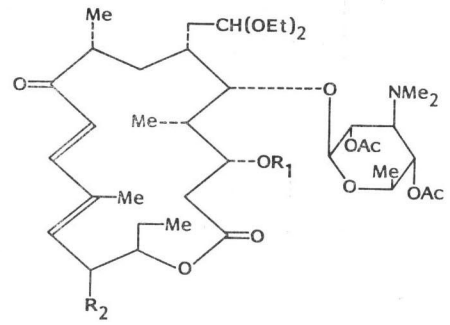
SYNTHESES OF 23-*C*-SUBSTITUTED DERIVATIVES OF MYCAMINOSYL TYLONOLIDE

Sir:

In previous papers[1~4] we have reported the syntheses of several types of active derivatives of mycaminosyl tylonolide (MT) and other related compounds which have various substituents at the C-23. This communication describes another kind of derivation at the C-23 of MT, that is, 23-*C*-alkylation or -arylation. 2′,4′-Di-*O*-acetylmycaminosyl tylonolide diethyl acetal (**1**)[5] was treated with *t*-butylchlorodimethylsilane in the presence of imidazole in DMF at 75°C, overnight. The resulting 3,23-bis(*O*-*tert*-butyldimethylsilyl) derivative (**2**) obtained in 75% yield, $[\alpha]_D^{22}$ −11° (*c* 1, $CHCl_3$), was treated with NBu_4F in oxolane (1 mol equivalent, room temperature, 1 hour) to give the 3-*O*-silyl derivative (**3**) (95%), $[\alpha]_D^{22}$ −10° (*c* 1, $CHCl_3$). Oxidation of **3** with DMSO-benzene (1:1) in the presence of pyridinium trifluoroacetate and dicyclohexylcarbodiimide gave the corresponding 23-aldehyde (**4**) (86%): $[\alpha]_D^{22}$ −40° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.67 (1H d, 23-H). Treatment of **4** with MeMgBr in oxolane (−78°C, 1.5 hours, then room temperature, 1 hour) gave the (23*S*)-23-*C*-methyl (**5a**) and (23*R*)-23-*C*-methyl (**5b**) derivatives in 36 and 10% yields. **5a**: $[\alpha]_D^{21}$ −10° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.12 (d, 24-CH_3). **5b**: $[\alpha]_D^{21}$ +11° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.22 (d, 24-CH_3). Compounds **5a** and **5b** were deacetylated (in MeOH, 50°C, overnight), and deblocked with 0.5 M HCl in CH_3CN (37°C, overnight) to give the final products, **6a** (74%): $[\alpha]_D^{22}$ −10° (*c* 1, $CHCl_3$) and **6b** (78%): $[\alpha]_D^{22}$ +16° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): **6a**: δ 1.15 (24-CH_3), **6b**: δ 1.24 (24-CH_3). Absolute configurations at C-23 of these products were determined[6] by the nuclear Overhauser effect difference spectroscopy. Irradiation of **6a** at the δ 1.15 (24-CH_3) caused pronounced positive signal enhancements of 13-H and 14-H, whereas irradiation of **6b** at the δ 1.24 (24-CH_3) caused similar enhancements of 13-H and 15-H. These results led to the conclusion[6], from the stereochemical requirements, that the absolute configurations at C-23 in **6a** and **6b** should be specified L and D, respectively as shown in Fischer projection (see Fig. 2).

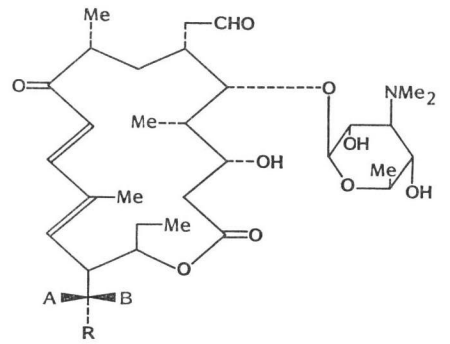
Fig. 1.



1	R_1=H	R_2=CH_2OH
2	R_1=$SiMe_2(^tBu)$	R_2=$CH_2OSiMe_2(^tBu)$
3	R_1=$SiMe_2(^tBu)$	R_2=CH_2OH
4	R_1=$SiMe_2(^tBu)$	R_2=CHO
5a	R_1=$SiMe_2(^tBu)$	R_2=(*S*)CH(OH)Me
5b	R_1=$SiMe_2(^tBu)$	R_2=(*R*)CH(OH)Me

^{t}Bu: *tert*-Butyl.

