2β-Alkyl Derivatives of Gibberellin A_1

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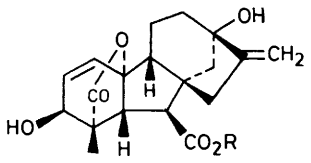
In the reaction of gibberellin A_3 (**1**) with lithium dialkylcuprates, *anti*-S_N2'-type substitution occurred with the displacement of the lactone function. The resultant 2β-alkyl-1(10)-enedioic acids (**4**)—(**7**) were iodolactonised, then reductively de-iodinated to give 2β-methyl, 2β-ethyl, 2β-n-propyl, and 2β-n-butyl gibberellin A_1 (**16**)—(**19**). The reaction of lithium dimethylcuprate with 3-didehydrogibberellin A_3 was complex but there was no evidence for the occurrence of conjugate addition to the α,β-unsaturated ketone in competition with the *anti*-S_N2'-type reaction.

The alkylation of esters of allylic alcohols by lithium dialkylcuprates was first noted by Rona *et al.*[1] Subsequently the reaction has been used, with and without allylic rearrangement, in many syntheses.[2] This paper describes the alkylation of gibberellin A_3 (GA_3) (**1**) by lithium dialkylcuprates and the elaboration of the alkylation products to give a homologous series of 2β-alkyl GAs, required for biological testing.

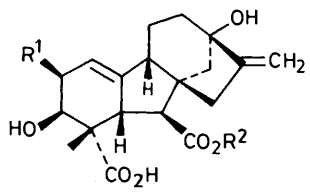
Initially the alkylation of GA_3 methyl ester (**2**) was studied. As expected from precedents in the literature,[1–4] methylation with lithium dimethylcuprate occurred at the less hindered 2-position with double bond rearrangement. The major product was the 2β-methyl isomer (**3**); evidence for this stereochemistry is given later. No 2α-methyl isomer was detected. Treatment of the 2β-methyl compound (**3**) with two equivalents of iodine in a biphasic system of tetrahydrofuran–dichloromethane–aqueous sodium hydrogen carbonate[5] gave the iodolactone (**8**). The 1β-stereochemistry, predicted mechanistically, was confirmed by the ^{1}H n.m.r. spectrum in which the 5-proton was deshielded by 0.56 p.p.m. from its position at δ 3.16 in 2β-methyl GA_1 methyl ester (**15**) (see later). Iodination of the acid (**3**) with an excess of iodine gave the ring C/D rearranged compound (**13**) which was reduced to compound (**14**) by tri-n-butylstannane; both compounds (**13**) and (**14**) were characterised by their spectroscopic properties. Reductive de-iodination of the iodolactone (**8**) with tri-n-butylstannane gave 2β-methyl GA_1 methyl ester (**15**) which was hydrolysed to 2β-methyl GA_1 (**16**) with sodium n-propanethiolate in hexamethylphosphoramide.

To avoid the need to hydrolyse the methyl ester (**15**) in the last step of this sequence, the alkylation of the free acid, GA_3 (**1**), was investigated. The reaction of GA_3 (**1**) with lithium dimethyl-, diethyl-, di-n-propyl-, and di-n-butyl-cuprates gave the 2β-methyl, 2β-ethyl, 2β-n-propyl, and 2β-n-butyl diacids (**4**)—(**7**). The yields were lower than those obtained in the methylation of GA_3 methyl ester (**2**). The total products from the methylation of GA_3 (**1**) were examined by g.l.c.-mass spectrometry after methylation and trimethylsilylation, the by-products appears to be di- and tri-olefins of the type (**20**). In all cases the 2β-alkyl epimers were the major products (see later for evidence for the stereochemical assignments). By g.l.c.-mass spectrometry of the derived products, no 2α-methyl, traces of 2α-ethyl, 15—20% of 2α-n-propyl, and 30—40% of 2α-n-butyl isomers were detected. This trend can be explained by the increasing steric interaction between the 3β-hydroxy group and the lithium dialkylcuprates in the intermediate π-allyl complex (**21**).[3,6,7]

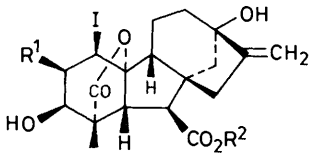
Iodolactonisation of the 2β-alkyl diacids (**4**)—(**7**) proceeded smoothly, but reduction of the iodolactones (**9**)—(**12**) with tri-n-butylstannane presented problems. One difficulty—the insolubility of the iodolactones—was overcome by using the 7-tri-n-butylstannyl esters, prepared by briefly refluxing the iodolactones (**9**)—(**12**) with bis(tri-n-butyltin) oxide in toluene. Reduction of the stannyl esters of the 2β-methyl- and 2β-ethyl-



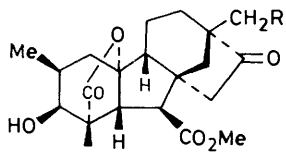
(**1**) R = H
(**2**) R = Me



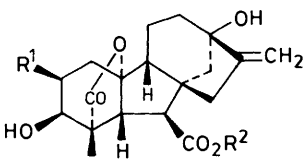
(**3**) $R^1 = R^2$ = Me
(**4**) R^1 = Me, R^2 = H
(**5**) R^1 = Et, R^2 = H
(**6**) R^1 = ^{n}Pr, R^2 = H
(**7**) R^1 = ^{n}Bu, R^2 = H



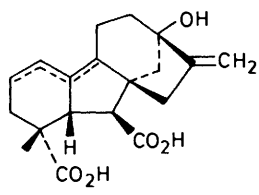
(**8**) $R^1 = R^2$ = Me
(**9**) R^1 = Me, R^2 = H
(**10**) R^1 = Et, R^2 = H
(**11**) R^1 = ^{n}Pr, R^2 = H
(**12**) R^1 = ^{n}Bu, R^2 = H



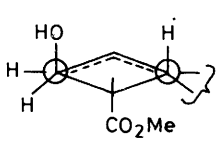
(**13**) R = I
(**14**) R = H



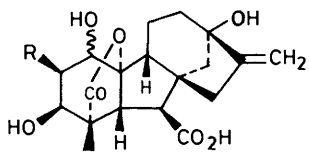
(**15**) $R^1 = R^2$ = Me
(**16**) R^1 = Me, R^2 = H
(**17**) R^1 = Et, R^2 = H
(**18**) R^1 = ^{n}Pr, R^2 = H
(**19**) R^1 = ^{n}Bu, R^2 = H



