Preparation of *ent*-Gibberellane and 16-*epi*-*ent*-Gibberellane

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A mixture of *ent*-gibberellane **1** and 16-*epi*-*ent*-gibberellane **2**, the parent hydrocarbons of the gibberellin plant hormones, has been prepared from gibberellin A_{14} dimethyl ester **5** by deoxygenation sequentially at carbons 3, 7 and 19 and then hydrogenation. The most direct route proceeded by dehydration of the 3-ol in **5** to the 2-ene **27**, hydride reduction to the 7,19-diol **28**, hydride reduction of the corresponding 7,19-dimethanesulfonate **29** to the 19-monomethanesulfonate **30**, and then hydrolysis to the 19-ol **31** which was converted into the phenyl selenide **38**. Hydrogenolysis of the selenide **38**, with concomitant hydrogenation of the 2- and 16-double bonds, gave a mixture of *ent*-gibberellane **1** and 16-*epi*-*ent*-gibberellane **2** in the ratio of 73:27. This mixture was separated on the analytical scale by capillary GLC and the two epimers were characterised by GLC–MS to provide reference mass spectra and KRI as fossil markers. The structures **1** and **2** were assigned on the basis that the major component was the *endo*-16-methyl epimer.

The preparation of *ent*-gibberellane **1** was undertaken for two reasons. Firstly, this hydrocarbon is the hitherto unknown parent upon which semi-systematic nomenclature for the gibberellin plant hormones (GAs) is based.[1] Secondly the related hydrocarbons, *ent*-kaurane **3** and *ent*-beyerane **4**, have been identified[2,3] in crude oil and geological sediments, suggesting a contribution to the fossil record from higher plants. Since the GAs occur in many, and perhaps all, higher plants the availability of *ent*-gibberellane **1** would provide another fossil marker. This paper describes the preparation of a mixture of *ent*-gibberellane **1** and 16-*epi*-*ent*-gibberellane **2** and the characterisation of both isomers by GLC-mass spectrometry. The structures **1** and **2** were assigned from many precedents that hydrogenation of *ent*-gibberell-16-enes provides mainly the 16α*H* (*endo*-16-methyl)-isomer.

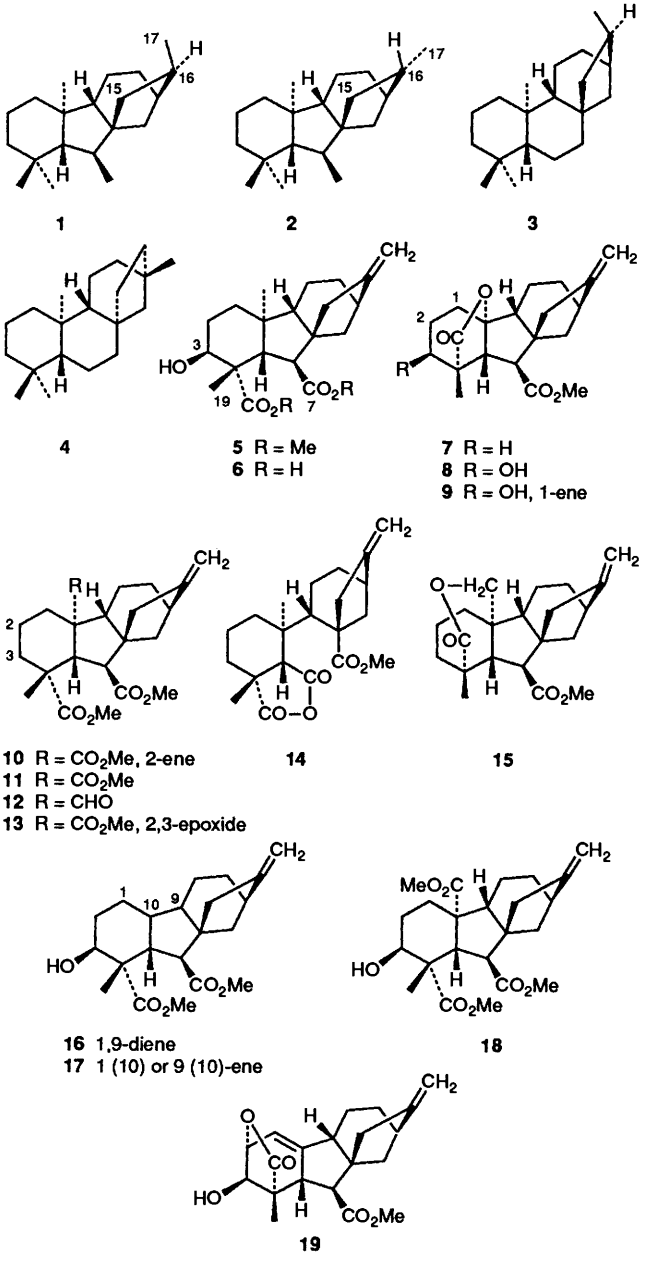
The starting material for the preparation of *ent*-gibberellane **1** was GA_{14} dimethyl ester **5**, obtained from the mother liquors of a commercial fermentation of *Gibberella fujikuroi*. The residue from these mother liquors was methylated and fractionated by flash chromatography (Table 1).

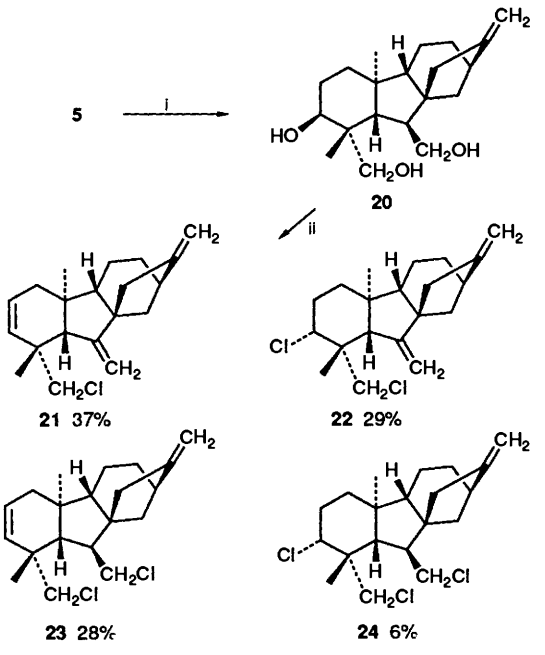
Three broad fractions were collected and analysed by GLC-mass spectrometry after trimethylsilylation (Table 1). Fraction 2 contained 67% GA_{14} dimethyl ester and was used without further purification; a middle cut of the fraction was analysed by ^1H and ^{13}C NMR and was hydrolysed to give pure GA_{14} **6**.

