Partial Synthesis of the 15β-Hydroxygibberellins A_{67} and A_{68} and of 15β-Hydroxygibberellins A_1 and A_3

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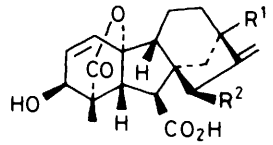
The structures of two new higher plant gibberellins, A_{67} (**7**) and A_{68} (**4**), have been established by their partial synthesis from gibberellin A_3 (**2**). In addition, 15β-hydroxyGA_1 (**8**) and 15β-hydroxyGA_3 (**3**) have also been prepared from GA_3 (**2**). The preparation of GA_{68} (**4**) from GA_3 (**2**) involves the novel displacement of a bridgehead hydroxy group by chlorine under the conditions of the Swern oxidation in which di-isopropylethylamine is replaced by triethylamine.

In a previous publication[1] we described a general route from gibberellin A_7 (GA_7) (**1**) to 15β-hydroxyGAs which do not possess a 13-hydroxy group. Thereby the structures were established for GA_{45} (**5**) and GA_{63} (**6**), two GAs tentatively identified[2,3] in extracts of apple and pear seeds by combined g.l.c.–mass spectrometry. This paper addresses the problem of the partial synthesis of 13,15β-dihydroxylated GAs from GA_3 (**2**) and, in particular, the synthesis of 15β-hydroxyGA_{20} (**7**), the structure tentatively deduced[4] by combined g.l.c.–mass spectrometry, for a new GA in extracts of seeds of *Helianthus annuus*. In the event, structure (**7**) was established for this new GA which is accorded[5] the number GA_{67}. In addition 15β-hydroxyGA_1 (**8**) and 15β-hydroxyGA_3 (**3**) were also synthesised from GA_3 (**2**) but they have not yet been found to occur naturally. In the course of this work a new method of 13-deoxygenation of GAs was uncovered, leading to the preparation of 15β-hydroxyGA_7 (**4**) from GA_3 (**2**). The 15β-hydroxyGA_7 (**4**) was identical with a new GA, occurring in seeds of apple and pear, and is therefore allocated the number GA_{68}.[5]

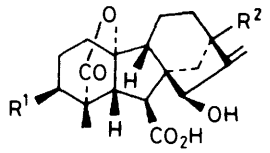
The route from GA_3 (**2**) to GA_{67} (**7**), 15β-hydroxyGA_1 (**8**), and 15β-hydroxyGA_3 (**3**), shown in Scheme 1, is essentially that previously described[1] except that the 7-oic acid was protected as the methyl ester, rather than the phenacyl ester, to provide improved yields of allylic hydroxylation and of Swern oxidation. Also it was necessary to protect the 3β- and 13-hydroxy groups as the acetates.

For the synthesis of GA_{67} (**7**) (Scheme 1), GA_3 (**2**) was converted into GA_{20} methyl ester 13-acetate (**16**) as described by Beale *et al.*[6] and hence, by oxidation with selenium dioxide and t-butyl hydroperoxide,[7] into the 15α-alcohol (**19**). No lactonisation of the 15α-alcohol (**19**) was observed, in contrast to the corresponding 13,15α-diol (**9**), obtained by hydrolysis of compound (**19**), and the 13-deoxy 15α-alcohols (**10**) and (**11**)[1] which readily formed the corresponding 7,15α-lactones (**12**), (**13**), and (**14**). The reason for non-lactonisation of compound (**19**) by the presence of the remote 13-acetoxy group is not clear. Oxidation of the 15α-alcohol (**19**) by the Swern procedure[8] gave the 15-ketone (**22**) which was reduced with zinc and acetic acid to give a mixture of the 1,2- and 1,4-reduction products (**25**) and (**28**). The ^1H n.m.r. spectrum of the less polar 1,4-reduction product (**28**) indicated stereospecific reduction to a single isomer, the stereochemistry of which was established as follows. Sodium borohydride reduction of compound (**28**), followed by ester hydrolysis, gave the hydroxy acid (**31**) which did not form a lactone, indicating the presence of a 15β-hydroxy group, and which showed a doublet (δ 4.05) for the 15-carbinol proton in the ^1H n.m.r. spectrum with a large coupling constant (*J* 11 Hz) indicative of a 16α-hydrogen.

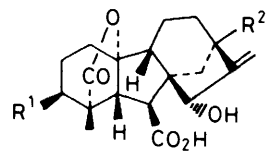
The 1,2-reduction product (**25**) from the α,β-unsaturated ketone (**22**) was epimeric with the alcohol (**19**) from the



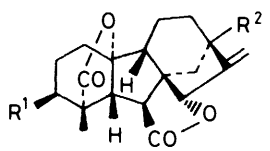
	R^1	R^2	
(**1**)	H	H	(GA_7)
(**2**)	OH	H	(GA_3)
(**3**)	OH	OH	
(**4**)	H	OH	(GA_{68})



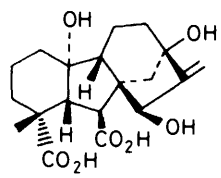
	R^1	R^2	
(**5**)	H	H	(GA_{45})
(**6**)	OH	H	(GA_{63})
(**7**)	H	OH	(GA_{67})
(**8**)	OH	OH	



