MYCINAMICINS, NEW MACROLIDE ANTIBIOTICS. VII STRUCTURES OF MINOR COMPONENTS, MYCINAMICIN VI AND VII

MITSUO HAYASHI, KENJI KINOSHITA, YASUHIRO SUDATE, SHUZO SATOI, HIDEO SAKAKIBARA

Research Center, Toyo Jozo Co., Ltd., Ohito, Shizuoka, 410-23, Japan

KEN-ICHI HARADA and MAKOTO SUZUKI

Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya, 468, Japan

(Received for publication September 30, 1982)

The mycinamicins are a new family of basic 16-membered macrolide antibiotics with novel skeletons[1,2]. During the isolation and purification of mycinamicins I (**1**), II (**2**), III (**3**), IV (**4**), and V (**5**) from the culture filtrate of *Micromonospora griseorubida* sp. nov., we have discovered two new minor components designated mycinamicin VI (**6**) and VII (**7**). Compounds **6** and **7** like **1**~**5**[3] possess strong antibacterial activity against Gram-positive bacteria. In this paper, the structural characterizations of **6** and **7** are presented.

The mycinamicin complex was separated by repeated chromatography on silica gel to give two new minor components, **6** and **7**. The physicochemical data of **6** and **7** are shown in Table 1.

Mycinamicin VI (**6**) was crystallized from hexane and acetone to afford colorless prisms. The composition of **6** was established by the elemental analysis and the high resolution mass spectrum [M^+, m/z 667.3924, Calcd. for $C_{35}H_{57}NO_{11}$: 667.3929]. The UV spectrum suggested the presence of an α,β-unsaturated lactone (215 nm) and an $\alpha,\beta,\gamma,\delta$-unsaturated ketone (281.5 nm). The IR spectrum showed also the presence of hydroxyl (3400 cm^{-1}), α,β-unsaturated lactone (1710, 1650 cm^{-1}) and $\alpha,\beta,\gamma,\delta$-unsaturated ketone (1670, 1625, 1590 cm^{-1}) functions. These data were very similar to those for structures **3** and **4**[3].

The chemical ionization (CI) mass spectrum of **6** was also closely similar to those of **3** and **4** using isobutane as the reagent gas (Fig. 1). The diagnostic ions indicated the presence of desosamine[4] (m/z 158, 174 and 176) and the same aglycone part as **3** or **4** (m/z 347 and 365). However, the protonated molecule ion (m/z 668) and the ion derived from neutral sugar (m/z 147) in the CI mass spectrum of **6** appeared at 14 u. or 28 u. lower than the corresponding ions of **3** (m/z 682 and 161) or **4** (m/z 696 and 175). In the ^1H NMR spectrum of **6** (Fig. 2), the signals of six olefinic (7.04 ppm, dd, J=10.0, 15.0 Hz,

Table 1. Physicochemical properties of **6** and **7**.

	6	**7**
Formula	$C_{35}H_{57}NO_{11}$	$C_{29}H_{47}NO_7$
Mp (°C)	198~200	243~245
$[\alpha]_D^{22}$	+13.5° (*c* 0.5, MeOH)	+50.1° (*c* 0.5, DMSO)
CIMS m/z	668 (MH^+), 522, 365, 347, 331,	522 (MH^+), 365, 347, 329,
(isobutane)	176, 174, 158, 147 (Fig. 1)	176, 174, 158
UV λ_{max}^{MeOH} nm (log ε)	215 (4.31), 281.5 (4.33)	215 (4.29), 281 (4.32)
IR ν_{max}^{KBr} cm^{-1}	3400, 1710, 1670, 1650, 1625, 1590	3510, 3400, 1710, 1670, 1650, 1625, 1595
^1H NMR δ	2.28 (6H, s, $N(CH_3)_2$)	—
(CD_3COCD_3)	4.29 (1H, d, J=7.0 Hz, H-1′)	2.28 (6H, s, $N(CH_3)_2$)
	4.55 (1H, d, J=8.0 Hz, H-1″)	4.29 (1H, d, J=7.5 Hz, H-1′)
	4.92 (1H, m, H-15)	4.93 (1H ddd, J=3.0, 9.0, 10.0 Hz, H-15)
	(Fig. 2)	
Elemental analysis (%)		
Found (Calcd.) C:	62.68 (62.95)	66.67 (66.77)
H:	8.78 (8.60)	9.31 (9.08)
N:	1.94 (2.10)	2.72 (2.68)

Fig. 1. CI mass spectra of **3**, **4** and **6**.

