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Diterpenoides. XXI. Hydration of Stereoisomers of Dimethyl 1,2,3,4,5,10,11,14-Octahydro-4β,10α-dimethyl-fluorene-4α, 6-dicarboxylate[1]

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Syntheses of 12- and 13-hydroxy diesters (XIII, XIV, XXI, and XXII) regarded as important intermediates for the formation of D-ring as in gibberellin, were accomplished in the unstable *trans*-(II) and stable *cis*-A/B-ring fused isomer (V) by reduction in lithium-liq. ammonia system and then by hydration with mercuric acetate. It is noticeable that 12-hydroxy diester (XX) obtained by epimerization at C-6 of the unstable form (XIII) has the same skeleton as in A- and B-ring of gibberallin A_{12}.

In our previous studies,[3] hydrofluorene diacid (IV) regarded as gibberellin skeleton (*e.g.* gibberellin A_{12}) and its stereoisomers (II, III and V) were synthesized from *l*-abietic acid (I). For an attempt on formation of D-ring on the hydrofluorenes as in gibberellin, substitution on the C-ring was examined.

Basing on the above idea, the selective substitution at 12- and 13- position of the four stereoisomers (II, III, IV and V) was succeeded by nitration method and published in our last report.[4]

Now, the same object have been achieved by another way, reduction of aromatic C-ring and successive hydration. The results will be described hereafter.

Hydrogenation of the aromatic C-ring of hexahydrofluorene diacids (II, III, IV and V) were examined using the lithium–liquid ammonia system. Among the four stereoisomers, (II) of *trans*-A/B-ring fused diacid and V of *cis* isomer could be reduced to pure octahydrofluorene (VI), mp 243—245°, and VII, mp 169.5—170.5°, respectively. Since the other hydrofluorenes (III and IV) gave an unseparable mixture, acids (II) and (V) only became the object of our study.

In general, on the reduction of substituted aromatic compounds by lithium-liquid ammonia, a 1,4-addition of hydrogens takes place so that the minimum possible number of alkyl groups are on the reduced positions.[5] Therefore, it is assumed that II and V were reduced at 11- and 14- positions. The structure of the hydrogenated compounds (VI and VII) was proved by following NMR spectra. In the corresponding dimethyl esters (VIII), mp 89.5—90.5°, and IX, mp 71—73°, the NMR pattern due to the aromatic C-ring disappeard and two signals attributed to allylic (VIII: 7.38 τ (width of half height: 2.4 cps) and IX: 7.44 τ

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[1] Part XX: A. Tahara and Y. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **20**, 1637 (1972). This was partly presented at the 90th Annual Meeting of the Pharmaceutical Society of Japan at Sapporo, July 1970 (Meeting Abstract, p. II-23); Melting points were determined on a micro hot-stagea nd uncorrected. Nuclear magnetic resonance (NMR) spectra were measured at 60 Mc in $CDCl_3$ (5—10% solution, tetramethylsilane as internal reference). Mass spectra were measured on JEOL's JMS-01S mass spectrometer with the direct sample inlet system (ionizing potential at 75 eV). Retention times (t_R) of gas-liquid chromatography were detected by using of the column (1.5% OV-17 on Shimalite W (100—120 mesh), 4 mm × 2 m) and carrier N_2 gas.

[2] Location: *Wako-shi, Saitama.*

[3] A. Tahara and Y. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **18**, 859 (1970); A. Tahra and Y. Ohtsuka, *J. Chem. Soc.* (Perkin I), **1972**, 320.

[4] A. Tahara and Y. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **20** 1637 (1972).

[5] A.J. Birch, *Quart. Rev.*, **4**, 69 (1950); E. Giovannini and H. Wegmüller, *Helv. Chim. Acta*, **41**, 933 (1958).