	R^1	R^2
(**9**)	H	OH
(**10**)	H	H
(**11**)	OH	H

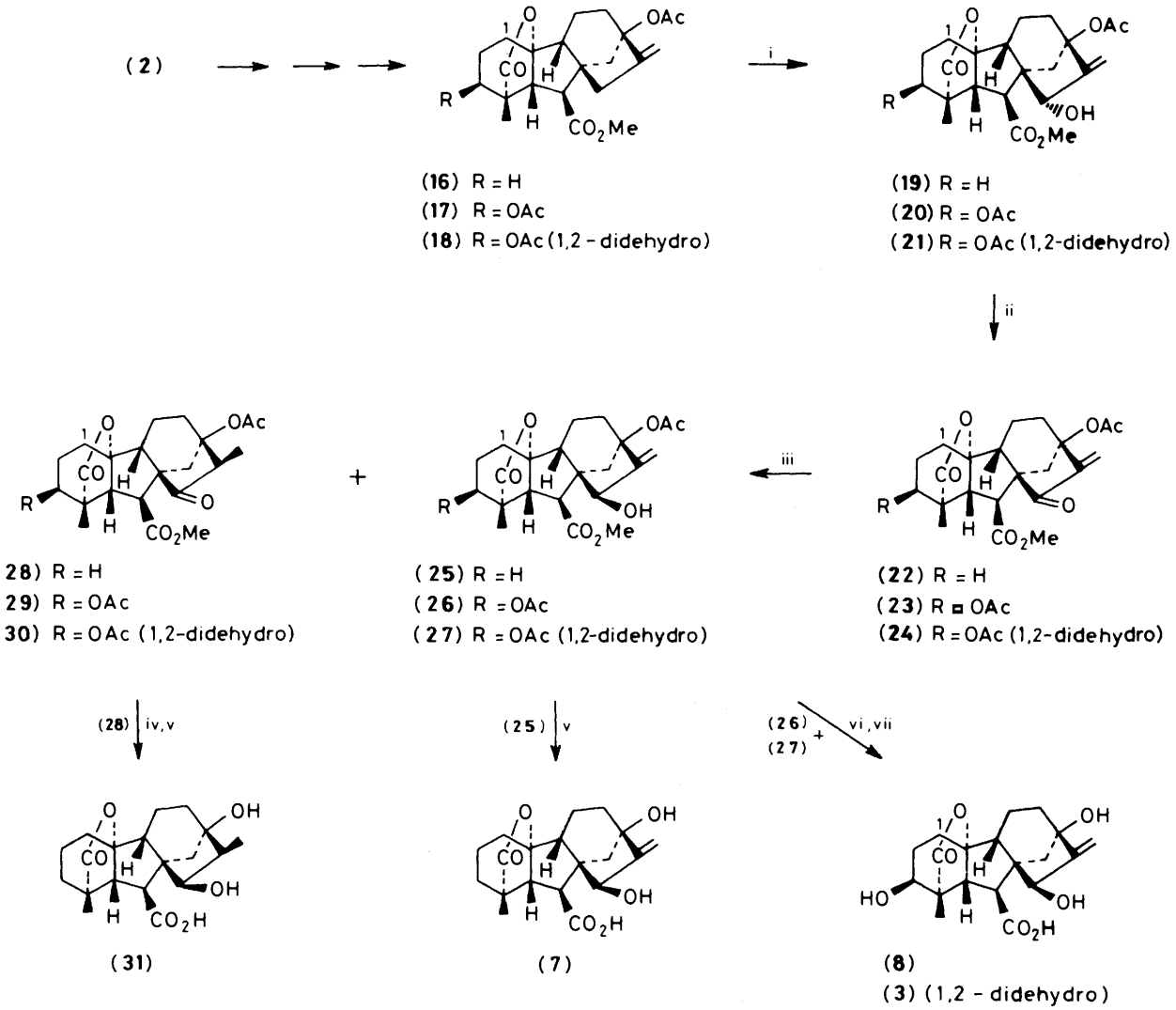


	R^1	R^2
(**12**)	H	OH
(**13**)	H	H
(**14**)	OH	H



(**15**)