(**20**)

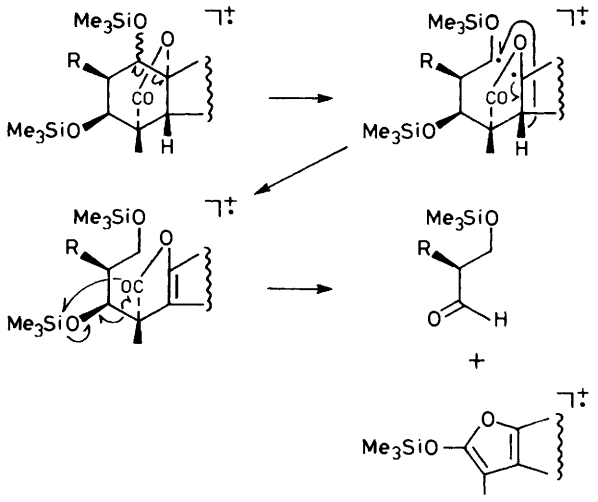


(**21**)



(**22**) R = ^{n}Pr
(**23**) R = ^{n}Bu

iodolactones (**9**) and (**10**), followed by hydrolysis of the stannyl esters with acetic acid, gave 2β-methyl GA_1 (**16**) and 2β-ethyl GA_1 (**17**) in good yield. However another difficulty arose in the reduction of the stannyl esters of 2β-n-propyl- and 2β-n-butyl-iodolactones (**11**) and (**12**) with tri-n-butylstannane. In addition to the required products (**18**) and (**19**), the epimeric 1-hydroxy compounds (**22**) and (**23**) were found in 10—15 and 40% respectively. These by-products were not isolated but were detected and characterised by g.l.c.-mass spectrometric comparison of the methyl ester trimethylsilyl ethers (MeTMSi derivatives) with the MeTMSi derivatives of GA_{55} (**24**) and GA_{57} (**25**). The more polar isomer of the pairs, (**22**) and (**23**), appeared to be the 1α-hydroxy compounds. For example, the MeTMSi derivatives of (**22**) and (**23**) like that of GA_{55}, which is more polar than GA_{57} MeTMSi, gave base peaks at *m/z* 448; a possible fragmentation sequence is shown in the Scheme. In

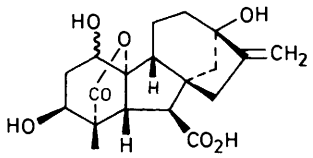


Scheme.

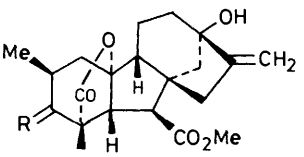
contrast the MeTMSi derivatives of GA_{57} and the less polar of each of the isomeric pairs, (**22**) and (**23**), gave weak *m/z* 448 ions. Like all known 1,3-dihydroxy GAs, the MeTMSi derivatives of all four epimers (**22**) and (**23**) gave ions derived from the M^+ ion by loss of C-1 and -2 (plus the substituent R), *i.e.* ($M^+ - 116$) for (**24**) and (**25**) and ($M^+ - 158$) and ($M^+ - 172$) for (**22**) and (**23**) respectively; a possible mechanism for this fragmentation is given by Beale and MacMillan.[8]

Formation of the 1-hydroxy compounds (**22**) and (**23**) was prevented by rigorous deoxygenation of the reaction mixture. Thereby reduction of the tri-n-butylstannyl esters of the iodolactones (**11**) and (**12**), followed by hydrolysis of the stannyl esters, gave 2β-n-propyl and 2β-n-butyl GA_1 (**18**) and (**19**) in acceptable yields. The observation that oxygen can compete with tri-n-butylstannane for the intermediate 1-radical in the reduction of the n-propyl- and n-butyl-iodolactones, but not of the methyl- and ethyl-iodolactones, is consistent with the β-stereochemistry of the 2-alkyl substituents. More direct evidence for this stereochemistry was obtained as follows.

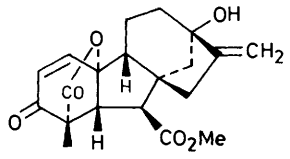
2β-Methyl GA_1 methyl ester (**15**) was subjected to Swern oxidation.[9] The resultant ketone (**26**) was reduced with sodium borohydride to give equal proportions of 2β-methyl GA_1 methyl ester (**15**) and its 3α-hydroxy epimer (**27**). In the ^{1}H n.m.r. spectra of these epimers, the 3β-hydroxy compound (**15**) was distinguished from the 3α-epimer (**27**) by the lower field chemical shift of the 5-proton. The $J_{2,3}$ in the 3α-epimer was 9.8 Hz establishing the diaxial disposition of the 2- and 3-protons and therefore the 2β-stereochemistry of the 2-methyl group. The $J_{2,3}$ value for the 3β-epimer was not measurable in the



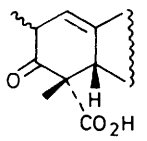
(**24**) 1β-OH
(**25**) 1α-OH



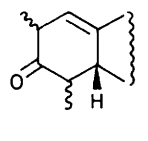
(**26**) R = O
(**27**) R = H, α-OH



(**28**)



(**29**)



(**30**)

broad singlet ($w_{\frac{1}{2}}$ 8 Hz) of the 3-proton. The 2β-stereochemistry in all other alkylation products, and derived compounds, is indicated by the ^{1}H n.m.r. data. In particular in all alkylation products the 3-proton occurred as a broad singlet and the 1-proton in the iodolactones had the typical $J_{ax.eq}$ value of 4.0—5.0 Hz.

Having established that GA_3 (**1**) and its methyl ester (**2**) were alkylated at C-2 by dialkylcuprates, it was of interest to investigate the reaction of the enone (**28**) where conjugate addition is an alternative. The reaction mixture from the enone (**28**) and lithium dimethylcuprate was complex and no pure products were isolated. However analysis of the mixture by capillary g.l.c.-mass spectrometry of the MeTMSi derivatives showed the presence of major amounts of 2α- and 2β-epimers (**29**). Other products tentatively identified included 2-epimers of (**30**), but no 1-methylated products were detected. It is of interest to note that 2α- as well as 2β-alkylation occurred in the enone (**28**) but not, as noted earlier, in the 3β-alcohol (**2**). Reaction of the enone (**28**) with methylmagnesium iodide in the presence of copper(I) bromide gave a similar reaction mixture.

