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SYNTHESIS OF SUBSTANCES RELATED TO GIBBERELLINS—XX*

MODIFICATION OF THE A-RING OF GIBBERIC ACID AND RELATED COMPOUNDS

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Abstract—The A-ring of methyl gibberate was modified through nitration, reduction, diazotization and hydrolysis to give methyl 2-hydroxygibberate. The same sequence of reactions was applied to methyl (±)-gibberate, the C-10 epimer of methyl (±)-epigibberate, methyl deoxogibberate and methyl (±)-deoxoepigibberate to yield the corresponding 2-hydroxy derivatives. Catalytic hydrogenation of 2-hydroxygibbanes with aromatic A-ring to saturated gibbanes was also investigated.

SINCE the total syntheses of (±)-gibberic (I)[1,2] ‖ and (±)-epigibberic (II)[2] acids had been completed, our efforts were directed to the conversion of gibberic acid and its derivatives into 2-oxogibbane compounds such as an oxo ester (III). This could be a possible precursor of a dienone ester (IV) which was the starting material in our partial synthesis of gibberellin C (V)[3]. This work has culminated in the total synthesis of some of the C_{19}-gibberellins.[4]

This paper describes the results obtained in the earlier phase of our study which provided valuable hints for the successful synthesis of the oxo ester (III).[4] A preliminary account of this work was briefly reported.[5]

Preparation of the starting materials

Methyl gibberate (IXa) was prepared from gibberellic acid by the standard method.[6] The synthesis of methyl (±)-gibberate (IXb) was carried out on a large scale by a combination of our own[2,7] with Loewenthal's method.[1]

The C-10 epimer (IXc) of methyl (±)-epigibberate was prepared as follows. The C-10 epimer of methyl (±)-6ξ-hydroxyepigibberate ethylene ketal (VI),[2] formerly described as an oil and now obtained in crystalline form, was treated with phosphorus oxychloride and pyridine to give a chloro ester (VIIa). Subsequent hydrogenolytic removal of the chlorine atom with W-7 Raney nickel yielded the ketal (VIII). Dekatalization by acid-hydrolysis gave the desired product (IXc). The assigned structure (IXc)

* Biochemical Studies on "Bakanae" Fungus—78. Part XIX, K. Mori, M. Shiozaki, M. Matsui and Y. Sumiki, *Proc. Japan Acad.* 44, 717 (1968).

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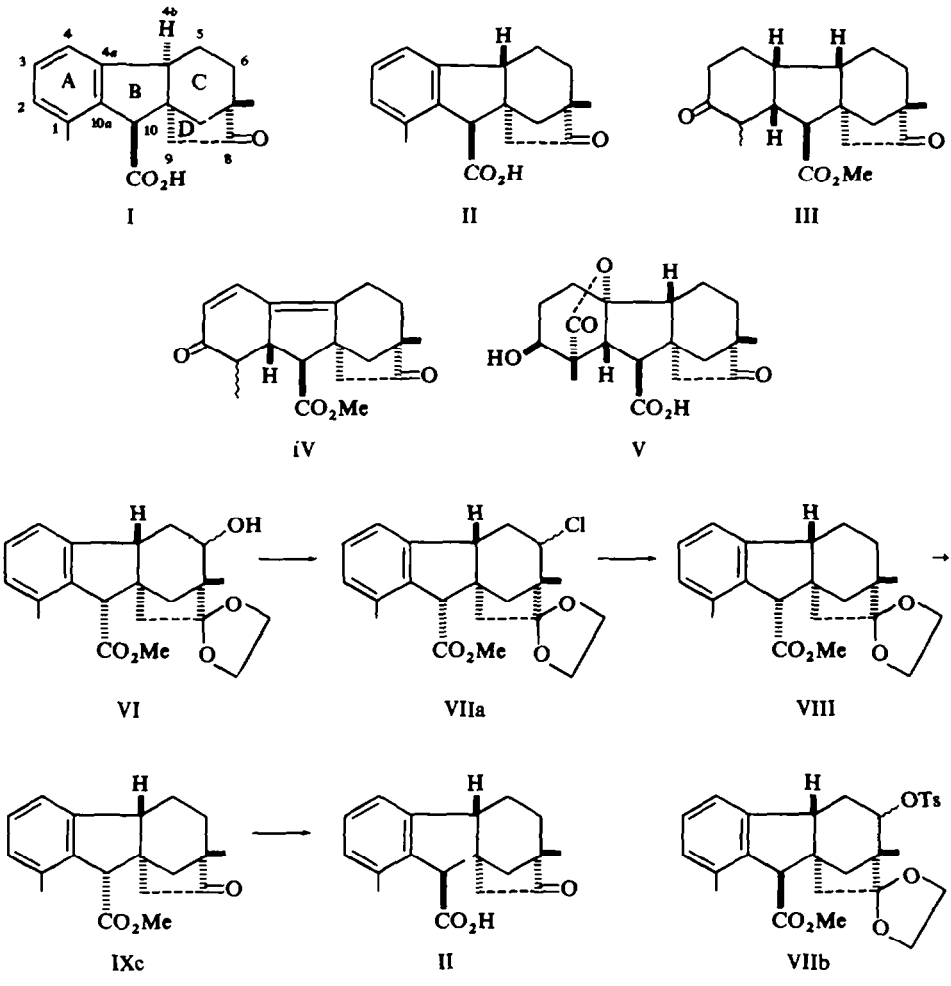
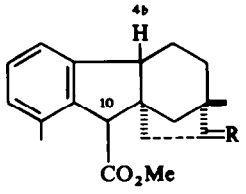
‖ Although the formulas depicted represent only one enantiomer, they are taken to mean a racemate with the exception of degradation products of gibberellic acid.



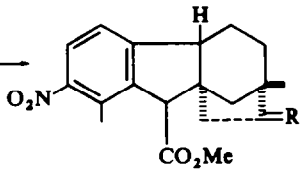
was proved by its conversion into (±)-epigibberic acid (II). The tosylate (VIIb) of the alcohol (VI) remained unchanted when it was treated with W-7 Raney nickel. Methyl deoxogibberate (IXd) and methyl (±)-deoxoepigibberate (XIe) were prepared as described previously.[8]

Modification of the aromatic A-ring

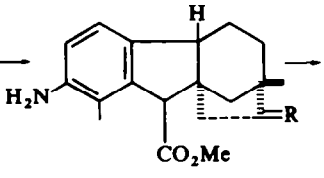
Functionalization at C-2 of the aromatic A-ring of methyl gibberate (IXa) and its derivatives (IXb–e) was carried out by nitration with nitric acid in acetic anhydride. In compounds (IXc, e) with a β-hydrogen atom at C-4b, the major products (Xc, e) were accompanied with their positional isomers, probably 4-nitro isomers, which could be removed by fractional crystallization. The nitro derivatives obtained (Xa–e) were hydrogenated over Pd–C to give amino derivatives (XIa–e). Diazotization followed by acid-hydrolysis of the diazonium salts afforded 2-hydroxy esters (XIIa–e).



