Preparation of Gibberellins A_9 and A_{20} from Gibberellic Acid

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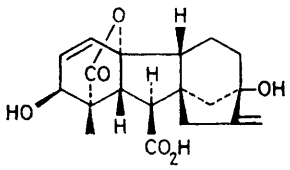
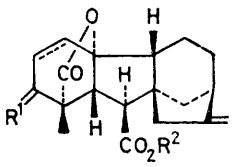
Methyl gibberellate has been converted *via* the methyl ester of 3-epigibberellin A_1 into the 3β-chloro- and 3β,13-dichloro-derivatives using triphenylphosphine and carbon tetrachloride. Hydrogenolysis of the chlorides with tributyltin hydride afforded gibberellins A_{20} and A_9 as their methyl esters. Gibberellin A_9 methyl ester was also prepared from the gibberellin A_4/A_7 mixture. The stereochemistry of the conjugate reduction of the ring-A-unsaturated ketone is defined.

ALTHOUGH there are fifty-six gibberellin plant hormones known at present, only the fungal metabolites, gibberellic acid (gibberellin A_3) (1), the gibberellin A_4/A_7 mixture (2), and gibberellin A_{13} (3) are relatively easily obtained. Hence for metabolic and structure–activity studies, there is a need to develop routes to the less-abundant gibberellin plant hormones. Simple preparations, permitting labelling, of the methyl esters of the ring-A-desoxygibberellins, A_9 (4) [1] and A_{20} (5),[2] from gibberellic acid (1) [3] form the subject of this paper. The hydrolysis of the esters has been described previously.[1,4] Previous preparations of gibberellin A_{20} have involved the reduction of gibberellin A_5 (6) or its 16,17-epoxide [2,4] or the microbiological transformation of steviol acetate.[5]

Starting from gibberellic acid (1) the preparation involves the selective reduction of the 1,2-double bond and removal of the hydroxy-groups. The catalytic



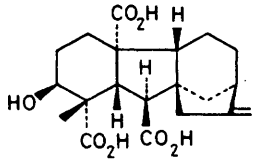
(1)



(2) R^1 = β-OH, α-H; R^2 = H
(17) R^1 = β-OH, α-H; R = Me
(18) R^1 = O; R^2 = Me

reduction of the 1,2-double bond has been described [6] using a partially poisoned palladium-on-barium carbonate catalyst but the yield is low and the reduction is accompanied by hydrogenolysis of the lactone ring. However, the two double bonds may be differentiated by oxidation of methyl gibberellate with manganese dioxide [7] or pyridinium dichromate [8] to the αβ-unsaturated ketone (7). The conjugate reduction of this ketone has been described previously [9] but mixtures were obtained. However sodium borohydride in the presence of copper(I) chloride gave the 3α-alcohol (8) (methyl 3-epigibberellin A_1) together with a small amount of gibberellin A_1 methyl ester (9). The reaction was not accompanied by hydrogenolysis of the lactone ring.

Treatment of gibberellin A_1 methyl ester (9) with triphenylphosphine and carbon tetrachloride [10] gave the elimination product, gibberellin A_5 methyl ester (6). On one occasion the reaction gave the dichloride (10). On the other hand, treatment of the 3α-alcohol with triphenylphosphine–carbon tetrachloride–acetone gave the 3β-chloro-compound (11) with inversion of configur-



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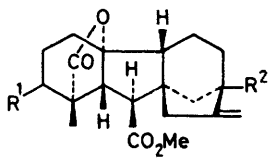
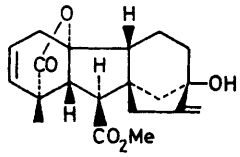


(4) R^1 = R^2 = H
(5) R^1 = H; R^2 = OH
(8) R^1 = α-OH; R^2 = OH
(9) R^1 = β-OH; R^2 = OH
(10) R^1 = α-Cl; R^2 = Cl
(11) R^1 = β-Cl; R^2 = OH
(12) R^1 = β-Cl; R^2 = Cl
(14) R^1 = β-OH; R^2 = H
(15) R^1 = α-OH; R^2 = H
(19) R^1 = β-Cl; R^2 = H



