Cladinose Analogues of Sixteen-membered Macrolide Antibiotics

VI. Synthesis of Metabolically Programmed, Highly Potent Analogues of Sixteen-membered Macrolide Antibiotics

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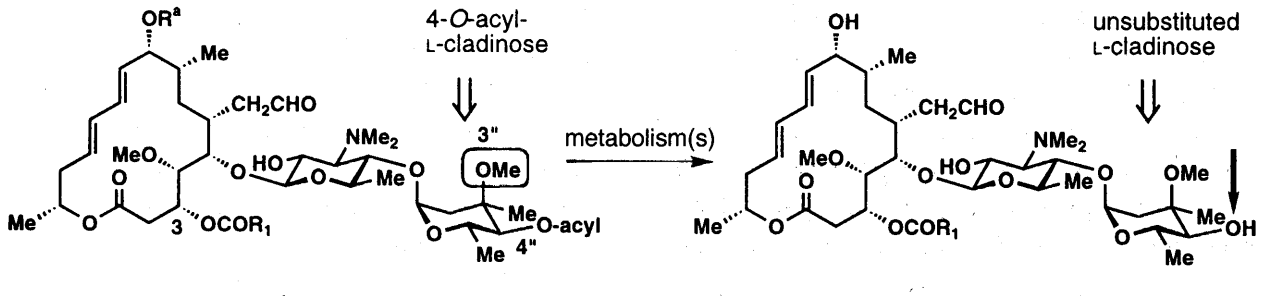
Five novel 3-hydroxyl derivatives of sixteen-membered macrolide possessing 4-*O*-acyl-α-L-cladinose as a neutral sugar moiety were synthesized by using a combination of structurally stable silyl acetal protection and selective hydrogenolysis of a 3″-methylthiomethyl ether to a 3″-OMe group. Several derivatives having *n*-butyryl, *i*-butyryl and *n*-valeryl substituent at the 4″-OH group exhibited significant antibacterial activity *in vitro*. One of them, 4″-*O*-*n*-butyryl-3″-*O*-methylleucomycin V, showed improved therapeutic effect in mice.

In search on sixteen-membered macrolides,[1] consideration of metabolism at the neutral sugar moiety is one of the key elements to design and generate efficient derivatives. Generally, biological deacylation at the neutral sugar moiety decreases antibacterial activity of a parent molecule to $1/8 \sim 1/64$ *in vitro*.[2] We have recently reported preparations of metabolically stable sixteen-membered macrolide derivatives,[3,4] which showed enhanced efficiency *in vivo*.

We set up an alternative strategy for preparation of novel analogues, which we propose metabolically programmed sixteen-membered macrolide derivatives exhibiting excellent activity both *in vitro* and *in vivo*. As part of this study, we demonstrated that one of the metabolically programmed derivatives (Scheme 1), **1x** [R=Ac, R_1=Et, acyl=COEt], exhibited strong therapeutic effect in mice.[5] Improved protective effect of **1x** could be mainly explained by its antibiotically active metabolite,[6] *i.e.* **2x** [R_1=Et]. Since a metabolite (**2**) having unsubstituted L-cladinose just like of fourteen-membered macrolides is much more active than that having L-mycarose (a diol-type neutral sugar), the parent antibiotic (**1**) clearly showed improved activity *in vivo* in comparison with the known acylated sixteen- membered macrolides. Thus, we have extensively investigated chemical modifications of **1** to enhance its antibacterial

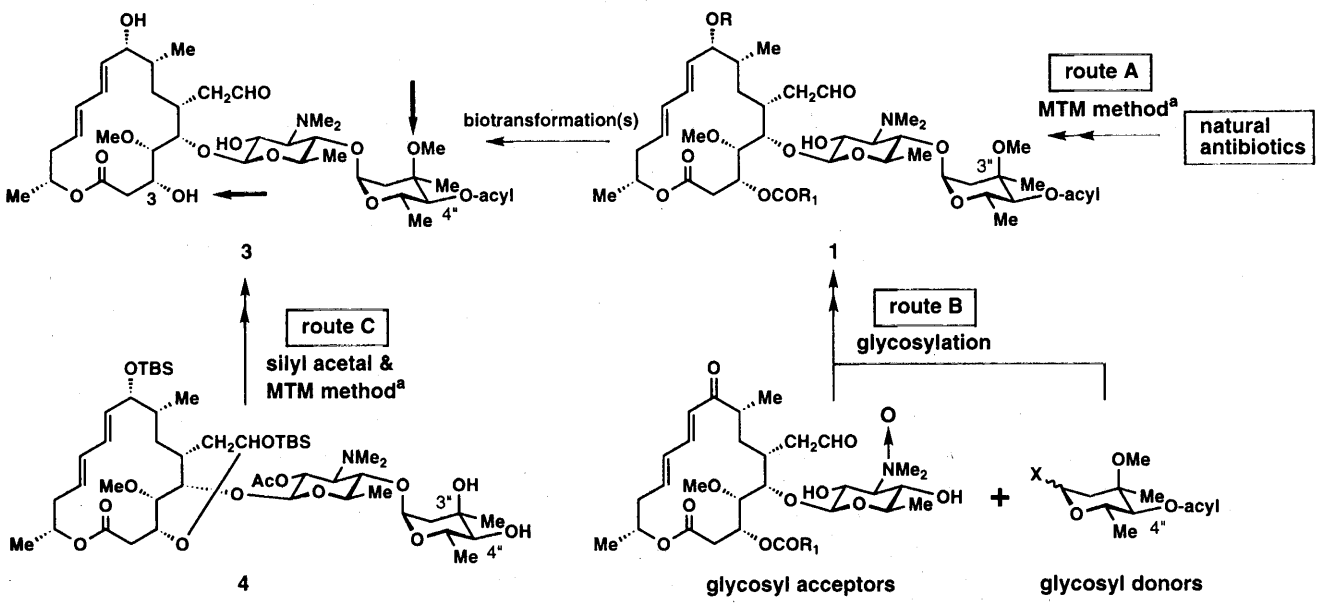
Scheme 1. Design and biological conversion of metabolically programmed 16-membered macrolide derivatives (**1**).



1 **2**: active metabolites[b]

[a] R=an acyl group or a hydrogen atom. [b] A cladinose-type metabolite (**2**) is more potent than a mycarose-type metabolite.

Scheme 2. Possible routes for preparation of metabolically programmed, highly potent 16-membered macrolide derivatives (**3**).



MTM method: Selective hydrogenolysis of a 3″-methylthiomethyl ether to a 3″-OMe group.

activity especially *in vitro*. Although the first sixteen-membered macrolide possessing a 4-*O*-acyl-α-L-cladinosyl residue was synthesized by TATSUTA *et al.*[7] However, no one did unveil dramatically improved *in vivo* activity of this class of antibiotic, since that synthesis in 1977.

Three years-analogue study of the leucomycin family (platenomycin skeleton) in our research group have concluded to design metabolically programmed, highly potent derivatives **3**, belonging to the leucomycin Fr group (Scheme 2). In this paper, we wish to describe general synthesis of some of the most active derivatives of the leucomycin family and their improved therapeutic effects. We also suggest SAR between a neutral sugar moiety and its antibacterial activity.

Chemistry

To generate metabolically programmed, highly potent leucomycin derivatives (**3**) we have focused on the followings; (i) screening of an appropriate acyl group at the C-4″ position, and (ii) an efficient synthetic method for biological evaluations *in vivo*. As we have reported in our previous paper,[5] the effect of introducing a methyl group at the 3″-hydroxyl group (mycarose to cladinose) may be different depending on the parent structure. These reasons prompted us to optimize the structure of the acyl group at C-4″. Among many possible routes for preparation of **3** (Scheme 2), biotransformations using **1** have been published.[6,8] Route A[5] starting from natural antibiotics has limitation for designs of the 4″-acyl group, because molecules possessing an unnatural acyl group (for example, *n*-valeryl) cannot be synthesized efficiently. Even though various kinds of derivatives can be constructed *via* route B,[7,9],† the luck of its convergency opted this out. We reasoned that a use of a relatively stable diol **4** to build the 4-*O*-acyl-L-cladinose moiety would enable us to prepare compounds **3** in a practical scale (route C) for *in vivo* evaluation. Thus, metabolically programmed, highly potent derivatives (**3**) were synthesized by utilizing a combination of structurally stable silyl acetal protection[10] and methylthiomethyl (MTM) method[5] including selective hydrogenolysis of a 3″-MTM ether to a 3″-OMe group.

The secondary hydroxyl groups and the aldehyde in leucomycion A_7[8],†† (LM-A_7) were protected by the published method[10] to give the acetyl silyl acetal **6** in 83% yield in two steps (Scheme 3). Upon carefully controled, heterogeneous basic hydrolysis of **6** afforded a diol (**4**) chemoselectively. The exceptional stability of

† TATSUTA *et al.* used cladinal (a glycal of 4-*O*-acyl-cladinose) as a glycosyl donor in reference 7.

†† A large amount of LM-A_7 was produced from midecamycin A_1 *via* biotransformation using a fungus PF1083. See ref. 8.

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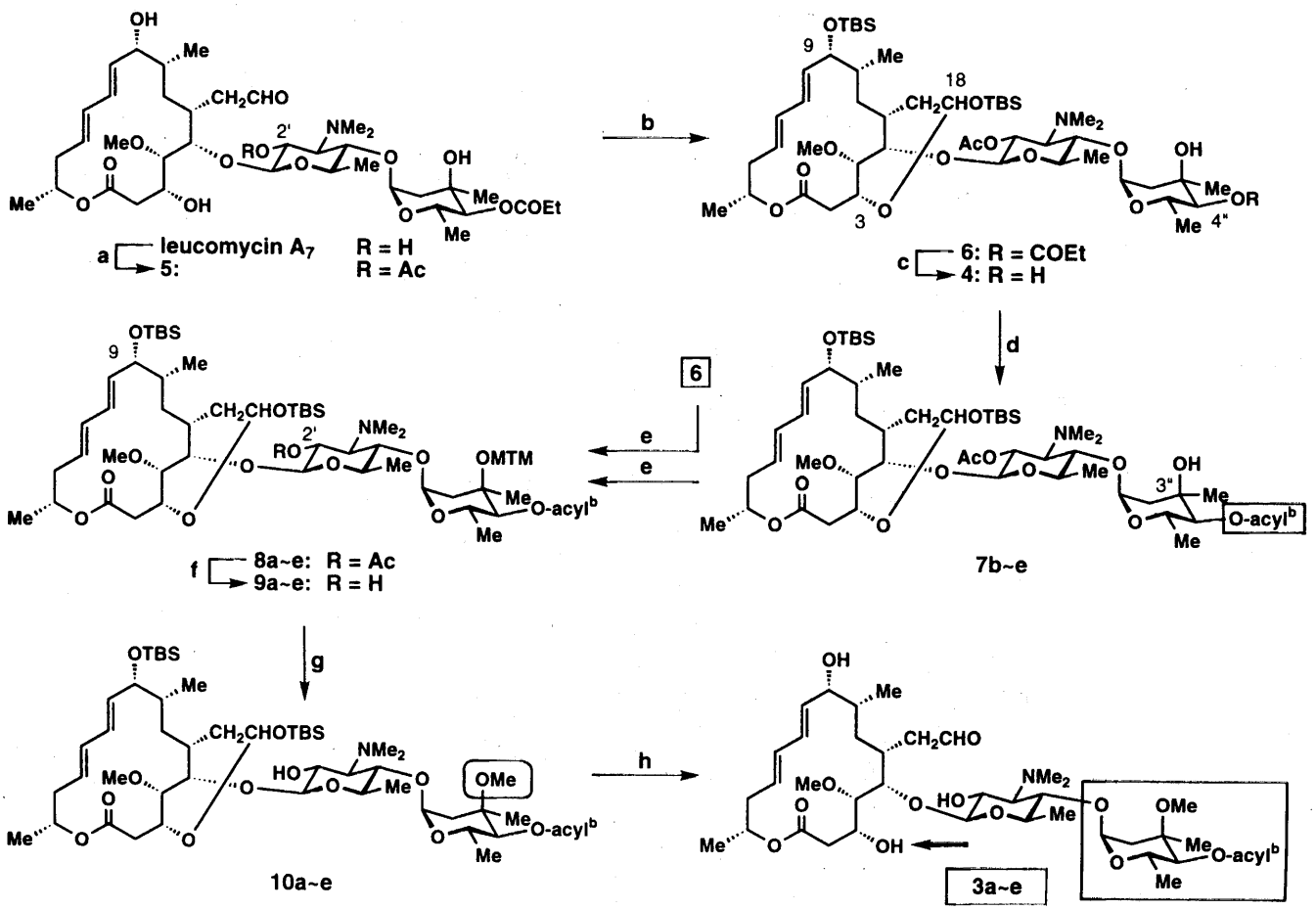
Scheme 3. Synthesis of metabolically programmed, highly potent 16-membered macrolide derivatives (3)[a].



