Reactions of 2-Chloro-*NN*-diethyl-1,1,2-trifluoroethylamine with Alcohols. Part I. Preparation of 2β- and 4β-Fluorogibberellins

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The allylic 2β-hydroxy-group in esters of gibberellic acid (9) reacts with 2-chloro-*NN*-diethyl-1,1,2-trifluoroethylamine to give the corresponding esters of 2β-fluoro-4aα,7-dihydroxy-1β-methyl-8-methylenegibb-3-ene-1α,10β-dicarboxylic acid 1,4a-lactone (5) and its allylic isomer 4β-fluoro-4aα,7-dihydroxy-1β-methyl-8-methylenegibb-2-ene-1α,10β-dicarboxylic acid 1,4a-lactone (14). The fluoro-acids (5) and (14) themselves were obtained by de-esterification of the corresponding *p*-bromophenacyl esters (7) and (15).

THE case for preparing fluoro-derivatives of the gibberellins has been outlined in an earlier paper [1] which described three fluorogibberellins; their biological activity is of considerable interest.[2,3]

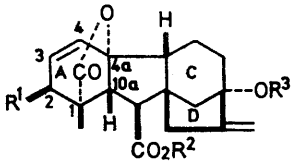
2-Chloro-*NN*-diethyl-1,1,2-trifluoroethylamine is a convenient reagent for converting alcohols into fluoro-derivatives under mild conditions,[4] and the mechanism of the reaction has been discussed.[5-8] However, its reaction with allylic alcohols does not appear to have been investigated. We have studied the reaction of methyl gibberellate (1) with the fluoro-amine in the hope that it would lead to a new fluorogibberellin, and also in order to examine the fluorination of anallylic alcohol.† The reaction with the fluoro-amine in the cold gave two major products, the 2β-fluoro-ester (2) (44%) and the 4β-fluoro-isomer (10) (31%). The ring A structures of these esters were deduced from their n.m.r. spectra. Although in each case the ring A protons were further coupled to the fluorine atom, the spectrum of the 2β-fluoro-3-ene (2) showed the ring A olefinic proton resonances as separate signals at τ 4·06 and 3·62, characteristic of Δ^3-gibberellins; [9] in contrast, the spectrum of the 4β-fluoro-2-ene showed the signals of both ring A olefinic protons as one complex multiplet at τ 3·98, as found in Δ^2-gibberellins [9] and -kaurenolides.[10,11] Additional support for these

† For a preliminary account see J. H. Bateson and B. E. Cross, *Tetrahedron Letters*, 1973, 1783.

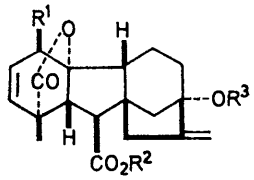
[1] J. H. Bateson and B. E. Cross, *J.C.S. Perkin I*, 1974, 1131.
[2] J. L. Stoddart, *Planta*, 1972, **107**, 81.
[3] J. L. Stoddart, personal communication.
[4] J. Fried and J. A. Edwards, 'Organic Reactions in Steroid Chemistry,' vol. 1, Van Nostrand-Reinhold, New York, 1972, 436.
[5] D. E. Ayer, *Tetrahedron Letters*, 1962, 1065.
[6] L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, 1964, **29**, 2187.
[7] M. Mousseron-Canet and J. C. Lanet, *Bull. Soc. chim. France*, 1969, 1745.
[8] M. Mousseron-Canet and J. L. Borgna, *Bull. Soc. chim. France*, 1969, 613.
[9] N. Murofushi, T. Yokota, and N. Takahashi, *Agric. Biol. Chem. (Japan)*, 1970, **34**, 1436.
[10] E. L. Ghisalberti, P. R. Jefferies, and E. J. Middleton, *Austral. J. Chem.*, 1969, **22**, 455.
[11] J. H. Bateson and B. E. Cross, *J.C.S. Perkin I*, 1972, 1117.

assignments was provided by u.v. spectra. That of the 2-ene (10) showed absorption [$\lambda_{max.}$ 222sh nm (ε 1160)] similar to that for other gibb-2-ene 1,4a-lactones,[12,13] whereas the 3-ene (2) showed only end-absorption.