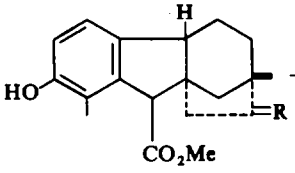
IX



X

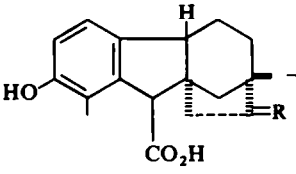


XI



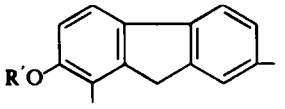
XII

	4b-H	10-CO_2Me	R
a(−)	α	β	O
b(±)	α	β	O
c(±)	β	α	O
d(−)	α	β	H_2



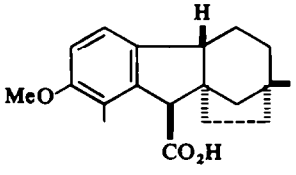
XIII

	4b-H	10-CO_2Me	R
e(±)	β	β	H_2
f(−)	α	α	O
g(±)	β	β	O

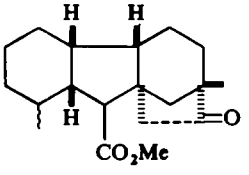


XIV

a′ R′ = H
b′ R′ = Me

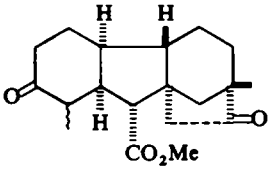


XV

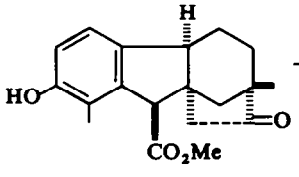


XVI 10-CO_2Me

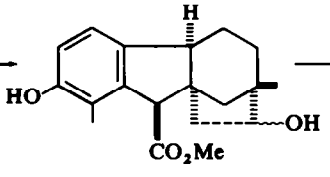
a	α
b	β



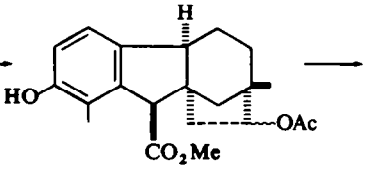
XVII



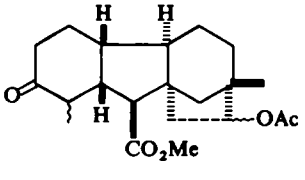
XIIa, b



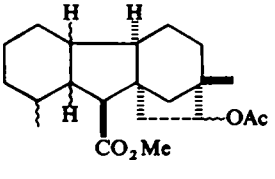
XVIIIa, b



XIXa, b

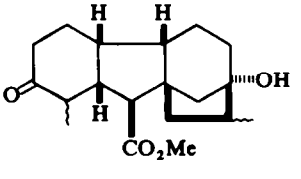


XXa, b



XXIa, b

a(−)
b(±)



XXII

The location of the OH group was determined by selenium dehydrogenation of phenolic keto acids (XIIIf, g) obtained by alkaline hydrolysis of the hydroxy esters (XIIa, c). The CO_2H group at C-10 epimerized during the hydrolysis. In both cases 2-hydroxy-1,7-dimethylfluorene (XIVa') was obtained which was methylated and identified as the corresponding methyl ether (XIVb')[9] with an authentic sample.* In the deoxo esters (XIId, e) the position of the OH group was assumed to be C-2 by analogy with the oxo esters (XIIa, b, c). The over-all yield of the hydroxy ester (XIIa) from the starting oxo ester (IXa) was 58%. The yield was lower in the compounds with a β-hydrogen atom at C-4b.†

Reduction of the aromatic A-ring

In spite of the wide-spread use of the Birch reduction in steroid total synthesis,[11] attempts to reduce the A-ring of a methoxy acid (XV) derived from (±)-2-hydroxy-deoxoepigibberic acid (XIIIe) by either the Dryden[12] or the Johnson modification,[13] were unsuccessful. Consequently, we turned our attention to catalytic hydrogenation. As the results hitherto obtained[1,2,14] indicated that the configuration of the C-10 carboxyl group determines the steric course of the reduction of the 4b(5) double bond, hydrogenation occurring *trans* to the C-10 substituent, we expected the C-10 carbomethoxyl group to be operative in the reduction of the A-ring.

Therefore the hydroxy ester (XIIc), in which both the C-10 carbomethoxyl group and the C-8, 9 two-carbon bridge are α-oriented, was chosen. It was anticipated that hydrogenation of the A-ring would proceed from the less hindered β-side and that subsequent epimerization[2,15] of the C-10 substituent followed by oxidation would generate the desired dioxo ester (III). T-1 Raney nickel[16] or rhodium-platinum oxides[17] were employed as catalysts. The oily product, after oxidation,[18] was chromatographed on alumina to give two crystalline substances. The one, easily eluted from the column, was an oxo ester (XVIa) resulting from the hydrogenolytic removal of the C-2 OH group. This, upon treatment with methanolic potash, epimerized to give a stereoisomer (XVIb) with an IR spectrum different from that of the starting material. The other, more slowly eluted from the column, was a dioxo ester (XVII). Attempted alkaline epimerization of this ester, however, gave back the starting material (XVII). The IR spectrum of the dioxo ester (XVII) in chloroform differed from that of the degradation product (III)[4] of gibberellic acid and our expectation to obtain the ester (III) could not be realized. The stereochemistry depicted in the formulas XVI and XVII were tentatively assigned to the products by inspection of molecular models after two assumptions had been made: (i) hydrogenation of the 4a(10a) double bond gave a product with rings A/B *cis* and (ii) no alteration of the β-configuration of the hydrogen atom at C-4b occurred during the hydrogenation. Construction of the models showed the crowded position at C-10 with its consequent epimerization. In compounds with β-hydrogens at C-4a and C-10a the α-oriented C-10 carbomethoxyl group would be unstable and epimerize as was the case with the oxo ester (XVIa). On the other hand, in compounds with α-hydrogens at C-4a and C-10a the α-orientated C-10 carbomethoxyl group was more stable as is the case

* Kindly provided by Professor B. E. Cross and Dr. R. H. B. Galt.

