Hydrolysis of Gibberellin 7-Methyl Esters: Anchimeric Assistance by a 15-Alcohol

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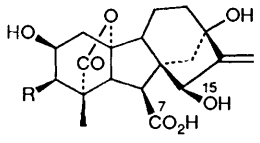
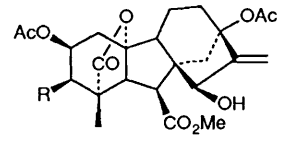
The neighbouring group effects of 15α- and 15β-hydroxy groups on the rates of hydrolysis of gibberellin 7-methyl esters are described. The presence of a 15-alcohol increases the rate of ester hydrolysis and a 15α- has a greater influence than a 15β-alcohol. The 15α-alcohol may be effective either through hydrogen bonding between the hydroxy proton and the ester carbonyl thus stabilising the tetrahedral intermediate formed on hydrolysis of the ester, or *via* 7,15α-lactonisation followed by hydrolysis of the lactone. The 15β-hydroxy may act through hydrogen bonding of a water molecule between the proton of the 15β-alcohol and the 7-carbonyl function. The effect is enhanced by the presence of a 13-acetate.

The gibberellin (GA) plant hormones, *e.g.* **1**, are densely functionalised structures, prone to acid- and base-catalysed rearrangements.[1] Hence a range of protecting groups have been employed in the manipulation of these compounds. For example, many reactions of GAs have been conducted on the methyl esters of the 7-oic acid. However, regeneration of the 7-oic acid from the methyl ester is difficult to achieve. These difficulties arise from the hindered nature of the methyl ester necessitating the use of prolonged reaction times and elevated temperatures during the deprotection reaction. Additionally when using aqueous bases, it is essential to protect a 3β-hydroxy to avoid epimerisation at C-3.[2]

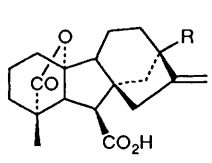
In a recently described synthesis[3] of two naturally occurring 15β-hydroxylated gibberellins, GA_{75} **1** and GA_{76} **2**, it was noted that reaction of the corresponding methyl esters **3** and **4**



1 R = OH, GA_{75}
2 R = H, GA_{76}

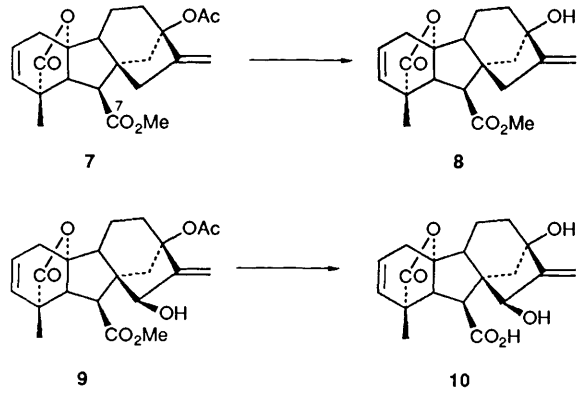


3 R = OAc
4 R = H



5 R = H, GA_9
6 R = OH, GA_{20}

with aqueous potassium carbonate in methanol at room temperature resulted in complete hydrolysis of the ester functions. The 7-methyl esters of GAs are usually resistant to hydrolysis under these conditions. For example (Scheme 1), reaction of GA_5 methyl ester 13-acetate **7** with aqueous potassium carbonate gives GA_5 methyl ester **8** as the sole product. However, under the same reaction conditions, 15β-hydroxy-GA_5 methyl ester 13-acetate **9** gives 15β-hydroxy-GA_5 **10**.[3] An investigation of the neighbouring group effect of the 15α- and 15β-hydroxy groups on the hydrolysis of gibberellin 7-methyl esters is now reported.



7 **8**

9 **10**

Scheme 1 *Reaction conditions:* Aqueous K_2CO_3 (1 mol dm^{-3}) in MeOH, 14 h, room temperature

