Syntheses of gibberellins A_{93} and A_{94}, natural products detected in wheat grain

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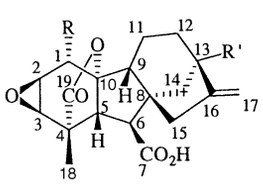
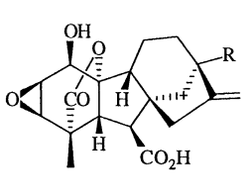
Extracts of mature wheat grain have been analysed by GC–MS and found to contain two new metabolites. The syntheses of the two new gibberellins, 1β-hydroxy-2β,3β-epoxyGA_9 4 and 1β-hydroxy-2β,3β-epoxy-GA_{20} 5 from the fungal gibberellins, GA_7 and GA_3 are described. A range of protecting groups for the 7-carboxylic acid which can be removed under mild conditions, are compared. The allyl ester proved most valuable in the manipulation of these multifunctional molecules and it is removed with tetrakis(triphenylphosphine)palladium(0), triphenylphosphine and potassium isobutyrate. The structures of the new natural products in wheat were confirmed to be 4 and 5 by comparison with the GC–MS data from the synthetic samples and are assigned the trivial names GA_{94} and GA_{93} respectively.

We have described previously the synthesis of two gibberellins **1** and **2** containing a 1α-hydroxy-2β,3β-epoxide moiety in ring A.[1] Only one of the known gibberellins, GA_6 **3**, has the 2β,3β-epoxide function.[2] Hydroxylation at C-1 occurs in both plant and fungal systems,[3] however, comparison of the GC–mass spectra of **1** and **2** with detected but uncharacterised gibberellins[4] revealed that neither compound is a natural product. On recent examination of extracts of mature wheat grain (*Triticum aestivum* cv Maris Huntsman) by GC–MS, two new compounds were detected with similar, but not identical, mass spectral data to **1** and **2** (Table 1). A series of 1β-hydroxygibberellins have been identified previously by GC–MS in extracts of wheat and their structures confirmed by direct comparison with synthetic samples.[5] Hence we proposed that the two new natural products were **4** and **5** with the 1β-hydroxy-2β,3β-epoxide functionality in ring A. We now describe the syntheses of **4** and **5** which confirm the structures of the natural products (now assigned the trivial names[6] GA_{93} **5** and GA_{94} **4**) and enable the metabolic grid to account for the presence of the 1β-hydroxy-GAs in wheat to be completed.[5]



1 R = OH, R' = H
2 R = R' = OH
3 R = H, R' = OH (GA_6)



4 R = H (GA_{94})
5 R = OH (GA_{93})

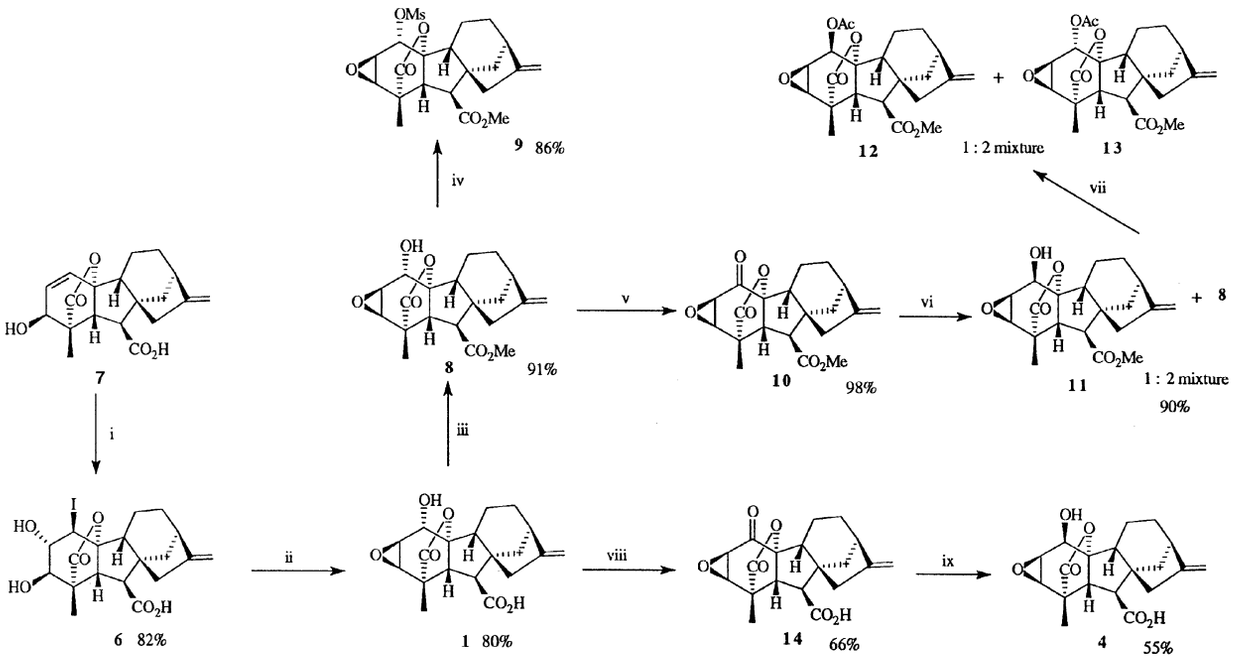
Results and discussion

Synthesis of 1β-hydroxy-2β,3β-epoxide 4 (Scheme 1)

Gibberellin A_7 **7** was converted to the 1α-hydroxy-2β,3β-epoxide **8** *via* a Payne-type rearrangement of the iododiol **6** as previously described.[1] A method for inversion of the stereochemistry of the 1-hydroxy group was then required. The most obvious choice was an S_N2 displacement of a suitable derivative of the 1α-alcohol. As with other sterically crowded systems[6] the direct inversion of a secondary alcohol under standard or modified Mitsunobu reaction conditions[7] has proven to be unsuccessful.[8] Caesium acetate has been successfully used for the inversion of alcohols at C-2 and C-3 of gibberellins *via* the corresponding methanesulfonates.[9] Thus **8** was converted to the methanesulfonate **9** under standard conditions. However, treatment of **9** with caesium acetate in refluxing toluene simply returned starting material whereas in *N*,*N*-dimethylformamide (DMF) at 80 °C an intractable gum was obtained. The density of functionality surrounding C-1 (the lactone and epoxide) appeared to be interfering with selective attack of the nucleophile and so the use of a two-stage oxidation procedure for inversion of the alcohol was investigated.

