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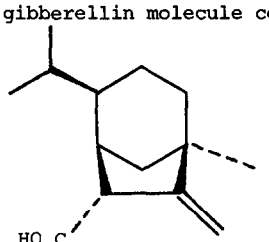
SYNTHESIS OF RING-A-NORGIBBERELLINS

Ailsa L. Cossey and Lewis N. Mander*

Research School of Chemistry, Australian National University,

P.O. Box 4, Canberra, A.C.T. 2600, Australia

The simple bicyclic acid 1 modelled on helminthosporic acid 2 has been shown to be more potent than GA_9 3 in the barley endosperm assay for gibberellin activity.[1] This result was consistent with the hypothesis that the "right-hand" portion (B,C,D rings) of the gibberellin molecule constitutes the "effector part", and that helminthosporic acid 2



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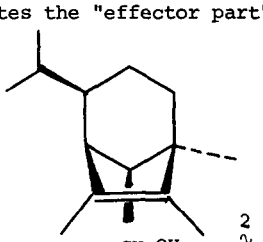

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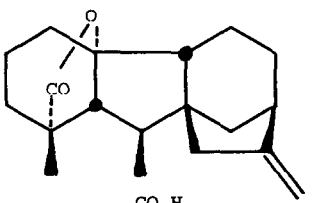

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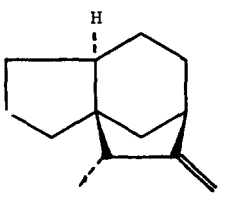
mimics this moiety.[2] The nor-gibberellin-helminthosporane hybrid molecule 4[3], however, has only 20% of the activity of 2 in this bioassay. In order to examine the hypothesis more closely, we have prepared and bioassayed ring A-nor-gibberellins 5 and 6. The former isomer 5 has the same relative configuration as that of the natural gibberellins, while 6, by having the same chirality as 4, provides a link between 4 and 5.



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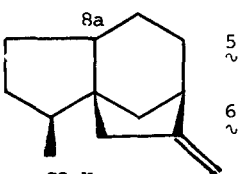
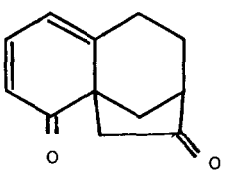


5 8aβH

6 8aαH



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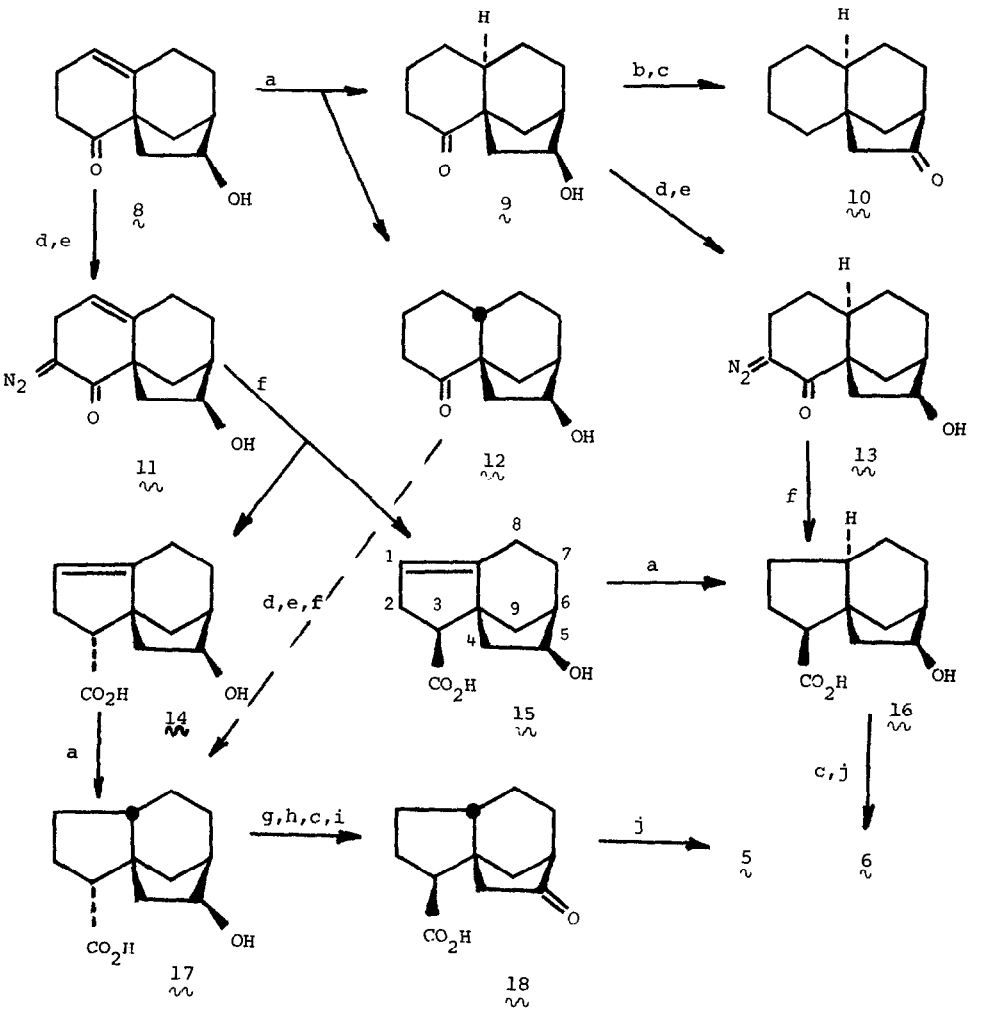
The syntheses (Scheme) of acids 5 and 6 were based on divergent routes from ketol 8, m.p. 69-70°,[4] which was prepared in 76% yield by K-selectride reduction[5] (THF, 2 equiv. *t*-BuOH, -65°, 1hr; 0° 1hr) of dienedione 7.[6] A 4:1 mixture of 9 and 12 was obtained from hydrogenation of 8, and resolution was effected by chromatography of the derived benzoates. The less polar, major compound, m.p. 92-94°, was identified as the A,B-*trans*-isomer by conversion (Wolff-Kishner reduction, Jones oxidation) to the known ketone 10 (g.l.c. and i.r. comparison; semicarbazone : m.p., mixed m.p. 225°);[7] the



