Neighbouring Group Participation on the Bromination of Methyl Gibberellate: *X*-Ray Molecular Structure of Methyl 3,13-Di-*O*-acetylgibberellate 16β,17-Dibromide and *ent*-3α, 13-Diacetoxy-17-bromo-10β,16β-dihydroxy-20-norgibberell-1-ene-7,19-dioic Acid 19,10-Lactone 7-Methyl Ester

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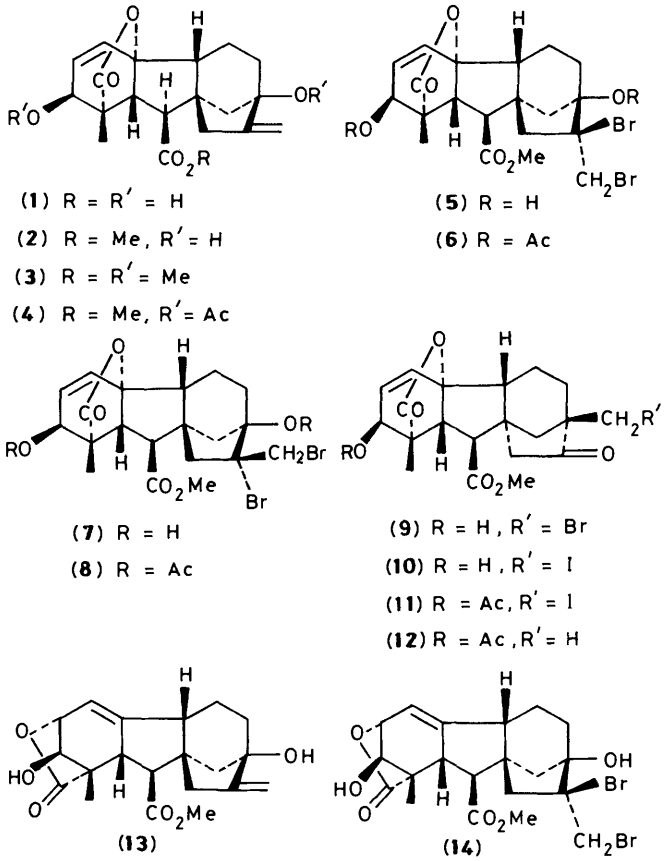
Bromination of methyl gibberellate at C-16 with trimethyl(phenyl)ammonium perbromide has been shown to be non-stereospecific. However only the (16*R*)-epimer readily rearranged to the 8,13-epigibberellin. The stereochemistry of the (16*S*)-epimer was established by *X*-ray analysis. Bromination of methyl diacetylgibberellate afforded a (16*R*)-hydroxy-17-bromide. Bromination under strictly anhydrous conditions led to the isomerization of ring A to the Δ[1]-19,2-lactones. Reaction with bromine in the presence of sodium hydrogen carbonate also gave a 1β,2α-dibromo adduct.

The acid-catalysed Wagner–Meerwein rearrangement of rings C and D of the plant hormone gibberellic acid to form the 8,13-epigibberellins is a characteristic rearrangement reaction of those gibberellins containing a 13-hydroxy group. In the specific case of gibberellic acid (**1**), the reaction with aqueous mineral acid is also preceded by the aromatization of ring A and by epimerization at C-9.[1] However, the bromination of gibberellic acid with bromine in tetrahydrofuran (THF)[2] or with pyridinium perbromide[3] leads to the rearrangement of rings C and D whilst retaining the structure of ring A. We have re-examined the bromination of methyl gibberellate (**2**) and some derivatives under carefully controlled conditions. The results shed some further light on the rearrangement reaction and the participation of the 13-oxygen function.

The addition of bromine to methyl gibberellate (**2**) was carried out using trimethyl(phenyl)ammonium perbromide[4] (TMPAP), initially in moist 1,4-dioxane, with t.l.c. control. Provided that the reaction mixture was worked up rapidly without the intervention of a base, this gave a separable mixture of a stable dibromo compound (**5**) (25% yield) and a second, less stable, isomer (**7**) (65% yield). The ^{1}H n.m.r. spectrum of the former showed that it retained the ring A structure of methyl gibberellate (δ 6.41, 1-H; 5.90, $J_{1,2}$ 9.5 Hz, 2-H; 4.05, $J_{2,3}$ 3.5 Hz, 3-H) whilst the 16-ene was replaced by a 16,17-dibromide (δ_H 4.00, CH_2Br; δ_C 82.3, C-16; 54.1, C-17). The compound formed a diacetate (**6**) [δ 2.04 and 2.09 (each 3 H, s, OAc)] on acetylation with acetic anhydride–toluene-*p*-sulphonic acid (AA–PTSA). When the reaction mixture was separated by flash chromatography and the less stable dibromide (**7**) immediately acetylated (AA–PTSA), it also formed a stable diacetate compound (**8**). The ^{1}H and ^{13}C n.m.r. spectra of this compound (see Tables 1 and 3) showed that it was a C-16 epimer of the diacetate (**6**). Hence in contrast to the previous work,[2,3] the addition of bromine to the 16-ene of 13-hydroxygibberellins had not led to the immediate Wagner–Meerwein rearrangement.[5] However, when the crude reaction mixture (shown by chromatography of an aliquot to contain just the two dibromides) was stirred with aqueous sodium hydrogen carbonate for 10 min and then worked up, the stable dibromide (**5**) and the known Wagner–Meerwein rearrangement product (**9**)[2] were obtained.

