The Partial Synthesis of 6-*epi*-Gibberellin A_{13} and 6-*epi*-Gibberellin A_{25} Derivatives

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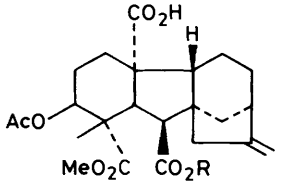
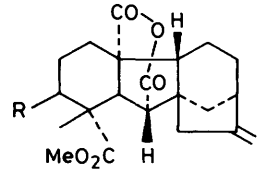
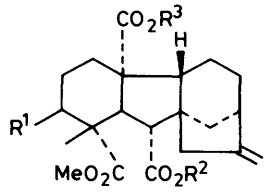
The preparation of 6-*epi*-GA_{13} and 6-*epi*-GA_{25} derivatives has been carried out from GA_{13} by epimerization at C-6 through an internal C-7,C-20 anhydride.

In previous work we have synthesized gibberellin analogues from diterpenes isolated from the genus *Sideritis*[1] or from other gibberellins.[2] Continuing these studies, we attempted to prepare the mixed anhydride (**1**) from the diacid (**2**) by treatment with tosyl chloride in triethylamine. However, we did not obtain the target product but instead the anhydride (**3**) by epimerization at C-6. This result permitted the preparation of the methyl esters of 6-*epi*-GA_{13} (**7**) and 6-*epi*-GA_{25} (**8**) as described here.





(**1**) R = Ts
(**2**) R = H
(**3**) R = OAc
(**4**) R = OH
(**5**) R = Imidazol-1-yl-C(S)O
(**6**) R = H

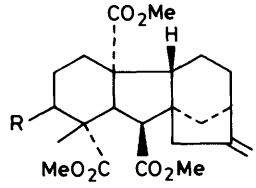


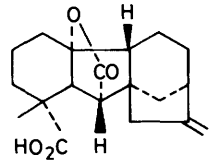
(**7**) R^1 = OH, R^2 = R^3 = Me
(**8**) R^1 = H, R^2 = R^3 = Me
(**9**) R^1 = OH, R^2 = Me, R^3 = H
(**10**) R^1 = Imidazol-1-yl-C(S)O, R^2 = R^3 = Me
(**11**) R^1 = R^2 = R^3 = H
(**12**) R^1 = OH, R^2 = H, R^3 = Me

Treatment of the anhydride (**3**) with methanolic potassium hydroxide gave the monoacid (**9**) and the hydrolysis product (**4**). When pure methanol or methanol–toluene-*p*-sulphonic acid was used in the methanolysis, starting material was recovered. Methylation of (**9**) with diazomethane afforded the trimethyl ester of 6-*epi*-GA_{13} (**7**). The coupling constant observed between 5-H and 6-H in this compound was 9 Hz, while in the trimethyl ester of GA_{13} (**13**) it was 12 Hz. In general, the ^{1}H n.m.r. spectra of these two epimeric compounds are different, while their mass spectra are very similar.

The trimethyl ester of 6-*epi*-GA_{13} (**7**) was transformed into the corresponding derivatives of 6-*epi*-GA_{25} (**8**) by formation of its thiocarbonylimidazole derivative (**10**) and reduction with tributyltin hydride; similarly the GA_{13} trimethyl ester (**13**) was transformed into the GA_{25} trimethyl ester (**15**).[3] The ^{13}C n.m.r. data of compounds of this 6-*epi* series are presented in the Table.

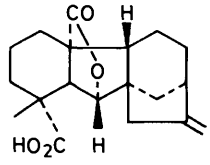
With the idea of preparing the GA_9 isomers, (**16**) and (**17**),





(**13**) R = OH
(**14**) R = Imidazol-1-yl-C(S)O
(**15**) R = H

(**16**)



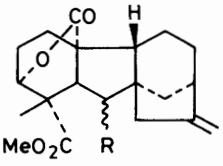
(**17**)

Table. Assignment of ^{13}C n.m.r. spectra of 6-*epi*-C_{20} gibberellin derivatives