[a] Reagents and conditions: (a) 2.0 equiv of Ac_2O, MeCN, 25°C, 16 hours, quant.; (b) 3.0 equiv of TBSCl, 6.0 equiv of imidazole, DMF, 45°C, 24 hours, 83%; (c) 25% aqueous NaOH, 1.0 equiv of n-Bu_4NHSO_4, PhH - H_2O (2 : 1), 25°C, 1 hour, 86%; (d) 1.2 equiv of acyl chloride, Pyr, 25°C, 0.5 hour, 90~92%; (e) DMSO - Bz_2O (3 : 1), 45°C, 3 days, 58~64% plus starting materials; (f) MeOH, 25°C, 16 hours, 97~99%; (g) Raney Nickel, EtOH, 25°C, 20 minutes 55~65%; (h) 2.0 M of TBAF in THF, 45°C, 1 hour, 65~70%.

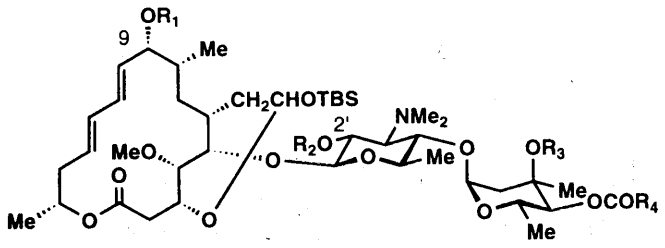
[b] 4″-Acyl side chains: (a) propionyl; (b) n-butyryl; (c) i-butyryl; (d) n-valeryl; (e) i-valeryl.

the 2′-*O*-acetyl group under those phase transfer conditions is worth mentioning. The reaction condition is so critical that it is not applicable to the other substrates *viz.* the corresponding silyl acetal of leucomycin A_1 possessing an *i*-valeryl group at C-4″. At this stage, four kinds of acyl groups including an unnatural substituent, *n*-valeryl group, were selectively introduced at the 4″-OH group.

Direct methylation at the 3″-hydroxyl group in **7** possessing a *cis*-vicinal acyloxy group led to complicated results. Also the same reaction conditions using model compounds **11a**[4] and **11e** which were rather stable at C-2′ (Fig. 1), showed messy spots in TLC Thus, after careful study the MTM method was finally adopted to construct the 3″-OMe group. Practical methylthiomethylation of **7b~7e** by published methods[5,11] proceeded in low yields. The 3″-hydroxyl group in **7** seems to be highly hindered sterically in addition to its low reactivity[12]. We reasoned that the substrates **11a** and **11e** might change their molecular conformation by introducing a large substituent in the C-2′ position, and thus might relieve steric factors. Although the yield could not be improved using the 2′-silyl derivatives (**11a** and **11e**), methylthiomethylation of **7** was accomplished by addition of benzoic anhydride[13] to afford **8** in moderate yield.

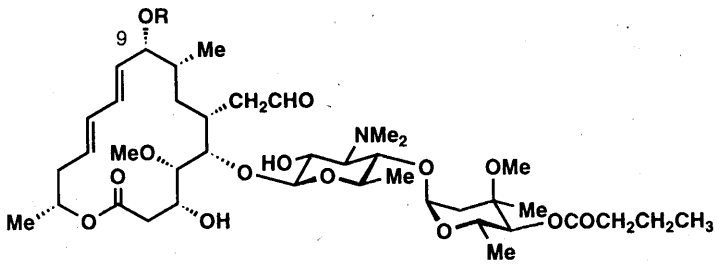
After quantitative methanolysis of **8a~8e**, the MTM group in **9a~9e** was transformed to the corresponding methyl group[14] by selective hydrogenolysis using deactivated Raney Nickel prepared by known method[5], albeit in low yield. Applying the conformational sug-

Fig. 1. Alternative synthetic intermediates.



	R_1	R_2	R_3	R_4
11a	TBS	TBS	H	Et
11e	TBS	TBS	H	CH_2CHMe_2
12	TBS	TBS	MTM	CH_2CHMe_2
13	Ac	H	MTM	Et

Fig. 2. 9-*O*-Acyl derivatives of compound (**3b**).



13b: R=H
14: R=Ac
15: R=COEt

gestions (*vide supra*), we used an alternative MTM intermediate **12** (Fig. 1) to overcome this steric hindrance, but the yields was not improved. Previously, we have reported[5], the reduction of an MTM ether to a methoxy group was influenced by the substituent at the C-9 position. Hydrogenolysis of 9-*O*-acetyl substrate (**13**) did not improve the yield either. Then, we noted that a labile aldehyde was protected and that 3″-OCH_2OEt by product[15] caused by reaction of solvent (EtOH) could not be observed in this reaction. Accordingly, we used Raney Nickel without deactivation, which successfully rose the yield up to 65%. Finally, removal of the two TBS groups from **10a**～**10e** was achieved with 2.0 M TBAF[4] in THF furnishing **3a**～**3e** in 65～70% yields.

The structures of **3a**～**3e** were confirmed by comparison of the degraded products with those derived from authentic samples as follows. Treatment of **3a** with *p*-toluenesulfonic acid and ethanol smoothly gave ethyl 4-*O*-propionyl-β-L-cladinoside[9] with a trace of its α-anomer, which indicated a methyl group was correctly introduced at C-3″. Moreover, the same acidic solvolysis of **3e** and **1y** [R=H, R_1=Me, acyl=$COCH_2CH(CH_3)_2$][5] (Scheme 1) prepared from josamycin, directly gave an identical product, ethyl 4-*O*-*i*-valeryl-L-cladinoside. These results suggested that the chemical acylation of **4** to **7** (Scheme 3) took place at the C-4″ position correctly without any acyl migrations. To design a more convergent synthetic scheme, an attempt was made to remove the 4″-*O*-propionyl group at the later stage, but efficient deacylation at the C-4″ position was not feasible at the stage of compounds **8**, **9** or **10**. These results could be explained by not only steric hindrance of the 3″-substituent but intramolecular effects of the free hydroxyl group at C-3″ for 4″-deacylation also.

Regioselective acylation of **3b** with acyl chloride in toluene gave 9-*O*-acetyl derivative (**14**) and 9-*O*-propionate (**15**) (Fig. 2).

Table 1. Antibacterial activities of 4-*O*-acyl-L-cladinose analogues and reference chemotherapeutics (MIC, μg/ml).

Test organisms	3a	3b	3c	3d	3e	14	15	LM-A_7	LM-A_1	RKM	CAM
Staphylococcus aureus 209P JC-1	0.10	0.05	0.05	0.05	0.05	0.20	0.20	0.20	0.10	0.10	0.05
S. aureus M133	0.20	0.20	0.20	0.20	0.39	0.78	0.78	0.39	0.20	0.39	3.13
S. aureus M126	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
S. aureus MS15026	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
S. aureus MS15027	0.20	0.20	0.20	0.20	0.20	0.39	0.78	0.39	0.20	0.78	6.25
S. epidermidis ATCC14990	0.20	0.20	0.20	0.20	0.20	0.39	0.78	0.20	0.20	0.78	0.10
Micrococcus luteus ATCC9341	<0.025	<0.025	<0.025	<0.025	<0.025	0.05	0.10	0.05	0.05	0.05	<0.025
Enterococcus faecalis W-73	0.39	0.78	0.78	0.78	0.78	1.56	3.13	0.78	0.39	0.39	0.78
Streptococcus pneumoniae IP692	<0.025	<0.025	<0.025	<0.025	0.05	0.10	0.10	0.20	0.10	0.10	<0.025
S. pneumoniae Type I	0.05	0.05	<0.025	<0.025	0.05	0.10	0.10	0.10	0.10	0.10	<0.025
S. pyogenes Cook	0.05	0.05	<0.025	<0.025	0.05	0.05	0.10	0.05	0.05	0.05	<0.025
Escherichia coli NIHJ JC-2	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	50
Klebsiella pneumoniae PCI602	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	50
Branhamella catarrhalis W-0500	0.39	0.20	0.20	0.10	0.20	0.78	0.78	0.20	0.20	0.20	0.10
B. catarrhalis W-0506	0.39	0.20	0.20	0.20	0.20	0.78	0.78	0.78	0.78	0.20	0.10
Haemophilus influenzae 9334	0.78	0.78	0.39	0.78	0.78	1.56	1.56	0.39	0.78	1.56	1.56

Biological Evaluation

Antibacterial activities *in vitro* of the novel 4-*O*-acyl-α-L-cladinosyl derivatives (**3a**～**3e**, **14** and **15**), compared with those of natural antibiotics, LM-A_7, LM-A_1, semisynthetic rokitamycin[16] (RKM), and clarithromycin (CAM) are shown in Table 1. As judged from the MIC values, compounds **3b**, **3c** and **3d** exhibited two times or more potent activity than that of RKM evaluated as one of the most potent derivatives in the leucomycin family. Unprecedentedly, their antibacterial activities are close to that of CAM. In this class of derivatives, enhancement of antibacterial activity by introducing a methyl group at 3″-OH was remarkable in the 4″-*O*-propionyl analogues (**3a** *vs.* LM-A_7), but only small effects were observed in the 4″-*O*-*i*-valeryl series (**3e** *vs.* LM-A_1). These results are compatible with other classes of 3″-*O*-methyl derivatives in sixteen-membered macrolides.[5,7] 9-*O*-Acyl analogues of **3b**, **14** and **15**, exhibited slightly depressed activity *in vitro*. These SAR informations might be similar to those of 3″-*O*-propionyl derivatives of leucomycin[17] reported by ŌMURA *et al.* It is interesting to note that **3d** showed excellent activity *in vitro* despite having an unnatural *n*-valeryl substituent.

Compound **3b** was selected as a representative derivative of a series of **3a**～**3e** for further biological study, as we envisioned to synthesize **3b** from LM-A_5 without replacements of the 4″-acyl group.††† The preliminary antibacterial activity *in vivo* of the test compounds was determined by measuring their protective effect against systemic infections in mice, compared with one of the most potent antibiotics, RKM. The *in vivo* activities against *Streptococcus pneumoniae* DP-I type I of the three new analogues **3b** and its 9-acyl derivatives, **14** and **15**, were two times potent than that of RKM. 9-Hydroxyl analogue (**3b**) also was two times potent than RKM in protective effects against *Staphylococcus aureus* Smith I (a detailed *in vivo* evaluation will be published in a separate paper). The excellent *in vivo* potency of **3b** is most probably related to potent activity *in vitro* of both the parent molecule and one of its major metabolites, 3″-*O*-methylleucomycin V[6].

In conclusion, a series of leucomycin Fr group analogues (3-OH type) possessing a 4-*O*-acyl-α-L-cladinose moiety were synthesized *via* MTM intermediates. These derivatives showed significantly increased antibacterial activity *in vitro*, and the representative compound (**3b**) exhibited improved activity *in vivo*.

Experimental

General Methods

MP's were determined with a Yanagimoto micro melting point apparatus and were uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Mass spectra were obtained on a Hitachi M-80A

††† To synthesis unnatural **3d**, replacement of 4″-acyl group is needed. And 3-OH-4″-*i*-butyryl sixteen-membered macrolide is not available as a starting material for synthesizing **3c**.

or M-80B mass spectrometer for EI-MS or FD-, SI-MS, respectively. ^{1}H NMR spectra were measured with a Jeol JNM-GSX 400 NMR spectrometer for 400 MHz in $CDCl_3$ using TMS as internal standard. Silica gel chromatography and preparative TLC were performed on Merck Kieselgel 60 and Merck TLC $60F_{254}$, respectively. In general, organic layer was dried with anhydrous Na_2SO_4, evaporation and concentration were carried out under reduced pressure below 30°C, unless otherwise noted.

Antibacterial Activity *In Vitro*

Minimum inhibitory concentrations (MICs) were determined by the agar dilution method. Test strains were subjected to seed culture using Sensitivity test broth (STB, Nissui Pharmaceutical) except the strains belonging to the genus *Streptococcus*, *Moraxella* and *Haemophilus* which were cultured on blood agar plate. A 5 μl portion of cell suspension of the test strains having about 10^6 CFU/ml was inoculated into Sensitivity disk agar (SDA, Nissui Pharmaceutical) supplemented with 5% horse blood in cases of *Streptococcus*, *Moraxella* and *Haemophilus* sp. After incubation at 37°C for 20 hours, MICs were determined.