Several procedures for the oxidation of the 1α-alcohol **8** to the ketone **10** were compared. Although Fetizon's reagent[10] and pyridinium dichromate (PDC)[11] returned mainly starting material, oxidation was successfully achieved under both Swern conditions[12] and with tetrapropylammonium perruthenate (TPAP), *N*-morpholine *N*-oxide (NMO) and molecular sieves[13] giving the required ketone **10** in 90% and 98% yield respectively. Ketone **10** was then reduced with sodium borohydride in methanol giving a 2:1 mixture (by ^{1}H-NMR spectroscopy) of the 1α-alcohol **8** and the required 1β-alcohol **11**. It has previously been shown that reduction of a ketone at C-3 of the gibberellins with aluminium isopropoxide in propan-2-ol gives predominantly the 3β-alcohol.[14] However reduction of the 1-oxo-2β,3β-epoxide **10** under these conditions gave a mixture of 1α:1β-alcohols **8** and **11** in a disappointing 10:1 ratio. The mixture of alcohols proved to be inseparable by either flash chromatography or medium pressure chromatography. In an attempt to prepare derivatives of **8** and **11** which may be separated, the mixture was treated with acetic anhydride in pyridine giving the acetates **12** and **13**; these were also inseparable. Therefore it was apparent that a stereoselective method was required for ketone reduction in which hydride delivery was exclusively from the α-face at C-1.

Bell and Turner[15] reported that reduction of 3-oxogibberellin 7-carboxylic acids with K-Selectride gives >95% yield of the 3β-alcohol (*i.e.* with delivery of hydride from the α-face at C-3). The stereochemical outcome has been rationalised in terms of steric and Coulombic inhibition of approach of the reagent to the β-face of the gibberellin by a borate complex with the 7-carboxylic acid. This hypothesis is supported by the fact that reduction of 3-oxogibberellin 7-methyl esters with K-Selectride

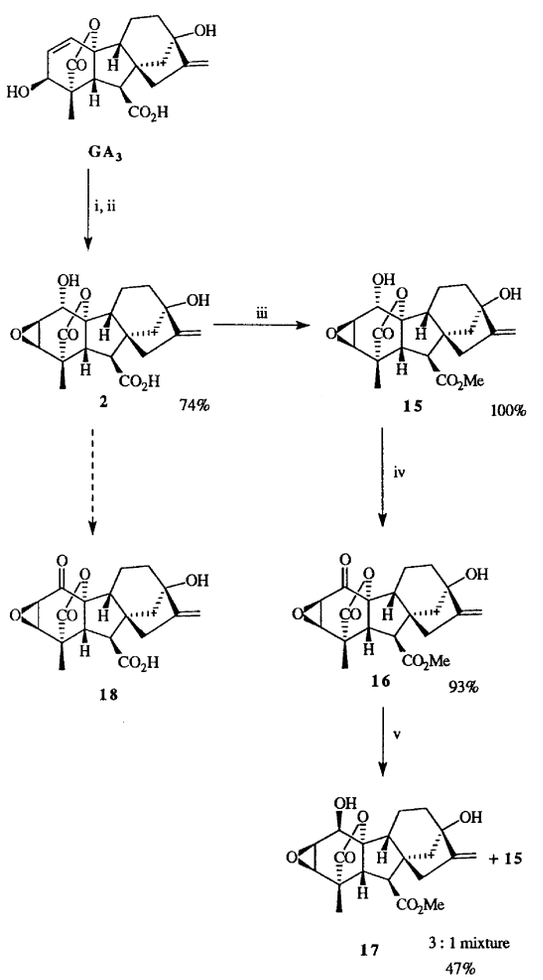


Scheme 1 *Reagents and conditions:* i, aq. KOH (0.8 mol dm^{-3}), THF, 14 h, room temp. then adjust to pH 9, I_2, CH_2Cl_2, 2 h; ii, aq. KOH (0.1 mol dm^{-3}); iii, CH_2N_2, MeOH; iv, MsCl, pyridine; v, TPAP, NMO, mol. sieves; vi, $NaBH_4$, MeOH; vii, Ac_2O, pyridine; viii, Me_2SO, $(COCl)_2$ Pr^i_2EtN, CH_2Cl_2, Me_2CO; ix, K-Selectride, KH_2PO_3

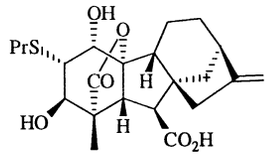
gives the 3α-alcohol in 93% yield.[16] Thus the 1α-hydroxy-2β,3β-epoxide 7-acid **1** was oxidised under Swern conditions to give the required keto acid **14** in 66% yield. Due to the increased polarity of the acid **14** compared with the methyl ester **10**, it proved necessary to add **14** as a solution in acetone to the activated sulfonium species in dichloromethane. Finally reduction of keto acid **14** with K-Selectride proceeded with excellent stereofacial selectivity to give the required 1β-alcohol **4** as a crystalline solid in 24% overall yield from GA_7.

Synthesis of 1β,13-dihydroxy-2β,3β-epoxide 5

Following the successful synthesis of **4**, it was proposed to use a similar approach for the preparation of the 13-hydroxylated compound **5**. Gibberellin A_3 was readily converted to the 1α-hydroxy-2β,3β-epoxide **2** as previously described (Scheme 2).[1] However, it was found that although oxidation of the 1-hydroxy 7-methyl ester **15** proceeded smoothly with either TPAP or under Swern conditions giving **16** (in 93% and 65% yield respectively), attempted oxidation of the corresponding 1-hydroxy 7-carboxylic acid **2** under similar conditions simply returned starting material. The problem was believed to be due to the polar nature of the dihydroxy acid compared with either the dihydroxy ester **15** or hydroxy acid **1**. Further attempts to oxidise the dihydroxy acid **2** with PDC in DMF or using the Parikh modification of the Moffatt oxidation[17] gave an intractable gum. Reduction of the keto ester **16** with K-Selectride gave a 3:1 mixture of the 1β:1α-alcohol **17** and **15** (by ^1H NMR spectroscopy) which proved to be inseparable by flash chromatography or MPLC. It was therefore apparent that the presence of the 7-carboxylic acid is essential to achieve good stereofacial selectivity in the reduction of the 1-ketone with K-Selectride. Since keto acid **18** could not be prepared *via* direct oxidation of the dihydroxy acid **2**, methods for converting a 7-methyl ester to an acid in the presence of a 2β,3β-epoxide were investigated. Treatment of **8** with aqueous sodium hydroxide gave a complex mixture of products and reaction with sodium propanethiolate in hexamethylphosphoramide (HMPA)[18] resulted in attack on the 2β,3β-epoxide as well as deprotection at C-7 giving **19** as the major product.

