S_N2 and S_N2' Alkylation of some Gibberellin Allylic Lactones by Lithium Methylcuprates

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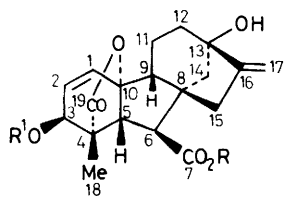
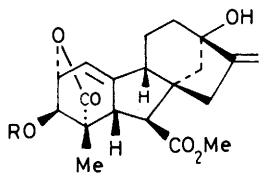
A detailed study is described of the reaction of methyl gibberellate (**2**), methylisogibberellate (**4**) and their corresponding tetrahydropyranyl ethers (**3**) and (**5**) with three cuprates, $(LiCuMe_2)_2$, $Li_2Cu_3Me_5$, and $(LiCu_2Me_3)_2$. The structures of the products, produced by displacement of the allylic lactone system by S_N2 or S_N2' *syn* and *anti* mechanisms, were deduced by extensive n.m.r. studies.

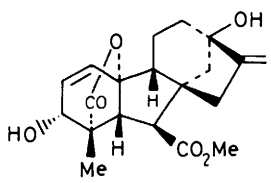
In a recent paper Taylor and MacMillan[1] described the preparation of 2β-alkylgibberellins *via* the *anti* S_N2' alkylation of the allylic lactone system in gibberellic acid (**1**) by lithium dialkylcuprates. This reaction was intriguing to us in connection with our project aimed at the synthesis of 10-methyl compounds.[2] We realised that it might be possible to influence this reaction such that the displacement occurred to yield C-10 methylated products. This paper describes a detailed study of the reaction of methyl gibberellate (**2**) and some of its derivatives with three different lithium methylcuprates. These investigations resulted in conditions where the reaction could be made to proceed by S_N2 or S_N2' (*syn* and *anti*) mechanisms to give intermediates useful for the synthesis of 2β-, 2α-, or 10β-methylgibberellins.



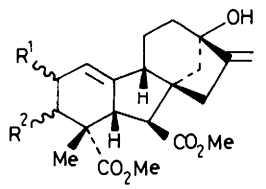
(**1**) R = H, R^1 = H
(**2**) R = Me, R^1 = H
(**3**) R = Me, R^1 = THP



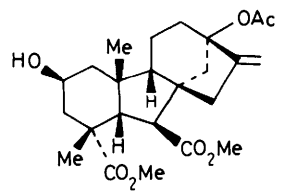
(**4**) R = H
(**5**) R = THP



(**6**)



(**7**) R^1 = β-Me, R^2 = β-OH
(**8**) R^1 = α-Me, R^2 = β-OH
(**9**) R^1 = β-Me, R^2 = α-OH



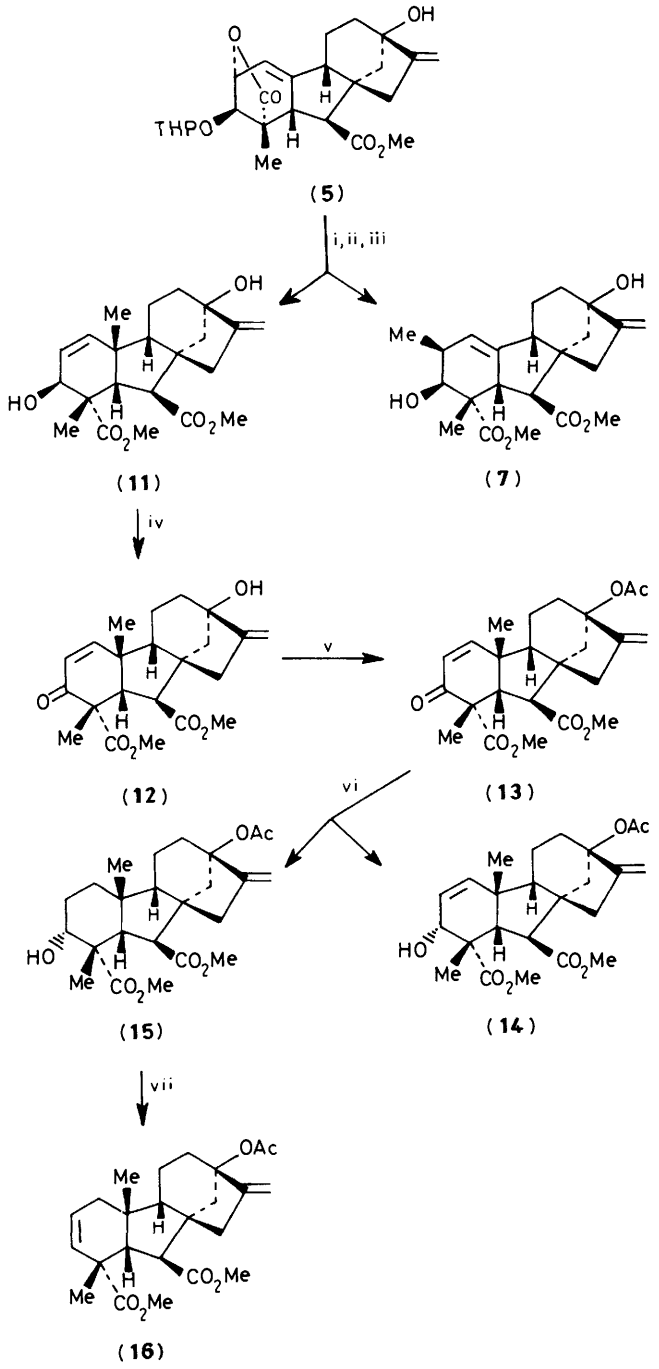
(**10**)