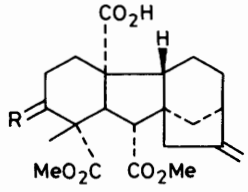
Carbon atom	(9)	(22)	(8)	Carbon atom	(9)	(22)	(8)
1	31.87	37.30	37.60	11	18.80	18.86	19.01
2	28.86	30.12	20.61	12	32.12	31.72	32.11
3	71.77	79.85	41.23	13	39.65	39.58	39.68
4	49.80	50.74	44.43	14	33.00	33.03	32.93
5	50.98	56.81	58.24	15	53.00	52.98	53.50
6	50.11	51.43	50.11	16	157.47	157.08	157.96
7	174.60[a]	173.38[a]	173.97[a]	17	106.60	106.78	106.43
8	50.60	50.74	49.86	18	21.50	23.18	26.43
9	59.49	59.13	60.21	19	174.93[a]	175.19[a]	175.33[a]
10	57.11	57.40	55.46	20	177.21[a]	175.62[a]	172.23[a]

[a] Resonances may be interchanged.

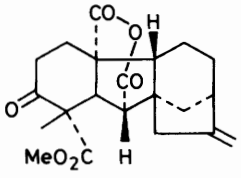
the following reactions were carried out. Treatment of the anhydride (**4**) with *N,N'*-thiocarbonyldi-imidazole in 1,2-dichloroethane afforded (**5**), which was reduced by tributyltin-hydride to give (**6**). The anhydride (**6**) was then treated with aqueous potassium hydroxide in tetrahydrofuran and the diacid (**11**) was obtained. Reaction of this with lead tetra-acetate gave an intractable mixture of products from which the methyl ester of the GA_9 isomers could not be isolated. This oxidative decarboxylation reaction with 19,20-diacid gibberellin derivatives has been used to prepare C_{19} gibberellins from C_{20} gibberellins albeit in very low yield.[4] When the diacid (**11**) was treated with diazomethane the trimethyl ester of 6-*epi*-GA_{25} (**8**) was again obtained.



(**18**) R = α-CO_2Me
(**19**) R = α-CO_2H
(**20**) R = β-CO_2H



(**21**) R = O
(**22**) R = α-OH



(**23**)

The methanolysis of (**3**) was shown to occur with attack at the C-7 carbonyl group to form (**9**), and not at the C-20 carbonyl group to give (**12**). The lactone (**18**) was obtained as follows. The monoacid (**9**) was oxidized with Jones reagent to give the ketone (**21**). This was reduced with sodium borohydride to afford the 3α-alcohol (**22**). Treatment of (**22**) with acetic anhydride gave the lactone (**18**). This compound was also obtained by reaction of (**4**) with aqueous potassium hydroxide in tetrahydrofuran and methylation with diazomethane. Alternatively, (**18**) was prepared *via* the keto anhydride (**23**), obtained by oxidation of (**4**). Reduction of this with sodium borohydride gave the lactone (**19**), which was treated with diazomethane to afford (**18**). The lactone (**19**) offers the possibility of also obtaining 6-*epi*-GA_{37} (**24**) in a manner similar to the preparation of GA_{37} (**25**) from (**20**).[5]

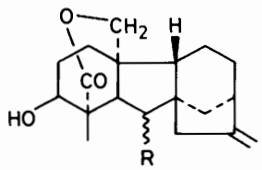
The epimerization at C-6 on chemical precursors of gibberellins has been carried out by Corey *et al.*[6] in the synthesis of GA_3 (**26**) by capture of the C-7 carbonyl by the C-19 carboxylic group in (**28**) to form the anhydride (**29**), using dicyclohexyl-carbodi-imide in tetrahydrofuran–triethylamine as reagent. In our case, the role of the C-19 acid has been substituted by the C-20 acid.

The partial synthesis of 6-*epi*-GA_3 (**27**) has been achieved through the epimerization of a 6β-aldehyde to a 6α-aldehyde.[7]

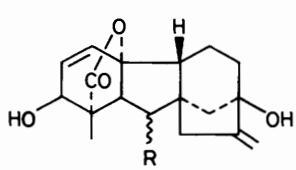
Experimental

M.p.s are determined with a Kofler hot-plate apparatus and are uncorrected. I.r. were taken for solutions in $CHCl_3$. Silica gel Merck (0.05—0.2 mm) was used for column chromatography.