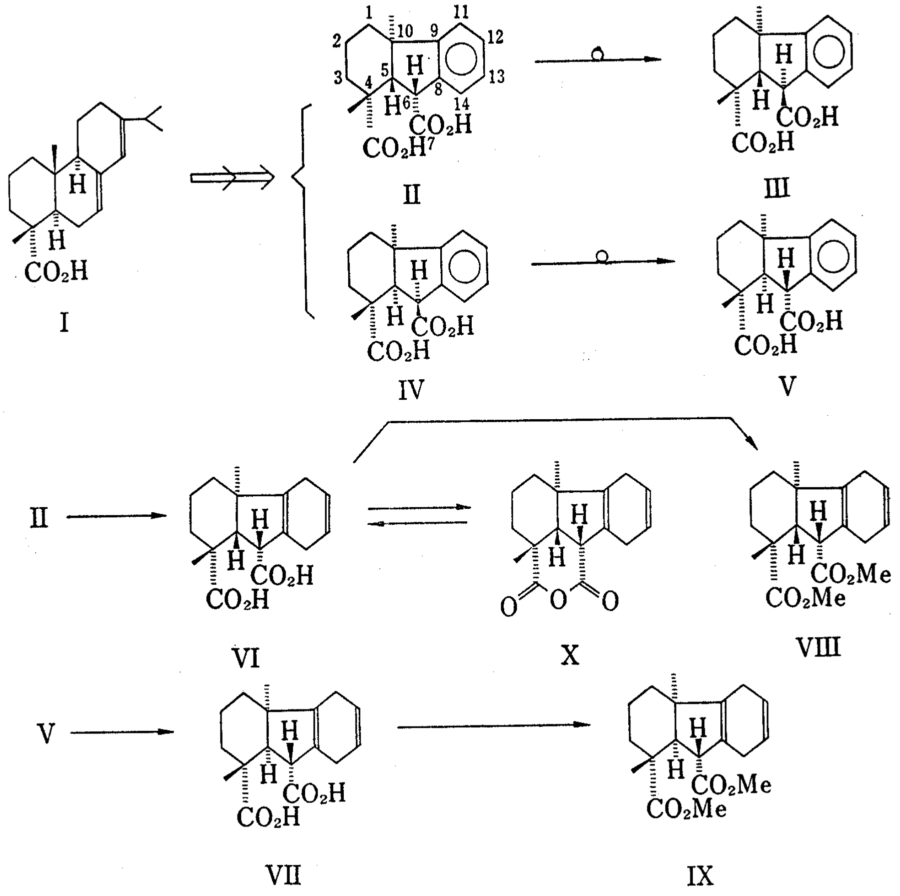

Fig. 1

(w.h.h.: 2.4 cps)) and olefinic protons (VIII: 4.29 τ (w.h.h.: 3 cps) and IX: 4.79 τ (w.h.h.: 3 cps)) newly appeared as single peak, respectively.

As described in the previous report,[3] configuration of 6α-carboxyl group of (II) is unstable to be epimerized to the stable 6β isomer. Thus, the doubt on the epimerization at C-6 of (VI) during the reduction was dispelled by a formation of an anhydride (X), mp 170—173°, because the stable 6β isomer should not form an anhydride ring. The anhydride (X) was readily returned to the original acid (VI) by alkaline hydrolysis.

Subsequently, the introduction of a hydroxyl group in octahydrofluorenes (VIII and IX) was examined by hydration on 12(13)-double bond. In both *trans*- and *cis*-A/B-ring series, the resulting hydrofluorenes having 12- and 13-hydroxyl groups are very similar to each other and, thus, it is difficult to observe subtle differences between the position isomers during the whole course of the experiment.

In our hydrations, the oxymercuration has advantages over the hydroboration in the following points: i) The experiment can be carried out in aqueous solution. ii) The end of the reaction is readily detected by the disappearance of the yellow color of the reaction mixture. iii) A generating apparatus is not needed.

With the exception of the hydration of dihydrobenzene (XI) to XII by mercuric acetate,[6] the example of this type of hydration of the diene system was not reported till now.

According to the condition of the above example,[6] hydrofluorene diester (VIII) having *trans*-A/B-ring fusion was treated with mercuric acetate in tetrahydrofuran–H_2O and then with sodium borohydride in alkaline solution. The resulting product was chromatographed to separate the two oily parts. Both parts was only distinguished by the retention time of

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[6] S. Moon, J.M. Takakis and B.H. Waxman, *J. Org. Chem.*, **34**, 2951 (1969).

gas-liquid chromatography (A-part (XIII): t_{R}=11.65—11.70 min and B-part (XIV+XVII): t_{R}=11.10 min (210°)). In the NMR spectra, signal due to a proton (A-part: 6.15—5.70 τ and B-part: 6.17—5.80 τ; 1H) attached to the hydroxyl-substituted carbon atom newly appeared.

The position of the hydroxyl-substituent was demonstrated by the chemical relation to the known 12- (XVIII) or 13-phenol (XIX) as follows. The A-part (XIII), bp 116—118° (bath temp.)/10^{-3} mmHg, was oxidized with Jones reagent[7] to give an oily ketone (XV), which was reduced by sodium borohydride not to return to the original hydroxy compound (XIII: t_{R}=7.25 min (220°)) but to give another isomer (XVII: t_{R}=7.35 min (220°)) having a different configuration of the hydroxyl group. The configuration is now hard to estimate clearly. The ketone (XV) was aromatized by bromination (bromine) and consecutive dehydrobromination (heat) to give pure crystals, mp 64.5—66.5°. Aromatization reaction, using N-bromosuccinimide instead of bromine, produced only an unseparable mixture. Since these crystals were completely identical with the authentic 12-phenol (XVIII)[4] and clearly different from the corresponding 13-phenol (XIX),[4] by comparison of gas-chromatographic retention time (XVIII: t_{R}=10.70 min and XIX: t_{R}=10.40 min (200°)), the original hydrated product (A-part (XIII)) should have a hydroxyl group on the 12-position.

