Terpenoids. Part 9.[1] 10α ⟶ 9α-Methyl Migration in Derivatives of Grandiflorenic Acid

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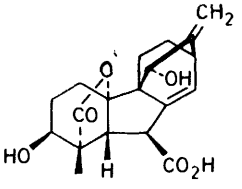
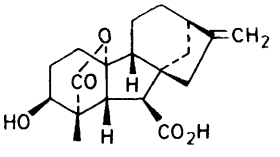
Attempts to rearrange grandiflorenic acid [*ent*-kaura-9(11),16-dien-19-oic acid] to rings C/D analogues of antheridiogen (A_{An}) were unsuccessful. The norketones of grandiflorenic acid and the methyl ester underwent 10α ⟶ 9α-methyl migration when treated with acetyl hypobromite, aqueous sulphuric acid, and bromine.

THE structural similarity between antheridiogen, A_{An} (1),[2] the antheridium-inducing factor from *Anemia phyllitidis*, and gibberellin A_4 (2) prompted the investigations reported here. The aim was to convert grandiflorenic acid (3) into rings C/D-analogues of antheridiogen (1) and to investigate the microbiological conversion of



(1)



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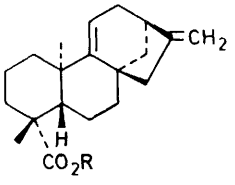
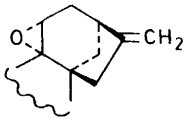


(3) R = H
(4) R = Me



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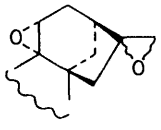

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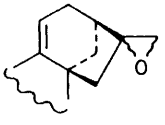

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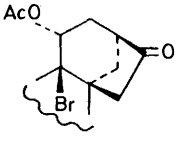

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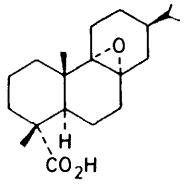

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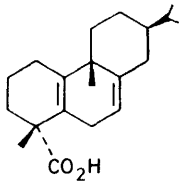


(10)

these analogues into antheridiogen-type compounds by mutant B1-41a of the fungus, *Gibberella fujikuroi*. In the event, a 10α ⟶ 9α-methyl migration was observed.

The original plan was to examine the acid-catalysed rearrangement of 9α,11α-epoxygrandiflorenic acid (5), prepared by selective deoxygenation of the di-epoxide (6). However, although Piozzi *et al.*[3] used titration with perbenzoic acid to determine the presence of two double bonds in grandiflorenic acid (3), reaction of methyl grandiflorenate (4) with *m*-chloroperbenzoic acid gave only the 16ξ,17ξ-monoepoxide (7). Purification of the *m*-chloroperbenzoic acid [4] and the addition of sodium carbonate [5] or disodium hydrogenphosphate [6] gave cleaner reaction products but no diepoxide (6).

As an alternative, the reaction of methyl grandiflorenate norketone (11) (see Scheme) with acetyl hypobromite [7] was tried. However, the required 9β-bromo-11α-acetate (8) was not formed. Instead an unstable compound was obtained which, from its spectroscopic properties, appeared to possess the structure (13) (see Scheme). The effect of other electrophiles on the norketone (11) and the corresponding acid (12) was then examined. The results, and inter-relationship of the products, are shown in the Scheme. The structures of all compounds shown in the Scheme were assigned from the ^1H n.m.r., ^{13}C n.m.r., and mass spectra, and they were confirmed [8] by the *X*-ray crystal structure of the bromo-acid (19), determined by Dr. C. J. Gilmore, Glasgow University.

The 10α ⟶ 9α-methyl migration, noted for the grandiflorenic acid derivatives (11) and (12), has been previously observed for other diterpenes [9-13] and in the preceding paper. In the free acid (12), lactone formation did not accompany rearrangement nor was the product (17) lactonised on treatment with glacial acetic acid, hydrochloric acid, or boron trifluoride–ether. Attempts to iodo-lactonise [14] the acid (15) also gave no reaction. Hertz and Wahlborg [15] also found that the rearrangement of the abietic acid epoxide (9) to (10), with acidic reagents, occurred without lactonisation.