The first approach (Scheme 1) to the conversion of GA_{14} dimethyl ester **5** into *ent*-gibberellane **1** was the concurrent

Table 1 Compounds identified by GLC-mass spectrometry after flash chromatography of mother liquors from *Gibberella fujikuroi*

Fraction	Eluent	Compound	% in Fraction	% of Total
1	10–20% ethyl acetate in light petroleum	**13**	30	2.5
		7	17	1.5
		Unknown	12	1.0
		14	9	0.5
		10	7	0.5
		11	7	0.5
		15	6	<0.5
		12	3	≪0.5
2	20–25% ethyl acetate in light petroleum	**6**	67	23
		13	18	6
		16	9	3
		17	6	2
3	25–50% ethyl acetate in light petroleum	**9** and **19**	54	32
		8	46	27



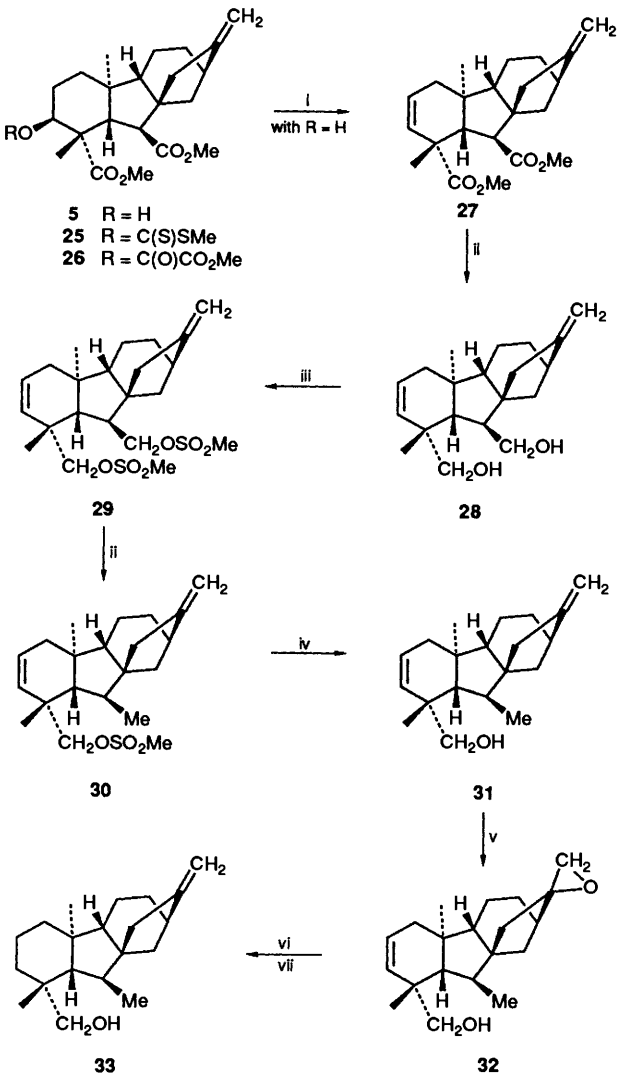


Scheme 1 *Reagents:* i, $LiAlH_4$; ii, CCl_4, Ph_3P

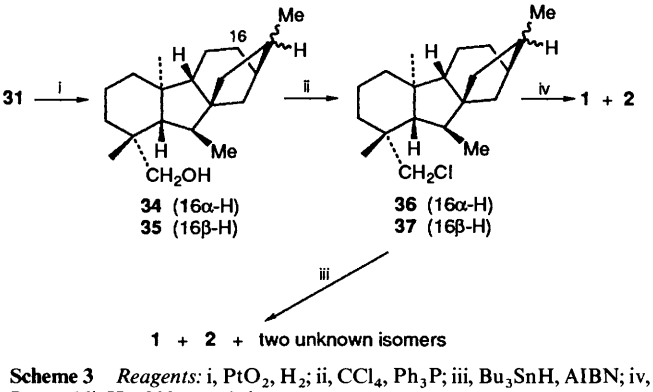
deoxygenation of all three oxygen functions. To that end GA_{14} dimethyl ester **5** was reduced with lithium aluminium hydride to the known[4] triol **20**. However, treatment of the triol **20** with carbon tetrachloride and triphenylphosphine gave a mixture of four products, possibly **21**–**24** (Scheme 1). This approach was, therefore, abandoned because of the low yield of the triol and the expected production of two pairs of epimers on hydrogenation of the two exocyclic double bonds in the mixture **21**–**24**. The individual carbon resonances and most of the hydrogen resonances in the triol **20** were assigned from the ^1H–^1H homonuclear, ^{13}C–^1H heteronuclear correlated and ^{13}C-coupled and decoupled spectra.

The next approach (Scheme 2) was based on the sequential deoxygenation of each of the oxygen functions in GA_{14} dimethyl ester **5** beginning with the 3-ol. Direct radical deoxygenation of the dithiocarbonate **25**[5] or the methyloxalyl ester **26**[6,7] was unproductive. Deoxygenation of **25** was accompanied by up to 50% isomerisation to the 15-ene; and **26** was converted into the original alcohol **5**. The 3-ol in **5** was removed by dehydration with phosphorus oxychloride. The resulting ene **27** was then reduced with lithium aluminium hydride to the diol **28** as the first step towards the deoxygenation of the two ester functions. The 7,19-dimethanesulfonate **29** of the diol **28** was selectively hydrogenolysed at C-7 with lithium aluminium hydride to give the 19-monomethanesulfonate **30**. The deoxygenation of **30** and the free alcohol **31** was investigated by a number of methods as described later. With the availability of the 19-ol **31** the opportunity was taken to prepare **33** *via* the epoxide **32**, to add to the list of similar compounds, prepared by Hanson *et al.*[8,9] as possible inhibitors of GA biosynthesis.

