2β-Isopropylidene-, 2β-t-Butyl-, and 2β-Isopropyl-gibberellin A_4 and Spiro[gibberellin A_4-2,1′-cyclopropane]

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2-Bis(methylthio)methylene-3-oxogibberellin A_9 methyl ester (**9**), prepared from 3-oxogibberellin A_9 methyl ester (**25**), was used as a synthon to prepare 2-isopropylidenegibberellin A_4 (**14**), 2β-t-butylgibberellin A_4 (**18**), 2β-isopropylgibberellin A_4 (**22**), and spiro[gibberellin A_4-2,1′-cyclopropane] (**48**). Spiranation of 3-oxogibberellin A_9 methyl ester (**25**) was also achieved directly by reaction with 2-chloroethyldimethylsulphoxonium iodide. The preparation of 2α-alkyl derivatives of gibberellin A_4 from the synthon (**9**) was not achieved, hydride reduction of the 2α-alkyl 3-ketones giving the 3α-hydroxy epimers.

Previously we have reported[1,2] that 2,2-dimethylgibberellin A_4 (2,2-dimethyl-GA_4) (**1**)[3,4] and 2,2-dimethylgibberellin A_1 (2,2-dimethyl-GA_1) (**2**)[4] are 10—100 times more active than the parent compounds, GA_4 (**3**) and GA_1 (**4**), in stem elongation assays based on monocotyledonous plants. This enhanced biological activity of the 2,2-dimethyl derivatives is not attributable to the 2β-alkyl substituent since 2β-methyl-GA_4 (**5**) and 2β-methyl-GA_1 (**6**) have[1,2] about the same activities as the parent gibberellins and the activities[2] of 2β-methyl-GA_1, 2β-ethyl-GA_1, 2β-propyl-GA_1 and 2β-butyl-GA_1[5] decrease in that order. Continuing our investigation into the effect of 2-alkylation on the biological properties of GA_4 (**3**) and GA_1 (**4**), we have prepared a series of bulky 2β-substituted derivatives of GA_4 (**3**) as described in this paper. The synthesis of a homologous series of 2α-alkyl derivatives of GA_4 (**3**) and GA_1 (**4**) is presented in the following paper.

Results and Discussion

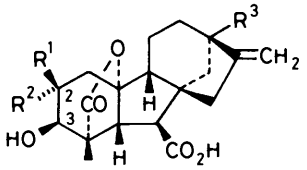
Corey and Chen[6] have described the reaction of lithium dimethylcuprate with α-bis(methylthio)methylene ketones to give α-isopropylidene ketones and α-t-butyl ketones. Applying these procedures, we have used the 2-bis(methylthio)methylene 3-ketone (**9**) to prepare 2β-isopropylidene-GA_4 (**14**) and 2β-t-butyl-GA_4 (**18**). Partial reduction of (**9**) to give the (*E*)-2-methylthiomethylene ketone (**12**) allowed preparation of 2β-isopropyl-GA_4 (**22**) by the method used to prepared 2β-t-butyl-GA_4 (**18**) from (**9**). The synthon (**9**) was prepared in 86% yield by treatment of 3-oxo-GA_9 methyl ester (**25**) with carbon disulphide and lithium 2,4,6-tri-t-butylphenoxide followed by methyl iodide.

2-Isopropylidenylgibberellin A_4 (**14**).—Reaction of the 2-bis(methylthio)methylene 3-ketone (**9**) with 2 mol equiv. of lithium dimethylcuprate gave the 2-isopropylidene 3-ketone (**10**). 1,2-Reduction of this ketone (**10**) with sodium borohydride and cerium(III) chloride in methanol at −70 °C gave 2-isopropylidene-3-*epi*-GA_4 methyl ester (**15**) which, on demethylation with sodium propane-1-thiolate in hexamethylphosphoramide, afforded a mixture of 2-isopropylidene-GA_4 (**14**) and 2-isopropylidene-3-*epi*-GA_4 (**16**) in the ratio 4:1. The stereochemistry at C-3 in the alcohols (**14**)—(**16**) was assigned from the chemical shifts of the 5- and 6-protons[7] in their ^1H n.m.r. spectra. and confirmed by an *X*-ray crystal structure determination[8] for 2-isopropylidene-GA_4 (**14**).

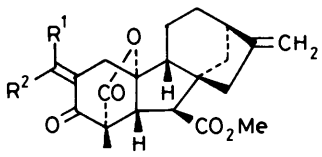
Epimerisation at C-3 during demethylation of the methoxycarbonyl group of the 3α-hydroxy ester (**15**) with sodium propane-1-thiolate was unexpected, since these conditions do not lead to 3-epimerisation in the demethylation of 3-hydroxy-C_{19}-GA methyl esters.[9] However the epimerisation of GA_4 methyl ester (**35**) and 3-*epi*-GA_4 methyl ester (**36**) with aqueous alkali is known to occur by a retro-aldol condensation,[10,11] and it is possible that the observed epimerisation of (**15**) was catalysed by adventitious aqueous base during the reaction or work-up. The predominance of the 3β-epimer (**14**) over the 3α-epimer (**16**) is also notable since the 3α-epimer is the major product[10,11] when 3-hydroxygibberellins are treated with dilute aqueous alkali. Here the 3α(*eq*)-epimer (**16**) may be less stable than the 3β-(*ax*)-epimer (**14**) because of the steric interaction between the 3α-hydroxy group and the proximate methyl of the 2-isopropylidene group. For example, with potassium carbonate in refluxing aqueous methanol, 2-isopropylidene-3-*epi*-GA_4 methyl ester (**15**) gave the 3β-epimer (**17**), while 2-methylene-3-*epi*-GA_4 methyl ester (**42**) and (*E*)-2-ethylidene-3-*epi*-GA_4 methyl ester (**43**) (both described later) were unchanged. The interaction of the 2-isopropylidene group and the 3-substituent was also indicated by the *X*-ray crystal structure[8] of 2-isopropylidene-GA_4 (**14**), in which ring *A* was flattened with an angle of 33° for O(3),C(3),C(2),C(2′). Further evidence for this interaction is provided by the u.v. spectra of the enone chromophores of the 2-isopropylidene 3-ketone (**10**) and the 2-bis(methylthio)methylene 3-ketone (**9**), which showed lower molecular extinction coefficients (6300 and 6970 l mol^{-1} cm^{-1}, respectively) than the (*E*)-2-ethylidene (**11**) and (*E*)-2-mono(methylthio)methylene (**12**) ketones (10 157 and 15 252 l mol^{-1} cm^{-1}, respectively).

2β-t-Butylgibberellin A_4 (**18**).—The synthon (**9**) and 4 mol equiv. of lithium dimethylcuprate gave the 2β- and 2α-t-butyl ketones (**26**) and (**27**) in the ratio 11:1. A similar mixture was also obtained from the 2-isopropylidene ketone (**10**) and 1.5 mol equiv. of lithium dimethylcuprate. The 2β-t-butyl isomer (**26**), obtained by flash chromatography of the mixture, was reduced by sodium borohydride in methanol to give a separable mixture of the 3β- and 3α-alcohols (**19**) and (**20**) in the ratio of 4:1. Demethylation of 2β-t-butyl-GA_4 methyl ester (**19**) with sodium propane-1-thiolate gave 2β-t-butyl-GA_4 (**18**) and a minor amount of 2β-t-butyl-3-*epi*-GA_4 (**21**), which was not obtained pure. The stereochemistry of 2β-t-butyl-GA_4 (**18**) was determined by *X*-ray crystallography,[8] which showed that ring *A* was close to a normal chair conformation with an equatorial 2β-butyl and an axial 3β-hydroxy group.

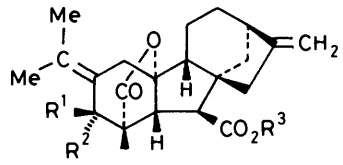
2β-Isopropyl-GA_4 (**22**).—Treatment of the synthon (**9**) with a zinc–copper couple in refluxing acetone gave the (*E*)-2-



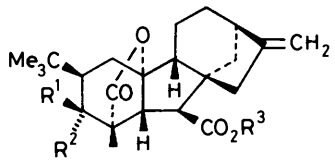
(1) R^1 = R^2 = Me, R^3 = H
(2) R^1 = R^2 = Me, R^3 = OH
(3) R^1 = R^2 = R^3 = H
(4) R^1 = R^2 = H, R^3 = OH
(5) R^1 = Me, R^2 = R^3 = H
(6) R^1 = Me, R^2 = H, R^3 = OH
(7) R^1 = H, R^2 = Et, R^3 = H
(8) R^1 = H, R^2 = Pr^i, R^3 = H



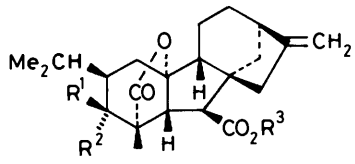
(9) R^1 = R^2 = SMe
(10) R^1 = R^2 = Me
(11) R^1 = Me, R^2 = H
(12) R^1 = SMe, R^2 = H
(13) R^1 = R^2 = H



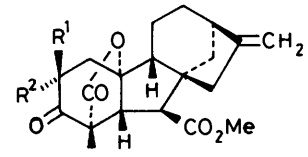
(14) R^1 = OH, R^2 = R^3 = H
(15) R^1 = H, R^2 = OH, R^3 = Me
(16) R^1 = R^3 = H, R^2 = OH
(17) R^1 = OH, R^2 = H, R^3 = Me



(18) R^1 = OH, R^2 = R^3 = H
(19) R^1 = OH, R^2 = H, R^3 = Me
(20) R^1 = H, R^2 = OH, R^3 = Me
(21) R^1 = R^3 = H, R^2 = OH



(22) R^1 = OH, R^2 = R^3 = H
(23) R^1 = OH, R^2 = H, R^3 = Me
(24) R^1 = H, R^2 = OH, R^3 = Me

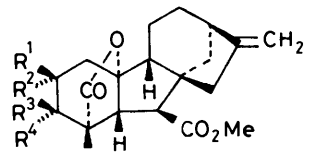


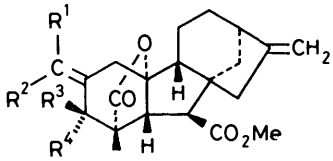
(25) R^1 = R^2 = H
(26) R^1 = Bu^t, R^2 = H
(27) R^1 = H, R^2 = Bu^t
(28) R^1 = Pr^i, R^2 = H
(29) R^1 = H, R^2 = Pr^i
(30) R^1 = Me, R^2 = H
(31) R^1 = H, R^2 = Me
(32) R^1 = R^2 = Me
(33) R^1 = Et, R^2 = H
(34) R^1 = H, R^2 = Et

mono(methylthio)methylene 3-ketone (**12**) in 74% yield; a slightly improved yield (78%) was obtained at room temperature by ultrasonication. The *E*-stereochemistry in the product (**12**) was established by nuclear Overhauser effect (n.O.e.) experiments: irradiation at the frequency of the *S*-methyl signal enhanced the 2′-H and upfield 1-H signals, and irradiation at the 2′-H and upfield 1-H frequencies enhanced the *S*-methyl signal, but no mutual enhancement of 2′-H and 1-H signals was observed.