2′-*O*-Acetyl-9,18-di-*O*-*tert*-butyldimethylsilylleucomycin A_7 3,18-Acetal (**6**)

To 10.0 g (13.2 mmol) of leucomycin A_7 (LM-A_7) was added dry CH_3CN (200 ml), and 2.50 ml (26.4 mmol) of acetic anhydride (Ac_2O) was added. The mixture was stirred at room temperature for 16 hours. After slowly adding saturated aqueous $NaHCO_3$ (500 ml), the reaction mixture was extracted with CH_2Cl_2 (500 ml). Then organic layer was dried and concentrated to afford crude **5** (10.55 g, quant.). To 10.55 g of **5** was added dry DMF (100 ml), and 5.97 g (39.6 mmol) of *t*-butyldimethylsilyl chloride (TBSCl) and 5.39 g (79.2 mmol) of imidazole were added. The mixture was stirred at 45°C for 24 hours. The reaction mixture was extracted with benzene (1 liter) and the benzene layer was successively washed with saturated aqueous $NaHCO_3$ (1 liter) twice and brine (1 liter) twice. Then the organic layer was dried and concentrated to afford 13.2 g of crude **6**. A 50 mg portion of this crude compound was purified by preparative TLC [hexane-AcOEt (5:1)] to afford **6** (42 mg, 83%) as a colorless solid.

6: MP 103~107°C; SI-MS *m/z* 1028 $(M+H)^+$; $[\alpha]_D^{14}$ −24° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.40 (1H, br dd, 7-H), 0.91 (3H, d, 19-H_3), 1.11 (3H, s, 3″-CH_3), 1.14 (3H, d, 6″-H_3), 1.17 (3H, t, 4″-$OCOCH_2CH_3$), 1.29 (3H, d, 6′-H_3), 1.29 (3H, d, 16-H_3), 1.46 (1H, br d, 17-H), 1.52 (1H, m, 8-H), 1.62 (1H, dt, 17-H), 1.85 (1H, dd, 2″-Hax), 2.00 (1H, d, 2″-Heq), 2.11 (3H, s, 2′-$OCOCH_3$), 2.28 (1H, m, 6-H), 2.41 (6H, s, 3′-$N(CH_3)_2$), 2.43 and 2.44 (2H, 2×apparent q, 4″-$OCOCH_2CH_3$), 2.67 (1H, dd, 2-H), 2.74 (1H, t, 3′-H), 2.94 (1H, br s, 4-H), 3.30 (1H, br d, 5-H), 3.30 (1H, t, 4′-H), 3.30 (1H, dq, 5′-H), 3.40 (3H, s, 4-OCH_3), 4.13 (1H, br dd, 3-H), 4.17 (1H, m, 9-H), 4.26 (1H, d, 1′-H), 4.37 (1H, dq, 5″-H), 4.53 (1H, br d, 18-H), 4.62 (1H, d, 4″-H), 4.64 (1H, ddq, 15-H), 5.09 (1H, d, 1″-H), 5.10 (1H, dd, 2′-H), 5.47 (1H, ddd, 13-H), 5.95 (1H, m, 10-H), 5.95 (1H, m, 11-H), 6.31 (1H, br dd, 12-H).

2′-*O*-Acetyl-9,18-di-*O*-*tert*-butyldimethylsilylleucomycin V 3,18-Acetal (**4**)

334 ml of benzene was added to 6.68 g (6.5 mmol) of **6**, and 25% aqueous NaOH (167 ml) and 2.19 g (6.45 mmol) of tetra-*n*-butylammonium hydrogensulfate were added. After vigorous stirring at 25°C for 1 hour, the benzene layer was collected and washed with brine (500 ml) twice. Then the organic layer was dried and concentrated to afford 5.88 g of crude **4**. A 50 mg portion of this crude compound was purified by preparative TLC [hexane-AcOEt (1:1)] to afford **4** (46 mg, 86%) as a colorless solid.

4: MP 102~106°C; SI-MS *m/z* 972 $(M+H)^+$; $[\alpha]_D^{14}$ −24° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.40 (1H, br dd, 7-H), 0.91 (3H, d, 19-H_3), 1.23 (3H, s, 3″-CH_3), 1.45 (1H, br d, 17-H), 1.52 (1H, m, 8-H), 1.62 (1H, dt, 17-H), 1.77 (1H, dd, 2″-Hax), 2.02 (1H, d, 2″-Heq), 2.11 (3H, s, 2′-$OCOCH_3$), 2.28 (1H, m, 6-H), 2.39 (6H, s, 3′-$N(CH_3)_2$), 2.66 (1H, dd, 2-H), 2.73 (1H, t, 3′-H), 2.94 (1H, br s, 4-H), 2.94 (1H, t, 4″-H), 3.29 (1H, t, 4′-H), 3.29 (1H, dq, 5′-H), 3.40 (3H, s, 4-OCH_3), 3.42 (1H, m, 5-H), 3.98 (1H, dq, 5″-H), 4.18 (1H, br dd, 3-H), 4.18 (1H, m, 9-H), 4.26 (1H, d, 1′-H), 4.52 (1H, br d, 18-H), 4.64 (1H, ddq, 15-H), 5.08 (1H, dd, 2′-H), 5.10 (1H, d, 1″-H), 5.47 (1H, ddd, 13-H), 5.95 (1H, m, 10-H), 5.95 (1H, m, 11-H), 6.31 (1H, br dd, 12-H).

2′-*O*-Acetyl-9,18-di-*O*-*tert*-butyldimethylsilylleucomycin A_5 3,18-Acetal (**7b**)

To a stirred mixture of **4** (500 mg, 0.52 mmol) in pyridine (5.0 ml) was added butyrylchloride (66 mg, 0.62 mmol). The resulting mixture was stirred at room temperature for 15 minutes. After slowly adding saturated aqueous $NaHCO_3$ (500 ml), the reaction mixture was extracted with $CHCl_3$ (250 ml) twice. The organic layers were combined, washed with brine (500 ml)

twice and dried. Then the organic layer was dried and concentrated to afford 544 mg of crude **7b**. A 40 mg portion of this crude compound was purified by preparative TLC [$CHCl_3$-MeOH (40:1)] to afford **7b** (36 mg, 92%) as a colorless solid.

7b: MP 78~81°C; EI-MS *m/z* 1041 $(M)^+$; $[\alpha]_D^{20}$ −41° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.41 (1H, br dd, 7-H), 0.91 (3H, d, 19-H_3), 0.96 (3H, t, 4″-$OCOCH_2CH_2CH_3$), 1.11 (3H, s, 3″-CH_3), 1.15 (3H, d, 6″-H_3), 1.29 (3H, d, 16-H_3), 1.29 (3H, d, 6′-H_3), 1.46 (1H, br d, 17-H), 1.52 (1H, m, 8-H), 1.62 (1H, dt, 17-H), 1.68 (2H, tq, 4″-$OCOCH_2CH_2CH_3$), 1.85 (1H, dd, 2″-Hax), 2.00 (1H, d, 2″-Heq), 2.11 (3H, s, 2′-$OCOCH_3$), 2.38 and 2.39 (2H, 2 × apparent t, 4″-$OCOCH_2CH_2CH_3$), 2.41 (6H, s, 3′-$N(CH_3)_2$), 2.67 (1H, dd, 2-H), 2.74 (1H, t, 3′-H), 2.95 (1H, br s, 4-H), 3.30 (1H, br d, 5-H), 3.30 (1H, t, 4′-H), 3.30 (1H, dq, 5′-H), 3.40 (3H, s, 4-OCH_3), 4.12 (1H, br dd, 3-H), 4.18 (1H, m, 9-H), 4.27 (1H, d, 1′-H), 4.38 (1H, dq, 5″-H), 4.53 (1H, br d, 18-H), 4.62 (1H, d, 4″-H), 4.64 (1H, ddq, 15-H), 5.09 (1H, d, 1″-H), 5.10 (1H, dd, 2′-H), 5.47 (1H, ddd, 13-H), 5.94 (1H, m, 10-H), 5.94 (1H, m, 11-H), 6.31 (1H, br dd, 12-H).

2′-*O*-Acetyl-9,18-di-*O*-*tert*-butyldimethylsilyl-4″-*O*-*iso*-butyrylleucomycin V 3,18-Acetal (**7c**)

Reaction of **4** with *iso*-butyrylchloride gave **7c** in 90% yield by a similar procedure to **7b**.

7c: MP 103~106°C; SI-MS *m/z* 1042 $(M+H)^+$; $[\alpha]_D^{13}$ −20° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.40 (1H, br dd, 7-H), 0.91 (3H, d, 19-H_3), 1.10 (3H, s, 3″-CH_3), 1.13 (3H, d, 6″-H_3), 1.19 and 1.20 (6H, 2 × d, 4″-$OCOCH(CH_3)_2$), 1.29 (3H, d, 16-H_3), 1.29 (3H, d, 6′-H_3), 1.45 (1H, br d, 17-H), 1.52 (1H, m, 8-H), 1.62 (1H, dt, 17-H), 1.84 (1H, dd, 2″-Hax), 1.99 (1H, d, 2″-Heq), 2.10 (3H, s, 2′-$OCOCH_3$), 2.28 (1H, m, 6-H), 2.41 (6H, s, 3′-$N(CH_3)_2$), 2.67 (1H, dd, 2-H), 2.68 (1H, septet, 4″-$OCOCH(CH_3)_2$), 2.74 (1H, t, 3′-H), 2.94 (1H, br s, 4-H), 3.30 (1H, br d, 5-H), 3.30 (1H, t, 4′-H), 3.30 (1H, dq, 5′-H), 3.40 (3H, s, 4-OCH_3), 4.12 (1H, br dd, 3-H), 4.18 (1H, m, 9-H), 4.26 (1H, d, 1′-H), 4.38 (1H, dq, 5″-H), 4.52 (1H, br d, 18-H), 4.60 (1H, d, 4″-H), 4.64 (1H, ddq, 15-H), 5.09 (1H, d, 1″-H), 5.10 (1H, dd, 2′-H), 5.47 (1H, ddd, 13-H), 5.95 (1H, m, 10-H), 5.95 (1H, m, 11-H), 6.31 (1H, br dd, 12-H).

2′-*O*-Acetyl-9,18-di-*O*-*tert*-butyldimethylsilyl-4″-*O*-valerylleucomycin V 3,18-Acetal (**7d**)

Reaction of **4** with *n*-valerylchloride gave **7d** in 91% yield by a similar procedure to **7b**.

7d: MP 80~83°C; SI-MS *m/z* 1056 $(M+H)^+$; $[\alpha]_D^{13}$ −23° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.40 (1H, br dd, 7-H), 0.91 (3H, d, 19-H_3), 0.91 (3H, t, 4″-$OCOCH_2CH_2CH_2CH_3$), 1.11 (3H, s, 3″-CH_3), 1.14 (3H, d, 6″-H_3), 1.28 (3H, d, 16-H_3), 1.28 (3H, d, 6′-H_3), 1.36 (2H, m, 4″-$OCOCH_2CH_2CH_2CH_3$), 1.45 (1H, br d, 17-H), 1.52 (1H, m, 8-H), 1.62 (1H, dt, 17-H), 1.62 (2H, tq, 4″-$OCOCH_2CH_2CH_2CH_3$), 1.85 (1H, dd, 2″-Hax), 2.00 (1H, d, 2″-Heq), 2.10 (3H, s, 2′-$OCOCH_3$), 2.28 (1H, m, 6-H), 2.39 and 2.40 (2H, 2 × apparent t, 4″-$OCOCH_2CH_2CH_2CH_3$), 2.41 (6H, s, 3′-$N(CH_3)_2$), 2.67 (1H, dd, 2-H), 2.74 (1H, t, 3′-H), 2.94 (1H, br s, 4-H), 3.30 (1H, br d, 5-H), 3.30 (1H, t, 4′-H), 3.30 (1H, dq, 5′-H), 3.40 (3H, s, 4-OCH_3), 4.12 (1H, br dd, 3-H), 4.18 (1H, m, 9-H), 4.26 (1H, d, 1′-H), 4.37 (1H, dq, 5″-H), 4.53 (1H, br d, 18-H), 4.62 (1H, d, 4″-H), 4.64 (1H, ddq, 15-H), 5.09 (1H, d, 1″-H), 5.10 (1H, dd, 2′-H), 5.47 (1H, ddd, 13-H), 5.94 (1H, m, 10-H), 5.94 (1H, m, 11-H), 6.30 (1H, br dd, 12-H).

