Structures of Mycinamicins

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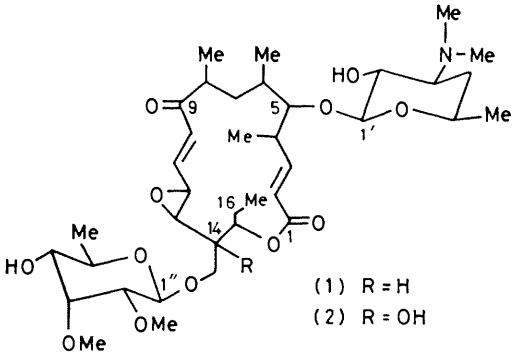
Summary A new family of basic 16-membered macrolide antibiotics with novel skeletons was isolated from *Micromonospora sp* A-11725 and their structures were determined on the basis of physico-chemical properties.

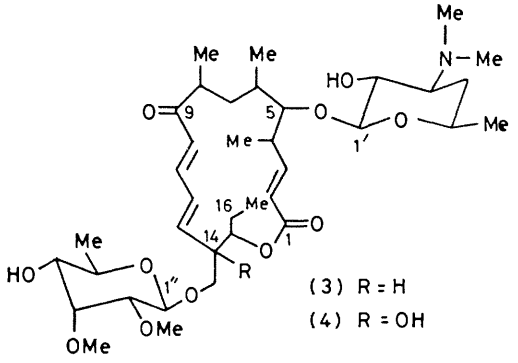
MYCINAMICINS, a new group of macrolide antibiotics, have been obtained from *Micromonospora sp.* A-11725, and named as mycinamicin I (**1**), II (**2**), IV (**3**), and V (**4**),† respectively; they were characterized as in Table 1.

The mass spectral fragmentation pattern of mycinamicin II was very similar to that of mycinamicin I. The molecular ion (*m/z* 727) and the fragment ions containing the aglycone unit (*m/z* 553, 536, and 361) of II appeared at 16 a.m.u. (oxygen atom) higher than the corresponding ions (*m/z* 711, 537, 520, and 345) of I, suggesting that II had an additional oxygen in the aglycone structure. Furthermore, in comparing the ^{1}H n.m.r. spectrum of II with that of I, it became apparent that the splitting pattern

TABLE 1. Physicochemical properties of mycinamicins.

	I	II	IV	V
Formula	$C_{37}H_{61}NO_{12}$	$C_{37}H_{61}NO_{13}$	$C_{37}H_{61}NO_{11}$	$C_{37}H_{61}NO_{12}$
M.p./°C	103—107	102—106	174—176	148—150
$[\alpha]_D^{25}$ (*c*, 1·0, MeOH)	−40·0°	−31·0°	+2·7°	+18·7°
λ_{max}/nm (MeOH)	218	218	215	215
(ϵ)	(23,700)	(23,200)	(20,700)	(20,800)
	240	240	281·5	280
	(sh., 12,900)	(sh., 12,200)	(21,500)	(21,400)
ν_{max}/cm^{-1} (KBr)	3470, 1715, 1685, 1645, 1620	3460, 1715, 1690, 1645, 1620	3460, 1715, 1675, 1645, 1625, 1590	3440, 1710, 1675, 1640, 1595





These data suggested that (**1**) and (**2**) resemble the neutral macrolide, chalcomycin,[1] except in the aminosugar unit. Comparison of the ^{13}C n.m.r. spectra of mycinamicins with those of chalcomycin and tylosin[2] afforded evidence for the presence of an aglycone unit with a novel skeleton in the mycinamicins. The data in Table 2 clearly demonstrate that the ^{13}C n.m.r. spectra of the aglycone part of (**1**) and of chalcomycin were quite similar to each other except for the signals due to C-8, C-16, C-17, and 8-Me in (**1**). The ^{1}H n.m.r. spectra (in CD_3COCD_3) showed similar features for all the compounds [*i.e.*, resonances in the ranges δ 2·28—2·31 (s, NMe_2), 4·29—4·32 (d, *J* 7·3 Hz), 3·49—3·55 (2 × OMe), and 4·57—4·60 (d, *J* 7·8 Hz)]. These ^{1}H and ^{13}C n.m.r. spectra suggested that desosamine and mycinose comprise the sugar units in mycinamicin and accordingly structure (**1**) was proposed for mycinamicin I.