The β-configuration of the fluorine atoms in both esters was shown by their deshielding of the 10a-protons [14] (1,3-diaxial effect). Thus in the n.m.r. spectrum of the fluoro-ester (10), the 10a-proton signal occurred 0·38 p.p.m. downfield from that in the methyl ester (11) of gibberellin A_5,[15] and was broadened by long-range coupling with the 4β-fluorine atom. Similarly the 10a proton resonance in the fluoro-ester (2) may be compared

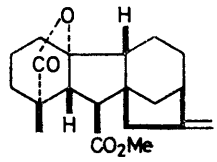


	R^1	R^2	R^3
(1)	OH	Me	H
(2)	F	Me	H
(3)	F	Me	CO·CHClF
(4)	Pr^nS	H	H
(5)	F	H	H
(6)	HO	*p*-BrC_6H_4·CO·CH_2	H
(7)	F	*p*-BrC_6H_4·CO·CH_2	H
(8)	F	*p*-BrC_6H_4·CO·CH_2	CO·CHClF
(9)	HO	H	H



	R^1	R^2	R^3
(10)	F	Me	H
(11)	H	Me	H
(12)	F	Me	CO·CHClF
(13)	Pr^nS	H	H
(14)	F	H	H
(15)	F	*p*-BrC_6H_4·CO·CH_2	H
(16)	H	H	H
(17)	F	*p*-BrC_6H_4·CO·CH_2	CO·CHClF
(18)	F	H	CO·CH_2F

with that in the methyl ester (19) of gibberellin A_9, since the effect of a 3,4-double bond on the chemical shift of the 10a-proton is known to be small.[14] In compound (2), the 10a-proton resonance appeared 0·48 p.p.m. downfield of the corresponding signal in compound (19),[14] and showed long-range coupling ($^4J_{HF}$ 1·5 Hz) with the 2β-fluorine

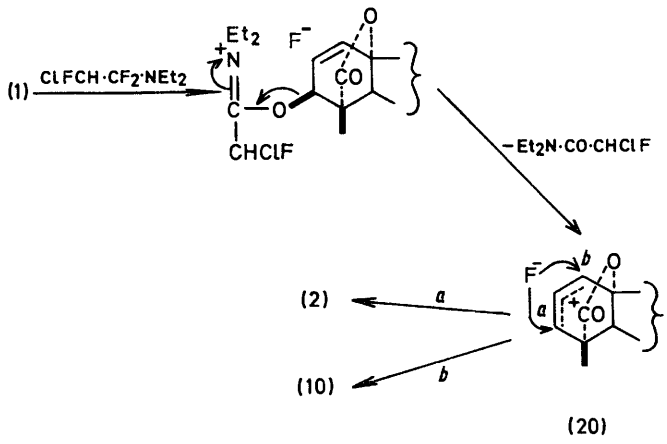


(19)

atom. The isomeric fluoro-esters could also be readily distinguished by their ^{19}F n.m.r. spectra. The spectrum of the 4β-fluoro-ester (10) showed a double doublet at ϕ* 178·1 (J 47 and 2·5 Hz), whereas the 2β-fluoro-isomer (2) showed an eight-line multiplet (J 47, 7, and *ca.* 1·5 Hz) at ϕ* 180·4.

The chlorofluoroacetates (3) and (12) were isolated as minor products from the fluorination of methyl gibberellate and were characterised by spectroscopic evidence (see Experimental section) (*cf.* ref. 6).

The structure and stereochemistry of the two fluoro-esters (2) and (10) suggests that the fluorination of ring A of methyl gibberellate may proceed as shown in the Scheme *via* the allylic carbonium ion (20) (*cf.* refs. 6—8). This ion could be quenched by fluoride ion attacking the less-hindered β-face at either position 2 or 4.†



SCHEME

Attempts to demethylate the 2β-fluoro-ester (2) and its 4β-fluoro-isomer (10) with lithium propane-1-thiolate [1,16] failed to give the required fluoro-acids. In each case acidic sulphur-containing gums were formed indicating that the allylic fluorine atoms had been displaced by thiolate ions. These acids are believed to have structures (4) and/or (13) since they showed molecular ions at *m/e* 404 in their mass spectra.

In order to prepare the fluoro-acids (5) and (14), the *p*-bromophenacyl ester (6) [17] of gibberellic acid was

† In another series, fluorination of the α- and β-epimers of an allylic alcohol with the fluoro-amine resulted in each case in substitution on the α-face (J. H. Bateson and B. E. Cross, unpublished work).

[12] J. MacMillan, J. Seaton, and P. J. Suter, *Tetrahedron*, 1960, **11**, 60.

[13] J. C. Brown, B. E. Cross, and J. R. Hanson, *Tetrahedron*, 1967, **23**, 4095.

[14] J. R. Hanson, *J. Chem. Soc.*, 1965, 5036.

[15] J. MacMillan and R. J. Pryce, *J. Chem. Soc.* (*C*), 1967, 550.

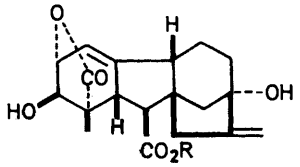
[16] P. A. Bartlett, and W. S. Johnson, *Tetrahedron Letters*, 1970, 4459; E. J. Corey, T. M. Brennan, and R. L. Carney, *J. Amer. Chem. Soc.*, 1971, **73**, 7316.