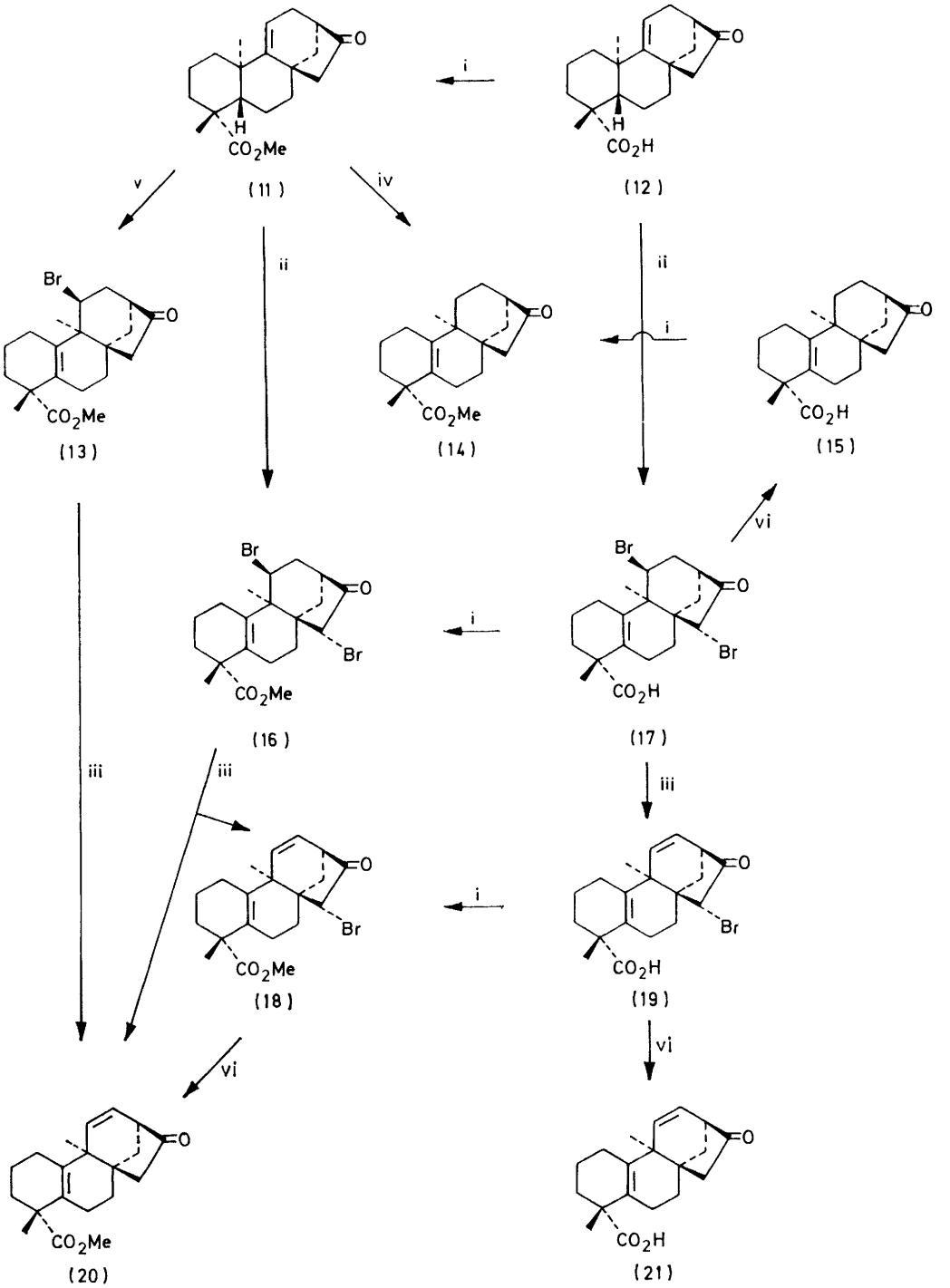
EXPERIMENTAL

For general procedures see Part 8.[1] Except where stated otherwise, i.r. spectra are for Nujol mulls and n.m.r. spectra are for solutions in deuteriochloroform with tetramethylsilane as internal standard. Usual work-up refers to acidification to pH 2 with concentrated hydrochloric acid and extraction with ethyl acetate, followed by removal of the ethyl acetate *in vacuo*. Light petroleum had b.p. 60—80 °C.

