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AN EFFICIENT SYNTHESIS OF 2-HYDROXY-GIBBERELLINS

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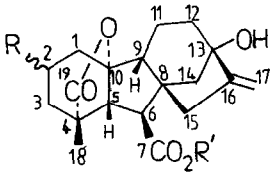
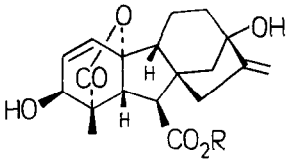
Methyl gibberellate(**4**) has been converted into 2-epi-gibberellin A_{29} methyl ester(**2**)in 48% overall yield by a route avoiding protection of the ring D functionality.

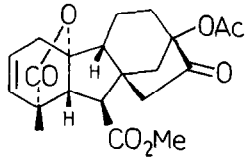
Ongoing biochemical investigations, within this laboratory, into the biosynthesis and mode of action of the gibberellin plant growth hormones (GAs) require quantities of the rare gibberellin A_{29} (**1**). Our previous routes[1] to 2-hydroxy-gibberellins from the available fungal GAs, e.g. GA_3 (**3**), have all involved electrophilic addition of ROBr to 2,3-olefins such as (**5**). This route required "protection" of the more reactive 16,17-olefin by oxidative cleavage to the 16-ketone before the 2,3-olefin was introduced. Reconstruction of the 16,17-olefin at a later stage was achieved by Wittig methylenation, a reaction made difficult by the low reactivity of such bicyclo-octanones, especially in the presence of a 13-hydroxy function[2] , which has to be protected in order to avoid a keto-carbinol rearrangement[3]. We now report a new method for the synthesis of 2-hydroxy-gibberellins, illustrated by the preparation of 2-epi-gibberellin A_{29} methyl ester (**2**), which requires no protection or manipulation of rings C/D.



(1) R= β-OH R'=H
(2) R= α-OH, R'=Me



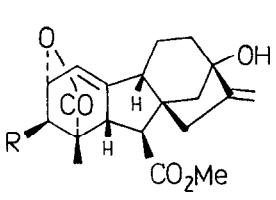
(3) R = H
(4) R = Me



(5)

Corey et al[4] , in their early work on the total synthesis of gibberellic acid, described the hydrolysis and iodolactonisation of iso-GA_3 methyl ester (**6**) which gave the iodolactone (**10**). Our initial strategy was to attempt to prepare the 3-deoxy-analogue (**7**) which by the Corey procedure would lead to the iodolactone (**11**) and hence by Bu_3SnH reduction to 2-epi-GA_{29} methyl ester (**2**).

Treatment of iso-GA_3 methyl ester(**6**) with KH/18crown6/CS_2(THF,12hr,20°) followed by MeI(1hr) gave, not the expected S-methyl-dithiocarbonate(**8**), but a mixture (1:5) of the triene-acid (**12**)[12] and the cyclic-dithiocarbonate (**13**)[12], formed by intramolecular displacement of the lactone system by the intermediate 3-dithiocarbonate anion.These compounds could be separated, with difficulty, by flash chromatography but treatment of the mixture with Bu_3SnH (toluene, AIBN, 1hr, reflux) resulted in fragmentation of the cyclic dithiocarbonate to the triene-acid (**12**) in an analogous reaction to the Corey-Winter alkene synthesis[5]. As an alternative to thioesters, we then examined the possibility of deoxygenation at C-3 by chlorination followed by Bu_3SnH reduction. However, treatment of iso-GA3 methyl ester (**6**), or its 13-acetate, with PCl_5 or with $POCl_3$ gave intractable mixtures.



