Partial Synthesis of Gibberellin A_{37} from Gibberellin A_{13}

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The partial synthesis of gibberellin A_{37} (1) from gibberellin A_{13} (5) is described. Selective reduction of the least reactive carboxy-group (that at position 10) in gibberellin A_{13} was achieved through formation of the 20,3-lactone (24), which yielded the 3α-hydroxy-epimer (3) of gibberellin A_{37}. This epimer was converted into gibberellin A_{37} (1) by Meerwein–Ponndorf reduction of the derived 3-ketone (2). Meerwein–Ponndorf reduction of the 3-oxogibberellins (2), (12), and (31) gave 50% or greater yields of the 3β-epimers, whereas the 3-oxo-20,19-lactone (18) gave the 3α-hydroxy-epimer predominantly.

Reduction of gibberellin A_{13} trimethyl ester with lithium aluminium hydride in ether, followed by acetylation, gave the 20,19-lactone diacetate (21) and the triacetate (23). Similar reduction of the monomethyl ester (7) unexpectedly yielded the 20,19-lactone (28) rather than a gibberellin A_{37} derivative.

GIBBERELLIN A_{37} (1) occurs [1] as the β-D-glucosyl ester in mature seed of *Phaseolus vulgaris* and has been detected [2] by g.l.c.–mass spectrometry in extracts of the culture filtrates of *Gibberella fujikuroi*. This paper describes studies on the conversion of the relatively accessible gibberellin A_{13} (5) into gibberellin A_{37} (1) and includes details of a successful route which has been briefly reported.[3]

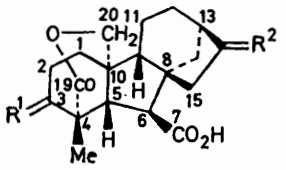
The crucial step in the partial synthesis of gibberellin A_{37} (1) from gibberellin A_{13} (5) is the selective reduction of the most hindered of the three carboxy-groups in the latter. Cross and Stewart [4] approached this problem in two ways. First, they reduced the anhydride (14) of acetylgibberellin A_{13} with lithium aluminium hydride in the expectation that the lactone (1) would be formed, by analogy with the previously reported [5] observation that the most hindered carbonyl group in some five-membered ring anhydrides was reduced. In the event, reduction in tetrahydrofuran at −55° afforded [4] the isomeric lactone (17). In another approach Cross and Stewart [4,6] reduced gibberellin A_{13} trimethyl ester (6) to the tetraol (20) which, on oxidation and concomitant lactonisation, gave the isomeric oxo-lactones (2) and (18), isolated as their methyl esters in low yield. However, Meerwein–Ponndorf reduction of the oxo-lactone (18) yielded the 3α-hydroxy-lactone (19), and similar reduction of the oxo-lactone (2) was not attempted.

Our concurrent studies began with a re-examination of the reduction with lithium aluminium hydride of gibberellin A_{13} trimethyl ester, which had been found [4] to give the tetraol (20) at 160° in dioxan. In boiling ether we obtained two products, which were isolated as the acetates (21) and (23). These structures were assigned from spectroscopic data, from the alkaline hydrolysis of both acetates to the same gummy lactone diol (22), and from the alternative preparation of the diacetate (21) as described later. The formation of compounds (21) and (23) confirmed that the 4- and 6-methoxycarbonyl groups in gibberellin A_{13} trimethyl ester (6) were more readily reduced than the 10-methoxycarbonyl group, and that lactonisation between the 10-methoxycarbonyl and the 4α-hydroxymethyl groups occurred readily.

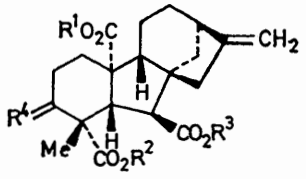
To increase the reactivity of the 10-carboxy-group in gibberellin A_{13} the monomethyl ester (7) was prepared by partial demethylation of the 3-tetrahydropyranyl (thp) ether (8) with potassium t-butoxide in dimethyl sulphoxide. The 3β-hydroxy-group was protected to prevent formation of the lactone (24) (see later). Structure (7) for the monomethyl ester was confirmed (*a*) by hydrolysis to the free alcohol (9), which was distinct from the monomethyl ester (10) obtained [4] by methanolysis of gibberellin A_{13} anhydride (16), and (*b*) by oxidation and decarboxylation to give a product which appeared to be a mixture of the 4-methyl epimers (27), since the n.m.r. spectrum contained two methyl doublets which were simplified to two singlets on irradiation at τ *ca.* 7·5.

