2α-Alkyl Gibberellins A_1 and A_4

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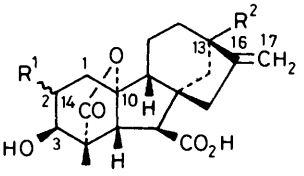
An alkylcopper–magnesium complex, prepared from alkylmagnesium bromide, copper(I) iodide, and hexamethylphosphoric triamide in tetrahydrofuran, is described as a reagent for the *syn*-S_N2' displacement of the allylic lactonic oxygen in gibberellin A_3 methyl ester (**13**). The resultant 2α-alkyl-1(10)-enes (**24**), (**27**), and (**29**) have been converted by known procedures into 2α-methyl (**7**), 2α-ethyl (**9**), and 2α-propyl (**11**) derivatives of gibberellin A_1 (**2**). The 2α-ethyl (**5**) and 2β-ethyl (**6**) derivatives of gibberellin A_4 (**1**) have been prepared by 13-deoxygenation of the corresponding derivatives of gibberellin A_1 (**2**). The direct preparation of 2α-alkyl derivatives of gibberellin A_4 by *syn*-S_N2' displacement of the allylic lactonic oxygen in the 3-tetrahydropyranyl ether of gibberellin A_7 methyl ester (**15**) with lithium dialkylcuprates works for methyl but not for higher alkyl groups. Attempts to prepare 2-methylgibberellin A_3 and 2-methylgibberellin A_7 gave the 2-methyl isomeric lactones (**58**) and (**60**).

Continuing our studies on the effect of 2-alkyl substituents on the biological activity of gibberellins (GAs) we now describe the preparation of 2α-alkyl derivatives of GA_4 (**1**) and GA_1 (**2**). As described in the preceding paper[1] the attempted preparation of 2α-methyl- and 2α-isopropyl-GA_4 by reduction of the 2α-alkyl 3-ketones was unsuccessful, giving only the 2α-alkyl 3α-alcohols. Thus methods were required that introduced a 2α-alkyl substituent with a 3β-hydroxy group already in the molecule. Such methods have been developed, based upon the *syn*-S_N2' displacement of the allylic lactone in GA_3 methyl ester (**13**) using a novel alkylcopper–magnesium complex.

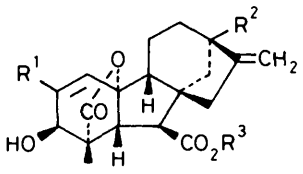
The reactions of GA_3 (**14**) and its methyl ester (**13**) with lithium dimethylcuprate have been shown[2] to give the *anti*-S_N2' products (**22**) and (**23**), respectively. In the case of GA_3 methyl ester (**13**), *ca.* 5% of the S_N2 product (**31**) was also isolated.[3] However, Beale[3] has shown that reaction of the 3-tetrahydropyranyl ether of GA_3 methyl ester (**13**) with lithium dimethylcuprate gave, after hydrolysis of the ether, a mixture of the 2α- and 2β-methyl derivatives (**24**) and (**23**). Applying this procedure to the 3-tetrahydropyranyl ether of GA_7 methyl ester (**15**), we obtained a 1:1 mixture of the 2α- and 2β-methyl derivatives (**25**) and (**26**). These compounds were then separately converted into 2α- and 2β-methyl-GA_4 (**3**) and (**4**) *via* the iodo lactones (**32**) and (**33**) and methyl esters (**41**) and (**42**), by the procedures described by MacMillan and Taylor.[2] The stereochemistry of 2α-methyl-GA_4 (**3**) follows from the established[4] stereochemistry of the known 2β-methyl-GA_4 (**4**). However this stereochemistry was independently confirmed by using the previously established fact[5] that the 16α,17-epoxide of GA_7 methyl ester (**15**) was catalytically [^{2}H]hydrogenated to the 1β,2β-[$^2H_2$]epoxide of GA_4 methyl ester (**43**). Thus treatment of the 2β-methyl iodo lactone (**33**) with 1,8-diazabicyclo[5.4.0]undec-7-ene gave 2-methyl GA_7 methyl ester (**16**). Conversion of this ester (**16**) into the corresponding 16α,17-epoxide followed by hydrogenation over palladium–calcium carbonate, then de-epoxidation and demethylation, afforded 2α-methyl-GA_4 (**3**). The ^{1}H n.m.r. spectra of 2α-methyl-GA_4 (**3**) and its precursors were unexceptional except for the 2α-methyl-1(10)-ene (**25**). As for the corresponding product (**24**),[3] obtained from the 3-tetrahydropyranyl ether of GA_3 methyl ester (**13**), the 6-H signal in the spectrum of the 2α-methyl-1(10)-ene (**25**) occurred at an unusually high field (2.33 p.p.m.; *J* 9.3 Hz), and $J_{2,3}$ was unusually large (9.0 Hz). These data were subsequently useful in distinguishing the 2α- and 2β-epimers of the corresponding 2α- and 2β-ethyl-1(10)-enes (**27**) and (**28**); they indicate a boat conformation for ring *A* in which interaction between the 19-oic acid group and the 6-hydrogen atom is minimised.

Attempts to prepare 2α-ethyl-GA_4 (**5**) by the method described for 2α-methyl-GA_4 (**3**) were unsuccessful. Many products were formed in the reaction between the 3-tetrahydropyranyl ether of GA_7 methyl ester (**15**) and lithium diethylcuprate; the only isolated product, after hydrolysis of the tetrahydropyranyl ether, was the diene (**57**). The most likely explanation for the formation of the diene (**57**) is that lithium diethylcuprate undergoes β-elimination to a hydrido metal species which brings about S_N2' attack of hydride at C-2, followed by acid-catalysed dehydration during hydrolysis of the ether group.

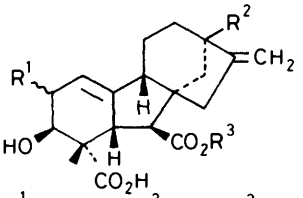
A general route to 2α-alkyl-GAs was developed from a re-investigation of copper(I)-catalysed Grignard reactions with GA_3 methyl ester (**13**). Previously MacMillan and Taylor[2] showed that GA_3 methyl ester (**13**) reacted with methylmagnesium iodide in the presence of copper(I) bromide to give the *anti*-S_N2' product (**23**). However with ethylmagnesium halide and copper(I) halide no reaction occurred with GA_3 methyl ester (**13**)[6] and, in the present work, several unidentified products were obtained in low yield from the 3-tetrahydropyranyl ether of GA_7 methyl ester (**15**). Nevertheless the Cu^I-catalysed S_N2' reaction of ethyl- (and other alkyl-) magnesium bromides with GA_3 methyl ester (**13**) occurred in the presence of hexamethylphosphoric triamide to give both *syn*- and *anti*-products in acceptable yields. After experimentation a general alkylcopper–magnesium reagent was developed from the alkylmagnesium bromide (2 mol equiv.), copper(I) iodide (1 mol equiv.) and hexamethylphosphoric triamide (1 mol equiv.) in tetrahydrofuran at −15 °C. This reagent was then treated with GA_3 methyl ester (**13**) (0.5—1.0 mol equiv.) in tetrahydrofuran at −40 °C. Under these conditions, ethylmagnesium bromide gave the 2α-ethyl- and 2β-ethyl-1(10)-enes (**27**) and (**28**) in the ratio *ca.* 1:1, in 47% overall yield; propylmagnesium bromide gave the 2α-propyl- and 2β-propyl-1(10)-enes (**29**) and (**30**) in the ratio 3:1 in an overall yield of 41%; and methylmagnesium bromide gave 2α-methyl- and 2β-methyl-1(10)-enes (**24**) and (**23**) in the ratio 3:1 in an overall yield of 70%. It is important that GA_3 methyl ester (**13**) is added to the alkylcopper reagent at −40 °C and that the reaction temperature is kept below −15 °C. The nature of the alkylcopper–magnesium reagent is not known, but it is presumably solvated and sterically demanding, to account for the high stereoselectivity for the 2α-alkylation products. The reagent is violet like the solid (Ph_2CuPh_2Mg·*n*THF), prepared



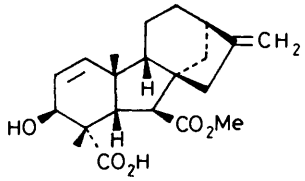
(1) $R^1 = R^2 = H$
(2) $R^1 = H$, $R^2 = OH$
(3) $R^1 = \alpha$-Me, $R^2 = H$
(4) $R^1 = \beta$-Me, $R^2 = H$
(5) $R^1 = \alpha$-Et, $R^2 = H$
(6) $R^1 = \beta$-Et, $R^2 = H$
(7) $R^1 = \alpha$-Me, $R^2 = OH$
(8) $R^1 = \beta$-Me, $R^2 = OH$
(9) $R^1 = \alpha$-Et, $R^2 = OH$
(10) $R^1 = \beta$-Et, $R^2 = OH$
(11) $R^1 = \alpha$-Pr, $R^2 = OH$
(12) $R^1 = \beta$-Pr, $R^2 = OH$



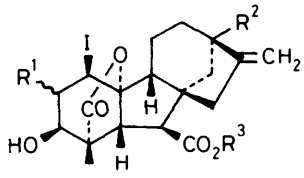
(13) $R^1 = H$, $R^2 = OH$, $R^3 = Me$
(14) $R^1 = R^3 = H$, $R^2 = OH$
(15) $R^1 = R^2 = H$, $R^3 = Me$
(16) $R^1 = R^3 = Me$, $R^2 = H$
(17) $R^1 = R^2 = R^3 = H$
(18) $R^1 = Et$, $R^2 = OH$, $R^3 = Me$
(19) $R^1 = Me$, $R^2 = OH$, $R^3 = H$
(20) $R^1 = Et$, $R^2 = OH$, $R^3 = H$
(21) $R^1 = Me$, $R^2 = R^3 = H$



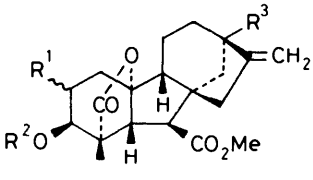
(22) $R^1 = \beta$-Me, $R^2 = OH$, $R^3 = H$
(23) $R^1 = \beta$-Me, $R^2 = OH$, $R^3 = Me$
(24) $R^1 = \alpha$-Me, $R^2 = OH$, $R^3 = Me$
(25) $R^1 = \alpha$-Me, $R^2 = H$, $R^3 = Me$
(26) $R^1 = \beta$-Me, $R^2 = H$, $R^3 = Me$
(27) $R^1 = \alpha$-Et, $R^2 = OH$, $R^3 = Me$
(28) $R^1 = \beta$-Et, $R^2 = OH$, $R^3 = Me$
(29) $R^1 = \alpha$-Pr, $R^2 = OH$, $R^3 = Me$
(30) $R^1 = \beta$-Pr, $R^2 = OH$, $R^3 = Me$



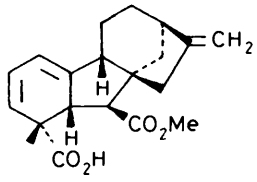
(31)



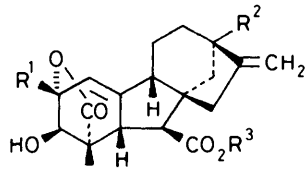
(32) $R^1 = \alpha$-Me, $R^2 = H$, $R^3 = Me$
(33) $R^1 = \beta$-Me, $R^2 = H$, $R^3 = Me$
(34) $R^1 = \alpha$-Me, $R^2 = OH$, $R^3 = Me$
(35) $R^1 = \alpha$-Et, $R^2 = OH$, $R^3 = Me$
(36) $R^1 = \beta$-Et, $R^2 = OH$, $R^3 = Me$
(37) $R^1 = \alpha$-Pr, $R^2 = OH$, $R^3 = Me$
(38) $R^1 = \beta$-Pr, $R^2 = OH$, $R^3 = Me$
(39) $R^1 = \beta$-Me, $R^2 = OH$, $R^3 = H$
(40) $R^1 = \beta$-Me, $R^2 = OH$, $R^3 = SnBu_3$