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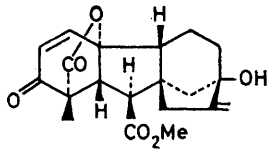

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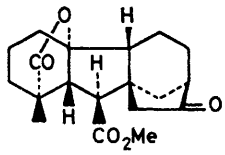

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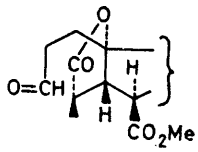


(16)

ation.[11] When pyridine was used as a co-solvent, displacement of the 13-hydroxy-group also occurred to afford the 3β, 13-dichloride (12).

The stereochemistry of the 3α-alcohol (8) and the 3β-chloro-compounds was assigned by examination of the

chemical shift of the 5β-^{1}H n.m.r. signal (see Table 1).[12] A 1 : 3-diaxial interaction with an electronegative substituent brings about a deshielding of the 5β-H. The assignment of the 5β : 6α-^{1}H resonances was made by deuterium exchange in gibberellin A_9 methyl ester norketone (13),[13] gibberellin A_4 methyl ester (14), and its

TABLE 1

5- and 6-H N.m.r. signals of gibberellins (determined in $CDCl_3$)

Compound	5-H	6-H
(13)	2.55	2.70 *
(14)	3.16	2.67 *
(15)	2.52	2.76 *
(8)	2.54	2.75
(19)	3.25	2.68
(11)	3.24	2.66
(12)	3.24	2.72
(10)	2.56	2.72
(5)	2.52	2.70

* Confirmed by deuterium exchange.

3-epimer (15). Both the latter also underwent exchange at C-2 as shown by the ^{13}C n.m.r. spectrum and by the sharpening of the 3-H proton resonance. The exchange at C-2 involves the intervention of a 3,4-seco-ring-A aldehyde (16) formed by retro-aldol cleavage. This deuteriation provides direct evidence for the intervention of this intermediate in the epimerization.[14] The epimerization of the 3-epigibberellins to afford a separable

TABLE 2

^{13}C N.m.r. spectra of 3-epigibberellin A_1 and A_9 methyl esters (determined in $CDCl_3$)

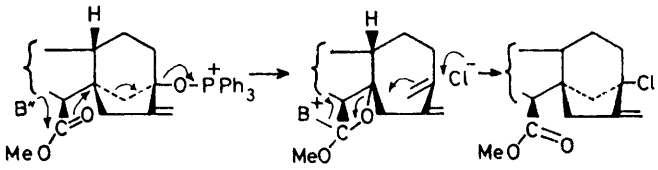
Carbon atom	3-Epigibberellin A_1 methyl ester	Gibberellin A_9 methyl ester
1	30.1 [a]	30.8
2	29.9 [b]	19.4
3	73.0 [c]	34.3 [d]
4	54.9	48.9
5	57.5	58.0
6	51.7	51.8
7	173.2	173.2
8	50.8	51.3
9	52.9	53.9
10	92.0	93.2
11	17.8	16.2
12	39.7	31.4
13	77.6	38.9 [d]
14	43.6	36.8
15	45.9	44.5
16	158.4	156.7
17	106.8	107.3
18	13.8	17.2
19	177.2	179.2
OMe	51.7	51.8

[a] Signal absent from the spectra of [1,3-$^2H_2$]- and [1,2,3-$^2H_3$]-3-epigibberellin A_1 methyl ester. [b] Signal absent from the spectra of [2-^{2}H]- and [1,2,3-$^2H_3$]-3-epigibberellin A_1 ester. [c] Signal absent from the spectrum of [1,2,3-$^2H_3$]-3-epigibberellin A_1 methyl ester. [d] Signals absent from the spectrum of [3,13-$^2H_2$]-gibberellin A_9 methyl ester.

mixture of the normal and epi series suggests that the route to the ring-A-saturated gibberellins possessing an axial hydroxy-group *via* hydride reduction of the unsaturated ketone, may be competitive with the catalytic hydrogenation of the 1,2-double bond. The ease of bridgehead substitution in this series has been noted previously.[15] A plausible explanation may lie in participation of the 7-carbonyl group in the fragmentation of the 8,14-bond to which it bears a *trans* relationship (Scheme).