[1] K. Hirago, T. Yokota, N. Murofushi, and N. Takahashi, *Agric. and Biol. Chem. (Japan)*, 1972, **36**, 345.
[2] J. R. Bearder and J. MacMillan, *J.C.S. Perkin I*, 1973, 2824.
[3] D. H. Bowen, D. M. Harrison, and J. MacMillan, *J.C.S. Chem. Comm.*, 1972, 808.
[4] B. E. Cross and J. C. Stewart, *J. Chem. Soc.* (*C*), 1971, 245.
[5] J. J. Bloomfield and S. L. Lee, *J. Org. Chem.*, 1967, **32**, 3919.
[6] B. E. Cross, K. Norton, and J. C. Stewart, *J. Chem. Soc.* (*C*), 1968, 1054.

Reduction of the monomethyl ester (7) with lithium aluminium hydride in boiling tetrahydrofuran gave an

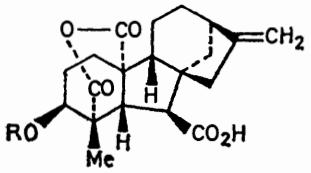


(1) R^1 = H,β-OH, R^3 = CH_2
(2) R^1 = O, R^2 = CH_2
(3) R^1 = H,α-OH, R^2 = CH_2
(4) R^1 = H,α-OH, R^2 = O



	R^1	R^2	R^3	R^4
(5)	H	H	H	H,β-OH
(6)	Me	Me	Me	H,β-OH
(7)	Me	H	H	H,β-OThp
(8)	Me	Me	Me	H,β-OThp
(9)	Me	H	H	H,β-OH
(10)	H	Me	H	H,β-OH
(11)	H	H	H	O
(12)	Me	Me	Me	O
(13)	Me	Me	Me	H,α-OH

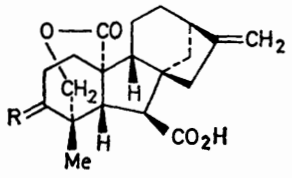
Thp = tetrahydropyran-2-yl



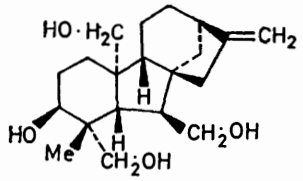
(14) R = Ac
(15) R = Thp
(16) R = H

intractable mixture which was treated with acetic anhydride in pyridine to give the lactones (28) and (29). The acetate lactone (29) was characterised by alkaline hydrolysis then oxidation (Cr_3O_3–C_5H_5N) to give the lactone (28). Compound (28) was in turn, characterised by acidic hydrolysis to the free alcohol (17), obtained [4] by reduction of the anhydride (14). The acetate (29) was converted by acidic hydrolysis and acetylation into the diacetate (21), previously obtained by hydride reduction of gibberellin A_{13} trimethyl ester. Reduction of the monomethyl ester (7) to the lactone (28) and not to the tetrahydropyranyl ether of gibberellin A_{37} was unexpected, and indicates that the anhydride (15) or its equivalent is formed under the conditions of reduction.

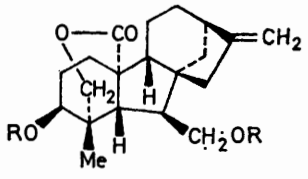
The successful route from gibberellin A_{13} (5) to gibberellin A_{37} (1) employed the 20,3-lactone (24), which was prepared by heating the borohydride reduction product of gibberellin A_{13} 3-ketone (11) at 135° under vacuum. Reduction of the 20,3-lactone (24) with lithium borohydride yielded the 3α-epimer (3) of gibberellin A_{37}, which was oxidised to the 3-ketone (2). Compound (2) was characterised as the methyl ester, which had the same physical constants as the methyl ester of the 3-ketone (2) obtained by Cross and Stewart [4] from oxidation of the tetraol (20). Contrary to the results of Cross and Stewart [4] with the 3-oxo-19,20-lactone (18), Meerwein–Ponndorf reduction of the 3-oxo-20,19-lactone (2)



(17) R = H,β-OH
(18) R = O
(19) R = H,α-OH

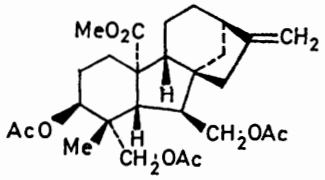


(20)



(21) R = Ac
(22) R = H

gave a 1 : 1 mixture of gibberellin A_{37} (1) and the 3α-hydroxy-epimer (3), separated by preparative layer chromatography (p.l.c.).

