# The fungal metabolite austdiol

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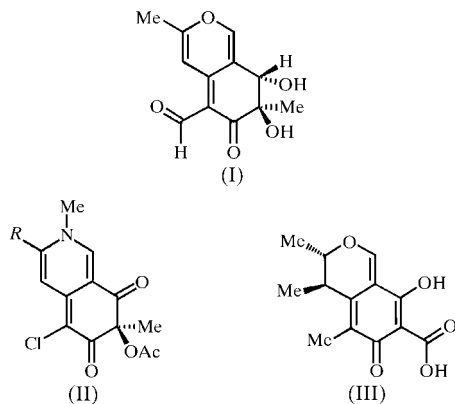Correspondence e-mail: raffaella.soave@istm.cnr.it

**Figure 1**
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

The title compound, (7*R*,8*S*)-7,8-dihydroxy-3,7-dimethyl-6-oxo-7,8-dihydro-6*H*-isochromene-5-carbaldehyde, $C_{12}H_{12}O_5$, is a *trans*-vicinal diol. Of the two fused rings, which lie approximately in the same plane, the pyran ring is almost perfectly planar, while the cyclohexenone ring adopts a slightly distorted half-chair conformation. The crystal packing is dictated by two strong intermolecular O—H⋯O interactions, one involving hydroxy and keto groups, the other involving two hydroxy groups. Molecules are linked together through twofold axes, forming zigzag ribbons extended along the *a* axis.

## Comment

The fungal metabolite austdiol, (I), is the main toxic component of a mixture of substances produced in mouldy maize meal by cultures of *Aspergillus Ustus* (Steyn, 1973; Vleggaar *et al.*, 1974). Fungal secondary metabolites are important because of the wide range of biological activities which they



can elicit (Paterson & Kemmelmeier, 1990). The effects can be beneficial (*e.g.* antibiotics) or detrimental (*e.g.* mycotoxins). Accurate knowledge of their molecular structure and properties is crucial in the search for new drugs, insecticides and
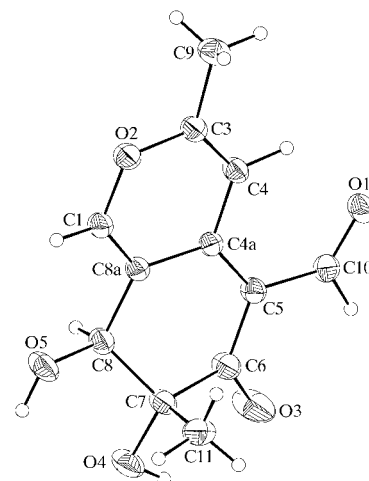
herbicides, so they have been the subject of increasing interest in recent decades (Paterson, 1986). In the 1970s, austdiol was investigated by means of chemical and spectroscopic techniques (Vleggaar *et al.*, 1974; Steyn & Vleggaar, 1976), and the X-ray structure of its 5-bromo derivative (Engel & Kruger, 1976) was determined to verify the absolute configuration of the two stereocentres. Other physicochemical data, including UV absorbance and thin-layer chromatography retention indices, were obtained subsequently (International Union of Pure and Applied Chemistry, 1982; Paterson, 1986; Frisvald & Thrane, 1987; Paterson & Kemmelmeier, 1990), and studies to elucidate the biosynthetic path that leads to austdiol were also performed (Colombo *et al.*, 1981, 1983). The core of austdiol has been found recently in the structures of four new fungi pigments (Wang *et al.*, 1997).

