© 1983 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 56, 3042—3046 (1983) [Vol. 56, No. 10

The Crystal and Molecular Structure of Albocycline

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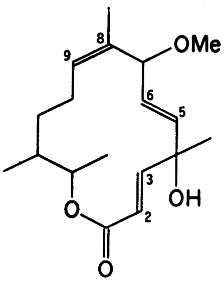
(Received March 11, 1983)

The detailed molecular geometry of albocycline ($C_{18}H_{28}O_4$) has been examined by X-ray crystal analysis. The crystals are monoclinic, with four molecules in a unit cell with dimensions of a=16.177(2), b=9.562(1), c=11.742(2) Å, and β=90.43(1)°; the space group is $P2_1$. 3062 unique intensity data were collected on a four-circle diffractometer with graphite-monochromated Mo $K\alpha$ radiation. The structure was elucidated by the Monte Carlo direct method, using the 30 reflections with the greatest $|E|$ values as the starting set; the 174th random phase set led to the correct solution. The R value reached 0.057 by block-diagonal least-squares refinements. The two crystallographically-independent molecules are connected by two O–H···O hydrogen bonds, forming a hydrogen-bonded dimer. The conformations of the fourteen-membered macrolide rings in these two molecules are considerably different from each other; *e.g.*, great differences of 165, 153, and 108° are found for the torsion angles around the C(4)–C(5), C(6)–C(7), and C(7)–C(8) single bonds respectively.

Albocycline is a macrolide antibiotic isolated from such strains of *Streptomyces* as *S. brunneogriseus*[1] and *S. maizeus*,[2] and is active mainly against staphylococci. On the basis of degradative and spectroscopic experiments,[3–5] the **1** structure was proposed for this antibiotic. A nuclear-Overhauser-effect study later suggested that the C(8)=C(9) double bond might be not *cis* but *trans*.[6] Therefore, in order to establish the molecular structure, we undertook an X-ray crystal structure analysis of albocycline itself. However, soon after this analysis has completed, the results of the X-ray study of (*p*-bromobenzoyl)albocycline (**2**) were published.[7] According to that report, albocycline has the **3** structure, which agrees with our conclusion. The present paper gives a detailed description of the two different molecular conformations found in the albocycline crystal.



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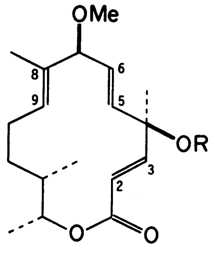

2 : R = p-BrC6H4CO
3 : R = H

Experimental

Colorless single crystals of albocycline were grown from a hexane–diethyl ether solution. The sample used for the X-ray experiment had dimensions of about 0.3×0.4×0.5 mm³. The crystal data are summarized in Table 1. The unit-cell dimensions and diffraction intensities were measured on a Rigaku four-circle diffractometer with graphite-monochromated Mo $K\alpha$ radiation (λ=0.71069 Å). The ω-2θ scan technique was applied at a 2θ scan rate of 4° min^{-1}; the scan width in ω was (0.9+0.34 tan θ)°. The background was measured for 10 s at each end of the scan range. The intensities were corrected for the Lorentz and polarization factors, but not for the absorption or the extinction effect. In the range of 2θ values up to 55°, 3062 independent structure factors above the $\sigma(F)$ level were selected for the structure determination.

Table 1. The crystal data

$C_{18}H_{28}O_4$	Mol wt 308 42
Crystal system	Monoclinic
Space group	$P2_1$
Cell dimensions	a = 16.177(2) Å
	b = 9.562(1) Å
	c = 11.742(2) Å
	β = 90.43(1)°
V	1816.2 Å³
Z	4
D_c	1.128 g cm^{-3}
μ(Mo $K\alpha$)	0.730 cm^{-1}

Structure Determination

In the early stage of the structure determination, various attempts were made to solve the structure with the MULTAN-78 program,[8] but all such attempts were unsuccessful. The structure was finally elucidated by the Monte Carlo direct method,[9] using the reflections with 2θ values less than 50°. The starting set was composed of the 30 reflections having the greatest $|E|$ values. In order to extend each of the tentative-phase sets derived from random numbers, 12 cycles of the tangent procedure were carried out by the use of 711 $|E|$ values above 1.30. Since the 174th random phase set showed a low R_K value of 0.316 ($R_K=\sum||E_o|-k|E_c||/\sum|E_o|$), 6 additional cycles of the tangent procedure were performed using 861 $|E|$ values above 1.20; consequently, the R_K value was reduced to 0.266. An E-map based on 828 phases revealed the locations of all the 44 non-hydrogen atoms.