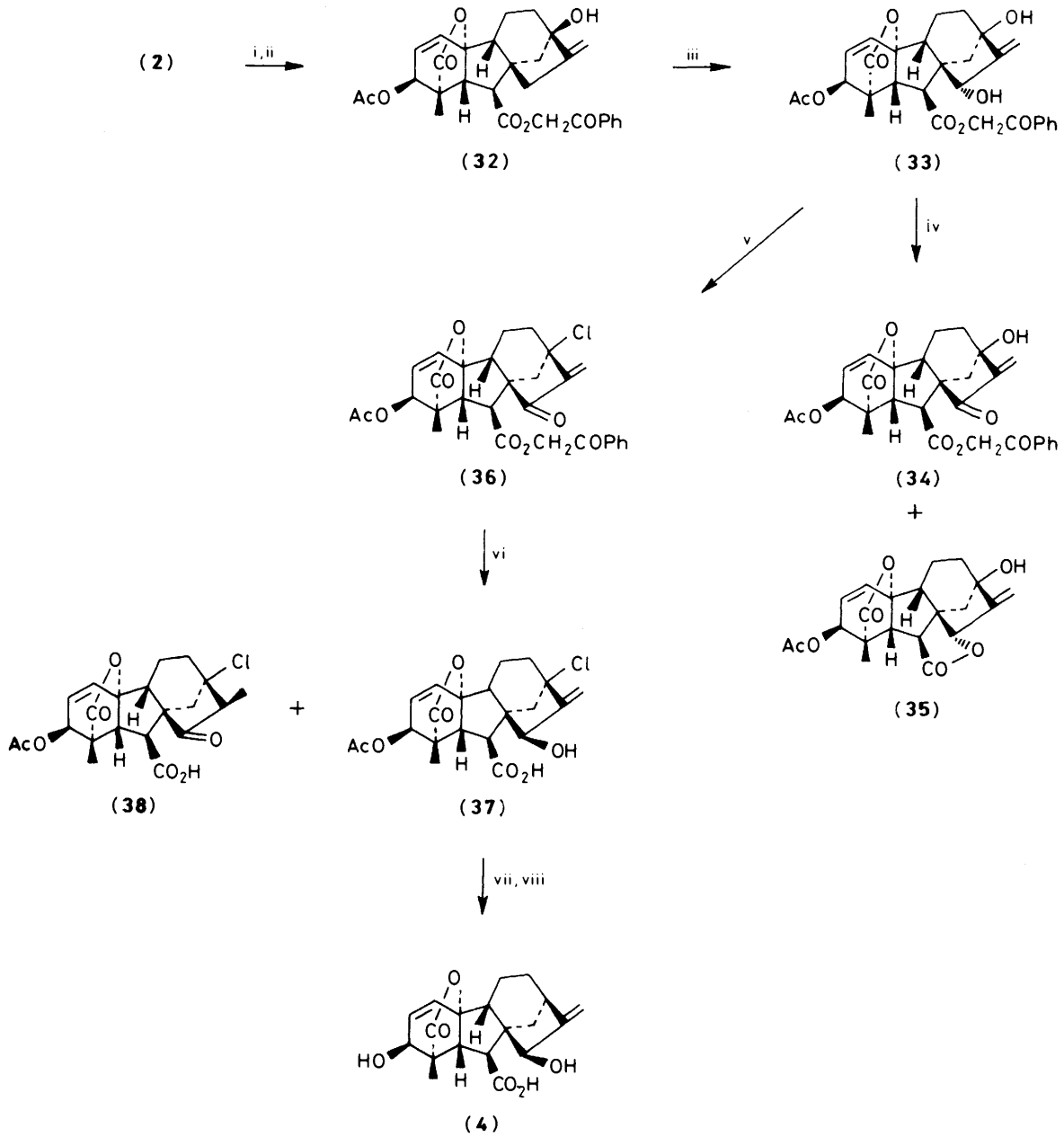
selenium dioxide oxidation of GA_{20} methyl ester 13-acetate (**16**) by comparison of the ^1H n.m.r. and mass spectra. Hydrolysis of the 1,2-reduction product (**25**) with aqueous sodium hydroxide initially gave the trihydroxy dicarboxylic acid (**15**) which was relactonised at pH 2.0 to give 15β-hydroxyGA_{20} (GA_{67}) (**7**). The methyl ester bis(trimethylsilyl) ether of the synthesised GA_{67} (**7**) had the same Kovat's Retention Index (2 614) and mass spectrum as that of the putative GA,[4] detected by combined g.l.c.–mass spectrometry in extracts of *Helianthus annuus* seeds. The β-stereochemistry of the 15-hydroxy group in GA_{67} (**7**) is deduced on the following evidence. First, the 15-alcohols (**19**) and (**25**) from selenium dioxide oxidation of GA_{20} methyl ester 13-acetate (**16**) and from



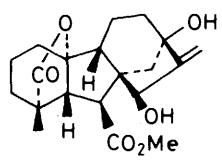
Scheme 1. *Reagents*: i, SeO_2–Bu^tO_2H; ii, $(COCl)_2$–DMSO, Pr^i_2EtN; iii, Zn–AcOH; iv, $NaBH_4$–MeOH; v, NaOH–H_2O–MeOH; vi, MeOH–K_2CO_3; vii, HMPA–PrSH

the 1,2-reduction of the 15-one (**22**) are epimeric. Secondly, photo-oxygenation of steroidal olefins occurs from the less hindered face of the molecule[9] and has been shown[10] also to give a compound identical with that of selenium dioxide oxidation. Thirdly, the allyl couplings (*ca.* 2.5 Hz) between the 17-H_2 of the 15-alcohol (**25**) and the newly elaborated carbinol proton at C-15 were not observed for the epimeric alcohol (**19**). This indicates that the 15α(*exo*)-hydrogen is more nearly at right angles to the plane of the double bond than is the 15β(*endo*)-hydrogen as reported elsewhere.[11,12] Finally, the 13,15-diol (**9**) obtained by hydrolysis of the selenium dioxide oxidation product (**19**) is readily lactonised to the 7,15-lactone (**12**) whereas the 1,2-reduction product (**25**), the corresponding 13,15β-diol (**39**), and GA_{67} (**7**) do not form lactones.

15β-HydroxyGA_1 (**8**) and 15β-hydroxyGA_3 (**3**) were prepared in an analogous manner from GA_1 methyl ester 3,13-diacetate (**17**) and GA_3 methyl ester 3,13-diacetate (**18**) respectively. The latter compounds were obtained from GA_3 (**2**) by published methods.[13,14] In these syntheses, however, the methyl esters were hydrolysed to the free 7-oic acids using sodium propanethiolate[15] in hexamethylphosphoramide (HMPA) to avoid epimerisation at C-3.[16] Good recovery of the free acids (**8**) and (**3**) required exhaustive extraction from the aqueous phase. The high water solubility of these compounds (**8**) and (**3**) may explain why they have not yet been detected in extracts from plant tissue. The β-phenacyl esters which can be reductively hydrolysed in non-aqueous media by zinc and acetic acid were used in an attempt to avoid the problem of recovery of these acids (**8**) and (**3**) from aqueous hydrolysis conditions (Scheme 2). Thus, GA_3 (**2**) was converted into the 3-acetyl phenacyl ester (**32**) which was oxidised with selenium dioxide and t-butyl hydroperoxide to give the 15α-alcohol (**33**). Oxidation of the latter compound (**33**) under the Swern conditions [oxalyl chloride, dimethyl sulphoxide (DMSO), di-isopropylethylamine] afforded the 15-ketone (**34**), together with some 7,15α-lactone (**35**). However, when triethylamine (TEA) was used as a base, a much less polar product was formed which was characterised as the 13-chloro-15-one (**36**) by ^1H n.m.r. and mass spectrometry. The generally accepted mechanism of the Swern oxidation involves an alkoxysulphonium salt, nucleophilic displacement of which by chloride ion may account for the formation of the 13-chloro compound (**36**). Why triethylamine and not di-isopropylethylamine should promote such nucleophilic substitution is not easy to explain. Treatment of the chloride (**36**) with zinc in acetic acid reductively hydrolysed the phenacyl ester and reduced the D-ring enone to



