SYNTHESES OF 23-*C*-ALKYLIDENE, AND 23-*N*-CONTAINING DERIVATIVES OF 5-*O*-MYCAMINOSYLTYLONOLIDE

NORIO KAJIKAWA, TSUTOMU TSUCHIYA and SUMIO UMEZAWA

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

HAMAO UMEZAWA

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

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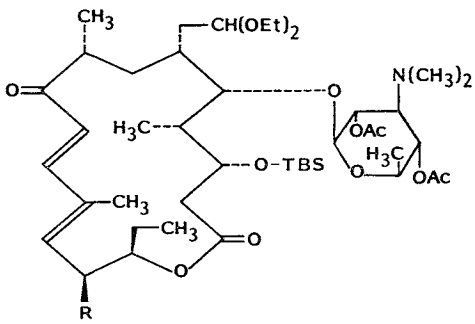
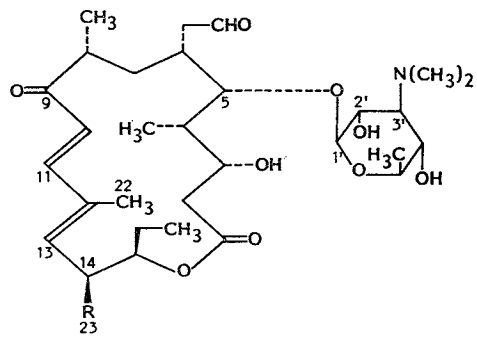
Several derivatives of 5-*O*-mycaminosyltylonolide substituted at C-23 have been prepared; these are 23-deoxy-23-*C*-methylene (**3**), 23-deoxy-23-*C*-(methoxycarbonylmethylene) (**5**), 23-deoxy-23-*C*-(ethoxycarbonylmethylene) (**7**), and 23-deoxy-23-*C*-(butoxycarbonylmethylene) (**9**), 23-deoxy-23-*C*-[(2*E*)-3-(ethoxycarbonyl)-2-propenylene] (**11**), and 23-deoxy-23-(dimethylaminoimino) (**13**), and 14-de(hydroxymethyl)-14-nitrile (**16**) derivatives. The key steps in these syntheses are the reactions of 2′,4′-di-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-23-deoxy-23-oxo-5-*O*-mycaminosyltylonolide diethyl acetal (**1**) with several Wittig reagents, 1,1-dimethylhydrazine and hydroxylamine. Antibacterial activities of these compounds are also described.

In previous papers,[1,2] we described the syntheses of 23-*C*-substituted derivatives (alkyl, phenyl, allyl, vinyl and ethynyl) of 5-*O*-mycaminosyltylonolide from a protected 23-oxo derivative (**1**) with several Grignard reagents, and found that most of these derivatives had marked antibacterial activities. This paper describes the syntheses of some derivatives having an unsaturated bond at C-23 from **1** by





1 R = CH=O
2 R = CH=CH$_2$
4 R = CH=CHCOOCH$_3$
6 R = CH=CHCOOEt
8 R = CH=CHCOOBu
10 R = CH=CHCH=CHCOOEt
12 R = CH=NN(CH$_3$)$_2$
14 R = CH=NOH
15 R = C≡N

3 R = CH=CH$_2$
5 R = CH=CHCOOCH$_3$
7 R = CH=CHCOOEt
9 R = CH=CHCOOBu
11 R = CH=CHCH=CHCOOEt
13 R = CH=NN(CH$_3$)$_2$
16 R = C≡N

TBS = Si(CH$_3$)$_2$^{t}Bu

reaction with the Wittig reagents, 1,1-dimethylhydrazine and hydroxylamine.