† A similar work was carried out in England at Akers Research Laboratories, I.C.I. Gibberic, dihydro-allogibberic and dihydroepiallogibberic acids were converted into nitro-, amino- and hydroxy-derivatives. (Personal communication from Dr. W. B. Turner to K.M. dated 28 September, 1964, Cf. ref. 10).

with the dioxo ester (XVII). It should be emphasized, however, that these stereochemical arguments are only tentative.

Methyl (±)-2-hydroxygibberate (XIIb), more readily accessible than the ester (XIIc), was then selected as the starting material. In our initial synthetic plan we thought that the incorrect stereochemistry at C-4b of gibberic acid in contrast to the ester (XIIc) might possibly be eliminated during the later conversion into the dienone (IV). The oxo ester (XIIb) was hydrogenated over W-7 Raney nickel to give an epimeric mixture of hydroxy esters, from which one epimer (XVIIIb) crystallized. This was treated with *p*-toluenesulphonic acid in methyl acetate to give an acetoxy ester (XIXb) after chromatography on alumina. Hydrogenation of the phenol (XIXb) over rhodium–platinum oxides[17] followed by chromic acid oxidation gave a crystalline oxo ester (XXb) in 2% yield after chromatographic purification. When this was hydrolyzed with base, the hydroxy oxo acid obtained regenerated the starting acetoxy ester (XXb) after methylation and acetylation. This suggested the stereochemistry depicted in the formula XXb. If the hydrogenation had taken place from the α-side yielding a compound with α-hydrogens at C-4a and C-10a, the C-10β-carbomethoxyl group should have been in a very crowded position and hence should have yielded an epimer after treatment with base. Although a compound with correct stereochemistry at C-4a and C-10a was thus obtained, the yield was disappointing and further transformation of the ketone (XXb) into the dienone (IV) was abandoned. In this case the hydrogenolysis product (XXIb) could not be obtained in crystalline form.

In order to confirm the suggested stereochemistry by ORD measurements, an optically active oxo ester (XXa) was prepared from methyl 2-hydroxygibberate (XIIa).

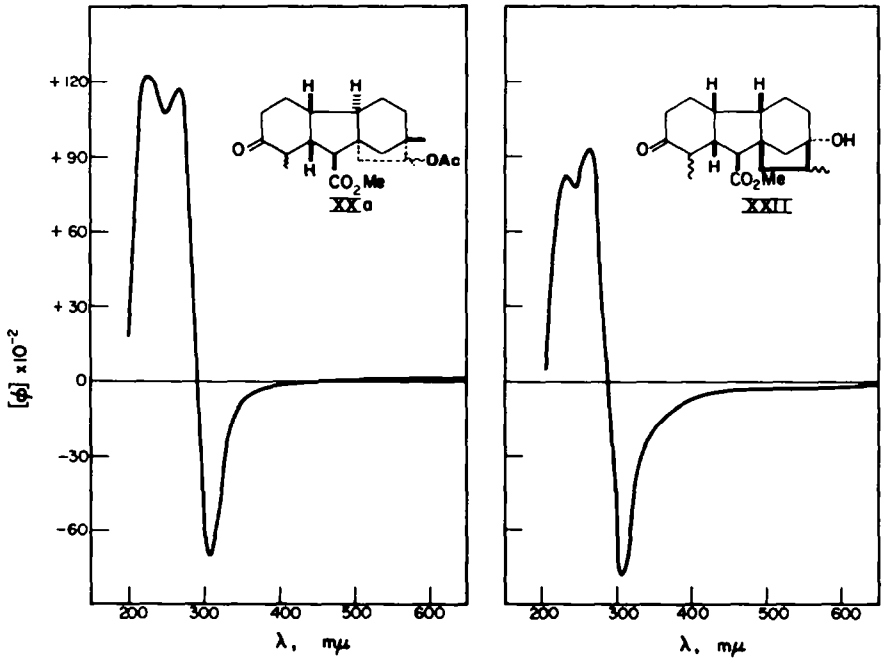


FIG. 1

In this case the two epimeric diols were obtained as crystals melting at 253–255° and 144–146°, respectively. The higher melting XVIIIa was converted into an acetoxy ester (XIXa) and hydrogenated over rhodium–platinum oxides. The crystalline oxo ester (XXa) was obtained in 5% yield after oxidation and chromatographic purification. The ORD curve (see Fig. 1) for this ketone (XXa) was similar in shape and amplitude to that for an authentic ketone (XXII),[19] m.p. 122–124°, kindly provided by Professor J. MacMillan. Since the stereochemistry of the authentic ketone (XXII) has been reported as depicted in the formula,[19] it seems reasonable to assume that our ketone (XXa) possesses the A/B *cis* ring junction with β-hydrogen atoms at C-4a and C-10a as suggested by the inspection of a molecular model.*

The results so far obtained indicated that the desired compounds with β-hydrogen atoms at C-4a and C-10a would be obtained from gibbane-10β-carboxylic esters with aromatic A-ring. This prompted the use of (±)-epigibberic acid (II) as the key intermediate in our total synthesis of C_{19}-gibberellins which will be described in the accompanying paper.

EXPERIMENTAL

All m.ps are uncorrected.

The C-10 *epimer of methyl* (±)-6ξ-*hydroxyepigibberate ethylene ketal* (VI). This crystallized after standing for a long period and was obtained as needles from EtOAc–pet. ether, m.p. 133–134°; ν_{max} (Nujol) 3570, 1735, 1600, 1160, 1125, 1058, 796 cm^{-1}. (Found: C, 70·14; H, 7·29. $C_{21}H_{26}O_5$ requires: C, 70·37; H, 7·31%).

The C-10 *epimer of methyl* (±)-6ξ-*chloroepigibberate ethylene ketal* (VIIa). The alcohol VI (700 mg) in dry pyridine (70 ml) was mixed with $POCl_3$ (14 ml) and the mixture was heated under reflux for 2 hr. The dark soln was poured onto ice and extracted with EtOAc. The extract was washed with water, sat $NaHCO_3$ aq and brine. Concentration of the soln after drying (Na_2SO_4) gave 546 mg of dark-coloured oil. After tritu aration with ether 252 mg (34%) of crystalline VIIa was obtained. Recrystallization from $CHCl_3$–MeOH gave needles, m.p. 145°; ν_{max} (Nujol) 1742, 1595 cm^{-1}. (Found: C, 67·02; H, 6·85; Cl, 10·04. $C_{21}H_{25}O_4Cl$ requires: C, 66·92; H, 6·69; Cl, 9·41%).