2′-*O*-Acetyl-9,18-di-*O*-*tert*-butyldimethylsilylleucomycin A_1 3,18-Acetal (**7e**)

Reaction of **4** with *iso*-valerylchloride gave **7e** in 90% yield by a similar procedure to **7b**.

7e: MP 101~105°C; SI-MS *m/z* 1056 $(M+H)^+$; $[\alpha]_D^{14}$ −19° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.40 (1H, br dd, 7-H), 0.90 (3H, d, 19-H_3), 0.96 (6H, d, 4″-$OCOCH_2CH(CH_3)_2$), 1.10 (3H, s, 3″-CH_3), 1.14 (3H, d, 6″-H_3), 1.28 (3H, d, 16-H_3), 1.28 (3H, d, 6′-H_3), 1.44 (1H, br d, 17-H), 1.51 (1H, m, 8-H), 1.61 (1H, dt, 17-H), 1.84 (1H, dd, 2″-Hax), 1.98 (1H, d, 2″-Heq), 2.10 (3H, s, 2′-$OCOCH_3$), 2.13 (1H, m, 4″-$OCOCH_2CH(CH_3)_2$), 2.28 (2H, 2 × d, 4″-$OCOCH_2CH(CH_3)_2$), 2.40 (6H, s, 3′-$N(CH_3)_2$), 2.65 (1H, dd, 2-H), 2.73 (1H, t, 3′-H), 2.94 (1H, br s, 4-H), 3.29 (1H, br d, 5-H), 3.29 (1H, t, 4′-H), 3.29 (1H, dq, 5′-H), 3.39 (3H, s, 4-OCH_3), 4.12 (1H, br dd, 3-H), 4.17 (1H, m, 9-H), 4.26 (1H, d, 1′-H), 4.37 (1H, dq, 5″-H), 4.52 (1H, br d, 18-H), 4.61 (1H, d, 4″-H), 4.63 (1H, ddq, 15-H), 5.08 (1H, d, 1″-H), 5.09 (1H, dd, 2′-H), 5.46 (1H, ddd, 13-H), 5.94 (1H, m, 10-H), 5.94 (1H, m, 11-H), 6.30 (1H, br dd, 12-H).

2′-*O*-Acetyl-9,18-di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methylthiomethylleucomycin A_7 3,18-Acetal (**8a**)

A solution of **6** (1.00 g, 0.97 mmol) in dry DMSO (9.0 ml) and benzoic anhydride (Bz_2O) (3.0 ml) was kept at 45°C for 3 days, then poured into toluene (200 ml). The organic layer was washed with H_2O (200 ml) three times, and dried. Evaporation gave a residue which was purified by silica gel column chromatography [100 g, hexane-EtOAc (2:1)] to afford **8a** (612 mg, 58%) as a

colorless solid.

8a: MP 96~100°C; FD-MS *m/z* 1088 $(M+H)^+$; $[\alpha]_D^{21}$ −28° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.40 (1H, br dd, 7-H), 0.91 (3H, d, 19-H_3), 1.05 (3H, d, 6″-H_3), 1.17 (3H, s, 3″-CH_3), 1.17 (3H, t, 4″-$OCOCH_2CH_3$), 1.24 (3H, d, 6′-H_3), 1.29 (3H, d, 16-H_3), 1.44 (1H, br d, 17-H), 1.51 (1H, m, 8-H), 1.63 (1H, dt, 17-H), 1.70 (1H, dd, 2″-Hax), 2.09 (3H, s, 2′-$OCOCH_3$), 2.21 (3H, s, 3″-OCH_2SCH_3), 2.41 (2H, q, 4″-$OCOCH_2CH_3$), 2.42 (6H, s, 3′-$N(CH_3)_2$), 2.66 (1H, dd, 2-H), 2.75 (1H, t, 3′-H), 3.15 (1H, t, 4′-H), 3.26 (1H, dq, 5′-H), 4.13 (1H, br dd, 3-H), 2.95 (1H, br s, 4-H), 3.41 (3H, s, 4-OCH_3), 3.28 (1H, br d, 5-H), 4.17 (1H, br dd, 9-H), 4.25 (1H, d, 1′-H), 4.52 (1H, br d, 18-H), 4.52 and 4.64 (2H, 2×d, 3″-OCH_2SCH_3), 4.58 (1H, dq, 5″-H), 4.64 (1H, ddq, 15-H), 4.67 (1H, d, 4″-H), 4.83 (1H, d, 1″-H), 5.05 (1H, dd, 2′-H), 5.46 (1H, ddd, 13-H), 5.94 (1H, m, 10-H), 5.94 (1H, m, 11-H), 6.30 (1H, br dd, 12-H).

2′-*O*-Acetyl-9,18-di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methylthiomethylleucomycin A_5 3,18-Acetal (**8b**)

Reaction of **7b** with DMSO and Bz_2O gave **8b** in 62% yield by a similar procedure to **8a**.

8b: MP 78~81°C; EI-MS *m/z* 1101 $(M)^+$; $[\alpha]_D^{20}$ −41° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.40 (1H, br dd, 7-H), 0.91 (3H, d, 19-H_3), 0.97 (3H, t, 4″-$OCOCH_2CH_2CH_3$), 1.05 (3H, d, 6″-H_3), 1.18 (3H, s, 3″-CH_3), 1.24 (3H, d, 6′-H_3), 1.28 (3H, d, 16-H_3), 1.44 (1H, br d, 17-H), 1.51 (1H, m, 8-H), 1.68 (2H, m, 4″-$OCOCH_2CH_2CH_3$), 1.69 (1H, dd, 2″-Hax), 2.10 (3H, s, 2′-$OCOCH_3$), 2.21 (3H, s, 3″-OCH_2SCH_3), 2.36 and 2.37 (2H, 2×apparent t, 4″-$OCOCH_2CH_2CH_3$), 2.42 (6H, s, 3′-$N(CH_3)_2$), 2.67 (1H, dd, 2-H), 2.75 (1H, t, 3′-H), 2.95 (1H, br s, 4-H), 3.15 (1H, t, 4′-H), 3.26 (1H, dq, 5′-H), 3.28 (1H, br d, 5-H), 3.41 (3H, s, 4-OCH_3), 4.13 (1H, br dd, 3-H), 4.18 (1H, br dd, 9-H), 4.25 (1H, d, 1′-H), 4.52 (1H, br d, 18-H), 4.52 and 4.63 (2H, 2×d, 3″-OCH_2SCH_3), 4.58 (1H, dq, 5″-H), 4.63 (1H, ddq, 15-H), 4.68 (1H, d, 4″-H), 4.83 (1H, d, 1″-H), 5.05 (1H, dd, 2′-H), 5.46 (1H, ddd, 13-H), 5.94 (1H, m, 10-H), 5.94 (1H, m, 11-H), 6.30 (1H, br dd, 12-H).

2′-*O*-Acetyl-9,18-di-*O*-*tert*-butyldimethylsilyl-4″-*O*-*iso*-butyryl-3″-*O*-methylthiomethylleucomycin V 3,18-Acetal (**8c**)

Reaction of **7c** with DMSO and Bz_2O gave **8c** in 64% yield by a similar procedure to **8a**.

8c: MP 71~73°C; SI-MS *m/z* 1102 $(M+H)^+$; $[\alpha]_D^{16}$ −42° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.40 (1H, br dd, 7-H), 1.04 (3H, d, 6″-H_3), 1.18 (3H, s, 3″-CH_3), 1.24 (3H, d, 6′-H_3), 1.28 (3H, d, 16-H_3), 1.44 (1H, br d, 17-H), 1.51 (1H, m, 8-H), 1.69 (1H, dd, 2″-Hax), 2.10 (3H, s, 2′-$OCOCH_3$), 2.21 (3H, s, 3″-OCH_2SCH_3), 2.23 (1H, d, 2″-Heq), 2.41 (6H, s, 3′-$N(CH_3)_2$), 2.65 (1H, septet, 4″-$OCOCH(CH_3)_2$), 2.67 (1H, dd, 2-H), 2.75 (1H, t, 3′-H), 2.95 (1H, br s, 4-H), 3.16 (1H, t, 4′-H), 3.26 (1H, dq, 5′-H), 3.28 (1H, br d, 5-H), 3.41 (3H, s, 4-OCH_3), 4.13 (1H, br dd, 3-H), 4.17 (1H, br dd, 9-H), 4.25 (1H, d, 1′-H), 4.51 and 4.62 (2H, 2×d, 3″-OCH_2SCH_3), 4.52 (1H, br d, 18-H), 4.59 (1H, dq, 5″-H), 4.63 (1H, ddq, 15-H), 4.67 (1H, d, 4″-H), 4.83 (1H, d, 1″-H), 5.05 (1H, dd, 2′-H), 5.46 (1H, ddd, 13-H), 5.94 (1H, m, 10-H), 5.94 (1H, m, 11-H), 6.30 (1H, br dd, 12-H).

2′-*O*-Acetyl-9,18-di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methylthiomethyl-4″-*O*-*n*-valerylleucomycin V 3,18-Acetal (**8d**)

Reaction of **7d** with DMSO and Bz_2O gave **8d** in 60% yield by a similar procedure to **8a**.

8d: MP 65~68°C; SI-MS *m/z* 1116 $(M+H)^+$; $[\alpha]_D^{18}$ −36° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.40 (1H, br dd, 7-H), 0.90 (3H, d, 19-H_3), 0.90 (3H, t, 4″-$OCOCH_2CH_2CH_2CH_3$), 1.04 (3H, d, 6″-H_3), 1.17 (3H, s, 3″-CH_3), 1.23 (3H, d, 6′-H_3), 1.28 (3H, d, 16-H_3), 1.35 (2H, tq, 4″-$OCOCH_2CH_2CH_2CH_3$), 1.43 (1H, br d, 17-H), 1.50 (1H, m, 8-H), 1.62 (2H, m, 4″-$OCOCH_2CH_2CH_2CH_3$), 1.68 (1H, dd, 2″-Hax), 2.09 (3H, s, 2′-$OCOCH_3$), 2.20 (3H, s, 3″-OCH_2SCH_3), 2.24 (1H, d, 2″-Heq), 2.37 and 2.39 (2H, 2×apparent t, 4″-$OCOCH_2CH_2CH_2CH_3$), 2.41 (6H, s, 3′-$N(CH_3)_2$), 2.66 (1H, dd, 2-H), 2.74 (1H, t, 3′-H), 2.94 (1H, br s, 4-H), 3.15 (1H, t, 4′-H), 3.26 (1H, dq, 5′-H), 3.28 (1H, br d, 5-H), 3.40 (3H, s, 4-OCH_3), 4.12 (1H, br dd, 3-H), 4.17 (1H, br dd, 9-H), 4.24 (1H, d, 1′-H), 4.52 (1H, br d, 18-H), 4.52 and 4.63 (2H, 2×d, 3″-OCH_2SCH_3), 4.58 (1H, dq, 5″-H), 4.62 (1H, ddq, 15-H), 4.67 (1H, d, 4″-H), 4.82 (1H, d, 1″-H), 5.05 (1H, dd, 2′-H), 5.45 (1H, ddd, 13-H), 5.94 (1H, m, 10-H), 5.94 (1H, m, 11-H), 6.30 (1H, br dd, 12-H).

2′-*O*-Acetyl-9,18-di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methylthiomethylleucomycin A_1 3,18-Acetal (**8e**)

Reaction of **7e** with DMSO and Bz_2O gave **8e** in 61% yield by a similar procedure to **8a**.

