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SYNTHESIS OF A FULLY FUNCTIONALISED TETRACYCLIC GIBBERELLIN INTERMEDIATE

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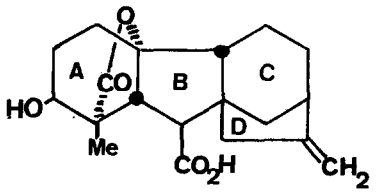
In our previous studies on gibberellin synthesis we have described a general approach to the construction of the ring A lactone system as present in gibberellins such as Gibberellic acid and Gibberellin A_4 (1), based on the reductive alkylation of a 2-methoxybenzoic acid [1,2]. We have also described an approach to the bicyclo[3,2,1] octane system present in rings C,D of these compounds [3,4,5].

With a view to combining these two approaches and, in addition, to illustrate a simple method of functionalisation in ring B we now describe the synthesis of a tetracyclic intermediate (6, R=CO_2Me, R'= $-OCH_2CH_2O-$) which contains all the functional groups necessary for elaboration to Gibberellin A_4.

7-Methoxyindan-1-one [6] was formylated, and the α-formyl ketone treated with hydrogen peroxide in refluxing t-butanol to give the dicarboxylic acid (2, R=R'=H), double m.p. 98°, 110°. Its half-ester (2, R=Me, R'=H) was treated with oxalyl chloride and then with aluminium chloride in 1,2-dichloromethane, to give after remethylation (Me_2SO_4/NaOH/THF) the keto-ester (3, R=H), m.p. 110°. Acid-catalysed condensation of this with n-butyl glyoxalate, followed by catalytic hydrogenation and methanolysis led to the diester (3, R= CH_2CO_2Me), m.p. 98-99°, in 76% overall yield. Treatment of the latter with methyl vinyl ketone in methanolic sodium

methoxide gave the half-ester (4), which was cyclised ($CF_3CO_2H/[CF_3CO]_2O$) to the diketo-ester (5), m.p. 215° in 82% overall yield.

The latter was now hydrogenolysed using a special catalyst prepared by prehydrogenation of palladium chloride in acetic acid [7], to give in 65% yield the keto-ester (6, R=H, R'=O), double m.p. 145°, 154°, together with a small amount of its 4b-epimer of m.p. 113-114° [8], found to be identical with an authentic sample [9].



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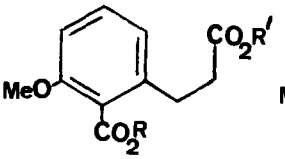

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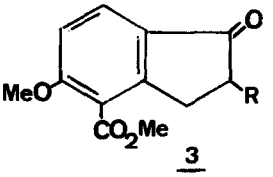

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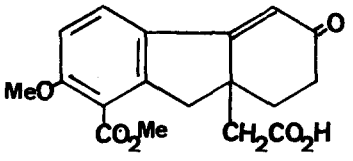

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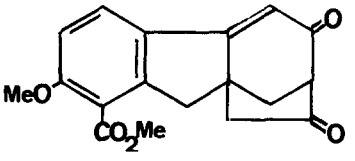

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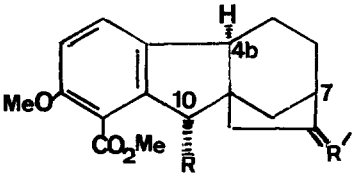

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The corresponding ketal (6, R=H, R'= $-OCH_2CH_2O-$), m.p. 159-160°, prepared in 91% yield by exchange with ethyl methyl dioxolan, was treated in THF/HMPTA with the lithio derivative of t-butyl cyclohexylamine [10,11], followed by carbonation and esterification, giving in 78% overall yield the ketal diester (6, R=CO_2Me, R'= $-OCH_2CH_2O-$), m.p. 187-188°, $\nu_{max}^{CHCl_3}(cm^{-1})$ 1710-1745 (CO_2Me); NMR ($CDCl_3$)(ppm) - 1.2-2.8/m, 9H(methylene and 7-H), 3.15/m, 1H(4b-H), 3.88/s, 3H(MeO), 3.91/s, 1H(10β-H), 3.96/broad s, 10H(2MeO and ketal), 6.95/d, 1H and 7.12/d, 1H(J-8)(aromatic H).

Alkaline hydrolysis of this to the corresponding dicarboxylic acid and reesterification (CH_2N_2) returned the original diester without significant epimerisation at C_{10}, thus indicating the relative stereochemistry of this compound to be as shown [12,13].

All the intermediates described gave consistent analyses and spectral (n.m.r., i.r. and u.v.) data.

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