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SYNTHESIS OF SUBSTANCES RELATED TO GIBBERELLINS
PART XVIII. TOTAL SYNTHESIS OF (±)-GIBBERELLINS A_2, A_4, A_9 AND A_{10}*

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In spite of several attempts (1) which have been made recently to synthesize the gibberellins (2), no successful total synthesis of them has been reported. We now wish to describe the total synthesis of some of the C-19 gibberellins in their racemic forms.

(±)-Epigibberic acid (I), of which total synthesis was accomplished by us in 1962 (3), was converted into a dienone ester (II) employing three new degradation products (XI, XVI and XVIII) of gibberellic acid as relay compounds. Since the dienone ester (II) was the starting material in our partial synthesis of gibberellin C (III)(4), this completed the total synthesis of (±)-gibberellin C (III). Cross, Hanson and Speake (5) have transformed the keto acid (III) into gibberellin A_4 (V), from which gibberellins A_2 (IV)(6) and A_9 (VI)(7) have been derived. Conversion of gibberellin A_9 (VI) into A_{10} (VII) has also been reported (8). Thus, the present work constitutes the formal total synthesis of (±)-gibberellins A_2 (IV), A_4 (V), A_9 (VI) and A_{10} (VII).

Methyl (±)-epigibberate (I, CO_2CH_3 instead of C-10 CO_2H), m.p. 99-100° (9), in acetic anhydride was nitrated with nitric acid to give a nitro ester (VIII), m.p. 128-129°, in 58 % yield (10). This was hydrogenated over palladium-charcoal to yield an amino ester (IX), m.p. 189-190°. Diazotization followed by hydrolysis of the amino ester (IX) afforded a hydroxy ester (X), m.p. 165-167°. The position of the hydroxyl group was confirmed by the selenium dehydrogenation of an acid obtained by alkaline hydrolysis of the ester (X). The dehydrogenation product was methylated with dimethyl sulfate and alkali to give 2-methoxy-1,7-dimethylfluorene (11) identified with an authentic sample by i.r. and m.m.p (12).

Hydrogenation of the phenol (X) over Raney nickel T-1 (13) resulted in only the reduction of the C-8 carbonyl group. The obtained dihydroxy ester was hydrogenated

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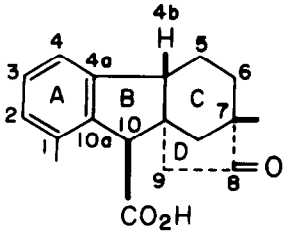
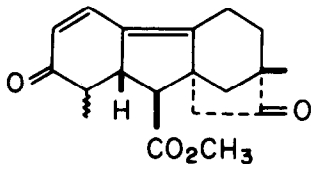


I



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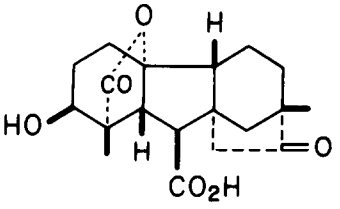
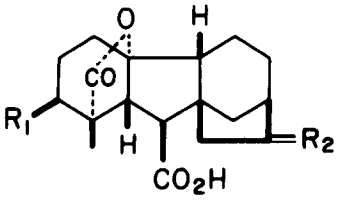
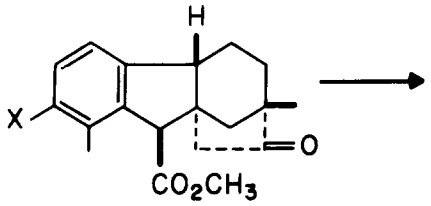


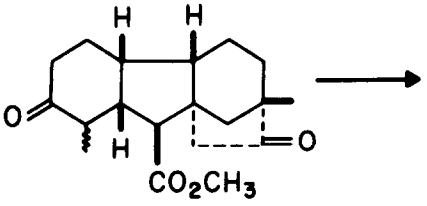
III



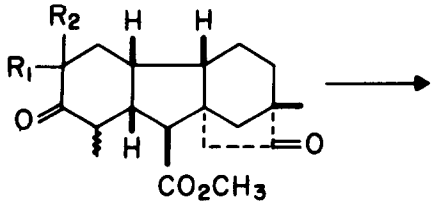
	R_1	R_2
IV	OH	$\overset{CH_3}{\underset{OH}{<}}$
V	OH	$=CH_2$
VI	H	$=CH_2$
VII	H	$\overset{CH_3}{\underset{OH}{<}}$



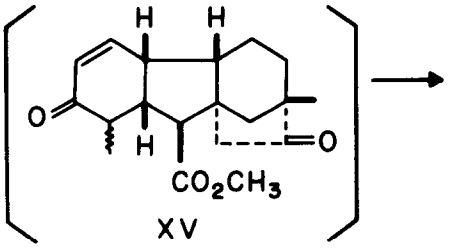
XIII $X = NO_2$; IX $X = NH_2$
X $X = OH$



