The Preparation of some *ent*-7-Nor-5β-gibberell-16-enes as Potential Gibberellin Biosynthesis Inhibitors

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Three routes for the preparation of *ent*-7-nor-5β-gibberell-16-enes from fujenal are described. Evidence is presented for the stereochemistry of the products.

THE ring contraction step in the biosynthesis of the plant growth hormone, gibberellic acid (3), involves the conversion of *ent*-7α-hydroxykaur-16-en-19-oic acid (1) into gibberellin A_{12} aldehyde (2).[1] The development of competitive inhibitors to block gibberellin biosynthesis at this step may provide a source of potential plant growth regulators. In this paper we describe the preparation of some *ent*-6-hydroxy-7-nor-5β-gibberell-16-enes as possible mimics of *ent*-7α-hydroxykaur-16-en-19-oic acid (1).† These compounds [*e.g.* (4)] possess the same B/C/D ring fusion together with an adjacent oxygen function but lack the methylene equivalent to C-6 of the kaurenoid intermediate. It is this centre from which hydrogen is abstracted during the ring-contraction process. These compounds also possess a *cis* A/B ring fusion although this was not intended at the outset of the work. Ring B norditerpenoids have been prepared [2] previously from the aldehyde-anhydride, fujenal (5) which also formed the starting point for the present work. The biological activity of these compounds, some of which are powerful gibberellin biosynthesis inhibitors, will be described elsewhere.

Methanolysis of fujenal (5) [3] in a sealed tube at 160 °C or with methanolic hydrochloric acid affords the pseudo-ester (6). However when fujenal was heated with sodium methoxide, the 19-monomethyl ester (7) was obtained. On oxidation with the 8N-chromium trioxide reagent,[4] this ester afforded a mixture of the 6,7-dicarboxylic acid (8) and the 6,7-anhydride (9) ($\nu_{max.}$ 1 775 and 1 735 cm^{-1}). Treatment of the dicarboxylic acid (8) with acetic anhydride gave the 6,7-anhydride (9). The ready formation of the anhydride served to locate the free carboxy-group in the methanolysis product (7) at C-6 rather than at C-19. Pyrolysis of the anhydride at 220 °C gave the 7-norgibberell-16-ene (10) [ν_{max} 1 735 (C=O) cm^{-1}; δ 5-H 3.02]. Two epimeric diols were obtained on reduction with lithium aluminium hydride in tetrahydrofuran. The less-polar minor product was the 6β,19-diol (11) whilst the major product was the 6α,19-diol (12). The evidence for the stereochemistry of the alcohols is presented below. Acetylation of the diol (11) gave the 19-mono-acetate (13) whilst the diol (12) gave a 6,19-diacetate.

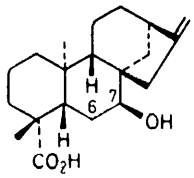
A second route involved reduction of fujenal with sodium borohydride in tetrahydrofuran–methanol to afford the known hydroxy-lactone (14).[2] The latter was oxidized with the 8N-chromium trioxide reagent to the aldehyde (15). This underwent an internal aldol condensation in the presence of 0.5N-methanolic sodium hydroxide, to give the hydroxy-lactone (16) which was then oxidized with 8N-chromium trioxide to form the β-keto-lactone (17). Decarboxylation of this in refluxing sodium hydroxide afforded the hemiacetal (18) [δ(^{1}H) 3.24 and 3.44 (AB quartet J 11 Hz, 19-CH_2O), and 2.12 (5-H); $\nu_{max.}$ 3 440 cm^{-1} (OH) no C=O absorption]. Reduction of the hemiacetal with lithium aluminium hydride gave the 6β,19-diol (11) and the 6α,19-diol (12).

A third more efficient route employed the internal Perkin condensation of fujenal (5) by sodium hydride in dimethylformamide. This gave the alcohol (19) [δ(^{1}H) 4.18 (6-H); $\nu_{max.}$ 3 550, 1 830, and 1 760 cm^{-1}]. When methanol was added to destroy the excess of sodium hydride, a neutral monomethyl ester, $C_{21}H_{28}O_4$, (20) was also obtained. The structure of the ester was assigned on the basis of the spectral data [δ(^{1}H) 5.41 (s, 6-H) and 3.56 (s, 3 H, OMe); $\nu_{max.}$ 1 750 (γ-lactone), 1 730 (ester) cm^{-1}]. The formation of this lactonic by-product suggests that the hydroxy-group in (19) may have the α-configuration. Oxidation of the alcohol (19) with the 8N-chromium trioxide reagent gave the keto-anhydride (21) ($\nu_{max.}$ 1 845, 1 780, and 1 725 cm^{-1}). Hydrolysis of the anhydride (21) with refluxing sodium hydroxide afforded the 6-keto-7-norgibberellin (22) which on methylation with diazomethane, gave the keto-ester (10) described above.

