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

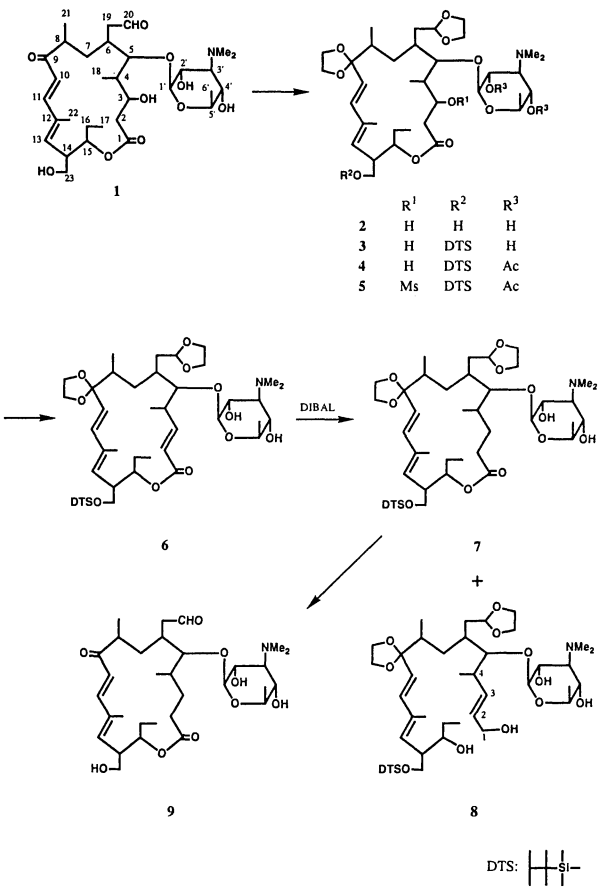
Shunji KAGEYAMA, Tsutomu TSUCHIYA,* Sumio UMEZAWA, and Masaya ORITA†
Institute of Bioorganic Chemistry, 1614 Ida, Nakahara-ku, Kawasaki 211
†Central Research Laboratories Yamanouchi Pharmaceutical Co., Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305
(Received July 18, 1992)

The title compounds, which proved highly antibacterial, have been prepared by selective hydrogenation of the corresponding 2,3-unsaturated compounds with $LiAlH_4$, diisobutylaluminium hydride, or $NaBH_4$–$NiCl_2$ 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*-(dimethylthexylsilyl)tylonolide 9,20-bis(ethylene acetal) with Raney Ni–K_2CO_3 involing three steps in it.

Some macrolide antibiotics such as tylosin,[1] josamycin,[2] niddamycin,[3] spiramycin I,[4] and rosamicin[5] 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. Removed of the OH-3 group will, therefore, give light to its biological role. Previously we prepared[6] a 4′-deoxymacrolide, 5-*O*-(4-deoxymycaminosyl)tylonolide (DT) and this compound showed remarkably enhanced antibacterial activity, compared to the parent compound, 5-*O*-mycaminosyltylonolide[7] (**1**). This is a successful example that deoxygenation exhibited a positive effect. In this paper we describe[8] 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

Sythesis of **9** is first described. The 9,20-bis(ethylene acetal) (**2**) of **1** had been prepared[9] 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 orthocarbonate[10] 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 dimethylthexylsilyl (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 deoxygenation[11] 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** with[12] tributylstannane (Bu_3SnH)–azobis(isobutyronitrile) (AIBN), treatment of **3** with halogens (Br_2 and I_2) in the presence of triphenylphosphine[13] (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 $NaBH_4$ in MeOH or in pyridine,[14] Mg in MeOH,[15] Zn–$NiCl_2 \cdot 6H_2O$[16] in aqueous methyl Cellosolve, $Na[(CH_3OCH_2CH_2O)_2AlH_2]$ (Red-Al by Aldrich Co.) in toluene, or Bu_3SnH–AIBN[12] in benzene all recovered the starting material; however, use of $LiAlH_4$ (LAH) in a ratio of LAH/**6** ca. 1.7 in tetrahydrofuran (THF) (at room temperature) or diisobutylaluminium 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 Me_2N-3′, which will readily attack the C-4′ to give the 3′,4′-aziridinium ion intermediate.[17] Treatmet 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 Bu_3SnH–AIBN[12] 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 ^{13}C 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 $CDCl_3$ at 27 °C

