Substitution Reactions of the 3-Epimeric Methanesulphonates of Methyl Gibberellate

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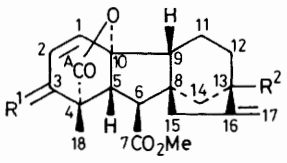
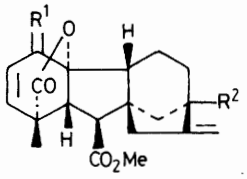
Whereas displacement of the 3β-(axial)-methylsulphonyloxy group from methyl gibberellate with lithium chloride or buffered aqueous acetone proceeds predominantly with *syn* rearrangement to afford the 1β-chloro- or 1β-hydroxy-gibberellin, the corresponding 3α-(equatorial) epimer reacts with simple inversion of configuration. This affords on the one hand a facile route to the 1-hydroxygibberellins and, on the other, a means of labelling gibberellins at C-3.

The stereochemistry of allylic displacement reactions has recently attracted considerable attention.[1,2] The presence of a lactone ring across the α-face of ring A of methyl gibberellate (**1**) ensures that this is a rigid system in which the stereochemistry of substituents at C-1 and C-3 are well-defined. The ^{1}H n.m.r. signals of the Δ^1- and Δ^2-olefinic protons are quite different whilst it is possible to distinguish between axial and equatorial electronegative substituents at C-1 and C-3 by the effect of the diaxial transannular interactions with 5β-H on its chemical shift (see for example refs. 3—7). This is particularly the case where epimers can be compared. Hence methyl gibberellate provides a suitable substrate for the study of the stereochemistry of allylic substitution reactions. The allylic displacement of the 3β-axial hydroxy group of methyl gibberellate by halides has been reported on a number of occasions.[3-5] The allylic substitution proceeds with *syn* stereochemistry and, depending upon the reagent, it is accompanied by varying amounts of nucleophilic substitution at C-3 with inversion of configuration. In their work on the reconstruction of ring A of methyl gibberellate, Corey *et al.* described[3] the reaction of the 3β-toluene-*p*-sulphonate with lithium bromide in HMPA which gave a mixture of 1α- and 1β-bromo compounds. It was later suggested[5] that these were the 1β- and 3α-bromides. Reaction of methyl gibberellate with fluoroamine and lithium chloride gave[4] entirely 1β-chloro compounds differing in the nature of the 13-substituents. MacMillan has described[5] the chlorination of methyl gibberellate with toluene-*p*-sulphonyl chloride and lithium chloride which gave predominantly the 3α-chloride (63%) with only a little (11%) 1β-chloride. In connection with gibberellin partial synthesis,[6] we contrasted[7] the reaction of methyl gibberellate (**1**) and triphenylphosphine–carbon tetrachloride with that of its 3-epimer (**2**). This reaction gave products derived from both simple bimolecular substitution and from rearrangement. In the rearrangement reaction, the 3β-(axial) alcohol gave the *syn* 1β-chloro compounds whilst the 3α-(equatorial) epimer gave the same *anti* 1β-chloro products. This result conformed with the analysis of Toromanoff[8] who suggested that when a leaving group is quasi-axial the allylic substitution product would possess the *syn* stereochemistry whilst its quasi-equatorial epimer would afford the *anti*-product. In an effort to extend these stereochemical studies, we have examined the displacement of the 3-methanesulphonates derived from methyl gibberellate and its 3-epimer with chloride and hydroxide ions. Our results, which differ in some respects from those reported earlier with the fluoroamine–lithium chloride and toluene-*p*-sulphonyl chloride–lithium chloride systems, form the subject of this paper.

Treatment of methyl gibberellate (**1**) with methanesulphonyl chloride in pyridine gave the 3β,13-dimethanesulphonate (**3**) and the 1β-chloro-13-methanesulphonate (**17**) with which it co-crystallized. Shorter reaction times gave the 3β-monomethanesulphonate (**16**).[9] In view of the nature of the investigations alternative preparations were tried. Although the methanesulphonyl chloride–sulphur dioxide system was not successful, methanesulphonic anhydride in pyridine gave the pure dimethanesulphonate (**3**). The 3α,13-dimethanesulphonate (**4**) was obtained from the 3α,13-diol (**2**) using methanesulphonyl chloride. Unless they were purified rigorously both dimethanesulphonates decomposed easily. Gibberellin A_7 methyl ester gave a 3-methanesulphonate on brief treatment with methanesulphonyl chloride.





	R^1	R^2
(**1**)	α-H,β-OH	OH
(**2**)	α-OH,β-H	OH
(**3**)	α-H,β-OMs	OMs
(**4**)	α-OMs,β-H	OMs
(**5**)	αCl,β-H	OMs
(**6**)	αH,β-Cl	OMs
(**7**)	α-OMs,β-^{2}H	OMs
(**8**)	α-OH,β-H	OMs
(**9**)	α-H,β-OTs	OH
(**10**)	α-OTs,β-H	OH
(**11**)	α-H,β-OH	OMs
(**12**)	α-H,β-OH	H
(**13**)	α-OH,β-^{2}H	OH
(**14**)	α-OH,β-H	H
(**15**)	α-H,β-OMs	H
(**16**)	α-H,β-OMs	OH

	R^1	R^2
(**17**)	α-H,β-Cl	OMs
(**18**)	α-H,β-OH	OMs
(**19**)	α-H,β-OH	OH
(**20**)	=O	OMs
(**21**)	α-OH,β-H	OMs
(**22**)	α-OH,β-H	OH
(**23**)	α-OH,β-H	H
(**24**)	α-H,β-OH	H