The 3β-chloro-compound (11) was then hydrogenolysed with tri-n-butyltin hydride in the presence of azobisisobutyronitrile to afford gibberellin A_{20} methyl ester (5).

Gibberellin A_9 methyl ester (4) was obtained in two ways. Oxidation of the gibberellin A_4/A_7 methyl ester mixture (17) with 8N-chromium trioxide in acetone gave the corresponding mixture of 3-ketones (18) which was reduced with sodium borohydride–copper(I) chloride to afford the 3α-epimer of gibberellin A_4 methyl ester (15). This was converted into the 3β-chloride (19) with triphenylphosphine and carbon tetrachloride. The



SCHEME

chloride was then hydrogenolysed with tri-n-butyltin hydride to afford gibberellin A_9 methyl ester (4).[1] Alternatively the dichloride (11), obtained from methyl gibberellate, was treated with tri-n-butyltin hydride to give gibberellin A_9 methyl ester.

The reduction reactions provide a means of labelling gibberellins suitably for metabolic studies. The 3-epigibberellin A_1 methyl ester (8) produced by reduction of the αβ-unsaturated ketone with sodium borodeuteride–copper chloride and protic work-up contained two deuterium atoms (M^+ 364) which were located by the absence of ^{13}C n.m.r. signals (see Table 2) at δ 30.1 and 73.0 at C-1 and C-3. The presence of deuterium on these carbon atoms 'quenches' their ^{13}C n.m.r. signal through C–D coupling and the absence of the nuclear Overhauser enhancement inherent in proton decoupling. When the reaction was carried out in methan[^{2}H]ol, the product contained three deuterium atoms (M^+ 365) located at C-1, C-2, and C-3 (absence of ^{13}C n.m.r. signals at δ 29.7, 30.1, and 73.0 p.p.m.). Reduction with sodium borohydride–copper(I) chloride in methan[^{2}H]ol gave 3-epigibberellin A_1 methyl ester containing one deuterium atom (M^+ 363) at C-2 (no ^{13}C n.m.r. signal at δ 29.7 p.p.m.). This latter method of deuteriation affords a simple stereo- (see later) and regio-specific method of labelling which may have more general application.

The stereochemistry of deuteriation was established by an examination of the high-field (360 MHz) ^{1}H n.m.r. spectrum kindly determined by Dr. I. H. Sadler (University of Edinburgh). In [2,2,6-$^2H_3$]-3-epigibberellin A_4 methyl ester, apart from the 6-H signal (δ 2.53, J 10.3 Hz), two groups of resonances at δ 2.23 and 2.13 disappear. The latter, which also appear at δ 2.24 and 2.11 in 3-epigibberellin A_1 methyl ester, are assigned to the

H-2 signals. The signal at δ 2.24 contains a large J_{gem} 13.6 Hz and three smaller (*ca.* 6 Hz) couplings corresponding to two *eq–ax* and one *eq–eq* couplings, and hence this signal is assigned to the equatorial 2-H signal. In the monodeuteriated [2-^{2}H]-3-epigibberellin A_1 methyl ester, this signal disappears and the two multiplets at δ 1.54 and 1.45 are modified. The former collapses to a doublet (*J* 13.2 Hz) and the latter to a less complex multiplet. In the [1,2,3-$^2H_3$]-3-epigibberellin A_1 methyl ester, the signal at δ 1.54 disappears and the multiplet at δ 1.45 collapses to a broad doublet (*J* 7—8 Hz). The latter corresponds to an axial–equatorial coupling. Thus the proton which is deuteriated at C-1 is the 1β (axial) proton and at C-2, it is the 2β (equatorial) proton. The reduction has therefore taken place from the β-face of the molecule. The reaction may proceed in two stages. First the conjugate reduction of the αβ-unsaturated ketone by pseudo-axial attack from the less hindered face at C-1 to generate a $\Delta^{2,3}$-enol borate, which then undergoes a *cis*-anti-Markownikoff hydroboronation to afford the C-2 borane which in the last step undergoes protonolysis.[16]

