Reactions of 2-Chloro-*NN*-diethyl-1,1,2-trifluoroethylamine with Alcohols. Part 4.[1] In the Presence of Lithium Bromide and Dimethyl Sulphide: Preparation of Bromo- and Methylsulphinyl-gibberellins

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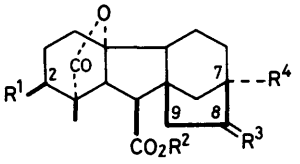
Tetrahydrogibberellic acid (1) was treated with 2-chloro-*N,N*-diethyl-1,1-2-trifluoroethylamine in the presence of lithium bromide to give *inter alia* 7α-bromo-4aα-hydroxy-1β,8β-dimethylgibb-2-ene-1α,10β-dicarboxylic acid 1,4a-lactone (10); its dihydro-derivative was active in the Tanginbozu dwarf rice bioassay. When the reaction was carried out on methyl tetrahydrogibberellate (2) in dimethyl sulphide and the products were oxidized, they included 10β-methoxycarbonyl-1β,8β-dimethyl-7α-methylsulphinylgibb-2-ene-1α,4aα-carbolactone (20).

HYDROXYGIBBERELLINS react with 2-chloro-*NN*-diethyl-1,1,2-trifluoroethylamine (fluoroamine) in the presence of lithium chloride to afford biologically active chlorogibberellins.[1] The observation [2] that fluoroamine in the presence of lithium bromide converts alcohols into the corresponding bromides suggested that this reagent could be used to prepare bromogibberellins.†

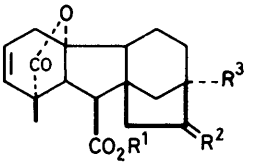
Reaction of the tetrahydrogibberellic acid (1) [1] with fluoroamine–lithium bromide in tetrahydrofuran, followed by a work-up procedure that involved treatment with aqueous sodium hydrogencarbonate, which presumably hydrolyzed the expected acid bromides,[1] gave a



	R¹	R²	R³	R⁴
(1)	OH	H	α-H, β-Me	OH
(2)	OH	Me	α-H, β-Me	OH
(3)	H	Me	α-H, β-Me	Br
(4)	H	Me	α-Me, β-H	Br
(5)	H	H	α-H, β-Me	Br
(6)	H	H	α-Me, β-H	Br
(7)	H	H	H, Me	F
(8)	O·CO·CHClF	Me	α-H, β-Me	F

mixture of the 7-(4-bromo-n-butoxy)-acid (9) (*cf.* ref. 1) and the 7α-bromogibberellin (10). The presence of the acid (9) was established by its n.m.r. spectrum and the accurate masses of its molecular ions (*i.e.* of $C_{23}H_{31}BrO_5$). P.l.c. of the mixture gave the nearly pure bromogibberellin (10) which was identified by its n.m.r. spectrum and by accurate mass. However, the n.m.r. spectrum also showed weak signals at δ 5.23br and 5.54br, which suggests the presence of an impurity that contained an 8-methylene group with its resonances shifted downfield, compared with the corresponding signals in its 7-chloro-analogue,[1] by the large 7-bromine atom. In addition the mass spectrum revealed the presence of the three molecular ions of a dibromo-species, $C_{19}H_{22}Br_2O_4$; this was confirmed by high resolution mass spectroscopy. It seemed likely that the acid (10) had undergone free-radical bromination at C-8 to give the dibromo-compound (11), which then partially lost hydrogen bromide to yield the olefin (12).

Support for the free-radical mechanism was provided by carrying out the bromination in the dark, under an atmosphere of nitrogen, and in the presence of *p*-benzoquinone. N.m.r. spectroscopy showed that resultant bromo-acid (10) contained much less of the olefin (12) than the product described above.