2′,4′-Di-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-23-deoxy-23-oxo-5-*O*-mycaminosyltylonolide diethyl acetal[1,2] (**1**) was treated with methylene-triphenylphosphorane in oxolane to give the 23-methylene derivative (**2**) in 40% yield. Presence of the terminal methylene (24-H_a, H_b) was proved by the ^1H NMR spectrum, in which two protons resonated at δ 5.14 and 5.15 coupled to 23-H with 11 ($J_{23,24(cis)}$) and 18 Hz ($J_{23,24(trans)}$). The moderate yield of **2** may, in part, be ascribed to the side reaction occurred at the C-9 carbonyl with the Wittig reagent. Treatment of **1** with other Wittig reagents containing alkoxycarbonyl groups, that is, methoxy-, ethoxy-, and butoxycarbonylmethylenetriphenylphosphorane and *trans*-3-(ethoxycarbonyl)-2-propenylenetriphenylphosphorane, each being readily prepared from the corresponding commercially available triphenylphosphonium bromide, gave the (23*E*)-23-*C*-

Table 1. Selected ^1H NMR data of **3**, **5**, **7**, **9**, **11**, **13** and **16** (in $CDCl_3$ at room temp).

	H-atom	Mult.	**3**	**5**	**7**	**9**	**11**	**13**	**16**
CH_3	17	t	0.92	0.93	0.93	0.93	0.92	0.92	1.01
	18	d	1.02	1.02	1.02	1.02	1.02	1.02	1.02
	21	d	1.22	1.22	1.22	1.22	1.22	1.22	1.22
	22	s*	1.82	1.83	1.83	1.82	1.83	1.84	1.83
	6′	d	1.27	1.27	1.27	1.27	1.27	1.27	1.26
	$N(CH_3)_2$	s	2.50	2.50	2.50	2.50	2.50	2.50, 2.79	2.51
CHC_2	2a	d	1.95	1.95	1.95	1.95	1.96	1.96	1.93
	2b	dd	2.52	2.55	2.55	2.55	2.55	2.54	2.58
	14	m	~3.27	3.46	3.46	3.46	3.42	3.52 dt	3.65 t
	19b	dd	2.94	2.96	2.96	2.96	2.97	2.95	3.00
CHO or CHN	3	d	3.86	3.86	3.86	3.86	3.86	3.86	3.84
	5	d	3.73	3.73	3.73	3.73	3.72	3.73	3.69
	15	dt	4.87	4.94	4.95	4.95	4.89	5.00	5.17
	1′	d	4.26	4.26	4.25	4.25	4.25	4.26	4.23
	2′	dd	3.48	3.48	3.48	3.49	3.48	3.49	3.46
	3′	t	2.36	2.36	2.36	2.36	2.36	2.36	2.36
	4′	t	3.05	3.06	3.06	3.05	3.07	3.05	3.07
	5′	dq		3.27	3.27	3.27	3.27	3.27	3.25
=CH	10	d	6.28	6.32	6.31	6.31	6.30	6.29	6.40
	11	d	7.30	7.28	7.28	7.28	7.29	7.32	7.30
	13	d	5.76	5.73	5.73	5.73	5.73	5.84	5.78
	23		5.73 ddd	6.83 dd	6.82 dd	6.82 dd	5.97 dd	6.37 d	—
	24a		5.18 d	5.94 d	5.94* d	5.93* d	6.28 dd	—	—
	24b	d	5.18*	—	—	—	—	—	—
	20	s	9.71	9.71	9.71	9.72	9.72	9.71	9.71
	COOCH			3.76 s	4.21 q	4.16 t	4.21 q	—	—
	CH_2CH_3	t			1.30	0.95	1.30	—	—
	$J_{14,23}$ (Hz)		8.0	8.2	8.2	8.8	8.8	6.3	—
	$J_{23,24}$ (Hz)		10.5, 17.5	15.5	15.5	15.5	15.5	—	—

Additional data for **11**: δ 5.87 (1H, d, 26-H), 7.25 (1H, dd, 25-H); $J_{24,25}$=10.5, $J_{25,26}$=15 Hz. Other J values common for the seven compounds were: $J_{2a,2b}$=16.5, $J_{2a,3}$=0, $J_{2b,3}$=10~10.5, $J_{3,4}$~1, $J_{4,5}$=9~10, $J_{5,6}$=0, $J_{4,18}$=6.8, $J_{8,21}$=6.8, $J_{16,17}$=7.5, $J_{13,14}$=$J_{14,15}$=10, $J_{15,16a}$=9.5~10, $J_{15,16b}$=3, $J_{6,19b}$=10, $J_{19a,19b}$=18, $J_{10,11}$=15.5, $J_{1',2'}$=7.5, $J_{2',3'}$=$J_{3',4'}$=10, $J_{4',5'}$=9.3 and $J_{5',6'}$=6.3 Hz.