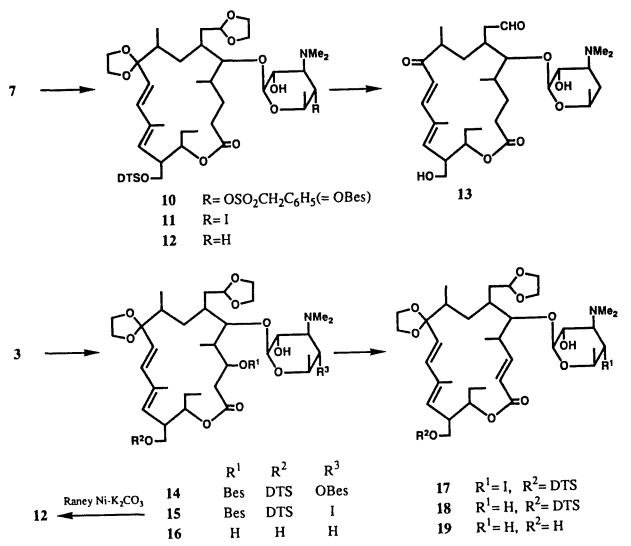
	9	1	13	DT
H-2	1.83, 2.42	1.96, 2.53	1.84, 2.44	1.96, 2.52
H-3	1.30, 1.44	3.85	1.26, 1.43	3.86
H-4	1.69	1.65	1.73	1.72
H-5	3.40	3.74	3.36	3.69
H-6	1.99	2.16	1.97	2.06
H-7	1.46, 1.67	1.49, 1.63	1.52, 1.73	1.62, 1.83
H-8	2.53	2.62	2.53	2.56
H-10	6.33	6.29	6.35	6.32
H-11	7.29	7.33	7.30	7.34
H-13	5.86	5.89	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–^{13}C correlated spectra with aid of, in some cases, Hohaha method.

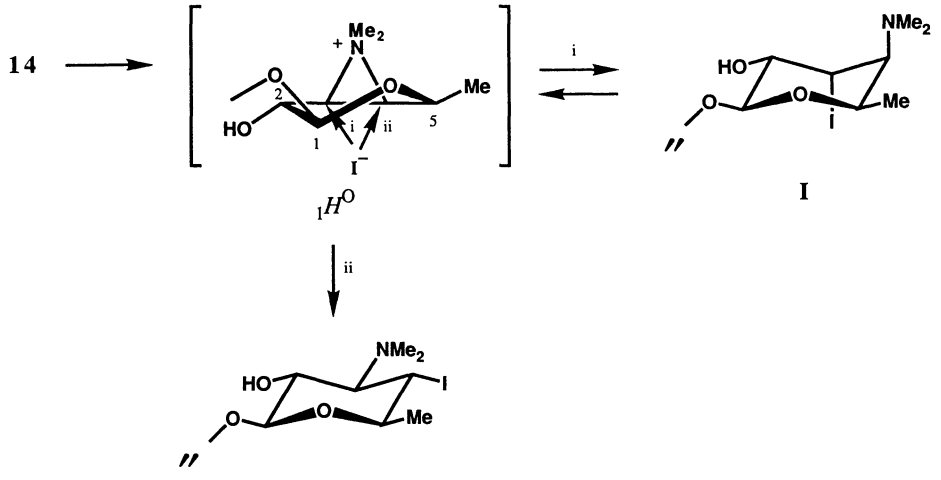
Table 2. ^{13}C NMR[a] Chemical Shifts[b] of **9** and **13** with 5-*O*-Mycaminosyltylonolide (**1**) and 5-*O*-(4-Deoxymycaminosyl)tylonolide (DT) in $CDCl_3$ at 27 °C