Reaction of the (*E*)-2-mono(methylthio)methylene 3-ketone (**12**) with 3.5 mol equiv. of lithium dimethylcuprate at 5 °C in diethyl ether gave equal amounts of 2β- and 2α-isopropyl 3-ketones (**28**) and (**29**), which were separated by flash chromatography. In the ^{1}H n.m.r. spectra of both isomers the prochiral isopropyl groups showed pairs of methyl doublets with *J* 7.1 Hz. Reduction of the 3-ketone (**28**) with sodium borohydride in propan-2-ol gave equal amounts of the 3β-ol (**23**) and the 3α-ol (**24**). An *X*-ray crystal structure determination[8] for the 3β-ol (**23**) confirmed the assignment of stereochemistry at C-2 and C-3. Demethylation of the 3β-ol (**23**) with sodium propane-1-thiolate in hexamethylphosphoramide gave 2β-isopropyl-GA_4 (**22**) without epimerisation.

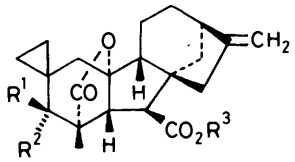
Spiro[*gibberellin* A_4-2,1′-*cyclopropane*] (**48**).—The first approach to the preparation of the spiran (**48**) was *via* 2-methylene-3-oxo-GA_9 methyl ester (**13**). The reductive removal of both methylthio groups in the synthon (**9**) was under several reducing conditions was investigated. With Raney nickel either over-reduction or no reaction occurred. Nickel boride and tributylstannane, either palladium-(0)-catalysed or with nonacarbonyldi-iron, gave the (*E*)-2-mono(methylthio)methylene 3-ketone (**12**) in low yield. Sodium borohydride with copper(I) bromide below −20 °C and tributylstannane with 2,2′-azobis-(2-methylpropiononitrile) gave no reaction. With sodium borohydride and tetrakis(triphenylphosphine)palladium(0) in tetrahydrofuran a mixture of 2-bis(methylthio)methylene-GA_4 methyl ester (**44**) and (*E*)-2-mono(methylthio)methylene-GA_4 methyl ester (**45**) was obtained in the ratio 6:4, respectively. The 3β-stereochemistry of both products (**44**) and (**45**) was assigned from the ^{1}H n.m.r. chemical shift of the 5-protons, and the (*E*)-stereochemistry in (**45**) was assigned from the chemical shift of the 3α-proton [4.08 p.p.m., similar to that (3.86 p.p.m.) in GA_4 methyl ester (**35**) and different from that (5.01 p.p.m.) in 2-bis(methylthio)methylene-GA_4 methyl ester (**44**)]. In the absence of the palladium(0) catalyst, reduction of (**9**) with sodium borohydride gave the 2-bis(methylthio)methylene-3β-ol (**44**) in tetrahydrofuran and the epimeric 3α-ol (**46**) in methanol. Thus the palladium(0) catalyst appears to promote 1,4-reduction and the solvent appears to control the stereochemistry of 1,2-reduction.



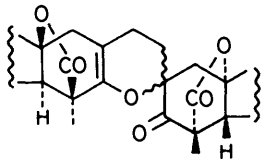


	R^1	R^2	R^3	R^4
(35)	H	H	OH	H
(36)	H	H	H	OH
(37)	H	Pr^i	H	OH
(38)	H	Me	H	OH
(39)	Me	H	OH	H
(40)	Me	H	H	OH
(41)	H	Me	OH	H

	R^1	R^2	R^3	R^4
(42)	H	H	H	OH
(43)	Me	H	H	OH
(44)	SMe	SMe	OH	H
(45)	SMe	H	OH	H
(46)	SMe	SMe	H	OH
(47)	SMe	H	H	OH



(48) R^1 = OH, R^2 = R^3 = H
(49) R^1R^2 = O, R^3 = Me
(50) R^1 = OH, R^2 = H, R^3 = Me
(51) R^1 = H, R^2 = OH, R^3 = Me



(52)

Didesulphurisation of the 2-bis(methylthio)methylene 3-ketone (**9**) was achieved in low yield by treatment with a zinc–copper couple in refluxing acetone containing a trace of acetic acid for 16 h. The 1,4-reduction products (**30**) and (**31**) and the 1,2-reduction product (**42**) were obtained in yields of 18, 18, and 12% respectively. A higher yield (29%) of the enol (**42**) was obtained by adding a large excess of freshly prepared zinc–copper couple in portions over 2 h; the 2β-methyl 3-ketone (**30**) was the only other product in this case. In the ^{1}H n.m.r. spectrum of the enol (**42**) the 2-methylene protons appear as two broad singlets at 5.12 and 5.40 p.p.m. and the signals for the geminally coupled 1-protons (J 15.1 Hz) occurred at 2.34 and 2.89 p.p.m. Irradiation at the frequency of the methylene proton signal at 5.12 p.p.m. gave an n.O.e. enhancement of the 1-H signal at 2.89 p.p.m. and the methylene proton signal at 5.40 p.p.m. Irradiation at the frequency of the 1-H signal at 2.34 p.p.m.. coupled (J 2.4 Hz) to both the methylene protons, enhanced only the 1-H signal at 2.89 p.p.m. Thus the signal at 5.12 p.p.m. was assigned to the methylene proton *cis* to C-1.

Oxidation of the methylene 3α-ol (**42**) with Jones reagent, manganese dioxide, or pyridinium dichromate yielded, not the enone (**13**). but the dimer (**52**), characterised by ^{1}H and ^{13}C n.m.r. The dimerisation of α-methylene ketones by 1,4-cycloaddition is well documented.[12,13] Thermal reversal of the dimerisation was indicated by the mass spectrum of the dimer (**52**); the electron impact spectrum, obtained by direct insertion, gave an ion at m/z 356, corresponding to the molecular ion of the monomer (**13**). as the highest significant ion, and g.l.c.–mass spectrometry showed only one g.l.c. peak, with M^+ 356. Indeed, reaction of the dimer (**52**) with dimethylsulphoxonium methylide in dimethyl sulphoxide at 140 °C gave the spiro ketone (**49**) in 84% yield. However the overall yield of the spiro ketone (**49**) from 3-oxo-GA_9 methyl ester (**25**) was only *ca.* 10%.

An improved yield (28%) of the spiro ketone (**49**) was obtained directly from 3-oxo-GA_9 methyl ester (**25**) by treatment with lithium di-isopropylamide and 2-chloroethyldimethylsulphonium iodide[14] in tetrahydrofuran, containing hexamethylphosphoramide. Reduction of the spiro ketone (**49**) with sodium borohydride in propan-2-ol gave about equal amounts of the 3β- and 3α-ols (**50**) and (**51**), the stereochemistry being assigned from the chemical shifts for the 5-protons in the ^{1}H n.m.r. spectra. The magnetic anisotropy of the cyclopropane ring was evident from the chemical shift of the 3α-proton in the 3β-ol (**50**) [2.85 p.p.m.; *cf.* that (3.86 p.p.m.) for the 3α-proton in GA_4 methyl ester (**35**); the signal for the 3β-proton in the 3α-ol (**51**) is unaffected, occurring at 3.80 p.p.m. as compared with 3.73 p.p.m. for the 3β-proton in 3-*epi*-GA_4 methyl ester (**36**)]. The π-character of the cyclopropyl ring may also account for the observation that the 3β-ol (**50**) is more polar than the 3α-ol (**51**) which is the reverse of the situation found for the methyl ester (**35**) and its 3-epimer (**36**). The 1:1 ratio of 3β- and 3α-epimers (**50**) and (**51**) from reduction of the spiro ketone (**49**) contrasts with the 1:9 ratio obtained[4] by reduction of 2,2-dimethyl-3-oxo-GA_9 methyl ester (**32**) under the same conditions. Demethylation of the spiran methyl ester (**50**) with sodium propane-1-thiolate in hexamethylphosphoramide gave spiro[gibberellin A_4-2,1′-cyclopropane] (**48**).

Attempted Preparation of 2α-Substituted Gibberellin A_4 Derivatives.—(*E*)-2-Mono(methylthio)methylene-3-oxo-GA_9 methyl ester (**12**), described earlier, is a potential precursor of 2α-ethyl-GA_4 (**7**) and 2α-isopropyl-GA_4 (**8**). Preparation of the latter (**8**) was attempted from 2β-isopropyl-3-oxo-GA_9 (**28**), formed as described earlier from the reaction of the (*E*)-2-mono(methylthio)methylene ketone (**12**) and 2.5 mol equiv. of lithium dimethylcuprate. Treatment of the 2β-isopropyl ketone (**28**) with lithium di-isopropylamide in diethyl ether, then quenching with dilute aqueous acid, gave the 2α-isopropyl ketone (**29**) in 71% yield. Reduction of the 2α-isopropyl ketone (**29**) with sodium borohydride in propan-2-ol resulted in epimerisation at C-2, affording the 2β-isopropyl 3β-and 3α-epimers (**23**) and (**24**) in equal amounts. Reduction of the 2α-isopropyl ketone (**29**) with sodium borohydride in tetrahydrofuran was slow and incomplete, giving 2β-isopropyl ketone (**28**) as well as the 3β- and 3α-alcohols (**23**) and (**24**); this result indicates that epimerisation of C-2 occurs before borohydride reduction. Under neutral conditions (zinc borohydride in diethyl ether or dimethoxyethane) no reduction occurred. However with sodium cyanoborohydride the 2α-isopropyl ketone (**29**) was reduced in 55% yield to a single alcohol which was neither the 3β- nor the 3α-epimer [(**23**) or (**24**)] with 2β-isopropyl stereochemistry. This reduction product must therefore retain the 2α-isopropyl group, but the stereochemistry of the 3-hydroxy group is uncertain. The structure (**37**) with a 3α-OH is the more probable since the ^{1}H n.m.r. spectrum showed $J_{2,3}$ 4.4 Hz, and since the analogous reduction of 2α-methyl-3-oxo-GA_9 methyl ester (**31**) gave a single product, identified as 2α-methyl-3-*epi*-GA_4 methyl ester (**38**) by its difference from the known 2β-methyl-GA_4 methyl ester (**39**),[3] 2β-methyl-3-*epi*-GA_4 methyl ester (**40**),[3] and 2α-methyl-GA_4 methyl ester (**41**).[15] Reduction of 2α-alkylated GA_4 3-ketones by metal hydrides is therefore not a viable route to 2α-alkyl derivatives of GA_4.

In parallel studies directed towards 2α-ethyl-GA_4 (**7**), (*E*)-2-ethylidene-3-oxo-GA_9 methyl ester (**11**) was prepared in 71% yield from (*E*)-2-mono(methylthio)methylene-3-oxo-GA_9 methyl ester (**12**) and 1.1 mol equiv. of lithium dimethylcuprate at −50 °C. However, catalytic hydrogenation of the 2-ethylidene 3-ketone (**11**), after prior protection of the 16,17-double bond by epoxide formation, gave back unchanged epoxide. Reduction of the 2-ethylidene 3-ketone (**11**) with zinc–copper couple gave mainly the 1,2-reduction product (**43**) and traces of 1,4-reduction products [the 2β- and 2α-ethyl 3-ketones

(**33**) and (**34**)]. The products (**33**) and (**34**) were also obtained by reduction with tributylstannane and tetrakis(triphenylphosphine)palladium(0) but only in moderate yield. Hydride reduction of the 2α-ethyl 3-ketone (**34**) was not attempted in view of the earlier results with the 2α-isopropyl and 2α-methyl ketones (**29**) and (**31**). A successful route to 2α-alkylated gibberellins is described in the following paper.[15]

Experimental

All solvents were redistilled and purified, where necessary, as described by Perrin *et al.*[16] Light petroleum refers to the fraction of boiling range 60—80 °C. T.l.c. was performed on aluminium-backed Kieselgel 60 F_{254} (0.2 mm thickness), eluted with ethyl acetate–light petroleum (3:1 for GA_1/GA_3 derivatives and 1:2 for GA_4/GA_7 derivatives plus 1% acetic acid for carboxylic acids); compounds were located by spraying with 5% sulphuric acid in ethanol then heating at 80 °C, or occasionally by use of iodine vapour or u.v. light. For flash chromatography, column sizes and solvent volumes suggested by Still *et al.*[17] were used; columns of Kieselgel (200—400 mesh ASTM) were washed with light petroleum, loaded with sample, and then washed with a solvent mixture of ethyl acetate–light petroleum equal in volume to, and containing 5 or 10% less ethyl acetate than, the eluting solvent mixture. M.p.s were determined with a Kofler hot-stage apparatus. N.m.r. spectra were recorded with a JEOL FX200 instrument for $CDCl_3$ solutions, unless stated otherwise, with tetramethylsilane as internal standard. U.v. spectra were determined for ethanolic solutions using a Perkin-Elmer 551 spectrophotometer. Capillary g.l.c. and g.l.c.–mass spectrometric analyses for Me ester *O*-$SiMe_3$ derivatives were carried out on WCOT OV-1 columns (10 m × 0.2 mm; 0.25 μm phase thickness). Low and high resolution probe mass spectra were obtained by using an AEI-GEC MS902 instrument.