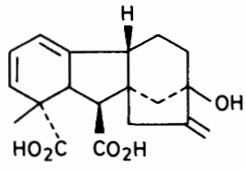
Preparation of ent-3α-*Acetoxygibberell*-16-*ene*-7,19,20-*trioic Acid* 7,20-*Anhydride* 19-*Methyl Ester* (**3**).—The anhydride (**30**)



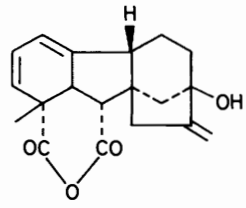
(**24**) R = α-CO_2H
(**25**) R = β-CO_2H



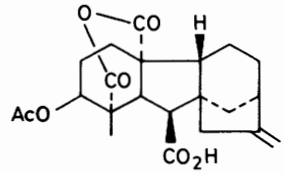
(**26**) R = β-CO_2H
(**27**) R = α-CO_2H



(**28**)



(**29**)



(**30**)

(450 mg)[8] in dry methanol (15 ml) was refluxed for 40 h. The solvent was evaporated off and the dicarboxylic acid (**2**) was obtained.[9] Compound (**2**) without purification in dry tetrahydrofuran (18 ml) and triethylamine (1.2 ml) was treated with toluene-*p*-sulphonyl chloride (275 mg) and stirred at room temperature, under argon, for 17 h. The solvent was evaporated off and the crude product was dissolved in ethyl acetate, washed with water, and dried. The extract obtained was chromatographed on silica using ethyl acetate–light petroleum (15%, v/v) as the eluant to give *the anhydride* (**3**) (350 mg), m.p. 168—169 °C (Found: C, 66.05; H, 7.0. $C_{23}H_{28}O_7$ requires C, 66.33; H, 6.78); $\nu_{max.}$ 3 010, 1 800, 1 755, 1 735, and 880 cm^{-1}; δ_H (200 MHz) 1.29 (3 H, s, 18-H), 2.08 (3 H, s, OAc), 2.25 and 3.20 (each 1 H, d, *J* 3 Hz, 5-H, and 6-H), 3.62 (3 H, s, OMe), 4.91 and 5.02 (each 1 H, br s, 17-H), and 5.32 (1 H, t, 3-H); *m/z* 372 (M^+ − 44, 26%), 346(3), 344(5), 329(3), 313(15), 284(70), 269(10), 253(9), 225(56), 171(14), 157(12), 146(35), 133(38), and 119(78).

Methanolysis Experiments.—(*a*) The anhydride (**3**) (125 mg) was refluxed with dry methanol (15 ml) for 24 h. The solvent was evaporated off and (**3**) was recovered unaltered. When toluene-*p*-sulphonic acid (2.5 mg) was added to the same reaction the starting material was again recovered.

(*b*) The anhydride (**3**) (125 mg) in a minimum quantity of chloroform was treated with methanolic potassium hydroxide (6 ml) (13 mg/ml methanol) for 2.5 h at room temperature. The solvent was evaporated off, water was added, and the product was recovered in ethyl ether to afford a gum which was chromatographed on silica. Elution with ethyl acetate–light petroleum (30%, v/v) gave ent-3α-*hydroxy*-6-epi-*gibberell*-16-*ene*-7,19,20-*trioic acid* 7,20-*anhydride* 19-*methyl ester* (**4**) (55 mg), m.p. 209.5—211 °C (from acetone–light petroleum) (Found: M^+, 374.1719. $C_{21}H_{25}O_6$ requires *M*, 374.1729), $\nu_{max.}$ 3 610, 3 020, 1 800, 1 755, 1 725, and 880 cm^{-1}; δ_H (90 MHz) 1.43 (3 H, s, 18-H), 2.42 and 3.19 (each 1 H, d, *J* 3 Hz, 5-H and 6-H), 3.63 (3 H, s, OMe), 4.12 (1 H, t, 3-H), and 4.98 (2 H, d, 17-H); *m/z* 374 (M^+), 346, 330, 302, and 284. Further elution gave ent-3α-