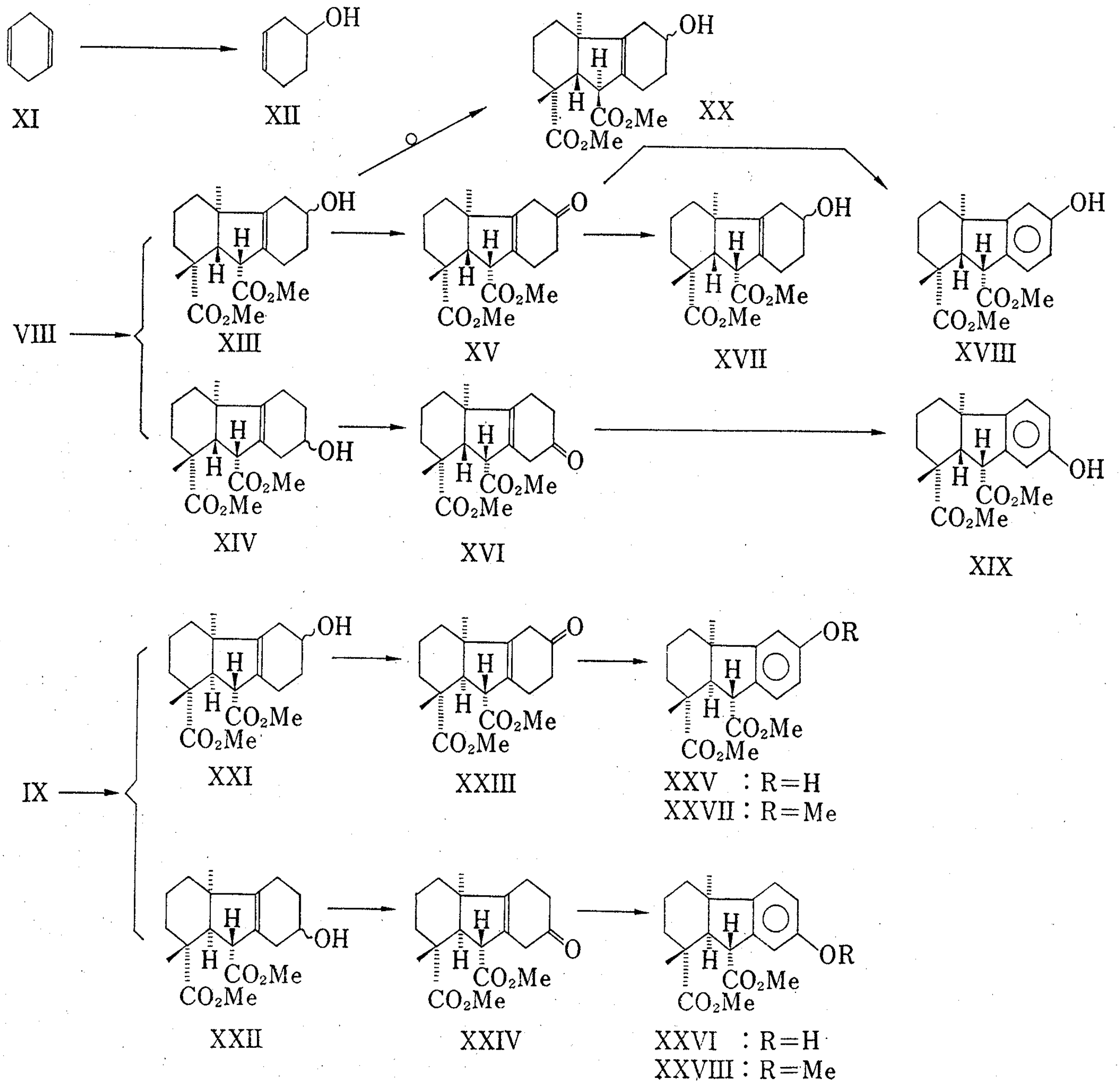

Fig. 2

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[7] C. Djerassi, R.R. Engle and A. Bowers, *J. Org. Chem.*, 21, 1547 (1956).

In other hand, the B-part (XIV+XVII), bp 118—120° (bath temp.)/10^{-3} mmHg, was oxidized and then aromatized in the same way as the A-part. The resulting phenolic product (XVIII+XIX) was purified by chromatography and subsequent recrystallization to separate two kinds of crystals, mp 64—66.5° and mp 137.5—139°, which were identical with authentic 12-(XVIII)[4] and 13-phenol (XIX),[4] respectively. The experimental result showed that the original B-part was a mixture consisting of 12-(XVII) (stereoisomer of XIII at C-12) and 13-hydroxy diesters (XIV).

12-Hydroxy diester (XIII) determined on its structure was treated under alkaline condition to be epimerized to the stable isomer having 6β-methoxycarbonyl group (XX). The epimerized oily diester (XX) has the same skeleton as the A- and B-ring of gibberellin A_{12}.

On the other hand, hydration of dihydro diester (IX) having *cis*-A/B-ring fusion was carried out in the same way as for the *trans* isomer. The hydration product of IX was separated by chromatography into two parts (C-part (XXI)), mp 54—57°, bp 116—118° bp 116—118° (bath temp.)/10^{-3} mmHg, and (D-part XXII)), mp 119—120°, bp 118—120° (bath temp.)/10^{-3} mmHg. These two parts were distinguished from each other by comparison of the retention time of gas-liquid chromatography (XXI: t_R=15.63 min and XXII: t_R=15.35 min (200°)). The NMR patterns were reasonable for the structure having two allylic protons (C-part: 6.95—6.65 τ and D-part: 6.9—6.7 τ) and a proton attached to the hydroxyl-substituted carbon atom (C-part: 6.2—5.75 τ and D-part: 6.5—6.0 τ).

Chemical evidence for the substituted position was adduced in the same way as for the *trans* isomers (A-part (XIII) and B-part (XVII+XIV)). The corresponding oily oxo diesters (XXIII and XXIV) oxidized by Jones reagent[7] were not clearly aromatized by bromination (bromine) and subsequent thermal dehydrobrominations, but our objective was attained using N-bromosuccinimide. The phenol (XXV) from thr C-part was obtained as crystals in pure state, mp 158—160°, and the phenol (XXVI) from the D-part was also obtained as a solid, but it was unsuccessful to purify it by recrystallization. The former phenol from the C-part was different from the specimen of 13-phenol (XXVI),[4] mp 206—207.5°, (*cf.* 12-phenol (XXV) has not been found yet in the literature), but the corresponding oily methoxy diester was completely identical with the authentic 12-substituted sample (XXVII).[4] In other way, the latter phenol from the D-part was identical with the authentic sample (XXVI)[4] by their comparison of retention time (t_R=13.50 min (220°)) of gas-liquid chromatography and, furthermore, the physical data of the corresponding methoxy diester, mp 99—101°, were superimposable with those of the authentic one (XXVIII).[4] Accordingly, the original hydrated compounds could be assigned as 12-(C-part (XXI)) and 13-hydroxy diester (D-part (XXII)), respectively.

