# An Unusual Gibberellin Transannular Ketol

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Spectroscopic evidence is presented for a revised structure for the product obtained by treatment of methyl di-*O*-acetylgibberellate with zinc and acetic anhydride. It is formed *via* a Diels–Alder type of addition across the 1(10),2(3)-diene by the carbonyl group of a mixed anhydride between the 19-carboxy and acetic acids.

Treatment of methyl gibberellate (1) or its 3,13-di-*O*-acetyl derivative (2) with zinc and boiling acetic anhydride affords a compound, $C_{24}H_{28}O_7$ which has been assigned [1] structure (3). This work, in turn, constituted a revision of an earlier study [2] in which it had been alleged that the reaction of a 13,16-ketol derived from gibberellin A_1 with zinc and acetic anhydride afforded the corresponding gibberellin A_4 derivatives through hydrogenolysis of the bridgehead 13-*O*-acetyl group. We repeated this reaction in the course of our studies [3] on the carbon-13 n.m.r. spectra of the gibberellins. However the carbon-13 data were incompatible with structure (3). In


(1) R = H

(2) R = Ac

(3)
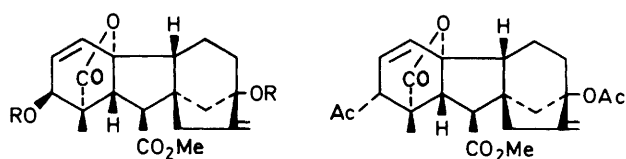
particular, whilst possessing three ester carbonyl resonances at δ 169.8, 172.8, and 178.4, the product lacked a signal in the range 200—220 p.p.m. which might be assigned to the $CH_3C(:O)C$ functionality. Furthermore, the ^1H n.m.r. spectrum contained [1] a C-methyl signal at δ 1.40 which was outside the range normally associated with CH_3CO groups. The carbon-13 n.m.r. spectrum contained a signal at δ 106.6 p.p.m. Subsequent studies on the chemistry of gibberellin A_{13} have revealed [4] the formation of acetals exemplified by (4) in which a carbon-13 n.m.r. signal at δ 108 was assigned to C-19—the carbon atom bearing two singly bonded oxygen atoms. By analogy this suggested that the zinc and acetic anhydride product might have structure (5). Recently an independent X-ray study has come to
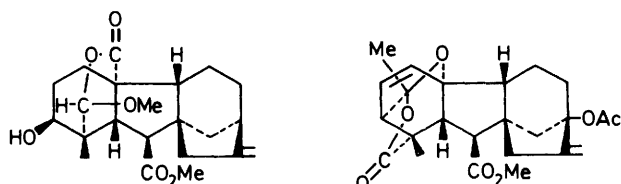

(4)

(5)

the same conclusion.[5] Here we present our spectroscopic evidence for the structure of this unusual adduct and some of the chemistry associated with its formation.

The ^1H n.m.r. spectrum of the zinc–acetic anhydride product (redetermined at 360 MHz) revealed two olefinic C–H reso-

nances at δ 6.63 (q, *J* 1.1 and 8.1 Hz) and 6.25 (q, *J* 8.1 and 6.4 Hz). A two-dimensional plot of the coupling constant (*J*) *versus* chemical shift (δ) revealed that these were coupled to a proton at δ 3.09 as vicinal and long-range couplings. These relationships, which were also confirmed by decoupling experiments, led to the identification of the fragment –C–CH(O)CH=CH–C–. The 2-D plot also revealed the typical gibberellin 5-H,6-H coupling (δ 2.05 and δ 2.89) (*J* 12 Hz) at higher field than normal. This was again confirmed by conventional decoupling studies. The olefinic 17-H protons, δ 4.98 and 5.16, were readily identified. The latter showed a long-range coupling (*J* 2.8 Hz) to one of the 15-H protons (δ 2.18) which was located from the 2-D plot and by spin-decoupling. The magnitude of the geminal coupling constant on this signal (*J* 15 Hz) enabled the other 15-H resonance (δ 2.08) to be identified. The position of the methyl group ^1H n.m.r. signal at δ 1.40 is in accord with a methyl group attached to a carbon atom bearing at least one oxygen function. The earlier work [1] had clearly established the presence of an extra CH_3CO moiety on ring A. The key to the position of the extra two-carbon unit came from the carbon-13 n.m.r. spectrum which showed a singlet at δ 106.6 which could be assigned to a carbon atom bearing two oxygen functions (*cf.* the anomeric carbon atom of sugars, δ 100—105 p.p.m.).[6] Since the carbon-13 n.m.r. spectrum contained singlet signals at δ 43.6 and 84.5 p.p.m. which were readily assigned by analogy with gibberellin derivatives,[3] to C-4 and C-10 respectively, the extra two-carbon unit must form part of a ketal bridge across ring A as in (5).

