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1,2,3,5a,6,11,12,14a-Octahydro-9-methoxy-12-(2-methylprop-1-enyl)-5*H*,14*H*-pyrrolo-[1″,2″:4′,5′]pyrazino[1′,2′:1,6]pyrido[3,4-*b*]-indole-5,14-dione

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.007 Å
R factor = 0.044
wR factor = 0.136
Data-to-parameter ratio = 7.8

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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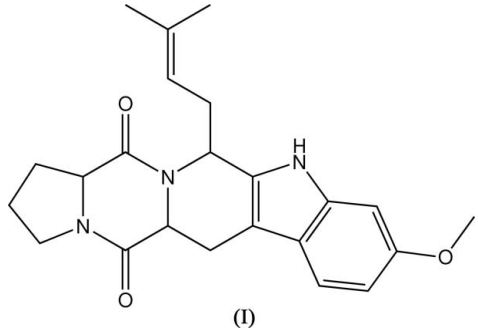
The title compound, $C_{22}H_{25}N_3O_3$, also known as fumitremorgine C, was isolated from the ethyl acetate extract of Penicillium *sp*. To a first approximation, the molecule is flat with the exception of the –C(H)═CMe_2 side arm, which is perpendicular to the remaining atoms. Molecules associate into one-dimensional chains *via* N—H···O and C—H···O interactions involving both carbonyl O atoms.

Comment

The isolation and chemical structure of the title compound, fumitremorgine C, (I), a mycotoxin produced by the *Aspergillus fumigatus* species, was first described in 1977 (Cole, 1977; Cole *et al.*, 1977). Interest in this and related compounds arises from their biological activity (*e.g.* Plate *et al.*, 1987; Cui *et al.*, 1997; Limbach *et al.*, 2005). We isolated (I) as a part of our continuing study characterizing bioactive metabolites from various endophyte cultures (Liu *et al.*, 2004; Shu *et al.*, 2004; Zhang *et al.*, 2005). Thus, a detailed bioassay-guided fractionation of the ethyl acetate extract of Penicillium *sp*., an endophytic fungus in *Vatica mangachapoi* Blanco, yielded (I), which was characterized crystallographically (Fig. 1 and Table 1).



(I)

The r.m.s. deviation of atoms O1, N1–N3, C1–C17 and C22 from their least-squares plane is 0.207 Å, with the maximum deviations being observed for the C*sp*^{3} atoms C15 [0.553 (5) Å] and C17 [−0.444 (4) Å]. The –C(H)═CMe_2 side arm is approximately perpendicular to this plane, as seen in the values of the C16—N2—C17—C18 and N3—C22—C17—C18 torsion angles of 76.2 (5) and 77.8 (5)°, respectively. The absolute configuration was determined assuming an *S*-configuration for atom C15 in the 'proline' residue, *i.e.* comprising atoms N1 and C12–C16. This allows assignment of the configurations of atoms C10 and C17 as *S* in each case.

Molecules associate in the crystal structure to form one-dimensional chains running parallel to the *c* axis. The N3-

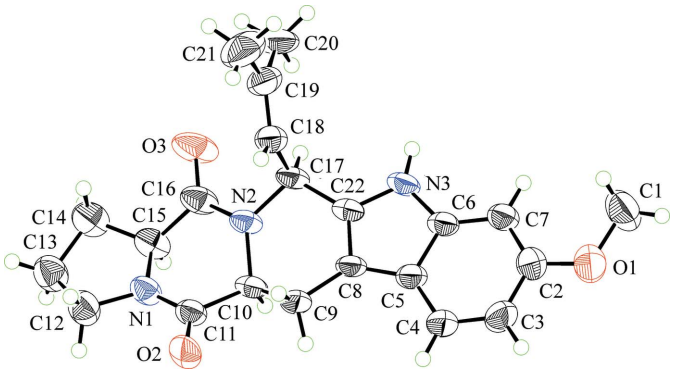


Figure 1
The molecular structure of (I), showing 50% probability displacement ellipsoids and the atom-numbering scheme.

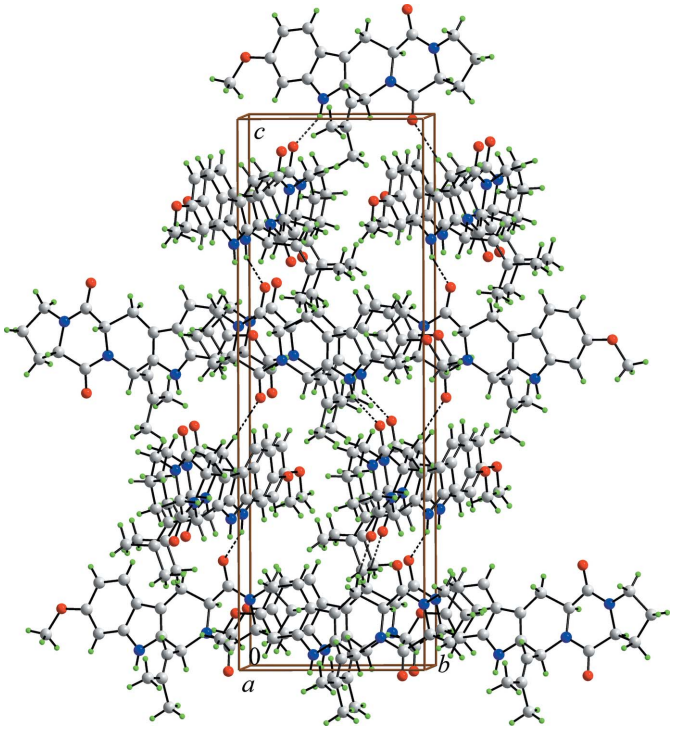


Figure 2
Packing diagram for (I) (Crystal Impact, 2002). Colour code: O (red), N (blue), C (gray) and H (green). Hydrogen bonds are shown as dashed lines.