XI



	R_1	R_2
XII	H	CHO
XIII	Br	CHO
XIV	Br	H



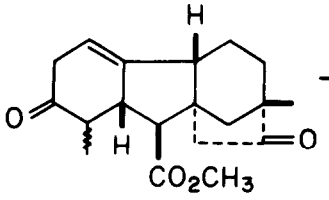
XV

over rhodium-platinum oxides (14) to give a complex mixture of esters with hydroaromatic A ring. This was oxidized with the Jones chromic acid reagent (15) and the product was chromatographed on silicic acid. Elution with petrol-benzene (6:1) gave a keto ester (XI, H_2 instead of C-2 O, unknown 4a, 10a-configurations), m.p. 110.5-111.5°, in 8 % yield. Petrol-benzene (3:1) eluted another stereoisomeric keto ester (XI, H_2 instead of C-2 O, unknown 4a, 10a-configurations), m.p. 98.5-99.5°, in 2 % yield. These two compounds were obviously obtained by the hydrogenolysis of the C-2 hydroxyl group. Then elution with benzene afforded a diketo ester [(XI) with unknown configurations at C-4a and C-10a (probably 4aα, 10aα)] in 12 % yield, m.p. 178-179°, νmax. (nujol) 1740, 1724, 1715 (sh.) cm^{-1}, δ (ppm from TMS at 100 MHz) 0.95 (3H, d, J=5Hz), 1.05 (3H, s), 3.68 (3H, s). Successive elution with benzene gave a racemic diketo ester (XI), m.p. 112-113°, νmax. (nujol) 1730, 1705 cm^{-1}, in 4 % yield. Its spectral properties in solution as well as gas chromatographic behavior were indistinguishable from those of an optically active diketo ester (XI), m.p. 128-129°, νmax. (nujol) 1742, 1730, 1720; ($CHCl_3$) 1744, 1736, 1716 cm^{-1}; δ (ppm from TMS at 100 MHz) 1.06 (3H, s) 1.08 (3H, d, J=5Hz), 3.70 (3H, s); g.l.c. retention time 10.8 min (1.5 % OV - 17, 4mm i.d. x 2m, 220°, N_2)(16).

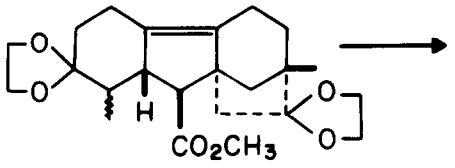
The diketo ester (XI) prepared from gibberellic acid was treated with methyl formate and sodium methoxide to give a formyl ketone (XII), m.p. 129-130°, in 69 % yield. This was dissolved in aqueous sodium hydroxide and treated with bromine to give a bromide (XIII). Alkaline hydrolysis of this α-bromo-α-formyl ketone (XIII) with an equimolar amount of sodium hydroxide gave a bromoketone (XIV) as a crude oil (17,18). This was heated with lithium bromide and lithium carbonate in dimethylformamide (19) to give a crude gummy product containing an α,β-unsaturated ketone (XV, δ ca. 6.1 and 7.1 C<u>H</u> = C<u>H</u>) and its $\Delta^{1(10a)}$ -isomer (δ 2.02, C=C C<u>H</u>$_3$). After equilibration with boiling dilute hydrochloric acid, the dehydrobromination product was separated into acid and neutral fractions. The acid fraction was esterified with diazomethane and chromatographed on alumina. Elution with petrol-ether (4:1) gave a diketo ester (XVI) in 7 % yield (from XII) which was identified by i.r., n.m.r. and m.m.p. with the authentic ester (XVI), m.p. 122-123°, νmax. (nujol) 1744, 1732, 1724 cm^{-1}, δ (ppm from TMS at 100 MHz) 1.08 (3H, s), 1.12 (3H, d, J=5Hz, partly overlapped on the 3H singlet), 3.73 (3H, s), 5.44 (1H, broad) (20).

This β,γ-unsaturated ketone (XVI) was treated with ethylene glycol and p-toluenesulfonic acid in dichloroethane. The oily product was chromatographed on alumina to give the $\Delta^{4a(4b)}$ bis-ketal (XVII) in 15 % yield, m.p. 145-146°, νmax. (nujol) 1738 cm^{-1}, δ (ppm from TMS at 100 MHz) 0.80 (3H, d, J=6Hz), 0.90 (3H, s), 3.68 (3H, s), 3.83-3.94 (8H, m), no olefinic proton (21). Hydrolysis of the ketal (XVII) with dilute hydrochloric acid in dioxan afforded a diketo ester (XVIII) in 86 % yield, identical with an authentic sample (XVIII), m.p. 167-168°, νmax. (nujol) 1742, 1714 cm^{-1}, δ (ppm from TMS at 100 MHz) 0.98 (3H, d, J=5Hz), 1.06 (3H, s), 3.80 (3H, s).