When the 3β,13-dimethanesulphonate (**3**) was treated with lithium chloride in pyridine, two products were obtained. The first of these (56%) was the 1β-chloro-13-methanesulphonate (**17**). In accordance with this structural assignment, the ^{1}H n.m.r. signal at δ 4.53 (d, *J* 3 Hz, 1-H) was coupled to the 2-H signal (δ 5.95, dd, *J* 3 and 10 Hz) which in turn was coupled to the 3-H signal (δ 5.86, d, *J* 10 Hz). The magnitude (3 Hz) of the 1-H,2-H coupling constant together with the position of the 2-H signal and the 5-H signal (δ 3.13) were indicative of a 1β- rather than a 1α-chloro compound (1β,13-dichloride, $J_{1,2}$ 3 Hz; 2-H, δ 5.95; 5-H, δ 3.10; 1α,13-dichloride, $J_{1,2}$ 3.5 Hz; 2-H, δ 5.84; 5-H, δ 2.98).[5,7] The second minor product (15%) was the 3α-chloro-13-methanesulphonate (**5**) in which the 3-H signal appeared as a multiplet (δ 4.63) whilst the 2-H resonance was at δ 5.85 (*J* 2 and 9 Hz) and the 1-H resonance appeared at δ 6.22 (*J* 2 and 9 Hz), a separation which is characteristic of the Δ^1- rather than the

Table. ^{1}H N.m.r. solvent shifts for some gibberellin 1-alcohols

	Compound								
	(19)			(21)			(22)		
Proton	$CDCl_3$	C_5D_5N	Δ	$CDCl_3$	C_5D_5N	Δ	$CDCl_3$	C_5D_5N	Δ
1	4.20	4.52	0.32	4.36	4.73	0.37	4.36	4.75	0.37
2	5.96	6.21	0.25	5.82	6.05	0.17	5.88	6.05	0.17
3	5.96	5.96	0.00	5.90	5.83	−0.07	5.88	5.85	−0.03
5	2.96	3.45	0.49	3.04	3.31	0.27	3.05	3.31	0.26
6	2.70	3.03	0.33	2.77	3.06	0.29	2.73	3.03	0.30
9	2.48	2.95	0.47						
17	5.05	5.10	0.07	5.20	5.19	0.01	5.02	5.10	0.08
	5.32	5.65	0.33	5.42	5.51	0.09	5.32	5.66	0.34
18	1.23	1.34	0.11	1.21	1.29	0.08	1.21	1.29	0.08
OCH_3	3.78	3.65	−0.13	3.78	3.69	−0.09	3.78	3.66	0.12

Δ^2-gibberellins. The position of the 5-H signal at δ 3.01 was indicative of a 3α-chloro compound rather than the 3β-chloride (3α,13-dichloride, δ 3.05; 3β,13-dichloride, δ 3.35). These results contrast with those of MacMillan who found that the 3α-chloro compound predominated on chlorination of methyl gibberellate with toluene-*p*-sulphonyl chloride and lithium chloride.[5]

Treatment of the 3α,13-dimethanesulphonate (**4**) with lithium chloride in pyridine gave the 3β-chloro-13-methanesulphonate (**6**) (70%) without rearrangement. To substantiate this result the reaction was repeated with the [3β-^{2}H]-3α,13-dimethanesulphonate (**7**). The product lacked the 3-H (CHCl) signal at δ 4.56 whilst the 2-H signal (δ 5.98) was now a doublet (*J* 10 Hz) instead of a quartet (*J* 3.5 and 10 Hz). The chloride was assigned the 3β-stereochemistry since the 5-H signal was significantly deshielded and appeared at δ 3.41 rather than at higher field.

Two major products were obtained when the 3β,13-dimethanesulphonate (**3**) was heated in aqueous acetone buffered with potassium acetate. The first product (50%) was the 1β-hydroxy-13-methanesulphonate (**18**) which was contaminated with *ca.* 10% (n.m.r.) of its 1α-epimer (**21**). The second product (40%) was the 3α-hydroxy-13-methanesulphonate (**8**). The structure of the latter was confirmed by treatment with methanesulphonyl chloride which gave the known 3α,13-dimethanesulphonate (**4**). The hydrogenolysis of the 13-methylsulphonyloxy group by tri-n-butyltin hydride has been described.[10] The 13-monomethanesulphonate (**8**) was reduced with tri-n-butyltin hydride to afford 3-*epi*-gibberellin A_7 methyl ester (**14**). The mixture of 1α- and 1β-alcohols could not be separated. Hydrogenolysis of the 13-methanesulphonate with tri-n-butyltin hydride gave a mixture of 13-desoxy-1α- and 1β-alcohols (**23**) and (**24**) which were then separated by flash chromatography.

Oxidation of the 1-alcohols with chromium trioxide gave an αβ-unsaturated ketone (**20**) [δ 6.15 (2-H); 7.00 (3-H), *J* 9.5 Hz]. Reduction of the αβ-unsaturated ketone with sodium borohydride in methanolic 0.1M-cerium(III) chloride or with lithium tri-t-butoxyaluminium hydride gave the 1α-alcohol (**21**). The stereochemistry of the 1-alcohols was assigned by a comparison of the solvent shifts of the 5β-H resonance between [$^2H_5$]pyridine and [$^2H_5$]chloroform[11] (see Table).