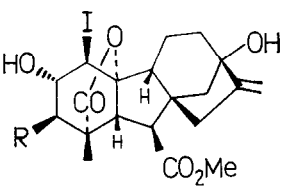
R

(6) OH

(7) H

(8) OC(=S)SMe

(9) I



R

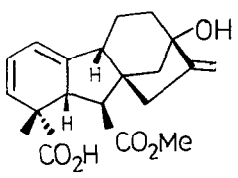
(10) OH

(11) H

Having failed to prepare (**7**) by direct deoxygenation of (**6**) we turned our attention to the triene-acid (**12**). This compound, previously used as a relay in the Corey total synthesis of gibberellic acid[4,6] is more readily obtained from methyl gibberellate (**4**) by bromination with CBr_4/PPh_3 (acetone/pyridine,10:1,reflux,5hr), a reaction which in our hands[7] consistently gave a mixture (3:1) of the 1β- and 3α -allylic bromides (**14**) and (**15**) in a combined yield of 84%. Reduction of (**14**) and (**15**) with activated zinc (EtOAc/CH_3COOH, 6:1, 1hr.) gave the triene-acid (**12**) in 93% yield[8]. Treatment of (**12**) with $NaHCO_3/I_2$ (THF/CH_2Cl_2/H_2O,1:1:2, 1hr.) resulted in a single iodolactone (91% yield), identified by its ^{1}H-n.m.r. spectrum [5.82(H-1); 4.93(t,H-2); 4.52(d,H-3); $J_{1,2}=J_{2,3}=5Hz$] as the 3β-iodo-19,2- lactone (**9**)[12].The regiospecificity of this reaction was surprising to us, particularly as Corey and Danheiser[9] in studies on the bicyclic model compound (**16**), obtained a mixture of bromolactones (**17**) and (**18**) after treatment with KBr_3. Similarly these workers[10] have also shown that iodoetherisation of the triene-triol (**19**) gave the 1β-iodo- 19,10-ether(**20**)[11].

Reduction of (**9**) with Bu_3SnH (toluene,AIBN,reflux,1hr) proceeded as expected to give 3-deoxy-iso-GA_3 (**7**) in 98% yield. Thus the original intermediate target (**7**), was achieved, albeit by a longer route than originally intended, in reasonable overall yield (70%) from methyl

gibberellate. Lactone hydrolysis, followed by iodolactonisation onto the 1,10-olefinic bond was accomplished in "one pot" as described by Corey et al[4]. viz:-(7) was treated with aqueous KOH (0.4M)/THF,1:1 (4hr, room temperature) and then, after adjustment of the pH to 9.0, with a solution of I_2 in CH_2Cl_2 for 1.5hr (vigorous stirring). This gave the 1β-iodo-2α-hydroxy-19,10-lactone (**11**)(72% yield), which on treatment with Bu_3SnH in the normal way produced 2-epi-GA_{29} methyl ester (**2**) in 97% yield.



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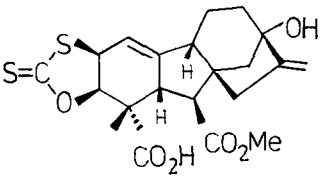

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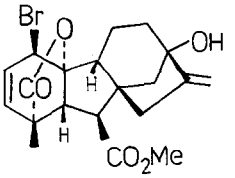

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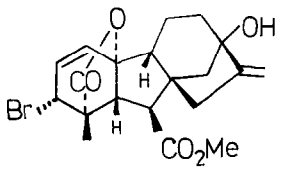

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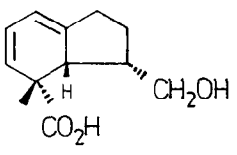

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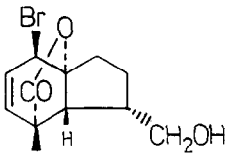

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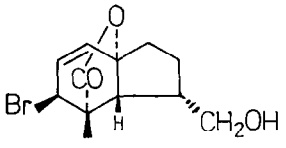

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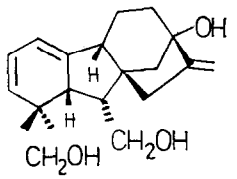

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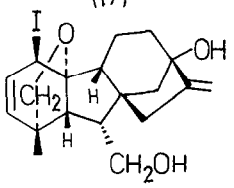

(20)

The overall yield of (**2**) from methyl gibberellate (**4**) was 48%. (**2**) has been converted into gibberellin A_{29} (**1**) by oxidation to the 2-ketone followed by $NaBH_4$ reduction[1]. In this work (**2**) was recovered unchanged when the more desirable Mitsunobu inversion (PPh_3,DEAD,PhCOOH,THF,24hr) was attempted. However, the route described above is the most efficient yet reported for the synthesis of gibberellin A_{29} and should also be applicable to the preparation of other 2-hydroxy-gibberellins such as GA_{40} and GA_{51}.

REFERENCES AND NOTES

1. L.J.Beeley and J.MacMillan, J.Chem.Soc. Perkin I, 1022,1976 ; M.H.Beale and J.MacMillan, J.Chem.Soc. Perkin I, 394,1981 ; P.S.Kirkwood, J.MacMillan and M.H.Beale, J.Chem.Soc. Perkin I, 699,1982.

2. For a discussion of the Wittig methylenation of gibberellin-16-ketones see L.N.Mander and J.V.Turner, Tetrahedron Lett., 22,4149,1981.

3.J.R.Bearder, V.M.Frydman, P.Gaskin, J.MacMillan, C.M.Wels and B.O.Phinney, J.Chem.Soc. Perkin I, 173,1976.