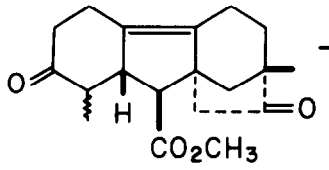
The $\Delta^{4a(4b)}$ diketo ester (XVIII) was submitted to the same sequence of reactions



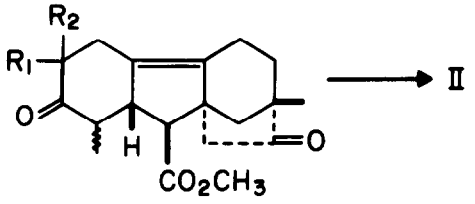
XVI



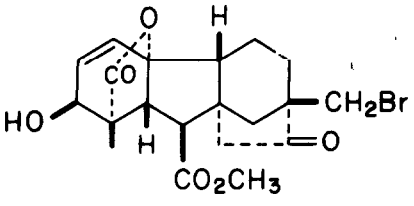
XVII



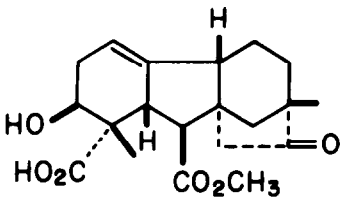
XVIII



	R_1	R_2
XIX	H	CHO
XX	Br	CHO
XXI	Br	H



XXII



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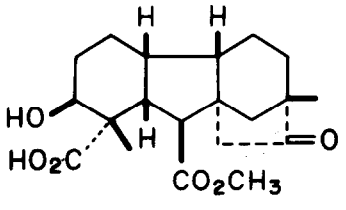
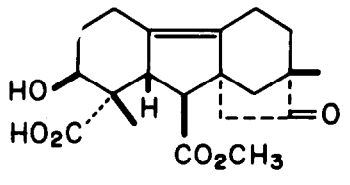
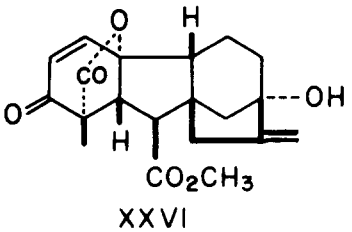


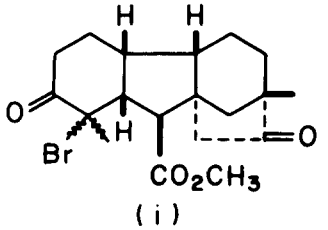
XXIV



XXV



XXVI



(i)

as described for the ester (XI). A formyl ketone (XIX) was obtained in 92 % yield as a gum. This was brominated to give an α-bromo-α-formyl ketone (XX). Removal of the formyl group with aqueous sodium hydroxide yielded a bromoketone (XXI). Chromatographic purification on alumina of the dehydrobromination ($LiBr$-Li_2CO_3-DMF) product afforded the dienone ester (II) in 3.4 % yield from the formyl ketone (XIX). This was identical with an authentic sample (II), m.p. 107-108°, $\nu_{max.}$ (nujol) 1736, 1672, 1660, 1574 cm^{-1}, δ (ppm from TMS at 100 MHz) 1.08 (3H, s), 1.10 (3H, d, J=5Hz), 3.80 (3H,s), 6.04 (1H, d, J=5Hz), 7.27 (1H, d, J=5Hz) by spectral comparisons and m.m.p. Thus we have connected the total synthesis of (±)-epigibberic acid (I) with the partial synthesis of gibberellin C (III).

Three relay compounds were prepared from gibberellic acid in the following manner. Methyl bromogibberellate (XXII)(22) in tetrahydrofuran-methanol was hydrogenated over palladium-charcoal in the presence of pyridine (23) under high pressure to give an unsaturated acid (XXIII), m.p. 191-192°, in 82 % yield. Gibberellin C methyl ester (III, CO_2CH_3 instead of C-10 CO_2H) was also obtained (14 % yield) as a by-product. Hydrogenation of the acid (XXIII) over Adams platinum oxide gave a saturated acid (XXIV), m.p. 274-276°, in 62 % yield after chromatography on silicic acid. Another expected product (XXV)(cf. 16) could not be obtained in pure form. Jones oxidation (15) followed by decarboxylation of the acid (XXIV) gave the first relay compound (XI). More conveniently, the crude hydrogenation product obtained from the acid (XXIII) was directly oxidized, decarboxylated and equilibrated with methanolic sodium methoxide to give the diketo ester (XI) in 49 % yield. The second relay compound (XVI) was obtained in 37 % yield from the acid (XXIII) by oxidation and decarboxylation. Alternatively, a keto lactone (XXVI)(24) was treated with zinc dust in hot acetic acid to effect reductive cleavage of the lactone ring. The product was heated with dilute hydrochloric acid, esterified with diazomethane and chromatographed on alumina to give the keto ester (XVI) in 44 % yield. The third relay compound (XVIII) was prepared from the dienone ester (II) in 73 % yield by borohydride reduction, catalytic hydrogenation over palladium-charcoal and oxidation with the Jones reagent (15).

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