The remaining ^1H and ^{13}C resonances were related through a series of Birdsall-Feeney plots.[7] The carbon signals associated with rings C and D could be assigned by analogy with gibberellin derivatives of known structure. In particular, a ^{13}C n.m.r. signal at δ 51.13 assigned to C-9, was related to a ^1H quartet at δ 1.89 (*J* 6 and 12 Hz). This quartet was then irradiated and two multiplets, δ 1.54 and 1.76, attributed to 11-H, collapsed. Irradiation at these positions not only affected the 9-H signal but also perturbed a multiplet at δ 2.38 attributed to one of the 12-H protons. This signal showed a long range (2 Hz) coupling to 14-H (δ 2.44, *J* 2 and 11 Hz). The remaining 12-H signal at δ 2.1 was partially obscured by other resonances. The other 14-H signal (δ 2.20) was identified by spin decoupling studies based on δ 2.44. Hence the spectroscopic data (see Table) are in accord with the structure (5).

Treatment of the compound (5) with aqueous methanolic potassium hydroxide gave the hydroxy acid (6) [1] which, in turn, gave a dimethyl ester with diazomethane. Relactonization of the hydroxy-acid (6) in glacial acetic acid gave the unsaturated ketone (7).[1] The highfield 360 MHz ^1H n.m.r. data and ^{13}C n.m.r. data (see Table) of the unsaturated ketone (7) were compatible with the structure which had been assigned previously.[1] In particular, the olefinic 2-H resonance (δ 6.53) appeared as a triplet (*J* 3.5 Hz) coupled to the 1-H protons (δ 2.54 and 2.75) whilst the extra methyl signal (C-21) had moved downfield to δ 2.31.

(6) R = H

(12) R = Me

(7)
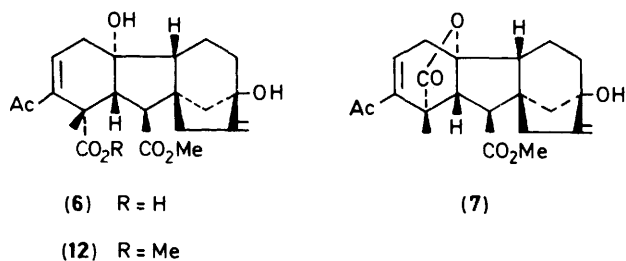
Some investigations were then carried out on the scope of the reaction. Treatment of the diacetate of methyl 3-*epi*-gibberellate gave the same ketal (5) and hence, surprisingly, the reaction is insensitive to C-3 stereochemistry. When the methyl 3,13-di-*O*-acetylgibberellate was treated with activated zinc in acetonitrile, the product was the diene-acid (8) ($\lambda_{max.}$ 274 nm, ϵ 3 400).[8] This compound had the ^{1}H n.m.r. characteristics of a ring A homoannular diene. Thus the C-3 proton resonated at δ 5.44 as

(8) R = H

(9) R = Me

(10)

