

Synthesis of 3-Deoxy-5-*O*-mycaminosyltylonolide and 3-Deoxy-5-*O*-(4-deoxymycaminosyl)tylonolide

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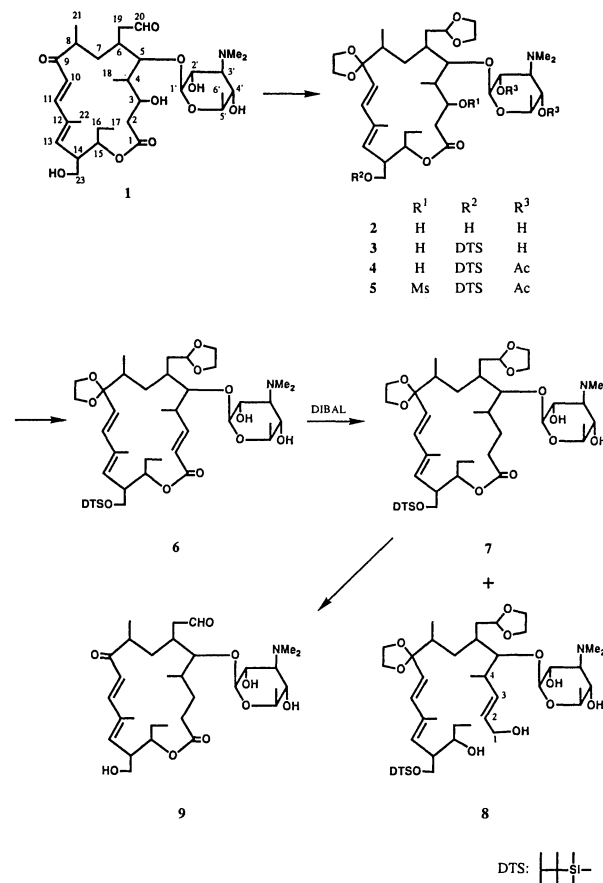
The title compounds, which proved highly antibacterial, have been prepared by selective hydrogenation of the corresponding 2,3-unsaturated compounds with LiAlH_4 , diisobutylaluminum hydride, or $\text{NaBH}_4\text{-NiCl}_2$ as the key steps. Further, the latter title compound was prepared effectively through the reaction of 3-*O*-benzylsulfonyl-5-*O*-(4-deoxy-4-iodomycaminosyl)-23-*O*-(dimethylhexylsilyl)tylonolide 9,20-bis(ethylene acetal) with Raney Ni- K_2CO_3 involving three steps in it.

Some macrolide antibiotics such as tylosin,¹⁾ josamycin,²⁾ niddamycin,³⁾ spiramycin I,⁴⁾ and rosamicin⁵⁾ have a hydroxyl (or acetoxyl) group at C-3 in their macrocyclic lactones. The therapeutic role of the hydroxyl group, however, has neither been discussed nor clarified. Removal of the OH-3 group will, therefore, give light to its biological role. Previously we prepared⁶⁾ a 4'-deoxymacrolide, 5-*O*-(4-deoxymycaminosyl)tylonolide (DT) and this compound showed remarkably enhanced antibacterial activity, compared to the parent compound, 5-*O*-mycaminosyltylonolide⁷⁾ (1). This is a successful example that deoxygenation exhibited a positive effect. In this paper we describe⁸⁾ the synthesis of 3-deoxy-5-*O*-mycaminosyltylonolide (9) and 3-deoxy-5-*O*-(4-deoxymycaminosyl)tylonolide (13) to prove the deoxygenation effect (at C-3) or combinative deoxygenation effects (at C-3 and C-4'), respectively, on their antibacterial activity.

Results and Discussion

Synthesis of 9 is first described. The 9,20-bis(ethylene acetal) (2) of 1 had been prepared⁹⁾ first by us by treatment of the 20-(diethyl acetal) of 1 with ethylene glycol in sulfolane–benzene in the presence of an acid-catalyst coupled with Soxhlet-type apparatus. However, this method took long time (48 h) to complete, met difficulty in removing the sulfolane, and the yield of 2 was moderate (62%); the major difficulty is in the protection of the less-reactive 9-carbonyl group. Here we found that 2 was readily prepared from 1 by use of diethylene orthocarbonate¹⁰⁾ in benzene- CH_3CN in a short period (2 h) (see Experimental). The product 2 was converted into the 23-*O*-silyl derivative 3 by treatment with dimethylhexylsilyl (DTS) chloride, and 3 was acetylated with acetic anhydride in CH_3CN (use of pyridine as the solvent was unsuitable) to give the 2',4'-di-*O*-acetyl derivative (4) having free OH-3, in high yield. After mesylation, the 3-*O*-mesyl derivative (5) was treated with ammonia in MeOH–water to give the 2,3-unsaturated product (6). Before carrying out this

reaction, direct deoxygenation of the HO-3 group was attempted; such as photochemical deoxygenation¹¹⁾ of the 3-*O*-acetyl derivative of 4 in HMPA- H_2O (95:5), treatment of the 2',4'-di-*O*-acetyl-3-*O*-(1-imidazolylthiocarbonyl) or 2',4'-di-*O*-acetyl-3-*O*-(phenoxythiocarbonyl) derivatives (their preparations are not described here) of 2 with¹²⁾ tributylstannane (Bu_3SnH)–azobis(isobutyronitrile) (AIBN), treatment of 3 with halogens (Br_2 and I_2) in the presence of triphenylphosphine¹³⁾ (followed by reductive dehalogenation), and treatment of the 3-*O*-mesyl derivative (5) with a halogenide (followed



by reductive dehalogenation). However, all of the trials failed to give the 3-deoxy or 3-halo derivatives, and when reaction occurred, 2,3-unsaturated derivatives were the major products in most cases. This led us prepare the 3-deoxy compound through the 2,3-unsaturated derivative.