We report here the crystal structure of austdiol, (I), at room temperature, as a preliminary step in the detailed investigation of its electrostatic properties [as in our previous study of another fungal metabolite, citrinin (Roversi *et al.*, 1996)] by X-ray diffraction at a temperature below 25 K. Fig. 1 shows the labelling scheme of the asymmetric unit of (I); the absolute configuration of the molecule was based on the known configuration of the 5-bromo derivative (Engel & Kruger, 1976). The six-membered ring of the cyclohexenone system has a distorted half-chair conformation, with puckering parameters (Cremer & Pople, 1975) $Q = 0.457$ (2) Å, $\theta = 125.0$ (2)° and $\varphi = 277.9$ (3)° for the atom sequence C8a—C8—C7—C6—C5—C4a. Atoms C8 and C7 are 0.258 (4) and −0.441 (4) Å, respectively, from the mean plane defined by atoms C8a, C6, C5 and C4a, and the r.m.s. deviation of these latter four atoms is 0.016 Å. The pyran ring, defined by atoms C4a—C4—C3—O2—C1—C8a, is almost perfectly planar, with deviations from the mean plane ranging between −0.028 (1) (for C4a) and 0.022 (1) Å (for C8a). The only other 6,8a-dihydroisochromene whose structure has been deposited with the Cambridge Structural Database (Allen, 2002) is the 5-bromo derivative of austdiol (Engel & Kruger, 1976), which
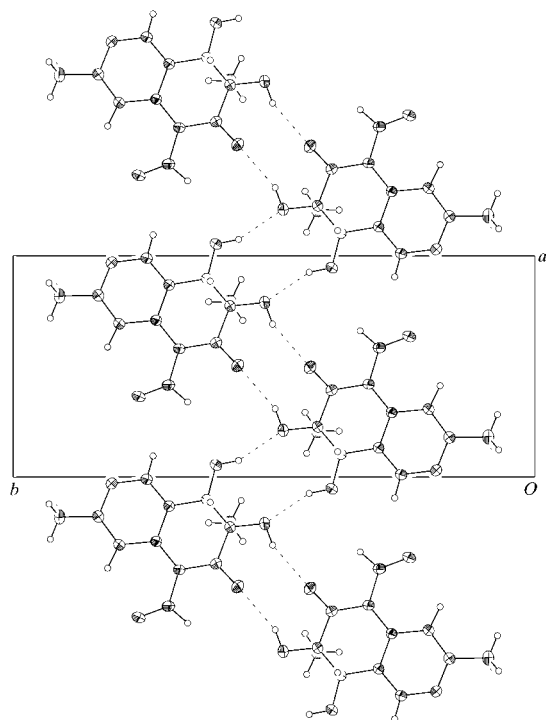
**Figure 2**
Packing diagram of (I), viewed down the *c* axis. Intermolecular O—H···O hydrogen bonds are shown as dashed lines.

crystallizes with four independent molecules in the asymmetric unit. We have calculated the puckering parameters for the ring systems of the four molecules of this austdiol derivative and found them to be very similar to those of the parent compound [$Q = 0.45$ (2) Å, $\theta = 124$ (2)° and $\varphi = 272$ (4)° for the cyclohexenone ring (mean values); deviations from planarity are between $-0.041$ and $0.036$ Å for the pyran ring]. In (I), the methyl substituent at C7 (7*R*) is oriented axially, while the two hydroxy groups at C7 and C8 (8*S*) are oriented equatorially, again in agreement with the orientation reported for the 5-bromo derivative. The molecule of austdiol is therefore nearly planar; the largest deviation is observed at the methyl C11 atom, which is located 1.902 (3) Å from the plane through the ten atoms of the two fused rings.

Other fungal metabolites showing structural similarities with austdiol are *N*-methylsclerotioramine, (II) (Whalley *et al.*, 1976), which contains an N atom instead of an O atom in the heterocyclic ring, and citrinin, (III), which has been extensively studied in our laboratory (Destro & Marsh, 1984; Destro, 1991; Roversi *et al.*, 1996). The molecules of both compounds are composed of two fused six-membered rings, as in austdiol, which are differently substituted. Furthermore, the positions of the double bonds in the fused rings are exactly the same in (I) and (II), while it differs in (III) (see *Scheme*). For this reason, the heterocyclic ring of (II) is essentially planar and the cyclohexenone ring adopts a distorted half-chair conformation, as in (I), while (III) has a planar cyclohexadienone ring [with the atoms at a distance from the mean plane of between $-0.031$ (1) and $0.017$ (1) Å] and a dihydropyran ring with puckering coordinates [$Q = 0.455$ (2) Å, $\theta =$

124.5 (3)° and $\varphi = 270.7$ (3)°] very similar to those reported above for the cyclohexenone ring of (I).