* Each signal has a small splitting.

Mult.: Multiplicity.

Table 2. Antibacterial spectra (MIC, μg/ml) of the products.

	Test organisms	MT	3	5	7	9	11	13	16
1	*Staphylococcus aureus* 193	1.56	<0.2	<0.2	<0.2	0.39	0.78	0.39	0.78
2	*S. aureus* EMf	50	100	50	25	50	>100	>100	>100
3	*S. aureus* 209P	1.56	<0.2	<0.2	<0.2	0.39	0.78	0.39	<0.2
4	*S. aureus* MS 9351	>100	>100	>100	>100	>100	>100	>100	>100
5	*S. aureus* MS 9610	>100	>100	>100	>100	>100	>100	>100	>100
6	*S. aureus* MS 9861	1.56	0.39	0.39	0.39	0.78	1.56	0.78	0.78
7	*S. aureus* MS 10225	3.12	0.39	0.39	0.39	0.39	1.56	0.78	0.78
8	*S. aureus* MS 10246	>100	>100	>100	>100	>100	>100	>100	>100
9	*S. aureus* Smith	1.56	0.39	0.39	0.39	0.78	1.56	0.78	0.78
10	*Micrococcus luteus* PCI 1001	<0.2	<0.2	<0.2	<0.2	0.39	1.56	0.39	0.39
11	*Bacillus subtilis* NRRL B-558	3.12	<0.2	0.39	<0.2	0.39	3.12	0.78	1.56
12	*Corynebacterium bovis* 1810	3.12	<0.2	<0.2	<0.2	0.39	1.56	0.78	0.78
13	*Escherichia coli* NIHJ	12.5	3.12	12.5	6.25	12.5	>100	6.25	6.25
14	*E. coli* K-12	25	6.25	12.5	12.5	25	>100	25	12.5
15	*E. coli* K-12 R-5	50	12.5	12.5	12.5	50	>100	50	25
16	*E. coli* K-12 ML 1629	100	50	50	50	100	>100	>100	100
17	*E. coli* K-12 ML 1410	>100	50	25	50	100	>100	>100	100
18	*E. coli* K-12 ML 1410 R81	100	100	50	50	100	>100	>100	100
19	*E. coli* K-12 LA290 R55	100	50	25	25	100	>100	>100	50
20	*Klebsiella pneumoniae* PCI 602	3.12	3.12	12.5	6.25	1.56	100	3.12	6.25
21	*Shigella dysenteriae* JS 11910	1.56	0.78	0.78	1.56	0.78	3.12	1.56	1.56
22	*Salmonella enteritidis* 1891	3.12	1.56	3.12	3.12	3.12	50	6.25	3.12
23	*S. typhi* T-63	100	25	50	50	100	>100	100	25
24	*Enterobacter aerogenes* ATCC 13048	100	25	50	50	100	>100	100	100
25	*Providencia* sp. Pv 16	>100	100	100	50	100	>100	>100	>100
26	*Serratia marcescens*	50	12.5	50	50	50	>100	50	50
27	*Proteus vulgaris* OX-19	50	12.5	25	25	50	>100	100	25
28	*Pseudomonas aeruginosa* A3	25	6.25	12.5	12.5	25	100	25	12.5
Geometrical mean for No. 1~12		6.6	1.4	1.8	1.5	3.1	7.4	4.2	4.2
Geometrical mean for No. 13~28		35	13	19	19	30	>100	42	25

(alkoxycarbonylmethylene) derivatives (**4**, **6** and **8**), and (23*E*)-23-*C*-[(2*E*)-3-(ethoxycarbonyl)-2-propenylene] derivative (**10**) in moderate to high yields. The 23-*trans* structure of these compounds was concluded by their ^{1}H NMR spectra (see Experimental). Removal of the protecting groups of **2**, **4**, **6**, **8** and **10** in warm methanol (deacetylation) and with 0.5 M hydrochloric acid in 50% aqueous acetonitrile (deblocking the acetal and *O*-silyl groups) gave the final products (**3**, **5**, **7**, **9** and **11**).