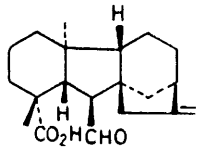
The 6-keto-acid (22) was resistant to reduction by sodium borohydride. However under forcing conditions (excess of sodium borohydride, refluxing tetrahydrofuran–aqueous sodium hydroxide for 20 h) [5] a separable mixture of hydroxy-acids was obtained. The less-polar major product (4) was inter-related with the 6β,19-diol (11) by methylation and reduction of the ester (23) with lithium aluminium hydride. The minor alcohol (24) was similarly related *via* the ester (25) with the 6α,19-diol (12).

The stereochemistry of these compounds was established as follows. The 6-alcohols fall into two series in which $J_{5,6}$ (established by spin decoupling studies) is 10—11 Hz (6α-alcohols) or 4—5 Hz (6β-alcohols). The former corresponds to a *trans*-coupling and the latter to a

† Part of this work has been described in a preliminary communication: J. R. Hanson, K. P. Parry, and C. L. Willis, *J.C.S. Chem. Commun.*, 1981, 285.



(1)



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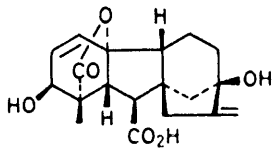

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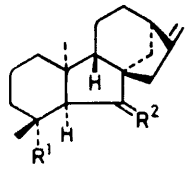
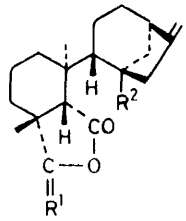
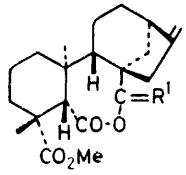


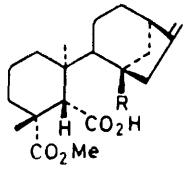
(4) R^1 = CO_2H, R^2 = α–H, β–OH
(10) R^1 = CO_2Me, R^2 = O
(11) R^1 = CH_2OH, R^2 = α–H, β–OH
(12) R^1 = CH_2OH, R^2 = α–OH, β–H
(13) R^1 = CH_2OAc, R^2 = α–H, β–OH
(22) R^1 = CO_2H, R^2 = O
(23) R^1 = CO_2Me, R^2 = α–H, β–OH
(24) R^1 = CO_2H, R^2 = α–OH, β–H
(25) R^1 = CO_2Me, R^2 = α–OH, β–H
(28) R^1 = CH_2OMs, R^2 = α–OMs, β–H
(29) R^1 = CH_2OAc, R^2 = O



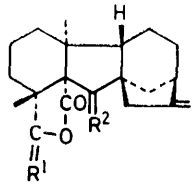
(5) R^1 = O, R^2 = CHO
(14) R^1 = H_2, R^2 = CH_2OH
(15) R^1 = H_2, R^2 = CHO



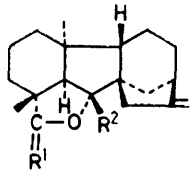
(6) R^1 = H, OMe
(9) R^1 = O



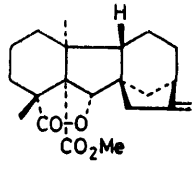
(7) R = CHO
(8) R = CO_2H



(16) R^1 = H_2, R^2 = H, OH
(17) R^1 = H_2, R^2 = O
(19) R^1 = O, R^2 = H, OH
(21) R^1 = R^2 = O



(18) R^1 = H_2, R^2 = OH
(26) R^1 = O, R^2 = H
(27) R^1 = H_2, R^2 = H



(20)

