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Diterpenoids. XII.[1] Catalytic Hydrogenation of $\Delta^{5,6}$- and 6-Enol Acetoxyhydrofluorene Derivatives. A Synthesis of Hydrofluorene Derivatives (cis-A/B-Ring Fusion (α C_5-H))[2]

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Hydrofluorene (III) and (IV) prepared by alkaline treatment of *cis*-dioxo ester (II), was already considered, without reliable evidence, to have *cis*-A/B-ring fusion. Now, in comparison with standard *trans*-hydrofluorene (XII) previously reported, the assumption on the structure of IV has been confirmed.

Otherwise, stereochemical analysis on catalytic hydrogenation of $\Delta^{5,6}$-unsaturated hydrofluorene (XIV and XV) is also carried out.

In the preceding paper,[1] an indisputable synthesis of hydrofluorene derivatives (XII) having *trans*-A/B-ring fusion (β C_5-H) from *l*-abietic acid (I) was accomplished.

On synthesis of the other type of hydrofluorene derivative from the resin acid (I), M. Ohta firstly reported that hydrofluorenone (IV) was obtained from methyl 6,7-dioxo-*allo-enantio*-podocarpa-8,11,13-triene-19-oate (II) through tricarboxylic acid (VII).[4] In succession, benzilic acid rearrangement was applied to the dioxoester (II) for the synthesis of III and IV by our[5] and Englishg roups[6] independently. Since the dioxo ester (II), used as starting material in the above two ways, has *cis*-A/B-ring fusion (α C_{10}-Me and α C_5-H), the hydrofluorene products (III) and (IV) would be probably assumed to retain its configuration if an epimerisation was not occurred at C_5-H during the reaction. However, sufficient evidence for it was not adduced until that time. Thus, in order to confirm the stereochemistry of hydrofluorenes (III) and (IV), the above mentioned *trans*-hydrofluorene (XII)[1] will be herein compared as standard with the corresponding compound derived from III and IV.

A convenient preparation of hydrofluorenone (V), methyl ester of the corresponding acid (IV) stated above, was performed from dioxo ester (II) through its oxidatively cleaved product, dicarboxylic acid ester (VIII). First attempt for removal of carbonyl group in the fluorenone ester (V) was carried out by Wolff–Kishner reduction. Thereupon, the treatment of oxo ester (V) with hydrazine hydrate and potassium hydroxide, gave the acid (IX), mp 156—160° (74% yield), which, without purification, was methylated as usual to the corresponding ester (X), mp 58—60°. Considering that both the isomeric esters (X and XII) have the same configurations except C_5-H as described in our previous papers, the discrepancy between the physical constants of the isomers indicates that the ester (X) should be the stereoisomer at C_5 of standard *trans*-ester (XII); that is, ester (X) has *cis*-A/B-ring fusion.

1) Previous communication: *Tetrahedron Letters*, **1966**, 5031; Part XI: A. Tahara, O. Hoshino, and T. Ohsawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 64 (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) M. Ohta, *Chem. Pharm. Bull.* (Tokyo), **5**, 256 (1957).
5) 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).
6) J.F. Grove and B.J. Riley, *J. Chem. Soc.*, **1961**, 1105.