8e: MP 80~82°C; SI-MS *m/z* 1116 $(M+H)^+$; $[\alpha]_D^{13}$ −39° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.41 (1H, br dd, 7-H), 0.91 (3H, d, 19-H_3), 0.97 (6H, d, 4″-$OCOCH_2CH(CH_3)_2$), 1.06 (3H, d, 6″-H_3), 1.18 (3H, s, 3″-CH_3), 1.24 (3H, d, 6′-H_3), 1.29 (3H, d, 16-H_3),

1.45 (1H, br d, 17-H), 1.51 (1H, m, 8-H), 1.62 (1H, dt, 17-H), 1.69 (1H, dd, 2″-Hax), 2.10 (3H, s, 2′-OCOCH$_3$), 2.14 (1H, m, 4″-OCOCH$_2$C*H*(CH$_3$)$_2$), 2.20 (3H, s, 3″-OCH$_2$SC*H*$_3$), 2.26 and 2.28 (2H, 2×d, 4″-OCOC*H*$_2$CH(CH$_3$)$_2$), 2.42 (6H, s, 3′-N(CH$_3$)$_2$), 2.67 (1H, dd, 2-H), 2.75 (1H, t, 3′-H), 2.95 (1H, br s, 4-H), 3.15 (1H, t, 4′-H), 3.27 (1H, dq, 5′-H), 3.29 (1H, br d, 5-H), 3.42 (3H, s, 4-OCH$_3$), 4.13 (1H, br dd, 3-H), 4.18 (1H, br dd, 9-H), 4.25 (1H, d, 1′-H), 4.52 (1H, br d, 18-H), 4.52 and 4.64 (2H, 2×d, 3″-OC*H*$_2$SCH$_3$), 4.59 (1H, dq, 5″-H), 4.64 (1H, ddq, 15-H), 4.68 (1H, d, 4″-H), 4.83 (1H, d, 1″-H), 5.05 (1H, dd, 2′-H), 5.46 (1H, ddd, 13-H), 5.95 (1H, m, 10-H), 5.95 (1H, m, 11-H), 6.31 (1H, br dd, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methylthiomethylleucomycin A$_7$ 3,18-Acetal (**9a**)

A solution of **8a** (580 mg, 0.53 mmol) in MeOH (12 ml) was allowed to stand at 25°C for 16 hours. Evaporation gave a residue which was purified by silica gel column chromatography [50 g, CHCl$_3$ - MeOH (10 : 1)] to afford **9a** (550 mg, 99%) as a colorless solid.

9a: MP 75~78°C; SI-MS *m/z* 1046 $(M+H)^+$; $[\alpha]_D^{21}$ −17° (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.41 (1H, br dd, 7-H), 0.91 (3H, d, 19-H$_3$), 1.05 (3H, d, 6″-H$_3$), 1.16 (3H, t, 4″-OCOCH$_2$C*H*$_3$), 1.17 (3H, s, 3″-CH$_3$), 1.20 (3H, d, 6′-H$_3$), 1.29 (3H, d, 16-H$_3$), 1.42 (1H, br d, 17-H), 1.59 (1H, m, 8-H), 1.65 (1H, dt, 17-H), 1.70 (1H, dd, 2″-Hax), 2.15 (1H, m, 6-H), 2.17 (3H, s, 3″-OCH$_2$SC*H*$_3$), 2.24 (1H, d, 2″-Heq), 2.27 (1H, m, 14-H), 2.39 and 2.40 (2H, 2×q, 4″-OCOC*H*$_2$CH$_3$), 2.53 (6H, s, 3′-N(CH$_3$)$_2$), 3.23 (1H, br s, 4-H), 3.23 (1H, t, 4′-H), 3.23 (1H, dq, 5′-H), 3.41 (1H, dd, 2′-H), 3.43 (3H, s, 4-OCH$_3$), 3.47 (1H, br d, 5-H), 4.02 (1H, br dd, 3-H), 4.18 (1H, br dd, 9-H), 4.26 (1H, d, 1′-H), 4.50 and 4.63 (2H, 2×d, 3″-OC*H*$_2$SCH$_3$), 4.55 (1H, br d, 18-H), 4.59 (1H, dq, 5″-H), 4.65 (1H, d, 4″-H), 4.81 (1H, ddq, 15-H), 4.87 (1H, d, 1″-H), 5.60 (1H, dt, 13-H), 5.70 (1H, br dd, 10-H), 6.08 (1H, m, 11-H), 6.08 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methylthiomethylleucomycin A$_5$ 3,18-Acetal (**9b**)

Reaction of **8b** with MeOH gave **9b** in 97% yield by a similar procedure to **9a**.

9b: MP 65~68°C; EI-MS *m/z* 1059 $(M)^+$; $[\alpha]_D^{20}$ −26° (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.42 (1H, br dd, 7-H), 0.92 (3H, d, 19-H$_3$), 0.96 (3H, t, 4″-OCOCH$_2$CH$_2$C*H*$_3$), 1.07 (3H, d, 6″-H$_3$), 1.18 (3H, s, 3″-CH$_3$), 1.21 (3H, d, 6′-H$_3$), 1.30 (3H, d, 16-H$_3$), 1.44 (1H, br d, 17-H), 1.61 (1H, m, 8-H), 1.65 (1H, dt, 17-H), 1.68 (2H, m, 4″-OCOCH$_2$C*H*$_2$CH$_3$), 1.71 (1H, dd, 2″-Hax), 2.18 (3H, s, 3″-OCH$_2$SC*H*$_3$), 2.25 (1H, d, 2″-Heq), 2.27 (1H, m, 14-H), 2.36 and 2.37 (2H, 2×t, 4″-OCOC*H*$_2$CH$_2$CH$_3$), 2.53 (6H, s, 3′-N(CH$_3$)$_2$), 3.24 (1H, br s, 4-H), 3.24 (1H, t, 4′-H), 3.24 (1H, dq, 5′-H), 3.42 (1H, dd, 2′-H), 3.44 (3H, s, 4-OCH$_3$), 3.48 (1H, br d, 5-H), 4.04 (1H, br dd, 3-H), 4.19 (1H, br dd, 9-H), 4.28 (1H, d, 1′-H), 4.52 and 4.64 (2H, 2×d, 3″-OC*H*$_2$SCH$_3$), 4.57 (1H, br d, 18-H), 4.60 (1H, dq, 5″-H), 4.67 (1H, d, 4″-H), 4.83 (1H, ddq, 15-H), 4.88 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.71 (1H, br dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-4″-*O*-*iso*-butyryl-3″-*O*-methylthiomethylleucomycin V 3,18-Acetal (**9c**)

Reaction of **8c** with MeOH gave **9c** in 98% yield by a similar procedure to **9a**.

9c: MP 70~72°C; SI-MS *m/z* 1060 $(M+H)^+$; $[\alpha]_D^{15}$ −30° (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.42 (1H, br dd, 7-H), 0.92 (3H, d, 19-H$_3$), 1.06 (3H, d, 6″-H$_3$), 1.17 (3H, s, 3″-CH$_3$), 1.19 (6H, d, 4″-OCOCH(C*H*$_3$)$_2$), 1.30 (3H, d, 16-H$_3$), 1.43 (1H, br d, 17-H), 1.60 (1H, m, 8-H), 1.67 (1H, dt, 17-H), 1.71 (1H, dd, 2″-Hax), 2.16 (1H, m, 6-H), 2.18 (3H, s, 3″-OCH$_2$SC*H*$_3$), 2.24 (1H, d, 2″-Heq), 2.29 (1H, m, 14-H), 2.55 (6H, s, 3′-N(CH$_3$)$_2$), 2.64 (1H, septet, 4″-OCOC*H*(CH$_3$)$_2$), 3.25 (1H, br s, 4-H), 3.25 (1H, t, 4′-H), 3.25 (1H, dq, 5′-H), 3.42 (1H, dd, 2′-H), 3.44 (3H, s, 4-OCH$_3$), 3.48 (1H, br d, 5-H), 4.04 (1H, br dd, 3-H), 4.19 (1H, br dd, 9-H), 4.28 (1H, d, 1′-H), 4.50 and 4.63 (2H, 2×d, 3″-OC*H*$_2$SCH$_3$), 4.57 (1H, br d, 18-H), 4.61 (1H, dq, 5″-H), 4.65 (1H, d, 4″-H), 4.82 (1H, ddq, 15-H), 4.89 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.71 (1H, br dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methylthiomethyl-4″-*O*-*n*-valerylleucomycin V 3,18-Acetal (**9d**)

Reaction of **8d** with MeOH gave **9d** in 99% yield by a similar procedure to **9a**.

9d: MP 63~66°C; SI-MS *m/z* 1074 $(M+H)^+$; $[\alpha]_D^{15}$ −17° (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.42 (1H, br dd, 7-H), 0.89 (3H, d, 19-H$_3$), 0.91 (3H, t, 4″-OCOCH$_2$CH$_2$CH$_2$C*H*$_3$), 1.06 (3H, d, 6″-H$_3$), 1.17 (3H, s, 3″-CH$_3$), 1.20 (3H, d, 6′-H$_3$), 1.30 (3H, d, 16-H$_3$), 1.35 (2H, tq, 4″-OCOCH$_2$CH$_2$C*H*$_2$CH$_3$), 1.44 (1H, br d, 17-H), 1.60 (1H, m, 8-H), 1.63 (2H, m,4″-OCOCH$_2$C*H*$_2$CH$_2$CH$_3$), 1.66 (1H, dt, 17-H), 1.70 (1H, dd, 2″-Hax), 2.16 (1H, m, 6-H), 2.18 (3H, s, 3″-OCH$_2$SC*H*$_3$), 2.25 (1H, d, 2″-Heq), 2.28 (1H, m, 14-H), 2.38 and 2.39 (2H, 2×apparent t, 4″-OCOC*H*$_2$CH$_2$-

CH_2CH_3), 2.54 (6H, s, 3'-$N(CH_3)_2$), 3.24 (1H, br s, 4-H), 3.24 (1H, t, 4'-H), 3.24 (1H, dq, 5'-H), 3.42 (1H, dd, 2'-H), 3.44 (3H, s, 4-OCH_3), 3.48 (1H, br d, 5-H), 4.03 (1H, br dd, 3-H), 4.18 (1H, br dd, 9-H), 4.27 (1H, d, 1'-H), 4.51 and 4.60 (2H, 2×d, 3''-OCH_2SCH_3), 4.56 (1H, br d, 18-H), 4.60 (1H, dq, 5''-H), 4.67 (1H, d, 4''-H), 4.82 (1H, ddq, 15-H), 4.87 (1H, d, 1''-H), 5.61 (1H, dt, 13-H), 5.70 (1H, br dd, 10-H), 6.09 (1H, m, 11-H), 6.09 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3''-*O*-methylthiomethylleucomycin A_1 3,18-Acetal (**9e**)

Reaction of **8e** with MeOH gave **9e** in 99% yield by a similar procedure to **9a**.

9e: MP 72~75°C; SI-MS *m/z* 1074 $(M+H)^+$; $[\alpha]_D^{18}$ −21° (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.43 (1H, br dd, 7-H), 0.93 (3H, d, 19-H_3), 0.97 (6H, d, 4''-$OCOCH_2CH(CH_3)_2$), 1.07 (3H, d, 6''-H_3), 1.18 (3H, s, 3''-CH_3), 1.22 (3H, d, 6'-H_3), 1.31 (3H, d, 16-H_3), 1.44 (1H, br d, 17-H), 1.61 (1H, m, 8-H), 1.67 (1H, dt, 17-H), 1.72 (1H, dd, 2''-Hax), 2.14 (1H, m, 6-H), 2.15 (1H, m, 4''-$OCOCH_2CH(CH_3)_2$), 2.18 (3H, s, 3''-OCH_2SCH_3), 2.26 (1H, d, 2''-Heq), 2.27 and 2.28 (2H, 2×d, 4''-$OCOCH_2CH(CH_3)_2$), 2.29 (1H, m, 14-H), 2.54 (6H, s, 3'-$N(CH_3)_2$), 3.24 (1H, br s, 4-H), 3.24 (1H, t, 4'-H), 3.24 (1H, dq, 5'-H), 3.42 (1H, dd, 2'-H), 3.45 (3H, s, 4-OCH_3), 3.49 (1H, br d, 5-H), 4.04 (1H, br dd, 3-H), 4.19 (1H, br dd, 9-H), 4.28 (1H, d, 1'-H), 4.52 and 4.65 (2H, 2×d, 3''-OCH_2SCH_3), 4.57 (1H, br d, 18-H), 4.61 (1H, dq, 5''-H), 4.67 (1H, d, 4''-H), 4.83 (1H, ddq, 15-H), 4.88 (1H, d, 1''-H), 5.62 (1H, dt, 13-H), 5.72 (1H, br dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3''-*O*-methylleucomycin A_7 3,18-Acetal (**10a**)

To a solution of **9a** (300 mg, 0.29 mmol) in EtOH (6.0 ml) was added Raney-Nickel (7.5 ml) with EtOH (4.0 ml). The mixture was vigorously stirred at 25°C for 20 minutes exactly. Insoluble matter was filtered off, and it was washed with EtOH (10 ml) twice. Combined filtrate and washings were concentrated to give a residue which was purified with preparative TLC [toluene-acetone (3:1)] to afford **10a** (172 mg, 60%) as a colorless solid.