Attempted Diepoxidation of Grandiflorenic Acid Methyl Ester (4).—Grandiflorenic acid (3) [1] (60 mg) was methylated

using an excess of ethereal diazomethane. The residue, obtained after removal of solvent, was dissolved in chloroform (10 ml) and treated with *m*-chloroperbenzoic acid (*B.D.H.* 85%; 120 mg) at 3 °C for 24 h. The reaction was worked up by adding ethyl acetate, washing with 1M-sodium hydroxide, and then with water. Evaporation of the organic phase gave a gum which was purified by p.l.c. in ethyl acetate–light petroleum (2 : 3). The band at R_F 0.7 gave *methyl* ent-16ξ17ξ-*epoxykaur*-9(11)-*en*-19-*oate* (7) (23 mg) as a gum (Found: M^+, 330.218. $C_{21}H_{30}O_3$ requires M, 330.219); $\nu_{max.}$ (CH_2Cl_2), 1 715 (CO_2Me), 1 217 (epoxide), 1 150, and 822 cm^{-1}; δ 0.96 (s, 20-H_3), 1.18 (s, 18-H_3), 2.83 (d, J 2 Hz, 17-CH_2), 3.67 (s, CO_2Me), and 5.25 (t, J 3 Hz, 11-H); *m/e* (%) 330 (M^+, 11), 315 (11), 273 (64), 271 (40), 255 (44), 213 (55), 131 (83), 109 (52), 105 (81), and 91 (100).

Reaction for longer periods at 3 °C or at room temperature gave many products (t.l.c.). Purified peracid,[4] and



Scheme Reagents: i, CH_2N_2; ii, Br_2; iii, KOH–MeOH; iv, H_2SO_4–H_2O–MeOH; v, MeCONHBr–LiOAc·$2H_2O$–AcOH; vi, Bu^n_3SnH

the addition of sodium carbonate [5] or disodium hydrogenphosphate [6] gave a cleaner reaction but no useful amounts of the diepoxide (6). With disodium hydrogenphosphate and purified peracid in refluxing chloroform the monoepoxide (5) was formed in 1 h but longer reaction times gave a complex mixture of products.

Acetyl Hypobromite Reaction on Methyl Grandiflorenate Norketone (11).—Grandiflorenic acid norketone (12) [1] (200 mg) was methylated using an excess of ethereal diazomethane. The residue, after evaporation of solvent, was dissolved in acetic acid (20 ml) and treated with lithium acetate dihydrate (1.452 g) and *N*-bromoacetamide (144 mg). The mixture was stirred at room temperature for 6 h. The solution was added to water which was extracted with ethyl acetate. Removal of the organic phase *in vacuo* gave crude methyl-*ent*-11α-bromo-9β-methyl-16-oxo-17,20-dinorkaur-1(5)-en-19-oate (13) (318 mg) which was found to be unstable. This crude product was used for subsequent reactions without purification. Spectroscopic data were obtained on the crude product: $\nu_{max.}$ (CH_2Cl_2) 1 741 (C=O), 1 723 (CO_2Me), and 1 678 (C=C) cm^{-1}; δ_H 1.27 (s, t-Me), 1.39 (s, t-Me), 3.64 (s, CO_2Me), and 4.34 (t, *J* 3 Hz, 11-H); δ_C 135.2 and 130.6 p.p.m. (fully substituted olefin); *m/e* (%) 394/396 (M^+, 15/13), 335/337 (59/58), 315 (25), 314 (26), 225 (100), 213 (39), 105 (27), and 91 (20); g.l.c.–m.s. analysis on 2% SE31 gave *m/e* (%) 314 (28), 255 (100), 253 (13), 213 (58), 197 (7), 159 (4), 157 (8), 155 (6), 145 (5), 143 (5), 131 (6), 119 (9), 105 (21), and 91 (5).

