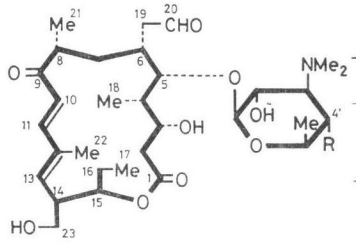
SYNTHESIS OF 4′-DEOXYMYCAMINOSYL TYLONOLIDE

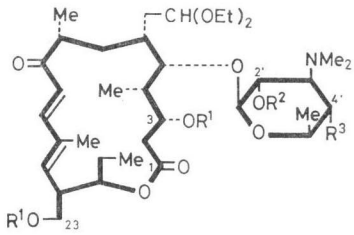
Sir:

Mycaminosyl tylonolide[1] (**1**) easily obtained by acidic hydrolysis of tylosin[2], a typical 16-membered macrolide antibiotic, has fairly strong antibacterial activity in spite of its relatively simple structure. An important characteristic of mycaminosyl tylonolide (**1**) is that the compound has an antibacterial activity, though it is weak, against *Escherichia coli* NIHJ for which the parent antibiotic tylosin has no activity. In order to study the role of the 4′-hydroxyl group of **1** in the antibacterial activity, the titled compound was prepared.

Selective acetylation of the hydroxyl groups on the sugar portion was successful by treatment of mycaminosyl tylonolide diethylacetal[3] (**2**) in acetonitrile with acetic anhydride in the absence of an external base[4], giving 2′,4′-di-*O*-acetyl mycaminosyl tylonolide diethylacetal (**3**) (98%), $[\alpha]_D^{25}+34°$ (*c* 1, chloroform). The structure was confirmed by the ^1H NMR spectrum. Tetrahydrofuranylation of **3** in dichloromethane with 2,3-dihydrofuran in the presence of pyridinium *p*-toluenesulfonate[5] gave the 3,23-bis(*O*-tetrahydrofuranyl) derivative (**4**) (quantitative). Re-



	R
1	OH
9	H



	R^1	R^2	R^3
2	H	H	OH
3	H	Ac	OAc
4	~THF	Ac	OAc
5	~THF	H	OH
6	~THF	H	$OSO_2CH_2C_6H_5$
7	~THF	H	I
8	~THF	H	H

Table 1. The ^{13}C NMR[a] chemical shifts[b] of **9** and **1** in $CDCl_3$ (at 20°C).

Carbon	**9**[c]	**1**[d]	Carbon	**9**[c]	**1**[d]
1	173.87	173.85	16	25.58	25.52
2	39.70	39.54	17	8.80	8.98
3	67.47	67.8 (br)	18	9.71	9.68
4	47.28	47.14	19	43.92	43.75
5	81.33	81.15	20	203.37	203.02
6	31.74	31.96	21	17.50	17.35
7	32.68	32.75	22	13.11	13.06
8	41.01	40.42	23	62.45	62.73
9	203.50	203.61	1′	104.31	104.03
10	118.69	118.72	2′	70.47	70.90
11	148.01	148.14	3′	65.75	70.16
12	135.87	135.65	4′	28.73	70.90
13	141.85	142.10	5′	69.59	73.32
14	44.95	44.61	6′	21.11	17.81
15	75.02	75.10	NMe_2	40.32	41.68

a) Measured at 62.9 MHz with a Bruker WM250 spectrometer.
b) In ppm downfield from TMS.
c) Assignments were confirmed by off-resonance technique.
d) Shift assignments were based, in part, on the shift-values of tylosin reported[6].

Table 2. Antibacterial spectra of **9** and **1**.

