The Stereochemistry of a Rearrangement and Fragmentation Reaction of Ring D of 13-Hydroxygibberellins

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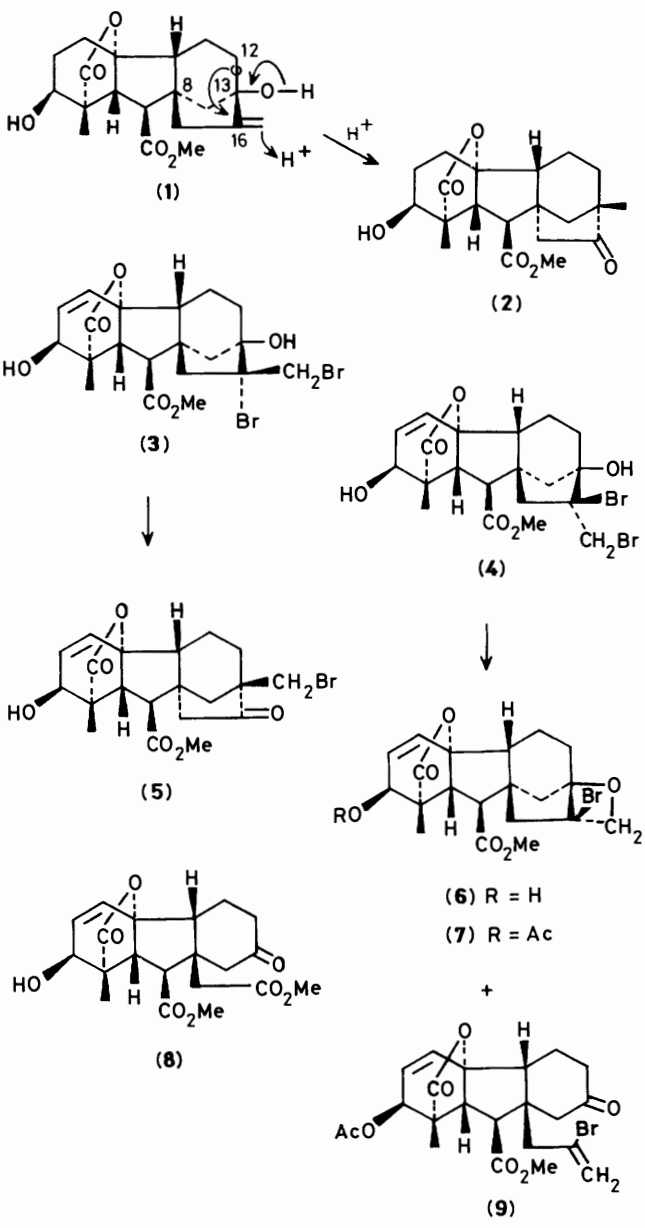
Treatment of methyl 16(*R*)- and 16(*S*)-16,17-dibromo-16,17-dihydrogibberellate with aqueous potassium carbonate at room temperature affords an 8,13-epigibberellin from the 16(*R*)-epimer whilst the 16(*S*)-epimer reacts much more slowly to give a 16-bromo-13,16,17-fused oxetane and a 16-bromo-13,16-secogibberellin, indicating the importance of the stereochemistry of the 16-substituent in determining the reaction pathway.

A characteristic feature of the 13-hydroxygibberellins [*e.g.* (**1**)] is the participation of the 13-hydroxy group in the acid-catalysed Wagner–Meerwein rearrangement of the 16-enes, leading to the formation of the 8:13-epigibberellins [*e.g.* (**2**)].[1,2] This skeletal rearrangement involves the migration of the C-12–C-13 bond to C-16 and may be initiated in a variety of ways. Hitherto there have been no investigations into the stereochemical dependence of this rearrangement (leading to 8:13-epigibberellins) on the configuration of a C-16 leaving group. The availability of the 16-epimeric 16,17-dibromo-16,17-dihydrogibberellins (**3**) and (**4**) of defined stereochemistry[3] prompted an investigation into stereochemical aspects of the participation of the neighbouring 13-hydroxy group in the displacement of the 16- and 17-bromine atoms. This has revealed two novel reactions of this system and the importance of the stereochemistry of the C-16 substituent in determining the reaction pathway. Bromination of methyl gibberellate with phenyltrimethylammonium perbromide in aqueous dioxane affords[3] the two epimeric 16,17-dibromides (**3**) and (**4**) which, provided a non-basic work-up is used, may be separated. The 16(*S*) stereochemistry of the more stable minor product (**4**) was established[3] by an *X*-ray crystallographic analysis of its diacetate.