Experimental

General details have been previously described.[10]

Preparation of Lithium Dialkylcuprates.—(*a*) *Lithium dimethylcuprate.* Copper(I) iodide (1 equiv., purified by the method of Kauffmann and Teter[11]), slurried in tetrahydrofuran (4 ml; distilled from calcium hydride), was cooled to 0 °C and stirred with 1.4M-solution of methyl lithium in diethyl ether (2 equiv.). The reaction was conducted under nitrogen in a flask sealed with a rubber septum. The yellow solution was used directly.

(*b*) *Lithium diethyl-, di-n-propyl- and di-n-butyl-cuprates.* These reagents were prepared as for the dimethylcuprate at between −20 and −10 °C. The black or brown solutions were used directly at the same temperature.

ent-3α,13-*Dihydroxy*-7-*methoxycarbonyl*-2α-*methyl*-20-*nor-gibberella*-1(10),16-*dien*-19-*oic Acid* (**3**).—Gibberellin A_3 methyl ester (**2**) (2.5 g) in tetrahydrofuran (30 ml) was added to a solution of lithium dimethylcuprate (3 equiv.) at 0 °C. The reaction mixture was allowed to warm to 20 °C. After 3 h it was poured into 0.5M-aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a gum (2.7 g) which was flash chromatographed on a silica column (45-mm diam.), eluted with ethyl acetate–light petrol-

eum–acetic acid (60:40:1). 2β-*Methyl*-1,10-*dehydrogibberellin* A_1 *methyl ester* (**3**) was recovered as a solid (1.4 g), m.p. 199—202 °C (from acetone–light petroleum) (Found: C, 66.6; H, 7.7. $C_{21}H_{28}O_6$ requires C, 67.0; H, 7.5%); δ_H ([$^2H_6$]acetone) 1.80 (d, *J* 7 Hz, 2β-CH_3), 1.29 (s, 18-H_3), 3.10 (m, 5-H), 3.24 (d, *J* 6 Hz, 6-H), 3.65 (s, CO_2Me), 3.89 (d, *J* 3 Hz, 3-H), and 4.87, 4.95, and 5.05 (each br s, 17-H_2 and 1-H); *m/z* 376 (M^+, 7%), 358 (49), 326 (21), 316 (17), 298 (18), 253 (100), and 235 (11). Later fractions contained more 2β-methyl compound (**3**) but were contaminated with unidentified polar compounds.

Treatment of ent-3α,10,13-*Trihydroxy*-7-*methoxycarbonyl*-20-*norgibberella*-1,16-*dien*-19-*oic Acid* 19,10-*Lactone* (**2**) *with Methylmagnesium Iodide and Copper*(I) *Bromide*.—Methylmagnesium iodide (3 ml; *ca.* 0.5M-solution in diethyl ether) was added to gibberellin A_3 methyl ester (**2**) (200 mg) and copper(I) bromide (50 mg) in tetrahydrofuran (20 ml). The reaction mixture was stirred at 20 °C for 6 h, then worked-up as usual to give a gum which had the same R_F value as the product described in the previous experiment, as shown by t.l.c. on Kieselgel HF using ethyl acetate–light petroleum (70:30) as solvent.

ent-1α-*Iodo*-3α,10,13-*trihydroxy*-7-*methoxycarbonyl*-2α-*methyl*-20-*norgibberell*-16-*en*-19-*oic Acid* 19,10-*Lactone* (**8**).—2β-Methyl-1,10-dehydrogibberellin A_1 methyl ester (3) (1.4 g), in tetrahydrofuran (40 ml) and dichloromethane (80 ml), was vigorously stirred with saturated aqueous sodium hydrogen carbonate (120 ml) and iodine (1.8 g) at 20 °C for 1 h. The organic phase was decanted and washed with saturated sodium thiosulphate solution (100 ml), followed by water (100 ml). Removal of the solvents under reduced pressure gave a foam (2.0 g), which was pure 1β-*iodo*-2β-*methylgibberellin* A_1 *methyl ester* (**8**), m.p. 171—173 °C (from acetone) (Found: C, 50.3; H, 5.7; I, 25.5. $C_{21}H_{27}O_6I$ requires C, 50.2; H, 5.4; I, 25.3%); $\nu_{max.}$($CHCl_3$) 3 600, 2 950, 2 880, 1 780, 1 740, 1 380, and 905 cm^{-1}; δ_H($CHCl_3$) 1.16 (s, 18-H_3), 1.20 (d, *J* 7 Hz, 2β-CH_3), 2.65 (d, *J* 10 Hz, 6-H), 3.62 (br s, 3-H), 3.68 (s, CO_2Me), 3.72 (d, *J* 10 Hz, 5-H), 4.31 (d, *J* 4.5 Hz, 1-H), 4.92 (br s, 17-H), and 5.20 (br s, 17-H); *m/z* 502 (M^+, 26%), 443 (70), 375 (13), 357 (44), 343 (34), 329 (64), 315 (42), 297 (43), 269 (64), and 253 (100).

ent-3α,10,13-*Trihydroxy*-7-*methoxycarbonyl*-2α-*methyl*-20-*norgibberell*-16-*en*-19-*oic Acid* 19,10-*Lactone* (**15**).—The 2β-methyliodolactone (**8**) (2.0 g) from the previous experiment in toluene (200 ml) was treated at 20 °C for 1 h with crude tri-n-butylstannane, prepared from tri-n-butylstannyl chloride (12.5 ml) and lithium aluminium hydride (750 mg) in diethyl ether (60 ml) for 30 min at 20 °C. The toluene was removed under reduced pressure to give an oil which was adsorbed onto silica gel and placed on a column (30 × 0.25 cm) of silica gel. The tin residues were removed by repeated elution with 10% ethyl acetate in light petroleum. Elution with 80—90% ethyl acetate afforded a yellow solid (1.04 g) which, on recrystallisation from chloroform–light petroleum, gave 2β-*methylgibberellin* A_1 *methyl ester* (**15**), m.p. 198—200 °C (Found: C, 66.1; H, 7.8%; M^+, 376.189. $C_{21}H_{28}O_6$ requires C, 67.0; H, 7.5%; *M*, 376.189); $\nu_{max.}$ (Nujol mull) 3 380, 1 770, 1 730, 1 705, 1 258, and 1 030 cm^{-1}; δ_H($CDCl_3$) 1.03 (d, *J* 6 Hz, 2β-CH_3), 1.18 (s, 18-H_3), 2.65 (d, *J* 11 Hz, 6-H), 3.16 (d, *J* 11 Hz, 5-H), 3.58 (br s, 3-H), 3.70 (s, CO_2Me), 4.90 (br s, 17-H), and 5.21 (br s, 17-H); *m/z* 376 (M^+, 92%), 344 (100), 316 (35), 298 (26), and 135 (24).

