

The Crystal and Molecular Structure of the Cyclic Isomer of Fusicoccin Deacetyl- aglycone

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Abstract

The cyclic isomer of fusicoccin deacetylglucose ($C_{21}H_{34}O_5$) crystallizes in the space group $P2_12_12_1$ with $a = 9.212$ (2), $b = 12.507$ (2), $c = 16.886$ (3) Å, $Z = 4$. The structure was refined to $R = 0.048$ for 2475 observed reflexions. The conformations of the saturated eight-membered ring and of the three five-membered rings are discussed. The packing is governed by intermolecular hydrogen bonds and methyl–methyl interactions.

Introduction

Crystallographic and extensive chemical work has been done to establish the structure of the major phytotoxic metabolite, fusicoccin A (Ballio, Brufani, Casinovi, Cerrini, Fedeli, Pellicciari, Santurbano & Vaciago, 1968; Barrow, Barton, Chain, Conlay, Smale, Thomas & Waight, 1968, 1971; Hough, Hursthouse, Neidle & Rogers, 1968; Barrow, Barton, Chain, Ohnsorge & Thomas, 1968, 1971), which was isolated from culture filtrates of the fungus *Fusicoccum amygdali* (Ballio, Chain, De Leo, Erlanger, Mauri & Tonolo, 1964). This substance, initially characterized as a phytotoxin, has remarkable growth-promoting activity for higher plants (Marré, 1977, and references quoted therein). Chemical work has also been directed towards the characterization and the elucidation of the structures of related metabolites (Ballio, Casinovi, Randazzo & Rossi, 1970; Ballio, Casinovi, Framondino, Grandolini, Menichini, Randazzo & Rossi, 1972; Ballio, Casinovi, Framondino, Grandolini, Randazzo & Rossi, 1972; Ballio, Casinovi, D'Alessio, Grandolini, Randazzo & Rossi, 1974; Ballio, Casinovi, Grandolini, Randazzo, Rossi & Sorrentino, 1974; Ballio, Casinovi, Grandolini, Pomponi, Randazzo & Rossi, 1975; Ballio, Casinovi, Grandolini, Marta & Randazzo, 1975) which, besides fusicoccin, have been found in the culture filtrates.

The acid hydrolysis of fusicoccin A yields the deacetylglucose (I), Fig. 1, together with a mixture of other products among which the most abundant is (II),

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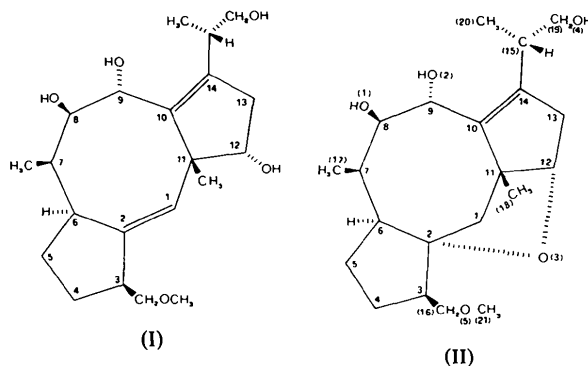


Fig. 1. The deacetylglucose of fusicoccin (I) and its cyclic isomer (II).

which is isomeric with (I). (II) can also be obtained from (I) by treatment with acids.

A tricyclic structure with two cyclopentene rings condensed on to a cyclooctane ring was initially proposed for (II) (Barrow, Barton, Chain, Ohnsorge & Thomas, 1971). Structure (II), where the tetrahydrofuran system is formed by interaction of the hydroxyl group of the cyclopentene ring with C(2) of the cyclooctene ring, has been assigned on the basis of NMR and MS data (Casinovi, Santurbano, Conti, Malorni & Randazzo, 1974). To establish the structure of the title compound, to gain deeper knowledge of the stereochemical features of this family of compounds and to investigate the conformational changes which chemical modifications may cause on the tricyclic system (Cerrini, Gavuzzo & Fedeli, 1975), we have undertaken the crystallographic analysis of (II).

Experimental

The crystal data are: $C_{21}H_{34}O_5$, $M_r = 366.5$, space group $P2_12_12_1$, $a = 9.212$ (2), $b = 12.507$ (2), $c = 16.886$ (3) Å, $V = 1945.5$ (6) Å³, $Z = 4$, $D_c = 1.25$ Mg m⁻³.

Suitable single crystals were obtained as colourless prisms by evaporation of an ethyl acetate solution. © 1979 International Union of Crystallography

Space group and preliminary cell dimensions were determined from Weissenberg photographs.

