Communications to the Editor

ALDECALMYCIN, A NEW ANTIMICROBIAL ANTIBIOTIC FROM *STREPTOMYCES*

Sir:

In the course of our screening from soil microorganisms for antibiotics, we have isolated a new antibiotic, aldecalmycin (**1**) from a culture broth of streptomycete. **1** shows antimicrobial activities against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). In this communication, we report the production, isolation, physico-chemical and biological properties of **1**.

The producing microorganism was isolated from a soil sample collected at Setagaya-ku, Tokyo, Japan, which was classified as *Streptomyces*. A well-grown agar slant of the strain MJ147-72F6 was used to inoculate sixteen 500-ml Erlenmeyer flasks containing 110-ml of seed medium composed of galactose 2.0%, dextrin 2.0%, Bacto-soytone 1.0%, corn steep liquor 0.5%, $(NH_4)_2SO_4$ 0.2% and $CaCO_3$ 0.2% (pH 7.4 before sterilization). The culture was incubated for 3 days at 27°C on a rotary shaker. Four hundred ml of this seed culture were transferred to four 20-liter jar fermenters each containing 12 liters of production medium consisting of glucose 2.0%, meat extract 3.0%, $(NH_4)_2SO_4$ 0.6%, $MgSO_4$ 0.3%, K_2HPO_4 0.6%, $CaCO_3$ 0.2% and Pronal 502 (Toho Chemical Industry) as an antifoaming reagent. The fermentation was continued for 3 days at 27°C with agitation at a rate of 200 rpm and aeration of 12 liters per minute.

The isolation of aldecalmycin is shown in Fig. 1 which was carried out using a silica gel column, Sephadex LH-20 column, preperative TLC, reverse phase HPLC and centrifugal partition chromatography. The antibiotic activity was monitored by bioassay using *Bacillus stearothermophilus*.

Physico-chemical properties of aldecalmycin (**1**) are summarized in Table 1. **1** was obtained as a white powder. The molecular formula of **1** was determined as $C_{33}H_{54}O_9$ by HRFAB-MS and elemental analysis. **1** shows characteristic UV absorption at 304 nm ($E^{1\%}_{1cm}$, 395) in alkaline MeOH as shown in Fig. 2. The substance gave positive color reactions to 2,4-dinitrophenylhydrazine and molybdophosphoric acid-sulfuric acid reagents, and negative to ninhydrin and Rydon-Smith reagents. The structure of aldecalmycin (**1**) (Fig. 3) was determined by NMR spectral analysis of its derivative **2** because the NMR spectra of **1** were complicated by a presence of aldehyde group. The ^1H and ^{13}C NMR data of **2** are shown in Table 2. Aldecalmycin (**1**) is related to lydicamycin[1] on its bicyclic ring system. Details of the structure determination of **1** and **2** will be reported later.

Table 1. Physico-chemical properties of aldecalmycin (**1**) and its derivative **2**.

	1	**2**
Appearance	White powder	White powder
Molecular formula	$C_{33}H_{54}O_9$	$C_{35}H_{58}O_{10}$
Elemental analysis		
Calcd:	C 65.64, H 9.18, O 25.18 (as $C_{33}H_{54}O_9 \cdot \frac{1}{2}H_2O$)	
Found:	C 65.48, H 9.29, O 25.47	
FAB-MS (*m/z*, $(M-H)^-$)	593	637
HRFAB-MS (*m/z*)		
Calcd:	593.3689 (as $C_{33}H_{53}O_9$)	637.3952 (as $C_{35}H_{57}O_{10}$)
Found:	593.3687 $(M-H)^-$	637.3935 $(M-H)^-$
UV λ_{max} nm ($E^{1\%}_{1cm}$)		
in MeOH	272 (30), 299 (31)	End absorption
in HCl-MeOH	271 (24), 303 (sh, 13)	
in NaOH-MeOH	304 (395)	
IR ν_{max} (KBr) cm^{-1}	3430, 2960, 2910, 1694, 1626, 1456, 1379, 1074, 1038, 995	3440, 2960, 2910, 1698, 1636, 1456, 1379, 1134, 1076, 1019
TLC (Rf value)[a]	0.39	0.46

[a] Silica gel TLC (Merck Art. No. 5715) $CHCl_3$-MeOH (20:3).

Fig. 1. Isolation and purification of aldecalmycin.

