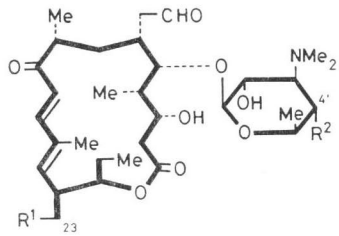
SYNTHESES OF DERIVATIVES OF 4′-DEOXYMYCAMINOSYL TYLONOLIDE AND MYCAMINOSYL TYLONOLIDE MODIFIED AT C-23

Sir:

In the foregoing communication[1] we reported the synthesis of 4′-deoxymycaminosyl tylonolide (**1a**) which showed fairly strong antibacterial activity. This paper describes the syntheses of derivatives of **1a** and of mycaminosyl tylonolide (**1b**) modified at C-23.

Treatment of the diethylacetal (**2a**) of **1a** with acetic anhydride in acetonitrile as described previously[1] gave the 2′-*O*-acetyl derivative (**3**) (93%), m.p. 187~190°C, $[\alpha]_D^{23}$ +28° (*c* 1, chloroform). Acylation of **3** with acetyl chloride, propanoyl chloride, *n*- or isobutanoyl chloride and benzoyl chloride in pyridine (−20°C, ≃1 hour) followed by treatment of the acyl derivatives with methanol (50°C, overnight[1]) to remove the 2′-*O*-acetyl group, gave 23-*O*-acetyl (**4**), 23-*O*-propanoyl (**5**), 23-*O*-*n*-butanoyl (**6**), 23-*O*-isobutanoyl (**7**) and 23-*O*-benzoyl (**8**) derivatives in higher than 90% yields (after purification) in all cases; the values of $[\alpha]_D^{19}$ (*c* 1, chloroform) were: **4**, +10°; **5**, +13°; **6**, +13°; **7**, +17°; **8**, +11°. The acylated positions (the 23-hydroxyl group) were confirmed, in their ^{1}H NMR spectra (**4**~**8**), by the appearance of two proton signals assignable to 23-CH_2O-acyl at δ 4.2~4.4 (*cf.* the shift values of H-3 and -23 of 3,23-di-*O*-acetylmycaminosyl tylonolide diethylacetal[2]). Deacetalation of the acyl derivatives with 0.1 M aqueous hydrochloric acid in acetonitrile (3: 2 v/v, 25°C, 1 hour) gave the desired 23-*O*-acetyl- (**9a**, m.p. 106~108°C, $[\alpha]_D^{19}$ −12° (*c*, 1, chloroform)), 23-*O*-propanoyl- (**10a**, −6°), 23-*O*-*n*-butanoyl- (**11a**, −9°), 23-*O*-isobutanoyl- (**12a**, −6°) and 23-*O*-benzoyl-4′-deoxymycaminosyl tylonolides (**13a**, −19°) in higher than 90% yields (after purification). As the reference compounds, 23-*O*-acetyl- (**9b**), 23-*O*-propanoyl- (**10b**), 23-*O*-*n*-butanoyl- (**11b**), 23-*O*-isobutanoyl- (**12b**) and 23-*O*-benzoyl-mycaminosyl tylonolides (**13b**) were also prepared similarly from mycaminosyl tylonolide diethylacetal[2] (**2b**) by way of 2′,4′-*O*-acetylation, selective 23-*O*-acylation, de(2′,4′-di-*O*-acetyl)ation and deacetalation.

C-23-halo derivatives of **1a** were next prepared. Treatment of **2a** with triphenylphosphine and carbon tetrachloride (molar ratio of 1: 2.2: 1.1)



	R^1	R^2		R^1	R^2
1a	OH	H	**13b**	$OCOC_6H_5$	OH
1b	OH	OH	**17a**	Cl	H
9a	OAc	H	**17b**	Cl	OH
9b	OAc	OH	**18a**	Br	H
10a	$OCOCH_2CH_3$	H	**18b**	Br	OH
10b	$OCOCH_2CH_3$	OH	**19a**	I	H
11a	$OCO(CH_2)_2CH_3$	H	**19b**	I	OH
11b	$OCO(CH_2)_2CH_3$	OH	**21a**	O~THF	H
12a	$OCOCH(CH_3)_2$	H	**21b**	O~THF	OH
12b	$OCOCH(CH_3)_2$	OH	**22a**	O~THP	H
13a	$OCOC_6H_5$	H	**22b**	O~THP	OH