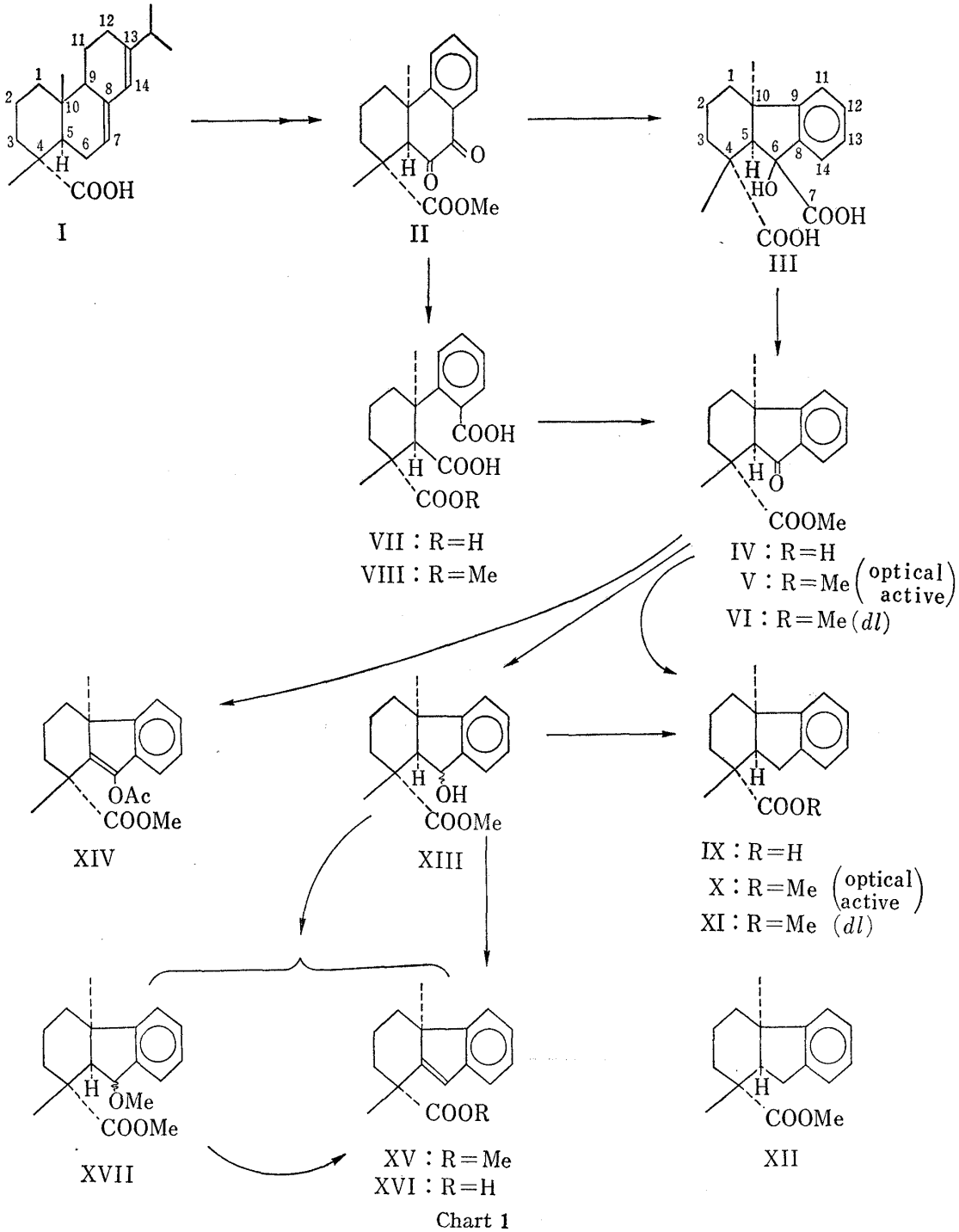


Chart 1

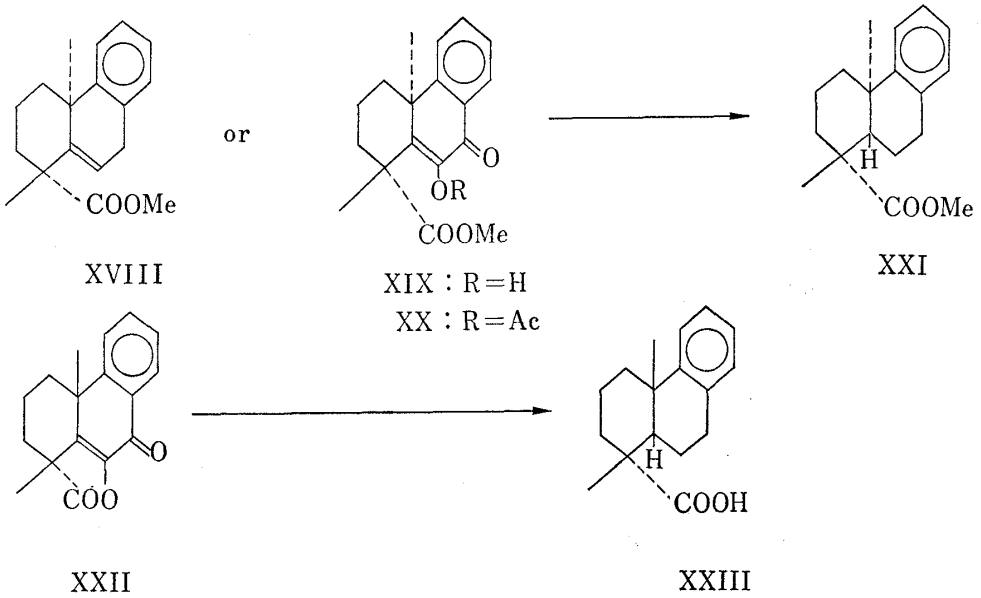
However, it would be premature to assume that the starting hydrofluorene (V) should also has *cis*-A/B-ring fusion only upon the above observation, for there is some fear of an epimerisation at C_5-H under the reduction condition. Accordingly, for the purpose of elucidation on stereochemistry of the oxo ester (V), the carbonyl group should be removed by the following reduction. Oxo ester (V) and also hydroxyl ester (XIII), bp 195—200°/6 mmHg, quantitatively obtained by $NaBH_4$-reduction of V, were hydrogenolized with palladium charcoal to yield the *cis*-hydrofluorene (X) as main product in both cases. An assumption of the main route of hydrogenolysis *via.* dehydrated product (XV) was canceled by the experimental fact that the ratio of the isomeric products (X and XII) (only *cis*-isomer (X) from V, and isomeric mixture (*cis–trans* ratio; 11:1) from XIII) is completely different from that in hydrogenation of dehydrated ester (XV) (*cis–trans* ratio; 4.5:1) to be described later.