cis-coupling. Treatment of the 6β-hydroxy-acid ($J_{5,6}$ 4 Hz) (4) with methanesulphonyl chloride gave the 6,19-γ-lactone (26) [δ(^{1}H) 4.60 (6-H) and 2.32 (5-H, $J_{5,6}$ 11 Hz)] whilst the 6β,19-diol (11) gave a 6α,19-ether (27) ($J_{5,6}$ 11 Hz). In both cases the change of coupling constant showed that inversion of configuration had taken place at C-6 with the formation of the 6,19-oxygen bridge. When the corresponding 6α,19-diol (12) was treated with methanesulphonyl chloride, a dimethanesulphonate (28) was obtained. The ready formation of a 19-6 bridge from the β-series is indicative of an internal nucleophilic substitution of a β-oriented C-6 methanesulphonate by the α-oriented C-19 substituent. The β-alcohols possess the small (4—5 Hz) 5-H,6-H coupling constant and hence the 5-hydrogen atom must have the α-configuration. Thus the A/B ring junction in these compounds is *cis*-fused. A further piece of evidence comes from the i.r. spectra of the epimeric hydroxy-acids. Whereas the 6β-hydroxy-acid (4) shows a sharp non-hydrogen bonded hydroxy-absorption at 3 600 cm^{-1}, the 6α-hydroxy-acid (24) in which the two groups are on the same face of the molecule, possesses a broad hydrogen-bonded absorption at 3 400 cm^{-1}. The *cis* A/B fusion has subsequently been confirmed by *X*-ray analysis of the hydroxy-acid (4).[6] The formation of the *cis*-ring junction, although less desirable in a mimic of *ent*-7α-hydroxykaur-16-en-19-oic acid (1) has precedent in the formation of perhydrofluorene-7-carboxylic acids from the resin acids.[7]

A number of attempts were made to prepare 6-deoxy-7-nor-compounds as possible mimics of earlier stages in gibberellin biosynthesis. Wolff-Kishner reduction of the keto-acid (22), even under forcing conditions, failed and the starting material was recovered. Reduction of the 6α,19-dimethanesulphonate (28) with lithium aluminium hydride occurred with attack on sulphur and the formation of the 6α,19-diol (12). Oxidation of the 19-monoacetate (13) with the 8N-chromium trioxide reagent gave the corresponding 6-ketone (29) from which the hemiacetal (18) was obtained after hydrolysis.

The ready formation of these *ent*-7-nor-5β-gibberellenes with a *cis* A/B ring junction is in marked contrast to the gibberellin series in which C-5 epimers are hitherto unknown. It should be noted that in the C-20 gibberellin series (*e.g.* gibberellin A_{13}), a potential pathway exists for their formation *via* a C-6 carbanion and a retro-Michael reaction. The formation of the *cis* A/B ring junction affords relief of the diaxial C-19,C-20 interaction present in the *trans*-series.

EXPERIMENTAL

I.r. spectra were recorded as Nujol mulls; n.m.r. spectra were recorded at 90 MHz in deuteriochloroform. Silica (Merck 7734) was used for column chromatography. Light petroleum refers to the fraction, b.p. 60—80 °C. Ethyl acetate extracts were dried over sodium sulphate.

Reaction of Fujenal with Sodium Methoxide.—Fujenal (5.0 g) was treated with a solution of sodium (0.35 g) in dry methanol (100 ml) for 1 h at room temperature. The solution was concentrated, acidified, and the product recovered in ethyl acetate. It was recrystallized from ethyl acetate–light petroleum to afford ent-7-*oxo*-6,7-*secokaur*-16-*ene*-6,19-*dioic acid* 19-*methyl ester* (7) (4.2 g) as needles, m.p. 149—151 °C (Found: C, 69.8; H, 8.3. $C_{21}H_{30}O_5$ requires C, 69.6; H, 8.3%), $\nu_{max.}$ 3 280br, 2 700, 1 730, 1 715, 1 690, and 880 cm^{-1}; δ 1.02 (3 H, s, 20-H), 1.35 (3 H, s, 18-H), 3.41 (1 H, s, 5-H), 3.67 (3 H, s, OMe), 4.78 (2 H, m, 17-H_2), and 9.73 (1 H, s, CHO); mass spec. 362 (15%), 348 (28), 344 (32), 330 (100), 316 (48), 284 (19), 269 (35), 181 (70), and 167 (25) a.m.u.

