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Diterpenoids. XI.[1] A Synthesis of Hydrofluorene Derivatives (*trans*-A/B-Ring Fusion (β C_5-H))[2]

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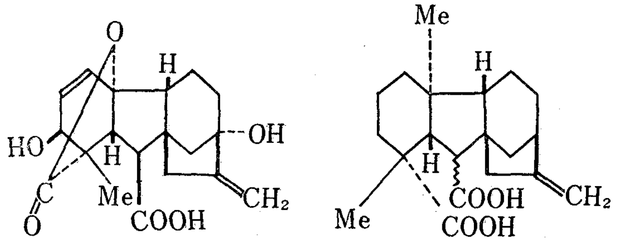
c-Homofluorene (VI) having undeniable *trans*-A/B-ring fusion has been previously synthesized from 1-abietic acid (I). In order to have a standard *trans*-A/B-ring hydrofluorene (XIII), basic skeleton of gibberellin, c-homofluorene (VI) was chosen as starting material and its seven membered alicyclic C-ring was contracted to benzene ring.

An approach to gibberellin skeleton from resin acid (*e.g.* *l*-abietic acid (I)) has been attempted by application of benzilic acid rearrangement of methyl 6,7-dioxo-*allo-enantio*-podocarpa-8,11,13-triene-19-oate (II).[4] The structure of the rearranged product (III) has undeniable perhydrofluorene skeleton, however, which still remains obscure on C_5-configuration (In the succeeding paper,[5] its stereochemistry will be clearly proved to be α C_5–H configuration (*cis*-A/B-ring fusion)).

General structure of gibberellin group (*e.g.* gibberellin A_3 (gibberellic acid) (IV) and A_{12} (V)) has *trans*-A/B-ring fusion (α C_{10}–O or α C_{10}–Me and β C_5–H), nevertheless, the basic skeleton having the above mentioned *trans*-fusion, has not yet been synthesized by chemical conversion from the other natural product. As shown in the previous paper,[1] c-homofluorene (VI) having *trans*-A/B-ring fusion has been already synthesized from *l*-abietic acid (I) and its structure was validly determined.



IV V

Chart 1

So, c-homofluorene (VI) was herein chosen as starting material and its seven membered alicyclic C-ring was contracted to benzene ring in order to have a standard *trans*-A/B-ring hydrofluorene. The expected compound (XIII) is regarded as one of the basic gibberellin skeleton (*trans*-A/B-ring fusion) and is also comparable with the compound (III)[4] (*cis*-A/B-ring fusion) obtained by the benzilic acid rearrangement. Accordingly, a synthesis of the compound (XIII) would be significant for making a standard in stereochemical study of the related compounds.

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1) Previous communication: *Tetrahedron Letters*, **1966**, 5031; Part X: A. Tahara, O. Hoshino, and T. Ohsawa *Chem. Pharm. Bull.* (Tokyo), **17**, 52 (1969).

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

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

4) 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**.

5) A. Tahara, O. Hoshino, and T. Ohsawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 68 (1969).

