Structure and Absolute Configuration of Versiol, a Metabolite from *Aspergillus versicolor*

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X-Ray analysis has established the structure and absolute configuration of versiol (1), a metabolite isolated from *Aspergillus versicolor*. Crystals are orthorhombic, space group $P2_12_12_1$, with a = 9.140(3), b = 6.118(2), c = 25.201(7) Å, Z = 4. The structure was solved by direct methods and refined by least-squares techniques to R 0.048 for 1 249 reflections. The absolute configuration determined by the Bijvoet method has verified that assigned by application of the Horeau asymmetric synthesis, but shown that that assigned by taking into account the Cotton effect was incorrect. Intermolecular hydrogen bonds link the molecules into infinite chains along the a axis.

DURING an investigation of the metabolites of the genus *Aspergillus*,[1] a new metabolite named versiol (1) was isolated from a strain of *Aspergillus versicolor* (Vuillemin) Tiraboschi NI 5 346. The physical properties and relative configuration of versiol determined by *X*-ray diffraction were reported briefly,[2] while McGahren and his co-workers[3] isolated from *Sporormia affinis* a metabolite named LL N313ζ whose structure was identical with that of versiol, except in its stereochemistry. Recently both metabolites were found to be identical by comparison of their *X*-ray diffraction patterns. This fact prompted us to investigate further the absolute

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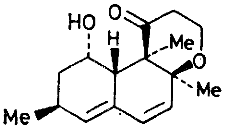
[1] T. Hamasaki, T. Nakagomi, Y. Hatsuda, K. Fukuyama, and Y. Katsube, *Tetrahedron Letters*, 1977, 2765.

[2] K. Fukuyama, T. Tsukihara, Y. Katsube, T. Hamasaki, and Y. Hatsuda, *Tetrahedron Letters*, 1976, 189.

[3] W. J. McGahren, G. A. Ellestad, J. E. Lancaster, G. O. Morton, and M. P. Kunstmann, *J. Amer. Chem. Soc.*, 1974, **96**, 1616; W. J. McGahren, G. A. Ellestad, G. O. Morton, and M. P. Kunstmann, *J. Org. Chem.*, 1976, **41**, 66.

configuration of versiol in order to ascertain whether the application of Horeau's asymmetric synthesis[4] or of Beecham's idea,[5] which took into account the Cotton effect due to the diene system with allylic oxygen, had led to an incorrect result. Since a crystal of a heavy-atom derivative was not available, we utilized the small anomalous scattering of light atoms for the determination of the absolute configuration.[6,7] We now describe the absolute stereochemistry of versiol elucidated by X-ray diffraction.



(1)

EXPERIMENTAL

The isolation and n.m.r. data are described in ref. 2. The compound was crystallized from acetone as colourless prisms elongated along the *b* axis.

Crystal Data.—$C_{16}H_{22}O_3$, $M = 262.35$. Orthorhombic, $a = 9.140(3)$, $b = 6.118(2)$, $c = 25.201(7)$ Å, $U = 1\,409.2$ Å^3, $Z = 4$, $D = 1.24$ g cm^{-3}. Cu-K_α radiation, $\lambda = 1.541\,8$ Å; μ(Cu-K_α) = 6.8 cm^{-1}. Space group $P2_12_12_1$ from systematic absences.

Crystallographic Measurements.—Preliminary unit-cell data were obtained from Weissenberg photographs. Accurate cell constants were determined by the least-squares treatment of the angular settings of 13 reflections. Intensities were initially measured up to $\sin\theta/\lambda$ 0.53 with Ni-filtered Cu-K_α radiation on a Toshiba four-circle diffractometer by means of the stationary-crystal–stationary-counter method, with a counting time of 30 s. Since it was desirable to obtain a more accurate molecular structure, the intensities were remeasured, after the structure determination,* on a Rigaku computer-controlled four-circle diffractometer using Ni-filtered Cu-K_α radiation. The θ—2θ scan technique was used with a scan speed of 2° min^{-1} in θ, and backgrounds were measured for 8 s at both the start and end points of a scan. A total of 1 250 independent intensities were measured in the range, $0 < \sin\theta/\lambda \leq 0.56$. The intensities of three reference reflections measured every sixty reflections showed no significant variation during data collection. The crystal used was so small (*ca.* 0.10 × 0.30 × 0.15 mm) that no absorption correction was considered necessary. Intensities were corrected for the Lorentz and polarization factors.