Preferential hydrogenation of the 2,3-double bond without reducing the 10,11- and 12,13-double bonds was not easily attained. As catalytic hydrogenation of the 2,3-double bond by use of Pd or Pt in various reaction conditions all failed, giving only a mixture of randomly hydrogenated products, metal hydride-type of reducing reagents were tested. Treatment of **6** with NaBH₄ in MeOH or in pyridine,¹⁴ Mg in MeOH,¹⁵ Zn–NiCl₂·6H₂O¹⁶ in aqueous methyl Cellosolve, Na[(CH₃OCH₂CH₂O)₂AlH₂] (Red-Al by Aldrich Co.) in toluene, or Bu₃SnH–AIBN¹² in benzene all recovered the starting material; however, use of LiAlH₄ (LAH) in a ratio of LAH/**6** ca. 1.7 in tetrahydrofuran (THF) (at room temperature) or diisobutylaluminum hydride (DIBAL) in a ratio of DIBAL/**6** ca. 5 in toluene (–60°C) (see Experimental) gave the desired **7** in 51 and 55% yield, respectively. Less or excess use of the reagents resulted low yield of **7** or formation of higher proportion of the

open lactone ring product **8**, respectively. Deprotection of **7** gave the desired 3-deoxy-5-*O*-mycaminosyltylonolide **9**.

3-Deoxy-5-*O*-(4-deoxymycaminosyl)tylonolide (**13**) was prepared next and this was readily obtained from **7**. Preferential sulfonylation of the HO-4' of **7** was performed by use of phenylmethanesulfonyl chloride to give a slightly unstable product **10**. This instability may be resulted from the neighboring Me₂N-3', which will readily attack the C-4' to give the 3',4'-aziridinium ion intermediate.¹⁷ Treatment of **10** with NaI in 2-butanone gave the 4'-deoxy-4'-iodo derivative **11**. The configuration of I-4' of **11** was assumed to be *R*, that is, the same orientation with the starting HO-4', deduced by analogy of the reaction of **14** with NaI, which is described next. Radical deiodination of **11** with Bu₃SnH–AIBN¹² gave the 4'-deoxy derivative **12**, which was deprotected to give the final product **13**. The structures of **9** and **13** were determined by the ¹H and ¹³C NMR spectra (Tables 1 and 2).

As **13** was prepared from **1** in 10 steps, a shorter synthetic route was searched. Sulfonylation of **3** with phenylmethanesulfonyl chloride gave selectively the

Table 1. ¹H NMR^{a)} Chemical Shifts^{b)} of **9** and **13** with 5-*O*-Mycaminosyltylonolide (**1**) and 5-*O*-(4-Deoxymycaminosyl)tylonolide (DT) in CDCl₃ at 27°C

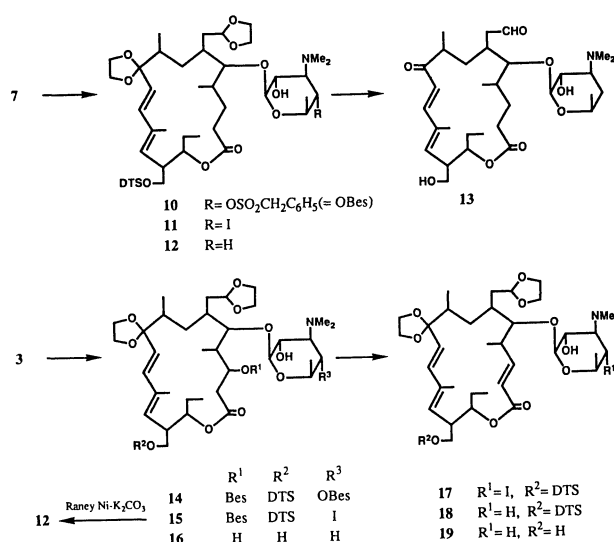
	9	1	13	DT
H-2	1.83, 2.42	1.96, 2.53	1.84, 2.44	1.96, 2.52
H-3	1.30, 1.44	3.85	1.26, 1.43	3.86
H-4	1.69	1.65	1.73	1.72
H-5	3.40	3.74	3.36	3.69
H-6	1.99	2.16	1.97	2.06
H-7	1.46, 1.67	1.49, 1.63	1.52, 1.73	1.62, 1.83
H-8	2.53	2.62	2.53	2.56
H-10	6.33	6.29	6.35	6.32
H-11	7.29	7.33	7.30	7.34
H-13	5.86	5.89	5.83	5.87
H-14	2.89	2.88	2.90	2.89
H-15	4.89	4.97	4.88	4.95
H-16	1.60, 1.84	1.61, 1.85	1.61, 1.86	1.61, 1.84
Me-17	0.94	0.95	0.94	0.95
Me-18	0.98	1.02	1.05	1.09
H-19	2.45, 2.93	2.40, 2.94	2.45, 3.00	2.46, 3.02
H-20	9.68	9.70	9.70	9.72
Me-21	1.22	1.22	1.21	1.21
Me-22	1.85	1.83	1.85	1.82
H-23	3.73, 3.73	3.75, 3.75	3.73, 3.73	3.74, 3.74
H-1'	4.23	4.26	4.19	4.21
H-2'	3.48	3.48	3.19	3.20
H-3'	2.49	2.36	2.49	2.46
H-4'	3.06	3.06	1.23, 1.60	1.20, 1.66
H-5'	3.23	3.27	3.43	3.47
H-6'	1.24	1.26	1.20, 1.21	1.20
NMe-3'	2.52	2.50	2.27	2.27

a) Measured at 500 MHz with a JEOL Alpha 500 NMR spectrometer. b) In ppm downfield from TMS. The shifts were confirmed by 2D ¹H–¹H and ¹H–¹³C correlated spectra with aid of, in some cases, Hohaha method.