So, the hydrogenolysis should be concluded to mainly proceed without epimerization at C_5-H. Therefore A/B-ring juncture of the fluorene (XIII and V) should be the same configuration as in *cis*–hydrofluorene (X) confirmed by comparison with standard *trans*–isomer (XII). Previously, hydrofluorene (III) prepared by alkaline treatment of *cis*–dioxo ester (II), was considered, without reliable evidence, to have *cis*-A/B-ring fusion. The present structural determination of the fluorene (XIII and V) strongly supports the assumption upon the structure (III).

Recently, U.R. Ghatak and co–workers reported a synthesis of *dl*-hydrofluorene series (VI) and (XI) by cyclic condensation.[7] In order to verify their assumption of the stereochemistry, Ghatak's *dl*-compounds (VI and XI) were compared with the respective our compounds (optical active) (V and X). Identification in the comparison gave another evident proof to the inference that Ghatak's samples were regarded as *cis*-A/B-ring compounds.

Now *trans*- (XII) and *cis*-hydrofluorene (X) are in our hand as authentic samples. Using these comparative standards, catalytic reduction mode of $\Delta^{5,6}$-unsaturated hydrofluorene skeleton will be consecutively studied.

Stereochemical analysis on a catalytic hydrogenation of $\Delta^{4,5}$- and $\Delta^{5,6}$-unsaturated 10-methyl decaline type skeletons, has been widely and precisely reported in terpene and steroid fields. Concerning the hydrogenation in resin acid field, for example, it is very noticeable that only the *trans*–isomer (XXI) was obtained by reduction of $\Delta^{5,6}$-unsaturated ester (XVIII, XIX and XX)[8] and, on the contrary, only *cis*-compound (XXIII) was yielded from $\Delta^{5,6}$-unsaturated lactone (XXII).[9] Therefore, the study on hydrogenation in the untapped hydrofluorene field, stimulates our interest.



XVIII XIX : R=H XX : R=Ac XXI XXII XXIII

Chart 2

The $\Delta^{5,6}$-unsaturated hydrofluorenes (XIV and XV) were synthesized for the above project. Enol–acetylation of oxo-ester (V) with acetic anhydride in the presence of potassium acetate, readily proceeded to give enol acetate (XIV), mp 150—153° (50% yield), whose infrared (IR) spectrum (ν (KBr): 1755 (OAc), 1635 (C=C), 1210 (C–O) cm^{-1}) showed that

7) U.R. Ghatak, J. Chakravarty and A.K. Benerjee, *Tetrahedron Letters*, **1967**, 3145.
8) A. Tahara, O. Hoshino and Y. Hamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 1328 (1963): *Sci. Papers Inst. Phys. Chem. Res.*, **58**, 15 (1964); A. Tahara, K. Hirao and Y. Hamazaki, *Chem. Pharm. Bull.* (Tokyo), **12**, 1498 (1964); A. Tahara and K. Hirao, *ibid.*, **12**, 984 (1964): *Tetrahedron*, **21**, 2133 (1965).
9) E. Wenkert, A. Afonso, P. Beak, R.W.J. Carney, P.W. Jeffs and J.D. McChesney, *J. Org. Chem.*, **30**, 713 (1965).