Treatment of **1** with 1,1-dimethylhydrazine or hydroxylamine gave the corresponding hydrazone (**12**) or oxime (**14**), the latter being a mixture of two geometrical isomers. Treatment of **14** with thionyl chloride in dichloromethane in the presence of 4-dimethylaminopyridine gave the corresponding nitrile (**15**) by dehydration. Removal of the protecting groups of **12** and **15** gave the final 23-(dimethylaminoimino) (**13**) and 14-nitrile (**16**) derivatives.

Antibacterial activities of these products are shown in Table 2. The compounds having a double bond between C-23 and C-24, especially **3**, showed enhanced antibacterial activities in comparison with the activity of the parent substance, 5-*O*-mycaminosyltylonolide (MT).

Experimental

2′,4′-Di-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-23-deoxy-23-*C*-methylene-5-*O*-mycaminosyltylonolide Diethyl Acetal (**2**)

To a solution of methyltriphenylphosphonium bromide (26.7 mg) in dry oxolane (0.33 ml) was added 2 M sodium hydride in dimethyl sulfoxide (0.057 ml) and the mixture was stirred at room temperature for 4 hours, then at 50°C for 5 minutes. To the resulting yellow solution was added **1** (32.8 mg) in oxolane (0.16 ml) and the mixture was stirred at 50°C for 5 minutes. The solution showed, on TLC with hexane - ethyl acetate, two spots at Rf 0.1 and 0.38 (**2**). After addition of benzene, the organic solution was washed with aqueous sodium sulfate solution (saturated), dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the residue with hexane - ethyl acetate (3 : 1) gave a solid of **2**, 13.2 mg (40%) and an unknown product (Rf 0.1), 6.6 mg. **2**: $[\alpha]_D^{22}$ +5° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1750 (lactone), 1680 (COCH=CH), 1595 (diene); ^{1}H NMR ($CDCl_3$) δ −0.04 and 0.18 (each 3H, s, $Si(CH_3)_2$), 0.87 (9H, s, Si-*tert*-Bu), 1.81 (3H, d, $J \leqq 1$ Hz, 22-CH_3), 2.06 and 2.08 (each 3H, s, Ac×2), 2.35 (6H, s, $N(CH_3)_2$), 2.49 (1H, dd, $J_{2a,2b}$=19, $J_{2b,3}$=7.5 Hz, 2-H_b), 2.74 (1H, t, $J_{3',4'}$=10 Hz, 3′-H), 3.20 (1H, ddd, 14-H), 3.57 (1H, d, J=9 Hz, 5-H), 3.68 (1H, dq, 5′-H), 3.99 (1H, d, 3-H), 4.36 (1H, d, $J_{1',2'}$=7.5 Hz, 1′-H), 4.69 (1H, m, 20-H), 4.75 (1H, t, J=10 Hz, 4′-H), 4.83 (1H, dt, $J_{14,15}=J_{15,16a}$=9.5, $J_{15,16b}$=2.5 Hz, 15-H), 4.89 (1H, dd, $J_{2',3'}$=10 Hz, 2′-H), 5.14 (1H, d, $J_{23,24a}$=11, $J_{24a,24b}$=0 Hz, 24-H_a), 5.15 (1H, d, $J_{23,24b}$=18 Hz, 24-H_b), 5.69 (1H, d, 13-H), 5.70 (1H, ddd, $J_{14,23}$=8.3 Hz, 23-H), 6.26 (1H, d, $J_{10,11}$=15 Hz, 10-H), 7.18 (1H, d, 11-H).