'Work-up' means that the reaction mixture was added to water, acidified with hydrochloric acid to pH 2, and extracted with ethyl acetate; drying over anhydrous sodium or magnesium sulphate and evaporation under reduced pressure were carried out where appropriate.

Reagents.—(a) *Sodium propane-1-thiolate.* Redistilled propane-1-thiol (0.4 ml) was added dropwise to a stirred suspension of sodium hydride (160 mg of a 50% dispersion in oil prewashed with light petroleum) in dry hexamethylphosphoramide (3.5 ml). After being stirred under nitrogen for 1 h, the mixture was left for 0.5 h before use.

(b) *Tributylstannane.* Tributylstannyl chloride in dry diethyl ether was stirred with lithium aluminium hydride (2 mol equiv.) for 0.5 h. The reaction was quenched by addition of water and the ether layer was decanted and evaporated to give crude tributylstannane.

(c) *Lithium dimethylcuprate.* Methyl-lithium (2 mol equiv.; 1.5M in diethyl ether) was added to a stirred suspension of copper(I) iodide in tetrahydrofuran or diethyl ether at 0 °C under nitrogen.

(d) *Zinc–Copper couple.* Zinc powder (6 g) was stirred sequentially with aqueous 0.2M hydrochloric acid (2 × 30 ml) for 1 min, 2% (w/v) aqueous copper sulphate (3 × 30 ml), water (2 × 20 ml), and acetone (3 × 30 ml). The resultant couple was used immediately.

(e) *Dimethylsulphoxonium methylide solution.* To sodium hydride (130 mg of a 60% dispersion in oil, pre-washed with light petroleum) were added dry dimethyl sulphoxide (10 ml) and trimethylsulphoxonium iodide (500 mg) in an atmosphere of nitrogen. The mixture was stirred for 1 h to give a slightly cloudy solution (0.23M).

(f) 0.5M *Lithium di-isopropylamide solution.* Butyl-lithium (5.45 ml; 1.6M in hexane) was added dropwise to a stirred solution of di-isopropylamine (1.7 ml) in dry diethyl ether (7.5 ml) under nitrogen. The solution was kept for 0.5 h without stirring before use.

ent-2-[*Bis(methylthio)methylene*]-10β-*hydroxy*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**9**).—To 2,4,6-tri-t-butylphenol (2.66 g) in dry diethyl ether (20 ml), under nitrogen at 0 °C, was added, with stirring, methyl-lithium (6.8 ml; 1.5M solution in diethyl ether). To the resultant cloudy yellow solution, warmed to room temperature, was added redistilled carbon disulphide (1.0 ml) followed, after 5 min, by 3-oxo-GA_9 methyl ester (**25**) (1.16 g) in dry tetrahydrofuran (3 ml). After 16 h redistilled methyl iodide (1.7 ml) was added and stirring was continued for a further 4 h. Work-up gave a semi-crystalline yellow gum. Purification by flash chromatography and elution with ethyl acetate–light petroleum (15:85) gave the 2-[*bis(methylthio)methylene*]-3-*oxo*-GA_9 *methyl ester* (**9**), yellow needles (1.3 g), m.p. 216—217 °C (from ethyl acetate–light petroleum) (Found: C, 62.0; H, 5.8; S, 14.0. $C_{23}H_{28}O_5S_2$ requires C, 61.6; H, 6.3; S, 14.3%); $\lambda_{max.}$ 340 nm (ε 6 970 l mol^{-1} cm^{-1}); δ 1.28 (3 H, s, 18-H_3), 2.42 (3 H, s, SMe), 2.43 (3 H, s, SMe), 2.67 (1 H, br t, *J* 8.0 Hz, 9- or 13-H), 2.78 (1 H, d, *J* 17.3 Hz, 1-H), 2.82 (1 H, d, *J* 10.3 Hz, 6-H), 3.16 (1 H, d, *J* 10.3 Hz, 5-H), 3.49 (1 H, d, *J* 17.3 Hz 1-H), 3.72 (3 H, s, OMe), 4.88 (1 H, br s, 17-H), and 5.00 (1 H, br s, 17-H); *m/z* 448 (M^+, 100%), 433 (46), 401 (12), 133 (14), 117 (19), 91 (29), 85 (24), and 75 (17).

ent-10β-*Hydroxy*-2-*isopropylidene*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**10**).—The dithio ketone (**9**) (368 mg) in dry dichloromethane or tetrahydrofuran (3 ml) was added to lithium dimethylcuprate (2.1 mmol) in dry diethyl ether (20 ml) at −78 °C under nitrogen. After 15 min, work-up followed by flash chromatography with ethyl acetate–light petroleum (10:90) gave the 2-*isopropylidene*-3-*oxo*-GA_9 *methyl ester* (**10**) (265 mg), needles, m.p. 192—194 °C (from ethyl acetate–light petroleum) (Found: C, 71.7; H, 7.5. $C_{23}H_{28}O_5$ requires C, 71.9; H, 7.3%); $\lambda_{max.}$ 258 nm (ε 6 300 l mol^{-1} cm^{-1}); δ 1.24 (3 H, s, 18-H_3), 1.84 and 2.15 (each 3 H, br s, =CMe_2), 2.49 (1 H, dm, *J* 16.6 Hz, 1-H), 2.68 (1 H, t, *J* 6.0 Hz, 9- or 13-H), 2.83 (1 H, d, *J* 10.0 Hz, 6-H), 3.13 (1 H, br d, *J* 16.6 Hz, 1-H), 3.15 (1 H, d, *J* 10.0 Hz, 5-H), 3.72 (3 H, s, OMe), 4.88 (1 H, br s, 17-H), and 5.00 (1 H, br s, 17-H); 2-D *J*-resolved ^{1}H n.m.r. δ 1.84 (dd, *J* 1.6 and 1.6 Hz), 2.15 (dd, *J* 2.6 and 1.6 Hz), and 2.49 (ddd. *J* 16.6, 2.6, and 1.6 Hz) (the 1-H signal at 3.13 p.p.m. was obscured by the 5-H signal); *m/z* 384 (M^+, 100%), 366 (20), 352 (62), 349 (72), 324 (47), 309 (22), 297 (31), 280 (100), and 269 (11).

ent-3β,10β-*Dihydroxy*-2-*isopropylidene*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**15**).—A solution of the 2-isopropylidene-3-oxo-GA_9 methyl ester (**10**) (265 mg) in methanol (20 ml) containing cerium(III) chloride (catalytic amount) was stirred at −70 °C with sodium borohydride (400 mg). After 1.5 h at −70 °C, work-up followed by flash chromatography with ethyl acetate–light petroleum (15:85) gave, sequentially, starting material (**10**) (79 mg) and 2-isopropylidene-3-*epi*-GA_4 methyl ester (**15**) (120 mg). Recycling the enone (**10**) gave (in total) 38 mg of starting material (**10**) and 155 mg of 2-*isopropylidene*-3-epi-GA_4 *methyl ester* (**15**), m.p. 165—171 °C (from ethyl acetate–light petroleum) (Found: C, 70.8; H, 8.0. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%); δ 1.26 (3 H, s, 18-H_3), 1.64 (3 H, d, *J* 1.0 Hz, =CMe), 1.86 (3 H, br s, =CMe), 2.36 (1 H, br d, *J* 17.7 Hz, 1-H), 2.64 (1 H, br t, 9- or 13-H), 2.69 (1 H, d, *J* 10.2 Hz, 5-H), 2.78 (1 H, d, *J* 10.0 Hz, 6-H), 2.92 (1 H, d, *J* 17.7 Hz, 1-H), 3.72 (3 H, s, OMe), 4.41 (1 H, d, *J* 7.0 Hz, 3β-H), 4.86 (1 H, br s, 17-H), and 4.97 (1 H, br s, 17-H) (on addition of D_2O the signal at 4.41 p.p.m. collapsed to a singlet); *m/z* 386

(M^+, 16%), 355 (8), 350 (13), 340 (28), 323 (100), 280 (18), and 264 (50).

Demethylation of ent-3β,10β-*Dihydroxy*-2-*isopropylidene*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**15**).—2-Isopropylidene-3-*epi*-GA_4 methyl ester (**15**) (150 mg) was stirred for 4 h with sodium propane-1-thiolate solution (1.5 mol) under nitrogen. After work-up the ethyl acetate extract (60 ml) was washed with saturated aqueous sodium hydrogen carbonate (5 × 20 ml). Acidification of the aqueous phase to pH 2 and extraction with ethyl acetate (4 × 20 ml) gave a gum which was fractionated by flash chromatography with ethyl acetate–light petroleum–acetic acid (30:70:1), to give sequentially: (a) 2-*isopropylidene*-GA_4 (**14**), prisms (59 mg), m.p. 192—199 °C (from methanol–water) (Found: M^+, 372.1951. $C_{22}H_{28}O_5$ requires *M*, 372.1937); δ[$(CD_3)_2CO$] 1.17 (3 H, s, 18-H_3), 1.65 (3 H, d, *J* 1.2 Hz, =CMe), 1.76 (3 H, d, *J* 2.2 Hz, =CMe), 2.31 (1 H, br d, *J* 15.6 Hz, 1-H), 2.62 (1 H, d, *J* 10.5 Hz, 6-H), 2.94 (1 H, d, *J* 15.8 Hz, 1-H), 3.28 (d, *J* 10.5 Hz, 5-H; superimposed on 9- or 13-H signal), 4.40 (1 H, s, 3α-H), 4.85 (1 H, br s, 17-H), and 4.98 (1 H, br s, 17-H); *m/z* 372 (M^+, 16%), 354 (9), 326 (29), 310 (100), 265 (25), 105 (24), 91 (29), and 59 (38); g.l.c.–mass spectrum of Me ester *o*-$SiMe_3$ derivative: 458 (M^+, 100%), 443 (12), 398 (13), 368 (20), 360 (21), 324 (29), 264 (40), 171 (51), and 75 (85); and (b) 2-*isopropylidene*-3-epi-GA_4 (**16**) (13 mg), prisms, m.p. 145—157 °C (from methanol–water) (Found: M^+, 372.1951. $C_{22}H_{28}O_5$ requires *M*, 372.1937); δ[$(CD_3)_2CO$] 1.21 (3 H, s, 18-H_3), 1.64 (3 H, br s, =CMe), 1.84 (3 H, br s, =CMe), 2.41 (1 H, d, *J* 17.6 Hz, 1-H), 2.64 (3 H, br m, 5- and 6-H + 9- or 13-H), 2.85 (1 H, br d, *J* 17.6 (Hz, 1-H), 4.40 (1 H, br s, 3β-H), 4.85 (1 H, br s, 17-H), and 4.97 (1 H, br s, 17-H); *m/z* 372 (M^+, 16%), 354 (9), 326 (32), 309 (100), 265 (19), 263 (17), and 91 (22).

