SYNTHESIS OF 3-DEOXY-3,4-DIDEHYDRO DERIVATIVES OF 5-*O*-MYCAMINOSYLTYLONOLIDE, 5-*O*-(4-DEOXYMYCAMINOSYL) TYLONOLIDE, AND DESMYCOSIN

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The 3-deoxy-3,4-didehydro derivatives of 5-*O*-mycaminosyltylonolide, 5-*O*-(4-deoxymycaminosyl)tylonolide, and desmycosin have been prepared by treatment of the corresponding 3-*O*-sulfonyl derivatives with NaI in 2-butanone as the key step. The mechanistic difference in the formation of the 2,3- and 3,4-unsaturated derivatives from the same 3-*O*-sulfonyl derivative is discussed.

Recently we reported[1,2] the synthesis and antibacterial activities of 3-deoxy-5-*O*-mycaminosyltylonolide and 3-deoxy-5-*O*-(4-deoxymycaminosyl)tylonolide (3,4′-DT) and it was found that removal of the 3-hydroxyl group in the macrolactone ring of mycaminosyltylonolides enhances the activity in comparison to the parent antibiotics. In the course of the synthesis of the 3-deoxy derivatives we obtained the 2,3-unsaturated intermediates and these were selectively hydrogenated to give the desired products. Deprotection of the above intermediates should give the corresponding 2,3-unsaturated analogs of the 3-deoxy compounds. Accordingly, 3-deoxy-5-*O*-(4-deoxymycaminosyl)-2,3-didehydro-23-*O*-(dimethylthexylsilyl)tylonolide 9,20-bis(ethylene acetal)[2] was deprotected to give the 2,3-unsaturated analog (De-2,3-DT) of 3,4′-DT, and was found to be identical with that prepared by a different route by TANAKA[3]. This analog had less than one-half the activity of 3,4′-DT, suggesting that the 2,3-unsaturation does not enhance antibacterial activity as does 3-deoxygenation. In connection with this study we were interested to prepare the corresponding 3,4-unsaturated compounds. Such compounds are possible to give antibacterial spectra different from those for the 2,3-unsaturated compounds. This paper describes the synthesis of 3,4-unsaturated analogs of mycaminosyltylonolides and desmycosin.

5-*O*-Mycaminosyltylonolide dimethyl acetal[4] (**3**) was treated with *tert*-butyldimethylsilyl chloride in DMF to give the 23-*O*-silyl product (**4**). Selective acetylation of **4** with acetic anhydride in toluene - acetonitrile gave the 2′,4′-di-*O*-acetyl derivative (**5**). Sulfonylation of **5** with phenylmethanesulfonyl chloride gave the 3-*O*-sulfonyl derivative (**6**).

In a foregoing paper[2] we reported that treatment of 5-*O*-(4-deoxy-4-iodomycaminosyl)-23-*O*-(dimethylthexylsilyl)-3-*O*-phenylmethanesulfonyltylonolide 9,20-bis(ethylene acetal), a structurally analogous compound to **6**, with ammonia in aqueous methanol gave the corresponding 2,3-unsaturated compound, and the iodo precursor was prepared from the corresponding 3,4′-bis(*O*-phenylmethanesulfonyl) compound by treatment with NaI in 2-butanone (30 minutes at 80°C). In the present study we utilized the same reaction conditions (NaI in 2-butanone), instead of ammonia in aqueous methanol, only extending the reaction period (8 hours at 80°C), whereupon the corresponding 3,4-unsaturated product (**9**) was produced in 84% yield, together with the C-20-deblocked 3-*O*-phenylmethanesulfonyl derivative (**8**). The 3-deoxy-3-iodo and 2,3-unsaturated products were not detected. This synthetic method effectively makes 3,4-unsaturated products. The 3,4-unsaturated structure **9** was confirmed by ^{1}H NMR spectrum, and also

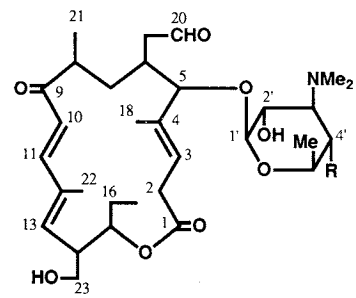
Table 1. ^{1}H NMR[a] chemical shifts[b] of **1**, **2**, 5-*O*-(4-deoxymycaminosyl)tylonolide (DT), 3-deoxy-2,3-didehydro-5-*O*-mycaminosyltylonolide[3] (De-2,3-MT), and 3-deoxy-5-*O*-(4-deoxymycaminosyl)-2,3-didehydrotylonolide[3] (De-2,3-DT) in $CDCl_3$ at 27°C.

	1	2	De-2,3-MT	De-2,3-DT	DT
2-H	2.98, 3.02	2.99, 2.99	5.65	5.66	1.96, 2.52
3-H	5.59	5.55	6.81	6.83	3.86
4-H	—	—	2.68	2.73	1.72
5-H	4.34	4.35	3.65	3.62	3.69
6-H	2.11	1.96	1.74	1.60	2.06
7-H	1.40, 1.66	1.50, 1.67	1.29, 1.29	1.71, 1.71	1.62, 1.83
8-H	2.77	2.65	2.50	2.48	2.56
10-H	6.17	6.21	6.22	6.24	6.32
11-H	7.16	7.15	7.20	7.20	7.34
13-H	5.77	5.78	5.78	5.77	5.87
14-H	2.91	2.90	2.90	2.90	2.89
15-H	4.95	4.95	4.88	4.87	4.95
16-H	1.63, 1.84	1.63, 1.87	1.65, 1.86	1.65, 1.84	1.65, 1.84
17-CH_3	0.96	0.96	0.97	0.97	0.95
18-CH_3	1.69	1.75	1.12	1.21	1.09
19-H	2.35, 2.63	2.37, 2.72	2.53, 2.86	2.53, 2.92	2.46, 3.02
20-H	9.74	9.76	9.69	9.70	9.72
21-CH_3	1.17	1.18	1.16	1.21	1.21
22-CH_3	1.84	1.84	1.83	1.83	1.82
23-H	3.69, 3.74	3.68, 3.73	3.74, 3.77	3.74, 3.74	3.73, 3.74
1′-H	4.05	4.02	4.24	4.20	4.21
2′-H	3.56	3.29	3.50	3.24	3.20
3′-H	2.44	2.47	2.45	2.48	2.46
4′-H	3.08	1.26, 1.67	3.10	1.21, 1.65	1.20, 1.66
5′-H	3.25	3.46	3.25	3.45	3.47
6′-CH_3	1.28	1.21	1.22	1.21	1.20
3′-$N(CH_3)_2$	2.57	2.40	2.56	2.34	2.27

[a] Measured at 500 MHz with a JEOL Alpha 500.
[b] In ppm downfield from TMS. The shifts were confirmed by the ^{1}H-^{1}H correlated 2D spectra with aid of, in some cases, HOHAHA method.

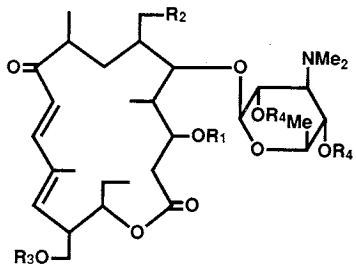
by the ^{1}H and ^{13}C NMR spectra of the final product (**1**) (see Tables 1 and 2).

To examine the effect of the 3-*O*-sulfonyl group the 3-*O*-mesyl (instead of 3-*O*-phenylmethanesulfonyl) derivative (**7**) was prepared, and this was treated with NaI. Again the same 3,4-unsaturated product **9** was obtained in 67% yield, although the reaction time required was longer, suggesting that any sulfonyl group will give the 3,4-unsaturation compound under similar conditions. Deacetylation of **9** gave **10**, and desilylation of **10** gave the 3-deoxy-3,4-didehydro compound (**1**).