Scheme 2. *Reagents:* i, $PhCOCH_2Br$, KH_2PO_4; ii, Ac_2O, pyridine; iii, SeO_2–Bu^tO_2H; iv, $(COCl)_2$–DMSO–Pr^i_2EtN; v, $(COCl)_2$–DMSO–TEA; vi, Zn–AcOH; vii, Bu^n_3SnH–$PhCH_3$–ABIN; viii, MeOH–K_2CO_3



(39)

a mixture of the 1,2- and 1,4-reduction products (**37**) and (**38**). The 1,2-reduction product (**37**), as the tri-n-butylstannyl ester, was reductively dechlorinated with tri-n-butylstannane and 2,2′-azo-bis-(2-methylpropionitrile) (ABIN), then hydrolysed with potassium carbonate in methanol. The product, 15β-hydroxyGA_7 (GA_{68}) (**4**) was identical, by g.l.c. retention time and mass spectrum of the methyl ester bis(trimethylsilyl ether), with the methyl ester bis(trimethylsilyl ether) of a putative GA detected in extracts of pear and apple[2,3] seeds.

The biological activity of the four 15β-hydroxyGAs, prepared in this study, will be reported elsewhere but they are similar to those of their non-15β-hydroxylated counterparts.

Experimental

General experimental details have been described in a previous paper.[17]

ent-3α-*Acetoxy*-10β,13-*dihydroxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic Acid* 7-*Phenacyl Ester* 19,10-*Lactone* (**32**).—Gibberellin A_3(**2**) (500 mg) was added to a solution of phenacyl

bromide (200 mg), 18-crown-6 ether (50 mg), and potassium hydrogen carbonate (400 mg) in acetonitrile (50 ml) and the mixture was heated under reflux for 1 h. The reaction mixture was diluted with water (50 ml), and acidified to pH 3, extracted with ethyl acetate (3 × 50 ml), and the extract was dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure gave the phenacyl ester. The product was treated with a solution of acetic anhydride (1 ml) in pyridine (5 ml) and the mixture was stirred for 1 h. The reaction mixture was transferred into water (50 ml), acidified to pH 3 with hydrochloric acid, and extracted with ethyl acetate (3 × 50 ml). The combined organic layers were evaporated under reduced pressure with the addition of toluene to assist removal of residual pyridine and acetic acid by azeotropic distillation. The ester lactone (**32**) (500 mg) was obtained as a gum with a weak molecular ion (Found: M^+, 506.1985. $C_{29}H_{30}O_8$ requires M, 506.1940); δ ($CDCl_3$) 1.26 (s, 18-H_3), 2.12 (s, $OCOCH_3$), 2.98 (d, J 11 Hz, 6-H), 3.37 (d, J 11 Hz, 5-H), 5.01 and 5.35 (each br s, together 17-H_2), 5.35 (d, J 4 Hz, 3-H), 5.42 (m, CO_2CH_2CO), 5.87 (dd, J 9.5 and 4 Hz, 2-H), 6.40 (d, J 9.5 Hz, 1-H), and 7.60 and 7.90 (ArH); m/z 488 (M^+ − 18, 1%), 446 (3), 401 (33), 283 (53), 266 (25), 237 (100), 209 (23), 155 (22), and 105 (86).

General Procedure for the Formation of 15α-Alcohols.—The starting material (~400 mg) in dichloromethane (5 ml) was added to a solution of selenium dioxide (80 mg) and t-butyl hydroperoxide (320 μl) in dichloromethane (10 ml) and the mixture was stirred at room temperature for 14 h. Examination by t.l.c. showed complete conversion into a more polar product. The reaction mixture was washed with water, the pH adjusted to 3.0 with hydrochloric acid, and the solution was dried over anhydrous sodium sulphate and the solvent removed. In this way the following compounds were prepared.

(i) ent-13-*Acetoxy*-10β,15β-dihydroxy-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**19**) (380 mg) was obtained from GA_{20} methyl ester 13-acetate (**16**) (400 mg) and crystallised (from acetone–light petroleum) as needles, m.p. 183—184 °C (Found: C, 65.0; H, 7.05. $C_{22}H_{28}O_7$ requires C, 65.3; H, 7.0%); δ($CDCl_3$) 1.10 (s, 18-H_3), 2.04 (s, $OCOCH_3$), 2.48 (m, 5- and 6-H), 2.89 (d, J 11 Hz, 14-H_1), 3.69 (s, CO_2CH_3), 3.76 (d, J 8.8 Hz, 15-OH), 4.02 (d, J 8.8 Hz, 15-H), 5.19 and 5.40 (each s, together 17-H_2); m/z 404 (M^+, 1%), 372(4), 330(100), 312(22), 298(20), 284(32) and 239(22).

(ii) ent-3α,13-*Diacetoxy*-10β,15β-*dihydroxy*-20-*norgibberella*-1,16-*diene*-17,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**21**) (375 mg) was obtained from GA_3 methyl ester 3,13-diacetate (**18**) (390 mg) and crystallised (from ethyl acetate–light petroleum), m.p. 172—174 °C (Found: C, 63.2; H, 6.3. $C_{24}H_{28}O_9$ requires C, 62.6; H, 6.1%); δ ($CDCl_3$) 1.16 (s, 18-H_3), 2.05 (s, 13-$OCOCH_3$), 2.12 (s, 3-$OCOCH_3$), 2.65 (d, J 11 Hz, 6-H), 2.94 (d, J 11 Hz, 14-H_1), 3.37 (d, J 11 Hz, 5-H), 3.71 (s, CO_2CH_3), 3.84 (d, J 8.8 Hz, 15-OH), 4.08 (d, J 8.8 Hz, 15-H), 5.23 and 5.43 (each br s, together 17-H_2), 5.31 (d, J 3.7 Hz, 3-H), 5.87 (dd, J 9.5 and 3.7 Hz, 2-H), and 6.35 (d, J 9.5 Hz, 1-H); m/z 460 (M^+, 1%), 429 (2), 386 (38), 340 (48), 308 (33), 236 (54), 235 (39), 209 (23), 180 (27), and 43 (100).

