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SOME 19-NORGIBBERELL-16-ENES AS INHIBITORS OF GIBBERELLIN PLANT HORMONE BIOSYNTHESIS

Mark K.Baynham and James R. Hanson*

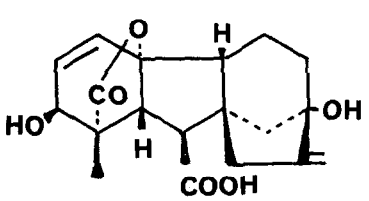
School of Molecular Sciences, University of Sussex, Brighton, Sussex, BN1 9QJ

Abstract: Methyl ent-7-hydroxy-4β(H)-19-norgibberell-16-en-20-oate, the corresponding 7,20-diol and 20-desoxy derivative, have been prepared from gibberellins A_{13} and A_{14} respectively and shown to act as inhibitors of gibberellic acid biosynthesis in Gibberella fujikuroi; further investigation of the 7-hydroxy-20-methyl ester suggests that this may be acting at the ring contraction step.

We have recently shown that ent-kauran-16,17-epoxide[1] and some B-norkaurenes[2] act as mimics of intermediates in gibberellin biosynthesis and, by blocking key steps in the formation of these plant hormones, lead to novel plant growth regulators. The C-19 carboxyl group plays an important role in several biosynthetic steps, providing for example, the lactone ring of the C_{19} gibberellins such as gibberellic acid (1). We have prepared some 19-norgibberell-16-enes lacking this group and investigated them as potential inhibitors of the formation of gibberellic acid (1) in Gibberella fujikuroi.

Gibberellins A_{13} (2)[3] and A_{14} (3)[4] were oxidized to their 3-ketones (4 and 5) and the resultant β-keto-acids, decarboxylated. The C-3 carbonyl group was then removed by Wolff-Kishner reduction and the 3-desoxy acids methylated to afford (6) and (7). In the case of gibberellin A_{13} a cleaner product was obtained by methylation of the 19-nor-3-ketone (8), reduction to the 3α-alcohol(9) with sodium borohydride under carefully controlled conditions, conversion to the 3β-chloro compound with triphenylphosphine and carbon tetrachloride and reduction of (10) with tri-n-butyl tin hydride to afford the 3-desoxy compound (6). Reduction of the 7- and 20-ester groups with lithium aluminium hydride proceeded in a stepwise manner in the gibberellin A_{13} series to afford the

7-mono-ol (11) (major product) and the 20-mono-ol (12) (minor product) and the 7,20-diol (13). In the gibberellin A_{14} series reduction of the ester (7) gave the 7-mono-ol (14). The stereochemistry of the 4-methyl group followed from the ^1H n.m.r. spectrum of (15) in which $J_{4:5}$ = 12.5 Hz and $J_{5:6}$ = 12 Hz (δ 0.93 H-18; 2.80 , H-4; 2.40, H-5; 3.52, H-6).



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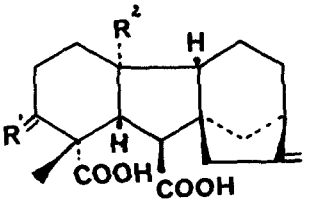
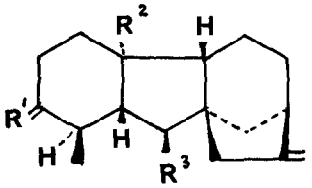
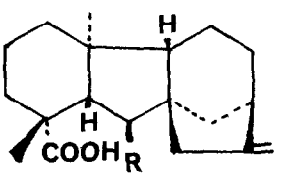


2 R^1 = α-H, β-OH; R^2 = CO_2H
3 R^1 = α-H, β-OH; R^2 = Me
4 R^1 = =O; R^2 = CO_2H
5 R^1 = =O; R^2 = Me



6 R^1 = H_2; R^2 = R^3 = CO_2Me
7 R^1 = H_2; R^2 = Me; R^3 = CO_2Me
8 R^1 = =O; R^2 = R^3 = CO_2H
9 R^1 = α-OH, β-H; R^2 = R^3 = CO_2Me
10 R^1 = β-Cl, α-H; R^2 = R^3 = CO_2Me
11 R^1 = H_2; R^2 = CO_2Me; R^3 = CH_2OH
12 R^1 = H_2; R^2 = CH_2OH; R^3 = CO_2Me
13 R^1 = H_2; R^2 = R^3 = CH_2OH
14 R^1 = H_2; R^2 = Me; R^3 = CH_2OH
15 R^1 = O; R^2 = R^3 = CO_2Me



16 R = CH_2OH
17 R = CHO

Our strain of Gibberella fujikuroi(ACC 917) produces gibberellic acid (1) at a concentration of approximately 40 mg. litre^{-1} and hence the 19-norgibberellenes were tested at this level. The hydroxy-ester (11), the diol (13) and the mono-ol (14) substantially (67 - 80%) inhibited the incorporation of [2-^{14}C] mevalonic acid into gibberellic acid (1) (see table)

Table: % Incorporation of [2-^{14}C]MVA into (1) and (2)

Substrate	Metabolite	
	Gibberellic acid (1)	Gibberellin A_{13} (2)
Control	2.44	0.128
(11)	0.47	0.016
(13)	0.61	0.051
(14)	0.81	0.086

10μC 2-^{14}C MVA and 40 mg substrate were incubated with G. fujikuroi in 1 litre medium (50 ml per flask) on shake culture for 4 days.

Gibberellin A_{13} (2) is a terminal metabolite on the C_{20} pathway. If these three compounds were blocking the loss of C-20 and the formation of the 19 → 10 lactone, we would expect some additional radioactivity in the gibberellin A_{13} in the presence of the inhibitors. Instead the amount of radioactivity in the gibberellin A_{13} decreased and hence inhibition was prior to this step. The mono-hydroxy-ester (11) was therefore investigated further. Gibberellin A_{12} 7-alcohol (16), although not a true intermediate in gibberellin biosynthesis, is a stable relative of the first gibbane intermediate, gibberellin A_{12} 7-aldehyde (17). It is converted into gibberellic acid in comparable yield to the aldehyde.[5] The mono-hydroxy-ester (11) had no effect on the incorporation of [17-^{14}C]-gibberellin A_{12} alcohol (16) into gibberellic acid (1) (8.89% incorporation in the control, 8.71% incorporation in the presence of the substrate). In contrast the incorporation of ent-[^{14}C]-kaurene was inhibited (0.18% in the control, 0.04% in the presence of the substrate). A radio-active metabolite with the t.l.c. characteristics of ent-7α-hydroxykaurenoic acid accumulated. Consequently this 19-norgibberell-16-ene

is blocking gibberellin biosynthesis at a stage in the oxidative metabolism of ent-kaurene, possibly that of ring contraction. In this context it is interesting to note that although esters of ent-kaur-16-en-19-oic acid in which the 19-carboxylic acid is blocked, are hydroxylated on ring B they do not undergo ring contraction unless they are readily hydrolysed.[6,7] It is possible that the 19-carboxylic acid plays a more important role in this step than has hitherto been realized.

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