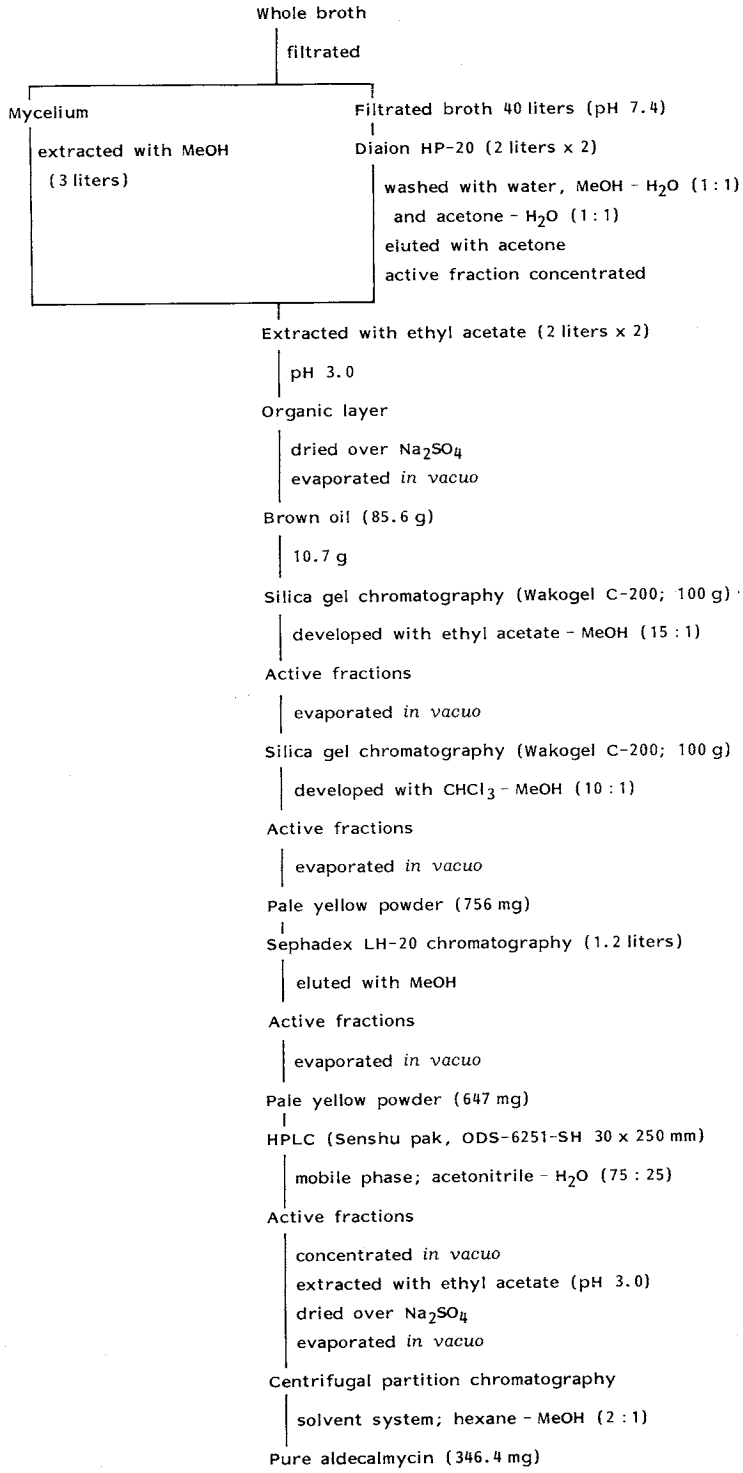

Fig. 2. The UV spectrum of aldecalmycin (**1**).

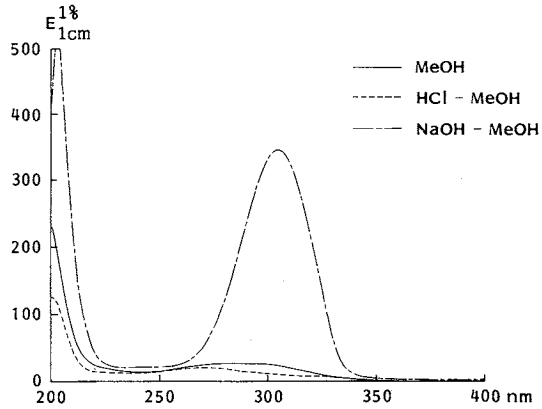

Fig. 3. The structure of aldecalmycin (**1**) and its derivative **2**.