(iii) ent-3α,13-*Diacetoxy*-10β,15β-*dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**20**) (380 mg) was obtained from GA_1 methyl ester 3,13-diacetate (**17**) (400 mg) as a gum (Found: M^+, 462.1884. $C_{24}H_{30}O_9$ requires M, 462.1889); δ($CDCl_3$) 1.07 (s, 18-H_3), 2.04 (s, 13-$OCOCH_3$), 2.13 (s, 3-$OCOCH_3$), 2.56 (d, J 10.5 Hz, 6-H), 2.92 (d, J 11.2 Hz, 14-H_1), 3.19 (d, J 10.5 Hz, 5-H), 3.69 (s, CO_2CH_3), 3.78 (d, J 8.8 Hz, 15-OH), 4.06 (d, J 8.8 Hz, 15-H), 4.94 (br s, 3-H), and 5.21 and 5.41 (each s, together 17-H_2); m/z 462 (M^+, 1%), 431 (2), 430 (2), 418 (1), 402 (18), 388 (91), 342 (23), 282 (22), 247 (29), and 43 (100).

(iv) 15α-*HydroxyGA*$_3$ *phenacyl ester* 3-*acetate* (**33**) (390 mg) was obtained from GA_3 phenacyl ester 3-acetate (**32**) (400 mg) as a gum; δ($CDCl_3$) 1.28 (s, 18-H), 2.15 (s, $OCOCH_3$), 2.85 (d, J 10 Hz, 6-H), 3.36 (d, J 10 Hz, 5-H), 4.24 (br s, 15-H), 5.29 and 5.49 (each d, J 16.6 Hz, together CO_2CH_2CO), 5.37 (d, J 4 Hz, 3-H), 5.42 and 5.48 (each s, together 17-H_2), 5.86 (dd, J 9.5 and 4 Hz, 2-H), 6.40 (d, J 9.5 Hz, 1-H), and 7.60 and 7.90 (ArH). This compound lactonised after a time to give compound (**35**), and therefore could not be analysed fully.

Swern Oxidation of Allylic Alcohols.—Oxalyl chloride (78 μl) was added to dry dichloromethane (10 ml) in a dry flask under nitrogen and the solution was cooled to −72 °C. After 10 min dimethyl sulphoxide was added and allowed to react for 3 min before addition of the 15α-alcohol (~200 mg) in dry dichloromethane (2 ml). The reaction mixture was stirred at −72 °C for 45 min and at −60 °C for a further 15 min. Di-isopropylethylamine (1.0 ml) was added dropwise and the reaction mixture was then allowed to warm to ambient temperature. The solvent was removed under reduced pressure and the products were separated by flash column chromatography[18] with 20—50% ethyl acetate in light petroleum as eluant.

(i) *Oxidation of* 15α-*hydroxyGA*$_{20}$ *methyl ester* 13-*acetate* (**19**) (200 mg). The first compound eluted, ent-13-*acetoxy*-10β-*hydroxy*-15-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**22**) (110 mg), was obtained as a gum [Found: (M^+ − 31), 371.1502. $C_{22}H_{26}O_7$ requires (M − 31), 371.1494]; δ($CDCl_3$) 1.14 (s, 18-H_3), 2.11 (s, $OCOCH_3$), 2.26 (d, J 11.2 Hz, 14-H), 2.63 (d, J 10.5 Hz, 5-H), 2.72 (d, J 10.5 Hz, 6-H), 3.08 (d, J 11.2 Hz, 14-H), 3.62 (s, CO_2CH_3), and 5.60 and 6.08 (each s, together 17-H_2); m/z 402 (M^+, 6%), 371 (22), 360 (47), 342 (18), 328 (41), 314 (100), 300 (32), 282 (25), 268 (22), and 254 (31). Starting material (**19**) was recovered from the later fractions.

(ii) *Oxidation of* 15α-*hydroxyGA*$_3$ *methyl ester* 3,13-*diacetate* (**21**) (200 mg). The first compound eluted, ent-3α,13-*diacetoxy*-10β-*hydroxy*-15-*oxo*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**24**) (110 mg), was crystallised (from ethyl acetate) m.p. 267—268 °C (Found: C, 63.1; H, 5.8. $C_{24}H_{26}O_9$ requires C, 62.9; H, 5.7%); δ($CDCl_3$) 1.23 (s, 18-H_3), 2.12 (s, 3-$OCOCH_3$), 2.15 (s, 13-$OCOCH_3$), 2.30 (d, J 11.2 Hz, 14-H), 2.71 (d, J 10.7 Hz, 6-H), 3.11 (d, J 11.2 Hz, 14-H_1), 3.48 (d, J 10.7 Hz, 5-H), 3.64 (s, CO_2CH_3), 5.35 (d, J 4 Hz, 3-H), 5.64 and 6.13 (each s, together 17-H_2), 5.91 (dd, J 9 and 4 Hz, 2-H), and 6.33 (d, J 9 Hz, 1-H); m/z 458 (M^+, absent), 428 (7), 387 (31), 386 (100), 281 (16), 280 (14), 253 (14), 238 (23), 237 (24), 209 (25), and 43 (84). Starting material (**21**) was recovered from the later fractions.