ent-3α,10,13-*Trihydroxy*-2α-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 19,10-*Lactone* (**16**).—2β-Methylgibberellin A_1 methyl ester (**15**) (150 mg), in a round-bottomed flask, fitted with a rubber septum and flushed with dry nitrogen, was treated with sodium propanethiolate–hexamethylphosphoramide (5 ml; 0.5M-solution, prepared from propanethiol in the usual way[10]) for 6 h at 20 °C. The product, recovered in the usual way, consisted (t.l.c. and g.l.c.) of one major component and a minor one (< 5%). The minor product was found to be 2β-methyl-3-epigibberellin A_1 (**30**) by comparison (t.l.c. and g.l.c.) with a sample obtained from the reduction of 2β-methyl-3-oxogibberellin A_1 methyl ester (**24**) (see later).

The major product was isolated by flash chromatography on a silica column (20-mm diam.), eluted with ethyl acetate–light petroleum–acetic acid (70:30:1), and characterised as 2β-*methylgibberellin* A_1 (**4**), m.p. 203—205 °C (from methanol–chloroform) (Found: C, 65.8; H, 7.5. $C_{20}H_{26}O_6$ requires C, 66.3; H, 7.2%); δ_H([$^2H_6$]acetone–[$^2H_5$]pyridine) 1.06 (d, *J* 6 Hz, 2β-CH_3), 1.32 (s, 18-H_3), 3.42 (d, *J* 10 Hz, 5-H), 3.59 (d, *J* 3 Hz, 3-H), 4.87 (br s, 17-H), and 5.27 (br s, 17-H); *m/z* 362 (M^+, 11%), 344 (33), 316 (15), 298 (12), 135 (11), 122 (29), and 105 (100).

Treatment of 2β-*Methyl*-1,10-*dehydrogibberellin* A_1 *Methyl ester* (**3**) *with a Ten-fold Excess of Iodine*.—The 2β-methyl monoacid (**3**) (300 mg), in tetrahydrofuran (10 ml) and dichloromethane (20 ml), was vigorously stirred with saturated aqueous sodium hydrogen carbonate (15 ml) and iodine (1.2 g) for 2 h. The usual work-up gave a gum which by t.l.c. consisted of two products. Recovery of the two compounds by flash chromatography on a silica column (20-mm diam.), eluted with ethyl acetate–light petroleum (60:40), showed that the more polar product was the 2β-methyliodolactone (**8**).

The less polar product was characterised as ent-3α,10-*dihydroxy*-1α-*iodo*-13-*iodomethyl*-7-*methoxycarbonyl*-2α-*methyl*-17,20-*bisnor*-13β-*gibberellan*-19-*oic acid* 19,10-*lactone* (**13**), m.p. 198—201 °C (from methanol–water) (Found: C, 39.8; H, 4.0. $C_{21}H_{26}O_6I_2$ requires C, 40.15; H, 4.2%); δ_H([$^2H_5$]pyridine) 1.28 (d, *J* 7.5 Hz, 2β-CH_3), 1.49 (s, 18-H_3), 3.14 (d, *J* 5.5 Hz, 6-H), 3.38 (d, *J* 6.5 Hz, CH_2I), 3.64 (s, CO_2Me), 3.85 (d, *J* 3 Hz, 3-H), 4.35 (d, *J* 5.5 Hz, 5-H), and 4.62 (d, *J* 4 Hz, 1-H); δ_H([$^2H_6$]acetone) 1.20 (d, *J* 7 Hz, 3-H), 1.22 (s, 18-H_3), 2.82 (d, *J* 6 Hz, 6-H), 3.37 (br s, CH_2I), 3.75 (s, CO_2Me and 3-H), 3.93 (d, *J* 6 Hz, 5-H), and 4.65 (d, *J* 5 Hz, 1-H); *m/z* 628 (M^+, 0.8%), 597 (2), 525 (1), 501 (22), 331 (100), and 299 (24).

Tri-n-Butyltin Hydride Reduction of ent-3α,10-*Dihydroxy*-1α-*iodo*-13-*iodomethyl*-7-*methoxycarbonyl*-2α-*methyl*-17,20-*bisnor*-13β-*gibberellan*-19-*oic Acid* 19,10-*lactone* (**13**).—The diiodide (**13**) (30 mg), in toluene (3 ml), was treated with crude tri-n-butyltin hydride (0.25 ml), prepared as described earlier, for 1 h at 20 °C. Recovery of the product as usual gave a brown oil which was adsorbed onto silica gel and applied to the top of a short column of silica gel. The bulk of the tin residues were removed by repeated elution with 10% ethyl acetate in light petroleum. Elution with acetone afforded ent-3α,10-*dihydroxy*-7-*methoxycarbonyl*-2α,13-*dimethyl*-16-*oxo*-17,20-*bisnor*-13β-*gibberellan*-19-*oic acid* 19,10-*lactone* (**14**) as a gum (Found: M^+, 376.191. $C_{21}H_{28}O_6$ requires *M*, 376.189); δ_H($CDCl_3$) 0.98 (d, *J* 4.5 Hz, 2-H_3), 1.06 (s), 1.26 (s) (18-H_3 and 17-H_3), 2.61 (d, *J* 7 Hz, 6-H), 3.15 (d, *J* 7 Hz, 5-H), 3.61 (br s, 3-H), and 3.67 (s, CO_2Me); *m/z* (trimethylsilylated), 448 (34%), 420 (12), 378 (9), 305 (15), 249 (18), 143 (100), 130 (18), and 73 (34).