Structure Determination and Refinement.—The structure was solved by use of 232 reflections with $|E| \geq 1.2$ by the multiple-solution weighted-tangent formula procedure.[8] The set with the highest figure-of-merit yielded an E map revealing the positions of all non-hydrogen atoms. At an early stage of refinement, the co-ordinates and isotropic temperature factors were refined by a block-diagonal least-squares method[9] by use of the carbon-atom scattering factors. The atoms were identified and the types of bonds assigned on the basis of temperature factors and bond lengths and angles. All twenty-two hydrogen atoms were located in a difference-Fourier synthesis after anisotropic refinement, so that the structure of versiol was determined unambiguously. The refinement, including hydrogen atoms with isotropic temperature factors, reduced R to 0.08 for 996 reflections. The structure was further refined by use of the recollected data. The strongest reflection, 012, was omitted from subsequent calculation. A weighting scheme, with $w = 0.3$ for $F_o = 0$, $w = 1.0$ for $0 < F_o \leq 17$, and $w = [1.0 + 0.25\,(F_o - 17)]^{-1}$ for $17 < F_o$, was used in the final refinement. The final R was 0.048 for 1 249 reflections (R 0.040 for non-zero reflections). Final atomic parameters

TABLE 1

Final atomic parameters * (× 10^4), with estimated standard deviations in parentheses, for non-hydrogen atoms

	x	*y*	*z*
C(1)	3 962(3)	5(5)	1 176(1)
C(2)	2 485(4)	−20(6)	887(1)
C(3)	1 446(3)	1 564(6)	1 157(1)
C(4)	1 158(4)	969(6)	1 736(1)
C(5)	2 575(4)	499(7)	2 014(1)
C(6)	3 794(4)	−116(6)	1 774(1)
C(7)	5 167(4)	−401(6)	2 060(1)
C(8)	6 442(4)	−723(6)	1 828(1)
C(9)	6 631(4)	−1 002(6)	1 239(1)
C(10)	5 128(3)	−1 673(5)	977(1)
C(11)	5 326(3)	−1 442(6)	384(1)
C(12)	5 917(4)	726(6)	191(1)
C(13)	7 294(4)	1 292(6)	497(1)
C(14)	297(5)	2 757(8)	2 012(2)
C(15)	7 836(4)	−2 660(6)	1 122(2)
C(16)	4 741(4)	−4 046(5)	1 124(1)
O(1)	1 864(3)	−2 169(4)	881(1)
O(2)	5 099(3)	−2 949(5)	78(1)
O(3)	7 058(2)	1 155(4)	1 052(1)

TABLE 2

Fractional co-ordinates (× 10^3) for hydrogen atoms

	x	*y*	*z*	Distance/ Å
H(C1)	442(5)	159(7)	109(1)	1.08
H(C2)	266(4)	44(6)	48(1)	1.07
H(C3)	47(4)	154(7)	94(1)	1.04
H(C3)	188(5)	312(7)	115(1)	1.03
H(C4)	48(4)	−50(7)	175(2)	1.09
H(C5)	257(4)	56(6)	242(1)	1.02
H(C7)	513(5)	−34(6)	248(2)	1.06
H(C8)	743(5)	−94(7)	206(2)	1.08
H(C12)	512(4)	200(6)	24(1)	1.08
H(C12)	614(4)	65(7)	−21(1)	1.03
H(C13)	763(4)	288(7)	40(1)	1.05
H(C13)	808(4)	15(7)	38(1)	1.04
H(C14)	18(5)	230(7)	237(2)	0.96
H(C14)	−57(5)	319(8)	183(2)	0.95
H(C14)	97(5)	416(8)	199(2)	1.05
H(C15)	766(4)	−398(7)	135(1)	1.00
H(C15)	795(5)	−307(7)	73(2)	1.03
H(C15)	880(4)	−198(7)	122(2)	1.00
H(C16)	458(5)	−413(7)	150(1)	0.97
H(C16)	561(5)	−497(7)	104(1)	1.00
H(C16)	382(5)	−463(8)	91(2)	1.06
H(O1)	121(4)	−225(7)	64(2)	0.86

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* In the preliminary communication, only the first set of intensities was used.