Epimerisation of 2-*Isopropylidene*-3-epi-GA_4 *Methyl Ester* (**15**).—2-Isopropylidene-3-*epi*-GA_4 methyl ester (**15**) (*ca.* 10 mg) in methanol (5 ml) was refluxed with saturated aqueous potassium carbonate (10 ml) for 1 h. Work-up gave a gum which by g.l.c. comparison (OV210; 230 °C; as the *O*-$SiMe_3$ derivative) with authentic samples described earlier was shown to contain 2-isopropylidene-GA_4 methyl ester (**17**) (80%) and an unidentified product (20%) which was not starting material.

ent-2α-*t*-*Butyl*-10β-*hydroxy*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**26**) *and* ent-2β-*t*-*Butyl*-10β-*hydroxy*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**27**).—The dithio ketone (**9**) (130 mg) in dry dichloromethane or tetrahydrofuran (1 ml) was added to lithium dimethylcuprate (1.2 mmol) in diethyl ether (20 ml) at 0 °C under nitrogen. After stirring for 50 min at 0 °C work-up gave a crystalline product which t.l.c. indicated to be a mixture of two compounds of similar polarity. Careful separation by flash chromatography with ethyl acetate–light petroleum (5:95) gave, sequentially, the 2β-*t*-*butyl*-3-*oxo*-GA_9 *methyl ester* (**26**), needles (99 mg), m.p. 190—216 °C with sublimation (from ethyl acetate–light petroleum) (Found: C, 72.2; H, 7.9. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.0%); δ 1.01 (9 H, s, 2-CMe_3), 1.15 (3 H, s, 18-H_3), 2.80 (1 H, d, *J* 10.2 Hz, 6-H), 2.91 (1 H, d, *J* 10.2 Hz, 5-H), 3.72 (3 H, s, OMe), 4.87 (1 H, br s, 17-H), and 4.99 (1 H, br s, 17-H); *m/z* 400 (M^+, 100%), 372 (25), 368 (17), 340 (29), 326 (36), 312 (49), 289 (54), 229 (35), 201 (33), 91 (36), 57 (48), 55 (49), 43 (55), and 41 (46); and the 2α-t-butyl-3-oxo-GA_9 methyl ester (**27**) as a gum (9 mg) contaminated with *ca.* 10% 2β-isomer; δ 0.99 (9 H, s, 2-CMe_3), 1.21 (3 H, s, 18-H_3), 2.79 (1 H, d, *J* 10.0 Hz, 6-H), 3.26 (1 H, d, *J* 10.0 Hz, 5-H), 3.73 (3 H, s, OMe), 4.99 (1 H, br s, 17-H), and 5.01 (1 H, br s, 17-H); *m/z* 400 (M^+, 18%), 372 (14), 344 (26), 340 (10), 326 (13), 312 (16), 289 (23), 57 (29), and 43 (100).

Reaction of the 2-*Isopropylidene*-3-*oxo*-GA_9 *Methyl Ester* (**10**) *with Lithium Dimethylcuprate*.—The 2-isopropylidene ketone (**10**) (262 mg) in dry dichloromethane or tetrahydrofuran (2 ml) was added to lithium dimethylcuprate (1.0 mmol) in diethyl ether (20 ml) at 0 °C. After 1 h, work-up followed by flash chromatography with ethyl acetate–light petroleum (5:95 then 10:90) gave, sequentially, the 2β-t-butyl-3-oxo-GA_9 methyl ester (**26**) (113 mg), the 2α-t-butyl-3-oxo-GA_9 methyl ester (**27**) (16 mg, contaminated with traces of 2β-isomer), starting material (**10**) (11 mg), and a mixture of unidentified compounds (30 mg). Identifications were made by comparisons of ^1H n.m.r. spectra and gas chromatograms (OV210; 230 °C) with those of authentic samples (described earlier). Conditions employed in this reaction were not optimised.

ent-2α-*t*-*Butyl*-3α,10β-*dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**19**) *and* ent-2α-*t*-*Butyl*-3β,10α-*dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**20**).—2β-t-Butyl-3-oxo-GA_9 methyl ester (**26**) (110 mg) in methanol (15 ml) at 30 °C was stirred with sodium borohydride (*ca.* 40 mg). After 1 h work-up followed by flash chromatography with ethyl acetate–light petroleum (15:85) gave, sequentially, the 2β-t-butyl-GA_4 methyl ester (**19**) (67 mg), the 2β-t-butyl-3-*epi*-GA_4 methyl ester (**20**) (2 mg), and a mixture of both epimers (27 mg). Flash chromatography of the mixture returned sufficient 2β-t-butyl-3-*epi*-GA_4 methyl ester (**20**) for analysis. 2β-*t*-*Butyl*-GA_4 *methyl ester* (**19**) had m.p. 250—257 °C (with sublimation above 230 °C) (from acetone–ethyl acetate–light petroleum) (Found: C, 71.5; H, 8.4. $C_{24}H_{34}O_5$ requires C, 71.5; H, 8.3%); δ 1.01 (9 H, s, 2-CMe_3), 1.13 (3 H, s, 18-H_3), 2.44 (1 H, d, *J* 4.4 Hz, 3β-OH), 2.70 (1 H, d, *J* 11.0 Hz, 6-H), 3.22 (1 H, d, *J* 11.0 Hz, 5-H), 3.70 (3 H, s, OMe), 3.92 (1 H, dd, *J* 4.4 and 3.2 Hz, 3α-H), 4.85 (1 H, br s, 17-H), and 4.98 (1 H, br s, 17-H) [on addition of D_2O the signal at 3.92 p.p.m. collapsed to a doublet (*J* 3.2 Hz) and the signal at 2.44 p.p.m. disappeared]; *m/z* (M^+, 2%), 384 (18), 370 (28), 356 (26), 352 (66), 342 (24), 340 (15), 328 (22), 324 (31), 283 (20), 267 (17), 223 (100), and 57 (75).

The 2β-*t*-*butyl*-3-epi-GA_4 *methyl ester* (**20**) had m.p. 221—224 °C (from ethyl acetate–light petroleum (Found: M^+, 402.2399. $C_{24}H_{34}O_5$ requires *M*, 402.2406); δ 1.00 (9 H, s, 2-CMe_3), 1.18 (3 H, s, 18-H_3), 2.45 (1 H, d, *J* 10.5 Hz, 5-H), 2.76 (1 H, d, *J* 10.5 Hz, 6-H), 3.59 (1 H, br t, *J* 9.2 and 4.0 Hz, 3β-H), 3.72 (3 H, s, OMe), 4.85 (1 H, br s, 17-H), and 4.97 (1 H, br s, 17-H) [on addition of D_2O the signal at 3.59 p.p.m. collapsed to a doublet (*J* 9.2 Hz)]; *m/z* 402 (M^+, 16%), 384 (28), 371 (17), 370 (17), 356 (74), 342 (73), 328 (55), 242 (33), 230 (30), 223 (34), 91 (31), and 57 (100).

ent-2α-*t*-*Butyl*-3α,10β-*dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 19,10-*Lactone* (**18**).—2β-t-Butyl-GA_4 methyl ester (**19**) (56 mg) was stirred for 4 h with sodium propane-1-thiolate solution (1.5 ml) under nitrogen. After work-up, as described for 2-isopropylidene-GA_4 (**14**), flash chromatography with ethyl acetate–light petroleum–acetic acid (20:80:1) gave 2β-*t*-*butyl*-GA_4 (**18**) (35 mg), m.p. 264—284 °C (exhibits dimorphism at *ca.* 270 °C) (from acetone–light petroleum) (Found: C, 71.4; H, 8.5. $C_{23}H_{32}O_5$ requires C, 71.1; H, 8.3%); δ 1.03 (9 H, s, CMe_3), 1.10 (3 H, s, 18-H_3), 2.62 (2 H, br s, 6-H and 9- or 13-H), 3.21 (1 H, d, *J* 11.0 Hz, 5-H), 3.87 (1 H, d, *J* 3.4 Hz, 3α-H), 4.85 (1 H, br s, 17-H), and 4.97 (1 H, br s, 17-H); *m/z* 388 (M^+, 2%), 370 (13), 352 (25), 342 (42), 324 (20), 314 (16), 269 (20), 223 (59), 57 (71), and 43 (100) [g.l.c.–mass spectrum of the Me ester, *O*-$SiMe_3$ derivative: 474 (M^+, 73%), 459 (10), 446 (58), 384 (51), 356 (26), 289 (84), and 185 (100)]; and a mixture of 2β-t-butyl-GA_4 (**18**) and 2β-t-butyl-3-*epi*-GA_4 (**21**) (8 mg), identified by g.l.c. comparison (OV210; 230 °C, as Me ester, *O*-$SiMe_3$ derivative) with authentic samples described earlier.

Zinc–Copper Couple Reduction of ent-2-[*Bis*(*methylthio*)-*methylene*]-10β-*hydroxy*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**9**).—(a) *In refluxing acetone.* The dithio ketone (**9**) (310 mg) in acetone (20 ml) was refluxed with zinc–copper couple, prepared from zinc powder (3 g). After 2 h some starting material remained (t.l.c.). Addition of a second portion of zinc–copper couple [from zinc powder (3 g)] and refluxing for a further 0.5 h gave, after evaporation under reduced pressure and flash chromatography with ethyl acetate–light petroleum (15:85), ent-10β-*hydroxy*-2-[(E)-(*methylthiomethylene*]-3-*oxo*-20-*norgibberell*-16-*ene* 7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**12**), needles (205 mg), m.p. 188—189 °C (from ethyl acetate–light petroleum) (Found: M^+, 402.1494. $C_{22}H_{26}O_5S$ requires M, 402.1501); $\lambda_{max.}$ 316 nm (ε 15 252 l mol^{-1} cm^{-1}); δ 1.26 (3 H, s, 18-H_3), 2.44 (1 H, dd, J 17.1 and 2.7 Hz, 1-H), 2.51 (3 H, s, SMe), 2.67 (1 H, t, 9- or 13-H), 2.83 (1 H, d, J 10.0 Hz, 6-H), 2.95 (1 H, dd, J 17.2 and 1.7 Hz, 1-H), 3.21 (1 H, d, J 9.8 Hz, 5-H), 3.72 (3 H, s, OMe), 4.88 (1 H, br s, 17-H), 5.00 (1 H, br s, 17-H), and 7.80 (1 H, dd, J 2.7 and 1.7 Hz, 2′-H) (^{1}H n.O.e: irradiation at 7.80 and 2.44 p.p.m. gave enhancement at 2.51 p.p.m. in both cases; irradiation at 2.51 p.p.m. gave enhancement at 2.40 and 7.80 p.p.m.); m/z 402 (M^+, 100%), 387 (22), 371 (11), 355 (14), 343 (29), 311 (61), 298 (23), 283 (25), 251 (46), 223 (57), 169 (25), 119 (33), 91 (49), and 86 (52).

Dichloromethane may be used in place of acetone in this reaction.