If the dioxane which was used as a solvent was freshly distilled, a third compound in addition to (**5**) and (**7**) was formed. This dibromide (**14**) formed the major product when



the dioxane was rigorously dried. Its ^{1}H n.m.r. spectrum (δ 5.90, *J* 3 and 5 Hz, 1-H; 4.72, *J* 5 Hz, 2-H; 4.28, *J* 5 Hz, 3-H; 3.23, *J* 3 and 6 Hz, 5-H) showed that rearrangement of ring A had taken place to form compound (**14**). Spin-decoupling experiments confirmed the long-range coupling between 1-H and 5-H (3 Hz) which is a characteristic of this system. When compound (**13**), which was obtained from methyl gibberellate (**2**) by rearrangement of ring A with dilute alkali,[6] was treated with TMPAP in very dry dioxane, the same compound (**14**) was obtained. The 3-hydroxy group has been shown[7] to play an

Table 1. ^{1}H N.m.r. signals for bromogibberellin derivatives

	Compound						
Solvent	(5) $(CD_3)_2$-CO	(6) $(CD_3)_2$-CO	(7) $CDCl_3$	(8) $CDCl_3$	(14) $(CD_3)_2$-CO	(15) $CDCl_3$	(17) $(CD_3)_2$-CO
1-H	6.41	6.61	6.25	6.36	5.90	6.37	6.55
2-H	5.90	5.88	5.97	5.90	4.72	6.02	5.88
3-H	4.05	5.26	4.21	5.32	4.28	3.62	5.25
5-H	3.22	3.28	3.31	3.28	3.23	3.22	3.23
6-H	2.68	2.77	2.77	2.75	2.44	2.77	2.73
14-H_2	N.a.	2.75, 2.11	N.a.	2.53, 2.65	1.64, 1.42	2.55, 2.23	1.87, 1.64
15-H_2	2.46, 2.11	2.47, 2.14	N.a.	2.52, 2.29	2.73, 2.07	2.66, 2.14	2.27, 2.63
17-H_2	4.00	4.08, 4.11	3.87, 3.96	4.14, 4.04	3.97, 4.07	3.82, 3.92	3.86
18-H_3	1.18	1.06	1.29	1.13	1.13	1.21	1.06
OMe	3.75	3.78	3.76	3.80	3.73	3.29, 3.43, 3.77	3.72
OAc		2.04, 2.09		2.07, 2.11			2.08

Selected coupling constants: 1-H, 2-H, 9.5 Hz; 2-H, 3-H, 3.5 Hz; 5-H, 6-H, 11 Hz; 14-H_α, 14-H_β, 11—12 Hz; 14-H_α, 15-H_β, 2.5 Hz; 15-H_α, 15-H_β, 14—15 Hz; 17-H, 17-H′, 11 Hz [except for compounds (**5**), (**6**), and (**17**) which showed singlets]. The coupling constants for compound (**14**) are given in the text, N.a. = not assigned.

Table 2. ^{1}H N.m.r. signals for the 8,13-epigibberellin derivatives

	Compound						
Solvent	(9) $(CD_3)_2$-CO	(10) $(CD_3)_2$-CO	(11) $CDCl_3$	(12) $CDCl_3$	(19) $(CD_3)_2$-CO	(20) $CDCl_3$	(21) $CDCl_3$
1-H	6.41	6.47	6.45	6.43	4.76	N.a.	N.a.
2-H	5.94	5.92	5.89	5.86	4.89	N.a.	N.a.
3-H	4.14	4.11	5.38	5.36	4.22	3.86	3.86
5-H	3.31	3.28	3.35	3.32	3.93	3.21	3.28
6-H	2.90	2.87	2.72	2.70	2.88	2.63	2.62
14-H_2	2.30, 2.28	2.24, 2.19	2.07, 2.17	N.a.	N.a.	N.a.	N.a.
15-H_2	2,82, 2.31	2.82, 2.27	3.04, 2.18	2.91, 2.12	2.86, 2.32	3.03, 2.15	3.05, 2.13
17-H_2	3.50, 3.63	3.29, 3.38	3.23, 3.28	1.03	3.48, 3.62	3.37, 3.48	3.20, 3.25
18-H_3	1.26	1.24	1.22	1.20	1.25	1.21	1.20
OMe	3.77	3.74	3.74	3.75	3.77	3.74	3.74
OAc			2.11	2.08			

Selected coupling constants: 1-H, 2-H, 9.5 Hz; 2-H, 3-H, 3.5 Hz; 5-H, 6-H, 7 Hz; 14-H_α, 14-H_β, 12 Hz; 14-H_β, 15-H_α, 3.5 Hz; 15-H_α, 15-H_β, 19 Hz, 17-H, 17-H′, 10 Hz. N.a. = not assigned.

