New Biosynthetically Patterned Inhibitors of Gibberellin Plant Hormone Formation

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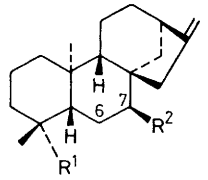
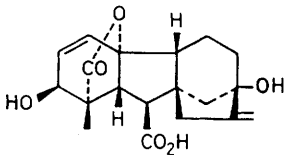
ent-19-Hydroxy-7-norgibberella-5,16-diene (**13**) and the corresponding 19-aldehyde (**14**) and acid (**12**), have been prepared from the fungal metabolite, fujenal (**8**) and shown to act as inhibitors of gibberellic acid biosynthesis in *Gibberella fujikuroi* and to act as plant growth regulators when tested against rice seedlings.

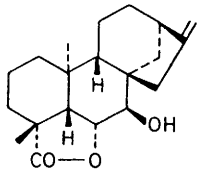
The oxidative metabolism of *ent*-kaur-16-en-19-oic acid (**1**) by hydroxylation to afford (**2**)[1–3] or dehydrogenation to (**3**)[4,5] are key steps in the divergence of the gibberellin plant hormone [*e.g.* (**5**)] and kaurenolide [*e.g.* (**6**)] biosynthetic pathways. Recently we have shown[6] that the B-*nor*-hydroxy-acid (**11**) was an effective mimic of *ent*-7α-hydroxykaurenoic acid (**2**) and thereby blocked its biosynthetic ring contraction to afford gibberellin A_{12} 7-aldehyde (**7**). Consequently the compound behaved as an inhibitor of gibberellic acid (**5**) biosynthesis and as a plant growth regulator in rice seedlings. *X*-Ray studies have revealed[7] a close fit between the B/C/D ring system of *ent*-7α-hydroxykaur-16-en-19-oic acid (**2**) and (**11**). We have now prepared some *ent*-7-norgibberella-5,16-dienes (**12**)—(**14**) in which C-6 (= kaurenoid C-7) has been



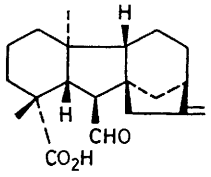
(1) $R^1 = CO_2H$, $R^2 = H$
(2) $R^1 = CO_2H$, $R^2 = OH$
(3) $R^1 = CO_2H$, $R^2 = H$, $\Delta^{6,7}$
(4) $R^1 = Me$, $R^2 = H$



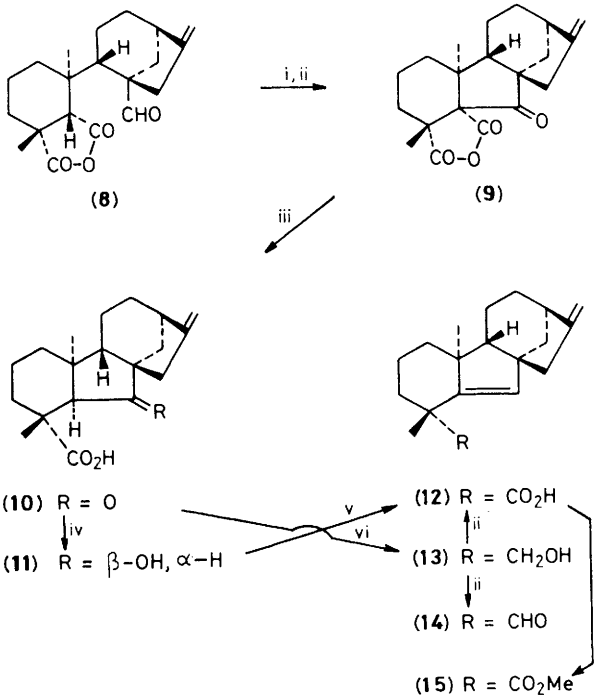
(5)



(6)



(7)



Scheme 1. *Reagents*, i, NaH, *N*,*N*-dimethylformamide; ii, CrO_3, Me_2CO; iii, aq. NaOH; iv, $NaBH_4$; v, $SOCl_2$, pyridine; vi, $LiAlH_4$; vii, CH_2N_2.

converted into a trigonal centre and examined them as potential inhibitors of the hydroxylation of *ent*-kaur-16-en-19-oic acid (**1**).

The *ent*-7-norgibberella-5,16-dienes were prepared from the easily accessible fungal metabolite, fujenal (**8**)[8] as shown in Scheme 1.[9]

Incubation of the 19-alcohol (**13**), 19-aldehyde (**14**), and 19-acid (**12**) with *Gibberella fujikuroi* at a concentration of 40 mg l^{-1} over periods of 3—7 days completely blocked the formation of gibberellic acid (**5**) from [2-^{14}C]mevalonic acid (MVA) and led to the accumulation of *ent*-[^{14}C]kaurene (**4**) and [^{14}C]fujenal (**8**). Thus, in the case of the 19-alcohol (**13**) after a 7 day incubation, there was a 0.78% incorporation of [2-^{14}C]MVA into *ent*-kaur-16-ene (**4**) compared to a 0.03% incorporation in the controls and a 2.7% incorporation into fujenal (**8**) (0.35% in the control). The 19-alcohol (**13**) was oxidized by *G. fujikuroi* to the 19-acid (**12**). However the corresponding 19-methyl ester (**15**) was without effect on gibberellic acid biosynthesis. Incubation of the 19-alcohol (**13**) and *ent*-[^{14}C]kaur-16-ene (**4**) for 6 days led to an increase in the amount of recovered kaurene (50% *vs.* 17.7% in the control) and an enhancement of the incorporation of the kaurene into fujenal (6.4% *vs.* 0.89% in the control). There was a substantial decrease in the incorporation of *ent*-[^{14}C]kaurene into gibberellic acid (**5**) (0.19% *vs.* 5.16% in the control). However the first of the known gibberellin intermediates, [6α-^{3}H]-gibberellin A_{12} 7-aldehyde (**7**), was efficiently incorporated into gibberellic acid (**5**) (26% *vs.* 1.6% in the control) after 5 days incubation in the presence of the 19-alcohol (**13**). These dienes are thus blocking a post-kaurene but pre-gibberellin step in the biosynthesis. Unlike the incubations with the hydroxy-acid (**11**), we did not detect[6] any accumulation of ent-7α-hydroxykaur-16-en-19-oic acid (**2**).

When applied to rice seedlings at a concentration of $< 400\,\mu g$ per plant, the 19-alcohol (**13**) showed significant plant growth regulatory activity (40% reduction in height over a 7 day period) and also diminished the 'bakanae' effect of a *G. fujikuroi* infection of the rice seedlings.

We thank the S.R.C. for a CASE award (to C. L. W.) and I.C.I. for generous support.

Received, 30th October 1981; Com. 1270

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