Oxidation of the Aldehyde (7).—The above aldehyde (7) (4.1 g) in acetone (100 ml) was treated with the 8N-chromium trioxide reagent [4] (3 ml) for 2 h at room temperature. Methanol (3 ml) was added and the mixture was concentrated under reduced pressure. The product was recovered in ethyl acetate and separated into acidic and neutral fractions with aqueous sodium hydrogencarbonate. Chromatography of the neutral fraction on silica and elution with 12.5% ethyl acetate–light petroleum gave ent-6,7-*secokaur*-16-*ene*-6,7,19-*trioic acid* 6,7-*anhydride* 19-*methyl ester* (9) (1.6 g) which crystallized from light petroleum as needles, m.p. 178—181 °C (Found: C, 70.3; H, 7.9. $C_{21}H_{28}O_5$ requires C, 70.0; H, 7.8%), $\nu_{max.}$ 1 775, 1 730, 1 655, and 890 cm^{-1}; δ 1.30 (6 H, s, 18- and 20-H), 3.49 (1 H, s, 5-H), 3.67 (3 H, s, OMe), 4.88 (2 H, s, 17-H_2), *m/z* 360 (40%), 346 (39), 342 (45), 330 (78), 282 (19), 254 (27), 181 (51), and 149 (100). Chromatography of the acid fraction on silica gave, on elution with 25% ethyl acetate–light petroleum, ent-6,7-*secokaur*-16-*ene*-6,7,19-*trioic acid* 19-*methyl ester* (8) (1.2 g) which crystallized from ethyl acetate–light petroleum as needles, m.p. 181—182 °C (Found: C, 66.5; H, 8.0. $C_{21}H_{30}O_6$ requires C, 66.6; H, 8.0%), $\nu_{max.}$ 3 415, 1 730, 1 710, 1 655, and 880 cm^{-1}; δ 1.20 (3 H, s, 20-H), 1.35 (3 H, s, 18-H), 3.40 (1 H, s, 5-H), 3.63 (3 H, s, OMe), and 4.78 (2 H, m, 17-H_2); mass spec. 360 (20%, M − 18), 342 (24), 332 (30), 328 (100), 320 (44), 300 (23), 294 (15), and 181 (39). The dicarboxylic acid (8) (1.1 g) on heating in acetic anhydride (15 ml) under reflux for 6 h gave, after chromatography, the anhydride (9) (0.89 g).

Pyrolysis of the Anhydride (9).—The above anhydride (9) (2.5 g) was heated at 230 °C under nitrogen in a sealed Pyrex tube overnight. The product was recovered in ethyl acetate and the neutral fraction chromatographed on silica. Elution with 5% ethyl acetate–light petroleum gave *methyl* ent-6-*oxo*-7-*nor*-5β-*gibberell*-16-*en*-19-*oate* (10) (0.9 g) which crystallized from aqueous methanol as prisms, m.p. 115—118 °C (Found: C, 75.9; H, 9.0. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%), $\nu_{max.}$ 1 735, 1 730, 1 655, and 890 cm^{-1}; δ 0.90 (3 H, s, 20-H), 1.51 (3 H, s, 18-H), 3.02 (1 H, s, 5-H), 3.67 (3 H, s, OMe), and 4.82 and 4.93 (2 H, m, 17-H); mass spec. 326 (35%), 308 (52), 256 (21), 181 (69), 109 (63), 107 (75), 105 (100), and 91 (48).