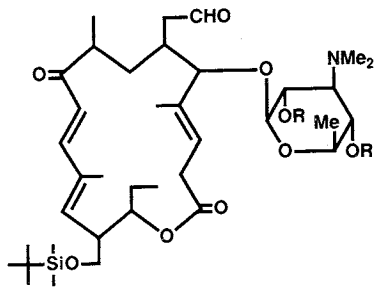


1 R=OH
2 R=H

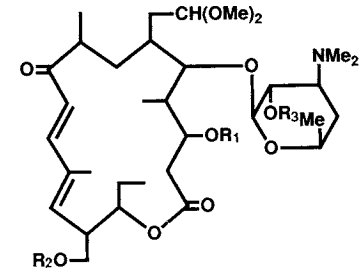
4′-Deoxy analog (**2**) of **1** was also prepared using a similar route. 5-*O*-(4-Deoxymycaminosyl)tylonolide dimethyl acetal[5] (**11**) was converted into the 23-*O*-silyl derivative (**12**), and after acetylation, the 2′-*O*-acetyl derivative (**13**) was converted to the 3-*O*-phenylmethanesulfonyl derivative (**14**). Similar treatment of **14** with NaI, as described for **6** gave the 3,4-unsaturated product (**15**) in 73% yield. Deacetylation (to give



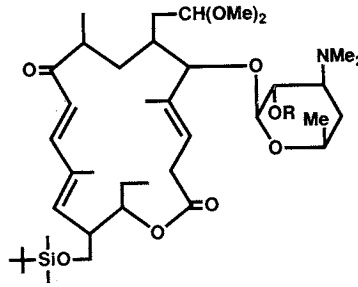
	R_1	R_2	R_3	R_4
3	H	$CH(OMe)_2$	H	H
4	H	$CH(OMe)_2$		H
5	H	$CH(OMe)_2$		Ac
6	Bes	$CH(OMe)_2$		Ac
7	SO_2CH_3	$CH(OMe)_2$		Ac
8	Bes	CHO		Ac



9 R=Ac
10 R=H



	R_1	R_2	R_3
11	H	H	H
12	H		H
13	H		Ac
14	Bes		Ac



15 R=Ac
16 R=H

Bes: $SO_2CH_2C_6H_5$

16) followed by acid-catalyzed desilylation and deacetalation gave **2**.

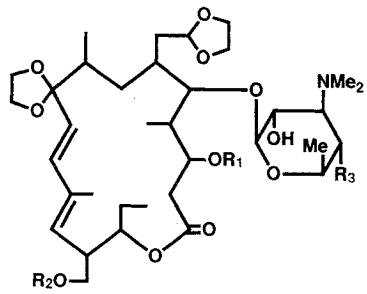
Preparation of **2** from 5-*O*-mycaminosyltylonolide[6] was attempted by conducting simultaneous 3,4-unsaturation and 4′-iodination by treatment of a 3,4′-disulfonyl derivative with NaI. 5-*O*-Mycaminosyltylonolide 9,20-bis(ethylene acetal)[2] (**17**) was treated with *tert*-butyldimethylsilyl chloride to give the 23-*O*-silyl derivative (**18**), which was selectively sulfonylated with phenylmethanesulfonyl chloride to give the 3,4′-bis(*O*-phenylmethanesulfonyl) derivative (**19**). Iodination of **19** for a short period with NaI gave the 4′-deoxy-4′-iodo-3-*O*-phenylmethanesulfonyl derivative (**20**, 73%). Longer reaction of **19** or **20** gave the 4′-deoxy-4′-iodo-3,4-unsaturation product (**21**) in 31 and 40% yields, respectively. The configuration at C-4′ of **20** and **21** is assumed to be *R* (I down) on the basis of the discussion reported[2] for the same iodination. The decreased yields of **21** compared with **9** and **15** are not clear, but possibly the unstable 4′-deoxy-4′-iodo intermediate(s) initially formed decomposes.

Table 2. ^{13}C NMR[a] chemical shifts[b] of **1**, **2**, DT, De-2,3-MT, and De-2,3-DT in $CDCl_3$ at 27°C.

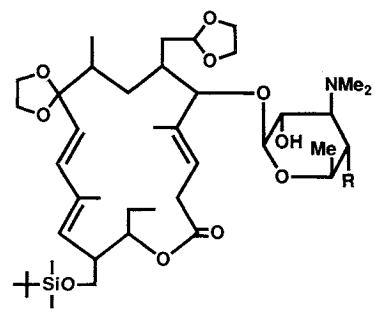
Carbon	1	2	De-2,3-MT	De-2,3-DT	DT
1	171.4	171.5	166.0	166.1	173.9
2	33.3	33.2	122.4	120.6	39.6
3	123.0	121.4	150.9	151.4	67.2
4	136.0	137.5	40.4	40.5	40.9
5	81.6	81.7	81.9	82.2	81.0
6	38.8	39.2	33.3	30.6	31.4
7	34.3	33.4	30.6	33.3	32.4
8	42.6	43.8	44.5	44.7	44.9
9	204.5	204.1	203.2	203.5	203.5
10	122.3	120.9	118.5	118.4	118.6
11	147.4	146.9	147.8	147.7	147.9
12	136.5	136.3	137.5	137.5	136.1
13	139.0	139.0	140.1	140.0	141.7
14	46.7	46.7	47.4	47.4	47.2
15	74.9	74.6	74.7	74.7	74.8
16	25.8	25.7	26.2	26.1	25.5
17	9.5	9.5	9.9	9.8	9.7
18	14.5	14.1	19.6	19.3	8.7
19	45.2	44.5	42.9	42.9	43.8
20	202.2	202.4	201.9	202.2	203.5
21	16.5	16.9	17.5	17.4	17.5
22	13.3	13.3	13.7	13.7	13.0
23	62.9	62.8	62.9	62.9	62.4
1′	100.5	101.5	103.9	104.5	104.2
2′	70.3	69.8	70.8	70.2	70.3
3′	70.6	65.7	70.4	65.6	65.6
4′	70.5	28.7	70.6	28.3	28.4
5′	73.3	69.5	73.3	69.6	69.5
6′	17.9	21.2	17.7	21.0	21.0
$N\text{-}(CH_3)_2$	41.8	40.3	41.8	40.2	40.2

[a] Measured at 125 MHz with a JEOL Alpha 500.
[b] In ppm downfield from TMS. The shifts were confirmed by the ^1H-^{13}C correlated 2D spectra with aid of, in some cases, HMBC method.

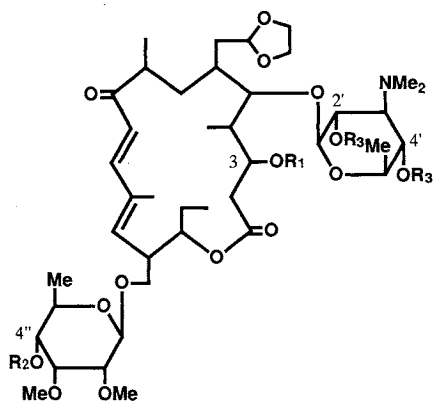
To examine the difference in effectiveness of the halo anions (I^-, Br^-, and Cl^-) in this reaction, **19** was treated with LiBr or Et_4NCl in 2-butanone, whereupon similar 3,4-unsaturated 4′-bromo-4′-deoxy (**22**) and 4′-chloro-4′-deoxy derivatives (**23**) were prepared in 41 and 37% yields, respectively. The configurations at C-4′ of **22** and **23** were determined to be *R* (halo atom down) on the basis of large coupling constants (10 Hz) of $J_{3',4'}$ (for **22**) and $J_{3',4'}$ and $J_{4',5'}$ (for **23**), which were confirmed by the ^1H-^1H 2D spectra. The above results indicate that all halo anions (excluding F^-) catalyze the 3,4-unsaturation. Reaction mechanism of these reactions is not clear, but it is possible that a halo anion, which is a more neutral species than ammonia, attacks the 4-H to abstract it as a proton to form C-4 carbanion, which then induces elimination of the 3-sulfonyloxy group to give 3,4-unsaturation. As the 3-*O*-phenylmethanesulfonyl group and C(4)-*H* are expected to be (nearly) antiperiplanar relationship (a situation at which elimination readily occurs), formation of the 3,4-double bond will be facilitated by the catalysis of almost neutral halo anion. The spacial relationship between the groups concerned in **6** was ascertained by the HOHAHA measurement (see Fig. 1); lack of observation of a cross peak between 3-H and 4-H (this indicates no coupling) suggests that the projection angle between the two hydrogens should be $\sim 90°$. As C-2 and 4-H is considered to be difficult to take antiperiplanar relationship by the nature of