Results and Discussion

A careful re-examination of the product from the treatment of methyl gibberellate (**2**) with lithium dimethylcuprate in ether–tetrahydrofuran by t.l.c. and capillary g.l.c.–mass spectrometry revealed the presence of a second isomeric product (5%) along with the 2β-methyl compound (**7**) (95%) described by Taylor and MacMillan.[1] The new product was isolated, after treatment with diazomethane, by preparative layer chromatography and assigned the 10-Me structure (**11**) (see Scheme) on the following n.m.r. evidence. The ^1H n.m.r. in deuteriochloroform showed two singlet methyl signals at δ 1.24 and 1.30, two methyl ester singlets at δ 3.63 and 3.68, an allylic carbinol proton (3-H) at δ 4.51 and a two-proton olefinic signal at δ 5.61 (1-H and 2-H) which was resolved into two doublets (*J* 10 Hz) at δ 5.34 and 5.52 when the spectrum was run in deuteriochloroform plus deuteriobenzene. The ^{13}C n.m.r. (see Table 3) supported the assigned structure with C-1 and C-2 appearing as doublets in the off-resonance decoupled spectrum at 128.1 and 133.6 p.p.m. and the introduced C-10 methyl group as a quartet at 29.1 p.p.m. Confirmation of the 10β-stereochemistry in (**11**) was achieved spectroscopically and chemically (see Scheme) as follows. ^1H N.O.e. difference spectra were obtained for irradiation at each of the two methyl singlets at δ 1.24 and 1.30. This revealed an equal enhancement (11%) of the doublet at δ 2.78 (5-H) and no enhancement of the doublet at δ 2.30 (6-H) when either methyl group was irradiated. Thus both methyl groups are on the same side of the molecule as 5β-H. The higher field methyl singlet (δ 1.24) was assigned to the C-10β methyl group on account of an observed n.O.e. of 5.3% to the olefinic signal at δ 5.61 and a similar enhancement of the broad signal at δ 1.82 (assigned to 9-H). Very little n.O.e. was observed from the 4β-methyl group (δ 1.30) to 3α-H at δ 4.51.

Treatment of (**11**) with manganese dioxide in acetone gave an enone (**12**) which was acetylated with acetic anhydride and toluene-*p*-sulphonic acid to give (**13**) (see Scheme). Reduction of this enone acetate with L-Selectride gave the 3α-allylic alcohol (**14**) and the saturated alcohol (**15**) in 47 and 30% yields respectively. For the allylic alcohol (**14**) n.O.e. difference spectroscopy as above revealed enhancements of the doublet at δ 2.79 (5-H) and of 3β-H at δ 4.29 when the methyl group at δ 1.25 (4β-Me) was irradiated, whereas irradiation at the other methyl singlet at δ 1.21 (10-Me) gave n.O.e.'s to 5β-H, to 1-H at δ 5.79 and to the broad signal at δ 1.91 which is assigned to 9-H. The observation of a n.O.e. from the 4β-methyl group to 3(ax)-H in the 3α-alcohol (**14**) but not to 3(eq)-H in the 3β-alcohol (**11**) is interesting and may be useful in the determination of stereochemistry at C-3 in this type of compound. Further comparison of the ^1H spectra of the 3β-allylic alcohol (**11**) and 3α-allylic alcohol (**14**) shows that the chemical shift of 5-H is very similar in both compounds [δ 2.78 in (**11**) and δ 2.79 in (**14**)], but 6-H which occurs at δ 2.30 in the 3β-alcohol (**11**) is moved downfield to δ 3.17 in the 3α-alcohol (**14**). The reason for this is not clear but could be attributed to a change in the effect of the 19-carboxylate on 6-H.