bound H atom forms a hydrogen-bonding interaction to a symmetry-related carbonyl O2 atom (see Table 2 for details). The remaining carbonyl O atom, O3, is associated with a methylene H atom bound to C9. A view of the unit-cell contents is shown in Fig. 2

Experimental

The isolated Penicillium *sp*. originated from fresh leaves of *Vatica mangachapoi* Blanco, collected in August 2003 from Hainan Island, China. The strain was cultured in a liquid medium (sucrose, 30 g; $NaNO_3$, 3 g; K_2HPO_4, 1 g; yeast extract, 1 g; KCl, 0.5 g; $MgSO_4{\cdot}7H_2O$, 0.5 g; $FeSO_4$, 0.01 g; H_2O, 1000 ml), followed by shaking incubation at 140 r.p.m. for two weeks at 301 K. The ferment broth was filtered and further extracted with ethyl acetate. Evaporation of the solvent *in vacuo* gave a brown residue (13.2 g), which was subjected to chromatography over a silica gel column (80 g) eluting with $CHCl_3$/MeOH (1:0–0:1), to yield seven fractions (F-1: 1.2 g; F-2: 2.4 g; F-3: 1.5 g; F-4: 2.2 g; F-5: 0.9 g; F-6: 1.1 g; F-7: 2.5 g). F-2, showing pronounced cytotoxic activity against the human nasopharyngeal epidermoid tumor KB cell line, was rechromatographed on a silica-gel column, eluting with petroleum ether/acetone (1:0–1:1) to afford five subfractions (F-2-1: 0.3 g; F-2-2: 0.5 g; F-2-3: 0.6 g; F-2-4: 0.4 g; F-2-5: 0.1 g). F-2-3 was subjected to gel filtration over Sephadex LH-20 (MeOH), followed by repeated recrystallization to give fumitremorgin C as a colorless powder (23.3 mg, m.p. 401–403 K). Crystals were obtained by slow evaporation of a $CHCl_3$/MeOH (1:1) solution of the compound; m.p. 401-403 K.

Crystal data

$C_{22}H_{25}N_3O_3$
M_r = 379.45
Tetragonal, $P4_3$
a = 8.7795 (12) Å
c = 26.020 (5) Å
V = 2005.6 (5) Å^3
Z = 4
D_x = 1.257 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 10.0–13.0°
μ = 0.09 mm^{-1}
T = 293 (2) K
Block, colorless
0.40 × 0.30 × 0.20 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
φ and ω scans
Absorption correction: none
2264 measured reflections
2004 independent reflections
1408 reflections with $I > 2\sigma(I)$
R_{int} = 0.071
θ_{max} = 26.0°
$h = 0 \rightarrow 10$
$k = 0 \rightarrow 10$
$l = 0 \rightarrow 31$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.136
S = 1.21
2004 reflections
257 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0569P)^2 + 0.2013P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ <0.001
$\Delta\rho_{max}$ = 0.14 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0095 (18)

Table 1
Selected geometric parameters (Å, °).

O1—C1	1.423 (7)	N2—C10	1.492 (5)
O1—C2	1.375 (6)	N2—C16	1.364 (6)
O2—C11	1.239 (5)	N2—C17	1.487 (5)
O3—C16	1.225 (6)	N3—C6	1.377 (5)
N1—C11	1.321 (6)	N3—C22	1.382 (5)
N1—C12	1.463 (6)	C8—C22	1.357 (6)
N1—C15	1.479 (6)	C18—C19	1.325 (7)
C1—O1—C2	118.3 (4)	C10—N2—C17	124.3 (3)
C11—N1—C12	124.3 (4)	C16—N2—C17	114.9 (3)
C11—N1—C15	123.1 (4)	C6—N3—C22	108.4 (3)
C12—N1—C15	112.5 (4)	C17—C18—C19	127.7 (5)
C10—N2—C16	120.4 (3)	C20—C19—C21	114.9 (5)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3···O2^{i}	0.86	2.08	2.812 (5)	143
C9—H9b···O3^{ii}	0.97	2.32	3.281 (6)	171

Symmetry codes: (i) $-y+1, x, z-\frac{1}{4}$; (ii) $y-1, -x+1, z+\frac{1}{4}$.

All H atoms were allowed to ride on their parent atoms in the riding-model approximation at distances of 0.93–0.98 (C—H) and 0.86 Å (N—H), and with U_{iso}(H) values of $1.2U_{eq}$(C,N) and $1.5U_{eq}(C_{methyl})$. In the absence of significant anomalous scattering effects, Friedel pairs were averaged in the final refinement.

Data collection: *CAD-4 Software* (Enraf– Nonius, 1989); cell refinement: *XCAD4* (Harms & Wocadlo, 1995); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97*.

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