(b) *In acetone–acetic acid at ambient temperature with ultrasonication.* To the dithio ketone (**9**) (310 mg) in acetone (30 ml) were added zinc–copper couple [from zinc powder (6 g)] and acetic acid (0.25 ml). The mixture was subjected to ultrasound (Mettler Electronics Corporation Ultrasonic Cleaner). After 1 h some starting material remained (t.l.c.). More acetic acid (0.25 ml) was added and, after 15 min, the mixture was filtered through Celite and the filtrate was evaporated under reduced pressure. Flash chromatography with ethyl acetate–light petroleum (20:80) gave, sequentially, the 2β-methyl-3-oxo-GA_9 methyl ester (**30**) (identical by ^{1}H n.m.r. and t.l.c. with an authentic sample, described later) and the (*E*)-monothio ketone (**12**) (217 mg) [identical by ^{1}H n.m.r. and t.l.c. with that prepared in (a)].

(c) *Prolonged reflux in acetone containing acetic acid.* The dithio ketone (**9**) (608 mg) in acetone (30 ml) was refluxed for 1 h with zinc–copper couple [from zinc powder (5 g)] after which time t.l.c. analysis indicated the presence of starting material (**9**) and the (*E*)-monothio ketone (**12**). More zinc–copper couple [from zinc powder (5 g)] and acetic acid (1 ml) were added. After refluxing for 16 h the mixture was cooled, filtered through Celite, and evaporated under reduced pressure. Flash chromatography of the resultant gum gave, sequentially: (i) 2β-methyl-3-oxo-GA_9 methyl ester (**30**) (86 mg), eluted with ethyl acetate–light petroleum (20:80) and identical by ^{1}H n.m.r. and t.l.c. with an authentic sample, described later; (ii) 2α-methyl-3-oxo-GA_9 methyl ester (**31**) (86 mg), eluted with ethyl acetate–light petroleum (20:80) and identical by ^{1}H n.m.r. and t.l.c. with an authentic sample, described later; and (iii) 2-*methylene*-3-epi-GA_4 *methyl ester* (**42**) (57 mg), eluted with ethyl acetate–light petroleum (60:40) as a gum (Found: M^+, 358.1766. $C_{21}H_{26}O_5$ requires M, 358.1780); δ 1.24 (3 H, s, 18-H_3), 2.34 (1 H, dt, J 15.1, 2.4, and 2.4 Hz, 1-H), 2.78 (2 H, s, 5-H and 6-H), 2.89 (1 H, d, J 15.1 Hz, 1-H), 3.73 (3 H, s, OMe), 4.14 (1 H, d, J 10.5 Hz, 3β-H), 4.86 (1 H, br s, 17-H), 4.98 (1 H, br s, 17-H), 5.12 (1 H, br s, 2 =CH), and 5.40 (1 H, br s, 2 =CH) [on addition of C_6D_6 the 5-H and 6-H signals separated to give signals at 2.68 p.p.m. (1 H, d, J 10.3 Hz, 5-H) and 2.75 p.p.m. (1 H, d, J 10.3 Hz, 6-H); on addition of D_2O the signal at 4.14 p.p.m. collapsed to a broad singlet; ^{1}H n.O.e: irradiation at 5.12 p.p.m. gave enhancement at 2.89 and 5.40 p.p.m.; irradiation at 2.34 p.p.m. gave enhancement at 2.89 p.p.m.; irradiation at 5.40 p.p.m. gave enhancement at 5.12 p.p.m.]; m/z 358 (M^+, 21%), 340 (16), 326 (36), 312 (81), 298 (100), 280 (23), 269 (54), 267 (40), 125 (52), and 91 (45).

The 2α-methyl-3-oxo-GA_9 methyl ester (**31**) contained some non-gibberellin impurities and so was subjected to further flash chromatography. The recovered material was identical (^{1}H n.m.r. and t.l.c.) with the 2β-methyl-3-oxo-GA_9 methyl ester (**30**) described later.

(d) *In refluxing acetone with an excess of zinc–copper couple.* The dithio ketone (**9**) (393 mg) in acetone (50 ml) was refluxed with zinc–copper couple [from zinc powder (31 g)]. After 1 h t.l.c. indicated the formation of a trace of a polar product, as well as of the (*E*)-monothio ketone (**12**). More zinc–copper couple [from zinc powder (20 g)] was added and the mixture refluxed for a further 1 h. Filtration and evaporation under reduced pressure gave a gum which after flash chromatography yielded 2β-methyl-3-oxo-GA_9 methyl ester (**30**) (149 mg), eluted with ethyl acetate–light petroleum (25:75) and identical by ^{1}H n.m.r. and t.l.c. with an authentic sample described later; and 2-methylene-3-*epi*-GA_4 methyl ester (**42**) (91 mg), eluted with ethyl acetate–light petroleum (40:60) and identical by ^{1}H n.m.r. and t.l.c. with that prepared in (c).

ent-10β-*Hydroxy*-2α-*methyl*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**30**).—2β-Methyl-GA_4 methyl ester (**39**)[3] (140 mg) in acetone (30 ml) was stirred with Jones reagent (1 ml). After 0.75 h methanol (5 ml) was added, followed by water (100 ml). Methanol and acetone were removed by evaporation under reduced pressure and the residue was extracted with ethyl acetate (3 × 40 ml). The extracts were washed with water and dried ($MgSO_4$). Evaporation under reduced pressure and flash chromatography with ethyl acetate–light petroleum (1:4) gave 2β-*methyl*-3-*oxo*-GA_9 *methyl ester* (**30**) (98 mg) as a gum (Found: M^+, 358.1781. $C_{21}H_{26}O_5$ requires M, 358.1780); δ 1.15 (3 H, d, J 6.1 Hz, 2β-Me), 1.19 (3 H, s, 18-H_3), 2.81 (1 H, d, J 10.3 Hz, 6-H), 3.00 (1 H, d, J 10.3 Hz, 5-H), 3.72 (3 H, s, OMe), 487 (1 H, br s, 17-H), and 4.99 (1 H, br s, 17-H); m/z 358 (M^+, 69%), 326 (100), 314 (27), 313 (26), 298 (42), 254 (26), 217 (28), 91 (50), and 77 (41).

ent-10β-*Hydroxy*-2β-*methyl*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**31**).—2α-Methyl-GA_4 methyl ester (**39**)[15] (55 mg) in acetone (10 ml) was stirred with Jones reagent (0.5 ml). After 1 h, work-up as for the 2β-methyl isomer gave 2α-*methyl*-3-*oxo*-GA_9 *methyl ester* (**31**) (*ca.* 40 mg) as a gum (Found: M^+, 358.1780. $C_{21}H_{26}O_5$ requires M, 358.1780); δ 1.21 (3 H, s, 18-H_3), 1.25 (3 H, d, J 7.6 Hz, 2α-Me), 2.68 (1 H, br t, 9- or 13-H), 2.81 (1 H, d, J 9.8 Hz, 6-H), 3.21 (1 H, d, J 10.0 Hz, 5-H), 3.72 (3 H, s, OMe), 4.88 (1 H, br s, 17-H), and 5.01 (1 H, br s, 17-H); m/z 358 (M^+, 15%), 326 (17), 298 (9), 126 (100), 84 (62), and 71 (53).

ent-10β-*Hydroxy*-2α-*isopropyl*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**28**) *and* ent-10β-*Hydroxy*-2β-*isopropyl*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**29**).—The (*E*)-monothio ketone (**12**) (307 mg) in dry tetrahydrofuran (5 ml) was added to lithium dimethylcuprate (2.5 mmol) solution in dry diethyl ether (20 ml) at −5 °C under nitrogen. After 40 min stirring, work-up, followed by flash chromatography, gave: (i) 2β-*isopropyl*-3-*oxo*-GA_9 *methyl ester* (**28**) (99 mg), eluted with ethyl acetate–light petroleum (5:95), m.p. 199—201 °C (from ethyl acetate–acetone) (Found: C, 71.3; H, 7.7%; M^+ 386.2015. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%; M 386.2093); δ 0.87 (3 H, d, J 6.6 Hz, 2-$CHMe_2$), 0.92 (3 H, d, J 7.1 Hz, 2-$CHMe_2$), 1.17 (3 H, s, 18-H_3), 2.66 (1 H, br t, 9- or 13-H), 2.81 (1 H, d, J 10.0 Hz, 6-H), 2.91 (1 H, d, J 10.3 Hz, 5-H), 3.72 (3 H, s, OMe), 4.87 (1 H, br s, 17-H), and 5.00 (1 H, br s, 17-H); m/z 386 (M^+, 11%), 358 (9), 354 (8),

326 (8), 290 (19), 289 (100), and 239 (11); and (ii) 2α-*isopropyl*-3-*oxo*-GA_9 *methyl ester* (**29**) (94 mg), eluted with ethyl acetate–light petroleum (10:90), m.p. 124—125 °C (from ethyl acetate–light petroleum) (Found: M^+, 386.2080. $C_{23}H_{30}O_5$ requires *M*, 386.2093): δ 0.831 (3 H, d, *J* 6.6 Hz, 2-$CHMe_2$), 0.834 (3 H, d, *J* 7.1 Hz, 2-$CHMe_2$), 1.21 (3 H, s, 18-H_3), 2.66 (1 H, br t, 9-or 13-H), 2.82 (1 H, d, *J* 10.0 Hz, 6-H), 3.17 (1 H, d, *J* 9.8 Hz, 5-H), 3.72 (3 H, s, OMe_3), 4.88 (1 H, br s, 17-H), and 4.99 (1 H, br s, 17-H); *m/z* 386 (M^+, 100%), 358 (25), 354 (20), 326 (22), 298 (22), 289 (70), 239 (24), and 91 (27).

Reduction of ent-10β-*Hydroxy*-2α-*isopropyl*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**28**) *with Sodium Borohydride*.—2β-Isopropyl-3-oxo-GA_9 methyl ester (**28**) (99 mg) in propan-2-ol (15 ml) was stirred with sodium borohydride (excess) for 1 h. Work-up followed by flash chromatography with ethyl acetate–light petroleum (20:80) gave sequentially: (i) 2β-*isopropyl*-GA_4 *methyl ester* (**23**) (45 mg), m.p. 274—277 °C (exhibits dimorphism above 230 °C) (from tetrahydrofuran–water) (Found: M^+, 388.2230. $C_{23}H_{32}O_5$ requires *M*, 388.2250); δ 0.89 (3 H, d, *J* 6.6 Hz, 2-$CHMe_2$), 0.97 (3 H, d, *J* 6.6 Hz, 2-$CHMe_2$), 1.16 (3 H, s, 18-H_3), 2.61 (1 H, br t, 9- or 13-H), 2.69 (1 H, d, *J* 11.0 Hz, 6-H), 3.16 (1 H, d, *J* 11.0 Hz, 5-H), 3.70 (3 H, s, OMe), 3.82 (1 H, br s, 3α-H), 4.85 (1 H, br s, 17-H), and 4.98 (1 H, br s, 17-H); *m/z* 388 (M^+, 2%), 370 (6), 356 (15), 338 (12), 326 (12), 266 (11), 223 (34), 123 (15), 91 (17), and 28 (100); and (ii) 2β-*isopropyl*-3-epi-GA_4 *methyl ester* (**24**) (41 mg), m.p. 220—221 °C (exhibits dimorphism above 200 °C) (from tetrahydrofuran–water) (Found: M^+, 388.2262. $C_{23}H_{32}O_5$ requires *M*, 388.2250); δ 0.88 (3 H, d, *J* 6.8 Hz, 2-$CHMe_2$), 0.93 (3 H, d, *J* 7.1 Hz, 2-$CHMe_2$), 1.19 (3 H, s, 18-H_3), 2.46 (1 H, d, *J* 10.3 Hz, 5-H), 2.63 (1 H, br t, 9- or 13-H), 2.76 (1 H, d, *J* 10.5 Hz, 6-H), 3.45 (1 H, br d, *J* 9.3 Hz, 3β-H), 3.72 (3 H, s, OMe), 4.85 (1 H, br s, 17-H), and 4.98 (1 H, br s, 17-H); *m/z* 388 (M^+, 15%), 370 (51), 356 (41), 342 (90), 328 (97), 314 (75), 310 (50), 300 (36), 91 (69), and 28 (100).