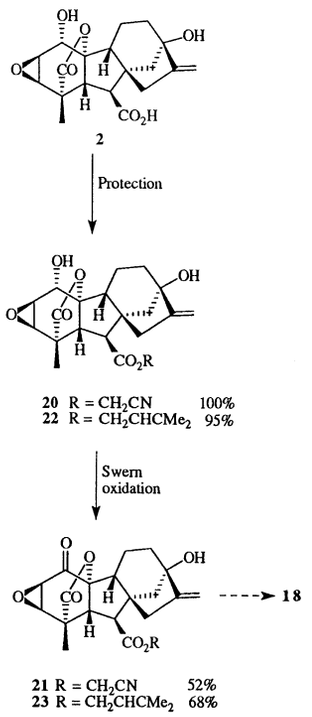


Scheme 2 *Reagents and conditions:* i, aq. KOH (0.8 mol dm^{-3}), THF, 14 h, room temp. then adjust to pH 9, I_2, CH_2Cl_2, 2 h; ii, aq. KOH (0.1 mol dm^{-3}); iii, CH_2N_2, MeOH; iv, TPAP, NMO, mol. sieves; v, K-Selectride, KH_2PO_3, THF



19

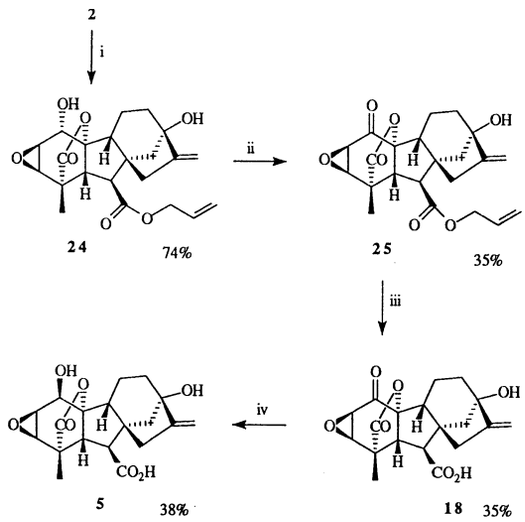
In the light of these problems the approach to the synthesis of **5** had to be modified. A protecting group for the 7-acid was required which would effectively reduce the polarity of the dihydroxy acid **2** to enable oxidation of the 1-alcohol to a ketone and which then could be removed prior to reduction of the 1-ketone to the required 1β-alcohol. A range of protecting groups was examined (Scheme 3).



Scheme 3

Recently it has been reported that a cyanomethyl ester may be used to protect the 7-carboxylic acid of gibberellins.[19] The acid **2** was heated to reflux with chloroacetonitrile to give the cyanomethyl ester **20** in quantitative yield. Oxidation of **20** under Swern conditions gave the keto epoxide **21** but attempts to remove the protecting group with either a mixture of potassium carbonate–potassium hydrogen carbonate in acetone–water or with potassium hydroxide gave an intractable mixture. Therefore, although the protecting group was simple to put on and compatible with the oxidation conditions, the route failed at the deprotection step, the reaction conditions proving incompatible with the epoxy, keto and lactone moieties in ring A. Another protecting group we considered was the 3-methylbut-2-enyl ester.[20] The ester **22** was formed in 95% yield *via* a 1,3-dicyclohexylcarbodiimide (DCC)–4-(*N*,*N*-dimethylamino)pyridine (DMAP) mediated coupling reaction. Oxidation of **22** with TPAP proceeded smoothly giving the keto ester **23** in 68% yield. Again, however, attempts to remove the ester to give the required 1-keto-2β,3β-epoxide 7-acid proved unsuccessful. Treatment of **23** with iodine in cyclohexane returned starting material when the reaction was conducted at room temperature and gave an intractable mixture at elevated temperatures. In this case, it is possible that not only is the densely functionalised A ring sensitive to the reaction conditions but also a Wagner–Meerwein type rearrangement of the C/D rings may occur in the presence of iodine.

Finally the allyl ester **24** was prepared from **2** using a DCC–DMAP mediated coupling with prop-2-en-1-ol (Scheme 4).



Scheme 4 *Reagents and conditions:* i, CH_2=$CHCH_2OH$, DCC, DMAP; ii, TPAP, NMO, mol. sieves; ii, Me_2CHCO_2K, Ph_3P, $Pd(PPh_3)_4$, CH_2Cl_2, EtOAc; v, K-Selectride, KH_2PO_3 THF

Oxidation of alcohol **24** with TPAP successfully gave the ketone **25** (52% yield over the two steps). Removal of the protecting group was achieved with a mixture of potassium isobutyrate, triphenylphosphine and tetrakis(triphenylphosphine)palladium(0)[21] giving the required 1-keto-2β,3β-epoxide **18** in 35% yield. Reduction of **18** with K-Selectride gave the 1β-hydroxy-2β,3β-epoxide **5** as a crystalline product in 5% overall yield from GA_3.

Comparison of 4 and 5 with the new metabolites in extracts of wheat grain and proposed biosynthesis.

Mature grain of *Triticum aestivum* (cv Maris Huntsman) was extracted and the GAs were purified from the BuOH-soluble fraction as described in the Experimental section. The purified extract was methylated with diazomethane and derivatised with trimethylsilyl chloride–1,1,1,3,3,3-hexamethyldisilazane–pyridine prior to analysis by GC–MS.[3] The extract contained two new metabolites which had not previously been identified.[4] The synthetic samples of the 1β-hydroxy-2β,3β-epoxides **4** and **5** were separately derivatised as the trimethylsilyl ether methyl esters and the GC–MS data compared with those of the metabolites in wheat (Table 1). These data confirm the tentative assignments of the natural products and **4** is now assigned the trivial name GA_{94} and **5** is GA_{93}.

One of the most dramatic biological effects of gibberellins is their enhancement of stem elongation.[3] The biological activities of GA_{93} and GA_{94} were assessed in a Tan-ginbozu dwarf rice immersion assay. It was found that in comparison with GA_3 and GA_7, neither GA_{93} nor GA_{94} is a potent stem elongation promoter (Table 2). Further bioassays are required to discover the significance of 1β-hydroxylation and the 2β,3β-epoxide in the role of GAs in plant growth and development in wheat.