(41) $R^1 = \alpha$-Me, $R^2 = R^3 = H$
(42) $R^1 = \beta$-Me, $R^2 = R^3 = H$
(43) $R^1 = R^2 = R^3 = H$
(44) $R^1 = \alpha$-Me, $R^2 = H$, $R^3 = OH$
(45) $R^1 = \alpha$-Et, $R^2 = H$, $R^3 = OH$
(46) $R^1 = \beta$-Et, $R^2 = H$, $R^3 = OH$
(47) $R^1 = \alpha$-Pr, $R^2 = H$, $R^3 = OH$
(48) $R^1 = \beta$-Pr, $R^2 = H$, $R^3 = OH$
(49) $R^1 = \alpha$-Et, $R^2 = Ac$, $R^3 = OH$
(50) $R^1 = \beta$-Et, $R^2 = Ac$, $R^3 = OH$
(51) $R^1 = \alpha$-Et, $R^2 = Ac$, $R^3 = OCOCO_2Me$
(52) $R^1 = \beta$-Et, $R^2 = Ac$, $R^3 = OCOCO_2Me$
(53) $R^1 = \alpha$-Et, $R^2 = Ac$, $R^3 = H$
(54) $R^1 = \beta$-Et, $R^2 = Ac$, $R^3 = H$
(55) $R^1 = \alpha$-Et, $R^2 = R^3 = H$
(56) $R^1 = \beta$-Et, $R^2 = R^3 = H$



(57)



(58) $R^1 = Me$, $R^2 = OH$, $R^3 = H$
(59) $R^1 = Et$, $R^2 = OH$, $R^3 = Me$
(60) $R^1 = Me$, $R^2 = R^3 = H$
(61) $R^1 = R^3 = Me$, $R^2 = H$

by Costa *et al.*[7] from phenylmagnesium bromide and copper(I) bromide in tetrahydrofuran.

By previously described methods,[2] the 2α- and 2β-alkyl-1(10)-enes (**24**) and (**27**)—(**30**) were converted into the 2α- and 2β-alkyl esters (**44**)—(**48**) *via* the iodo lactones (**34**)—(**38**). Demethylation of the methyl esters then gave 2α-methyl-GA_1 (**7**), 2α-ethyl-GA_1 (**9**), 2α-propyl-GA_1 (**11**), and 2β-propyl-GA_1 (**12**). This sequence of reactions was not applied to the 2β-methyl-1(10)-ene (**23**), since the preparation of 2β-methyl-GA_1 (**8**) by this route has been described[2] previously. Similarly since 2β-ethyl-GA_1 (**10**) has also been previously prepared,[2] the 2β-ethyl-GA_1 methyl ester (**46**) was retained for conversion into 2β-ethyl-GA_4 (**6**) as described later. The stereochemistry of the 2α- and 2β-alkyl groups in all the compounds was assigned from their ^1H n.m.r. spectra and from the results of treatment of the iodo lactones (**34**)—(**36**) with 1,8-diazabicyclo[5.4.0]undec-7-

ene in refluxing toluene. As expected the 2α-alkyl-1β-iodo lactones (**34**) and (**35**) did not react, but the 2β-ethyl-1β-iodo lactone (**36**) underwent *trans*-dehydroiodination to give a mixture of 2-ethyl-GA_3 methyl ester (**18**) and the corresponding 19,2-isomeric lactone (**59**). The formation of the isomeric lactone (**59**) is discussed later.

2α-Ethyl-GA_4 (**5**) and 2β-ethyl-GA_4 (**6**) were prepared from 2α- and 2β-ethyl-GA_1 methyl esters (**45**) and (**46**). 13-Deoxygenation[8] of the 3-acetyl 13-oxalyl esters (**51**) and (**52**) with tributylstannane gave the 3-acetates (**53**) and (**54**), which were hydrolysed in two steps *via* the methyl esters (**55**) and (**56**) to 2α- and 2β-ethyl-GA_4 (**5**) and (**6**).

Attempts to prepare 2-methyl-GA_3 (**19**), 2-ethyl-GA_3 (**20**), and 2-methyl-GA_7 (**21**) were unsuccessful. 1β-Iodo-2β-methyl-GA_1 (**39**), prepared from GA_3 (**14**) by the method of MacMillan and Taylor,[2] was converted into the tributylstannyl ester (**40**) and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene in refluxing toluene. After hydrolysis of the stannyl ester, the isomeric 19,2-lactone (**58**) of 2-methyl-GA_3 (**19**) was obtained as the sole product. As noted earlier, treatment of 1β-iodo-2β-ethyl-GA_1 methyl ester (**36**) with 1,8-diazabicyclo[5.4.0]undec-7-ene gave a mixture of 2-ethyl-GA_3 methyl ester (**18**) and the isomeric lactone (**59**). Similarly, demethylation of 2-methyl-GA_7 methyl ester (**16**), obtained as described earlier, with sodium propane-1-thiolate in hexamethylphosphoric triamide, yielded the isomeric lactone (**60**) and no 2-methyl-GA_7 (**21**). Since 19,10 ⟶ 19,2-lactone isomerisation in aqueous alkali occurs *via* a 2β,3β-epoxide,[9] the 3β-hydroxy group of 2-methyl-GA_3 methyl ester was protected by formation of the 3-tetrahydropyranyl ether. However hydrolysis of the methyl ester of this tetrahydropyranyl ether with sodium hydroxide in aqueous methanol, followed by acid hydrolysis of the ether, again gave the isomeric lactone (**58**) as the sole product. This latter result suggested that isomerisation of the lactone can also occur under acidic conditions, and this was demonstrated by conversion of 2-methyl-GA_7 methyl ester (**16**) into the isomeric lactone (**61**) by treatment with toluene-*p*-sulphonic acid in either dichloromethane or acetone–methanol (1:1). The mechanism of this acid-catalysed lactone isomerisation is not known but the ready rearrangement of the lactone system in 2-alkyl derivatives of GA_3 and GA_7 is probably facilitated by the electron-donating 2-alkyl groups.

The biological activities of the 2β- and 2α-alkyl derivatives described in this and the preceding paper will be presented elsewhere. However these results show that 2α-methyl and 2α-ethyl substituents confer high biological activity of GA_4 (**1**) and GA_1 (**2**).

Experimental

General experimental details and the preparation of tributylstannane, sodium propanethiolate, and lithium dialkylcuprate solutions are given in the preceding paper.[1]

Lithium Dialkylcuprate Reactions.—(a) *Lithium dimethylcuprate and* 3-O-*tetrahydropyranylgibberellin* A_7 *methyl ester.* A mixture (657 mg) containing 24% GA_4 (**1**) and 73% GA_7 (**17**) in methanol was treated with ethereal diazomethane. The crystalline mixture of the methyl esters (**15**) and (**43**) obtained on evaporation was stirred with 2,3-dihydropyran (0.35 ml; freshly distilled from potassium hydroxide) and a few crystals of toluene-*p*-sulphonic acid in dry dichloromethane (10 ml). After 3.5 h the solution was evaporated under reduced pressure and the resultant gum in dry dichloromethane (4 ml) was added to a solution of lithium dimethylcuprate (3.8 mmol) in dry diethyl ether (20 ml). The mixture was stirred at 0 °C for 1 h, then at room temperature for 3 h. Work-up gave a gum which was stirred in acetone (27 ml) and methanol (3 ml) containing a few crystals of toluene-*p*-sulphonic acid. After 4 h the mixture was evaporated under reduced pressure and the residue in ethyl acetate (30 ml) was extracted with saturated aqueous sodium hydrogen carbonate (3 × 30 ml). The aqueous fractions were acidified to pH 2 and extracted with ethyl acetate (3 × 30 ml). Evaporation under reduced pressure followed by flash chromatography with ethyl acetate–light petroleum–acetic acid (50:150:1 then 60:140:1) gave, sequentially, 2β-*methyl*-1,10-*didehydro-*GA_4 7,19-*diacid* 7-*methyl ester* (**26**) as a gum (81 mg) (Found: M^+, 360.1925. $C_{21}H_{28}O_5$ requires *M*, 360.1936); δ 1.11 (3 H, d, *J* 7.3 Hz, 2β-Me), 1.34 (3 H, s, 18-H_3), 3.04 (1 H, br m, 5-H), 3.13 (1 H, d, *J* 6.3 Hz, 6-H), 3.70 (3 H, s, OMe), 3.87 (1 H, d, *J* 2.7 Hz, 3α-H), 4.89 (2 H, br s, 17-H_2 or 17-H and 1-H), and 4.99 (1 H, br s, 17- or 1-H); *m/z* 360 (M^+, 4%), 342 (26), 328 (4), 300 (15), 283 (12), 282 (17), 238 (21), 237 (100), 195 (11), 169 (12), 119 (10), and 9 (13); and 2α-*methyl*-1,10-*didehydro-*GA_4 7,19-*diacid* 7-*methyl ester* (**25**) (88 mg) (Found: M^+, 360.1956. $C_{21}H_{28}O_5$ requires *M*, 360.1936); δ 1.18 (3 H, d, *J* 6.8 Hz, 2α-Me), 1.34 (3 H, s, 18-H_3), 2.38 (1 H, d, *J* 9.3 Hz, 6-H), 3.00 (1 H, br d, *J* 9.4 Hz, 5-H), 3.52 (1 H, d, *J* 9.0 Hz, 3α-H), 3.67 (3 H, s, OMe), 4.89 (2 H, br s, 17-H_2 or 17-H and 1-H), and 5.07 (1 H, br s, 17- or 1-H); *m/z* 360 (M^+, 4%), 342 (11), 328 (7), 300 (10), 296 (22), 283 (17), 282 (28), 237 (82), 169 (16), and 91 (20).

(b) *Lithium diethylcuprate and* 3-O-*tetrahydropyranyl-gibberellin* A_7 *methyl ester.* To lithium (1.0 g, sliced strips) in dry diethyl ether (30 ml) at 0 °C under nitrogen was added 1/8th of a solution of ethyl bromide (5.3 ml; distilled from phosphorus pentaoxide) in dry diethyl ether (20 ml). When attack of the lithium was established the remainder of the ethereal ethyl bromide was added dropwise over 2 h. The cloudy solution was allowed to settle overnight at −20 °C. Titration against diphenylacetic acid[10] indicated the ethyl-lithium concentration to be 0.33M. A portion (27 ml) of this solution was added to a stirred suspension of copper(I) iodide (840 mg) in dry tetrahydrofuran (20 ml) at −20 °C under nitrogen. To the resultant maroon–black solution was added a mixture of the tetrahydropyranyl ethers of GA_4 and GA_7 methyl esters, (**43**) and (**15**), containing 0.75 mmol GA_7 derivative and prepared as described in (a), in tetrahydrofuran (5 ml). The temperature was kept between −20 and 0 °C for 1 h and the mixture was then allowed to warm to room temperature. After 4 h (total reaction time) work-up and cleavage of the tetrahydropyranyl ether as described in (a) gave GA_4 methyl ester (**43**) (125 mg), identical (^{1}H n.m.r. and t.l.c.) with an authentic sample, and a gum, believed to be 20-norgibberella-1(10),2,16-triene-7,19-dioic acid 7-methyl ester (**57**) (*ca.* 40 mg) as a gum; δ 1.34 (3 H, s, 18-H_3), 2.98 (1 H, d, *J* 4.6 Hz, 6-H), 3.36 (1 H, br m, 5-H), 3.71 (3 H, s, OMe), 4.89 (2 H, br s, 17-H_2), 5.37 (1 H, d, *J* 9.5 Hz, 3-H), 5.63 (1 H, ddd, *J* 5.2, 2.6, and 2.6 Hz, 1-H), and 6.12 (1 H, dd, *J* 9.6 and 5.2 Hz, 2-H); *m/z* 328 (M^+, 7%), 313 (16), 282 (19), 281 (19), 223 (100), 222, (59), and 155 (27).