Reduction of the Keto-ester (10).—The above keto-ester (10) (750 mg) in dry tetrahydrofuran (150 ml) was heated with lithium aluminium hydride (750 mg) for 6 h under reflux. Ethyl acetate and water were added. The products were recovered in ethyl acetate and separated by chromatography on silica. Elution with 20% ethyl acetate–light petroleum gave ent-6α,19-*dihydroxy*-7-*nor*-5β-*gibberell*-16-*ene* (11) (150 mg) which crystallized from light petroleum as needles, m.p. 33 °C (Found: C, 78.2; H, 10.4. $C_{19}H_{30}O_2$ requires C, 78.6; H, 10.4%), $\nu_{max.}$ 3 400, 1 655, and 878 cm^{-1}; δ 1.11 (3 H, s, 20-H), 1.15 (3 H, s, 18-H), 1.76 (1 H, d, J 4 Hz, 5-H), 3.31 (2 H, 19-H), 3.8 (1 H, d, J 4 Hz, 6-H), and 4.86, (2 H, m, 17-H). Irradiation at δ 3.8 caused the doublet at δ 1.76 to collapse to a singlet; mass spec. 290 (1%), 272 (19), 242 (38), 205 (22), 186 (29), 185 (42), 138 (33), and 105 (100). The 19-*mono-acetate*, prepared by reaction with acetic anhydride in pyridine overnight, had m.p. 28—29 °C (Found: C, 76.2; H, 9.8. $C_{21}H_{32}O_3$ requires C, 75.9; H, 9.6%); $\nu_{max.}$ 3 470, 1 740, 1 655, 1 245, 1 030, and 870 cm^{-1}; δ 1.10 (3 H, s, 20-H), 1.19 (3 H, s, 18-H), 1.75 (1 H, d, J 6 Hz, 5-H), 2.03 (3 H, s, OAc), 3.87 (1 H, d, J 6 Hz, 6-H), 3.95 (2 H, s, 19-H), and 4.85 (2 H, m, 17-H). Irradiation at δ 3.87 caused the doublet at δ 1.75 to collapse to a singlet; mass spec. 332 (1%), 314 (75), 299 (16), 257 (36), 255 (47), 241 (100), 189 (69), 123 (70), 119 (82), 109 (90), 107 (61), 105 (54), and 91 (72). Further elution with 30% ethyl acetate–light petroleum gave ent-6β,19-*dihydroxy*-7-*nor*-5β-*gibberell*-16-*ene* (12) (0.32 g) which crystallized from ethyl acetate–light petroleum as needles, m.p. 159—161 °C (Found: C, 78.6; H, 10.5. $C_{19}H_{30}O_2$ requires C, 78.6; H, 10.4%), $\nu_{max.}$ 3 170 (br), 1 655 and 880 cm^{-1}; δ 1.08 (3 H, s, 20-H), 1.12 (3 H, s, 18-H), 1.59 (1 H, d, J 10 Hz, 5-H), 3.28 (2 H, s, 19-H), 3.52 (1 H, s, O*H* exchanged with deuterium oxide), 3.69 (1 H, d, J 10 Hz, 6-H), and 4.82 (2 H, m, 17-H). Irradiation at δ 3.69 caused the doublet at δ 1.59 to collapse to a singlet; mass spec. 290 (15%), 272, 242, 186, 133, 122, 109, and 105 (100). The diacetate, prepared with acetic anhydride in pyridine, was a gum, $\nu_{max.}$ 1 740, 1 657 cm^{-1}; δ 0.94 (3 H, s, 20-H), 1.15 (3 H, s, 18-H), 2.05 and 2.15 (each 3 H, s, OAc), 3.84 (2 H, s, 19-H), 4.88 (2 H, m, 17-H), 5.25 (1 H, d, J 11 Hz, 6-H); mass spec. 314 (100%, M − 60), 299 (23), 254 (29), 241 (55), 239 (40), 185 (38), 145 (20), 109 (26), 107 (15), and 105 (34).

Reaction of the β-*Keto-lactone* (17) *with Alkali.*—The keto-lactone (17) [2] (1 g) in methanol (20 ml) was heated with 6N-sodium hydroxide (100 ml) for 4 h under reflux. The solution was cooled, acidified, and the product recovered in ethyl acetate. Chromatography on silica and elution with 25% ethyl acetate–light petroleum gave ent-19-*hydroxy*-6-*oxo*-7-*nor*-5β-*gibberell*-16-*ene* 6,19-*hemiacetal* (18) (570 mg) which crystallized from aqueous methanol as prisms, m.p. 80—82 °C (Found: C, 79.4; H, 9.9. $C_{19}H_{28}O_2$ requires C, 79.1; H, 9.8%), $\nu_{max.}$ 3 425, 1 685, and 860 cm^{-1}; δ 0.93 (3 H, s, 20-H), 1.03 (3 H, s, 18-H), 2.12 (1 H, s, 5-H), 3.24 and 3.44 (1 H each, AB q, J 11 Hz, 19-H), and 4.72 and 4.89 (1 H each, m, 17-H).

Reduction of the Hemiacetal (18).—The above hemiacetal (18) (500 mg) in dry tetrahydrofuran (100 ml) was heated with lithium aluminium hydride (400 mg) for 2 h under reflux. The mixture was cooled, treated with ethyl acetate and water, and the products recovered in ethyl acetate and chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave *ent*-6α,19-dihydroxy-7-nor-5β-gibberell-16-ene (11) (190 mg) whilst further elution with 30% ethyl acetate–light petroleum gave *ent*-6β,19-dihydroxy-7-nor-5β-gibberell-16-ene (12) (230 mg), which were identified by their i.r. and n.m.r. spectra.