[17] B. E. Cross, *J. Chem. Soc.*, 1954, 4670.

fluorinated with a 1·2 molar excess of 2-chloro-*NN*-diethyl-1,1,2-trifluoroethylamine. The resultant esters (7) (49%) and (15) (26%), which were identified by their n.m.r. spectra (see Experimental section), were de-esterified with zinc dust in glacial acetic acid to give the new fluorogibberellins (5) and (14). The structures of these acids were confirmed by methylation, which gave the esters (2) and (10), respectively (see above). The biological activity of these two fluorogibberellins is under investigation, but tests already completed indicate that the 4β-fluoro-acid (14) is less active than gibberellin A_5 (16) and the 2β-fluoro-acid (5) is inhibitory in the dwarf pea and dwarf-5 maize assays.[3]

Minor products from the fluorination of the *p*-bromophenacyl ester (6) were the 7-chlorofluoroacetates (8) and (17). De-esterification of the latter with zinc dust in acetic acid also dechlorinated the acetyl residue to yield the fluoro-acetate (18).

One attempted preparation of the *p*-bromophenacyl ester of gibberellic acid gave the ester (21) of the rearranged [18] 1,3-lactone (22). The ester was identified by



(21) R = *p*-Br C$_6$H$_4$·CO·CH$_2$
(22) R = H

its spectroscopic data (see Experimental section) and by de-esterfication to give the acid lactone (22).[18]

EXPERIMENTAL

Details of chromatographic materials and conditions used for the determination of physical data *etc.* are reported in refs. 1 and 19.

Reaction of Methyl Gibberellate (1) *with* 2-*Chloro*-NN-*diethyl*-1,1,2-*trifluoroethylamine*.—Methyl gibberellate chloroform solvate (860 mg) was suspended in dry dichloromethane (45 ml) with stirring at 0° and the fluoro-amine (0·5 ml) was added from a syringe during 15 min. The homogeneous solution was stirred at room temperature for 2 h and then evaporated *in vacuo* at 25°. The residual gum was chromatographed on silica gel (20 × 2·5 cm). Elution with ethyl acetate–light petroleum (1 : 9) gave a gum which was shown (n.m.r.) to be a mixture of a fluorinated gibberellin and chloro-*NN*-diethylfluoroacetamide. P.l.c. [development with ethanol–benzene (3 : 97)] gave 7-*chlorofluoroacetoxy*-4β-*fluoro*-10β-*methoxycarbonyl*-1β-*methyl*-8-*methylenegibb*-2-*ene*-1α,4aα-*carbolactone* (12) as a gummy solid (29 mg) (Found: *m/e* 456·1137. $C_{22}H_{23}{}^{35}ClF_2O_6$ requires *M*, 456·1151), $\nu_{max.}$ ($CHCl_3$ film) 1790, 1775, 1739, 907, 818, and 732 cm^{-1}; τ 8·74 (3H, s, 1β-Me), 7·32 (1H, d, *J* 10 Hz, 10-H), 6·93 (1H, d, *J* 10 Hz, 10a-H), 6·22 (3H, s, OMe), 5·12 (1H, dd, *J* 47 and 3 Hz, 4α-H), 4·90br (1H) and 4·72br (1H) (8-CH_2), 3·95 (2H, m, $W_{\frac{1}{2}}$ 5 Hz, 2-H and 3-H), and 3·75 (1H, d, *J* 50 Hz, 7-O_2C·CHClF); *m/e* 458 (M^+, 3%), 456 (M^+, 8), 344 (37), 334 (37), 333 (48), and 332 (100).

Elution with ethyl acetate–light petroleum (3 : 17 and 1 : 4) gave a gum which crystallised from ethyl acetate–light petroleum as needles (32 mg), m.p. 156—159° of 7-*chlorofluoroacetoxy*-2β-*fluoro*-10β-*methoxycarbonyl*-8-*methylenegibb*-3-*ene*-1α,4aα-*carbolactone* (3) (Found: C, 58·05; H, 5·2; F, 8·2%; *m/e* 456·1154. $C_{22}H_{23}{}^{35}ClF_2O_6$ requires C, 57·9; H, 5·1; F, 8·3%; *M*, 456·1151), $\nu_{max.}$ 1791, 1769, 1740, 1670, and 901 cm^{-1}; τ 8·65 (3H, s, 1β-Me), 7·22 (1H, d, *J* 11 Hz, 10-H), 6·97 (1H, dd, *J* 11, $^4J_{HF}$ 1·5 Hz, 10a-H), 6·23 (3H, s, OMe), 4·91 (1H, dm, *J* 47 Hz, 2α-H), 4·91br (1H) and 4·7br (1H) (8-CH_2), 4·03 (1H, m, $W_{\frac{1}{2}}$ 9·5 Hz, 3-H), 3·77 (1H, d, *J* 50 Hz, 7-O_2C·CHClF), and 3·61 (1H, dm, *J* 9·5 Hz, 4-H); *m/e* 458 (M^+, 2%), 456 (M^+, 6), and 334 (28).