The C-10 *epimer of methyl* (±)-*epigibberate ethylene ketal* (VIII). The ester VIIa (177 mg) dissolved in dioxan (80 ml) was hydrogenated over Raney nickel W-7 (15 g) in the presence of $BaCO_3$ (0·5 g) at 70° and an initial press of 70 kg/cm^2 for 5·3 hr. The catalyst was filtered off and the filtrate concentrated *in vacuo* to give crystalline VIII (150 mg, 93%). Recrystallization from EtOAc–MeOH gave needles, m.p. 115–116°; ν_{max} (Nujol) 1743, 1599 cm^{-1}. (Found: C, 73·43; H, 7·68. $C_{21}H_{26}O_4$ requires: C, 73·66; H, 7·66%).

The C-10 *epimer of methyl* (±)-*epigibberate* (IXc). The ketal VIII (104 mg) dissolved in dioxan-2N HCl (20 ml: 8 ml) was heated for 15 min on a boiling water bath. The mixture was diluted with water and extracted with EtOAc. The extract was washed with water, sat $NaHCO_3$ aq and brine. Concentration of the soln after drying (Na_2SO_4) gave crystalline IXc (88 mg, 98%). Recrystallization from EtOAc gave plates, m.p. 112–113°; ν_{max} (Nujol) 1745, 1595 cm^{-1}. (Found: C, 76·19; H, 7·51. $C_{19}H_{22}O_3$ requires: C, 76·48; H, 7·43%).

(±)-*Epigibberic acid* (II). The ester IXc (86 mg) was heated under reflux with 20% KOH in MeOH–H_2O (1:1, 10 ml) for 3·5 hr. After cooling, the soln was acidified with HCl to give 80 mg (96%) of II. Its IR spectrum was identical with that of an authentic sample; ν_{max} (Numol) 1730, 1708, 1600 cm^{-1}.

The C-10 *epimer of methyl* (±)-6ξ-*tosyloxyepigibberate ethylene ketal* (VIIb). The alcohol VI (617 mg) in pyridine (12 ml) was treated with *p*-TsCl (1 g) for 40 hr at room temp. After conventional work-up 656 mg of VIIb was obtained. Recrystallization from EtOAc gave needles, m.p. 148–150°; ν_{max} (Nujol) 1700, 1602 cm^{-1}. (Found: C, 65·43; H, 6·22. $C_{28}H_{32}O_7S$ requires: C, 65·18; H, 5·88%).

Methyl 2-*nitrogibberate* (Xa). To a stirred and cooled soln of IXa (5·8 g) in Ac_2O (50 ml), a mixture of fuming HNO_3 (*d*, 1·50; 4·8 ml), conc HNO_3 (*f*, 1·38; 4·8 ml) and Ac_2O (30 ml) was added dropwise at −3—−4° during 15 min. After the addition, the mixture was stirred for 1 hr at −1–4°. It was poured into ice–water and left to stand overnight to hydrolyse Ac_2O. The solid product was taken into EtOAc. The

* The ketone (XX and XXII) have the C-1 methyl group in the thermodynamically more stable configuration, although it is difficult to decide whether it is α or β.[19]

extract was washed with water, sat $NaHCO_3$ aq and brine. Concentration of the soln after drying (Na_2SO_4) gave 6·2 g of semi-solid. Recrystallization from MeOH gave 4·55 g (70%) of needles, m.p. 174–175°; ν_{max} (Nujol) 1725, 1605, 1590, 1520 cm^{-1}. (Found: C, 66·60; H, 5·96; N, 4·46. $C_{19}H_{21}O_5N$ requires: C, 66·46; H, 6·16; N, 4·08%).

Methyl (±)-2-*nitrogibberate* (Xb). The ester Xa (12 g) in Ac_2O (120 ml) was nitrated with fuming HNO_3 (11 ml) and conc HNO_3 (11 ml) in Ac_2O (70 ml); yielding 11 g of crystalline Xb. This was employed for the next step without further characterization; ν_{max} (Nujol) 1728, 1605, 1590, 1520 cm^{-1}.

The C-10 *epimer of methyl* 2-*nitroepigibberate* (Xc). The ester IXc (11 g) in Ac_2O (100 ml) was nitrated with fuming HNO_3 (9·6 ml) and conc HNO_3 (9·6 ml) in Ac_2O (60 ml) to give 10·5 g of crude crystalline product. Recrystallization from $CHCl_3$–MeOH gave 6·8 g (51%) of Xc as prisms, m.p. 171–172°; ν_{max} (Nujol) 1740, 1608, 1592, 1520 cm^{-1}. (Found: C, 66·45; H, 6·34; N, 4·11. $C_{19}H_{21}O_5N$ requires: C, 66·46; H, 6·16; N, 4·08%). The second and the third crops from the mother liquor were the mixture of Xc and its probable positional isomer.

Methyl 2-*nitrodeoxogibberate* (Xd). The ester IXd (1·6 g) in Ac_2O (30 ml) was nitrated with conc HNO_3 (8 ml) in Ac_2O (20 ml) to give an oil which was chromatographed on alumina (19 × 2 cm). Elution with EtOAc–pet. ether (1:4) gave crystalline Xd (700 mg, 40%). Recrystallization from EtOAc–pet. ether gave needles, m.p. 103–104°; ν_{max} (Nujol) 1735, 1605, 1590, 1523 cm^{-1}. (Found: C, 69·06; H, 7·03; N, 4·20. $C_{19}H_{23}O_4N$ requires: C, 69·28; H, 7·04; N, 4·25%).

Methyl (±)-2-*nitrodeoxoepigibberate* (Xe). The ester IXe (5·5 g) in Ac_2O (50 ml) was nitrated with fuming HNO_3 (4·5 ml) and conc HNO_3 (4·5 ml) in Ac_2O (30 ml) to give 1·0 g of crystalline Xe. The mother liquor was chromatographed on alumina (25 × 2 cm). Elution with EtOAc–pet. ether (1:3) gave 0·9 g of Xe improving the total yield to 1·9 g (29%). Recrystallization from MeOH gave needles, m.p. 106–108°, ν_{max} (Nujol) 1722, 1600, 1588, 1515 cm^{-1}. (Found: C, 69·08; H, 6·60; N, 4·49; $C_{19}H_{23}O_4N$ requires: C, 69·28; H, 7·04; N, 4·25%).