The lattice constants and intensities were measured with a crystal $0.3 \times 0.3 \times 0.6$ mm on an automatic Syntex P_2 diffractometer with Mo $K\alpha$ radiation monochromatized by a graphite crystal. Refined cell parameters were obtained by a least-squares fit of the θ angles of 15 high-order reflexions. The intensities were collected within the range $2.0 \leq 2\theta \leq 60.0^\circ$ by the ω -scan technique, with a scan speed in the interval 0.5 to $29.3^\circ \text{ min}^{-1}$ over a range of 0.7° . Background counts were taken for a time equal to that of the scan. Of ca 2810 independent reflexions the intensities of 2475 were considered observed [$I > 3\sigma(I)$].

Three standard reflexions monitored after every 100 remained essentially constant. In the estimation of $\sigma(I)$ the uncertainty factor p was set equal to 0.0001, as indicated by the variances of the standard reflexions (McCandlish, Stout & Andrews, 1975). Lorentz and polarization factors (Azaroff, 1955), but no absorption corrections were applied [$\mu(\text{Mo } K\alpha) = 0.094 \text{ mm}^{-1}$].

Structure solution and refinement

The absolute scale factor and the overall B were derived by the Wilson method. The structure was solved with *MULTAN* (Germain, Main & Woolfson, 1971) from 236 reflexions with $|E| > 1.65$. An E map calculated with the phases of the set having the highest

Table 1. *Final fractional coordinates of the non-hydrogen atoms with e.s.d.'s in parentheses*

	x	y	z
C(1)	0.5308 (3)	0.5781 (2)	0.2131 (1)
C(2)	0.6150 (3)	0.5306 (2)	0.1435 (1)
C(3)	0.5334 (3)	0.4479 (2)	0.0927 (2)
C(4)	0.6334 (4)	0.4370 (3)	0.0204 (2)
C(5)	0.6725 (4)	0.5521 (3)	0.0022 (2)
C(6)	0.6931 (3)	0.6075 (2)	0.0836 (1)
C(7)	0.6586 (3)	0.7288 (2)	0.0773 (1)
C(8)	0.7394 (3)	0.7999 (2)	0.1369 (2)
C(9)	0.7053 (3)	0.7883 (2)	0.2251 (1)
C(10)	0.7571 (3)	0.6815 (2)	0.2553 (1)
C(11)	0.6470 (3)	0.5952 (2)	0.2761 (1)
C(12)	0.7407 (3)	0.4950 (2)	0.2666 (1)
C(13)	0.8962 (3)	0.5294 (2)	0.2845 (2)
C(14)	0.8939 (3)	0.6469 (2)	0.2626 (1)
C(15)	1.0341 (3)	0.7072 (2)	0.2505 (2)
C(16)	0.3789 (3)	0.4800 (3)	0.0682 (2)
C(17)	0.4979 (3)	0.7591 (3)	0.0685 (2)
C(18)	0.5829 (3)	0.6116 (3)	0.3588 (2)
C(19)	1.1284 (4)	0.6978 (3)	0.3248 (2)
C(20)	1.1154 (4)	0.6651 (4)	0.1777 (3)
C(21)	0.1564 (5)	0.3987 (4)	0.0322 (3)
O(1)	0.7124 (3)	0.9085 (2)	0.1133 (1)
O(2)	0.7752 (2)	0.8775 (2)	0.2629 (1)
O(3)	0.7296 (2)	0.4676 (1)	0.1836 (1)
O(4)	1.2662 (3)	0.7463 (2)	0.3159 (2)
O(5)	0.2895 (3)	0.3892 (2)	0.0744 (2)

figure of merit revealed all the non-hydrogen atoms. The structure was refined by a diagonal least-squares method, isotropically (4×4 blocks) and anisotropically (9×9 blocks) successively. The function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = (a + |F_o| + c|F_o|^2)^{-1}$ with a and c of the order of $2F_{o(\text{min})}$ and $2/F_{o(\text{max})}$ respectively. Scattering factors were taken from *International Tables for X-ray Crystallography* (1974). A difference synthesis showed all the H atoms in stereochemically feasible positions. These were included in the refinement with an overall isotropic B of 4.5 \AA^2 keeping their positional parameters fixed. When the refinement was stopped the sum of the square of the ratios between the parameter shifts and the e.s.d.'s was 0.1. The adequacy of the weighting scheme was checked by inspection of the mean of $w|\Delta F^2|$ as a function of the $|F_o|$ and $\sin \theta/\lambda$ ranges: in both cases the function was nearly constant. The final R and R_w are 0.048 and 0.067 respectively for all observed reflexions. All the calculations were performed on the HP 21MX minicomputer of the CNR Research Area (Cerrini & Spagna, 1977). The final coordinates of the non-hydrogen atoms are reported in Table 1, those of