Base Treatment of the Acetyl Hypobromite Product (13).—The product (13) (230 mg), in methanol (5 ml), and potassium hydroxide (200 mg) were stirred at room temperature for 2 h, and then at 60 °C for 2 h. The mixture was added to water and worked-up in the usual way to give an oil which was purified by p.l.c. with ethyl acetate–light petroleum (1 : 1). The band at R_F 0.8 gave *methyl* ent-9β-*methyl*-16-*oxo*-17,20-*dinorkaur*-1(5),11-*dien*-19-*oate* (20) (41 mg) as a gummy solid (Found: M^+, 314.187. $C_{20}H_{26}O_3$ requires *M*, 314.188); $\nu_{max.}$ (CH_2Cl_2) *ca.* 1 725br. (C=O + CO_2Me) cm^{-1}; δ_H 1.27 (s, 2 × t-Me), 3.68 (s, CO_2Me), 5.65 (ddd, *J* 9, 7, and 2 Hz, 12-H), 5.93 (d, *J* 9 Hz, 11-H); δ_C 134.0 and 129.0 (fully substituted olefin) and 135.5 and 123.4 p.p.m. (1,2-disubstituted olefin); *m/e* (%) 314 (M^+, 33), 299 (44), 296 (9), 272 (8), 257 (23), 255 (76), 254 (34), 237 (34), 233 (18), 213 (77), 197 (100), 173 (68), 172 (27), 159 (66), 149 (16), 143 (22), 141 (19), 131 (20), 119 (23), 117 (27), 109 (23), 105 (48), 96 (26), and 91 (70); g.l.c.–m.s. analysis on 2% SE31 gave the same m.s.

Reaction of Methyl Grandiflorenate (11) *Norketone with Acid.*—Grandiflorenic acid norketone (12) [1] (50 mg) was methylated in the usual way and dissolved in methanol (1 ml) and 10% aqueous sulphuric acid (2 ml). This mixture was refluxed for 3 h under nitrogen gas before dilution with water and extraction with ethyl acetate. The residue obtained after removal of the organic phase was purified by p.l.c. with ethyl acetate–light petroleum (1 : 1). The band at R_F 0.7 gave *methyl* ent-9β-*methyl*-16-*oxo*-17,20-*dinorkaur*-1(5)-*en*-19-*oate* (14) (21 mg) as a gum (Found: M^+, 316.203. $C_{20}H_{28}O_3$ requires *M*, 316.204); $\nu_{max.}$ (CH_2Cl_2) 1 730br. (C=O and CO_2Me) and 1 669 (C=C) cm^{-1}; δ_H 1.21 (s, t-Me), 1.24 (s, t-Me), and 3.64 (s, CO_2Me); δ_C 137.0 and 128.0 p.p.m. (fully substituted olefin); *m/e* (%) 316 (M^+, 13), 301 (2), 257 (100), 241 (43), 147 (20), and 105 (23).