Fig. 2.



	a.c.*	A	B	R
6a	*S*	OH	H	Me
6b	*R*	H	OH	Me
7a	*S*	OH	H	Et
7b	*R*	H	OH	Et
8a	*S*	OH	H	Bu
8b	*R*	H	OH	Bu
9a	*R*	OH	H	C_6H_5
9b	*S*	H	OH	C_6H_5
10a	*S*	OH	H	$CH_2CH=CH_2$
10b	*R*	H	OH	$CH_2CH=CH_2$
11a	*S*	OH	H	$CH=CH_2$
11b	*R*	H	OH	$CH=CH_2$
12a	*R*	OH	H	C≡CH
12b	*S*	H	OH	C≡CH

* Absolute configuration at C-23 by CAHN-INGOLD-PRELOG specifications.

Table 1. Antibacterial activity (MIC, μg/ml) of derivatives of mycaminosyl tylonolide (MT).

Test organisms	MT	**6a**	**6b**	**7a**	**7b**	**8a**	**8b**
Staphylococcus aureus 193	1.56	1.56	0.78	0.39	0.39	<0.2	<0.2
S. aureus EMf	50	>100	>100	>100	100	25	50
S. aureus 209P	1.56	0.78	0.39	0.39	0.39	<0.2	<0.2
S. aureus MS 9610	>100	>100	>100	>100	>100	>100	>100
S. aureus MS 9351	>100	>100	>100	>100	>100	>100	>100
S. aureus MS 9861	1.56	1.56	0.78	0.78	0.78	0.39	0.39
S. aureus MS 10225	3.12	3.12	1.56	1.56	0.78	0.39	0.78
S. aureus MS 10246	>100	>100	>100	>100	>100	>100	>100
S. aureus Smith	1.56	1.56	1.56	0.78	0.78	0.39	0.39
Micrococcus luteus PCI 1001	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2
Bacillus subtilis NRRL B-558	3.12	0.78	0.78	0.78	0.39	0.39	<0.2
Corynebacterium bovis 1810	3.12	3.12	0.78	3.12	0.78	<0.2	<0.2
Escherichia coli NIHJ	12.5	6.25	3.12	3.12	3.12	6.25	3.12
E. coli K-12	25	25	12.5	12.5	12.5	25	12.5
E. coli K-12 R-5	50	50	25	25	12.5	25	12.5
E. coli K-12 ML 1629	100	>100	100	100	100	100	50
E. coli K-12 ML 1410	>100	>100	100	100	100	100	50
E. coli K-12 ML 1410 R81	100	>100	100	100	100	100	100
E. coli K-12 LA290 R55	100	50	50	50	50	25	25
Klebsiella pneumoniae PCI 602	3.12	3.12	3.12	12.5	6.25	3.12	6.25
Shigella dysenteriae JS 11910	1.56	0.78	0.78	1.56	1.56	0.78	0.78
Salmonella enteritidis 1891	3.12	3.12	3.12	3.12	3.12	3.12	3.12
S. typhi T-63	100	100	50	100	50	50	50
Enterobacter aerogenes ATCC 13048	100	100	100	100	100	100	50
Providencia sp. Pv 16	>100	>100	>100	>100	>100	>100	100
Serratia marcescens	50	25	12.5	50	50	50	12.5
Proteus vulgaris OX-19	50	50	25	50	50	25	25
Pseudomonas aeruginosa A3	25	12.5	12.5	6.25	6.25	50	6.25
Geometrical mean	17.25	15.62	10.78	12.50	10.26	8.03	6.12

LD_{50} (mice, iv; mg/kg): MT; 220, **6a**; 110, **6b**; 280, **7a**; 60.

