Reactions of 2-Chloro-*NN*-diethyl-1,1,2-trifluoroethylamine with Alcohols. Part 2.[1] Bridgehead Fluorination of Gibberellins

By **Robert E. Banks** and **Brian E. Cross,*** Department of Organic Chemistry, The University, Leeds LS2 9JT

Four new fluoro-gibberellins, *viz.* 2β,7α-difluoro-4aα-hydroxy-1β-methyl-8-methylenegibb-3-ene-1α,10β-dicarboxylic acid 1,4a-lactone (4), 4β,7α-difluoro-4aα-hydroxy-1β-methyl-8-methylenegibb-2-ene-1α,10β-dicarboxylic acid 1,4a-lactone (7), and the 8-epimers of 7α-fluoro-4aα-hydroxy-1β,8-dimethylgibb-2-ene-1α,10β-dicarboxylic acid 1,4a-lactones[(18) and (19)] and of 7α-fluoro-4aα-hydroxy-1β,8-dimethylgibbane-1α,10β-dicarboxylic acid 1,4a-lactone [(12) and 13)], containing bridgehead fluorine atoms have been prepared by the fluorination of esters of gibberellins with the title reagent, followed by de-esterification.

BRIDGEHEAD and tertiary hydroxy-groups do not usually react with 2-chloro-*NN*-diethyl-1,1,2-trifluoroethylamine at room temperature, and on heating rearrangement is often the predominant reaction.[2,3] Treatment of the *p*-bromophenacyl ester (1) of gibberellic acid with a

[1] Part 1, J. H. Bateson and B. E. Cross, *J.C.S. Perkin I*, 1974, 2409.

[2] J. Kopecky, J. Smejkal, and M. Hudlicky, *Chem. and Ind.*, 1969, 271.

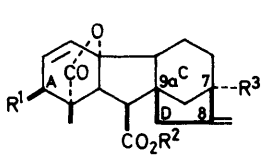
[3] C. M. Sharts and W. A. Sheppard, *Org. Reactions*, 1974, **21**, 160.

small excess of the fluoro-amine gave [1] the fluoro-esters (2) and (5), in which ring A had been fluorinated, whereas the 7-hydroxy-group was unaffected. However, the discovery that the 7-hydroxy-group of esters of gibberellic acid is smoothly replaced by fluorine when they are treated with a large excess of the fluoro-amine at room temperature † has provided a means of preparing several new biologically active [4] fluoro-gibberellins (*cf.* refs. 1 and 5).

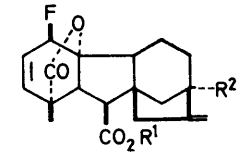
Fluorination of *p*-bromophenacyl gibberellate (1) with a large excess of the fluoro-amine (*cf.* ref. 1) afforded the two isomeric difluoro-esters (3) and (6), whose structures were determined by spectroscopy. Their ^{1}H n.m.r. spectra (see Experimental section) readily distinguished the 2-ene (6) from the Δ^3-gibberellin (3) [1,6] and showed that the ring A fluorine atom in each ester possessed the β-configuration.[1] These structural assignments were supported by the ^{19}F n.m.r. spectra in which the signal due to the 2β- and 4β-fluorine atoms appeared as expected (*cf.* ref. 1); in each ester the other fluorine atom gave rise to a complex multiplet at ϕ* 147 with no evidence of geminal H,F coupling, *i.e.* the fluorine was on a tertiary carbon atom. Hence it appeared that replacement of the 7-hydroxy-group by fluorine had occurred without rearrangement, and this conclusion was confirmed by evidence [$\nu_{max.}$ 900 cm^{-1}; τ 4.91 (1 H) and 4.72 (1 H)] that the terminal methylene group at C-8 remained intact. De-esterification of the fluoro-esters (3) and (6) with zinc dust in glacial acetic acid at room temperature gave the required difluorogibberellins (4) and (7). The latter showed the u.v. absorption [$\lambda_{max.}$ 222 nm (ε 1 500)] of a gibb-2-ene 1,4a-lactone,[1,7] thus confirming the identity of the ring A isomers.