Reactions with Bromine.—(a) *Grandiflorenic acid norketone* (12). The norketone (100 mg), in chloroform (2.5 ml), was treated with bromine (45 μl) and stirred at room temperature for 1.5 h. The solvent was removed and the residue was purified by p.l.c. with ethyl acetate–light petroleum–acetic acid (40 : 60 : 1). The band at R_F 0.35 gave ent-11α,15β-*dibromo*-9β-*methyl*-16-*oxo*-17,20-*dinorkaur*-1(5)-*en*-19-*oic acid* (17) (120 mg), decomposing above 125 °C (from ethyl acetate) (Found: C, 49.1; H, 5.5. $C_{19}H_{24}Br_2O_3$ requires: C, 49.6; H, 5.3%); $\nu_{max.}$ 3 400 (CO_2H), 3 070 (CO_2H), 1 757 (C=O), and 1 711 (CO_2H); in CH_2Cl_2 3 070, 1 753, 1 698, 1 610, and 822 (C=C) cm^{-1}; δ 1.33 (s, t-Me), 1.50 (s, t-Me), 4.36 (t, *J* 3 Hz, 11-H), and 5.40 (d, *J* 3 Hz, 15-H); *m/e* (%) 458/460/462 (M^+, 1/3/1), 413/415/417 (3/7/3), 378/380 (12/13), 333/335 (19/22), 300 (9), 299 (11), 298 (9), 255 (17), 254 (16), 253 (13), 225 (10), 213 (13), 211 (10), 197 (10), 157 (11), 155 (10), 129 (9), 105 (15), 91 (17), 82 (100), 81 (45), and 80 (98).

(b) *Methyl grandiflorenate norketone* (11). The methyl ester (11) (40 mg) was treated as in (a). P.l.c. of the product with ethyl acetate–light petroleum (1 : 1) gave, at R_F 0.6, *methyl* ent-11α,15β-*dibromo*-9β-*methyl*-17,20-*dinorkaur*-1(5)-*en*-19-*oate* (16) (40 mg), m.p. 128—135 °C (from ethyl acetate) (Found: C, 50.9; H, 5.8. $C_{20}H_{26}Br_2O_3$ requires: C, 50.7; H, 5.5%); $\nu_{max.}$ 1 753 (C=O), 1 732 (CO_2Me), 1 260, 1 170, 1 113, and 824 (C=C) cm^{-1}; δ 1.34 (s, t-Me), 1.53 (s, t-Me), 3.68 (s, CO_2Me), 4.43 (t, *J* 3 Hz, 11-H), and 5.47 (d, *J* 3 Hz, 15-H); *m/e* (%) 472/474/476 (M^+, 6/11/4), 413/415/417 (59/100/54), 333 (82), 269 (32), 253 (43), 225 (27), 172 (32), 82 (42), and 80 (51).

Reaction of the Dibromides (16) *and* (17) *with Tri-n-butylstannane.*—(a) The dibromide (17) (120 mg), in dry benzene (36 ml), was treated with tri-n-butylstannane (48 μl) and a few crystals of 2,2′-azobis-(2-methylpropionitrile).[16] This mixture was refluxed for 1 h under nitrogen gas. The benzene was then removed to give a gum which was partitioned between ethyl acetate and 2M-sodium hydroxide. The usual work-up gave a gum (119 mg) which was purified by p.l.c. with ethyl acetate–light petroleum–acetic acid (40 : 60 : 1). The band at R_F 0.6 gave ent-9β-*methyl*-16-*oxo*-17,20-*dinorkaur*-1(5)-*en*-19-*oic acid* (15) as a gum (Found: M^+, 302.188. $C_{19}H_{26}O_3$ requires *M*, 302.188); $\nu_{max.}$ (CH_2Cl_2) 3 070 (CO_2H), 1 738 (C=O), and 1 694 (CO_2H) cm^{-1}; δ 1.19 (s, t-Me), and 1.25 (s, t-Me); *m/e* (%) 302 (M^+, 30), 287 (6), 257 (100), 241 (70), 197 (18), 147 (17), 105 (24), and 91 (29).

(b) In the methyl ester series the dibromide (16) (60 mg), on treatment with tri-n-butylstannane, and purification of the product by p.l.c. in ethyl acetate–light petroleum (1 : 1) gave, at R_F 0.6, the compound (14) (26 mg) identical (t.l.c., m.s., and n.m.r.) to the compound described earlier.