N.O.e. difference spectroscopy on the 3α-saturated alcohol (**15**) again revealed the position of 5-H (δ 2.38) which was enhanced when both the 4-Me (δ 1.34) and the 10-Me (δ 1.16)



Scheme. *Reagents:* i, $Li_2Cu_3Me_5$; ii, IR120(H^+); iii CH_2N_2; iv, MnO_2; v, Ac_2O, TsOH; vi, $LiBu^s{}_3BH$; vii, $POCl_3$, py

were irradiated. The n.O.e. observed between the δ 1.34 Me group and 3β-H confirmed the assignment of the Me signals. Again 6-H occurred at low field (δ 3.42) in this 3α-alcohol. Further chemical evidence for the 10β-stereochemistry was obtained by treatement of the saturated alcohol (**15**) with phosphorus oxychloride in pyridine which gave a single olefinic product (**16**) which was identical by capillary g.l.c.–mass spectrometry and ^1H n.m.r. to the minor component of the mixture of olefins obtained from dehydration of the 2β-alcohol (**10**) previously described.[2]

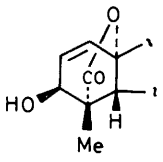
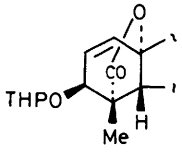
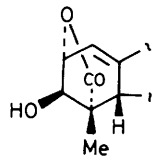
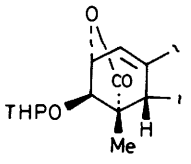
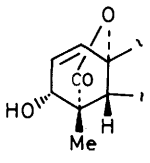
The effect of changing the bulk and reactivity of the methylcuprate on the regiochemistry of this substitution reaction was next examined. Methyl gibberellate (**2**) was treated with $Li_2Cu_3Me_5$ and $(LiCu_2Me_3)_2$, prepared as described by Ashby *et al.*[3] The more reactive $Li_2Cu_3Me_5$ gave a similar result to $(LiCuMe_2)_2$ and formed the 2β-methyl compound (**7**) (80%) with some 10β-methyl compound (**11**) (14%) and a little of the isolactone (**4**) (5%) (see Table 1). From the reaction of (**2**) with the less reactive $(LiCu_2Me_3)_2$ two new isomers were detected by capillary g.l.c.–mass spectrometry in 14 and 18% yield, in addition to the 2β-methyl compound (**7**) (47%) and the isolactone (**4**) (21%). The new isomers were isolated and identified as the 2α-methyl 3β-alcohol (**8**) and the 2β-methyl 3α-alcohol (**9**) on the following evidence. The 2β-methyl 3α-alcohol (**9**) on the following evidence. The 2β-methyl 3α-alcohol (**9**) was the sole product when methyl 3-*epi*-gibberellate (**6**) was treated with $(LiCuMe_2)_2$, $Li_2Cu_3Me_5$, or $(LiCu_2Me_3)_2$ and its ^1H n.m.r. (see Table 2) confirmed the *trans*-di-equatorial arrangement of the 2-Me and 3-OH groups with 3-H resonating as a doublet with $J_{ax,ax}$ 9 Hz. The 2α-methyl 3β-alcohol (**8**) also showed a large (10 Hz) axial-axial coupling on 3α-H. This would indicate that the 1,3-interaction between the 2α-methyl and 19-carboxylate groups has caused a change to a boat conformation in ring A. The upfield shift of 6-H from *ca.* δ 3.0 in (**7**) and (**11**) to δ 2.18 in (**8**) may also be explained by a change in the relative position of the 19-carboxylate. The ^{13}C n.m.r. spectra (Table 3) of the three isomeric 2-methyl-3-hydroxy-1(10)enes (**7**), (**8**), and (**9**), although very different from the 10-methyl isomer (**11**), were very similar to each other. The only significant differences observed were for the 3α-alcohol (**9**) relative to the 3β-alcohols (**7**) and (**8**) and there are downfield shifts of C-3 (*ca.* 7 p.p.m.) and C-2 (*ca.* 4 p.p.m.).

The formation of (**9**) when methyl gibberellate (**2**) was the substrate indicates that the alcohol is epimerising at C-3 before reaction with $(LiCu_2Me_3)_2$. This retro-aldol epimerisation is known[4] to occur in basic solution. Another base-catalysed rearrangement of methyl gibberellate is the 1,3-lactone shift to give the isolactone (**4**).[5] The occurrence of this rearrangement before reaction with the cuprate is probably the best explanation for the formation of the 10-methyl compound (**11**) from methyl gibberellate (**2**). In reactions that were incomplete the starting material was always recovered as the isolactone (**4**). This may indicate that the isolactone (**4**) was being formed in the reaction. However the occurrence of this isomerisation during the aqueous work-up is also possible.

To clarify the above results the reaction of the isolactone (**4**) with the three cuprates was examined. Similar results (see Table 1) to those observed with methyl gibberellate were obtained when $(LiCuMe_2)_2$ and $Li_2Cu_3Me_5$ were the reactants. Once again, the low reactivity of $(LiCu_2Me_3)_2$ was evident and mostly starting material was recovered from this reaction. As expected, the 2β-methyl 3α-alcohol (**9**) was not observed when the isolactone (**4**) was substrate as the 3-epimerisation does not occur[6] in 2-oxygenated compounds. Thus it appears that the reaction of the isolactone (**4**) with methylcuprates proceeds mainly by an S_N2 pathway. With methyl gibberellate (**2**) the major pathway is apparently S_N2' *anti*. However, since there is a possibility of base-catalysed conversion of methyl gibberellate (**2**) into the isolactone (**4**) before reaction with cuprate, no definitive conclusions about the reaction pathway in (**2**) can be reached.