Table 2. ¹³C NMR^{a)} Chemical Shifts^{b)} of **9** and **13** with 5-*O*-Mycaminosyltylonolide (**1**) and 5-*O*-(4-Deoxymycaminosyl)tylonolide (DT) in CDCl₃ at 27°C

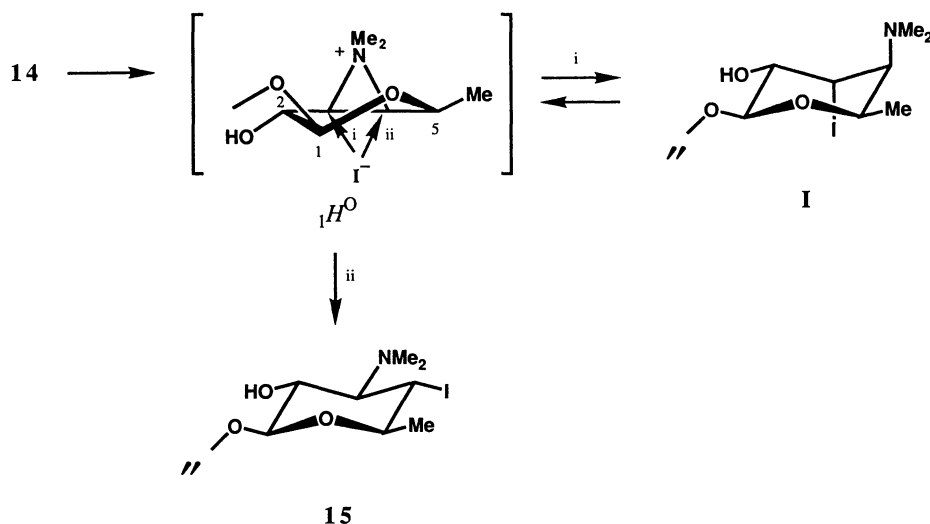
Carbon	9	1	13	DT
1	173.3	174.0	173.4	173.9
2	32.2	39.5	32.3	39.6
3	27.8	68.0	27.7	67.2
4	35.9	40.3	36.1	40.9
5	83.2	81.4	83.6	81.0
6	31.5	32.0	31.3	31.4
7	31.8	32.7	31.8	32.4
8	44.7	44.5	44.9	44.9
9	203.4	203.5	203.7	203.5
10	118.6	119.0	118.5	118.6
11	148.0	148.0	147.9	147.9
12	136.3	136.1	136.4	136.1
13	141.6	141.6	141.4	141.7
14	47.2	47.2	47.1	47.2
15	74.3	75.0	74.2	74.8
16	25.7	25.6	25.6	25.5
17	9.6	9.6	9.5	9.7
18	15.6	8.9	15.2	8.7
19	43.4	43.8	43.5	43.8
20	202.1	203.0	202.4	203.5
21	17.5	17.3	17.5	17.5
22	13.2	13.1	13.2	13.0
23	62.6	62.5	62.6	62.4
1'	103.7	104.0	104.2	104.2
2'	71.0	70.9	70.3	70.3
3'	70.1	70.2	65.6	65.6
4'	70.8	70.8	28.4	28.4
5'	73.2	73.1	69.5	69.5
6'	17.7	17.8	21.0	21.0
N-Me ₂	41.7	41.7	40.2	40.2

a) Measured at 125 MHz with a JEOL Alpha 500 NMR spectrometer. b) In ppm downfield from TMS. The shifts were confirmed by 2D ¹H–¹³C correlated spectra.



3,4'-bis(*O*-benzylsulfonyl) derivative (**14**). If, in this reaction, tosyl chloride or mesyl chloride was used instead, the corresponding 4'-*O*-tosyl or 3,2',4'-tri-*O*-mesyl derivative was the major product formed, respectively. This means that the bulk of benzylsulfonyl group is suitable for this reaction. Treatment of **14** with NaI similarly as described for **11** gave the 4'-iodo derivative (**15**) with the 3-*O*-benzylsulfonyl group remained intact. To determine the configuration at C-4', the splitting pattern of the H-4' in its ¹H NMR spectrum was searched, but the signals (δ = ca. 3.5 in C₆D₆) were overlapped with many other ones. However, irradiation of Me-6' (δ = 1.65) converted the isolated multiplet (δ = 3.84) of H-5 into a clear doublet ($J_{4,5}$ = 10.4 Hz), which indicates that H-4' should be axial. This result shows that iodine was introduced at C-4' with retention of configuration. The mechanism may be explained as that the initially formed *galacto*-3',4'-aziridinium ion intermediate¹⁷⁾ having a half-chair

conformation (${}_1H^O$) is iodinated through the Skew form to give **15** (route ii). However, this mechanism is against the Fürst-Plattner rule (trans-diaxial ring opening) of epimines; we propose therefore that intermediate will first be opened, according to the rule (route i) to give the unstable 4'-dimethylamino-3'-iodogulopyranoside (I), and then the I, which is equilibrated with the intermediate (${}_1H^O$), is gradually converted into the thermodynamically more stable 3'-dimethylamino-4'-iodogluco derivative (**15**) through the ${}_1H^O$ form, as shown below. A similar reaction mechanism was reported by us in the fluorinations of 3,23-di-*O*-acetyl-5-*O*-(4-*O*-benzylsulfonyl- β -D-mycaminosyl)tylonolide 9,20-bis(ethylene acetal)¹⁷⁾ and 2,3-*allo*-(*N*-tosylepimine)s.¹⁸⁾ No isolation of I in the present reaction will be ascribed to its instability caused by the low C-I bond energy, compared to C-F. Compound **15** was then treated with NH₃ in aq MeOH as described for **6** to give the 2,3-unsaturated product (**17**) by removal of the elements of phenylmethanesulfonic acid. Reductive deiodination of **17** gave **18**. Here the selective hydrogenation of the 2,3-double bond was again tested using the reducing agents described before and CuI-MeLi-DIBAL¹⁹⁾ (**18** was recovered), NaBH₄-DMF (to give **18** and glycoside-cleaved products), and KB[CH(CH₃)-C₂H₅]²⁰⁾ (K-Selectride by Aldrich Co.) (to give **19** and glycoside-cleaved products). Among them, LAH in THF, and NaBH₄-NiCl₂²¹⁾ in MeOH were found to give **12** in good to high yields, respectively (52 and 82%; see Experimental). These synthetic routes made the reaction steps reduce to 8, increasing the overall yields of **13** to 17—25%. At this stage, to examine the role of the protecting group at C-23, the 23-de(*O*-DTS) derivative (**19**) of **18** was prepared, and it was treated with several reducing agents involving LAH-THF or NaBH₄-NiCl₂-MeOH [compound **19** was prepared from DT through its 9,20-bis(ethylene acetal) (**16**)]. However, in these reactions, 10,11- and/or 12,13-double bonds were par-



Scheme 1.

tially reduced along with the 2,3-double bond giving a mixture of products involving **12**. This indicates that the protection of the HO-23 is necessary; this suggests that the HO-23 attracts the reagents to come close to the double bonds making reaction with them.