Anal Calcd for $C_{46}H_{79}NO_{12}Si$: C 63.81, H 9.13, N 1.62.
Found: C 64.04, H 9.12, N 1.79.

23-Deoxy-23-*C*-methylene-5-*O*-mycaminosyltylonolide (**3**)

A solution of **2** (41.6 mg) in MeOH (0.8 ml) was kept at 50°C for 12 hours. On TLC with $CHCl_3$ - MeOH - 28% aqueous ammonia (15 : 1 : 0.1), the solution showed a single spot (deacetyl product, Rf 0.12; *cf.* **2**, Rf 0.65). Concentration gave a residue, that was dissolved in 0.5 M hydrochloric acid in 50% aqueous acetonitrile (0.4 ml) and the solution was kept at 37°C for 14 hours. TLC of the solution with $CHCl_3$ - MeOH - 28% aqueous ammonia (10 : 1 : 0.1) showed a single spot of **3** (Rf 0.2; *cf.* the deacetyl product, Rf 0.3). After addition of sodium hydrogencarbonate (40 mg) followed by chloroform, the organic solution was washed with aqueous sodium sulfate (saturated), dried (Na_2SO_4), and concentrated. The residue was purified by short column chromatography with $CHCl_3$ - MeOH - 28% aqueous ammonia (25 : 1 : 0.1) to give a solid of **3**, 27.4 mg (96%): $[\alpha]_D^{22}$ +5° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1720 (lactone and CHO), 1680, 1595.

Anal Calcd for $C_{32}H_{51}NO_9 \cdot H_2O$: C 62.85, H 8.67, N 2.29.
Found: C 63.02, H 8.58, N 2.24.

General Procedure for Preparation of (23*E*)-2′,4′-Di-*O*-acetyl-23-*C*-(alkoxycarbonylmethylene)-3-*O*-*tert*-butyldimethylsilyl-23-deoxy-5-*O*-mycaminosyltylonolide Diethyl Acetals (**4**, **6** and **8**), and (23*E*)-2′,4′-Di-*O*-acetyl-23-*C*-[(2*E*)-3-(ethoxycarbonyl)-2-propenylene]-3-*O*-*tert*-butyldimethylsilyl-23-deoxy-5-*O*-mycaminosyltylonolide Diethyl Acetal (**10**)

To a solution of a (alkoxycarbonylmethyl)triphenylphosphonium bromide (0.5 mmol) or [(2*E*)-3-(ethoxycarbonyl)-2-propenyl]triphenylphosphonium bromide in dry oxolane (2.2 ml) was added 2 M sodium hydride in dimethyl sulfoxide (0.3 ml) and the mixture was vigorously stirred at room temperature for 30 minutes. To the resulting suspension was added **1** (217 mg, 0.25 mmol) in dry oxolane (1.0 ml), and the mixture was stirred at room temperature for 30 minutes. Addition of water (0.8 ml) followed by concentration gave a residue, that was extracted with benzene. The organic solution was washed with aqueous sodium sulfate (saturated), dried (Na_2SO_4), and concentrated. Purification of the crude product by column chromatography with hexane - ethyl acetate (3 : 1) gave solids of the titled compounds in yields of 64% (**4**), 63% (**6**), 94% (**8**) and 53% (**10**), respectively.