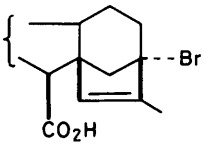


	R¹	R²	R³
(9)	H	α-H, β-Me	O[CH₂]₄Br
(10)	H	α-H, β-Me	Br
(11)	H	Br, Me	Br
(12)	H	CH_2	Br
(13)	Me	α-H, β-Me	Br
(14)	Me	CH_2	Br
(15)	Me	Br, Me	Br
(16)	H	α-H, β-Me	O[CH₂]₂OMe
(17)	Me	α-H, β-Me	SMe
(18)	Me	α-H, β-Me	Cl
(19)	Me	α-H, β-Me	F
(20)	Me	α-H, β-Me	SO·Me

Methylation of the above impure 7α-bromo-acid (10), followed by p.l.c. of the product, gave the ester (13), shown by its n.m.r. and mass spectra to contain small amounts of the olefin (14) and the dibromide (15). Hydrogenation of the ester over palladized charcoal gave a mixture of the 8-epimers of the bromo-esters [(3) and (4)], which was shown by g.l.c. analysis to contain only 9% of the 8α-methyl epimer. The formation of the latter confirmed the presence of the olefin (12) in the impure bromo-acid (10).

Bromination of the acid (1) with fluoroamine–lithium bromide in 1,2-dimethoxyethane, followed by the usual work-up, gave the 7α-(2-methoxyethoxy)-acid (16) [1] (18%) and the 7α-bromo-acid (10) (32%), which were more readily separated than the acids (9) and (10). Hydrogenation of the bromo-acid (10) [which contained a small amount of the olefin (12)] over palladized charcoal followed by purification by p.l.c. gave a gum, believed to contain a small amount of the rearranged olefin (21) as impurity [δ 5.40br (9-H)]. Further hydrogenation over

† Preliminary account, B. E. Cross and I. C. Simpson, *Tetrahedron Lett.*, 1980, 215.



(21)

Adams catalyst, followed by purification by p.l.c., yielded a crystalline mixture of the 8-epimers of the 7α-bromogibberellins (5) and (6) which, however, contained some of the fluoro-analogue (7).[3] Further purification by multidip p.l.c. and recrystallization reduced the amount of the fluoro-acid (7), but g.l.c. analysis of a methylated sample showed that 8% of the fluoro-compound remained.

In the Tanginbozu dwarf rice bioassay the above 7α-bromogibberellins (5) and (6) showed activity comparable with that of their 7α-chloro- and 7α-fluoro-analogues, but greater than that of dihydrogibberellin A_5.[1,4]

The reaction of 7-hydroxy-groups in gibberellins with fluoroamine has been shown to proceed *via* a carbocation type of intermediate.[1,3] In some cases nucleophilic attack by oxygenated solvents has occurred (*cf.* ref. 1 and see above), which suggests that if the reaction was carried out in the presence of appropriate sulphur compounds thiogibberellins could be prepared. Treatment of the tetrahydro-ester (2) with fluoroamine in dimethyl sulphide as solvent gave, as the only isolable product, a gum believed to be the 2β-chlorofluoroacetoxy 7α-fluoro-ester (8) on the basis of its spectroscopic data (see Experimental section). However, when lithium chloride was added to the reaction mixture the required thio-compound (17) was formed, but not in good yield (28%); the chloride ion acted as the more successful nucleophile and gave 48% of the 7α-chloro-ester (18).[1] The larger bromide ions attack the 7-position less readily than the chloride ions and it seemed possible that addition of lithium bromide in place of lithium chloride might give a better yield of the thio-compound.

In the event, analysis of the product by g.l.c. showed that it contained the methylthio-ester (17) (32%), the bromo-ester (13) (27%), and the fluoro-ester (19) (41%). This indicates that the fluoride ion predominates in the attack on the 7-carbocation, presumably because despite its weaker nucleophilicity, it is the smallest nucleophile present. The function of the lithium halide in assisting nucleophilic attack by sulphur is uncertain, but it may co-ordinate with the 7-oxygen atom, thus aiding the departure of the latter.

The mixture of esters (13), (17), and (19) was oxidized with *m*-chloroperbenzoic acid and then chromatographed to yield the 7α-methylsulphinyl ester (20). The structure of the latter was confirmed by high resolution mass spectroscopy and by its n.m.r. spectrum, which was very similar to that of the chloro-ester (18),[1] except for an extra signal at δ 2.81 (3 H, s) due to the SO·Me grouping. Thus it seems likely that fluoroamine in the presence of suitable nucleophiles could provide a route to a number of novel 7-substituted gibberellins.