The direct route, shown in Scheme 3, from the 19-ol **31** (Scheme 2) to the *ent*-gibberellanes **1** and **2** was next investigated. Hydrogenation of **31** with a PtO_2 catalyst gave a mixture (3:2) of **34** and **35** and chlorination of this mixture proceeded in good yield. Treatment of the chlorides **36** and **37** with tributylstannane in toluene was complete but gave a mixture of products, not separable by TLC. GLC–MS analysis showed four isomers which, in order of retention times, were in the ratio of 8:4:5:3. Only the two lower retention time isomers were obtained, in the ratio of 7:3, when the chloro compounds



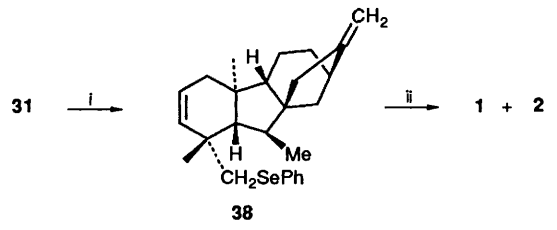
Scheme 2 *Reagents:* i, $POCl_3$, pyridine; ii, $LiAlH_4$, tetrahydrofuran; iii, $MeSO_2Cl$, pyridine; iv, 2 mol dm^{-3} NaOH; v, 3-$ClC_6H_4CO_3H$; vi, Pd-C, H_2; vii, KSeCN.



Scheme 3 *Reagents:* i, PtO_2, H_2; ii, CCl_4, Ph_3P; iii, Bu_3SnH, AIBN; iv, Raney Ni, H_2, 200 atm, 3 d

were treated with Raney nickel and hydrogen at 200 atm for 3 d. These isomers were identified (see later) as *ent*-gibberellane **1** and 16-*epi*-*ent*-gibberellane **2**. The pair of isomers with longer retention were probably the products of rearrangement of the intermediate 19-radical, formed from the epimeric 19-chloro compounds and tributylstannane.

More efficient ways of deoxygenating the 19-ol **31** were next investigated and a more successful route is shown in Scheme 4.



38

Scheme 4 *Reagents:* i, *N*-Phenylselenophthalimide, tetrahydrofuran; ii, Raney Ni, H_2, 35 psi, 18 h

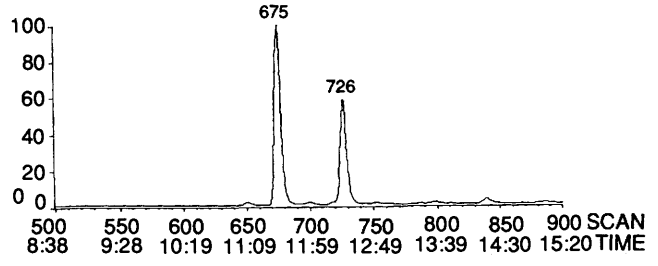


Fig. 1 Total ion current (TIC) trace from the GLC–mass spectrometry of the mixture of *ent*-gibberellane (scan 675, KRI 1926) and 16-*epi*-*ent*-gibberellane (scan 726, KRI 1957). The line diagrams of the mass spectra from scans 675 and 726 are shown in Fig. 2

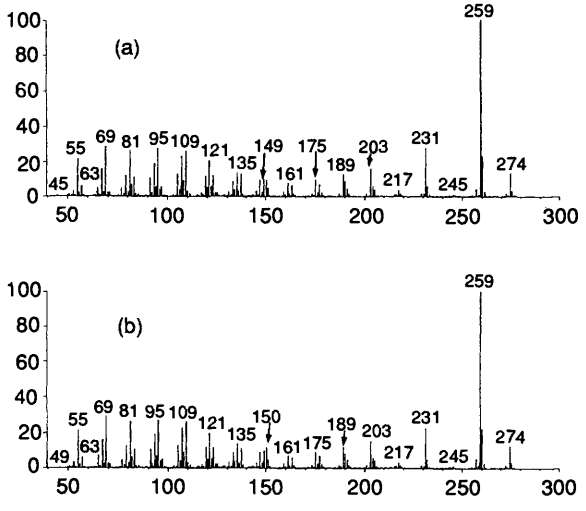


Fig. 2 GLC–mass spectra of (a) *ent*-gibberellane **1** and (b) 16-*epi*-*ent*-gibberellane **2**

Reaction of **31** with *N*-phenylselenophthalimide[10,11] gave the selenide **38** in 68% yield based on amount of **31** consumed. Deselenation of **38** with Raney nickel and hydrogen for 18 h at room temperature and 35 psi gave a mixture (73:27) of *ent*-gibberellane **1** and 16-*epi*-*ent*-gibberellane **2** in 63% yield. This 7 step synthesis of **1** and **2** from GA_{14} dimethyl ester **5** was accomplished in 11% overall yield.

Although *ent*-gibberellane **1** and 16-*epi*-*ent*-gibberellane **2** were obtained as an inseparable mixture, the epimers were separated on an analytical scale by capillary GLC–mass spectrometry. The Kovats retention indices were 1926 for *ent*-gibberellane **1** and 1957 for 16-*epi*-*ent*-gibberellane **2**. The total ion current trace from GLC–mass spectrometry is shown in Fig. 1 and the GLC mass spectra are shown in Fig. 2.