ent-3α,13-*Dihydroxy*-2α-*methyl*-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic Acid* (**4**).—Treatment of gibberellin A_3 (**1**) (1.5 g) with lithium dimethylcuprate, in the manner described for gibberellin A_3 methyl ester (**2**), and the usual work-up gave a gum. Flash chromatography of this gum on a 40-mm diameter column eluted with ethyl acetate–light petroleum–acetic acid (70:30:1) yielded 2β-*methyl*-1-10- *dehydrogibberellin* A_1 *diacid* (**4**) (560 mg), m.p. decomp. over 250 °C (Found: M^+, 362.1744. $C_{20}H_{26}O_6$ requires *M*, 362.1729); δ_H([$^2H_6$]acetone) 1.08 (d, *J* 7.3 Hz, 2-CH_3), 1.34 (s, 18-(H_3), 3.11 (br s, 5-H), 3.19 (d, *J* 5.9 Hz,

6-H), 3.88 (br s, 3-H), 4.91 (br s, 17-H), 4.97 (br s, 1-H), and 5.08 (br s, 17-H).

ent-3α,13-*Dihydroxy*-2α-*ethyl*-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic Acid* (**5**).—The preparation was as described in the previous experiment but gibberellin A_3 (**1**) (0.69 g), in tetrahydrofuran (40 ml), was precooled to −20 °C before addition to the lithium diethylcuprate solution, which was also at −20 °C. The mixture was stirred at between −15 and −10 °C for 3 h. The usual work-up gave a gum which was purified by flash chromatography on a 40-mm diameter column eluted with ethyl acetate–light petroleum–acetic acid (80:20:1) to give, after recrystallisation from methanol–acetone–chloroform, pure 2β-*ethyl*-1,1-*dehydrogibberellin* A_1 *diacid* (**5**) (210 mg), m.p. 228—230 °C (Found: C, 66.8; H, 7.7. $C_{21}H_{28}O_6$ requires C, 67.0; H, 7.5%); $\nu_{max.}$ (Nujol mull) 3 260, 1 770, 1 680, 1 125, and 900 cm^{-1}; δ_H([$^2H_5$]pyridine) 1.21 (t, *J* 7 Hz, CH_3), 2.00 (s, 18-H_3), 4.04 (br s, 5-H and 6-H), 4.58 (br s, 3-H), 5.16 (br s, 17-H), and 5.52 (br s, 17-H and 1-H); *m/z* 376 (M^+, 3%), 358 (33), 340 (24), 330 (16), 313 (40), 312 (27), and 267 (100).

ent-3α,13-*Dihydroxy*-2α-*n-propyl*-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic Acid* (**6**).—Gibberellin A_3 (**1**) (580 mg) was treated with lithium di-n-propylcuprate following the procedure described in the previous experiment. Recovery of the product as usual gave a gum which was flash chromatographed on a silica column (40-mm diam.), eluted with ethyl acetate–light petroleum–acetic acid (70:30:2) to give, after recrystallisation from methanol–chloroform 2β-*n-propyl*-1,10-*dehydrogibberellin* A_1 *diacid* (**6**) (190 mg), m.p. 238—241 °C (Found: C, 67.5; H, 7.5. $C_{22}H_{30}O_6$ requires C, 67.7; H, 7.7%); *m/z* 390 (M^+, 3%), 372 (27), 354 (21), 344 (13), 327 (38), 311 (9), and 281 (100).

Later fractions from flash chromatography contained more 2β-n-propyl product (**6**), admixed with a second product and other unidentified material (not propylated by g.l.c.-m.s.). This second component of the product mixture was shown to be present in amounts of *ca.* 15% by g.l.c. on a SP-2100 column at 225 °C. Combined g.l.c.-m.s. suggested it was 2α-n-propyl-1,10-dehydrogibberellin A_1 diacid: *m/z* (dimethyl ester bistrimethylsilyl ether) 562 (M^+, 30%), 547 (38), 502 (11), 472 (100), 440 (92), 412 (75), 374 (43), 353 (98), and 263 (32).

ent-2α-*n-Butyl*-3α,13-*dihydroxy*-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic Acid* (**7**).—Gibberellin A_3 (**28**) (1.0 g), in tetrahydrofuran (60 ml) was added to lithium di-n-butylcuprate (3 equiv.) as for the lithium diethylcuprate reaction. Recovery of the product in the usual way gave a yellow gum (1.2 g). Flash chromatography on a silica column (40-mm diam.), eluted with ethyl acetate–light petroleum–acetic acid (65:35:1), afforded the major product, 2β-*n-butyl*-1,10-*dehydrogibberellin* A_1 *diacid* (**7**) (290 mg), m.p. 215—218 °C (from methanol–water) (Found: C, 67.8; H, 8.8. $C_{23}H_{32}O_6$ requires C, 68.3; H, 8.0%); $\nu_{max.}$ (Nujol mull) 3 380, 1 750, 1 700, 1 045, and 722 cm^{-1}; δ_H([$^2H_6$]acetone) 0.88 (br m, CH_3), 1.29 (s, 18-H_3), 3.16 (br m, 5-H and 6-H), 3.98 (br s, 3-H), 4.90 (br s, 17-H), and 5.06 (br s, 17-H and 1-H); *m/z* 404 (M^+, 4%), 386 (47), 368 (27), 358 (20), 341 (45), and 295 (100). The methylation product was a gum; $\nu_{max.}$($CHCl_3$) 3 600, 3 450, 2 920, 2 880, 1 735, 1 665, 1 140, 1 010, and 910 cm^{-1}; δ_H($CDCl_3$) 0.93 (br m, CH_3), 1.30 (s, 18-H_3), 3.03 (m, 6-H), 3.17 (d, *J* 6.5 Hz, 5-H), 3.63 (s, CO_2Me), 3.70 (s, CO_2Me), 3.94 (br s, 3-H), 4.98 (br s, 17-H), 5.0 (br s, 1-H), and 5.11 (br s, 17-H).