10a: MP 68~70°C; SI-MS *m/z* 1000 $(M+H)^+$; $[\alpha]_D^{21}$ −4° (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.42 (1H, br dd, 7-H), 0.92 (3H, d, 19-H_3), 1.07 (3H, d, 6''-H_3), 1.09 (3H, s, 3''-CH_3), 1.16 (3H, t, 4''-$OCOCH_2CH_3$), 1.22 (3H, d, 6'-H_3), 1.30 (3H, d, 16-H_3), 1.43 (1H, br d, 17-H), 1.60 (1H, m, 8-H), 1.64 (1H, dd, 2''-Hax), 1.67 (1H, dt, 17-H), 2.17 (1H, m, 6-H), 2.27 (1H, d, 2''-Heq), 2.30 (1H, m, 14-H), 2.42 and 2.43 (2H, 2×apparent q, 4''-$OCOCH_2CH_3$), 2.47 (1H, t, 3'-H), 2.54 (6H, s, 3'-$N(CH_3)_2$), 3.26 (3H, s, 3''-OCH_3), 3.31 (1H, t, 4'-H), 3.38 (1H, dd, 2'-H), 3.44 (3H, s, 4-OCH_3), 3.48 (1H, br d, 5-H), 4.04 (1H, br dd, 3-H), 4.19 (1H, br dd, 9-H), 4.30 (1H, d, 1'-H), 4.57 (1H, br d, 18-H), 4.59 (1H, dq, 5''-H), 4.71 (1H, d, 4''-H), 4.82 (1H, ddq, 15-H), 4.90 (1H, d, 1''-H), 5.62 (1H, dt, 13-H), 5.71 (1H, br dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3''-*O*-methylleucomycin A_5 3,18-Acetal (**10b**)

Reaction of **9b** with Raney-Nickel gave **10b** in 58% yield by a similar procedure to **10a**.

10b: MP 72~75°C; FAB-MS *m/z* 1014 $(M+H)^+$; $[\alpha]_D^{20}$ −15° (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.42 (1H, br dd, 7-H), 0.92 (3H, d, 19-H_3), 0.95 (3H, t, 4''-$OCOCH_2CH_2CH_3$), 1.07 (3H, d, 6''-H_3), 1.08 (3H, s, 3''-CH_3), 1.22 (3H, d, 6'-H_3), 1.31 (3H, d, 16-H_3), 1.44 (1H, br d, 17-H), 1.61 (1H, m, 8-H), 1.64 (1H, dd, 2''-Hax), 1.67 (2H, m, 4''-$OCOCH_2CH_2CH_3$), 2.17 (1H, m, 6-H), 2.28 (1H, d, 2''-Heq), 2.30 (1H, m, 14-H), 2.37 and 2.38 (2H, 2×apparent t, 4''-$OCOCH_2CH_2CH_3$), 2.48 (1H, t, 3'-H), 2.55 (6H, s, 3'-$N(CH_3)_2$), 3.26 (3H, s, 3''-OCH_3), 3.32 (1H, t, 4'-H), 3.38 (1H, dd, 2'-H), 3.44 (3H, s, 4-OCH_3), 3.48 (1H, br d, 5-H), 4.05 (1H, br dd, 3-H), 4.19 (1H, br dd, 9-H), 4.29 (1H, d, 1'-H), 4.56 (1H, br d, 18-H), 4.58 (1H, dq, 5''-H), 4.70 (1H, d, 4''-H), 4.82 (1H, ddq, 15-H), 4.90 (1H, d, 1''-H), 5.62 (1H, dt, 13-H), 5.72 (1H, br dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-4''-*O*-*iso*-butyryl-3''-*O*-methylleucomycin V 3,18-Acetal (**10c**)

Reaction of **9c** with Raney-Nickel gave **10c** in 55% yield by a similar procedure to **10a**.

10c: MP 82~85°C; SI-MS *m/z* 1014 $(M+H)^+$; $[\alpha]_D^{15}$ −20° (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.42 (1H, br dd, 7-H), 0.94 (3H, d, 19-H_3), 1.07 (3H, d, 6''-H_3), 1.08 (3H, s, 3''-CH_3), 1.19 and 1.20 (6H, 2×d, 4''-$OCOCH(CH_3)_2$), 1.22 (3H, d, 6'-H_3), 1.31 (3H, d, 16-H_3), 1.43 (1H, br d, 17-H), 1.61 (1H, m, 8-H), 1.65 (1H, dd, 2''-Hax), 1.68 (1H, dt, 17-H), 2.17 (1H, m, 6-H), 2.30 (1H, m, 14-H), 2.55 (6H, s, 3'-$N(CH_3)_2$), 2.67 (1H, septet, 4''-$OCOCH(CH_3)_2$), 3.25 (3H, s, 3''-OCH_3), 3.32 (1H, t, 4'-H), 3.38 (1H, dd, 2'-H), 3.44 (3H, s, 4-OCH_3), 3.48 (1H, br d, 5-H), 4.04 (1H, br dd, 3-H), 4.19 (1H, br dd, 9-H), 4.30 (1H, d, 1'-H), 4.57 (1H, br d, 18-H), 4.59 (1H, dq, 5''-H), 4.69 (1H, d, 4''-H), 4.82 (1H, ddq, 15-H), 4.90 (1H, d, 1''-H), 5.62 (1H, dt, 13-H), 5.71 (1H,

br dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methyl-4″-*O*-*n*-valerylleucomycin V 3,18-Acetal (**10d**)

Reaction of **9d** with Raney-Nickel gave **10d** in 65% yield by a similar procedure to **10a**.

10d: MP 70~72°C; SI-MS *m/z* 1028 $(M+H)^+$; $[\alpha]_D^{15}$ −16° (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.42 (1H, br dd, 7-H), 0.89 (3H, t, 4″-OCOCH$_2$CH$_2$CH$_2$C*H*$_3$), 0.92 (3H, d, 19-H$_3$), 1.06 (3H, d, 6″-H$_3$), 1.08 (3H, s, 3″-CH$_3$), 1.22 (3H, d, 6′-H$_3$), 1.30 (3H, d, 16-H$_3$), 1.35 (2H, tq, 4″-OCOCH$_2$CH$_2$C*H*$_2$CH$_3$), 1.42 (1H, br d, 17-H), 1.63 (2H, m, 4″-OCOCH$_2$C*H*$_2$CH$_2$CH$_3$), 1.67 (1H, dt, 17-H), 2.17 (1H, m, 6-H), 2.27 (1H, d, 2″-Heq), 2.30 (1H, m, 14-H), 2.39 and 2.40 (2H, 2 × apparent t, 4″-OCOC*H*$_2$CH$_2$CH$_2$CH$_3$), 2.54 (6H, s, 3′-N(CH$_3$)$_2$), 3.25 (3H, s, 3″-OCH$_3$), 3.31 (1H, t, 4′-H), 3.38 (1H, dd, 2′-H), 3.44 (3H, s, 4-OCH$_3$), 3.47 (1H, br d, 5-H), 4.04 (1H, br dd, 3-H), 4.18 (1H, br dd, 9-H), 4.29 (1H, d, 1′-H), 4.56 (1H, br d, 18-H), 4.58 (1H, dq, 5″-H), 4.70 (1H, d, 4″-H), 4.82 (1H, ddq, 15-H), 4.90 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.71 (1H, br dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methylleucomycin A$_1$ 3,18-Acetal (**10e**)

Reaction of **9e** with Raney-Nickel gave **10e** in 58% yield by a similar procedure to **10a**.

10e: MP 75~78°C; SI-MS *m/z* 1028 $(M+H)^+$; $[\alpha]_D^{16}$ −24° (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.42 (1H, br dd, 7-H), 1.07 (3H, d, 6″-H$_3$), 1.09 (3H, s, 3″-CH$_3$), 1.22 (3H, d, 6′-H$_3$), 1.30 (3H, d, 16-H$_3$), 1.42 (1H, br d, 17-H), 1.60 (1H, m, 8-H), 1.63 (1H, dd, 2″-Hax), 1.67 (1H, dt, 17-H), 2.17 (1H, m, 6-H), 2.27 (1H, d, 2″-Heq), 2.28 (2H, 2 × d, 4″-OCOC*H*$_2$CH(CH$_3$)$_2$), 2.54 (6H, s, 3′-N(CH$_3$)$_2$), 3.25 (3H, s, 3″-OCH$_3$), 3.31 (1H, t, 4′-H), 3.39 (1H, dd, 2′-H), 3.44 (3H, s, 4-OCH$_3$), 3.48 (1H, br d, 5-H), 4.04 (1H, br dd, 3-H), 4.19 (1H, br dd, 9-H), 4.30 (1H, d, 1′-H), 4.57 (1H, br d, 18-H), 4.59 (1H, dq, 5″-H), 4.71 (1H, d, 4″-H), 4.82 (1H, ddq, 15-H), 4.90 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.71 (1H, br dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

3″-*O*-Methylleucomycin A$_7$ (**3a**)

To 163 mg (0.16 mmol) of **10a** was added 1.22 ml of a 2.0 M solution of TBAF in THF and the mixture was allowed to react at 45°C for 1 hour. Then the reaction mixture was dropped into 5% aqueous $KHSO_4$ (50 ml) and then extracted with $CHCl_3$ (300 ml) twice. The organic layers were combined and successively washed with saturated aqueous $NaHCO_3$ (600 ml) twice and brine (600 ml) twice. The organic layer was dried and concentrated. The resulting residue was purified by silica gel column chromatography [10 g, $CHCl_3$-MeOH-NH_4OH (400:20:1)] to afford **3a** (88 mg, 70%) as a colorless solid.

3a: MP 111~113°C; EI-MS *m/z* 771 $(M)^+$; $[\alpha]_D^{17}$ −79° (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (1H, br ddd, 7-H), 0.99 (3H, d, 19-H$_3$), 1.07 (3H, d, 6″-H$_3$), 1.10 (3H, s, 3″-CH$_3$), 1.17 (3H, t, 4″-OCOCH$_2$C*H*$_3$), 1.19 (3H, d, 6′-H$_3$), 1.30 (3H, d, 16-H$_3$), 1.60 (1H, br dt, 7-H), 1.66 (1H, dd, 2″-Hax), 1.90 (1H, m, 8-H), 2.12 (1H, dt, 14-H), 2.22 (1H, d, 2-H), 2.29 (1H, d, 2″-Heq), 2.34 (1H, br dd, 17-H), 2.42 (1H, t, 3′-H), 2.42 and 2.43 (2H, 2 × apparent q, 4″-OCOC*H*$_2$CH$_3$), 2.51 (1H, br dt, 14-H), 2.57 (6H, s, 3′-N(CH$_3$)$_2$), 2.70 (1H, dd, 2-H), 2.87 (1H, br dd, 17-H), 3.09 (1H, br d, 4-H), 3.22 (1H, dd, 2′-H), 3.26 (3H, s, 3″-OCH$_3$), 3.28 (1H, dq, 5′-H), 3.45 (1H, t, 4′-H), 3.54 (3H, s, 4-OCH$_3$), 3.79 (1H, br d, 3-H), 4.10 (1H, dd, 9-H), 4.11 (1H, br d, 5-H), 4.54 (1H, dq, 5″-H), 4.58 (1H, d, 1′-H), 4.72 (1H, d, 4″-H), 4.93 (1H, d, 1″-H), 5.29 (1H, ddq, 15-H), 5.61 (1H, ddd, 13-H), 5.68 (1H, dd, 10-H), 6.03 (1H, br dd, 12-H), 6.26 (1H, dd, 11-H), 9.80 (1H, br s, 18-H).

3″-*O*-Methylleucomycin A$_5$ (**3b**)

Reaction of **10b** with a 2.0 M solution of TBAF in THF gave **3b** in 68% yield by a similar procedure to **3a**.