Experimental

General experimental details have been described in a previous publication[12] except that NMR spectra were recorded with JEOL FX270 or FX400 instruments for $CDCl_3$ solutions, unless the solvent is specified. *J*-Values are given in Hz. GLC–mass spectrometric analyses were carried out with a bonded FSOT OV-101 column (25 m × 0.2 mm i.d., 0.25 μm phase thickness) in a Dani 3800HR and coupled to a VG 7035 mass spectrometer with a VG 2050 data system. The GLC conditions were: injector, 250 °C; detector, 280 °C; helium carrier gas, 0.8 bar; splitless injection; temperature programme, 10 °C per min to 140 °C then 3 °C per min to 320 °C. The mass spectrometric conditions were: source, 210 °C; 24 eV; scan speed, 0.6 s per mass decade; cycle time, 1.3 s. The KRI values for *ent*-gibberellane **1** and 16-*epi*-*ent*-gibberellane **2** were determined by co-injection with n-alkalnes on a bonded FSOT OV-1 column (25 m, 0.25 μm phase thickness); injector, 250 °C; detector, 280 °C; helium carrier gas, 0.8 bar; splitless injection; temperature programme, 50 °C for 2 min then 10 °C per min to 150 °C, then to 300 °C at 3 °C per min.

Isolation of GA_{14} *Dimethyl Ester* **5** (*Table 1*).—The butyl acetate mother liquors from the isolation of GA_3 from a commercial fermentation of *Gibberella fujikuroi* were evaporated on a rotary evaporator and azeotroping with toluene. A portion (*ca.* 20 g) of the resultant viscous oil was dissolved in ethyl acetate (10 cm^3) and acetic acid (3 cm^3) and loaded on to a column (40 mm o.d.), packed with flash silica. The column was eluted with 10–60% ethyl acetate in light petroleum containing 1% acetic acid. The fraction eluted with ethyl acetate–light petroleum–acetic acid (40:60:1) was evaporated to give an orange gum (8.5 g) co-running with GA_4 and GA_7 on TLC. This fraction in methanol was methylated with diazomethane in ether and then divided into two. Each half was re-chromatographed as before except that acetic acid was omitted from the eluting solvent mixture. Elution with 10–20% ethyl acetate in light petroleum gave a 'non polar' fraction (260 mg). A sample was trimethylsilylated and analysed by GLC–mass spectrometry. The following components were identified as the methyl esters by comparison with reference spectra.[13] They are listed in order of increasing retention times with % of total fraction in parenthesis after structure number: GA_9 **7** (17%); GA_{25}-2-ene **10** (7%); GA_{25} **11** (7%); GA_{24} **12** (3%); fujenoic acid **14** (9%); GA_{25} 2,3-epoxide **13** (30%); GA_{15} **15** (6%).

Further elution of the column with 20–25% ethyl acetate in light petroleum gave the GA_{14}-containing fraction. An aliquot was trimethylsilylated and analysed by GLC–mass spectrometry. The following compounds were identified as the methyl ester trimethylsilyl ether derivatives by comparison with reference spectra.[13] They are in order of increasing retention times with % of total fraction in parentheses; **16** (7%); **17** (6%); GA_{14} **5** (67%); GA_{13} **18** (18%). A cut from the middle of this fraction contained >85% GA_{14} dimethyl ester **5** by GLC–mass spectrometry; it gave an intractable gum (lit.,[14] gum) (Found: M^+, 376.222. Calc. for $C_{22}H_{32}O_5$, 376.225); δ_H and δ_C ($CDCl_3$) contained all the signals of reference spectra.

Elution of the column with 25–30% ethyl acetate in light petroleum gave a GA_4/GA_7-containing fraction (2.3 g) that was analysed in the same way as the previous fractions; GA_7-isomeric lactone **19** (30%); GA_4 **8** (46%); GA_7 **9** (24%).

ent-3α-*Hydroxygibberell*-16-*ene*-7,19-*dioic Acid* **6**.—Gibberellin A_{14} dimethyl ester **5** (500 mg) in hexamethylphosphoramide (5 cm^3) was treated with the supernatant (25 cm^3), obtained from hexamethylphosphoramide (30 cm^3), sodium hydride (50% oil dispersion; 3 g) and redistilled propanethiol (5 cm^3). After 16 h at room temperature the solution was poured into water and was worked up in the usual way. Flash chromatography of the crude product and elution with ethyl acetate–light petroleum–acetic acid (35:65:1) gave GA_{14} **6** (203 mg) as platelets, m.p. 230–233.5 °C (from ethyl acetate–light petroleum) (lit.,[14] m.p. 232–233 °C); δ_H and probe mass spectrum, same as for authentic sample.

ent-3α,7,19-*Trihydroxygibberell*-16-*ene* **20**.—Gibberellin A_{14} dimethyl ester **5** (1.0 g) in tetrahydrofuran (20 cm^3) was added cautiously to a cold solution of lithium aluminium hydride (1.0 g) in tetrahydrofuran (50 cm^3). The mixture was heated at reflux for 3.5 h and then excess of hydride was quenched by the slow addition of methanol. Addition of water, followed by acidification and extraction with ethyl acetate gave a solid which was purified by flash chromatography. Elution with 85% ethyl acetate–light petroleum gave the required GA_{14} triol **20** (463 mg) crystallising from ethyl acetate–light petroleum in needles, m.p. 187–188 °C (lit.,[4] m.p. 182–184 °C) (Found: C, 75.0; H, 10.2%; M^+, 320.235. Calc. for $C_{20}H_{32}O_3$: C, 75.0; H, 10.1%; *M*, 320.239); $\delta_H(C_5D_5N)$ 1.11 (s, 20-H_3), 1.46 (dd, *J* 11 and 2, 14α-H), 1.54 (d, br, *J* 8, 2β-H), 1.71 (dd, *J* 11 and 5, 14β-H), 1.86 (s, 18-H_3), 2.06 (d, *J* 13, 5-H), 2.46 (dt, *J* 15 and 2.5, 15α-H), 2.51 (m, 13-H), 2.68 (m, 6-H), 3.91 (d, *J* 10.5), 3.98 (s, br, 3-H), 4.00 (dd, *J* 10.5 and 5, 7-H), 4.24 (dd, *J* 10.5 and 7, 7-H), 4.30 (d, *J* 10.5, 19-H), 4.86 (s, br, 17-H) and 5.01 (s, br, 17-H); $\delta_C(C_5D_5N)$ 27.95 (C-1), 34.84 (C-2), 72.37 (C-3), 48.96 (C-4), 51.64 (C-5), 47.42 (C-6), 63.07 (C-7), 44.34 (C-8), 58.84 (C-9), 43.05 (C-10), 17.58 (C-11), 32.70 (C-12), 39.65 (C-13), 35.81 (C-14), 42.89 (C-15), 159.93 (C-16), 105.61 (C-17), 17.74 (C-18), 67.94 (C-19) and 24.92 (C-20); *m*/*z* 320 (M^+, 45), 302 (20), 287 (37), 284 (57), 271 (85), 269 (55), 253 (100), 105 (66) and 91 (71).