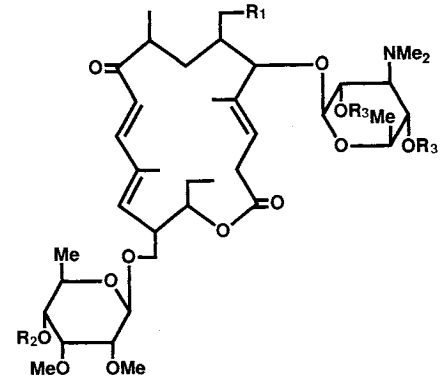
	R_1	R_2	R_3
17	H	H	OH
18	H	Si	OH
19	Bes	Si	OBes
20	Bes	Si	I



21 R=I
22 R=Br
23 R=Cl
24 R=H



	R_1	R_2	R_3
25	H	H	H
26	H	Ac	Ac
27	Bes	Ac	Ac



	R_1	R_2	R_3
28	$CH(OCH_2)_2$	Ac	Ac
29	$CH(OCH_2)_2$	Ac	H
30	CHO	Ac	H
31	CHO	H	H

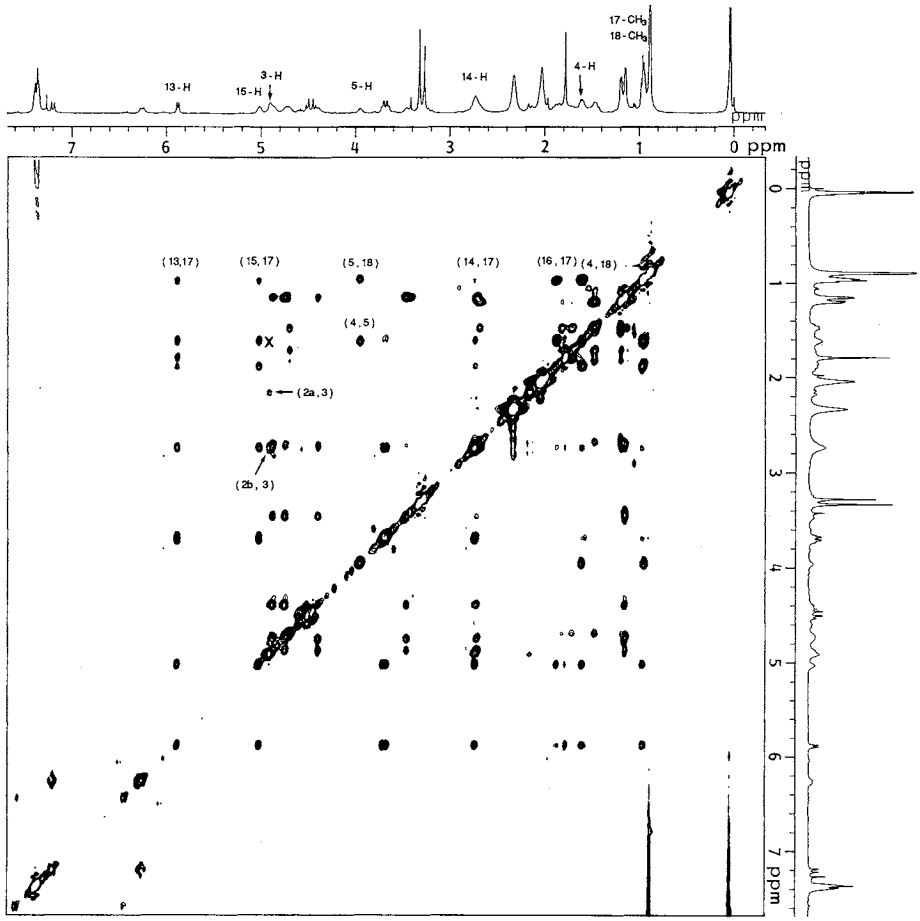
Bes: $SO_2CH_2C_6H_5$

the macrolactone ring, the remaining 3-*O*-phenylmethanesulfonyl and 4-H should take antiperiplanar relationship. On the contrary, the more basic ammonia in aqueous methanol withdraws one of the protons at C-2, rather than the proton at C-4, to give 2,3-unsaturation[1,2], because 2-H hydrogens are activated by the neighboring, electron-withdrawing carboxyl group.

Reductive deiodination of **21** with Bu_3SnH-azobis(isobutyronitrile) (AIBN) gave the 4'-deoxy derivative (**24**) in high yield. Acid-catalyzed deprotection of **24** as described for **16** gave **2**.

3-Deoxy-3,4-didehydrodesmycosin (**31**) was also prepared by taking a similar route. Desmycosin

Fig. 1. HOHAHA spectrum of compound **6**.



In $CDCl_3$ at 27°C measured at 500 MHz with a JEOL Alpha 500; mixing time: 120 msec. The shift values of 3-H and 4-H were δ 4.92 and δ 1.61, respectively. The crossing of the 3-H and 4-H is shown by x.

20-(ethylene acetal) (**25**), prepared from tylosin by acid-catalyzed hydrolysis in the presence of ethylene glycol, was acetylated to give the 2′,4′,4″-tri-*O*-acetyl derivative (**26**). After phenylmethanesulfonylation, the 3-sulfonate (**27**) was treated with NaI, and the 3,4-unsaturated derivative (**28**) was obtained in 67% yield. Successive deacetylation of **28** (to give **29**), deacetalation (to give **30**) and deacetylation gave 3-deoxy-3,4-didehydrodesmycosin (**31**).

Antibacterial spectra of **1**, **2**, and **31** are shown in Table 3. Compounds **1** and **2** showed similar antibacterial activity with that for the corresponding 3-deoxy-2,3-didehydro analogs (De-2,3-MT and De-2,3-DT), however, **2** showed activity against some resistant bacteria.

Experimental

General

Optical rotations were determined with a Perkin-Elmer 241 polarimeter. ^1H NMR spectra were recorded with Bruker WM 250 (250 MHz) and JEOL Alpha 500 (500 MHz) spectrometers, and the chemical

Table 3. Antibacterial activity (MIC μg/ml) of **1**, **2** and **31** together with 5-*O*-(4-deoxymycaminosyl)tylonolide (DT), 3-deoxy-2,3-didehydro-5-*O*-mycaminosyltylonolide[3] (De-2,3-MT), 3-deoxy-5-*O*-(4-deoxymycaminosyl)-2,3-didehydrotylonolide[3] (De-2,3-DT), and erythromycin (EM).

Test organism[a]	**1**	**2**	**31**	De-2,3-MT	De-2,3-DT	DT	EM
Staphylococcus aureus FDA 209P JC-1	3.13	1.56	0.39	3.13	3.13	0.2	0.2
S. aureus MS 8710[b]	>50	12.5	>50	>50	>50	>50	>50
S. aureus MS 9610[b]	>50	6.25	>50	>50	>50	>50	>50
S. epidermidis IID 866	1.56	1.56	0.2	1.56	1.56	0.1	0.1
Streptococcus pyogenes Cook	0.78	1.56	0.2	1.56	3.13	0.2	0.05
S. pyogenes CAY 2303[c]	>50	25	>50	>50	>50	>50	>50
S. pneumoniae IID 552	0.78	0.78	3.13	1.56	1.56	0.1	0.05
Enterococcus faecalis IID 682	6.25	6.25	6.25	6.25	6.25	0.39	0.1
Branhamella catarrhalis CAY1267	1.56	0.39	1.56	1.56	0.78	0.2	0.2
Escherichia coli O-1	>50	50	>50	>50	>50	6.25	>50
Citrobacter freundii NIH10018-68	25	12.5	>50	50	6.52	1.56	12.5
Shigella sonnei II 37148	>50	50	>50	>50	>50	12.5	25
Klebsiella pneumoniae ATCC 10031	6.25	3.13	25	25	6.25	0.78	3.13
Proteus vulgaris OX-19	>50	12.5	>50	>50	>50	25	>50
Pseudomonas aeruginosa NCTC10490	>50	50	>50	>50	>50	25	>50

[a] Mueller-Hinton agar, inoculum size 10^6 cfu/1 ml, incubation time: 18 hours at 37°C.
[b] Multi-resistant strain.
[c] Clinical origin.

shifts (δ) were measured downfield from internal TMS. Mass spectra (MS) were determined using the fast atom bombardment method with a JMS-DX300 (HF) mass spectrometer. Thin-layer chromatography (TLC) was performed on Kieselgel 60 F_{254} (Merck), and column chromatography on Kieselgel 60, 230~400 mesh (Merck).