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–^{13}C 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*-mesyi 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 ^{1}H NMR spectrum was searched, but the signals (δ=ca. 3.5 in C_6D_6) 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 intermediate[17] having a half-chair conformation ($_1H^\circ$) 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 ($_1H^\circ$), is gradually converted into the thermodynamically more stable 3′-dimethylamino-4′-iodogluco deriative (**15**) therough the $_1H^\circ$ 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 NH_3 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–DIBAL[19] (**18** was recovered), $NaBH_4$–DMF (to give **18** and glycoside-cleaved products), and KB[$CH(CH_3)$-C_2H_5]H[20] (K-Selectride by Aldrich Co.) (to give **19** and glycoside-cleaved products). Among them, LAH in THF, and $NaBH_4$–$NiCl_2$[21] 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 $NaBH_4$–$NiCl_2$–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–K_2CO_3 readily gave **12** in one step from **15** in high yield (40% **13** from **1**); in this reaction, selective deiodination 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**) showed[8] stronger antibacterial activities than 5-*O*-mycaminosyltylonolide,[7] josamycin,[2] and erythromycin. Characteristic feature was that they showed[8] activity against Gram-negative bacteria, and **13** showed strong activity against *Haemophillis influenzae* IID 985. As the corresponding 2,3-unsaturated analog[22] 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. ^{1}H 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 Me_4Si. Mass spectra (MS) were determined using fast atom bomberdment method and the data are recorded as m/z. Thin-layer chromatography (TLC) was performed on Kieselgel 60 F_{254} (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 CH_3CN (1.5 ml), and the mixture was kept for 2 h at room temperature. The solution was poured into aq $NaHCO_3$ (saturated, 10 ml) under stirring and the mixture was extracted with benzene. The organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed with $CHCl_3$–MeOH–28% aq NH_3 (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 $CHCl_3$, and the solution was washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed with $CHCl_3$–CH_3OH–aq 28% NH_3 (15 : 1 : 0.1) to give a solid of **3**, 1.12 g (93%), $[\alpha]_D^{23}$ −9°(*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.07 (6H, s, $SiMe_2$), 0.84 (6H, s, $SiCMe_2$), 0.88 (6H, d, $SiCCH\underline{Me_2}$), 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, Me_2N-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 $C_{43}H_{77}NO_{12}Si$: 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 CH_3CN (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 $NaHCO_3$ (saturated), dried ($MgSO_4$), 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° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=1.17 (3H, d, Me-6′), 2.00 and 2.04 (each 3H, s, Ac×2), 2.33 (6H, s, Me_2N-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%. Caled for $C_{47}H_{81}NO_{14}Si$: 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 $NaHCO_3$ (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° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=2.02 and 2.04 (each 3H, s, Ac×2), 2.33 (6H, s, Me_2N-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 $C_{48}H_{83}NO_{16}S$ Si: 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 NH_3 (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 $CHCl_3$ was washed with water, dried ($MgSO_4$), and concentracted. The residual syrup was purified by a short column with $CHCl_3$–MeOH–28% aq NH_3 (15 : 1 : 0.1) to give a solid of **6**, 39.9 mg (96%), $[\alpha]_D^{25}$ −34° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 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, Me_2N-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 $C_{43}H_{75}NO_{11}Si$: C, 63.75; H, 9.33; N, 1.73%.

3-Deoxy-23-*O*-(dimethylthexylsilyl)-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 $Na_2SO_4 \cdot 10\ H_2O$ (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**: $[\alpha]_D^{21}$ −27° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.06 (6H, s), 0.83 (6H, s), and 0.87 (6H, d) (Me ×6 of dimethylthexylsilyl), 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 $C_{43}H_{77}NO_{11}Si \cdot 0.5\ H_2O$: C, 62.89; H, 9.57; N, 1.71%.