The reaction conditions that were used to examine the solvolysis were aqueous acetone containing potassium carbonate and were sufficiently mild to avoid rearrangement of ring A of methyl gibberellate.[4,5] The reactions were followed by t.l.c. Under these conditions methyl 16(*R*)-16,17-dibromo-16,17-dihydrogibberellate (**3**) rapidly (30 min, room temperature) gave the 8,13-epigibberellin (**5**) which was identified by its i.r. and n.m.r. spectra.[3] On the other hand the 16(*S*)-epimer reacted much more slowly, requiring 2—3 days at room temperature for complete reaction, to afford two main products. Although one product (**6**) could be separated by chromatography, the products were best purified and characterized by acetylation and chromatography.

The first product, $C_{20}H_{23}BrO_6$, to which the unusual bromo-oxetane structure (**6**) was assigned, formed a monoacetate (**7**) which lacked any hydroxy absorption in the i.r. The parent alcohol possessed ^{1}H n.m.r. signals characteristic of ring A (δ 6.27, dd, *J* 0.7 and 9.3 Hz, 1-H; 5.87, dd, *J* 3.7 and 9.3 Hz, 2-H; 4.07, dd, *J* 0.7 and 3.7 Hz, 3-H) and ring B (δ 3.15 and 2.81, *J* 11.4 Hz, 5- and 6-H). As expected the signals assigned 3-H and 5-H were shifted downfield (to δ 5.32 and 3.31 respectively) in the monoacetate (**7**). The nature of the oxygen functions was established from the ^{13}C n.m.r. spectrum of the alcohol (**6**) (see Table 1) which contained signals from the 19,10-γ-lactone,



7-ester, and C-3 alcohol functions. Hence the remaining oxygen atom must be present as a cyclic ether. Although a bromo-oxetane structure was originally deduced from these spectral data, in view of its novelty this structure and the stereochemistry particularly at C-16 were established by *X*-ray crystallographic analysis of the acetate (**7**) (see Figure). The ^{13}C n.m.r. signals at

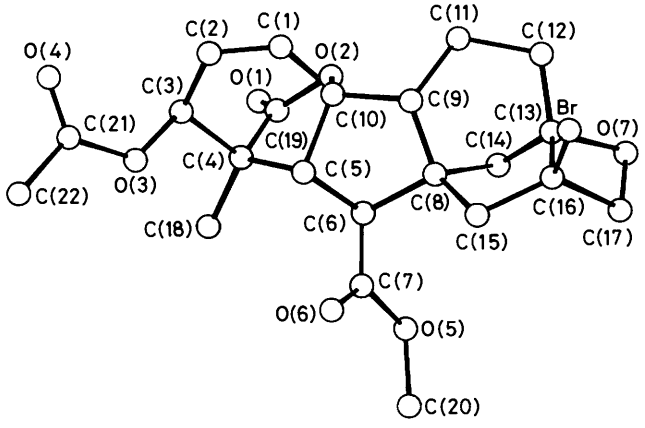


Figure. *X*-Ray molecular structure of compound (**7**)