3b: MP 100~104°C; FD-MS *m/z* 786 $(M+H)^+$; $[\alpha]_D^{15}$ −76° (*c* 0.9, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, 4″-OCOCH$_2$CH$_2$C*H*$_3$), 0.99 (3H, d, 19-H$_3$), 1.08 (3H, d, 6″-H$_3$), 1.11 (3H, s, 3″-CH$_3$), 1.20 (3H, d, 6′-H$_3$), 1.31 (3H, d, 16-H$_3$), 1.60 (1H, br dt, 7-H), 1.67 (1H, dd, 2″-Hax), 1.69 (2H, tq, 4″-OCOCH$_2$C*H*$_2$CH$_3$), 1.91 (1H, m, 8-H), 2.12 (1H, dt, 14-H), 2.22 (1H, br d, 2-H), 2.29 (1H, d, 2″-Heq), 2.34 (1H, br dd, 17-H), 2.39 (2H, m, 4″-OCOC*H*$_2$CH$_2$CH$_3$), 2.58 (6H, s, 3′-N(CH$_3$)$_2$), 2.70 (1H, dd, 2-H), 2.87 (1H, br dd, 17-H), 3.10 (1H, br d, 4-H), 3.23 (1H, dd, 2′-H), 3.26 (3H, s, 3″-OCH$_3$), 3.28 (1H, dq, 5′-H), 3.46 (1H, t, 4′-H), 3.54 (3H, s, 4-OCH$_3$), 3.79 (1H, br d, 3-H), 4.10 (1H, dd, 9-H), 4.11 (1H, br d, 5-H), 4.54 (1H, dq, 5″-H), 4.59 (1H, d, 1′-H), 4.72 (1H, d, 4″-H), 4.94 (1H, d, 1″-H), 5.29 (1H, ddq, 15-H), 5.61 (1H, ddd, 13-H), 5.69 (1H, dd, 10-H), 6.04 (1H, br dd, 12-H), 6.26 (1H, dd, 11-H), 9.80 (1H, s, 18-H).

4″-*O*-*iso*-Butyryl-3″-*O*-methylleucomycin V (**3c**)

Reaction of **10c** with a 2.0 M solution of TBAF in THF gave **3c** in 65% yield by a similar procedure to **3a**.

3c: MP 98~102°C; EI-MS *m/z* 785 $(M)^+$; $[\alpha]_D^{17}$ −71° (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, br ddd, 7-H), 0.97 (3H, d, 19-H_3), 1.05 (3H, d, 6″-H_3), 1.08 (3H, s, 3″-CH_3), 1.18 and 1.19 (6H, 2×d, 4″-OCOCH(CH_3)$_2$), 1.29 (3H, d, 16-H_3), 1.58 (1H, br dt, 7-H), 1.66 (1H, dd, 2″-Hax), 1.89 (1H, m, 8-H), 2.10 (1H, dt, 14-H), 2.20 (1H, d, 2-H), 2.26 (1H, d, 2″-Heq), 2.32 (1H, br dd, 17-H), 2.47 (1H, t, 3′-H), 2.49 (1H, br dt, 14-H), 2.57 (6H, s, 3′-N(CH_3)$_2$), 2.67 (1H, septet, 4″-OCOC*H*(CH_3)$_2$), 2.69 (1H, dd, 2-H), 2.86 (1H, br dd, 17-H), 3.08 (1H, br d, 4-H), 3.22 (1H, dd, 2′-H), 3.24 (3H, s, 3″-OCH_3), 3.27 (1H, dq, 5′-H), 3.44 (1H, t, 4′-H), 3.53 (3H, s, 4-OCH_3), 3.77 (1H, br d, 3-H), 4.08 (1H, dd, 9-H), 4.09 (1H, br d, 5-H), 4.52 (1H, dq, 5″-H), 4.57 (1H, d, 1′-H), 4.69 (1H, d, 4″-H), 4.92 (1H, d, 1″-H), 5.28 (1H, ddq, 15-H), 5.59 (1H, ddd, 13-H), 5.67 (1H, dd, 10-H), 6.02 (1H, br dd, 12-H), 6.25 (1H, dd, 11-H), 9.79 (1H, br s, 18-H).

3″-*O*-Methyl-4″-*O*-*n*-valerylleucomycin V (**3d**)

Reaction of **10d** with a 2.0 M solution of TBAF in THF gave **3d** in 67% yield by a similar procedure to **3a**.

3d: MP 98~102°C; EI-MS *m/z* 799 $(M)^+$; $[\alpha]_D^{17}$ −68° (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, 4″-OCOCH$_2$CH$_2$CH$_2$C*H*$_3$), 0.98 (3H, d, 19-H_3), 1.06 (3H, d, 6″-H_3), 1.09 (3H, s, 3″-CH_3), 1.18 (3H, d, 6′-H_3), 1.29 (3H, d, 16-H_3), 1.34 (2H, tq, 4″-OCOCH$_2$CH$_2$C*H*$_2$CH$_3$), 1.58 (1H, br dt, 7-H), 1.62 (2H, m, 4″-OCOCH$_2$C*H*$_2$CH$_2$CH$_3$), 1.65 (1H, dd, 2″-Hax), 1.90 (1H, m, 8-H), 2.10 (1H, dt, 14-H), 2.21 (1H, d, 2-H), 2.28 (1H, d, 2″-Heq), 2.33 (1H, br dd, 17-H), 2.39 and 2.40 (2H, 2×apparent t, 4″-OCOC*H*$_2$CH$_2$CH$_2$-CH$_3$), 2.49 (1H, br dt, 14-H), 2.55 (6H, s, 3′-N(CH_3)$_2$), 2.69 (1H, dd, 2-H), 2.86 (1H, br dd, 17-H), 3.08 (1H, br d, 4-H), 3.21 (1H, dd, 2′-H), 3.24 (3H, s, 3″-OCH_3), 3.27 (1H, dq, 5′-H), 3.43 (1H, t, 4′-H), 3.53 (3H, s, 4-OCH_3), 3.78 (1H, br d, 3-H), 4.09 (1H, dd, 9-H), 4.10 (1H, br d, 5-H), 4.52 (1H, dq, 5″-H), 4.57 (1H, d, 1′-H), 4.70 (1H, d, 4″-H), 4.92 (1H, d, 1″-H), 5.28 (1H, ddq, 15-H), 5.60 (1H, ddd, 13-H), 5.67 (1H, dd, 10-H), 6.02 (1H, br dd, 12-H), 6.25 (1H, dd, 11-H), 9.79 (1H, br s, 18-H).

3″-*O*-Methylleucomycin A_1 (**3e**)

Reaction of **10e** with a 2.0 M solution of TBAF in THF gave **3e** in 66% yield by a similar procedure to **3a**.

3e: MP 100~104°C; EI-MS *m/z* 799 $(M)^+$; $[\alpha]_D^{18}$ −66° (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (6H, d, 4″-OCOCH$_2$CH(C*H*$_3$)$_2$), 0.97 (3H, d, 19-H_3), 0.98 (1H, br ddd, 7-H), 1.07 (3H, d, 6″-H_3), 1.09 (3H, s, 3″-CH_3), 1.18 (3H, d, 6′-H_3), 1.29 (3H, d, 16-H_3), 1.58 (1H, br dt, 7-H), 1.65 (1H, dd, 2″-Hax), 1.99 (1H, m, 8-H), 2.10 (1H, dt, 14-H), 2.13 (1H, m, 4″-OCOCH$_2$C*H*-(CH$_3$)$_2$), 2.20 (1H, d, 2-H), 2.27 (1H, d, 2″-Heq), 2.28 (2H, d, 4″-OCOC*H*$_2$CH(CH$_3$)$_2$), 2.32 (1H, br dd, 17-H), 2.42 (1H, t, 3′-H), 2.50 (1H, br dt, 14-H), 2.56 (6H, s, 3′-N(CH_3)$_2$), 2.69 (1H, dd, 2-H), 2.86 (1H, br dd, 17-H), 3.08 (1H, br d, 4-H), 3.22 (1H, dd, 2′-H), 3.24 (3H, s, 3″-OCH_3), 3.27 (1H, dq, 5′-H), 3.44 (1H, t, 4′-H), 3.53 (3H, s, 4-OCH_3), 3.78 (1H, br d, 3-H), 4.08 (1H, dd, 9-H), 4.10 (1H, br d, 5-H), 4.53 (1H, dq, 5″-H), 4.57 (1H, d, 1′-H), 4.71 (1H, d, 4″-H), 4.92 (1H, d, 1″-H), 5.28 (1H, ddq, 15-H), 5.59 (1H, ddd, 13-H), 5.67 (1H, dd, 10-H), 6.02 (1H, br dd, 12-H), 6.25 (1H, dd, 11-H), 9.79 (1H, br s, 18-H).

9,18,2′-Tri-*O*-*tert*-butyldimethylsilylleucomycin A_7 3,18-Acetal (**11a**)

To 1.00 g (1.32 mmol) of LM-A_7 was added dry DMF (12 ml), and 1.18 g (7.82 mmol) of TBSCl and 1.08 g (15.8 mmol) of imidazole were added. The mixture was stirred at 50°C for 24 hours. The reaction mixture was cooled to room temperature, and MeOH (50 ml) was added followed by stirring at room temperature for 30 minutes. Evaporation gave a residue which was extracted with benzene (500 ml) and the benzene layer was successively washed with saturated aqueous $NaHCO_3$ (500 ml) twice and brine (500 ml) twice. Then the organic layer was dried and concentrated to afford 1.22 g of crude **11a**. A 60 mg portion of this crude compound was purified by preparative TLC [$CHCl_3$ - MeOH (50 : 1)] to afford **11a** (59 mg, 83%) as a colorless solid.

11a: MP 105~107°C; $[\alpha]_D^{17}$ −17° (*c* 1.0, MeOH); SI-MS *m/z* 1100 $(M+H)^+$; ^{1}H NMR δ 0.41 (1H, br dd, 7-H), 1.11 (3H, s, 3″-CH_3), 1.17 (3H, t, 4″-OCOCH$_2$C*H*$_3$), 1.25 (3H, d, 6′-H), 1.30 (3H, d, 16-H), 1.38 (1H, dt, 17-H), 1.66 (1H, br d, 17-H), 1.86 (1H, dd, 2″-Hax), 2.00 (1H, d, 2″-Heq), 2.53 (6H, s, 3′-N(CH_3)$_2$), 2.55 (1H, t, 3′-H), 2.61 (1H, dd, 2-H), 3.14 (1H, br s, 4-H), 3.35 (1H, t, 4′-H), 3.38 (3H, s, 4-OCH_3), 3.42 (1H, br dd, 5-H), 3.52 (1H, dd, 2′-H), 4.21 (1H, d, 1′-H), 4.22 (1H, m, 3-H), 4.23 (1H, m, 9-H), 4.37 (1H, dq, 5″-H), 4.62 (1H, d, 4″-H), 4.63 (1H, br dd, 18-H), 4.85 (1H, ddq, 15-H), 5.10 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.75 (1H, dd, 10-H), 6.12 (1H, m, 11-H), 6.12 (1H, m, 12-H).

9,18,2′-Tri-*O*-*tert*-butyldimethylsilylleucomycin A_1 3,18-Acetal (**11e**)

One hundred thirty ml of benzene was added to 1.16 g (1.05 mmol) of crude **11a**, and 25% aqueous NaOH

(65 ml) and 358 mg (1.05 mmol) of tetra-*n*-butylammonium hydrogensulfate were added. After vigorous stirring at room temperature for 2 hours, the benzene layer was collected and washed with brine (150 ml) twice. The organic layer was dried and concentrated. The residue thus obtained was purified by silica gel column chromatography [200 g, $CHCl_3$-MeOH (30:1)] to give 795 mg (0.76 mmol, 72% overall 2 steps) of diol. To a stirred mixture of diol (430 mg, 0.41 mmol) in pyridine (4.3 ml) was added *iso*-valeryllchloride (248 mg, 2.06 mmol). The resulting mixture was stirred at room temperature for 10 minutes. After slowly adding saturated aqueous $NaHCO_3$ (50 ml), the reaction mixture was extracted with $CHCl_3$ (50 ml) twice. The organic layers were combined, washed with brine (100 ml) twice and dried. Then the organic layer was dried and concentrated to afford crude **11e**. This crude compound was purified by silica gel column chromatography [30 g, hexane-AcOEt (2:1)] to afford 11e (326 mg, 71%) as a colorless solid.