The structure thus obtained was refined by the block-diagonal least-squares method with anisotropic temperature factors, using all the 3062 reflections. After all the 56 hydrogen atoms had been located in a difference Fourier map, further least-squares refine-

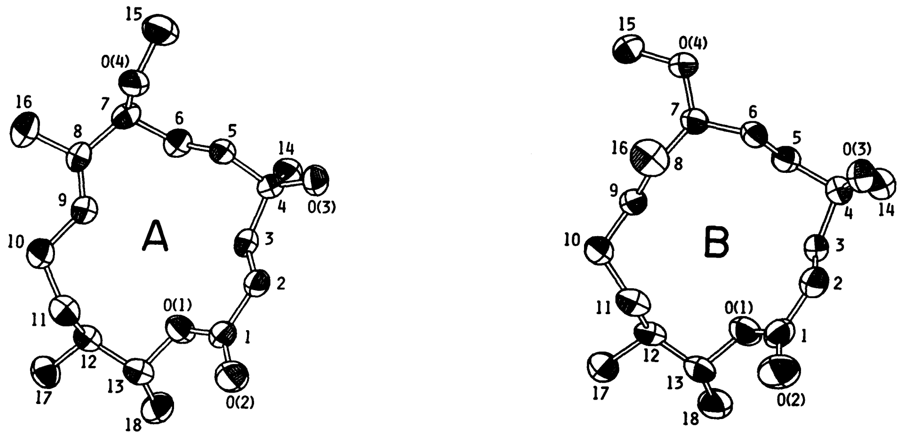

Fig. 1. The skeletons of the two crystallographically-independent albocycline molecules, A and B, viewed perpendicularly to their respective ring planes. Each non-hydrogen atom is represented as a thermal ellipsoid enclosing a 50% probability.

Table 2. The final atomic parameters and estimated standard deviations. The coordinates and B_{eq}[a)] values are multiplied by 10^4 and 10^2 respectively.

Atom	x	y	z	$B_{eq}/Å^2$	Atom	x	y	z	$B_{eq}/Å^2$
O(A1)	60(2)	4466(4)	5275(3)	436	O(B1)	5068(2)	4724(5)	9356(3)	524
O(A2)	856(2)	5718(6)	6451(3)	606	O(B2)	4361(3)	3584(6)	10685(4)	686
O(A3)	2528(2)	4936(4)	2861(3)	419	O(B3)	2341(2)	5092(5)	7696(3)	498
O(A4)	343(2)	6669(4)	328(3)	465	O(B4)	3650(2)	3078(5)	4163(3)	471
C(A1)	757(3)	5075(5)	5575(4)	367	C(B1)	4370(3)	4294(6)	9849(4)	455
C(A2)	1388(3)	4926(6)	4674(4)	362	C(B2)	3641(3)	4741(7)	9183(4)	444
C(A3)	1265(3)	4166(5)	3762(4)	326	C(B3)	3683(3)	5651(6)	8363(4)	380
C(A4)	1790(3)	4149(5)	2701(3)	339	C(B4)	3030(3)	5949(6)	7461(4)	403
C(A5)	1256(3)	4978(5)	1861(3)	338	C(B5)	3480(3)	5455(6)	6394(4)	381
C(A6)	554(3)	4533(5)	1413(4)	367	C(B6)	3412(2)	4238(5)	5937(4)	355
C(A7)	-37(3)	5433(6)	739(4)	404	C(B7)	4058(3)	3636(6)	5144(4)	382
C(A8)	-798(3)	5869(6)	1406(4)	398	C(B8)	4561(3)	2574(5)	5809(3)	342
C(A9)	-922(3)	5521(6)	2480(4)	402	C(B9)	5321(3)	2855(6)	6134(4)	373
C(A10)	-1633(3)	5945(6)	3216(4)	453	C(B10)	5858(3)	1981(6)	6911(5)	465
C(A11)	-1404(3)	6009(6)	4478(4)	418	C(B11)	5760(3)	2314(6)	8174(4)	450
C(A12)	-1375(3)	4607(5)	5082(4)	380	C(B12)	6243(3)	3578(6)	8612(4)	422
C(A13)	-676(3)	4590(6)	5979(4)	394	C(B13)	5867(3)	4134(7)	9708(4)	498
C(A14)	1976(3)	2678(6)	2315(4)	448	C(B14)	2794(4)	7467(8)	7416(5)	563
C(A15)	846(5)	6471(10)	-633(6)	698	C(B15)	4205(4)	2495(9)	3353(4)	582
C(A16)	-1387(4)	6770(11)	744(6)	776	C(B16)	4103(4)	1262(7)	6132(5)	538
C(A17)	-2217(3)	4220(6)	5591(5)	479	C(B17)	7150(3)	3181(8)	8795(5)	571
C(A18)	-676(4)	3388(8)	6809(5)	597	C(B18)	6333(5)	5304(9)	10294(6)	713