Reagents: (a) H_2, 5% Pd-C, EtAc, (b) NH_2NH_2, KOH, $HOCH_2CH_2OH$, 210°, (c) CrO_3, H_2SO_4, H_2O, acetone, (d) MeOCHO, NaOMe, PhH, (e) p-$MeC_6H_4SO_2N_3$, Et_3N, MeCN, (f) 450w Hanovier medium pressure Hg lamp, T.H.F., H_2O, $NaHCO_3$, (g) CH_2N_2, Et_2O, (h) NaOMe, MeOH, (i) NaOH, H_2O, Et_2O, (j) $Ph_3\overset{+}{P}CH_3\bar{B}r$, KOt-Bu, T.H.F.-t-BuOH (9:1).

minor benzoate had m.p. 108-110°. "Diazo-transfer"[8] to the ketol mixture 9/12 followed by a photo-Wolff rearrangement[9] gave (72% overall yield) a 12:4:1 mixture of hydroxyacids A,B, and C. The major product A, m.p. 125-127°, which must be derived from ketol 9, was converted (CH_2N_2; NaOMe, MeOH, reflux) to a 4:1 mixture of C-3 epimeric methyl esters at equilibrium. The major isomer was identified as the original ester from acid A, which was thus shown to have structure 16, since the 3β-carboxyl group occupies the less crowded pseudo-equatorial conformation in this epimer. The minor isomer corresponded to acid C (5-oxo-derivative m.p. 109-111°), which was therefore the 3α-epimer of 16; acid B, m.p. 201-204°, must accordingly derive from ketol 12.

Diazo-transfer to ketol 8 followed by Wolff rearrangement gave (60% overall) a 3:1 mixture of acids 14, m.p. 220-222°, and 15, m.p. 207-208°, respectively. Catalytic hydrogenation of 15 gave 16, while 14 was similarly converted to acid B, which therefore has the carboxyl group in the 3α-configuration and must be assigned structure 17. Hydrogenation of both 14 and 15, therefore, has occurred on the face opposite to the carboxyl function, a result which has been observed with similar structures.[10] Equilibration of 17-methyl ester, as before, gave a 4:3 mixture favouring the parent ester. The minor, more polar epimer was oxidized and hydrolyzed (10%NaOH, ether, 2-phase system, 16hr vigorous stirring) to acid 18, m.p. 90-93°, which afforded, after Wittig methylenation,[7] target acid 5, m.p. 73-76°. Acid 16 was similarly oxidized (ketoacid m.p. 101-102°) and methylenated to give acid 6, m.p. 112-113°.

Preliminary bioassays (barley endosperm) show acid 6 to have half the potency of 4, whereas 5 is slightly more active. Further syntheses and assays are in progress, and the results will be published in due course.

Acids 14 and 15 are clearly potential substrates[11] for the synthesis of natural gibberellins, also, and the utilization of 14 and analogues towards this end is well advanced.

Acknowledgements: We are indebted to Dr B.G. Coombe and Mrs P.E. Phillips, Waite Agricultural Institute, University of Adelaide, for bioassays on acids 5 and 6.

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4. All structures except 2 and 3 represent racemates; numbering (Structure 15) is based on 4H-3a,6-methanoazulene. All compounds were fully characterized by ^{1}H and ^{13}C nmr, i.r. and m.s. measurements;[12] all crystalline compounds gave satisfactory combustion analyses (±0.3%).

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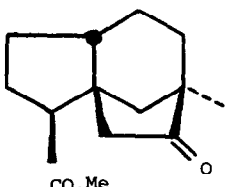
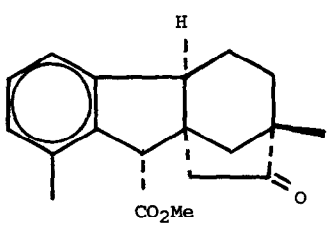
11. cf. L.J. Dolby, S. Estandiari, C.A. Elliger, K.S. Marshall, J. Org. Chem., 36, 1277 (1971).

12. ^{13}C N.m.r. chemical shifts were especially useful for the confirmation of stereochemical assignments. Typically, relatively higher field resonances were observed for C6-C9 in the *cis*-fused isomers, i.e., 17 and 18; C4 was also relatively shielded by the carboxyl function in the 3β-configuration and C9 by a 3α-carboxyl group. Excellent correlations ($\Delta\delta \leq 1.0$ ppm) were observed for resonances arising from C-3a,4,5,6,7,8, and 9 of the 6-methyl-homologue of 18-methyl ester (i) and the corresponding nuclei in methyl 6-*epi*gibberate (ii).[13]



(i)



(ii)

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