For this reason the tetrahydropyranyl ethers (**3**) and (**5**) were prepared and their alkylation was examined. In these compounds epimerisation at C-3 or allylic lactone rearrangement is not possible as both require formation of the 3-alkoxide.[4,5] Reaction of the methyl 3-tetrahydropyranyloxygibberellate (**3**) with lithium dimethylcuprate, followed by acid hydrolysis of the tetrahydropyranyl ether function with the ion exchange resin IR120 and methylation with diazomethane gave equal amounts of the 2β-and 2α-methyl 3β-alcohols (**7**) and (**8**), the products of S_N2' *anti* and S_N2' *syn* addition (see Table 1). Similar reaction

Table 1. Reactions of $MeGA_3$ and derivatives with $Li_xCu_yMe_z$

Substrate	Cuprate[a]	Products (%, g.l.c.)[b] (4)	(7)	(8)	(9)	(11)
 (2)	A	0	95	0	0	5
	B	5	80	0	0	14
	C	21	47	14	18	0
 (3)	A	0	52	48	0	0
	B	0	63	37	0	0
	C	0	75	25	0	0
 (4)	A	0	93	0	0	7
	B	21	63	0	0	16
	C	67	28	0	0	4
 (5)	A	0	98	0	0	2
	B	0	56	0	0	44
	C	37	8	0	0	55
 (6)	A	0	0	0	100	0
	B	0	0	0	100	0
	C	0	0	0	100	0

[a] A = $(LiCuMe_2)_2$, B = $Li_2Cu_3Me_5$, C = $(LiCu_2Me_3)_2$. [b] By capillary g.l.c.–mass spectrometry of $SiMe_3$ derivatives, relative R_t—(4) = 1.00, (11) = 0.94, (7) = 1.02, (8) = 0.97, (9) = 1.08.

with $Li_2Cu_3Me_5$ and $(LiCu_2Me_3)_2$ gave the same products, but with an increase in the amount of S_N2' *anti* attack (63 and 75% respectively) *versus* S_N2' *syn* attack. $(LiCuMe_2)_2$ in ether and $(LiCu_2Me_3)_2$ in tetrahydrofuran are reported to be dimeric whereas $Li_2Cu_3Me_5$ in ether is monomeric.[7] Empirically, as the size of the cuprate increases from $(LiCuMe_2)_2$ through $Li_2Cu_3Me_5$ to $(LiCu_2Me_3)_2$ the amount of S_N2' *syn* attack on (3) decreases. It has been recently suggested[8] that S_N2' *syn* attack of cuprate reagents only occurs when severe steric constraints prevent S_N2' *anti* displacement. If this were the case then the amount of S_N2' *syn* attack on (3) should increase as the size of the cuprate species increases. However, although the square planar structure of $(LiCuMe_2)_2$ now seems certain,[9] no structural information on $Li_2Cu_3Me_5$ and $(LiCu_2Me_3)_2$ is available and speculation about the relative sizes of the three cuprates may be inappropriate. In reaction of the isolactone THP-ether (5) with the three cuprates only S_N2 and S_N2' *anti* addition were observed (Table 1). In this case, increasing steric interaction between the 3β-tetrahydropyranyloxy substituent and the cuprate can explain the observed change from 98% displacement at C-2 with $(LiCuMe_2)_2$ through *ca.* 1:1 C(2):C(10) attack with $Li_2Cu_3Me_5$ to *ca.* 1:7 C(2):C(10) attack with $(LiCu_2Me_3)_2$.

Several conclusions concerning the mode of attack of methyl-

Table 2. ^{1}H N.m.r. ($CDCl_3$) of the 2-methyl-1(10)-enes.

Compd.	2-Me	18-Me	5-H	6-H	3-H	1-H	17-H_2	
(7)	1.10 (d, *J* 7)	1.30	3.02 (br, s)	3.15 (d, *J* 6)	3.86 (br, s)	4.98	4.98	5.11
(8)	1.18 (d, *J* 7)	1.35	3.05 (dt, *J* 8, 2)	2.18 (d, *J* 8)	3.50 (d, *J* 10)	5.10	4.97	5.10
(9)	1.16 (d, *J* 7)	1.35	2.95 (br, s)	3.06 (d, *J* 5)	3.18 (d, *J* 9)	5.18	4.92	5.09

Table 3. ^{13}C N.m.r. of the alkylation products.