Table 3. ^{13}C N.m.r. assignments

	Compound						
Solvent	(5) $(CD_3)_2$-CO	(6) $(CD_3)_2$-CO	(8) $CDCl_3$	(9) $(CD_3)_2$-CO	(10) $(CD_3)_2$-CO	(11) $CDCl_3$	(19) $(CD_3)_2$-CO
C-1	132.5	129.7	129.6	131.3	131.2	130.0	48.4[a]
C-2	134.3	135.3	133.6	134.7	134.7	132.5	47.7[a]
C-3	70.4	70.8	70.2	71.2	71.1	71.0	78.2
C-4	54.3	52.9	52.2	53.4	53.3	51.2	51.5
C-5	53.7	53.7	54.3	56.2	56.2	55.8	52.1
C-6	51.9	53.2	53.2	51.5	51.6	51.0	51.3
C-7	173.0	172.4	172.0	173.8	173.7	173.7	173.6
C-8	51.2	51.1	48.9	50.5	50.2	49.5	49.2
C-9	52.7	52.7	51.9	50.3	50.3	49.4	50.2
C-10	91.4	90.8	89.6	89.9	89.7	88.6	93.8
C-11	17.1	17.3	16.5	19.5	19.6	18.9	18.9
C-12	40.3	35.8	41.8[a]	33.5[a]	35.2[a]	34.6[a]	33.6[a]
C-13	78.4	77.3	76.8	56.0	55.1	54.6	55.8
C-14	43.0	38.5	42.1[a]	36.7[a]	35.2[a]	34.6[a]	36.5[b]
C-15	48.3	46.2	48.9	44.7	46.7	46.4	44.6
C-16	82.3	88.2	85.7	214.0	213.5	212.7	213.8
C-17	54.1	51.7	54.8	51.6	10.9	9.7	50.7
C-18	14.9	14.7	14.3	14.7	14.7	14.1	15.0
C-19	178.8	177.2	176.7	178.9	178.8	176.7	176.0
OMe	52.4	52.7	52.3	52.4	52.2	52.3	52.4
OAc		20.6, 21.1	20.7, 21.5			20.7	
		170.4, 169.8	169.9, 170.0			169.8	

[a,b] Assignments may be interchanged within a column.

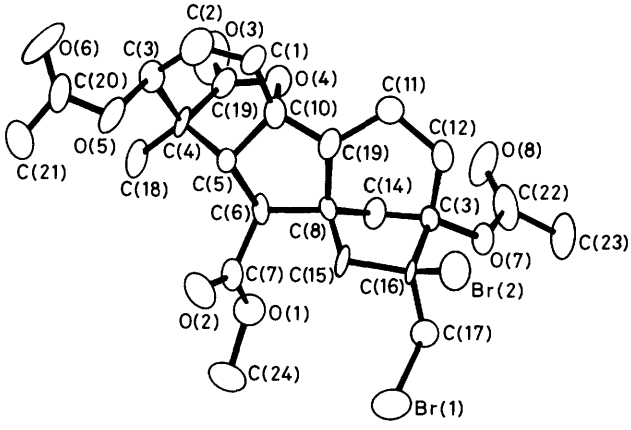
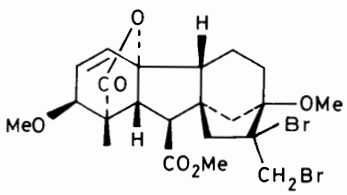


Figure 1. *X*-Ray molecular structure of compound (**6**)

important neighbouring-group role in the base-catalysed rearrangement of the lactone (**2**) to (**13**). In order to examine the role of the 3-hydroxy group in the present case, the permethylated derivative (**3**) of gibberellic acid was brominated under the same very dry conditions. In this case the addition of bromine to the 16-ene proceeded slowly. After 6 h a poor yield of a 16,17-dibromide (**15**) was obtained, the ^{1}H n.m.r. spectrum of which (δ 6.37, 1-H; 6.02, $J_{1,2}$ 9.5 Hz, 2-H; 3.62, $J_{2,3}$ 3.5 Hz, 3-H) showed that the rearrangement of ring A had not taken place.

The C-16 stereochemistry of the products was determined as follows. The stable dibromide (**5**), as its diacetate (**6**), was examined by *X*-ray crystallography and shown to have the stereochemistry as in Figure 1 in which the bromine has the β configuration (*i.e.*, configuation at C-16 is *S*). Catalytic reduction of this compound with hydrogen over palladium–charcoal gave the methyl tetrahydrogibberellate, m.p. 271—272 °C,[8] to which the stereochemistry (**16**) has been assigned.[9] The same isomer of methyl tetrahydrogibberellate was obtained by the catalytic reduction of the less stable dibromide (**7**). Since reduction may proceed *via* the 16-ene, this is not unexpected. However, it established that the dibromides are only epimeric at C-16. Their difference in reactivity may then be rationalized in terms of the differing geometry of the bromine relative to the C-12–C-13 bond. The sluggish rate of bromination of the 13-methyl ether suggested that the 13-oxygen function was affecting the rate of addition.

Bromination of the diacetate of methyl gibberellate, compound (**4**), revealed the participation of the 13-acetoxy group.



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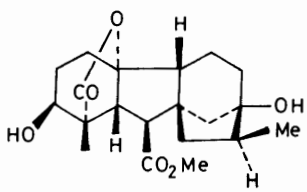

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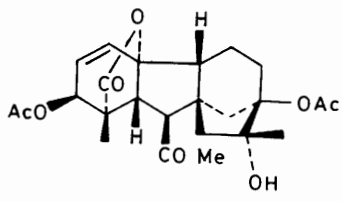

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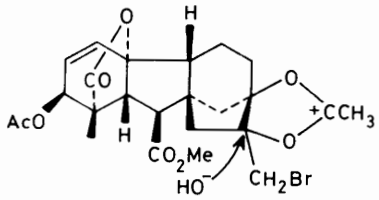

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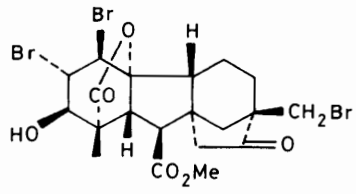

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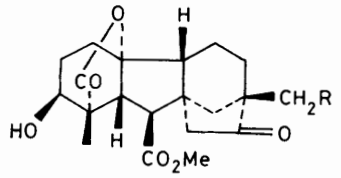

(20) R = Br

(21) R = I

The only isolable product was a diacetoxy bromohydrin (**17**), the structure and stereochemistry of which was established by *X*-ray crystallographic analysis (see Figure 2). Its formation may be rationalized in terms of an intermediate acetoxylinium ion (**18**).