Experimental

General experimental details have been described in a previous paper.[22] For the numbering scheme used throughout the paper, see structure **1**. Unless otherwise stated, all reactions were worked-up by the following standard procedure. The reaction mixture was poured into water and ethyl acetate. The pH was adjusted to 2 with 2 M hydrochloric acid and the products extracted with ethyl acetate. The combined organic extracts

Table 1 Comparison of the mass spectra of methylated, trimethylsilylated derivatives of synthetic and wheat grain GA_{94} **4** and GA_{93} **5** and the 1α-hydroxy-2β,3β-epoxides **1** and **2**

GA/source	KRI	Characteristic ions *m/z* (% base peak)
1α-Hydroxy-2β,3β-epoxy GA_9 **1** Synthetic	2606	432 (M^+, 2), 417 (3), 385 (100), 288 (30), 201 (59), 145 (88), 73 (90)
GA_{94} **4** (1β-2β,3β-epoxy GA_9) Synthetic	2505	432 (M^+, 2), 414 (1), 403 (3), 400 (3), 382 (2), 370 (3), 356 (4), 313 (12), 310 (13), 301 (41), 300 (44), 283 (6), 268 (9), 255 (6), 241 (100), 240 (44), 221 (11), 211 (9), 132 (18)
Wheat grain	2504	432 (M^+, 2), 414 (1), 403 (3), 400 (3), 382 (2), 370 (2), 356 (4), 313 (12), 310 (12), 301 (39), 300 (41), 283 (6), 268 (10), 255 (6), 241 (100), 240 (41), 221 (11), 211 (9), 132 (17)
1α-Hydroxy-2β,3β-epoxy GA_{20} **2** Synthetic	2646	520 (M^+, 41), 473 (11), 376 (41), 303 (100), 235 (77), 207 (49), 73 (87)
GA_{93} **5** (1β-2β,3β-epoxy GA_{20}) Synthetic	2663	520 (M^+, 100), 505 (9), 491 (8), 461 (22), 447 (2), 401 (5), 389 (5), 376 (7), 347 (8), 329 (15), 305 (30), 303 (98), 279 (10), 235 (41), 208 (40), 207 (90), 194 (16), 193 (15)
Wheat grain	2662	520 (M^+, 77), 505 (9), 491 (8), 461 (22), 447 (2), 401 (4), 389 (6), 376 (7), 347 (9), 329 (15), 305 (31), 303 (100), 279 (9), 235 (40), 208 (37), 204 (89), 194 (16), 193 (24)

Table 2 Rice seedling bio-assay

	Second leaf Sheath/mm	Total/mm
Control	15	23
GA_3	40	55
GA_7	50	64
GA_{93}	16	26
GA_{94}	21	33

were washed with water, dried over anhydrous sodium sulfate and the solvent removed *in vacuo*.

ent-2α,3α-Epoxy-10β-hydroxy-1β-methylsulfonyloxy-20-nor-gibberell-16-ene-7,19-dioic acid 19,10-lactone 7-methyl ester 9

1α-Hydroxy-2β,3β-epoxide methyl ester **8** (76 mg, 0.21 mmol) in pyridine (2.5 cm^3) was stirred with methanesulfonyl chloride (26 ml) for 1 h at room temperature. The usual work-up was followed by purification by flash chromatography. Elution with 30% ethyl acetate–light petroleum gave methanesulfonate **9** as a foam (79 mg) (Found: M^+, 438.1349. $C_{21}H_{26}O_8S$ requires *M*, 438.1348); δ_H 1.31 (s, 18-H_3), 2.61 (m, 13-H), 2.72 (d, *J* 11, 6-H), 3.09 (d, *J* 11, 5-H), 3.16 (s, OSO_2Me), 3.25 and 3.29 (2 × d, each *J* 3.5, 2- and 3-H), 3.72 (s, CO_2Me), 4.86 (br s, 17-H) and 4.9 (br s, 17-H and 1-H); *m/z* 438 (M^+, 48%), 406 (39), 402 (31), 378 (30), 360 (65), 254 (93), 221 (68) and 43 (100).

Oxidation of hydroxy ester 8

Under Swern oxidation conditions. Oxalyl chloride (freshly distilled, 0.28 mmol, 0.25 μl) and dimethyl sulfoxide (7 mmol, 0.51 μl) were stirred in dichloromethane (5 cm^3) at −78 °C for 5 min. 1-Hydroxy-2,3-epoxide **8** (107 mg, 0.30 mmol) was added dropwise in dichloromethane (5 cm^3) and the reaction mixture stirred for 1.5 h at −78 °C. *N*,*N*-Diisopropylethylamine (5.6 mmol, 1 μl) was added and the reaction allowed to warm to room temperature over 1.5 h. The usual work-up was followed by purification by flash chromatography. Elution with 40% ethyl acetate–light petroleum gave *ent*-2α,3α-epoxy-10β-hydroxy-1-oxo-20-norgibberell-16-ene-7,19-dioic acid 19,10-lactone 7-methyl ester **10**, which was crystallised from ethyl acetate–light petroleum as needles (12 mg), mp 155–157 °C (Found: M^+, 358.1412. $C_{20}H_{22}O_6$ requires *M*, 358.1416); δ_H 1.41 (s, 18-H_3), 2.80 (d, *J* 11, 6-H), 3.31 and 3.51 (2 × d, *J* 3.5, 2- and 3-H), 3.39 (d, *J* 11, 5-H), 3.74 (s, CO_2Me), 4.99 and 5.26 (2 × br s, 17-H_2); *m/z* 358 (M^+, 48%), 326 (40), 298 (13), 241 (22), 228 (100), 201 (19) and 91 (45).

With tetrapropylammonium perruthenate (TPAP). Hydroxy ester **8** (104 mg, 0.29 mmol), *N*-methylmorpholine *N*-oxide (51 mg, 0.43 mmol) and molecular sieves (crushed and dried, 145 mg) were stirred at room temperature under nitrogen in dichloromethane (900 μl) and acetonitrile (100 μl). Tetrapropylammonium perruthenate (TPAP) (5 mg, 0.015 mmol, catalytic) was added and the reaction stirred for 2 h. To work-up the mixture, it was passed through a short column of silica, which was eluted with dichloromethane (100 cm^3) and then ethyl acetate (100 cm^3). The ketone **10** was obtained in 100% yield, the ^1H NMR and mass spectral data being identical to those previously obtained.

Reduction of keto ester 10

With sodium borohydride. Sodium borohydride (12.7 mg, 0.34 mmol) in methanol (1 cm^3) was added to a stirred solution of the epoxy ketone **10** (60 mg, 0.17 mmol) in methanol (4 cm^3). The mixture was stirred for 1 h at room temperature and then worked-up as usual. Purification by flash chromatography and elution with 25% ethyl acetate in light petroleum gave a 2:1 mixture of the 1α-hydroxy- and 1β-hydroxy-epoxides **8** and **11** (55 mg). The epimeric mixture showed as a single spot in three different solvent systems. δ_H(major 1α-alcohol **8**; as previously described); δ_H(minor 1β-alcohol **11**) 1.29 (s, 18-H_3), 2.61 (m, 13-H), 2.69 (d, *J* 10.5, 6-H), 3.13 (d, *J* 10.5, 5-H), 3.41 (m, 2-H and 3-H), 3.71 (s, OCH_3), 3.90 (d, *J* 8, 1-H), 4.86 and 4.98 (2 br s, 17-H_2). The trimethylsilyl derivative of **11** gave KRI† 2505; *m/z* 432 (M^+, 1%), 400 (3), 370 (3), 356 (4), 324 (2), 300 (41), 283 (6), 268 (10), 241 (100), 240 (43), 221 (13), 211 (10), 195 (9), 132 (19), 119 (10), 93 (20), 73 (66), 55 (11) and 44 (30).