Unlike the case of *trans*-isomer, the sodium borohydride reduction products of 12-(XXIII) and 13-oxo diesters (XXIV) could not be distinguished from the respective original hydroxy compounds (XXI and XXII) by comparison of their physical constants (IR, NMR and t_R). Thus, it is not clear whether or not the hydration product is a stereoisomeric mixture due to the configuration of the hydroxyl group.

In conclusion, the hydroxy diesters (XIII, XIV, XXI and XXII) were accomplished to synthesize by reduction and hydration of the unstable *trans*-(II) and stable *cis*-isomers (V). The substituents at 12- and 13-position were regarded as the starting point for the formation of a D-ring as in gibberellin. Furthermore, it is noticeable that the 12-hydroxy diester (XX) obtained by epimerization at C-6 of the unstable form (XIII) has the same skeleton as the A- and B-ring of gibberellin A_{12}.

Experimental

Reduction of Benzene Ring of Stereoisomers (II and V) with Lithium-Ammonia-*tert*-Butanol System——i) Reduction of 1,2,3,4,5β,10-Hexahydro-4β,10α-dimethylfluorene-4α,6α-dicarboxylic Acid (II). 1,2,3,4,5β,10,11,14-Octahydro-4β,10α-dimethylfluorene-4α,6α-dicarboxylic Acid (VI): To a solution of dicarboxylic acid

(II)³⁾ (750 mg) in liq. NH_3 (120 ml), *tert*-BuOH (7.5 ml) and tetrahydrofuran (7.5 ml), granular Li-metal (430 mg) was added at once under dry ice–acetone cooling (−40— −50°). The reaction mixture was stirred at −40— −50° for 6 hr and then was left standing overnight at room temperature after MeOH (5 ml) was carefully added. The residue resulted by removal of solvent was dissolved in H_2O, then acidified and extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and the solvent was removed to give crystals (VI) (720 mg), which were pure enough for the further experiments. A part of the crystals (150 mg) was purified by chromatography on silicic acid–celite (1: 1) (20 g) for an analytical sample. The crystals obtained from petr. ether–ether (2: 1) elution were recrystallized from MeOH–H_2O to colorless fine prisms (VI) (134 mg), mp 243—245°. *Anal.* Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.53; H, 7.73. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1710, 1695.

Dimethyl Ester (VIII): Usual methylation (CH_2N_2) of dicarboxylic acid (VI) (270 mg) gave crystals, which were recrystallized from MeOH–H_2O to colorless needles (VIII) (255 mg), mp 89.5—90.5°. *Anal.* Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.56; H, 8.02. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1734, 1726. NMR τ: 9.08 (s, 3H, 10-Me), 8.68 (s, 3H, 4-Me), 6.43 (s, 3H, COOMe), 6.31 (s, 3H, COOMe), 7.90 (d, 1H, J=8.7 cps, 5β-H), 6.65 (d, 1H, J=8.7 cps, 6β-H), 7.38 (s (width of half height: 2.4 cps), 4H, allylic H), 4.29 (s (width of half height: 2.4 cps), 2H, olefinic H). t_R=8.6 min (190°).

Anhydride (X): A solution of dicarboxylic acid (VI) (100 mg) in Ac_2O (6 ml) was refluxed for 100 min. The reaction mixture was evaporated under reduced pressure and the resulted solid was recrystallized from petr. ether–ether to give colorless plates (X) (79 mg), mp 170—173°. *Anal.* Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.10; H, 7.29. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1794, 1763. NMR τ: 9.03 (s, 3H, 10-Me), 8.64 (s, 3H, 4-Me), 8.04 (d, 1H, J=6.75 cps, 5β-H), 6.62 (d, 1H, J=6.75 cps, 6β-H), 4.25 (s (width of half height: 2.7 cps), 2H, olefinic H). t_R=4.6 min (220°).

The anhydride (X) was returned to the dimethyl ester (VIII) *via* diacid (VI) as follows. A suspension of anhydride (X) (45 mg) in 1N KOH aq. (10 ml) was stirred for 17 hr at room temperature under N_2 atmosphere. After the mixture was acidified with HCl aq. and then extracted with ether, the extract was washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave crude crystals (VI) (46 mg), which were directly methylated by CH_2N_2–ether solution to give crystals (VIII) (47 mg). NMR analysis clearly showed the crystals consisted of diester (VIII) and C-aromatic diester (diester of II) in ratio of 4.5: 1. The crystals were purified by recrystallization from MeOH–H_2O to give colorless needles (32 mg), mp 103—110°, whose physical constants (t_R (200°), IR (KBr), and mp (mixed mp)) were identical with those of diester (VIII).

ii) Reduction of 1,2,3,4,5α,10-Hexahydro-4β,10α-dimethylfluorene-4α,6α-dicarboxylic Acid (V). 1,2,3,4,5α,10,11,14-Octahydro-4β,10α-dimethylfluorene-4α,6α-dicarboxylic Acid (VII): Dicarboxylic acid (V)³⁾ (580 mg) was similarly reduced in liq. NH_3 (70 ml), *tert*-BuOH (7 ml) and tetrahydrofuran (7 ml) with granular Li-metal (400 mg) as in the case of the isomeric diacid (II). The resulted crystals (VII) (567 mg) was pure enough for the further experiments.