The bridgehead fluorination of gibberellins has been extended to the reaction of a *ca.* 1 : 1 mixture of the 8-epimeric methyl tetrahydrogibberellates [8] [(8) and (9)] with a large excess of the fluoro-amine. As expected [9] the 2β-hydroxy-group was eliminated, but fluorination occurred at C-7 to give the esters (16) and (17). After purification by chromatography and crystallisation, the product was shown to be mainly (*ca.* 75%) the 8β-Me epimer (16) by comparison of its ^{1}H n.m.r. spectrum with that of the pure epimer (see below). Presumably partial separation of the 8α- and 8β-epimers had occurred during purification.

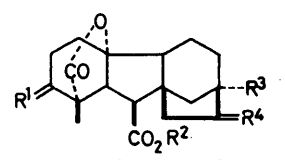
The ^{19}F n.m.r. spectrum of the mixture of esters (16) and (17) showed no geminal H,F coupling, in agreement with the placement of the fluorine atom at C-7. This conclusion was rigorously established by ^{13}C n.m.r. spectroscopy. In comparison with the spectra of derivatives of gibberellin A_1 (15),[10,11] the spectrum of the tetrahydroesters (8) and (9) showed additional high-field signals at δ 18.1 and 26.6. These were provisionally assigned to the 8β- and 8α-methyl groups in the esters (8) and (9), respectively, since models show that the 8-methyl group in the former suffers greater steric compression [12]



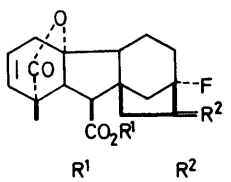
	R^1	R^2	R^3
(1)	HO	*p*-BrC_6H_4·CO·CH_2	OH
(2)	F	*p*-BrC_6H_4·CO·CH_2	OH
(3)	F	*p*-BrC_6H_4·CO·CH_2	F
(4)	F	H	F



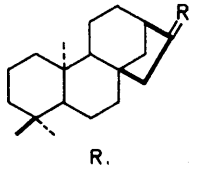
	R^1	R^2
(5)	*p*-BrC_6H_4·CO·CH_2	OH
(6)	*p*-BrC_6H_4·CO·CH_2	F
(7)	H	F



	R^1	R^2	R^3	R^4
(8)	α-H,β-OH	Me	OH	α-H,β-Me
(9)	α-H,β-OH	Me	OH	α-Me,β-H
(10)	H_2	Me	F	α-H,β-Me
(11)	H_2	Me	F	α-Me,β-H
(12)	H_2	H	F	α-H,β-Me
(13)	H_2	H	F	α-Me,β-H
(14)	α-OH,β-H	Me	OH	α-H,β-Me
(15)	α-H,β-OH	H	OH	CH_2



	R^1	R^2
(16)	Me	α-H,β-Me
(17)	Me	α-Me,β-H
(18)	H	α-H,β-Me
(19)	H	α-Me,β-H



	R
(20)	α-H,β-Me
(21)	CH_2

† For a preliminary account see R. E. Banks and B. E. Cross, *Chem. and Ind.*, 1975, 90.

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[9] Ref. 3, p. 163.

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[12] J. B. Stothers, 'Carbon-13 NMR Spectroscopy,' Academic Press, New York, 1972, p. 404.

than it does in the latter. Support for these assignments was provided by the ^{13}C n.m.r. spectrum of *ent*-kaurane (20),[13] whose ring D methyl group is found in a stereochemical environment closely similar to that in the ester (8), and which gave rise to a ^{13}C signal at δ 15.8. Many of the other resonances in the spectrum of *ent*-kaurane were assigned provisionally (see Experimental section) by comparison with the ^{13}C n.m.r. spectrum[14] of *ent*-kaurene (21).

Most of the remaining ^{13}C resonances in the spectrum of the esters (8) and (9) have been assigned provisionally (see Experimental section) by analogy with literature values[10,11] for closely related gibberellins. Low power broad-band decoupling was used to confirm the assignment of the quaternary carbon signals; in particular the resonances due to C-7 in the epimers were observed at δ 75.35 and 76.8.