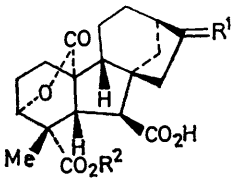


(23)

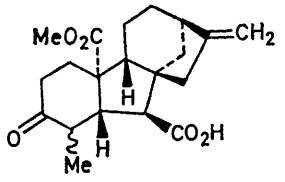
This partial synthesis of gibberellin A_{37} (1) also confirms the structure (30) for gibberellin A_{36},[7] previously converted into gibberellin A_{37} (1) by borohydride reduction. It does not, however, provide a good preparative route since, in some experiments, the 20,3-lactone (24)

[7] J. R. Bearder and J. MacMillan, *Agric. and Biol. Chem. (Japan)*, 1972, **36**, 342.

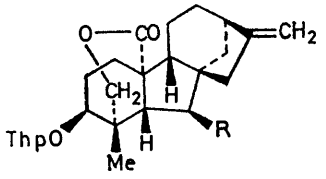
and the 19,20-lactone (3) were contaminated with 10—30% of their Δ^{15}-isomers. An alternative route *via* the nor-ketone (26) [4] would avoid this complication.



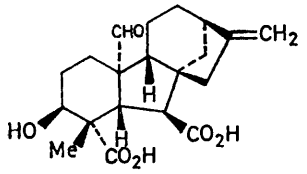
(24) $R^1 = CH_2$, $R^2 = H$
(25) $R^1 = CH_2$, $R^2 = Me$
(26) $R^1 = O$, $R^2 = H$



(27)



(28) $R = CO_2H$
(29) $R = CH_2 \cdot OAc$



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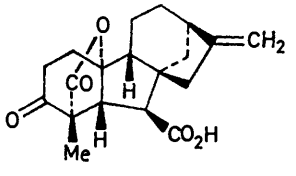

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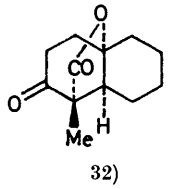
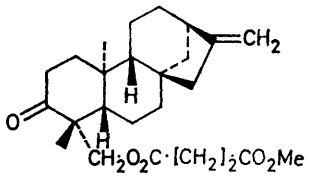


32)



(33)

Cross and Stewart [4] found that Meerwein–Ponndorf reduction of the 3-ketone (18) gave the 3α-hydroxy-epimer (19) with only a trace (t.l.c.) of the 3β-epimer (17). We obtained a similar result in which an 85 : 15 ratio (t.l.c.) of the 3α- and 3β-epimers (19) and (17) was obtained. The contrast between the two ketones (18) and (2) led us to investigate the Meerwein–Ponndorf reduction of other 3-ketones. From the 3-ketone (12) of gibberellin A_{13} trimethyl ester we obtained gibberellin A_{13} trimethyl ester (6) as the major product (87%) by g.l.c.; the 3α-hydroxy-epimer (13) was not detected although the dimethyl ester of the lactone (24), readily obtained from the 3α-hydroxy-epimer (13) was detected in 13% yield by g.l.c. An authentic sample of the 3α-hydroxy-epimer (13) was prepared for reference by reduction with sodium borohydride of the 3-ketone (12), although this reduction has been reported [8] to give the dimethyl ester of the lactone (24) directly. Meerwein–Ponndorf reduction of the 3-ketone (31) from gibberellin A_4 methyl ester afforded a 1 : 1 mixture of the 3α- and 3β-hydroxy-epimers. Thus Meerwein–Ponndorf reduction of *ent*-3-oxogibberellanes may only exceptionally yield the unnatural *ent*-3β-(*i.e.* 3α-) hydroxy-isomers as the predominant product. It may be significant that the 3-ketone (18) which gives predominantly the 3α-hydroxy-epimer is the only one without a 4α-carbonyl-containing substituent. A similar distinction obtains for the ketones (32) and (33), and Meerwein–Ponndorf reduction of (32) gives a 1 : 1 mixture of epimers [9] whereas the latter compound (33) affords the 3β-epimer in only 21% yield.[10]

EXPERIMENTAL

For general experimental details see ref. 11; for g.l.c.–mass spectrometry see ref. 12.

Reduction of Gibberellin A_{13} Trimethyl Ester (6) *with Lithium Aluminium Hydride*.—The trimethyl ester (6) (1·57 g) and lithium aluminium hydride (3·88 g) were refluxed for 2·25 h in sodium-dried ether (450 ml). The crude product (1·63 g) was treated overnight at room temperature with pyridine (15 ml) and acetic anhydride (15 ml). The solution was poured into water and, after 1 h, adjusted to pH 2 with 2N-hydrochloric acid. The ethyl acetate extract was washed with water at pH 2, aqueous sodium hydrogen