Continued elution with ethyl acetate–light petroleum (9 : 31) gave 4β-*fluoro*-7-*hydroxy*-10β-*methoxycarbonyl*-1β-*methyl*-8-*methylenegibb*-2-*ene*-1α,4aα-*carbolactone* (10), which crystallised as prisms (287 mg), m.p. 145—146°, $[\alpha]_D^{23}$ −111·1° (*c* 0·51 in $CHCl_3$) (Found: C, 66·1; H, 6·25; F, 5·1. $C_{20}H_{23}FO_5$ requires C, 66·3; H, 6·35; F, 5·25%), $\nu_{max.}$ ($CHBr_3$) 3565, 1786, 1735, 1660, 1630, 902, and 732 cm^{-1}; τ (90 MHz) 8·76 (3H, s, 1β-Me), 7·33 (1H, d, *J* 10 Hz, 10-H), 6·98br (1H, d, *J* 10 Hz, 10a-H), 6·26 (3H, s, OMe), 5·15 (1H, dd, *J* 47 and 3 Hz, 4α-H), 5·02br (1H) and 4·74br (1H), (8-CH_2), and 3·98 (2H, m, $W_{\frac{1}{2}}$ 12 Hz, 2-H and 3-H); τ ([$^2H_5$]pyridine) 8·68 (3H, s, 1β-Me), 7·07 (1H, d, *J* 10 Hz, 10-H), 6·76 (1H, d, *J* 10 Hz, 10a-H), 6·35 (3H, s, OMe), 4·96 (1H, dd, *J* 47 and 3 Hz, 4α-H), 4·93br (1H) and 4·40br (1H) (8-CH_2), and 3·94 (2H, m, $W_{\frac{1}{2}}$ 12 Hz, 2-H and 3-H); *m/e* 362 (M^+, 100%), 330 (65), 303 (98), and 238 (61).

Elution of the column with ethyl acetate–light petroleum (1 : 4 and 2 : 3) gave 2β-*fluoro*-7-*hydroxy*-10β-*methoxycarbonyl*-1β-*methyl*-8-*methylenegibb*-3-*ene*-1α,4aα-*carbolactone* (2), which crystallised from ethyl acetate–light petroleum as rosettes of prisms (198 mg), m.p. 182—184°, $[\alpha]_D^{23}$ +4·1° (*c* 0·47 in $CHCl_3$) (Found: C, 66·4; H, 6·35; F, 5·25. $C_{20}H_{23}FO_5$ requires C, 66·3; H, 6·35; F, 5·25%), $\nu_{max.}$ ($CHBr_3$) 3570, 1783, 1733, 1661, and 900 cm^{-1}; τ (90 MHz), 8·68 (3H, s, 1β-Me), 7·23 (1H, d, *J* 11 Hz, 10-H), 7·03 (1H, dd, *J* 11, $^4J_{HF}$ 1·5 Hz, 10a-H), 6·26 (3H, s, OMe), 5·04br (1H) and 4·72br (1H) (8-CH_2), 4·94 (1H, d of dd, *J* 47, 2·5, and 1·5 Hz, 2α-H), 4·06 (1H, 7 lines, 3-H), and 3·62 (1H, dt, *J* 9·5 and 1·5 Hz, 4-H) [irradiation at the frequency of the signal at τ 4·06 simplified the signal centred at τ 4·94 to a broadened doublet, *J* 47 Hz]; τ ([$^2H_5$]pyridine) 8·50 (3H, s, 1β-Me), 6·97 (1H, d, *J* 11 Hz, 10-H), 6·75 (1H, dd, *J* 11, $^4J_{HF}$ 1·5 Hz, 10a-H), 6·33 (3H, s, OMe), 4·90br (1H) and 4·35br (1H) (8-CH_2), 4·73 (1H, dm, *J* 47 Hz, 2α-H), 3·99 (1H, 7 lines, $W_{\frac{1}{2}}$ 9·5 Hz, 3-H), and 3·48br (1H, d, *J* 9·5 Hz, 4-H); *m/e* 362 (M^+, 90%), 330 (100), and 303 (57).

On t.l.c. analysis [development with ethanol–benzene (2 : 23)] the 4β-fluoro-ester (10), the 2β-fluoro-ester (2), and methyl gibberellate gave R_F values of 0·43, 0·41, and 0·25, respectively.