Chlorination of Gibberellin A_{14} *Triol* **20**.—Gibberellin A_{14} triol **20** (300 mg) and triphenylphosphine (1.6 g) were dissolved in a mixture of carbon tetrachloride (30 cm^3) and pyridine (10 cm^3). The solution was heated to reflux for 2 h and then allowed to cool. The supernatant liquid was decanted from a dark semicrystalline residue and the solvent was removed under reduced pressure. Flash chromatography of the resultant residue gave a gum (147 mg), eluting with 10% ethyl acetate–light petroleum. Analysis of this gum by GLC–mass spectrometry showed the following 4 components in order of elution (5% of total fraction in parenthesis): (i) *ent*-19-chlorogibberella-2,6,16-triene **21** (37%); *m*/*z* 304 (M^+ + 2, 14%), 302 (M^+, 45), 287 (23), 273 (10), 267 (49), 259 (16), 253 (72), 185 (32), 169 (24), 105 (72), 93 (44), 91 (100), 81 (47), 79 (68), 77 (48), 67 (37), 57 (42), 55 (43), 43 (24) and 41 (65); (ii) *ent*-7,19-dichlorogibberella-2,16-diene **23** (28%); *m*/*z* 340 (M^+, 2, 12%), 338 (M^+, 19), 311 (17), 309 (23), 303 (52), 291 (10), 289 (24), 273 (19), 253 (25), 235 (35), 221 (27), 185 (36), 169 (31), 105 (31), 91 (100), 79 (87), 75 (46), 67 (40), 55 (51) and 41 (68); (iii) *ent*-3β,19-dichlorogibberella-6,16-diene **22** (29%); *m*/*z* 340 (M^+ + 2, 9%), 338 (M^+ 17), 327 (32), 326 (40), 325 (94), 324 (64), 323 (100), 302 (48), 289 (74), 279 (52), 253 (68), 221 (56), 155 (73), 139 (78), 105 (82), 93 (81), 91 (84), 81 (75), 78 (76), 67 (60), 55 (68) and 41 (74); (iv) *ent*-3β,7,19-trichlorogibberell-16-ene **24** (6%); *m*/*z* 378 (M^+ + 2, 11%), 376 (M^+, 33), 361 (70), 359 (10), 341 (13), 339 (51), 333 (51), 331 (50), 327 (63), 325 (76), 283 (14), 265 (79), 263 (100), 159 (58), 146 (65), 119 (79), 105 (78), 93 (76), 91 (72), 80 (77), 67 (65), 55 (68) and 41 (68).

Dimethyl ent-3α-*Methyldithiocarboxygibberell*-16-*ene*-7,19-*dioate* **25**.—Gibberellin A_{14} dimethyl ester **5** (1.36 g, 80% purity) in tetrahydrofuran (10 cm^3) was added dropwise to a cooled and stirred suspension of potassium hydride (suspension in oil, washed with light petroleum; 900 mg) and 1,4,7,10,13,16-hexaoxacyclooctadacane (18-crown-6) (5 mg) in tetrahydrofuran (20 cm^3). The mixture was stirred for 30 min and then carbon disulfide was added. Stirring was continued for 34 h after which time iodomethane (2 cm^3) was added and stirring was continued for 1 h. Excess of hydride was quenched and the mixture was poured into acidified water. Recovery in ethyl acetate followed by flash chromatography and elution with 10% ethyl acetate in light petroleum gave the dithiocarbonate **25** (692 mg) as an orange foam (Found: M^+, 466.189. $C_{24}H_{34}O_5S_2$ requires M^+, 466.185); δ_H 0.74 (s, 20-H_3), 1.14 (s, 18-H_3), 2.42 (d, *J* 12.5, 5-H), 2.60 (s, SMe), 3.35 (d, *J* 12.5, 6-H), 3.70 (s, OMe), 3.73 (s, OMe), 4.85 (s, br, 17-H), 4.91 (s, br, 17-H) and 6.91 (s, br, 3-H); *m*/*z* 466 (M^+, 3%), 450 (2), 435 (12), 418 (14), 403 (13), 358 (58), 327 (62), 326 (41), 299 (98), 283 (36), 277 (73), 239 (100) and 91 (61).

Starting material **5** (510 mg) was eluted with 25% ethyl acetate–light petroleum.

Radical Reduction of Gibberellin A_{14} *Dithiocarbonate* **25**.—The dithiocarbonate **25** (690 mg) in benzene (30 cm^3) was added dropwise to a refluxing solution of tributylstannane (1.5 cm^3) and 2,2′-azo(2-methylpropionitrile) (30 mg) in benzene (50 cm^3). Heating under reflux was continued for a further 2.5 h after which time TLC indicated complete conversion into a single product. The solvent was reduced under reduced pressure and the residue was purified by flash chromatography. Elution with 1% ethyl acetate in light petroleum removed tin residues. Further elution with 5% ethyl acetate in light petroleum gave a gum (307 mg) shown to be a mixture (1:2) of GA_{12} dimethyl ester and its 15-*endo*-isomer by ^1H NMR and GLC–mass spectrometry.