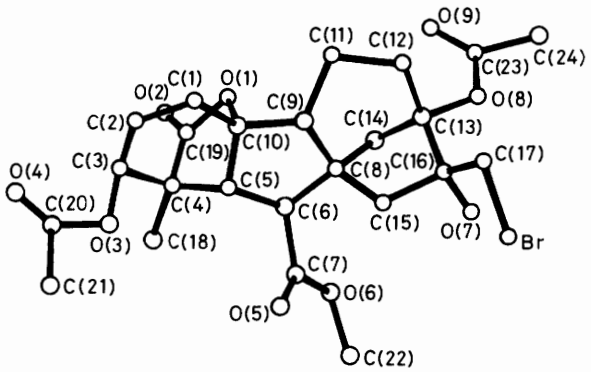

Figure 2. *X*-Ray molecular structure of compound (**17**)

Treatment of a solution of methyl gibberellate (**2**) in methylene dichloride–THF with bromine and saturated aq. sodium hydrogen carbonate gave the epigibberellin (**9**) and the corresponding ring A addition product (**19**). The stereochemistry of the 1β-bromine in the latter was assigned on the basis of the shift to lower field of the 5-H signal [δ 3.93 in (**19**), 3.31 in (**9**)] (*c.f.* Tables 1 and 2). The multiplicity of the ring A resonances, showing small ($J_{1,2}$ 0.9 Hz, $J_{2,3}$ 1.2 Hz) coupling constants and a long-range 'W' $J_{1,3}$ coupling constant (0.9 Hz), are in accord with the 1β,2α-diaxial configuration of the dibromide (**19**).

An interesting stereochemical contrast was observed on reduction of the (16*R*) and (16*S*) dibromides with tributyltin hydride (TBTH). The (16*S*)-dibromide (**5**) regenerated methyl gibberellate (**2**) whilst the (16*R*)-dibromide (**7**) gave the 8,13-epigibberellin (**9**). The bromomethyl group in the latter was only very slowly reduced to the 13-methyl group. This rearrangement is in accord with the stereochemistry (**7**) in which the C-16 bromine is *trans* to the migrating bond. Since the dibromide (**14**) regenerated the 16-ene (**13**) by reduction with TBTH, it was tentatively assigned the (16*S*) configuration. Hydrogenation of the unsaturated bromo compound (**9**) gave the corresponding gibberellin A_1 analogue (**20**).

Iodination with iodine in methylene dichloride–THF in the presence of aqueous sodium hydrogen carbonate gave the iodo compound (**10**) which could be hydrogenated to give the iodo compound (**21**). Acetylation of (**10**) gave the 3-acetate (**11**). In contrast to the bromomethyl derivative, the iodomethyl group in (**11**) was readily reduced with TBTH to afford compound (**12**).

In conclusion we have shown that bromination of methyl gibberellate (**2**) at C-16 is not stereospecific and, in contrast to previous reports, it does not necessarily lead directly to rearrangement. Indeed the participation of the 13-acetoxy group leading to bromohydrin formation as in structure (**17**) revealed that the bromonium ion may be stabilized in ways that do not lead to the rearrangement of rings C and D and the formation of the epigibberellins. The influence of the stereochemistry of the 16-bromine atoms on their subsequent reactions is reflected in the ease of rearrangement of the (16*R*)-epimer in contrast to the (16*S*)-compound.

Experimental

Silica for flash chromatography was Merck 9385. Light petroleum refers to the fraction boiling in the range 60—80 °C. ^{1}H and ^{13}C N.m.r. spectra were determined on a Bruker WH 360 spectrometer. I.r. spectra are for Nujol mulls. Ether refers to diethyl ether.

Bromination of Methyl Gibberellate (**2**) *with Trimethyl(phenyl)ammonium Perbromide.*—(*a*) A solution of methyl gibberellate (**2**) (500 mg) in freshly redistilled dioxane (6 ml) was treated with TMPAP (500 mg) for 40 min at room temperature. Ether was added to precipitate the reagent and the reaction mixture was then filtered and the solvent evaporated off under reduced pressure. The residue was chromatographed on silica in ethyl acetate–light petroleum (3:7) to give *methyl gibberellate* 16β,17-*dibromide* (75 mg) (**5**), which crystallized from ethanol as prisms, m.p. 160—162 °C (Found: C, 46.2; H, 4.4. $C_{20}H_{24}Br_2O_6$ requires C, 46.2; H, 4.65%); $\nu_{max.}$ 3 500, 1 770 and 1 735 cm^{-1}. Further elution gave a mixture (350 mg) (1:1 by ^{1}H n.m.r.) of dibromides (**7**) and (**14**).