EXPERIMENTAL

Details of chromatographic materials and conditions for the determination of physical data, *etc.*, have been reported.[5] All g.l.c. analyses were carried out on the methyl esters. The abundance of ions in mass spectra are relative.

Reaction of Tetrahydrogibberellic Acid (1) *with* 2-*Chloro*-NN-*diethyl*-1,1,2-*trifluoroethylamine in the presence of Lithium Bromide.*—(a) *In tetrahydrofuran.* A stirred suspension of the acid (1.0 g) and anhydrous lithium bromide (3.87 g) in tetrahydrofuran (100 ml) at 0 °C was treated with an excess of fluoroamine (12 ml) over 45 min. The mixture was stirred for a further 90 min at 0 °C and for 3 h at room temperature. Evaporation followed by distillation of the chloro-*NN*-diethylfluoroacetamide under reduced pressure (75 °C and 0.2 mmHg) during 69 h afforded a black oil which was chromatographed on silica gel (330 g). Elution with ethyl acetate–light petroleum (1 : 1) gave a gum, which was dissolved in ethyl acetate and extracted with sodium hydrogencarbonate solution. The combined aqueous extracts were acidified at 0 °C with 2N hydrochloric acid. Recovery in ethyl acetate followed by preparative layer chromatography (p.l.c.) [development with formic acid–benzene ×2 (3 : 97) and formic acid–ethanol–benzene (3 : 3 : 94)] gave one broad band; elution of the lower portion of the band gave a gum believed to be a mixture of the 7α-bromo-acid (10) (see later for details) and the 7α-(4-bromo-n-butoxy)-4aα-hydroxy-1β,8β-dimethylgibb-2-ene-1α,10β-dicarboxylic acid 1,4α-lactone (9); δ 3.42 (m, $W_{\frac{1}{2}}$ 6 Hz, OCH_2), 3.56 (t, *J* 6 Hz, CH_2Br), 1.27 (s) and 1.29 (s) (1β-Me), and 0.98 (d, *J* 7 Hz) and 1.13 (d, *J* 7 Hz) (8β-Me) (Found: *m/z* 466.1351 and 468.1343. $C_{23}H_{31}{}^{79}BrO_5$ and $C_{23}H_{31}{}^{81}BrO_5$ require *M*, 466.1356 and 468.1336, respectively). Material recovered from the upper portion of the band was further purified by p.l.c. [development with formic acid–benzene ×2 (3 : 97) and formic acid–ethanol–benzene (3 : 3 : 94)] and afforded a gum (116 mg) which was mainly 7a-bromo-4aα-hydroxy-1β,8β-dimethylgibb-2-ene-1α,10β-dicarboxylic acid 1,4aα-lactone (10) (Found: *m/z* 396.0758. $C_{19}H_{23}{}^{81}BrO_4$ requires *M*, 396.0760); δ 1.14 (3 H, d, *J* 7 Hz, 8β-Me), 1.29 (3 H, s, 1β-Me), 2.72 (2 H, m, 10- and 10a-H), and 5.78 (2 H, m, $w_{\frac{1}{2}}$ 12 Hz, 2- and 3-H); *m/z* 396 (*M*, ^{81}Br, 1.1), 394 (*M*, ^{79}Br, 0.9), 350 (60), 348 (59), 303 (23), and 269 (90). Its mass spectrum also contained peaks believed to be due to the dibromo-species (11) (Found: *m/z* 475.9858 and 471.9877. $C_{19}H_{22}{}^{81}Br_2O_4$ and $C_{19}H_{22}{}^{79}Br_2O_4$ require *M*, 475.9846 and 471.9886 respectively), whilst the n.m.r. spectrum revealed the presence of the 8-ene (12); δ 5.23br and 5.54br (8-CH_2); *m/z* 476 (1.1), 474 (0.9), and 472 (0.9).