23-*O*-*tert*-Butyldimethylsilyl-5-*O*-mycaminosyltylonolide Dimethyl Acetal (**4**)

A mixture of **3** (9.50 g, 14.8 mmol), imidazole (1.81 g), and *tert*-butyldimethylsilyl chloride (2.67 g, 17.7 mmol) in dry DMF (95 ml) was kept for 8 hours at room temperature. After addition of toluene (500 ml), the whole mixture was washed with aq $NaHCO_3$ and aq NaCl (both saturated) and the solution was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography with $CHCl_3$-MeOH-28% aq NH_3 (15:1:0.1) to give a solid of **4**, 9.64 g (86%), mp 183.5~184.5°C (ether), $[\alpha]_D^{20}$ +3° (*c* 1, $CHCl_3$); MS *m/z* 758 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.89 (9H, s, *tert*-butyl), 1.01 (3H, d, 18-CH_3), 1.79 (3H, s, 22-CH_3), 2.50 (6H, s, 3′-$N(CH_3)_2$), 3.25 and 3.30 (each 3H, s, $OCH_3 \times 2$).

Anal Calcd for $C_{39}H_{71}NO_{11}Si \cdot \frac{1}{2}H_2O$: C 61.06, H 9.46, N 1.83.
Found: C 61.39, H 9.52, N 1.80.

5-*O*-(2,4-Di-*O*-acetylmycaminosyl)-23-*O*-*tert*-butyldimethylsilyltylonolide Dimethyl Acetal (**5**)

A mixture of **4** (1.00 g, 1.32 mmol) and acetic anhydride (0.3 ml, 3.2 mmol) in toluene-acetonitrile (1:1, 40 ml) was kept overnight at room temperature. After concentration of the solution, the residue dissolved in toluene was washed with aq $NaHCO_3$ (saturated), dried ($MgSO_4$), and concentrated. The residue was purified by a short column with hexane-acetone (7:3) to give a solid of **5**, 1.06 g (95%), $[\alpha]_D^{20}$ +4° (*c* 1, $CHCl_3$); MS *m/z* 842 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.89 (9H, s, *tert*-butyl), 0.93 (3H, d, 18-CH_3), 1.79 (3H, s, 22-CH_3), 2.05 and 2.06 (each 3H, s, Ac × 2), 2.34 (6H, s, 3′-$N(CH_3)_2$), 3.23 and 3.29 (each 3H, s, $OCH_3 \times 2$).

Anal Calcd for $C_{43}H_{75}NO_{13}Si$: C 61.33, H 8.98, N 1.66.
Found: C 61.27, H 9.14, N 1.64.

5-*O*-(2,4-Di-*O*-acetylmycaminosyl)-3-*O*-phenylmethanesulfonyl-23-*O*-*tert*-butyldimethylsilyltylonolide Dimethyl Acetal (**6**)

To a cold (−30°C) solution of **5** (906 mg, 1.08 mmol) in dry pyridine (18 ml) was added phenylmethanesulfonyl chloride (370 mg, 1.95 mmol) and the solution was kept at −20°C for 3 hours. Water (~0.4 ml) was added, and the solution was gradually warmed to room temperature. After concentration to a half of its volume, the mixture was extracted with toluene. The organic solution was washed with aq $NaHCO_3$ (saturated), dried ($MgSO_4$), and concentrated to give a solid of **6**, 1.1 g (quant.), which was slightly unstable, and used for the next step without purification, TLC: Rf 0.3 (hexane-acetone, 7:3) (*cf.* **5**: Rf 0.4); analytical sample was purified by column chromatography (hexane-acetone, 7:3), $[\alpha]_D^{20}$ +12° (*c* 1, $CHCl_3$); MS *m/z* 996 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.89 (9H, s, *tert*-butyl), 1.78 (3H, s, 22-CH_3), 2.02 and 2.03 (each 3H, s, Ac×2), 2.32 (6H, s, 3′-$N(CH_3)_2$), 3.27 and 3.33 (each 3H, s, OCH_3×2), 5.88 (1H, d, $J_{13,14}$=10.5 Hz, 13-H), 6.26 (1H, d, $J_{10,11}$=15.3 Hz, 10-H), 7.21 (1H, d, 11-H), ~7.4 (5H, m, *Ph*CH_2SO_2).

Anal Calcd for $C_{50}H_{81}NO_{15}SSi$: C 60.28, H 8.19, N 1.41, S 3.22.
Found: C 60.12, H 8.25, N 1.29, S 3.19.

5-*O*-(2,4,-Di-*O*-acetylmycaminosyl)-23-*O*-*tert*-butyldimethylsilyl-3-*O*-mesyltylonolide Dimethyl Acetal (**7**)

To a solution of **5** (400 mg, 0.48 mmol) in dry pyridine (8 ml) was added methanesulfonyl chloride (110 μl, 1.43 mmol) and the solution was kept at room temperature for 3 hours. Usual work-up as described for **6** gave, after chromatography (hexane-acetone, 7:3), a solid of **7**, 402 mg (92%), $[\alpha]_D^{20}$ −9° (*c* 1, $CHCl_3$); MS *m/z* 920 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 2.05 (6H, s, Ac×2), 3.11 (3H, s, SO_2CH_3).

Anal Calcd for $C_{44}H_{77}NO_{15}SSi$: C 57.43, H 8.43, N 1.52, S 3.48.
Found: C 57.42, H 8.42, N 1.42, S 3.44.

5-*O*-(2,4-Di-*O*-acetylmycaminosyl)-23-*O*-*tert*-butyldimethylsilyl-3-deoxy-3,4-didehydrotylonolide (**9**)

From **6**: To a solution of **6** (980 mg, 0.84 mmol) in dry 2-butanone (20 ml) was added NaI (443 mg, 2.95 mmol) and the mixture was stirred for 8 hours at 80°C under the atmosphere of nitrogen. After cooled to room temperature, the mixture was filtered, and the solution was concentrated. The residue was extracted with toluene, and the solution was washed with 10% aq $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated. The residue gave two spots at Rf 0.33 (major, **9**) and 0.25 (**8**); the products were separated by column chromatography with hexane-acetone (7:3) to give solids of **9**, 641 mg (84% based on **5**) and **8**, 87 mg (11%).

8: $[\alpha]_D^{20}$ +2° (*c* 1, $CHCl_3$); MS *m/z* 950 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.90 (9H, s, *tert*-butyl), 1.80 (3H, s, 22-CH_3), 2.02 and 2.03 (each 3H, s, Ac×2), 2.32 (6H, s, 3′-$N(CH_3)_2$), 4.33 (1H, d, $J_{1'2'}$=7.9 Hz, 1′-H), 4.55 (2H, s, PhCH_2SO_2), 4.71 (1H, t, *J*=9.8 Hz, 4′-H), 4.85 (1H, dd, $J_{2',3'}$=10 Hz, 2′-H), 4.95 (1H, br d, 3-H), 5.97 (1H, d, $J_{13,14}$=10.4 Hz, 13-H), 6.28 (1H, d, $J_{10,11}$=15.9 Hz, 10-H), 7.34 (1H, d, 11-H), and 9.74 (1H, s, 20-H).

9: $[\alpha]_D^{22}$ −28° (*c* 1, $CHCl_3$); MS *m/z* 778 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.89 (9H, s, *tert*-butyl), 1.61 (3H, s, 18-CH_3), 1.79 (3H, s, 22-CH_3), 2.05 (6H, s, Ac×2), 2.34 (6H, s, 3′-$N(CH_3)_2$), 4.13 (1H, br d, 1′-H), 4.31 (1H, br s, 5-H), 5.57 (1H, br s, 3-H), 5.81 (1H, d, $J_{13,14}$=10.4 Hz, 13-H), 6.17 (1H, d, $J_{10,11}$=15.3 Hz, 10-H), 7.12 (1H, d, 11-H), and 9.70 (1H, s, 20-H).