A part of the crystals (100 mg) was chromatographed on silicic acid–celite (1: 1) (15 g) to elute colorless crystals (93 mg) in petr. ether–ether (2: 1) fraction. The crystals were further recrystallized from petr. ether–ether to colorless prisms (VII) (85 mg), mp 169.5—170.5°. *Anal.* Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.54; H, 7.42. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1694. NMR τ: 8.94 (s, 3H, 10-Me), 8.74 (s, 3H, 4-Me), 7.32 (s (width of half height: 3 cps), 4H, allylic H), 4.25 (s (width of half height: 3 cps), 2H, olefinic H).

Dimethyl Ester (IX): Usual methylation (CH_2N_2) of diacid (VII) (300 mg) gave crystals, which were recrystallized from MeOH–H_2O to colorless plates (IX) (270 mg), mp 71—73°. *Anal.* Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.91; H, 8.01. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1743, 1738 (sh), 1725. NMR τ: 9.03 (s, 3H, 10-Me), 8.91 (s, 3H, 4-Me), 6.32 (s, 3H, COOMe), 6.28 (s, 3H, COOMe), 6.92 (d, 1H, J=10.5 cps, 5α-H), 6.65 (d, 1H, J=10.5 cps, 6β-H), 7.44 (s (width of half height: 3 cps), 4H, allylic H), 4.79 (s (width of half height: 3 cps), 2H, olefinic H). t_R=4.30 min (200°).

Hydration of Stereoisomers (VIII) and (IX) with $Hg(OAc)_2$——i) Hydration of Dimethyl 1,2,3,4,5β,10,11,14-Octahydro-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (VIII). Dimethyl 1,2,3,4,5β,10,11,12,13,14-Decahydro-12-(XIII) and 13-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (XIV): Hg $(OAc)_2$ (480 mg, 1.2 eq. mole) was added to a solution of diester (VIII) (400 mg) in tetrahydrofuran–H_2O (2: 1) (32 ml). The yellow solution was stirred at room temperature under N_2 atmosphere until the yellow color disappeared (48—185 hr). To the reaction mixture, 3N NaOH (8 ml) and $NaBH_4$ (800 mg) were added and it was refluxed for 60 min under N_2 atmosphere. After cooling, it was extracted with ether and the extract was washed with H_2O, dried over Na_2SO_4. Removal of the solvent gave a colorless oil (523 mg). The oil was chromatographed on neutral Al_2O_3 (110 g) to separate two fractions, a colorless oil (A-part (XIII)) (141 mg) and (B-part (XVII+XIV)) (111 mg), in petr. ether–ether (1: 1) elution, successively.

The former oil (XIII), bp 116—118° (bath temp.)/10^{-3} mmHg, had the following properties. *Anal.* Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.73; H, 8.38. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3420, 1735 (sh), 1730. NMR τ: 9.10 (s, 3H, 10-Me), 8.62 (s, 3H, 4-Me), 6.38 (s, 3H, COOMe), 6.27 (s, 3H, COOMe), 7.83 (d, 1H, J=8.5 cps, 5β-H), 6.62 (d, 1H, J=8.5 cps, 6β-H), *ca.* 7.4 (broad, 1H, OH (disappeared by D_2O)), 6.15—5.70 (m, 1H, 12-H). t_R=11.65—11.70 min (210°).

On the other hand, the latter oil (XVII+XIV), bp 118—120° (bath temp.)/10^{-3} mmHg, had the following physical constants. *Anal.* Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.54; H, 8.39. IR ν_{max}^{film} cm^{-1}: 3420, 1735 (sh), 1730. NMR τ: 9.10 (s, 3H, 10-Me), 8.62 (s, 3H, 4-Me), 6.38 (s, 3H, COOMe), 6.26 (s, 3H, COOMe), 7.87 (d, 1H, J=8.5 cps, 5β-H), 6.61 (d, 1H, J=8.5 cps, 6β-H), *ca.* 7.42 (broad, 1H, OH (disappeared by D_2O)), 6.17—5.80 (m, 1H, 13-H and 12-H). t_R=11.10 min (210°). It was clearly showed by chemical conversion to the corresponding phenol that the fraction was a mixture consisting of 12-(XVII) and 13-hydroxy diesters (XIV) as described later. 13-Hydroxy ester (XIV) could not be isolated in pure state.

ii) Hydration of Dimethyl 1,2,3,4,5α,10,11,14-Octahydro-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (IX). Dimethyl 1,2,3,4,5α,10,11,12,13,14-Decahydro-12-(XXI) and 13-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (XXII): To a solution of diester (IX) (500 mg) in tetrahydrofuran–H_2O (2: 1) (40 ml), Hg $(OAc)_2$ (600 mg; 1.2 eq. mole) was added. The reaction mixture was treated as in the case of the isomer (VIII). The resulted colorless oil (480 mg) was carefully chromatographed on neutral Al_2O_3 (54 g) to separate two compounds, colorless crystals (XXI) (138 mg) in petr. ether–ether (1: 1) elution and (XXII) (105 mg) in successive petr. ether–ether (1: 1—1: 2) elution.

The former crystals (XXI), mp 54—57°, bp 116—118° (bath temp.)/2×10^{-3} mmHg, had the following properties. *Anal.* Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.66; H, 8.33. IR ν_{max}^{KBr} cm^{-1}: 3525, 1724. NMR τ: 9.06 (s, 3H, 10-Me), 8.94 (s, 3H, 4-Me), 6.95—6.67 (m, 2H, 11-H_2), 6.33 (s, 3H, COOMe), 6.28 (s, 3H, COOMe), 6.2—5.75 (m, 1H, 12-H), *ca.* 8.0 (broad, 1H, OH (disappeared by D_2O)). t_R=7.50 min (210°).