[8] R. H. B. Galt, *J. Chem. Soc.*, 1965, 3143.
[9] M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzly, and H. J. E. Loewenthal, *J. Org. Chem.*, 1969, **34**, 126.
[10] E. L. Ghisalberti, P. R. Jefferies, and E. S. Middleton, *Austral. J. Chem.*, 1969, **22**, 455.
[11] J. MacMillan and T. J. Simpson, *J.C.S. Perkin I*, 1973, 1487.
[12] J. R. Bearder, J. MacMillan, and B. O. Phinney, *Phytochemistry*, 1973, **12**, 2655.

carbonate, and water again. Recovery gave an oil (1·96 g) which was adsorbed on silica gel (6 g) and eluted through a column of silica gel (100 g) with increasing concentrations of ethyl acetate in light petroleum. The triacetate (23) (829 mg) was eluted with 25—26% ethyl acetate; a mixture (293 mg) of acetates (23) and (21) was eluted with 27% ethyl acetate; and the 20,19-lactone diacetate (21) (377 mg) was eluted with 28—29% ethyl acetate.

ent-3α,7-*Diacetoxy*-19-*hydroxygibberell*-16-*en*-20-*oic acid* 20,19-*lactone* (21) crystallised from methanol–acetone in prisms, m.p. 166·5—168·5°; $[\alpha]_D^{29}$ −9·5° (*c* 1 in EtOH) (Found: C, 69·5; H, 7·6. $C_{24}H_{32}O_6$ requires C, 69·2; H, 7·75%); $\nu_{max.}$ (Nujol) 3062, 3013, 1740, 1725, 1658, and 872 cm^{-1}; $\nu_{max.}$ (CCl_4) 3060, 1745, 1658, 890, and 875 cm^{-1}; τ 9·02 (4-Me), 8·1 (m, 6-H, located by INDOR), 7·95 (2 × OAc), 5·63 (d, *J* 13 Hz, 19-H), 5·98 (dd, *J* 1·5 and 13 Hz, 19-H), 5·83 (dd, *J* 2·5 and 11 Hz, 7-H), 6·02 (dd, *J* 6 and 11 Hz, 7-H), and 5·12br (17-H_2 and 3-H).

Methyl ent-3α,7,19-*triacetoxygibberell*-16-*en*-20-*oate* (23) was a gum even after repeated p.l.c. on silica gel with ethyl acetate–light petroleum (3 : 1) (Found: M^+, 490·255. $C_{27}H_{38}O_8$ requires *M*, 490·257); τ 8·96 (4-Me), 7·96 (2 × OAc), 7·94 (s, OAc), 6·5—5·5 (complex, 2 × CH_2OAc), 5·18br (3- and 17-H), and 5·08br (17-H).

Hydrolysis of the Acetates (21) *and* (23).—The acetate (21) (145 mg) was refluxed for 2 h with 2% potassium hydroxide in methanol. The usual work-up gave a gum (132 mg) which was chromatographed on a column of silica gel (16 g). Elution with 22—26% acetone in light petroleum gave the diol (22) as a gum (111 mg), homogeneous by t.l.c. and >98% pure by g.l.c.; $\nu_{max.}$ 3400, 1725, 1658, and 880 cm^{-1}. Re-acetylation of this diol (22) gave the acetate (21), identified by g.l.c. comparison.

Similar hydrolysis of the acetate (23) gave the same diol (22), identified by i.r. ($CHCl_3$) and g.l.c. comparison and by re-acetylation to give the acetate (21), identified by g.l.c. comparison.

3-O-*Tetrahydropyranylgibberellin* A_{13} *Trimethyl Ester* (8).—Gibberellin A_{13} trimethyl ester (6) (2 g) was refluxed for 3 days in ether (100 ml) with dihydropyran (2 ml; freshly distilled from potassium hydroxide pellets) and toluene-*p*-sulphonic acid dihydrate (5 mg). The gum (4 g) obtained by evaporation under vacuum was chromatographed on a column of silica gel (100 g). Elution with ethyl acetate–light petroleum (1 : 10) gave a gum which was crystallised from aqueous methanol to give *ether* (8) as a diastereoisomeric mixture (1·3 g), m.p. 111—116° (Found: C, 66·9; H, 7·9. $C_{28}H_{40}O_8$ requires C, 66·7; H, 8·0%); $\nu_{max.}$ (Nujol) 3070, 1730, 1655, and 880 cm^{-1}; τ 8·84 and 8·72 (s, 4-Me), 7·45 and 7·40 (d, *J* 13 Hz, 5-H), 6·41, 6·35, and 6·30 (s, OMe), 6·16 and 6·08 (t, 3-H), 6·17 and 6·14 (d, *J* 13 Hz, 6-H), 5·44 and 5·32 (t, O·CH·O), and 5·20br and 5·11br (17-H_2).