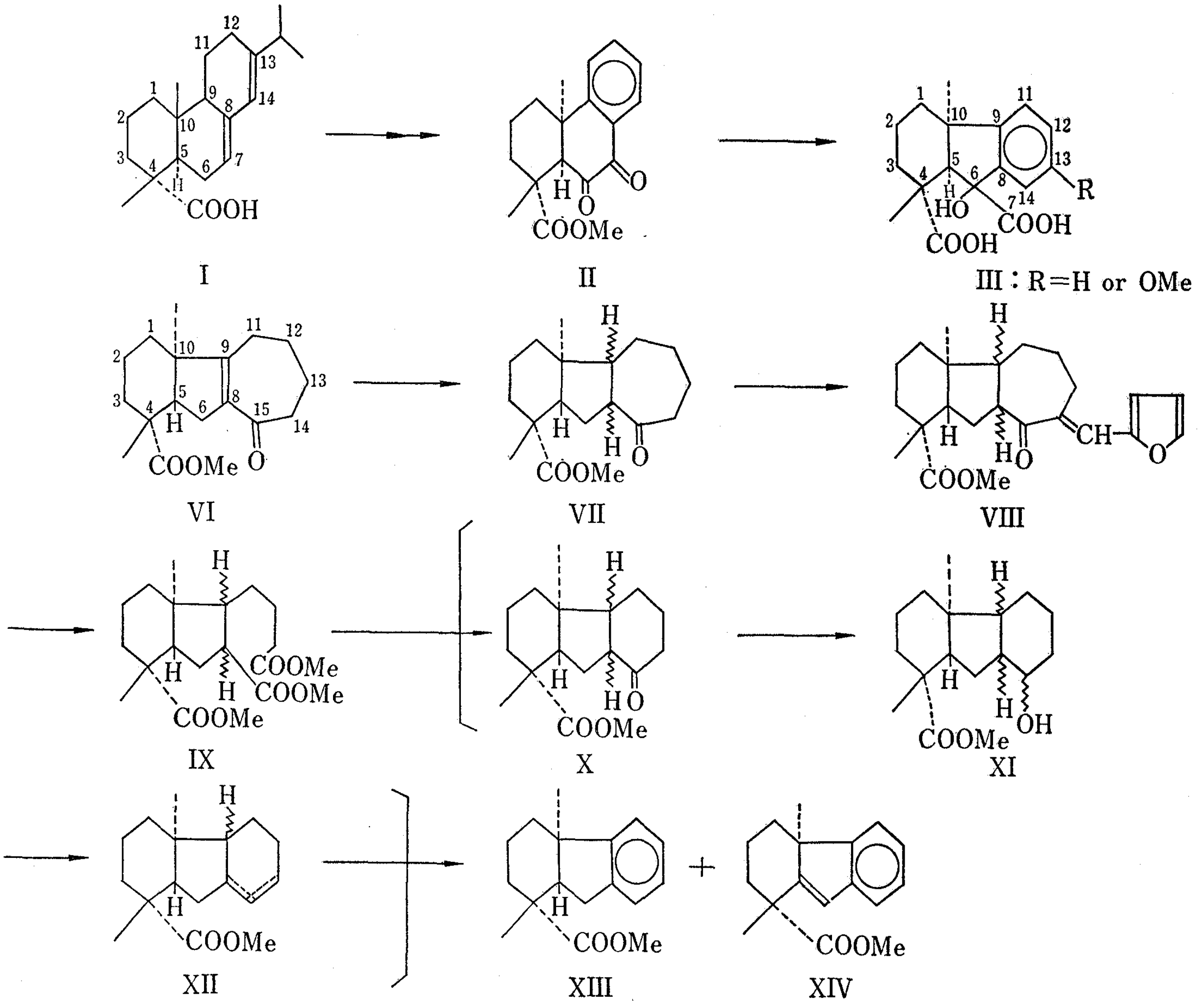

Chart 2

At first, for the hydrogenation of double bond of the homofluorene ester (VI),[1] VI was catalytically reduced in the presence of palladium charcoal under 45 lbs./in^2 hydrogen pressure. The hydrogenated product, whose thin-layer chromatogram (TLC) showed two main and one small spots, is considered as mixture of stereoisomers at B/C ring fusion. The mixture was heated with mineral acid to induce an epimerization at C_8 adjacently attached to the carbonyl group. In a thin-layer chromatogram of the epimerized mixture, one main spot (two main spots became one by the acid treatment) together with a small one remained. The main spot was chromatographically separated on alumina to give saturated c-homohydrofluorene (VII), mp 104—106°, IR ν_{max}^{KBr}: 1715, 1695 cm^{-1} in pure state. Since the asymmetric centre of B/C-ring juncture will be canceled afterwards as benzene ring, reliable evidence on its stereochemistry was not adduced.

For the selective fission of the saturated oxo ester (VII) at C_{14}–C_{15} bond and the contraction of seven to six membered ring, VII was converted to the corresponding furfuridene oxo ester (VIII), mp 103—105° by the usual treatment of furfural under alkaline condition. C-ring of VIII was smoothly cleaved by ozone gas treatment and successively the decomposition of the resulted ozonide. The obtained acidic product was methylated as usual to afford the corresponding ester (IX) as colorless oil, bp 225—230° (bath temp.)/1 mmHg. Dieckmann condensation of the trimethyl ester (IX) was carried out with sodium hydride in xylene and the neutral product was purified by chromatography to give isomeric mixture (X), mp 55—75°. It could be assumed that the mixture consisted of two stereoisomers due to C_8-configuration by observation of its thin-layer chromatogram.

For the purpose of aromatization of ring-C, the carbonyl group of the ester (X) was removed as follows. Thereupon, sodium borohydride reduction of the isomeric mixture of the esters (X) afforded the corresponding alcohol (XI), whose gas liquid-chromatogram showed four peaks depending on stereoisomers at C_8-angular proton and C_{14}-hydroxyl configuration. Successively, the alcohol (XI), without purification, was dehydrated with phosphorus oxychloride in pyridine. The location of the double bond of dehydrated ester (XII) in gas chromatographically pure state is still obscure.

At last, the unsaturated ester (XII) was readily aromatized by reflux with sulfur in quinoline. Gas liquid-chromatographical investigation of the aromatized mixture showed a small amount of unsaturated ester (XIV)[6] was mingled in the aimed ester (XIII). Successive chromatography on alumina of the reaction mixture afforded major product, mp 83—84°, IR $\nu_{\max}^{\text{KBr}}$: 1715 cm^{-1} and NMR τ: 9.18 (s, 3H), 8.75 (s, 3H), 6.38 (s, 3H). Since the configuration of *trans*-A/B-ring fusion in the starting material (VI) should not be varied during the sequence of the reaction (VI—XIII), it can be reasonably stated that the hydrofluorene compound has stereochemical structure as shown in XIII.