Methyl 2-*aminogibberate* (XIa). The nitro ester Xa (1·3 g) dissolved in 95% EtOH (150 ml) was hydrogenated over 5% Pd–C (0·5 g) in the presence of conc HCl (0·5 ml) at room temp under atmospheric press for 1 hr (270 ml H_2 uptake). The catalyst was filtered off and the filtrate concentrated *in vacuo*. The residue was neutralized with 0·2% KOH aq (200 ml) and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 1·15 g (97%) of crystalline XIa. Recrystallization from MeOH gave needles, m.p. 154–155°; ν_{max} (Nujol) 3460, 3380, 1730, 1625, 1490, 1162, 825 cm^{-1}. (Found: C, 73·20; H, 6·96; N, 4·32; $C_{19}H_{23}O_3N$; C, 72·82; H, 7·40; N, 4·49%).

Methyl (±)-2-*aminogibberate* (XIb). The nitro ester Xb (11 g) suspended in 99% EtOH (200 ml) was hydrogenated over 10% Pd–C (3 g) in the presence of conc HCl (4 ml) at room temp under atmospheric press for 10 hr (2·4 l. H_2 uptake). Conventional work-up gave 9·5 g of crystalline XIb. This was employed for the next step without recrystallization. ν_{max} (Nujol) 3500, 3420, 1740, 1632, 1492, 1170, 820 cm^{-1}.

The C-10 *epimer of methyl* (±)-2-*aminoepigibberate* (XIc). The nitro ester Xc (6·5 g) suspended in 99% EtOH (200 ml) containing conc HCl (4 ml) was hydrogenated over 10% Pd–C (2 g). After conventional work-up, 5·5 g (94%) of crystalline XIc was obtained. Recrystallization from MeOH gave prisms, m.p. 203–204°; ν_{max} (Nujol) 3400, 3360, 1730, 1645, 1610, 1598, 1492, 1174, 842 cm^{-1}. (Found: C, 73·14; H, 7·32; N, 4·49. $C_{19}H_{23}O_3N$ requires: C, 72·82; H, 7·40; N, 4·49%).

Methyl 2-*aminodeoxogibberate* (XId). The nitro ester Xd (317 mg) dissolved in 99% EtOH (40 ml) containing conc HCl (1 ml) was hydrogenated over 10% Pd–C (100 mg) to give 260 mg of XId. Recrystallization from EtOAc–pet. ether gave needles, m.p. 157–160°; ν_{max} (Nujol) 3490, 3410, 1710, 1630, 1600, 1590, 1488, 1290, 1265, 1043 cm^{-1}. (Found: C, 76·29; H, 8·42; N, 4·54. $C_{19}H_{25}O_2N$ requires: C, 76·22; H, 8·42; N, 4·68%).

Methyl (±)-2-*aminodeoxoepigibberate* (XIe). The nitro ester Xe (1·0 g) dissolved in MeOH (150 ml) containing conc HCl (0·5 ml) was hydrogenated over 10% Pd–C (0·3 g) to give 800 mg (90%) of XIe. Recrystallization from MeOH gave needles, m.p. 130–131°; ν_{max} (Nujol) 3440, 3380, 3260, 1720, 1638, 1612, 1492, 1172, 828 cm^{-1}. (Found: C, 76·55; H, 8·12; N, 5·17. $C_{19}H_{25}O_2N$ requires: C, 76·22; H, 8·42; N, 4·68%).

Methyl 2-*hydroxygibberate* (XIIa). The amino ester XIa (1·1 g) in pyridine (6 ml) was added with stirring and cooling to a soln of $NaNO_2$ (0·8 g) in 80% (v/v) H_2SO_4 (30 ml) at −5–0° during 20 min. (The $NaNO_2$ soln was prepared by portionwise addition of $NaNO_2$ to H_2SO_4 under ice-cooling. The mixture was once warmed (30°) to dissolve $NaNO_2$ and then cooled to −5v–6° before the addition of XIa). Then water (15 ml) was added carefully at 0–5° and within 50 min followed with urea (0·7 g). The mixture was poured into boiling water (200 ml). After cooling, the product was extracted with EtOAc. The extract was washed with water, $NaHCO_3$ aq and brine. Concentration of the soln after drying (Na_2SO_4) gave 950 mg (86%)

of XIIa. Recrystallization from MeOH gave needles, m.p. 199–200°; ν_{max} (Nujol) 3470, 1736, 1692, 1600, 816 cm^{-1}. (Found: C, 72·37; H, 6·96. $C_{19}H_{22}O_4$ requires: C, 72·59; H, 7·05%).

Methyl (±)-2-*hydroxygibberate* (XIIb). The amino ester XIb (9·5 g) in pyridine (50 ml) was added with stirring and ice-cooling to a soln of $NaNO_2$ (7·8 g) in 80% (v/v) H_2SO_4 (300 ml) at −5–0° during 30 min. Subsequent operations as described above for XIIa gave 7·5 g (79%) of XIIb. Recrystallization from EtOAc–pet. ether gave needles, m.p. 181–183°; ν_{max} (Nujol) 3490, 1738, 1704, 1602, 1122, 875, 820 cm^{-1}. (Found: C, 72·80; H, 7·33. $C_{19}H_{22}O_4$ requires: C, 72·59; H, 7·05%).

The C-10 *epimer of methyl* (±)-2-*hydroxyepigiberate* (XIIc). The amino ester XIc (5·3 g) in pyridine (80 ml) was added with stirring and ice-cooling to a soln of $NaNO_2$ (4 g) in 80% (v/v) H_2SO_4 (200 ml) at −5–0°. Subsequent operations as described above for XIIa gave 4·7 g (89%) of XIIc. Recrystallization from $CHCl_3$ gave needles, m.p. 203–205°; ν_{max} (Nujol) 3380, 1742, 1714, 1600, 1506, 1200, 1178, 834, 820, 810, 798, 775 cm^{-1}. (Found: C, 72·65; H, 6·81. $C_{19}H_{22}O_4$ requires: C, 72·59; H, 7·05%).

Methyl 2-*hydroxydeoxogibberate* (XIId). The amino ester XId (210 mg) in pyridine (1·5 ml) was added with stirring and ice-cooling to a soln of $NaNO_2$ (200 mg) in 80% (v/v) H_2SO_4 (5 ml) at −5–−6°. Subsequent operations as described above for XIIa gave 203 mg (97%) of XIId. Recrystallization from MeOH–H_2O gave prisms, m.p. 189–190°; ν_{max} (Nujol) 3465, 1698, 1600, 1498, 1280, 1067, 1044 cm^{-1}.