the structure is reasonable. In the other way, the above mentioned hydroxy ester (XIII) was dehydrated with phosphorus oxychloride in pyridine to give $\Delta^{5,6}$-unsaturated ester (XV), mp 74—76° (40% yield), whose NMR spectrum due to an olefinic proton indicates the accurate location of its double bond. Reflux of the hydroxy ester (XIII) in methanol containing conc. hydrochloric acid afforded methoxy ester (XVII, 30% yield), mp 66—68°, whose NMR spectrum appeared at 6.70, 7.16 and 5.13τ due to OMe, C_5-H and C_6-H respectively, in addition to the above mentioned unsaturated ester (XV, 42% yield). The methoxy ester (XVII) was demethanolized in acetic acid with 40% HBr aq. to give the unsaturated ester (XV) in satisfactory yield. Alkaline hydrolysis of the unsaturated ester (XV) readily gave the corresponding acid (XVI), mp 100—101°.

Table I. Hydrogenation of $\Delta^{5,6}$-Hydrofluorene Derivative

Reduction condition	Ratio of *cis*- (X) and *trans*-hydrofluorene (XII)
5% Pd–C, AcOH, conc. H_2SO_4	7.7:1
10% Pd–C, AcOH, conc. H_2SO_4	4.5:1
60% Pd–C, AcOH, conc. H_2SO_4	5.0:1
Raney Ni(W=7), EtOH, 50 lbs.	1.9:1 (starting material (XV) 1.5)
10% Pd–C, AcOH conc. H_2SO_4	4.5:1[a]
Li–$EtNH_2$–NH_4Cl	16.5:1[a] (starting material (XVI) 10.0)

Ratio of product was determined by gas liquid chromatographic analysis (1% NGS on Anakrom, glass column 4 mm×1.75 m, 160°).
a) The ratio was detected as the corresponding ester.

The enol acetate (XIV) and unsaturated ester (XV) were hydrogenated in acetic acid with palladium charcoal in the presence of sulfuric acid. Gas liquid-chromatogram of the resulted mixtures (obtained from XIV and XV) showed that they consisted of *cis*- (X) and *trans*–isomers (XII) in the ratio of 4.5:1 and 4:1 respectively. Also the isomeric mixtures were chromatographed on alumina to preparatively separate *cis*- (X) and *trans*–isomer (XII) (76% and 11% yield from (XIV); 70% and 8.4% yield from XV).

Successively, gas liquid chromatographic analysis of hydrogenated mixtures obtained under the different hydrogenation conditions indicated an interesting variety in the ratio of the stereoisomers as shown in Table 1. Thereupon, in the hydrogenation of $\Delta^{5,6}$-unsaturated ester (XV) with 5%, 10% and 60% palladium charcaol, the ratio of the obtained isomer (X and XII) was observed as 7.7:1, 4:1 and 5.0:1 respectively; reduction of the compound (XV) with Raney nickel (W–7) in ethanol under 50 lbs. pressure, gave *cis*- (X), *trans*–isomer (XII) and starting material (XV) in the ratio of 1.9:1:1.5. From the result, it can be reasonably stated that hydrogenation under palladium charcoal as catalyst predominantly yielded *cis*–isomer (X), while with Raney nickel catalyst *trans*–isomer was relatively increased. In the reduction of the corresponding acid (XVI) by lithium–ethylamine, *cis*–isomer (IX) was predominantly produced; 16.5 (*cis*–isomer (X)):1 (*trans*–isomer (XII)):10 (starting material (XVI)).[10] Thus, it can be stated that *cis*–isomer (IX) is more thermodynamically stable in these hydrofluorene systems. The result finely contrasted with that of usual hydrogenation of the acid (XVI) in the presence of 10% palladium charcoal catalyst (4.5 (*cis*–isomer (X):1 (*trans*–isomer (XII)).

As above mentioned, hydrogenation mode of $\Delta^{5,6}$-unsaturated fluorene system in company with stereochemistry of isomeric hydrofluorene due to C_5-configuration is clearly ascertained herein.

10) The ratio was detected as the corresponding methyl ester by gas liquid chromatography.