Carbon no. (multiplicity)	(7)	(8)	(9)	(11)
1(d)	115.67	119.64	119.91	128.09
2(d)	33.34	32.27	37.67	133.55
3(d)	75.58	75.09	82.26	67.71
4(s)	50.04[a]	49.37[a]	50.13[a]	50.30[a]
5(d)	49.26[b]	50.39[b]	49.59[b]	54.26[b]
6(d)	50.49[b]	51.52[b]	51.54[b]	52.96[b]
7(s)	174.55	174.92	174.51	175.66
8(s)	49.45[a]	48.49[a]	49.75[a]	49.32[a]
9(d)	45.81[b]	45.71[b]	45.74[b]	55.11[b]
10(s)	141.60	139.55	138.92	45.88
11(t)	18.65	19.00	18.60	18.98
12(t)	37.63[c]	37.62[c]	37.40[c]	38.21[c]
13(s)	79.28	79.00	79.17	78.90
14(t)	39.12[c]	39.28[c]	38.64[c]	40.94[c]
15(t)	45.94	49.10	48.78	47.11
16(s)	154.67	154.30	154.09	154.02
17(t)	106.12	106.69	106.20	105.99
18(q)	18.66[d]	19.21	19.41[d]	18.98
19(s)	176.50	177.31	175.97	177.87
2 Me or 10 Me(q)	22.03[d]	19.21[d]	22.93[d]	29.11
OMe(q)	51.66	51.52	51.70	51.47
OMe(q)	51.47	51.94	51.38	51.66

[a,b,c,d] Assignments may be interchanged.

cuprates on this system can be drawn from the data obtained. They are (1) attack at the tertiary position, C-10 is only possible by an S_N2' pathway; (2) attack at the secondary carbon, C-2, whether by S_N2 or S_N2' mechanisms, is the most favoured reaction; (3) S_N2' *syn* attack at C-2 can be forced by steric crowding, and is a more favourable reaction than S_N2 displacement at the tertiary carbon. Thus, by selection of suitable substrates and cuprates, compounds bearing 2β-, 2α-, or 10β-methyl groups can be produced in synthetically useful yields. This was confirmed by a large-scale reaction of the isolactone tetrahydropyranyl ether (**5**) with $Li_2Cu_3Me_5$ which gave the 10β-methyl compound (**11**) and the 2β-methyl compound (**7**) in 41 and 28% isolated yields respectively.

Experimental

For general details see ref. 10.

Methyl 3-*epi*-gibberellin A_3) (**6**) was prepared as described by Taylor in Kirkwood *et al.*[4] and purified by flash chromatography. Methyl 3-tetrahydropyranyloxygibberellate (**3**) was prepared as a diastereoisomeric mixture from methyl gibberellate and dihydropyran (1.2 equiv.) in dichloromethane with toluene-*p*-sulphonic acid catalysis in the normal way.

Methyl Isogibberallate (*Methylisogibberellin* A_3) (**4**) *and Methyl* 3-*Tetrahydropyranyloxyisogibberellate* (3-*Tetrahydropyranyloxymethylisogibberellin* A_3) (**5**).—Gibberellic acid (gibberellin A_3) (**1**) (2 g) was stirred on 0.05M aqueous potassium hydroxide (230 ml) for 3 h at room temperature. The solution was then acidified to pH 3 with hydrochloric acid and extracted with ethyl acetate. The extract was concentrated under reduced pressure and then treated with an excess of ethereal diazomethane. Evaporation gave methyl isogibberellate (**4**) (1.9 g) which was shown by n.m.r. spectroscopy to be pure: δ(C_5D_5N) 1.24 (3 H, s, 18-Me), 2.72 (1 H, d, *J* 7, 6-H), 3.53 (3 H, s, CO_2Me), 3.66 (1 H, dd, *J* 2, 5-H), 4.38 (1 H, d, *J* 5, 3-H), 4.76 (1 H, t, *J* 5, 2-H), 4.90 and 5.28 (2 H, 2 × br, s, 17-H_2), and 5.77 (1 H, m, 1-H).

Methyl isogibberellate (**4**) (1.9 g) in dichloromethane (100 ml) was treated with dihydropyran (575 μl, 1.2 equiv.) and toluene-*p*-sulphonic acid (5 mg) for 2 h at room temperature. The solution was then washed with saturated aqueous sodium hydrogen carbonate and water. The oil obtained by evaporation of the dichloromethane was fractionated by stepped, flash chromatography. After elution of the least polar material (300 mg) with 30% ethyl acetate in light petroleum, the required 3-tetrahydropyranyl ether (**5**) (1.27 g) was eluted with 40% ethyl acetate and consisted of a diastereoisometic mixture (*ca.* 2:1) as shown by its n.m.r. spectrum: δ($CDCl_3$) 1.19 and 1.16 (3 H, 2 s, 18-Me), 3.68 (3 H, s, CO_2Me), 3.98 and 4.20 (1 H, d, *J* 5, 3-H), 4.72 (2 H, m, 2-H and 2'-H), 4.90 and 5.04 (2 H, 2 × br s, 17-H_2), and 5.68 (1 H, m, 1-H); *m/z* 444 (M^+, 1%), 412 (2), 360 (3), 342 (3), 328 (3), 314 (2), 297 (25), and 85 (100). Further elution with 50% ethyl acetate gave starting material (500 mg).