Reactions of Gibberellin A_3 *Methyl Ester* (**13**) *and Alkylcopper–Magnesium Reagents.*—(a) *Methylcopper–magnesium reagent.* To copper(I) iodide (338 mg) slurried in tetrahydrofuran (20 ml) under nitrogen was added hexamethylphosphoric triamide (0.31 ml), and the mixture was cooled to −15 °C. Dropwise addition of methylmagnesium bromide (1.16 ml; 3M solution in diethyl ether) gave a purple supernatant and a yellow solid. The mixture was cooled to −40 °C and GA_3 methyl ester (**13**) (314 mg) was added in tetrahydrofuran (6 ml). The temperature was allowed to rise and the mixture was stirred for 1 h at between −25 and −15 °C and then for 1 h at room temperature. After work-up the ethyl acetate extracts were washed with saturated aqueous sodium hydrogen carbonate (× 4). Evaporation of the ethyl acetate fraction under reduced pressure afforded crude starting material (**13**) (84 mg). Acidification of the aqueous washings to pH 2 and extraction

with ethyl acetate (× 5) gave a gum. Flash chromatography with ethyl acetate–light petroleum–acetic acid (50:50:1) yielded, sequentially, the known *ent*-3α,13-dihydroxy-2α-methyl-20-norgibberell-1(10),16-diene-7,19-dioic acid 7-methyl ester (**23**) (54 mg), identified by ^{1}H n.m.r. and mass spectrometry; and ent-3α,13-*dihydroxy*-2β-methyl-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic acid* 7-*methyl ester* (**24**) as a gum (177 mg) (Found: M^+, 376.1869; $M^+ - 18$, 358.1768. $C_{21}H_{28}O_6$ requires *M*, 376.1886; $M - 18$, 358.1780); δ 1.17 (3 H, d, *J* 6.8 Hz, 2α-Me), 1.36 (3 H, s, 18-H_3), 2.39 (d, *J* 8.3 Hz, 6-H; superimposed on other signals), 3.01 (1 H, br d, *J* 8.3 Hz, 5-H), 3.52 (1 H, d, *J* 8.3 Hz, 3α-H), 3.68 (3 H, s, OMe), 4.97 (1 H, br s, 17- or 1-H), and 5.11 (2 H, br s, 17-H_2 or 17-H and 1-H); *m/z* 376 (M^+, 6%), 358 (24), 317 (30), 316 (92), 312 (39), 298 (54), 254 (32), 253 (100), and 91 (34).

(b) *Ethylcopper–magnesium reagent.* To copper(I) iodide (2.56 g), slurried in dry tetrahydrofuran under nitrogen, was added hexamethylphosphoric triamide (2.4 ml), and the mixture was cooled to −15 °C. Dropwise addition of ethylmagnesium bromide (8.9 ml; 3M solution in diethyl ether) gave a purple solution (on a smaller scale slight warming may be required to form the complex). After cooling to −40 °C and stirring at this temperature for 5 min, GA_3 methyl ester (**13**) (1.73 g) in dry tetrahydrofuran (9 ml) was added slowly. The reaction mixture thickened markedly but was sheared by rapid stirring. The temperature was allowed to rise to −15 °C and stirring was continued for 3 h (the mixture became dark purple). Work-up as in (a) gave starting material (**13**) (284 mg) and an acidic gum which was subjected to flash chromatography with ethyl acetate–light petroleum (55:45) to give sequentially: (i) ent-2α-*ethyl*-3α,13-*dihydroxy*-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic acid* 7-*methyl ester* (**28**) (496 mg) as a gum (Found: $M^+ - 18$, 372.1943. $C_{22}H_{30}O_6$ requires $M - 18$, 372.1937); δ[$(CD_3)_2$CO] 1.00 (3 H, t, *J* 7.3 Hz, 2-CH_2*Me*), 1.29 (3 H, s, 18-H_3), 3.07 (1 H, br m, 5-H), 3.21 (1 H, d, *J* 6.1 Hz, 6-H), 3.67 (3 H, s, OMe), 4.01 (1 H, d, *J* 2.2 Hz, 3α-H), 4.90 (1 H, br s, 17-H), and 5.07 (2 H, br s, 17- and 1-H) [^{1}H n.m.r. homonuclear decoupling: on irradiation at 3.07 p.p.m. the signal at 3.15 p.p.m. collapsed to a singlet; on irradiation at 3.21 p.p.m. the signal at 3.07 p.p.m. became a broad singlet; on irradiation of the singlet at 5.07 p.p.m. the signal at 3.07 p.p.m. sharpened (*i.e.* some coupling lost)]; *m/z* 390 (M^+, 2%), 372 (32), 340 (17), 331 (10), 330 (10), 313 (11), 312 (15), 297 (12), 268 (27), 267 (100), 239 (12), and 91 (14); δ(7,19-dimethyl ester) 1.02 (3 H, t, *J* 7.3 Hz, CH_2*Me*), 1.31 (3 H, s, 18-H_3), 3.01 (1 H, br m, 5-H), 3.15 (1 H, d, *J* 6.1 Hz, 6-H), 3.64 (3 H, s, OMe), 3.70 (3 H, s, OMe), 3.96 (1 H, br s, 3α-H), 4.98 (1 H, br s, 17-H), 5.06 (1 H, br s, 1-H), and 5.11 (1 H, br s, 17-H); (ii) ent-2β-*ethyl*-3α,13-*dihydroxy*-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic acid* 7-*methyl ester* (**27**) (427 mg) as a gum (Found: $M^+ - 18$, 372.1925. $C_{22}H_{30}O_6$ requires $M - 18$, 372.1937); δ[$(CD_3)_2$CO] (7-methyl ester 19-acid) 0.99 (3 H, t, *J* 7.3 Hz, 2-CH_2*Me*), 1.32 (3 H, s, 18-H_3), 2.56 (1 H, d, *J* 7.8 Hz, 6-H), 3.00 (1 H br d, *J* 8.1 Hz, 5-H), 3.63 (3 H, s, OMe), 4.88 (1 H, br s, 17-H), 5.08 (1 H, br s, 17-H), and 5.21 (1 H, ddd, *J* 2.2 Hz, × 3, 1-H) [^{1}H n.m.r. homonuclear decoupling: on irradiation at 2.56 p.p.m. the signal at 3.00 p.p.m. collapsed to a broad singlet; on irradiation at 3.00 p.p.m. the signal at 2.56 p.p.m. collapsed to a sharp singlet and the signal at 5.25 p.p.m. collapsed to a broad singlet (triplet substructure, *J ca.* 2 Hz); on irradiation at 5.25 p.p.m. the signal at 3.00 p.p.m. became a ddd ($J_{5,6}$ 7.6, $J_{5,9}$ 2.1, $J_{5,2}$ 0.5 Hz)]; *m/z* 390 (M^+, 4%), 372 (21), 331 (22), 330 (68), 326 (25), 313 (18), 312 (37), 268 (25), 267 (100), 239 (30), and 91 (30); δ(7,19-dimethyl ester) 0.99 (3 H, t, *J* 7.3 Hz, 2-CH_2*Me*), 1.35 (3 H, s, 18-H_3), 2.18 (1 H, d, *J* 8.1 Hz, 6-H), 3.05 (1 H, br dt, $J_{5,6}$ 7.8 Hz, $J_{5,1} \simeq J_{5,9} = 2.0$ Hz, 5-H), 3.62 (3 H, s, OMe), 3.65 (1 H, d, *J* 6.4 Hz, 3α-H), 3.71 (3 H, s, OMe), 4.97 (1 H, br s, 17-H), 5.12 (1 H, br s, 17-H), and 5.20 (1 H, ddd, $J \simeq 2.0$ Hz × 3, 1-H).

On a smaller scale (*ca.* 0.33 of above) repetition afforded 2β-ethyl- and 2α-ethyl-1,10-didehydro-GA_1 7,19-diacid 7-methyl esters (**28**) and (**27**) in the ratio 36:64.

(c) *Propylcopper–magnesium reagent.* The procedures described in (b) were followed with the following quantities: copper(I) iodide (1.12 g) in tetrahydrofuran (40 ml) containing hexamethylphosphoric triamide (1 ml); 2M propylmagnesium chloride in diethyl ether (6 ml); and gibberellin A_3 methyl ester (**13**) (1.06 g) in tetrahydrofuran (10 ml). Starting material (**13**) (258 mg) was recovered in the neutral fraction. The acidic product was subjected to flash chromatography using ethyl acetate–light petroleum–acetic acid (55:45:1) to give, sequentially: (i) ent-3α,13-*dihydroxy*-2α-*propyl*-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic acid* 7-*methyl ester* (**30**) as a gum (193 mg) (Found: M^+, 404.2183. $C_{23}H_{32}O_6$ requires *M*, 404.2199); δ 0.97 (3 H, t, *J* 6.1 Hz, 2-CH_2CH_2*Me*), 1.33 (3 H, s, 18-H_3), 3.12 (1 H, d, *J* 6.1 Hz, 6-H), 3.71 (3 H, s, OMe), 3.95 (1 H, br s, 3α-H), 4.94 (1 H, br s, 17-H), and 5.06 (2 H, br s, 17- and 1-H); *m/z* 404 (M^+, 2%), 386 (35), 354 (15), 345 (9), 344 (9), 327 (10), 326 (14), 311 (10), 282 (23), 281 (100), 239 (8), 105 (7), and 91 (9); and (ii) ent-3α,13-*dihydroxy*-2β-*propyl*-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic acid* 7-*methyl ester* (**29**) (300 mg) as a gum (Found: M^+, 404.2208. $C_{23}H_{32}O_6$ requires *M*, 404.2199); δ 0.96 (3 H, t, *J* 6.4 Hz, 2-CH_2CH_2*Me*), 1.36 (3 H, s, 18-H_3), 3.61 (1 H, superimposed on signal at 3.67 p.p.m., 5-H), 3.67 (3 H, s, OMe_3), 3.72 (1 H, d, *J* 7.1 Hz, 3α-H), 4.97 (1 H, br s, 17-H), 5.12 (1 H, br s, 17-H), and 5.22 (1 H, br s, 1-H); *m/z* 404 (M^+, 5%), 386 (20), 345 (27), 344 (63), 340 (30), 327 (19), 326 (41), 282 (26), 281 (100), 239 (24), 105 (15), and 91 (26).

Iodo Lactones.—(a) ent-3α,10β-*Dihydroxy*-1α-*iodo*-2α-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**33**). The 2β-methyl-1(10),16-diene-7,19-dioic acid 7-methyl ester (**23**) (937 mg) in tetrahydrofuran (25 ml) and dichloromethane (40 ml) was stirred vigorously with saturated aqueous sodium hydrogen carbonate (40 ml) and iodine (1.67 g) for 1 h. The organic phase was washed with saturated aqueous sodium thiosulphate (2 × 50 ml) followed by water (2 × 30 ml). After drying ($MgSO_4$), evaporation under reduced pressure gave 1β-*iodo*-2β-*methyl*-GA_4 *methyl ester* (**33**) (1.06 g), m.p. 137—140 °C (from ethyl acetate–light petroleum) (Found: M^+, 486.0875. $C_{21}H_{27}IO_5$ requires *M*, 486.0905); δ 1.18 (3 H, s, 18-H_3), 1.26 (3 H, d, *J* 6.6 Hz, 2β-Me), 2.64 (1 H, d, *J* 10.3 Hz, 6-H), 3.70 (2 H, m, 3β-OH and 3α-H), 3.73 (3 H, s, OMe), 3.77 (1 H, d, *J* 10.5 Hz, 5-H), 4.39 (1 H, d, *J* 4.9 Hz, 1α-H), 4.90 (1 H, br s, 17-H), and 5.00 (1 H, br s, 17-H); δ[$(CD_3)_2$CO] 1.10 (3 H, s, 18-H_3), 1.20 (3 H, d, *J* 6.6 Hz, 2β-Me), 2.63 (d, *J* 10.4 Hz, 6-H; superimposed on other signals), 3.63 (1 H, br m, 3α-H), 3.71 (3 H, s, OMe), 3.87 (1 H, d, *J* 10.5 Hz, 5-H), 4.61 (2 H, d, *J* 5.1 Hz, 1-H and 3β-OH), 4.93 (1 H, br s, 17-H), and 5.03 (1 H, br s, 17-H); *m/z* 486 (M^+, 17%), 454 (62), 426 (37), 359 (12), 341 (11), 327 (33), 313 (25), 299 (43), 237 (100), 105 (18), and 91 (30).