[3,13-^{2}H]-Gibberellin A_9 methyl ester was prepared by the [^{2}H]-tri-n-butyltin hydride reduction of the corresponding dichloride. Examination of the ^{13}C n.m.r. spectrum (Table 2) confirmed the location of the labels, particularly that at C-13.

EXPERIMENTAL

General experimental details have been described previously.[17]

Oxidation of Methyl Gibberellate with Pyridinium Dichromate.—Methyl gibberellate (1 g) in dimethylformamide (6 ml) was stirred with pyridinium dichromate (2 g) at 0 °C for 30 min. The solution was poured into water (142 ml) and the product was recovered in ethyl acetate, washed with water, filtered through alumina, and dried. The solvent was evaporated off to afford the αβ-unsaturated ketone (7) (880 mg) which crystallized from acetone–light petroleum as plates, m.p. 185—187 °C (lit.,[7] 186—187 °C), $\nu_{max.}$ 3 300, 1 750, and 1 660 cm^{-1}, δ 1.27 (3 H, s, 18-H), 2.85 (1 H, d, *J* 11 Hz, 6-H), 3.49 (1 H, d, *J* 11 Hz, 5-H), 3.70 (3 H, s, OMe), 4.95 and 5.28 (1 H, m, each 17-H), 6.03 (1 H, d *J* 9 Hz, 2-H), and 7.25 (1 H, d, *J* 9 Hz, 1-H).

Reduction of the αβ-Unsaturated Ketone (7) with Sodium Borohydride: Copper(I) Chloride.—The αβ-unsaturated ketone (7) (2 g) in methanol (250 ml) containing copper(I) chloride (3 g) was treated with sodium borohydride (3 g) at 0 °C for 1 h. The solution was acidified, concentrated *in vacuo*, and poured into water. The product was recovered in ethyl acetate and chromatographed on silica to afford gibberellin A_1 methyl ester (350 mg), m.p. 227—233 °C (lit.,[18] 233—235 °C) (identified by its n.m.r. spectrum). Further elution afforded 3-epigibberellin A_1 methyl ester (8) (1 g), m.p. 188—189 °C (lit.,[9] 182—184 °C) (Found: C, 66.2; H, 7.0. Calc. for $C_{20}H_{26}O_6$ requires C, 66.3; H, 7.2%), $\nu_{max.}$ 3 300br, 1 770, and 1 710 cm^{-1}, δ 1.18 (3 H, s, 18-H), 2.54 (1 H, d, *J* 10.3 Hz, 5-H), 2.75 (1 H, d, *J* 10.3 Hz, 6-H), 3.50br, 3.72 (3 H, s, OMe), and 4.92 and 5.22 (each 1 H, m, 17-H).

Deuteriation Experiments.—(*a*) The αβ-unsaturated ketone (7) (300 mg) in [^{2}H]methanol (15 ml) was treated with sodium borohydride (400 mg) and copper(I) chloride (400 mg) at 0 °C for 30 min to afford, after work-up as above, the [2-^{2}H]-ester (8) (150 mg), m.p. 188—190 °C, M^+ 363.

(*b*) The αβ-unsaturated ketone (7) (400 mg) in methanol (15 ml) was treated with sodium [^{2}H]borohydride (400 mg) and copper(I) chloride (400 mg) at 0 °C for 30 min to afford, after work-up as above, the [1,3-$^2H_2$]-ester (8) (170 mg), m.p. 184—187 °C, M^+ 364.

