Crystal Structure of Verrucarin A

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The trichothecene compounds constitute an important group of mycotoxins whose biological activities have attracted our attention, because of their high potency and diversity.¹ Recently, the macrocyclic trichothecane, such as Verrucarrin A, became of our interest, because of its high cytotoxicity and cytostaticity. Verrucarrin A has been isolated from the soil fungi *Myrothecium verrucaria*, and it is one of the most toxic compounds. The next-most toxic compounds are the non-macrocyclic members, which have bulky ester side chains, such as the T-2 toxin. However, unsubstituted trichothecenes that contains 12,13-epoxy and 9-ene substitution still retain appreciable toxicity.

The crystal structure of Verrucarrin A *p*-iodobenzene-sulfonate acetone derivative was determined using rotation, oscillation and Weissenberg photographs by McPhail and Sim, 1966. The compound crystallized in the orthorhombic system and space group $P2_12_12_1$, with a final *R* value of 12.5%.² In this paper we describe the X-ray structure determination of Verrucarrin A in order to confirm its formulation, conformation and stereochemistry at high resolution. The title compound crystallizes in the monoclinic system and space group $P2_1$. The X-ray data were collected by graphite-monochromatized Mo K_α radiation. No absorption correction was

applied. Table 1 summarizes the crystal and experimental data. The molecular structure of the title compound is shown in Fig. 2. The chirality is shown in Fig. 2, and its inferred from the known absolute configuration of Verrucarrin A previously determined.² The mol-

Table 1 Crystal and experimental data

Formula: C ₂₇ H ₃₄ O ₉
Formula weight=502.6
Crystal system: monoclinic
Space group: $P2_1$ $Z=2$
$a=10.603(1)\text{\AA}$
$b=8.795(1)\text{\AA}$
$c=14.285(1)\text{\AA}$
$\beta=97.96(1)^\circ$
$V=1319.3(2)\text{\AA}^3$
$D_x=1.265\text{ g/cm}^3$
$D_m=1.260\text{ g/cm}^3$ (measured by flotation)
$\mu(\text{MoK}\alpha)=0.946\text{ mm}^{-1}$
$T=293\text{ K}$
colorless
$F(0\ 0\ 0)=536$
0.28×0.18×0.15 mm
Radiation=Mo K_α
$\theta/2\theta$ scans with $2\theta_{\text{max}}=60^\circ$
$R=0.049(\text{on } I)$
$R_w=0.110(\text{on } I)$
$(\Delta\sigma)$
$(\Delta\rho)_{\text{min}}$
$(\Delta\rho)_{\text{max}}$
No. of reflections measured=2640
No. of reflections used=2490
No. of parameters=461
Goodness-of-fit=1.116
Minimum residual density=-0.18 e/ $\text{\AA}^3$
Maximum residual density=0.16 e/ $\text{\AA}^3$
Measurement: Siemens P4 diffractometer
Program system: SHELXL-Plus
Structure determination: direct method (SHELXS-86)
Refinement: full matrix (SHELXL-93)

Fig. 1 Chemical structure.

Fig. 2 The molecular structure of the title compound with the atom labeling. Thermal ellipsoids are drawn at the 50% probability level.

Fig. 3 A perspective drawing of the packing arrangement of the title compound in the crystal.

ecule comprises a system of two six-membered rings (A and B), a five-membered ring (C), a three-membered ring at C12 and an eighteen-membered ring. The A and B rings are *cis* fused at C6–C11 and the C ring is fused at C2–C12–C5 to the B-ring. According to the puckering parameter values (ϕ_2 , θ_2 and Q)³, the A and B rings occur in envelope ³E₁ and half-chair ²H₁ conformations, respectively, while ring C (ϕ_2 and Q)³, adopts an envelope conformation. The epoxy ring at C12 is almost perpendicular to the B ring; the angle between normals to the best planes through B and the epoxy ring is 85.7(3)°. The dihedral angle between the B and eighteen-membered rings is only 31.9(1)°. The arrangement of the molecules in the unit cell is shown in Fig. 3. The molecules in the crystal are packed at normal van der Waals distances. There is one intramolecular hydrogen bond between the O35–H hydroxyl group and the O36 carbonyl group. The O35...O36 and H35...O36 distances are 2.706(8) and 2.36(12) Å and the O35–H35...O36 angle is 101(8)°. In addition, there are five