Reaction of Fujenal with Sodium Hydride.—Fujenal (5 g) in dry dimethylformamide (140 ml) was heated with sodium hydride (1 g) for 1 h under reflux. Methanol was added and the solvent was removed under reduced pressure. The residue was acidified, taken up in ethyl acetate, washed with water, dried and the solvent evaporated to afford a gum which was chromatographed on silica. Elution with 15% ethyl acetate–light petroleum gave methyl *ent*-6β-hydroxy-5β-methoxycarbonyl-7-nor-5β-gibberell-16-en-19-oic acid 6,19-lactone (20) (200 mg) as a gum, $\nu_{max.}$ 1 730, 1 655, and 877 cm^{-1}; δ 0.98 (3 H, s, 20-H), 1.13 (3 H, s, 18-H), 3.56 (3 H, s, OMe), 4.81 (2 H, m, 17-H), 5.41 (1 H, s, 6-H); mass spec. 300 ($M - CO_2$, 25%), 242 (100), 197 (24), 159 (22), 119 (64), 105 (30), and 91 (72). Further elution with 25% ethyl acetate–light petroleum gave ent-5-*carboxy*-6-*hydroxy*-7-*nor*-5β-*gibberell*-16-*en*-19-*oic acid anhydride* (19) (4.55 g) which crystallized from ethyl acetate–light petroleum as needles, m.p. 195—196 °C (Found: C, 72.7; H, 7.9. $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9%), $\nu_{max.}$ 3 550sharp, 1 830, 1 760, 1 655, and 885 cm^{-1}; δ 0.93 (3 H, s, 20-H)) 1.39 (3 H, s, 18-H), 4.18 (1 H, s, 6-H), 4.85 (2 H, m, 17-H);, mass spec. 330 (12%), 312 (18), 258 (28), 242 (40), 197 (29), 181 (69), 153 (100), 107 (52), and 91 (42).

Oxidation of the Anhydride (19).—The anhydride (4.5 g) in acetone (200 ml) was treated with 8N-chromium trioxide (3 ml) for 1 h at room temperature. Methanol was added, the mixture was concentrated under reduced pressure, diluted with water, and the product recovered in ethyl acetate to afford ent-5-*carboxy*-6-*oxo*-7-*nor*-5β-*gibberell*-16-*en*-19-*oic acid anhydride* (21) (4.25 g) which crystallized from ethyl acetate–light petroleum as needles, m.p. 109—111 °C (Found: C, 72.9; H, 7.3. $C_{20}H_{24}O_4$ requires C, 73.2; H, 7.3%), $\nu_{max.}$ 1 845, 1 780, 1 724, 1 660, and 885 cm^{-1}; δ 1.28 (3 H, s, 20-H), 1.41 (3 H, s, 18-H), and 4.95 (2 H, m, 17-H); mass spec. 328 (100%), 296 (3), 256 (52), 254 (27), 241 (44) 147 (23), 131 (20), 119 (17), 105 (41), and 91 (51).

Hydrolysis of the Anhydride (21).—The above anhydride (21) (4.0 g) was heated under reflux with 3N-aqueous sodium hydroxide (100 ml) for 4 h. The solution was cooled, acidified, and the product recovered in ethyl acetate. Chromatography on silica and elution with 20% ethyl acetate–light petroleum gave ent-6-*oxo*-7-*nor*-5β-*gibberell*-16-*en*-19-*oic acid* (22) (3 g) which crystallized from ethyl acetate–light petroleum as needles, m.p. 166—168 °C (Found: C, 75.3; H, 8.5. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.6%), $\nu_{max.}$ 3 000br, 1 730, 1 695, 1 655, and 873 cm^{-1}; δ 1.02 (3 H, s, 20-H), 1.59 (3 H, s, 18-H), 3.05 (1 H, s, 5-H), and 4.87 (2 H, m, 17-H). Methylation with diazomethane in ether gave methyl *ent*-6-oxo-7-nor-5β-gibberell-16-en-19-oate (10), m.p. 115—118 °C, identical with the material described above.

