Absolute Stereochemistry of the Fungal Product, Wortmannin

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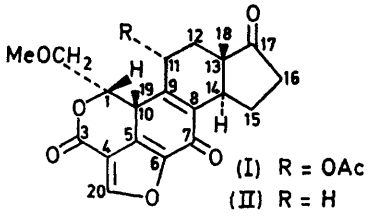
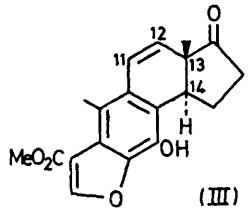
Summary The absolute stereochemistry at C-10, C-11, C-13, and C-14 in the fungal product, wortmannin, has been deduced from biogenetic and spectroscopic evidence

THE *X*-ray study, described in the accompanying communication,[1] confirms the structure, proposed by us,[2] for the fungal metabolite, wortmannin, and it defines the absolute stereochemistry (I). We have independently deduced the same absolute stereochemistry (I) except for that at C-1 which we were unable to determine.

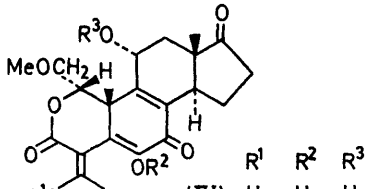
The 13β-Me,14α-H configuration was indicated by the o.r.d. (*a* + 138) of the 11,12-dihydromethyl ether of the



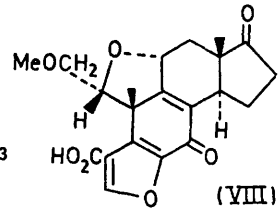
(I) R = OAc
(II) R = H



(III)



	R^1	R^2	R^3
(IV)	H	H	H
(V)	Ac	Ac	Ac
(VI)	Ac	Ac	H
(VII)	H	H	Ac



(VIII)

hydrolysis product (III).[2] The normal stereoidal stereochemistry at C-10, C-13, and C-14 was established by the conversion (0·2—0·5%) of 2-[^{3}H]-lanosterol[3] into [^{3}H]-wortmannin (I) and -11-desacetoxywortmannin (II) in shake-cultures of *Penicillium wortmannii*. The specific incorporation of tritium was demonstrated by acidic hydrolysis[2] to methoxyacetaldehyde which contained all of the label. The 11α-acetoxy-configuration was indicated by the down-field shift (0·07 p.p.m.) of the 18-protons in the n.m.r. spectrum of wortmannin (I) compared with 11-desacetoxywortmannin (II). Similar downfield shifts (0·06 p.p.m.) have been observed[5] for the 18-protons in steroids when substituted by an 11α-acetoxygroup. Similar n.m.r. evidence for an 11α-acetoxy-group in wortmannin was obtained from the products of mild alkaline hydrolysis. 1N-K_2CO_3 gave the triol (IV) (enolic-OH at τ 2·74 and −3·50, the 13 Hz coupling of the latter to 20-H removed by addition of D_2O) which formed a triacetate (V) and a diacetate (VI). Hydrolysis of wortmannin with $KHCO_3$ afforded the diol (VII) with enolic hydroxy-signals in the n.m.r. spectrum at τ 2·82 and −3·75, the latter being coupled (13 Hz) to 20-H. The negligible changes in the chemical shift of the 18-protons in going from the mono-

TABLE

[^{3}H]:[^{14}C]-*Ratios derived from* 2S-[^{3}H]- *and* 2R-[^{3}H]-2-[^{14}C]-*mevalonic acid lactone.*

Compound	2*R*-Isomer	2*S*-Isomer
(II)	0·50:1	0·18:1
Methoxyacetaldehyde	0·56:1	0·10:1
11,12-Dihydro-(III)	0·38:1	0·13:1

acetate (VII) to the triol (IV), and from the triacetate (V) to the diacetate (VI) are consistent only with an 11α-acetoxy configuration; replacement of an 11β-acetoxy-group by 11β-hydroxy usually leads to downfield shifts of *ca.* 0·20 p.p.m.[5] An 11β-pseudo-axial hydrogen in a half-boat ring c conformation of wortmannin (I) is also consistent with the observed long-range coupling (3 Hz) to 14α-H, similar to that between the pseudo-axial 9- and 12-H in eleutherin.[6] Moreover, the previously described[2] acid hydrolysis product, $C_{21}H_{22}O_7$, for which the ether structure (VIII) will be substantiated in the full paper, requires an 11-α-acetoxy-configuration for its formation.

In an attempt to decide the absolute stereochemistry at C-1 in wortmannin (I) and desacetoxywortmannin (II), 2*S*-[^{3}H]- and 2R-[^{3}H]-2-[^{14}C]-mevalonic acid lactones were separately fed to *P. wortmannii*, each with a [^{3}H]:[^{14}C] ratio of 2:1. Incorporations of 1—6% based upon the [^{14}C]-isotope were obtained. The labelled desacetoxywortmannin (II) was hydrolysed by acid to methoxyacetaldehyde and 11,12-dihydro-(III) with the [^{3}H]:[^{14}C] ratios shown in the Table. These ratios clearly showed substantial loss of the [^{3}H]-label from both the 2*S*- and 2*R*-isomers[7] and, unexpectedly, a considerable interchange between the 2*S*- and 2*R*-[^{3}H]-atoms. These results will be discussed in detail in the full paper but it is salutary to note that the greater retention of the 2*R*-[^{3}H], compared to the 2*S*-[^{3}H], at C-1 suggests the opposite C-1 stereochemistry to that established by the accompanying[1] *X*-ray determination.

(*Received*, 31*st July* 1972; *Com.* 1331.)

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