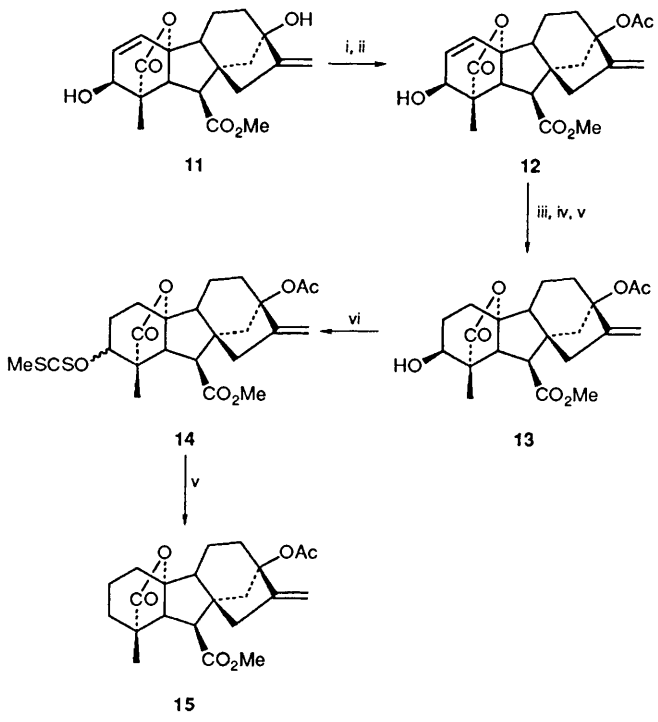
Results and Discussion

It has been previously observed[4] that 7,15-lactonisation occurs between a 15α-alcohol and the 7-methyl ester of non-13-hydroxylated GAs while no such lactonisation is seen in systems with an alcohol or acetate at position-13. This implies that the substituent at C-13 in some way affects the relationship between the 15α-alcohol and the 7-ester function. To further investigate this relationship, as well as the neighbouring group effect of a 15-alcohol on the hydrolysis of a 7-methyl ester, a series of derivatives of GA_9 **5** and GA_{20} **6** were prepared. These are respectively the least substituted non-13-hydroxy and 13-hydroxy C_{19}-gibberellins.

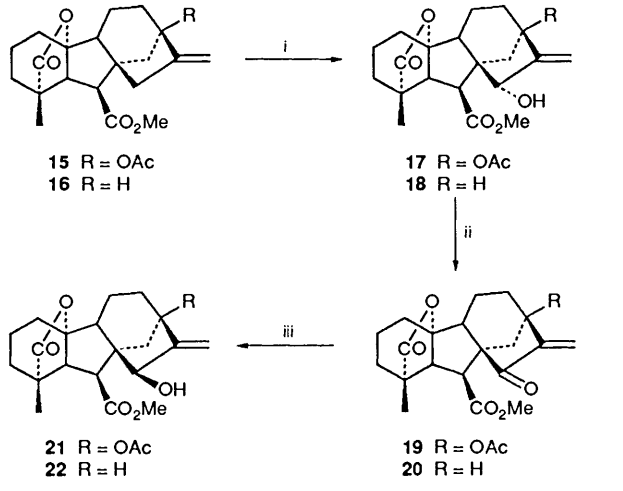
As shown in Scheme 2, GA_{20} methyl ester 13-acetate **15** was prepared in 30% overall yield from GA_3 methyl ester **11**, *via* radical reduction of the xanthate **14** prepared from GA_1 methyl ester 13-acetate **13**.[5] Gibberellin A_9 **6** was isolated[6] from large scale fermentation of the fungus *Gibberella fujikuroi* and was subsequently methylated with ethereal diazomethane to give GA_9 methyl ester **16**.

Allylic hydroxylation (Scheme 3) of GA_{29} methyl ester 13-acetate **15** and GA_9 methyl ester **16** afforded excellent yields of the 15α-alcohols **17** and **18**. Inversion of the 15α-hydroxy group to the β-orientation was achieved by Swern oxidation followed by reduction with zinc in acetic acid to give 15β-hydroxy-GA_{20} methyl ester 13-acetate (GA_{67} methyl ester 13-acetate, **21**) and 15β-hydroxy-GA_9 methyl ester (GA_{45} methyl ester, **22**).[7]

The non-15-hydroxy-, 15α-hydroxy- and 15β-hydroxy-GA_{20} methyl ester 13-acetates **15**, **17** and **21** and the non-15-hydroxy-,



Scheme 2 Preparation of GA_{20} 7-methyl ester 13-acetate 15. *Reagents:* i, Ac_2O, TsOH; ii, aq. K_2CO_3, MeOH; iii, H_2, 10% Pd on $CaCO_3$, py., MeOH; iv, I_2, aq. $NaHCO_3$, CH_2Cl_2; v, Bu_3SnH, AIBN; vi, CS_2, NaH, MeI



Scheme 3 Preparation of 15-hydroxygibberellin derivatives. *Reagents:* i, SeO_2, Bu^tO_2H; ii, DMSO, $(COCl)_2$, Pr^i_2EtN; iii, Zn, AcOH

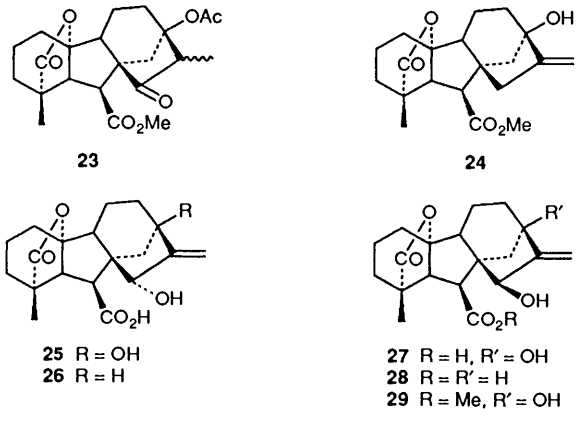
15α-hydroxy- and 15β-hydroxy-GA_9 methyl esters **16**, **18** and **22** were each treated with aqueous potassium carbonate (1 mol dm^{-3}) in methanol at room temperature for 60 h. The results of these experiments are shown in Table 1. The C-7 methyl esters of the non-15-hydroxylated derivatives **15** and **16** were not hydrolysed under the reaction conditions although the 13-acetate in **15** was cleaved to give **24**. In the presence of a 15α-hydroxy function **17** and **18**, the corresponding 7-carboxylic acids **25** and **26** were the only products. The effect of the 15β-hydroxy on the rate of hydrolysis of a 7-methyl ester depended on the substituent at C-13. In the presence of a 13-acetate **21** hydrolysis was complete whereas in the case of 15β-hydroxy-GA_9 methyl ester **22** only 37% hydrolysis was observed. The above reactions were repeated using aqueous sodium hydroxide (0.5 mol dm^{-3}) in methanol at room temperature for 16 h. The results are shown in Table 2. It is apparent that the same