As described above, we can have **13** in good yield, however, for large-scale preparation, further rising of the yield and reduction of the steps with avoiding the troublesome procedure were necessary. After fruitless trials, we found that the use of Raney nickel–K₂CO₃ readily gave **12** in one step from **15** in high yield (40% **13** from **1**); in this reaction, selective diiodination at C-4', 2,3-double bond formation, and selective hydrogenation of the double bond occurred simultaneously.

The synthetic 3-deoxy (**9**) and 3,4'-dideoxy compounds (**13**) showed⁸⁾ stronger antibacterial activities than 5-*O*-mycaminosyltylonolide,⁷⁾ josamycin,²⁾ and erythromycin. Characteristic feature was that they showed⁸⁾ activity against Gram-negative bacteria, and **13** showed strong activity against *Haemophilus influenzae* IID 985. As the corresponding 2,3-unsaturated analog²²⁾ of **13** gave approximately one-half of the activity of **13**, deoxygenation at C-3 was suggested to be an important factor to enhance antibacterial activity.

Experimental

General. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. ¹H NMR spectra were recorded with a Bruker WM 250 (250 MHz) or JEOL Alpha 500 (500 MHz) spectrometers, and the chemical shifts (δ) were measured downfield from internal Me₄Si. Mass spectra (MS) were determined using fast atom bombardment method and the data are recorded as *m/z*. Thin-layer chromatography (TLC) was performed on Kieselgel 60 F₂₅₄ (Merck), and column chromatography on Wakogel C-200.

5-*O*-Mycaminosyltylonolide 9,20-Bis(ethylene acetal) (2). A mixture of ethylene glycol (0.3 ml, 5.4 mmol) and *p*-toluenesulfonic acid monohydrate (34 mg, 0.18 mmol) in benzene (2 ml) was refluxed for 2 h, coupled with Dean–Stark trap (azeotropic distillation). After cooled, tetramethyl orthocarbonate (0.32 ml, 2.4 mmol) was added, and the solution was kept for 2 h at room temperature. To this was added a solution of **1** (100 mg, 0.17 mmol) and anhydrous *p*-toluenesulfonic acid (36 mg, 0.21 mmol) in dry CH₃CN (1.5 ml), and the mixture was kept for 2 h at room temperature. The solution was poured into aq NaHCO₃ (saturated, 10 ml) under stirring and the mixture was extracted with benzene. The organic layer was dried (MgSO₄) and concentrated. The residue was chromatographed with CHCl₃–MeOH–28% aq NH₃ (30:1:0.1→10:1:0.1) to give a solid of **2**, 80 mg (70%), identical with the specimen reported.⁹⁾

23-*O*-(Dimethylthexylsilyl)-5-*O*-mycaminosyltylonolide 9,20-Bis(ethylene acetal) (3). To a solution of **2** (1.00 g, 1.46 mmol) in dry DMF (8 ml) were added dimethylthexylsilyl chloride (0.43 ml, 2.19 mmol) and imidazole (0.2 g), and the solution was kept at room temperature for 6 h. After concentration, the residue was dissolved in CHCl₃, and the solution was washed with water, dried (MgSO₄), and concentrated. The residue was chromatographed with CHCl₃–CH₃OH–aq 28% NH₃ (15:1:0.1) to give a solid of **3**, 1.12 g (93%),

$[\alpha]_D^{25} -9.0^\circ$ (c 1, CHCl₃); ¹H NMR (CDCl₃) δ =0.07 (6H, s, SiMe₂), 0.84 (6H, s, SiCMe₂), 0.88 (6H, d, SiCCHMe₂), 1.33 (3H, d, Me-6'), 1.71 (3H, br s, Me-22), 2.35 (1H, t, *J*_{2',3'}=*J*_{3',4'}=10 Hz, H-3'), 2.48 (6H, s, Me₂N-3'), 3.00 (1H, t, *J*_{4',5'}=10 Hz, H-4'), 4.30 (1H, d, *J*_{1',2'}=8 Hz, H-1'), 5.40 (1H, br d, *J*_{13,14}=10 Hz, H-13), 5.69 (1H, d, *J*_{10,11}=16 Hz, H-10), and 6.31 (1H, d, H-11); MS *m/z* 828 (M⁺+1).

Found: C, 61.95; H, 9.20; N, 1.68%. Calcd for C₄₃H₇₇NO₁₂Si: C, 62.36; H, 9.37; N, 1.69%.

5-*O*-(2,4-Di-*O*-acetylmycaminosyl)-23-*O*-(dimethylthexylsilyl)tylonolide 9,20-Bis(ethylene acetal) (4). To a solution of **3** (2.20 g) in dry CH₃CN (22 ml) was added acetic anhydride (0.6 ml) and the solution was kept overnight at room temperature. After concentration, the residue dissolved in toluene was washed with aq NaHCO₃ (saturated), dried (MgSO₄), and concentrated. The residue was purified by a short column with cyclohexane–acetone (7:2) to give a solid of **4**, 2.04 g (84%), $[\alpha]_D^{25} -40.0^\circ$ (c 1, CHCl₃); ¹H NMR (CDCl₃) δ =1.17 (3H, d, Me-6'), 2.00 and 2.04 (each 3H, s, Ac×2), 2.33 (6H, s, Me₂N-3'), 2.76 (1H, t, H-3'), 4.66 (1H, br d, H-1'), 4.75 (1H, t, H-4'), 4.94 (1H, dd, H-2'), 5.41 (1H, br d, H-13), 5.65 (1H, d, H-10), and 6.36 (1H, d, H-11); MS *m/z* 912 (M⁺+1).