Methylation of the 7α-bromo-acid (10) in the usual manner using diazomethane, followed by purification by p.l.c. [development with formic acid–ethanol–benzene (1 : 1 : 48)] afforded mainly 7α-bromo-10β-methoxycarbonyl-1β,8β-dimethylgibb-2-ene-1α,4aα-carbolactone (13) as a gum (85 mg); δ 1.12 (3 H, d, *J* 7 Hz, 8β-Me), 1.25 (3 H, s, 1β-Me), 2.69 (2 H, m, 10- and 10a-H), 3.73 (3 H, s, OMe), and 5.77 (2 H, m, $w_{\frac{1}{2}}$ 12 Hz, 2- and 3-H) (Found: *m/z* 410 and 408. $C_{20}H_{25}{}^{81}BrO_4$ and $C_{20}H_{25}{}^{79}BrO_4$ require *M*, 410 and 408, respectively). Its mass spectrum also contained peaks at *m/z* 490, 488, and 486, corresponding to the molecular ions of the dibromo-species (15) and the n.m.r. spectrum revealed the presence of some of the diene (14), δ 5.18br and 5.51br (8-CH_2).

(b) *In* 1,2-*dimethoxyethane.* A stirred suspension of the acid (1) (705 mg) and lithium bromide (2.75 g) in 1,2-dimethoxyethane (25 ml) was treated with an excess of fluoro-

amine as described in method (a). Evaporation under reduced pressure afforded an oil, which was mixed with ethyl acetate and sodium hydrogencarbonate and heated under reflux at 100 °C for 15 min. The layers were separated, the organic layer was washed with sodium hydrogencarbonate, and the combined alkaline extracts were acidified using 2N hydrochloric acid at 0 °C. Recovery in ethyl acetate gave a gum which, on purification by p.l.c. [development with formic acid–ethanol–benzene (2 : 3 : 45) and (2 : 5 : 43)], afforded two major bands. Material from the band of lower R_F was 7α-(2-methoxyethoxy)-4aα-hydroxy-1β,8β-dimethylgibb-2-ene-1α,10β-dicarboxylic acid 1,4α-lactone (16), as a gum (140 mg) identical (n.m.r. spectrum) with a sample previously reported.[1]

Material from the band of higher R_F was a gum (258 mg) which contained mainly 7α-bromo-4aα-hydroxy-1β,8β-dimethylgibb-2-ene-1a,10β-dicarboxylic acid 1,4α-lactone (10) [n.m.r. spectrum identical with the sample prepared in (a)]; the n.m.r. spectrum also contained peaks due to the diene (12); δ 5.22br and 5.54br (8-CH_2).

(c) *In the presence of a radical inhibitor.* The reaction of the tetrahydrogibberellic acid (1) (500 mg) in 1,2-dimethoxyethane (20 ml) with fluoroamine (5 ml) in the presence of lithium bromide (2.0 g) was repeated, as in (b) except that *p*-benzoquinone (10 mg) was added, and the reaction was performed in the dark under an atmosphere of nitrogen. The usual work-up gave a gum which, after purification by p.l.c. [development with formic acid–ethanol–benzene ×2 (2 : 5 : 43) and (2 : 7 : 41)] afforded the 7α-bromo-acid (10) as a gum. Its n.m.r. spectrum showed that the peaks due to the diene (12) [δ 5.23br and 5.54br (8-CH_2)] were much weaker than in the n.m.r. spectrum of the same compound prepared in (b).

Hydrogenation of the 7α-Bromo-ester (13).—The ester (13) (85 mg) in ethyl acetate (10 ml) was hydrogenated in the usual way over 10% palladium-on-charcoal (90 mg). Recovery afforded a gum which was purified by p.l.c. [development with ethanol–benzene (3 : 47)] and gave a mixture of the 8-epimers of 7α-bromo-10β-methoxycarbonyl-1β,8-dimethylgibbane-1α,4aα-carbolactone [(3) and (4)] as a *gum* (51 mg) (Found: C, 58.85; H, 6.7; Br, 19.75%; *m/z* 412.1063. $C_{20}H_{27}{}^{81}BrO_4$ requires C, 58.4; H, 6.6; Br, 19.4%; *M*, 412.1073); δ 1.03 (d, *J* 7 Hz, 8α-Me), 1.13 (d, *J* 7 Hz, 8β-Me), 1.26 (3 H, s, 1β-Me), 2.53 (2 H, m, 10- and 10a-H), and 3.72 (3 H, s, OMe); *m/z* 412 (*M*, 9.3), 410 (*M*, 20), 388 (35), 367 (43), 307 (57), 305 (61), and 287 (100). The n.m.r. spectrum contained no olefinic signals and the mass spectrum had no peaks that corresponded to dibromo-species. G.l.c. analysis revealed the presence of 9% of the 8α-methyl epimer (4).