Anal Calcd for $C_{41}H_{67}NO_{11}Si \cdot \frac{1}{2}H_2O$: C 62.56, H 8.71, N 1.78.
Found: C 62.80, H 8.56, N 1.76.

From **7**: To a solution of **7** (170 mg, 0.19 mmol), in dry 2-butanone (3.4 ml) was added NaI (83 mg, 0.55 mmol) and the mixture was stirred for 18 hours at 80°C under the atmosphere of nitrogen. After usual post-treatment, the crude product was purified by column chromatography with hexane-acetone (14:5) to give a solid of **9**, which was identical with the specimen prepared from **6**, 96 mg (67%), and another solid (possibly the 3-*O*-mesyl analog of **8**), 17 mg (11%), MS *m/z* 874 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 3.19 (3H, s, SO_2CH_3).

23-*O*-*tert*-Butyldimethylsilyl-3-deoxy-3,4-didehydro-5-*O*-mycaminosyltylonolide (**10**)

A solution of **9** (550 mg) in methanol (11 ml) was heated at 60°C for 3 hours. Concentration gave a

residue, which was washed with aq $NaHCO_3$. The product was purified by chromatography with $CHCl_3$-MeOH-28% aq NH_3 (18:1:0.1) to give a solid of **10**, 431 mg (88%), $[\alpha]_D^{20}$ −32° (*c* 1, $CHCl_3$); MS *m/z* 694 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.95 (3H, t, $J_{16,17}=7.3$ Hz, 17-CH_3), 1.18 (3H, d, $J_{8,21}=6.8$ Hz, 21-CH_3), 1.28 (3H, d, $J_{5',6'}=6.3$ Hz, 6'-CH_3), 1.69 (3H, s, 18-CH_3), 1.80 (3H, s, 22-CH_3), 2.49 (6H, s, 3'-$N(CH_3)_2$), 4.04 (1H, d, 1'-H), 5.60 (1H, br s, 3-H), 5.81 (1H, d, 13-H), 6.16 (1H, d, 10-H), 7.14 (1H, d, 11-H), and 9.74 (1H, s, 20-H).

Anal Calcd for $C_{37}H_{63}NO_9Si\cdot\frac{1}{2}H_2O$: C 63.21, H 9.17, N 1.99.
Found: C 63.48, H 9.08, N 1.88.

3-Deoxy-3,4-didehydro-5-*O*-mycaminosyltylonolide (**1**)

To an ice-cold solution of **10** (230 mg) in THF (4.6 ml) was added 1 M aq HCl (2.3 ml), and the solution was heated for 2 hours at 40°C. TLC ($CHCl_3$-MeOH-28% aq NH_3, 10:1:0.1) of the solution gave a single spot at Rf 0.25 (*cf.* **10**: Rf 0.35). Concentration to a small volume was followed by extraction of the residue with chloroform. The organic solution was washed with aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed with $CHCl_3$-MeOH-28% aq NH_3 (15:1:0.1) to give a solid of **1**, 163 mg (85%), $[\alpha]_D^{20}$ −21° (*c* 1, $CHCl_3$); MS *m/z* 580 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.96 (3H, t, $J=7.3$ Hz, 17-CH_3), 1.18 (3H, d, $J=6.8$ Hz, 21-CH_3), 1.28 (3H, d, $J=5.9$ Hz, 6'-CH_3), 1.70 (3H, s, 18-CH_3), 1.84 (3H, s, 22-CH_3), 2.52 (6H, s, 3'-$N(CH_3)_2$), 4.05 (1H, d, $J_{1',2'}=7.8$ Hz, 1'-H), 4.35 (1H, br s, 5-H), 4.96 (1H, m, 15-H), 5.60 (1H, br s, 3-H), 5.78 (1H, d, $J_{13,14}=10$ Hz, 13-H), 6.18 (1H, d, $J_{10,11}=16$ Hz, 10-H), 7.15 (1H, d, 11-H), and 9.73 (1H, s, 20-H).

Anal Calcd for $C_{31}H_{49}NO_9\cdot\frac{1}{2}H_2O$: C 63.24, H 8.56, N 2.38.
Found: C 63.51, H 8.71, N 2.33.

23-*O*-*tert*-Butyldimetylsilyl-5-*O*-(4-deoxymycaminosyl)tylonolide Dimethyl Acetal (**12**)

Compound **11**[5] (10.00 g) was treated with *tert*-butyldimethylsilyl chloride (2.88 g) in a manner as described for **4**. The crude product obtained (without chromatography) was recrystallized from ether to give **12** as crystals, 10.40 g (88%), mp 178.5~179°C, $[\alpha]_D^{20}$ −4° (*c* 1, $CHCl_3$); MS *m/z* 742 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.89 (9H, s, *tert*-butyl), 1.09 (3H, d, 18-CH_3), 1.77 (3H, s, 22-CH_3), 2.27 (6H, s, 3'-$N(CH_3)_2$), 3.24 and 3.45 (each 3H, s, $OCH_3\times2$).

Anal Calcd for $C_{39}H_{71}NO_{10}Si\cdot H_2O$: C 61.62, H 9.68, N 1.84.
Found: C 61.94, H 9.51, N 1.81.

5-*O*-(2-*O*-Acetyl-4-deoxymycaminosyl)-23-*O*-*tert*-butyldimethylsilyltylonolide Dimethyl Acetal (**13**)

Compound **12** (1.00 g) was treated with acetic anhydride (0.2 ml) as described for **5** to give, after chromatography ($CHCl_3$-MeOH, 15:1), a solid of **13**, 1.00 g (95%), $[\alpha]_D^{20}$ +21° (*c* 1, $CHCl_3$); MS *m/z* 784 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 2.10 (3H, s, Ac), 2.30 (6H, s, 3'-$N(CH_3)_2$), 3.22 and 3.30 (each 3H, s, $OCH_3\times2$).

Anal Calcd for $C_{41}H_{73}NO_{11}Si$: C 62.80, H 9.38, N 1.79.
Found: C 62.53, H 9.11, N 1.77.

5-*O*-(2-*O*-Acetyl-4-deoxymycaminosyl)-3-*O*-phenylmethanesulfonyl-23-*O*-*tert*-butyldimethylsilyltylonolide Dimethyl Acetal (**14**)

Compound **13** (884 mg) was treated with phenylmethanesulfonyl chloride (390 mg) as described for **6** to give a solid of **14**, 1.05 g (quant.), which was used for the next step without purification, TLC: Rf 0.6 ($CHCl_3$-MeOH, 10:1) (*cf.* **11**: Rf 0.5); MS *m/z* 938 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.89 (9H, s, *tert*-butyl), 2.09 (3H, s, Ac), 3.27 and 3.33 (each 3H, s, $OCH_3\times2$), 5.89 (1H, d, 13-H), 6.26 (1H, d, 10-H), ~7.4 (5H, m, *Ph*CH_2SO_2).

5-*O*-(2-*O*-Acetyl-4-deoxymycaminosyl)-23-*O*-*tert*-butyldimethylsilyl-3-deoxy-3,4-didehydrotylonolide Dimethyl Acetal (**15**)

A mixture of **14** (950 mg, 1.01 mmol) and NaI (456 mg, 3.04 mmol) in dry 2-butanone (19 ml) was stirred for 6.5 hours at 80°C. TLC (benzene-acetone, 2:1) of the solution showed a major spot at Rf 0.55 with weak spots (Rf 0.5, 0.65, and 0.7; *cf.* **14**: Rf 0.6). Similar treatment as described for **9** gave, after

chromatography (benzene - acetone, 3 : 1), a solid of **15**, 567 mg (73% based on **13**), $[\alpha]_D^{20}$ 0° (*c* 1, $CHCl_3$); MS *m/z* 766 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.89 (9H, s, *tert*-butyl), 1.61 (3H, br s, 18-CH_3), 1.80 (3H, s, 22-CH_3), 2.08 (3H, s, Ac), 2.30 (6H, s, 3'-$N(CH_3)_2$), 3.27 and 3.30 (each 3H, s, $OCH_3 \times 2$), 4.13 (1H, d, $J_{1',2'}=7.9$ Hz, 1'-H), 4.33 (1H, br s, 5-H), 4.83 (1H, dd, 2'-H), 4.98 (1H, br s, 3-H), 5.74 (1H, d, $J_{13,14}=10.4$ Hz, 13-H), 6.15 (1H, d, $J_{10,11}=15.9$ Hz, 10-H), and 7.09 (1H, d, 11-H).