(11)
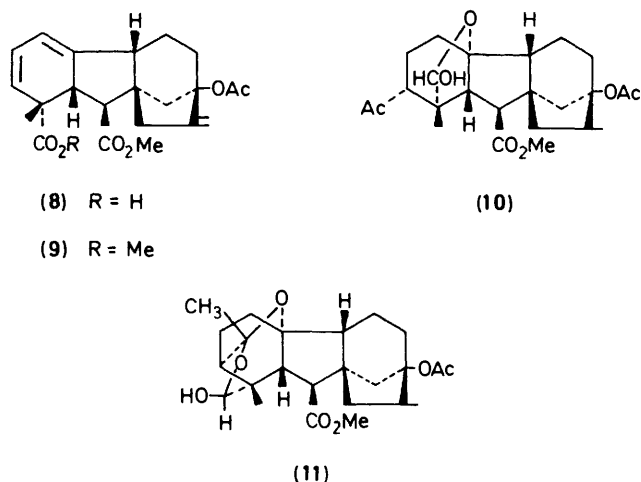
a doublet (J 9.6 Hz) coupled to the C-3 proton (δ 6.13) which, in turn, was coupled (J 5.2 Hz) to the C-1 proton. The latter showed allylic couplings (J 2.7 Hz) to 5-H (δ 3.34) and possibly to 9-H. This reaction affords a simple means of preparing the diene-acid (8) and suggests that it could be an intermediate in the formation of the ketal (5). Whilst the diene-acid (8) gave a good yield of the ketal on treatment with zinc and acetic anhydride, the dimethyl ester (9) did not undergo the cyclization reaction. However, the most interesting feature of the second stage of the reaction was that it also proceeded rapidly from the diene-acid (8) in acetic anhydride alone, *i.e.* in the absence of
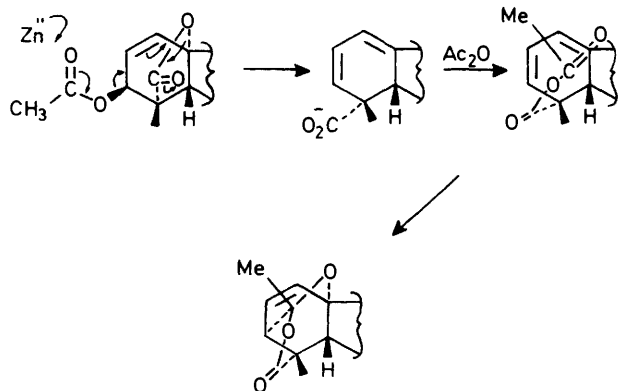

Scheme.

Table. ^{1}H (360 MHz) and ^{13}C (90 MHz) spectra (determined in CDCl$_3$)[b]

Carbon atom	Compound (5)		Compound (7)	
	^{1}H	^{13}C	^{1}H	^{13}C
1	6.63 q	138.59	2.54 q	35.86
			2.75 q	
2	6.25 q	126.64	6.53 t	134.55
3	3.09 q	51.97		143.58
4		43.62		48.86
5	2.05 d	53.29	2.72 d	56.36
6	2.89 d	50.87	2.88 d	53.16
7		172.79		172.73
8		50.21		50.90
9	1.89 q	51.13		51.10
10		84.5		90.24
11	1.54 m	16.44		17.51
	1.76 m			
12	2.38 m	36.39		38.28
	2.0			
13		84.03		78.18
14	2.44 q	40.23		43.02[a]
	2.20 d			
15	2.18 m	42.38		46.08[a]
	2.09 d			
16		153.82		156.28
17	4.98 m	107.66	4.97 m	107.32
	5.16 m		5.26 m	
18	1.17 s	19.76	1.38 s	13.14
19		178.43		175.96
OMe	3.72 s	51.90	3.73 s	52.10
Me	1.40 s	22.85	2.31 s	28.62
$>C<^O_O$		106.61		198.07
Ac	2.03 s	22.00		
		169.78		