Experimental

Methyl 4β,10α-Dimethyl-6-oxohydrofluore(α 5-H)-8,11,13-triene-4α-carboxylate (V)——A solution of tricarboxylic acid monoester (VIII) (1.0 g), previously reported,[4] in acetic anhydride (5 ml) was refluxed for 3 hr and the solvent was evaporated at 230—260°. The resulted oil was distilled at 260—270°/40 mmHg to give oil (0.83 g), which was redistilled to afford colorless oil (V) (0.58 g, 71% yield), bp 175—177°/4 mmHg. *Anal.* Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.38; H, 7.51. IR ν_{max}^{film} cm^{-1}: 1730 (COOMe), 1710 (α, β-unsat. five membered ring ketone), 1605 (C=C). NMR τ: 8.66 (s, 3H), 8.49 (s, 3H), 6.98 (s, 1H; C_5–H), 6.32 (s, 3H; COOMe). t_R: 12.2 (2% XE-60, 165°). Physical constants of the above mentioned oxo ester (V) was identical with oxo ester previously obtained by methylation of the known optical active[4,5] and racemic[7] acid.

Methyl 4β,10α-Dimethylhydrofluore(α 5-H)-8,11,13-triene-4α-carboxylate (X) from Methyl 4β,10α-Dimethyl-6-oxohydrofluore(α 5-H)-8,11,13-triene-4α-carboxylate (V) *via* 4β,10α-Dimethyl-6-oxohydrofluore-(α 5-H)-8,11,13-triene-4α-carboxylic Acid (IX)——A solution of oxo ester (V) (200 mg) in diethylene glycol (5 ml) was heated with 90% hydrazine hydrate (0.25 ml) and KOH (0.35 g) for 1.5 hr at 130—140° and further for 4 hr at 210—220°. After excess hydrazine hydrate was distilled off in vacuum and then H_2O was added, the H_2O-layer was extracted with ether, then acidified with conc. HCl and extracted with ether. The ether extract was washed with H_2O and dried over Na_2SO_4. Removal of the solvent afforded crystals (132 mg), mp 135—157°, which were recrystallized from MeOH–H_2O to give colorless prisms (86 mg, 48% yield), mp 156—160°. The crystals were used in the next step without further purification. An ether solution of the above acid (IX) (30 mg) was treated as usual with diazomethane–ether solution. The resulted crystals (30 mg), mp 52—57°, were recrystallized from EtOH–H_2O to give colorless prisms (27 mg, 85% yield), mp 54—60°, whose analytical sample had mp 58—60°. *Anal.* Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.37; H, 8.31. IR ν_{max}^{KBr} cm^{-1}: 1730. NMR τ: 8.84 (s, 6H; C_4– and C_{10}-Me), 7.23 (broad, 2H), 6.37 (COOMe). t_R: 5.10 (1.0% SE-30 on shimalite, 4 m×3 mm, 169°). Physical constants (IR-spectrum and t_R) of this ester (X) were identical with those of *dl*-compound synthesized through the other route by Dr. U.R. Ghatak, *et al.*,[7] but were completely different from those of the *trans*-isomer (XII) previously reported.[1]

Methyl 4β,10α-Dimethyl-6-hydroxyhydrofluore(α 5-H)-8,11,13-triene-4α-carboxylate (XIII)——A solution of oxo ester (V) (500 mg) in MeOH (10 ml) was refluxed with $NaBH_4$ (400 mg) for 6 hr and the solvent was evaporated in vacuum. The obtained residue was diluted with H_2O, acidified with 10% HCl aq. and extracted with ether. The ether extract was washed with H_2O, then dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resulted oil (530 mg) was distilled to give colorless oil (XIII), bp 195—200°/6 mmHg. *Anal.* Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.11; H, 7.84. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3590 (OH), 1730 (COOMe). NMR τ: 8.91 (s, 3H; C_{10}-Me), 8.70 (s, 3H; C_4-Me), 6.43 (s, 3H; COOMe).

Methyl 4β,10α-Dimethylhydrofluore(α 5-H)-8,11,13-triene-4α-carboxylate (X)——i) Catalytic Hydrogenolysis of Methyl 4β,10α-Dimethyl-6-oxohydrofluore(α 5-H)8,11,13-tiene-4α-carboxylate (V) : A solution of oxo ester (V) (100 mg) in AcOH (10 ml) containing conc. H_2SO_4 (0.02 ml) was shaken under hydrogen atmosphere in the presence of 10% Pd–C (50 mg). After an absorption of H_2 had almost ceased, the catalyst was filtered off and the filtrate was evaporated in vacuum. An ether solution of the resulted residue was washed with sat. $NaHCO_3$ aq., then H_2O and dried over Na_2SO_4. Removal of the solvent gave crystals (59 mg, 62% yield), whose gas liquid chromatogram shows it consists of only *cis*-ester (X) (t_R: 7.70 (1% XE-60, 157°; *cf. trans*-isomer, t_R: 6.85)).