Table 2. *Fractional coordinates of the H atoms from the final difference synthesis*

	x	y	z
H1(C1)	0.477	0.641	0.196
H2(C1)	0.462	0.530	0.233
H(C3)	0.516	0.385	0.122
H1(C4)	0.713	0.389	0.041
H2(C4)	0.595	0.391	-0.023
H1(C5)	0.752	0.556	-0.031
H2(C5)	0.586	0.581	-0.031
H(C6)	0.788	0.605	0.096
H(C7)	0.707	0.741	0.030
H(C8)	0.827	0.785	0.127
H(C9)	0.601	0.794	0.232
H(C12)	0.717	0.436	0.295
H1(C13)	0.913	0.519	0.338
H2(C13)	0.964	0.494	0.250
H(C15)	1.013	0.779	0.243
H1(C16)	0.332	0.519	0.101
H2(C16)	0.361	0.521	0.028
H1(C17)	0.453	0.715	0.030
H2(C17)	0.493	0.814	0.040
H3(C17)	0.457	0.764	0.118
H1(C18)	0.528	0.553	0.371
H2(C18)	0.533	0.670	0.365
H3(C18)	0.653	0.625	0.395
H1(C19)	1.105	0.740	0.368
H2(C19)	1.153	0.622	0.340
H1(C20)	1.196	0.691	0.169
H2(C20)	1.054	0.677	0.137
H3(C20)	1.150	0.599	0.186
H1(C21)	0.114	0.324	0.032
H2(C21)	0.083	0.454	0.062
H3(C21)	0.176	0.427	-0.028
H(O1)	0.743	0.941	0.159
H(O2)	0.750	0.864	0.311
H(O4)	1.255	0.818	0.315

Table 3. Bond distances (Å) and angles (°) with *e.s.d.*'s in parentheses

C(1)—C(2)	1.527 (3)	C(9)—O(2)	1.438 (3)
C(1)—C(11)	1.525 (3)	C(10)—C(11)	1.523 (3)
C(2)—C(3)	1.540 (4)	C(10)—C(14)	1.338 (3)
C(2)—C(6)	1.570 (4)	C(11)—C(12)	1.530 (4)
C(2)—O(3)	1.482 (3)	C(11)—C(18)	1.529 (4)
C(3)—C(4)	1.536 (4)	C(12)—C(13)	1.526 (4)
C(3)—C(16)	1.536 (4)	C(12)—O(3)	1.446 (3)
C(4)—C(5)	1.516 (5)	C(13)—C(14)	1.516 (4)
C(5)—C(6)	1.552 (4)	C(14)—C(15)	1.510 (4)
C(6)—C(7)	1.553 (4)	C(15)—C(19)	1.531 (5)
C(7)—C(8)	1.535 (4)	C(15)—C(20)	1.532 (5)
C(7)—C(17)	1.536 (4)	C(16)—O(5)	1.406 (4)
C(8)—C(9)	1.530 (4)	C(19)—O(4)	1.416 (4)
C(8)—O(1)	1.436 (3)	C(21)—O(5)	1.424 (5)
C(9)—C(10)	1.507 (3)		
C(2)—C(1)—C(11)	103.6 (2)	C(9)—C(10)—C(11)	119.7 (2)
C(1)—C(2)—C(3)	116.2 (2)	C(9)—C(10)—C(14)	128.1 (2)
C(1)—C(2)—C(6)	119.4 (2)	C(11)—C(10)—C(14)	112.1 (2)
C(1)—C(2)—O(3)	102.6 (2)	C(1)—C(11)—C(10)	113.9 (2)
C(3)—C(2)—C(6)	106.0 (2)	C(1)—C(11)—C(12)	101.9 (2)
C(3)—C(2)—O(3)	104.2 (2)	C(1)—C(11)—C(18)	112.7 (2)
C(6)—C(2)—O(3)	107.0 (2)	C(10)—C(11)—C(12)	100.4 (2)
C(2)—C(3)—C(4)	102.1 (2)	C(10)—C(11)—C(18)	111.9 (2)
C(2)—C(3)—C(16)	115.3 (2)	C(12)—C(11)—C(18)	115.1 (2)
C(4)—C(3)—C(16)	111.5 (2)	C(11)—C(12)—C(13)	106.1 (2)
C(3)—C(4)—C(5)	102.7 (3)	C(11)—C(12)—O(3)	104.9 (2)
C(4)—C(5)—C(6)	105.8 (2)	C(13)—C(12)—O(3)	109.0 (2)
C(2)—C(6)—C(5)	104.0 (2)	C(12)—C(13)—C(14)	102.3 (2)
C(2)—C(6)—C(7)	123.2 (2)	C(10)—C(14)—C(13)	110.4 (2)
C(5)—C(6)—C(7)	110.5 (2)	C(10)—C(14)—C(15)	129.1 (2)
C(6)—C(7)—C(8)	115.0 (2)	C(13)—C(14)—C(15)	120.4 (2)
C(6)—C(7)—C(17)	116.5 (2)	C(14)—C(15)—C(19)	109.6 (3)
C(8)—C(7)—C(17)	112.8 (2)	C(14)—C(15)—C(20)	110.8 (3)
C(7)—C(8)—C(9)	118.9 (2)	C(19)—C(15)—C(20)	110.7 (3)
C(7)—C(8)—O(1)	106.4 (2)	C(3)—C(16)—O(5)	108.2 (3)
C(9)—C(8)—O(1)	108.9 (2)	C(15)—C(19)—O(4)	112.8 (3)
C(8)—C(9)—C(10)	110.4 (2)	C(2)—O(3)—C(12)	111.5 (2)
C(8)—C(9)—O(2)	105.4 (2)	C(16)—O(5)—C(21)	113.6 (3)
C(10)—C(9)—O(2)	113.3 (2)		