(*b*) The reaction was repeated using dioxane which had been dried and freshly distilled from sodium, to afford, after chromatography, ent-16α,17-*dibromo*-2β,3α,13-*trihydro*-20-*nor*-*gibberell*-1(10)-*ene*-7,19-*dioic acid* 19,2-*lactone* 7-*methyl ester** (**14**) (330 mg), which crystallized from ethanol as prisms, m.p.

* Methyl isogibberellate 16β-17-dibromide.

Table 4. Fractional atomic co-ordinates ($\times 10^4$) with estimated standard deviations in parentheses for compound (**6**)

	x	*y*	*z*
Br(1)	5 862(1)	0(0)	4 228(1)
Br(2)	3 236(1)	−1 575(1)	5 125(1)
O(1)	3 348(7)	3 102(8)	2 209(6)
O(2)	2 543(7)	1 699(11)	852(5)
O(3)	−2 108(9)	4 313(8)	1 768(6)
O(4)	−1 409(6)	2 512(6)	2 645(5)
O(5)	−1 651(6)	1 488(8)	−931(5)
O(6)	−3 512(9)	1 773(22)	−2 187(7)
O(7)	2 946(6)	1 283(6)	6 399(4)
O(8)	1 434(8)	2 685(8)	6 753(5)
C(1)	−2 116(9)	582(10)	1 670(8)
C(2)	−2 729(10)	939(11)	622(9)
C(3)	−2 218(10)	2 023(11)	−14(7)
C(4)	−1 025(9)	2 735(9)	769(7)
C(5)	−52(8)	1 763(9)	1 433(7)
C(6)	1 213(9)	2 262(9)	2 235(6)
C(7)	2 440(10)	2 284(11)	1 656(7)
C(8)	1 495(8)	1 359(9)	3 333(6)
C(9)	50(9)	710(9)	3 208(7)
C(10)	−873(9)	1 315(9)	2 279(7)
C(11)	−338(9)	691(10)	4 393(8)
C(12)	854(8)	292(9)	5 335(7)
C(13)	2 202(8)	971(9)	5 276(7)
C(14)	1 876(8)	2 107(9)	4 425(7)
C(15)	2 587(9)	383(9)	3 380(6)
C(16)	3 180(8)	194(9)	4 676(6)
C(17)	4 596(8)	706(10)	5 007(8)
C(18)	−428(10)	3 726(11)	103(8)
C(19)	−1 603(9)	3 298(11)	1 739(7)
C(20)	−2 379(12)	1 481(15)	−1 965(9)
C(21)	−1 629(11)	1 018(14)	−2 856(8)
C(22)	2 468(11)	2 120(10)	7 074(7)
C(23)	3 364(12)	2 151(12)	8 203(8)
C(24)	4 635(10)	3 138(17)	1 765(9)

Table 5. Fractional atomic co-ordinates ($\times 10^4$) with estimated standard deviations in parentheses for compound (**17**)

	x	*y*	*z*
Br	9 295(2)	0(0)	4 807(2)
O(1)	2 473(10)	3 880(9)	2 247(7)
O(2)	1 776(12)	5 568(9)	1 337(9)
O(3)	2 264(11)	2 934(11)	−1 327(8)
O(4)	64(11)	3 015(16)	−2 605(10)
O(5)	6 729(12)	2 993(11)	787(8)
O(6)	7 546(11)	4 369(10)	2 141(9)
O(7)	8 546(11)	2 652(10)	4 980(8)
O(8)	6 812(10)	2 836(10)	6 357(7)
O(9)	5 019(12)	4 048(10)	6 492(8)
C(1)	1 706(17)	2 096(15)	1 215(11)
C(2)	1 035(14)	2 469(16)	94(13)
C(3)	1 667(16)	3 461(16)	−457(12)
C(4)	2 927(15)	4 106(13)	404(12)
C(5)	3 898(14)	3 131(13)	1 125(11)
C(6)	5 263(14)	3 614(13)	2 040(10)
C(7)	6 560(16)	3 612(14)	1 564(11)
C(8)	5 483(14)	2 799(13)	3 147(12)
C(9)	3 938(14)	2 131(13)	2 932(12)
C(10)	2 978(15)	2 753(14)	1 898(11)
C(11)	3 482(16)	2 030(15)	4 051(12)
C(12)	4 802(15)	1 683(13)	5 086(13)
C(13)	6 109(14)	2 532(14)	5 137(11)
C(14)	5 763(16)	3 543(12)	4 280(11)
C(15)	6 717(15)	1 902(14)	3 383(11)
C(16)	7 313(14)	1 874(12)	4 731(10)
C(17)	7 702(16)	692(14)	5 298(14)
C(18)	3 563(17)	5 027(20)	−241(13)
C(19)	2 332(15)	4 640(12)	1 371(13)
C(20)	1 162(20)	2 797(15)	−2 441(10)
C(21)	2 152(19)	2 288(18)	−3 187(14)
C(22)	8 914(18)	4 361(20)	1 862(17)
C(23)	6 122(18)	3 578(13)	6 942(12)
C(24)	7 064(23)	3 692(19)	8 240(14)

167—168 °C (Found: C, 45.9; H, 4.6. $C_{20}H_{24}Br_2O_6$ requires C, 46.2; H, 4.65%); $\nu_{max.}$ 3 570, 3 450, 1 760, and 1 730 cm^{-1}. The above compound (50 mg), identified by its i.r. and n.m.r. spectra, was obtained when a solution of the 19,2-lactone (**13**) (100 mg) in dry dioxane (6 ml) was treated with TMPAP (100 mg). The diacetate, prepared with AA–PTSA, was a gum, $\nu_{max.}$ 1 770, 1 740, and 1 730 cm^{-1}, δ_H 1.18, 1.99, 2.09 (each 3 H, s), 2.52 (d, *J* 6 Hz), 3.25 (dd, *J* 3 and 6 Hz), 3.75 (OMe), 3.75 and 3.92 (each 1 H), 5.00 (2 H), and 5.80 (dd, *J* 3 and 5 Hz).