Meerwein–Verley–Ponndorf reduction. Aluminium foil (0.35 g, 13.0 mmol) and mercuric chloride (3.5 mg, 0.013 mmol) in propan-2-ol (15 cm^3) were heated to reflux. Carbon tetrachloride (60 μl) was added and the mixture was heated at a gentle reflux for 3 h. Keto ester **10** (20 mg, 5.59×10^{-2} mmol) in propan-2-ol (2 cm^3) was added and the mixture was heated for a further 3 h with distillation of the acetone produced. The mixture was then cooled to room temperature and worked-up as usual. The crude product was purified by flash chromatography. Elution with 25% ethyl acetate in light petroleum gave the 1-alcohols **8** and **10** as a ~10:1 (α:β) epimeric mixture; spectroscopic data as previously described.

ent-1α- and 1β-Acetoxy-2α,3α-epoxy-10β-hydroxy-20-nor-gibberell-16-ene-7,19-dioic acid 19,10-lactones 7-methyl ester 12 and 13

The mixture of epimeric alcohols **8** and **10** (27 mg) in pyridine (750 μl) and acetic anhydride (700 μl) was stirred at room temperature for 2 h. The usual work-up gave a gum which was purified by flash chromatography. Elution with 10% ethyl acetate in light petroleum gave the epimeric acetates **12** and **13** in a ratio of 2:1 (α:β). The acetates also showed as one spot by TLC in three different solvent systems [ethyl acetate–light petroleum (1:5), diethyl ether–hexane (3:10) and dichloromethane–methanol (9:1)] (Found: M^+, 402.1671. $C_{22}H_{26}O_7$ requires *M*, 402.1679); δ_H(major 1α-acetate **13**) 1.31 (s, 18-H_3), 2.15 (s, $OCOCH_3$), 2.62 (m, 13-H), 2.72 (d, *J* 11, 6-H), 2.97 (d, *J* 3.5, 2- or 3-H), 3.08 (d, *J* 11, 5-H), 3.20 (d, *J* 3.5, 2- or 3-H), 3.72 (s, OCH_3), 4.86 and 4.97 (2 br s, 17-H_2) and 5.18 (d, *J* <0.5, 1-H); δ_H(minor 1β-acetate **12**) 1.32 (s, 18-H_3), 2.19 (s, $OCOCH_3$), 2.64 (m, 13-H), 2.69 (d, *J* 10.5, 6-H), 3.28 (d, *J* 10.5, 5-H), 3.31 (d, *J* 4, 3-H),

† KRI (Kovats Retention Index) is described in detail in ref. 4.

3.44 (t, *J* 4, 2-H), 3.72 (s, OCH_3), 4.86 and 4.97 (2 br s, 17-H_2) and 5.01 (d, *J* 4, 1-H); *m/z* 402 (M^+, 13%), 384 (5), 370 (74), 342 (13), 310 (55), 280 (37), 254 (100), 240 (55), 239 (78), 238 (80), 221 (51), 171 (35), 105 (38) and 91 (76).

ent -2α,3α-Epoxy-10β-hydroxy-1-oxo-20-norgibberell-16-ene-7, 19-dioic acid 19,10-lactone 14

Dichloromethane (5 cm^3) and freshly distilled oxalyl chloride (0.24 cm^3, 2.9 mmol) were added to a 10 cm^3 flame-dried, round-bottomed flask under nitrogen at −78 °C . Dimethyl sulfoxide (0.49 cm^3, 7.22 mmol) was added dropwise to the solution and the reaction stirred for 5 min. 1α-Hydroxy 2β,3β-epoxide **1** (100 mg, 0.29 mmol) was dissolved in a minimum of acetone and dichloromethane and added dropwise to the reaction mixture. After 1.5 h at −78 °C, *N*,*N*-diisopropylethylamine (0.97 cm^3, 5.7 mmol) was added and the reaction mixture allowed to warm to room temperature for 1.5 h. The reaction was diluted with dichloromethane (2 cm^3) and water (1 cm^3) and then the usual work-up was carried out. Purification by column chromatography, eluting with 40% ethyl acetate–light petroleum gave the epoxy ketone **14** as a white solid which was recrystallised from ethyl acetate–light petroleum as needles (66 mg), mp 155–156 °C (Found: C, 66.3; H, 5.8. $C_{19}H_{20}O_6$ requires C, 66.28; H, 5.81%); δ_H 1.46 (s, 18-H_3), 2.82 (d, *J* 11, 6-H), 3.31 and 3.50 (2 × d, *J* 3.5, 2- and 3-H), 3.35 (d, *J* 11, 5-H) and 4.94 (2 × br s, 17-H_2); *m/z* 344 (M^+, 38%), 326 (30), 274 (32), 255 (32), 228 (56), 211 (28) and 91 (100).

ent-2α,3α-Epoxy-1α,10β-dihydroxy-20-norgibberell-16-ene-7, 19-dioic acid 19,10-lactone 4

A solution of the epoxy ketone **14** (100 mg, 0.29 mmol) in tetrahydrofuran was added to dry powdered potassium dihydrogen orthophosphate (0.24 g, 2.03 mmol) under nitrogen. The reaction was cooled to −78 °C and K-Selectride (potassium tri-*sec*-butylborohydride) (1.2 cm^3, 1 M solution in tetrahydrofuran) was added dropwise over 5 min stirring continuously. The solution was allowed to warm to room temperature over 2 h and then worked-up as usual. Purification by column chromatography, eluting with 40% ethyl acetate–light petroleum gave GA_{94} **4**, which was crystallised from ethyl acetate–light petroleum as a white solid (55 mg), mp 142–144 °C (Found: C, 65.5; H, 6.2. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%); δ_H 1.36 (s, 18-H_3), 2.63 (m, 13-H), 2.72 (d, *J* 10.5, 6-H), 3.14 (d, *J* 10.5, 5-H), 3.42 (2 × s, 2- and 3-H), 3.92 (d, *J* 4, 1-H) and 5.92 (2 × br s, 17-H_2); δ_C 14.2 (C-18), 17.6 (C-11), 31.6 (C-12), 39.4 (C-13), 42.5, 44.2 (C-14 and C-15), 47.2 and 47.6 (C-3 and C-9), 48.6 and 49.3 (C-4 and C-8), 51.4, 51.9 (C-5 and C-6), 59.7 (C-2), 69.2 (C-1), 92.4 (C-10), 107.7 (C-17), 156.2 (C-16), 172.2 and 176 (C-7 and C-19); *m/z* 346 (M^+, 28%), 328 (18), 310 (17), 287 (96), 240 (65), 195 (36) and 91 (100).