4: $[\alpha]_D^{22}$ −11° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1750, 1675, 1590; ^1H NMR ($CDCl_3$) δ −0.04 and 0.17 (each 3H, s, $Si(CH_3)_2$), 0.87 (9H, s, Si-*tert*-Bu), 1.81 (3H, d, $J \leqq 1$ Hz, 22-CH_3), 2.06 and 2.08 (each 3H, s, Ac×2), 2.35 (6H, s, $N(CH_3)_2$), 2.49 (1H, dd, $J_{2a,2b}=19$, $J_{2b,3}=7.5$ Hz, 2-H_b), 2.73 (1H, t, $J_{3',4'}=10$ Hz, 3′-H), ~3.38 (1H, m, 14-H), 3.58 (1H, d, $J_{4,5}=9$ Hz, 5-H), 3.68 (1H, dq, one of OCH_2CH_3), 3.75 (3H, s, $COOCH_3$), 3.99 (1H, d, 3-H), 4.35 (1H, d, $J_{1',2'}=7.5$ Hz, 1′-H), 4.68 (1H, m, 20-H), 4.75 (1H, t, $J=10$ and 10 Hz, 4′-H), 4.89 (1H, dd, 2′-H), 4.90 (1H, dt, 15-H), 5.67 (1H, d, $J_{13,14}=10.5$ Hz, 13-H), 5.92 (1H, dd, $J_{23,24}=16.3$, $J_{14,24}=1$ Hz, 24-H), 6.28 (1H, d, $J_{10,11}=15$ Hz, 10-H), 6.81 (1H, dd, $J_{14,23}=8.5$ Hz, 23-H), 7.16 (1H, d, 11-H).

Anal Calcd for $C_{48}H_{81}NO_{14}Si$: C 62.40, H 8.78, N 1.52.
Found: C 62.65, H 8.86, N 1.73.

6: $[\alpha]_D^{22}$ −10° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1750, 1680, 1590; ^1H NMR ($CDCl_3$) δ 1.30 (3H, t, $J=7$ Hz, $COOCH_2CH_3$), 2.06 and 2.08 (each 3H, s, Ac×2), 2.35 (6H, s, $N(CH_3)_2$), 4.20 (2H, q, $COOCH_2CH_3$), 5.67 (1H, d, 13-H), 5.92 (1H, dd, 24-H), 6.28 (1H, d, 10-H), 6.81 (1H, dd, 23-H), 7.16 (1H, d, 11-H).

Anal Calcd for $C_{49}H_{83}NO_{14}Si$: C 62.75, H 8.86, N 1.49.
Found: C 62.90, H 8.67, N 1.53.

8: $[\alpha]_D^{22}$ −9° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1750, 1680, 1590; ^1H NMR ($CDCl_3$) δ 4.14 (2H, t, $COOCH_2C_3H_7$).

Anal Calcd for $C_{51}H_{87}NO_{14}Si$: C 63.42, H 9.02, N 1.45.
Found: C 63.53, H 8.91, N 1.32.

10: $[\alpha]_D^{22}$ +19° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1755, 1720, 1680, 1645, 1600; ^1H NMR ($CDCl_3$) δ 1.30 (3H, t, $COOCH_2CH_3$), 2.05 and 2.07 (each 3H, s, Ac×2), 2.35 (6H, s, $N(CH_3)_2$), 4.20 (2H, q, $COOCH_2CH_3$), 4.34 (1H, d, 1′-H), 4.88 (1H, dd, 2′-H), 5.66 (1H, d, 13-H), 5.85 (1H, d, $J_{25,26}=15$ Hz, 26-H), 5.94 (1H, dd, $J_{14,23}=8.3$, $J_{23,24}=16$ Hz, 23-H), 6.25 (1H, dd, $J_{24,25}=10.5$ Hz, 24-H), 6.27 (1H, d, 10-H), 7.16 (1H, d, 11-H), 7.23 (1H, dd, 25-H).

Anal Calcd for $C_{51}H_{85}NO_{14}Si$: C 63.55, H 8.83, N 1.45.
Found: C 63.80, H 8.78, N 1.63.

2′,4′-Di-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-23-deoxy-23-(dimethylaminoimino)-5-*O*-mycaminosyltylonolide Diethyl Acetal (**12**)