(b) ent-3α,10β-*dihydroxy*-1α-*iodo*-2β-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**32**). The 2α-methyl-1(10),16-diene-7,19-dioic acid 7-methyl ester (**25**) (71 mg) in tetrahydrofuran (8 ml) and dichloromethane (10 ml) was stirred vigorously with saturated aqueous sodium hydrogen carbonate (10 ml) and iodine (125 mg). After 1 h the mixture was worked up as described in (a). Flash chromatography with ethyl acetate–light petroleum (30:70) gave 1β-*iodo*-2α-*methyl*-GA_4 *methyl ester* (**32**), needles (54 mg; low yield through spillage during work-up), m.p. 142—143 °C (from ethyl acetate–light petroleum) (Found: C, 51.7; H, 5.9. $C_{21}H_{27}IO_5$ requires C, 51.9; H, 5.6%); δ 1.16 (3 H, d, *J* 8.3 Hz, 2α-Me), 1.21 (3 H, s, 18-H_3), 2.34 (1 H, d, *J* 5.6 Hz, 3β-OH), 2.69 (1 H, d, *J* 10.3 Hz, 6-H), 3.66 (1 H, d, *J* 5.6 Hz, 3α-H), 3.74 (3 H, s, OMe), 3.80 (1 H, d, *J* 10.3 Hz, 5-H), 4.21 (1 H, s, 1α-H), 4.94 (1 H, br s, 17-H), and 5.00 (1 H, br s, 17-H); *m/z* 486 (M^+, 6%), 454 (12), 359 (12), 341 (11), 327 (43), 313 (17), 299 (74), 281 (43), 237 (100), 105 (17), and 91 (28).

(c) ent-3α,10β,13-*Trihydroxy*-1α-*iodo*-2β-*methyl*-20-*nor*-*gibberell*-16-ene-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**34**). The 2α-methyl-1(10),16-diene 7,19-diacid 7-methyl ester (**24**) (175 mg) in tetrahydrofuran (5 ml) and dichloromethane (10 ml) was vigorously stirred with saturated aqueous sodium hydrogen carbonate (10 ml) and iodine (146 mg) for 1 h. Work-up as described in (a) gave 1β-*iodo*-2α-*methyl*-GA_1 *methyl ester* (**34**), prisms (169 mg), m.p. 185 °C (decomp.) (from acetone–tetrahydrofuran–light petroleum) (Found: C, 49.9; H, 5.3%; M^+, 502.0833. $C_{21}H_{27}O_6$ requires C, 50.2; H, 5.4%; *M*, 502.0854); δ(C_5D_5N) 1.25 (3 H, d, *J* 8.1 Hz, 2α-Me), 1.55 (3 H, s, 18-H_3), 3.04 (1 H, t, *J* 8.5 Hz, 9-H; under signal at 3.08 p.p.m.), 3.08 (1 H, d, *J* 9.5 Hz, 6-H; superimposed on signal at 3.04 p.p.m.), 3.26 (1 H, q, *J* 8.2 Hz, 2β-H), 3.63 (3 H, s, OMe), 4.03 (1 H, s, 3α-H), 4.47 (1 H, d, *J* 9.3 Hz, 5-H), 4.67 (1 H, s, 1α-H), 5.10 (1 H, br s, 17-H), and 5.61 (1 H, br s, 17-H); *m/z* 502 (M^+, 64%), 470 (38), 443 (98), 375 (28), 357 (79), 343 (87), 329 (100), 315 (72), 297 (66), 269 (68), 253 (93), 135 (76), 91 (69), 69 (69), and 43 (93).

(d) ent-2α-*Ethyl*-3α,10β,13-*trihydroxy*-1α-*iodo*-20-*nor*-*gibberell*-16-ene-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**36**). The 2β-ethyl-1(10),16-diene 7,19-diacid 7-methyl ester (**28**) (496 mg) in tetrahydrofuran (10 ml) and dichloromethane (20 ml) was stirred vigorously with saturated aqueous sodium hydrogen carbonate (20 ml) and iodine (355 mg) for 1 h. Work-up as described in (a) gave 2β-*ethyl*-1β-*iodo*-GA_1 *methyl ester* (**36**) (637 mg) as a gum (Found: M^+, 516.0997. $C_{22}H_{29}IO_6$ requires *M*, 516.1011); δ 0.94 (3 H, t, *J* 7.3 Hz, 2-CH_2Me), 1.19 (3 H, s, 18-H_3), 2.68 (1 H, d, *J* 9.8 Hz, 6-H; superimposed on the signal at 2.78 p.p.m.), 2.78 (1 H, br t, 9-H; under signal at 2.68 p.p.m.), 3.74 (4 H, s, OMe and 3α-H), 3.77 (1 H, d, *J* 9.8 Hz, 5-H), 4.36 (1 H, d, *J* 3.9 Hz, 1-H), 5.01 (1 H, br s, 17-H), and 5.28 (1 H, br s, 17-H); δ[$(CD_3)_2CO$] 0.93 (3 H, t, *J* 7.3 Hz, 2-CH_2Me), 1.11 (3 H, s, 18-H_3), 2.62 (1 H, d, *J* 9.8 Hz, 6-H), 2.79 (1 H, br t, 9-H), 3.72 (3 H, s, OMe), 3.88 (1 H, d, *J* 10.0 Hz, 5-H), 3.90 (1 H, br s, 3α-H), 4.58 (2 H, d, *J* 5.1 Hz, 1-H and 3β-OH), 4.93 (1 H, br s, 17-H), and 5.22 (1 H, br s, 17-H); *m/z* 516 (M^+, 39%), 457 (66), 389 (14), 371 (61), 357 (28), 344 (17), 343 (60), 339 (18), 329 (33), 325 (18), 311 (45, 283 (47), 267 (81), 265 (34), and 71 (100).

(e) ent-2β-*Ethyl*-3α,10β,13-*trihydroxy*-1α-*iodo*-20-*nor*-*gibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**35**). The 2α-ethyl-1(10),16-diene 7,19 diacid 7-methyl ester (**27**) (332 mg) in tetrahydrofuran (15 ml) and dichloromethane (20 ml) was stirred vigorously with saturated aqueous sodium hydrogen carbonate (20 ml) and iodine (237 mg) for 1 h. Work-up as described in (a) gave 2α-*ethyl*-1β-*iodo*-GA_1 *methyl ester* (**35**) (440 mg), m.p. 140—145 °C (decomp.) (from acetone–ethyl acetate–light petroleum) (Found: C, 51.1; H, 5.6; I, 24.4. $C_{22}H_{29}IO_6$ requires C, 51.2; H, 5.6; I, 24.6%); δ 0.99 (3 H, t, *J* 7.3 Hz, 2-CH_2Me), 1.21 (3 H, s, 18-H_3), 2.66 (2 H, m; under signal at 2.68 p.p.m.), 2.68 (1 H, d, *J* 9.5 Hz, 6-H; superimposed on signal at 2.66 p.p.m), 3.75 (4 H, s, OMe and 3α-H), 3.83 (1 H, d, *J* 9.5 Hz, 5-H), 4.30 (1 H, s, 1α-H), 5.00 (1 H, br s, 17-H), and 5.27 (1 H, br s, 17-H); δ[$(CD_3)_2CO$] 0.97 (3 H, t, *J* 7.3 Hz, 2-CH_2Me), 1.15 (3 H, s, 18-H_3), 2.62 (1 H, d, *J* 9.3 Hz, 6-H; superimposed on signal at 2.66 p.p.m.), 2.66 (1 H, t, 9-H; under signal at 2.62 p.p.m.), 3.73 (4 H, s, OMe and 3α-H), 3.90 (1 H, s, 13-OH; superimposed on upfield arm of signal at 3.91 p.p.m.), 3.91 (1 H, d, *J ca.* 9 Hz, 5-H; upfield arm is superimposed on signal at 3.90 p.p.m.), 4.50 (1 H, s, 1α-H), 4.80 (1 H, d, *J* 4.2 Hz, 3β-OH), 4.93 (1 H, br s, 17-H), and 5.20 (1 H, br s, 17-H) [on addition of D_2O the signals at 4.80 p.p.m. (3β-OH) and 3.90 p.p.m. (13-OH) disappeared, that of 3α-H collapsed to 1 H, s at 3.72 p.p.m. and that of 5-H became obvious as 1 H, d, *J* 9.3 Hz, at 3.87 p.p.m.]; *m/z* 516 (M^+, 47), 484 (25), 457 (95), 389 (33), 371 (93), 357 (85), 343 (100), 339 (39), 330 (67), 325 (36), 311 (79), 283 (61), and 267 (73).

(f) ent-3α,10β,13-*Trihydroxy*-1α-*iodo*-2α-*propyl*-20-*nor*-*gibberell*-16-ene-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**38**). The 2β-propyl-1(10),16-diene-7,19-dioic acid 7-methyl ester (**30**) (232 mg) in tetrahydrofuran (20 ml) and dichloromethane (40 ml) was stirred vigorously with saturated aqueous sodium hydrogen carbonate (40 ml) and iodine (161 mg) for 1 h. Work-up as in (a) gave 1β-*iodo*-2β-*propyl*-GA_1 *methyl ester* (**38**) (254 mg) as a gum (Found: M^+, 530.1176. $C_{23}H_{31}IO_6$ requires *M*, 530.1167); δ 0.96 (3 H, t, *J* 7.1 Hz, 2-CH_2CH_2Me), 1.19 (3 H, s, 18-H_3), 2.90 (1 H, d, *J* 10.0 Hz, 6-H; superimposed on signal at 2.95 p.p.m.), 3.75 (4 H, s, OMe and 3α-H), 3.79 (1 H, d, *J* 10.3 Hz, 5-H), 4.35 (1 H, d, *J* 3.9 Hz, 1-H), 5.00 (1 H, br s, 17-H), and 5.28 (1 H, br s, 17-H); *m/z* 530 (M^+, 73%) 471 (100), 403 (25), 385 (82), 371 (39), 357 (95), 343 (22), 339 (20), 325 (51), 297 (49), 281 (65), 279 (30), 105m (19), and 91 (36).

(g) ent-3α,10β,13-*Trihydroxy*-1α-*iodo*-2β-*propyl*-20-*nor*-*gibberell*-16-*ene*-7,19- *dioic acid* 7-*methyl ester* 19,10-*lactone* (**37**). The 2α-propyl-1(10),16-diene-7,19-dioic acid 7-methyl ester (**29**) (220 mg) in tetrahydrofuran (20 ml) and dichloromethane (40 ml) was stirred vigorously with saturated aqueous sodium hydrogen carbonate (40 ml) and iodine (155 mg) for 1 h. Work-up as in (a) gave 1β-*iodo*-2α-*propyl*-GA_1 *methyl ester* (**37**) (294 mg) as a gum (Found: M^+, 530.1143. $C_{23}H_{31}IO_6$ requires *M*, 530.1167); δ 0.90 (3 H, t, *J* 7.4 Hz, 2-CH_2CH_2Me), 1.21 (3 H, s, 18-H_3), 2.68 (1 H, d, *J* 9.5 Hz, 6-H; superimposed on signal at 2.6 p.p.m.), 3.75 (4 H, br s, OMe and 3α-H), 3.83 (1 H, d, *J* 9.5 Hz, 5-H), 4.29 (1 H, s, 1-H), 5.00 (1 H, br s, 17-H), and 5.27 (1 H, br s, 17-H); *m/z* 530 (M^+, 37%), 499 (45), 471 (65), 403 (37), 385 (80), 371 (67), 357 (100), 353 (33), 343 (61), 339 (35), 325 (78), 297 (61), 281 (96), 128 (67), 105 (41), and 91 (65).