ent-3α,10β-*Dihydroxy*-2α-*isopropyl*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 19,10-*Lactone* (**22**).—2β-Isopropyl-GA_4 methyl ester (**23**) (98 mg) was stirred with sodium propane-1-thiolate solution (2 ml) for 4.5 h under nitrogen. Work-up as described for 2-isopropylidene-GA_4 (**14**), followed by flash chromatography with ethyl acetate–light petroleum–acetic acid (40:60:1) gave 2β-*isopropyl*-GA_4 (**22**) (30 mg) as a gum (Found: M^+, 374.2112; *M* − 18, 356.2007. $C_{22}H_{30}O_5$ requires *M*, 374.2093; *M* − 18, 356.1987); δ[$(CD_3)_2CO$] 0.90 (3 H, d, *J* 6.6 Hz, 2-$CHMe_2$), 0.97 (3 H, d, *J* 6.3 Hz, 2-$CHMe_2$), 1.13 (3 H, s, 18-H_3), 2.59 [1 H, d, *J* 10.7 Hz; superimposed on 1 H, br m (9- or 13-H)], 3.16 (1 H, d, *J* 10.7 Hz, 5-H), 3.73 (1 H, d, *J* 3.7 Hz, 3α-H), 4.85 (1 H, br s, 17-H), and 4.97 (1 H, br s, 17-H) (on addition of D_2O no change was observed); *m/z* 374 (M^+, 3%), 356 (43), 338 (56), 328 (59), 312 (80), 310 (52), 300 (38), 269 (52), 223 (100), and 43 (76) [g.l.c.–mass spectrum of the Me ester *O*-$SiMe_3$ derivative: *m/z* 460 (M^+, 65%), 370 (49), 289 (79), 261 (36), 233 (42), and 171 (100)].

Reduction of ent-2-[*Bis*(*methylthio*)*methylene*]-10β-*hydroxy*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**9**) *with Sodium Borohydride*.—(a) *With tetrakis*(*triphenylphosphine*)*palladium*(0) *in tetrahydrofuran*. To the dithio ketone (**9**) (127 mg) in dry tetrahydrofuran (20 ml), containing tetrakis(triphenylphosphine)palladium(0) (33 mg) under nitrogen was added sodium borohydride (27 mg). After stirring for 16 h, work-up and flash chromatography gave, sequentially: (i) ent-3α,10β-*dihydroxy*-2-[*bis*(*methylthio*)-*methylene*]-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**44**) (56 mg) as a gum (Found: M^+, 450.1492; *M* − 17, 433.1515. $C_{23}H_{30}O_5S_2$ requires *M*, 450.1534; *M* − 17, 433.1507); δ 1.23 (3 H, s, 18-H_3), 2.26 (3 H, s, SMe), 2.29 (3 H, s, SMe), 2.38 (1 H, d, *J* 17.0 Hz, 1-H), 2.64 (1 H, t, 9- or 13-H), 2.71 (1 H, d, *J* 10.5 Hz, 6-H), 3.32 (1 H, d, *J* 10.7 Hz, 5-H), 3.52 (1 H, d, *J* 16.6 Hz, 1-H), 3.72 (3 H, s, OMe), 4.86 (1 H, br s, 17-H), 4.98 (1 H, br s, 17-H), and 5.01 (1 H, s, 3α-H); *m/z* 450 (M^+, 48%), 433 (19), 432 (19), 387 (65), 358 (100), 325 (30), 311 (59), 251 (76), 223 (78), 119 (55), and 105 (32); and (ii) (*E*)-2-(methylthiomethylene)-GA_4 methyl ester (**45**) (37 mg) as a gum, δ 1.20 (3 H, s, 18-H_3), 2.08 (3 H, s, SMe), 2.71 (1 H, d, *J ca.* 11 Hz, 6-H), 2.92 (1 H, d, *J ca.* 16 Hz, 1-H), 3.37 (1 H, d, *J ca* 11 Hz, 5-H), 3.72 (3 H, s, OMe), 4.08 (1 H, s, 3α-H), 4.88 (1 H, br s, 17-H), 4.98 (1 H, br s, 17-H), and 6.28 (1 H, d, *J ca* 2 Hz, 2 =CH); *m/z* 404 (M^+; 8%), 387 (46), 343 (100), 312 (61), 295 (41), 283 (92), 252 (67), 105 (52), and 91 (66).

(b) *In tetrahydrofuran*. The dithio ketone (**9**) (85 mg) in tetrahydrofuran (15 ml), was stirred under nitrogen with sodium borohydride (excess). After 1 h, work-up followed by flash chromatography with ethyl acetate–light petroleum (20:80) gave 2-[bis(methylthio)methylene]-GA_4 methyl ester (**44**) (61 mg), identical by ^1H n.m.r., mass spectrometry, and t.l.c. with that prepared in (a), as well as slightly impure fractions (26 mg).

(c) *In methanol*. To the dithio ketone (**9**) (95 mg), partially dissolved in methanol (25 ml), was added sodium borohydride (excess). The mixture formed a colourless, homogeneous solution within 5 min. After 0.25 h, work-up followed by flash chromatography with ethyl acetate–light petroleum (25:75) gave ent-3β,10β-*dihydroxy*-2-[*bis*(*methylthio*)*methylene*]-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**46**) (72 mg) as a gum (Found: M^+, 450.1523. $C_{23}H_{30}O_5S_2$ requires *M*, 450.1534); δ 1.30 (3 H, s, 18-H_3), 2.31 (3 H, s, SMe), 2.32 (3 H, s, SMe), 2.67 (1 H, d, *J* 19.1 Hz, 1-H), 2.70 (1 H, d, *J* 9.8 Hz, 5-H), 2.78 (1 H, d, *J* 10.0 Hz, 6-H), 3.22 (1 H, dd, *J* 18.3 and 1.0 Hz, 1-H), 3.72 (3 H, s, OMe), 4.63 (1 H, br s, 3β-H), 4.89 (1 H, br s, 17-H), and 4.97 (1 H, br s, 17-H); *m/z* 450 (M^+, 3%), 434 (5), 387 (9), 371 (10), 358 (97), 311 (67), 298 (22), 251 (98), 223 (100), 119 (64), and 105 (26).

Oxidation of 2-*Methylene*-3-epi-GA_4 *Methyl Ester* (**42**).—The enol (**42**) (37 mg) was stirred in acetone (20 ml) with Jones reagent (0.5 ml) for 10 min. The reaction was quenched by addition of methanol (5 ml). Work-up (including back-washing of ethyl acetate extracts with water) followed by flash chromatography with ethyl acetate–light petroleum (20:80) yielded the dimer (**52**) (18 mg) as a gum [fast atom bombardment–mass spectrum (thioglycerol matrix): $M^+ + 1$, 713.30 (weak). $C_{42}H_{48}O_{10}$ requires $M + 1$, 713.32]; $\lambda_{max.}$ 208 (ε 2 400 l mol^{-1} cm^{-1}) and 231 nm (ε 648); δ 1.23 (3 H, s, 18-H_3), 1.25 (3 H, s, 18-H_3), 2.67 (1 H, d, *J* 10.5 Hz, 5- or 6-H), 2.80 (1 H, d, *J* 10.3 Hz, 5- or 6-H), 2.99 (1 H, d, *J* 10.5 Hz, 5- or 6-H), 3.46 (1 H, d, *J* 10.3 Hz, 5- or 6-H), 3.72 (3 H, s, OMe), 3.73 (3 H, s, OMe), 4.86 (2 H, br s, 17-H_2), and 4.98 (2 H, br s, 17-H_2); *m/z* (electron impact; scanned up to *m/z* 800) 356 [M^+ of enone (**28**), 73%], 324 (100), 296 (31), 252 (50), 123 (35), and 91 (62). (*N.B.* Some very weak higher *m/z* peaks were evident.) G.l.c.–mass spectrometry gave a single g.l.c. peak with *m/z* 356 [M^+ of enone (**28**), 64%], 324 (100), 296 (32), 287 (19), 268 (20), and 252 (47).

Similar results were obtained from oxidation of (**42**) with manganese dioxide or pyridinium dichromate.

Spiro-[3-*oxogibberellin* A_9 *methyl ester*-2,1′-*cyclopropane*] (**49**).—(a) *From the dimer* (**52**) *and dimethylsulphoxonium methylide*. To a solution of the dimer (**52**) (146 mg) in dry dimethyl sulphoxide (10 ml) under nitrogen at 140 °C was added dimethylsulphoxonium methylide solution (1.8 ml) and the mixture was stirred at 140 °C for 0.75 h. Work-up followed by flash chromatography with ethyl acetate–light petroleum (10:90) gave *spiro*-[3-*oxo*-GA_9 *methyl ester*-2,1′-

cyclopropane] (**49**) as a gum (128 mg) (Found: M^+, 370.1727; $M - 32$, 338.1494. $C_{22}H_{26}O_5$ requires M, 370.1780; $M - 32$, 338.1518); δ: 0.80 (2 H, m, cyclopropyl H), 0.95 (1 H, m, cyclopropyl H), 1.20 (3 H, s, 18-H_3), 2.67 (1 H, br t, 9- or 13-H), 2.86 (1 H, d, *J* 10.0 Hz, 6-H), 3.26 (1 H, d, *J* 10.3 Hz, 5-H), 3.73 (3 H, s, OMe), 4.88 (1 H, br s, 17-H), and 4.99 (1 H, br s, 17-H); *m/z* 370 (M^+, 73%), 338 (100), 310 (25), 266 (32), 238 (32), 189 (29), 160 (34), 128 (35), 105 (37), 91 (65), and 55 (52).

(b) *From 3-oxo-GA$_9$ methyl ester* (**25**) *and 1-chloro-2-(dimethylsulphonio)ethylene iodide.* To 3-oxo-GA_9 methyl ester (**25**) (69 mg) in dry tetrahydrofuran (15 ml) under nitrogen were added lithium di-isopropylamide (0.44 ml; 0.5M solution in tetrahydrofuran) and hexamethylphosphoramide (0.5 ml). After stirring for 2 min, 1-chloro-2-(dimethylsulphonio)ethylene iodide (51 mg) was added and stirring was continued for 1 h. Work-up followed by flash chromatography with ethyl acetate–light petroleum (12:88) gave the spiro ketone (**49**) (20 mg) (identical by ^{1}H n.m.r. and t.l.c. with that described earlier).

Repetition of the reaction with addition of a second equivalent of lithium di-isopropylamide solution after 1 h and continued stirring for a further 0.5 h gave the spiro ketone (**49**) (6% yield) and starting material (**6**) (30%).