[4] A. Horeau and H. B. Kagan, *Tetrahedron*, 1964, **20**, 2431.

[5] A. F. Beecham, A. M. Mathieson, S. R. Johns, J. A. Lamberton, A. A. Sioumis, T. J. Batterham, and I. G. Young, *Tetrahedron*, 1971, **27**, 3725.

[6] D. W. Engel, *Acta Cryst.*, 1972, **B28**, 1496.

[7] K. Fukuyama, K. Hamada, T. Tsukihara, and Y. Katsube, *Bull. Chem. Soc. Japan*, 1978, **51**, 37.

[8] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.

[9] T. Ashida, HBLS V, The Osaka Universal Crystallographic Computing System, The Computation Center, Osaka University, 1973, p. 55.

are given in Tables 1 and 2. Observed and calculated structure factors and atom thermal parameters are listed in Supplementary Publication No. SUP 22234 (11 pp., 1 microfiche).*

Absolute Configuration.—The absolute configuration was determined by the Bijvoet method with the technique described by Engel.[6] The Bijvoet differences were calculated with $\Delta f''_{O:C} = 0.02$, and seventeen sets of Bijvoet pairs and reference-reflection pairs were chosen by hand. A specimen of size *ca.* 0.20 × 0.30 × 0.15 mm was mounted with its *b* axis parallel to the ϕ axis of a Rigaku off-line four-circle diffractometer. The intensities of the Bijvoet pair, $h_1k_1l_1$ and $\bar{h}_1\bar{k}_1\bar{l}_1$, and its reference-reflection pair, $h_2k_2l_2$ and $\bar{h}_2\bar{k}_2\bar{l}_2$, were measured alternately 10 times by use of Ni-filtered Cu-K_α radiation. The θ—2θ scan technique was applied with a scan speed of 0.5° min^{-1} in θ, and backgrounds were counted for 26 s at each end of the scan range. The results are also deposited in the Supplementary Publication, and clearly indicate the correct enantiomer. The probability that the absolute configuration of versiol shown as (1) is wrong may be estimated by assuming *t*-distribution of DELA's,[6] and is calculated to be $\leqslant 0.01\%$.

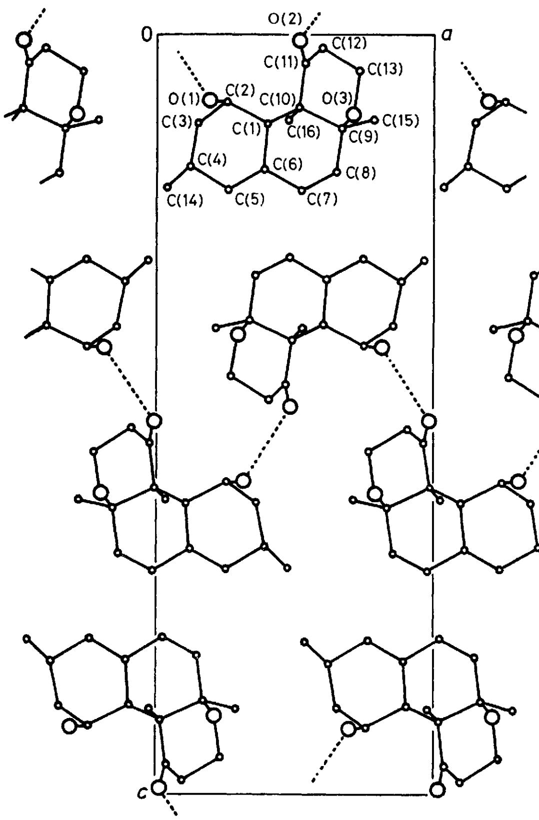

FIGURE 1 Crystal structure of versiol, viewed along the *b* axis. Broken lines indicate hydrogen bonds. Hydrogen atoms are omitted for clarity

Atomic scattering factors were taken from ref. 10. Computations were carried out on a TOSBAC 3400 computer at the Tottori University Computing Centre, and on an NEAC 2200 N700 computer at the Computation Centre of Osaka University.