Reduction of the Keto-acid (22).—The above keto-acid (1 g) in tetrahydrofuran (20 ml) was treated with sodium borohydride (1 g) in methanol (20 ml) and 2.5% aqueous sodium hydroxide (4 ml) under reflux for 20 h. The solvents were removed under reduced pressure and the residue acidified and extracted with ethyl acetate. The products were chromatographed on silica. Elution with 15% ethyl acetate–light petroleum gave ent-6α-*hydroxy*-7-*nor*-5β-*gibberell*-16-*en*-19-*oic acid* (4) (540 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 143—144 °C (Found: C, 75.0; H, 9.1. $C_{19}H_{28}O_3$ requires C, 75.0; H, 9.2%), $\nu_{max.}$ 3 600sharp, 3 000br, 1 690, 1 655, and 870 cm^{-1}; δ 0.95 (3 H, s, 20-H), 1.42 (3 H, s, 18-H), 2.57 (1 H, d, *J* 5 Hz, 5-H), 4.03 (1 H, d, *J* 5 Hz, 6-H), and 4.92 (2 H, m, 17-H). Irradiation at δ 4.03 caused the doublet at δ 2.57 to collapse to a singlet. The *methyl ester*, prepared with diazomethane, crystallized from light petroleum as needles, m.p. 158—159 °C (Found: C, 75.0; H, 9.3. $C_{20}H_{30}O_3$ requires C, 75.4; H, 9.4%), $\nu_{max.}$ 3 530, 1 720, 1 655, and 875 cm^{-1}; δ 0.90 (3 H, s, 20-H), 1.38 (3 H, s, 18-H), 2.55 (1 H, d, *J* 5 Hz, 5-H), 3.68 (3 H, s, OMe), 4.04 (1 H, d, *J* 5 Hz, 6-H), and 4.91 (2 H, m, 17-H). Irradiation at δ 4.04 caused the doublet at δ 2.55 to collapse to a singlet. Further elution with 25% ethyl acetate–light petroleum gave ent-6β-*hydroxy*-7-*nor*-5β-*gibberell*-16-*en*-19-*oic acid* (380 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 164—165 °C (Found: C, 74.7; H, 9.2. $C_{19}H_{28}O_3$ requires C, 75.0; H, 9.2%), $\nu_{max.}$ 3 400br, 3 000br, 1 690, 1655, and 880 cm^{-1}; δ ([$^2H_5$]pyridine) 1.20 (3 H, s, 20-H), 1.72 (3 H, s, 18-H), 2.91 (1 H, d, *J* 11 Hz, 5-H), 4.40 (1 H, d, *J* 11 Hz, 6-H), 4.98 (2 H, d, 17-H), and 7.12 (1 H, s, OH, exchanged with D_2O). Irradiation at δ 4.4 caused the doublet at δ 2.9 to collapse to a singlet. The *methyl ester* (25), prepared with diazomethane, crystallized from light petroleum as needles, m,p. 94—96 °C (Found: C, 75.4; H, 9.2. $C_{20}H_{30}O_3$ requires C, 75.5; H, 9.4%), $\nu_{max.}$ 3 400br, 1 720, 1 655, and 875 cm^{-1}; δ 0.90 (3 H, s, 20-H), 1.32 (3 H, s, 18-H), 2.30 (1 H, d, *J* 11 Hz, 5-H), 3.68 (3 H, s, OMe), 4.12 (1 H, d, *J* 11 Hz, 6-H), and 4.90 (2 H, m, 17-H). Irradiation at δ 2.30 caused the doublet at δ 4.12 to collapse to a singlet.

Reduction of the Methyl Esters (23) *and* (25).—(*a*) The hydroxy-ester (23) (100 mg) in dry tetrahydrofuran (50 ml) was heated with lithium aluminium hydride (100 mg) for 6 h under reflux. Ethyl acetate and water were added. The product was recovered in ethyl acetate and chromatographed on silica to afford the diol (11) (65 mg) which crystallized as needles, m.p. 33 °C, identical (i.r. and n.m.r.) with the material described above.

(*b*) Under similar conditions, the hydroxy-ester (25) (100 mg) gave the diol (12) (68 mg), m.p. 159—161 °C, identified by its i.r. and n.m.r. spectra.

Reaction of the Hydroxy-acid (4) *with Methanesulphonyl Chloride*.—The acid (4) (300 mg) in dry pyridine (10 ml) was treated with methanesulphonyl chloride (0.5 ml) at room temperature overnight. The solution was poured into dilute hydrochloride acid and the product recovered in ethyl acetate to afford ent-6β-*hydroxy*-7-*nor*-5β-*gibberell*-16-*en*-19-*oic acid* 6,19-*lactone* (26) (140 mg) which crystallized as prisms, m.p. 102—105 °C (Found: C, 79.5; H, 9.2. $C_{19}H_{26}O_2$ requires C, 79.7; H, 9.3%), $\nu_{max.}$ 1 790, 1 660, and 880 cm^{-1}; δ 1.02 (3 H, s, 20-H), 1.52 (3 H, s, 18-H), 2.32 (1 H, d, *J* 11 Hz, 5-H), 4.60 (1 H, d, *J* 11 Hz, 6-H), and 4.90 (2 H, d, 17-H). Irradiation at δ 4.60 caused the doublet at δ 2.32 to collapse to a singlet; mass spec. 286 (4%), 242 (31), 227 (52), 199 (37), 174 (20), 159 (19), 137 (23), 109 (100), 105 (46), and 91 (55).

