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EVIDENCE FOR CONFIGURATIONAL IDENTITY BETWEEN LEUCOMYCIN AND TYLOSIN

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Basic 16-membered macrolide antibiotics[1] can be classified, in terms of the carbon skeleton of the aglycone moiety, into two large groups; one is the magnamycin-leucomycin group, such as spiramycin, maridomycin, medicamycin and YL-704 antibiotics etc., and the other is the tylosin-cirramycin group, such as rosamicin, angolamycin and juvenimicin etc. The absolute structures and conformation in the magnamycin-leucomycin group are now defined by powerful X-ray crystallographic and spectrometric analyses[2,3,4]. However, those of the macrolide belonging to tylosin[5,6] group have not been clarified to date. A deep insight as to the configurational model[7] advanced by Celmer for these macrolides deduced that the absolute configuration at each asymmetric center has the same "biosynthetically-expected" chirality. Our attention was called to obtain the evidence for Celmer's suggestion on stereochemical correlation of tylosin and leucomycin having known configuration.

In order to study the absolute configuration and conformation of both aglycone moieties for tylosin (1) and leucomycin-A_3 (2), we attempted to obtain the aglycone moiety of 1 by applying modified Polonovski reaction[8]. Acid hydrolysis of 1 gave mycaminosyl-tylonolide(3) in which mycarose and mycinose moieties are removed from the original antibiotic. Compound 3 was converted to its N-oxide (4) by treatment with m-chloroperbenzoic acid in $CHCl_3$. The N-oxide was refluxed in $CHCl_3$ and acetic anhydride and then hydrolyzed with aqueous sodium bicarbonate. The product was subjected to silica gel column chromatography to isolate aglycone, tylonolide-5,20-hemiacetal (5), mp. 103-105°C, $C_{23}H_{36}O_7$ (M^+=424) which was produced by cleavage between lactone and mycaminose moieties. The CrO_3 oxidation of 5 in pyridine afforded tylonolide-dilactone (6), mp. 186-188°C, $C_{23}H_{34}O_7$ (M^+=422). In a similar manner, aglycone, leuconolide-A_3-5,18-hemiacetal (7) isolated from 2, was oxidized to 9-dehydro-leuconolide-A_3-dilactone (8), mp. 89-91°C, $C_{22}H_{30}O_8$ (M^+=422). The ^{1}H-n.m.r. spectral data of 6 and 8, both chemical shift values and coupling constants for the corresponding protons at 3-, 4-, 5- and 6-positions in