† Formerly named A 11725 I, II, Ia and IIa, respectively.

TABLE 2. ^{13}C n.m.r. chemical shifts for mycinamicin I[a], II[a], IV[a], V[a], chalcomycin (A), and tylosin (B)

	I	II	IV	V	(A)	(B)
C-1	165·7	165·9	166·1	166·3	164·7	173·9
C-2	120·1	120·0	120·9	120·7	120·3	39·4
C-3	151·5	151·9	151·6	151·8	151·0	71·7
C-4	41·9	42·0	41·3	41·3	41·5	45·1
C-5	87·5	87·5	87·9	87·7	87·5	81·6
C-6	34·2	34·4	34·1	34·1	36·7	32·3[b]
C-7	32·1	32·0	32·6	32·7	33·9	32·9[b]
C-8	44·7	44·6	44·9	44·8	78·4	40·3
C-9	200·8	200·8	203·4	203·8	199·4	202·8[c]
C-10	125·6	126·2	123·2	123·8	124·5	118·8
C-11	143·7	143·0	141·7	141·4	145·8	148·0
C-12	59·6[b]	60·4	133·0	130·5	59·4[b]	134·9
C-13	59·0[b]	54·0	141·3	143·5	58·8[b]	142·2
C-14	47·5	73·1	49·2	77·4	49·4	44·7
C-15	72·4	74·2	72·7	75·8	68·5	75·3
C-16	24·7	21·2	25·3	21·4	18·3[c]	25·5
C-17	8·9	10·1	9·6	10·4	—	9·0[d]
4-Me	18·9[c]	19·0[b]	19·4[b]	19·5[b]	19·1[c]	9·6[d]
6-Me	17·1[c]	17·1[b]	17·4[b]	17·4[b]	18·5[c]	—
6-CH_2	—	—	—	—	—	43·9
8-Me	17·5[c]	17·4[b]	17·8[b]	17·6[b]	27·7	17·4[e]
12-Me	—	—	—	—	—	13·0
14-CH_2	67·1	72·6	68·6	75·2	66·7	68·2
CHO	—	—	—	—	—	203·0[e]
C-1′	105·5	105·0	104·9	104·8	—	—
C-2′	70·3	70·3	70·4	70·4	—	—
C-3′	65·8	65·8	65·8	65·8	—	—
C-4′	28·5	28·5	28·3	28·4	—	—
C-5′	69·4	69·4	69·5	69·4	—	—
C-6′	21·1	21·2	21·2	21·2	—	—
NMe_2	40·1	40·2	40·2	40·2	—	—
C-1″	100·9	101·2	101·0	101·6	100·5	101·1
C-2″	81·9	81·9	81·9	81·7	81·6	82·0
C-3″	79·3	79·3	79·9	79·2	79·4	79·9
C-4″	72·7	72·6	72·7	72·5	72·5	72·9
C-5″	70·6	70·7	70·5	70·7	70·4	70·6
C-6″	17·8[c]	17·7[b]	17·8[b]	17·6[b]	17·7[b]	17·8[e]
2″-OMe	59·0	59·3	59·7	59·1	58·5	59·6
3″-OMe	61·6	61·6	61·7	61·7	61·4	61·7

[a] ^{13}C n.m.r. spectra were recorded in $CDCl_3$ solution on a JEOL FX-100 Fourier transform spectrometer. Chemical shifts are given in p.p.m. with respect to Me_4Si as internal standard. [b–e] Assignments within any vertical column may be reversed.

(dd) at δ 5·42 (H-15) in II was different from the splitting pattern (ddd) at δ 5·37 (H-15) in I. These facts indicated that II had an additional hydroxy group in the aglycone unit. In the ^{13}C n.m.r. spectrum of II, a downfield shift of C-14 (47·5 → 73·1 p.p.m.) was observed. Therefore, this additional hydroxy group was finally determined to be located at position 14 [structure (**2**)].

In order to investigate the structural relationships of mycinamicin I and II to IV and V, we studied their de-epoxidation ($CrCl_2$–acetic acid)[3]. Reaction products from I (**1**) and II (**2**) are completely identical with natural mycinamicin IV (**3**) and V (**4**) in all respects. Details of these isolation[4] and structural[5] studies will be published elsewhere.

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