[a] These assignments may be interchanged. [b] Coupling constants (in Hz) compound (5) $J_{1,2}$ 8.1; $J_{2,3}$ 6.4; $J_{5,6}$ 12; $J_{9,11}$ 6 and 12; $J_{14,14'}$ 11; $J_{15,15'}$ 15; $J_{15,17}$ 2; Hz. Compound (7) $J_{1,1'}$ 19.5; $J_{1,2}$ 3.5; $J_{5,6}$ 9.7 Hz.

any Lewis acid catalysis. This suggests that the unusual adduct may arise (see Scheme) through the [4 + 2] cyclo-addition of the mixed anhydride (9) which is held beneath the diene by the axial carboxy group at C-4. The ability of a carbonyl group to function as a heterodienophile in an apparent Diels–Alder reaction with conjugated dienes, whilst unusual, nevertheless has precedent in the synthesis of dihydropyrans.[9]

The ketal structure (5) also accounts for the difference in the sodium borohydride reduction[1] of the tetrahydro derivative of (5) compared with the tetrahydro derivative of the unsaturated ketone (7), the former giving a mono-ol and the latter a diol. The reduction product which was originally formulated as (10) should now be reformulated as (11). The formation of this ketal (5) represents a further example of the propensity of the C-4 axial substituents to dominate the chemistry of ring A of the gibberellins.

Experimental

The ^{1}H and ^{13}C n.m.r. spectra were determined on a Bruker WH 360 spectrometer in deuteriochloroform. Standard pulse sequences and programmes were used. Zinc was activated by washing with 5% hydrochloric acid, water, methanol, and ether and then dried *in vacuo*.

Reaction of Methyl Gibberellate with Zinc and Acetic Anhydride.—Methyl gibberellate (2 g) was dissolved in acetic anhydride (35 ml) and heated under reflux for 1 h. Activated

zinc (10 g) was then added and the solution was heated under reflux for a further 30 min. Two further batches of activated zinc (5 g each) were added at 30 min intervals and the mixture was then refluxed for a further hour. The mixture was cooled and filtered. The acetic anhydride was distilled off under reduced pressure and the residue chromatographed on silica. Elution with 15% ethyl acetate–light petroleum gave the ketol (5) (980 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 177—178 °C (lit.,[1] 183—184 °C (from benzene–light petroleum) (Found: C, 67.4; H, 6.7. Calc. for $C_{24}H_{28}O_7$: C, 67.3; H, 6.6%); $v_{max.}$ 1 775, 1 740, 1 725, and 1 655 cm^{-1}.

Hydrolysis of the Ketol.—The above ketol (650 mg) in methanol (25 ml) and 10% aqueous potassium hydroxide (12 ml) was heated under reflux for 1 h. The methanol was evaporated and the solution acidified and extracted with ethyl acetate. The solvent was dried and evaporated to give the hydroxy acid (6) (490 mg) which crystallized from ethyl acetate–light petroleum as large prisms, m.p. 195—196 °C (lit.,[1] 210—212 °C) (Found: C, 65.6; H, 7.0. Calc. for $C_{22}H_{28}O_7$: C, 65.35; H, 6.9%); $v_{max.}$ 3 420, 1 740, 1 700, and 1 660 cm^{-1}; δ (90 MHz) 1.28 (3 H, s, 18-Me), 2.24 (3 H, s, 21-Me), 3.62 (3 H, s, OMe), 4.81 and 5.10 (each 1 H, s, 17-H), and 7.16 (1 H, q, 2-H). The dimethyl ester, prepared with diazomethane, had m.p. 161—163 °C (lit.,[1] 164—165 °C); $v_{max.}$ 3 400, 1 739, 1 700, 1 680, and 1 620 cm^{-1}; δ (90 MHz), 1.30 (3 H, s, 18-Me), 2.27 (3 H, s, 21-Me), 3.68 and 3.70 (each 3 H, s, OMe), 4.80 and 5.15 (each 1 H, s, 17-H), and 7.04 (1 H, q, 2-H).