Exploratory Lithium Alkyl Cuprate Reactions.—Substrates [*ca.* 100 mg of (**2**), (**3**), **4**), (**5**), or (**6**)] in tetrahydrofuran (1 ml) were added at room temperature to solutions of the alkyl cuprates prepared as follows: (a) $(LiCuMe_2)_2$ from CuI (3 equiv.), MeLi (6 equiv.) in ether (7 ml); (b) $Li_2Cu_3Me_5$ from CuI (3 equiv.), MeLi (5 equiv.) in ether (7 ml); and (c) $(LiCu_2Me_3)_2$ from CuI (3 equiv.), MeLi (4.5 equiv.) in tetrahydrofuran (7 ml).

After 1 h the reactions were added to ice–water and acidified with dilute hydrochloric acid. The products were recovered in ethyl acetate and then methylated with diazomethane. For reactions of the tetrahydropyranyl ethers (**3**) and (**5**) some hydrolysis of the tetrahydropyranyl ether occurred on work-up. In these cases the crude product was first treated with Amberlite IR-120(H^+) resin in methanol at 5 °C overnight to complete the hydrolysis before filtration and treatment with diazomethane.

The products were then analysed by g.l.c. and g.l.c.-mass spectrometry as their Me_3Si ethers on a 25 m × 0.2 mm i.d. WCOT OV-1 column with H_2 carrier at 0.6 bar at 180 °C for 1 min then 3 °C per min to 280 °C. The results are shown in Table 1. Where necessary for identification the products were separated by p.t.l.c. on silica gel using ethyl acetate–light petroleum mixtures and characterised by ^{1}H and ^{13}C n.m.r. The products were as follows.

ent-3α-*Hydroxy*-10α-*gibberella*-1,16-*diene*-7,19-*dioic Acid* 7,19-*Dimethyl Ester* (**11**): δ_H($CDCl_3$) 1.24 and 1.30 (6 H, 2 s, 20-Me and 18-Me), 2.30 (1 H, d, *J* 6, 6-H), 2.78 (1 H, d, *J* 6, 5-H), 3.63 and 3.68 (6 H, 2 s, 2 × CO_2Me), 4.51 (1 H, br, s, $w_{\frac{1}{2}}$ 4, 3-H), 4.93 and 5.08 (2 H, 2 × br, s, 17-H_2), and 5.61 (2 H, s, 1-H and 2-H); δ_H($CDCl_3$ + C_6D_6) 5.34 and 5.52 (2 H, 2d, *J* 10, 1-H and 2-H); δ_C—see Table 3; *m/z* 390 (M^+, 29%), 372 (9), 358 (80), 340 (33), 330 (100), 312 (18), 298 (20), 296 (25), 253 (21), and 237 (12).

ent-3α-*Hydroxy*-2α-*methyl*-20-*norgibberella*-1(10), 16-*diene*-7,19-*dioic Acid* 7,19-*Dimethyl Ester* (**7**): $\delta_H(CDCl_3)$ 1.10 (3 H, d, *J* 7, 2-Me), 1.30 (3 H, s, 18-Me), 3.02 (1 H, br, 5-H), 3.15 (1 H, d, *J* 6 Hz, 6-H), 3.64 and 3.70 (6 H, 2 s, 2 × OMe), 3.86 (1 H, br, s, 3-H), 4.98 (2 H, br, s, 1-H and 17-H), and 5.11 (1 H, br, s, 17-H); δ_C—see Table 3; *m/z* 390 (M^+, 2%), 372 (23), 358 (6), 340 (36), 330 (10), 313 (16), 312 (16), 297 (13), 253 (100), and 235 (10).

ent-3α-*Hydroxy*-2β-*methyl*-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic Acid* 7,19-*Dimethyl Ester* (**8**): $\delta_H(CDCl_3)$ 1.18 (3 H, d, *J* 7 Hz, 2-Me), 1.35 (3 H, s, 18-Me), 2.18 (1 H, d, *J* 8 Hz, 6-H), 3.05 (1 H, dt, *J* 8, 2 Hz, 5-H), 3.50 (1 H, d, *J* 10 Hz, 3-H), 3.62 and 3.71 (6 H, 2 s, 2 × OMe), 4.97 (1 H, br, s, 17-H), 5.1 (2 H, br, s, 1-H and 17-H); δ_C—see Table 3; *m/z* 390 (M^+, 3%), 372 (26), 358 (10), 340 (51), 330 (64), 312 (58), 297 (18), 253 (100), 237 (11), and 235 (14).

ent-3α-*Hydroxy*-2α*methyl*-20-*norgibberella*-1(10),16-*diene*-7,19-*dioic Acid* 7,19-*Dimethyl Ester* (**9**): $\delta_H(CDCl_3)$ 1.16 (3 H, d, *J* 7, 2-Me), 1.35 (3 H, s, 18-Me), 2.95 (1 H, br, s, 5-H), 3.06 (1 H, d, *J* 5 Hz, 6-H), 3.18 (1 H, d, *J* 9 Hz, 3-H), 3.67 and 3.72 (6 H, 2 s, 2 × OMe), 4.92 and 5.09 (2 H, 2 s, 17-H_2), and 5.18 (1 H, q, *J* 2 Hz, 1-H); δ_C—see Table 3; *m/z* 390 (M^+, absent), 372 (27%), 357 (13), 340 (30), 313 (14), 312 (16), 297 (44), 253 (100), and 235 (10).

