Synthesis of a Hydrofluorenone Derivative, a Promising Intermediate for Synthesis of C_{19} Gibberellins

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Summary 4-Acetoxy-1,2,3,4,4a,9a-hexahydro-4a-hydroxy-7-methoxy-1-methyl-9-oxo-fluorene-1-carboxylic acid (1′ → 4a)-lactone has been synthesized in high yield, in several steps, from simple starting materials.

RECENTLY a formal total synthesis of the (±)-gibberellins A_2, A_4, A_9, and A_{10} was achieved;[1] syntheses of several hydrofluorene derivatives which may serve as intermediates or models for the total synthesis of gibberellins have also been reported.[2,3] We describe here an efficient synthesis of 4-acetoxy-1,2,3,4,4a,9a-hexahydro-4a-hydroxy-7-methoxy-1-methyl-9-oxofluorene-1-carboxylic acid (1′ → 4a)-lactone (X), a promising intermediate in the synthesis of C_{10} gibberellins, using the route shown.

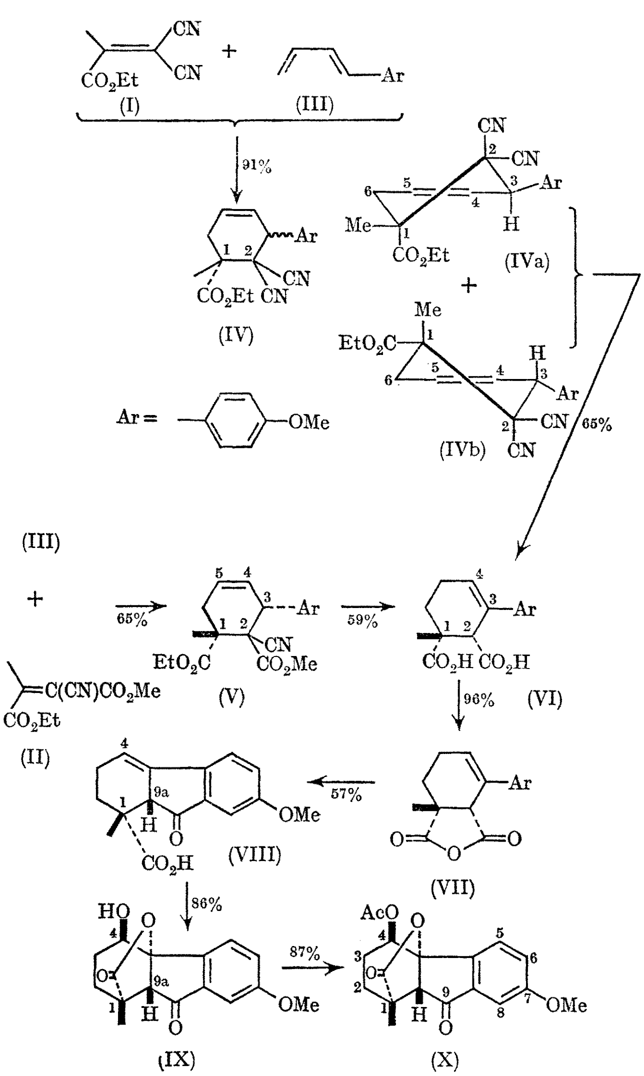
The Knoevenagel reaction of ethyl pyruvate and malononitrile in ethanol at room temperature afforded the dienophile (I),† b.p. 80—95°/2 mm. Hg., yield 44%, which was condensed with 1-(*p*-methoxyphenyl)butadiene (III)[4] by heating under reflux in benzene to give the adducts (IVa), m.p. 126·0—126·5°, and (IVb), m.p. 130·5—131·0°, separable by silica gel chromatography. The ratio of (IVa) to (IVb) was 2·2 : 1 as estimated by the n.m.r. peak intensities of the C-1 methyl groups. Assignment of structures (IVa) and (IVb) to the stereoisomeric adducts is based on n.m.r. data ($CDCl_3$); the lower chemical shift of the benzylic 3-H in (IVa) (4·38 p.p.m.) as compared with that in (IVb) (3·85 p.p.m.) due to deshielding by the axial ester group in (IVa), and the broader shape of the quasi-axial C-1 methyl signal in (IVb) due to the W-shaped long-range coupling with the quasi-axial 6-H.

Hydrolysis of the mixture of (IVa) and (IVb) with 30% aqueous KOH under reflux for 60 hr. yielded the styrenoid dicarboxylic acid (VI), m.p. 200° (dec.).

The alternative dienophile (II) was synthesized in 43% yield by condensation of ethyl pyruvate with methyl cyanoacetate in the presence of anhydrous $ZnCl_2$–acetic anhydride, which gave only one of the double-bond isomers, b.p. 104—111°/0·8 mm. Hg. Diels–Alder condensation of (II) with the diene (III) afforded the adduct (V), m.p. 107—108°, which was then converted into the dicarboxylic acid (VI) by heating under reflux in 35% aqueous KOH for 24 hr.

Heating the acid (VI) in acetic anhydride furnished the anhydride (VII), m.p. 100·5—101·5°; the same dicarboxylic acid (VI) was recovered upon base treatment of anhydride (VII) with base, so the orientations of the two carbonyl functions in (VII) and (VI) are identical. The intramolecular Friedel–Crafts cyclization of this anhydride (VII) was achieved by treatment with $AlCl_3$ in benzene at room temperature for 5 hr. to give the keto-acid (VIII) (57%) after recrystallization from aqueous ethanol, m.p. 214—217° (decomp.). Hydroxy-lactonization[5] of the keto-acid (VIII) with *p*-nitroperbenzoic acid in chloroform yielded the γ-lactone (IX), m.p. 177—178°, which on acetylation with acetic anhydride in pyridine diluted with methylene chloride gave 4-acetoxy-1,2,3,4,4a,9a-hexahydro-4a-hydroxy-7-methoxy-1-methyl-9-oxofluorene-1-carboxylic acid (1′ → 4a)-lactone (X), m.p. 176·3—177·0°.

Subsequent steps which would lead to the C_{19} gibberellins are introduction of a C_1-unit at C-9 and transformation of the aromatic ring into rings C and D. The C-4 oxygen function has a dual purpose; it will serve to elaborate ring A and also to re-introduce an oxygen function at C-4a if the lactone is hydrogenolysed during reduction of the atomatic ring.



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† Compounds (I)—(X) gave elemental analyses and spectroscopic data in agreement with the structures shown. Yields quoted are or recrystallised or distilled products.

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