CRYSTAL AND MOLECULAR STRUCTURE OF (14*R*)-14-HYDROXY-6-*O*-METHYLERYTHROMYCIN A

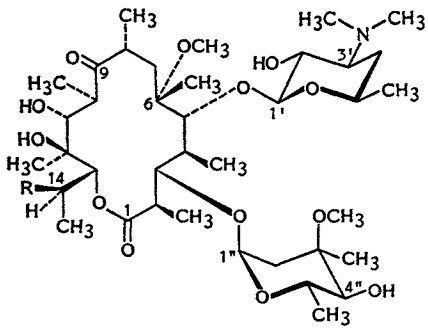
Sir:

In the previous studies[1], we isolated (14*R*)-14-hydroxy-6-*O*-methylerythromycin A (**1**) as an active metabolite from human urine after oral administration of 6-*O*-methylerythromycin A (**2**). The antimicrobial activity of **1** was equal to or 2-fold less than that of **2** *in vitro*, whereas **1** was more effective than **2** against systemic infections in mice[2]. In order to elucidate the structure-activity relationships, we have determined the molecular structure of **1** by the X-ray crystallographic analysis.

The colorless single crystals were grown from acetonitrile - water. The crystal data are summarized in Table 1.

The reflection intensities up to 2θ of 120° were measured by a Rigaku automated four-circle diffractometer with graphite-monochromated CuKα radiation. The 3354 independent reflections with $|Fo|>3\sigma$ (F) were used for the struc-

Fig. 1. Structures of **1** and **2**.



1 R=OH
2 R=H

Table 1. Crystal data of **1**.

Formula	$C_{38}H_{69}NO_{14}\cdot 3H_2O$
MW	818.02
Space group	$P2_12_12_1$
a	19.785(1)
b	25.901(1)
c	8.732(1) Å
Z	4
U	4474.7 Å^3
D_{calcd}	1.21 gcm^{-3}
D_{obsd}	1.20 gcm^{-3}

Table 2. Atomic coordinates ($\times 10^4$) with the esd's in parentheses.

Atom	*X*	*Y*	*Z*	Atom	*X*	*Y*	*Z*
C1	11975 (4)	1234 (3)	3016 (11)	O11	12025 (4)	2039 (3)	−775 (9)
C2	11626 (4)	844 (3)	3968 (10)	O12	11958 (4)	2885 (3)	931 (11)
C3	11180 (4)	500 (3)	2912 (10)	O13	11756 (3)	1720 (2)	3265 (8)
C4	10496 (4)	780 (3)	2507 (11)	O14	12682 (4)	2931 (3)	3478 (11)
C5	10146 (4)	477 (3)	1189 (9)	C1′	9191 (4)	−39 (3)	1946 (10)
C6	10244 (4)	744 (3)	−406 (10)	C2′	8478 (4)	29 (3)	2617 (11)
C7	9829 (5)	1258 (3)	−472 (11)	C3′	8208 (4)	−512 (3)	3044 (11)
C8	9972 (6)	1575 (4)	−1959 (11)	C4′	8184 (5)	−837 (4)	1560 (12)
C9	10645 (6)	1828 (4)	−1999 (11)	C5′	8894 (5)	−875 (3)	919 (12)
C10	10792 (5)	2252 (3)	−797 (13)	C6′	8920 (6)	−1147 (4)	−630 (13)
C11	11425 (5)	2084 (4)	132 (13)	C7′	7383 (7)	−924 (4)	4722 (14)
C12	11602 (5)	2441 (4)	1549 (13)	C8′	6985 (5)	−269 (5)	2972 (15)
C13	12109 (5)	2153 (3)	2600 (13)	N3′	7564 (4)	−444 (3)	3881 (10)
C14	12345 (6)	2470 (4)	4019 (15)	O2′	8504 (3)	331 (2)	3979 (8)
C15	12837 (7)	2174 (4)	4972 (17)	O5′	9160 (3)	−362 (2)	625 (7)
C16	12163 (5)	551 (4)	4887 (13)	C1″	11488 (4)	−386 (3)	3213 (12)
C17	10041 (5)	848 (4)	3953 (11)	C2″	11447 (5)	−819 (4)	4393 (13)
C18	10016 (5)	371 (3)	−1656 (10)	C3″	10885 (5)	−1206 (3)	4124 (12)
C19	9404 (6)	1981 (4)	−2147 (14)	C4″	10918 (5)	−1384 (3)	2411 (12)
C20	10887 (7)	2767 (4)	−1683 (17)	C5″	10829 (5)	−902 (3)	1389 (11)
C21	10986 (6)	2628 (5)	2393 (15)	C6″	10905 (5)	−1049 (4)	−340 (12)
C22	11428 (6)	552 (5)	−1124 (13)	C7″	10994 (7)	−1681 (4)	5209 (14)
O1	12406 (3)	1140 (2)	2104 (9)	C8″	10048 (7)	−772 (5)	5702 (13)
O3	11020 (3)	8 (2)	3599 (7)	O3″	10219 (3)	−995 (3)	4271 (7)
O5	9424 (3)	441 (2)	1435 (7)	O4″	10400 (4)	−1741 (3)	2071 (9)
O6	10931 (3)	900 (2)	−509 (7)	O5″	11390 (3)	−558 (2)	1676 (8)
O9	11073 (4)	1719 (3)	−2941 (9)				

Fig. 2. Molecular structure of **1** with the atomic numbering.