Eluted in the later fractions was impure 2α-n-butyl-1,10-dehydrogibberellin A_1 diacid; δ_H([$^2H_6$]acetone) 0.93 (br m, CH_3), 1.32 (s, 18-H_3), 3.71 (d, *J* 7 Hz, 6-H), 4.83 (br s), 5.00 (br s), 5.16 (br s) (17-H_2 and 1-H); *m/z* (dimethyl ester, bistrimethylsilyl ether) 576 (M^+, 8%), 561 (15), 516 (5), 486 (46), 454 (65), 426 (79), 411 (15), 388 (16), 367 (100), 277 (74), 221 (28), 207 (9), and 157 (25). The crude 2α-n-butyl diacid in acetone was treated with ethereal diazomethane. Evaporation of the solvents gave a gum which was purified by preparative t.l.c. on silica gel using ethyl acetate–light petroleum (50:50). Recovery of the band at R_F 0.2—0.3 yielded the 2α-n-butyl dimethyl ester as a gum, (M^+ − 18) 414.240 ($C_{25}H_{34}O_5$ requires 414.240). δ_H($CDCl_3$) 0.98 (t, *J* 6.7 Hz, CH_3), 1.35 (s, 18-H_3), 3.04 (m, 5-H), 3.62 (d, *J* 8.1 Hz, 6-H), 3.62 (s), 3.71 (s), (2 × CO_2Me), 4.98 (br s), 5.12 (br s) (17-H_2), and 5.21 (br s, 1-H).

ent-1α-*Iodo*-2α-*methyl*-3α,10,13-*trihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 19,10-*Lactone* (**9**).—The diacid (**4**) (400 mg), in tetrahydrofuran (80 ml) and dichloromethane (80 ml), was stirred with saturated sodium hydrogen carbonate solution (100 ml) and iodine (480 mg) at 20 °C for 1 h. The aqueous layer was decanted and acidified to pH 3 with concentrated hydrochloric acid, followed by extraction with ethyl acetate (2 × 80 ml). The combined organic layers were washed with saturated sodium thiosulphate solution and then with water. The solvents were removed under reduced pressure to give a colourless solid which was purified by flash chromatography on a column (30-mm diam.) in silica, eluted with ethyl acetate–light petroleum–acetic acid (65:35:1), to give 1β-*iodo*-2β-*methylgibberellin* A_1 (**9**) (400 mg), m.p. 189—193 °C (from acetone–light petroleum) (Found: M^+, 488.068. $C_{20}H_{25}O_6I$ requires *M*, 488.070); δ_H([$^2H_6$]acetone–[$^2H_5$]pyridine) 1.23 (d, *J* 6.5 Hz, CH_3), 1.24 (s, 18-H_3), 2.74 (m, 6-H and 2-H), 3.69 (d, *J* 3.5 Hz, 3-H), 4.02 (d, *J* 10 Hz, 5-H), 4.64 (d, *J* 5 Hz, 1-H), 5.00 (br s, 17-H), and 5.27 (br s, 17-H); *m/z* 488 (M^+, 49%), 443 (48), 361 (20), 343 (100), 315 (76), 297 (31), and 135 (31).

ent-2α-*Ethyl*-3α,10,13-*trihydroxy*-1α-*iodo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 19,10-*Lactone* (**10**).—The 2β-ethyl diacid (**5**) (163 mg), in tetrahydrofuran (25 ml) and dichloromethane (20 ml), was vigorously stirred with saturated sodium hydrogen carbonate solution (45 ml) and iodine (220 mg) for 50 min. The product was recovered by the method described in the previous experiment. The product was flash chromatographed on a column (30-mm diam.) of silica, eluted with ethyl acetate–light petroleum–acetic acid (65:35:1), to give 1β-*iodo*-2β-*ethylgibberellin* A_1 (**10**) as a gum (190 mg) (Found: M^+, 502.085. $C_{21}H_{27}O_6I$ requires *M*, 502.085); δ_H([$^2H_6$]acetone) 0.93 (m, CH_3), 1.16 (s, 18-H_3), 2.61 (d, *J* 10 Hz, 6-H), 2.81 (m, 2-H), 3.75 (d, *J* 3.5 Hz, 3-H), 3.89 (d, *J* 10 Hz, 5-H), 4.59 (d, *J* 5 Hz, 1-H), 4.93 (br s, 17-H), and 5.22 (br s, 17-H); *m/z* 502 (M^+, 50%), 457 (57), 375 (16), 357 (97), 329 (100), 311 (52), 267 (22), 254 (75), and 128 (43). The *methyl ester*, prepared with diazomethane, was a gum (Found: M^+, 516.102. $C_{22}H_{29}O_6I$ requires M^+, 516.101).

ent-1α-*Iodo*-3α,10,13-*trihydroxy*-2α-*n-propyl*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 19,10-*Lactone* (**11**).—The 2β-n-propyl diacid (**6**) (150 mg), in tetrahydrofuran (50 ml) and dichloromethane (50 ml), was stirred with saturated sodium hydrogen carbonate solution (100 ml) and iodine (250 mg) for 1 h at 20 °C. The usual work-up afforded a gum which was purified by flash chromatography on a column (30-mm diam.) of silica, eluted with ethyl acetate–light petroleum–acetic acid (60:40:1), to give 1β-*iodo*-2β-*propylgibberellin* A_1 (**11**) (160 mg) as a gum (Found: M^+, 516.101. $C_{22}H_{29}O_6I$ requires *M*, 516.101); $\nu_{max.}$($CHCl_3$) 3 600, 2 950, 2 880, 1 780, 1 760, 1 715, 1 370, and 905 cm^{-1}; δ_H([$^2H_6$]acetone) 0.93 (m, CH_3), 1.16 (s, 18-H_3), 2.61 (d, *J* 10 Hz, 6-H), 2.81 (m, 2-H), 3.72 (br s, 3-H), 3.89 (d, *J* 10 Hz, 5-H), 4.58 (d *J* 5 Hz, 1-H), 4.93 (br s, 17-H), and 5.23 (br s, 17-H); *m/z* 516 (M^+, 36%), 471 (45), 387 (2), 371 (76), 343 (100), 325 (50), 297 (29), 245 (21), and 128 (23).

ent-2α-*n-Butyl*-3α,10,13-*trihydroxy*-1α-*iodo*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 19,20-*Lactone* (**12**).—The 2β-n-butyl

diacid (**7**) (170 mg), in tetrhahydrofuran (30 ml) and dichloromethane (20 ml), was vigorously stirred with saturated sodium hydrogen carbonate solution (45 ml) and iodine (200 mg) at 20 °C for 1 h. The product was recovered and was purified by flash chromatography as described in the previous experiment to give 1β-*iodo*-2β-*n*-*butylgibberellin* A_1 (**12**) as a gum (155 mg) (Found: M^+, 530.117. $C_{23}H_{31}O_6I$ requires *M*, 530.117); δ_H([$^2H_6$]acetone) 0.91 (m, CH_3), 1.16 (s, 18-H_3), 2.61 (d, *J* 10 Hz, 6-H), 2.80 (m, 2-H), 3.72 (br s, 3-H), 3.88 (d, *J* 10 Hz, 5-H), 4.59 (d, *J* 5 Hz, 1-H), 4.92 (br s, 17-H), and 5.23 (br s, 17-H); *m*/*z* 530 (M^+, 56%), 485 (46), 403 (20), 385 (85), 357 (100), 339 (44), 311 (25), 295 (25), 259 (20), and 128 (18).