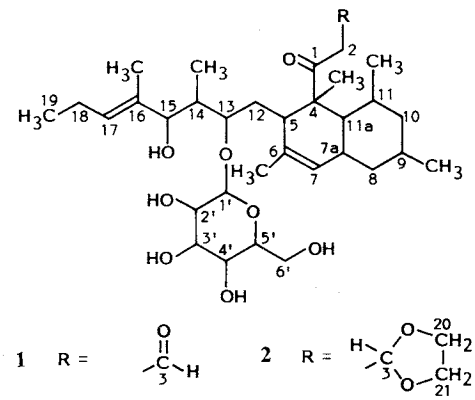

Table 2. ^{13}C NMR data (100 MHz) and ^{1}H NMR data (400 MHz) of the aldecalmycin derivative **2** in CD_3OD-C_6D_6 (10:1).

Position	^{13}C	^{1}H	Position	^{13}C	^{1}H
16-Me	10.5	1.61	4	52.8	
14-Me	10.6	0.66	6′	62.4	3.88, 4.04
19	14.3	0.92	20[a]	65.5	~3.8, ~3.9
4-Me	17.5	1.25	21[a]	65.7	~3.8, ~3.9
18	21.6	1.99	4′	71.6	3.51
6-Me	22.6	1.76	2′	75.1	3.25
9-Me	22.7	0.85	5′	77.3	3.3[b]
11-Me	24.1	0.63	3′	78.1	3.45
12	32.3	1.21, 1.84	13	78.1	3.52
9	34.5	1.54	15	80.2	3.83
11	38.0	1.33	1′	101.7	4.33
14	40.9	2.03	3	102.0	5.28
7a	42.4	1.68	7	124.4	5.01
8	43.6	0.84, 1.74	17	131.1	5.29
5	45.1	2.27	16	136.0	
2	45.6	3.22, 3.37	6	137.1	
11a	46.1	1.68	1	214.7	
10	47.5	0.91, 1.59			

Chemical shifts in ppm from TMS as an internal standard.

[a] These values may be interchanged.

[b] It is overlapped by solvent signal.

Table 3. The antimicrobial activities of aldecalmycin.

Test organism	MIC (μg/ml)	Test organism	MIC (μg/ml)
Staphylococcus aureus FDA 209P	6.25	*Corynebacterium bovis* 1810	12.5
S. aureus Smith	12.5	*Escherichia coli* NIHJ	>100
S. aureus MS9610	6.25	*E. coli* K-12	>100
S. aureus No. 5 (MRSA)	12.5	*Shigella dysenteriae* JS11910	>100
S. aureus No. 17 (MRSA)	12.5	*Salmonella typhi* T-63	>100
Micrococcus luteus FDA 16	12.5	*Proteus vulgaris* OX19	>100
M. luteus IFO 3333	12.5	*Serratia marcescens*	>100
M. luteus PCI 1001	50	*Pseudomonas aeruginosa* A3	>50
Bacillus anthracis	6.25	*P. aeruginosa* GN315	100
B. subtilis NRRL B-558	6.25	*Klebsiella pneumoniae* PCI 602	>100
B. subtilis PCI 219	6.25	*Mycobacterium smegmatis* ATCC 607	100
B. cereus ATCC 10702	6.25	*Candida albicans* 3147	100

Biological properties of aldecalmycin (**1**) are shown in Table 3. **1** shows the antimicrobial activities against Gram-positive bacteria including MRSA. The MICs of **1** against Gram-positive bacteria are 6.25~25 μg/ml. The acute toxicity of **1** (LD_{50} in mice) was 100 mg/kg with iv administration.

Ryuichi Sawa
Yoshikazu Takahashi
Sakiko Itoh
Kazuo Shimanaka
Naoko Matsuda
Masa Hamada
Tsutomu Sawa
Hiroshi Naganawa
Tomio Takeuchi

Institute of Microbial Chemistry,
3-14-23 Kamiosaki, Shinagawa-ku,
Tokyo 141, Japan

(Received September 20, 1991)

Reference

1) Hayakawa, Y.; N. Kanamaru, N. Morisaki, K. Furihata & H. Seto: Lydicamycin, a new antibiotic of a novel skeletal type II. Physico-chemical properties and structure elucidation. J. Antibiotics 44: 288~292, 1991