Found: C, 61.79; H, 8.96; N, 1.48%. Calcd for C₄₇H₈₁NO₁₄Si: C, 61.88; H, 8.95; N, 1.54%.

5-*O*-(2,4-Di-*O*-acetylmycaminosyl)-23-*O*-(dimethylthexylsilyl)-3-*O*-mesyltylonolide 9,20-Bis(ethylene acetal) (5). To a solution of **4** (7.00 g) in dry pyridine (2 ml) was added methanesulfonyl chloride (0.18 ml), and the solution was kept for 3 h at room temperature. The solution was poured into aq NaHCO₃ (saturated) under vigorous stirring and the mixture was extracted with toluene. The product obtained by evaporation was purified by a short column with cyclohexane–acetone (3:1) to give a solid of **5**, 723 mg (95%), $[\alpha]_D^{25} -51.0^\circ$ (c 1, CHCl₃); ¹H NMR (CDCl₃) δ =2.02 and 2.04 (each 3H, s, Ac×2), 2.33 (6H, s, Me₂N-3'), 3.15 (3H, s, Ms), 5.46 (1H, br d, H-13), 5.57 (1H, d, H-10), and 6.35 (1H, d, H-11); MS *m/z* 990 (M⁺+1).

Found: C, 58.04; H, 8.62; N, 1.36%. Calcd for C₄₈H₈₃NO₁₆Si: C, 58.22; H, 8.45; N, 1.41%.

3-Deoxy-2,3-didehydro-23-*O*-(dimethylthexylsilyl)-5-*O*-mycaminosyltylonolide 9,20-Bis(ethylene acetal) (6). To a solution of **5** (51 mg) in MeOH (1 ml) was added 28% aq NH₃ (0.5 ml) and the solution was kept for 3 h at room temperature (2,3-double bond formation with partial removal of the 2'- and 4'-*O*-acetyl groups). After concentration, the residue dissolved in MeOH (1 ml) was heated overnight at 50°C (deacetylation). The solution was concentrated and the residue dissolved in CHCl₃ was washed with water, dried (MgSO₄), and concentrated. The residual syrup was purified by a short column with CHCl₃–MeOH–28% aq NH₃ (15:1:0.1) to give a solid of **6**, 39.9 mg (96%), $[\alpha]_D^{25} -34.0^\circ$ (c 1, CHCl₃); ¹H NMR (CDCl₃) δ =0.07 (6H, s), and 0.84 (6H, s), and 0.87 (6H, d) (Me×6 of dimethylthexylsilyl), 0.95 (3H, t, *J*=7.5 Hz, Me-17), 1.02 (3H, d, *J*_{8,21}=7 Hz, Me-21), 1.12 (3H, d, *J*_{4,18}=7 Hz, Me-18), 1.32 (3H, d, Me-6'), 1.71 (3H, br s, Me-22), 2.36 (1H, t, H-3'), 2.49 (6H, s, Me₂N-3'), 3.05 (1H, t, H-4'), 3.57 (1H, dd, *J*_{1',2'}=7.5 and *J*_{2',3'}=10 Hz, H-2'), 4.35 (1H, d, H-1'), 5.00 (1H, m, H-20), 5.32 (1H, br d, *J*_{13,14}=11 Hz, H-13), 5.49 (1H, d, *J*_{10,11}=16 Hz, H-10), 5.58 (1H, d, *J*_{2,3}=16 Hz, H-2), 6.25 (1H, d, H-11), and 6.74 (1H, dd, *J*_{3,4}=10 Hz, H-3); MS *m/z* 810 (M⁺+1).

Found: C, 63.47; H, 9.36; N, 1.68%. Calcd for C₄₃H₇₅NO₁₁Si: C, 63.75; H, 9.33; N, 1.73%.

3-Deoxy-23-O-(dimethylhexylsilyl)-5-O-mycaminosyltylonolide 9,20-Bis(ethylene acetal) (7) and a By-product (8). To a cold (-60°C) solution of **6** (2.00 g, 2.45 mmol) in dry toluene (80 ml) was added dropwise 1.5 M DIBAL (1 M = 1 mol dm $^{-3}$) in toluene (7.4 ml), and the solution was kept at the temperature for 30 min. In TLC with CHCl_3 - CH_3OH -28% aq NH_3 (10:1:0.1), the solution showed mainly three spots at R_f 0.4, 0.25, and 0.2. Excess DIBAL was destroyed by addition of $\text{Na}_2\text{SO}_4 \cdot 10 \text{ H}_2\text{O}$ (powder, 3 g), and the mixture was neutralized with 1 M aq AcOH (22 ml). After addition of CHCl_3 (600 ml), the organic solution was washed with aq NaCl (saturated), dried (MgSO_4), and concentrated. The residue was chromatographed with CHCl_3 - MeOH -28% aq NH_3 (18:1:0.1) to give solids of **7**, 1.09 g (55%), **8**, 0.59 g (29%), and a mixture of **8** and a product of R_f 0.2, 0.31 g.

Compounds **7**: $[\alpha]_D^{25} -27^{\circ}$ (c 1, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ =0.06 (6H, s), 0.83 (6H, s), and 0.87 (6H, d) (Me $\times$ 6 of dimethylhexylsilyl), 0.89 (3H, t, Me-17), 0.93 (3H, d, $J_{4,18}$ =7 Hz, Me-18), 1.01 (3H, d, Me-21), 1.31 (3H, d, Me-6'), 1.73 (3H, br s, Me-22), 2.35 (1H, t, H-3'), 2.48 (6H, s, Me_2N -3'), 3.01 (1H, t, H-4'), 4.31 (1H, d, $J_{1,2}$ =7.5 Hz, H-1'), 4.95 (1H, br t, H-20), 5.40 (1H, br d, $J_{13,14}$ =11 Hz, H-13), 5.62 (1H, d $J_{10,11}$ =16 Hz, H-10), and 6.37 (1H, d, H-11); MS m/z 812 (M^+ +1).