(c) The reaction was repeated using dioxane (6 ml) to which two drops of water had been added. Flash chromatography on silica in ethyl acetate–light petroleum (3:7) gave methyl gibberellate 16β,17-dibromide (**5**) (125 mg) and crude methyl gibberellate (16α,17-dibromide (**7**) (300 mg). Each fraction was immediately acetylated with AA (3 ml) and catalytic amount of PTSA (100 mg) for 3 h. The solvent was evaporated off under reduced pressure at 25 °C and the products were purified by chromatography on silica in ethyl acetate–light petroleum (3:7) to afford (a) *methyl* 3,13-*di*-O-*acetylgibberellate* 16β,17-*dibromide* (**6**), which recrystallized from ethanol as prisms, m.p. 174—176 °C (Found: C, 47.8; H, 4.55. $C_{24}H_{28}Br_2O_8$ requires C, 47.7; H, 4.7%); $\nu_{max.}$ 1 775, 1 730, and 1 720 cm^{-1}, and (b) *methyl* 3,13-di-O-*acetylgibberellate* 16α,17-*dibromide* (**8**), which crystallized from ethanol as prisms, m.p. 179—181 °C (Found: C, 48.3; H, 4.8%); $\nu_{max.}$ 1 775 and 1 735br cm^{-1}.

(d) Methyl gibberelllate (**2**) (300 mg) was treated with a solution of TMPAP (500 mg) in dioxane (6 ml) containing water (2 drops) for 40 min. Ether was added, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Chromatography of an aliquot showed that the mixture contained (**5**) (75 mg) and (**7**) (180 mg). The remainder was taken up in THF (5 ml) and the solution was stirred with saturated aqueous sodium hydrogen carbonate (10 ml) for 10 min. The organic products were recovered in ethyl acetate and chromatographed on silica in ethyl acetate–light petroleum (3:7) to afford methyl gibberelate 16β,17-dibromide (**5**) (60 mg) and *ent*-13-bromomethyl-3α,10β-dihydroxy-16-oxo-8,13-epi-17,20-dinorgibberell-1-ene-7,19-dioic acid 19,10-lactone 7-methyl ester (**9**) (150 mg), which crystallized from ethanol as prisms, m.p. 218—219 °C (253—254 °C from ethyl acetate) (lit.,[2] 214—216 °C) (Found: C, 55.0; H, 4.95. Calc. for $C_{20}H_{23}BrO_6$: C, 54.7; H, 5.3%); $\nu_{max.}$ 3 480, 1 770, 1 755, and 1 740 cm^{-1}.

Bromination of the Methoxy Compound (**3**).—A solution of compound (**3**) (500 mg) in very dry dioxane (6 ml) was treated with TMPAP (500 mg) for 6 h The reaction was slow (t.l.c. monitor). Ether was added, the solution was filtered, and the solvent was evaporated off to give a gum, which was chromatographed on silica to afford *methyl* 3,13-*di*-O-*methylgibberellate* 16ξ,17-*dibromide* (**15**) (25 mg), which crystallized from ethanol as needles, m.p. 135—137 °C (Found: C, 47.6; H, 5.4. $C_{22}H_{28}Br_2O_6 \cdot \frac{1}{2}H_2O$ requires C, 47.5; H, 5.4%); $\nu_{max.}$ 1 770 and 1 735 cm^{-1}. Reduction with tributyltin hydride regenerated the starting material.

Reaction of Methyl Gibberellate (**2**) *with Bromine.*—A solution of methyl gibberellate (**3**) (600 mg) in a mixture of THF (20 ml) and methylene dichloride (40 ml) was vigorously stirred at room temperature with aqueous sodium hydrogen

carbonate (30 ml) and bromine (1.5 ml) for 1.5 h. The organic layer was separated, washed successively with aqueous sodium thiosulphate and water, and then dried, and the solvent was evaporated off. The residue was chromatographed on silica in ethyl acetate–light petroleum (6:4) to afford compound (**9**) (300 mg) and ent-1α,2β-*dibromo*-13-*bromomethyl*-3α,10β-*dihydroxy*-16-*oxo*-8,13-epi-17,20-*dinorgibberellane*-7,19-*dioic acid* 19,10-*lactone* 7-*methyl ester* (**19**) (130 mg), which crystallized from ethanol as prisms, m.p. 271—272 °C (Found: C, 40.4; H, 3.9. $C_{20}H_{23}Br_3O_6$ requires C, 40.1; H, 3.8%); $\nu_{max.}$ 3 500, 1 795, 1 740, and 1 715 cm^{-1}.