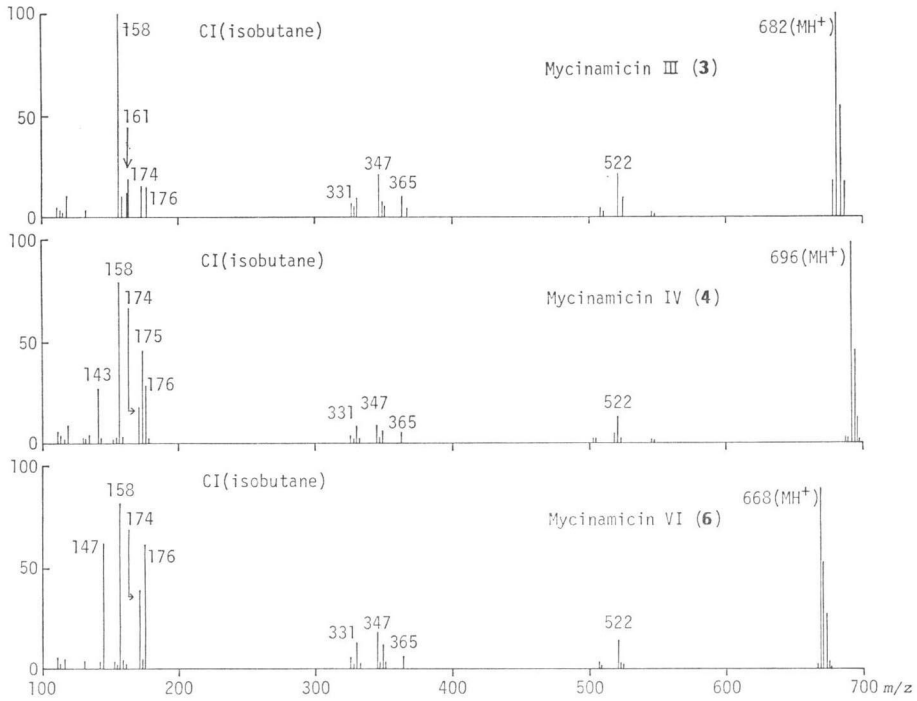
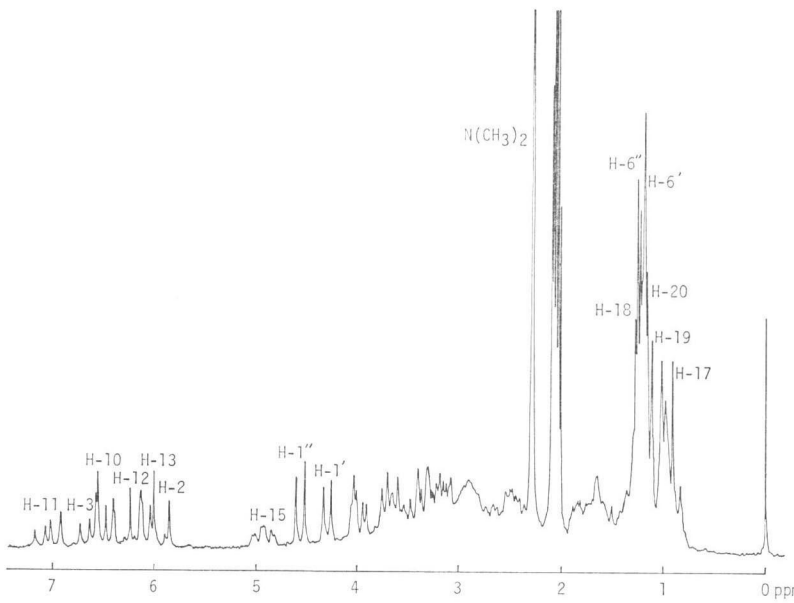


Fig. 2. ^{1}H NMR spectrum of mycinamicin VI (**6**) in CD_3COCD_3.