Hydrogenation of the 7α-Bromo-acid (10).—The acid (120 mg) in ethyl acetate (10 ml) was hydrogenated in the usual way over 10% palladium-on-charcoal (150 mg) during 2 h. Recovery followed by purification by p.l.c. [development with formic acid–ethanol–benzene (2 : 5 : 43) and (1 : 3 : 21)] gave a gum which was believed to be mainly a mixture of the 8-epimers of 7α-bromo-4aα-hydroxy-1β,8-dimethylgibbane-1α,10β-dicarboxylic acid 1,4a-lactone (5) and (6); δ 1.04 (d, *J* 7 Hz, 8α-Me) and 1.09 (d, *J* 7 Hz, 8β-Me), 1.15 (3 H, s, 1β-Me), 2.53 (1 H, d, *J* 10.5 Hz, 10-H), and 2.75 (1 H, d, *J* 10.5 Hz, 10a-H); a broad peak at δ 5.40 (9-H) was believed to be due to the olefin (21).

Hydrogenation of the above impure 7α-bromo-acids (5) and (6) in ethyl acetate (10 ml) with Adams catalyst (57 mg) afforded, on recovery, a semi-solid which was purified by p.l.c. [development with formic acid–ethanol–benzene (2 : 5 : 43)]. The recovered material crystallized from ethyl acetate–light petroleum as prisms (127 mg), m.p. 213—219 °C (decomp.), of the 8-epimers of the 7α-bromo-acids (5) and (6), and contained some of the fluoro-acid (7) (Found: C, 61.45; H, 7.1; Br, 14.25; F, 2.1%; *m/z* 396.0923. $C_{19}H_{25}{}^{79}BrO_4$ requires C, 57.4; H, 6.3; Br, 20.1%; *M*, 396.0936); *m/z* 352, 274, 273, 249, and 231. G.l.c. analysis indicated the presence of 8% of the fluoro-ester (7).

Reaction of Methyl Tetrahydrogibberellate (2) *with* 2-*Chloro*-NN-*diethyl*-1,1,2-*trifluoroethylamine in Dimethyl Sulphide.*—A suspension of the ester (400 mg) in dimethyl sulphide (15 ml) at 0 °C was treated with an excess of fluoroamine (4 ml) in the usual way, and the mixture was stirred for 1 h. It was allowed to warm to room temperature, stirred for a further 1 h, and then 1,2-dimethoxyethane (10 ml) was added and the stirring was continued overnight. The resultant solution was evaporated under reduced pressure to afford a semi-solid which was purified by p.l.c. [development with formic acid–ethanol–benzene (2 : 3 : 45)] to give, in addition to chloro-*NN*-diethylfluoroacetamide, a gum believed to be 2β-chlorofluoroacetoxy-7a-fluoro-10β-methoxycarbonyl-1β,8β-dimethylgibbane-1α,4aα-carbolactone (8) (Found: S, 0.6%); $\nu_{max.}$ (film) 1 780, 1 740, and 1 725 cm^{-1}; δ 1.03 (3 H, d, *J* 6 Hz, 8β-Me), 1.09 (3 H, s, 1β-Me), 2.65 (1 H, d, *J* 11 Hz, 10-H), 3.17 (1 H, d, *J* 11 Hz, 10a-H), 3.74 (3 H, s, OMe), 5.12br (1 H, m, 2α-H), and 6.38 (1 H, d, *J* 51 Hz, CHClF); δ_F ([$^2H_6$]acetone) 144.27br (m, 7α-F) and 145.32 (d, *J* 50 Hz, CHClF); *m/z* 348 (*M* − ClFCH.CO_2H), 304, 284, and 261.