The Purity of the Iodolactones (**9**)—(**12**).—The purity of the four iodolactones (**9**)—(**12**) was established by h.p.l.c. of their methyl esters on a 25 cm × 4.6 mm column of Spherisorb ODS (reverse-phase packing). The compounds were eluted with methanol–water (70:30) and detected by u.v. monitoring at 210 nm.

ent-3α,10,13-*Trihydroxy*-2α-*methyl*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 19,10-*Lactone* (**16**).—Powdered 2β-methyliodolactone (**9**) (100 mg), toluene (25 ml), and bis(tri-n-butyltin) oxide (100 mg) were refluxed under a Dean and Stark trap for 30 min. The flask was cooled and the solution treated with tri-n-butyltin hydride (0.5 ml), prepared by the usual method, for 1 h at 20 °C. The reaction mixture was poured into acetic acid (40 ml) and stirred for 20 min. The solvents were removed under reduced pressure. The resultant oil was taken up in ethyl acetate and was extracted with saturated sodium hydrogen carbonate solution (2 × 30 ml). The material from the combined basic layers was recovered and was purified by flash chromatography on a column (20-mm diam.) of silica eluted with ethyl acetate–light petroleum–acetic acid (70:30:1). A crystalline solid was obtained which was identical (^{1}H n.m.r. and m.p.) with 2β-methylgibberellin A_1 (**16**) prepared earlier from gibberellin A_1 methyl ester (**2**).

ent-2α-*Ethyl*-3α,10,13-*trihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 19,10-*Lactone* (**17**).—Powdered 1β-iodo-2β-ethylgibberellin A_1 (**10**) (80 mg), in toluene (25 ml), was refluxed with bis(tri-n-butyltin) oxide (100 mg) under a Dean and Stark trap for 20 min. The flask was cooled and the tri-n-butyltin ester solution was treated with tri-n-butyltin hydride (0.5 ml) for 1 h at 20 °C. The usual work-up, followed by flash chromatography on a column (20-mm diam.) of silica, eluted with ethyl acetate–light petroleum–acetic acid (60:40:1), afford 2β-*ethylgibberellin* A_1 (**17**) (36 mg) as a gum (Found: M^+, 376.188. $C_{21}H_{28}O_6$ requires *M*, 376.189); δ_H([$^2H_6$]acetone) 0.91 (t, *J* 6 Hz, CH_3), 1.14 (s, 18-H_3), 2.58 (d, *J* 10.5 Hz, 6-H), 3.19 (d, *J* 10.5 Hz, 5-H), 3.64 (br s, 3-H), 4.86 (br s, 17-H), and 5.20 (br s, 17-H); *m*/*z* 375 (18), 358 (47), 330 (13), 312 (13), 290 (17), 149 (38), and 43 (100). The *methyl ester*, prepared with diazomethane, was a gum (Found: M^+, 390.202. $C_{22}H_{30}O_6$ requires *M*, 390.204).

ent-3α,10,13-*Trihydroxy*-2α-*n*-*propyl*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 19,10-*Lactone* (**18**).—Nitrogen was bubbled through a solution of the tri-n-butyltin ester of 1β-iodo-2β-n-propylgibberellin A_1 (**11**) (80 mg), in a rubber-septum-sealed flask for 90 min. A solution of crude tri-n-butyltin hydride (0.5 ml) in toluene (5 ml) was deoxygenated in a similar manner. The reagent and substrate solutions were mixed under nitrogen. After 30 min the product was recovered and purified by flash chromatography as described in the previous experiment, to give 2β-*n*-*propylgibberelin* A_1 (**18**) as a gum (30 mg) (Found: M^+, 390.204. $C_{22}H_{30}O_6$ requires *M*, 390.204); δ_H([$^2H_6$]acetone) 0.88 (m, CH_3), 1.14 (s, 18-H_3), 2.57 (d, *J* 10 Hz, 6-H), 3.19 (d, *J* 10 Hz, 5-H), 3.59 (br s, 3-H), 4.87 (br s, 17-H), and 5.20 (br s, 17-H); *m*/*z* 390 (M^+, 60%), 372 (100), 344 (24), 326 (18), and 290 (33).

ent-2α-*n*-*Butyl*-3α,10,13-*trihydroxy*-20-*norgibberell*-16-*ene*-7,19-*dioic Acid* 19,10-*Lactone* (**19**).—1β-Iodo-2β-butylgibberellin A_1 (**12**) (80 mg) was treated in the same way as the 2β-propyliodolactone. The usual work-up and flash chromatography using ethyl acetate–light petroleum–acetic acid (58:42:1) afforded a gum (28 mg), 2β-*n*-*butylgibberellin* A_1 (**19**) (Found: M^+, 404.2205. $C_{23}H_{32}O_6$ requires *M*, 404.220); δ_H([$^2H_6$]acetone) 0.88 (m, CH_3), 1.13 (s, 18-H_3), 2.57 (d, *J* 10 Hz, 6-H), 3.19 (d, *J* 10 Hz, 5-H), 3.59 (br s, 3-H), 4.87 (br s, 17-H), and 5.20 (br s, 17-H); *m*/*z* 404 (M^+, 60%), 386 (100), 358 (27), and 290 (46).