Found: C, 63.08; H, 9.49; N, 1.73%. Calcd for $\text{C}_{43}\text{H}_{77}\text{NO}_{11}\text{Si} \cdot 0.5 \text{ H}_2\text{O}$: C, 62.89; H, 9.57; N, 1.71%.

Compounds **8**: $[\alpha]_D^{25} -27^{\circ}$ (c 1, CHCl_3); $^1\text{H NMR}$ (CDCl_3 - C_6D_6 =1:1) δ =0.06 (6H, s), 0.84 (6H, s), and 0.88 (6H, d) (Me $\times$ 6 of dimethylhexylsilyl). 0.94 (3H, t, Me-17), 1.09 (3H, d, $J_{4,18}$ =7 Hz, Me-18), 1.13 (3H, d, Me-21), 1.36 (3H, d, Me-6'), 1.72 (3H, br s, Me-22), 2.43 (6H, s, Me_2N -3'), 3.06 (1H, t, H-4'), 4.03 (2H, d, $J_{1,2}$ =5 Hz, H-1), 4.31 (1H, d, H-1'), 4.92 (1H, m, H-20), 5.55 (1H, d, $J_{10,11}$ =16 Hz, H-10), 5.64 (1H, dd, $J_{2,3}$ =16 Hz, H-2), 5.68 (1H, br d, $J_{13,14}$ =10 Hz, H-13), 5.75 (1H, dd, $J_{3,4}$ =8 Hz, H-3), and 6.48 (1H, d, H-11); MS m/z 814 (M^+ +1).

3-Deoxy-5-O-mycaminosyltylonolide (9). To a solution of **7** (600 mg) in THF (9 ml) was added 1 M Bu_4NF in THF (1.1 ml) and the solution was kept for 5 h at room temperature. TLC (CHCl_3 - MeOH -28% aq NH_3 =10:1:0.1) of the solution showed a single spot at R_f 0.3. Concentration gave a residue, that was extracted with CHCl_3 . The organic solution was washed with water, dried (MgSO_4), and concentrated. The residue dissolved in CH_3CN (6 ml) was mixed with 0.1 M aq HCl (24 ml) and the turbid solution was stirred for 5 h at room temperature, to give a clear solution. Addition of aq NaHCO_3 (saturated, 60 ml) followed by extraction of the mixture with CHCl_3 gave a crude product, that was chromatographed with CHCl_3 - MeOH -28% aq NH_3 (15:1:0.1) to give a solid of **9**, 383 mg (89%), $[\alpha]_D^{25} -23^{\circ}$ (c 1, CHCl_3); MS m/z 582 (M^+ +1).

Found: C, 62.29; H, 8.80; N, 2.29%. Calcd for $\text{C}_{31}\text{H}_{51}\text{NO}_9 \cdot \text{H}_2\text{O}$: C, 62.08; H, 8.73; N, 2.33%.

5-O-[4-O-(Benzylsulfonyl)mycaminosyl]-3-deoxy-23-O-(dimethylhexylsilyl)tylonolide 9,20-Bis(ethylene acetal) (10). To a cold (-40°C) solution of **7** (1.30 g, 1.60 mmol) in dry pyridine (26 ml) was added phenylmethanesulfonyl chloride (459 mg, 2.40 mmol), and the solution was kept at the temperature for 3 h. Water (0.5 ml) was added, and the solution was warmed to room temperature. In TLC with cyclohexane-acetone (7:2), the solution showed a major spot at R_f 0.3. Concentration gave a residue, that was extracted with CHCl_3 . The organic solution was washed with aq NaHCO_3 (satu-

rated), dried (MgSO_4), concentrated, and the residue was dried under vacuum to give **10** as a slightly unstable solid, 1.55 g, which was used in the next step without purification.

3-Deoxy-5-O-(4-deoxy-4-iodomycaminosyl)-23-O-(dimethylhexylsilyl)tylonolide 9,20-Bis(ethylene acetal) (11). To a solution of **10** (1.56 g) in dry 2-butanone (24 ml) was added NaI (366 mg), and the mixture was stirred, under the atmosphere of N_2 , for 30 min at 80°C . In TLC with cyclohexane-acetone (7:2), the solution showed a major spot at R_f 0.4. Concentration gave a residue, that was extracted with EtOAc . The organic solution was washed with 0.1 M aq $\text{Na}_2\text{S}_2\text{O}_3$ and water, dried (MgSO_4), and concentrated. The residual syrup was chromatographed with cyclohexane-acetone (7:2) to give a solid of **11**, 1.04 g (71 % based on **7**), $[\alpha]_D^{25} -73^{\circ}$ (c 1, CHCl_3); MS m/z 922 (M^+ +1).

Found: C, 56.39; H, 8.24; N, 1.46; I, 14.14%. Calcd for $\text{C}_{43}\text{H}_{76}\text{INO}_{10}\text{Si}$: C, 56.01; H, 8.31; N, 1.56; I, 13.76%.

3-Deoxy-5-O-(4-deoxymycaminosyl)-23-O-(dimethylhexylsilyl)tylonolide 9,20-Bis(ethylene acetal) (12) From **11**. To a solution of **11** (1.04 g, 1.13 mmol) in dry benzene (20 ml) were added Bu_3SnH (0.91 ml, 3.4 mmol) and AIBN (37 mg), and the solution was heated under the atmosphere of N_2 for 2 h at 80°C . Concentration gave a residue, that was chromatographed by successive use of cyclohexane-acetone (3:1, 500 ml) $\rightarrow$ CHCl_3 (600 ml) $\rightarrow$ CHCl_3 - MeOH -28% aq NH_3 (10:1:0.1) to give a stannane-free solid of **12**, 790 mg (88%), $[\alpha]_D^{25} -38^{\circ}$ (c 1, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ =0.06 (6H, s), 0.83 (6H, s), and 0.87 (6H, d), (Me $\times$ 6 of dimethylhexylsilyl), 0.91 (3H t, Me-17), 0.96 (3H, d, Me-18), 1.01 (3H, d, Me-21), 1.24 (3H, d, Me-6'), 1.73 (3H, br s, Me-22), 2.40 (6H, s, Me_2N -3'), 3.33 (1H, dd, $J_{1,2}$ =7 and $J_{2,3}$ =10 Hz, H-2'), 4.29 (1H, d, H-1'), 4.99 (1H, br t, H-20), 5.38 (1H, br d, H-13), 5.60 (1H, d, $J_{10,11}$ =16 Hz, H-10), and 6.38 (1H, d, H-11); MS m/z 796 (M^+ +1).