To a cold (0°C) solution of **1** (292 mg) in MeOH (2.9 ml) was gradually added 1,1-dimethylhydrazine (1.4 ml) under stirring for 15 minutes and the mixture was kept at the temperature for 10 minutes. TLC of the solution with $CHCl_3$ - MeOH - 28% aqueous ammonia (15 : 1 : 0.1) showed a single spot of **12** (Rf 0.55; *cf.* **1**, Rf 0.4). Concentration gave a residue, that was extracted with chloroform. The organic solution was washed with aqueous sodium hydrogensulfate (saturated), dried (Na_2SO_4), and concentrated. The residue was purified by short column chromatography with hexane - ethyl acetate (2 : 1) to give a solid of **12**, 194 mg (63%): $[\alpha]_D^{22}$ −18° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1750 (lactone), 1680 (C=N), 1595; ^1H NMR ($CDCl_3$) δ −0.04 and 0.16 (each 3H, s, $Si(CH_3)_2$), 2.05 and 2.07 (each 3H, s, Ac×2), 2.35 (6H, s, 3′-$N(CH_3)_2$), 2.77 (6H, s, $NN(CH_3)_2$), 4.36 (1H, d, 1′-H), 4.89

(1H, dd, 2′-H), 4.95 (1H, dt, 15-H), 5.78 (1H, d, 13-H), 5.78 (1H, d, 13-H), 6.27 (1H, d, 10-H), 6.37 (1H, d, $J_{14,23}$=6.3 Hz, 23-H), 7.19 (1H, d, 11-H).

Anal Calcd for $C_{47}H_{83}N_3O_{12}Si$: C 62.05, H 9.13, N 4.62.
Found: C 61.98, H 9.00, N 4.75.

2′,4′-Di-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-23-deoxy-23-(hydroximino)-5-*O*-mycaminosyltylonolide Diethyl Acetal (**14**)

A mixture of **1** (423 mg) and hydroxylamine sulfate (400 mg) in MeOH (4.2 ml) was kept at room temperature for 2 hours. TLC of the solution with $CHCl_3$ - MeOH - 28% aqueous ammonia (15 : 1 : 0.1) showed two spots at Rf 0.35 (major) and 0.3 (minor). Concentration gave a residue, that was extracted with $CHCl_3$. The organic solution was treated as described for **12**, and concentrated. The residue was purified by column chromatography with hexane - ethyl acetate (4 : 1) to give a solid of **14**, 237 mg (63%): $[\alpha]_D^{21}$ −14° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1750, 1680, 1595; ^1H NMR ($CDCl_3$) δ −0.04 and 0.16 (each 3H, s, $Si(CH_3)_2$), 2.06 and 2.08 (each 3H, s, Ac×2), 2.35 (6H, s, $N(CH_3)_2$), 4.37 (1H, d, 1′-H), 4.89 (1H, dd, 2′-H), 4.98 (1H, dt, 15-H), 5.71 (1H, d, 13-H), 6.29 (1H, d, 10-H), 7.18 (1H, d, 11-H), 7.33 (1H, d, $J_{14,23}$=7.5 Hz, 23-H), 6.92 (1H, slightly br s, NOH).

Anal Calcd for $C_{45}H_{78}N_2O_{13}Si$: C 61.12, H 8.80, N 2.85.
Found: C 61.22, H 8.84, N 3.17.

2′,4′-Di-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-14-de(hydroxymethyl)-5-*O*-mycaminosyltylonolide Diethyl Acetal 14-Nitrile (**15**)

To a cold (−10°C) mixture of 4-dimethylaminopyridine (11.7 mg) and thionyl chloride (6.1 μl) in dichloromethane (0.33 ml) was added **14** (33.8 mg) in dichloromethane (0.17 ml), and the mixture was stirred at the temperature for 2 minutes, then, after addition of 4-dimethylaminopyridine (11.7 mg), at room temperature for 15 minutes. TLC of the mixture with hexane - ethyl acetate (2 : 1) showed a single spot (**15**, Rf 0.33; *cf.* **14**, Rf 0.23). Dichloromethane (1 ml) was added, and the organic solution was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography with hexane - ethyl acetate (4 : 1) to give a solid of **15**, 24.4 mg (74%): $[\alpha]_D^{21}$ −20° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1750, 1685, 1600; ^1H NMR ($CDCl_3$) δ −0.04 and 0.16 (each 3H, s, $Si(CH_3)_2$), 2.05 and 2.26 (each 3H, s, Ac×2), 2.34 (6H, s, $N(CH_3)_2$), 4.34 (1H, d, 1′-H), 4.38 (1H, dd, 2′-H), 5.11 (1H, dt, 15-H), 5.69 (1H, d, 13-H), 6.37 (1H, d, 10-H), 7.15 (1H, d, 11-H).