Demethylation of the Tetrahydropyranyl Ether (8).—The ether (1 g) in dimethyl sulphoxide (50 ml; freshly distilled from calcium hydride) was heated at 105° for 3 h with resublimed potassium t-butoxide (700 mg). The cooled mixture was poured into water and potassium carbonate (5 g) was added. The aqueous solution was extracted with ethyl acetate, then adjusted to pH 2 with 2N-hydrochloric acid and re-extracted with ethyl acetate. Recovery of material from the second extract gave a brown gum (1 g) which was purified by p.l.c. on silica gel HF plates developed four times with acetone–light petroleum–acetic acid (1 : 3 : 0·04). Recovery from the band at R_F 0·5 in ethyl acetate gave the *diacid* (7) as a diastereomeric mixture, crystallising from ethyl acetate–light petroleum in needles (500 mg), m.p. 213—223° (Found: C, 65·6; H, 7·8. $C_{26}H_{36}O_8$ requires C, 65·5; H, 7·6%); $\nu_{max.}$ (Nujol) 3500—2500, 1735, 1700, 1670, and 880 cm^{-1}; τ (C_5D_5N) 8·16 and 7·96 (s, 4-Me), and 6·83 and 6·78 (d, *J* 13 Hz, 5-H), 6·38 and 6·36 (s, OMe), 5·71 and 5·55 (t, 3-H), 5·36 and 5·34 (d, *J* 13 Hz, 6-H), and 5·18br and 5·06br (17-H_2).

Demethylation of Gibberellin A_{13} *Trimethyl Ester* (6) (with J. R. Bearder).—The trimethyl ester (6) (1 g) and potassium t-butoxide (1 g) in dimethyl sulphoxide (150 ml) were kept at 20° for 3 h. Water (750 ml) was added and the pH was adjusted to 2·5 with 2N-hydrochloric acid. Extraction with ethyl acetate gave an oil (1·06 g) which was subjected to p.l.c. on silica gel [multiple development with ethyl acetate–light petroleum–acetic acid (50 : 50 : 1)]. The band at R_F 0·5 was eluted with ethyl acetate to give ent-3β-*hydroxygibberell*-16-*ene*-7,19,20-*trioic acid* 20,3-*lactone* 19-*methyl ester* (25), crystallising from ethyl acetate–light petroleum in needles (284 mg), m.p. 228—231° (Found: M^+, 374·171. $C_{21}H_{26}O_6$ requires *M*, 374·173); $[\alpha]_D^{32}$ −59° (*c* 0·4); $\nu_{max.}$ (Nujol) 3235, 3077, 1742, 1712, 1657, and 877 cm^{-1}; τ (C_5D_5N) 8·37 (4-Me), 7·41 (d, *J* 12 Hz, 5-H), 6·41 (d, *J* 12 Hz, 6-H), 6·33 (OMe), 5·16br and 5·05br (17-H_2), and 4·92 (m, 3-H). The dimethyl ester crystallised from ethyl acetate–light petroleum in needles m.p. 154—155° (lit.,[8] 167—169° for mixture of 15- and 16-enes) (Found: M^+, 388·188. Calc. for $C_{22}H_{28}O_6$: *M*, 388·189), $[\alpha]_D^{32}$ −61° (*c* 0·6); $\nu_{max.}$ (CCl_4) 3060, 1766, 1739, 1656, and 877 cm^{-1}; τ 8·57 (4-Me), 7·70 (d, *J* 12 Hz, 5-H), 7·05 (d, *J* 12 Hz, 6-H), 6·38 and 6·33 (2 × OMe), 5·25 (m, 3- and 17-H), and 5·14br (17-H); *m/e* 388 (1%), 356 (100), 296 (50), 284 (23), and 283 (43).

ent-3α-*Hydroxygibberell*-16-*en*-7,19,20-*trioic Acid* 20-*Methyl Ester* (9).—The tetrahydropyranyl ether (7) (50 mg) was heated for 24 h in acetic acid (2 ml) and methanol (18 ml). Evaporation yielded the crystalline *alcohol* (9) (45 mg), which crystallised from acetone–light petroleum in needles, m.p. *ca.* 260° (Found: C, 64·5; H, 7·0. $C_{21}H_{28}O_7$ requires C, 64·3; H, 7·2%); $\nu_{max.}$ (Nujol) 3610, 3400—2400, 1725, 1690, 1650, and 880 cm^{-1}; τ (C_5D_5N) 7·93 (s, 4-Me), 6·53 (d, *J* 13 Hz), 6·33 (s, OCH_3), 5·45 (t, 3-H), 5·30 (d, *J* 13 Hz, 6-H), and 5·16br and 5·06br (17-H_2).