Demethylation of the 4β-*Fluoro-ester* (10).—The fluoro-ester (152 mg) was treated with an excess (3 ml) of a solution of lithium propane-1-thiolate reagent in hexamethylphosphoramide [1,16] and the solution was stirred in an atmosphere of argon at room temperature for 2·5 h. Recovery in ethyl acetate was followed by extraction with sodium hydrogen carbonate solution; these extracts were acidified with dilute hydrochloric acid at 0° and extracted with ethyl acetate.

[18] B. E. Cross, *J. Chem. Soc.*, 1960, 3022.
[19] B. E. Cross and R. E. Markwell, *J. Chem. Soc.* (*C*), 1971, 2980.

Evaporation gave an acidic gum, which was chromatographed on silica gel (10 × 1 cm). Elution with ethyl acetate–light petroleum (1 : 1) gave an intractable foam (94 mg), believed to be the acid (4) and/or (13) (Found: S, 7·35. Calc. for $C_{22}H_{28}O_5S$: S, 7·9%), $\nu_{max.}$ ($CHCl_3$ film) 3400br, 2600br, 1770, 1715br, and 915 cm^{-1}; τ 9·0 (3H, t, *J* 6·5 Hz, $S{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$) and 8·72 (3H, s, 1β-Me); *m/e* 404 (M^+, 24%), 386 (26), 358 (80), 284 (100), 239 (92), and 105 (58).

Demethylation of the 2β-*Fluoro-ester* (2).—Treatment of the 2β-fluoro-ester (121 mg) with lithium propane-1-thiolate, as described above, gave an intractable gum (79 mg) which was believed to be the acid (4) and/or (13) (Found: S, 7·7. Calc. for $C_{22}H_{28}O_5S$: S, 7·9%); τ ([$^2H_6$]acetone) 9·0 (3H, t, *J* 6·5 Hz, $S{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$) and 8·58 (3H, s, 1β-Me); *m/e* 404 (M^+, 17%), 386 (20), 358 (65), 328 (52), and 105 (55).

Reaction of Gibberellic Acid with p-*Bromophenacyl Bromide.*—Gibberellic acid (500 mg) in ethanol (20 ml) and water (20 ml) was titrated with 2N-sodium hydroxide to pH 6·7, *p*-bromophenacyl bromide (500 mg) in ethanol (15 ml) was added, and the solution was heated under reflux for 1 h. Recovery, after evaporation of the ethanol *in vacuo*, gave *p*-bromophenacyl gibberellate (6), which crystallised from ethanol as needles (870 mg), m.p. 219—221° (lit.,[17] 218—219°); τ ([$^2H_5$]pyridine) 8·25 (3H, s, 1β-Me), 6·67 (1H, d, *J* 11 Hz, 10-H), 6·18 (1H, d, *J* 11 Hz, 10a-H), 5·49 (1H, d, *J* 3·5 Hz, 2α-H), 4·9br (1H, 8-*H*CH) and 4·39br (3H, s, 8-HC*H* and $O{\cdot}CH_2{\cdot}COAr$), 3·84 (1H, d, *J* 9·5 Hz, 4-H), 3·55 (1H, d, *J* 9·5 Hz, 4-H), and 2·34 (2H, d, *J* 9 Hz) and 2·05 (2H, d, *J* 9 Hz) (aromatic H).

A similar experiment in which gibberellic acid (500 mg) solution was neutralised (B.D.H. universal indicator) and then made slightly acidic by addition of one drop of dilute hydrochloric acid, gave, after recovery followed by crystallisation from benzene, 10β-p-*bromophenacyloxycarbonyl*-7-*hydroxy*-1β-*methyl*-8-*methylenegibb*-4-*ene*-1α,3α-*carbolactone* (21) as prisms (715 mg), m.p. 122—123° (Found: C, 59·95; H, 5·05; Br, 14·95. $C_{27}H_{27}BrO_7$ requires C, 59·7; H, 5·0; Br, 14·7%), $\nu_{max.}$ 3410br, 1770, 1750, 1705, 1661, and 896 cm^{-1}; τ 8·7 (3H, s, 1β-Me), 7·3 (1H, d, *J* 5·5 Hz, 10-H), 6·66 (1H, dd, *J* 5·5 and 3 Hz, 10a-H), 5·76br (1H, d, *J* 5 Hz, 2α-H), 5·29 (1H, t, *J* 5 Hz, 3β-H), 5·03br (1·H) and 4·9br (1H) (8-CH_2), 4·69 (2H, s, $O{\cdot}CH_2COAr$), 42·2 (1H, m, *W*- 5 Hz, 4-H), and 2·39 (2H, d, *J* 9 Hz) and H2 (2H, d, *J* 9 Hz) (aromatic H); τ ([$^2H_5$]-pyridine) 8·36[5](362 s, 1β-Me), 6·89 (1H, d, *J* 6 Hz, 10-H), 6·03 (1H, dd, *J* 7 and 3 Hz, 10a-H), 5·43 (1H, d, *J* 5·5 Hz, 2α-H), and 5·0, (1H, t, *J* 5·5 Hz, 3β-H).