H atoms in Table 2.* Table 3 lists all the bond distances and angles.

Discussion

The structure of the cyclic isomer (Fig. 2) is consistent with that proposed by Casinovi, Santurbano, Conti, Malorni & Randazzo (1974). The conformational features of the molecule can be deduced from the torsion angles (Table 4). The cyclooctane ring assumes a boat-chair conformation with an approximate mirror plane passing through C(1) and C(8). The boat-chair form is the lowest-energy conformation of all the

symmetric forms analysed for cyclooctane (Bucourt, 1974). The largest deviation of 27.6° from the theoretical torsion angles of the boat-chair form occurs for C(2)—C(6) which is common with the cyclopentane ring. The cyclopentane ring assumes a $C_2(4)-C_2(6)$ conformation while the cyclopentene ring has C(12) in the flap of an envelope conformation. The tetrahydrofuran ring has a half-chair conformation with an approximate twofold axis passing through the O atom. Table 5 shows the deviations from planarity of the three five-membered rings. The fusion between the

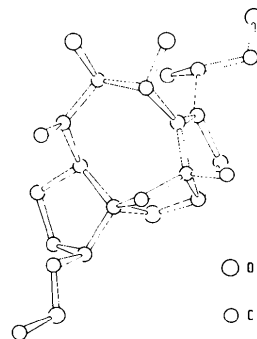


Fig. 2. The molecular skeleton of the cyclic isomer of fusicoccin deacetylaglycone.

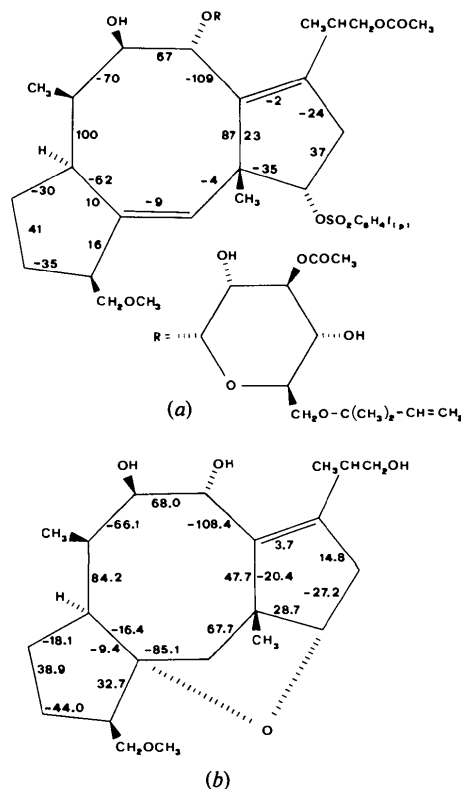


Fig. 3. The torsion angles of the tricycyclic system of (a) fusicoccin aglycone and (b) the cyclic isomer of fusicoccin deacetylaglycone.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33986 (21 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 4. Torsion angles ($^{\circ}$) with e.s.d.'s in parentheses