Table 1 Hydrolysis of gibberellin derivatives in aqueous K_2CO_3 (1 mol dm^{-3}) in MeOH, 60 h, room temperature

Substrate	7-Carboxylic acid in recovered product (%)
GA_{20} methyl ester 13-acetate **15**	0
15α-OH-GA_{20} methyl ester 13-acetate **17**	100
15β-OH-GA_{20} methyl ester 13-acetate **19**	100
GA_9 methyl ester **16**	0
15α-OH-GA_9 methyl ester **18**	100
15β-OH-GA_9 methyl ester **20**	37
15α-OH-GA_9 7,15α-lactone **35**	100
15β-OTHP-GA_9 methyl ester **38**	0

Table 2 Hydrolysis of gibberellin derivatives in aqueous K_2CO_3 (0.5 mol dm^{-3}) in MeOH, 16 h, room temperature

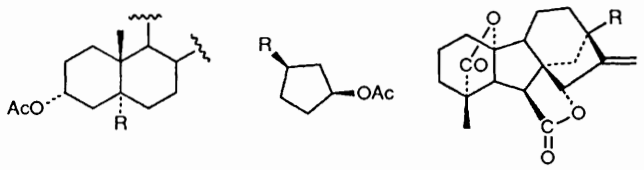
Substrate	7-Carboxylic acid in recovered product (%)
GA_{20} methyl ester 13-acetate **15**	0
15α-OH-GA_{20} methyl ester 13-acetate **17**	100
15β-OH-GA_{20} methyl ester 13-acetate **19**	94
GA_9 methyl ester **16**	0
15α-OH-GA_9 methyl ester **18**	100
15β-OH-GA_9 methyl ester **20**	65



pattern emerges as with reaction with aqueous potassium carbonate, *i.e.* the presence of a 15-hydroxy group increases the rate of hydrolysis of the 7-methyl ester, and the 15α- has a more pronounced effect than the 15β-alcohol and in the latter case a 13-acetate increases the rate of hydrolysis.

One explanation for the increase in the rate of hydrolysis of the 7-methyl esters of the 15α- and 15β-hydroxygibberellins could be hydrogen bonding between the hydroxy proton and the carbonyl oxygen stabilising the tetrahedral intermediate formed on hydrolysis of the ester. This phenomenon has previously been observed in the cholestane series.[8] For example, it was noted that the *cis* diaxial 3α-acetoxy-5α-hydroxy derivative **30** was hydrolysed under conditions in which the non-hydroxy acetate **31** remained unaffected.

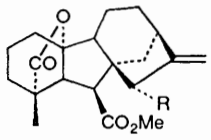
There is evidence for hydrogen bonding between the hydroxy proton and the carbonyl of the 7-methyl ester in the case of the 15α-hydroxygibberellins. Firstly, the methyl ester carbonyl stretch appears at ν 1732 cm^{-1} (in CCl_4) in the infra-red spectrum of 15α-hydroxy-GA_9 methyl ester **18**, whereas this signal appears at a higher frequency, ν 1740 cm^{-1} (in CCl_4) in GA_9 methyl ester **16** as a result of a stronger bond. This difference in vibrational frequency of 8 cm^{-1} is comparable to the case of 1-acetoxy-3-hydroxycyclopentane **32** where the carbonyl stretch is 11 cm^{-1} lower than in the non-hydroxy acetate **33** and is hydrolysed at seven times the rate.[9] Secondly



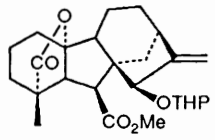
30 R = OH
31 R = H

32 R = OH
33 R = H

34 R = OH
35 R = H



36 R = OTHP
37 R = OMOM



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the ^{1}H NMR spectra of the 15α-hydroxygibberellin **17** displays a doublet at δ 3.76, attributed to the 15α-hydroxy proton, which disappears on shaking with D_2O. Hydroxy protons are not usually apparent in the ^{1}H NMR spectra of gibberellins because of rapid exchange with the solvent. The appearance of the signal at δ 3.76 as a sharp doublet implies that the 15α-hydroxy proton is hydrogen bonded to the carbonyl of the 7-ester and does not readily exchange. Finally computer generated models [Fig. 1(*a*)] of 15α-hydroxy-GA_9 methyl ester **18** indicate that the distance between the carbonyl oxygen and the hydroxy proton is 2.09 Å, very close to the predicted length of a hydrogen bond of 2.07 Å.[10]