Reduction of Iodo Lactones with Tri-butylstannane and 2,2′-*Azoisobutyronitrile* (AIBN).—(a) ent-3α,10β-*Dihydroxy*-2α-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**42**). 1β-Iodo-2β-methyl-GA_4 methyl ester (**33**) (76 mg) was refluxed in toluene (30 ml) with AIBN (catalytic) and tributylstannane, prepared from tributyltin chloride (222 μl). After 1 h, evaporation under reduced pressure followed by flash chromatography with ethyl acetate–light petroleum (30:70) gave 2β-methyl-GA_4 methyl ester (**42**) (56 mg), m.p. 135—136 °C (from ethyl acetate–light petroleum) [lit.,[4] m.p. 154—155 °C (from acetone–light petroleum] (Found: M^+ 360.1932. Calc. for $C_{21}H_{28}O_5$: *M*, 360.1936); identical by n.m.r. and mass spectrometry with the compound described previously.[4]

(b) ent-3α,10β-*Dihydroxy*-2β-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**41**). Reduction of 1β-iodo-2α-methyl-GA_4 methyl ester (**32**) (50 mg), as in (a) under the same conditions and with the same quantities of reagents, with purification by flash chromatography [ethyl acetate–light petroleum (45:55)] gave 2α-*methyl*-GA_4 *methyl ester* (**41**) (23 mg), m.p. 175—178 °C (from ethyl acetate–light petroleum) (Found: M^+, 360.1968. $C_{21}H_{28}O_5$ requires *M*, 360.1936); δ 1.09 (3 H, d, *J* 8.1 Hz, 2α-Me), 1.16 (3 H, s, 18-H_3), 2.65 (1 H, d, *J* 10.7 Hz, 6-H), 3.16 (1 H, d, *J* 10.7 Hz, 5-H), 3.56 (1 H, s, 3α-H), 3.71 (3 H, s, OMe), 4.85 (1 H, br s, 17-H), and 4.98 (1 H, br s, 17-H); *m/z* 360 (M^+, 5%), 342 (12), 328 (43), 300 (15), 298 (100), 282 (20), 238 (74), 223 (24), and 91 (28).

(c) ent-3α,10β,13-*Trihydroxy*-2β-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**44**). 1β-Iodo-2α-methyl-GA_1 methyl ester (**34**) (128 mg) was refluxed, as a suspension, in toluene (40 ml) containing AIBN (catalytic) and tributylstannane [from tributyltin chloride (550 μl]. After 1 h the mixture was evaporated under reduced pressure and the resultant gum was subjected to flash chromatography. After removal of tin residues by elution with ethyl acetate–light petroleum (5:95) further elution with ethyl acetate–light petroleum (60:40) gave 2α-methyl-GA_1 methyl ester (**44**) (100 mg) as a gum (Found: M^+, 376.1886. $C_{21}H_{28}O_6$ requires *M*,

376.1886); δ 1.08 (3 H, d, *J* 8.1 Hz, 2α-Me), 1.15 (3 H, s, 18-H_3), 2.69 (1 H, d, *J* 10.3 Hz, 6-H; superimposed on 1 H, br m, 9-H), 3.17 (1 H, d, *J* 10.3 Hz, 5-H), 3.55 (1 H, br s, 3α-H), 3.72 (3 H, s, OMe), 4.95 (1 H, br s, 17-H), and 5.25 (1 H, br s, 17-H); *m/z* 376 (M^+, 29%), 361 (18), 359 (16), 358 (16), 345 (26), 344 (100), 317 (23), and 298 (21).

(d) ent-2α-*Ethyl*-3α,10β,13-*trihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**46**). 2β-Ethyl-1β-iodo-GA_1 methyl ester (**36**) (637 mg) in toluene (30 ml) was refluxed for 1 h with AIBN (catalytic) and tributylstannane (670 μl). Flash chromatography of the product, first with light petroleum and ethyl acetate–light petroleum (1:9) to remove tin residues, and then with ethyl acetate–light petroleum (55:45), gave 2β-*ethyl*-GA_1 *methyl ester* (**46**) as a gum (Found: M^+, 390.2056; $M^+ - 32$, 358.1787. $C_{22}H_{30}O_6$ requires *M*, 390.2042; $M - 32$, 358.1780); δ 0.92 (3 H, t, *J* 7.3 Hz, 2-CH_2Me), 1.16 (3 H, s, 18-H_3), 2.68 (1 H, d, *J* 10.5 Hz, 6-H), 3.19 (1 H, d, *J* 10.5 Hz, 5-H), 3.72 (4 H, s, OMe and 3α-H), 4.95 (1 H, br s, 17-H), and 5.26 (1 H, br s, 17-H); δ(C_5D_5N) 0.88 (3 H, t, *J* 7.1 Hz, 2-CH_2Me), 1.05 (3 H, s, 18-H_3), 3.01 (1 H, d, *J* 10.5 Hz, 6-H), 3.60 (3 H, s, OMe), 3.71 (1 H, d, *J* 10.5 Hz, 5-H), 3.96 (1 H, dd, *J* 5.4 and 3.2 Hz, 3α-H), 5.08 (1 H, br s, 17-H), 5.63 (1 H, br s, 17-H), 6.46 (1 H, br s, 13-OH), and 7.08 (1 H, d, *J* 5.9 Hz, 3β-OH) (on addition of D_2O the signals at 7.08 and 6.46 p.p.m. disappeared and the signal at 3.96 p.p.m. collapsed to 1 H, d, *J* 2.7 Hz); *m/z* 390 (M^+, 69%), 372 (14), 358 (100), 344 (20), 333 (24), 331 (40), 330 (35), 313 (20), 312 (32), 304 (31), 267 (24), and 239 (23).

(e) ent-2β-*Ethyl*-3α,10β,13-*trihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**45**). 2α-Ethyl-1β-iodo-GA_1 methyl ester (**35**) (467 mg) in toluene (30 ml) was refluxed for 1 h with AIBN (catalytic) and tributylstannane (0.5 ml). Flash chromatography of the product as in (d) [except that the product was eluted with ethyl acetate–light petroleum (6:4)] gave 2α-*ethyl*-GA_1 *methyl ester* (**45**) (239 mg) as a gum (Found: M^+, 390.2074; $M^+ - 32$, 358.1757. $C_{22}H_{30}O_6$ requires *M*, 390.2042; $M - 32$, 358.1780); δ 0.91 (3 H, t, *J* 7.3 Hz, 2-CH_2Me), 153 (3 H, s, 18-H_3), 2.68 (1 H, d, *J* 10.0 Hz, 6-H), 3.19 (1 H, d, *J* 10.3 Hz, 5-H), 3.61 (1 H, s, 3α-H), 3.72 (3 H, s, OMe), 4.95 (1 H, br s, 17-H), and 5.25 (1 H, br s, 17-H); *m/z* 390 (M^+, 27%), 372 (13), 358 (100), 344 (11), 331 (20), 330 (13), 312 (21), 304 (18), 267 (10), and 239 (13); later column fractions gave slightly impure 2α-ethyl-GA_1 methyl ester (**45**) (80 mg).

(f) ent-3α,10β,13-*Trihydroxy*-2β-*propyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**47**). The product, obtained as in (a) from 1β-iodo-2α-propyl-GA_1 methyl ester (**37**) (180 mg) in toluene (30 ml; deoxygenated with nitrogen), AIBN (catalytic), and tributylstannane (0.3 ml), was subjected to flash chromatography. After elution of tin residues with ethyl acetate–light petroleum (5:95) elution with ethyl acetate–light petroleum (1:1) gave 2α-*propyl*-GA_1 *methyl ester* (**47**) (73 mg), m.p. 203—205 °C (from ethyl acetate–light petroleum) (Found: C, 68.4; H, 7.9. $C_{23}H_{32}O_6$ requires C, 68.3; H, 8.0%); δ 0.87 (3 H, t, *J* 5.6 Hz, 2-CH_2CH_2Me), 1.16 (3 H, s, 18-H_3), 2.69 (1 H, d, *J* 10.0 Hz, 6-H), 3.19 (1 H, d, *J* 10.2 Hz, 5-H), 3.61 (1 H, s, 3α-H), 3.72 (3 H, s, OMe), 4.95 (1 H, br s, 17-H), and 5.25 (1 H, br s, 17-H); *m/z* 404 (M^+, 26%), 386 (15), 372 (100), 358 (19), 345 (26), 344 (22), 326 (33), 304 (30), 281 (12), 239 (37), 135 (37), 128 (33), 121 (33), 115 (30), 105 (37), and 91 (89).

(g) ent-3α,10β,13-*Trihydroxy*-2α-*propyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**48**). The product, obtained as in (a) from 1β-iodo-2β-propyl-GA_1 methyl ester (**38**) (352 mg) in toluene (30 ml; deoxygenated with nitrogen), AIBN (catalytic), and tributylstannane (0.5 ml), was flash chromatographed. After elution of tin residues as in (f), elution with ethyl acetate–light petroleum (1:1) gave 2β-*propyl*-GA_1 *methyl ester* (**48**) (261 mg) as a gum (Found: M^+, 404.2186. $C_{23}H_{32}O_6$ requires *M*, 404.2199); δ 0.92 (3 H, t, *J* 6.4 Hz, 2-CH_2CH_2Me), 1.15 (3 H, s, 18-H_3), 2.68 (1 H, d, *J* 10.2 Hz, 6-H), 3.18 (1 H, d, *J* 10.5 Hz, 5-H), 3.67 (1 H, superimposed on signal at 3.71, 3α-H), 3.71 (3 H, s, OMe), 4.95 (1 H, br s, 17-H), and 5.25 (1 H, br s, 17-H); *m/z* 404 (M^+, 81%), 373 (39), 372 (100), 345 (51), 344 (58), 327 (28), 326 (55), 304 (49), 281 (49), 239 (62), 135 (65), 121 (46), 105 (47), and 91 (89).

(h) ent-3α-*Acetoxy*-2β-*ethyl*-10β-*hydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**53**). To 2α-ethyl-GA_1 3-acetate 13-methyl oxalate 7-methyl ester (**51**) (158 mg) in refluxing toluene (20 ml) were added tributylstannane (170 μl) and AIBN (catalytic). The reaction was monitored by t.l.c. After 0.5 h more tributylstannane (250 μl) and AIBN (catalytic) were added, and after a further 15 min AIBN (catalytic) was again added. After 0.5 h (total reflux time 1.25 h) the reaction was complete. Tin residues were removed from the crude product by gravity elution through silica gel (60—120 mesh) with light petroleum and then ethyl acetate–light petroleum (5:95). Elution with ethyl acetate–light petroleum (1:1) gave 2α-*ethyl*-GA_4 3-*acetate methyl ether* (**53**) (74 mg) as a gum (Found: $M^+ - 31$, 385.2014; $M^+ - 60$, 356.1974. $C_{24}H_{32}O_6$ requires $M - 31$, 385.2015; $M - 60$, 356.1987); δ 0.87 (3 H, t, *J* 7.3 Hz, 2-CH_2Me), 1.03 (3 H, s, 18-H_3), 2.17 (3 H, s, COMe), 2.63 (1 H, br t, 9- or 13-H; under signal at 2.67 p.p.m.), 2.67 (1 H, d, *J* 11.0 Hz, 6-H; superimposed on signal at 2.63 p.p.m.), 3.11 (1 H, d, *J* 11.0 Hz, 5-H), 3.70 (3 H, s, OMe), 4.86 (1 H, br s, 17-H), 4.99 (1 H, br s, 17-H), and 5.16 (1 H, d, *J* 3.9 Hz, 3α-H); *m/z* 385 ($M^+ - 31$, 6%), 356 (15), 312 (100), 296 (22), 283 (23), 253 (39), 252 (44), 223 (90), and 43 (38).