Compounds: **8**: $[\alpha]_D^{22}$ −27° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$–C_6D_6=1 : 1) δ=0.06 (6H, s), 0.84 (6H, s), and 0.88 (6H, d) (Me ×6 of dimethylthexylsilyl). 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%), $[\alpha]_D^{21}$ −23° (*c* 1, $CHCl_3$); MS *m/z* 582 (M^++1).

Found: C, 62.29; H, 8.80; N, 2.29%. Calcd for $C_{31}H_{51}NO_9 \cdot H_2O$: C, 62.08; H, 8.73; N, 2.33%.

5-*O*-[4-*O*-(Benzylsulfonyl)mycaminosyl]-3-deoxy-23-*O*-(dimethyltheoxylsilyl)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 temprature. 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 $NaHCO_3$ (saturated), 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*-(dimethylthexylsilyl)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 $Na_2S_2O_3$ 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**), $[\alpha]_D^{21}$ −73° (*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 $C_{43}H_{76}INO_{10}Si$: C, 56.01; H, 8.31; N, 1.56; I, 13.76%.

3-Deoxy-5-*O*-(4-deoxymycaminosyl)-23-*O*-(dimethylthexylsilyl)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)→$CHCl_3$ (600 ml)→$CHCl_3$–MeOH–28% aq NH_3 (10 : 1 : 0.1) to give a stannane-free solid of **12**, 790 mg (88%), $[\alpha]_D^{20}$ −38° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.06 (6H, s), 0.83 (6H, s), and 0.87 (6H, d) , (Me ×6 of dimethylthexylsilyl), 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 $C_{43}H_{77}NO_{10}Si$: 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 temprature. 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 $Na_2SO_4 \cdot 10H_2O$ (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 $NiCl_2 \cdot 6H_2O$ (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%), $[\alpha]_D^{19}$ −21° (*c* 1, $CHCl_3$); MS *m/z* 566 (M^++1).

Found: C, 63.81; H, 8.80; N, 2.50%. Calcd for $C_{31}H_{51}NO_8 \cdot H_2O$: 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-forth 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 cloromatography (cyclohexane–acetone 7 : 2), a solid of **15**, 93.6 mg (71% based on **3**), TLC (benzene–EtOAc 4 : 1): R_f 0.55, $[\alpha]_D^{20}$ −54° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ=0.04 (6H, s), 0.87 (6H, d), and 0.87 (6H, s) (Me ×6 of dimethylthexylsilyl), 1.645 (3H, d, Me-6′), 1.651 (3H, s, Me-22), 2.40 (6H, s, Me_2N-3′), 2.72 (1H, t, H-3′), 3.84 (1H, m, H-5′), 4.34 (2H, br s, $PhC\underline{H}_2SO_2$), 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 $C_{50}H_{82}INO_{13}S$ Si: 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 similarily 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, $[\alpha]_D^{20}$ −51° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.08 (6H, s,), 0.84 (6H, s), and 0.88 (6H, d), (Me ×6 of dimethylthexylsilyl), 1.70 (3H, br s, Me-22), 2.60 (6H, s, Me_2N-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 $C_{43}H_{74}NIO_{10}Si$: 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 dm^3) 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 dm^3)→$CHCl_3$ (3 dm^3)→$CHCl_3$–MeOH–28% aq NH_3 (15 : 1 : 0.1)], a solid of **18**, 52.0 g (89%), $[\alpha]_D^{20}$ −20° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.07 (6H, s, MeSi), 1.25 (3H, d, Me-6′), 1.70 (3H, d, Me-22), 2.27 (6H, s, Me_2N-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 $C_{43}H_{75}NO_{10}Si \cdot 0.5\ H_2O$: 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%), $[\alpha]_D^{20}$ −5° (*c* 1, $CHCl_3$); MS *m/z* 670 (M^++1).