Dimethyl ent-3α-*Methyloxalyloxygibberell*-16-*ene*-7,19-*dioate* **26**.—Gibberellin A_{14} dimethyl ester **5** (380 mg) in tetrahydrofuran (20 cm^3) and pyridine (2 cm^3) was stirred with methyloxalyl chloride (0.5 cm^3) for 1 h. The reaction mixture was poured into water at pH 2 and the product was extracted with ethyl acetate. Flash chromatography of the recovered product and elution with 20% ethyl acetate in light petroleum gave the oxalate **26** as a gum (207 mg) (Found: M^+, 462.227. $C_{25}H_{34}O_8$ requires *M*, 462.225); δ_H 0.72 (s, 20-H_3), 1.14 (s, 18-H_3), 2.35 (d, *J* 12.5, 5-H), 3.22 (d, *J* 12.5, 6-H), 3.70 (s, CO_2Me), 3.93 (s, $OCOCO_2Me$), 4.83 (s, br, 17-H), 4.90 (s, br, 17-H) and 5.54 (s, br, 3-H); δ_C 14.59, 16.81, 23.67, 24.53, 32.08, 33.89, 38.86, 39.88, 43.65, 45.99, 47.76, 49.67, 50.62, 51.38, 51.83, 53.53, 56.46, 76.59, 105.33, 157.23, 158.43 and 175.80; *m*/*z* 462 (M^+, 8%), 431 (15), 430 (42), 416 (22), 376 (17), 344 (100), 342 (21), 329 (29), 328 (21), 283 (30), 164 (21) and 91 (29).

Attempted Hydride Reduction of Gibberellin A_{14} *Dimethyl Ester* 3β-*Methyl Oxalate* **26**.—The oxalate **26** (105 mg) in toluene (15 cm^3) was treated with tributylstannane (0.2 cm^3) and 2,2′-azo(2-methylpropionitrile) (10 mg) under reflux for 4 h. Analysis of the product by TLC showed a single spot co-running with GA_{14} dimethyl ester **5**.

Dimethyl ent-*Gibberella*-2,16-*diene*-7,19-*dioate* **27**.—Phosphorus oxychloride (4.0 cm^3) was added to a solution of GA_{14} dimethyl ester **5** (4.0 g) in pyridine (50 cm^3) and the mixture was heated under reflux for 45 min with the exclusion of moisture. The cooled reaction mixture was poured into water and adjusted to pH 2 with 2 mol dm^{-3} hydrochloric acid. Extraction with ethyl acetate gave a yellow gum that was subjected to flash chromatography. Elution with 10% ethyl acetate in light petroleum gave the olefin **27** (2.38 g) as an intractable gum (lit.,[15] gum) (Found: M^+, 358.216. Calc. for $C_{22}H_{30}O_4$: *M*, 358.214); δ_H 0.72 (s, 20-H_3), 1.28 (s, 18-H_3), 2.13 (d, *J* 12.5, 5-H), 3.33 (d, *J* 12.5, 6-H), 3.66 (s, CO_2Me), 3.73 (s, CO_2Me), 4.81 (s, br, 17-H), 4.91 (s, br, 17-H) and 5.63 (m, 2-H and 3-H); δ_C 15.37, 17.54, 28.81, 32.10, 37.59, 39.72, 41.13, 42.34, 45.65, 45.88, 49.35, 51.40, 51.53, 51.76, 54.07, 56.53 (C-9), 105.99 (C-17), 124.96 (C-2), 131.78 (C-3), 157.15 (C-16), 175.50 (C-7) and 176.44 (C-19); *m*/*z* 358 (M^+, 8%), 326 (41), 298 (100), 239 (40), 223 (27), 206 (28), 135 (23), 119 (15), 105 (24) and 91 (28).

ent-5,19-*Dimethylsulfonyloxygibberella*-2,16-*diene* **29**.—The

diol **28** (560 mg) in pyridine (25 cm^3) was treated with methanesulfonyl chloride (1.5 cm^3) for 4 h at room temperature. The cooled reaction mixture was poured into water and worked up in the usual way. The resultant dark oil was purified by flash chromatography. Elution with 30% ethyl acetate in light petroleum gave the required 7,19-dimesylate **29** (776 mg), crystallised from ethyl acetate–light petroleum as needles, decomp. pt. <80 °C (Found: M^+, 458.181. $C_{22}H_{34}O_6S_2$ requires *M*, 458.180); δ_H 0.90 (s, 20-H_3), 1.20 (s, 18-H), 1.41 (d, *J* 13, 5-H), 2.18 (m, 6-H), 3.03 (s, OSO_2Me), 3.05 (s, OSO_2Me), 4.22 (d, *J* 9.5, 19-H), 4.38 (d, *J* 9.5, 19-H), 4.41 (d, *J* 11, 7-H), 4.43 (d, *J* 11, 7-H), 4.85 (s, br, 17-H), 4.96 (s, br, 17-H), 5.44 (m, 2-H) and 5.75 (m, 3-H); *m/z* 458 (M^+, 67%), 443 (15), 362 (57), 347 (51), 267 (38), 266 (55), 253 (90), 251 (87), 119 (91), 105 (100), 91 (89) and 79 (88).

Lithium Aluminium Hydride Reduction of ent-7,19-*Dimethylsulfonyloxygibberella*-2,16-*diene* **29**.—The dimethanesulfonate **29** (1.23 g) in tetrahydrofuran (50 cm^3) was added to a cold solution of lithium aluminium hydride (1.2 g) in tetrahydrofuran (50 cm^3), after which the mixture was heated under reflux for 50 min. Methanol was added to the reaction mixture at 0 °C. After the addition of water and acidification with 2 mol dm^{-3} hydrochloric acid, the mixture was extracted with ethyl acetate. The recovered solid was purified by flash chromatography. Elution with 15% ethyl acetate in light petroleum gave *ent*-19-methylsulfonyloxygibberella-2,16-diene **30** (703 mg) as a gum (Found: M^+, 364.205. $C_{21}H_{32}O_3S$ requires M, 364.207); δ_H 0.86 (s, 20-H_3), 1.08 (d, *J* 7, 7-H_3), 1.21 (s, 18-H_3), 3.01 (s, OSO_2Me), 4.22 (d, *J* 9.5, 19-H), 4.35 (d, *J* 9.5, 19-H), 4.79 (s, br, 17-H), 4.93 (s br, 17-H), 5.44 (dd, *J* 10 and 2.5, 2-H) and 5.71 (m, 3-H); *m/z* 364 (M^+, 28%), 349 (70), 268 (22), 255 (100) and 253 (31).