hydroxy-6-epi-*gibberell*-16-*ene* 7,19-20-*methyl ester* (**9**) (65 mg) as a gum (Found: M^+, 406.1965. $C_{22}H_{30}O_7$ requires M, 406.1991); δ_H (200 MHz) 1.37 (3 H, s, 18-H), 2.65 and 3.08 (each 1 H, d, J 9 Hz, 5-H and 6-H), 3.60 and 3.65 (each 3 H, s, OMe), 3.88 (1 H, t, 3-H), and 4.79 and 4.92 (each 1 H, s, 17-H); *m/z* 406 (M^+), 388, 374, 356, 346, 330, and 312.

6-epi-*Gibberellin* A_{13} *Trimethyl Ester* (**7**).—Treatment of (**9**) with diazomethane afforded quantitatively (**7**), as a gum (Found: M^+, 420.2140. $C_{23}H_{32}O_7$ requires M, 420.2148); δ_H (90 MHz) 1.41 (3 H, s, 18-H), 2.45 and 2.91 (each 1 H, d, J 9 Hz, 5-H and 6-H), 3.58 and 3.63 (each 3 H, s, OMe), 3.78 (1 H, t, 3-H), and 4.99 (2 H, d, 17-H); *m/z* 420 (M^+), 388, 370, 360, 328, 310, and 300.

ent-3α-*Imidazol*-1-*ylthiocarbonyloxy*-6-epi-*gibberell*-16-*ene*-7,19,20-*trioic Acid* 7,19,20-*Trimethyl Ester* (**10**).—6-*epi*-Gibberellin A_{13} trimethyl ester (**7**) (110 mg) and *N,N'*-thiocarbonyldi-imidazole (175 mg) in dry 1,2-dichloromethane (1.5 ml) were heated under reflux for 25 h. Work-up and chromatography of the residue eluting with ethyl acetate–light petroleum afforded (**10**) (120 mg), m.p. 182—183 °C (from acetone–light petroleum) (Found: M^+, 530.2074. $C_{27}H_{34}N_2O_7S$ requires M, 530.2086); δ_H (200 MHz) 1.40 (3 H, s, 18-H), 2.36 and 2.97 (each 1 H, d, J 8 Hz, 5-H and 6-H), 4.87 and 4.98 (each 1 H, br s, 17-H), 5.73 (1 H, t, 3-H), and 7.10, 7.65, and 8.30 (each 1 H, br s, imidazole H); *m/z* 530 (M^+, 3%), 498(5), 419(5), 403(12), 387(9), 371(14), 356(14), 342(5), 311(9), 283(22), 251(4), 223(39), 181(13), and 143(12).

Reduction of the Imidazolylthiocarbonyloxy Derivative (**10**).—Compound (**10**) (108 mg) in dry toluene (5 ml) was added dropwise to a refluxing solution of tributyltin hydride (0.5 ml) and azoisobutyronitrile (trace) in dry toluene (5 ml). The mixture was allowed to reflux for a further 18 h when the solvent was evaporated off and the residue dissolved in acetonitrile (50 ml). The solution was washed with light petroleum (5 × 10 ml) to eliminate the excess of the tin hydride and the acetonitrile evaporated off. The residue was chromatographed using 10% ethyl acetate–light petroleum as the eluant to afford 6-epi-*gibberellin* A_{25} *trimethyl ester* (**8**) (40 mg), m.p. 127—129 °C (from ethyl acetate–light petroleum) (Found: M^+, 404.2177. $C_{23}H_{32}O_6$ requires M, 404.2199); δ_H (200 MHz) 1.34 (3 H, s, 18-H), 1.86 and 2.95 (each 1 H, d, J 8 Hz, 5-H and 6-H), 3.51, 3.53 and 3.58 (each 3 H, s, OMe), 4.79 and 4.92 (each 1 H, br s, 17-H); *m/z* 404 (M^+, 3%), 372(18), 344(5), 349(3), 312(10), 284(24), and 225(19). Further elution gave 6-epi-*gibberellin* A_{13} *trimethyl ester* (**7**) (11 mg). When the light petroleum extract was chromatographed, compounds (**8**) (20 mg) and (**7**) (3 mg) were again obtained.