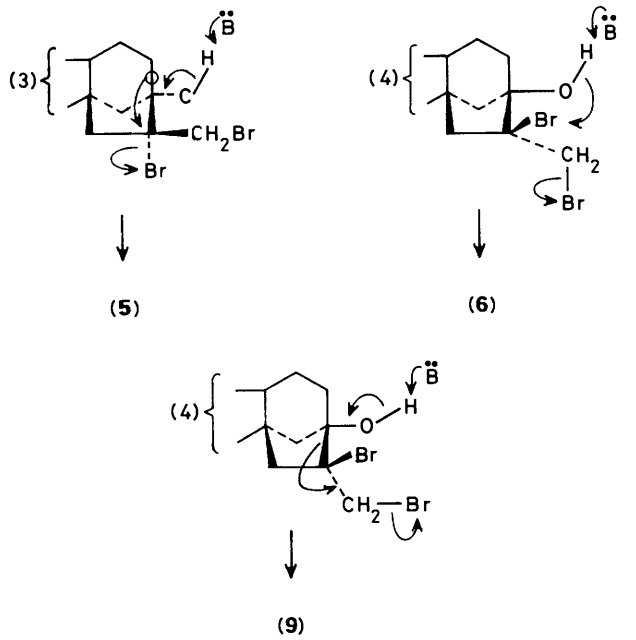
δ 68.2, 83.8, and 96.2 and the ^1H n.m.r. AB doublets at δ 4.60 and 4.90 (*J* 8.3 Hz) were assigned to the bromo-oxetane (**6**). Selective population-transfer ^1H n.m.r. experiments for acetate (**7**) linked the ^1H n.m.r. signals at δ 2.15 with δ 2.18 and at δ 2.17 with δ 2.33 (*J* 12 Hz) which were assigned to 14-H and 15-H. Nuclear Overhauser enhancement experiments based on irradiation of the signal at δ 4.95 led to enhancement of those at δ 4.65, 2.18, and 2.33 whilst irradiation at δ 4.65 only gave enhancement of the signal at δ 4.95. These n.O.e. experiments reflect the geometry of ring D established in this case by *X*-ray crystallographic analysis. They may have diagnostic value in determining the C-16 stereochemistry of other compounds of this type.

The second product was isolated pure only as its mono-acetate, $C_{22}H_{25}BrO_7$ (**9**). This monoacetate lacked any hydroxy absorption in the i.r. spectrum. Its ^{13}C n.m.r. spectrum contained carbonyl signals attributable to lactone, ester, and acetoxy carbons (δ 175.3, 169.2, and 170.9 respectively) together with a cyclohexanone (δ 209.7). Apart from the ring A olefinic signals there were two further alkene resonances (δ_C 126.0, quaternary carbon, and 124.2, methylene; δ_H 5.67 and 5.71, *J* 2.0 Hz) which were assigned to a bromoethylene grouping ($CBr=CH_2$). Apart from carbonyl absorption ($\nu_{max.}$ 1 715 cm^{-1}, cyclohexanone; 1 740, ester and acetoxy; 1 775, γ-lactone) the i.r. spectrum also contained a stronger than usual alkene absorption at 1 625 cm^{-1} which was attributed to an alkene bearing an electronegative substituent. The ^1H n.m.r. spectrum showed that rings A and B had again remained intact (δ 6.53, dd, *J* 0.7 and 9.3 Hz, 1-H; 5.91, dd, *J* 3.8 and 9.3 Hz, 2-H; 5.34, dd, *J* 0.7 and 3.8 Hz, 3-H; 3.31 and 2.61, *J* 11.9 Hz, 5- and 6-H). However, it also contained two further pairs of AB doublets (δ 2.31 and 2.72, *J* 14.5 Hz, 15-H_2; 2.58 and 2.96, *J* 15.7 Hz, 14-H_2), and a pair of doublets of triplets (δ 2.36 and 2.59, *J* 6.5 and 18 Hz) assigned to 12-H_2. In the latter the large coupling represents the geminal coupling. The smaller couplings must arise because one proton at C-12 bisects those at C-11 whilst the other subtends dihedral angles of approximately 30° and 130°. The spectrum is reminiscent of that of the 13,16-secogibberellin (**8**)[6,7] which showed doublets at 3.28 and 2.53 (*J* 11.5 Hz, 5- and 6-H respectively), 2.81 and 2.61 (*J* 15 Hz), and 2.48 and 2.16 (*J* 16 Hz) (14- and 15-H_2) overlapping with signals at 2.20 and 2.64

Table 1. ^1H and ^{13}C N.m.r. data determined in $CDCl_3$

Carbon atom	(6) ^1H	(6) ^{13}C	(7) ^1H	(9) ^1H	(9) ^{13}C
1	6.27	132.7[a]	6.40	6.53	128.7[a]
2	5.87	132.6[a]	5.88	5.91	134.1[a]
3	4.07	69.5	5.32	5.34	69.5
4		53.5			51.3
5	3.15	52.7	3.31	3.31	55.1
6	2.81	50.3	2.85	2.61	51.6
7		171.7			169.2
8		56.2			48.8
9		49.4		3.08	51.3
10		90.2			89.8
11		17.4		2.13	19.9
12		30.2		2.36, 2.59	35.3
13		68.2			209.7
14	2.15	41.7	2.15, 2.18	2.58, 2.96	43.2
15	2.17, 2.29	51.5	2.17, 2.33	2.31, 2.72	48.1
16		96.2			126.0
17	4.60, 4.90	83.8	4.65, 4.95	5.67, 5.71	124.2
18	1.17	14.4	1.13	1.12	13.9
19		177.9			175.3
OAc			2.12	2.16	20.1, 170.9
OMe	3.73	53.9	3.79	3.76	51.7

[a] Assignments may be interchanged.