Cyclooctane ring		Cyclopentene ring		Side chains	
C(11)–C(1)–C(2)–C(6)	–85.1 (3)	C(14)–C(10)–C(11)–C(12)	–20.4 (3)	C(2)–C(3)–C(16)–O(5)	–139.6 (3)
C(1)–C(2)–C(6)–C(7)	–16.4 (3)	C(10)–C(11)–C(12)–C(13)	28.7 (2)	C(4)–C(3)–C(16)–O(5)	104.6 (3)
C(2)–C(6)–C(7)–C(8)	84.2 (3)	C(11)–C(12)–C(13)–C(14)	–27.2 (2)	C(3)–C(16)–O(5)–C(21)	–162.5 (3)
C(6)–C(7)–C(8)–C(9)	–66.1 (3)	C(12)–C(13)–C(14)–C(10)	14.8 (3)	C(10)–C(14)–C(15)–C(19)	125.5 (2)
C(7)–C(8)–C(9)–C(10)	68.0 (3)	C(13)–C(14)–C(10)–C(11)	3.7 (3)	C(10)–C(14)–C(15)–C(20)	–112.1 (3)
C(8)–C(9)–C(10)–C(11)	–108.4 (2)			C(13)–C(14)–C(15)–C(19)	–56.2 (3)
C(9)–C(10)–C(11)–C(1)	47.7 (3)	Ether ring		C(13)–C(14)–C(15)–C(20)	66.3 (3)
C(10)–C(11)–C(1)–C(2)	67.7 (3)	C(11)–C(1)–C(2)–O(3)	33.0 (2)	C(14)–C(15)–C(19)–O(4)	175.9 (2)
		C(1)–C(2)–O(3)–C(12)	–14.0 (2)	C(20)–C(15)–C(19)–O(4)	53.4 (4)
Cyclopentane ring		C(2)–O(3)–C(12)–C(11)	–10.6 (3)		
C(6)–C(2)–C(3)–C(4)	32.7 (3)	O(3)–C(12)–C(11)–C(1)	30.8 (2)		
C(2)–C(3)–C(4)–C(5)	–44.0 (3)	C(12)–C(11)–C(1)–C(2)	–39.4 (2)		
C(3)–C(4)–C(5)–C(6)	38.9 (3)				
C(4)–C(5)–C(6)–C(2)	–18.1 (3)				
C(5)–C(6)–C(2)–C(3)	–9.4 (3)				

Table 5. Displacements from least-squares planes (\AA)

Equations of the planes in the form $Ax + By + Cz = D$ are in the crystal system and x, y and z are in fractional coordinates.

Plane 1: $7.3610x - 7.3695y + 2.0200z = 0.8496$
 Plane 2: $0.2372x + 3.2883y + 16.2861z = 6.5973$
 Plane 3: $6.1761x + 8.8561y - 3.7421z = 7.9605$
 Plane 4: $0.0379x - 3.7074y - 16.1270z = -6.5858$

	Plane 1	Plane 2	Plane 3	Plane 4
C(1)			–0.360*	
C(2)	0.056		0.000	
C(3)	–0.037			
C(4)	0.634*			
C(5)	0.037			
C(6)	–0.056			
C(9)				0.060
C(10)		–0.019		–0.029
C(11)		0.011	0.273*	–0.050
C(12)		–0.453*	0.000	
C(13)		–0.011		0.069
C(14)		0.019		–0.014
C(15)				–0.036
O(3)			0.000	

* Atom not included in the calculation of the plane.

cyclooctane and cyclopentane rings is *cis*, while that between the cyclooctane and cyclopentene rings is quasi-*trans*.

The formation of the cyclic isomer from fusicocin deacetylglucoside involves an attack of the hydroxyl group of the cyclopentene ring on the C double bond of the eight-membered ring. The conformational changes associated with this process can be visualized from Fig. 3 where the torsion angles of the tricyclic system of the fusicocin aglycone, as present in the *p*-iodobenzenesulphonyl derivative (Brufani, Cerrini, Fedeli & Vaciego, 1971), and of the cyclic isomer are compared.