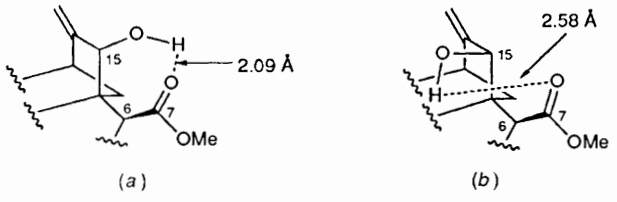

Fig. 1 (*a*) 15α-hydroxy-GA_9 methyl ester; (*b*) 15β-hydroxy-GA_9 methyl ester

Attempts were made to prepare the tetrahydropyranyl and methoxymethyl ether derivatives of 15α-hydroxy-GA_9 methyl ester **18** in which no hydrogen bonding is possible to the carbonyl of the 7-methyl ester. However, in both cases the 7,15α-lactone **35** was the sole product. Indeed, an alternative explanation for the increased rate of base hydrolysis of the C-7 methyl ester in the presence of a 15α-alcohol is *via* the 7,15-lactone followed by hydrolysis. Treatment of the lactones **34** and **35** with aqueous potassium carbonate in methanol gave the hydroxy acids **25** and **26** respectively in good yield. It was originally believed[4] that lactonisation of a 15α-hydroxy acid would occur instantly. However after being set aside in methanol for 5 d, 15α-hydroxy-GA_9 **26** showed only 17% lactonisation, and 15α-hydroxy-GA_{20} **25**, 40% lactonisation. These results indicate that a 13-hydroxy promotes the 7,15-lactonisation reaction.

The effect of the 15β-hydroxy group on the rate of hydrolysis of the 7-methyl ester is significant although less marked than that of a 15α-alcohol. It is unlikely that there is direct hydrogen bonding between the hydroxy proton and the carbonyl of the methyl ester. Molecular modelling [Fig. 1(*b*)] indicates a distance of 2.58 Å. Additionally, the infra-red spectra of GA_9 methyl ester **16** and 15β-hydroxy-GA_9 methyl ester **22** showed carbonyl stretchings at ν 1740 and 1739 cm^{-1} respectively (in CCl_4) and the ^{1}H NMR spectra of 15β-hydroxy-GAs had no signals attributable to hydroxy protons. However, it is speculated that, in aqueous solutions, a water molecule could be captured by hydrogen bonding between the carbonyl oxygen of the 7-methyl ester and the 15-hydroxy proton, so stabilising the tetrahedral intermediate in the hydrolysis of the methyl ester. Indeed, reaction of the 15β-tetrahydropyranyl ether derivative **38** with aqueous potassium carbonate returned only starting material. Additional support for this possibility is derived from comparison of the reaction of 15β-hydroxy-GA_{20} methyl ester 13-acetate **21** and 15β-hydroxy-GA_9 methyl ester **22** with aqueous potassium carbonate; in the former case 100% hydrolysis of the 7-methyl ester occurs whereas in the latter only 37% hydrolysis is evident. Computer-generated models indicate that water could be trapped between the three functional groups of GA_{20} 7-methyl ester 13-acetate **21**, so increasing the rate of hydrolysis of the methyl ester more than in the case of 15β-hydroxy-GA_9 methyl ester **22**. Indeed, as would be expected, treatment of 15β-hydroxy-GA_{20} methyl ester **24** (with the free alcohol at C-13) with aqueous potassium carbonate led to only 40% hydrolysis of the 7-methyl ester.

Conclusions

The presence of a 15-alcohol in a gibberellin molecule increases the rate of base hydrolysis of the C-7-methyl ester. A 15α- has a greater affect than a 15β- hydroxy group. Experimental results indicate that the 15β-hydroxy group may be effective *via* hydrogen bonding of a water molecule between the carbonyl of the 7-methyl ester and the proton on the 15-alcohol, so stabilising the tetrahedral intermediate formed on hydrolysis of the 7-methyl ester. The effect is enhanced by the presence of a 13-acetate.

The increase in the rate of ester hydrolysis in the presence of a 15α-hydroxy may be caused either by hydrogen bonding between the hydroxy proton and the ester carbonyl oxygen or *via* 7,15α-lactonisation followed by hydrolysis of the lactone.

Experimental

General experimental details have been described in a previous paper.[11] *J* Values are given in Hz.

ent-13-*Acetoxy*-3α,10β-*dihydroxy*-20-*norgibberell*-16-*ene*-17,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* 3α-S-*Methyl Dithiocarbonate* **14**.—Gibberellin A_1 methyl ester 13-acetate **13** (700 mg) in freshly distilled tetrahydrofuran (20 cm^3) was stirred at room temperature under nitrogen gas for 16 h with sodium hydride (1.5 g, 60% dispersion in oil), carbon disulphide (3 cm^3) and 18-crown-6-ether (30 mg). Dry iodomethane (2 cm^3) was added and the reaction was stirred at room temperature under nitrogen gas for a further 2h. The reaction mixture was slowly diluted with water (50 cm^3) and worked up as usual. The crude product was purified by flash column chromatography. Elution with ethyl acetate–light petroleum (20:80) and (30:70) yielded a 1:1 mixture (by ^{1}H NMR) of 3α- and 3β-dithiocarbonate **14** (760 mg). 3α-Dithiocarbonate δ 1.10 (s, 18-H_3), 2.03 (s, $OCOCH_3$), 2.55 (s, OCS_2CH_3), 2.74 (d, *J* 11, 6-H), 2.79 (d, *J* 11, 5-H), 3.74 (s, CO_2CH_3), 5.00 and 5.16 (2 br s, 17-H_2) and 5.77 (m, 3-H); 3β-dithiocarbonate δ 1.10 (s, 18-H_3), 2.03 (s, $OCOCH_3$), 2.61 (s, OCS_2CH_3), 2.71 (d, *J* 10.5, 6-H), 3.28 (d, *J* 10.5, 5-H), 3.74 (s, CO_2CH_3), 5.00 and 5.16 (2 br s, 17-H_2), and 5.77 (m, 3-H); *m/z* 494 (M^+, 10%), 386 (24), 343 (46), 342 (27), 302 (25), 301 (100), 283 (72), 282 (38), 269 (48), 267 (33), 241 (26), 223 (32), 91 (23) and 43 (55).