Anal Calcd for $C_{45}H_{76}N_2O_{12}Si$: C 62.47, H 8.85, N 3.24.
Found: C 62.19, H 8.81, N 3.44.

General Procedure for Preparation of (23*E*)-23-*C*-(Alkoxycarbonylmethylene)-23-deoxy-5-*O*-mycaminosyltylonolides (**5**, **7** and **9**), (23*E*)-23-*C*-[(2*E*)-3-(Ethoxycarbonyl)-2-propenylene]-23-deoxy-5-*O*-mycaminosyltylonolide (**11**) and 14-De(hydroxymethyl)-5-*O*-mycaminosyltylonolide 14-Nitrile (**16**)

A solution of **4**, **6**, **8**, **10** or **15** (0.12 mmol) in MeOH (2.2 ml) was kept at 50°C for 13 hours. Concentration gave a residue, that was dissolved in 0.5 M hydrochloric acid in 50% aqueous acetonitrile (1.1 ml) and the solution was kept at 37°C for 25 hours. After neutralization with aqueous sodium hydrogencarbonate (saturated), the mixture was extracted with $CHCl_3$. The organic solution was washed with aqueous sodium sulfate (saturated), dried (Na_2SO_4), and concentrated. Purification of the residue with column chromatography with $CHCl_3$ - MeOH - 28% aqueous ammonia (15 : 1 : 0.1) gave solids of the titled compounds in yields of 85% (**5**), 82% (**7**), 83% (**9**), 53% (**11**) and 27% (**15**, unstable), respectively.

5: $[\alpha]_D^{22}$ −26° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1725, 1680, 1595.
Anal Calcd for $C_{34}H_{53}NO_{11}\cdot H_2O$: C 60.99, H 8.22, N 2.15.
Found: C 61.00, H 8.02, N 2.19.

7: $[\alpha]_D^{22}$ −25° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1720, 1680, 1595.
Anal Calcd for $C_{35}H_{55}NO_{11}\cdot 1\frac{1}{3}H_2O$: C 60.96, H 8.37, N 2.03.
Found: C 61.08, H 8.16, N 2.27.

9: $[\alpha]_D^{22}$ −25° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1715, 1675, 1590.
Anal Calcd for $C_{37}H_{59}NO_{11}$: C 63.25, H 8.40, N 1.99.
Found: C 63.49, H 8.28, N 2.24.

11: $[\alpha]_D^{22}$ +6° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1715, 1680, 1640, 1590.

Anal Calcd for $C_{37}H_{57}NO_{11} \cdot \frac{2}{3}H_2O$: C 63.16, H 8.30, N 1.99.

Found: C 62.97, H 8.00, N 1.69.

16: $[\alpha]_D^{18}$ −31° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1725, 1680, 1600.

Anal Calcd for $C_{31}H_{48}N_2O_9 \cdot H_2O$: C 60.98, H 8.20, N 4.59.

Found: C 61.02, H 7.93, N 4.57.

23-Deoxy-23-(dimethylaminoimino)-5-*O*-mycaminosyltylonolide (**13**)

A solution of **12** (143 mg) in MeOH (2.9 ml) was kept at room temperature for 2 days. The product was then treated with 0.5 M HCl in 50% aqueous acetonitrile (1.4 ml) at 37°C for 18 hours and processed as described for **5** to give, after column chromatography ($CHCl_3$ - EtOH - 28% aqueous ammonia, 20 : 1 : 0.1), a solid of **13**, 45.5 mg (46%): $[\alpha]_D^{22}$ −18° (*c* 1, $CHCl_3$); IR (KBr) cm^{-1} 1720, 1675, 1595.

Anal Calcd for $C_{33}H_{55}N_3O_9 \cdot H_2O$: C 60.46, H 8.40, N 6.41.

Found: C 60.40, H 8.54, N 6.87.

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