The conformation of the cyclopentane ring is shifted from $C_5(4)–C_2(2)$ to $C_5(4)–C_2(6)$. The conformation of

Table 6. Short interatomic contacts (\AA)

C(1)···C(7)	3.19	C(9)···C(17)	3.28
C(1)···C(9)	3.09	C(9)···C(18)	3.35
C(1)···C(16)	3.07	C(10)···C(20)	3.56
C(1)···C(17)	3.34	C(10)···O(3)	2.95
C(2)···C(10)	2.97	C(13)···C(18)	3.31
C(2)···C(17)	3.31	C(13)···C(19)	3.08
C(3)···C(21)	3.67	C(13)···C(20)	3.20
C(4)···O(3)	2.92	C(14)···C(18)	3.32
C(5)···C(16)	3.06	C(14)···O(2)	3.08
C(5)···C(17)	3.25	C(14)···O(3)	3.02
C(6)···C(9)	3.29	C(16)···C(17)	3.66
C(6)···C(10)	3.10	C(17)···O(1)	2.82
C(6)···C(11)	3.28	C(18)···C(21) ^I	3.67
C(6)···C(16)	3.32	C(20)···O(4)	2.90
C(7)···C(10)	3.19	O(1)···O(2)	2.62
C(8)···C(14)	3.19	O(2)···C(14)	3.08
C(9)···C(15)	3.22	O(2)···O(5) ^{II}	2.82
		O(3)···O(4) ^{III}	2.77

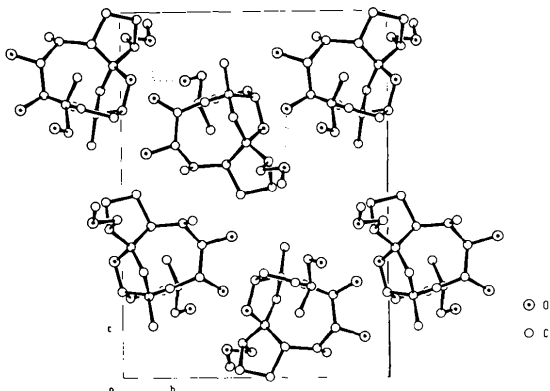
Symmetry code: (I) $\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$; (II) $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$; (III) $2 - x, y - \frac{1}{2}, \frac{1}{2} - z$.

the cyclopentene ring is retained as $C_5(12)$ although an inversion of the torsion angles does occur so that C(12) is on the opposite side of the plane of the other four atoms in the two compounds. This inversion which brings O(3) closer to C(2) is a prerequisite for ring closure. As far as the eight-membered ring is concerned, substantial changes do occur in the torsion angles of the bonds which are common to the three five-membered rings, while the remaining part of the ring maintains its conformation, so that the stereochemistry of the α -glycol system is the same in the two compounds. Furthermore the boat–chair conformation assumed by the cyclooctane moiety maintains the approximate mirror plane, present in the aglycone of fusicocin, through the same atoms C(1) and C(8).

The relevant intra- and intermolecular contacts are reported in Table 6. The two O atoms of the α -glycol

Table 7. Geometry of the intermolecular hydrogen bonds

	Distances (Å)		Angles (°)		
	O...O	H...O	O-H...O	C(16)-O(5)...H	C(21)-O(5)...H
O(2)-H...O(5)	2.82	1.99	159.4	107.8	109.9
O(3)...H-O(4)	2.77	1.87	169.0	126.2	102.6

Fig. 4. The packing of the cyclic isomer molecules viewed down *a*.

system are engaged in a hydrogen bond: the distance between the two O atoms is 2.62 Å, while the distance between O(2) and the H atom bound to O(1) is 1.95 Å and the system C(8)-O(1)-H...O(2)-C(9) is fairly planar.

The packing is mainly governed by hydrogen bonds and methyl-methyl interactions. One hydrogen bond, 2.82 Å long, occurs between the hydroxyl O(2) of a molecule and the acceptor O(5) of another molecule which is generated by the symmetry operation $1-x, \frac{1}{2}+y, \frac{1}{2}-z$. The other hydrogen bond of 2.77 Å occurs between the acceptor O(3) and the hydroxyl O(4) generated by the symmetry operation $2-x, y-\frac{1}{2}, \frac{1}{2}-z$. The geometry of the hydrogen bonds is given in Table 7. The methyl-methyl interaction of 3.67 Å occurs between the C(18) and C(21) methyl groups of two different molecules related by the symmetry operation $\frac{1}{2}-x, 1-y, \frac{1}{2}+z$.

Fig. 4 gives a view of the packing down *a*.

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