RESULTS AND DISCUSSION

The present *X*-ray crystallographic analysis has established the structure and absolute configuration of versiol as in (1). The absolute configuration is correctly represented by the atomic parameters in Tables 1 and 2, if the right-handed co-ordinate system is adopted. The arrangement of molecules in the crystal and scheme of atomic numbering used in this paper are shown in Figure 1, and a stereoscopic view of the molecule plotted by a local version of PLUTO[11] in Figure 2. Bond lengths and angles are given in Table 3, selected torsion angles in Table 4, and intermolecular distances <3.8 Å in Table 5.

TABLE 3

Bond lengths (Å) and angles (°), with estimated standard deviations in parentheses

(*a*) Bond lengths

C(1)–C(2)	1.535(5)	C(1)–C(6)	1.515(5)
C(1)–C(10)	1.562(4)	C(2)–C(3)	1.518(5)
C(2)–O(1)	1.432(5)	C(3)–C(4)	1.527(5)
C(4)–C(5)	1.501(6)	C(4)–C(14)	1.517(6)
C(5)–C(6)	1.323(6)	C(6)–C(7)	1.458(5)
C(7)–C(8)	1.318(5)	C(8)–C(9)	1.506(5)
C(9)–C(10)	1.577(4)	C(9)–C(15)	1.525(5)
C(9)–O(3)	1.455(4)	C(10)–C(11)	1.512(5)
C(10)–C(16)	1.540(5)	C(11)–C(12)	1.513(5)
C(11)–O(2)	1.219(4)	C(12)–C(13)	1.516(5)
C(13)–O(3)	1.419(4)		

(*b*) Bond angles

C(2)–C(1)–C(6)	112.5(3)	C(2)–C(1)–C(10)	116.2(3)
C(6)–C(1)–C(10)	110.9(3)	C(1)–C(2)–C(3)	109.3(3)
C(1)–C(2)–O(1)	111.2(3)	C(3)–C(2)–O(1)	110.0(3)
C(2)–C(3)–C(4)	112.6(3)	C(3)–C(4)–C(5)	110.1(3)
C(3)–C(4)–C(14)	110.8(3)	C(5)–C(4)–C(14)	111.8(3)
C(4)–C(5)–C(6)	124.5(4)	C(1)–C(6)–C(5)	121.8(4)
C(1)–C(6)–C(7)	114.2(3)	C(5)–C(6)–C(7)	122.1(4)
C(6)–C(7)–C(8)	124.0(4)	C(7)–C(8)–C(9)	123.8(4)
C(8)–C(9)–C(10)	110.0(3)	C(8)–C(9)–C(15)	110.4(3)
C(8)–C(9)–O(3)	104.3(3)	C(10)–C(9)–C(15)	112.0(3)
C(10)–C(9)–O(3)	109.6(3)	C(15)–C(9)–O(3)	110.3(3)
C(1)–C(10)–C(9)	106.8(2)	C(1)–C(10)–C(11)	109.7(3)
C(1)–C(10)–C(16)	112.6(3)	C(9)–C(10)–C(11)	106.5(3)
C(9)–C(10)–C(16)	110.2(3)	C(11)–C(10)–C(16)	110.7(3)
C(10)–C(11)–C(12)	116.3(3)	C(10)–C(11)–O(2)	122.3(3)
C(12)–C(11)–O(2)	121.3(3)	C(11)–C(12)–C(13)	109.4(3)
C(12)–C(13)–O(3)	111.2(3)	C(9)–O(3)–C(13)	114.4(3)

TABLE 4

Selected torsion angles (°)

C(6)–C(1)–C(2)–C(3)	46.1
C(2)–C(3)–C(4)–C(5)	47.6
C(4)–C(5)–C(6)–C(1)	11.9
C(10)–C(1)–C(6)–C(7)	40.0
C(6)–C(7)–C(8)–C(9)	−4.6
C(8)–C(9)–C(10)–C(1)	50.8
O(3)–C(9)–C(10)–C(11)	54.0
C(10)–C(11)–C(12)–C(13)	51.2
C(12)–C(13)–O(3)–C(9)	60.7
C(5)–C(6)–C(7)–C(8)	−170.5
C(1)–C(2)–C(3)–C(4)	−60.6
C(3)–C(4)–C(5)–C(6)	−23.4
C(5)–C(6)–C(1)–C(2)	−23.2
C(1)–C(6)–C(7)–C(8)	−5.7
C(7)–C(8)–C(9)–C(10)	−19.7
C(9)–C(10)–C(1)–C(6)	−62.2
C(9)–C(10)–C(11)–C(12)	−51.9
C(11)–C(12)–C(13)–O(3)	−51.7
C(13)–O(3)–C(9)–C(10)	−62.0
C(7)–C(8)–C(9)–O(3)	97.7

* See Notice to Authors in *J.C.S. Perkin II*, 1977, Index issue.