(iii) *Oxidation of* 15α-*hydroxyGA*$_1$ *methyl ester* 3,13-*diacetate* (**20**) (200 mg). The first compound eluted, ent-3α,13-*diacetoxy*-10β-*hydroxy*-15-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**23**) (103 mg), was obtained as a gum (Found: M^+, 460.1759. $C_{24}H_{28}O_9$ requires M, 460.1733); δ($CDCl_3$) 1.21 (s, 18-H_3), 2.12 (s, 3-$OCOCH_3$), 2.15 (s, 13-$OCOCH_3$), 2.27 (d, J 11.2 Hz, 14-H), 2.62 (d, J 10.5 Hz, 6-H), 3.11 (d, J 11.2 Hz, 14-H_1), 3.35 (d, J 10.5 Hz, 5-H), 3.63 (s, CO_2CH_3), 4.99 (br s, 3-H), and 5.63 and 6.11 (each s, together 17-H_2); m/z 460 (M^+, 10%), 429 (36), 418 (84), 400 (27), 388 (34), 372 (100), 358 (38), 326 (33), 312 (63), 298 (26), 280 (28), 268 (80), 253 (37), 252 (24), and 209 (32). The starting material (**20**) was recovered from later fractions.

(iv) *Oxidation of* 15α-*hydroxyGA*$_3$ *phenacyl ester* 3-*acetate* (**33**) (200 mg). The first compound eluted, ent-3α-*acetoxy*-10β,13,15β-*trihydroxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 7,15;19,10-*dilactone* (**35**) (53 mg), was obtained as a gum (Found: M^+, 386.1365. $C_{21}H_{22}O_7$ requires M, 386.1365); δ($CDCl_3$) 1.40 (s, 18-H_3), 2.12 (s, $OCOCH_3$), 2.73 (d, J 9 Hz,

6-H), 3.13 (d, *J* 9 Hz, 5-H), 4.66 (br s, 15-H), 5.32 and 5.42 (each s, together 17-H_2), 5.39 (d, *J* 4 Hz, 3-H), 5.93 (dd, *J* 9 and 4 Hz, 2-H), and 6.42 (d, *J* 9 Hz, 1-H); *m/z* 386 (M^+, 73%), 282 (26), 237 (40), 209 (65), 105 (36), and 43 (100). The second compound eluted, ent-3α-*acetoxy*-10β,13-*dihydroxy*-15-*oxo*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 7-*phenacyl ester* 19,10-*lactone* (**34**) (103 mg), was also obtained as a gum (Found: M^+, 520.1741. $C_{29}H_{28}O_9$ requires *M*, 520.1733); δ($CDCl_3$) 1.30 (s, 18-H_3), 2.13 (s, $OCOCH_3$), 2.95 (d, *J* 10.7 Hz, 6-H), 3.41 (d, *J* 10.7 Hz, 5-H), 5.10 and 5.49 (each d, *J* 16.6 Hz, together CO_2CH_2CO), 5.36 (d, *J* 4 Hz, 3-H), 5.70 and 6.10 (each s, together 17-H_2), 5.91 (dd, *J* 9.3 and 4 Hz, 2-H), 6.34 (d, *J* 9.3 Hz, 1-H), and 7.60 and 7.90 (ArH); *m/z* 478 (*M* − 105, 1%), 386 (5), 365 (5), 324 (4), 296 (3), 270 (5), 181 (36), and 105 (100).

(v) *Oxidation of* 15α-*hydroxyGA*$_3$*phenacyl ester* 3-*acetate* (**33**) (200 mg) *with triethylamine base.* The first compound eluted, ent-3α-*acetoxy*-13-*chloro*-10β-*hydroxy*-15-*oxo*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 7-*phenacyl ester* 19,10-*lactone* (**36**) (110 mg), was obtained as a gum (Found: M^+, 536.1253. $C_{29}H_{25}ClO_8$ requires *M*, 536.1238); δ($CDCl_3$) 1.31 (s, 18-H_3), 2.13 (s, $OCOCH_3$), 2.98 (d, *J* 10.7 Hz, 5-H), 3.50 (d, *J* 10.7 Hz, 6-H), 5.09 and 5.50 (each d, *J* 16.4 Hz, together CO_2CH_2CO), 5.37 (d, *J* 4.5 Hz, 3-H), 5.89 and 6.24 (each s, together 17-H_2), 5.95 (dd, *J* 9 and 4.5 Hz, 2-H), 6.34 (d, *J* 9 Hz, 1-H), and 7.60 and 7.90 (ArH); *m/z* 536 (M^+, 1%), 433 (2), 403 (6), 374 (7), 270 (14), 207 (9), and 105 (100). Small amounts of the lactone (**35**) and the ketone (**34**) were obtained from later fractions.

Reduction of 15-*Ketones with Zinc and Acetic Acid.*—Zinc dust (activated in 2M-hydrochloric acid, washed with methanol and light petroleum) was added to the starting material in acetic acid (5 ml) and the mixture was stirred at room temperature for 2 h. Excess of zinc was filtered off and the acetic acid was removed with toluene and methanol under reduced pressure.

(i) *Reduction of* 15-*oxoGA*$_{20}$ *methyl ester* 13-*acetate* (**22**) (140 mg). The products were separated by flash column chromatography with 15—35% ethyl acetate in light petroleum as eluant. The first compound eluted, ent-13-*acetoxy*-10β-*hydroxy*-15-*oxo*-20-*norgibberellane*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**28**) (62 mg), was crystallised (from ethyl acetate–light petroleum) as needles, m.p. 176—178 °C (Found: C, 65.1; H, 7.1. $C_{22}H_{28}O_7$ requires C, 65.3; H, 7.0%); δ($CDCl_3$) 1.13 (s, 18-H_3), 1.14 (d, *J* 6.4 Hz, 17-H_3), 2.06 (s, $OCOCH_3$), 2.64 (br s, 5- and 6-H), 3.18 (d, *J* 11.2 Hz, 14-H), and 3.62 (s, CO_2CH_3); *m/z* 404 (M^+, 27%), 376 (4), 362 (20), 344 (100), 318 (73), 313 (23), 284 (39), and 256 (22).

