

## Synthesis of 3-Methoxy-6,16-dioxo-9 $\alpha$ H-gibba-A-triene and Stereochemistry of a Diels–Alder Reaction

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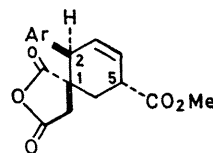
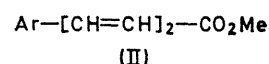
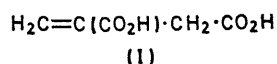
**Summary** A stereospecific synthesis of 3-methoxy-6,16-dioxo-9 $\alpha$ H-gibba-A-triene has been achieved in good yield, starting with a Diels–Alder reaction, the major products from which violate the *cis*-addition principle.

RECENTLY syntheses of several hydrofluorene<sup>1</sup> and gibbane<sup>2</sup> derivatives, potential intermediates for the total synthesis of gibberellins, have been described. We report here an efficient synthesis of 3-methoxy-6,16-dioxo-9 $\alpha$ H-gibba-A-triene<sup>3</sup> (IX) and the unexpected *trans*-orientation in the Diels–Alder reaction of itaconic acid (I) with methyl-5-*p*-methoxyphenyl-*trans,trans*-penta-2,4-dienoate (II)<sup>†</sup> of rigorously established stereochemistry.

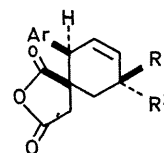
Condensation of (I) with (II) without solvent for 8 h at 160° produced in 80% yield a mixture of three stereoisomeric adducts. 60% of the mixture consisted of the quasi-axial and quasi-equatorial esters (IIIa) and (IIIb) in the ratio 1:2.3; the third adduct was the quasi-equatorial ester (IIIc) epimeric with (IIIb) at C-1.<sup>4</sup> Stereochemistry to these adducts was assigned as follows. Hydrogenation (ethyl acetate, PtO<sub>2</sub>) to the corresponding cyclohexane derivatives (IVa, b, and c) followed by methanolysis afforded a mixture of acids (Va, b, and c) in the same isomer ratio as the initial adducts (determined by g.l.c.). The acid (Va), m.p. 150–152°, was separated readily, because of its very low solubility in methanol, and shown to be axial at C-5 by its quantitative epimerisation (MeOH, NaOMe) to (Vb).

The fact that the equatorial trimethyl ester (VIb), m.p. 102–103°, [from (Vb) with diazomethane] underwent quantitative Dieckmann cyclisation (benzene, NaOMe)—of necessity in the alternative chair diaxial conformation—to the bicyclo[3,2,1]octan-6-one (VII) m.p. 112–114°, whereas similar conversion of the axial trimethyl ester (VIa), m.p. 98–99°, into (VII) proceeded more slowly, and *via* (VIb), established the *cis*-diequatorial relationship of the C-1-CH<sub>2</sub>·CO<sub>2</sub>Me and C-5-CO<sub>2</sub>Me groups in (VIb) and hence in (IIIb).

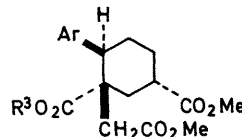
Compound (VII) was converted by standard methods in 70% yield into 1-carboxy-*anti*-2-(*p*-methoxyphenyl)bicyclo[3,2,1]octan-6-one (VIIIa), m.p. 188–190°. The intramolecular Friedel–Crafts reaction of the derived acid chloride (VIIIb), using AlCl<sub>3</sub> (2 mol) in benzene, afforded (90%) 3-methoxy-6,16-dioxo-9 $\alpha$ H-gibba-A-triene (IX) [m.p.



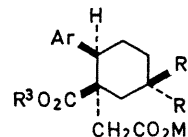
(IIIc)



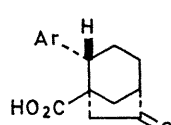
(IIIa) R<sup>1</sup> = CO<sub>2</sub>Me, R<sup>2</sup> = H  
(IIIb) R<sup>1</sup> = H, R<sup>2</sup> = CO<sub>2</sub>Me



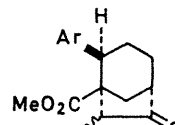
(IVc) R<sup>3</sup> = H  
(IVc) R<sup>3</sup> = Me



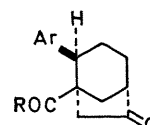
(IVa) R<sup>1</sup> = CO<sub>2</sub>Me, R<sup>2</sup> = R<sup>3</sup> = H  
(IVb) R<sup>1</sup> = R<sup>3</sup> = H, R<sup>2</sup> = CO<sub>2</sub>Me  
(IVa) R<sup>1</sup> = CO<sub>2</sub>Me, R<sup>2</sup> = H, R<sup>3</sup> = Me  
(IVb) R<sup>1</sup> = H, R<sup>2</sup> = CO<sub>2</sub>Me, R<sup>3</sup> = Me



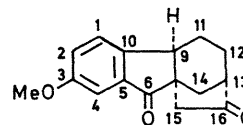
(Vc)



(VIa)



(VIb) R = OH  
(VIb) R = Cl



(IX)

184–185°,  $\lambda_{\text{max}}$  (EtOH) 220, (log  $\epsilon$  4.40), 251 (4.00), and 321 nm, (3.58);  $\nu_{\text{max}}$  (CCl<sub>4</sub>) 1711 and 1751 cm<sup>-1</sup>], thereby establishing the *cis*-relationship of the C-1-carboxy and the

† Compounds (II)—(X) gave satisfactory analytical and spectral data.

C-2-*p*-methoxyphenyl groups and therefore the equatorial configuration of the latter group in (IIIa), (IIIb)—(VIa), and (VIb).

Application of the sequence (VI) → (IX) to the mixture of trimethyl esters (VI) gave a readily separable mixture of (IX) and 1-carboxy-*syn*-2-(*p*-methoxyphenyl)bicyclo[3,2,1]-octan-6-one (X), m.p. 203—205°, [epimeric with (VIII) at C-2]. The stability of (VIc) in admixture with (VIa) and (VIb) to epimerisation (as determined by g.l.c.) and its conversion into (X) established the structure of (IIIc) as shown, *i.e.* *trans*-diequatorial at C-2 and C-5.

The violation of the “*cis*-addition principle”<sup>5</sup> in the production of (IIIb) and (IIIc) (82% of the total mixture) is considered to occur by a thermally catalysed process,<sup>6</sup> either in the transition state or after initial product formation to relieve the 1,3-quasi-diaxial interactions at C-1 and C-5 which result in the normal Diels–Alder product (IIIa).

Studies of this aspect of the Diels–Alder reaction and on the conversion of (IX) into C<sub>19</sub> gibberellins are in progress.

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<sup>1</sup> T. Hori and K. Nakanishi, *Chem. Comm.*, 1969, 528, and ref. 1 and 3 therein.

<sup>2</sup> E. J. Corey, M. Narisada, T. Hiraoka, and R. A. Ellison, *J. Amer. Chem. Soc.*, 1970, **92**, 396.

<sup>3</sup> Gibberellane numbering, J. MacMillan, *J. Chem. Soc. (C)*, 1970, 1341.

<sup>4</sup> Cf. N. Gerber, *J. Amer. Chem. Soc.*, 1960, **82**, 5216.

<sup>5</sup> K. Alder and G. Stein, *Angew. Chem.*, 1937, **50**, 510.

<sup>6</sup> T. M. Lyssy, *J. Org. Chem.*, 1962, **27**, 5.