The introduction of an oxygen substituent at C-1 in the gibberellins has added interest since a number of rare gibberellins including a group recently isolated[12] from wheat possess hydroxy groups at this centre. Solvolysis of the 3β-sulphonates provides an alternative and simpler partial synthesis of these compounds.[12] Thus the methanesulphonate of gibberellin A_7 methyl ester (**15**) gave a separable mixture of gibberellin A_{62} methyl ester (**24**), its 1α-epimer (**23**), and 3-*epi*-gibberellin A_7 methyl ester (**14**). The structures of these products were assigned on the basis of the n.m.r. resonances assigned to the ring A protons. The corresponding 3-monomethanesulphonate of methyl gibberellate gave 1β-hydroxygibberellin A_5 methyl ester (**19**),[12] its 1α-epimer (**22**) and methyl 3-*epi*-gibberellate (**2**) whilst the 3-monotoluene-*p*-sulphonate gave only 1β-hydroxygibberellin A_5 (**19**) and its 1α-epimer (**22**). A simple route to gibberellin A_{62} methyl ester (**24**) from methyl gibberellate (**1**) involved conversion into the 3β,13-dimethanesulphonate, solvolysis as above, separation of the 1α- and 1β-alcohols from the 3α-alcohol, and then hydrogenolysis of the 13-methylsulphonyloxy group[10] in the mixed 1α/1β-alcohols to afford the 13-desoxy-1-alcohols from which gibberellin A_{62} methyl ester was separated chromatographically.

In contrast to these results buffered hydrolysis of the 3α-(equatorial) epimers proceeded without rearrangement and led to the 3β-hydroxy compounds. Thus treatment of the 3-*epi*-monotoluene-*p*-sulphonate (**10**) of methyl gibberellate with buffered aqueous acetone gave methyl gibberellate (**1**) whilst the 3α,13-dimethanesulphonate (**4**) gave the 13-monomethanesulphonate of methyl gibberellate (**11**). This was characterized by hydrogenolysis of the 13-monomethanesulphonate with tri-n-butyltin hydride to give gibberellin A_7 methyl ester (**12**).[10] This affords an effective means of labelling methyl gibberellate and gibberellin A_7 methyl ester at the 3-position. Thus methyl [3β-^{2}H]-3-*epi*-gibberellate (**13**), prepared by reduction of the corresponding 3-ketone with sodium borodeuteride–cerium(III) chloride, was converted into its 3-monotoluene-*p*-sulphonate and 3α,13-dimethanesulphonate and thence into methyl [3α-^{2}H]gibberellate and methyl [3α-^{2}H]gibberellin A_7. Both samples lacked the 3-H signal whilst the 2-H signal was a simple doublet (*J* 10 Hz).

In conclusion *syn* rearrangement appears to predominate on displacement of the axial 3β-methanesulphonate whilst simple inversion of configuration occurs with the equatorial epimer. Although rearrangement was observed[7] when both epimeric alcohols were treated with triphenylphosphine–carbon tetrachloride this is not a simple displacement reaction and the allylic halides appear to undergo further reactions in the presence of the reagent.[13]

Experimental

General experimental details have been described previously.[14]

Preparation of Methanesulphonates.—(*a*) Methyl gibberellate (2 g) in pyridine (10 ml) was treated with methanesulphonyl chloride (0.9 ml) at room temperature overnight. The mixture was poured into dilute hydrochloric acid and the products

recovered in ethyl acetate. The extract was washed with dilute hydrochloric acid and water and then dried. The solvent was evaporated and the residue chromatographed on silica. Elution with 25% ethyl acetate–light petroleum gave ent-1α-*chloro*-10β-*hydroxy*-13-*methylsulphonyloxy*-20-*norgibberella*-2,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (100 mg) (**17**) which crystallized as needles, m.p. 150—152 °C (Found: C, 54.6; H, 5.3. $C_{21}H_{25}ClO_7S$ requires C, 55.3; H, 5.5%), *m/z* 424.072 ($M^+ - CH_3OH$ requires *m/z* 424.074), $\nu_{max.}$ 1 780, 1 730, 1 170, 820, and 720 cm^{-1}; δ 1.50 (3 H, s, 18-H), 2.70 (1 H, d, *J* 10.5 Hz, 6-H), 3.04 (3 H, s, SO_2Me) 3.13 (1 H, d, *J* 10.5 Hz, 5-H), 3.77 (3 H, s, OMe), 4.53 (1 H, d, *J* 3 Hz, 1-H), 5.20 and 5.40 (each 1 H, m, 17-H), 5.86 (1 H, d, *J* 10 Hz, 3-H), and 5.95 (1 H, dd, *J* 10 and 3 Hz, 2-H). Further elution with 35% ethyl acetate–light petroleum gave ent-3α,13-*dimethylsulphonyloxy*-10β-*hydroxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**3**) (1.8 g) which crystallized as plates, m.p. 100—102 °C (Found: C, 51.2; H, 5.6. $C_{22}H_{28}O_{10}S_2$ requires C, 51.2; H, 5.42%), $\nu_{max.}$ 1 780, 1 730, 1 640, 1 180, 920, 870, and 770 cm^{-1}; δ 1.29 (3 H, s, 18-H), 3.06 and 3.13 (each 3 H, s, SO_2Me), 2.84 (1 H, d, *J* 11 Hz, 6-H), 3.33 (1 H, d, *J* 11 Hz, 5-H), 3.78 (3 H, s, OMe), 5.08 (1 H, d, *J* 3.5 Hz, 3-H), 5.18 and 5.48 (each 1 H, m, 17-H), 6.06 (1 H, dd, *J* 3.5 and 9.5 Hz, 2-H), and 6.54 (1 H, d, *J* 9.5 Hz, 1-H).