Spiro[gibberellin A$_4$ methyl ester-2,1′-cyclopropane] (**50**) *and Spiro-[3-epigibberellin A$_4$ methyl ester-2,1′-cyclopropane]* (**51**).—The spiro ketone (**49**) (107 mg) in propan-2-ol (10 ml) was stirred with sodium borohydride (*ca.* 40 mg) for 40 min. Work-up followed by flash chromatography with ethyl acetate–light petroleum (35:65) gave, sequentially: (i) *spiro-[3-epi-GA$_4$ methyl ester-2,1′-cyclopropane]* (**51**) (25 mg) as a gum (Found: M^+, 372.1945; $M - 18$, 354.1823. $C_{22}H_{28}O_5$ requires M, 372.1937; $M - 18$, 354.1831); δ 0.52 (1 H, d, *J* 3.7 Hz, cyclopropyl H), 0.57 (1 H, d, *J* 3.2 Hz, cyclopropyl H), 0.65 (1 H, m, cyclopropyl H), 0.93 (1 H, M, cyclopropyl H), 1.17 (3 H, s, 18-H_3), 2.63 (1 H, br t, 9- or 13-H), 2.68 (1 H, d, *J* 10.5 (Hz, 5-H), 2.80 (1 H, d, *J* 10.5 Hz, 6-H), 3.72 (3 H, s, OMe), 3.80 (1 H, s, 3β-H), 4.85 (1 H, br s, 17-H, and 4.98 (1 H, br s, 17-H); *m/z* 372 (M^+, 5%), 354 (42), 326 (100), 312 (37), 294 (24), 267 (24), 239 (26), and 91 (48); and (ii) *spiro[GA$_4$ methyl ester-2,1′-cyclopropane]* (**50**) (20 mg) as a gum (Found: M^+, 372.1900; $M - 18$, 354.1813. $C_{22}H_{28}O_5$ requires M, 372.1937; $M - 18$, 354.1831; δ 0.5 (4 H, m, cyclopropyl H), 1.16 (3 H, s, 18-H_3), 1.27 (1 H, d, *J* 13.4 Hz, 1-H), 2.16 (1 H), d, *J* 13.7 Hz, 1-H), 2.64 (1 H, br t, 9- or 13-H), 2.75 (1 H, d, *J* 11.0 Hz, 6-H), 2.85 (1 H, s, 3α-H), 3.29 (1 H, d, *J* 10.7 Hz, 5-H), 3.71 (3 H, s, OMe), 4.86 (1 H, br s, 17-H), and 4.98 (1 H, br s, 17-H) (on addition of D_2O no change was observed); *m/z* 372 (M^+, 4%), 354 (40), 340 (37), 327 (26), 326 (100), 312 (41), 310 (60), 294 (34), 267 (34), 250 (58), 222 (62), and 91 (85).

Spiro[gibberellin A$_9$-2,1′-cyclopropane] (**48**).—Spiro[gibberellin A_4 methyl ester-2,1′-cyclopropane] (**50**) (20 mg) was stirred with sodium propane-1-thiolate solution (1.5 ml) under nitrogen. After 4.5 h work-up followed by flash chromatography with ethyl acetate–light petroleum–acetic acid (120:80:1) gave spiro[GA_4-2,1′-cyclopropane] (**48**) (13 mg) as a gum (Found: M^+, 358.1796; $M - 18$, 340.1700. $C_{21}H_{26}O_5$ requires M, 358.1780; $M - 18$, 340.1674); δ[$(CD_3)_2CO$] 0.35 (2 H, m, cyclopropyl H), 0.61 (1 H, m, cyclopropyl H), 1.11 (3 H, s, 18-H_3), 1.28 (1 H, d, *J* 13.4 Hz, 1-H), 2.63 (d, *J* 11.0 Hz, 6-H; superimposed on other signals), 2.77 (1 H, s, 3α-H), 3.29 (1 H, d, *J* 11.0 Hz, 5-H), 4.85 (1 H, br s, 17-H), and 4.98 (1 H, br s, 17-H); *m/z* 358 (M^+, 4%), 340 (21), 312 (100), 296 (35), 294 (25), and 91 (41) [g.l.c.–mass spectrum of the Me ester *O*-$SiMe_3$ derivative: *m/z* 444 (M^+, 100%), 384 (23), 326 (66), 310 (52), 298 (44), 294 (38), 251 (67), and 250 (72)].

Epimerisation of the 2β-Isopropyl-3-oxogibberellin A$_9$ Methyl Ester (**28**).—2β-Isopropyl-3-oxo-GA_9 methyl ester (**28**) (94 mg) in dry tetrahydrofuran (2 ml) and dry diethyl ether (15 ml), under nitrogen, was stirred with 0.5M lithium di-isopropylamide solution (1.0 ml). After 7 min, the reaction was quenched by addition to acidified water. Extraction with ethyl acetate and evaporation under reduced pressure gave a gum. Flash chromatography yielded starting material (**28**) (*ca.* 25 mg), eluted with ethyl acetate–light petroleum (5:95); and the 2α-isopropyl-3-oxo-GA_9 methyl ester (**29**) (67 mg), eluted with ethyl acetate–light petroleum (10:90). The two isomers were identical (^{1}H n.m.r. and t.l.c.) with samples described earlier.

Hydride Reduction of 2α-Isopropyl-3-oxogibberellin A$_9$ Methyl Ester (**29**).—(a) *With sodium borohydride in propan-2-ol.* The ketone (**29**) in propan-2-ol (15 ml) was stirred with an excess of sodium borohydride for 1 h. Work-up, followed by flash chromatography with ethyl acetate–light petroleum (20:80) gave, sequentially, 2β-isopropyl-GA_4 methyl ester (**23**) (49 mg) and 2β-isopropyl-3-epi-GA_4 methyl ester (**24**) (49 mg), identical with the compounds described earlier.

(b) *With sodium borohydride in tetrahydrofuran.* The ketone (**29**) (54 mg) in dry tetrahydrofuran (10 ml) was stirred with an excess of sodium borohydride under nitrogen. After 30 min, t.l.c. showed the presence of 2β-isopropyl-3-oxo-GA_9 methyl ester (**28**), 2β-isopropyl-GA_4 methyl ester (**23**), and 2β-isopropyl-3-*epi*-GA_4 methyl ester (**24**).

(c) *With sodium cyanoborohydride.* To the ketone (**29**) (67 mg) and an excess of sodium cyanoborohydride in tetrahydrofuran (10 ml) was added acetic acid (to pH 4.5). After 30 min, t.l.c. indicated no reaction. A few drops of aqueous 2M hydrochloric acid were added and the mixture was stirred for a further 30 min. T.l.c. again indicated no reaction. Potassium dihydrogen phosphate (*ca.* 30 mg) was added. T.l.c. still indicated no reaction. Work-up and flash chromatography with ethyl acetate–light petroleum (30:70) gave *2α-isopropyl-3-epi-gibberellin A$_4$ methyl ester* (**37**) (*ca.* 10 mg) as a gum (Found: M^+, 388.2257. $C_{23}H_{32}O_5$ requires M, 388.2250); δ 0.89 (3 H, d, *J* 6.1 Hz, 2-CHMe), 0.99 (3 H, d, *J* 6.1 Hz, 2-CHMe), 1.20 (3 H, s, 18-H_3), 2.62 (1 H, br t, 9- or 13-H), 2.67 (1 H, d, *J* 10.5 Hz, 5- or 6-H), 3.01 (1 H, d, *J* 10.3 Hz, 5- or 6-H), 3.72 (3 H, s, OMe), 3.91 (1 H, d, *J* 4.4 Hz, 3β-H), 4.84 (1 H, br s, 17-H), and 4.97 (1 H, br s, 17-H); *m/z* 388 (M^+, 9%), 386 (100), 370 (34), 358 (32), 356 (28), 342 (58), 328 (49), 326 (42), 314 (49), 289 (77), 223 (63), 105 (48), 91 (82), and 41 (82).

The same product (**37**) (10 mg) was obtained by reduction of (**29**) (15 mg) with sodium borohydride in diethyl ether (15 ml) and t-butyl alcohol (0.5 ml).

Epimerisation of 2β-Methyl-3-oxogibberellin A$_9$ Methyl Ester (**30**).—2β-Methyl-3-oxo-GA_4 methyl ester (**30**) (238 mg) in dry tetrahydrofuran (1 ml) and dry diethyl ether (15 ml), under nitrogen, was stirred with lithium di-isopropylamide (2.7 ml; 0.5M solution/suspension in diethyl ether). T.l.c. after 1 min indicated a 1:1 mixture of 2β- and 2α-methyl ketones, (**30**) and (**31**). After 7 min, work-up followed by flash chromatography with ethyl acetate–light petroleum (15:85) gave mixed fractions of (**30**) and 2α-methyl-3-oxo-GA_9 methyl ester (**31**) (123 mg), followed by 2α-methyl-3-oxo-GA_9 methyl ester (**31**) (41 mg) (contaminated with *ca.* 20% 2β-isomer by ^{1}H n.m.r.), identical by ^{1}H n.m.r. with an authentic sample, described earlier.

Reaction of 2α-Methyl-3-oxogibberellin in A$_9$ Methyl Ester (**31**) *with Sodium Borohydride in the Presence of t-Butyl Alcohol.*—2α-Methyl-3-oxo-GA_9 methyl ester (**31**) [*ca.* 10 mg; contaminated with *ca.* 20% 2β-isomer (**30**)] in dry tetrahydrofuran and dry diethyl ether (15 ml) under nitrogen was stirred for 1 h with sodium borohydride (excess) and t-butyl alcohol (1.5 ml). Work-up followed by flash chromatography with ethyl acetate–light petroleum (35:65) gave traces of 2β-methyl-GA_4

methyl ester (**39**) and 2β-methyl-3-*epi*-GA_4 methyl ester (**40**), both identified by ^1H n.m.r. and t.l.c. comparison with authentic samples.[3]

The main product was ent-3β,10β-*dihydroxy*-2β-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**38**), a gum (*ca.* 5 mg) (Found: $M^+ - 18$, 342.1850. $C_{21}H_{28}O_5$ requires $M - 18$, 342.1831); δ 1.10 (3 H, d, *J* 7.8 Hz, 2α-CH_3), 1.17 (3 H. s, 18-H_3), 2.61 (1 H, br m, 9-or 13-H; under signal at 2.63 p.p.m.). 2.63 (1 H, d, *J* 10.5 Hz, 5-H; superimposed on signal at 2.61 p.p.m.), 2.75 (1 H, d, *J* 10.3 Hz, 6-H), 3.71 (3 H, s, OMe), 3.87 (1 H. d, *J* 7.6 Hz, 3β-H), 4.85 (1 H, br s, 17-H), and 4.98 (1 H, br s, 17-H); *m/z* 360 (M^+, 11%), 342 (78), 328 (55), 314 (100), 300 (66), 298 (38), 286 (48), 282 (50), 277 (47), 233 (74), and 91 (75); it was distinct (^1H n.m.r. and t.l.c.) from 2α-methyl-GA_4 methyl ester (**41**),[15] 2β-methyl-GA_4 methyl ester (**39**),[3] and 2β-methyl-3-*epi*-GA_4 methyl ester (**40**).[3]

ent-2-[(E)-*Ethylidene*]-10β-*hydroxy*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**11**).—The (*E*)-monothio ketone (**12**) (470 mg) in dry tetrahydrofuran (4 ml) was added to lithium dimethylcuprate solution (1.3 mmol) in dry diethyl ether (15 ml) at −50 °C in an atmosphere of nitrogen. Work-up after 20 min followed by flash chromatography [ethyl acetate–light petroleum (10:90)] gave 2β- and 2α-isopropyl-3-oxo-GA_9 methyl esters (**28**) (24 mg) and (**29**) (54 mg), described earlier, followed by (E)-2-*ethylidene*-3-*oxo*-GA_9 *methyl ester* (**11**) (308 mg), m.p. 228—230 °C (from ethyl acetate–light petroleum) (Found: M^+, 370.1754, $C_{22}H_{26}O_5$ requires *M*, 370.1780); $\lambda_{max.}$ 245 nm (ε 10 157 l mol^{-1} cm^{-1}); δ 1.26 (3 H, s. 18-H_3), 1.77 (3 H, ddd, *J* 7.3, 1.5, and 1.5 Hz, =CHMe), 2.51 (1 H, dm, *J* 17.0 Hz, 1-H), 2.84 (1 H, d, *J* 10.0 Hz, 6-H), 3.13 (1 H. dm, *J* 17.0 Hz, 1-H), 3.18 (1 H, d, *J* 9.8 Hz, 5-H), 3.73 (3 H. s. OMe), 4.88 (1 H, br s, 17-H), 5.00 (1 H, br s, 17-H), and 7.02 (1 H, ddq, *J* 7.3, 2.8, and 2.0 Hz, =CHMe) [^1H n.O.e.: irradiation at 2.51, 7.02, and 1.77 p.p.m. (in turn) gave enhancement at 1.77, 1.77, and 7.02 p.p.m., respectively; irradiation at 3.13 p.p.m. gave enhancement at 2.51 and 1.77 p.p.m.]; *m/z* 370 (M^+, 96%), 352 (17), 342 (23), 338 (100), 326 (30), 310 (44), 282 (32), 266 (96), 243 (43), and 91 (60).

