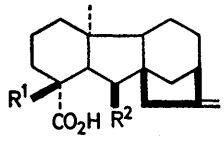
Production of Fluorogibberellins by *Gibberella fujikuroi* from a Fluorinated Analogue of a Gibberellin Precursor

By J. H. BATESON and B. E. CROSS*
(*Department of Organic Chemistry, The University, Leeds* LS2 9JT)

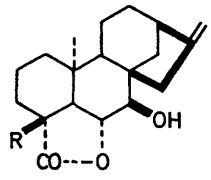
Summary Fluorogibberellic acid (**10**) and fluorogibberellin A_9 (**8**) were produced by a fermentation of *G. fujikuroi* to which 1α-carboxy-1β-fluoromethyl-10β-formyl-4aα-methyl-8-methylenegibbane (**2**) had been added.

THE preparation of fluorogibberellins was undertaken for the reasons, (i) the introduction of fluorine into biologically active molecules often modifies or enhances their activity,[1] (ii) it would be of great value to be able to prepare fluro-

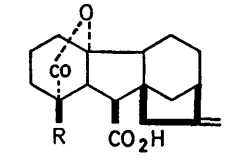
inated, or other analogues, of mould metabolites by feeding modified precursors to cultures of the appropriate mould,[2] and (iii) it is of interest to examine how far the natural precursors of metabolites can be modified before being rejected by the enzyme systems of the fungus.



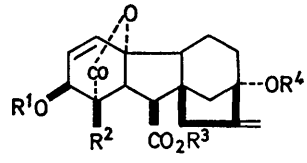
	R^1	R^2
(1)	Me	CHO
(2)	CH_2F	CHO
(3)	CH_2F	CO_2H



	R
(4)	CH_2OH
(5)	p-$MeC_6H_4 \cdot SO_2 \cdot OCH_2$
(6)	CH_2F
(7)	Me



	R
(8)	CH_2F
(9)	Me



	R^1	R^2	R^3	R^4
(10)	H	CH_2F	H	H
(11)	H	Me	H	H
(12)	Ac	CH_2F	Me	Ac

Since the aldehyde (**1**) is a good precursor[3] of gibberellic acid, its 1β-fluoromethyl analogue (**2**) has been prepared from 7,18-dihydroxykaurenolide (**4**) by the following route. Treatment of the monotoluene-*p*-sulphonate[4] (**5**) of the kaurenolide with caesium fluoride in dimethylacetamide at 150°, gave 18-fluoro-7-hydroxykaurenolide (**6**).†‡ The latter was converted into the gummy fluoro-aldehyde (**2**)†‡ by the method previously used[3] to prepare the aldehyde (**1**) from 7-hydroxykaurenolide (**7**). The fluoroaldehyde (1 g), which was characterised by oxidation with Jones reagent to give fluorogibberellin A_{12} (**3**), was added all at once, in ethanol solution, to a 5 l stirred fermentation[5] of *G. fujikuroi* during the gibberellic acid production phase.

The acidic metabolites were isolated from the fermentation in the usual way[5] and were chromatographed on silica gel. A crystalline fraction (30 mg), which was identified as fluorogibberellin A_9 (**8**)† by i.r., n.m.r., and mass spectroscopy, was shown to contain 8% of gibberellin A_9 (**9**) by g.l.c. of its methyl ester. Preparative layer chromatography (p.l.c.) [development (× 3) in acetic acid–di-isopropyl ether (1 : 99)] separated the fluorogibberellin A_9, m.p. 204—205° (pure by g.l.c. of its methyl ester), as the faster running band.

Further elution of the silica gel column gave crystalline gibberellic acid (**11**) (*ca.* 900 mg). The leading gibberellic acid fractions†‡ (500 mg) contained (fluorine analysis and ^{1}H n.m.r. spectrum) 28 ± 2% of fluorogibberellic acid (**10**), showing that *ca.* 140 mg of the latter had been produced which corresponds to the utilisation of >12% of the fluoroaldehyde (**2**). Attempts to separate the mixture into its components have not yet succeeded. However, methylation and acetylation of part of the mixture, followed by p.l.c. [development (× 20) in ethanol–benzene (1 : 99)] gave pure methyl diacetylfluorogibberellate (**12**)† as the faster running band.

The biological activity of fluorogibberellins A_9 and A_{12} is under investigation and preliminary results[6] show that at low dose rates the former is five to six times more active in the lettuce hypocotyl extension test, though less active in the barley endosperm system, than gibberellin A_9.

All new compounds gave satisfactory spectral and analytical data.

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† In the ^{1}H n.m.r. spectra of these compounds the $-CH_2F$ group gave signals at τ *ca.* 5·5 (AB of ABX, J_{HF} *ca.* 48 Hz).

‡ Each ^{19}F spectrum showed a triplet (*J ca.* 48 Hz) at 60—70 p.p.m. upfield from hexafluorobenzene.

[1] For refs. see K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, 1971, **93**, 3060.
[2] *Cf.* M. Gorman, R. L. Hamill, R. P. Flander, and J. Mabe, *Biochem. Biophys. Res. Comm.*, 1968, **31**, 294.
[3] B. E. Cross, K. Norton, and J. C. Stewart, *J. Chem. Soc.* (*C*), 1968, 1054.
[4] B. E. Cross, R. H. B. Galt, and J. R. Hanson, *J. Chem. Soc.*, 1963, 3783.
[5] B. E. Cross and P. L. Myers, *Phytochemistry*, 1969, **8**, 79.
[6] J. L. Stoddart, personal communication.