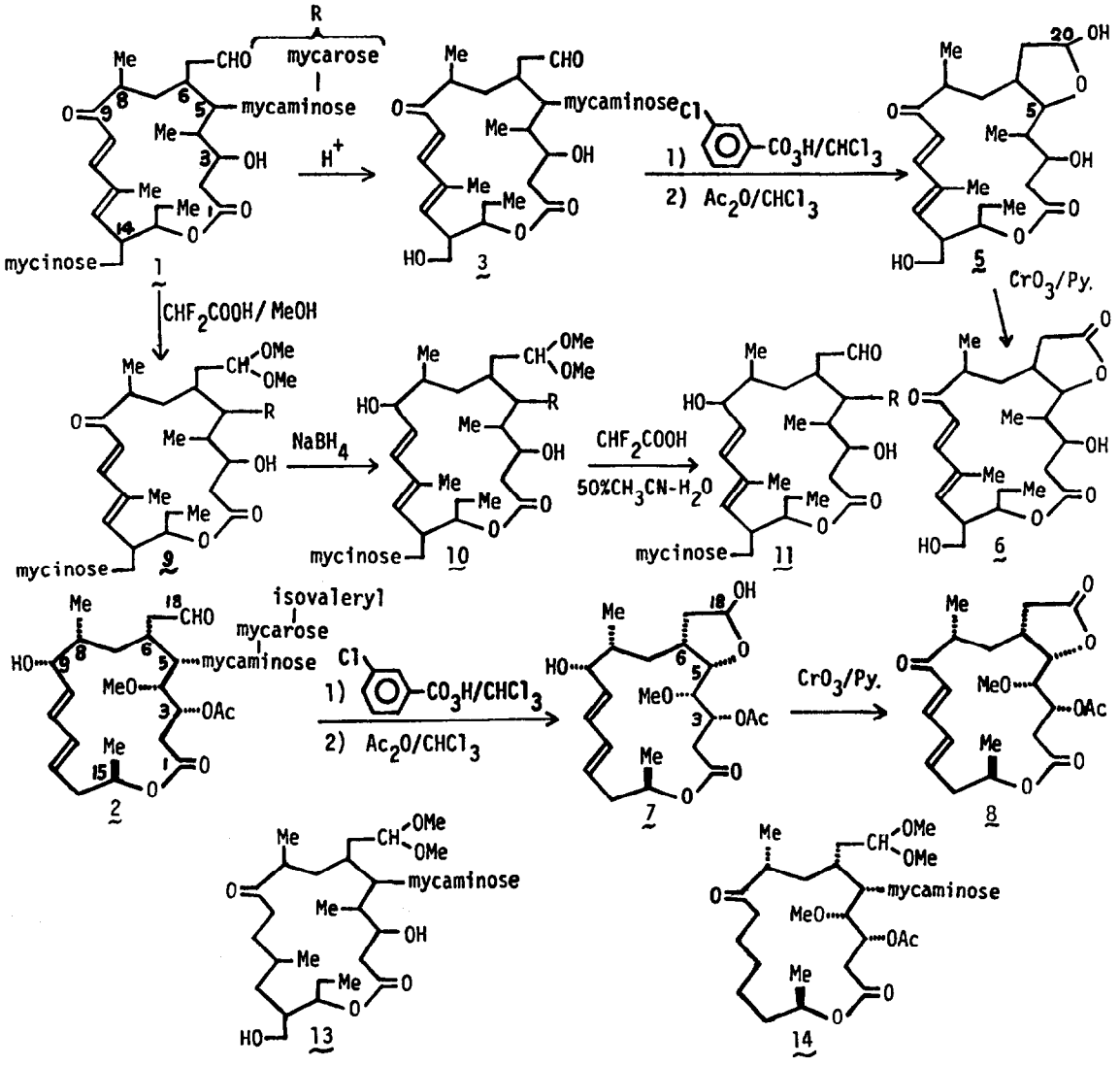


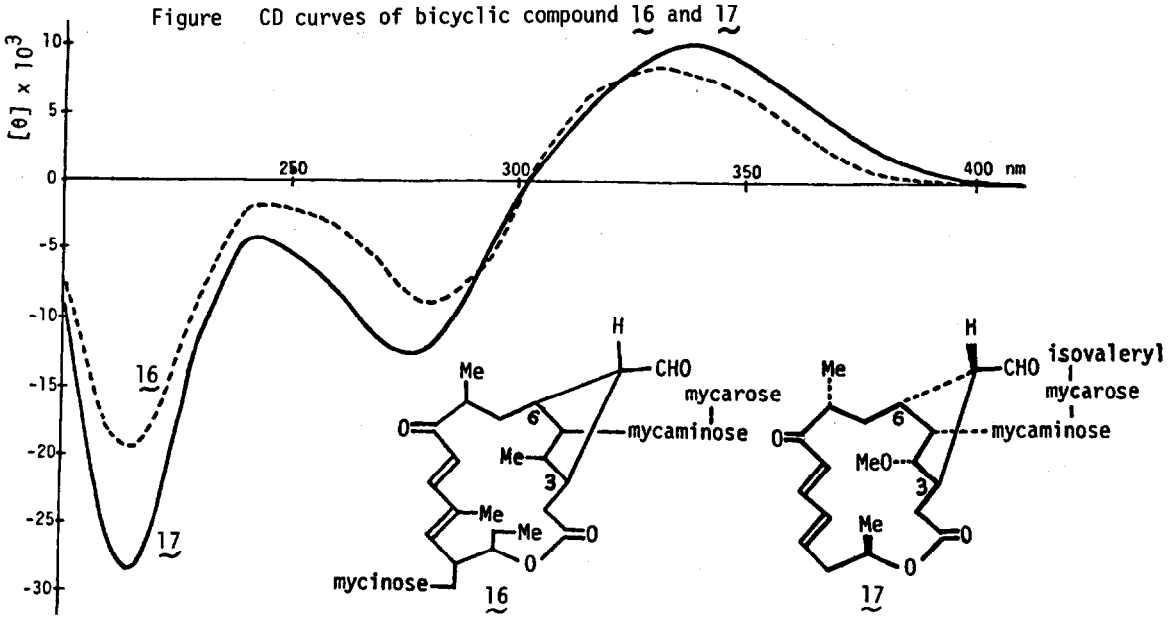
Table Chemical shift values and coupling constants in ^{1}H-n.m.r. spectra (in $CDCl_3$, 100 MHz) of 6 and 8

