MYCINAMICINS, NEW MACROLIDE ANTIBIOTICS

X. X-RAY CRYSTALLOGRAPHY AND THE ABSOLUTE CONFIGURATION OF MYCINAMICIN IV

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Mycinamicins are 16-membered macrolide antibiotics produced by *Micromonospora griseorubida* sp. nov., and possess strong antibacterial activity against Gram-positive bacteria[1]. On the basis of degradative and spectroscopic experiments[2~4], the structures of mycinamicins were elucidated. Also the X-ray crystal structure of mycinolide IV (**2**), which is an aglycone of mycinamicin IV (**1**), was reported[5]. In the present paper we report the X-ray crystal structure analysis of **1**, thus proving the absolute configuration of the macrolide ring, since the absolute configuration of D-desosamine and D-mycinose have been determined previously[6]. The knowledge of the complete three-dimensional structure of **1** is particularly important in connection with the biosynthesis of mycinamicins and the relationship between molecular structure and biological activity.

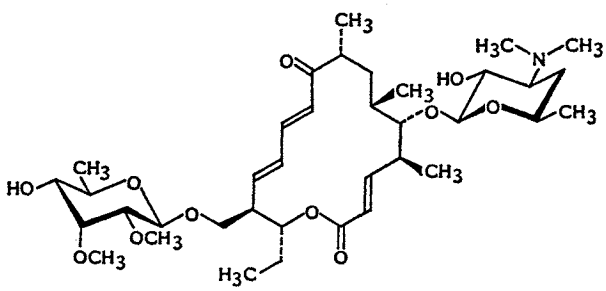
Colorless single crystals of **1** were grown from an acetone solution. Preliminary X-ray photographs indicated unambiguously the space group $P2_12_12$. The sample used for the X-ray experiment had dimensions of about $0.3\times0.4\times0.5$ mm^3. The crystal data are summarized in Table 1. The unit-cell dimensions and diffraction intensities were measured on a Rigaku four-circle diffractometer with graphite-monochromated MoKα radiation (λ=0.71069 Å). The $\omega-2\theta$ scan technique was applied at a 2θ scan rate of 8° minutes^{-1}; the scan width in ω was $(0.9+0.34\tan\theta)°$. The background was measured for 8s at each end of the scan range. 2753 independent reflections ($2\theta\leqq50°$) at the 3σ (F) level were obtained for the structure determination.

In the early stage of the structure determination, various attempts were made to solve the structure with the MULTAN 78 program[7], but all such attempts were unsuccessful. The structure was finally elucidated by the Monte Carlo direct method[8]. The *E*-map revealed the locations of all the 49 non-hydrogen atoms. The structure thus obtained was refined by the block-

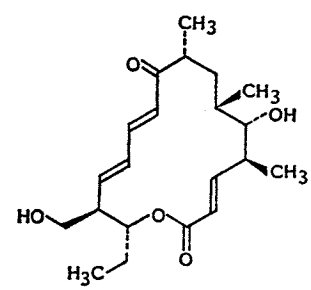
Table 1. Crystal data for mycinamicin IV.

Formula	$C_{37}H_{61}NO_{11}$
MW	695.89
Space group	$P2_12_12$
a	17.895(3) Å
b	38.449(13) Å
c	5.804(1) Å
Z	4
U	3993.3(17) Å^3
D_{calc}	1.157 gcm^{-3}

Fig. 1. Absolute configuration of mycinamicins.



Mycinamicin IV (present study)



Mycinolide IV[5]

Fig. 2. The molecular structure of mycinamicin IV.