Scheme.

assigned to 12-H_2. Hence the structure (**9**) was assigned to this fragmentation product.

The formation of these compounds (see Scheme) represents two unusual reactions which have not previously been detected in gibberellin chemistry. The absence of major products arising from migration of the C-12–C-13 bond in the case of the 16(*S*) isomer and its much slower rate of reaction compared with the 16(*R*) isomer clearly reflects the importance of C-16 stereo-

Table 2. Fractional atomic co-ordinates ($\times 10^4$), with estimated standard deviations in parentheses, compound (7)

	x	*y*	*z*
Br	1 793.1(27)	5 338.8(24)	895.6(9)
O(1)	9 698(13)	1 282(12)	1 922(4)
O(2)	8 086(14)	2 739(11)	1 507(4)
O(3)	8 625(12)	−788(11)	441(4)
O(4)	10 878(16)	−643(14)	23(5)
O(5)	3 451(13)	−109(12)	2 012(4)
O(6)	3 732(16)	−548(16)	1 163(5)
O(7)	2 492(14)	5 350(15)	2 210(5)
C(1)	7 943(23)	2 777(19)	556(7)
C(2)	8 882(22)	1 776(19)	388(7)
C(3)	9 033(19)	434(18)	745(6)
C(4)	7 981(20)	428(19)	1 239(6)
C(5)	6 390(17)	1 087(16)	1 105(6)
C(6)	5 332(18)	1 161(16)	1 549(6)
C(7)	4 155(21)	89(18)	1 534(7)
C(8)	4 568(20)	2 692(17)	1 516(6)
C(9)	5 629(19)	3 561(17)	1 141(6)
C(10)	7 020(18)	2 638(16)	1 055(6)
C(11)	6 123(21)	5 031(19)	1 371(7)
C(12)	4 790(21)	5 827(19)	1 656(7)
C(13)	3 636(19)	4 764(19)	1 844(7)
C(14)	4 473(22)	3 493(20)	2 073(7)
C(15)	2 847(21)	2 722(18)	1 318(7)
C(16)	2 343(19)	4 240(17)	1 504(6)
C(17)	1 262(22)	4 534(21)	2 951(7)
C(18)	7 888(21)	−1 092(19)	1 489(7)
C(19)	8 674(21)	1 466(19)	1 583(7)
C(20)	2 191(21)	−1 159(18)	2 047(7)
C(21)	9 697(22)	−1 272(19)	112(7)
C(22)	9 335(23)	−2 664(20)	−111(7)

chemistry in determining the reaction pathway under these mildly basic conditions.

Experimental

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

Rearrangement of Methyl 16(R),17-*Dibromo*-16,17-*dihydrogibberellate* (**3**).—A solution of methyl gibberellate (500 mg) in dioxane (6 ml) containing water (2 drops) was treated with phenyltrimethylammonium perbromide (500 mg) for 40 min at room temperature. Ether was added to precipitate the reagent. The solution was filtered and the solvent was evaporated off. The residue was subjected to flash chromatography on silica. Elution with ethyl acetate–light petroleum (3:7) gave methyl 16(*S*),17-dibromo-16,17-dihydrogibberellate (**4**) (120 mg) and crude methyl 16(*R*),17-dibromo-16,17-dihydrogibberellate (**3**) (300 mg). A solution of the latter (200 mg) in acetone (2 ml) was immediately stirred with 5% aqueous potassium carbonate (5 ml) for 30 min with t.l.c. monitoring. The solution was diluted with water and the product was recovered with ethyl acetate. Flash chromatography on silica in ethyl acetate–light petroleum (1:1) gave the 8:13-epigibberellin (**5**) (80 mg), which crystallized from ethanol as needles, m.p. 218—219 °C (lit.,[3] 214—216 °C), identified by its ^{1}H n.m.r. spectrum.