The alcohol (9) (30 mg) was oxidised at 0° with Jones reagent to give a solid (25 mg) which was heated for 1·5 h with water in a stream of nitrogen. Evaporation left a gum which after t.l.c. showed, in its n.m.r. spectrum, two 3-proton doublets at τ *ca.* 9·1 (*J* 6 Hz) which were assigned to the 4-methyl groups of the epimeric ketones and which collapsed to two singlets on irradiation at τ 7·5.

Reduction of the Monomethyl Ester (7).—The monomethyl ester (7) (160 mg) and lithium aluminium hydride (200 mg) in tetrahydrofuran (35 ml; freshly distilled from lithium aluminium hydride) were refluxed for 24 h. The excess of hydride was destroyed with water and the solution was acidified to pH 2 with 2N-hydrochloric acid. The gum (180 mg) obtained by recovery in ethyl acetate was stirred at 80° for 3 h with acetic anhydride (1 ml) in pyridine (10 ml). Acidification and extraction with ethyl acetate gave a gum which was separated by p.l.c. on silica gel HF [four developments with acetone–light petroleum (1 : 10)], into the acetate (29) (higher R_F) and the acid (28).

ent-19-*Hydroxy*-3α-*tetrahydropyranyloxygibberell*-16-*ene*-7,20-*dioic acid* 20,19-*lactone* (28) (40 mg), crystallised from ethyl acetate–light petroleum, had m.p. *ca.* 180° (Found: C, 69·6; H, 8·1. $C_{25}H_{34}O_6$ requires C, 69·7; H, 8·0%),

$\nu_{max.}$ (CCl_4) 3500—2500, 1730, 1700, 1660, and 890 cm^{-1}; τ 9·11 and 9·00 (s, 4-Me), 7·37br (5- and 6-H), 6·02 and 5·96, and 5·68 and 5·66 (each d, J 12 Hz, 20-H_2), *ca.* 5·35br (3-H and O·CH·O), and 5·10br (17-H_2).

ent-7-Acetoxy-19-*hydroxy*-3-tetrahydropyranyloxygibberell-16-en-20-oic acid 20,19-lactone (29) was obtained as a gum (110 mg), τ 7·95 (1 × OAc). It was characterised by heating for 1 h with 1% potassium hydroxide in methanol, then oxidising the product with chromium trioxide in pyridine at 60° for 2 h. The product, after p.l.c. on silica gel HF with acetone–light petroleum (2 : 3) (elution of the band at R_F 0·5) was identified (i.r., n.m.r., and mass spectra) as the acid (28).

Hydrolysis of the Tetrahydropyranyl Ether (28).—The ether (30 mg) in methanol (18 ml) and acetic acid (20 ml) was heated under reflux for 24 h. Evaporation under vacuum gave the δ-lactone (17), which crystallised from ethyl acetate–light petroleum to give needles, m.p. 219—223°, identical (mixed m.p., i.r., n.m.r., and mass spectra) with the product obtained by reduction of 3-acetylgibberellin A_{13} anhydride as described by Cross and Stewart.[4]

Hydrolysis and Acetylation of the Tetrahydropyranyl Ether (29).—The ether (80 mg) was refluxed for 24 h in methanol (18 ml) and glacial acetic acid (2 ml). Half the product (40 mg) was treated at 18° for 24 h with acetic anhydride (1 ml) in acetic acid (4 ml). The mixture was acidified with hydrochloric acid, then extracted with ethyl acetate. The recovered product was chromatographed on silica gel HF (4 mm) with acetone–light petroleum (3 : 2). Crystallisation of the material from the band at R_F 0·4 gave the diacetate (21), m.p. 160—163°, identical (mixed m.p., i.r., n.m.r., and mass spectra, and g.l.c. on 2% SE-33 and OV-1 columns) with the diacetate (21) obtained by reduction of gibberellin A_{13} trimethyl ester with lithium aluminium hydride.