Anal Calcd for $C_{41}H_{71}NO_{10}Si \cdot \frac{1}{2}H_2O$: C 63.53, H 9.36, N 1.81.
Found: C 63.78, H 9.11, N 1.80.

23-*O*-*tert*-Butyldimethylsilyl-3-deoxy-5-*O*-(4-deoxymycaminosyl)-3,4-didehydrotylonolide Dimethyl Actal (**16**)

Compound **15** (396 mg) in methanol (8 ml) was treated as described for **10** to give a solid of **15**, 324 mg (87%), $[\alpha]_D^{20}$ −16° (*c* 1, $CHCl_3$); MS *m/z* 724 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 1.75 (3H, s, 18-CH_3), 1.81 (3H, s, 22-CH_3), 2.28 (6H, s, 3'-$N(CH_3)_2$), 5.47 (1H, br s, 3-H), 5.78 (1H, d, 13-H), 6.20 (1H, d, 10-H), and 7.12 (1H, d, 11-H).

Anal Calcd for $C_{39}H_{69}NO_9Si \cdot \frac{1}{4}H_2O$: C 64.29, H 9.62, N 1.92.
Found: C 64.21, H 9.45, N 1.94.

3-Deoxy-5-*O*-(4-deoxymycaminosyl)-3,4-didehydrotylonolide (**2**)

From **16**: A solution of **16** (199 mg) in THF (4 ml) was treated with 1 M aq HCl (2 ml) as described for **1** to give a solid of **2**, 135 mg (87%). $[\alpha]_D^{27}$ −28° (*c* 1, $CHCl_3$); MS *m/z* 564 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.96 (3H, t, 17-CH_3), 1.18 (3H, d, $J=6.35$ Hz, 21-CH_3 or 6'-CH_3), 1.20 (3H, d, $J=5.86$ Hz, 6'-CH_3 or 21-CH_3), 1.76 (3H, s, 18-CH_3), 1.83 (3H, d, $J_{13,22}=\sim 1$ Hz, 22-CH_3), 2.27 (6H, s, 3'-$N(CH_3)_2$), 2.35 (1H, dd, 2a-H), 2.45 (1H, m, 3'-H), 2.75 (1H, dd, 2b-H), 3.22 (1H, dd, $J_{1',2'}=7.3$ Hz and $J_{2',3'}=10$ Hz, 2'-H), 4.00 (1H, d, 1'-H), 4.36 (1H, br s, 5-H), 4.94 (1H, m, 15-H), 5.55 (1H, t, 3-H), 5.57 (1H, br d, $J_{13,14}=10$ Hz, 13-H), 6.23 (1H, d, $J_{10,11}=16$ Hz, 10-H), 7.14 (1H, d, 11-H), and 9.76 (1H, s, 20-H).

Anal Calcd for $C_{31}H_{49}NO_8 \cdot \frac{1}{4}H_2O$: C 65.53, H 8.69, N 2.47.
Found: C 65.55, H 8.57, N 2.13.

From **24**: A solution of **24** (155 mg) in acetonitrile (2.3 ml) - 0.5 M aq HCl (4.6 ml) was heated for 2 hours at 40°C, and treated as described above to give a solid of **2**, 86.6 mg (76%), the product being identical with **2** obtained from **16**.

23-*O*-*tert*-Butyldimethylsilyl-5-*O*-mycaminosyltylonolide 9,20-Bis(ethylene acetal) (**18**)

A mixture of **17**[7] (3.00 g), imidazole (536 mg) and *tert*-butyldimethylsilyl chloride (990 mg) in dry DMF (24 ml) were treated as described for **4** to give a solid of **18**, 3.01 g (86%), $[\alpha]_D^{21}$ −10° (*c* 1, $CHCl_3$); MS *m/z* 800 $(M+1)^+$.

Anal Calcd for $C_{41}H_{73}NO_{12}Si \cdot \frac{1}{2}H_2O$: C 60.86, H 9.22, N 1.73.
Found: C 60.84, H 9.04, N 1.83.

3-*O*-Phenylmethanesulfonyl-5-*O*-[4-*O*-(phenylmethanesulfonyl)mycaminosyl]-23-*O*-*tert*-butyldimethylsilyl)tylonolide 9,20-Bis(ethylene acetal) (**19**)

To a cold (−40°C) solution of **18** (1.00 g, 1.25 mmol) in dry pyridine (20 ml) was added phenylmethanesulfonyl chloride (670 mg, 3.51 mmol) and the solution was kept at −20°C for 1.5 hours. Water (0.7 ml) was added and working-up as described for **6** gave a solid of **19**, 1.38 g (quant.), which was unstable, and used for the next step without purification.

3-*O*-Phenylmethanesulfonyl-23-*O*-*tert*-butyldimethylsilyl-5-*O*-(4-deoxy-4-iodomycaminosyl)tylonolide 9,20-Bis(ethylene acetal) (**20**)

A mixture of **19** (415 mg, 0.38 mmol) and NaI (141 mg, 0.94 mmol) in dry 2-butanone (6.2 ml) was stirred for 30 minutes at 80°C under the atmosphere of nitrogen. On TLC (cyclohexane - acetone, 3 : 1), the solution showed a major spot at Rf 0.4 with a very weak spot at Rf 0.33 (*cf.* **19**: Rf 0.28). Work-up as described for **9** (for chromatography, cyclohexane - acetone, 7 : 2 was used) gave a solid of **20**, 290 mg (73%), $[\alpha]_D^{27}$ −70° (*c* 1, $CHCl_3$); MS *m/z* 1,064 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.88 (9H, s, *tert*-butyl), 0.93 (3H, t, $J=7.5$ Hz, 17-CH_3), 0.97 (3H, d, 18-CH_3 or 21-CH_3), 1.02 (3H, d, 21-CH_3 or 18-CH_3), 1.48

(3H, d, $J_{5',6'}=6$ Hz, 6'-CH_3), 1.71 (3H, br s, 22-CH_3), 2.54 (6H, s, $N(CH_3)_2$), ~3.37 (1H, m, 2'-H), 4.38 (1H, d, $J_{1',2'}=7.5$ Hz, 1'-H), 4.50 (2H, br s, $PhCH_2SO_2$), 5.48 (1H, br d, $J_{13,14}=10$ Hz, 13-H), 5.59 (1H, d, $J_{10,11}=16$ Hz, 10-H), and 6.37 (1H, d, 11-H).

Anal Calcd for $C_{48}H_{78}INO_{13}SSi$: C 54.17, H 7.39, N 1.32, I 11.92.
Found: C 54.09, H 7.27, N 1.08, I 11.95.

23-*O*-*tert*-Butyldimethylsilyl-3-deoxy-5-*O*-(4-deoxy-4-iodomycaminosyl)-3,4-didehydrotylonolide 9,20-Bis(ethylene acetal) (**21**)

From **19**: A mixture of **19** (1.32 g, 1.19 mmol) and NaI (940 mg, 6.27 mmol) in dry 2-butanone (25 ml) was stirred for 6 hours at 80°C under the atmosphere of nitrogen. On TLC (benzene - ethyl acetate, 4 : 1), the solution showed several spots at Rf 0 (major), 0.3 (major, **21**), 0.43 (minor, **20**), 0.47 (slight, **19**), and 0.6 (slight). Subsequent work-up as described for **9** followed by chromatography (benzene - ethyl acetate, 5.5 : 1) gave a solid of **21**, 330 mg (31% based on **18**) and a solid of **20**, 130 mg (10% based on **18**).

21: $[\alpha]_D^{27}$ −72° (*c* 1, $CHCl_3$); MS *m/z* 892 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.95 (3H, t, 17-CH_3), 0.97 (3H, d, 21-CH_3), 1.51 (3H, d, 6'-CH_3), 1.57 (3H, br s, 18-CH_3), 1.70 (3H, s, 22-CH_3), 2.54 (6H, s, 3'-$N(CH_3)_2$), 3.39 (1H, dd, 2'-H), 4.14 (1H, d, 1'-H), 5.41 (1H, d, 13-H), 5.43 (1H, t, 3-H), 5.56 (1H, d, 10-H), and 6.31 (1H, d, 11-H).