De-esterification of the Ester (21).—The ester (140 mg) in glacial acetic acid (5 ml) was stirred with activated zinc dust (150 mg) for 2 h. The mixture was filtered, the zinc was washed with ethyl acetate, and the combined filtrates were evaporated to dryness. The residue was redissolved in ethyl acetate and the solution was extracted with sodium hydrogen carbonate solution. Acidification of these extracts at 0°, followed by recovery in ethyl acetate, gave the 1,3-lactone (22) as a gum (89 mg), M^+ 346; $\nu_{max.}$ ($CHCl_3$ film) 3400br, 2600br, 1755, and 1710br cm^{-1}; τ ([$^2H_6$]acetone) 8·84 (3H, s, 1β-Me), 6·65 (1H, dd, 10a-H), 5·72 (1H, d, *J* 5·5 Hz, 2α-H), 5·29 (1H, t, *J* 5·5 Hz, 3β-H), 5·05br (1H) and 4·9br (1H) (8-CH_2), and 4·2 (1H, m, 4-H).

Its methyl ester crystallised from ethyl acetate–light petroleum as prisms, m.p. 172—173° (lit.,[18] 174°), identical (i.r. and n.m.r. spectra) with an authentic specimen; τ 8·82 (3H, s, 1β-Me), 7·45 (d, *J* 6 Hz, 10-H), 6·70 (1H, dd, 10a-H), 6·26 (3H, s, OMe), 5·75br (1H, d, *J ca.* 6 Hz, 2α-H), 5·25 (1H, t, *J* 5·5 Hz, 3β-H), 5·0br (1H) and 4·86br (1H) (8-CH_2), and 4·20 (1H, m, 4-H).

Reaction of p-*Bromophenacyl Gibberellate* (6) *with* 2-*Chloro*-NN-*diethyl*-1,1,2-*trifluoroethylamine.*—A stirred suspension of the ester (800 mg) in dichloromethane (50 ml) was treated with a 1·2 molar excess of the fluoro-amine (300 mg) at −10° during 15 min. Stirring was continued at 0° for 30 min and then the homogeneous solution was allowed to warm to room temperature. Evaporation *in vacuo* at room temperature gave a gum which was chromatographed on silica gel (20 × 2·5 cm). Elution with ethyl acetate–light petroleum (3 : 17) gave 10β-p-*bromophenacyloxycarbonyl*-7-*chlorofluoroacetoxy*-4β-*fluoro*-1β-*methyl*-8-*methylenegibb*-2-*ene*-1α,4aα-*carbolactone* (17) (148 mg), which after purification by p.l.c. gave a foam (Found: C, 54·65; H, 4·1; Br + Cl, 17·6; F, 6·1%; *m/e* 642/640/638. $C_{29}H_{26}BrClF_2O_7$ requires C, 54·5; H, 4·1; Br + Cl, 18·0; F, 5·9%; *M*, 642/640/638), $\nu_{max.}$ ($CHCl_3$ film) 1790, 1774, 1750, 1710, 1667, 1630, 901, 819, and 732 cm^{-1}; τ (90 MHz), 8·61 (3H, s, 1β-Me), 7·11 (1H, d, *J* 10·5 Hz, 10-H), 6·94br (1H, d, *J* 10·5 Hz, 10a-H), 5·15 (1H, dd, *J* 47 and 3 Hz, 4α-H), 4·89br (1H) and 4·74br (1H) (8-CH_2), 4·63 (2H, m, $O{\cdot}CH_2{\cdot}COAr$), 3·97 (2H, m, $W_{\frac{1}{2}}$ 13 Hz, 2-H and 3-H), 3·77 (1H, d, *J* 50 Hz, 7-$O_2C{\cdot}$CHClF), and 2·38 (2H, d, *J* 9 Hz) and 2·21 (2H, d, *J* 9 Hz) (aromatic H).

Elution of the column with ethyl acetate–light petroleum (1 : 4 and 1 : 3) gave 10β-p-*bromophenacyloxycarbonyl*-7-*chlorofluoroacetoxy*-2β-*fluoro*-1β-*methyl*-8-*methylenegibb*-3-*ene*-1α,4aα-*carbolactone* (8), which crystallised from ethanol as needles (68 mg), m.p. 180—181° (Found: C, 54·4; H, 4·0; Br + Cl, 17·9; F, 6·1%; *m/e* 642/640/638. $C_{29}H_{26}BrClF_2O_7$ requires C, 54·5; H, 4·1; Br + Cl, 18·0; F, 5·9%; *M*, 642/640/638), $\nu_{max.}$ 1782, 1771, 1749, 1708, 1661, and 899 cm^{-1}; τ (90 MHz) 8·52 (3H, s, 1β-Me), 6·99 (2H, s, 10-H and 10a-H), 4·93 (1H, d of dd, *J* 47 Hz, 2α-H), 4·91br (1H) and 4·74br (1H) (8-CH_2), 4·64 (2H, m, $O{\cdot}CH_2{\cdot}COAr$), 4·02 (1H, 7 lines, 3-H), 3·77 (1H, d, *J* 50 Hz, 7-$O_2C{\cdot}CHClF$),, 3·61 (1H, dt, *J* 9·5 and 1·5 Hz, 4-H), and 2·35 (2H, d, *J* 9 Hz) and 2·2 (2H, d, *J* 9 Hz) (aromatic H).