(*b*) Methyl gibberellate (500 mg) in pyridine (5 ml) was treated with methanesulphonyl chloride (0.12 ml) at room temperature for 3 h. The reaction mixture was worked up as above and chromatographed on silica. Elution with 35% ethyl acetate–light petroleum gave *ent*-3α-methylsulphonyloxy-10,13-dihydroxy-20-norgibberella-1,16-diene-7,19-dioic acid 19,10β-lactone 7-methyl ester (480 mg), m.p. 143—145 °C (Found: C, 57.5; H, 5.9. $C_{21}H_{26}O_8S$ requires C, 57.5; H, 5.9%), $\nu_{max.}$ 3 550, 1 770, 1 730, 1 175, 925, and 725 cm^{-1}; δ 1.24 (3 H, s, 18-H), 2.74 (1 H, d, *J* 11 Hz, 6-H), 3.08 (3 H, s, SO_2Me), 3.28 (1 H, d, *J* 11 Hz, 5-H), 3.74 (3 H, s, OMe), 5.00 and 5.25 (each 1 H, m, 17-H), 5.04 (1 H, d, *J* 4 Hz, 3-H), 5.98 (1 H, dd, *J* 4 and 9 Hz, 2-H), and 6.45 (1 H, d, *J* 9 Hz, 1-H).

(*c*) Methyl gibberellate (500 mg) in pyridine (10 ml) was treated with methanesulphonic anhydride (300 mg) and left for 24 h. The mixture was poured into dilute hydrochloric acid and the product recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and water and dried. The solvent was evaporated and the residue crystallized to afford the above 3β,13-dimethanesulphonate which was identified by its n.m.r. spectrum.

(*d*) Methyl 3-*epi*-gibberellate (330 mg) in pyridine (5 ml) was treated with methanesulphonyl chloride (0.2 ml) at room temperature overnight. The reaction was worked up as above to afford ent-3β,13-*dimethylsulphonyloxy*-10β-*hydroxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (310 mg), m.p. 166—168 °C (Found: C, 51.2; H, 5.2. $C_{22}H_{28}O_{10}S_2$ requires C, 51.2; H, 5.4%), $\nu_{max.}$ 1 785, 1 735, 1 180, 1 170, 910, 810, and 770 cm^{-1}; δ 1.30 (3 H, s, 18-H), 2.82 (1 H, d, *J* 11 Hz, 5-H), 3.04 and 3.10 (each 3 H, s, SO_2Me), 3.05 (1 H, d, *J* 11 Hz, 6-H), 3.78 (3 H, s, OMe), 5.18 and 5.41 (each 1 H, m, 17-H), 5.32 (1 H, m, 3-H), 5.98 (1 H, dd, *J* 3 and 10 Hz, 2-H), and 6.43 (1 H, d, *J* 10 Hz, 1-H). The corresponding [3-^{2}H] derivative was prepared as above and lacked the δ5.32 signal in the n.m.r. spectrum. The signal at δ 5.98 appeared as a doublet (*J* 10 Hz).

(*e*) Gibberellin A_7 methyl ester (300 mg) in pyridine (4 ml) was treated with methanesulphonyl chloride (0.2 ml) at room temperature for 20 h. The reaction was worked up as above to afford ent-10β-*hydroxy*-3α-*methylsulphonyloxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (280 mg), m.p. 125—127 °C (Found: C, 59.8; H, 6.2. $C_{21}H_{26}O_7S$ requires C, 59.7; H, 6.2%), $\nu_{max.}$ 1 780, 1 735, 1 180, 930, and 760 cm^{-1}; δ 1.25 (3 H, s, 18-H), 2.70 (1 H, d, *J* 11 Hz, 6-H), 3.04 (3 H, s, SO_2Me), 3.24 (1 H, d, *J* 11 Hz, 5-H), 3.70 (3 H, s, OMe), 4.85 and 4.98 (each 1 H, m, 17-H), 5.00 (1 H, d, *J* 4 Hz, 3-H), 5.90 (1 H, dd, *J* 4 and 9 Hz, 2-H), 6.41 (1 H, d, *J* 9 Hz, 1-H).

Preparation of Toluene-p-*sulphonates.*—(*a*) Methyl 3-*epi*-gibberellate (150 mg) in pyridine (2 ml) was treated with toluene-*p*-sulphonyl chloride (79 mg) at room temperature for 4 days. The reaction was worked up as above to afford ent-10β,13-*dihydroxy*-3β-p-*tolylsulphonyloxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (140 mg) which crystallized as needles, m.p. 145—148 °C (Found: C, 62.85; H, 5.7. $C_{27}H_{30}O_8S$ requires C, 63.0; H, 5.8%), $\nu_{max.}$ 3 520, 3 475, 1 780, 1 775, 1 715, 1 600, 1 190, 860, and 725 cm^{-1}; δ 1.05 (3 H, s, 18-H), 2.45 (3 H, s, Ar-Me), 2.70 (1 H, d, *J* 11 Hz, 6-H), 2.98 (1 H, d, *J* 11 Hz, 5-H), 3.75 (3 H, s, OMe), 4.92 and 5.23 (each 1 H, m, 17-H), 5.15 (1 H, m, 3-H), 5.72 (1 H, dd, *J* 3 and 10 Hz, 2-H), 6.35 (1 H, d, *J* 10 Hz, 1-H), and 7.30 and 7.80 (each 2 H, d, *J* 8 Hz, ArH). The corresponding [3-^{2}H] derivative was prepared as above. The n.m.r. spectrum lacked the signal at δ 5.15 whilst the signal at δ 5.72 appeared as a doublet *J* 10 Hz.