Rearrangement of Methyl 16(S),17-*Dibromo*-16,17-*dihydrogibberellate* (**4**).—(*a*) A solution of methyl 16(*S*),17-dibromo-16,17-dihydrogibberellate (**4**) (200 mg) in acetone (5 ml) was stirred with aqueous potassium carbonate (5 ml) for 2 days. The solution was diluted with water and the product was recovered with ethyl acetate. The extract was dried and the solvent was evaporated off to give a residue, which was chromatographed on silica. Elution with ethyl acetate–light petroleum (1:1) gave ent-16α-*bromo*-13,17-*epoxy*-3α,10β-*dihydroxy*-20-*norgibberell*-1-*ene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**6**) (80 mg) as prisms, m.p. 210 °C (Found: C, 54.5; H, 5.3. $C_{20}H_{23}BrO_6$ requires C, 54.7; H, 5.2%); $\nu_{max.}$ 3 500, 1 760, and 1 730 cm^{-1}. The n.m.r. data are given in Table 1. Acetylation with acetic anhydride–toluene-*p*-sulphonic acid (PTSA) at room temperature overnight gave the acetate (**7**) (*vide infra*), identified by its n.m.r. spectrum.

(*b*) A solution of methyl 16(*S*),17-Dibromo-16,17-dihydrogibberellate (**4**) (190 mg) in acetone (3.5 ml) was stirred with aqueous potassium carbonate (5 ml) at room temperature for 40 h. The products were recovered in ethyl acetate, and the extract was washed with brine and dried over sodium sulphate. The solvent was evaporated off to give a residue (190 mg), which was treated with acetic anhydride (3 ml) and PTSA (40 mg) overnight. The products were poured into water, recovered in ethyl acetate, and flash chromatographed on silica. Elution with ethyl acetate–light petroleum (3:7) gave ent-3α-*acetoxy*-16α-*bromo*-13,17-*epoxy*-10β-*hydroxy*-20-*norgibberell*-1-*ene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**7**) (50 mg) as prisms, (from toluene–light petroleum), m.p. 164—165 °C (Found: C, 54.8; H, 5.5. $C_{22}H_{25}BrO_7$ requires C, 54.9; H, 5.2%); $\nu_{max.}$ 1 780, 1 745, and 1 735 cm^{-1}. Further elution gave ent-3α-*acetoxy*-16-*bromo*-10β-*hydroxy*-13-*oxo*-20-*nor*-13,16-*secogibberella*-1,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**9**) (120 mg) which crystallized as needles, m.p. 158—160 °C (Found: C, 54.65; H, 5.2. $C_{22}H_{25}BrO_7$ requires C, 54.9; H, 5.2%); $\nu_{max.}$ 1 775, 1 740, 1 715, and 1 625 cm^{-1}.

Crystallographic Data.—Compound (7), $C_{22}H_{25}BrO_7$, M = 481.4, orthorhombic, space group $P2_12_12_1$, a = 8.672(3), b = 9.549(4), c = 25.587(8) Å, V = 2 118.9 Å^3, Z = 4, $D_{calc.}$ = 1.51 g cm^{-3}, monochromated Mo-K_α radiation, λ = 0.710 69 Å, μ = 19.6 cm^{-1}.

Data were collected using a crystal of *ca.* 0.25 × 0.2 × 0.1 mm mounted on an Enraf–Nonius CAD4 diffractometer operating in the θ–2θ mode with $\Delta\theta = (0.8 + 0.35\tan\theta)°$ and a maximum scan time of 1 min. The crystal diffracted only weakly and out of 1 536 unique reflections measured with $2 < \theta < 22°$ and $+h$, $+k$, $+l$, only 900 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. An empirical absorption correction using DIFABS was applied after isotropic refinement with minimum and maximum corrections of 0.54 and 1.31.

The structure was solved by routine heavy-atom methods and refined by full matrix least-squares with Br anisotropic and C and O atoms isotropic. Hydrogen atoms were omitted. The weighting scheme was $w = 1/\sigma^2(F)$ and the final residuals were R = 0.076, R' = 0.082 (R = 0.086, R' = 0.094 for the opposite absolute structure). A final difference map was featureless. Programs from the Enraf–Nonius SDP-Plus package were run on a PDP11/34 computer. Final atomic co-ordinates are given in Table 2.*

* *Supplementary data* (see section 5.6.3 of Instructions for Authors, January Issue). Tables of bond lengths, bond and torsion angles, and temperature factors have been deposited at the Cambridge Crystallographic Data Centre.

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