Elution of the column with ethyl acetate–light petroleum (3 : 7 and 7 : 13) gave 10β-p-*bromophenacyloxycarbonyl*-4β-*fluoro*-7-*hydroxy*-1β-*methyl*-8-*methylenegibb*-2-*ene*-1α,4aα-*carbolactone* (15) as a gum (391 mg) (Found: C, 59·8; H, 5·0; Br, 14·35; F, 3·8%; *m/e* 546/544. $C_{27}H_{26}BrFO_6$ requires C, 59·5; H, 4·8; Br, 14·6; F, 3·5%; *M*, 546/544), $\nu_{max.}$ ($CHCl_3$ film) 1787, 1745, 1706, 1661, 1630, 900, and 731 cm^{-1}; τ 8·63 (3H, s, 1β-Me), 7·16 (1H, d, *J* 10·5 Hz, 10-H), 6·91 (1H, d, *J* 10·5 Hz, 10a-H), 5·02 (1H, dd, *J ca.* 47 and 3 Hz, 4a-H), 4·96br (1H) and 4·70br (1H) (8-CH_2), 4·64 (2H, s, $O{\cdot}CH_2{\cdot}COAr$), 3·96 (2H, m, $W_{\frac{1}{2}}$ 12 Hz, 2-H and 3-H), and 2·39 (2H, d, *J* 9 Hz) and 2·22 (2H, d, *J* 9 Hz) (aromatic H).

Further elution of the column with ethyl acetate–light petroleum (7 : 13 and 2 : 3) gave 10β-p-*bromophenacyloxycarbonyl*-2β-*fluoro*-7-*hydroxy*-1β-*methyl*-8-*methylenegibb*-3-*ene*-1α,4aα-*carbolactone* (7) as a solid (209 mg) (Found: C, 59·7; H, 4·7; Br, 14·9; F, 3·7%; *m/e* 546/544. $C_{27}H_{26}BrFO_6$ requires C, 59·5; H, 4·8; Br, 14·6; F, 3·5%; *M*, 546/544), $\nu_{max.}$ ($CHCl_3$ film) 1780, 1743, 1706, 1661, and 901 cm^{-1}; τ 8·56 (3H, s, 1β-Me), 7·02 (2H, s, 10-H and 10a-H), 4·93 (1H, dm, *J ca.* 47 Hz, 2α-H), 4·99br (1H, 8-*H*CH), 4·64br (3H, s, 8-HC*H* and 7-$O{\cdot}CH_2{\cdot}COAr$), 4·04 (1H, m, $W_{\frac{1}{2}}$ 10 Hz, 3-H), 3·6br (1H, d, *J* 9·5 Hz, 4-H), and 2·39 (2H, d, *J* 9 Hz) and 2·22 (2H, d, *J* 9 Hz) (aromatic H).

De-esterification of the 4β-*Fluoro-ester* (15).—The fluoro-

ester (150 mg) in glacial acetic acid (2 ml) was stirred with activated zinc dust (150 mg) at room temperature for 1 h. The mixture was filtered, the zinc was washed with ethyl acetate, and the combined filtrates were evaporated to dryness *in vacuo* at 40°. The residue, in ethyl acetate, was extracted with sodium hydrogen carbonate solution and the extracts were acidified, with dilute hydrochloric acid at 0°. Recovery in ethyl acetate gave a gum which after four crystallisations from ethyl acetate–light petroleum gave needles (66 mg), containing an impurity ($\nu_{max.}$ 1740 cm^{-1}). Purification by p.l.c. [development with acetic acid–di-isopropyl ether (3 : 47)] gave 4β-*fluoro*-4aα,7-*dihydroxy*-1β-*methyl*-8-*methylenegibb*-2-*ene*-1α,10β-*dicarboxylic acid* 1,4a-*lactone* (14), which crystallised from ethyl acetate–light petroleum as the hemihydrate (48 mg), m.p. 114—117° (Found: C, 64·1; H, 6·2; F, 5·55%; *m/e* 348·1374. $C_{19}H_{21}FO_5,0{\cdot}5H_2O$ requires C, 63·9; H, 6·2; F, 5·3%; *M*, 348·1373), $\nu_{max.}$ ($CHBr_3$), 3580, 3460br, 2600br, 1785, 1710, 1660, 1627, 904, and 732 cm^{-1}; *m/e* 348 (M^+, 15%), 330 (7), 284 (7), 180 (12), 136 (11), 135 (11), 105 (13), 85 (85), and 83 (100). Another crystalline form (identical i.r. spectrum in $CHBr_3$) had m.p. 140—142°.