[10] 'International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham 1962, p. 202.

[11] S. Motherwell, PLUTO, Cambridge Crystallographic File User Manual, May 1976.

McGahren and his co-workers assigned the configuration at C(2) by application of Horeau's asymmetric synthesis, and on the basis of that assigned the configurations at C(1) and C(4): these have been verified by the present analysis. They also assigned the configuration at the C(9) atom according to Beecham's method. They interpreted the diene system with an allylic oxygen as being of left-handed helicity, since it showed a negative Cotton effect in c.d. and o.r.d. spectra.[3] However, the present crystallographic analysis has contradicted the spectroscopic assignment: the helical sense of C(7)–C(8)–C(9)–O(3) is right-handed (the torsion angle is 97.7° in the crystalline state). The pyranone ring adopts a chair conformation. The C(9)–C(15) bond is axial, while C(10)–C(16) is equatorial with respect to the ring. The ring composed of atoms C(1)—(6) has a half-chair conformation; atoms C(2) and C(3) deviate by 0.39 and 0.33 Å respectively on opposite sides of the plane through atoms C(1), and C(4)—(6). As predicted by spectroscopy,[3] the atom H(C4) is 1,3-diaxal relative to the hydroxy-group.

TABLE 5

Intermolecular distances <3.8 Å

$C(2) \cdots O(2^{I})$	3.494	$O(1) \cdots C(11^{I})$	3.587
$O(1) \cdots C(12^{I})$	3.575	$O(1) \cdots O(2^{I})$	2.907 *
$O(2) \cdots C(13^{I})$	3.585	$O(2) \cdots C(15^{I})$	3.684
$C(15) \cdots O(1^{II})$	3.744	$C(1) \cdots C(16^{III})$	3.711
$O(3) \cdots C(16^{III})$	3.625	$C(7) \cdots C(7^{IV})$	3.791

* Hydrogen bond. Roman numeral superscripts refer to the following transformations of the co-ordinates relative to the reference molecule at x,y,z:

I $-\frac{1}{2} + x, -\frac{1}{2} - y, -z$
II $1 + x, y, z$
III $x, 1 + y, z$
IV $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$

An intermolecular hydrogen bond between the hydroxy-group and the carbonyl oxygen links the molecules into infinite chains along the *a* axis. The distance $H[O(1)] \cdots O(2)$ is 2.07 Å, and the angles $O(1)-H[O(1)] \cdots O(2)$ and $H[O(1)] \cdots O(2)-C(11)$ are 164 and 115°. The difference between the i.r. absorption bands due to the carbonyl group for KBr (1 680 cm^{-1}) and chloroform (1 700 cm^{-1}) samples, and the band due to its acetyl derivative (1 703 cm^{-1}) are explicable in terms of the intermolecular hydrogen bond. Other intermolecular distances require no special comment.

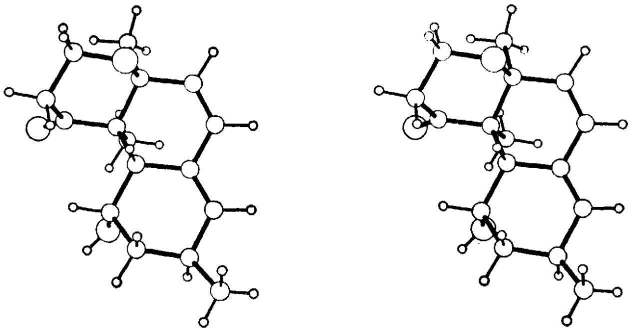

FIGURE 2 Stereoscopic view of versiol, showing the correct absolute configuration

We thank the staff of the Institute for Protein Research of Osaka University for the use of a Rigaku computer-controlled four-circle diffractometer, and Drs. W. J. McGahren and E. L. Patterson of the Cyanamid Company for supplying crystals of LL N313ζ.

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