The ^{13}C n.m.r. spectrum of the fluoro-esters (16) and (17) was complicated by extensive C-F coupling. However, low power broad-band decoupling revealed singlets at δ 54.0 and 92.4 due to the quaternary carbon atoms C-1 and C-4a, respectively; the spectrum also contained a low-field doublet at δ 99.9 (J_{CF} 198 Hz) and a weaker doublet at δ 101.2 (J_{CF} 191 Hz). These chemical shifts and couplings could only be assigned to C-7 in the major and minor epimers, (16) and (17), respectively. Hence the bridgehead hydroxy-groups in the esters (8) and (9) have been cleanly replaced by fluorine, presumably *via* a carbocation type of intermediate.

Alkaline hydrolysis of the fluoro-esters (16) and (17) afforded the new fluoro-gibberellins (18) and (19). Hydrogenation of the esters (16) and (17) gave the esters (10) and (11), which on alkaline hydrolysis afforded 7-fluorodihydrogibberellin A_9 [(12) and (13)].

Treatment of the single epimer (14) derived[15] from methyl tetrahydrogibberellate with an excess of the fluoro-amine gave the fluoro-ester (16), whose n.m.r. spectrum was used to identify the signals due to (16) in the epimeric mixture of (16) and (17) (see above).

EXPERIMENTAL

Details of chromatographic materials and conditions used for the determination of physical data, *etc.*, are reported in refs. 5 and 16 except that, unless otherwise stated, i.r. spectra were determine for solutions in chloroform. Fourier transform ^{13}C n.m.r. spectra were recorded with a Bruker HF 3 instrument at 22.62 MHz with tetramethylsilane as internal standard.

The 8-Epimeric Mixture of Methyl Tetrahydrogibberellates [(8) *and* (9)].—The ^{13}C n.m.r. spectrum of the mixture[8] in [$^2H_6$]dimethyl sulphoxide showed signals at δ 14.4 (1β-Me), 16.2 and 16.8 (C-5), 18.1 (8β-Me), 26.6 (8α-Me), 27.8 (C-4), 29.3 (C-3), 40.7 (C-6), 42.8 (C-11), 45.1 and 46.4 (C-9), 49.5 (C-9a), 50.2, 51.0, 51.9, and 52.3 (C-8, -10, and -10a), 51.5 (OMe), 54.1 (C-1), 54.4 (C-4b), 68.5 (C-2), 75.35 and 76.8 (C-7), and 93.3 (C-4a).

ent-*Kaurane* (20).—The ^{13}C n.m.r. spectrum in $CDCl_3$ included signals at δ 15.8 (C-17), 17.75 (C-20), 18.7 (C-2 and -11), 20.5 (C-6), 21.6 (C-19), 33.3 (C-4), 39.4 (C-10), 40.6 (C-7), 41.0 (C-1), 42.2 (C-3), 44.9 (C-8), 56.4 (C-5 or C-9), and 57.6 (C-9 or C-5).

