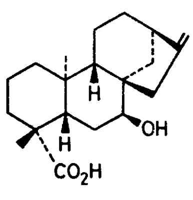
Mimics of Intermediates in Gibberellin Biosynthesis as Plant Growth Regulators

By JAMES R. HANSON, KEITH P. PARRY, and CHRISTINE L. WILLIS

(*The School of Molecular Sciences, The University of Sussex, Brighton* BN1 9QJ and
I.C.I. Plant Protection Ltd., Jealott's Hill, Bracknell, Berks., RG12 6EY)

Summary The ring-contracted *ent*-6α-hydroxy-5β(H)-B-norkaur-16-en-19-oic acid (**4**) and the corresponding alcohol (**6**) have been shown to act as inhibitors of gibberellin plant growth hormone biosynthesis at the ring contraction stage and to act as plant growth regulators in rice.

SELECTIVE inhibitors of gibberellin plant hormone biosynthesis may provide novel plant growth regulators. With this object in mind, we have prepared a number of compounds which resemble key biosynthetic intermediates but lack essential structural features.[1]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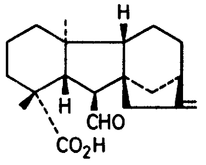
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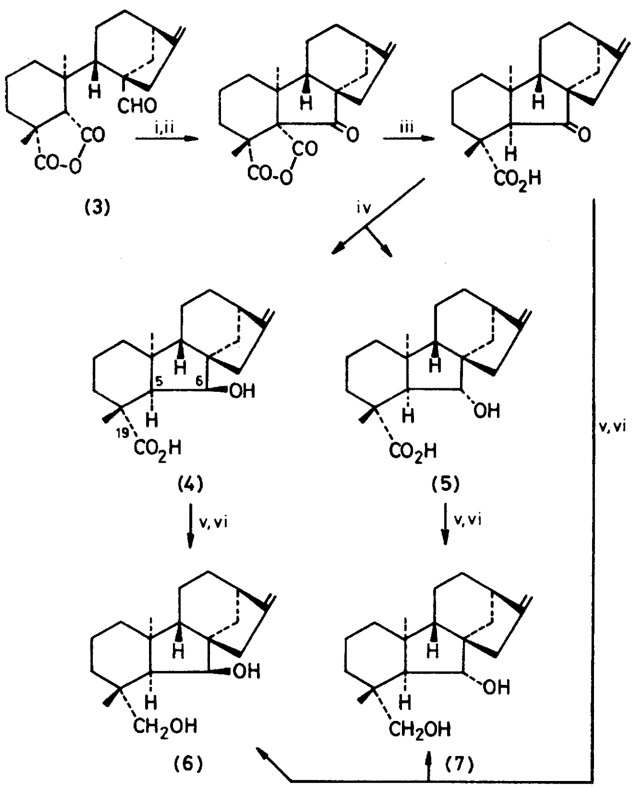
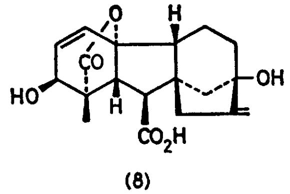


SCHEME. *Reagents*, i, NaH, *NN*-dimethylformamide, ii, CrO_3, iii, NaOH, iv, $NaBH_4$, tetrahydrofuran, aq. NaOH, v, CH_2N_2, vi, $LiAlH_4$.

ent-7α-Hydroxykaur-16-en-19-oic acid (**1**) is a substrate in *Gibberella fujikuroi* for the ring contraction of ring B to form gibberellin A_{12} aldehyde (**2**).[2] Compounds (**4**) and (**6**) resemble (**1**) in their ring B/C/D structure but differ from it in the size of ring B and in the stereochemistry of their A/B ring junction. The epimeric B-nor-diterpenoid hydroxy-acids (**4**) and (**5**) and the corresponding diols (**6**) and (**7**) were readily prepared from the naturally occurring fujenal (**3**).[3] The best route is shown in the Scheme whilst other methods will be described in our full paper.

The stereochemistry of the hydroxy-acids (**4**) (m.p. 143—144 °C) and (**5**) (m.p. 164—165 °C) and the diols (**6**) (m.p. 33 °C) and (**7**) (m.p. 159—161 °C) followed from the magnitude of the 5-H, 6-H coupling constants ($J_{5,6}$ 11 Hz, 6α-alcohols; $J_{5,6}$ 4 Hz, 6β-alcohols) and the ease of formation of a 6:19-γ-lactone and 6:19-ether which was accompanied by a change in $J_{5,6}$ to 11 Hz when the β-alcohols were treated with methanesulphonyl chloride. Under the same conditions the α-alcohols gave methanesulphonates. The structure of the hydroxy-acid (**4**) has been confirmed† by *X*-ray analysis.

The compounds were incubated with *Gibberella fujikuroi* in shake culture in the presence of [2-^{14}C]mevalonic acid. The concentration (40 mg l^{-1}) was typical of the level of gibberellic acid production under these conditions. The incorporations of [2-^{14}C]mevalonic acid into gibberellic acid (**8**) were compared with those of parallel control fermentations. Whereas the α-alcohols (**5**) and (**7**) had little effect on gibberellic acid biosynthesis, the β-alcohols (**4**) and (**6**) blocked its formation completely. Even at a concentration of 4 mg l^{-1}, the hydroxy-acid (**4**) reduced the incorporation of mevalonic acid into gibberellic acid in a 10-day fermentation from 1·44 to 0·12%. Radioactive *ent*-7α-hydroxykaur-16-en-19-oic acid (**1**) accumulated in these blocked fermentations. It was isolated as the methyl ester and identified by comparison with authentic material.[4] However when [6-^{3}H]gibberellin A_{12} aldehyde (**2**) was incubated with *Gibberella fujikuroi* in the presence of the β-hydroxy-acid (**4**), it was incorporated into gibberellic acid (**8**) (31 *vs.* 2·2% in the control). Consequently the β-alcohol is blocking the ring-contraction stage in gibberellin biosynthesis. This is the first demonstration of an inhibitor acting at this level. Most inhibitors of gibberellin biosynthesis such as CCC and AMO-1618 act on kaurene synthetase.[5]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† We thank Dr. P. B. Hitchcock for this determination.

When the β-diol (**6**) was applied to young rice seedlings (*ca.* 1 cm high) by direct droplet application (conc. 40 p.p.m.) to afford a maximum dose of 400 μg per plant, there was a 30% inhibition of growth after a further 7 days. The α-diol (**7**) was inactive. The β-diol (**6**) also inhibited the 'bakanae' effect of *Gibberella fujikuroi* infections of the rice seedlings.

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