ii) Catalytic Hydrogenolysis of Methyl 4β,10α-Dimethyl-6-hydroxyhydrofluore(α 5-H)-8,11,13-triene-4α-carboxylate (XIII): A solution of hydroxy ester (XIII) (100 mg) in AcOH (10 ml) containing a small amount of conc. H_2SO_4 was shaken under hydrogen atmosphere in the presence of 10% Pd–C (50 mg). After an absorption of H_2 had almost ceased, the reaction mixture was treated as stated above. Gas liquid chromatogram of the resulted oil (90 mg, 95% yield) shows it consists of *cis*- (X) and *trans*-isomer (XII) in the ratio of 11:1, t_R: 6.85 (*trans* (XII)), 7.75 (*cis* (X)).

Methyl 4β,10α-Dimethyl-6-acetoxyhydrofluore-5,8,11,13-tetraene-4α-carboxylate (XIV)——A solution of oxo ester (V) (100 mg) and potassium acetate (40 mg) in acetic anhydride (3 ml) was refluxed for 2 hr and the solvent was removed under reduced pressure. After H_2O was added to the resulted residue, it was extracted with ether. The ether extract was washed with sat. $NaHCO_3$ aq., then H_2O and dried over Na_2SO_4. Removal of the solvent gave crystals (63 mg, 55% yield), mp 135—145°, which were recrystallized from MeOH–H_2O to give colorless prisms (XIV) (55 mg), mp 150—153°. *Anal.* Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.73; H, 7.06. IR ν_{max}^{KBr} cm^{-1}: 1755 (C=C–OAc), 1720 (COOMe), 1635 (C=C), 1210 (C–O).

Dehydration of Methyl 4β,10α-Dimethyl-6-hydroxyhydrofluore(α 5-H)-8,11,13-triene-4α-carboxylate (XIII)—i) Methyl 4β,10α-Dimethylhydrofluore-5,8,11,13-tetraene-4α-crboxylate (XV): A solution of hydroxy ester (XIII) (144 mg) and $POCl_3$ (0.5 ml) in pyridine (2 ml) was left standing at 0° for 2 days. It was poured into ice–water and was extracted with ether. The ether extract was washed with 10% HCl aq., then with H_2O and dried over Na_2SO_4. Removal of the solvent afforded oil (87 mg), which was chromato-

graphed on neut. alumina (5.0 g) to give oil (60 mg, 45% yield) in petr. ether elution. The oil was distilled in vacuum to give colorless oil (52 mg), bp 185—200° (bath temp.)/8 mmHg, which was crystallized to mp 40—45°. The crystals were recrystallized from MeOH–H_2O to give colorless prisms (XV), mp 76—77°. *Anal.* Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.96; H, 7.93. IR ν_{max}^{KBr} cm^{-1}: 1730 (COOMe), 1610 (C=C). NMR τ: 8.92 (s, 3H; C_{10}-Me), 8.49 (s, 3H; C_4-Me), 6.44 (s, 3H; COOMe), 3.53 (s, 1H; C_6-H).

ii) XV and Methyl 4β,10α-Dimethyl-6-methoxyhydrofluore(α 5-H)-8,11,13-triene-4α-carboxylate (XVII): A solution of hydroxy ester (XIII) (530 mg) in MeOH (10 ml) and conc. HCl (0.5 ml) wasre fluxed for 1.5 hr and then the solvent was removed under reduced pressure. The resulted oil was dissolved in ether and the ether solution was washed with H_2O, and dried over Na_2SO_4. Removal of the ether afforded the oil (500 mg), which was chromatographed on neut. alumina (15 g) to following fraction. i) Petr. ether elution gave oil (250 mg). It was recrystallized from MeOH–H_2O to give colorless prims (210 mg, 42% yield), mp 65—70°, whose physical constants (mixed mp and IR spectrum) were identical with those of the unsaturated ester (XV) obtained previously. ii) Successive petr. ether elution gave crystals (177 mg), mp 55—65°. They were recrystallized from MeOH–H_2O to give colorless prisms (XVII) (165 mg, 30% yield), mp 60—67°, whose analytical sample had mp 66—68°. *Anal.* Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.23; H, 8.69. IR ν_{max}^{KBr} cm^{-1}: 1715 (COOMe). NMR τ: 8.83 (s, 3H; C_{10}-Me), 8.72 (s, 3H; C_4-Me), 6.70 (s, 3H; OMe), 6.37 (s, 3H; COOMe), 7.16 (d (9 cps), 1H; C_5-H), 5.13 (d (9 cps), 1H; C_6-H).

