Production of *gem*-Difluoronor-derivatives of Gibberellin A_7 and 7-Hydroxykaurenolide by *Gibberella fujikuroi*

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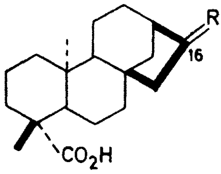
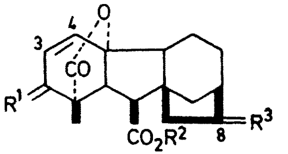
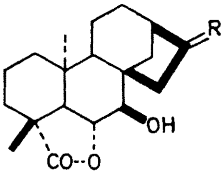
Summary *ent*-16,16-Difluoro-17-norkauranoic acid (**1**) has been fed to fermentations of *Gibberella fujikuroi* in the presence of AMO-1618, and the products have been shown to include 10β-carboxy-8,8-difluoro-1β-methyl-2-oxogibb-3-ene-1α,4aα-carbolactone (**3**) (a derivative of gibberellin A_7) and 16,16-difluoro-7β-hydroxy-17-norkauranolide (**5**).





	R
(1)	F_2
(2)	CH_2

	R^1	R^2	R^3
(3)	O	Me	F_2
(4)	α-H,β-OH	H	CH_2



	R
(5)	F_2
(6)	CH_2

In earlier work[1–4] fluorinated analogues of biosynthetic precursors of the gibberellins have been fed to fermentations of *G. fujikuroi*. Two of these precursors were transformed into novel gibberellins and related metabolites,[1,2] whilst a third acted as an enzyme inhibitor[3] in the same biological system.

In continuation of these studies *ent*-16,16-difluoro-17-norkauranoic acid (**1**) has been prepared.[5] In the latter, unlike the natural biosynthetic precursor kaurenoic acid (**2**),[6] the terminal methylene group is absent and C-16 is sp^3, rather than sp^2, hybridised.

Addition of the difluoro-acid (**1**) (40 mg l^{-1}) to a stirred fermentation[4] of *G. fujikuroi*, in the presence of AMO-1618 (10 mg l^{-1}), which blocks[2,7] the biosynthesis of diterpenoids by the fungus, followed by harvesting and work-up in the usual way,[1,4] gave crude acidic and neutral products. The former were chromatographed on a Kieselgel column and the fractions were methylated with diazomethane and purified by multi-dip p.l.c. using the methyl esters of authentic gibberellins as markers.

Material recovered from a spot with an R_F similar to that of the methyl ester of gibberellin A_9 gave a gum (5—10 mg per 4 l) shown by high resolution mass spectroscopy to have the formula $C_{19}H_{20}F_2O_5$. Its ^{1}H and ^{19}F n.m.r. spectra [δ 1·25 (s, 1β-Me), 2·84 (d, *J* 10 Hz, 10-H), 3·35 (d, *J* 10 Hz, 10a-H), 3·77 (s, OMe), 6·07 (d, *J* 9 Hz, 3-H), and 7·28 (d, *J* 9 Hz, 4-H); ϕ^* 102·0 (dm, *J ca.* 235 Hz, 7-F) and 85·1 (dm, *J ca.* 229 Hz, 7-F)]† showed that it had structure (**3**), *i.e.* that it is a derivative of gibberellin A_7 (**4**). This structure was confirmed by its u.v. (λ_{max} 232 nm, ε *ca.* 4000) and i.r. (ν_{max} 1785, 1734, and 1695 cm^{-1}) spectra which were very similar to those of other gibberellins with the same structure of ring *A*.[8]

Purification by multi-dip p.l.c. of the neutral products afforded the difluoro-7-hydroxy-17-norkauranolide (*ca.*

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† The ^{19}F n.m.r. spectrum of methyl *ent*-16,16-difluoro-17-norkauranoate showed ϕ^* 84·68 (2 × dd, *J* 230 and 16 Hz, 16-F) and 109·47 (dm, *J* 230 Hz, 16-F).

5 mg per 4 l) (**5**), whose ^{1}H n.m.r. spectrum closely resembled that of the normal fungal metabolite, 7-hydroxykaurenolide (**6**),[9] except for the absence of the 17-H_2 protons. Its ^{19}F n.m.r. spectrum showed ϕ^* 99·28 (dm, *J* 226 Hz) and 84·36 (dm, *J* 226 Hz).†

Thus, the enzyme systems in the two main biosynthetic pathways[6] in *G. fujikuroi, viz.* to the gibberellins and the kaurenolides, are both capable of utilising the difluoro-acid (**1**) as 'starting material' despite the absence of the terminal methylene group. It is also of interest that the gibberellin A_7 analogue (**3**) does not possess the commonly found hydroxy-group at position 2, but has undergone an 'unnatural' oxidation to give a 2-keto-group.

We thank the S.R.C. for a research grant and Drs. P. R. Brook and A. Crawshaw for determining the n.m.r. spectra on a Jeol FX90Q instrument.

(*Received, 21st August* 1980; *Com.* 920.)

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