The exocyclic C3—C9 bond, linking the methyl C9 atom to the unsaturated system, is markedly shorter than the other methyl bond C11—C7 [1.486 (3) *versus* 1.512 (4) Å]. Our preliminary results at $T = 20$ K confirm the short value of the C3—C9 bond also at low temperature. This feature may be due to some kind of hyperconjugative interaction of this methyl group with the unsaturated system of (I), as observed for citrinin (Roversi *et al.*, 1996).

The geometric parameters of the hydrogen bonds are given in Table 2. Each molecule of (I) is joined head-to-head to two different molecules by O—H···O hydrogen bonds through twofold axes (Fig. 2). In one dimer, the hydrogen bond involves the hydroxy group at C7 of the parent molecule and the keto group of the other, while in the second dimer, the hydrogen bond is formed by two hydroxy groups. The overall pattern is that of zigzag one-dimensional ribbons extended along the *a* axis. Similar patterns are common in vicinal diols (Brock, 2002). Ribbons of (I) are piled up along the *c* axis; the angle between the normal to the molecular plane (defined by all the atoms of the two fused rings) and the *c* axis is 3.60 (3)°. The layers are related by screw axes, so that the methyl group at C7 points towards the aldehyde O atom of the molecule of an adjacent layer, making a weak C—H···O interaction (Table 2).

## Experimental

The title compound was obtained as described by Colombo *et al.* (1983). Pale orange crystals of (I) (decomposition 528 K) were obtained upon slow crystallization from an MeOH–H₂O (95:5) solution.

*Crystal data*

| | |
|---|---|
| C₁₂H₁₂O₅ | $D_m$ measured by flotation in a |
| $M_r = 236.22$ | CCl₄/benzene solution |
| Orthorhombic, $P2_12_12$ | Mo $K\alpha$ radiation |
| $a = 8.448$ (1) Å | Cell parameters from 60 |
| $b = 19.938$ (1) Å | reflections |
| $c = 6.428$ (1) Å | $\theta = 2.1$–12.4° |
| $V = 1082.7$ (2) Å³ | $\mu = 0.11$ mm⁻¹ |
| $Z = 4$ | $T = 290$ (2) K |
| $D_x = 1.449$ Mg m⁻³ | Prism, pale orange |
| $D_m = 1.451$ Mg m⁻³ | $0.50 \times 0.30 \times 0.23$ mm |

**Table 1**
Selected geometric parameters (Å, °).

| | | | |
|---|---|---|---|
| O2—C3 | 1.357 (2) | O4—C7 | 1.424 (2) |
| O2—C1 | 1.358 (2) | O5—C8 | 1.417 (2) |
| O1—C10 | 1.214 (3) | C3—C9 | 1.486 (3) |
| O3—C6 | 1.221 (3) | C7—C11 | 1.512 (4) |
| | | | |
| C3—O2—C1 | 118.7 (2) | C8a—C1—O2 | 123.5 (2) |
| O3—C6—C5 | 123.6 (2) | O1—C10—C5 | 127.4 (2) |
| O3—C6—C7 | 117.6 (2) | | |
| | | | |
| C8a—C4a—C5—C10 | 177.2 (2) | C5—C4a—C8a—C8 | −7.4 (3) |
| C4a—C5—C6—O3 | 169.6 (3) | C4—C4a—C8a—C8 | 171.8 (2) |
| C5—C4a—C8a—C1 | 176.3 (2) | C6—C5—C10—O1 | −177.9 (2) |
| C4—C4a—C8a—C1 | −4.5 (3) | | |

**Table 2**
Hydrogen-bonding geometry (Å, °).

| $D$—H$\cdots A$ | $D$—H | H$\cdots A$ | $D\cdots A$ | $D$—H$\cdots A$ |
|---|---|---|---|---|
| O4—H04$\cdots$O3 | 0.88 (3) | 2.07 (3) | 2.623 (2) | 119 (2) |
| O4—H04$\cdots$O3$^{i}$ | 0.88 (3) | 2.18 (3) | 3.025 (2) | 159 (2) |
| O5—H05$\cdots$O4$^{ii}$ | 0.89 (3) | 2.06 (3) | 2.891 (2) | 156 (3) |
| C1—H1$\cdots$O1$^{iii}$ | 0.93 (2) | 2.34 (2) | 3.182 (2) | 150 (1) |

Symmetry codes: (i) $1 - x, 1 - y, z$; (ii) $-x, 1 - y, z$; (iii) $x - 1, y, z$.