Anal Calcd for $C_{41}H_{70}INO_{10}Si$: C 55.21, H 7.91, I 14.23, N 1.57.
Found: C 55.09, H 7.80, I 13.97, N 1.47.

From **20**: A mixture of **20** (120 mg) and NaI (85 mg) in dry 2-butanone - DMF (10 : 1, 2.6 ml) was stirred for 6 hours at 80° under the atmosphere of nitrogen. Work-up as described above gave a solid of **21**, 40 mg (40%).

5-*O*-(4-Bromo-4-deoxymycaminosyl)-23-*O*-*tert*-butyldimethylsilyl-3-deoxy-3,4-didehydrotylonolide 9,20-Bis(ethylene acetal) (**22**)

A mixture of **19** (150 mg, 0.14 mmol) and LiBr (59 mg, 0.68 mmol) in dry 2-butanone (3 ml) was stirred for 6 hours at 80°C. TLC (benzene - ethyl acetate, 4 : 1) of the solution showed spots at Rf 0 (major), 0.23 (major, **22**), 0.3 (slight), and 0.4 (slight). Subsequent work-up as described for **9** followed by chromatography (benzene - ethyl acetate, 4 : 1) gave a slightly unstable solid of **22**, 47 mg (41%), and a product mixture (41 mg) having Rf 0 (eluted with $CHCl_3$ - MeOH, 10 : 1).

22: $[\alpha]_D^{20}$ −47° (*c* 1, $CHCl_3$); MS *m/z* 844 and 846 (both $(M+1)^+$), 236 and 238, ^1H NMR ($CDCl_3$) δ 0.89 (9H, s, *tert*-butyl), 1.42 (3H, d, 6'-CH_3), 2.58 (3H, s, 3'-$N(CH_3)_2$), 2.69 (1H, t, $J_{2',3'}=J_{3',4'}=10$ Hz, 3'-H), 4.18 (1H, d, 1'-H), 5.41 (1H, d, $J=10$ Hz, 13-H), 5.42 (1H, br s, 3-H), 5.56 (1H, d, $J=16$ Hz, 10-H), and 6.32 (1H, d, 11-H).

Anal Calcd for $C_{41}H_{70}BrNO_{10}Si\cdot\frac{1}{2}H_2O$: C 57.66, H 8.50, N 1.64.
Found: C 57.85, H 8.25, N 1.58.

23-*O*-*tert*-Butyldimethylsilyl-5-*O*-(4-chloro-4-deoxymycaminosyl)-3-deoxy-3,4-didehydrotylonolide 9,20-Bis(ethylene acetal) (**23**)

A mixture of **19** (150 mg, 0.14 mmol) and Et_4NCl (68 mg, 0.41 mmol) in dry 2-butanone (3 ml) was stirred for 6 hours at 80°C. TLC (benzene - ethyl acetate, 4 : 1) of the solution showed spots at Rf 0 (major), 0.17 (major, **23**), and 0.2 (slight; possibly 3-*O*-benzylsulfonyl-4'-chloro-4'-deoxy derivative), together with several slight sports. Chromatography (benzene - ethyl acetate, 4 : 1) of the crude mixture gave a slightly unstable solid of **23**, 40 mg (37%), and a product mixture (36 mg) having Rf 0 (eluted with $CHCl_3$ - MeOH, 10 : 1).

23: $[\alpha]_D^{20}$ −45° (*c* 1, $CHCl_3$); MS *m/z* 800 [M + 1 (for the ^{35}Cl isomer)]$^+$, 192 and 194 (3 : 1 in strength), ^1H NMR ($CDCl_3$) δ 0.89 (9H, s, *tert*-butyl), 1.36 (3H, d, 6'-CH_3), 2.55 (3H, s, 3'-$N(CH_3)_2$), 3.58 (1H, t, $J_{3',4'}=J_{4',5'}=10$ Hz, 4'-H), 4.17 (1H, d, 1'-H), 5.40 (1H, d, $J=10$ Hz, 13-H), 5.41 (1H, br s, 3-H), 5.56 (1H, d, $J_{10,11}=16$ Hz, 10-H), and 6.31 (1H, d, 11-H).

Anal Calcd for $C_{41}H_{70}ClNO_{10}Si\cdot\frac{1}{2}H_2O$: C 60.82, H 8.84, Cl 4.38, N 1.73.
Found: C 60.93, H 8.82, Cl 4.52, N 1.70.

23-*O*-*tert*-Butyldimethylsilyl-3-deoxy-5-*O*-(4-deoxymycaminosyl)-3,4-didehydrotylonolide 9,20-Bis(ethylene Acetal) (**24**)

To a solution of **21** (230 mg, 0.26 mmol) in benzene (7.5 ml) were added Bu_3SnH (0.22 ml, 0.82 mmol) and AIBN (10 mg), and the solution was heated under the atmosphere of Ar for 2 hours at 80°C. On TLC with $CHCl_3$-MeOH-28% aq NH_3 (10:1:0.1), the solution showed a single spot at Rf 0.5 (*cf.* **21**: Rf 0.9). Concentration gave a residue, that was chromatographed by successive use of cyclohexane-acetone (3:1, 250 ml)→$CHCl_3$ (120 ml)→$CHCl_3$-MeOH-28% aq NH_3 (10:1:0.1) to give a stannane-free solid of **24**, 185 mg (94%), $[\alpha]_D^{27}$ −53° (*c* 1, $CHCl_3$); MS *m/z* 766 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.89 (9H, s, *tert*-butyl), 1.23 (3H, d, 6′-CH_3), 2.30 (6H, s, 3′-$N(CH_3)_2$), 3.30 (1H, dd, 2′-H), 4.08 (1H, d, J=7.3 Hz, 1′-H), 5.40 (1H, br s, 3-H), 5.40 (1H, d, J=10 Hz, 13-H), 5.57 (1H, d, $J_{10,11}$=16 Hz, 10-H), and 6.31 (1H, d, 11-H).

Anal Calcd for $C_{41}H_{71}NO_{10}Si \cdot H_2O$: C 62.80, H 9.13, N 1.79.
Found: C 63.02, H 9.12, N 1.76.

Desmycosin 20-(Ethylene Acetal) (**25**)

A mixture of tylosin (10.65 g), ethylene glycol (50 ml), camphorsulfonic acid (3.48 g) and acetonitrile (50 ml) was kept for 1 hour at room temperature. The solution was poured into a 0.1 M aq K_2CO_3 (170 ml) and the mixture was extracted with toluene. The organic solution was concentrated and the residue was chromatographed ($CHCl_3$-MeOH-28% aq NH_3, 15:1:0.1) to give a solid of **25**, 6.52 g (80%), $[\alpha]_D^{20}$ −26° (*c* 1, $CHCl_3$); MS *m/z* 816 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 1.26 (3H, d, 6″-CH_3), 1.31 (3H, d, 6′-CH_3), 2.50 (6H, s, 3′-$N(CH_3)_2$), 3.48 and 3.56 (each 3H, s, $OCH_3 \times 2$), 4.32 (1H, d, $J_{1',2'}$=7.3 Hz, 1′-H), 4.56 (1H, d, $J_{1'',2''}$=7.8 Hz, 1″-H), 5.88 (1H, unresolved s, 13-H), 6.23 (1H, unresolved s, 10-H), and 7.28 (1H, unresolved s, 11-H).

Anal Calcd for $C_{41}H_{69}NO_{15} \cdot H_2O$: C 59.05, H 8.58, N 1.68.
Found: C 59.23, H 8.60, N 1.64.

2′,4′,4″-Tri-*O*-acetyldesmycosin 20-(Ethylene Acetal) (**26**)

A solution of **25** (1.00 g, 1.23 mmol) and acetic anhydride (0.28 ml, 2.94 mmol) in acetonitrile (15 ml) was kept overnight at room temperature. After concentration to a small volume, toluene (40 ml) was added, and the solution was washed vigorously with aq $NaHCO_3$, dried ($MgSO_4$), and concentrated to give the corresponding crude 2′,4′-di-*O*-acetyl derivative, 1.1 g; Rf 0.7 (toluene-ethyl acetate, 1:2) (*cf.* **25**: Rf 0.35). After dryness, the solid was dissolved in dry pyridine (16 ml) containing acetic anhydride (0.116 ml, 1.23 mmol) and the solution was kept for 2 days at room temperature. On TLC (benzene-acetone, 2:1), the solution showed two spots at Rf 0.45 (minor, the 2′,4′-di-*O*-acetyl derivative) and 0.7 (**26**). After work-up in a usual manner, the product was chromatographed with benzene-acetone (3:1) to give a solid of **26**, 818 mg (71%) along with the di-*O*-acetyl derivative, 187 mg (17%).