In a repeat experiment the dimesylate **29** (503 mg) gave, as the sole product, *ent*-19-hydroxygibberella-2,16-diene **31** as a gum (234 mg) (Found: M^+, 286.229. $C_{20}H_{30}O$ requires *M*, 286.230); δ_H 0.84 (s, 20-H_3), 1.07 (d, *J* 7, 7-H_3), 1.16 (s, 18-H_3), 3.63 (d, *J* 11, 19-H), 3.84 (d, *J* 11, 19-H), 4.78 (s, br, 17-H), 4.92 (s, br, 17-H), 5.53 (dd, *J* 10 and 2.5, 2-H) and 5.64 (ddd, *J* 10, 5.5 and 2.0, 3-H); *m/z* 286 (M^+, 34%), 271 (11), 255 (100), 199 (12), 187 (43), 119, (32), 107 (49), 105 (39), 91 (46), 79 (27) and 45 (26).

ent-19-*Hydroxygibberella*-2,16-*diene* **31**.—A solution of *ent*-19-dimethylsulfonyloxygibberella-2,16-diene **30** (220 mg) in methanol (15 cm^3) and 2 mol dm^{-3} sodium hydroxide (10 cm^3) was stirred for 18 h at room temperature. After work-up the residue was purified by flash chromatography. Elution with 15% ethyl acetate in light petroleum gave the 19-hydroxy diene **31** (146 mg), spectroscopically identical with that described in the previous section.

ent-16β,17-*Epoxy*-19-*hydroxygibberell*-2-*ene* **32**.—The 2,16-diene **31** (750 mg) in chloroform (30 cm^3) was treated with 3-chloroperbenzoic acid (565 mg, 1.1 equiv.) overnight at 5 °C. The mixture was diluted with chloroform, washed with saturated aqueous sodium hydrogen carbonate and the organic phase was recovered. The solvent was removed under reduced pressure and the residual gum was fractionated by flash chromatography. Elution with 15% ethyl acetate in light petroleum gave starting material **31** (114 mg), followed by the 16,17-epoxide **32** (473 mg) as a gum (Found: M^+, 302.224. $C_{20}H_{30}O_2$ requires *M*, 302.225); δ_H 0.89 (s, 20-H_3), 1.10 (d, *J* 7, 7-H_3), 1.15 (s, 18-H_3), 1.86 (d, *J* 13, 5-H), 2.84 (s, br, 17-H_2), 3.64 (d, *J* 11, 19-H), 3.82 (d, *J* 11, 19-H), 5.54 (m, 2-H) and 5.65 (m, 3-H); *m/z* 302 (M^+, 12%), 287 (24), 271 (100), 253 (27), 203 (31), 145 (18), 107 (25) and 91 (19).

ent-19-*Hydroxygibberell*-16-*ene* **33**.—A solution of the epoxide **32** (470 mg) in methanol (20 cm^3) was stirred rapidly with palladium on carbon (50 mg) in an atmosphere of hydrogen until uptake had ceased. The catalyst was removed by filtration through Celite and the filtrate was evaporated under reduced pressure. The resultant gum, methanol (10 cm^3) and potassium selenocyanide (550 mg) were heated under reflux for 5 h. The supernatant was decanted from elemental selenium, reduced in volume under reduced pressure and poured into water. The product, recovered in ethyl acetate, was purified by flash chromatography. Elution with 10% ethyl acetate in light petroleum gave the 19-ol **33** (207 mg) as a gum (Found: M^+, 288.245. $C_{20}H_{32}O$ requires *M*, 288.245); δ_H 0.85 (s, 20-H_3), 1.03 (d, *J* 7, 7-H), 1.08 (s, 18-H_3), 3.74 (s, br, 19-H_2) and 4.77 and 4.91 (s, br, 17-H_2); *m/z* 288 (M^+, 81%), 286 (6), 273 (100), 259 (31), 275 (98), 255 (39), 187 (23), 156 (34), 139 (27), 119 (30), 95 (39), 55 (30) and 41 (34).

ent-19-*Hydroxygibberellane* 16-*Epimers* **34** *and* **35**.—The dienol **31** (80 mg) in ethyl acetate (20 cm^3) was stirred with platinum oxide (10 mg) under an atmosphere of hydrogen for 2 h at ambient temperature and pressure. The reaction mixture was filtered through Celite and the filtrate was evaporated to dryness under reduced pressure. Analysis of the resultant gum (73 mg) by GLC–mass spectrometry as the MeTMSi derivative showed the following two components: (a) *ent*-19-hydroxy-16αH-gibberellane **35** (38%); *m/z* (TMSi ether) 362 (M^+, 7%), 347 (22), 319 (3), 272 (23), 271 (10), 259 (100), 257 (29), 243 (13), 229 (31), 189 (34), 163 (44), 149 (45), 109 (84), 103 (21), 95 (73), 81 (52), 75 (34) and 73 (76); and (b) *ent*-19-hydroxygibberellane **34** (62%); *m/z* (TMSi ether) 362 (M^+, 16%), 247 (65), 319 (9), 272 (57), 259 (100), 257 (67), 241 (22), 229 (59), 215 (21), 203 (35), 189 (56), 163 (69), 149 (72), 109 (92), 103 (42), 95 (85), 81 (78), 75 (49) and 73 (84).

ent-19,*Chlorogibberellane* 16-*Epimers* **36** *and* **37**.—*ent*-19-Hydroxygibberellane 16-epimers **34** and **35** (209 mg) and triphenylphosphine (400 mg) in carbon tetrachloride (10 cm^3) and pyridine (5 cm^3) were allowed to react and the reaction mixture then worked up as described for the GA_{14} triol **20**. Flash chromatography of the crude product and elution with light petroleum afforded the 16-epimers **36** and **37** of *ent*-19-chlorogibberellane as an oil (153 mg) (Found: M^+, 308.227. $C_{20}H_{33}{}^{35}Cl$ requires *M*, 308.227); δ_H 0.83 (s, 20-H_3), 0.93 (d, *J* 6, 16β-Me), 0.94 (d, *J* 7, 16α-Me), 1.01 (d, 7, 7-H_3), 1.11 (s, 18-H_3), 3.60 (d, *J* 11, 19-H) and 3.86 (d, *J* 11, 19-H); *m/z* 310 (M^+ + 2, 4%), 308 (M^+, 10), 295 (36), 293 (100), 273 (6), 272 (6), 267 (13), 265 (38), 262 (55), 259 (11), 257 (5), 217 (5) and 183 (25).