Oxidation of Gibberellin A_{13} (5).—Gibberellin A_{13} (1·0 g) in acetone (60 ml) was treated at 0° for 0·5 h with an excess of Jones reagent. The usual work-up gave the ketone (11) as a gum (930 mg) which was directly reduced (see later) but which was characterised by methylation to give the trimethyl ester (12), obtained from acetone–light petroleum as needles, m.p. 121—124° (lit.,[8] 138—140°) (Found: M^+, 418·199. Calc. for $C_{23}H_{30}O_7$, M, 418·199); $\nu_{max.}$ 1728, 1720m, 1660m, and 887 cm^{-1}, τ 8·72 (s, 4-Me), 6·34, 6·32, and 6·28 (3 × OMe), and 5·19 and 5·10 (17-H_2); *m/e* 418 (44%), 386·163 (51) (Calc. for $C_{21}H_{24}O_5$: 386·162), 358 (33), 327 (47), 326 (100), 299 (32), and 298 (40).

ent-3β-*Hydroxygibberell*-16-*ene*-7,19,20-*trioic acid* 20,3-*Lactone* (24).—The ketone (11) (8·1 g) in ethanol (500 ml) was stirred at 0° for 0·5 h with sodium borohydride (8·0 g). The temperature was then raised to 25° and stirring was continued for a further 2 h. The mixture was poured into brine, which was adjusted to pH 2·5 and extracted with ethyl acetate. Recovery from the ethyl acetate extract gave a foam (6·5 g) which was heated at 135° for 40 min under vacuum. The product (5·9 g), which was shown to contain no endocyclic double bond isomer by g.l.c. of a methylated sample on OV-210 at 230°, was chromatographed on a column of silica gel (80 g). The *lactone* (24) was eluted with ethyl acetate–light petroleum (7 : 3) and purified in 200 mg portions by p.l.c. on silica gel with ethyl acetate–light petroleum–acetic acid (50 : 50 : 1); it crystallised from acetone–light petroleum as needles (37 mg), m.p. 263—268° (lit.,[8] 280—283° for isomeric mixture of 15- and 16-enes) (Found: M^+, 360·155. $C_{20}H_{24}O_6$ requires M, 360·157), *m/e* 360 (6%), 342·146 (100) (Calc. for $M^+ - H_2O$: 342·147), 314 (25), 296 (74), 270 (51), and 269 (77). The methyl ester was identical (m.p., i.r., n.m.r., and mass spectra) with that described earlier.

ent-3β,20-*Dihydroxygibberell*-16-*ene*-7,19-*dioic Acid* 19,20-*Lactone* (3).—The lactone (24) (100 mg) in dry tetrahydrofuran (50 ml) was stirred at 20° for 24 h with lithium borohydride (100 mg). The mixture was added to 1M-potassium hydrogen phosphate and the solution was adjusted to pH 2·5. The product was recovered by extraction with ethyl acetate as a gum (90 mg), which was purified by p.l.c. on silica gel developed twice with ethyl acetate–light petroleum–acetic acid (50 : 50 : 1). The band at R_F 0·45 gave the *alcohol* (3), crystallising from ethyl acetate–light petroleum as plates, m.p. 280—285° (Found: M^+, 346·177. $C_{20}H_{26}O_5$ requires M, 346·178); $\nu_{max.}$ (Nujol) 3430, 3100, 1740, 1660, and 887 cm^{-1}; τ (C_5D_5N) 8·09 (s, 4-Me), 7·42 and 6·74 (each d, J 12 Hz, 5- and 6-H), 6·10 (m, 3-H), 5·86 and 5·40 (each d, J 12 Hz, 20-H_2), and 5·16br and 5·04br (17-H_2); *m/e* 346 (9%), 318 (16), 282 (23), 178 (100), 177 (26), 176 (47), and 152 (47).

ent-20-*Hydroxy*-3-*oxogibberell*-16-*en*-7,19-*dioic Acid* 19,20-*Lactone* (2).—The alcohol (3) (9 mg) in acetone (10 ml) was treated with an excess of Jones reagent as described in an earlier experiment. The ketone (2) was obtained as a gum (7 mg), τ (C_5D_5N) 8·20 (s, 4-Me), 7·09 and 6·54 (each d, J 12 Hz, 5- and 6-H), 5·51 and 5·08 (each d, J 12 Hz, 20-H_2), and 5·16br and 5·02br (17-H_2). It was characterised as the methyl ester, crystallising from acetone–light petroleum as needles, m.p. 240—246° (lit.,[4] 248—250°) (Found: M^+, 358·178. Calc. for $C_{21}H_{26}O_5$: M, 358·178); $\nu_{max.}$ 1740, 1720, and 890 cm^{-1}; τ 8·76 (s, 4-Me), 7·04 (d, J 12 Hz, 5-H), 6·28 (s, OMe), 5·60 and 5·25 (each d, J 12 Hz, 20-H_2) and 5·17br and 5·05br (17-H_2); *m/e* 358 (82%), 326 (62), 298 (66), 254 (83), 253 (40), 211 (37), and 43 (100).

ent-3α,20-*Dihydroxygibberell*-16-*en*-7,19-*dioic Acid* 19,20-*Lactone* (*Gibberellin* A_{37}) (1).—The ketone (2) (6 mg) in propan-2-ol (10 ml) was heated with aluminium isopropoxide (500 mg). Propan-2-ol (5 ml) and the acetone formed were distilled from the mixture over 6 h. The product was recovered in ethyl acetate and separated by t.l.c. on silica gel with ethyl acetate–light petroleum–acetic acid (50 : 50 : 1). The lower band gave gibberellin A_{37} (1), crystallising from acetone–light petroleum in needles (2·3 mg), m.p. 226—228°, identified by mixed m.p. and n.m.r. spectrum and by conversion into the methyl ester (identified by n.m.r. and mass spectra of the ester and trimethylsilyl ether).

