The Absolute Stereochemistry of Phomin: *X*-Ray Analysis of the Phomin–Silver Fluoroborate Complex

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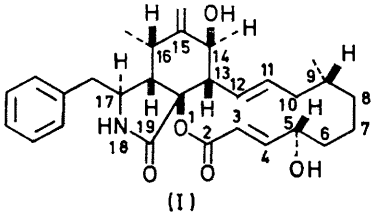
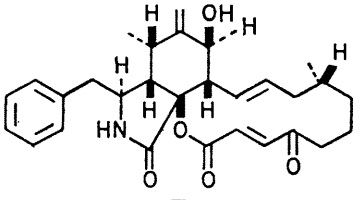
Summary The absolute stereochemistry of the macrolide antibiotic phomin has been determined by *X*-ray analysis of the phomin–silver fluoroborate complex and chemical correlation with (+)-3-methylpimelic acid.

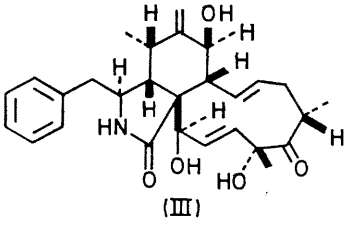
THE fungal metabolites phomin and 5-dehydrophomin, isolated from a *Phoma species*, were assigned the constitutions shown in (I) and (II) on the basis of chemical and spectroscopic studies.[1,2] The cytochalasins A and B whose constitutions were elucidated independently by Aldridge *et al.*[3,4] proved to be identical with 5-dehydrophomin and phomin, respectively. These cytostatic active metabolites represent a novel type of macrolide antibiotic in which the large lactone ring is fused to a highly substituted octahydroisoindole system.



(I)



(II)



(III)

Several papers[5–9] have recently reported investigations of crystal structures of metal salts of polyether antibiotics, *e.g.* silver monensate[5] and silver polyetherin A.[6] Since phomin contains three ethylenic groups we considered it likely that a complex containing a silver ion could be prepared, and an *X*-ray crystallographic study of such a complex would define the stereochemistry of phomin and provide additional information about the environment of the metal ion in a silver–antibiotic complex. The phomin–silver fluoroborate complex was obtained from isopropyl alcohol as very small needle-like crystals; these are orthorhombic, of space group $P2_12_12_1$, with four units of $C_{29}H_{37}NO_5AgBF_4,2(CH_3)_2CHOH$ in a cell of dimensions $a = 13{\cdot}95$, $b = 27{\cdot}48$, $c = 10{\cdot}06$ Å. The *X*-ray intensity data were collected by means of a Hilger and Watts' four-circle diffractometer controlled by a PDP-8 computer; Mo-K_α radiation was employed and 1404 independent reflections were obtained with $I > 2\sigma$ (I). Preliminary co-ordinates for the silver ion were derived from a Patterson synthesis, the other atoms were located in electron-density distributions, and the atomic co-ordinates and isotropic thermal parameters were subsequently adjusted by least-squares

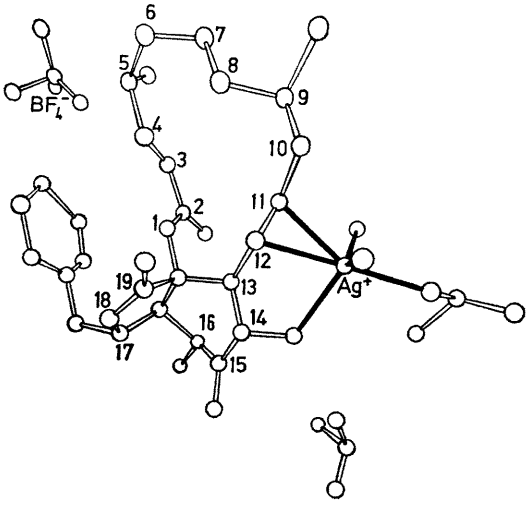


FIGURE. *The phomin-silver fluoroborate complex.*

calculations. The geometry of the complex is shown in the Figure, and this defines the relative stereochemistry shown in (I).

The absolute configuration of the antibiotic was established by two independent procedures. A correction for anomalous dispersion by the silver ion ($\Delta f'' = 1{\cdot}4$ electrons)[10] was incorporated in the structure-factor programme at the conclusion of the least-squares refinement of the crystal structure, and structure factors were calculated with co-ordinates appropriate to (I) and then with co-ordinates appropriate to the mirror image of (I). This resulted in $R = 10{\cdot}86\%$ for (I) and $R = 10{\cdot}98\%$ for the mirror image, suggesting that (I) represents the true absolute stereochemistry. An independent and conclusive proof of the

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absolute stereochemistry at position 9 was provided by the chemical degradation of phomin to *R*-(+)-3-methylpimelic acid, the absolute configuration of which has been established by interconnection with (+)-pulegone,[11] and this establishes that (I) represents the correct absolute configuration of phomin.

A further deduction from our results is that the diagram of the molecular geometry of the antibiotic isozygosporin A which appears in ref. 12 almost certainly represents the mirror image of the natural molecule and that isozygosporin A should be assigned the absolute sterochemistry (III).

The methylenecyclohexane ring in the phomin complex adopts a skew boat conformation, and since the diagram in ref. 12 shows that this is also true of compound (III) the departure from a chair conformation is unlikely to arise from crystal packing requirements. The skew boat conformation of the cyclohexanone ring in the alkaloid lunarine is connected with the *cis*-fusion of the cyclohexanone to a five-membered ring,[13] for this requires the torsion angle about the ring-junction bond to be appreciably smaller than 60°. Two recent preliminary publications have reported that the barrier to ring inversion in methylenecyclohexane is *ca.* 2·5 kcal. lower than the barrier in cyclohexane (though higher than the barrier in cyclohexanone). [14,15]

The silver ion in the phomin complex is co-ordinated to the C(11)=C(12) double bond and the oxygen atom on C(14). In the polyether salts the antibiotic molecules are wrapped around the metal cations whereas in the phomin–silver fluoroborate complex the silver ion is located on the exterior of the antibiotic molecule and is in contact with the oxygen atom of an isopropyl alcohol molecule and the oxygen atoms on C(2) and C(19) of neighbouring phomin molecules, the silver–oxygen distances being between 2·3 and 2·8 Å.

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