Methyl (±)-2-*hydroxydeoxoepigibberate* (XIIe). The amino ester XIe (1·50 g) in pyridine (6 ml) was added with stirring and ice-cooling to a soln of $NaNO_2$ (1·2 g) in 80% (v/v) H_2SO_4 (35 ml) at −5–0°. Subsequent operations as described above for XIIa gave 350 mg (17%) of XIIe. Recrystallization from MeOH gave prisms, m.p. 173–174°; ν_{max} (Nujol) 3440, 1698, 1600, 1500, 1250, 1158, 1060, 1038, 826, 816, 790 cm^{-1}. (Found: C, 75·71; H, 8·21. $C_{19}H_{24}O_3$ requires: C, 75·97; H, 8·05%).

The C-10 *epimer of* 2-*hydroxygibberic acid* (XIIIf). The phenol ester XIIa (800 mg) in MeOH (20 ml) was heated under reflux with 40% KOH aq (10 ml) for 2 hr. The mixture was acidified with dil HCl and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 750 mg (98%) of XIIIf. Recrystallization from EtOAc gave needles, m.p. 248–250°; ν_{max} (Nujol) 3400, 1712, 1684, 1604, 828 cm^{-1}. (Found: C, 71·59; H, 6·68. $C_{18}H_{20}O_4$ requires: C, 71·98; H, 6·71%).

(±)-2-*Hydroxyepigibberic acid* (XIIIg). The phenol ester XIIc (539 mg) in MeOH (20 ml) was heated under reflux with 30% KOH (10 ml) for 2 hr. Subsequent treatments as described above for XIIIf gave 460 mg (89%) of XIIIg. Recrystallization from MeOH–C_6H_6 gave plates, m.p. 266–268°; ν_{max} (Nujol) 3440, ~3200–~2600, 1710, 1695 (sh.), 1600 cm^{-1}. (Found: 72·11; H, 6·43. $C_{18}H_{20}O_4$ requires: C, 71·98; H, 6·71%).

Selenium dehydrogenation of (XIIIf). The acid XIIIf (650 mg) and Se powder (700 mg) were heated in a current of N_2 at 200°, rising to 320° in 30 min, and then at 325–340° for 2·5 hr. The mixture was extracted with ether–C_6H_6. The extract was concentrated and the residue was kept at 200° under 15 mm Hg. Crude crystalline 2-hydroxy-1,7-dimethylfluorene XIVa' (ca. 10 mg) was obtained as sublimate. The residue in ether was chromatographed on alumina (20 × 2 cm) in pet. ether to give the following fractions (100 ml each). No. 1–3 (pet. ether): crystalline compound (probably 1,7-dimethylfluorene, 2 mg). No. 4–5 (ether): oil. No. 6–9 (ether–MeOH 50:1): crystalline 2-hydroxy-1,7-dimethylfluorene XIVa' (ca. 100 mg). No. 8–10 (EtOAc): oil. The fraction 6 (=XIVa', 80 mg) in MeOH (6 ml) was mixed with 50% KOH aq (1 ml) and Me_2SO_4 (0·5 ml). After 30 min the mixture was diluted with water and extracted with ether. The extract was washed with dil KOH aq, water and brine. The soln was dried (Na_2SO_4), decolorized (activated charcoal) and concentrated to give 70 mg of crystalline 2-methoxy-1,7-dimethylfluorene (XIVb'). Recrystallization from MeOH gave needles, m.p. 163–164° (lit.[9] 168–169°); ν_{max} (Nujol) 1612, 1592, 1470, 1440, 1402, 1382, 1350, 1308, 1252s, 1232, 1208, 1192, 1162, 1130, 1092s, 1010, 814s cm^{-1}, λ^{max} (EtOH) 274–275. 280, 303, 314 mμ (log ε 4·37, 4·27, 3·80, 3·76). (Found: C, 85·52; H, 6·99. Calcd. for $C_{16}H_{16}O$: C, 85·68; H, 7·19%). The IR spectrum was identical with that of an authentic sample. The UV spectrum agreed well with that reported in the literature.[9]

Selenium dehydrogenation of (XIIIg). The acid XIIIg (450 mg) and Se powder (150 mg) was heated in the same manner as described above. Subsequent treatments gave 25 mg of crystalline XIVb', identified by IR spectrum.

(±)-2-*Methoxydesoxoepigibberic acid* (XV). The phenol ester XIIe (200 mg) in MeOH (5 ml) was mixed with 20% KOH aq (4 ml). To the mixture, Me_2SO_4 (0·5 ml) was added dropwise with shaking. At the end of the exothermic reaction, 30% KOH aq (10 ml) was added and the mixture was refluxed for 2 hr. After cooling, the mixture was acidified with dil HCl and extracted with EtOAc. Subsequent work-up gave 150 mg (77%) of XV. Recrystallization from EtOAc gave prisms, m.p. 194–195°; ν_{max} (Nujol) 1690, 1660, 826 cm^{-1}. (Found: C, 75·65; H, 8·16. $C_{19}H_{24}O_3$ requires: C, 75·97; H, 8·05%).

Catalytic hydrogenation of XIIc (*gibbane compounds* XVIa *and* XVII)