ent-13-*Acetoxy*-10β-*hydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* **15**.—The mixture of the 3α- and 3β-epimers of GA_1 methyl ester 13-acetate 3-dithiocarbonate **14** (650 mg), tributylstannane (2 cm^3) and 2,2′-azobis(2-methylpropionitrile) (30 mg) in toluene (50 cm^3) were

heated under reflux for 3 h, with addition of further tributylstannane (1 cm^3) and 2,2′-azobis(2-methylpropionitrile) (10 mg) after 1 h and 2 h. After being cooled, the solvent was removed under vacuum and the residue was purified by flash column chromatography. Elution with ethyl acetate–light petroleum (20:80) yielded the required GA_{20} methyl ester 13-acetate **15** (440 mg), m.p. 107–110 °C (lit.,[5] 111–113 °C); δ 1.08 (s, 18-H_3), 2.02 (s, $OCOCH_3$), 2.57 (d, *J* 10, 6-H), 2.70 (d, *J* 10, 5-H), 3.72 (s, CO_2CH_3), and 4.97 and 5.14 (2 br s, 17-H_2); *m/z* 388 (M^+, 36%), 347 (25), 346 (100), 328 (40), 314 (27), 300 (33), 286 (34), 284 (44), 268 (23), 258 (23), 244 (29) and 43 (56).

ent-13-*Acetoxy*-10β,15β-*dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* **17**.—Gibberellin A_{20} methyl ester 13-acetate **15** (440 mg) in dichloromethane (15 cm^3) was stirred with selenium dioxide (127 mg, 1 equiv.) and *tert*-butyl hydroperoxide (70% in water) (500 mm^3, 4 equiv.) for 24 h at room temperature. The crude product, recovered in the usual way, was purified by flash column chromatography. Elution with ethyl acetate–light petroleum (30:70) gave recovered starting material **15** (150 mg); elution with ethyl acetate–light petroleum (40:60) yielded the required 15α-hydroxy-GA_{20} methyl ester 13-acetate **17** (270 mg) which crystallised from acetone–light petroleum as needles, m.p. 179–181 °C (lit.,[4] 183–184 °C) (Found: M^+, 404.1804. $C_{22}H_{28}O_7$ requires *M*, 404.1835); δ 1.10 (s, 18-H_3), 2.04 (s, $OCOCH_3$), 2.58 (s, 6-H and 5-H), 3.69 (s, CO_2CH_3), 3.76 (d, *J* 8.5, 15-OH), 4.02 (d, *J* 8.5, 15-H), and 5.19 and 5.40 (2 s, 17-H_2); *m/z* 404 (M^+, 3%), 372 (5), 344 (68), 331 (25), 330 (91), 313 (26), 312 (76), 299 (47), 298 (77), 285 (30), 284 (100), 267 (28), 266 (40), 239 (78), 238 (42) and 43 (71).

ent-13-*Acetoxy*-10β-*hydroxy*-15-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* **19**.—Oxalyl chloride (200 mm^3) and dimethyl sulphoxide (400 mm^3) in dichloromethane (5 cm^3) were stirred at −78 °C for 5 min under nitrogen gas. 15α-Hydroxy-GA_{20} methyl ester 13-acetate **17** (88 mg) in dichloromethane (2 cm^3) was added and the mixture was stirred for a further 1 h at −78 °C. Diisopropylethylamine (1 cm^3) was added and the solution was allowed to warm to room temperature, with stirring, over 1 h. The crude product was recovered in the usual way and purified by flash column chromatography. Elution with ethyl acetate–light petroleum (50:50) gave recovered starting material **17** (15 mg); elution with ethyl acetate–light petroleum (40:60) yielded the required 15-oxo-GA_{20} methyl ester 13-acetate **19** (70 mg) as a gum (Found: M^+, 402.1665. $C_{22}H_{26}O_7$ requires *M*, 402.1678); δ 1.14 (s, 18-H_3), 2.11 (s, $OCOCH_3$), 2.63 (d, *J* 10, 6-H), 2.72 (d, *J* 10, 5-H), 3.08 (d, *J* 11, 14-H), 3.62 (s, CO_2CH_2) and 5.60 and 6.08 (2 s, 17-H_2); *m/z* 402 (M^+, 9%), 371 (23), 360 (54), 328 (28), 315 (35), 314 (100), 300 (28), 255 (36), 254 (33), 91 (23) and 43 (88).