Protons	6 Chem. shift δ(ppm)	6 Coupling constant (Hz)	8 Chem. shift δ(ppm)	8 Coupling constant (Hz)
C_2 -H	2.0-2.9		2.0-2.9	
C_3 -H	3.57	$J_{2,3}$=11.4 $J_{3,4}$= 0	5.00	$J_{2,3}$=11.1 $J_{3,4}$= 0
C_4 -H	ca 1.6	$J_{4,5}$=10.8	3.23	$J_{4,5}$=9.0
C_5 -H	4.41	$J_{5,6}$=4.2	4.20	$J_{5,6}$=4.8
C_6 -H	ca 2.2		ca2.1	

each aglycone, closely resembled as shown in Table.

Further, the configuration at C-6 on the lactone ring of 1 was determined by CD analysis as following. Treatment of 1 with difluoroacetic acid in MeOH gave tylosin-dimethylacetal (9) in high yield. The $NaBH_4$ reduction of the ketone carbonyl at 9-position in 9 afforded 9-dihydro-tylosin-dimethylacetal (10), which was converted to 9-dihydro-tylosin (11) by treatment with difluoroacetic acid in 50% H_2O-acetonitrile. The CD curve of 11 exhibited a characteristic Cotton effect[9] due to the asymmetric carbon neighbouring to ethyl formyl group linked to the 6-position on the lactone ring at 296 nm ([θ] -620, in EtOH). Therefore, the configuration at C-6 in 1 was decided to be identical with that of 2 (294 nm, [θ] -780, in EtOH). With regard to the configuration at C-8, we attempted to obtain the following tetrahydro compounds from 1 and 2 to examine the Cotton effect of the ketone carbonyl group at C-9 due to asymmetric center at C-8 on the lactone ring. Namely, tetrahydro-mycaminosyl-tylonolide-dimethylacetal (13), mp. 111-113°C, M^+=647, 3.22, 3.27 ppm (s. 2 x OMe), obtained by catalytic reduction of dimethylacetal (12) of 3 over PtO_2 and tetrahydro-demycarosyl-9-dehydro-LM-A_3-dimethylacetal (14), mp. 102-104°C, M^+=647, 3.18, 3.20 ppm (s. 2 x OMe), derived from 2 in a similar manner, were subjected to CD analysis. Compounds, 13 and 14 showed a similar Cotton effect at 282 nm ([θ] +1530 in 13) and 284 nm ([θ] +3900 in 14) in MeOH suggesting that the configuration at C-8 is identical in both compounds.

Figure CD curves of bicyclic compound 16 and 17



The acetate of 1 and 9-dehydro-LM-A_3 (magnamycin-B) (15) obtained by MnO_2 oxidation of 2 was treated with $LiOH \cdot H_2O$ in EtOH to afford the corresponding bicyclic lactone structure[4,10], 3-deoxyl-3,6-bicyclo-tylosin (16), mp. 133-135°C, 9.8 ppm (d. J=3.5 Hz, CHO) and 3-desacetoxyl-3,6-bicyclo-9-dehydro-LM-A_3 (17), mp. 113-115°C, 9.7 ppm (d. J=3.5 Hz, CHO), respectively. This reactivity indicates that the 3-position and the methylene adjacent to the formyl group are in close proximity within the lactone ring. Bicyclic lactone, 17, whose absolute configuration at C-3, -9 and -17 has been derived by X-ray crystallography[4] of 5,9-O-diacetyl-3-desacetoxyl-3,6-bicyclo-leuconolide-A_3, mp. 70-71°C, $C_{24}H_{40}O_8$ (M^+=450), and 16 showed the same Cotton effect due to lactone ester at 215 nm ([θ] -19400 in 16, [θ] -28400 in 17), π-π^* transition due to conjugated diene at 279 nm ([θ] -8940 in 16, [θ] -12260 in 17) and n-π transition (333 nm; [θ] +7890 in 16, 337 nm; [θ] +10270 in 17) as shown in figure. Although these observations cannot be considered complete, they are important in that they strongly suggest the appropriateness of Celmer's suggestion on the configurations between magnamycin-leucomycin group and tylosin group.

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