Methyl 4β,10α-Dimethylhydrofluore-5,8,11,13-tetraene-4α-carboxylate (XV)——A solution of methoxy ester (XVII) (50 mg) in AcOH (0.5 ml) and 40% HBr–H_2O (4 drops) was refluxed for 2 hr. After the solvent was evaporated in vacuum, the obtained residue was extracted with ether. Then the ether extract was washed with sat. $NaHCO_3$ aq., H_2O and dried over Na_2SO_4. Removal of the solvent gave crystals (37 mg, 83% yield), which were identical with unsaturated ester (XV) by comparison of their IR-spectra.

4β,10α-Dimethylhydrofluore-5,8,11,13-tetraene-4α-carboxylic Acid (XVI)——A solution of unsaturated ester (XV) (200 mg) and potassium hydroxide (100 mg) in ethylene glycol (6.0 ml) and H_2O (0.2 ml), was refluxed for 2.5 hr. After the reaction mixture was diluted with H_2O and extracted with ether, the alkaline aqueous layer was acidified with conc. HCl and then it was extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and the solvent was evaporated. The resulted crystals (196 mg), mp 86—90°, were recrystallized twice from MeOH–H_2O to colorless needles (XVI), mp 100—101°. *Anal.* Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.30; H, 7.56. IR ν_{max}^{KBr} cm^{-1}: 3600, 1695.

Methyl 4β,10α-Dimethylhydrofluore(β 5-H)-8,11,13-triene-4α-carboxylate (XII) and Methyl 4β,10α-Dimethylhydrofluore(α 5-H)-8,11,13-triene-4α-carboxylate (X)——i) Catalytic Hydrogenolysis of Methyl 4β,10α-Dimethyl-6-acetoxyhydrofluore-5,8,11,13-tetraene-4α-carboxylate (XIV): A solution of enol acetate (XX) (150 mg) in AcOH (20 ml) containing conc. H_2SO_4 (0.01 ml) was shaken under hydrogen atmosphere in the presence of 10% Pd–C (90 mg). The hydrogenation was continued for 21 hr at room temperature and then more 11 hr under IR-lamp heating. After the catalyst was filtered off and the filtrate was condensed under reduced pressure, ether solution of the obtained residue was washed with sat. $NaHCO_3$ aq., then H_2O and dried over Na_2SO_4. Removal of ether gave oil (130 mg) (its gas liquid chromatogram shows it consists of *cis*- (X) and *trans*-isomer (XII) in the ratio of 4.5:1), which was chromatographed on neut. alumina (10 g) to give following fractions. i) Petr. ether elution: The obtained oily crystals (40 mg) (its gas liquid chromatogram shows it still contains two compounds) were rechromatographed on neut. alumina (4.0 g) to give crystals (14 mg, 11% yield), mp 60—73° and successively other crystals (10 mg). The former crystals were recrystallized from MeOH–H_2O to give colorless prisms, mp 82—84°, whose physical constants (t_R and IR spectrum) were identical with those of *trans*-isomer (XII) previously reported. While IR spectrum indicated the latter crystals were *cis*-isomer (X), which was combined with next *cis*-isomer fraction. ii) Petr. ether–ether (100:1) and (20:1) elution: The obtained crystals (100 mg), mp 48—54°, were combined with the *cis*-isomer obtained from petr. ether elution and recrystallized from MeOH–H_2O to give colorless prisms (94 mg, 76% yield), mp 55—58°, whose physical constants (t_R and IR spectrum) were identical with those of *cis*-isomer (X) previously synthesized.