ent-13-*Acetoxy*-10β,15α-*dihydroxy*-20-*norgibberell*-16-*ene*-7,-19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* **21**.—15-Oxo-GA_{20} methyl ester 13-acetate **19** (70 mg) in acetic acid (1 cm^3) was stirred with activated zinc (170 mg) for 1 h at room temperature. The reaction mixture was filtered and the zinc was washed with ethyl acetate (3 × 10 cm^3). The combined filtrate and washings were evaporated under vacuum and the resultant residue was purified by flash column chromatography. Elution with ethyl acetate–light petroleum (40:60) gave the known[4] 16ξ,17-dihydro-15-oxo-GA_{20} methyl ester 13-acetate **23** (30 mg) as a gum (Found: M^+, 404.1835. Calc. for $C_{22}H_{28}O_7$: *M*, 404.1835); δ 1.13 (s, 18-H_3), 1.14 (d, *J* 7, 17-H_3), 2.05 (s, $OCOCH_3$), 2.61 (d, *J* 10, 6-H), 2.66 (d, *J* 10, 5-H), 3.17 (d, *J* 11, 14-H) and 3.62 (s, CO_2CH_3); *m/z* 404 (M^+, 31%), 362 (24), 344 (100), 316 (79), 313 (26), 284 (32), 260 (29), 257 (26), 212 (25) and 43 (71).

Elution with ethyl acetate–light petroleum (50:50) yielded the required 15β-hydroxy-GA_{20} methyl ester 13-acetate **21** (20 mg) as a gum (Found: M^+, 404.1812. $C_{22}H_{28}O_7$ requires *M*, 404.1835); δ 1.08 (s, 18-H_3), 2.01 (s, $OCOCH_3$), 2.48 (d, *J* 10.5, 6-H), 2.74 (d, *J* 10.5, 5-H), 3.78 (s, CO_2CH_3), 4.24 (m, 15-H), and 5.22 and 5.24 (2 d, *J* 2.5, 17-H_2); *m/z* 404 (M^+, 42%), 362 (31), 344 (78), 330 (76), 316 (26), 312 (56), 284 (48), 268 (29), 267 (25), 266 (31), 239 (38), 91 (30) and 43 (100).

ent-10β,15β-*Dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* **18**.—Gibberellin A_9 methyl ester **16** (310 mg) in dichloromethane (15 cm^3) was stirred with selenium dioxide (110 mg, 1 equiv.) and *tert*-butyl hydroperoxide (70% in water) (500 mm^3, 4 equiv.) for 17 h at room temperature. The reaction mixture was worked up as usual and the crude product purified by flash column chromatography. Elution with ethyl acetate–light petroleum (40:60) yielded the required 15α-hydroxy-GA_9 methyl ester **18** (240 mg) which crystallised from ethyl acetate–light petroleum, m.p. 169–170 °C (Found: M^+, 346.1767. $C_{20}H_{26}O_5$ requires *M*, 346.1780); δ 1.10 (s, 18-H_3), 2.53 (d, *J* 10, 6-H), 2.63 (d, *J* 10, 5-H), 3.67 (s, CO_2CH_3), 4.03 (br s, 15-H) and 5.15 and 5.26 (2 br s, 17-H_2); *m/z* 346 (M^+, 10%), 315 (23), 314 (100), 286 (25), 241 (20), 226 (30), 225 (17), 159 (16), 129 (17), 115 (16) and 91 (32).

ent-10β-*Hydroxy*-15-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* **20**.—Oxalyl chloride (200 mm^3) and dimethyl sulphoxide (400 mm^3) in dichloromethane (5 cm^3) were stirred at −78 °C for 5 min under nitrogen gas. 15α-Hydroxy-GA_9 methyl ester **18** (50 mg) in dichloromethane (2 cm^3) was added and the mixture stirred for a further 1 h at −78 °C. Diisopropylethylamine (1 cm^3) was added and the solution was allowed to warm to room temperature, with stirring, over 1 h. The crude product was recovered in the usual way and purified by flash column chromatography. Elution with ethyl acetate–light petroleum (30:70) yielded the required 15-oxo-GA_9 methyl ester **20** (30 mg) as a gum (Found: M^+, 344.1634. $C_{20}H_{24}O_5$ requires *M*, 344.1624); δ 1.15 (s, 18-H_3), 2.61 (d, *J* 10.5, 6-H), 2.69 (d, *J* 10.5, 5-H), 3.63 (s, CO_2CH_3), and 5.38 and 5.99 (2 s, 17-H_2); *m/z* 344 (M^+, 41%), 313 (26), 300 (23), 284 (25), 241 (32), 240 (100), 239 (30), 143 (15), 129 (17), 115 (17) and 91 (30).

ent-10β,15α-*Dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* **22**.—15-Oxo-GA_9 methyl ester **20** (30 mg) in acetic acid (0.5 cm^3) was stirred with activated zinc (125 mg) for 1 h at room temperature. The reaction mixture was filtered and the zinc was washed with ethyl acetate (3 × 10 cm^3). The combined filtrate and washings were evaporated under vacuum and the residue purified by flash column chromatography. Elution with ethyl acetate–light petroleum (40:60) yielded the required 15β-hydroxy-GA_9 methyl ester **22** (14 mg) as a gum (Found: M^+, 346.1762. $C_{20}H_{26}O_5$ requires *M*, 346.1780); δ 1.09 (s, 18-H_3), 2.46 (d, *J* 10.5, 6-H), 2.74 (d, *J* 10.5, 5-H), 3.77 (s, CO_2CH_3), 3.94 (br s, 15-H), and 5.08 and 5.12 (2 br s, 17-H_2); *m/z* 346 (M^+, 10%), 315 (27), 314 (100), 284 (9), 241 (10), 225 (9), 170 (12), 167 (10), 141 (10), 135 (15), 121 (18) and 105 (12).