(a) *With rhodium-platinum oxides.* The phenol XIIc (1 g) dissolved in AcOH (100 ml) was hydrogenated over RhO_2–PtO_2 (50 mg) at room temp and an initial press of 100 kg/cm² for 40 hr. Removal of the catalyst and the solvent gave an oil which was dissolved in acetone (100 ml) and treated with the Jones reagent (3 ml) under ice-cooling. After 30 min MeOH was added to the reaction mixture which was concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ether soln was washed with water, $NaHCO_3$ aq and brine. Concentration of the soln after drying (Na_2SO_4) gave an oil (751 mg). This was chromatographed on alumina (20 × 1·8 cm) in pet. ether to give the following fractions (100 ml each). No. 1–10 (ether–pet. ether, 1:10): none. No. 11–13 (ether–pet. ether, 1:10): 98 mg of crystalline oxo ester XVIa. Recrystallization from MeOH gave plates, m.p. 108–109°; ν_{max} (Nujol) 1743 (sh), 1736 cm^{-1}. (Found: C, 74·61; H, 9·17. $C_{19}H_{28}O_3$ requires: C, 74·96; H, 9·27%). No. 14–23 (ether–pet. ether, 1:10): oil. No. 24–33 (ether–pet. ether, 1:7): oil. No. 34–37 (ether–pet. ether, 1:4): oil. The oil (No. 14–37, 250 mg) was re-chromatographed on silica gel (15 g) impregnated with $AgNO_3$ aq (1·05 g in 5 ml). The column (18 × 1·9 cm) was successively eluted to give the following fractions (50 ml each). No. 1–10 (ether–pet. ether, 1:20): 10 mg of XVIa and another unknown crystalline compound (8 mg). No. 11–14 (ether–pet. ether, 1:10): none. No. 15–23 (ether–pet. ether, 1:10): 18 mg of crystalline dioxo ester XVII. Recrystallization from ether–pet. ether gave needles, m.p. 122–123°; ν_{max} (Nujol) 1742, 1710, 1185, 1150, 985; ($CHCl_3$) 1740, 1718, 1168, 1152 cm^{-1}. (Found: C, 71·64; H, 7·57. $C_{19}H_{26}O_4$ requires: C, 71·69; H, 8·23%). No. 15–20 (ether–pet. ether, 1:10): none.

(b) *With Reney nickel T-1.* The phenol XIIc (700 mg) in 99% EtOH (100 ml) was hydrogenated over Raney nickel T-1 (4 g) at 180–190° and an initial press of 100 kg/cm² for 3·5 hr. The oil (690 mg) obtained after Jones oxidation as described above was chromatographed on alumina (5 × 1·4 cm) to give the following fractions (10 ml each) by elution with ether–pet. ether (3:2). No. 1: 30 mg of XVIa. No. 2–4: oil (479 mg). No. 5: gum (30 mg). The oil (479 mg) was chromatographed on silica gel (15 g) containing water (5 ml). The column (20 × 1·8 cm) was eluted to give the following fractions (50 ml each). No. 1–7 (ether–pet. ether, 1:40): 99 mg of XVIa and 117 mg of gum. No. 8–14 (ether–pet. ether, 1:20): oil (15 mg). No. 15–21 (ether–pet. ether, 1:10): gum (84 mg). No. 22–24 (ether–pet. ether, 1:10): 51 mg of XVII. No. 25–27 (ether–pet. ether, 1:7) 22 mg of XVII. No. 28–32 (ether–pet. ether, 1:4): none. The total yield of XVIa was 129 mg (19%). XVII was obtained in 10·5% (73 mg) yield. XVIa and XVII obtained with Raney nickel catalyst were identified with those obtained with RhO_2–PtO_2 catalyst by IR comparisons. IR spectrum of XVII in $CHCl_3$ was different from that of III.

Epimerization at C-10 *of* XVIa (*gibbane compound* XVIb)

The ester XVIa (70 mg) in MeOH (2·5 ml) was heated at 50–60° with 20% KOH aq (1·5 ml) for 2 hr. The neutral fraction was recrystallized from MeOH to give plates of XVIb, m.p. 98–100°: ν_{max} (Nujol) 1743, 1731 cm^{-1}. (Found: C, 75·06; H, 8·91. $C_{19}H_{28}O_3$ requires: C, 74·96; H, 9·27%). The IR was clearly different from that of XVIa.

The attempted epimerization at C-10 *of* XVII. The ester XVII (11 mg) in MeOH (3 ml) was heated under reflux with 20% KOH aq (1·5 ml) for 2 hr. The product after esterification with CH_2N_2 was shown to be the starting XVII by IR comparison.

Reduction of methyl 2-hydroxygibberate (XIIa) [*methyl* 1,7-*dimethyl*-2,8-*dihydroxy*-4bα,7α-*gibba*-1,3,4a(10a)-*triene*-10β-*carboxylate* (XVIIIa)]

(a) *Catalytic reduction.* The phenol XIIa (2·0 g) dissolved in dioxan (70 ml) was hydrogenated over Raney nickel W-7 (4 g) at 40° and an initial press of 80 kg/cm² for 8 hr. The catalyst and the solvent were removed to give 850 mg (42%) of crystalline diol (XVIIIa). Recrystallization from EtOAc gave prisms, m.p. 253–255°; ν_{max} (Nujol) 3450, 3310, 1690, 1605 cm^{-1}. (Found: C, 72·00; H, 7·75. $C_{19}H_{24}O_4$ requires: C, 72·12; H, 7·65%). From the mother liquor, there was obtained a C-8 hydroxyl epimer (600 mg, 30%). Recrystallization from EtOAc–pet. ether gave leaflets, m.p. 144–146°; ν_{max} (Nujol) 3540, 3320, 1740, 1605 cm^{-1}. (Found: C, 71·85; H, 7·71. $C_{19}H_{24}O_4$ requires: C, 72·12; H, 7·65%).

(b) *Borohydride reduction.* The phenol XIIa (200 mg) in dioxan (5 ml) was treated with $NaBH_4$ (60 mg) at room temp for 3 hr. After acidification with dil AcOH, the mixture was extracted with EtOAc to give 170 mg (85%) of the epimer melting at 144–146°. The identity was proved on the basis of its IR spectrum.

Reduction of methyl (±)-2-*hydroxygibberate* (XIIb) [*methyl* (±)-1,7-*dimethyl*-2,8-*dihydroxy*-4bα,7α-*gibba*-1,3,4a(10a)-*triene*-10β-*carboxylate* (XVIIIb)]

The racemic phenol XIIb (7·5 g) in dioxan (100 ml) was hydrogenated over Raney nickel W-7 (15 g) at 60–70° and an initial press of 70 kg/cm² for 5 hr. The catalyst and the solvent were removed and the residue was triturated with ether to give 3·6 g (48%) of XVIIIb. Recrystallization from EtOAc–pet. ether gave rods, m.p. 235–237°; ν_{max} (Nujol) 3460, 3320, 1698, 1605 cm^{-1}. (Found: C, 72·12; H, 7·71. $C_{19}H_{24}O_4$ requires: C, 72·12; H, 7·65%). The C-8 epimer could not be obtained in crystalline form.