Hydrogenation Reactions.—(*a*) A solution of the bromo compound (**5**) (100 mg) in methanol (4 ml) containing 10% palladium–charcoal (50 mg) was stirred under an atmosphere of hydrogen for 2 h. The catalyst was filtered off and the filtrate was evaporated. The residue was chromatographed on silica in ethyl acetate–light petroleum (1:1) to afford methyl (16*S*)-tetrahydrogibberellate (**16**) (70 mg), m.p. 271—273 °C (lit.,[8] 271—272 °C) (Found: C, 65.6; H, 7.5. Calc. for $C_{20}H_{28}O_6$: C, 65.9; H, 7.7%), identified by its ^1H n.m.r. spectrum: δ 0.94 (3 H, d, *J* 7 Hz), 1.03 (3 H, s), 2.51 and 3.18 (each 1 H, d, *J* 10 Hz, together 6- and 5-H), and 3.68 (4 H, OMe, and 3-H).

(*b*) Repetition with the epimer (**7**) (200 mg) in methanol (5 ml) gave methyl (16*S*)-tetrahydrogibberellate (**16**) (110 mg), m.p. 271—273 °C, identical (i.r. and n.m.r.) with the above sample.

Reaction with Tributyltin Hydride.—(*a*) A solution of the dibromo compound (**5**) (200 mg) in toluene (5 ml) was treated with TBTH (1 ml) and azoisobutyronitrile (AIBN) (50 mg) under reflux for 3 h. The solvent was evaporated off, the residue was diluted with acetonitrile, and the solution was washed with light petroleum. The acetonitrile was evaporated off under reduced pressure to give methyl gibberellate (**2**) (120 mg), identified by its ^1H n.m.r. spectrum.

(*b*) The freshly prepared bromo compound (**7**) (100 mg) was dissolved in toluene (5 ml) containing a few drops of THF, and the solution was treated with TBTH (1 ml) and AIBN (50 mg) under reflux for 1.5 h. The solvent was evaporated off, the residue was diluted with acetonitrile, the solution was washed with light petroleum, and the acetonitrile was evaporated off. The residue was crystallized from ethyl acetate to afford the bromo compound (**9**) (60 mg), identified by its i.r. and n.m.r. spectra.

Reduction of Compound (**9**).—A solution of the bromo compound (**9**) (200 mg) in ethyl acetate (5 ml) was stirred under hydrogen in the presence of 10% palladium–charcoal (100 mg) for 2 h. The solution was filtered and the filtrate was evaporated to give *ent*-13-bromomethyl-3α,10β-dihydroxy-16-oxo-8,13-epi-17,20-dinorgibberellane-7,19-dioic acid 19,10-lactone 7-methyl ester (**20**) (170 mg), m.p. 270—271 °C (lit.,[2] 264 °C) (Found: C, 54.6; H, 5.8. Calc. for $C_{20}H_{25}BrO_6$: C, 54.4; H, 5.7%); $\nu_{max.}$ 3 510, 1 770, 1 750, and 1 745 cm^{-1}.

Iodination of Methyl Gibberellate (**2**).—A solution of methyl gibberellate (**2**) (300 mg) in a mixture of THF (10 ml) and methylene dichloride (20 ml) was vigorously stirred with saturated aqueous sodium hydrogen carbonate (15 ml) and iodine (1.2 g) for 2 h. The organic layer was separated, washed with aqueous sodium thiosulphate, and dried. The solvent was evaporated off and the residue was chromatographed on silica to afford ent-3α,10β-*dihydroxy*-13-*iodomethyl*-16-*oxo*-8,13-*epi*-17,20-*norgibberell*-1-*ene*-7,19-*dioic acid* 19,10-*lactone* 7-*methyl ester* (**10**) (180 mg), which crystallized from ethanol as needles, m.p. 222—223 °C (Found: C, 49.7; H, 4.7. $C_{20}H_{23}IO_6$ requires C, 49.4; H, 4.8%); $\nu_{max.}$ 3 500, 1 760, 1 740, and 1 735 cm^{-1}. The *acetate* (**11**), prepared with AA in pyridine, crystallized from ethanol as needles, m.p. 203—204 °C (Found: C, 50.5; H, 4.8. $C_{22}H_{25}IO_7$ requires C, 50.0; H, 4.8%); $\nu_{max.}$ 1 765, 1 740, and 1 730 cm^{-1}.

Reduction of the Iodo Compounds (**10**) *and* (**11**).—(*a*) A solution of compound (**10**) (200 mg) in ethyl acetate (5 ml) was stirred under hydrogen in the presence of 10% palladium–charcoal (100 mg) for 2 h. The solution was filtered and the solvent was evaporated off to give ent-3α,10β-*dihydro*-13-*iodomethyl*-16-*oxo*-8,13-*epi*-17,20-*dinorgibberellane*-7,19-*dioic acid* 19,10-*lactone* 7-*methyl ester* (**21**) (180 mg), which crystallized from ethanol as prisms, m.p. 241—242 °C (Found: C, 49.5; H, 5.1. $C_{20}H_{25}IO_6$ requires C, 49.2; H, 5.2%); $\nu_{max.}$ 3 490, 1 760, 1 740, and 1 725 cm^{-1}.