11e: MP 78~81°C; SI-MS *m/z* 1128 $(M+H)^+$; $[\alpha]_D^{14}$ −17° (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.41 (1H, br dd, 7-H), 0.93 (3H, d, 19-H_3), 0.97 (6H, d, 4″-OCOCH$_2$CH(CH_3)$_2$), 1.10 (3H, s, 3″-CH_3), 1.14 (3H, d, 6″-H_3), 1.25 (3H, d, 6′-H_3), 1.30 (3H, d, 16-H_3), 1.38 (1H, dt, 17-H), 1.65 (1H, br d, 17-H), 1.70 (1H, m, 8-H), 1.85 (1H, dd, 2″-Hax), 2.00 (1H, d, 2″-Heq), 2.13 (1H, m, 4″-OCOCH$_2$CH(CH$_3$)$_2$), 2.29 (2H, d, 4″-OCOCH_2CH(CH$_3$)$_2$), 2.38 (1H, dd, 2-H), 2.45 (1H, m, 14-H), 2.53 (6H, s, 3′-N(CH$_3$)$_2$), 2.55 (1H, t, 3′-H), 2.61 (1H, dd, 2-H), 3.14 (1H, br s, 4-H), 3.30 (1H, dq, 5′-H), 3.34 (1H, t, 4′-H), 3.38 (3H, s, 4-OCH$_3$), 3.42 (1H, br dd, 5-H), 3.53 (1H, dd, 2′-H), 4.20 (1H, d, 1′-H), 4.22 (1H, m, 3-H), 4.23 (1H, m, 9-H), 4.37 (1H, dq, 5″-H), 4.62 (1H, d, 4″-H), 4.63 (1H, br dd, 18-H), 4.84 (1H, ddq, 15-H), 5.10 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.74 (1H, br dd, 10-H), 6.11 (1H, m, 11-H), 6.11 (1H, m, 12-H).

9,18,2′-Tri-*O*-*tert*-butyldimethylsilyl-3″-*O*-methylthiomethylleucomycin A_1 3,18-Acetal (**12**)

Reaction of **11e** with DMSO and Bz_2O gave **12** in 58% yield by a similar procedure to **8a**.

12: MP 90~92°C; SI-MS *m/z* 1188 $(M+H)^+$; $[\alpha]_D^{14}$ −22° (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.38 (1H, br dd, 7-H), 0.92 (3H, d, 19-H_3), 0.97 (6H, d, 4″-OCOCH$_2$CH(CH_3)$_2$), 1.08 (3H, d, 6″-H_3), 1.20 (3H, s, 3″-CH_3), 1.22 (3H, d, 6′-H_3), 1.31 (3H, d, 16-H_3), 1.41 (1H, dt, 17-H), 1.62 (1H, br d, 17-H), 1.66 (1H, m, 8-H), 1.74 (1H, dd, 2″-Hax), 2.13 (1H, m, 4″-OCOCH$_2$CH(CH$_3$)$_2$), 2.18 (3H, s, 3″-OCH$_2$SCH_3), 2.25 (1H, d, 2″-Heq), 2.27 (2H, d, 4″-OCOCH_2CH(CH$_3$)$_2$), 2.42 (1H, dd, 2-H), 2.48 (1H, t, 3′-H), 2.50 (6H, s, 3′-N(CH$_3$)$_2$), 2.60 (1H, dd, 2-H), 3.14 (1H, br s, 4-H), 3.40 (3H, s, 4-OCH$_3$), 4.17 (1H, d, 1′-H), 4.19 (1H, m, 3-H), 4.21 (1H, m, 9-H), 4.52 and 4.65 (2H, 2×d, 3″-OCH_2SCH$_3$), 4.55 (1H, dq, 5″-H), 4.60 (1H, br dd, 18-H), 4.71 (1H, d, 4″-H), 4.80 (1H, ddq, 15-H), 4.98 (1H, d, 1″-H), 5.61 (1H, dt, 13-H), 5.74 (1H, dd, 10-H), 6.11 (1H, m, 11-H), 6.11 (1H, m, 12-H).

9-*O*-Acetyl-18-*O*-*tert*-butyldimethylsilyl-3″-*O*-methylthiomethylleucomycin A_7 3,18-Acetal (**13**)

To 5.00 g (6.60 mmol) of LM-A7 was added dry pyridine (100 ml), and 2.70 g (37.8 mmol) of Ac_2O was added. The mixture was stirred at room temperature for 2 days. After slowly adding saturated aqueous $NaHCO_3$ (500 ml), the reaction mixture was extracted with CH_2Cl_2 (500 ml). Then organic layer was dried and the resulting residue was purified by silica gel column chromatography [300 g, hexane-AcOEt (1:3)]. Thus, 3.30 g (60%) of 9,″-di-*O*-acetylleucomycin A_7 was obtained. To 3.05 g (3.62 mmol) of 9,2′-di-*O*-acetylleucomycin A_7 was added dry DMF (30 ml), and 1.10 g (7.29 mmol) of TBSCl and 989 mg (14.5 mmol) of imidazole were added. The mixture was stirred at 45°C for 24 hours. After slowly adding saturated aqueous $NaHCO_3$ (300 ml), the reaction mixture was extracted with CH_2Cl_2 (300 ml). Then the organic layer was dried and concentrated to afford crude compound. This crude compound was purified by silica gel column chromatography [200 g, hexane-AcOEt (2:1)] to give 1.85 g (54%) of 9,2′-di-*O*-Ac-18-*O*-TBS-LM-A_7 3,18-acetal. A solution of 9,2′-di-*O*-Ac-18-*O*-TBS-LM-A_7 3,18-acetal (1.80 g, 1.88 mmol) in dry DMSO (16.2 ml) and Bz_2O (5.4 ml) was kept at 45°C for 3 days, then poured into toluene (300 ml). The organic layer was washed with H_2O (300 ml) three times, and dried. Evaporation gave a residue which was purified by silica gel column chromatography [180 g, hexane-EtOAc, 2:1] to afford 9,2′-di-*O*-Ac-3″-*O*-MTM-18-*O*-TBS-LM-A_7 3,18-Acetal (460 mg, 24%). A solution of 9,2′-di-*O*-Ac-3″-*O*-MTM-18-*O*-TBS-LM-A_7 3,18-acetal (460 mg, 0.45 mmol) in MeOH (12 ml) was allowed to stand at 25°C for 16 hours. Evaporation gave a residue which was purified by silica gel column chromatography [50 g, $CHCl_3$-MeOH (10:1)] to afford **13** (435 mg, 99%) as a colorless solid.

13: MP 75~78°C; FD-MS *m/z* 973 $(M)^+$; $[\alpha]_D^{17}$ −21° (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.67 (1H, br dd, 7-H), 0.93 (3H, d, 19-H_3), 1.06 (3H, d, 6″-H_3), 1.17 (3H, t, 4″-OCOCH$_2$CH_3), 1.18 (3H, s, 3″-CH_3), 1.23

(3H, d, 6′-H_3), 1.29 (3H, d, 16-H_3), 1.40 (1H, br dt, 17-H), 1.72 (1H, dd, 2″-Hax), 1.79 (1H, br dd, 17-H), 1.86 (1H, m, 8-H), 2.13 (3H, s, 9-$OCOCH_3$), 2.17 (3H, s, 3″-OCH_2SCH_3), 2.26 (1H, d, 2″-Heq), 2.48 (1H, t, 3′-H), 2.55 (6H, s, 3′-$N(CH_3)_2$), 2.67 (1H, dd, 2-H), 3.27 (1H, dq, 5′-H), 3.28 (1H, br d, 4-H), 3.37 (1H, t, 4′-H), 3.39 (1H, dd, 2′-H), 3.47 (3H, s, 4-OCH_3), 3.59 (1H, br d, 5-H), 3.99 (1H, br dd, 3-H), 4.32 (1H, d, 1′-H), 4.51 and 4.64 (2H, 2 × d, 3″-OCH_2SCH_3), 4.58 (1H, br d, 18-H), 4.59 (1H, dq, 5″-H), 4.66 (1H, d, 4″-H), 4.87 (1H, ddq, 15-H), 4.91 (1H, d, 1″-H), 5.40 (1H, br d, 9-H), 5.61 (1H, dd, 10-H), 5.67 (1H, dt, 13-H), 6.06 (1H, m, 11-H), 6.06 (1H, m, 12-H).

9-*O*-Acetyl-3″-*O*-methylleucomycin A_5 (**14**)

To a stirred mixture of **3b** (20 mg, 0.025 mmol) in toluene (1.0 ml) was added acetylchloride (6.9 mg, 0.088 mmol) and pyridine (9.0 μl). The resulting mixture was stirred at room temperature for 15 minutes. After slowly adding saturated aqueous $NaHCO_3$ (50 ml), the reaction mixture was extracted with $CHCl_3$ (50 ml) twice. The organic layers were combined, washed with brine (100 ml) twice and dried. Then the organic layer was dried and concentrated to afford crude **14**. This crude compound was purified by preparative TLC [$CHCl_3$-MeOH (10:1)] to afford **14** (16 mg, 75%) as a colorless solid.

14: MP 102~105°C; EI-MS *m/z* 828 $(M+H)^+$; $[\alpha]_D^{17}$ −75° (*c* 0.6, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, 4″-$OCOCH_2CH_2CH_3$), 0.98 (3H, d, 19-H_3), 1.08 (3H, d, ‴-H_3), 1.10 (3H, s, 3″-CH_3), 1.20 (3H, d, 6′-H_3), 1.30 (3H, d, 16-H_3), 1.62 (1H, br dt, 7-H), 1.67 (1H, dd, 2″-Hax), 1.68 (2H, tq, 4″-$OCOCH_2CH_2CH_3$), 1.99 (1H, m, 8-H), 2.00 (3H, s, 9-$OCOCH_3$), 2.12 (1H, dt, 14-H), 2.22 (1H, br d, 2-H), 2.30 (1H, d, 2″-Heq), 2.39 (2H, m, 4″-$OCOCH_2CH_2CH_3$), 2.42 (1H, t, 3′-H), 2.46 (1H, br dd, 17-H), 2.50 (1H, br dt), 2.57 (6H, s, 3′-$N(CH_3)_2$), 2.71 (1H, dd, 2-H), 2.82 (1H, br dd, 17-H), 3.09 (1H, br d, 4-H), 3.20 (1H, dd, 2′-H), 3.26 (3H, s, 3″-OCH_3), 3.27 (1H, dq, 5′-H), 3.45 (1H, t, 4′-H), 3.54 (3H, s, 4-OCH_3), 3.79 (1H, br d, 3-H), 4.14 (1H, br d, 5-H), 4.54 (1H, dq, 5″-H), 4.57 (1H, d, 1′-H), 4.72 (1H, d, 4″-H), 4.93 (1H, d, 1″-H), 5.17 (1H, dd, 9-H), 5.29 (1H, ddq, 15-H), 5.60 (1H, dd, 10-H), 5.65 (1H, ddd, 13-H), 6.03 (1H, br dd, 12-H), 6.40 (1H, dd, 11-H), 9.80 (1H, s, 18-H).

3″-*O*-Methyl-9-*O*-propionylleucomycin V (**15**)

Reaction of **3b** with a propionylchloride gave **15** in 74% yield by a similar procedure to **14**.

15: MP 102~105°C; FD-MS *m/z* 841 $(M)^+$; $[\alpha]_D^{19}$ −73° (*c* 0.3, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, 4″-$OCOCH_2CH_2CH_3$), 0.98 (3H, d, 19-H_3), 1.07 (3H, d, 6″-H_3), 1.09 (3H, t, 9-$OCOCH_2CH_3$), 1.09 (3H, s, 3″-CH_3), 1.20 (3H, d, 6′-H_3), 1.30 (3H, d, 16-H_3), 1.62 (1H, br dt, 7-H), 1.67 (1H, dd, 2″-Hax), 1.69 (2H, tq, 4″-$OCOCH_2CH_2CH_3$), 2.00 (1H, m, 8-H), 2.12 (1H, dt, 14-H), 2.22 (1H, br d, 2-H), 2.28 (1H, d, 2″-Heq), 2.39 (2H, q, 9-$OCOCH_2CH_3$), 2.39 (2H, m, 4″-$OCOCH_2CH_2CH_3$), 2.47 (1H, br dd, 17-H), 2.51 (1H, br dt, 14-H), 2.57 (6H, s, 3′-$N(CH_3)_2$), 2.70 (1H, dd, 2-H), 2.82 (1H, br dd, 17-H), 3.09 (1H, br d, 4-H), 3.21 (1H, dd, 2′-H), 3.26 (3H, s, 3″-OCH_3), 3.28 (1H, dq, 5′-H), 3.45 (1H, t, 4′-H), 3.54 (3H, s, 4-OCH_3), 3.79 (1H, br d, 3-H), 4.14 (1H, br d, 5-H), 4.54 (1H, dq, 5″-H), 4.57 (1H, d, 1′-H), 4.72 (1H, d, 4″-H), 4.93 (1H, d, 1″-H), 5.18 (1H, dd, 9-H), 5.29 (1H, ddq, 15-H), 5.61 (1H, dd, 10-H), 5.65 (1H, ddd, 13-H), 6.03 (1H, br dd, 12-H), 6.40 (1H, dd, 11-H), 9.80 (1H, s, 18-H).

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