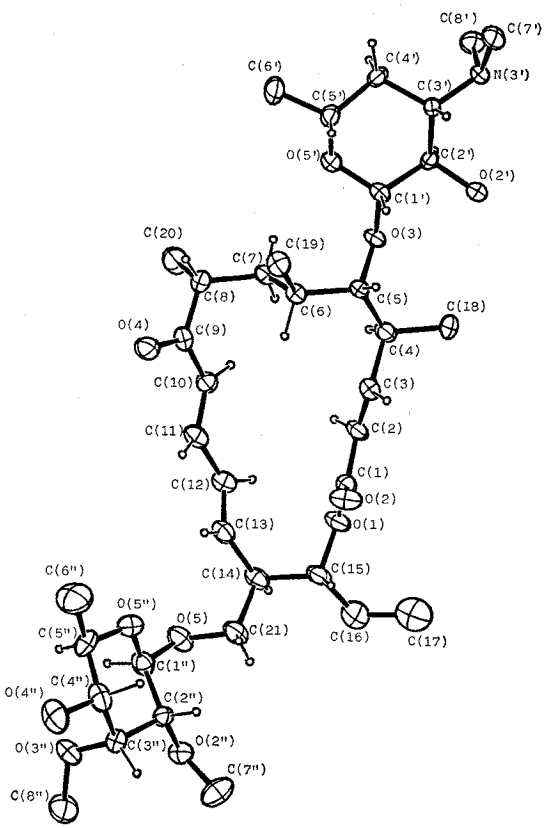
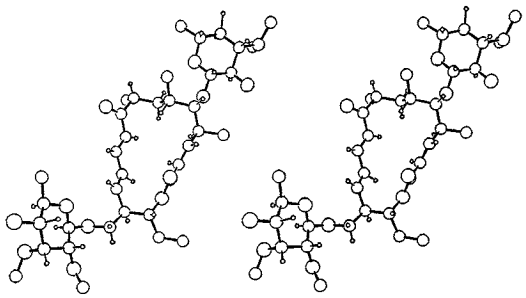


Fig. 3. A stereoscopic drawing of **1**.



diagonal least-squares method with anisotropic temperature factors, using all the 2753 non-zero reflections. 27 hydrogen atoms out of a total of 61 were located and included in the model. The final R-factor was 0.098. The molecular structure and the stereoscopic drawing of **1** are shown in Figs. 2 and 3, respectively.

The conformations of the two 16-membered macrolides, mycinamicin IV (**1**) and mycinolide IV (**2**) as determined in the crystal are compared in terms of the torsion angles of the 16-bonds constituting the macrocyclic lactone ring in Table 2. The lactone ring has a very similar conformation of that found in **2**. The presence of the desosamine and mycinose substituents have therefore little effect on the conformation of the 16-membered lactone ring. Since D-desosamine HCl and methyl β-D-mycinoside were obtained from hydrolysis and methanolysis of **1**[6], the relative stereochemistry obtained from the X-ray crystal structure analysis, permits the absolute configuration at C(4), C(5), C(6), C(8), C(14) and C(15) in the aglycone of **1** to be assigned as are *S*,*S*,*S*,*R*,*R* and *R*, respectively. With the excepting of the C(14) carbon atom, the lactone ring in **1** has the same absolute configuration in the dedesosaminyl derivative of mycinamicin I[9]. Aside from dissimilarities arising between the double bond (-C(2)=C(3)-) in **1** and the hydroxyl bearing single bond (-C(2)(OH)–C(3)-) in tylosin[10,11], the overall conformations and the absolute configurations of the 16-membered lactone rings are very similar in these two compounds.

Table 2. The conformation of the 16-membered ring.

Bond	Torsion angle[a]		
	1(°)	**2**(°)	Δ(°)[b]
O(1)-C(1)-C(2)-C(3)	−176	−177	1
C(1)-C(2)-C(3)-C(4)	175	177	2
C(2)-C(3)-C(4)-C(5)	140	144	4
C(3)-C(4)-C(5)-C(6)	−53	−62	9
C(4)-C(5)-C(6)-C(7)	−74	−69	5
C(5)-C(6)-C(7)-C(8)	177	180	3
C(6)-C(7)-C(8)-C(9)	−61	−56	5
C(7)-C(8)-C(9)-C(10)	−46	−52	6
C(8)-C(9)-C(10)-C(11)	172	169	3
C(9)-C(10)-C(11)-C(12)	−171	−175	4
C(10)-C(11)-C(12)-C(13)	163	163	0
C(11)-C(12)-C(13)-C(14)	−172	−170	2
C(12)-C(13)-C(14)-C(15)	76	94	18
C(13)-C(14)-C(15)-O(1)	−48	−62	14
C(14)-C(15)-O(1)-C(1)	106	112	6
C(15)-O(1)-C(1)-C(2)	−171	−167	4

[a] The angle A-B-C-D is considered positive if the A-B bond has to be rotated clockwise to eclipse the C-D bond when looking from B to C.

[b] Differences between **1** and **2**.

1: Mycinamicin IV (present study), **2**: mycinolide IV[5].

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