THF: Tetrahydrofuran
THP: Tetrahydropyran

in pyridine under nitrogen (room temperature, 20 hours) according to the method of ANISUZZAMAN and WHISTLER[3] gave 23-chloro-23,4′-dideoxymycaminosyl tylonolide diethylacetal (**14a**) (99%), m.p. 164~167°C, $[\alpha]_D^{23}$ +12° (*c* 1, chloroform); Found (Calcd. for $C_{35}H_{60}NO_9Cl$): C, 62.19 (62.34); H, 8.71 (8.97); N, 2.32 (2.08); Cl, 5.16 (5.26)%. The structure was confirmed by the ^{1}H NMR spectrum of the 3-*O*-acetyl derivative of **14a** (H-3: δ 5.17; H-3′; δ 2.47, dt, *J* 11.5×2 and 4 Hz). Similarly, 23-bromo-23-deoxy (**15a**) (95%) and 23-deoxy-23-iodo (**16a**) (87%) derivatives of **2a** were prepared by treating **2a** with triphenylphosphine and carbon tetrabromide (room temperature, 1 hour) or triphenylphosphine and carbon tetraiodide (room temperature, 1 hour); **15a**: $[\alpha]_D^{23}$ +31° (*c* 1, chloroform), **16a**: $[\alpha]_D^{23}$ +78° (*c* 1, chloroform); Found (Calcd. for $C_{35}H_{60}NO_9I$): C, 54.88 (54.90); H, 7.75 (7.90); N, 1.77 (1.83); I, 16.28 (16.57%). Deacetalation of the halo derivatives gave the corresponding 23-chloro-23,4′-dideoxy- [**17a**, $[\alpha]_D^{25}$ −8° (*c* 1, chloroform)], 23-bromo-23,4′-dideoxy- (**18a**, +11°), and 23,4′-dideoxy-23-iodo-mycaminosyl tylonolides (**19a**, +56°), in high yields. As the reference compounds, 23-chloro-23-deoxy- (**17b**), 23-bromo-23-deoxy- (**18b**) and 23-deoxy-

Table 1. Antibacterial spectra of

Test organisms*	1a	9a	9b	10a	10b	11a	11b	12a	12b
Staph. aureus 193	3.12	0.78	0.78	0.39	0.78	0.39	0.78	0.2	0.78
〃 EMf	>100	>100	>100	>100	>100	>100	>100	>100	>100
〃 209P	0.78	0.2	0.39	0.2	0.39	0.39	0.39	0.39	0.39
〃 MS 9610	>100	>100	>100	>100	>100	>100	>100	>100	>100
〃 MS 9351	>100	>100	>100	>100	>100	>100	>100	>100	>100
〃 MS 9861	6.25	1.56	1.56	3.12	1.56	1.56	1.56	0.39	1.56
〃 MS 10225	3.12	0.78	0.78	0.2	0.78	0.39	0.78	0.39	0.78
〃 MS 10246	>100	>100	>100	>100	>100	>100	>100	>100	>100
Micr. luteus PCI 1001	0.2	<0.2	0.2	<0.2	0.2	<0.2	0.2	<0.2	0.2
B. subtilis NRRL B-558	3.12	0.39	0.39	<0.2	0.39	<0.2	1.56	<0.2	0.39
Coryn. bovis 1810	3.12	0.39	3.12	<0.2	0.78	<0.2	0.78	<0.2	0.78
E. coli NIHJ	6.25	6.25	12.5	6.25	25	12.5	100	12.5	50
〃 K-12	25	25	>100	25	>100	25	>100	25	>100
〃 K-12 R-5	25	25	100	25	100	25	100	25	100
〃 K-12 ML-1629	25	25	>100	25	>100	25	>100	50	>100
〃 K-12 ML-1410	25	25	100	25	100	25	100	25	100
〃 K-12 ML-1410 R81	25	25	100	25	100	25	100	25	100
〃 K-12 LA 290 R55	12.5	6.25	25	3.12	25	6.25	25	6.25	25
Kl. pneumoniae PCI 602	1.56	6.25	3.12	1.56	3.12	1.56	6.25	3.12	3.12
Sh. dysenteriae JS 11910	0.39	0.78	1.56	0.2	1.56	0.39	1.56	0.78	1.56
Sal. enteritidis 1891	0.78	1.56	3.12	0.78	12.5	0.78	12.5	6.25	3.12
Sal. typhi T-63	50	50	100	50	100	50	100	50	100
Enter. aerogenes ATCC 13048 (MS-1)	>100	>100	>100	100	>100	>100	>100	>100	>100
Providencia sp Pv 16	>100	>100	>100	>100	>100	>100	>100	>100	>100
Serratia marcescens	>100	100	>100	50	>100	>100	>100	50	>100
Proteus vulgaris OX-19	12.5	12.5	50	6.25	50	6.25	50	12.5	50
Ps. aeruginosa A3	50	100	100	100	100	100	100	100	100
Mean MIC** (mcg/ml)	15.7	10.4	19.8	7.09	20.3	8.49	23.1	8.94	19.8

* Agar dilution streak method (nutrient agar, 37°C, 17 hours)

** Index value being taken as 0 for <0.2, 2 for 0.39, . . . , 10 for 100, and 11 for >10; see. Ref. 5. Mean

23-iodo-mycaminosyl tylonolides (**19b**) were prepared from the diethyl acetal of mycaminosyl tylonolide (**2b**) *via* the corresponding 23-halo-23-deoxy-mycaminosyl tylonolide diethylacetals (chloro: **14b**, bromo: **15b** and iodo: **16b**); **16b**: $[\alpha]_D^{25}+67°$ (*c* 1, chloroform); Found (Calcd. for $C_{35}H_{60}NO_{10}I$): C, 53.52 (53.77); H, 7.49 (7.74); N, 1.90 (1.79); I, 16.38 (16.23)%.