a) $B_{eq} = 8\pi^2(u_1^2+u_2^2+u_3^2)/3$, where u_i is the root-mean-square deviation in the i-th principal axis of the thermal ellipsoid.

ments were carried out including the hydrogen atoms with isotropic temperature factors. For these refinements, the following weighting scheme was used:

$$w=1/\{\sigma(F)^2 \exp(c_1X^2+c_2Y^2+c_3XY+c_4X+c_5Y)\},$$

where $X=|F_o|$ and $Y=\sin\theta/\lambda$. The c_1, c_2, c_3, c_4, and c_5 coefficients were evaluated from the $(\Delta F)^2$ distribution: $c_1=-0.377\times10^{-4}$, $c_2=24.1$, $c_3=0.0518$, $c_4=-0.265\times10^{-2}$, and $c_5=-27.3$. In this manner, the R value reached 0.057. The final atomic parameters are listed in Table 2.[10)]

The calculations were done on a HITAC M-200H computer at the Hokkaido University Computing Center, using our own programs. The atomic scattering factors were taken from the International Tables.[11)]

Results and Discussion

Molecular Structure. The frameworks of the two crystallographically-independent molecules, A and B, are illustrated in Fig. 1, while the bond distances and angles and the torsion angles are given in Tables 3 and 4 respectively. These results demonstrate that albocycline has the **3** structure in which the fourteen-membered macrolide ring contains a *trans,trans,trans*-triene system.

Notwithstanding the incorporation in the macrolide ring, the ester moiety in each of the A and B molecules keeps the geometry characteristic of secondary alcohol esters, *i.e.*, the synperiplanar configuration of the

TABLE 3. THE BOND DISTANCES AND ANGLES WITH THEIR STANDARD DEVIATIONS
The e.s.d.'s given in parentheses refer to the last decimal position.

Bond distance	l/Å		Bond distance	l/Å	
	Mol. A	Mol. B		Mol. A	Mol. B
C(1)-C(2)	1.482(6)	1.472(7)	C(7)-O(4)	1.419(7)	1.427(6)
C(1)-O(1)	1.315(6)	1.338(7)	C(8)-C(9)	1.321(7)	1.312(6)
C(1)-O(2)	1.208(6)	1.194(7)	C(8)-C(16)	1.498(10)	1.508(8)
C(2)-C(3)	1.308(6)	1.300(7)	C(9)-C(10)	1.499(7)	1.508(7)
C(3)-C(4)	1.513(6)	1.518(6)	C(10)-C(11)	1.527(7)	1.525(7)
C(4)-C(5)	1.528(6)	1.530(7)	C(11)-C(12)	1.516(7)	1.526(8)
C(4)-C(14)	1.509(8)	1.501(9)	C(12)-C(13)	1.541(6)	1.522(7)
C(4)-O(3)	1.422(5)	1.411(6)	C(12)-C(17)	1.536(7)	1.529(7)
C(5)-C(6)	1.318(6)	1.286(7)	C(13)-C(18)	1.507(9)	1.512(10)
C(6)-C(7)	1.507(7)	1.517(6)	C(13)-O(1)	1.459(6)	1.467(7)
C(7)-C(8)	1.523(7)	1.515(7)	C(15)-O(4)	1.410(8)	1.426(7)