Found: C, 64.55; H, 9.75; N, 1.71%. Calcd for $\text{C}_{43}\text{H}_{77}\text{NO}_{10}\text{Si}$: C, 64.87; H, 9.75; N, 1.76%.

From **15**. To a solution of **15** (305 mg, 0.28 mmol) in MeOH (6 ml) were added Raney Ni (0.5 ml) and anhydrous K_2CO_3 (116 mg, 0.84 mmol), and the mixture was shaken under the atmosphere of H_2 for 3 h at room temperature. After filtration, the solution was concentrated, and the residue was extracted with CHCl_3 . The crude product obtained was chromatographed with CHCl_3 - MeOH -28% aq NH_3 (15:1:0.1) to give a solid of **12**, 194 mg (87%), which was identical with the specimen prepared from **11** in all respects.

From **18** with LAH. To an ice-cold solution of **18** (10.0 g, 12.6 mmol) in THF (200 ml) was added LAH (960 mg, 25.2 mmol), and the mixture was stirred for 30 min at the temperature. Addition of powdered $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ (15 g; to destroy the excess LAH) followed by aq NH_4Cl (saturated, 30 ml) gave a neutral mixture. It was concentrated and the residue was extracted with toluene. The crude product obtained was chromatographed with CHCl_3 - MeOH -28% aq NH_3 (15:1:0.1) to give a solid of **12**, 5.21 g (52%).

From **18** with NaBH_4 - NiCl_2 . To a solution of **18** (100 mg, 0.13 mmol) in MeOH (2 ml) was added $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (15 mg, 0.063 mmol) and the solution was cooled to 0°C . To the solution was added piece by piece NaBH_4 (73 mg, 1.9 mmol) within 8 h. The resulting black suspension was poured into aq NH_4Cl (saturated, 6 ml) and the whole mixture was extracted with EtOAc . The organic solution was washed with water, dried (MgSO_4), and concentrated. The residue was chromatographed with CHCl_3 - MeOH -28% aq NH_3

(17:1:0.1) to give a solid of **12**, 81.9 mg (82%).

3-Deoxy-5-O-(4-deoxymycaminosyl)tylonolide (13). A solution of **12** (730 mg) in THF (12 ml) was treated similarly as described for **9** to give, after column chromatography with CHCl_3 -MeOH-28% aq NH_3 (12:1:0.1), a solid of **13**, 511 mg (99%), $[\alpha]_D^{25} -21^\circ$ (c 1, CHCl_3); MS m/z 566 ($M^+ + 1$).

Found: C, 63.81; H, 8.80; N, 2.50%. Calcd for $\text{C}_{31}\text{H}_{51}\text{NO}_8 \cdot \text{H}_2\text{O}$: C, 63.78; H, 8.97; N, 2.40%.

3-O-Benzylsulfonyl-5-O-[4-O-(benzylsulfonyl)mycaminosyl]-23-O-(dimethylthexylsilyl)tylonolide 9,20-Bis(ethylene acetal) (14). To a cold (-40°C) solution of **3** (100 mg, 0.12 mmol) in dry pyridine (2 ml) was added phenylmethanesulfonyl chloride (58 mg, 0.30 mmol) and the solution was kept at -20°C for 1.5 h. Water (0.06 ml) was added, and the solution was gradually warmed to room temperature. After concentration to one-fourth of its volume, the reaction mixture was extracted with toluene. The organic solution was then treated as described for **10** to give **14** as a slightly unstable solid, 132 mg, which was used to the next step without purification.

3-O-Benzylsulfonyl-5-O-(4-deoxy-4-iodomycaminosyl)-23-O-(dimethylthexylsilyl)tylonolide 9,20-Bis(ethylene acetal) (15). A mixture of **14** (132 mg, 0.12 mmol) and NaI (27 mg, 0.18 mmol) in 2-butanone (2.6 ml) was treated similarly as described for **11**, to give, after column chromatography (cyclohexane-acetone 7:2), a solid of **15**, 93.6 mg (71% based on **3**), TLC (benzene-EtOAc 4:1): R_f 0.55, $[\alpha]_D^{25} -54^\circ$ (c 1, CHCl_3); ^1H NMR (500 MHz, C_6D_6) $\delta=0.04$ (6H, s), 0.87 (6H, d), and 0.87 (6H, s) (Me $\times$ 6 of dimethylthexylsilyl), 1.645 (3H, d, Me-6'), 1.651 (3H, s, Me-22), 2.40 (6H, s, Me₂N-3'), 2.72 (1H, t, H-3'), 3.84 (1H, m, H-5'), 4.34 (2H, br s, PhCH_2SO_2), 4.69 (1H, d, $J_{1,2}=7$ Hz, H-1'), 5.66 (1H, d, $J_{13,14}=10.5$ Hz, H-13), 5.82 (1H, d, $J_{10,11}=15.5$ Hz, H-10), and 6.66 (1H, d, H-11); MS m/z 1092 ($M^+ + 1$).

Found: C, 54.86; H, 7.50; N, 1.18; I, 11.61%. Calcd for $\text{C}_{50}\text{H}_{82}\text{INO}_{13}\text{S}$: C, 54.98; H, 7.57; N, 1.28; I, 11.62%.