The latter crystals (XXII), mp 119—120°; bp 118—120° (bath temp.)/2×10^{-3} mmHg, had the following physical constants. *Anal.* Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.60; H, 8.29. IR ν_{max}^{KBr} cm^{-1}: 3470, 1720. NMR τ: 9.05 (s, 3H, 10-Me), 8.93 (s, 3H, 4-Me), 6.9—6.7 (m, 2H, 14-H_2), 6.33 (s, 3H, COOMe), 6.28 (s, 3H, COOMe), 6.5—6.0 (m, 1H, 13-H), *ca.* 7.9 (broad, 1H, OH (disappeared by D_2O)). t_R=7.30—7.23 min (210°).

Oxidation of 12-Hydroxy-(XIII and XXI) and 13-Hydroxy-decahydrofluorene Derivatives (XIV (mixture) and XXII)——i) Oxidation of Dimethyl 1,2,3,4,5β,10,11,12,13,14-Decahydro-12-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (XIII). Dimethyl 1,2,3,4,5β,10,11,12,13,14-Decahydro-4β,10α-dimethyl-12-oxofluorene-4α,6α-dicarboxylate (XV): Jones oxidizing reagent[7] (0.1 ml) was dropwise added to a solution of hydroxy diester (XIII) (38 mg) in acetone (3 ml) under ice-cooling. The reaction mixture was stirred under ice-cooling for 60 min and for 30 min more after MeOH (0.5 ml) was added.

After the solution was diluted with H_2O and extracted with ether, the extract was washed with sat. Na_2CO_3 aq., then sat. NaCl aq. and dried over Na_2SO_4. Removal of the solvent gave a colorless oil (32 mg), which was chromatographed on silica gel (5 g) to give a colorless oil (XV) (32 mg) in petr. ether–ether (4: 1) elution. *Anal.* by high resolution mass spectrometry. Calcd. for $C_{19}H_{26}O_5$ (M^+; *m/e*): 334.1780. Found: 334.1767. IR ν_{max}^{film} cm^{-1}: 1729. NMR τ: 9.03 (s, 3H, 10-Me), 8.59 (s, 3H, 4-Me), 6.35 (s, 3H, COOMe), 6.23 (s, 3H, COOMe). t_R=12.30 min (210°).

Reduced Product (XVII): 12-Oxo diester (XV) (56 mg) in MeOH (16 ml) was usually reduced with $NaBH_4$ (48 mg). The resulted oil (53 mg) was chromatographed on neut. Al_2O_3 (7 g) to give a colorless oil (XVII) (42 mg), bp 108—109° (bath temp.)/10^{-3} mmHg, in petr. ether–ether (1: 1) elution. *Anal.* Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 68.11; H, 8.12. IR ν_{max}^{film} cm^{-1}: 3420, 1735 (sh), 1730. NMR τ: 9.11 (s, 3H, 10-Me), 8.64 (s, 3H, 4-Me), 6.42 (s, 3H, COOMe), 6.30 (s, 3H, COOMe), *ca.* 7.89 (d, 1H, J=8.0 cps, 5β-H), 6.65 (d, 1H, J=8.0 cps, 6β-H), 7.87 (broad, 1H, OH (disappearance by D_2O-addition)), 6.15—5.80 (m, 1H, 12-H). t_R=10.45 min (220°) (*cf.* 12-hydrated compound (XIII): t_R=11.05 min under the same condition). The retention time was exactly same with that of the latter chromatographical fraction (B-part (XVII and XIV)) of hydration product.

ii) Oxidation of a Mixture consisting of Dimethyl 1,2,3,4,5β,10,11,12,13,14-Decahydro-12-(XVII) and 13-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (XIV). A Mixture consisting of Dimethyl 1,2,3,4,5β,10,11,12,13,14-Decahydro-4β,10α-dimethyl-12-(XV) and 13-oxofluorene-4α,6α-dicarboxylate (XVI): Mixed hydroxy diester (XVII+XIV) (47 mg) was oxidized with Jones reagent (0.12 ml) as in the case of 12-isomer (XIII). A part (41 mg) of the resulted colorless oil (47 mg) was chromatographed on silica gel (5 g) to give a colorless oil (XV+XVI) (36 mg) in petr. ether–ether (4: 1) elution. *Anal.* by high resolution mass spectrometry. Calcd. for $C_{19}H_{26}O_5$ (M^+: *m/e*): 334.1780. Found: 334.1803. IR ν_{max}^{film} cm^{-1}: 1729. NMR τ: 9.03 (s, 3H, 10-Me), 8.59 (s, 3H, 4-Me), 6.35 (s, 3H, COOMe), 6.23 (s, 3H, COOMe). t_R=12.20 min (210°). The fraction was a mixture consisting of 12-(XV) and 13-oxo compound (XVI).

iii) Oxidation of Dimethyl 1,2,3,4,5α,10,11,12,13,14-Decahydro-12-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (XXI). Dimethyl 1,2,3,4,5α,10,11,12,13,14-Decahydro-4β,10α-dimethyl-12-oxofluorene-4α,6α-dicarboxylate (XXIII): Hydroxy diester (XXI) (60 mg) was oxidized with Jones reagent (0.15 ml) as in the case of (XIII). The resulted colorless oil (58 mg) was chromatographed on silica gel (5 g) to give a colorless oil (XXIII) (35 mg) in petr. ether–ether (3: 1) elution. *Anal.* by high resolution mass spectrometry. Calcd. for $C_{19}H_{26}O_5$ (M^+; *m/e*): 334.1780. Found: 334.1767. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735 (sh), 1730, 1160. NMR τ: 9.04 (s, 3H, 10-Me), 8.92 (s, 3H, 4-Me), 6.30 (s, 3H, COOMe), 6.25 (s, 3H, COOMe). t_R=6.60 min (220°).