Table 2 Final atomic coordinates and equivalent isotropic temperature factors (Å²)^a

Atom	x	y	z	<i>U</i> _{eq}
O1	0.4790(3)	0.4074	0.4841(2)	0.047(1)
O14	0.1390(3)	0.4659(5)	0.4054(3)	0.062(1)
O16	0.4090(3)	0.0812(5)	0.2009(2)	0.056(1)
O22	0.0087(4)	-0.1670(8)	0.0403(3)	0.112(2)
O29	0.1363(3)	0.1120(4)	0.4317(2)	0.048(1)
O32	0.1641(4)	-0.0948(5)	0.3433(3)	0.063(1)
O33	-0.1817(5)	-0.2343(11)	-0.0250(4)	0.144(3)
O35	0.4708(5)	-0.1139(13)	-0.0055(4)	0.165(4)
O36	0.5619(5)	-0.0796(12)	0.1798(4)	0.186(5)
C2	0.3468(4)	0.3977(7)	0.4969(3)	0.046(1)
C3	0.3072(5)	0.2420(6)	0.5268(3)	0.045(1)
C4	0.2704(4)	0.1526(6)	0.4342(3)	0.040(1)
C5	0.2860(4)	0.2662(6)	0.3528(3)	0.039(1)
C6	0.4294(4)	0.2605(6)	0.3333(3)	0.040(1)
C7	0.4586(5)	0.3887(8)	0.2649(4)	0.053(1)
C8	0.5967(5)	0.3853(10)	0.2461(4)	0.065(2)
C9	0.6913(5)	0.3666(7)	0.3349(4)	0.060(2)
C10	0.6535(5)	0.3222(6)	0.4146(4)	0.051(1)
C11	0.5193(4)	0.2846(6)	0.4281(3)	0.042(1)
C12	0.2677(4)	0.4157(6)	0.4010(3)	0.045(1)
C13	0.2263(6)	0.5611(8)	0.3593(5)	0.068(2)
C15	0.4671(5)	0.1059(7)	0.2984(3)	0.047(1)
C17	0.4658(5)	-0.0158(11)	0.1506(4)	0.085(2)
C18	0.3919(6)	-0.0440(11)	0.0536(4)	0.079(2)
C19	0.2761(6)	-0.1383(9)	0.0605(4)	0.069(2)
C20	0.1916(7)	-0.1411(13)	-0.0362(4)	0.088(3)
C21	0.0660(8)	-0.2221(16)	-0.0405(5)	0.110(4)
C23	-0.1128(6)	-0.1883(10)	0.0405(5)	0.080(2)
C24	-0.1533(6)	-0.1488(10)	0.1309(4)	0.079(2)
C25	-0.0760(5)	-0.1085(8)	0.2072(4)	0.063(2)
C26	-0.1174(5)	-0.0667(8)	0.2960(4)	0.068(2)
C27	-0.0446(5)	-0.0206(8)	0.3730(4)	0.063(2)
C28	0.0963(5)	-0.0096(6)	0.3806(3)	0.047(1)
C30	0.1916(5)	0.2435(7)	0.2626(4)	0.048(1)
C31	0.8273(6)	0.4024(14)	0.3265(6)	0.087(2)
C34	0.2975(17)	-0.3024(18)	0.0978(11)	0.162(6)

$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} (a_i^* a_j^*) (a_i \cdot a_j).$$

intermolecular C–H...O interactions <3.42 Å, which help stabilize the molecules in the crystal: C8...O35 (–*x*+1, +*y*+1/2, –*z*), C13...O32 (*x*, +*y*+1, +*z*), C30...O33 (–*x*, +*y*+1/2, –*z*), C24...O36 (*x*–1, +*y*, +*z*), C31...O14 (*x*+1, +*y*, +*z*), 3.412(8), 3.098(8), 3.386(7), 3.250(9) and 3.387(7) Å, respectively. The methyl group at C19 and O33, O35 and O36 atoms have large thermal parameters, which indicate the presence of a disorder. All H-atoms positions were found at the final stages of the refinement and their position and isotropic thermal parameter were refined.

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