C-23-acetal derivatives of **1a** were further prepared. Selective acetylation of **1a** as previously described (Ac_2O/acetonitrile) gave the 2′-*O*-acetyl derivative (**20**) (94%) having the aldehyde group free. Selective 23-*O*-tetrahydrofuranylation or tetrahydropyranylation of **20** with dihydrofuran (2 mole equiv. for **1a**) or 3,4-dihydro-2*H*-pyran (2 mole equiv. for **1a**) in dichloromethane in the presence of pyridinium *p*-toluenesulfonate[4] (room temperature, 26 hours), followed by de(2′-*O*-acetyl)ation by treating the derivatives with methanol (50°C, 6 hours) gave 23-*O*-tetrahydrofuranyl- (**21a**) and 23-*O*-tetrahydropyranyl-4′-deoxymycaminosyl tylonolides (**22a**) in yields of 74 and 70%, respectively; **21a**: $[\alpha]_D^{19}$ −25° (*c* 1, chloroform); Found (Calcd. for $C_{35}H_{57}NO_{10}$): C, 64.42 (64.49); H, 8.75 (8.81); N, 2.14 (2.15)%. **22a**: $[\alpha]_D^{19}$ −17° (*c* 1, chloroform); Found (Calcd. for $C_{36}H_{59}NO_{10}$): C, 64.92 (64.94); H, 8.85 (8.93); N, 2.14 (2.10%). The structures were confirmed by the ^{13}C NMR spectra.

As reference compounds, 23-*O*-tetrahydro-

the products (mcg/ml).

13a	17a	17b	18a	18b	19a	19b	21a	21b	22a	22b
0.2	1.56	1.56	0.78	0.78	0.78	0.78	0.78	0.78	0.78	0.39
50	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
<0.2	0.78	1.56	0.39	0.39	0.2	0.2	<0.2	<0.2	<0.2	<0.2
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
1.56	3.12	3.12	0.78	0.78	0.39	0.39	0.78	0.78	1.56	1.56
0.39	1.56	1.56	0.78	0.78	0.39	0.39	0.78	0.78	0.78	0.78
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
<0.2	0.2	0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2
<0.2	0.2	0.39	<0.2	0.2	<0.2	0.2	0.2	0.2	0.78	0.78
<0.2	0.2	3.12	0.2	0.78	0.39	0.78	0.39	0.39	<0.2	0.2
25	6.25	25	6.25	12.5	3.12	12.5	12.5	25	25	50
25	25	100	25	100	25	100	50	>100	50	>100
25	25	100	25	100	50	100	25	100	25	100
25	25	100	50	>100	25	>100	50	100	50	100
25	25	>100	50	100	25	100	50	>100	50	>100
25	25	>100	50	100	25	100	50	100	50	100
6.25	6.25	50	25	50	12.5	50	12.5	100	50	100
6.25	1.56	3.12	1.56	1.56	1.56	0.78	1.56	3.12	1.56	3.12
0.78	0.39	0.78	0.39	0.39	0.39	0.78	0.39	0.78	0.39	0.78
1.56	0.78	1.56	0.78	0.39	0.78	0.78	1.56	1.56	1.56	3.12
50	25	>100	25	>100	25	>100	100	>100	100	>100
>100	>100	>100	100	>100	100	>100	>100	>100	>100	>100
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
50	12.5	>100	12.5	>100	25	>100	100	>100	100	>100
6.25	6.25	50	12.5	50	12.5	50	25	50	25	50
100	100	100	>100	100	>100	100	100	100	100	100
8.06	9.17	23.1	8.94	15.3	7.86	14.6	11.0	17.0	12.2	18.3

MIC of **1b**[1] was 34.8, and that of **13b** was 15.3.

furanyl- (**21b**) and 23-*O*-tetrahydropyranyl-mycaminosyl tylonolides (**22b**) were also prepared from mycaminosyl tylonolide (**1b**) by a similar synthetic pathway.

The antibacterial spectra of the compounds prepared are shown in Table 1. The results show that the C-23-modifications described here generally gave rise to compounds more active than the parent compounds (**1a** and **1b**) in terms of their antibacterial activity, and it is clearly shown that the 4′-deoxy compounds are always superior to the corresponding 4′-hydroxyl compounds. Among those prepared, prominent compounds in terms of the antibacterial activity are **10a**, **11a**, **13a**, and **19a**, as shown by mean MIC[5] in Table 1.

Akihiro Tanaka
Tsutomu Tsuchiya
Sumio Umezawa

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

Masa Hamada
Hamao Umezawa

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

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