Thiocarboxyimidazole Derivative (**5**).—The anhydride (**4**) (120 mg) was treated with *N,N'*-thiocarbonyldi-imidazole as described above for (**7**). In this way (**5**) was obtained, m.p. 186—189 °C (from ethyl acetate–light petroleum) (Found: M^+, 484.1635. $C_{25}H_{28}O_6N_2S$ requires M, 484.1668); δ_H (200 MHz) 1.41 (3 H, s, 18-H), 2.28 and 3.28 (each 1 H, d, J 3 Hz, H-5 and H-6), 3.67 (3 H, s, OMe), 4.97 and 5.07 (each 1 H, br s, 17-H), 6.07 (1 H, t, 3-H), and 7.09, 7.58 and 8.25 (each 1 H, br s, imidazole H); *m/z* 484 (M^+, 1%), 357(34), 328(7), 284(14), 269(21), 253(6), and 223(55).

Reduction of Compound (**5**).—The thiocarboxyimidazole derivative (**5**) (140 mg) was treated with tributyltin hydride as described for (**10**) but the reaction time in this case was 6 h. Elution with 10% ethyl acetate–light petroleum afforded 6-epi-*gibberell*-16-*ene*-7,19,20-*trioic acid* 7,20-*anhydride* 19-*methyl ester* (**6**) (100 mg), m.p. 229—231 °C (from ethyl acetate–light petroleum) (Found: M^+, 358.1791. $C_{21}H_{26}O_5$ requires M, 358.1780); $\nu_{max.}$ 1 810, 1 765, 1 730, and 895 cm^{-1}; δ_H (90 MHz) 1.34 (3 H, s, 18-H), 1.90 and 3.24 (each 1 H, d, J 3 Hz, 5-H and 6-H), 3.61 (3 H, s, OMe), and 4.96 (2 H, d, 17-H); *m/z* 358 (M^+, 0.5%), 314(36), 286(32), 282(20), 271(11), 254(8), 227(41), 146(43), 133(37), and 119(22).

Hydrolysis of Compound (**6**).—The anhydride (**6**) (100 mg) in tetrahydrofuran (9 ml) was treated with aqueous potassium hydroxide (1M; 3 ml) at room temperature for 10 days with stirring. The organic layer was separated and the aqueous solution acidified with 3% aqueous HCl and extracted with ethyl acetate. The tetrahydrofuran and ethyl acetate extracts were combined and the solvents evaporated off. The residue was chromatographed using 50% ethyl acetate–light petroleum as the eluant to give the 6-epi-GA_{25} 19-*monomethyl ester* (**11**) (50 mg) as a gum (Found: $M^+ - 18$, 358.1793. $C_{21}H_{26}O_5$ requires $M - 18$, 358.1780); δ_H (60 MHz) 1.35 (3 H, s, 18-H), 3.21 (1 H, d, J 9 Hz, 6-H), 3.60 (3 H, s, OMe), and 4.84 (1 H, d, 17-H); *m/z*: 358 ($M^+ - 18$, 0.2%), 344(2), 326(1), 314(7), 298(2), 286(6), 282(7), 272(20), 254(3), and 227(15). Methylation with diazomethane gave the trimethyl ester (**8**), identical with that obtained from (**10**).

Oxidation of Compound (**9**).—The monoacid (**9**) (400 mg) in acetone (10 ml) was treated dropwise with a slight excess of Jones reagent. The reaction was poured into water and worked up as usual, to yield quantitatively ent-3-*oxo*-6-epi-*gibberell*-16-*ene*-7,19,20-*trioic acid* 7,19-*dimethyl ester* (**21**), m.p. 220—222 °C (from ethyl acetate) (Found: M^+, 404.1801. $C_{22}H_{28}O_{27}$ requires M, 404.1832); δ_H (200 MHz) 1.51 (3 H, s, 18-H), 2.08 and 3.20 (each 1 H, d, J 8 Hz, 5-H and 6-H), 3.57 and 3.59 (each 3 H, s, OMe), and 4.79 and 4.93 (each 1 H, s, 17-H); *m/z* 404 (M^+, 1%), 372(16), 344(16), 340(8), 328(6), 312(10), 300(7), 294(5), 268(20), and 254(15).