Reaction of Methyl Tetrahydrogibberellate (2) *with* 2-*Chloro*-NN-*diethyl*-1,1,2-*trifluoroethylamine in Dimethyl Sulphide.*—(a) *In the presence of lithium chloride.* The ester (2) (500 mg) and lithium chloride (1.5 g) were stirred at 0 °C as a suspension in dimethyl sulphide (20 ml) and treated with an excess of fluoroamine (3 ml) in the usual manner, followed by stirring at 0 °C for a further 3 h and at room temperature for 7 h. Evaporation, followed by distillation of the chloro-*NN*-diethylfluoroacetamide at 70 °C/0.1 mmHg over 2 h, afforded a gum which was purified by p.l.c. [development with formic acid–ethanol–benzene (1 : 1 : 23) and formic acid–benzene ×2 (1 : 24)]. The resultant gum (226 mg) (Found: F, 1.7; Cl, 10.8; S, 2.65%) was shown by g.l.c. analysis to contain the 7α-fluoro-ester (19) (24%), the 7α-chloro-ester (18) (48%), and the thio-ester (17) (28%). Further purification by p.l.c. [development with formic acid–benzene ×8 (1 : 24)] yielded a gum (12 mg), shown by g.l.c. analysis to contain only the 7α-fluoro-ester (19) (17%) and 10β-methoxycarbonyl-7α-methylthio-1β,8β-dimethylgibb-2-ene-1α,4aα-carbolactone (17) (83%) (Found: *m/z* 376.1713. $C_{21}H_{28}O_4S$ requires *M*, 376.1708).

(b) *In the presence of lithium bromide.* The reaction was carried out as described above using the ester (2) (1.5 g), lithium bromide (4.0 g), dimethyl sulphide (60 ml), and fluoroamine (9 ml). The usual work-up afforded a black gum which was chromatographed on silica gel (110 g), but no useful separation was achieved. G.l.c. analysis of the combined fractions (907 mg) showed the gum to contain the 7α-fluoro-ester (19) (41%), the 7α-bromo-ester (13) (27%), and the 7α-methylthio-ester (17) (32%).

Oxidation of the Impure 7α-Methylthio-ester (17) *with* m-*Chloroperbenzoic Acid.*—The impure ester (17) (907 mg), obtained from the preceding experiment, in dichloromethane (30 ml) was stirred at 0 °C and treated with drops of *m*-chloroperbenzoic acid (70 mg) in dichloromethane (10 ml)

over 15 min. The mixture was allowed to warm to room temperature, stirred for a further 1 h, and then shaken with a solution of sodium sulphite (30 ml). The organic layer was washed with sodium hydrogencarbonate solution and water. Evaporation under reduced pressure afforded an oil which on purification by p.l.c. [development with ethanol–benzene (1 : 24)] gave two major bands; material recovered from the band of higher R_F yielded a foam (224 mg), shown by g.l.c. analysis to be mainly the 7α-fluoro- and 7α-bromo-esters (19) and (13), respectively, with only a trace of the 7α-methylthio-ester (17). Material recovered from the other band was further purified by p.l.c. [development with benzene and ethanol–benzene ×2 (3 : 47)] and afforded 10β-*methoxycarbonyl*-7α-*methylsulphinyl*-1β,8β-*dimethylgibb*-2-*ene*-1α,4aα-*carbolactone* (20) as a gum (72 mg) (Found: *m/z* 392.1649. $C_{21}H_{28}O_5S$ requires *M*, 392.1657); $\nu_{max.}$ (film) 1 778, 1 737, 1 640, 939, and 911 cm^{-1}; δ 1.12 (3 H, d, *J* 6 Hz, 8β-Me), 1.20 (3 H, s, 1β-Me), 2.59 (1 H, d, *J* 10.5 Hz, 10-H), 2.79 (1 H, d, *J* 10.5 Hz, 10a-H), 2.81 (3 H, s, SO·*Me*), 3.73 (3 H, s, OMe), and 5.74 (2 H, m, $w_{\frac{1}{2}}$ 12 Hz, 2- and 3-H); *m/z* 392 (*M*, 1.8), 329 (50), 297 (45), 269 (85), and 223 (100).

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