Oxidation of 1α,13-dihydroxy-2β,3β-epoxide methyl ester 15

Under Swern oxidation conditions. Oxalyl chloride (freshly distilled, 174 μl, 1.99 mmol) and dimethyl sulfoxide (350 μl, 4.99 mmol) were stirred in dichloromethane (5 cm^3) at −78 °C for 5 min. Diol **15**[1] (75 mg, 0.20 mmol) in dichloromethane (5 cm^3) was added dropwise and the reaction mixture stirred for 1.5 h at −78 °C. *N*,*N*-Diisopropylethylamine (690 μl, 3.99 mmol) was added and the resulting yellow solution was allowed to warm to room temperature over 1.5 h. The usual work-up was followed by purification by flash chromatography. Elution with 70% ethyl acetate–light petroleum gave *ent*-2α,3α-epoxy-10β,-13-dihydroxy-1-oxo-20-norgibberell-16-ene-7,19-dioic acid 19,-10-lactone 7-methyl ester **16** as a gum (49 mg, 65%) (Found: M^+, 374.1360. $C_{20}H_{22}O_7$ requires *M*, 374.1366); δ_H 1.42 (s, 18-H_3), 2.80 (d, *J* 10.5, 6-H), 3.31 and 3.52 (2 × d, each *J* 3.5, 2- and 3-H), 3.41 (d, *J* 10.5, 5-H), 3.75 (s, CO_2Me), 4.98 and 5.28 (2 × br s, 17-H_2); *m/z* 374 (M^+, 25%), 346 (3), 342 (13), 315 (10), 304 (9), 275 (21), 231 (61), 135 (100) and 91 (97).

With TPAP. To a stirred solution of diol **15** (50 mg, 0.14 mmol), molecular sieves (4 Å, vacuum oven dried, 100 mg) and *N*-methylmorpholine *N*-oxide (24 mg, 0.21 mmol) in dichloromethane–acetonitrile (2 cm^3: 200 μl) was added TPAP (2.4 mg, 0.007 mmol). After 2 h, the solvent was removed *in vacuo* and the resulting gum purified by flash chromatography. Elution with 70% ethyl acetate–light petroleum gave ketone **16** (48 mg) whose ^{1}H NMR and mass spectral data were identical to those previously obtained.

Reduction of keto ester 16 with K-Selectride

Keto ester **16** (169 mg, 0.45 mmol) in tetrahydrofuran (10 cm^3) was added to dry, powdered potassium hydrogen orthophosphate (374 mg, 3.16 mmol). The mixture was cooled to −78 °C, then K-Selectride (1 M in tetrahydrofuran, 2.26 cm^3, 2.25 mmol) was added dropwise over 5 min. The reaction was allowed to warm to 0 °C over 2 h with stirring. The usual work-up was followed by purification by flash chromatography. Elution with 50% ethyl acetate–light petroleum with three drops acetic acid added gave a mixture of 1α-alcohol **15** and 1β-alcohol **17** (80 mg) in the ratio 1:3. Separation was attempted using medium pressure liquid chromatography, eluting with 50% ethyl acetate–light petroleum (with three drops acetic acid added), which gave a 1:7 mixture (by ^{1}H NMR) of the 1α-alcohol **15** and the 1β-alcohol **17** as a white foam (13 mg) (Found: M^+, 376.1526. $C_{20}H_{24}O_7$ requires *M*, 376.1522); δ_H 1.31 (s, 18-H_3), 2.68 (d, *J* 10, 6-H), 3.18 (d, *J* 10, 5-H), 3.40 (m, 2- and 3-H), 3.74 (s, CO_2Me), 3.91 (br s, 1-H), 4.96 and 5.25 (2 × br s, 17-H_2). GC–MS of the trimethylsilyl derivative of **17** gave KRI 2663; *m/z* 376 (M^+, 38%), 344 (78), 326 (37), 317 (34), 275 (32), 231 (100), 163 (67) and 135 (49). Further elution gave 1α-alcohol **15** (24 mg); ^{1}H NMR and mass spectral data being identical to those previously assigned. The trimethylsilyl derivative of **15** gave KRI 2646.

Treatment of hydroxy ester 8 with sodium propanethiolate

Propanethiol (0.42 cm^3) was added to sodium hydride (144 mg) (previously washed with light petroleum and dried under vacuum) in hexamethylphosphoramide (HMPA) (3 cm^3) and the solution stirred for 2 h at room temperature under nitrogen. The complex formed was allowed to stand for 1 h before use.

1α-Hydroxy-2,3-epoxide methyl ester **8** (30 mg, 0.08 mmol) was treated with the sodium propanethiolate–hexamethylphosphoramide complex (2 cm^3) and the reaction stirred for 2 h at room temperature. The usual work-up was followed by purification by column chromatography. Elution with 35% ethyl acetate–light petroleum gave a gummy mixture (116 mg) of which the major compound was hydroxy thioether **19**; δ_H 0.90 (t, *J* 7, $SC_2H_4CH_3$), 1.12 (s, 18-H_3), 2.54 (apparent t, *J* 7, 2-H), 2.61 (d, *J* 10, 5-H), 3.23 (d, *J* 10, 6-H), 3.28 (d, *J* 7, 3-H), 3.98 (d, *J* 7, 1-H), 4.85 and 4.96 (2 × br s, 17-H_2); *m/z* 580 (M^+, 14%), 478 (15), 390 (45), 375 (13), 291 (14), 241 (17), 217 (100), 191 (23) and 91 (9); GC–MS (trimethylsilyl derivative) *m/z* 580 (M^+, 12%), 565 (9), 549 (5), 478 (15), 460 (4), 390 (33), 217 (72), 191(18) and 73 (100).

ent-2α,3α-Epoxy-1β,10β,13-trihydroxy-20-norgibberell-16-ene-7,19-dioic acid 7-cyanomethyl ester 19,10-lactone 20

13-Hydroxyepoxy alcohol **2** (100 mg, 0.28 mmol) in dichloromethane (3 cm^3) and triethylamine (194 μl, 1.12 mmol) were heated to reflux with chloroacetonitrile (21 μl, 0.34 mmol) for 4 h. The reaction mixture was allowed to cool and diluted with dichloromethane (5 cm^3). The usual work-up was followed by flash chromatography. Elution with 60% ethyl acetate–light petroleum gave hydroxy ester **20** as a yellow gum (116 mg); δ_H[$(CD_3)_2CO$] 1.24 (s, 18-H_3), 2.71 (d, *J* 10, 6-H), 2.97 (d, *J* 10, 5-H), 3.00 and 3.14 (2 × d, each *J* 3.5, 2- and 3-H), 3.93 (br s, 1-H), 4.72 (s, CH_2CN), 4.92 and 5.20 (2 × br s, 17-H_2); *m/z* 401 (M^+, 18%), 344 (5), 326 (16), 231 (100), 163 (33) and 135 (17).