Found: C, 62.54; N, 8.96; N, 2.07%. Calcd for $C_{35}H_{59}NO_{11}$: 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%), $[\alpha]_D^{20}$ −10° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ=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, Me_2N-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 $C_{35}H_{57}NO_{10} \cdot H_2O$: C, 62.76; H, 8.88; N, 2.09%.

References

1) J. M. McGuire, W. S. Boniece, C. E. Higgens, M. M. Hoehn, W. Stark, J. Westhead, and R. N. Wolfe, *Antibiot. Chemother. Basel.* (1954—1968), **11**, 320 (1961).

2) T. Osono, Y. Oka, S. Watanabe, Y. Numazaki, K. Moriyama, H. Ishida, K. Suzaki, Y. Okami, and H. Umezawa, *J. Antibiot.*, **20**, 173 (1967).

3) G. Huber, K. H. Wallhäußer, L. Fries, A. Steigler, and H. Weidenmüller, *Arzneim.-Forsch.*, **12**, 1191 (1962).

4) S. Pinnert-Sindico, L. Ninet, J. Preud'Homme, and C. Cosan, *Antibiot. Annu.*, **1955**, 724.

5) G. H. Wagman, J. A. Waitz, J. Marquez, A. Murawski, E. M. Oden, R. T. Testa, and M. J. Weinstein, *J. Antibiot.*, **25**, 641 (1972).

6) A. Tanaka, T. Tsuchiya, S. Umezawa, and H. Umezawa, *J. Antibiot.*, **34**, 1374 (1981).

7) R. L. Hamill, M. E. Haney, Jr., M. Stamper, and P. F. Wiley, *Antibiot. Chemothr. (Basel.)*, **11**, 328 (1961).

8) Short Communication: S. Kageyama, T. Tsuchiya, S. Umezawa, and T. Takeuchi, *J. Antibiot.*, **45**, 144 (1992).

9) S. Sakamoto, T. Tsuchiya, S. Umezawa, and H. Umezawa, *Bull. Chem. Soc. Jpn.*, **60**, 1481 (1987).

10) D. H. R. Barton, C. C. Dawes, and P. D. Magnus, *J. Chem. Soc., Chem. Commun.*, **1975**, 432.

11) H. Deshayes, J. P. Pete, C. Protella, and D. Scholler, *J. Chem. Soc., Chem. Commun.*, **1975**, 439.

12) D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574; M. J. Robins and J. S. Wilson, *J. Am. Chem. Soc.*, **103**, 932 (1981).

13) A. K. M. Anisuzzaman and R. L. Whistler, *Carbohydr. Res.*, **61**, 511 (1978).
14) W. R. Jacson and A. Zurqiyah, *J. Chem. Soc.*, **1965**, 5280.
15) T. Hudlicky, G. Sinai-Zingde, and M. G. Natchus, *Tetrahedron Lett.*, **28**, 5287 (1987).
16) C. Petrier and J. L. Luche, *Tetrahedron Lett.*, **28**, 2347 (1987).
17) S. Kageyama, T. Onoda, T. Tsuchiya, S. Umezawa, and H. Umezawa, *Carbohydr. Res.*, **169**, 241 (1987).
18) Y. Kobayashi, T. Tsuchiya, T. Ohgi, N. Taneichi, and Y. Koyama, *Carbohydr. Res.*, **230**, 89 (1992).
19) T. Tsuda, T. Hayashi, H. Satomi, T. Kawamoto, and T. Saegusa, *J. Org. Chem.*, **51**, 537 (1986).
20) B. Ganem and J. M. Fortunato, *J. Org. Chem.*, **40**, 2846 (1975).
21) D. Satoh and T. Hashimoto, *Chem. Pharm. Bull.*, **24**, 1950 (1976).
22) A. Tanaka. Ph. D. Thesis. University of Keio, Tokyo, Japan, (1984); H. Umezawa, S. Umezawa, T. Tsuchiya, and A. Tanaka, Japan Patent Appl. 101933 (1980); *Chem. Abstr.*, **97**, 56185j.