Reaction of the Dibromides (16) *and* (17) *with Base.*—(a) The dibromide (17) (119 mg), in methanol (4 ml), was treated with potassium hydroxide (300 mg). This mixture was stirred at room temperature for 1 h, and then for 2 h at 60 °C. The mixture was then added to water and worked up in the usual way to give a gum which was purified by p.l.c. with ethyl acetate–light petroleum–acetic acid (40 : 60 : 1). The band at R_F 0.45 gave ent-15β-*bromo*-9β-*methyl*-16-*oxo*-17,20-*dinorkaura*-1(5),11-*dien*-19-*oic acid* (19) (94 mg), m.p. 185—188 °C (from acetone) Found: C, 60.5; H, 6.4. $C_{19}H_{23}BrO_3$ requires: C, 60.2; H, 6.1%); $\nu_{max.}$ 3 200 (CO_2H), 1 730 (C=O and CO_2H), 1 160, 1 115, and 760 cm^{-1}; δ 1.32 (s, t-Me), 1.35 (s, t-Me), 3.01 (dd, *J* 8 and 3 Hz, 13-H), 4.66 (d, *J* 3 Hz, 15-H), 5.67 (ddd, *J* 9, 7, and 2 Hz, 12-H), and 5.94 (d, *J* 9 Hz, 11-H); *m/e* (%) 378/380 (M^+, 15/15), 363/365 (35/32), 333/335 (9/10),

299 (84), 297 (28), 285 (18), 281 (12), 253 (100), 243 (39), 235 (15), 225 (18), 213 (24), 211 (22), 197 (99), 183 (15), 181 (14), 173 (18), 169 (18), 165 (18), 159 (20), 155 (28), 143 (25), 141 (46), 131 (23), 129 (28), 128 (25), 117 (34), 115 (30), 105 (46), and 91 (60).

(b) The dibromide (16) (51 mg) was treated with methanolic potassium hydroxide as in (a). The product was subjected to p.l.c. with ethyl acetate–light petroleum (1 : 1) to give, at R_F 0.7, a mixture of (20), identified by m.s. and g.l.c.–mass spectrometry and the monobromide (18). The latter product had *m/e* (%) 392/394 (M^+, 28/27), 377/379 (39/40), 333/335 (56/53), 313 (63), 253 (100), 213 (39), 197 (79), 105 (42), and 91 (58), and was identified by comparison (m.s. and g.l.c.–mass spectrometry) with the methylation product of the acid (19), described in (a).

Reaction of the Monobromides (18) *and* (19) *with Tri-n-butylstannane.*—(a) The monobromide (19) (54 mg), in dry benzene (20 ml), was treated with tri-n-butylstannane (16 μl) and a few crystals of 2,2′-azobis-(2-methylpropionitrile). This mixture was refluxed for 6 h under nitrogen gas before work-up as described earlier. The gum obtained was purified by p.l.c. with ethyl acetate–light petroleum–acetic acid (40 : 60 : 1). The band at R_F 0.6 gave ent-9β *methyl*-16-*oxo*-17,20-*dinorkaura*-1(5),11-*dien*-19-*oic acid* (21) (23 mg), m.p. 167—169 °C (from ethyl acetate) (Found: C, 75.4; H, 8.3. $C_{19}H_{24}O_3$ requires: C, 76.0; H, 8.0%); $\nu_{max.}$ 1 741 (C=O), 1 693 (CO_2H), 751, and 728 cm^{-1}; δ 1.26 (s, t-Me), 1.27 (s, t-Me), 5.64 (ddd, *J* 9, 7, and 2 Hz, 12-H), and 5.94 (d, *J* 9 Hz, 11-H); *m/e* (%) 300 (M^+, 26), 285 (46), 282 (24), 254 (37), 243 (30), 237 (29), 213 (30), 197 (100), 173 (69), 172 (45), 159 (44), 155 (29), 143 (36), 141 (59), 131 (29), 129 (36), 128 (33), 119 (26), 117 (46), 115 (33), 105 (76), 96 (53), and 91 (97).

(b) Treatment of the methyl ester (18) from base treatment of the monobromide (16) with tri-n-butylstannane gave (20), identified by t.l.c., g.l.c., and m.s.

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