Epoxidation of ent-2-[(E)-*Ethylidene*]-10β-*hydroxy*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**11**). —(*E*)-2-Ethylidene-3-oxo-GA_9 methyl ester (**11**) (154 mg) in chloroform (10 ml) was stirred with *m*-chloroperbenzoic acid (93 mg) at room temprature. After 3 h the mixture was added to saturated aqueous sodium sulphite (10 ml). The chloroform layer was separated, washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a gum. Flash chromatography [ethyl acetate–light petroleum (40:60)] gave. sequentially, (E)-2-*ethylidene*-3-*oxo*-GA_9 16α,17-*epoxide methyl ester* (65 mg; spillage) as a gum (Found: M^+, 386.1697. $C_{22}H_{26}O_6$ requires *M*, 386.1729); δ 1.27 (3 H, s, 18-H_3), 1.79 (3 H. br d, *J* 7.3 Hz, =CHMe), 2.52 (1 H, br, d, *J* 17.8 Hz, 1-H), 2.85 (2 H, s, 17-H_2), 2.89 (1 H, d, *J* 9.8 Hz, 6-H), 3.14 (1 H, d, *J* 17.8 Hz, 1-H), 3.17 (1 H, d, *J* 9.3 Hz, 5-H), 3.73 (3 H, s, OMe), and 7.06 (1 H, m, =CHMe); *m/z* 386 (87%), 368 (14), 358 (30), 356 (50), 342 (35), 341 (31), 326 (45), 327 (37), 283 (47), 282 (74), 281 (48), and 71 (100); and (E)-2-*ethylidene*-3-*oxo*-GA_9 16β,17-*epoxide methyl ester* (1 mg) as a gum (Found: M^+, 386.1713. $C_{22}H_{26}O_6$ requires *M*, 386.1729); δ 1.26 (3 H, s, 18-H_3), 1.79 (3 H, dd, *J* 5.7 and 1.5 Hz, =CHMe), 2.56 (1 H, br, d, *J* 1.6 Hz, 1-H). 2.79 (1 H, d, *J* 5.1 Hz, 17-H), 2.82 (1 H, d, *J* 10.0 Hz, 6-H), 2.87 (1 H. d, *J* 5.1 Hz, 17-H), 3.17 (1 H, d, *J* 10.0 Hz, 5-H), 3.21 (1 H, br d, *J* 1.6 Hz, 1-H), 3.73 (3 H, s, OMe), and 7.10 (1 H, m, =CHMe); *m/z* 386 (M^+, 78%), 368 (16), 358 (26), 356 (29), 355 (33), 354 (32). 342 (45), 341 (34), 327 (58), 326 (45), 298 (29), 283 (58), 282 (100), and 281 (58).

Attempted Hydrogenation of the 2-[(E)-*Ethylidene*]-3-*oxogibberellin* A_9 16α,17-*Epoxide Methyl Ester*.—(*E*)-2-Ethylidene-3-oxo-GA_9 16α,17-epoxide methyl ester (65 mg) in tetrahydrofuran (10 ml) was stirred with 10% palladium on calcium carbonate (catalytic) under hydrogen at room temperature and pressure. After 0.5 h filtration through Celite and evaporation under reduced pressure gave a gum identical with starting material by ^1H n.m.r. and t.l.c.

The reaction was repeated in ethyl acetate and with a different batch of catalyst, with the same result.

Reduction of 2-[(E)-*Ethylidene*]-3-*oxogibberellin* A_9 *Methyl Ester* (**11**).—(a) *With zinc–copper couple in acetone.* The enone (**11**) (80 mg) in acetone (15 ml) was refluxed with zinc–copper couple. After 1 h some starting material was still present (t.l.c.). Acetic acid (1 ml) was added and refluxing continued for a further 15 min; no starting material then remained (t.l.c.). The cooled mixture was filtered through Celite and evaporated under reduced pressure to give a gum. Flash chromatography with ethyl acetate–light petroleum (10:90) gave, sequentially, ent-2α-*ethyl*-10β-*hydroxy*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**33**) (*ca.* 10 mg) as a gum (Found: M^+, 372.1968. $C_{22}H_{28}O_5$ requires *M*, 372.1937); δ 0.91 (3 H. t, *J* 7.6 Hz, 2-CH_2Me), 1.18 (3 H, s, 18-H_3), 2.81 (1 H, d, *J* 10.3 Hz, 6-H), 2.97 (1 H, d, *J* 10.3 Hz, 5-H , 3.72 (3 H, s, OMe), 4.87 (1 H, br s, 17-H), and 4.99 (1 H, br s, 17-H): *m/z* 372 (M^+, 74%), 344 (29), 340 (68), 328 (27), 327 (25), 312 (34), 289 (36), 285 (21), and 94 (100); and ent-2β-*ethyl*-10β-*hydroxy*-3-*oxo*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**34**) (*ca.* 10 mg) as a gum (Found: M^+, 372.1948. $C_{22}H_{28}O_5$ requires *M*, 372.1937); δ 0.89 (3 H, t, *J* 7.3 Hz, 2-CH_2Me), 1.20 (3 H, s, 18-H_3), 2.83 (1 H, d, *J* 10.0 Hz, 6-H), 3.17 (1 H, d, *J* 9.8 Hz, 5-H), 3.72 (3 H, s, OMe), 4.88 (1 H, br s, 17-H), and 5.00 (1 H, br s, 17-H); *m/z* 372 (M^+, 100%), 344 (42), 340 (55). 328 (31), 312 (32), 289 (40), 94 (62), 91 (60), and 55 (69).

Further elution, with ethyl acetate–light petroleum (35:65), gave ent-2-[(E)-*ethylidene*]-3β,10β-*dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**43**) (*ca.* 40 mg) as a gum (Found: M^+, 372.1914. $C_{22}H_{28}O_5$ requires *M*, 372.1937); δ 1.22 (3 H, s, 18-H_3), 1.64 (3 H, ddd, *J* 6.8, 2.0, and 1.0 Hz, =CHMe), 2.63 (1 H, br t, 9- or 13-H), 2.73 (1 H, d, *J* 10.0 Hz, 6-H), 2.79 (1 H, d, *J* 10.0 Hz, 5-H), 3.09 (1 H, d, *J* 15.4 Hz, 1-H), 3.73 (3 H, s, OMe_3), 4.10 (1 H, m, 3β-H), 4.87 (1 H, br s, 17-H), 4.98 (1 H, br s, 17-H), and 5.99 (1 H, ddq, *J* 6.6, 2.0, and 2.0 Hz. =CHMe) (on addition of D_2O the signal at 4.10 p.p.m. collapsed to a broad singlet) [^1H homonuclear decoupling: irradiation at 3.09 p.p.m. showed slight sharpening of the 1 H multiplet at 4.10 p.p.m.; on irradiation at 1.64 p.p.m. the signal at 4.10 p.p.m. sharpened to a broad singlet and that at 5.99 p.p.m. became a triplet (*J* 2.2 Hz); on irradiation at 5.99 p.p.m. the signal at 1.64 p.p.m. collapsed to a broad singlet; on irradiation at 2.04 p.p.m. (where the other arm of the 1-H_2 AB quartet may occur) the signal at 5.99 p.p.m. became a dq (*J* 5.5 and 2.2 Hz), the signal at 4.10 p.p.m. became less broad, and the 1-H doublet at 3.09 p.p.m. collapsed]; *m/z* 372 (M^+, 16%), 354 (23), 341 (22), 326 (98), 325 (100), 312 (65), 309 (88), 297 (56), 269 (79), 267 (82), 250 (60), and 91 (85).

(b) *With tributylstannane and tetrakis(triphenylphosphine)-palladium*(0). To (*E*)-2-ethylidene-3-oxo-GA_9 methyl ester (**11**) (111 mg) in dry tetrahydrofuran (7 ml) and dry diethyl ether (25 ml) containing tetrakis(triphenylphosphine)palladium(0) (14 mg), under nitrogen, was added tributyltin hydride [prepared from tributyltin chloride (212 μl)], over 1 h. After 2 h the mixture was filtered through Celite and evaporated under reduced pressure to give a gum. Flash chromatography with ethyl acetate–light petroleum (10:90) gave, sequentially, 2β-ethyl-3-oxo-GA_9 methyl ester (**34**) (46 mg). 2α-ethyl-3-oxo-GA_9 methyl ester (**33**) (15 mg), and starting material (**11**) (*ca.* 30

mg), all as gums. The ethyl compounds were identical (^{1}H n.m.r. and t.l.c.) with those described in (a).

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References

1 G. V. Hoad, B. O. Phinney, V. M. Sponsel, and J. MacMillan, *Phytochemistry*, 1981, **20**, 703.
2 G. V. Hoad, J. MacMillan, V. A. Smith, V. M. Sponsel, and D. A. Taylor, in 'Plant Growth Substances 1982. Proceedings of the XIth International Conference on Plant Growth Substances,' ed. P. W. Wareing, Academic Press, New York, 1982, pp. 91—100.
3 M. H. Beale and J. Macmillan, *Phytochemistry*, 1981, **20**, 693.
4 M. H. Beale, J. MacMillan, C. R. Spray, D. A. Taylor, and B. O. Phinney, *J. Chem. Soc., Perkin Trans. 1*, 1984, 541.
5 J. MacMillan and D. A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1985, 837.
6 E. J. Corey and R. H. K. Chen, *Tetrahedron Lett.*, 1973, 3817.
7 Z. V. Duri, B. M. Fraga, and J. R. Hanson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 161.
8 J. A. K. Howard and C. M. Nunn, unpublished results.
9 N. Takahashi, 'Plant Growth Substances 1973,' Hirokawa Publishing Co., Tokyo, 1974, pp. 228—240.
10 B. E. Cross, J. F. Grove, and A. Morrison, *J. Chem. Soc.*, 1961, 2498.
11 J. MacMillan and R. J. Pryce, *J. Chem. Soc. C*, 1967, 740.
12 J. Colonge and G. Descotis, in '1,4-Cycloaddition Reactions,' ed. J. Hamer, Academic Press, New York, 1967, pp. 217—253.
13 S. M. Ruder and R. C. Ronald, *Tetrahedron Lett.*, 1984, 5501.
14 D. F. Rane, A. G. Fishman, and R. E. Pike, *Synthesis*, 1984, 694.
15 A. M. Fowles and J. MacMillan, *J. Chem. Soc., Perkin Trans. 1*, 1988, following paper.
16 D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, 'Purification of Laboratory Chemicals,' 2nd edn., Pergamon, Oxford, 1980.
17 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

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