*Data collection*

| | |
|---|---|
| Siemens $P4$ diffractometer | $h = -10 \rightarrow 10$ |
| $2\theta/\omega$ scans | $k = 0 \rightarrow 25$ |
| 6711 measured reflections | $l = -8 \rightarrow 8$ |
| 1470 independent reflections | 3 standard reflections |
| 1269 reflections with $I > 2\sigma(I)$ | every 97 reflections |
| $R_{int} = 0.019$ | intensity decay: none |
| $\theta_{max} = 27.5°$ | |

*Refinement*

| | |
|---|---|
| Refinement on $F^2$ | $w = 1/[\sigma^2(F_o^2) + (0.0660P)^2$ |
| $R[F^2 > 2\sigma(F^2)] = 0.036$ | $+ 0.0091P]$ |
| $wR(F^2) = 0.102$ | where $P = (F_o^2 + 2F_c^2)/3$ |
| $S = 1.09$ | $(\Delta/\sigma)_{max} = 0.001$ |
| 1470 reflections | $\Delta\rho_{max} = 0.20$ e Å$^{-3}$ |
| 202 parameters | $\Delta\rho_{min} = -0.21$ e Å$^{-3}$ |
| All H-atom parameters refined | |

Due to the absence of significant anomalous scatterers in the title compound, the absolute configuration could not be determined and so was assigned to match the configuration of the chiral centres known from the X-ray analysis of the 5-bromo derivative (Engel & Kruger, 1976). All H atoms were located from difference Fourier maps and refined isotropically [C—H = 0.89 (3)–1.04 (2) Å].

Data collection: *XSCANS* (Siemens, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *SHELXL*97.

## References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Brock, C. P. (2002). *Acta Cryst.* B**58**, 1025–1031.
Burnett, M. N. & Johnson, C. K. (1996). *ORTEP*III. Report ORNL-6895. Oak Ridge National Laboratory, Tennessee, USA.
Colombo, L., Gennari, C., Poli, G., Scolastico, C. & Aragozzini, F. (1983). *J. Chem. Soc. Perkin Trans.* 1, pp. 2745–2749.
Colombo, L., Gennari, C., Ricca, G. S., Scolastico, C. & Aragozzini, F. (1981). *J. Chem. Soc. Chem. Commun.* pp. 575–576.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Destro, R. (1991). *Chem. Phys. Lett.* **181**, 232–236.
Destro, R. & Marsh, R. E. (1984). *J. Am. Chem. Soc.* **106**, 7269–7271.
Engel, D. W. & Kruger, G. J. (1976). *Acta Cryst.* B**32**, 2545–2548.
Frisvald, J. & Thrane, U. (1987). *J. Chromatogr.* **404**, 195–214.
International Union of Pure and Applied Chemistry (1982). *Pure Appl. Chem.* **54**, 2219–2284.
Paterson, R. R. M. (1986). *J. Chromatogr.* **368**, 249–264.
Paterson, R. R. M. & Kemmelmeier, C. (1990). *J. Chromatogr.* **511**, 195–221.
Roversi, P., Barzaghi, M., Merati, F. & Destro, R. (1996). *Can. J. Chem.* **74**, 1145–1161.
Sheldrick, G. M. (1997). *SHELXL*97 and *SHELXS*97. University of Göttingen, Germany.
Siemens (1991). *XSCANS User's Manual.* Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Steyn, P. S. (1973). *Tetrahedron*, **29**, 107–120.
Steyn, P. S. & Vleggaar, R. (1976). *J. Chem. Soc. Perkin Trans.* 1, pp. 204–206.
Vleggaar, R., Steyn, P. S. & Nagel, D. W. (1974). *J. Chem. Soc. Perkin Trans.* 1, pp. 45–49.
Wang, G. Y. S., Borgeson, B. M. & Crews, P. (1997). *Tetrahedron Lett.* **38**, 8449–8452.
Whalley, B. W., Ferguson, G., Marsh, W. C. & Restivo, R. J. (1976). *J. Chem. Soc. Perkin Trans.* 1, pp. 1366–1369.