The half acetate (XIXa) [*methyl* 1,7-*dimethyl*-2-*hydroxy*-8-*acetoxy*-4bα,7α-*gibba*-1,3,4a(10a)-*triene*-10β-*carboxylate*]

The high-melting XVIIIa (6·5 g) in MeOAc (860 ml) containing *p*-TsOH (7 g) was heated under reflux for 2·5 hr. Another 7 g of *p*-TsOH was added to the mixture and the heating was continued for 2 hr. After cooling, the soln was washed with water and $NaHCO_3$ aq, dried (Na_2SO_4) and concentrated. The residue was chromatographed on alumina (19·5 × 3·5 cm) in C_6H_6. Elution with C_6H_6–$CHCl_3$ (3:1–1:1) (7·5 l.) gave 5·35 g (73%) of XIXa. Recrystallization from EtOAc–pet. ether gave needles, m.p. 177–178°; ν_{max} (Nujol) 3360, 1718, 1688, 1598 cm^{-1}. (Found: C, 70·02; H, 7·51. $C_{21}H_{26}O_5$ requires: C, 70·37; H, 7·31%).

The low-melting isomer of XVIIIa (200 mg) gave 120 mg (53%) of half acetate which crystallized as prisms from EtOAc–pet. ether, m.p. 145–146°; ν_{max} (Nujol) 3460, 1730, 1695, 1605 cm^{-1}. (Found: C, 69·93; H, 7·78. $C_{21}H_{26}O_5$ requires: C, 70·37; H, 7·31%).

The half acetate (XIXb) [*methyl* (±)-1,7-*dimethyl*-2-*hydroxy*-8-*acetoxy*-4bα,7α-*gibba*-1,3,4a(10a)-*triene*-10β-*carboxylate*]

The racemic XVIIIb (3·5 g) in MeOAc (480 ml) containing *p*-TsOH (4 g) was heated under reflux for 4·5 hr. Subsequent treatments including chromatography on alumina gave 2·6 g (67%) of XIXb. Recrystallization from EtOAc–pet. ether gave rods, m.p. 165–166°; ν_{max} (Nujol) 3480, 1730, 1705, 1605 cm^{-1}. (Found: C, 70·58; H, 7·56. $C_{21}H_{26}O_5$ requires: C, 70·37; H, 7·31%).

Catalytic hydrogenation of XIXa [*methyl* 1,7-*dimethyl*-2-*oxo*-8-*acetoxy*-4aβ,4bα,7α,10aβ-*gibbane*-10β-*carboxylate* (XXa)]

The half acetate XIXa (5·0 g) in AcOH (70 ml) was hydrogenated over RhO_2–PtO_2 (0·2 g) at 50–60° and an initial press of 110 kg/cm² for 3 hr. Removal of the catalyst and the solvent gave an oil (5·0 g). This was dissolved in AcOH (100 ml) and oxidized by dropwise addition of CrO_3 (5·0 g) in AcOH (45 ml) and water (5 ml) with stirring and ice-cooling. After 40 hr at 6°, MeOH (20 ml) was added to the mixture which was concentrated *in vacuo*. The residue was diluted with water and extracted with C_6H_6–ether (1:1). The extract was washed with water, $NaHCO_3$ aq and brine. Concentration of the soln after drying (Na_2SO_4) gave an oil (4 g). This was chromatographed on alumina (21 × 2·5 cm) in benzene. Elution with C_6H_6 (1 l.) gave an oily hydrogenolysis product probably XXIa (360 mg). Then elution with C_6H_6–ether (5:1; 1 l.) gave 450 mg of semi-solid. Recrystallization from EtOAc–pet. ether gave 250 mg (5%) of XXa as rods, m.p. 175–176°; ν_{max} (Nujol) 1730s, 1710s, 1460, 1435, 1410, 1378, 1338, 1315, 1288, 1240s, 1225, 1165s; ($CHCl_3$) 1726s, 1710s, 1250s, 1210m, 1165m cm^{-1}. (Found: C, 69·76; H, 8·51. $C_{21}H_{30}O_5$ requires: C, 69·58; H, 8·34%). Further elution gave 620 mg of oil.

Catalytic hydrogenation of XIXb [*methyl* (±)-1,7-*dimethyl*-2-*oxo*-8-*acetoxy*-4aβ,4bα,7α,10aβ-*gibbane*-10β-*carboxylate* (XXb)]

The racemic XIXb (2·5 g) in AcOH (70 ml) was hydrogenated over RhO_2–PtO_2 (0·2 g) at 25° and an initial press of 98 kg/cm² for 5·5 hr. The oily product (2·5 g) in pyridine (20 ml) was added to the Sarett reagent prepared from CrO_3 (2 g) and pyridine (30 ml) under ice-cooling. The mixture was left to stand overnight at room temp, diluted with water and extracted with C_6H_6–ether (1:1). The extract was washed with water, dried (Na_2SO_4) and evaporated to give an oil which was chromatographed on alumina (21 × 2·5 cm) in C_6H_6. Elution with C_6H_6–ether (5:1; 1 l.) gave ca. 200 mg of oil. Then elution with C_6H_6–ether (4:1; 0·5 l. and 3:1; 1 l.) gave 50 mg (2%) of XXb. Recrystallization from EtOAc–pet. ether gave rods, m.p. 121–122°; ν_{max} (Nujol) 1730, 1715, 1255; ($CHCl_3$) 1726s, 1710s, 1250s, 1210m, 1165m cm^{-1}. (Found: C, 69·30; H, 8·42. $C_{21}H_{30}O_5$ requires: C, 69·58; H, 8·34%). The IR spectrum ($CHCl_3$ soln) was superimposable on that of XXa.

The attempted epimerization at C-10 *of* XXb. The XXb (40 mg) in MeOH (2·5 ml) was heated under reflux with 20% KOH aq (1·5 ml) for 2 hr. The product (30 mg) was treated with ethereal CH_2N_2 and the

resulting ester was acetylated with Ac_2O (1 ml) and pyridine (1 ml). After 2 days the solvents were removed and the residue was extracted with ether. The extract was washed with water, dil HCl, $NaHCO_3$ aq and brine. Concentration of the soln after drying (Na_2SO_4) gave back the starting material XXa (23 mg) identified by IR comparison.

ORD measurements. Values are for $[\phi]$, in MeOH (c = 0·1%), for the ketones. (XXa), m.p. 175–176°: negative Cotton effect curve (600 mμ) +100°; (308, trough 1) −6900°; (266, peak 1) +11,700°; (250, trough 2) +10,800°; (228, peak 2) +12,200°. A −18,600°. (XXII), m.p. 122–124°: negative Cotton effect curve (600 mμ) −100°; (308, trough 1) −7700°; (266, peak 1) +9100°; (245, trough 2) +7700°; (230, peak 2) +8200°. A −16,800°.

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