Reaction of p-*Bromophenacyl Gibberellate* (1) *with* 2-*Chloro*-NN-*diethyl*-1,1,2-*trifluoroethylamine*.—A stirred suspension of the ester (850 mg) in dry dichloromethane (20 ml) was treated with an excess of the fluoro-amine (4.5 ml) at 0 °C during 15 min. The homogeneous solution was allowed to warm to room temperature and stirring was continued for a further 1 h. Evaporation gave a liquid which was chromatographed on silica gel (2.5 × 22 cm). Elution with ethyl acetate–light petroleum (3 : 22) gave at first 2-chloro-*NN*-diethyl-2-fluoroacetamide; later fractions afforded 10β-p-*bromophenacyloxycarbonyl*-4β,7α-*difluoro*-1β-*methyl*-8-*methylenegibb*-2-*ene*-1α,4aα-*carbolactone* (6), which crystallised from ethyl acetate–light petroleum as prisms (99 mg), m.p. 144—146° or 176—178° (Found: C, 59.05; H, 4.3; F. 6.75. $C_{27}H_{25}BrF_2O_5$ requires C, 59.3; H, 4.6; F, 6.9%), $\nu_{max.}$ (Nujol) 1 785, 1 747, 1 709, 1 665, and 900 cm^{-1}; τ 8.61 (3 H, s, 1β-Me), 7.15 (1 H, d, *J* 10.5 Hz, 10-H), 6.92 (1 H, d, *J* 10.5 Hz, 10α-H), 5.15 (1 H, dd, *J* 47 and 3 Hz, 4α-H), 4.91br (1 H) and 4.72br (1 H) (8-CH_2), 4.65 (2 H, s, O·CH_2·COAr), 3.96 (2 H, m, $W_{\frac{1}{2}}$ 8 Hz, 2- and 3-H), and 2.34 (2 H, d, *J* 9 Hz) and 2.19 (2 H, d, *J* 9 Hz) (aromatic H); ϕ^* 176.0 (d, *J* 47 Hz, 4β-F) and 147.3 (m, 7α-F); *m/e* 548 and 546.

Elution with ethyl acetate–light petroleum (1 : 4) gave 10β-p-*bromophenacyloxycarbonyl*-2β,7α-*difluoro*-1β-*methyl*-8-*methylenegibb*-3-*ene*-1α,4aα-*carbolactone* (3), which crystallised from ethyl acetate–light petroleum as plates (111 mg), m.p. 176—178° (Found: C, 59.2; H, 4.55; F, 6.75. $C_{27}H_{25}BrF_2O_5$ requires C, 59.3; H, 4.6; F, 6.9%), $\nu_{max.}$ (Nujol) 1 785, 1 750, 1 714, 1 674, and 910 cm^{-1}; τ 8.54 (3 H, s, 1β-Me), 7.1 (2 H, s, 10-H and 10α-H), 4.94 (1 H, dm, *J* 47 Hz, 2α-H), 4.92br (1 H) and 4.71br (1 H) (8-CH_2), 4.64 (2 H, s, O·CH_2·COAr), 4.05 (1 H, m, $W_{\frac{1}{2}}$ 10 Hz, 3-H), 3.61 (1 H, dt, *J* 9 and 1.5 Hz, 4-H), 2.38 (2 H, d, *J* 9 Hz) and 2.19 (2 H, d, *J* 9 Hz) (aromatic H); ϕ^* 179.3 (dd, *J* 47 and 9 Hz, 2β-F) and 147.3 (m, 7α-F); *m/e* 548 and 546.

De-esterification of the 4β-*Fluoro-ester* (6).—The 4β-fluoro-ester (240 mg) in glacial acetic acid (20 ml) was stirred with activated zinc dust (350 mg) at room temperature for 2.5 h. The mixture was filtered, the zinc was washed with ethyl acetate, and the combined solutions were evaporated *in vacuo*. The residue, in ethyl acetate, was extracted with 2N-sodium hydrogen carbonate solution and the extracts were acidified with 2N-hydrochloric acid. Recovery in ethyl acetate gave a solid which crystallised from chloroform–light petroleum as blades (105 mg), m.p. 218—225°, of 4β,7α-*difluoro*-4aα-*hydroxy*-1β-*methyl*-8-*methylenegibb*-2-*ene*-1α,10β-*dicarboxylic acid* 1,4a-*lactone* (7) (Found: C, 65.0; H, 5.8; F, 10.95. $C_{19}H_{20}F_2O_4$ requires C, 65.1; H, 5.75; F, 10.8%), $\nu_{max.}$ 3 620—2 400, 1 790, 1 715, and 905 cm^{-1}; $\lambda_{max.}$ 225 nm (ε 1 570); *m/e* 286, 241, and 240.