Bond angle	θ/°		Bond angle	θ/°	
	Mol. A	Mol. B		Mol. A	Mol. B
C(2)-C(1)-O(1)	111.1(4)	110.9(4)	C(8)-C(7)-O(4)	107.5(4)	114.1(4)
C(2)-C(1)-O(2)	124.7(4)	125.9(5)	C(7)-C(8)-C(9)	123.4(4)	120.8(5)
O(1)-C(1)-O(2)	124.1(4)	123.1(5)	C(7)-C(8)-C(16)	113.9(4)	115.1(4)
C(1)-C(2)-C(3)	122.4(4)	122.8(5)	C(9)-C(8)-C(16)	122.7(5)	124.0(5)
C(2)-C(3)-C(4)	126.6(4)	127.1(4)	C(8)-C(9)-C(10)	127.2(5)	126.6(5)
C(3)-C(4)-C(5)	102.0(3)	100.4(4)	C(9)-C(10)-C(11)	112.9(4)	114.1(5)
C(3)-C(4)-C(14)	111.8(4)	112.4(4)	C(10)-C(11)-C(12)	115.2(4)	115.9(4)
C(3)-C(4)-O(3)	111.2(3)	107.5(4)	C(11)-C(12)-C(13)	110.4(4)	110.8(4)
C(5)-C(4)-C(14)	113.8(4)	113.1(4)	C(11)-C(12)-C(17)	111.8(4)	109.8(5)
C(5)-C(4)-O(3)	106.3(4)	111.3(4)	C(13)-C(12)-C(17)	112.4(4)	110.9(4)
C(14)-C(4)-O(3)	111.3(4)	111.6(4)	C(12)-C(13)-C(18)	116.5(5)	116.3(5)
C(4)-C(5)-C(6)	124.8(4)	125.6(4)	C(12)-C(13)-O(1)	102.2(3)	104.7(4)
C(5)-C(6)-C(7)	124.5(5)	122.8(4)	C(18)-C(13)-O(1)	108.0(4)	106.1(5)
C(6)-C(7)-C(8)	113.5(4)	108.0(4)	C(1)-O(1)-C(13)	120.9(4)	120.3(4)
C(6)-C(7)-O(4)	112.3(4)	108.7(3)	C(7)-O(4)-C(15)	114.5(5)	113.3(4)

TABLE 4. THE TORSION ANGLES[a)]

Torsion angle	ϕ/°		Torsion angle	ϕ/°	
	Mol. A	Mol. B		Mol. A	Mol. B
O(1)-C(1)-C(2)-C(3)	-5.9	-12.2	O(4)-C(7)-C(8)-C(9)	-123.4	132.4
O(2)-C(1)-C(2)-C(3)	176.9	171.4	O(4)-C(7)-C(8)-C(16)	54.8	-52.2
C(2)-C(1)-O(1)-C(13)	-174.1	-165.6	C(6)-C(7)-O(4)-C(15)	77.5	179.5
O(2)-C(1)-O(1)-C(13)	3.1	10.9	C(8)-C(7)-O(4)-C(15)	-156.9	-60.0
C(1)-C(2)-C(3)-C(4)	168.0	165.3	C(7)-C(8)-C(9)-C(10)	177.5	172.3
C(2)-C(3)-C(4)-C(5)	-104.6	-114.0	C(16)-C(8)-C(9)-C(10)	-0.6	-2.7
C(2)-C(3)-C(4)-C(14)	133.4	125.6	C(8)-C(9)-C(10)-C(11)	-151.4	-88.3
C(2)-C(3)-C(4)-O(3)	8.3	2.4	C(9)-C(10)-C(11)-C(12)	-79.2	-81.4
C(3)-C(4)-C(5)-C(6)	-70.0	95.3	C(10)-C(11)-C(12)-C(13)	144.1	158.7
C(14)-C(4)-C(5)-C(6)	50.6	-144.7	C(10)-C(11)-C(12)-C(17)	-90.1	-78.4
O(3)-C(4)-C(5)-C(6)	173.4	-18.3	C(11)-C(12)-C(13)-C(18)	168.1	174.6
C(4)-C(5)-C(6)-C(7)	169.6	-159.2	C(11)-C(12)-C(13)-O(1)	-74.5	-68.8
C(5)-C(6)-C(7)-C(8)	-103.6	103.1	C(17)-C(12)-C(13)-C(18)	42.6	52.3
C(5)-C(6)-C(7)-O(4)	18.6	-132.6	C(17)-C(12)-C(13)-O(1)	160.0	169.0
C(6)-C(7)-C(8)-C(9)	1.4	-106.6	C(12)-C(13)-O(1)-C(1)	145.9	124.6
C(6)-C(7)-C(8)-C(16)	179.7	68.8	C(18)-C(13)-O(1)-C(1)	-90.7	-112.0

a) The e.s.d.'s are 0.4—0.9°.