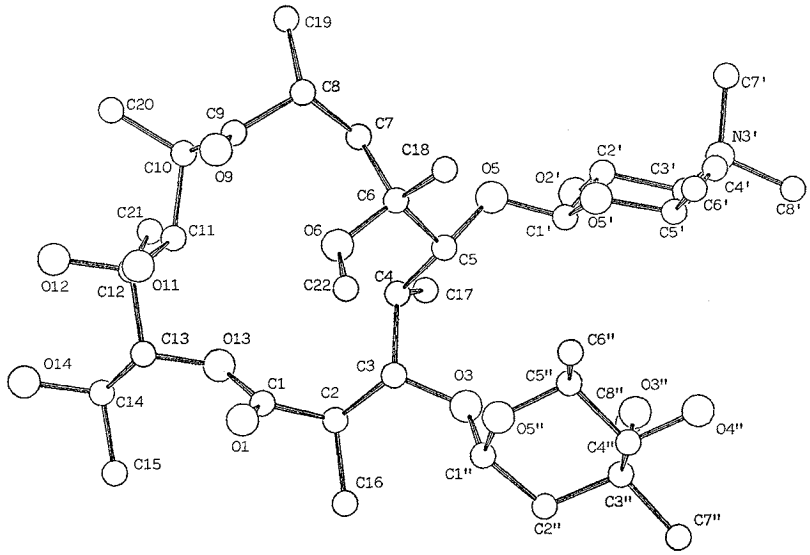


Table 3. Torsion angles of lactone ring (deg).

	1[a]	2[b]	3[c]
O13-C1-C2-C3	112	124	84
C1-C2-C3-C4	−80	−92	−119
C2-C3-C4-C5	168	157	175
C3-C4-C5-C6	−102	−86	−76
C4-C5-C6-C7	−70	−74	−73
C5-C6-C7-C8	173	−177	−172
C6-C7-C8-C9	−73	−74	−65
C7-C8-C9-C10	−64	−67	−70
C8-C9-C10-C11	122	117	107
C9-C10-C11-C12	−173	−172	−171
C10-C11-C12-C13	165	169	176
C11-C12-C13-O13	−68	−71	−73
C12-C13-O13-C1	120	114	154
C13-O13-C1-C2	171	175	−174

[a] (14*R*)-14-Hydroxy-6-*O*-methylerythromycin A.
[b] 6-*O*-Methylerythromycin A in ref 8.
[c] 11,4″-Bis(*O*-(*p*-bromobenzoyl))oleandomycin in ref 11.

ture determination and refinement. The structure was solved by direct methods using MULTAN 78[3]. Block-diagonal least-squares refinement of the positional and anisotropic thermal parameters for the non-hydrogen atoms converged to an R value of 8.9%. The program package and computer system used for the analysis were UNICS III[4] and FACOM M-780, respectively.

Based on the known absolute configurations of the sugar components cladinose and desosamine[5,6], we were able to define the configurations of the asymmetric centers in **1**. The final atomic coordinates are presented in Table 2, and the molecular structure of **1** is shown in Fig. 2.

The *R* configuration at C-14 of **1**, previously elucidated by NMR studies[1], is reaffirmed, and the absolute configruations of the other asymmetric centers in **1** are consistent with those established for erythromycin A[7].

We had previously carried out the X-ray crystallographic analysis of **2**[8]. The three-dimensional structures of **1** and **2** are quite similar. The torsion angles of the aglycone in **1** (Table 3) agree well with those in **2** with C6-C9-C1 region of the molecule, but slightly different with C2-C5 region.

The X-ray crystal structure of various macrolide antibiotics have been studied from the view point of the structure-activity relationships, and several "diamond lattice" conformation models have been proposed for the aglycons of the 14-membered macrolides[9]. The molecular structure of the aglycone in **1** is almost the same as PERUN's model III[10]. OGURA *et al.* proposed conformation model F for an oleandomycin derivative (**3**) from the X-ray crystallographic studies[11]. The torsion angles of the aglycone in **1** (Table 3) are somewhat different from those in **3**, indicating that the conformation of the aglycone may be different in the erythromycin and the oleandomycin derivatives.

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