The second compound eluted, 15β-hydroxyGA$_{20}$ methyl ester 13-acetate (**25**) (60 mg), was dissolved in methanol (10 ml) and the solution was refluxed for 6 h with 2M-sodium hydroxide (2 ml). Excess of ethyl acetate was added and the aqueous layer was adjusted to pH 2.0 and stirred at room temperature for 24 h. The organic phase was back-washed with distilled water, dried over anhydrous sodium sulphate, and the solvent was removed to yield ent-10β,13,15α-*trihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10-*lactone* (**7**) (32 mg) which was crystallised (from acetone–light petroleum) as prisms, m.p. 135—137 °C (Found: M^+, 348.1583. $C_{19}H_{24}O_6$ requires *M*, 348.1573); δ[$(CD_3)_2CO$] 1.05 (s, 18-H_3), 2.56 (d, *J* 11 Hz, 5-H), 2.63 (d, *J* 11 Hz, 6-H), 4.30 (br s, 15-H), and 5.11 and 5.29 (each br s, together 17-H_2); *m/z* 348 (M^+, 50%), 330 (100), 312 (15), 302 (69), 284 (75), 273 (27), 256 (39), 226 (25), 159 (34), 145 (30), and 135 (41).

(ii) *Reduction of* 15-*oxoGA*$_3$ *methyl ester* 3,13-*diacetate* (**24**) (140 mg). The products were separated by flash column chromatography with 15-35% ethyl acetate in light petroleum as eluant. The first compound eluted, ent-3α,13-*diacetoxy*-10β-*hydroxy*-15-*oxo*-20-*norgibberell*-1-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**30**) (68 mg), was crystallised (from ethyl acetate–light petroleum), m.p. 183—185 °C (Found: C, 62.0; H, 6.5. $C_{24}H_{28}O_9$ requires C, 62.6; H, 6.1%); δ($CDCl_3$) 1.16 (d, *J* 7.1 Hz, 17-H_3), 1.21 (s, 18-H_3), 2.06 (s, 13-$OCOCH_3$), 2.14 (s, 3-$OCOCH_3$), 2.70 (d, *J* 10.5 Hz, 6-H), 3.19 (d, *J* 11.2 Hz, 14-H), 3.42 (d, *J* 10.5 Hz, 5-H), 3.65 (s, CO_2CH_3), 5.34 (d, *J* 3.7 Hz, 3-H), 5.89 (dd, *J* 9.5 and 3.7 Hz, 2-H), and 6.32 (d, *J* 9.5 Hz, 1-H); *m/z* 460 (M^+, 7%), 432 (4), 401 (3), 400 (14), 372 (26), 296 (46), 281 (26), 256 (31), 237 (39), 236 (26), 209 (50), 208 (33), and 43 (100).

The second compound eluted, 15β-hydroxyGA$_3$ methyl ester 3,13-diacetate (**27**) (50 mg), was dissolved in methanol (5 ml). Potassium carbonate (10 mg) was added and the mixture was stirred at room temperature for 12 h. The product was washed with acidified water (20 ml) and extracted with ethyl acetate (3 × 50 ml). The extract was back-washed, dried over anhydrous sodium sulphate, and the solvent was removed under reduced pressure. The residual oil was treated with sodium propanethiolate (1.5 ml) [sodium hydride (50% in oil; 160 mg) was washed with light petroleum in a dry flask under N_2. Hexamethylphosphoramide (3.5 ml) and propanethiol (0.4 ml) were added and the mixture was stirred at room temperature for 1 h]. After 4 h the mixture was carefully acidified with acetic acid until a white suspension (produced on addition of acetic acid) was no longer present. Acetic acid was removed with toluene–methanol and the product was washed with aqueous sodium hydrogen carbonate. The aqueous phase was acidified and extracted into ethyl acetate during 48 h. The extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield ent-3α,10β,13,15α-*tetrahydroxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 19,10-*lactone* (**3**) (20 mg) which was crystallised (from acetone–light petroleum), m.p. 195—225 °C (decomp.) (Found for Me ester: M^+, 376.1534. $C_{20}H_{24}O_7$ requires *M*, 376.1522); δ(C_5D_5N) 1.83 (s, 18-H_3), 3.41 (d, *J* 11.2 Hz, 6-H), 4.13 (d, *J* 11.2 Hz, 5-H), 4.55 (d, *J* 3.9 Hz, 3-H), 4.99 (br s, 15-H), 5.59 and 5.81 (each br s, together 17-H_2), 6.15 (dd, *J* 10 and 3.9 Hz, 2-H), and 6.48 (d, *J* 10 Hz, 1-H); *m/z* (for Me ester) 376 (M^+, 12), 358 (11), 344 (100), 326 (37), 298 (31), 296 (23), 253 (55), 237 (48), 183 (46), 155 (34), and 55 (86).

(iii) *Reduction of* 15-*oxoGA*$_1$ *methyl ester* 3,13-*diacetate* (**23**) (160 mg). The products were separated by flash column chromatography as in the preceding experiment. The first compound eluted, ent-3α,13-*diacetoxy*-10β-*hydroxy*-15-*oxo*-20-*norgibberellane*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**29**) (62 mg), was crystallised (from acetone) as needles, m.p. 255—257 °C (Found: M^+, 462.1884. $C_{24}H_{30}O_9$ requires *M*, 462.1889); δ($CDCl_3$) 1.10 (s, 18-H_3), 1.15 (d, *J* 7.1 Hz, 17-H_3), 2.06 (s, 13-$OCOCH_3$), 2.15 (s, 3-$OCOCH_3$), 2.61 (d, *J* 10.3 Hz, 6-H), 3.19 (d, *J* 11.5 Hz, 14-H), 3.29 (d, *J* 10.3 Hz, 5-H), 3.63 (s, CO_2CH_3), and 4.98 (br s, 3-H); *m/z* 462 (M^+, 21%), 420 (13), 402 (56), 374 (31), 342 (22), 270 (49), and 43 (100).