(i) ent-3α-*Acetoxy*-2α-*ethyl*-10β-*hydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 7-*methyl ester* 19,10-*lactone* (**54**). To 2β-ethyl-GA_1 3-acetate 13-methyl oxalate 7-methyl ester (**52**) (214 mg) in refluxing toluene (20 ml) were added tributylstannane (300 μl) and AIBN (catalytic). After 1 h tin residues were removed from the recovered product by gravity feed elution through silica gel (60—120 mesh) with light petroleum and ethyl acetate–light petroleum (5:95). Elution with ethyl acetate–light petroleum (1:1) yielded product (127 mg), which was further purified by flash chromatography with ethyl acetate–light petroleum (30:70) to give 2β-*ethyl*-GA_4 3-*acetate methyl ester* (**54**) (71 mg) as a gum (Found: M^+, 416.2230. $C_{24}H_{32}O_6$ requires *M*, 416.2199); δ 0.87 (3 H, t, *J* 7.3 Hz, 2-CH_2Me), 1.03 (3 H, s, 18-H_3), 2.17 (3 H, s, COMe), 2.63 (1 H, br t, 9- or 13-H; under signal at 2.67 p.p.m.), 2.67 (1 H, d, *J* 11.0 Hz, 6-H; superimposed on signal at 2.63 p.p.m.), 3.11 (1 H, d, *J* 11.0 Hz, 5-H), 3.70 (3 H, s, OMe), 4.86 (1 H, br s, 17-H), 4.99 (1 H, br s, 17-H), and 5.16 (1 H, d, *J* 3.9 Hz, 3α-H); *m/z* 416 (M^+, 3%), 385 (10), 356 (34), 324 (48), 312 (100), 296 (49), 253 (37), 252 (41), 251 (29), 223 (85), and 43 (46).

Preparation of 2α-*Methylgibberellin* A_4 *Methyl Ester* (**41**) *from* 2-*Methylgibberellin* A_7 *Methyl Ester* (**16**).—(a) *Epoxidation.* 2-Methylgibberellin A_7 methyl ester (**16**) (164 mg), was stirred with *m*-chloroperbenzoic acid (94 mg) in chloroform (10 ml) for 16 h at 5 °C. Dilution with chloroform (10 ml) was followed by washing with saturated aqueous sodium hydrogen carbonate (15 ml) then water (15 ml). After drying ($MgSO_4$), evaporation under reduced pressure followed by flash chromatography with ethyl acetate–light petroleum (1:1) yielded 2-methyl-GA_7 16α,17-epoxide methyl ester (99 mg) as a gum; δ 1.24 (3 H, s, 18-H_3), 1.82 (3 H, d, *J* 1.5 Hz, 2-Me), 2.81 (d, *J* 11 Hz, 6-H; one arm under signal at 2.83 p.p.m.), 2.83 (2 H, s, 17-H_2), 3.73 (3 H, s, OMe), 3.93 (1 H, br s, 3α-H), and 6.03 (1 H, d, *J* 1.7 Hz, 1-H); earlier fractions (9 mg) contained a slightly less polar compound by t.l.c., presumably the 16β,17-epoxide.

(b) *Hydrogenation.* 2-Methyl-GA_7 16α,17-epoxide methyl ester (70 mg) in tetrahydrofuran (8 ml) containing 10% palladium–calcium carbonate (20 mg) was stirred in hydrogen at ambient temperature and pressure. After 1 h, filtration

through Celite and evaporation under reduced pressure gave a gum which lacked olefinic signals in its ^{1}H n.m.r. spectrum.

(c) *De-epoxidation.* To a solution of sodium iodide (400 mg) and sodium acetate (150 mg) in glacial acetic acid (7 ml), acetone (1 ml), and water (0.5 ml) was added zinc powder (400 mg; freshly activated with 2M hydrochloric acid), followed dropwise by a solution of the hydrogenation product in acetone (3 ml). After 3.5 h the mixture was diluted with ethyl acetate (20 ml) and washed with saturated aqueous sodium hydrogen carbonate (20 ml). After drying ($MgSO_4$), evaporation under reduced pressure gave a gum (16 mg). Although slightly impure, the major product was identified by t.l.c. and ^{1}H n.m.r. as 2α-methyl-GA_4 methyl ester (**41**), described earlier.

ent-3α-*Acetoxy*-2α-*ethyl*-10β,13-*dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**50**).—2β-Ethyl-GA_1 methyl ester (**46**) (317 mg) in pyridine (5 ml) was stirred with redistilled acetic anhydride (2 ml) for 10 h. Azeotropic removal of pyridine and acetic anhydride with toluene under reduced pressure gave 2β-*ethyl-GA*$_1$ 3-*acetate methyl ester* (**50**) (276 mg) as a gum (Found: M^+, 432.2164. $C_{24}H_{32}O_7$ requires M, 432.2148); δ 0.87 (3 H, t, J 7.3 Hz, 2-CH_2*Me*), 1.03 (3 H, s, 18-H_3), 2.16 (3 H, s, COMe), 2.66 (1 H, d, J 10.5 Hz, 6-H), 3.12 (1 H, d, J 10.5 Hz, 5-H), 3.72 (3 H, s, OMe), 4.96 (1 H, br s, 17-H), 5.15 (1 H, d, J 3.9 Hz, 3α-H), and 5.27 (1 H, br s, 17-H); m/z 432 (M^+, 13%), 414 (6), 401 (17), 400 (19), 372 (85), 354 (17), 340 (62), 328 (100), 312 (58), 304 (35), 267 (41), 239 (68), and 43 (64). The polarity of the product by t.l.c. was identical with that of starting material.

ent-3α-*Acetoxy*-2β-*ethyl*-10β,13-*dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**49**).—2α-Ethyl-GA_1 methyl ester (**45**) (179 mg) in pyridine (5 ml) was stirred with redistilled acetic anhydride (1 ml) for 5 h. Work-up as in the previous experiment gave 2α-*ethyl-GA*$_1$ 3-*acetate methyl ester* (**49**) (199 mg) as a gum (Found: M^+, 432.2148. $C_{24}H_{32}O_7$ requires M, 432.2139); δ 0.94 (3 H, t, J 7.3 Hz, 2-CH_2*Me*), 1.05 (3 H, s, 18-H_3), 2.13 (3 H, s, COMe), 2.68 (1 H, d, J 10.3 Hz, 6-H), 3.18 (1 H, d, J 10.3 Hz, 5-H), 3.73 (3 H, s, OMe), 4.83 (1 H, s, 3α-H), 4.96 (1 H, br s, 17-H), and 5.27 (1 H, br s, 17-H); m/z 432 (M^+, 9%), 401 (20), 400 (38), 372 (76), 340 (34), 328 (100), 313 (23), 312 (27), 304 (21), 299 (20), 269 (27), 268 (25), 267 (20), 239 (49), and 432 (41). (N.B. T.l.c. polarity of product was identical with that of starting material.)

ent-3α-*Acetoxy*-2α-*ethyl*-10β-*hydroxy*-13-(2-*methoxy*-2,3-*dioxoethoxy*)-20-*norgiberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**52**).—2β-Ethyl-GA_1 3-acetate methyl ester (**50**) (276 mg) in dry tetrahydrofuran (25 ml) was refluxed with oxalyl chloride (2 ml) for 1 h. The mixture was cooled in an ice-bath and water (15 ml) was added cautiously down the condenser. Extraction with ethyl acetate (3 × 30 ml) gave, after recovery, a brown gum. The crude product was methylated with ethereal diazomethane and then subjected to flash chromatography with ethyl acetate–light petroleum (40:60), which yielded the *oxalyl ester* (**52**) (214 mg) as a gum (pure by t.l.c. but ^{1}H n.m.r. shows a non-GA impurity, possibly dimethyl oxalate) (Found: $M^+ - 31$, 487.1931. $C_{27}H_{34}O_{10}$ requires $M - 31$, 487.1968); δ 0.87 (3 H, t, J 7.3 Hz, 2-CH_2*Me*), 1.03 (3 H, s, 18-H_3), 2.17 (3 H, s, COMe), 2.69 (1 H, d, J 10.8 Hz, 6-H), 3.15 (1 H, d, J 10.8 Hz, 5-H), 3.73 (3 H, s, OMe), 3.89 (3 H, s, 13-$OCOCO_2$Me), 5.07 (1 H, br s, 17-H), 5.15 (1 H, d, J 3.7 Hz, 3α-H), and 5.26 (1 H, br s, 17-H) (the impurity gave rise to two singlets at 3.973 and 3.966 p.p.m.); m/z 487 ($M^+ - 31$, 13%), 458 (68), 426 (40), 414 (100), 398 (57), 355 (63), 354 (80), 325 (79), 311 (63), 310 (52), 251 (43), 211 (56), 59 (48), and 43 (87).

ent-3α-*Acetoxy*-2β-*ethyl*-10β-*hydroxy*-13-(2-*methoxy*-2,3-*dioxoethoxy*)-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**51**).—2α-Ethyl-GA_1 3-acetate methyl ester (**49**) (199 mg) in dry tetrahydrofuran (15 ml) was refluxed with oxalyl chloride (2 ml) for 1 h. Quenching and work-up as for the 2β-ethyl isomer, as described in the previous experiment, gave crude product which was methylated with ethereal diazomethane. Flash chromatography with ethyl acetate–light petroleum (1:1) yielded the *oxalyl ester* (**51**) (158 mg) as a gum (Found: $M^+ - 31$, 487.1943. $C_{27}H_{34}O_{10}$ requires $M - 31$, 487.1968); δ 0.94 (3 H, t, J, 7.3 Hz, 2-CH_2*Me*), 1.05 (3 H, s, 18-H_3), 2.13 (3 H, s, COMe), 2.71 (1 H, d, J 10.7 Hz, 6-H), 3.20 (1 H, d, J 11.1 Hz, 5-H), 3.74 (3 H, s, Me), 3.89 (3 H, s, 13-$OCOCO_2$Me), 4.83 (1 H, s, 3α-H), 5.07 (1 H, br s, 17-H), and 5.25 (1 H, br s, 17-H); m/z 487 ($M^+ - 31$, 12%), 458 (73), 426 (21), 415 (30), 414 (100), 355 (54), 354 (63), 325 (79), 311 (64), 310 (51), 251 (37), 221 (42), 91 (20), 59 (24), and 43 (45).

ent-2α-*Ethyl*-3α,10β-*dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**56**).—2β-Ethyl-GA_4 3-acetate methyl ester (**54**) (70 mg) was stirred, in methanol (7 ml), with saturated aqueous potassium carbonate (7 ml), for 2 h. The mixture was diluted with water (10 ml), acidified to pH 2, and extracted with ethyl acetate (3 × 20 ml). Flash chromatography of the recovered gum with ethyl acetate–light petroleum (30:70) gave, sequentially, starting material (**54**) (6 mg) and 2β-*ethyl-GA*$_4$ *methyl ester* (**56**) (29 mg) as a gum (Found: M^+, 374.2011; $M^+ - 18$, 356.2024; $M^+ - 32$, 342.2796. $C_{22}H_{30}O_5$ requires M, 374.2095; $M - 18$, 356.1987; $M - 32$, 342.1831); δ 0.92 (3 H, t, J 7.3 Hz, 2-CH_2*Me*), 1.16 (3 H, s, 18-H_3), 2.63 (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 10.7 Hz, 5-H), 3.70 (4 H, s, OMe and 3α-H), 4.85 (1 H, br s, 17-H), and 4.97 (1 H, br s, 17-H); δ(C_5D_5N) 0.87 (3 H, t, J 7.3 Hz, 2-CH_2Me), 1.51 (3 H, s, 18-H_3), 2.54 (1 H, br t, 9- or 13-H), 2.99 (1 H, d, J 11.0 Hz, 6-H), 3.66 (3 H, s, OMe), 3.93 (1 H, d, 5-H; partly obscured by the signal at 3.66 p.p.m.), 3.96 (1 H, br dd, J *ca.* 5.9 and 2.2 Hz, 3α-H), 4.91 (1 H, br s, 17-H), 5.01 (1 H br s, 17-H), and 7.10 (1 H, d, J 5.9 Hz, 3β-OH) (on addition of D_2O the signal at 3.96 p.p.m. collapsed to a br d, J 2.2 Hz); m/z 374 (M^+, 1%), 356 (9), 342 (39), 312 (70), 296 (33), 252 (100), 223 (79), 91 (46), and 41 (47).