(*c*) The αβ-unsaturated ketone (7) (140 mg) in [^{2}H]methanol (10 ml) was treated with sodium [^{2}H]borohydride (140 mg) at 0 °C for 30 min. The reaction mixture was acidified with 20% [^{2}H]hydrochloric acid (0.5 ml) and the product recovered as above to afford the [1,2,3-$^2H_3$]-ester (8) (100 mg), m.p. 186—188 °C, M^+ 365.

Reaction of Giberrellin A_1 Methyl Ester with Triphenylphosphine and Carbon Tetrachloride.—Gibberellin A_1 methyl ester (220 mg) and triphenylphosphine (1 g) in carbon tetrachloride (25 ml) and pyridine (2.5 ml) were heated under reflux for 1 h. The solvents were evaporated off and the residue was chromatographed on silica to afford gibberellin A_5 methyl ester (80 mg) which was identified by its n.m.r. spectrum. On one occasion the reaction also gave ent-3β,13-*dichloro*-10β-*hydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester*, m.p. 153—154 °C, (Found: C, 60.3; H, 6.0. $C_{20}H_{24}O_4Cl_2$ requires C, 60.15; H, 6.0%), $\nu_{max.}$ 1 765, 1 720, and 1 660 cm^{-1}, δ 1.24 (3 H, s, 18-H), 2.56 (1 H, d, *J* 10 Hz, 5-H), 2.72 (1 H, d, *J* 10 Hz, 6-H), 3.69 (3 H, s, OMe), 3.9 (1 H, q, *J* 6 and 11 Hz, 3-H), and 5.08 and 5.40 (each 1 H, m, 17-H).

Reaction of 3-Epigiberellin A_1 Methyl Ester with Triphenylphosphine and Carbon Tetrachloride.—(*a*) The ester (500 mg) in acetone (10 ml) was heated under reflux with triphenylphosphine (1 g) and carbon tetrachloride (8 ml) for 1 h. The solvents were evaporated off and the products were chromatographed on silica to afford the 3β-*chloro-ester* (11) (250 mg) as a gum (Found: M^+, 380.139. $C_{20}H_{25}O_5{}^{35}Cl$ requires *M*, 380.139), $\nu_{max.}$ 3 300br, 1 765, 1 730, and 1 655 cm^{-1}, δ 1.16 (3 H, s, 18-H), 2.66 (1 H, d, *J* 10 Hz, 6-H), 3.24 (1 H, d, *J* 10 Hz, 5-H), 3.68 (3 H, s, OMe), 4.09 (1 H, m, 3-H), and 4.92 and 5.24 (each 1 H, m, 17-H).

(*b*) 3-Epigibberellin A_1 methyl ester (3 g) in pyridine (7 ml) was heated with carbon tetrachloride (30 ml) and triphenylphosphine (4.5 g) for 3 h. The solvent was evaporated off and the residue chromatographed on silica. Elution with 30% ethyl acetate–light petroleum afforded ent-3α,13-*dichloro*-10β-*hydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (12) (1.5 g) which crystallized from acetone–light petroleum as needles, m.p. 140—142 °C (Found: C, 60.2; H, 6.00. $C_{20}H_{24}O_4Cl_2$ requires C, 60.15; H, 6.0%), $\nu_{max.}$ 1 760, 1 710, and 1 660 cm^{-1}, δ 1.19 (3 H, s, 18-H), 2.72 (1 H, d, *J* 10 Hz, 6-H), 3.24 (1 H, d, *J* 10 Hz, 5-H), 3.71 (3 H, s, OMe), 4.10 (1 H, m, 3-H), and 5.13 and 5.45 (each 1 H, m, 17-H). Subsequent fractions gave the monochloro-compound described above.

Hydrogenolysis Reactions.—(*a*) The chloro-ester (11) (200 mg) in benzene (10 ml) was treated with tri-n-butyltin hydride (1 ml) and azobisisobutyronitrile (100 mg) under reflux for 45 min. The solution was diluted with ethyl acetate, washed with water and dilute hydrochloric acid, dried, and evaporated. The residue was chromatographed on silica to afford gibberellin A_{20} methyl ester (5) (130 mg), m.p. 182—185 °C (lit.,[2] 181 °C), $\nu_{max.}$ 3 500, 1 765, 1 715, 1 665, and 880 cm^{-1}, δ 1.08 (3 H, s, 18-H), 2.54 (1 H, d, *J* 10 Hz, 5-H), 2.68 (1 H, d, *J* 10 Hz, 6-H), 3.69 (3 H, s, OMe), and 4.92 and 5.23 (each 1 H, m, 17-H).