Large-scale Reaction of $Li_2Cu_3Me_5$ *with Methyl* 3-*Tetrahydropyranyloxyisogibberellate* (**5**).—A solution of $Li_2Cu_3Me_5$ was prepared by the addition of methyl-lithium 1.4M soln.; 10.0 ml, 15.44 mmol) to a suspension of cuprous iodide (1.74 g, 9.15 mmol) in dry ether (50 ml). To this stirred solution at room temperature the tetrahydropyranyl ether (**5**) (1.27 g, 2.86 mmol) in dry tetrahydrofuran (10 ml) was added dropwise during 10 min. After a further 1 h at room temperature the reaction mixture was added slowly to ice–water with stirring. After acidification to pH 3 with hydrochloric acid the product was recovered in ethyl acetate. Copper salts were removed from the ethyl acetate by the addition of anhydrous sodium sulphate and filtration through a glass sinter.

Hydrolysis of the tetrahydropyranyl ether was completed by treatment of product in methanol (50 ml) with acidic ion exchange resin (Amberlite IR-120(H^+), 10 g) at 5 °C overnight. The solution was then filtered and evaporated. The resulting gum in ethyl acetate was washed with water and then eluted through a short column of silica gel with ethyl acetate. The eluant was then treated with an excess of ethereal diazomethane and then evaporated. Stepped, flash chromatography on a column (16 × 3 cm) eluted with the following percentages of ethyl acetate in light petroleum, 50% (300 ml), 60% (300 ml), and 70% (300 ml) in 25-ml fractions, gave in fractions 9—15 the 2β-methyl-1(10)-ene (**7**) (324 mg) and in fractions 17—31 the 10β-methyl-1(2)-ene (**11**) (469 mg). See earlier for characterising data.

ent-13-*Hydroxy*-3-*oxo*-10α-*gibberella*-1,16-*diene*-7,19-*dioic acid* 7,19-*Dimethyl Ester* (**12**).—The 10β-methyl-allylic alcohol (**11**) (345 mg), dissolved in acetone (30 ml) in a centrifuge tube, was treated with active manganese dioxide (2.3 g) with stirring for 3 h. The mixture was then centrifuged at 5 000 r.p.m. for 5 min and the supernatant liquid collected. The residual oxidant suspended in a further 30 ml of acetone was immersed in a sonic bath for 10 min before centrifugation and collection of the supernatant liquid as before. The combined acetone solutions were evaporated to give the *enone* (**12**) (311 mg) as a gum (Found: M^+, 388.1884, $C_{22}H_{28}O_6$ requires M^+, 388.1886); $\delta(CDCl_3)$ 1.4 and 1.62 (6 H, 2 s, 4-Me and 10-Me), 2.89 (2 H, br s, 5-H and 6-H), 3.65 and 3.68 (6 H, 2 s, 2 × OMe), 4.95 and 5.12 (2 H, 2 × br, s, 17-H_2), 5.98 (1 H, d, *J* 10 Hz, 2-H), and 6.72 (1 H, d, *J* 10 Hz, 1-H); *m/z* 388 (M^+, 27), 356 (100), 328 (25), 313 (17), 297 (20), 269 (25), 181 (91), 122 (22), and 121 (21).

ent-13-*Acetoxy*-3-*oxo*-10α-*gibberella*-1,16-*diene*-7,19-*dioic Acid* 7,19-*Dimethyl Ester* (**13**).—The above 13-hydroxy enone (**12**) (356 mg) was treated with acetic anhydride (3 ml) and toluene-*p*-sulphonic acid (5 mg) at room temperature for 1.5 h. The solution was then diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate and then water. Evaporation of the ethyl acetate gave the acetate (**13**) (350 mg) as a gum (Found: M^+, 430.2002. $C_{24}H_{30}O_7$ requires M^+, 430.1991); $\delta(CDCl_3)$ 1.39 and 1.61 (6 H, 2 s, 4-Me and 10-Me), 2.00 (3 H, s, OCOMe), 2.86 and 2.95 (2 H, 2 d, *J* 8 Hz, 5-H and 6-H), 3.65 and 3.68 (6 H, 2 s, 2 × OMe), 5.00 (2 H, br, s, 17-H_2), 6.05 (1 H, d, *J* 10 Hz, 2-H), and 6.75 (1 H, d, *J* 10 Hz, 1-H); *m/z* 430 (M^+, 32%), 398 (96), 370 (16), 338 (100), 311 (31), 310 (26), 251 (26), 181 (100), 121 (26), and 43 (53).