(*b*) Treatment of methyl gibberellate as above afforded ent-10β,13-*dihydroxy*-3α-p-*tolylsulphonyloxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester*, m.p 168—170 °C (Found: C, 63.3; H, 6.1. $C_{27}H_{30}O_8S$ requires C, 63.0; H, 5.8%), ν_{max} 3 415, 1 780, 1 735, 1 600, 860, and 665 cm^{-1}; δ 1.31 (3 H, s, 18-H), 2.19 (3 H, s, ArMe), 2.74 (1 H, d, *J* 11 Hz, 6-H), 3.10 (1 H, d, *J* 11 Hz, 5-H), 3.78 (3 H, s, OMe), 4.70 (1 H, m, 3-H), 4.98 and 5.25 (each 1 H, m, 17-H), 5.91 (1 H, dd, *J* 3 and 9 Hz, 2-H), 6.30 (1 H, dd, *J* 1.5 and 9 Hz, 1-H), and 7.31 and 7.80 (each 2 H, d, *J* 8 Hz, ArH).

Reactions with Lithium Chloride.—(*a*) The 3,13-dimethanesulphonate of methyl gibberellate (500 mg) in pyridine (10 ml) was treated with lithium chloride (250 mg) at 0 °C. The mixture was allowed to warm to room temperature and then left for 2 days. The mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue, which contained two major products by t.l.c. analysis, was chromatographed on silica. Elution with 30% ethyl acetate–light petroleum gave the 1β-chloro compound (**17**) (250 mg), m.p. 150—152 °C, identified by its n.m.r. spectrum. Elution with 40% ethyl acetate–light petroleum gave ent-3β-*chloro*-13-*methylsulphonyloxy*-10β-*hydroxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**5**) (70 mg) as a gum (Found: *m/z* 424.073 ($C_{21}H_{25}ClO_7S - CH_3OH$ requires *m/z* 424.074), $\nu_{max.}$ 1 775 and 1 725 cm^{-1}; δ 1.30 (3 H, s, 18-H), 2.78 (1 H, d, *J* 10 Hz, 6-H), 3.02 (3 H, s, SO_2Me), 3.01 (1 H, d, *J* 10 Hz, 5-H), 3.73 (3 H, s, OMe), 4.63 (1 H, m, 3-H), 5.14 and 5.38 (each 1 H, m, 17-H), 5.85 (1 H, dd, *J* 2 and 9 Hz, 2-H), and 6.22 (1 H, dd, *J* 2 and 9 Hz, 1-H).

(*b*) The 3,13-dimethanesulphonate of methyl 3-*epi*-gibberellate (**4**) (400 mg) in pyridine (10 ml) was stirred with lithium chloride (200 mg) as above. The product was recovered as above to afford ent-3α-*chloro*-13-*methylsulphonyloxy*-10β-*hydroxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**6**) (250 mg) as a gum (Found: *m/z* 424.073. $C_{21}H_{25}ClO_7S - CH_3OH$ requires *m/z* 424.074), $\nu_{max.}$ 1 775, 1 725, 1 630, 900, and 810 cm^{-1}; δ 1.34 (3 H, s, 18-H), 2.86 (1 H, d, *J* 11 Hz, 6-H), 3.04 (3 H, s, SO_2Me), 3.41 (1 H, d, *J* 11 Hz, 5-H), 3.78 (3 H, s, OMe), 5.18 and 5.41 (each 1 H, m, 17-H), 4.56 (1 H, d, *J* 3.5 Hz, 3-H), 5.98 (1 H, dd, *J* 3.5 and 10 Hz, 2-H), and 6.30 (1 H, d, *J* 10 Hz, 1-H).

(*c*) Treatment of the 3,13-dimethanesulphonate of methyl 3-*epi*-[3-^{2}H]gibberellate (400 mg) under the same conditions gave the [3-^{2}H]-3-chloro compound (230 mg) (Found: *m/z* 425. $C_{21}H_{24}{}^2HClO_7S - CH_3OH$ requires *m/z* 425) which lacked

the n.m.r. signal at δ 4.56 whilst the signal at δ 5.98 was a doublet (*J* 10 Hz).

Solvolysis of the Dimethanesulphonate of Methyl Gibberellate.—The dimethanesulphonate (**3**) (1.2 g) in acetone (50 ml) was treated with potassium acetate (500 mg) in water (50 ml) for 3 h under reflux. The solution was concentrated and the products recovered in ethyl acetate and chromatographed on silica. Elution with 35% ethyl acetate–light petroleum gave a mixture of *ent*-1α,10β- and *ent*-1β,10β-dihydroxy-13-methylsulphonyloxy-20-norgibberella-2,16-diene-7,19-dioic acid 19,10β-lactone 7-methyl ester (**18**) and (**21**) (500 mg). Further elution with 40% ethyl acetate–light petroleum gave ent-3β,10β-*dihydroxy*-13-*methylsulphonyloxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**8**) (400 mg) as a gum (Found: C, 57.4; H, 6.0. $C_{21}H_{26}O_8S$ requires C, 57.5; H, 5.9%), $\nu_{max.}$ 3 400, 1 780, 1 740, 1 660, 910, and 760 cm^{-1}; δ 1.30 (3 H, s, 18-H), 2.84 (1 H, d, *J* 10.5 Hz, 6-H), 2.95 (1 H, d, *J* 10.5 Hz, 5-H), 3.03 (3 H, s, SO_2Me), 3.78 (3 H, s, OMe), 4.30 (1 H, m, 3-H), 5.18 and 5.41 (each 1 H, m, 17-H), 5.92 (1 H, dd, *J* 2.5 and 9 Hz, 2-H), and 6.24 (1 H, dd, *J* 1.5 and 9 Hz, 1-H). Treatment of the above gum (100 mg) with methanesulphonyl chloride in pyridine overnight afforded the 3,13-dimethanesulphonate (**4**) (90 mg) which was identified by its n.m.r. spectrum.