De-esterification of the 2β-*Fluoro-ester* (3).—Treatment of the 2β-fluoro-ester (120 mg) in glacial acetic acid (20 ml) with activated zinc dust (120 mg), as in the preceding experiment, afforded a gum (73 mg) (one spot on t.l.c.) which sublimed at 120 °C and 2 × 10^{-4} mmHg to give

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[14] J. R. Hanson, M. Siverns, F. Piozzi, and G. Savona, *J.C.S. Perkin I*, 1976, 114.

[15] B. E. Cross, J. F. Grove, and A. Morrison, *J. Chem. Soc.*, 1961, 2498.

[16] B. E. Cross and R. E. Markwell, *J. Chem. Soc.* (*C*), 1971, 2980.

2β,7α-*difluoro*-4aα-*hydroxy*-1β-*methyl*-8-*methylenegibb*-3-*ene*-1α,10β-*dicarboxylic acid* 1,4a-*lactone* (4) (Found: C, 64.7; H, 6.1; F, 10.6. $C_{19}H_{20}F_2O_4$ requires C, 65.1; H, 5.75; F, 10.8%), $\nu_{max.}$ 3 600—2 500, 1 785, 1 710, and 905 cm^{-1}; *m/e* 240.

Reaction of the 8-*Epimeric Mixture of Methyl Tetrahydrogibberellates* [(8) *and* (9)] *with* 2-*Chloro*-NN-*diethyl*-1,1,2-*trifluoroethylamine*.—A stirred suspension of methyl tetrahydrogibberellates (2 g) in dry dichloromethane (112 ml) was cooled to 0 °C and a large excess of the fluoro-amine (8 ml) was added over 1 h. The solution was allowed to reach room temperature and stirred for a further 1.5 h. Evaporation, followed by removal of the chloro-*NN*-diethylfluoroacetamide *in vacuo* (0.1 mmHg) at 60 °C, afforded a solid which was chromatographed on silica gel (2.7 × 25 cm). Elution with ethyl acetate–light petroleum (3 : 17) gave a gummy solid which crystallised from ethyl acetate–light petroleum as needles (580 mg), m.p. 136—143°, of the mixture of 8-epimers of 7α-*fluoro*-10β-*methoxycarbonyl*-1β,8-*dimethylgibb*-2-*ene*-1α,4aα-*carbolactone* [(16) and (17)], $[\alpha]_D^{25}$ −33.6° (*c* 0.03 in EtOH) (Found: C, 68.9; H, 7.2; F, 5.05. $C_{20}H_{25}FO_4$ requires C, 68.9; H, 7.2; F, 5.45%), $\nu_{max.}$ 1 770 and 1 735 cm^{-1}; $\lambda_{max.}$ 222 and 211sh nm (ε 1 500 and 1 280); τ 9.08 (3 H, d, *J* 6.8 Hz, 8α-Me), 9.00 (3 H, d, *J* 6.8 Hz, 8β-Me), 8.79 (3 H, s, 1β-Me), 7.31 (2 H, m, 10- and 10a-H), 6.25 (3 H, s, OMe), and 4.28 (2 H, m, 2- and 3-H); τ ([$^2H_5$]pyridine) 9.06 (3 H, d, *J* 6.8 Hz, 8β-Me), 8.89 (3 H, d, *J* 6.8 Hz, 8α-Me), 8.70 (3 H, s, 1β-Me), 7.6 (2 H, d, *J* 3 Hz, 4-H_2), 7.11 (2 H, s, 10- and 10a-H), 6.25 (3 H, s, OMe), and 4.30br (2 H, s, 2- and 3-H), ϕ* 159.7 [m, 7-F in (16)] and 147.2 [m, 7-F in (15)]; *m/e* 304, 261, and 244; δ_C 15.3 (1β-Me), 52.2 (OMe), 54.0 (C-1), 92.4 (C-4a), 127.8 (C-3), 132.6 (C-2), 173.0 (10β-CO), and 177.6 (1α-CO).