ii) Catalytic Hydrogenation of Methyl 4β,10α-Dimethylhydrofluore-5,8,11,13-tetraene-4α-carboxylate (XV): After a solution of unsaturated ester (XV) (1.0 g) in AcOH (80 ml) containing conc. H_2SO_4 (0.05 ml) was hydrogenated in the presence of 10% Pd–C (300 mg), it was worked up as in the case of enol acetate (XIV). The resulted oil (0.95 g) (its gas liquid chromatogram shows it consists of *cis*- (X) and *trans*-isomer (XII) in the ratio of 4.5:1 as shown in Table I) was chromatographed on neut. alumina (70 g) to give the following fractions. i) Petr. ether–ether (50:1) elution: The obtained crystals (27 mg), mp 79—82°, were recrystallized from MeOH–H_2O to give colorless prisms (25 mg), mp 83—84°, whose physical constants (mp, mixed mp, t_R and IR-spectrum) were identical with those of *trans*-isomer (XII). ii) Successive petr. ether–ether (50:1) elution: The resulted oil (150 mg) was rechromatographed on neut. alumina (10 g) to give crystals (70 mg), mp 69—78°, and successively give crystals (76 mg), mp 40—50°, in petr. ether–ether (200:3) elution. The former crystalls were recrystallized from MeOH–H_2O to give colorless prisms (58 mg), mp 77—80°, whose IR-spectrum and t_R were identical with those of the *trans*-isomer (XII). While, the latter crystals were recrystallized from MeOH–H_2O to give colorless prisms (60 mg), mp 53—55°, whose physical constants (mixed mp, IR-spectrum and t_R) were identical with those of *cis*-isomer (X). iii) Last petr. ether–ether (50:1 and 10:1) elution: The obtained crystals (656 mg), mp 44—55°, were recrystallized from

MeOH–H_2O to give colorless prisms (640 mg), mp 55—59°, whose physical constants (mixed mp, IR spectrum and t_R) were identical with those of *cis*-isomer (X). By the purification stated above *trans*-isomer (XII), (85 mg, 8.4% yield) and *cis*-isomer (X), (700 mg, 70% yield) were obtained as total yield.

Catalytic Hydrogenolysis under Various Conditions of Methyl 4β,10α-Dimethylhydrofluore-5,8,11,13-tetraene-4α-carboxylate (XV) and the Corresponding Acid (XVI)——Catalytic hydrogenation of the methyl ester (XV) or the corresponding acid (XVI) (50 mg) was carried out under the following conditions. Ratio of the yielded *cis*-(X) and *trans*-isomer (XII) was decided by peak area due to the corresponding isomer in the gas liquid-chromatogram (1.0% NGS on shimalite, 1.8 m×4 mm, 159°).

i) Methyl ester (XV) (50 mg) in AcOH (10 ml) containing conc. H_2SO_4 (0.05 ml) was hydrogenated in the presence of 5% Pd–C (25 mg). An oil (57 mg) obtained by usual treatment, consisted of *cis*-(X) and *trans*-ester (XII) in the ratio of 7.7:1 (t_R: 16.2 (*trans*), 18.4 (*cis*)).

ii) Hydrogenation of methyl ester (1 g scale) in the presence of 10% Pd–C was previously stated. The product consisted of *cis*-(X) and *trans*-ester (XII) in the ratio of 4.5:1.

iii) Methyl ester (XV) (50 mg) was hydrogenated in the presence of 60% Pd–C (25 mg) under the same condition. The hydrogenated oil consisted of *cis*-(X) and *trans*-ester (XII) in the ratio of 5.0:1 (t_R: 16.2 *trans*), 18.4 (*cis*)).

iv) A solution of methyl ester (XV) (50 mg) in EtOH (10 ml) was hydrogenated in the presence of Raney Ni (W-7) under hydrogen pressure 50 lbs./in^2. The catalyst was filtered off and the filtrate was evaporated in vacuum. The resulted oil (54 mg) consisted of *cis*-(X), *trans*-isomer (XII) and the starting material (XV) in the ratio of 1.9:1:1.5 (t_R: 18.2 (*trans*), 20.7 (*cis*), 23.9 (starting material)).

v) Acid (XVI) (50 mg) in AcOH (10 ml) containing conc. H_2SO_4 (0.05 ml) was hydrogenated in the presence of 10% Pd–C (25 mg). Crystals (50 mg), mp 117—151°, obtained by usual treatment, was methylated by diazomethane to give oil, which consisted of *cis*-(X) and *trans*-isomer (XII) in the ratio of 4.5:1 (t_R: 16.2 (*trans*), 18.3 (*cis*)).

vi) Lithium metal (4 mg) was added to a solution of acid (XVI) (50 mg) in absolute $EtNH_2$ and the reaction mixture was stirred at room temperature for 1.5 hr. After NH_4Cl (50 mg) was added and $EtNH_2$ was removed, 10% HCl aq. was added to the resulted residue and it was extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and the solvent was evaporated to give crystals (50 mg), mp 91—132° They were methylated by diazomethane–ether solution to afford an oil, which consisted of *cis*-(X), *trans*-isomer (XII) and the starting material in the ratio of 16.5:1:10 (t_R: 16.2 (*trans*), 18.6 (*cis*), 21.3 (starting material)).

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