Reduction of the 13-*Methanesulphonate* (**8**) *with Tri-n-Butyltin Hydride.*—The methanesulphonate (**8**) (100 mg) in benzene (10 ml) was treated with tri-n-butyltin hydride (0.5 ml) and azobisisobutyronitrile (10 mg) under reflux for 1 h. The solvent was evaporated and the residue chromatographed on silica. Elution with 25% ethyl acetate–light petroleum gave ent-3β,10β-*dihydroxy*-20-*norgibberella*-1,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**14**) (50 mg) which crystallized as needles, m.p. 138—141 °C (Found: C, 69.8; H, 7.12. $C_{20}H_{24}O_5$ requires C, 69.8; H, 7.0%), $\nu_{max.}$ 3 450, 1 770, 1 730, 1 660, and 890 cm^{-1}; δ 1.30 (3 H, s, 18-H), 2.75 (1 H, d, *J* 11 Hz, 6-H), 2.94 (1 H, d, *J* 11 Hz, 5-H), 3.70 (3 H, s, OMe), 4.30 (1 H, m, 3-H), 4.89 and 5.02 (each 1 H, m, 17-H), 5.89 (1 H, dd, *J* 3 and 10 Hz, 2-H), and 6.36 (1 H, dd, *J* 1.5 and 10 Hz, 1-H).

Reduction of the Methanesulphonates (**18**) *and* (**21**) *with Tri-n-butyltin Hydride.*—The above mixture of methanesulphonates (180 mg) in benzene (15 ml) was heated under reflux with tri-n-butyltin hydride (0.8 ml) and azobisisobutyronitrile (20 mg) for 1 h. The solvent was evaporated and the residue chromatographed on silica. Elution with 15% ethyl acetate–toluene afforded *ent*-1α,10β-dihydroxy-20-norgibberella-2,16-diene-7,19-dioic acid 19,10β-lactone 7-methyl ester (**24**) (55 mg) which crystallized as plates, m.p. 182—184 °C (lit.,[12] gum) (Found: C, 69.8; H, 6.9. Calc. for $C_{20}H_{24}O_5$: C, 69.8; H, 7.0%), $\nu_{max.}$ 3 600, 1 780, 1 730, 1 660, and 860 cm^{-1}; δ 1.20 (3 H, s, 18-H), 2.65 (1 H, d, *J* 10 Hz, 6-H), 2.90 (1 H, d, *J* 10 Hz, 5-H), 3.70 (3 H, s, OMe), 4.20 (1 H, m, 1-H), 4.86 and 4.95 (each 1 H, m, 17-H), 5.86 (2 H, s, 2- and 3-H). Further elution with 15% ethyl acetate–toluene gave ent-1β,10β-*dihydroxy*-20-*norgibberella*-2,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**23**) (15 mg) which crystallized as plates, m.p. 169—171 °C (Found: C, 69.7; H, 7.00. $C_{20}H_{24}O_5$ requires C, 69.8; H, 7.0%), $\nu_{max.}$ 3 600, 1 780, 1 735, 1 660, and 900 cm^{-1}; δ 1.20 (3 H, s, 18-H), 2.63 (1 H, d, *J* 10 Hz, 6-H), 2.95 (1 H, d, *J* 10 Hz, 5-H), 3.69 (3 H, s, OMe), 4.10 (1 H, m, 1-H), 4.86 and 4.95 (each 1 H, m, 17-H), and 5.85 (2 H, m, 2- and 3-H).

Oxidation of the Methanesulphonates (**18**) *and* (**21**).—The above mixture of methanesulphonates (300 mg) in acetone (15 ml) was treated with the 8N-chromium trioxide reagent (0.5 ml) at room temperature for 10 min. The excess of reagent was destroyed with methanol and the solvents evaporated. The residue was taken up in water and the products recovered in ethyl acetate. The extract was washed with water and dried. The solvent was evaporated to give ent-1-*oxo*-10β-*hydroxy*-13-*methylsulphonyloxy*-20-*norgibberella*-2,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**20**) (250 mg) as a gum (Found: C, 57.9; H, 5.6. $C_{21}H_{24}O_8S$ requires C, 57.8; H, 5.5%), $\nu_{max.}$ 1 790, 1 735, 1 720, 1 660, 890, and 722 cm^{-1}; δ 1.36 (3 H, s, 18-H), 2.84 (1 H d, *J* 11 Hz, 6-H), 3.08 (3 H, s, SO_2Me), 3.42 (1 H, d, *J* 11 Hz, 5-H), 3.80 (3 H, s, OMe), 5.15 and 5.40 (each 1 H, m, 17-H), 6.12 (1 H, d, *J* 10 Hz, 2-H), and 7.04 (1 H, d, *J* 10 Hz, 3-H).