H-11; 6.60 ppm, dd, J=10.0, 15.5 Hz, H-3; 6.47 ppm, d, J=15.0 Hz, H-10; 6.27 ppm, dd, J=10.0, 15.0 Hz, H-12; 6.01 ppm, dd, J=8.5, 15.0 Hz, H-13; 5.92 ppm, d, J=15.5 Hz, H-2), two anomeric (4.55 ppm, d, J=8.0 Hz, H-1″; 4.29 ppm, d, J=7.0 Hz, H-1′), one *N*-dimethyl (2.28 ppm, s) and six *C*-methyl (1.23 ppm, d, J=6.5 Hz, H-18; 1.22 ppm, d, J=6.0 Hz, H-6″; 1.19 ppm, d, J=

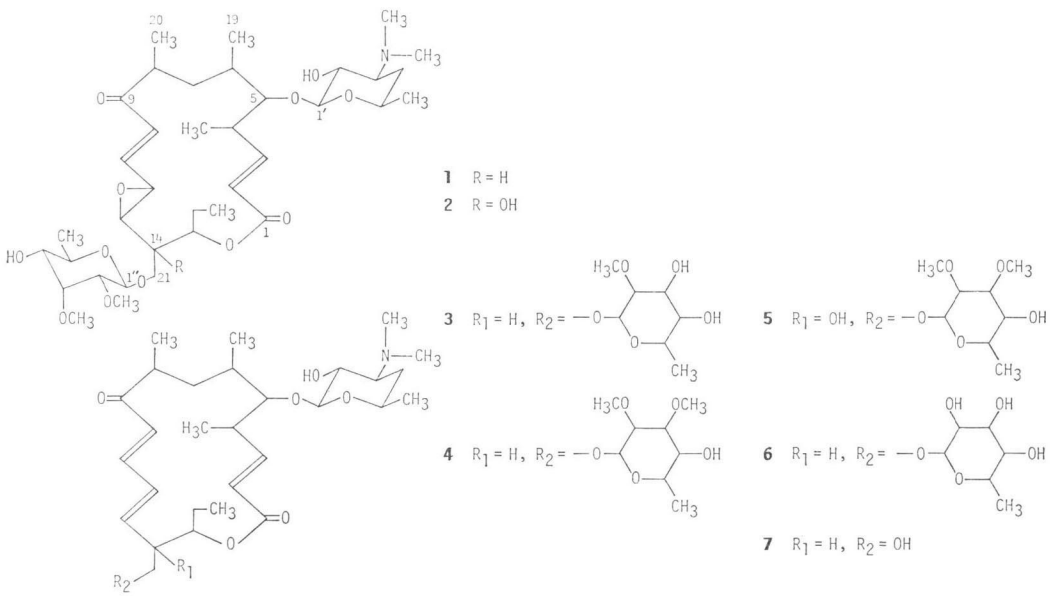
Table 2. ^{13}C NMR chemical shifts for **3**, **4** and **6**.