General Method for the Reaction of a Gibberellin 7-Methyl Ester with Aqueous Potassium Carbonate in Methanol.—The methyl ester in methanol (2 cm^3) was stirred with aqueous potassium carbonate (1 mol dm^{-3}; 1 cm^3) at room temperature for 60 h. The reaction mixture was worked up as usual.

Gibberellin A_{20} *7-methyl ester* 13-*acetate* **15** (72 mg) gave GA_{20} 7-methyl ester **24** (55 mg)[5] (Found: M^+, 346.1763. $C_{20}H_{26}O_5$ requires *M* − 18, 346.1780); δ 1.01 (s, 18-H_3), 2.60

(s, 5-H and 6-H), 3.71 (s, CO_2CH_3), and 4.85 and 5.18 (2 br s, 17-H_2); *m/z* 346 (M^+, 50%), 315 (33), 314 (100), 303 (46), 287 (27), 286 (33), 241 (17), 163 (15), 135 (17) and 91 (27).

15α-Hydroxygibberellin A_{20} *7-methyl ester 13-acetate* **17** (30 mg) gave *15α-hydroxy*-GA_{20} **25** (22 mg) as a gum (Found: $M^+ - 18$, 330.1473. $C_{19}H_{22}O_5$ requires *M*, 330.1467); δ 1.12 (s, 18-H_3), 2.42 (d, *J* 8.5, 6-H), 2.48 (d, *J* 8.5, 5-H), 4.18 (br s, 15-H), and 5.23 and 5.27 (2 br s, 17-H_2); *m/z* 330 ($M^+ - 18$, 100%), 269 (9), 257 (24), 241 (20), 213 (14), 115 (9) and 91 (13).

15β-Hydroxygibberellin A_{20} *7-methyl ester 13-acetate* **21** (20 mg) gave 15β-hydroxy-GA_{20} **27** (15 mg)[4] (Found: M^+, 348.1538. $C_{19}H_{24}O_6$ requires *M*, 348.1573); δ[$(CD_3)_2CO$] 1.05 (s, 18-H_3), 2.55 (d, *J* 10.5, 6-H), 2.62 (d, *J* 10.5, 5-H), 4.30 (br s, 15-H), and 5.11 and 5.29 (2 br d, *J* 2.5, 17-H_2); *m/z* 348 (M^+, 33%), 331 (24), 330 (100), 305 (49), 302 (41), 281 (42), 257 (39), 247 (35), 245 (30), 241 (35), 201 (34), 129 (34), 115 (37), 105 (35) and 91 (65).

Gibberellin A_9 *7-methyl ester* **16** (40 mg) gave unchanged starting material **16** (33 mg), δ 1.08 (s, 18-H_3), 2.54 (d, *J* 10.5, 6-H), 2.70 (d, *J* 10.5, 5-H), 3.71 (s, CO_2CH_3), and 4.85 and 4.97 (2 br s, 17-H_2); *m/z* 330 (M^+, 18%), 229 (30), 298 (100), 270 (65), 243 (35), 227 (37), 226 (39), 217 (23) and 159 (20).

15α-Hydroxygibberellin A_9 *7-methyl ester* **18** (40 mg) gave *15α-hydroxy*-GA_9 **26** (36 mg) as a gum (Found: $M^+ - 18$, 314.1505. $C_{19}H_{22}O_4$ requires $M - 18$, 314.1518); δ 1.15 (s, 18-H_3), 2.48 (d, *J* 10, 6-H), 2.61 (d, *J* 10, 5-H), 4.04 (br s, 15-H), and 5.24 and 5.28 (2 br s, 17-H_2); *m/z* 314 ($M^+ - 18$, 100%), 270 (19), 229 (18), 226 (75), 214 (15), 211 (41), 197 (16), 185 (19), 183 (25), 169 (19) and 155 (20).

15β-Hydroxygibberellin A_9 *7-methyl ester* **22** (14 mg) gave starting material **22** (9 mg) and 15β-hydroxy-GA_9 **28** (5 mg)[7] (Found: M^+, 332.1631. $C_{19}H_{24}O_5$ requires *M*, 332.1623); δ 1.15 (s, 18-H_3), 2.47 (d, *J* 10.8, 6-H), 2.77 (d, *J* 10.8, 5-H), 4.17 (br s, 15-H), and 5.11 (br s, 17-H_2); *m/z* 332 (M^+, 7%), 315 (23), 314 (100), 286 (8), 270 (14), 242 (9), 241 (9), 225 (9), 213 (7), 185 (9), 159 (8) and 91 (12).

15α-Hydroxygibberellin A_{20} *7,15-lactone* **34** (7 mg) gave 15α-hydroxy-GA_{20} **25** (5 mg) whose ^1H NMR and mass spectra were identical to those previously obtained.

15α-Hydroxygibberellin A_9 *7,15-lactone* **35** (5 mg) gave 15α-hydroxy-GA_9 **26** (4 mg) whose ^1H NMR and mass spectra were identical to those previously obtained.