C(13)-O(1)-C(1)=O(2) segment and the eclipsed conformation of the H(13)-C(13)-O(1)-C(1) segment. This geometry brings the O(2) and H(13) atoms close to each other; their distances are 2.49(4) and 2.30(5) Å for the A and B molecules respectively. The C(2)=C(3) and C(1)=O(2) conjugated double bonds are transoid and nearly coplanar for both molecules. Consequently, the C(13)-O(1)-C(1)(O(2))-C(2)=C(3)-C(4) segment as a whole has a rigid and nearly-planar configuration. This coplanarity of the five consecutive bonds makes it impossible for the ring to take a rectangular form.

As will be seen from Fig. 1, the ring conformations of the A and B molecules differ considerably from each other. The C(5) and C(6) atoms in the former molecule are situated above and below the mean plane of the ring respectively, while those in the latter are placed in the opposite way. This remarkable variation in the orientation of the C(5)=C(6) double bond is caused mainly by great changes (165, 153, and 108° respectively) of the C(3)–C(4)–C(5)=C(6), C(5)=C(6)–C(7)–C(8), and C(6)–C(7)–C(8)=C(9) torsion angles. These torsional changes further alter the orientations of the atomic groups at the C(4) and C(7) atoms in a regular manner; *i.e.*, the O(3)H, $C(14)H_3$, and $O(4)–C(15)H_3$ groups in the A molecule are pseudo-equatorial, pseudo-axial, and pseudo-axial respectively, whereas those in the B molecule are pseudo-axial, pseudo-equatorial, and pseudo-equatorial respectively. On the other hand, the $C(17)H_3$ and $C(18)H_3$ groups remote from the C(4)–C(5)=C(6)–C(7) segment are pseudo-equatorial for both molecules.

When the macrolide ring in the B molecule is viewed along the normal of its mean plane, it looks like a somewhat-deformed trapezoid having the nearly-planar C(13)–O(1)–C(1)(O(2))–C(2)=C(3)–C(4), C(4)–C(5)=C(6)–C(7), C(7)–C(8)(C(16))=C(9)–C(10), and C(10)–C(11)=C(12)–C(13) segments as the four sides (see Fig. 1). The mean planes for these segments make angles of 33, 12, 5, and 16° with the normal of the ring plane respectively. On the other hand, the macrolide ring in the A molecule is too greatly deformed to be regarded as having such a trapezoid form. That is to say, the mean planes for the C(13)–O(1)–C(1)(O(2))–C(2)=C(3)–C(4) and C(7)–C(8)(C(16))=C(9)–C(10) segments incline at large angles of 46 and 70° with the normal of the ring plane respectively, although those for the C(4)–C(5)=C(6)–C(7) and C(10)–C(11)–C(12)–C(13) segments are at small angles of 17 and 9° with this normal respectively. The marked inclination of the C(7)–C(8)(C(16))=C(9)–C(10) segment results mainly from the eclipsed conformation of the C(6)–C(7)–C(8)=C(9) segment. The (*p*-bromobenzoyl)albocycline molecule[7] has almost the same ring conformation as the A molecule of albocycline. A ring conformation such as the B molecule takes may be unfavorable for the derivative molecule because of the pseudo-axial orientation of the large *p*-bromobenzoyloxyl group.