Reduction of ent-19-*Chlorogibberellane* 16-*Epimers* **36** *and* **37**.—(a) *With tributylstannane*. A solution of the chlorides **36** and **37** (50 mg) in toluene (10 cm^3) was treated with tributylstannane (50 mm^3) and 2,2′-azo(2-methylpropionitrile) (5 mg) and heated under reflux for 2.5 h. TLC indicated complete conversion into a single product. Distillation of the solvent under reduced pressure followed by flash chromatography and elution with light petroleum gave a mobile oil (78 mg), containing organotin residues that precluded NMR analysis. GLC–mass spectrometric analysis detected the following four components in order of increasing retention times: **2** *m/z* 274 (M^+, 16%), 259 (100), 231 (41), 217 (4), 203 (28), 189 (19), 177 (12), 175 (15), 150 (15), 149 (16), 137 (19), 135 (21), 121 (26), 109 (32), 95 (35), 81 (41), 69 (28) and 55 (16); **1** *m/z* 274 (M^+, 23%), 259 (100), 231 (47), 217 (4), 203 (31), 189 (20), 177 (13), 175 (18), 150 (22), 149 (19), 137 (19), 135 (26), 121 (32), 109 (42), 95 (43), 81 (34), 69 (36) and 55 (15); (unknown) *m/z* 274 (M^+, 22%), 259 (100), 231 (20), 217 (43), 203 (10), 189 (15), 177 (12), 175 (7), 150 (32), 149 (19), 137 (4), 135 (17), 121 (24), 109

(23), 95 (47), 81 (32), 69 (25) and 55 (15); (unknown) *m/z* 274 (M^+, 24%), 259 (100), 231 (19), 217 (35), 203 (13), 189 (16), 177 (15), 175 (12), 150 (47), 149 (21), 137 (6), 135 (19), 121 (29), 109 (32), 95 (62), 81 (35), 69 (31) and 55 (16).

(b) *With Raney nickel.* A solution of the chloride **36** and **37** (60 mg) in ethanol (15 cm^3) and triethylamine (1 cm^3) and Raney nickel (*ca.* 600 mg) were pressurised to 200 atm with hydrogen in a rocking autoclave and heated at 60 °C for 3 d. The catalyst was removed by filtration through Celite and the filtrate was diluted with ethyl acetate, washed with 2 mol dm^{-3} hydrochloric acid and evaporated to dryness under reduced pressure. Analysis of the residual gum (51 mg) by GLC–mass spectrometry indicated a pure mixture of *ent*-gibberellane **1** (70%) and 16-*epi*-*ent*-gibberellane **2** (30%); see later for characterisation.

ent-19-*Phenylselenogibberella*-2,16-*diene* **38**.—A mixture of *N*-phenylselenophthalamide (200 mg, 2 equiv.) and tributylphosphine (300 mg, 2 equiv.) in tetrahydrofuran (6 cm^3) was stirred at room temperature for 10 min. *ent*-19-Hydroxygibberella-2,16-diene **31** (100 mg, 1 equiv.) was added and the mixture was stirred first at room temperature for 20 min, and then under reflux for 4 h. The solvent was removed by distillation under reduced pressure and the residual oil was purified by flash chromatography. Elution with 2% ethyl acetate in light petroleum gave the phenyl selenide **38** as an oil (59 mg) (Found: M^+, 426.180. $C_{26}H_{34}{}^{80}Se$ requires M, 426.183); δ_H 0.86 (s, 20-H_3), 1.04 (d, *J* 7, 7-H), 1.20 (s, 18-H_3), 3.08 (d, *J* 11, 19-H), 3.42 (d, *J* 11, 19-H), 4.78 (s, br, 17-H), 4.92 (s, br, 17-H), 5.58 (ddd, *J* 10, 5.5 and 1.5, 2-H), 5.70 (dd, *J* 10 and 2.5, 3-H), 7.23 (m, 3 H, SePh) and 7.50 (m, 2 H, SePh); *m/z* 428 (M^+, ^{82}Se, 14%), 427 (M^+, ^{81}Se, 20), 426 (M^+, ^{80}Se, 54), 424 (M^+, ^{78}Se, 28), 423 (M^+, ^{77}Se, 14), 269 (100), 255 (65), 213 (13), 199 (19), 187 (46), 157 (15), 121 (35), 119 (36), 105 (30) and 77 (16).

Elution with 5% ethyl acetate in light petroleum gave unchanged reagent and elution with 5% ethyl acetate in light petroleum gave starting material **31** (27 mg).

Reduction of ent-19-*Phenylselenogibberella*-2,16-*diene* **38**.—The 19-phenylseleno-2,16-diene **38** (52 mg), ethanol (15 cm^3), triethylamine (1 cm^3) and Raney nickel (*ca.* 300 mg) were shaken for 18 h with hydrogen at 35 psi in a Parr hydrogenator. The reaction mixture was filtered through Celite and the solvent was removed under reduced ressure. The resultant oil (21 mg) was characterised as a mixture of *ent*-gibberellane **1** (73%) and 16-*epi*-*ent*-gibberellane **2** (27%) by GLC–mass spectrometry (see Figs. 1 and 2).

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