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SYNTHESIS OF SUBSTANCES RELATED TO GIBBERELLINS
PART XV* A PARTIAL SYNTHESIS OF GIBBERELLIN C**

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SINCE the total synthesis of (±)-gibberic[1,2] and (±)-epigibberic[2] acids had been accomplished, our efforts were directed to the synthesis of gibbane compounds containing the 1→4a-lactone bridge which is characteristic to all gibberellins. We now wish to describe a partial synthesis of gibberellin C (I)[3], a biologically active lactonic acid obtained from gibberellin A_1.

A diketo ester (II)[4], m.p. 107-108°C, νmax. (Nujol) 1736,

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* Part XIV, K. Mori, M. Matsui and Y. Sumiki, Agr. Biol. Chem. (Tokyo), 28, 243 (1964).

** Biochemical Studies on "Bakanae" Fungus. Part 72. This is a part of a paper read at the 3rd I.U.P.A.C. International Symposium on the Chemistry of Natural Products held in Kyoto, Japan, in April, 1964.

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2 K. Mori, M. Matsui and Y. Sumiki, Agr. Biol. Chem. (Tokyo), 26, 783 (1962).

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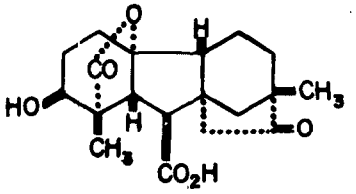
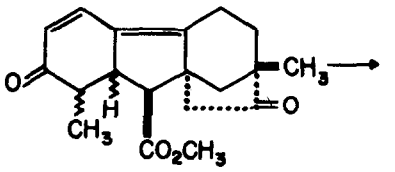
4 This new compound was prepared in the following manner. Methyl gibberellate (ia) was oxidized with manganese dioxide to give a keto lactone (ib) as described by Cross (J. Chem. Soc., 1960, 3022). This was boiled with dilute hydrochloric acid, treated with diazomethane and chromatographed over alumina to afford the diketo ester (II, gas chromatographically pure) in 48% yield.

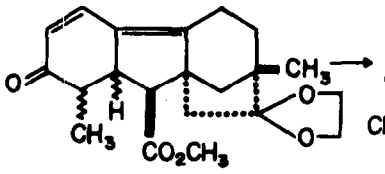
1672, 1660, 1574 cm^{-1}, λmax. (EtOH) 302 mμ (ε 16100), was boiled with ethylene glycol and p-toluenesulfonic acid in dichloroethylene to afford a monoketal (III), m.p. 180-181°C, νmax. (Nujol) 1730, 1650, 1572 cm^{-1}, λmax. (EtOH) 308 mμ (ε 17200). This monoketal (III)