Treatment of 1β-*Iodo*-2β-*n*-*propylgibberellin* A_1 (**11**) *with Tri-n-butyltin Hydride without Deoxygenation*.—2β-n-Propyliodolactone (**11**) was treated with tri-n-butyltin hydride by the method described for the reduction of 1β-iodo-2β-methylgibberellin A_1 (**9**). Recovery of the product yielded a gum which, by capillary g.l.c.-mass spectrometry of the methylated and trimethylsilylated sample, containing three compounds in a ratio of 16:1:2. In order of increasing retention times these were: (*a*) 2β-n-propylgibberellin A_1 (**18**); *m*/*z* (Me ester TMSi ether) 548 (M^+, 100%), 533 (7), 489 (7), 448 (21), 377 (20), 355 (11), 235 (19), 207 (29), 194 (12), and 171 (21); (*b*) 1β-hydroxy-2β-n-propylgibberellin A_1 (**22**); *m*/*z* (Me ester TMSi ether) 636 (M^+, 30%), 577 (8), 562 (15), 546 (14), 478 (20), 448 (22), 388 (18), 375 (20), 259 (28), 238 (14), 208 (27), 194 (30), 103 (20), and 73 (100); (*c*) 1α-hydroxy-2β-n-propylgibberellin A_1 (**22**); *m*/*z* (Me ester TMSi ether) 636 (M^+, 7%), 478 (6), 448 (100), 375 (12), 261 (10), 259 (7), 207 (7), 194 (5), 171 (7), 103 (26), and 73 (40).

Treatment of 1β-*Iodo*-2β-*n*-*butylgibberellin* A_1 (**12**) *with Tri-n-butyltin Hydride without Deoxygenation*.—The 2β-n-butyliodolactone (**12**) was treated with tri-n-butylstannane as described in the previous experiment. The product was recovered by the usual method to yield a gum. Inspection of this product by packed column g.l.c.-mass spectrometry after methylation and trimethylsilylation, revealed two peaks in a ratio of 3:1. The major peak (shorter retention time) was considered to contain both 2β-n-butylgibberellin A_1 (**19**) and 1β-hydroxy-2β-n-butylgibberellin A_1 (**23**), by comparison with the corresponding 2β-n-propyl analogues.

The longer retention time, minor peak was identified as 1α-hydroxy-2β-n-butylgibberellin A_1 (**2**); *m*/*z* (Me ester TMSi ether) 650 (M^+, 28%), 478 (14), 448 (100), 273 (15), 208 (12), 103 (40), and 73 (35).

ent-10,13-*Dihydroxy*-7-*methoxycarbonyl*-2α-*methyl*-3-*oxo*-20-*norgibberell*-16-*en*-19-*oic Acid* 19,10-*Lactone* (**26**).—Dichloromethane (1 ml; distilled from phosphorus pentaoxide) and dimethyl sulphoxide (90 μl; distilled under reduced pressure), in a flask fitted with a rubber septum, were cooled to −70 °C. The pressure was equalised by insertion of a nitrogen needle. Oxalyl chloride (60 μl; freshly distilled) was added. After 10 min at −78 °C 2β-methylgibberellin A_1 methyl ester (**15**) (100 mg) in dichloromethane (3 ml) was added dropwise and the reaction mixture was stirred at −70 °C for 1 h. Di-isopropylethylamine (400 μl) was added and the flask was allowed to warm to 20 °C. The solvents were evaporated to give a brown oil which was flash chromatographed on a column (20-mm diam.) of silica, eluted with ethyl acetate–light petroleum (60:40), to give 2β-*methyl*-3-*oxogibberellin* A_1 *methyl ester* (**26**) as a gum (60 mg) (Found: M^+, 374.173. $C_{21}H_{26}O_6$ requires *M*, 374.173); $\nu_{max.}$($CHCl_3$) 3 600, 2 950, 1 785, 1 630, 1 125, 1 000, and 910 cm^{-1}; δ_H($CDCl_3$) 1.16 (d, *J* 6 Hz, 2β-CH_3), 1.20 (s, 18-H_3), 2.66 (m, 2-H), 2.79 (d, *J* 10 Hz, 6-H), 3.01 (d, *J* 10 Hz, 5-H), 3.73 (s, CO_2Me), 4.98 (br s), 5.26 (br s) (17-H_2); *m*/*z* 374 (M^+, 52%), 342 (100), 315 (32), 163 (17), and 135 (19).

Later fractions contained more of the 3-ketone (**26**), but contaminated with starting material (**15**).

Reduction of ent-10,13-*Dihydroxy*-7-*methoxycarbonyl*-2α-*methyl*-3-*oxo*-20-*norgibberell*-16-*en*-19-*oic Acid* 19,10-*Lactone* (**26**).—The ketone (**26**) (40 mg), in methanol (2 ml), was stirred with sodium borohydride (6 mg) at 0 °C for 1 h. The usual work-up gave a gum which, by t.l.c. and g.l.c. (QF-1, 230 °C) contained two products in the ratio of *ca.* 1:1. The products were isolated by preparative t.l.c. using ethyl acetate–light petroleum (70:30). Recovery of the band at R_F 0.25 afforded ent-3β,10,13-*trihydroxy*-7-*methoxycarbonyl*-2α-*methyl*-20-*norgibberell*-16-*en*-19-*oic acid* 19,10-*lactone* (**27**) (Found: M^+, 376.187. $C_{21}H_{28}O_6$ requires M, 376.189); $\nu_{max.}(CHCl_3)$ 3 630, 2 880, 1 170, 1 725, 1 655, and 905 cm^{-1}; $\delta_H(CDCl_3)$ 1.16 (d, J 6 Hz, 2β-CH_3), 1.19 (s, 18-H_3), 2.54 (d, J 10.5 Hz, 5-H), 2.77 (d, J 10 Hz, 6-H), 3.24 (d, J 9.2 Hz, 3-H), 3.73 (s, CO_2Me), 4.95 (br s, 17-H), and 5.25 (br s, 17-H); m/z 376 (93), 358 (33), 344 (100), 316 (35), 304 (25), 298 (32), 253 (24), 135 (30), and 91 (27).

Recovery of the band of R_F 0.32 afforded a mixture of 2β-methylgibberellin A_1 and 2β-methyl-3-epigibberellin A_1 methyl esters (**15**) and (**27**) in a ratio of 2:1 respectively (by ^{1}H-n.m.r.).

Purity of the 2β-*Alkylgibberellin Derivatives* (**16**)—(**19**).—Each of the 2β-alkyl compounds, as their Me ester TMSi ether derivatives, gave one peak by capillary g.l.c. using a DANI 3800 HR fitted with a WCOT glass column of OV-1. The carrier gas was hydrogen at a pressure of 0.6 bar. The run was programmed from 180—280 °C at 3 °C min^{-1}.

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