26: $[\alpha]_D^{20}$ −3° (*c* 1, $CHCl_3$); MS *m/z* 942 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ ~1.18 (9H, br, 21-, 6′-, and 6″-CH_3), 2.05, 2.06 and 2.11 (each 3H, s, Ac×3), 2.43 (6H, s, 3′-$N(CH_3)_2$), 3.47 and 3.52 (each 3H, s, $OCH_3 \times 2$), ~4.40 (1H, br s, 1′-H), 4.43 (1H, dd, 4″-H), 4.62 (1H, d, 1″-H), 4.77 (1H, t, 4′-H), ~4.94 (3H, m, 15-H, 20-H, 2′-H), 5.88 (1H, d, 13-H), 6.27 (1H, d, 10-H), and 7.33 (1H, d, 11-H).

Anal Calcd for $C_{47}H_{75}NO_{18}$: C 59.92, H 8.02, N 1.49.
Found: C 59.75, H 8.02, N 1.42.

2′,4′,4″-Tri-*O*-acetyl-3-*O*-(phenylmethanesulfonyl)desmycocin 20-(Ethylene Acetal) (**27**)

Compound **26** (900 mg, 0.96 mmol) was treated with phenylmethanesulfonyl chloride (370 mg, 1.94 mmol) in pyridine (14 ml) in a manner as described for **6** to give a slightly unstable solid of **27**, 1.07 g (quant.); Rf 0.45 (toluene-ethyl acetate, 1:2) (*cf.* **26**: Rf 0.4).

2′,4′,4″-Tri-*O*-acetyl-3-deoxy-3,4-didehydrodesmycocin 20-(Ethylene Acetal) (**28**)

A mixture of **27** (1.10 g, 1.0 mmol) and NaI (450 mg, 3.0 mmol) in 2-butanone (17 ml) was stirred for 15 hours at 80°C. On TLC (toluene-ethyl acetate, 1:2) the upper solution showed a spot at Rf 0.38. Post-treatment as described for **9** gave, after chromatography (toluene-ethyl acetate, 4:5→3:5), a solid of **28**, 618 mg (67% based on **26**), $[\alpha]_D^{20}$ −18° (*c* 1, $CHCl_3$); MS *m/z* 924 $(M+1)^+$, ^1H NMR ($CDCl_3$)

δ 0.94 (3H, t, 17-CH_3), 1.14, 1.17, and 1.18 (each 3H, d, 21-, 6'-, and 6''-CH_3), 1.60 (3H, s, 18-CH_3), 1.79 (3H, s, 22-CH_3), 2.03, 2.05, and 2.11 (each 3H, s, Ac×3), 2.34 (6H, s, 3'-N(CH_3)$_2$), 3.46 and 3.52 (each 3H, s, OCH_3×2), 4.19 (1H, d, 1'-H), 4.43 (1H, br d, 4''-H), 4.61 (1H, d, 1''-H), 4.76 (1H, t, 4'-H), ~4.95 (3H, br, 15-, 20-, and 2'-H), 5.49 (1H, br, 3-H), 5.76 (1H, d, 13-H), 6.14 (1H, d, 10-H), and 7.10 (1H, d, 11-H).

Anal Calcd for $C_{47}H_{73}NO_{17}\cdot\frac{1}{2}H_2O$: C 60.50, H 7.99, N 1.51.
Found: C 60.33, H 8.00, N 1.47.

4''-*O*-Acetyl-3-deoxy-3,4-didehydrodesmycosin 20-(Ethylene Acetal) (**29**)

A solution of **28** (120 mg) in methanol (2.5 ml) was heated overnight at 50°C. The crude product obtained was chromatographed with $CHCl_3$-MeOH (10:1) to give a solid of **29**, 108 mg (99%), $[\alpha]_D^{20}$ −14° (*c* 1, $CHCl_3$); MS *m/z* 840 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 1.68 (3H, s, 18-CH_3), 1.83 (3H, s, 22-CH_3), 2.12 (3H, s, 4''-Ac), ~2.8 (6H, br s, 3'-N(CH_3)$_2$), 3.46 and 3.52 (each 3H, s, OCH_3×2), 4.09 (1H, d, 1'-H), 4.43 (1H, br d, 4''-H), 4.62 (1H, d, 1''-H), 5.37 (1H, br s, 3-H), 5.85 (1H, d, 13-H), 6.10 (1H, d, 10-H), and 7.29 (1H, d, 11-H).

Anal Calcd for $C_{43}H_{69}NO_{15}\cdot H_2CO_3$: C 58.58, H 7.93, N 1.55.
Found: C 58.41, H 7.78, N 1.56.

4''-*O*-Acetyl-3-deoxy-3,4-didehydrodesmycosin (**30**)

To an ice-cold solution of **29** (310 mg) in THF (6.2 ml) was added 1 M aq HCl (3.1 ml), and the solution was heated for 1.5 hours at 40°C. Work-up as described for **1** gave, after chromatography ($CHCl_3$-MeOH, 15:1→12:1), a solid of **30**, 245 mg (84%), $[\alpha]_D^{20}$ −15° (*c* 1, $CHCl_3$); MS *m/z* 796 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 1.68 (3H, s, 18-CH_3), 1.81 (3H, s, 22-CH_3), 2.12 (3H, s, 4''-Ac), 2.79 (6H, br s, 3'-N(CH_3)$_2$), 3.47 and 3.52 (each 3H, s, OCH_3×2), 4.07 (1H, d, 1'-H), 4.44 (1H, br d, 4''-H), 4.62 (1H, d, 1''-H), 5.54 (1H, br s, 3-H), 5.82 (1H, d, 13-H), 6.11 (1H, d, 10-H), 7.22 (1H, d, 11-H), and 9.73 (1H, s, 20-H).

Anal Calcd for $C_{41}H_{65}NO_{14}\cdot\frac{1}{2}H_2CO_3$: C 60.27, H 8.04, N 1.70.
Found: C 60.03, H 8.15, N 1.68.

3-Deoxy-3,4-didehydrodesmycosin (**31**)

To an ice-cold solution of **30** (100 mg) in methanol (1.5 ml) was added 0.1 M aq NaOMe in methanol (0.5 ml), and the solution was kept for 4 hours at the temperature. Neutralization (1 M aq HCl) followed by usual work-up gave, after chromatography ($CHCl_3$-MeOH-28% aq NH_3, 15:1:0.1), a solid of **31**, 80 mg (83%), $[\alpha]_D^{20}$ −38° (*c* $CHCl_3$); MS *m/z* 754 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.95 (3H, t, J=7.3 Hz, 17-CH_3), 1.18 (3H, d, J=6.7 Hz, 21-CH_3), 1.27 and 1.28 (each 3H, d, J=~6 Hz, 6'- and 6''-CH_3), 1.69 (3H, s, 18-CH_3), 1.80 (3H, s, 22-CH_3), 2.30 (6H, s, 3'-N(CH_3)$_2$), 3.48 and 3.61 (each 3H, s, OCH_3×2), 4.05 (1H, d, $J_{1',2'}$=7.3 Hz, 1'-H), 4.35 (1H, br s, 5-H), 4.56 (1H, d, $J_{1'',2''}$=7.9 Hz, 1''-H), 4.97 (1H, m, 15-H), 5.58 (1H, br s, 3-H), 5.83 (1H, d, $J_{13,14}$=10 Hz, 13-H), 6.14 (1H, d, $J_{10,11}$=16 Hz, 10-H), 7.16 (1H, d, 11-H), and 9.74 (1H, s, 20-H).

Anal Calcd for $C_{39}H_{63}NO_{13}$: C 62.13, H 8.42, N 1.86.
Found: C 62.20, H 8.69, N 1.79.

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