Relactonization of the Hydroxy-acid 1(6).—The hydroxy acid (250 mg) was dissolved in glacial acetic acid (15 ml) and heated under reflux for 30 min. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate. The solution was washed with aqueous sodium hydrogen carbonate and water and dried. The solvent was evaporated and the residue crystallized from ethyl acetate–light petroleum to afford 3-acetylgibberellin A₅ methyl ester (215 mg), m.p. 190—192° C (lit.,[1] 200—202° C) (Found: C, 67.9; H, 6.9. Calc. for $C_{22}H_{26}O_6$: C, 68.4; H, 6.7%); v_{max} 3 440, 1 760, 1 730, 1 660, and 1 610 cm^{-1}.

Reaction of Methyl 3-epi-Gibberellate with Zinc and Acetic Anhydride.—Methyl 3-*epi*-gibberellate [10] (300 mg) was dissolved in acetic anhydride (20 ml) and heated under reflux for 1 h. Activated zinc (5 g) was then added and the mixture was then heated for a further 30 min. A further portion of zinc (5 g) was then added and the mixture was then heated for a further 2 h. The solution was filtered and the zinc was washed with ethyl acetate; the solvents were then evaporated. The residue was recrystallized from ethyl acetate–light petroleum to afford the ketol (5) (138 mg), m.p. 179—181 °C which was identified by its n.m.r. spectrum.

Reaction of the 3,13-Diacetate of Methyl Gibberellate with Zinc in Acetonitrile.—The 3,13-diacetate (1 g) was dissolved in acetonitrile (freshly dried over calcium hydride) (40 ml) and heated under reflux. Activated zinc (10 g) was added. Two further 5-g portions were added at 30 min intervals. After 2 h the solution was cooled and filtered. The zinc was washed with

ethyl acetate and the solvents were evaporated. The residue was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave the starting material (54 mg) followed by the diene (8) (448 mg) as a white foam (Found: C, 64.9; H, 6.8. Calc. for $C_{22}H_{28}O_6\cdot H_2O$: C, 65.3; H, 7.0%); $\lambda_{max.}$ 274 nm (ε 3 400); $v_{max.}$ 1 735, 1 700, 1 660, 1 600 and 720 cm^{-1}; δ (360 MHz) 1.350 (3 H, s, 18-Me), 1.996 (3 H, s, OAc), 2.7116 (2 H, m, J 13 and 1.5 Hz, 15-H), 3.087 (1 H, d, J 4.5 Hz, 6-H), 3.338 (1 H, m, J 2.7 and 4.5 Hz, 5-H), 3.717 (3 H, s, OMe), 4.989 (2 H, m, 17-H), 5.444 (1 H, d, J 9.6 Hz, 3-H), 5.653 (1 H, m, J 2.7, 2.7 and 5.2 Hz, 1-H), and 6.128 (1 H, dd, J 5.2 and 9.6 Hz, 2-H). The methyl ester, prepared with diazomethane, was a gum, $v_{max.}$ 1 740, 1 720, 1 660, 1 595, 890, and 720 cm^{-1}; δ (90 MHz), 1.36 (3 H, s, 18-Me), 1.99 (3 H, s, OAc), 2.99 (1 H, d, J 3 Hz, 6-H), 3.32 (1 H, m, 5-H), 3.65 and 3.72 (each 3 H, s, OMe), 5.06 (2 H, br s, 17-H), 5.42 (1 H, m, J 3, 3, and 5 Hz, 1-H), 5.5 (1 H, d, 10 Hz), and 6.14 (1 H, dd, J 5 and 10 Hz, 2-H).

Reaction of the Diene (8) *with Acetic Anhydride.*—The diene (8) (169 mg) was dissolved in acetic anhydride (20 ml) and heated under reflux for 30 min. The solvent was evaporated under reduced pressure and the product recrystallized from ethyl acetate–light petroleum to afford the ketol (5) (141 mg), m.p. 177—178 °C, identified by its n.m.r. spectrum. When the reaction was carried out with zinc (total 20 g) (as above) the diene (320 mg) gave the ketol (147 mg).

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