Reduction of the Ketone (**20**).—(i) The above ketone (**20**) (200 mg) in methanolic cerium chloride (0.1M; 20 ml) was treated with sodium borohydride (200 mg) for 1 h in an ice-bath. The solvent was evaporated, dilute hydrochloric acid was added to the residue, and the product was recovered in ethyl acetate. The extract was washed thoroughly with water and dried. The solvent was evaporated to give ent-1β,10β-*dihydroxy*-13-*methylsulphonyloxy*-20-*norgibberella*-2,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**21**) (150 mg) as a gum (Found: C, 57.4; H, 5.8. $C_{21}H_{26}O_8S$ requires C, 57.5; H, 5.9%), $\nu_{max.}$ 3 450, 1 780, 1 735, 1 660, 925, and 890 cm^{-1}; δ 1.24 (3 H, s, 18-H), 2.72 (1 H, d, *J* 10.5, 6-H), 2.94 (1 H, d, *J* 10.5 Hz, 5-H), 3.05 (3 H s, SO_2Me), 3.78 (3 H, s, OMe), 4.17 (1 H, m, 1-H), 5.20 and 5.42 (each 1 H, m, 17-H), 5.82 (1 H, dd, *J* 3.5 and 10 Hz, 2-H), and 5.90 (1 H, dd, *J* 2 and 10 Hz, 3-H).

(ii) Lithium aluminium hydride (200 mg) was stirred with t-butyl alcohol (15 ml) for 30 min. The above ketone (**20**) (120 mg) in t-butyl alcohol (5 ml) was added and the mixture left for a further 1 h. Water was added and the product was recovered in ethyl acetate to afford the alcohol (**21**) (100 mg) identified by its n.m.r. spectrum.

Solvolysis of the Methanesulphonate of Gibberellin A_7 *Methyl Ester* (**15**).—The methanesulphonate (**15**) (240 mg) in acetone (10 ml) was heated with potassium acetate (120 mg) in water (20 ml) under reflux for 3 h. The acetone was evaporated and the aqueous residue extracted with ethyl acetate. The extract was washed with water and dried. The solvent was evaporated and the residue chromatographed on silica. Elution with 12% ethyl acetate–light petroleum gave *ent*-1β,10β-dihydroxy-20-norgibberella-2,16-diene-7,19-dioic acid 19,10β-lactone 7-methyl ester (**23**) (20 mg) which was identified by its n.m.r. spectrum. Further elution gave *ent*-1α,10β-dihydroxy-20-norgibberella-2,16-diene-7,19-dioic acid 19,10β-lactone 7-methyl ester (**24**) (60 mg) which was also identified by its n.m.r. spectrum. Elution with 15% ethyl acetate–light petroleum gave *ent*-3β,10β-dihydroxy-20-norgibberella-1,16-diene-7,19-dioic acid 19,10β-lactone 7-methyl ester (**14**) (85 mg) which crystallized as needles, m.p. 138—141 °C, and was identified by its n.m.r. spectrum.

Solvolysis of the 3-*Monomethanesulphonate of Methyl Gibberellate* (**16**).—The monomethanesulphonate (**16**) (400 mg) in acetone (20 ml) was heated under reflux with potassium acetate (200 mg) in water (20 ml) for 3.5 h. The acetone was evaporated and the aqueous residue extracted with ethyl acetate. The extract was washed with water and dried. The solvent was evaporated and the residue chromatographed on silica. Elution with 35% ethyl acetate–light petroleum gave ent-1β,10β,13-*trihydroxy*-20-*norgibberella*-2,16-*diene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**22**) (40 mg) as an amorphous solid (Found: C, 66.3; H, 6.8. $C_{20}H_{24}O_6$ requires C, 66.6; H, 6.7%), $\nu_{max.}$ 3 500, 1 780, 1 735, 1 660, 1 020, and 890 cm^{-1}; δ 1.21 (3 H, s, 18-H), 2.73 (1 H, d, *J* 10.5 Hz, 6-H), 3.00 (1 H, d, *J* 10.5 Hz, 5-H), 3.77 (3 H, s, OMe), 4.38 (1 H, m, 1-H), 5.02 and 5.32 (each 1 H, m, 17-H), and 5.88 (2 H, m, 2- and 3-H). Further elution gave *ent*-1α,10β,13-trihydroxy-20-norgibberella-2,16-diene-7,19-dioic acid 19,10β-lactone 7-methyl ester (**19**) (90

mg) as an amorphous solid (Found: C, 66.4; H, 6.9. Calc. for $C_{20}H_{24}O_6$: C, 66.6; H, 6.7%), $\nu_{max.}$ 3 550, 1 780, 1 735, 1 660, 1 020, and 890 cm^{-1}; δ 1.23 (3 H, s, 18-H), 2.70 (1 H, d, *J* 10.5 Hz, 6-H), 2.96 (1 H, d, *J* 10.5 Hz, 5-H), 3.78 (3 H, s, OMe), 4.2 (1 H, m, 1-H), 5.03 and 5.32 (each 1 H, m, 17-H), and 5.96 (2 H, m, 2- and 3-H). Further elution with 40% ethyl acetate–light petroleum gave *ent*-3β,10β,13-trihydroxy-20-norgibberella-1,16-diene-7,19-dioic acid 19,10β-lactone 7-methyl ester (160 mg) which crystallized as prisms, m.p. 176—177 °C (lit.,[15] 173—176 °C) identified by its i.r. and n.m.r. spectra. Treatment of the toluene-*p*-sulphonate (**9**) (300 mg) under comparable conditions gave the *ent*-1β-alcohol (**22**) (30 mg) and the *ent*-1α-alcohol (**19**) (90 mg) which were identified by their n.m.r. spectra.