ent-2β-*Ethyl*-3α,10β-*dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 7-*Methyl Ester* 19,10-*Lactone* (**55**).—To 2α-ethyl-GA_4 3-acetate methyl ester (**53**) (72 mg) in methanol (20 ml) was added saturated aqueous potassium carbonate (to pH 9—10). After stirring for 2.5 h, t.l.c. indicated *ca.* 70% conversion into a more polar product. Saturated aqueous potassium carbonate (6 ml) was added and the mixture stirred for 2 min. After acidification to pH 2 the mixture was extracted with ethyl acetate (3 × 20 ml). Flash chromatography of the recovered gum with ethyl acetate–light petroleum (30:70) gave, sequentially, a mixture (27 mg) of starting material (**53**) and 2α-ethyl-GA_4 methyl ester (**55**), and pure 2α-*ethyl-GA*$_4$ *methyl ester* (**55**) (43 mg) as a gum (Found: M^+, 374.2110. $C_{22}H_{30}O_5$ requires M, 374.2093); δ 0.91 (3 H, t, J 7.3 Hz, 2-CH_2*Me*), 1.16 (3 H, s, 18-H_3), 2.63 (1 H, br t, 9- or 13-H), 2.70 (1 H, d, J 10.7 Hz, 6-H), 3.18 (1 H, d, J 10.7 Hz, 5-H), 3.63 (1 H, s, 3-H), 3.71 (3 H, s, OMe), 4.85 (1 H, br s, 17-H), and 4.98 (1 H, br s, 17-H); m/z 374 (M^+, 4%), 356 (21), 343 (25), 342 (51), 328 (23), 312 (100), 253 (34), 252 (67), 223 (76), and 91 (30).

Hydrolyses of Methyl Esters with Sodium Propane-1-thiolate.—(a) ent-3α,10β-*Dihydroxy*-2α-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10-*lactone* (**4**). 2β-Methyl-GA_4 methyl ester (**42**) (50 mg) was stirred with sodium propane-1-thiolate solution (1.5 ml) for 5 h under nitrogen. After work-up the ethyl acetate extracts were washed with saturated aqueous sodium

hydrogen carbonate (3 × 20 ml). The aqueous washings were acidified to pH 2 and extracted with ethyl acetate (3 × 20 ml). The organic extracts were dried ($MgSO_4$); evaporation under reduced pressure followed by flash chromatography with ethyl acetate–light petroleum–acetic acid (40:60:1) yielded 2β-methyl-GA_4 (**4**) (28 mg) as a gum (Found: M^+, 346.1760. Calc. for $C_{20}H_{26}O_5$: M, 346.1773); identical (n.m.r. and mass spectrometry) with the previously prepared sample.[2] G.l.c.–mass spectrometric analysis indicated the presence of 6% *endo*-isomer.

(b) ent-3α,10β-*Dihydroxy*-2β-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10-*lactone* (**3**). 2α-Methyl-GA_4 methyl ester (**41**) (22 mg) was demethylated and the product worked up as described for the 2β-isomer (**42**) in the previous experiment. Purification by flash chromatography ethyl acetate–light petroleum–acetic acid (40:60:1) gave 2α-*methyl-GA*$_4$ (**3**) (20 mg) as a gum (Found: M^+, 346.1776. $C_{20}H_{26}O_5$ requires M, 346.1773); δ[$(CD_3)_2CO$] 1.03 (3 H, d, J 8.1 Hz, 2α-Me), 1.13 (3 H, s, 18-H_3), 2.60 (1 H, d, J 10.5 Hz, 6-H), 3.18 (1 H, d, J 10.7 Hz, 5-H), 3.45 (1 H, s, 3α-H), 4.84 (1 H, br s, 17-H), and 4.97 (1 H, br s, 17-H); g.l.c.–mass spectrum of the Me ester *O*-SiMe derivative: m/z 432 (M^+, 38%), 342 (51), 310 (21), 298 (100), 289 (67), 261 (32), 239 (50), 238 (57), 233 (56), 201 (29), and 143 (71). G.l.c.–mass spectrometry indicated the presence of 5% *endo*-isomer.

(c) ent-2β-*Ethyl*-3α,10β-*dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10-*lactone* (**5**). 2α-Ethyl-GA_4 methyl ester (**55**) (43 mg) was stirred with sodium propane-1-thiolate solution (1.5 ml) under nitrogen for 5 h. Work-up followed by flash chromatography [ethyl acetate–light petroleum–acetic acid (30:70:1)] gave 2α-*ethyl-GA*$_4$ (**5**) (30 mg) as a gum (Found: M^+, 360.1951. $C_{22}H_{30}O_5$ requires M, 360.1936); δ[$(CD_3)_2CO$] 0.89 (3 H, t, J 7.3 Hz, 2-CH_2*Me*), 1.13 (3 H, s, 18-H_3), 2.59 (1 H, d, J 10.7 Hz, 6-H; superimposed on signal at 2.61 p.p.m.), 2.61 (1 H, br t, 9- or 13-H; under signal at 2.59 p.p.m.), 3.20 (1 H, d, J 10.7 Hz, 5-H), 3.54 (1 H, s, 3α-H), 4.84 (1 H, br s, 17-H), and 4.97 (1 H, br s, 17-H); m/z 360 (M^+, 6%), 342 (19), 324 (16), 314 (43), 298 (100), 296 (43), 269 (59), 223 (65), and 91 (31); g.l.c.–mass spectrometery of the Me ester *O*-$SiMe_3$ derivative: m/z 446 (M^+, 45%), 356 (59), 312 (94), 289 (78), 261 (40), 253 (44), 252 (40), 233 (57), 223 (48), and 157 (100).

(d) ent-2α-*Ethyl*-3α,10β-*dihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10-*lactone* (**6**). 2α-Ethyl-GA_4 methyl ester (**56**) (28 mg) was stirred for 6 h with sodium propane-1-thiolate solution (1.8 ml) as in (a). Flash chromatography of the crude acidic product with ethyl acetate–light petroleum–acetic acid (35:65:1) gave 2β-*ethyl-GA*$_4$ (**6**) (23 mg) as a gum (Found: M^+, 360.1927. $C_{21}H_{28}O_5$ requires M, 360.1936); δ[$(CD_3)_2CO$] 0.91 (3 H, t, J 7.3 Hz, 2-CH_2*Me*), 1.13 (3 H, s, 18-H_3), 2.59 (1 H, d, J 10.7 Hz, 6-H; superimposed on signal at 2.62 p.p.m.), 2.62 (1 H, br t, 9- or 13-H; under signal at 2.59 p.p.m.), 3.16 (1 H, d, J 10.7 Hz, 5-H), 3.62 (1 H, d, J 2.9 Hz, 3α-H), 4.85 (1 H, br s, 17-H), and 4.97 (1 H, br s, 17-H); m/z 360 (M^+, 3%), 342 (28), 324 (34), 314 (38), 298 (100), 296 (38), 223 (54), and 91 (35); g.l.c.–mass spectrometry of the Me ester *O*-$SiMe_3$ derivative: m/z 446 (M^+, 71%), 418 (17), 356 (55), 312 (45), 289 (84), 261 (39), 253 (39), 233 (52), and 157 (100).

(3) ent-3α,10β,13-*Trihydroxy*-2β-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10-*lactone* (**7**). 2α-Methyl-GA_1 methyl ester (**44**) (99 mg) was stirred with sodium propane-1-thiolate solution (1.8 ml) for 6.5 h and the product worked up as described in (a). Flash chromatography with ethyl acetate–light petroleum (60:40) gave 2α-*methyl-GA*$_1$ (**7**) (20 mg) as a gum (Found: M^+, 362.1703. $C_{20}H_{26}O_6$ requires M, 362.1729); δ[$(CD_3)_2CO$] 1.03 (3 H, d, J 8.1 Hz, 2α-Me), 1.13 (3 H, s, 18-H_3), 2.58 (1 H, d, J 10.3 Hz, 6-H), 3.19 (1 H, d, J 10.3 Hz, 5-H), 3.45 (1 H, s, 3α-H), 4.86 (1 H, br s, 17-H), and 5.19 (1 H, br s, 17-H); m/z 362 (M^+, 31%), 344 (86), 316 (25), 298 (51), 277 (44), 230 (85), 228 (62), 154 (62), 152 (55), 91 (49), 77 (59), 55 (53), and 28 (100); g.l.c.–mass spectrum of the Me ester *O*-$SiMe_3$ derivative: m/z 520 (M^+, 100%), 448 (13), 377 (15), 207 (25), and 73 (22); earlier and later column fractions yielded slightly impure 2α-methyl-GA_1 (**7**) (41 mg).

(f) ent-2β-*Ethyl*-3α,10β,13-*trihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10-*lactone* (**9**). The crude acid, obtained as in (a) from 2α-ethyl-GA_1 methyl ester (**45**) (94 mg) and sodium propane-1-thiolate solution (1.4 ml) was subjected to flash chromatography. Elution with ethyl acetate–light petroleum–acetic acid (40:60:1) gave 2α-*ethyl-GA*$_1$ (**9**) (23 mg) as a gum (Found: M^+, 376.1861. $C_{21}H_{28}O_5$ requires M, 376.1886); δ[$(CD_3)_2CO$] 0.89 (3 H, t, J 7.3 Hz, 2-CH_2*Me*), 1.13 (3 H, s, 18-H_3), 2.28 (1 H, d, 6-H); partially obscured by other signals), 2.60 (1 H, br t, 9-H), 3.21 (1 H, d, J 10.3 Hz, 5-H), 3.54 (1 H, s, 3α-H), 4.87 (1 H, br s, 17-H), and 5.19 (1 H, br s, 17-H); m/z 390 (M^+, 27%), 372 (13), 359 (29), 358 (100), 344 (11), 331 (20), 330 (13), 312 (21), 304 (18), 239 (13), and 163 (18); g.l.c.–mass spectrometry of the Me ester *O*-$SiMe_3$ derivative: m/z 534 (M^+, 100%), 519 (6), 475 (5), 448 (12), 377 (15), 207 (19), and 73 (22); later column fractions yielded slightly impure 2α-ethyl-GA_1 (**9**) (37 mg).

(g) ent-3α,10β,13-*Trihydroxy*-2β-*propyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10-*lactone* (**11**). 2α-Propyl-GA_1 methyl ester (**47**) (50 mg) was stirred with sodium propane-1-thiolate solution (1.5 ml) for 4 h as in (a). Flash chromatography of the crude product with ethyl acetate–light petroleum–acetic acid (35:65:2) gave 2α-*propyl-GA*$_1$ (**11**) (35 mg) as a solid foam (Found: M^+, 390.2061; $M^+ - 18$, 372.1942. $C_{22}H_{30}O_6$ requires M^+, 390.2042; $M^+ - 18$, 372.1937); δ[$(CD_3)_2CO$] 0.88 (3 H, t, J 7.0 Hz, 2-CH_2CH_2*Me*), 1.13 (3 H, br s, 18-H_3), 2.75 (1 H, d, J 10.3 Hz, 6-H), 3.19 (1 H, d, J 10.5 Hz, 5-H), 3.60 (1 H, d, J 3.4 Hz, 3α-H), 4.87 (1 H, br s, 17-H), and 5.20 (1 H, br s, 17-H); m/z 390 (M^+, 63%), 372 (100), 345 (25), 344 (40), 328 (17), 326 (16), 326 (33), 290 (55), 281 (15), 239 (20), 163 (24), 136 (21), 135 (37), 129 (19), 128 (31), 127 (19), 121 (22), 120 (34) 105 (22), and 91 (36).