(*b*) The 3,13-dihalide (12) (400 mg) in benzene (10 ml) was heated under reflux with tri-n-butyltin hydride (1.5 ml) and azobisisobutyronitrile (200 mg) for 2 h. The solvent was evaporated off and the residue was chromatographed on silica. Elution with 15% ethyl acetate–light petroleum afforded gibberellin A_9 methyl ester (180 mg), m.p. 137—138 °C (lit.,[1] 136 °C) identified by comparison (n.m.r.) with an authentic sample. Repetition with the dihalide (250 mg) and tri-n-butyltin [^{2}H]hydride gave [3,13-$^2H_2$]gibberellin A_9 methyl ester (120 mg), *m/e* 332, 301, 288, 272, 245, 244, 239, 238, and 218.

Preparation of Gibberellin A_9 Methyl Ester from the Gibberellin A_4/A_7 Mixture.—3-Epigibberellin A_4 methyl ester (15), prepared as above from the mixture of gibberellin A_4 and A_7 3-ketone methyl esters, had m.p. 168—169 °C, (lit.,[19] 166—167 °C). Treatment with carbon tetrachloride–triphenyl phosphine, as above, gave ent-3α-*chloro*-10β-*hydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (19), m.p. 95—97 °C (Found: C, 67.4; H, 7.0. $C_{20}H_{25}O_4Cl$ requires C, 67.6; H, 7.1%), $\nu_{max.}$ 1 770, 1 730, 1 655, and 890 cm^{-1}, δ 1.2 (3 H, s, 18-H), 2.68 (1 H, d, *J* 11 Hz, 6-H), 3.25 (1 H, d, *J* 11 Hz, 5-H), 3.65 (3 H, s, OMe), 4.1 (1 H, m, 3-H), and 5.0 (2 H, m, 17-H). Reduction of the chloro-ester (350 mg) with tri-n-butyltin hydride as above, gave gibberellin A_9 methyl ester (250 mg), m.p. 136—137 °C, identified by comparison (n.m.r.) with an authentic sample.

Treatment of 3-Epigibberellin A_4 Methyl Ester with Sodium Methoxide in Methan[^{2}H]*ol.*—The ester (500 mg) in methan-[^{2}H]olic sodium methoxide {from methan[^{2}H]ol (10 ml) and sodium (230 mg)} was heated under reflux for 3 h. The solvent was evaporated off and the residue was acidified and recovered in ethyl acetate to afford after chromatography on silica [2,2,6-$^2H_3$]gibberellin A_4 methyl ester (100 mg), m.p. 173—175 °C (lit.,[19] 176 °C), $\nu_{max.}$ 3 495, 1 765, and 1 712 cm^{-1}, δ 1.13 (3 H, s, 18-H), 3.16 (1 H, s, 5-H), 3.70 (3 H, s, OMe), 3.81 (1 H, s, 3-H), and 4.87 and 4.98 (each 1 H, 17-H), *m/e* 349 (8%), 331 (63), 317 (83), 303 (50), and 239 (100). Further elution gave [2,2,6-$^2H_3$]-3-epigibberellin A_4 methyl ester (110 mg), m.p. 160—162 °C (lit.,[20] 166—167 °C), $\nu_{max.}$ 3 500, 1 765, and 1 712 cm^{-1}, δ 1.16 (3 H, s, 18-H), 2.52 (1 H, s, 5-H), 3.70 (3 H, s, OMe), and 4.86 and 4.98 (each 1 H, 17-H), *m/e* 349 (8%), 331 (63), 317 (83), 303 (88), 287 (30), 271 (18), and 239 (100).

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