Table 1. (Continued)

Test organisms	9a	9b	10a	10b	11a	11b	12a	12b
Staphylococcus aureus 193	0.39	0.2	<0.2	<0.2	<0.2	0.39	1.56	0.78
S. aureus EMf	>100	50	>100	100	>100	100	>100	>100
S. aureus 209P	0.78	<0.2	0.39	<0.2	<0.2	<0.2	1.56	0.78
S. aureus MS 9610	>100	>100	>100	>100	>100	>100	>100	>100
S. aureus MS 9351	>100	>100	>100	>100	>100	>100	>100	>100
S. aureus MS 9861	0.78	0.39	0.39	0.39	0.39	0.39	1.56	1.56
S. aureus MS 10225	1.56	0.39	0.78	0.39	0.39	0.39	3.12	3.12
S. aureus MS 10246	>100	>100	>100	>100	>100	>100	>100	>100
S. aureus Smith	0.78	0.39	0.39	<0.2	0.39	0.78	1.56	1.56
Micrococcus luteus PCI 1001	<0.2	<0.2	<0.2	<0.2	0.2	<0.2	<0.2	<0.2
Bacillus subtilis NRRL B-558	1.56	0.39	0.78	0.39	0.39	0.39	3.12	3.12
Corynebacterium bovis 1810	0.78	<0.2	0.39	<0.2	0.78	<0.2	6.25	3.12
Escherichia coli NIHJ	25	3.12	1.56	3.12	1.56	1.56	6.25	6.25
E. coli K-12	50	6.25	12.5	6.25	12.5	6.25	50	25
E. coli K-12 R-5	100	12.5	12.5	12.5	12.5	6.25	50	25
E. coli K-12 ML 1629	>100	50	100	50	100	50	>100	100
E. coli K-12 ML 1410	>100	50	100	100	100	50	>100	100
E. coli K-12 ML 1410 R81	>100	50	100	100	100	50	>100	100
E. coli K-12 LA290 R55	100	12.5	25	12.5	25	12.5	100	50
Klebsiella pneumoniae PCI 602	3.12	3.12	3.12	3.12	1.56	3.12	6.25	3.12
Shigella dysenteriae JS 11910	1.56	0.78	0.78	0.78	0.78	0.78	1.56	0.78
Salmonella enteritidis 1891	6.25	3.12	1.56	3.12	3.12	3.12	3.12	3.12
S. typhi T-63	>100	50	50	50	50	25	100	50
Enterobacter aerogenes ATCC 13048	>100	50	50	50	100	50	>100	100
Providencia sp. Pv 16	>100	100	>100	>100	>100	>100	>100	>100
Serratia marcescens	50	12.5	25	12.5	50	12.5	25	12.5
Proteus vulgaris OX-19	100	25	12.5	25	50	12.5	100	50
Pseudomonas aeruginosa A3	50	3.12	6.25	6.25	25	12.5	12.5	6.25
Geometrical mean	18.58	5.68	7.63	5.97	8.43	5.96	20.01	13.47

Other 23-*C*-substituted analogs (**7a,b**~**12a,b**) were prepared similarly by treatment of **4** with ethyl-, butyl-, phenyl-, allyl-, vinyl-, and ethynylmagnesium bromide, followed by deblocking. The faster-moving products on column chromatography (they are shown by attachment of "**a**" to the numbers) had, in all compounds including **6a**, small $J_{14,23}$ values (2~3 Hz) in their ^{1}H NMR spectra, and the slower-moving ones (shown by "**b**" after the numbers) including **6b**, larger $J_{14,23}$ values (5.5~6.8 Hz). The faster- and the slower-moving products were, therefore, concluded to have the same spatial arrangement with those of **6a** and **6b**, respectively. **7a**: $[\alpha]_D^{22}$ −6°, **7b**: +9°, **8a**: +7°, **8b**: +30°, **9a**: +81°, **9b**: +30°, **10a**: +40°, **10b**: −10°, **11a**: −3°, **11b**: 0°, **12a**: +65°, **12b**: −39°, all measured at *c* 1 in $CHCl_3$. The structures of these compounds were confirmed by the elemental analysis.

Antibacterial spectra (Table 1) of these products were diversified, but the slower-moving products (mimor products) always had, more or less, stronger activities than those of the corresponding faster-moving ones (major products). Among them, **8b**, **9b**, **10b** and **11b** were the most prominent. Acute toxicities (Table 1) of **6a**, **6b**, **7a**, and MT in mice suggest that the isomers having the same spatial arrangement with that of **6b** may have lower toxicity in comparison with the other series of isomers, respectively. Structure-toxicity relationships will be studied more in detail in the future.

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