Carbon	3	4	6	Carbon	3	4	6
1	166.1	166.1	166.3	1′	104.9	104.9	104.9
2	120.9	120.9	120.9	2′	70.4	70.4	70.5
3	151.7	151.6	152.0	3′	65.8	65.8	65.8
4	41.3	41.3	41.4	4′	28.4	28.3	28.4
5	87.8	87.9	87.8	5′	69.5	69.5	69.5
6	34.1	34.1	34.2	6′	21.1	21.2	21.2
7	32.6	32.6	32.7	$N(CH_3)_2$	40.2	40.2	40.3
8	44.9	44.9	44.8	1″	100.8	101.0	101.0
9	203.7	203.4	203.9	2″	80.1	81.9	71.4
10	123.2	123.2	123.4	3″	69.8	79.9	70.2*
11	141.8	141.7	141.9	4″	72.8	72.7	72.9
12	133.0	133.0	133.3	5″	69.8	70.5	70.7*
13	141.3	141.3	141.1	6″	17.7	17.8	17.8
14	49.2	49.2	49.3	$2''OCH_3$	59.4	59.7	—
15	73.7	73.7	73.7	$3''OCH_3$	—	61.7	—
16	25.2	25.3	25.4				
17	9.7	9.6	9.7				
18	19.4	19.4	19.5				
19	17.4	17.4	17.5				
20	17.7	17.8	17.8				
21	68.7	68.6	68.8				

^{13}C NMR spectra were recorded with a JEOL FX-100 spectrometer at 25.0 MHz in $CDCl_3$. Chemical shifts are given in ppm relative to Me_4Si as internal standard.

* Assignments may be reversed.

Fig. 3. Chemical structures of mycinamicins.



6.0 Hz, H-6′; 1.15 ppm, d, J=7.0 Hz, H-20; 0.99 ppm, d, J=6.5 Hz, H-19; 0.91 ppm, t, J=7.5 Hz, H-17) protons were observed, but the signals of the two *O*-methyl groups which are characteristic for the mycinose moiety of **4** were not recognized.

The ^{13}C NMR data of **6** are summarized in Table 2 together with those of **3** and **4**, and these data are very similar to each other except for the second sugar moiety. The important difference between **6** and **4** is the absence of two *O*-methyl groups at C-2″ and C-3″ in the former. The lack of the two *O*-methyl groups resulted in the up-field shifts for C-2″ (81.9→71.4 ppm) and C-3″ (79.9→70.2 ppm). From these results, the chemical structure for **6** is proposed as shown in Fig. 3.

Mycinamicin VII (**7**) crystallized from hexane and acetone as colorless needles. The UV and IR spectra of **7** were very similar to those of **4**. The CI mass spectrum showed predominantly the protonated molecule ion (MH^+) at m/z 522 using isobutane or ammonia as reagent gas. However, the diagnostic ion (m/z 175) for the mycinose moiety could not be detected at all. In addition, the characteristic signals for two *O*-methyl groups and one anomeric proton derived from the mycinose moiety observed in the ^1H NMR spectrum of **4** were not recognized in that of **7**. The above data suggested that **7** is 21-demycinosyl-mycinamicin IV. This compound was identical in all respects with 21-demycinosyl-mycinamicin IV which was isolated on acid hydrolysis of mycinamicin IV (**4**)[5].

References

1) HAYASHI, M.; M. OHNO & S. SATOI: Structures of mycinamicins. J. Chem. Soc., Chem. Commun. 1980: 119～121, 1980
2) HAYASHI, M.; M. OHNO, S. KATSUMATA, S. SATOI, K. I. HARADA, M. TAKEDA & M. SUZUKI: Mycinamicins, new macrolide antibiotics. IV. Structure of mycinamicin III. J. Antibiotics 34: 276～281, 1981
3) SATOI, S.; N. MUTO, M. HAYASHI, T. FUJII & M. OTANI: Mycinamicins, new macrolide antibiotics. I. Taxonomy, production, isolation, characterization and properties. J. Antibiotics 33: 364～376, 1980
4) SUZUKI, M.; K. I. HARADA, N. TAKEDA & A TATEMATSU: Chemical ionization mass spectra of new macrolide antibiotics, M-4365 A_2 and G_2. Heterocycles 8: 199～205, 1977
5) HAYASHI, M.; M. OHNO, K. KINOSHITA, S. SATOI, M. SUZUKI & K. I. HARADA: Mycinamicins, new macrolide antibiotics. III. Isolation and structures of mycinamicin aglycones, mycinolide IV and V. J. Antibiotics 34: 346～349, 1981