3-Deoxy-5-O-(4-deoxy-4-iodomycaminosyl)-2,3-didehydro-23-O-(dimethylthexylsilyl)tylonolide 9,20-Bis(ethylene acetal) (17). To a solution of **15** (18.0 g) in MeOH (750 ml) was added 28% aq NH_3 (100 ml), and the solution was treated similarly as described for **6** to give, after column chromatography (hexane-acetone 7:2), a solid of **17**, 11.5 g (76%), TLC (benzene-EtOAc 4:1): R_f 0.6, $[\alpha]_D^{25} -51^\circ$ (c 1, CHCl_3); ^1H NMR (CDCl_3) $\delta=0.08$ (6H, s), 0.84 (6H, s), and 0.88 (6H, d), (Me $\times$ 6 of dimethylthexylsilyl), 1.70 (3H, br s, Me-22), 2.60 (6H, s, Me₂N-3'), 4.37 (1H, d, H-1'), 4.97 (1H, m, H-20), 5.30 (1H, br d, $J_{13,14}=10$ Hz, H-13), 5.48 (1H, d, $J_{10,11}=16$ Hz, H-10), 5.59 (1H, d, $J_{2,3}=16$ Hz, H-2), 6.27 (1H, d, H-11), and 6.75 (1H, dd, $J_{3,4}=10$ Hz, H-3); MS m/z 920 ($M^+ + 1$).

Found: C, 56.08; H, 8.08; N, 1.41; I, 13.98%. Calcd for $\text{C}_{43}\text{H}_{74}\text{NIO}_{10}\text{Si}$: C, 56.14; H, 8.11; N, 1.52; I, 13.79%.

3-Deoxy-5-O-(4-deoxymycaminosyl)-2,3-didehydro-23-O-(dimethylthexylsilyl)tylonolide 9,20-Bis(ethylene acetal) (18). To a solution of **17** (67.5 g, 73.4 mmol) in dry benzene (1 dm³) were added, under the atmosphere of Ar, tributylstannane (59 ml, 220 mmol) and AIBN (2.5 g) and the solution was treated similarly as described for **12** to give, after column chromatographies [silica gel 750 g; hexane-acetone (3:1, 5 dm³) $\rightarrow$ CHCl_3 (3 dm³) $\rightarrow$ CHCl_3 -MeOH-28% aq NH_3 (15:1:0.1)], a solid of **18**, 52.0 g (89%), $[\alpha]_D^{25} -20^\circ$ (c 1, CHCl_3); ^1H NMR (500 MHz, CDCl_3) $\delta=0.07$ (6H, s, MeSi), 1.25 (3H, d, Me-6'), 1.70 (3H, d, Me-22), 2.27 (6H, s, Me₂N-3'), 4.31 (1H, d, H-1'), 5.05 (1H, br s, H-20), 5.29 (1H, d, H-13), 5.48 (1H, d, $J=16$ Hz, H-10) and

5.58 (1H, d, $J=16$ Hz, H-2), 6.25 (1H, d, H-11), and 6.76 (1H, dd, $J_{3,4}=9.3$ Hz, H-3); MS m/z 794 ($M^+ + 1$).

Found: C, 64.45; H, 9.46; N, 1.69%. Calcd for $\text{C}_{43}\text{H}_{75}\text{NO}_{10}\text{Si} \cdot 0.5 \text{H}_2\text{O}$: C, 64.30; H, 9.53; N, 1.74%.

5-O-(4-Deoxymycaminosyl)tylonolide 9,20-Bis(ethylene acetal) (16). Compound **DT** (1.00 g, 1.72 mmol) was treated similarly as described for **2** to give a solid of **16**, 944 mg (82%), $[\alpha]_D^{25} -5^\circ$ (c 1, CHCl_3); MS m/z 670 ($M^+ + 1$).

Found: C, 62.54; H, 8.96; N, 2.07%. Calcd for $\text{C}_{35}\text{H}_{59}\text{NO}_{11}$: C, 62.76; H, 8.88; N, 2.09%.

3-Deoxy-5-O-(4-deoxymycaminosyl)-2,3-didehydrotylonolide 9,20-Bis(ethylene acetal) (19). To a solution of **16** (800 mg, 1.20 mmol) in pyridine-DMF (4:1, 8 ml) was added acetic anhydride (3.0 ml, 27 mmol) and the solution was heated for 24 h at 60°C (peracetylation). After concentration to a small volume, the concentrate was extracted with toluene. The organic solution was washed with aq NaHCO_3 and water (removal of DMF), dried (MgSO_4), and concentrated. The residue was dissolved in MeOH (16 ml) and, after addition of K_2CO_3 (825 mg, 6 mmol), the mixture was stirred overnight at room temperature. Concentration followed by extraction of the residue with CH_2Cl_2 gave a solid, that was chromatographed with CHCl_3 -MeOH-aq 28% NH_3 (17:1:0.1) to give a solid of **19**, 561 mg (72%), $[\alpha]_D^{25} -10^\circ$ (c 1, CHCl_3); ^1H NMR (500 MHz, CDCl_3) $\delta=0.97$ (3H, t, Me-17), 1.02 (3H, d, Me-21), 1.21 (3H, d, Me-18), 1.25 (3H, d, Me-6'), 1.75 (3H, d, Me-22), 2.27 (6H, s, Me₂N-3'), 4.31 (1H, d, $J_{1,2}=7.3$ Hz, H-1'), 5.29 (1H, d, $J_{13,14}=10.4$ Hz, H-13), 5.52 (1H, d, $J_{10,11}=15.6$ Hz, H-10), 5.60 (1H, d, $J_{2,3}=15.6$ Hz, H-2), 6.29 (1H, d, H-11), 6.79 (1H, dd, $J_{3,4}=9.5$ Hz, H-3); MS m/z 652 ($M^+ + 1$).

Found: C, 63.07; H, 8.74; N, 2.02%. Calcd for $\text{C}_{35}\text{H}_{57}\text{NO}_{10} \cdot \text{H}_2\text{O}$: C, 62.76; H, 8.88; N, 2.09%.

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