(h) ent-3α,10β,13-*Trihydroxy*-2α-*propyl*-20-*norgibberell*-16-*ene*-7,19-*dioic acid* 19,10-*lactone* (**12**). 2β-Propyl-GA_1 methyl ester (**48**) (49 mg) was stirred with sodium propane-1-thiolate solution (1.5 ml) for 6 h as in (a). Flash chromatography of the crude product with ethyl acetate–light petroleum–acetic acid (35:65:2) gave 2β-*propyl-GA*$_1$ (**12**) (38 mg) as a solid foam (Found: M^+, 390.2047; $M^+ - 18$, 372.1927. $C_{22}H_{30}O_6$ requires: M, 390.2042; $M^+ - 18$, 372.1937); δ[$(CD_3)_2CO$] 0.88 (3 H, t, J 6.9 Hz, 2-CH_2CH_2*Me*), 1.13 (1 H, s, 18-H_3), 2.58 (1 H, d, J 10.5 Hz, 6-H), 3.18 (1 H, d, J 10.2 Hz, 5-H), 3.60 (1 H, d, J 3.4 Hz, 3α-H), 4.87 (1 H, br s, 17-H), and 5.20 (1 H, br s, 17-H); m/z 390 (M^+, 57%), 372 (100), 345 (19), 344 (32), 327 (15), 326 (30), 290 (54), 281 (13), 239 (20), 163 (25), 136 (17), 135 (26), 129 (12), 128 (13), 122 (15), 121 (20), 105 (17), and 91 (27).

(i) ent-2β,3α-*Dihydroxy*-2α-*methyl*-20-*norgibberella*-(10),16-*diene*-7,19-*dioic acid* 19,2-*lactone* (**60**). 2-Methyl-GA_7 methyl ester (**16**) (114 mg) was stirred for 5 h with sodium propane-1-thiolate solution (3 ml) under nitrogen. Work-up followed by flash chromatography with ethyl acetate–light petroleum–acetic acid (40:60:1) gave the 2β-*methyl* 19,2-*lactone* (**60**) (91 mg) as a gum (Found: M^+, 344.1635. $C_{20}H_{24}O_5$ requires M, 344.1624); δ 1.25 (3 H, s, 18-H_3), 1.59 (3 H, s, 2β-Me), 3.23 (1 H, dd, J 5.8 and 2.2 Hz, 5-H), 3.92 (1 H, s, 3α-H), 4.92 (2 H, br s, 17-H_2), and 5.52 (1 H, br t, J 2 Hz × 2, 1-H); δ[$(CD_3)_2CO$] 1.16 (3 H, s, 18-H_3), 1.51 (3 H, s, 2β-Me), 2.42 (1 H, d, J 6.4 Hz, 6-H), 3.28 (1 H, dd, J 6.4 and 2.4 Hz, 5-H), 3.94 (1 H, s, 3α-H), 4.91 (2 H, br s, 17-H_2), and 5.54 (1 H, br s, 1-H); m/z 344 (M^+, 22%), 326 (29), 299 (26), 298 (50), 282 (67), 281 (75), 253 (34), 237 (100), 193 (29), 167 (58), 93 (30), and 91 (57); g.l.c.–mass spectrum (of the Me ester *O*-$SiMe_3$ derivative): 430 (M^+, 9%), 398 (34), 370 (25), 312 (36),

296 (41), 295 (38), 283 (45), 256 (35), 237 (92), 236 (100), and 75 (57).

Treatment of Iodo Lactones with 1,8-*Diazabicyclo*[5.4.0]*undec-7-ene* (DBU).—(a) 1β-*Iodo*-2β-*methylgibberellin* A_4 *methyl ester* (**33**). The iodo lactone (**33**) (999 mg) was refluxed in toluene (40 ml) containing DBU (615 μl). After 35 min the mixture was cooled, washed with aqueous hydrochloric acid (pH 3; × 2) and the aqueous washings were back-extracted with ethyl acetate. The organic fractions were combined, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography with ethyl acetate–light petroleum (25:75) gave 2-*methyl-*GA_7 *methyl ester* (**16**) as prisms (571 mg), m.p. 168—172 °C [from ethyl acetate–acetone (trace)–light petroleum] (Found: C, 70.6; H, 7.5. $C_{21}H_{26}O_5$ requires C, 70.4; H, 7.3%); δ 1.24 (3 H, s, 18-H_3), 1.81 (3 H, d, *J* 1.0 Hz, 2-Me), 2.77 (1 H, d, *J* 11.0 Hz, 6-H), 3.17 (1 H, d, *J* 11.0 Hz, 5-H), 3.72 (3 H, s, OMe), 3.92 (1 H, br s, 3α-H), 4.85 (1 H, br s, 17-H), 4.99 (1 H, br s, 17-H), and 6.01 (1 H, q, *J* 1.5 Hz, 1-H); *m/z* 358 (M^+, 6%), 326 (21), 298 (17), 295 (100), 253 (30), 237 (74), 236 (55), 235 (42), 135 (18), and 91 (27).

(b) 1β-*Iodo*-2α-*methylgibberellin* A_1 *methyl ester* (**34**). The iodo lactone (**34**) (31 mg) was refluxed in toluene (20 ml) containing DBU (50 μl) for 1 h. After cooling, the mixture was evaporated under reduced pressure. Purification by flash chromatography with ethyl acetate–light petroleum (1:1) afforded starting material (**34**) (identified by ^{1}H n.m.r. and t.l.c.).

(c) 1β-*Iodo*-2β-*methylgibberellin* A_1 (**39**). The iodo lactone (**39**) (58 mg) was converted into the tributylstannyl ester by refluxing in toluene (15 ml) with bis(tributylstannyl) oxide (30 μl) and removing the water with a Dean–Stark trap. After 30 min, DBU (36 μl) was added and refluxing was continued for a further 30 min. Evaporation under reduced pressure gave a gum which was purified by flash chromatography with ethyl acetate–light petroleum–acetic acid (75:25:1) to give ent-3α,2β,13-*trihydroxy*-2α-*methyl*-20-*norgibberell*-1(10),16-*diene*-7,19-*dioic acid* 19,2-*lactone* (**60**) (*ca.* 45 mg) as a gum (Found: M^+, 360.1580. $C_{20}H_{24}O_6$ requires *M*, 360.1573); δ 1.16 (3 H, s, 18-H_3), 1.51 (3 H, s, 2β-Me), 2.43 (1 H, d, *J* 5.9 Hz, 6-H), 3.27 (1 H, dd, *J* 6.0 and 2.5 Hz, 5-H), 3.95 (1 H, s, 3α-H), 4.92 (1 H, br s, 17-H), 5.09 (1 H, br s, 17-H), and 5.55 (1 H, br s, 1-H); *m/z* 360 (M^+, 8%), 342 (26), 314 (20), 299 (19), 298 (84), 297 (15), 269 (18), 253 (49), 169 (28), 44 (100), and 43 (78); g.l.c.–mass spectrometry of the Me ester *O*-$SiMe_3$ derivative: *m/z* 518 (M^+, 100%), 503 (6), 489 (12), 384 (21), 383 (25), 369 (10), and 238 (19).

The same result was obtained when 1β-iodo-2β-methyl-GA_1 (**39**) (58 mg) was refluxed for 1 h in tetrahydrofuran (15 ml) containing DBU (36 μl).

(d) 2β-*Ethyl*-1β-*iodogibberellin* A_1 *methyl ester* (**36**). The iodo lactone (**36**) (140 mg) was refluxed for 1 h in toluene (20 ml) containing DBU (100 μl). Work-up as in (a) followed by flash chromatography with ethyl acetate–light petroleum (60:40) gave, sequentially, as gums, ent-2α-*ethyl*-3α,2β,13-*trihydroxy*-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic acid* 7-*methyl ester* 19,2-*lactone* (**59**) [19 mg; contaminated with traces of (**28**)] (Found: M^+, 388.1901. $C_{22}H_{28}O_6$ requires *M*, 388.1901); δ 1.07 (3 H, t, *J* 7.3 Hz, 2-CH_2Me), 1.20 (3 H, s, 18-H_3), 2.57 (1 H, d, *J* 5.9 Hz, 6-H), 3.22 (1 H, dd, *J* 6.0 and 2.6 Hz, 5-H), 3.99 (1 H, br d, *J* 6 Hz, 3α-H), 4.83 (br s, OH), 4.98 (1 H, br s, 17-H), 5.13 (1 H, br s, 17-H), and 5.57 (1 H, br s, 1-H) (on addition of D_2O the signal at 3.99 p.p.m. collapsed to a sharp singlet); *m/z* 388 (M^+, 17%), 357 (14), 356 (33), 329 (13), 328 (17), 326 (39), 325 (100), 284 (19), 283 (32), 267 (50), 266 (44), 265 (46), 237 (18), and 71 (88); and a 1:1 mixture (39 mg) of 2-ethyl-GA_3 ethyl ester (**18**) and (**59**) (Found: M^+, 388.1899. $C_{22}H_{28}O_6$ requires *M*, 388.1886); δ[spectrum of (**59**) substracted] 1.04 (3 H, t, *J* 7.3 Hz, 2-CH_2Me), 1.24 (3 H, s, 18-H_3), 2.77 (1 H, d, *J* 10.7 Hz, 6-H), 3.18 (1 H, d, *J* 10.7 Hz, 5-H), 3.74 (3 H, s, OMe), 3.99 (1 H, s, 3α-H), 4.96 (1 H, br s, 17-H), 5.28 (1 H, br s, 17-H), and 5.98 (1 H, br s, 1-H).

(e) 2α-*Ethyl*-1β-*iodogibberellin* A_1 *methyl ester* (**35**). The iodo lactone (**35**) (30 mg) and DBU (40 μl) were refluxed in toluene (15 ml) for 1 h. Flash chromatography of the product, recovered as in (a), with ethyl acetate–light petroleum (1:1) yielded only starting material, identified by ^{1}H n.m.r. and t.l.c.

Hydrolysis of 2-*Methyl-*GA_7 *Methyl Ester* (**16**) via *the* 3-*Tetrahydropyranyl Ether*.—2-Methyl-GA_7 methyl ester (**16**) (178 mg) was stirred in dry dichloromethane with 2,3-dihydropyran (150 μl) and toluene-*p*-sulphonic acid (catalytic). After 1.5 h the mixture was evaporated under reduced pressure and the resultant gum purified by flash chromatography with ethyl acetate–light petroleum (1:3). The product in methanol (10 ml) was refluxed for 16 h with aqueous 2M sodium hydroxide (20 ml). Work-up gave a gum which was stirred in acetone (27 ml) and methanol (3 ml) containing toluene-*p*-sulphonic acid (catalytic) for 1.5 h. Evaporation under reduced pressure followed by flash chromatography with ethyl acetate–light petroleum–acetic acid (30:70:1) gave the 2β-methyl 19,2-lactone (**60**), identical by ^{1}H n.m.r. and t.l.c. with that described earlier.

Reaction of 2-*Methyl-*GA_7 *Methyl Ester* (**16**) *with Toluene-p-sulphonic Acid in Acetone–Methanol*.—2-Methyl-GA_7 methyl ester (**16**) in acetone (13 ml) and methanol (2 ml) was stirred with toluene-*p*-sulphonic acid (catalytic). After 7 h, work-up gave ent-2β-3α-*dihydroxy*-2α-*methyl*-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic acid* 19,2-*lactone* 7-*methyl ester* (**61**) as a gum (Found: M^+, 358.1812. $C_{21}H_{26}O_5$ requires *M*, 358.1780); δ 1.20 (3 H, s, 18-H_3), 1.58 (3 H, s, 2β-Me), 2.54 (1 H, d, *J* 6.2 Hz, 6-H), 3.20 (1 H, dd, *J* 6.2 and 2.5 Hz, 5-H), 3.73 (3 H, s, OMe), 3.89 (1 H, s, 3α-H), 4.90 (2 H, br s, 17-H_2), and 5.51 (1 H, m, 1-H); *m/z* 358 (M^+, 3%), 326 (15), 298 (15), 295 (100), 253 (29), 237 (50), 236 (31), 235 (41), 169 (19), 105 (16), 94 (46), and 91 (27).

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