Reduction of Compound (**21**).—The ketone (**21**) (140 mg) in chloroform (1 ml) and methanol (3 ml) was treated with sodium borohydride (100 mg), at room temp with stirring for 50 min. Work-up afforded ent-3β-*hydroxy*-6-epi-*gibberell*-16-*ene*-7,19,20-*trioic acid* 7,19-*dimethyl ester* (**22**) (110 mg), m.p. 172—174 °C (from ethyl acetate–light petroleum) (Found: $M^+ - 18$, 388.1870. $C_{22}H_{28}O_6$ requires $M - 18$, 388.1884); δ_H (60 MHz) 1.47 (3 H, s, 18-H), 2.02 and 3.08 (each 1 H, d, J 9 Hz, 5-H and 6-H), 3.66 (6 H, s, 2 OMe), and 4.90 (2 H, d, 17-H); *m/z* 388 ($M^+ - 18$, 1%), 356(29), 342(6), 328(4), 314(4), 300(3), 283(3), 268(6), and 255(11).

Formation of the Lactone (**18**).—Compound (**22**) (100 mg) in acetic anhydride (1 ml) was set aside at room temp. for 20 h. Evaporation of the solvent gave ent-3β-*hydroxy*-6-epi-*gibberell*-16-*ene*-7,19,20-*trioic acid* 3,20-*lactone* 7,19-*dimethyl ester* (**18**) (22 mg), m.p. 208—210 °C (Found: M^+, 388.1901. $C_{22}H_{28}O_6$ requires 388.1886); $\nu_{max.}$ 3 020, 2 940, 1 750, 1 730, 1 430, 1 100, and 850 cm^{-1}; δ_H (200 MHz, C_6D_6) 1.16 (3 H, s, 18-H), 1.68 and 3.12 (each 1 H, d, J 9 Hz, 5-H and 6-H), 3.39 and 3.43 (each 3 H, s, OMe), 4.56 (1 H, d, 3-H), and 5.00 and 5.10 (each 1 H, br s, 17-H); *m/z* 388 (M^+, 7%) 356(85), 328(10), 300(2), 282(5), and 269(6).

Hydrolysis of the Anhydride (**4**).—The anhydride (**4**) (105 mg) in tetrahydrofuran (7.5 ml) was treated with aqueous potassium hydroxide (0.95M) (3 ml) and heated under reflux for 6 h. The solvent was evaporated (90%), diluted with water and extracted with ethyl acetate as usual. The residue obtained was methylated with diazomethane and the methyl ester formed was purified by crystallization to give *the lactone* (**18**), identical with that obtained above.

Oxidation of the Anhydride (**4**).—The alcohol (**4**) (180 mg) was oxidized as described for (**9**) to give quantitatively ent-3-*oxo*-6-epi-*gibberell*-16-*ene*-7,19,20-*trioic acid* 7,20-*anhydride* 19-*methyl ester* (**23**), m.p. 208—210 °C (from ethyl acetate–light petroleum) (Found: M^+, 372.1556. $C_{21}H_{24}O_6$ requires M, 372.1571); δ_H (90 MHz) 1.27 (3 H, s, 18-H), 2.27 and 3.26 (each 1 H, d, J 4 Hz, 5-H and 6-H), 3.69 (3 H, s, OMe), and 4.99 (2 H, d, 17-H); m/z 372 (M^+, 17%), 344(42), 340(18), 328(14), 312(17), 296(11), 285(18), 268(25), 254(71), 239(21), and 217(29).

Alternative Preparation of the Lactone (**18**).—Compound (**23**) (43 mg) in dry benzene (1 ml) and dry methanol (2 ml) was treated with sodium borohydride (30 mg) at room temp. with stirring for 25 min. Work-up afforded a gum which was methylated with diazomethane and chromatographed, using ethyl acetate–light petroleum (20%, v/v) as the eluant to give the lactone (**18**) (28 mg).

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