***ent*-2α,3α-Epoxy-10β,13-dihydroxy-1-oxo-20-norgibberell-16-ene-7,19-dioic acid 7-cyanomethyl ester 19,10-lactone 21**

Oxalyl chloride (freshly distilled, 0.25 cm^3, 2.87 mmol) and dimethyl sulfoxide (0.51 cm^3, 7.19 mmol) were stirred in dichloromethane (5 cm^3) at −78 °C for 5 min. Hydroxy ester **20** (100 mg, 0.25 mmol) in dichloromethane (5 cm^3) was added dropwise to the solution. After 1.5 h stirring *N*,*N*-diisopropylethylamine (1 cm^3, 5.78 mmol) was added and the solution became yellow. The reaction was allowed to warm to room temperature with stirring for 1.5 h. The usual work-up was carried out followed by purification by flash chromatography. Elution with 60% ethyl acetate–light petroleum (plus ten drops acetic acid) gave keto ester **21** as a gum (52 mg) (Found: M^+, 399.1302. $C_{21}H_{21}NO_7$ requires *M*, 399.1318); δ_H 1.43 (s, 18-H_3), 2.88 (d, *J* 10.5, 6-H), 3.53 and 3.54 (2 × d, each *J* 3.5, 2- and 3-H), 3.42 (d, *J* 10.5, 5-H), 4.80 (s, CH_2CN), 5.01 and 5.31 (2 × br s, 17-H_2); *m/z* 399 (M^+, 12%), 371 (2), 342 (3), 311 (9), 231 (69), 163 (38) and 135 (100).

***ent*-2α,3α-Epoxy-1β,10β,13-trihydroxy-20-norgibberell-16-ene-7,19-dioic acid 19,10-lactone 7-(3-methylbut-2-enyl) ester 22**

To a solution of the 1α,13-dihydroxy-2,3-epoxide **2** (50 mg, 0.14 mmol) in *N*,*N*-dimethylformamide (2 cm^3) was added a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (10 mg) and 3-methylbut-2-en-1-ol (30 ml, 0.28 mmol). The reaction was cooled to 0 °C and 1,3-dicyclohexylcarbodiimide (DCC) (60 mg, 0.28 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 6 h. The reaction was filtered to remove any white precipitate, which was washed with dichloromethane. The solvent was removed *in vacuo* and the crude product dissolved in dichloromethane and filtered again. The organic layer was washed sequentially with dilute hydrochloric acid and aqueous sodium hydrogen carbonate and then dried, filtered and the solvents removed *in vacuo*. Purification by flash chromatography, eluting with 40% ethyl acetate–light petroleum gave hydroxy ester **22** as a gum (57 mg) (Found: M^+, 430.2004. $C_{24}H_{30}O_7$ requires *M*, 430.1992); δ_H 1.30 (s, 18-H_3), 1.68 and 1.74 [2 × br s, $CO_2CH_2CHC(CH_3)_2$], 2.67 (d, *J* 11, 6-H), 3.04 and 3.18 (2 × d, each *J* 3.5, 2- and 3-H), partially masking 3.03 (d, *J* 11, 5-H), 3.98 (br s, 1-H), 4.61 (apparent t, *J* 7, $CO_2CH_2CHC(CH_3)_2$], 4.94 and 5.24 (2 × br s, 17-H_2) and 5.41 (apparent t, *J* 7, $CO_2CH_2CHC(CH_3)_2$]; *m/z* 430 (M^+, 10%), 412 (5), 361 (15), 317 (8), 231 (10), 224 (24), 143 (21) and 69 (100).

***ent*-2α,3α-Epoxy-10β,13-dihydroxy-1-oxo-20-norgibberell-16-ene-7,19-dioic acid 19,10-lactone 7-(3-methylbut-2-enyl) ester 23**

Hydroxy ester **22** (67 mg, 0.16 mmol), *N*-methylmorpholine *N*-oxide (28 mg, 0.24 mmol) and molecular sieves (crushed and dried, 80 mg) were stirred in dichloromethane (2 cm^3) and acetonitrile (0.5 cm^3) at room temperature. TPAP (3 mg, 0.008 mmol) was added and the reaction stirred for 2 h. Work-up was carried out by passing the reaction mixture through a short column of silica, washing with dichloromethane and then ethyl acetate to give keto ester **23** as a gum (66 mg) (Found: M^+, 428.1841. $C_{24}H_{28}O_7$ requires *M*, 428.1835); δ_H 1.41 (s, 18-H_3), 1.72 and 1.76 [2 × br s, $CO_2CH_2CHC(CH_3)_2$], 2.77 (d, *J* 10.5, 6-H), 3.30 and 3.50 (2 × d, each *J* 3.5, 2- and 3-H), 3.40 (d, *J* 10.5, 5-H), 4.11 (br s, 1-H), 4.65 [dd, *J* 12, 4, $CO_2CH_2CHC(CH_3)_2$], 4.96 and 5.27 (2 × br s, 17-H_2) and 5.33 [m, $CO_2CH_2CHC(CH_3)_2$]; *m/z* 428 (M^+, 5%), 410 (4), 359 (10), 224 (40), 143 (32), 99 (45), 69 (74) and 56 (100).

***ent*-2α,3α-Epoxy-1β,10β,13-trihydroxy-20-norgibberell-16-ene-7,19-dioic acid 19,10-lactone 7-(prop-2-enyl) ester 24**

To a solution of the 1α,13-dihydroxy-2,3-epoxide **2** (100 mg, 0.28 mmol) in *N*,*N*-dimethylformamide (4 cm^3) was added a catalytic amount of DMAP (10 mg) and prop-2-en-1-ol (37 μl, 0.28 mmol). The reaction was cooled to 0 °C and DCC (114 mg, 0.55 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was filtered to remove any white precipitate and the fitrate washed with dichloromethane. The solvent was removed *in vacuo* and the crude product dissolved in ethyl acetate and filtered again. The organic layer was washed sequentially with dilute hydrochloric acid and aqueous sodium hydrogen carbonate and then dried, filtered and the solvents removed *in vacuo*. Purification by flash chromatography, eluting with 50% ethyl acetate–light petroleum gave hydroxy ester **24** as a gum (83 mg) (Found: M^+, 402.1676. $C_{22}H_{26}O_7$ requires *M*, 402.1678); δ_H 1.31 (s, 18-H_3), 2.71 (d, *J* 10.5, 6-H), 3.06 and 3.19 (2 × d, each *J* 3.5, 2- and 3-H), partially masking 3.04 (d, *J* 10.5, 5-H), 4.02 (br s, 1-H), 4.65 (m, $CO_2CH_2CHCH_2$), 4.96 and 5.25 (2 × br s, 17-H_2), 5.31 and 5.37 (2 × m, $CO_2CH_2CHCH_2$) and 5.95 (m, $CO_2CH_2CHCH_2$); *m/z* 402 (M^+, 23%), 361 (22), 344 (36), 326 (100), 317 (38), 301 (46), 231 (94) and 163 (64).