(*b*) The iodo compound (**11**) (40 mg) was dissolved in toluene (2 ml) containing a few drops of THF, and the solution was treated with TBTH (0.3 ml) and AIBN (50 mg) under reflux for 3 h. The solvent was evaporated off, the residue was taken up in acetonitrile, and the solution washed with light petroleum. The acetonitrile was evaporated off and the residue was crystallized from ethanol to afford ent-3α-*acetoxy*-10-*hydroxy*-13-*methyl*-16-*oxo*-8,13-*epi*-17,20-*dinorgibberell*-1-*ene*-7,19-*dioic acid* 19,10-lactone 7-*methyl ester* (**12**) (26 mg), which crystallized from ethanol as needles, m.p. 136—137 °C (Found: C, 65.9; H, 6.4. $C_{22}H_{26}O_7$ requires C, 65.7; H, 6.5%); $\nu_{max.}$ 1 785, 1 745, and 1 735 cm^{-1}.

Bromination of the Diacetate (**4**).—The 3,13-diacetyl derivative (**4**) (500 mg) was dissolved in moist dioxane (6 ml) and the solution was treated with TMPAP (500 mg) for 5 h. Ether was added to precipitate the reagent. The reaction mixture was filtered, the filtrate was dried over sodium sulphate, and the solvent was evaporated off to give a gum. T.l.c. showed this contained one major product and only a trace of a second component. Chromatography of the product on silica gel in ethyl acetate–light petroleum (30:70) gave ent-3α,13-*diacetoxy*-17-bromo-10β,16β-*dehydroxy*-20-*norgibberell*-1-*ene*-7,19-*dioic acid* 19, 10-*lactone* 7-*methyl ester* (**17**), which crystallized from ethanol as prisms, m.p. 185—187 °C (Found: C, 52.9; H, 5.3. $C_{24}H_{29}BrO_9$ requires C, 53.2; H, 5.4%); $\nu_{max.}$ 3 500. 1 765, and 1 745br cm^{-1}.

Crystallographic Data.—(a) *Compound* (**6**). $C_{24}H_{28}Br_2O_8$, *M* = 604.3, monoclinic, space group $P2_1$, *a* = 10.113(1), *b* = 10.663(1), *c* = 11.961(2) Å β = 102.15(1)°, *V* = 1 260.9 $Å^3$, *Z* = 2, D_c = 1.59 g cm^{-3}. Monochromated Mo-K_α radiation, λ = 0.710 69 Å, μ = 32.3 cm^{-1}.

A crystal of size *ca.* 0.25 × 0.20 × 0.15 mm was mounted on a CAD 4 diffractometer operating in the θ—2θ mode, Δθ = (0.70 + 0.35 tanθ)° with a maximum scan time of 1 min. 2 610 Reflections were measured for 2 < θ < 25°. 1 740 Unique reflections with $|F^2| > \sigma(F^2)$ were used in the refinement, $\sigma(F^2) = [\sigma^2(I) + (0.04I)^2]^{\frac{1}{2}}/L_p$. Routine heavy-atom methods were used in the structure solution and refinement. A full-matrix least-squares refinement was done with all atoms anisotropic except for the hydrogen atoms which were held fixed at calculated positions (C–H 1.08 Å), with B_{iso} 6.0 $Å^2$. The hydrogen atoms for C(21), C(23), and C(24) were omitted. A weighting scheme = $1/\sigma^2(F)$ was used. The final *R* factors were *R* = 0.046, *R'* = 0.055 (the alternative absolute structure had *R* = 0.052, *R'* = 0.062). A final difference map was featureless. Programs were from the Enraf-Nonius SDP-Plus package run on a PDP 11/34 computer. Final atom co-ordinates are given in Table 4.

(b) *Compound* (**17**). $C_{24}H_{29}BrO_9$, *M* = 541.4, monoclinic, space group $P2_1$, *a* = 9701(2), *b* = 11.382(3), *c* = 11.887(2) Å, β = 105.97(2)°, *V* = 1 261.8 $Å^3$, *Z* = 2, D_c = 1.43 g cm^{-3}. Monochromated Mo-K_α radiation, λ = 0.710 69 Å, μ = 16.6 cm^{-1}.

A crystal of size 0.25 × 0.15 × 0.07 mm was mounted on a CAD 4 diffractometer operating in the θ—2θ mode, $\Delta\theta = (0.8 + 0.35 \tan\theta)^\circ$, with a maximum scan time of 1 min. 2 608 Total reflections were measured for $2 < \theta < 25^\circ$, $+h, +k, \pm l$. 1 162 Unique reflections with $|F^2| > \sigma(F^2)$ were used in the refinement where $\sigma(F^2) = [\sigma^2(I) + (0.04I)^2]^{\frac{1}{2}}/L_p$. There was no crystal decay. Absorption corrections were made by the DIFABS method after isotropic refinement. Routine heavy-atom methods were used in the structure solution and refinement. A full-matrix least-squares refinement was done with all the atoms held anisotropic. Hydrogen atoms could not be located and were omitted. A weighting scheme $\omega = 1/\sigma^2(F)$ was used. The final R factors were $R = 0.0623$, $R' = 0.0681$ ($R = 0.0625$, $R' = 0.0689$ for the opposite absolute configuration). Programs were from the Enraf-Nonius SDP-Plus package and were run on a PDP11/34 computer. Two non-positive definite temperature factors for O(4) and C(21) may indicate slight unresolved disorder of the C(20) acetyl group. Final atomic co-ordinates are given in Table 5. The intramolecular distances, bond angles, torsional angles, hydrogen atom co-ordinates, and anisotropic temperature factors for both crystal structures have been deposited with the Cambridge Crystallographic Data Centre.*

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* See section 5.6.3 of Instructions for Authors, in this issue.

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