Cladinose Analogues of Sixteen-membered Macrolide Antibiotics

III. Efficient Synthesis of 4-*O*-Alkyl-L-cladinose Analogues: Improved Antibacterial Activities Compatible with Pharmacokinetics

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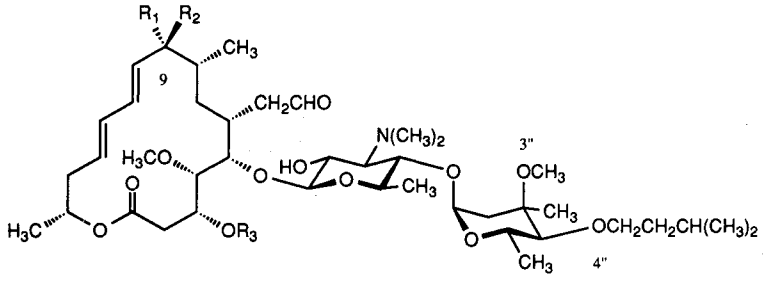
The synthesis and biological evaluation of sixteen-membered macrolides possessing a 4-*O*-alkyl-α-L-cladinosyl moiety as a neutral sugar are described. These potent novel derivatives have been efficiently synthesized avoiding glycosylations. Two hydroxyl groups in mycarose of the tri-(*tert*-butyldimethylsilyl) ether intermediate were successively alkylated. Sequential deprotections of silyl groups afforded 4-*O*-alkyl-L-cladinose analogues and 3,4-di-*O*-alkyl-L-mycarose analogues of leucomycin V. Some 4-*O*-alkyl-L-cladinose analogues exhibited potent antibacterial activities. The most active derivative, 3″-*O*-methyl-4″-*O*-(3-methylbutyl)leucomycin V, showed improved metabolic stability in rat plasma *in vitro* and extremely high concentrations in serum after oral administrations in mice and in hamsters.

Sixteen-membered macrolide antibiotics[1] are safe and useful in treating infections caused by Gram-positive bacteria and exert fewer interaction with other drugs and have less effect on the intestinal tract in comparison with the fourteen-membered macrolides. There seems to be some possibilities that their pharmacokinetics[2] and therapeutic effects will be improved with chemical modifications. KIRST proposed several important factors for the improvement of macrolide antibiotics[3]. Our work was focused on following two elements; 1) the improvement of chemical and metabolic stability, and 2) the improvement of serum concentrations. One explanation for the poor pharmacokinetics involves *in vivo* deacylation[4] at the neutral sugar moiety, which led us to design, synthesize and study of several stages of 4-*O*-alkyl-L-cladinose analogues (Fig. 1). As part of our program in this area, we have synthesized the 9-dehydro (a carbonyl group at the C-9 position) derivatives including compound (**1**) *via* glycosylations, and excellent metabolic stability of **1** was shown in rat plasma *in vitro*[5]. Recently, we have also prepared the 9-OH derivatives, such as compound (**2**), using bioconversion, and dramatic improvement of pharmacokinetics was demonstrated[6]. SAKAKIBARA and ŌMURA *et al.* have investigated many 3-OH derivatives of leucomycin, including rokitamycin (RKM), which is a very effective semi-synthetic sixteen-membered macrolide antibiotic.[7,8]

In this paper, we wish to report the efficient synthesis of 3-OH derivatives (Fig. 1), such as compound (**3f**)†,[9], a 4-*O*-alkyl-L-cladinose analogue of leucomycin V[10] (LM-V) (Fig. 2), without glycosylation or biotransformation. The reported compound (**3f**) exhibited not only potent antibacterial activities *in vitro* but also

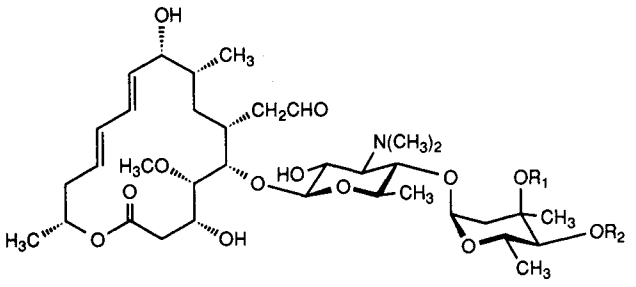
Fig. 1. 4-*O*-Alkyl-L-cladinose analogues of leucomycin.



	R_1	R_2	R_3
1	=O		$COCH_2CH_3$
2	OH	H	$COCH_2CH_3$
3f	OH	H	H

† A compound (**3f**) was originally prepared *via* glycosylation and biotransformations. See ref. 9. The preparation of **3f** using bioconversion will be reported elsewhere.

Fig. 2. A part of natural leucomycins and its analogue, RKM.



	R_1	R_2
LM-V	H	H
LM-A_7	H	$COCH_2CH_3$
RKM	$COCH_2CH_3$	$COCH_2CH_2CH_3$

excellent pharmacokinetics in spite of its 3-OH structure. Structure activity relationships (SAR) between the neutral sugars and antibacterial activities were also discussed.