15β-Hydroxygibberellin A_9 *7-methyl ester 15-tetrahydropyran* **38** (14 mg) gave unchanged starting material **38** (12 mg) whose ^1H NMR and mass spectra were identical to those previously obtained.

General Method for the Reaction of a Gibberellin 7-Methyl Ester with Aqueous Sodium Hydroxide in Methanol.—The methyl ester in methanol (2 cm^3) was stirred with aqueous sodium hydroxide (0.5 mol dm^{-3}; 1 cm^3) at room temperature for 16 h. The reaction mixture was worked up as usual.

Gibberellin A_{20} *7-methyl ester 13-acetate* **15** (35 mg) gave GA_{20} 7-methyl ester **24** (29 mg).

15α-Hydroxygibberellin A_{20} *7-methyl ester 13-acetate* **17** (30 mg) gave 15α-hydroxy-GA_{20} **25** (15 mg).

15β-Hydroxygibberellin A_{20} *7-methyl ester 13-acetate* **21** (20 mg) gave a 16:1 mixture of 15β-hydroxy-GA_{20} **27** and 15β-hydroxy-GA_{20} methyl ester **29** (12 mg).

Gibberellin A_9 *methyl ester* **16** (40 mg) returned unchanged starting material **16** (40 mg).

15α-Hydroxygibberellin A_9 *methyl ester* **18** (40 mg) gave 15α-hydroxy-GA_9 **26** (36 mg).

15β-Hydroxygibberellin A_9 *methyl ester* **22** (14 mg) gave a 2:1 mixture of 15β-hydroxy-GA_9 **28** and 15β-hydroxy-GA_9 methyl ester **22** (14 mg).

Attempted Preparation of 15α-*Hydroxy*-GA_9 *7-Methyl Ester 15-O-Tetrahydropyran* **36**.—15α-Hydroxy-GA_9 methyl ester **18** (50 mg) in dichloromethane (10 cm^3) was stirred with dihydropyran (50 mm^3) and toluene-*p*-sulphonic acid (10 mg) at room temperature for 3 h. The reaction was worked up as usual and the product purified by flash column chromatography. Elution with ethyl acetate–light petroleum (30:70) gave *ent*-10β,15β-dihydroxy-20-norgibberell-16-ene-7,19-dioic acid 7,15; 19,10-dilactone **35** (45 mg) which crystallised from acetone–light petroleum as needles, m.p. 215–217 °C (lit.,[7] 218–220 °C) (Found: M^+, 314.1509. $C_{19}H_{22}O_4$ requires *M*, 314.1518); δ 3.16 (s, 18-H_3), 2.29 (d, *J* 8.5, 6-H), 2.66 (d, *J* 8.5, 5-H), 4.54 (br s, 15-H), and 5.16 and 5.29 (2 br d, *J* 1.5, 17-H_2); *m/z* 314 (M^+, 100%), 270 (20), 227 (19), 226 (75), 211 (37), 197 (16), 185 (19), 183 (22), 169 (19), 155 (18), 129 (20) and 91 (31).

Attempted Preparation of 15α-*Hydroxy*-GA_9 *7-Methyl Ester 15-O-Methoxymethyl Ether* **37**.—15α-Hydroxy-GA_9 methyl ester **18** (40 mg) in triethylamine (2 cm^3) was treated dropwise with methyl chloromethyl ether (0.5 cm^3) for 5 h at room temperature. The reaction was worked up as usual to yield a 1:1 mixture (by ^1H NMR) of starting material **18** and the 7,15α-lactone **35** (35mg).

ent-10β,15α-*Dihydroxy*-20-*norgibberell*-16-*ene* 7,19-*dioic Acid 7-Methyl Ester* 19,10-*Lactone* 15α-O-*Tetrahydropyran* **38**.—15β-Hydroxy-GA_9 methyl ester **22** (14 mg) in dichloromethane (10 cm^3) was stirred with dihydropyran (50 mm^3) and toluene-*p*-sulphonic acid (10 mg) for 3 h at room temperature. The reaction mixture was worked up as usual and purified by flash column chromatography. Elution with ethyl acetate–light petroleum (30:70) yielded the required 15β-tetrahydropyran **38** as a 4:3 mixture of two stereoisomers as a gum (15 mg) (Found: M^+, 430.2321. $C_{25}H_{34}O_6$ requires *M*, 430.2355); δ 1.09 (s, 18-H_3), 2.45 (d, *J* 11, 6-H), 2.79 (d, *J* 11, 5-H), 3.77 (s, CO_2CH_3), 4.16 (br s, 15-H), 4.99 (br s, 17-H_2), and 5.09 (br s, O–CH–O); δ 1.25 (s, 18-H_3), 2.74 (d, *J* 11, 6-H), 3.21 (d, *J* 11, 5-H), 3.74 (s, CO_2CH_3), 4.16 (br s, 15-H), 4.99 and 5.12 (2 br s, 17-H_2), and 5.16 (br s, O–CH–O); *m/z* 430 (M^+, 1%), 402 (1), 360 (3), 314 (12), 284 (3), 280 (3), 221 (5), 186 (11), 169 (9), 101 (10), 97 (9) and 85 (100).

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