Solvolysis of the 3,13-*Dimethanesulphonate of Methyl* 3-epi-*Gibberellate* (**4**).—The dimethanesulphonate (**4**) (200 mg) in acetone (25 ml) and water (25 ml) containing potassium acetate (150 mg) was heated under reflux for 5 h. The acetone was evaporated and the products were recovered in ethyl acetate and chromatographed in silica. Elution with 35% ethyl acetate–light petroleum gave *ent*-3α,10β-dihydroxy-13-methylsulphonyloxy-20-norgibberella-1,16-diene-7,19-dioic acid 19,10β-lactone 7-methyl ester (**11**) (160 mg) as a gum, δ 1.25 (3 H, s, 18-H), 2.80 (1 H, d, *J* 10.5 Hz, 6-H), 3.04 (3 H, s, SO_2Me), 3.25 (1 H, d, *J* 10.5 Hz, 5-H), 3.80 (3 H, s, OMe), 4.25 (1 H, m, 3-H), 5.15 and 5.38 (each 1 H, m, 17-H), 5.90 (1 H, dd, *J* 3 and 10 Hz, 2-H), and 6.30 (1 H, d, *J* 10 Hz, 1-H). The n.m.r. spectrum indicated the presence of an impurity (*ca.* 10%) which would not be removed. The above 13-monomethanesulphonate (160 mg) in benzene (10 ml) was heated under reflux with tri-n-butyltin hydride (0.3 ml) and azobisisobutyronitrile (10 mg) for 1 h. The solvent was evaporated and the residue chromatographed on silica to afford gibberellin A_7 methyl ester (**12**) (120 mg) as needles, m.p. 153—154 °C (lit.,[16] 152—153 °C) identified by its i.r. and n.m.r. spectra. Repetition of the above experiment with the 3,13-dimethanesulphonate of methyl [3β-^{2}H]-3-*epi*-gibberellate (200 mg) gave [3α-^{2}H]gibberellin A_7 methyl ester (115 mg). The ^{1}H n.m.r. spectrum lacked a signal at δ 4.18 (3-H) whilst the signal at δ 5.80 was a doublet (*J* 10 Hz).

Solvolysis of the 3-*Monotoluene*-p-*sulphonate of Methyl* 3-epi-*Gibberellate* (**10**).—The monotoluene-*p*-sulphonate (**10**) (100 mg) in acetone (25 ml) and water (25 ml) was heated under reflux with potassium acetate (70 mg) for 5 h. The acetone was evaporated and the product recovered in ethyl acetate and chromatographed on silica. Elution with 45% ethyl acetate–light petroleum gave methyl gibberellate (**1**) (50 mg) which crystallized as needles, m.p. 203—205 °C (lit.,[17] m.p. 209—210 °C) identified by its i.r. and n.m.r. spectra. Repetition with the 3-monotoluene-*p*-sulphonate of methyl [3-^{2}H]-3-*epi*-gibberellate (100 mg) gave methyl [3α-^{2}H]gibberellate (45 mg), m.p. 204—205 °C. The ^{1}H n.m.r. spectrum (determined in [$^2H_5$]pyridine) lacked a signal at δ 4.42 whilst the signals at δ 6.10 (2-H) and 6.40 (1-H) were doublets with *J* 10 Hz.

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References

1 K. H. Overton, *Chemical Society Reviews*, 1979, **8**, 447.
2 R. M. Magid, *Tetrahedron*, 1980, **36**, 1901.
3 E. J. Corey, T. M. Brennan, and R. L. Carney, *J. Am. Chem. Soc.*, 1971, **93**, 7316.
4 R. E. Banks and B. E. Cross, *J. Chem. Soc., Perkin Trans. 1*, 1977, 512; B. E. Cross and I. C. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 98.
5 J. R. Bearder, P. S. Kirkwood, and J. MacMillan, *J. Chem. Soc., Perkin Trans. 1*, 1981, 672.
6 J. R. Hanson, in 'British Plant Growth Regulator Group, Monograph 5, 1980, Gibberellins,' ed. J. R. Lenton, p. 5.
7 Z. J. Duri, B. M. Fraga, and J. R. Hanson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3016.
8 E. Toromanoff, *Tetrahedron*, 1978, **34**, 1665.
9 N. Murofushi, R. C. Durley, and R. P. Pharis, *Agric. Biol. Chem.*, 1974, **38**, 475.
10 M. H. Beale and J. MacMillan, *J. Chem. Res.* 1980, (*S*), 289; (*M*) 3536.
11 J. R. Hanson, *J. Chem. Soc.*, 1965, 5036.
12 P. Gaskin, P. S. Kirkwood, J. R. Lenton, J. MacMillan, and M. E. Radley, *Agric. Biol. Chem.*, 1980, **44**, 1589; P. S. Kirkwood and J. MacMillan, *J. Chem. Soc., Perkin Trans. 1*, 1982, 689; P. S. Kirkwood, J. MacMillan, and M. Hutchinson, *J. Chem. Soc., Perkin Trans. 1*, 1982, 707.
13 Z. J. Duri and J. R. Hanson, unpublished results.
14 J. R. Hanson, J. Hawker, and A. F. White, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1892.
15 B. Voigt, G. Adam, N. S. Kobrina, E. P. Serebryakov, and N. D. Zelinsky, *Z. Chem.*, 1977, **17**, 372; I. A. Gurvich, N. S. Kobrina, and V. F. Kucherov, *Izv. Akad. Nauk. SSR, Ser. Khim.*, 1969, 1805.
16 B. E. Cross, R. H. B. Galt, and J. R. Hanson, *Tetrahedron*, 1962, **18**, 451.
17 B. E. Cross, *J. Chem. Soc.*, 1954, 4670.

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