Hydrolysis of the 7α-*Fluoro-esters* [(16) *and* (17)].—The fluoro-esters (83 mg) in methanol (9 ml) and 2N-sodium hydroxide (17 ml) were refluxed for 7 h in an atmosphere of nitrogen. Acidification of the solution with 2N-hydrochloric acid and recovery in ethyl acetate gave a mixture of the 8-epimers of 7α-*fluoro*-4aα-*hydroxy*-1β,8-*dimethylgibb*-2-*ene*-1α,10β-*dicarboxylic acid* 1,4α-*lactone* [(18) and (19)], which crystallised from ethyl acetate–light petroleum as prisms, m.p. 219—224° (Found: C, 68.25; H, 6.9; F, 5.7. $C_{19}H_{23}FO_4$ requires C, 68.25; H, 6.65; F, 5.7%), $\nu_{max.}$ 2 400—3 600, 1 770, and 1 710 cm^{-1}; *m/e* 290 and 247.

Hydrogenation of the 7α-*Fluoro-esters* [(16) *and* (17)].—The esters (300 mg) in ethyl acetate (30 ml) were hydrogenated over 10% palladium–charcoal (150 mg). Recovery gave the 8-epimeric mixture of 7α-*fluoro*-10β-*methoxycarbonyl*-1β,8-*dimethylgibbane*-1α,4aα-*carbolactones* [(10) and (11)], which crystallised from ethyl acetate–light petroleum as needles (230 mg), m.p. 128—142° (Found: C, 68.4; H, 7.65; F, 5.15. $C_{20}H_{27}FO_4$ requires C, 68.5; H, 7.8; F, 5.4%), $\nu_{max.}$ 1 770 and 1 730 cm^{-1}; τ 9.08 (3 H, d, *J* 6.8 Hz, 8α-Me), 9.01 (3 H, d, *J* 6.8 Hz, 8β-Me), 8.94 (3 H, s, 1β-Me), 7.52 (1 H, d, *J* 10 Hz, 10-H), 7.30 (1 H, d, *J* 10 Hz, 10α-H), and 6.26 (3 H, s, OMe); *m/e* 306, 263, and 246.

Hydrolysis of the 7α-*Fluoro-dihydro-esters* [(10) *and* (11)].—The esters (120 mg) in methanol (10 ml) and 2N-sodium hydroxide (15 ml) were refluxed under nitrogen for 7 h. Recovery in the usual manner gave the 8-epimeric mixture of 7α-*fluoro*-4aα-*hydroxy*-1β,8-*dimethylgibbane*-1α,10β-*dicarboxylic acid* 1,4a-*lactones* [(12) and (13)], which crystallised from ethyl acetate–light petroleum as plates (40 mg), m.p. 205—207° (Found: C, 67.8; H, 7.3; F, 5.6. $C_{19}H_{25}FO_4$ requires C, 67.8; H, 7.5; F, 5.65%), $\nu_{max.}$ 3 580—2 400, 1 765, and 1 710 cm^{-1}; *m/e* 292 and 249.

Reaction of the Diol (14) *with the Fluoro-amine*.—The diol (150 mg),[15] suspended in dry dichloromethane (9 ml), was stirred at 0 °C and the fluoroamine (0.6 ml) was added over 20 min. Work-up as in preceding fluorinations (see above) gave a solid which was chromatographed on silica gel (2.5 × 22 cm). Elution with ethyl acetate–light petroleum (1 : 4) gave a gum which crystallised from ethyl acetate–light petroleum as needles (21 mg), m.p. 129—137°, of 7α-*fluoro*-10β-*methoxycarbonyl*-1β,8β-*dimethylgibb*-2-*ene*-1α,-4aα-*carbolactone* (16) (Found: *m/e* 348.173 3. $C_{20}H_{25}FO_4$ requires *M*, 348.173 7), $\nu_{max.}$ ($CHCl_3$ film) 1 775 and 1 735 cm^{-1}; τ (90 MHz) 9.00 (3 H, d, *J* 6.8 Hz, 8β-Me), 8.78 (3 H, s, 1β-Me), 8.06 (2 H, s, 10- and 10α-H), 6.26 (3 H, s, OMe), and 4.28 (2 H, s, 2- and 3-H); ϕ* 147.1 (m, 7α-F); *m/e* 348, 304, and 244.

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