Experimental

Catalytic Reduction of Methyl 4β,10α-Dimethyl-15-oxo-c-homohydrofluore(β 5-H)-8-monoene-4α-carboxylate (VI). Stereoisomeric Mixture of 4β,10α-Dimethyl-15-oxo-c-homohydrofluore(β 5-H)-4α-carboxylate (VII)——A solution of α,β-unsaturated keto ester (VI) (150 mg) in EtOH (20 ml) was shaken in the presence of 10% Pd–C (50 mg) under hydrogen atmosphere (starting pressure, 45 lbs./in^2). After an absorption of H_2 had almost ceased in 5 hr, the catalyst was filtered off and the filtrate was evaporated to give oil (152 mg, TLC (Al_2O_3, petr. ether–$CHCl_3$ (1:1), 3 spots)). A solution of oil in 10% HCl aq. (0.1 ml) and MeOH (2 ml) was refluxed for 1 hr and usual treatment gave oil (152 mg, TLC (same condition stated above), 2 spots). Chromatography of the oil on alumina (7.5 g) gave crystals (121 mg) in petr. ether–ether (20:1) elution. They were recrystallized from MeOH–H_2O to give colorless prisms (VII) (109 mg, 72% yield), mp 98—104°, whose analytical sample is mp 104—106°. *Anal.* Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.12; H, 9.73. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1715 (COOMe), 1695 (sat. 7-membered ring CO). NMR τ: 9.47 (s, 3H; C_{10}-Me), 8.80 (s, 3H; C_4-Me), 6.41 (s, 3H; COOMe).

16-Furfuridene Derivative (VIII) of VII——A solution of oxo ester (VII) (250 mg) and freshly distilled furfural (1 ml) in EtOH (10 ml) and 15% NaOH aq. (4 ml) was left standing at room temperature for 45 hr. After the reaction mixture was diluted with H_2O, appeared crystals (311 mg, 98% yield), mp 96—102°, were collected and recrystallized from MeOH–H_2O to give colorless prisms (VIII), mp 103—105°. *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.61; H, 8.28. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1720 (COOMe), 1680 (sat. 7-membered ring CO), 1605 (C=C). NMR τ: 9.42 (s, 3H; C_{10}-Me), 8.75 (s, 3H; C_4-Me), 6.38 (COOMe).

Oxidative Cleavage of 16-Furfuridene Derivative (VIII). Cleaved Tricarboxylic Acid Methyl Ester (IX)——To a solution of furfuridene ester (VIII) (300 mg) in AcOEt (15 ml), ozone gas was bubbled at −70° until the solution changed to blue color (it took 1—2 hr) and the solvent was evaporated under reduced pressure. 30% H_2O_2 (0.25 ml) and conc. HCl (0.25 ml) was added to a solution of the resulted residue in AcOH (7 ml) under ice–cooling and it was left standing at room temperature for 19 hr. After a small amount of Pd–C was added to the reaction mixture to decompose excess H_2O_2, the solvent was evaporated *in vacuo* and ether extract of the residue was washed with H_2O and extracted with 10% Na_2CO_3 aq. The Na_2CO_3 aq. extract was acidified with conc. HCl under ice–cooling and then it extracted with ether. The ether extract was washed with H_2O and treated as usual with diazomethane–ether solution. The resulted oil (300 mg) was distilled at bp 225—230° (bath temp.)/1 mmHg to give colorless oil (IX) (290 mg, 97% yield). *Anal.* Calcd. for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 64.41; H, 8.76. IR $\nu_{\max}^{\text{CCl}_4}$ cm^{-1}: 1735, 1725 (COOMe). NMR τ: 9.50 (s, 3H; C_{10}-Me), 8.84 (s, 3H; C_4-Me), 6.42, 6.38 (COOMe). TLC (Al_2O_3, petr. ether–$CHCl_3$ (1:1)), one spot.

Dieckmann Condensationn of Tricarboxylic Acid Methyl Ester (IX). Stereoisomeric Mixture of Methyl 4β,10α-Dimethyl-14-oxo-hydrofluore(β 5-H)-4α-carboxylate (X)——A mixture o triester (IX) (260 mg) and sodium hydride (100 mg) in ab. xylene (15 ml) was refluxed for 5 hr under N_2–stream and, after sodium hydride (50 mg) was newly added, it was continued to reflux for more 11 hr. Then benzene (10 ml) containing AcOH (1 ml) were added to the reaction mixture and the organic solution was washed with H_2O. The organic solution was combined with ether solution extracted from aqueous layer and it was dried over Na_2SO_4, then the solvent was evaporated *in vacuo*. Solution of the obtained oil (202 mg) and conc. HCl (1 ml) in AcOH (5 ml)–H_2O (0.5 ml) was refluxed for 3 hr and then the solvent was removed *in vacuo*.