L-Selectride Reduction of the Enone Acetate (**13**).—The enone (**13**) (325 mg) in dry tetrahydrofuran (20 ml) with ethanol (90 μl) was cooled to −40 °C and treated with L-selectride (1M soln. in THF; 2 ml). The solution was then allowed to warm to room temperature during 1.5 h and then diluted with water. After acidification to pH 3 with dilute hydrochloric acid the product was recovered in ethyl acetate. The resultant gum was fractionated by stepped, flash chromatography on a 16 × 3 cm column using the following percentages of ethyl acetate in light petroleum, 15% (200 ml), 20% (250 ml), 30% (250 ml), and 40% (250 ml) in 20-ml fractions. Fractions 25—30 contained the saturated alcohol (**15**) (97 mg) as a gum (Found: M^+ −32, 402.2036. $C_{23}H_{30}O_6$ requires M^+ –CH_3OH, 402.2042); $\delta(CDCl_3)$ 1.16 (3 H, s, 10-Me), 1.34 (3 H, s, 4-Me), 2.00 (3 H, s, OCOMe), 2.38 (1 H, d, *J* 10, 5-H), 3.42 (1 H, d, *J* 10, 6-H), 3.62 and 3.65 (6 H, 2 s, 2 × OMe), 3.96 (1 H, br, s, 3-H), and 4.92 and 5.02 (2 H, 2 × br, s, 17-H_2); *m/z* 434 (M^+, 1.5%), 416 (15), 402 (100), 400 (22), 342 (63), 314 (27), and 282 (42).

Fractions 32—41 contained the unsaturated alcohol (**14**) (153 mg), isolated as a gum (Found: M^+, 432.2151. $C_{24}H_{32}O_7$ requires M^+, 432.2148); $\delta(CDCl_3)$ 1.21 (3 H, s, 10-Me), 1.25 (3 H, s, 4-Me), 1.97 (3 H, s, OCOMe), 2.79 (1 H, d, *J* 6 Hz, 5-H), 3.17 (1 H, d, *J* 6 Hz, 6-H), 3.66 and 3.68 (6 H, 2 s, 2 × OMe), 4.29 (1 H, dd, *J* 5 and 1.5 Hz, 3-H), 4.89 and 4.9 (2 H, 2 × br, s, 17-H_2), 5.79 (1 H, dd, *J* 10, 1.5 Hz, 1-H), and 5.85 (1 H, dd, *J* 10, 5 Hz, 2-H); *m/z* 432 (M^+, 19%), 414 (29), 382 (54), 372 (39), 354 (68), 340 (100), 339 (75), 322 (50), 312 (38), 295 (69), 279 (22), 253 (29), 235 (42), 165 (41), and 123 (54).

Treatment of the Alcohol (**15**) *with Phosphorus Oxychloride*.—The alcohol (**15**) (20 mg) in dry pyridine (2 ml) with phosphorus oxychloride (60 μl) was refluxed for 3 h. After normal work-up, capillary g.l.c.–mass spectrometry and t.l.c. showed the presence of a single product identified as the Δ^2-olefin (**16**) by n.m.r. and mass spectral comparison with a mixture of the Δ^1- and Δ^2-olefins obtained from the 2β-alcohol (**10**); $\delta_H(CDCl_3)$ 1.14 (3 H, s, 10-Me), 1.42 (3 H, s, 4-Me), 2.02 (3 H, s, OCOMe), 2.36 (1 H, d, *J* 11 Hz, 5-H), 2.89 (1 H, d, *J* 11 Hz, 6-H), 3.56 and 3.64 (6 H, 2 s, 2 × OMe), 4.92 and 5.10 (2 H, 2 × br, s, 17-H_2), 5.67 (1 H, d, *J* 10 Hz, 3-H), and 5.76 (1 H, dq, *J* 10, 4, 2 Hz, 2-H); *m/z* 416 (M^+, absent), 401 (1), 384 (3), 294 (2), 356 (72), 341 (8), 324 (16), 314 (60), 296 (100), 281 (20), 264 (5), 255 (20), 237 (33), and 230 (15).

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References

1 D. H. Taylor and J. MacMillan, *J. Chem. Soc., Perkin Trans. 1*, 1985, 837.
2 M. H. Beale, *J. Chem. Soc., Perkin Trans. 1*, preceding paper.
3 E. C. Ashby, J. J. Lin, and J. J. Watkins, *J. Org. Chem.*, 1977, **42**, 1099.

4 P. S. Kirkwood, J. MacMillan, and M. Hutchinson, *J. Chem. Soc., Perkin Trans. 1*, 1982, 707.
5 P. S. Kirkwood, J. MacMillan, and M. L. Sinnott, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2117.
6 J. MacMillan and R. J. Pryce, *J. Chem. Soc. C*, 1967, 740.
7 E. C. Ashby and J. J. Watkins, *J. Am. Chem. Soc.*, 1977, **99**, 5312.
8 E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, 1984, **25**, 3063.
9 K. R. Stewart, J. R. Lever, and M. H. Whangbo, *J. Org. Chem.*, 1982, **47**, 1472.
10 M. H. Beale, J. MacMillan, C. R. Spray, D. A. Taylor, and B. O. Phinney, *J. Chem. Soc., Perkin Trans. 1*, 1984, 541.

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