Reaction of the Diol (11) *with Methanesulphonyl Chloride*.—The diol (11) (300 mg) in dry pyridine (10 ml) was treated with methanesulphonyl chloride (0.5 ml) at room temperature overnight. The mixture was poured into dilute hydrochloric acid and the product recovered in ethyl acetate. Chromatography on silica and elution with 5% ethyl acetate–light petroleum gave ent-6,19-*epoxy*-6β,19-*dihydroxy*-7-*nor*-5β-*gibberell*-16-*ene* (27) (98 mg) which crystallized from light petroleum as needles, m.p. 50—52 °C (Found: C, 83.8; H, 10.3. $C_{19}H_{28}O$ requires C, 83.8; H, 10.3%), $\nu_{max.}$ 1 660 and 865 cm^{-1}; δ 0.97 (3 H, s, 20-H), 1.30 (3 H, s, 18-H), 1.98 (1 H, d, *J* 11 Hz, 3.25 and 3.49 (each

1 H, AB q, 19-H), 4.18 (1 H, d, *J* 11 Hz, 6-H), and 4.69 and 4.82 (2 H, br, m, 17-H). Irradiation at δ 4.18 caused the doublet at δ 1.98 to collapse to a singlet.

Reaction of the Diol (12) *with Methanesulphonyl Chloride*.—The diol (12) (250 mg) in dry pyridine (10 ml) was treated with methanesulphonyl chloride (0.5 ml) at room temperature overnight. The mixture was poured into dilute hydrochloric acid. The product was recovered in ethyl acetate and chromatographed on silica. Elution with 15% ethyl acetate–light petroleum gave the *dimethanesulphonate* (28) (200 mg) of *ent*-6β,19-dihydroxy-7-nor-5β-gibberell-16-ene which crystallized from ethyl acetate–light petroleum as needles, m.p. 134 °C (Found: C, 56.6; H, 7.6. $C_{21}H_{34}O_6S_2$ requires C, 56.5; H, 7.6%), $\nu_{max.}$ 1 660, 1 170, and 890 cm^{-1}; δ 1.08 (3 H, s, 20-H), 1.10 (3 H, s, 18-H), 2.01 (1 H, d, *J* 11 Hz, 5-H), 2.95 and 3.02 (each 3 H, s, SO_2Me), 3.98 (2 H, s, 19-H), 4.87 (2 H, m, 17-H), and 5.05 (1 H, d, *J* 11 Hz, 6-H); irradiation at δ 2.01 caused the doublet at δ 5.05 to collapse to a singlet.

Reduction of the Dimethanesulphonate (28).—The dimethanesulphonate (28) (150 mg) in dry tetrahydrofuran (50 ml) was heated with lithium aluminium hydride (150 mg) under reflux for 4 h. Ethyl acetate and water were added. The product was recovered in ethyl acetate and chromatographed on silica. Elution with 30% ethyl acetate : light petroleum gave the diol (12) (88 mg), m.p. 159—161 °C, which was identified by its i.r. and n.m.r. spectra.

Oxidation of the 19-*Monoacetate* (13).—The 19-monoacetate (13) (150 mg) in acetone (50 ml) was treated with the 8N-chromium trioxide reagent (1 ml) for 10 min at room temperature. Methanol was added and the solvents were removed under reduced pressure. The residue was diluted with water and the product recovered in ethyl acetate to afford the 19-*monoacetate* (29) of *ent*-19-hydroxy-6-oxo-7-nor-5β-gibberell-16-ene (145 mg) as a gum, $\nu_{max.}$ 1 740br, 1 655, 1 235, 1 035, and 880 cm^{-1}; δ 1.03 (3 H, s, 20-H), 1.09 (3 H, s, 18-H), 1.98 (3 H, s, OAc), 2.18 (1 H, s, 5-H), 3.98 (2 H, s, 19-H), and 4.82 (2 H, m, 17-H); mass spec. 330 (3%), 315 (10), 270 (18), 257 (44), 255(21), 189 (100), 119 (16), and 109 (28).

Hydrolysis of the 19-*Monoacetate* (29).—A solution of the above 19-monoacetate (130 mg) and potassium carbonate (400 mg) in water (2 ml) and methanol (15 ml) was heated under reflux for 1 h. The methanol was evaporated, the solution diluted with water, and the product recovered in ethyl acetate to give the hemiacetal (18) (112 mg) which slowly crystallized from light petroleum as needles, m.p. 84—85 °C.

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