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[6] A synthesis and this compound (XIV) will be described in our succeeding paper.[5]

An ether solution of the residue was washed with H_2O and extracted with 10% Na_2CO_3 aq. i) Acidic Part: Na_2CO_3 aq. extract was acidified with conc. HCl and it was extracted with ether. Usual treatment of the ether extract gave oil (28 mg). ii) Neutral Part: The ether layer was dried over Na_2SO_4 and evaporated. The resulted oil (124 mg) was chromatographed on alumina (6.0 g) to give in petr. ether–ether (20:1) elution oily crystals (X) (100 mg, 51% yield), mp 55—75°, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735 (its TLC (Al_2O_3, petr. ether–$CHCl_3$ (1:1)) shows 2 spots, which is presumably due to two stereoisomers at C_8-angular proton configuration), and they were used in the next step without purification.

Isomeric Mixture of Methyl 4β,10α-Dimethyl-hydrofluore(β 5-H)-monoene-4α-carboxylate (XII) from Stereoisomeric Mixture of 4β,10α-Dimethyl-14-oxo-hydrofluore(β 5-H)-4α-carboxylate (X) *via* Stereoisomeric Mixture of Methyl 4β,10α-Dimethyl-14-hydroxy-hydrofluore(β 5-H)-4α-carboxylate (XI)——After a mixture of oxo ester (X) (100 mg) and $NaBH_4$ (80 mg) in MeOH (5 ml) was refluxed for 3 hr, H_2O and 10% HCl aq. were added to the residue obtained by the evaporation of solvent and it was extracted with ether. The ether extract was washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave oil (XI) (100 mg), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3650 (OH), 1735 (COOMe), whose gas liquid chromatogram (t_R: 13.1, 14.0, 15.3 and 17.65; 2% XE–60, 1.75 m×4 mm, 165°) shows it presumably consists of four stereoisomers due to configuration of C_8-angular proton and C_{14}-hydroxyl group. It was used in next step without further purification.

A solution of the oil (XI) (98 mg) in pyridine (2.0 ml) and $POCl_3$ (0.1 ml) was left standing at room temperature for 3 hr. After ice–water was poured into the reaction mixture and it was extracted with ether, the ether extract was washed with 10% HCl aq., then H_2O and dried over Na_2SO_4. Removal of the solvent gave crystalline mass (66 mg), which were chromatographed on alumina (3.5 g) to give crystals (XII) (47 mg, 51% yield), mp 80—93°, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735 (COOMe), in petr. ether elution. They were in gas liquid chromatographically pure state (t_R: 3.15; 1% XE–60 on 1.75 m×4 mm, 152°) and used in the next step without further purification.

Aromatization of Isomeric Mixture of Methyl 4β,10α-Dimethyl-hydrofluore(β 5-H)-monoene-4α-carboxylate (XII). Methyl 4β,10α-Dimethyl-hydrofluore(β 5-H)-8,11,13-triene-4α-carboxylate (XIII) and Methyl 4β,10α-Dimethylhydrofluore-5,8,11,13-tetraene-4α-carboxylate (XIV)——A solution of ester (XII) (35 mg) in quinoline (1 ml) was refluxed with sulfur (13 mg) for 2.5 hr until evolution of H_2S gas was ceased. Ether was added to the reaction mixture and undissolved material was filtered off. The filtrate was washed with 10% HCl aq., 10% Na_2CO_3 aq., then H_2O and dried over Na_2SO_4. Removal of the solvent gave oil (24 mg), which was chromatographed on alumina (1.5 g) to give crystals (6 mg, 17% yield), mp 65—75° in petr. ether elution. They were recrystallized from MeOH–H_2O to give colorless prisms (XIII), mp 83—84°. *Anal.* Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.69; H, 8.69. IR ν_{max}^{KBr} cm^{-1}: 1715. NMR τ: 9.18 (s, 3H; C_{10}-Me), 8.75 (s, 3H; C_4–Me), 6.38 (s, 3H; COOMe). Retention time of the *trans*–isomer in gas liquid chromatography (t_R: 7.25; 1% XE–60, 152°) was completely different from that of *cis*–isomer (t_R: 8.05; under the same condition) reported in our successive article.[5] Gas liquid chromatogram of the mixed oil showed it consisted of a small amount of unsaturated ester (XIV) (t_R: 8.40; under the same condition) in addition to the main ester (XIII) before the chromatographical purification was carried out.

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