The second compound eluted, 15β-hydroxyGA$_1$ methyl ester 3,13-diacetate (**26**) (50 mg), was deacetylated and demethylated as described above and yielded ent-3α,10β,13,15α-*tetrahydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10-*lactone* (**8**) (20 mg) as a gum (Found for Me ester: M^+, 378.1687. $C_{20}H_{26}O_7$ requires *M*, 378.1678); δ(CD_3OD) 1.19 (s, 18-H_3), 3.65 (br s, 3-H), 4.37 (br s, 15-H), and 5.19 and 5.30 (each br s, together 17-H_2); *m/z* (for Me ester) 378 (M^+, 20%), 360 (10), 346 (41), 300 (23), 282 (25), 149 (55), and 129 (22).

(iv) *Reduction of* 13-*chloro*-15-*oxoGA*$_7$ *phenacyl ester* 3-*acetate* (**36**) (160 mg). The first compound eluted, ent-3α-*acetoxy*-13-*chloro*-10β-*hydroxy*-15-*oxo*-20-*norgibberell*-1-*ene*-7,19-*dioic acid* 19,10-*lactone* (**38**) (70 mg), was crystallised (from acetone–light petroleum), m.p. 256—257 °C (Found: C, 59.4; H, 5.8; Cl, 8.3. $C_{21}H_{23}ClO_7$ requires C, 59.6; H, 5.5; Cl, 8.4%); δ[$(CD_3)_2CO$] 1.16 (d, *J* 7 Hz, 17-H_3), 1.20 (s, 18-H_3), 2.97 (d, *J* 10.7 Hz, 6-H), 3.24 (d, *J* 10.7 Hz, 5-H), 5.28 (d, *J* 4 Hz, 3-H), 5.90 (dd, *J* 9 and 4 Hz, 2-H), and 6.53 (d, *J* 9 Hz, 1-H); *m/z* 422 (M^+,

4%), 406 (3), 404 (8), 349 (5), 347 (16), 331 (5), 329 (12), 298 (29), 272 (67), 254 (64), 253 (55), and 209 (100).

The second compound eluted, ent-3α-*acetoxy*-13-*chloro*-10β,15α-*dihydroxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 19,10-*lactone* (**37**) (45 mg), was obtained as a gum (Found for Me ester TMSi ether: M^+, 508.1683. $C_{25}H_{33}ClO_7Si$ requires M, 508.1684); δ[$(CD_3)_2CO$] 1.15 (s, 18-H_3), 2.80 (d, J 11 Hz, 6-H), 3.27 (d, J 11 Hz, 5-H), 4.49 (br s, 15-H), 5.27 (d, J 4 Hz, 3-H), 5.34 and 5.49 (each d, J 2 Hz, together 17-H_2), 5.86 (dd, J 10 and 4 Hz, 2-H), and 6.63 (d, J 10 Hz, 1-H); *m/z* (Me ester TMSi ether) 508 (M^+, 8%), 493 (12), 473 (6), 448 (4), 404 (7), 389 (3), 369 (40), 297 (26), 272 (24), 255 (27), 219 (54), and 147 (30).

ent-3α,10β,15α-*Trihydroxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic Acid* 19,10-*Lactone* (**4**).—The chloride (**37**) (40 mg), as a powder, was refluxed with toluene (20 ml) and bis(tri-n-butyltin) oxide (40 μl) under a Dean–Stark trap for 30 min. The solution was treated with tri-n-butyltin hydride (50 μl) and 2,2′-azobis-(2-methylpropionitrile) for 1 h at reflux. The solvent was removed under reduced pressure and the resultant oil was taken up in methanol (10 ml). The product was deacylated by the method earlier described, extracted with ethyl acetate, and purified by flash chromatography to give GA_{68} (**4**) (20 mg) (Found: M^+, 346.1401. $C_{19}H_{22}O_6$ requires M, 346.1416); $\nu_{max.}$($CHCl_3$) 3 420, 1 770, and 1 710 cm^{-1}; δ(C_5D_5N) 1.84 (s, 18-H_3), 3.33 (d, J 11.2 Hz, 6-H), 4.07 (d, J 11.2 Hz, 5-H), 4.55 (d, J 4 Hz, 3-H), 4.76 (br s, 15-H), 5.18 and 5.43 (each br s, together 17-H_2), 6.14 (dd, J 8 and 4 Hz, 2-H), and 6.45 (d, J 8 Hz, 1-H); *m/z* 346 (M^+, 2%), 328 (27), 266 (75), 238 (34), 221 (52), 193 (24), 155 (41), and 84 (93).

ent-10β,13,15α-*Trihydroxy*-20-*norgibberellane*-7,19-*dioic Acid* 19,10-*Lactone* (**31**).—The ketone (**28**) (40 mg) was dissolved in methanol (10 ml) and sodium borohydride (50 mg) was added. After 2 h excess of sodium borohydride was decomposed with water (10 ml), the mixture was extracted with ethyl acetate (3 × 50 ml), and the extract was concentrated under reduced pressure. The resultant oil was refluxed in methanol (10 ml) and 2M-sodium hydroxide (2 ml) as described in an earlier procedure and the 16,17-dihydro-15β-hydroxyGA_{20} (**31**) (20 mg) was obtained as a gum [Found for Me ester: (M^+ − 18), 332.1653. $C_{19}H_{21}O_5$ requires (M − 18), 336.1623]; δ[$(CD_3)_2CO$] 0.86 (d, J 7.5 Hz, 17-H_3), 1.03 (s, 18-H_3), 2.50 (m, 5- and 6-H), and 4.05 (d, J 11 Hz, 15-H); *m/z* 332 (M^+, 1%), 314 (1), 300 (3), 286 (1), 274 (1), 246 (6), 240 (4), 201 (3), 164 (48), 106 (25), and 58 (100).

Acknowledgements

We thank the S.E.R.C. for a research studentship (to S. C. D.).

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Received 10*th May* 1985; *Paper* 5/785