The upper band from t.l.c. gave the 3-epimer (3) (2 mg), m.p. 280—285°.

Reduction of Trimethyl ent-3-*Oxogibberell*-16-*ene*-7,19,20-*trioate* (12).—(a) *With sodium borohydride* (cf. *ref.* 8). The ketone (176 mg) in methanol (30 ml) was reduced with sodium borohydride (190 mg) at 0° for 0·5 h then at 25° for 2·5 h. After the addition of water and removal of the methanol under vacuum, the aqueous residue was extracted with ethyl acetate to give a foam (192 mg), which was purified by p.l.c. on silica gel HF with ethyl acetate–light petroleum–acetic acid (50 : 50 : 1). Recovery from the band at R_F 0·5 gave the 3α-*alcohol* (13) (110 mg), which crystallised from ethyl acetate–light petroleum in prisms, m.p. 107—108° (Found: C, 65·6; H, 7·9. $C_{23}H_{32}O_7$ requires C, 65·7; H, 7·7%); $\nu_{max.}$ 3550, 1730, 1660, and 885 cm^{-1}; τ 8·69 (4-Me), 7·86 (5-H, J 12 Hz), 6·72 (m, 3-H), 6·38, 6·30, and 6·28 (3 × OMe), 6·16 (6-H, J 12 Hz), and 5·19br and 5·11br (17-H_2); *m/e* 388 (5%), 356 (100), 296 (45), and 284 (28) (no M^+).

(b) *With aluminium isopropoxide–propan-2-ol.* The ketone (113 mg) in propan-2-ol (50 ml) was boiled for 6 h with aluminium isopropoxide (20 ml of distillate collected). The usual work-up gave a product (125 mg), g.l.c. of which on OV-210 at 200°, showed the presence of gibberellin A_{13} trimethyl ester (6) (93%), t_R 8·7 min, and the absence of the 3α-hydroxy-epimer (13), t_R 7·7 min, but the presence of the dimethyl ester of the derived δ-lactone (24) (7%), t_R 19·4 min. G.l.c. (on OV-210 at 200°) and g.l.c.–mass spectrometry (on QF-1 at 190°) of the trimethylsilylated product confirmed the presence of 93% of gibberellin A_{13} trimethyl ester as the trimethylsilyl derivative (t_R 4·1 min) and of the δ-lactone (24) dimethyl ester (no Me_3Si substituent). Similar results were obtained in a second experiment.

Reduction of the Keto-lactone (18) (cf. *ref.* 4).—The keto-lactone (50 mg) in propan-2-ol (15 ml) was boiled with aluminium isopropoxide (2·5 g) for 6 h with slow distillation (7 ml collected). The usual work-up gave a gum (35 mg). G.l.c. of the methylated trimethylsilylated derivative on OV-210 at 218° showed only two peaks. The major peak (83%), t_R 7·1 min, and the minor peak (17%), t_R 5·6 min, were identified as due to the 3α- and 3β-epimers (19) and (17), respectively, by g.l.c.–mass spectrometry.

Reduction of the 3-Ketone (31) *from Gibberellin* A_4 *Methyl Ester* (with D. A. Robinson).—The ketone (25 mg) [12] in propan-2-ol (40 ml) was reduced with aluminium isopropoxide (4 g) as described in the previous experiment. The gummy product (20 mg) was shown to be a 1 : 1 mixture of gibberellin A_4 methyl ester and its 3α-hydroxy-epimer [13] by g.l.c. and g.l.c.–mass spectrometry of the trimethylsilyl derivative on 2% QF-1 at 200°. P.l.c. of the product on silica gel with ethyl acetate–light petroleum (1 : 1) gave gibberellin A_4 methyl ester (R_F 0·38) and the 3α-hydroxy-epimer (R_F 0·26), m.p. 165—167°; τ 8·83 (4-Me), 7·66 (d, *J* 12 Hz, 6-H), 7·24 (d, *J* 12 Hz, 5-H), 6·30 (OMe), 6·33br (3-H), and 5·16br and 5·03br (17-H_2).

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