Reduction of 12-Oxo diester (XXIII): 12-Oxo diester (XXIII) (35 mg) in MeOH (10 ml) was usually reduced with $NaBH_4$ (30 mg). The resulted oil (34 mg) was chromatographed on neut. Al_2O_3 (10 g) to separate a colorless oil (27 mg), bp 111—114° (bath temp.)/10^{-3} mmHg, in petr. ether–ether (1: 1) elution. *Anal.* Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.62; H, 8.35. IR ν_{max}^{film} cm^{-1}: *ca.* 3420 (broad), 1730. NMR τ: 9.05 (s, 3H, 10-Me), 8.93 (s, 3H, 4-Me), 6.32 (s, 3H, COOMe), 6.27 (s, 3H, COOMe). t_R= 15.40 min (200°) (*cf.* 12-hydrated compound (XXII): t_R=15.63 min under the same condition).

iv) Oxidation of Dimethyl 1,2,3,4,5α,10,11,12,13,14-Decahydro-13-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (XXII). Dimethyl 1,2,3,4,5α,10,11,12,13,14-Decahydro-4β,10α-dimethyl-13-oxofluorene-4α,6α-dicarboxylate (XXIV): Hydroxy diester (XXII) (60 mg) was oxidized with Jones reagent (0.15 ml) as in the case of (XIII). The resulted colorless oil (45 mg) was chromatographed on silica gel (5 g) to separate a colorless oil (XXIV) (34 mg) in petr. ether–ether (4: 1) elution. *Anal.* by high resolution mass spectrometry. Calcd. for $C_{19}H_{26}O_5$ (M^+; *m/e*): 334.1780. Found: 334.1803. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735 (sh), 1730, 1160. NMR τ: 8.99 (s, 3H, 10-Me), 8.91 (s, 3H, 4-Me), 6.30 (s, 3H, COOMe), 6.27 (s, 3H, COOMe). t_R=6.65 min (220°).

Reduction of 13-Oxo Diester (XXIV): 13-Oxo diester (XXIV) (34 mg) in MeOH (10 ml) was usually reduced with $NaBH_4$ (30 mg). The resulted oil (32 mg) was chromatographed on neut. Al_2O_3 (10 g) to separate crystals (26 mg), mp 91—94°, in petr. ether–ether (1: 1) elution, which were recrystallized from petr. ether–ether to give colorless prisms, mp 115—121.5°. *Anal.* Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.87; H, 8.31. IR ν_{max}^{KBr} cm^{-1}: *ca.* 3480 (broad), 1723. NMR τ: 9.05 (s, 3H, 10-Me), 8.93 (s, 3H, 4-Me), 6.32 (s, 3H, COOMe), 6.27 (s, 3H, COOMe). t_R=15.35 min (200°) (*cf.* 13-hydrated compound (XXII): t_R=15.23 min).

Aromatization of 12-(XV and XXIII) and 13-Oxo Diesters (XVI and XXIV)——i) Aromatization of Dimethyl 1,2,3,4,5β,10,11,12,13,14-Decahydro-4β,10α-dimethyl-12-oxofluorene-4α,6α-dicarboxylate (XV). Dimethyl 1,2,3,4,5β,10-Hexahydro-12-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (XVIII): Bromine (23 mg, 1.20 eq. mole) in AcOH (1.0 ml) was dropwise added into a solution of 12-oxo diester (XV) (40 mg) in AcOH (2.5 ml) under ice-cooling. The reaction mixture was stirred at 15° for 30 min, refluxed for 60 min and then evaporated under reduced pressure. The resulted residue was extracted with ether and the extract was washed with sat. Na_2CO_3 aq., then sat. NaCl aq. and dried over Na_2SO_4. Removal of the solvent gave a yellow oil (34 mg). A solution of the oil (33 mg) in MeOH (5 ml) was stirred for 90 min in the presence of Pd-black (150 mg) under H_2 gas atmosphere. After the catalyst was filtered off, the filtrate was evaporated to give a pale yellow oil (32 mg), which was chromatographed on silica gel (10 g) to separate a colorless oil (24 mg) in petr. ether–ether (4: 1) elution. The oil crystallized and was recrystallized twice from MeOH–H_2O to give colorless prisms (XVIII), mp 64.5—66.5°, whose physical constants (mixed mp, IR spectrum and t_R (220°): 10.70 min, *cf.* 13-phenol (XIX): 10.40 min) were completely identical with those of the authentic sample (XVIII) (mp 66.5—67.5°).[4)]

ii) Aromatization of a Mixture consisting of Dimethyl 1,2,3,4,5β,10,11,12,13,14-Decahydro-4β,10α-dimethyl-12-(XV) and 13-oxofluorene-4α,6α-dicarboxylate (XVI). Mixture of Dimethyl 1,2,3,4,5β,10-Hexahydro-12-(XVIII) and 13-Hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (XIX): A mixture of oxo diesters (XV+XVI) (54 mg) was aromatized as in the case of the isomeric diester (XIII). The resulted pale yellow oil (43 mg) was chromatographed on silica gel (13 g) to separate the following three fractions: i) a colorless oil (5 mg) in petr. ether–ether (4: 1) elution, ii) a colorless oil (24 mg) in petr. ether–ether (3: 1) elution and iii) a colorless oil (2 mg) in successive petr. ether–ether (3: 1) elution. The second fraction was rechromatographed on silica gel (7.5 g) to successively give two oily parts (7 mg and 17 mg) in petr. ether–ether (4: 1) elution. The oily two parts were combined with the i) and iii)-fraction, respectively.