Test organisms*	Minimum inhibitory concentration (mcg/ml)			Test organisms*	Minimum inhibitory concentration (mcg/ml)		
	9	**1**	Tylosin		**9**	**1**	Tylosin
Staph. aureus 193	3.12	6.25	0.78	*E. coli* K-12 ML-1629	25	>100	>100
Staph. aureus EMf**	>100	>100	6.25	*E. coli* K-12 ML-1410	25	>100	>100
Staph. aureus 209P	0.78	3.12	0.78	*E. coli* K-12 ML-1410 R81	25	>100	>100
Staph. aureus MS 9610	>100	>100	>100	*E. coli* K-12 LA 290 R55	12.5	50	>100
Staph. aureus MS 9351	>100	>100	>100	*Kl. pneumoniae* PCI 602	1.56	3.12	25
Staph. aureus MS 9861	6.25	12.5	6.25	*Sh. dysenteriae* JS 11910	0.39	0.78	12.5
Staph. aureus MS 10225	3.12	12.5	3.12	*Sal. enteritidis* 1891	0.78	1.56	25
Staph. aureus MS 10246	>100	>100	>100	*Sal. typhi* T-63	50	100	>100
Micr. luteus PCI 1001	0.2	0.2	<0.2	*Enter. aerogenes* ATCC 13048 (MS-1)	>100	>100	>100
B. subtilis NRRL B-558	3.12	12.5	0.78	*Providencia* sp Pv 16	>100	>100	>100
Coryn. bovis 1810	3.12	25	0.2	*Serratia marcescens*	>100	>100	>100
E. coli NIHJ	6.25	12.5	100	*Proteus vulgaris* OX-19	12.5	50	>100
E. coli K-12	25	100	>100	*Ps. aeruginosa* A3	50	100	>100
E. coli K-12 R-5	25	100	>100				

* Agar dilution streak method (nutrient agar, 37°C, 17 hours)
** Erythromycin-resistant strain

moval of the acetyl groups of **4** by dissolving it in methanol (50°C, overnight) gave the corresponding 2′,4′-diol (**5**) (88%); *Anal.* Found (Calcd. for $C_{43}H_{73}NO_{13}$): C, 63.78 (63.60); H, 9.01 (9.06); N, 1.69 (1.72)%. Selective sulfonylation of the 4′-hydroxyl group of **5** was successful only when **5** was treated with benzylsulfonyl chloride (1.5 mole equivalents for **5**) in pyridine (−40°C, 4 hours) to give 4′-*O*-benzylsulfonyl derivative (**6**). The compound was unstable; however, when immediately reacted with sodium iodide (1.5 mole equivalents for **5**) in methyl ethyl ketone (80°C, 15 minutes), the 4′-iodo derivative (**7**) was obtained. Reductive deiodination of **7** with tri(*n*-butyl)stannane in benzene in the presence of 2.2′-azobis(isobutyronitrile) (80°C, 2 hours) gave, after purification, the 4′-deoxy derivative (**8**) (75% from **5**); *Anal.* Found (Calcd. for $C_{43}H_{73}NO_{12}$): C, 64.99 (64.88); H, 8.95 (9.24); N, 1.52 (1.76)%. Hydrolysis of **8** in 0.1 M aqueous hydrochloric acid-acetonitrile (2.5: 1 v/v) (25°C, 30 minutes) gave the desired 4′-deoxymycaminosyl tylonolide (**9**) (80% after purification), $[\alpha]_D^{25}$ −12° (*c* 1.2, chloroform), UV λ_{Max}^{MeOH} 282.5 nm (log ε 4.32); $Rf_{compound\ 1}$ 1.4 (Wakogel B-5, with chloroform - methanol, 6: 1). The structure was confirmed by the ^{13}C NMR spectrum (Table 1). *Anal.* Found (Calcd. for $C_{31}H_{51}NO_9$): C, 63.73 (64.00); H, 8.81 (8.84); N, 2.21 (2.41)%.

The antibacterial spectrum of **9** in comparison with that of **1** and tylosin (Table 2) shows that **9** has enhanced antibacterial activities against the strains tested. It is noteworthy that **9** inhibits the growth of *E. coli*, although the activity is still weak. This result shows that the deoxygenation of the 4′-hydroxyl group greatly enhances the activity of the parent antibiotic (**1**).

AKIHIRO TANAKA
TSUTOMU TSUCHIYA
SUMIO UMEZAWA

Institute of Bioorganic Chemistry,
1614 Ida, Nakahara-ku, Kawasaki 211,
Japan

HAMAO UMEZAWA

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

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