The ring formation results in considerable deformation of the vinylene groups. The deviations of the C(1)–C(2)=C(3)–C(4), C(4)–C(5)=C(6)–C(7), and C(7)–C(8)=C(9)–C(10) torsion angles from the value (180°) for the ideal planar *trans* configuration are 12.0, 10.4, and 2.5° for the A molecule respectively, and are 14.7, 20.8, and 7.7° for the B molecule respectively. It is of interest to note that each vinylene group in the B molecule is more greatly deformed than the corresponding group in the A molecule. Apart from the O(1)–C(1)–C(2)=C(3) segment which has the synperiplanar conformation because of the strong conjugation between the C(2)=C(3) and C(1)=O(2) double bonds, there are three and four synperiplanar segments of the C=C–C–X type in the A and B molecules respectively (see Table 5). Of these seven segments, two are the C(2)=C(3)–C(4)–O(3) segments in the two molecules. It is known that, in the preferred conformations of *unsym*-butene ($CH_2=CH-CH_2-CH_3$) and allyl alcohol ($CH_2=CH-CH_2-OH$), the C=C double bond eclipses one of the hydrogen atoms at the allylic position.[12] The C(5)=C(6)–C(7)–H(7) and H(7)–C(7)–C(8)=C(9) segments in the B molecule have such eclipsed conformations. On the other hand, the eclipsed conformations of the C(5)=C(6)–C(7)–O(4) and C(6)–C(7)–C(8)=C(9) segments in the A molecule result in significant enlargement of the C(5)=C(6)–C(7), C(6)–C(7)–O(4), C(6)–C(7)–C(8), and C(7)–C(8)=C(9) bond angles, the observed values of which are greater than the corresponding values in the B molecule by 1.7, 3.6, 5.5, and 2.6° respectively. The O(3)–C(4)–C(5) bond angle in the B molecule is greater than that in the A molecule by 5.0°. This is also explained by the fact that, while the C(5)=C(6) double bond in the former molecule eclipses the C(4)–O(3) bond, that in the latter is gauche to the C(3)–C(4) and C(4)–C(14) bonds.

Crystal Structure. The molecular arrangement viewed along the b axis is shown in Fig. 2. There are two kinds of hydrogen bonds, O(A3)–H···O(B4) and

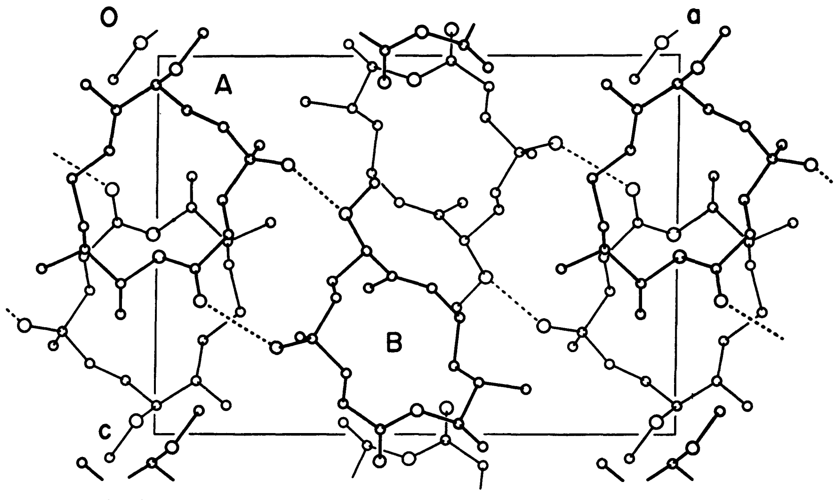

Fig. 2. The molecular arrangement viewed along the b axis.

TABLE 5. THE SYNPERIPLANAR SEGMENTS OF THE C=C–C–X TYPE AND THEIR TORSION ANGLES(ϕ/°)

(1) Molecule A	
C(2)=C(3)–C(4)–O(3)	8.3(7)
C(5)=C(6)–C(7)–O(4)	18.6(6)
C(6)–C(7)–C(8)=C(9)	1.4(7)
(2) Molecule B	
C(2)=C(3)–C(4)–O(3)	2.4(7)
O(3)–C(4)–C(5)=C(6)	−18.3(7)
C(5)=C(6)–C(7)–H(7)	−15(3)
H(7)–C(7)–C(8)=C(9)	9(3)

O(B3)–H···O(A2); their O···O distances are 2.957(5) and 2.867(5) Å respectively. Through these hydrogen bonds, the O(2)–C(1)–C(2)=C(3)–C(4)–O(3)–H(O3) segment in the A molecule and the H(O3)–O(3)–C(4)–C(5)=C(6)–C(7)–O(4) segment in the B molecule are connected to form a fourteen-membered ring; consequently, the two molecules form a hydrogen-bonded dimer oriented nearly in the [101] direction. The macrolide-ring planes of the A and B molecules in the same dimer make an angle of 30° with each other, and incline at angles of 15 and 37° to the (010) plane respectively. The hydrogen-bonded dimers are further held together mainly by the van der Waals interactions.

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