The former fraction (12 mg) was recrystallized from MeOH–H_2O to give colorless prisms, mp 64—66.5° (6 mg), whose physical constants (mixed mp, IR spectrum and t_R) were completely identical with those of authentic 12-hydroxy diester (XVIII).[4)]

While, the latter fraction was recrystallized from petr. ether–ether to give colorless prisms, mp 137.5—139°, whose physical constants (mixed mp, IR spectrum and t_R) were identical with those of authentic 13-hydroxy diester (XIX).[4)]

iii) Aromatization of Dimethyl 1,2,3,4,5α,10,11,12,13,14-Decahydro-4β,10α-dimethyl-12-oxofluorene-4α,6α-dicarboxylate (XXIII). Dimethyl 1,2,3,4,5α,10-Hexahydro-12-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (XXV): A solution of 12-oxo diester (XXIII) (50 mg) in CCl_4 (10 ml) was refluxed with N-bromosuccinimide (32 mg, 1.2 eq. mole) and benzoyl peroxide (5 mg) for 90 min under N_2 atmosphere. After filtration, the filtrate was evaporated and the residue was extracted with ether. The extract was washed with sat. Na_2CO_3 aq., then H_2O and dried over Na_2SO_4. Removal of the solvent gave a pale yellow oil (53 mg), which was chromatographed on silica gel (11 g) to give pale yellow crystals (38 mg). The crystals were recrystallized from petr. ether–ether to give colorless fine prisms (XXV) (10 mg), mp 158—160°. *Anal.* Calcd. for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.44; H, 7.29. IR ν_{max}^{KBr} cm^{-1}: 3440, 1727 (sh), 1717, 1618, 1593, 805. NMRτ: 8.85 (s, 3H, 10-Me), 8.79 (s, 3H, 4-Me), 6.30 (s, 3H, COOMe), 6.21 (s, 3H, COOMe). t_R=13.75 min (220°) (*cf.* the corresponding 13-hydroxy diester (XXVI): 13.50 min under the same condition).

12-Methoxy Diester (XXVII): 12-Hydroxy diester (XXV) (45 mg) was usually methylated with Me_2SO_4–KOH. The resulted colorless oil (41 mg) was chromatographed on silica gel (10 g) to give a colorless oil (23 mg) in petr. ether–ether (9: 1) elution. The physical constants (IR, NMR spectrum and t_R: 11.5 min (210°) (*cf.* the corresponding 13-methoxy diester (XXVIII): $t_R=11.1$ min under the same condition) were completely identical with those of the authentic 12-methoxy diester (XXVII).[4]

iv) Aromatization of Dimethyl 1,2,3,4,5α,10,11,12,13,14-Decahydro-4β,10α-dimethyl-13-oxofluorene-4α,6α-dicarboxylate (XXIV). Dimethyl 1,2,3,4,5α,10-Hexahydro-13-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (XXVI): 13-Oxo diester (XXIV) (27 mg) was aromatized with N-bromosuccinimide as in the case of the corresponding 12-oxo compound (XXIII). The resulted pale yellow oil (25.5 mg) was chromatographed on silica gel (10 g) to give pale yellow crystals in petr. ether–ether (4: 1) elution. Recrystallization from MeOH–H_2O was unsuccessful, but the physical constants (NMR and t_R) were completely identical with those of the authentic 13-hydroxy diester (XXVI).[4]

13-Methoxy Diester (XXVIII): 13-Hydroxy diester (XXVI) (25 mg) was usually methylated with Me_2SO_4–KOH. The resulted oil (16 mg) was chromatographed on silica gel (5 g) to separate a colorless oil (10 mg) in petr. ether–ether (9: 1) elution, which was crystallized from petr. ether–ether to give colorless fine prisms (XXVIII), mp 99—101°. The physical constants (mixed mp, t_R, IR and NMR spectrum) were identical with those of the authentic 13-methoxy diester (XXVIII).[4]

6-Epimerization of Dimethyl 1,2,3,4,5β,10,11,12,13,14,-Decahydro-12-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (XIII). Dimethyl 1,2,3,4,5β,10,11,12,13,14-Decahydro-12-hydroxy-4β,10α-dimethylfluorene-4α,6β-dicarboxylate (XX)——A solution of 12-hydroxy diester (XIII) (30 mg) and KOH (120 mg) in ethylene glycol (5 ml)–H_2O (0.15 ml) was refluxed for 90 min under N_2 atmosphere. The reaction mixture was diluted with H_2O, then acidified and extracted with ether. After the extract was washed with H_2O and dried over Na_2SO_4, the solvent was evaporated to give a colorless oil, which was usually methylated with CH_2N_2–ether solution. The resulted colorless crystals (25.5 mg) were chromatographed on neut. Al_2O_3 (10 g) to separate colorless oil (XX) (20 mg) in petr. ether–ether (1:1) elution. *Anal.* by high resolution mass spectrometry. Calcd. for $C_{19}H_{28}O_5$: 336.1937. Found: 336.1906. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3430, 1735 (sh), 1730. NMR τ: 9.30 (s, 3H, 10-Me), 8.81 (s, 3H, 4-Me), 6.33 (s, 3H, COOMe), 6.28 (s, 3H, COOMe), 6.25—5.85 (m, 1H, 12-H), 7.89 (d, 1H, $J=10.5$ cps, 5β-H). $t_R=13.20$ (210°).

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