Its methyl ester, prepared with diazomethane, crystallised from ethyl acetate–light petroleum with m.p. 143—144°, and was identical (i.r. spectrum) with the specimen described above.

The mother-liquors from the first crystallisation gave an intractable gum (28 mg), believed to be the ring C/D rearrangement product,[20] 4β-fluoro-4aα-hydroxy-1β,7β-dimethyl-8-oxo-7α-gibb-2-ene-1α,10β-dicarboxylic acid 1,4a-lactone, $\nu_{max.}$ 3450br, 2600br, 1788, 1740 (cyclopentanone), 1712, 1627, and 732 cm^{-1}; τ 8·92 (3H, s, 8-Me), 8·63 (3H, s, 1β-Me), 7·32 (1H, d, *J* 7 Hz, 10-H), 6·93 (1H, d, J 7 Hz, 10a-H), 5·03 (1H, dd, *J* 48 and 3 Hz, 4α-H), and 3·93 (2H, m, $W_{\frac{1}{2}}$ 12·5 Hz, 2-H and 3-H). This compound was responsible for the impurity ($\nu_{max.}$ 1740 cm^{-1}) in the crude 4β-fluorogibberellin.

De-esterification of the 2β-*Fluoro-ester* (7).—Treatment of the fluoro-ester (75 mg) in glacial acetic acid (3 ml) with zinc dust (75 mg) as in the preceding experiment gave a gum which was purified by p.l.c. [development with acetic acid–di-isopropyl ether (2 : 23)]. Recovery of the major band, followed by crystallisation from chloroform–light petroleum, gave 2β-*fluoro*-4aα,7-*dihydroxy*-1β-*methyl*-8-*methylenegibb*-3-*ene*-1α,10β-*dicarboxylic acid* 1,4a-*lactone* (5) as needles (33 mg) of the hemihydrate, m.p. 180—182° (Found: C, 63·8; H, 6·1; F, 5·3%; *m/e*, 348·1378. $C_{19}H_{21}FO_5,0{\cdot}5H_2O$ requires C, 63·9; H, 6·2; F, 5·3%; *M*, 348·1373), $\nu_{max.}$ ($CHBr_3$) 3580, 3460br, 2610br, 1781, 1710, 1660, and 904 cm^{-1}; *m/e* 348 (M^+, 35%), 330 (31), 284 (100), and 105 (82).

Its methyl ester, prepared with diazomethane in the usual way, crystallised from ethyl acetate–light petroleum with m.p. 180—182°, and was identical (i.r. spectrum) with the sample described above.

De-esterification of the 4β-*Fluoro*-7-*chlorofluoroacetoxy-ester* (17).—Treatment of the ester (140 mg) in glacial acetic acid (5 ml) with zinc dust (250 mg) for 4 h and recovery in the usual manner gave an acid fraction, which was purified by p.l.c. [development with acetic acid–di-isopropyl ether (1 : 19)]. Recovery of the major band in ethyl acetate gave 4β-*fluoro*-7-*fluoroacetoxy*-4aα-*hydroxy*-1β-*methyl*-8-*methylene-gibb*-2-*ene*-1α,10β-*dicarboxylic acid* 1,4a-*lactone* (18), which crystallised from chloroform–light petroleum as needles (52 mg), m.p. 185—187°, of the hemisolvate (Found: C, 55·75; H, 4·85; F, 8·2. $C_{21}H_{22}F_2O_6,0{\cdot}5CHCl_3$ requires C, 55·2; H, 4·9; F, 8·1%), $\nu_{max.}$ 3140br, 1783, 1718, 1664, 917, and 731 cm^{-1}; τ 8·68 (3H, s, 1β-Me), 7·27 (1H, d, *J* 10·5 Hz, 10-H), 6·97 (1H, d, *J* 10·5 Hz, 10a-H), 5·2 (2H, d, *J* 47 Hz, 7-$O_2C{\cdot}CH_2F$), 4·9br (1H) and 4·74br (1H) (8-CH_2), and 3·94 (2H, m, $W_{\frac{1}{2}}$ 13 Hz, 2-H and 3-H); *m/e* 408 (M^+, 10%), 375 (12), 232 (25), 221 (27), and 113 (100).

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[20] B. E. Cross, J. F. Grove, J. MacMillan, and T. P. C. Mulholland, *Chem. and Ind.*, 1956, 954.