4.E.J.Corey, T.M.Brennan and R.L.Carney, J.Am.Chem.Soc.,93,7316,1971.

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6.E.J.Corey, R.L.Danheiser, S.Chandrasekaran, G.E.Keck, B.Goplan, S.D.Larsen, P.Siret and J-L.Gras, J.Am.Chem.Soc.,100,8034,1978.

7.It has been reported by J.Z.Duri,B.M.Fraga and J.R.Hanson, J.Chem.Soc. Perkin I, 3016,1981. that treatment of methyl gibberellate(**4**) with CBr_4/PPh_3 in acetone at reflux gave solely the 1β-bromo-isomer(**14**), while in pyridine the 1β,13-dibromide was the only product. In this work we observed no reaction when acetone alone was solvent. When 10% pyridine in acetone was solvent we obtained the 1β- and 3α-mono-bromides in a 3:1 ratio (84% yield). In pyridine alone we again observed only these compounds (3:1 ratio,75% isolated yield), with no trace of dibromides. The isomers were separable by flash chromatography and were identified by ^1H nmr comparison with samples previously prepared in this laboratory (J.R.Bearder,P.S.Kirkwood and J.MacMillan, J.Chem.Soc. Perkin I, 672,1981).

8.Samples of the 1(10),2,16-triene-acid (**12**)[λmax270(5200)] prepared by this route were essentially pure. However, material prepared from Bu_3SnH reduction of the cyclic dithiocarbonate was contaminated with the isomeric 1,9,16-heteroannular-triene-acid [λmax247 (3590)], identified by its ^1H and ^{13}C nmr spectra. The formation of this isomer was also observed in solutions of (**12**) on standing at room temperature for several days.

9.E.J.Corey and R.L.Danheiser, Tetrahedron Letters,4477,1973.

10.For a discussion see R.L.Danheiser, in Strategies and Tactics in Organic Synthesis, Ed. T.Lindberg,p21,1984, Academic Press.

11.In addition to the halolactonisations discussed in refs. 9 and 10, other electrophile-assisted lactonisations of (**12**) have also been of variable regiospecificity; e.g. MCPBA gives the 3β-hydroxy-19,2-lactone (**6**)(ref.4) while CF_3COOH forms the 19,10-lactone-2,3-olefin (GA_5). (E.P.Serebryakov, J.General Chem. USSR, 1849,1981).

12.All compounds gave IR,nmr and high resolution mass spectra consistent with their assigned structures.
Selected ^1H nmr data (200 MHz,$CDCl_3$):-
(**12**)δ6.10(1H,q,J=10,5,2-H),5.62(1H,dt,J=5,2.5,2.5,1-H), 5.41(1H,d,J=10, 3-H),5.08and4.94(each 1H,br,s,17-H_2),3.70(3H,s,OMe),3.30(1H,br,5-H), 3.08(1H,d,J=4,6-H),1.33(3H,s,18-H_3).
(**13**)δ5.34(1H,br,1-H),5.20(1H,d,J=5.5,3-H),5.10and5.01(each 1H,br,s,17-H_2),4.96(1H,br,2-H),3.75(3H,s,OMe),3.21(2H,s,5-Hand6-H),1.56(3H,s,18-H_3)
(**9**)δ5.82(1H,dt,J=5,2.5,2.5,1-H),5.14and4.99(each 1H,br,s,17-H_2),4.93 (1H,t,J=5,2-H),4.52(1H,d,J=5,3-H),3.75(3H,s,OMe),3.26(1H,dd,J=7,2.5,5-H) 2.58(1H,d,J=7,6-H),1.16(3H,s,18-H_3).
(**7**)δ5.95(1H,dt,J=5,2.5,2.5,1-H),5.13and4.97(each 1H,br,s,17-H_2),4.86 (1H,t,J=5,2-H),3.74(3H,s,OMe),3.18(1H,dd,J=6,2.5,5-H),2.59(1H,d,J=6,6-H) 1.25(3H,s,18-H_3).
(**11**)δ5.27and4.99(each 1H,br,s,17-H_2),4.61(1H,d,J=4,2-H),4.49(1H,s,1-H), 3.75(3H,s,OMe),3.37(1H,d,J=10,5-H),2.66(1H,d,J=10,6-H),1.11(3H,s,18-H_3).
(**2**)δ5.25and4.95(each 1H,br,s,17-H_2),4.30(1H,t,J=4,2-H),3.72(3H,s,OMe), 2.73(1H,d,J=10,6-H),2.60(1H,d,J=10,5-H),1.10(3H,s,18-H_3).

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