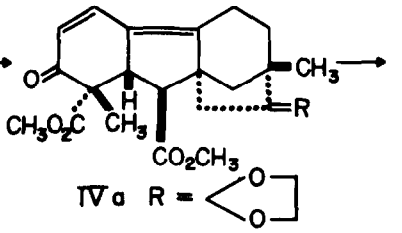
I



II

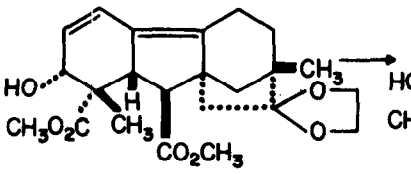


III

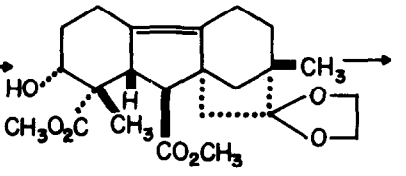


IVa R =

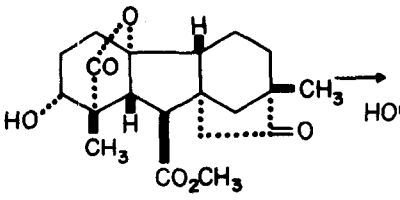
IVb R = O



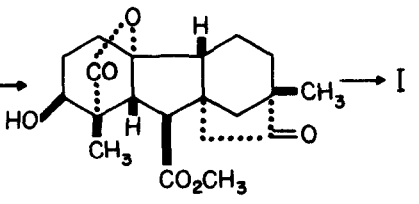
V



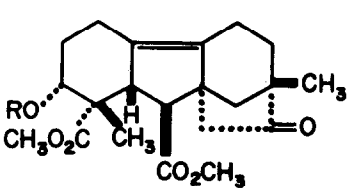
VI



VII

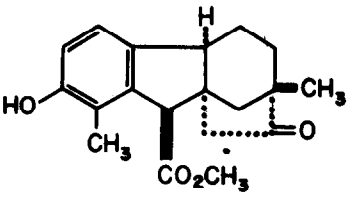


VIII

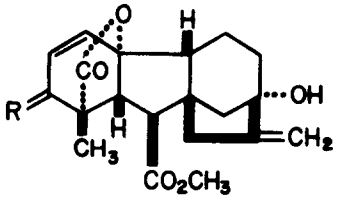


IXa R = H

IXb R = CH_3CO

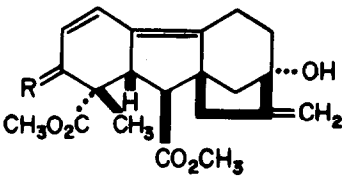


X



Ia R = 

Ib R = O



IIa R = 

IIb R = O

in tetrahydrofuran was carboxylated with ethereal triphenylmethyl sodium and carbon dioxide. After acidification, the product was treated with diazomethane and chromatographed over alumina. The crystalline starting material (III) was removed and the mother liquor in aqueous dioxane was heated with a trace of hydrochloric acid to regenerate the ring D ketone. Thus obtained oily mixture of the diketo ester (II) and the keto diester (IVb) was separated by gas-liquid chromatography[5]. A total of 3 mg of the oil was

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5 Presence of the desired α-carbomethoxylated product (IVb) in the oil was conclusively proved by comparison of the gas chromatogram of the authentic diester (IVb) with that of the oil, employing three kinds of columns, SE-30, QF-1 and CNSi. The retention times of the esters II and IVb are listed below.

Retention times (min.)[a]

Ester	1.5% SE-30[b]	2.0% QF-1[b]	2.0% CNSi[b]
II	3.9	10.4	18.4
IVb	5.8	16.2	29.5

a: All retention times were determined on a Shimadzu Seisakusho Model GC-1B, hydrogen flame detector, stainless steel column, 150cm x 4mm i.d.

b: Column temp., 220°C. Carrier gas, N_2, 90 ml/min.

chromatographed over SE-30 and about 0.5 mg of the diester (IVb) was collected as semi-solid mass contaminated with silicone oil[6]. After chromatographic purification over alumina, this substance showed a completely identical infrared spectrum with that of the authentic diester (IVb)[7,8], m.p. 107-108°C, νmax. (Nujol) 1730, 1680, 1660, 1560 cm^{-1}, λmax. (EtOH) 309 mμ (ε 14200).

The diester (IVb) was boiled with ethylene glycol and p-toluenesulfonic acid in dichloroethylene to give a monoketal (IVa), oil, νmax. (film) 1738(sh.), 1730, 1680, 1660, 1574 cm^{-1}, λmax. (EtOH) 313 mμ (ε 13100). Reduction of this monoketal (IVa) with sodium borohydride yielded a hydroxy ester (V), oil, νmax. (film) 3480, 1730, 1670(sh.)cm^{-1}. This was hydrogenated over palladium-charcoal. The resulting hydroxy ketal ester (VI), oil, νmax. (film) 3500, 1725 cm^{-1}, was boiled with dilute sulfuric acid to effect relactonization as well as hydrolysis of the ring D ketal. The product was treated with diazomethane and chromatographed over alumina to give 2-hydroxyl equatorial epimer (VII) of gibberellin C methyl ester, m.p. 223-226°C, which was identified with an authentic sample by mixed m.p. and infrared spectrum. From the earlier fractions of the chromatographic separation was obtained a hydroxy diester (IXa) which was characterized as its crystalline acetate (IXb)[9], m.p. 135-137°C.

Since the ester (VII) had been converted to gibberellin C (L)

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6 2% SE-30, 150cm x 6mm i.d. Carrier gas N_2, 180 ml/min. Column temp., 220°C. A part of the outlet gas was introduced into the detector, while the remaining part was passed through a U-tube immersed in a Dry Ice-acetone bath. Thus the separated material was collected.

7 The yield of the diester (IVb), calculated from the gas chromatographic analysis, was about 9%. The low yield of the diester (IVb) and the stereoselective introduction of the carboxyl group must be due to the large steric hindrance caused by the β-oriented C-10 carbomethoxyl group. No introduction of a carboxyl group at C-3 may be ascribed to the lack of enolizability of the C-2 ketone function to the direction of C-3 because of the extraordinary stability of the gibba-3,4a(4b)-diene system.

8 This new compound (IVb) was obtained by treatment of a keto-ester (iib) with boiling dilute hydrochloric acid. The keto-ester (iib) was obtained from methyl gibberellenate (iia) by manganese dioxide oxidation according to Moffatt (J. Chem. Soc., 1960, 3045).

by base-catalyzed epimerization of 2-hydroxyl group followed by acid hydrolysis[9], this completed a partial synthesis of gibberellin C (I) from the diketo ester (II). A synthesis of the ester (II) from methyl 2-hydroxygibberate (X)[10], m.p. 199-200°C, ν_{max}. (Nujol) 3470, 1736, 1692, 1600, 816 cm^{-1}, is in progress.

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9 K. Mori, M. Matsui and Y. Sumiki, Agr. Biol. Chem. (Tokyo) 28, 179 (1964).

10 K. Mori, T. Ogawa, M. Matsui and Y. Sumiki, unpublished.