***ent*-2α,3α-Epoxy-10β,13-dihydroxy-1-oxo-20-norgibberell-16-ene-7,19-dioic acid 19,10-lactone 7-(prop-2-enyl) ester 25**

Dihydroxy ester **24** (82 mg, 0.20 mmol), *N*-methylmorpholine *N*-oxide (36 mg, 0.31 mmol) and molecular sieves (crushed and dried, 100 mg) were stirred in dichloromethane (2 cm^3) and acetonitrile (0.2 cm^3) at room temperature. TPAP (3.5 mg, 0.01 mmol) was added and the reaction stirred for 3 h. Work-up was carried out by passing the reaction mixture through a short column of silica, washing with dichloromethane and ethyl acetate to give keto ester **25** as a gum (56 mg) (Found: M^+, 400.1512. $C_{22}H_{24}O_7$ requires *M*, 400.1522); δ_H 1.42 (s, 18-H_3), 2.81 (d, *J* 10.5, 6-H), 3.31 and 3.51 (2 × d, each *J* 3.5, 2- and 3-H), 3.41 (d, *J* 10.5, 5-H), 4.64 (m, $CO_2CH_2CHCH_2$), 4.98 and 5.28 (2 × br s, 17-H_2), 5.32 and 5.39 (2 × m, $CO_2CH_2CHCH_2$) and 5.91 (m, $CO_2CH_2CHCH_2$); *m/z* 400 (M^+, 28%), 359 (33), 342 (21), 315 (10), 301 (13), 224 (59), 143 (40), 99 (48) and 56 (100).

***ent*-2α,3α-Epoxy-10β,13-dihydroxy-1-oxo-20-norgibberell-16-ene-7,19-dioic acid 19,10-lactone 18**

Isobutyric acid (125 ml, 0.79 mmol) was stirred in aqueous potassium hydroxide (1.5 M, 2 cm^3) for 0.5 h. The solvent was removed *in vacuo*, using toluene to form an azeotrope. The resulting white powder was taken up in ethyl acetate (2 cm^3) and stirred at room temperature with tetrakis(triphenylphosphine)-palladium(0) (18 mg, 0.02 mmol) and triphenylphosphine (7 mg, 0.03 mmol). Keto ester **25** (210 mg, 0.53 mmol) was added to the reaction mixture in dichloromethane (2 cm^3) and ethyl acetate (1 cm^3) and stirring continued for 4 h. The usual work-up was carried out, then the combined organic phase was extracted with aqueous sodium hydrogen carbonate (2 × 75 cm^3). The aqueous extract was then acidified to pH 2 and extracted with ethyl acetate. The combined organic layers were dried, filtered and the solvent removed *in vacuo*. Elution of a flash column with 70% ethyl acetate–light petroleum gave keto acid **18** as a cream foam (67 mg) (Found: M^+, 360.1205. $C_{19}H_{20}O_7$ requires *M*, 360.1209); δ_H[$(CD_3)_2CO$] 1.41 (s, 18-H_3), 2.82 (d, *J* 10.5, 6-H), 3.44 and 3.74 (2 × d, each *J* 3.5, 2- and 3-H), partially masking 3.41 (d, *J* 10.5, 5-H), 4.90 and 5.23 (2 × br s, 17-H_2); *m/z* 360 (M^+, 39%), 342 (18), 318 (8), 290 (8), 272 (12), 231 (61), 163 (48) and 135 (100).

***ent*-2α,3α-Epoxy-1α,10β,13-trihydroxy-20-norgibberell-16-ene-7,19-dioic acid 19,10-lactone 5**

1-Keto-13-hydroxy-2,3-epoxide **18** (67 mg, 0.19 mmol) in tetrahydrofuran (10 cm^3) was added to dry, powdered potassium hydrogen orthophosphate (154 mg, 1.3 mmol). The mixture was cooled to −78 °C, then K-Selectride (1 M in tetrahydrofuran, 2.26 cm^3, 2.25 mmol) was added dropwise over 5 min. The reaction was allowed to warm to 0 °C over 2 h with stirring. The usual work-up was carried out. The organic phase was extracted with aqueous sodium hydrogen carbonate (3 × 20 cm^3) and then the aqueous extract was acidified to pH 3 and

extracted with ethyl acetate (3 × 30 cm^3). Purification by flash chromatography eluting with 70% ethyl acetate–light petroleum (plus three drops acetic acid) gave the 1β-hydroxy-2β,3β-epoxide, GA_{93} **5**, which was crystallised from ethyl acetate–light petroleum as a white powder (26 mg), mp 145–146 °C (Found: M^+, 362.1361. $C_{19}H_{22}O_7$ requires *M*, 362.1366); δ_H[$(CD_3)_2CO$] 1.26 (s, 18-H_3), 2.61 (d, *J* 10, 6-H), 3.21 (d, *J* 10, 5-H), 3.36 (m, 2- and 3-H), 3.91 (br s, 1-H), 4.88 and 5.19 (2 × br s, 17-H_2); δ_C[$(CD_3)_2CO$] 14.8 (C-18), 17.8 (C-11), 39.8 (C-12), 43.5, 46.2 (C-14 and C-15), 47.2 and 47.6 (C-3 and C-9), 49.1 and 49.6 (C-4 and C-8), 51.4, 51.6 (C-5 and C-6), 59.7 (C-2), 65.2 (C-1), 78.1 (C-13), 94.2 (C-10), 106 (C-17), 159 (C-16), 174 and 177 (C-7 and C-19); *m/z* 362 (M^+, 45%), 344 (100), 3 (15), 231 (79), 163 (45), 135 (63) and 91 (48).

Tan-ginbozu dwarf rice immersion assay

Tan-ginbozu dwarf rice seeds were soaked in water for 2 days at 28 °C under constant light (the water was changed at 12 h intervals), by which time the coleoptile had emerged. The germinated seeds were selected for uniformity and placed in groups of six in cylindrical vials (18 mm diameter and 50 mm depth), which contained sterile water (1 cm^3) and a methanolic solution of the substrate (10 μl). Gibberellins A_7, A_{93} and A_{94} at a concentration of 10 μg per 10 μl of methanol were tested in duplicate. Two vials containing sterile water (1 cm^3) and methanol (10 μl) were used as control standards. The seeds were allowed to grow at 28 °C, under constant lighting. After 5 days, the length of the second leaf-sheath, and the total length—from seed to longest leaf-tip—was recorded.

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