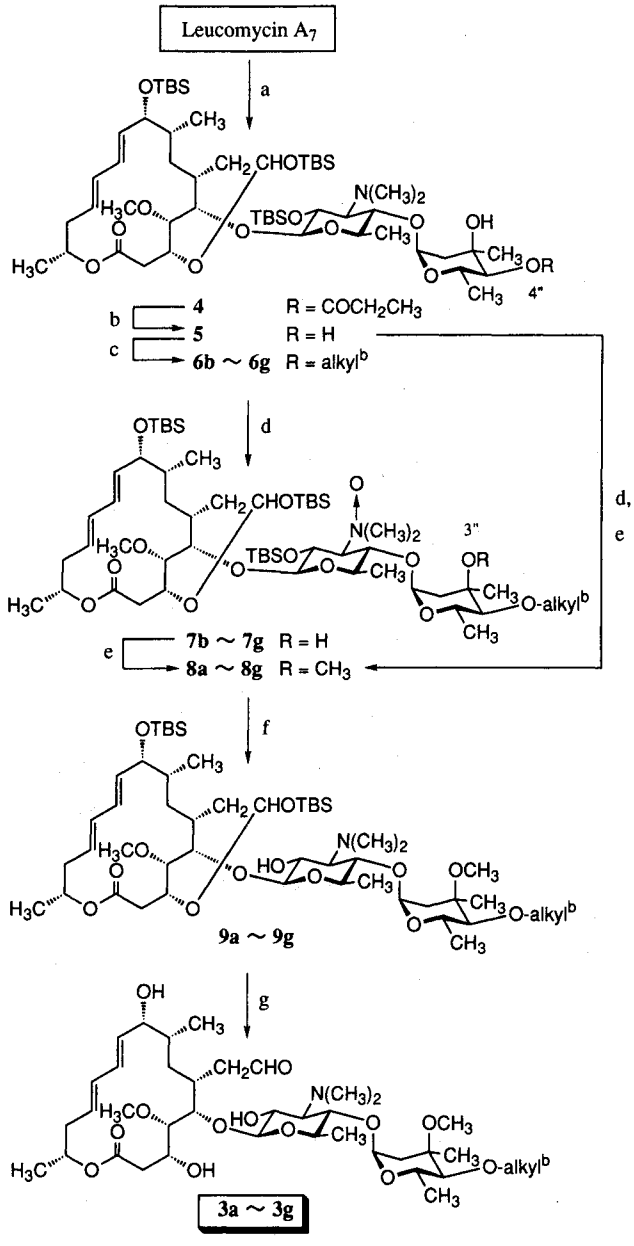
When SANO, ŌMURA *et al.* prepared 4″-*O*-substituted spiramycin I, a chemically stabilized silyl ether intermediate was used[11,12]. Because there seemed to be some difficulties in introducing general alkyl groups[††,13] to hydroxyl groups of the neutral sugar moiety in leucomycins, 3, 18-(*O*-silyl)acetal protection could be desired. 4″-*O*-Methylation of erythromycin, however, has been already reported[14]. On the other hand, introducing a methyl group onto the tertiary hydroxyl group at C-3″ position of a sixteen-membered macrolide antibiotic could be only done *via* glycosylation of a neutral sugar[5,15]. It is mainly because the 3″-hydroxyl group seems to be highly hindered sterically in addition to its low reactivity[12], that conversion of 3″-OH to 3″-OCH_3 has not been reported.

Chemistry

The *tert*-butyldimethylsilyl (TBS) protection of leucomycin A_7[†††,16] (LM-A_7) afforded tris-TBS ether (**4**) in a good yield. Selection of heterogeneous basic hydrolysis resulted in a quantitative chemoselective saponification at the C-4″ position to generate diol (**5**). Fortunately, these conditions using phase transfer catalyst did not affect the lactone bond with a fused seven-membered silyl acetal ring.

Chemoselective 4″-*O*-alkylations were completed under rather strong conditions to afford the mono alkyl

Scheme 1. Synthesis of compounds **3a**～**3g**[a,b].

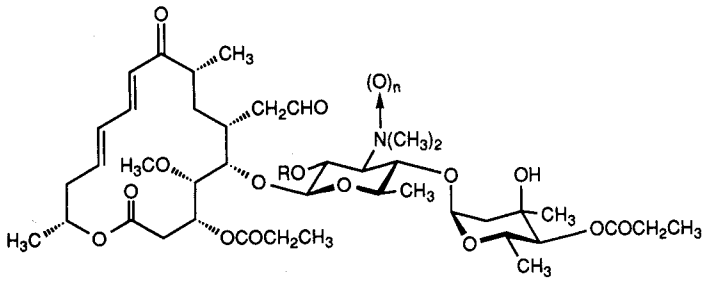


[a]Reagents and conditions: (a) 6.0 equiv of TBSCl, 12 equiv of imidazole, DMF, 50°C, overnight, 83%; (b) 25% aqueous NaOH, 1.0 equiv of *n*-Bu_4NHSO_4, PhH-H_2O (2:1), 25°C, 2 h, 87%; (c) 30 equiv of alkyl halide, 5.0 equiv of NaH, DMF, 45°C, 1 h, 67-90%; (d) 1.5 equiv of *m*CPBA, $CHCl_3$, 25°C, 5 min; (e) 30 equiv of MeI, 5.0 equiv of NaH, 45°C 1 h; (f) silica gel, 25°C, overnight, 51-65% overall 3 steps; (g) 2.0 M of TBAF in THF, 45°C, 1 h, 54-94%. TBS: *tert*-Butyldimethylsilyl.
[b]Alkyl side chains: (a) methyl; (b) ethyl; (c) *n*-propyl; (d) *n*-butyl; (e) *n*-pentyl; (f) 3-methylbutyl; (g) benzyl.

†† Some reactive alkylation (*i.e.* methoxymethyl or benzyl) did not require 3,18-(*O*-silyl)acetal protection. See ref. 13.

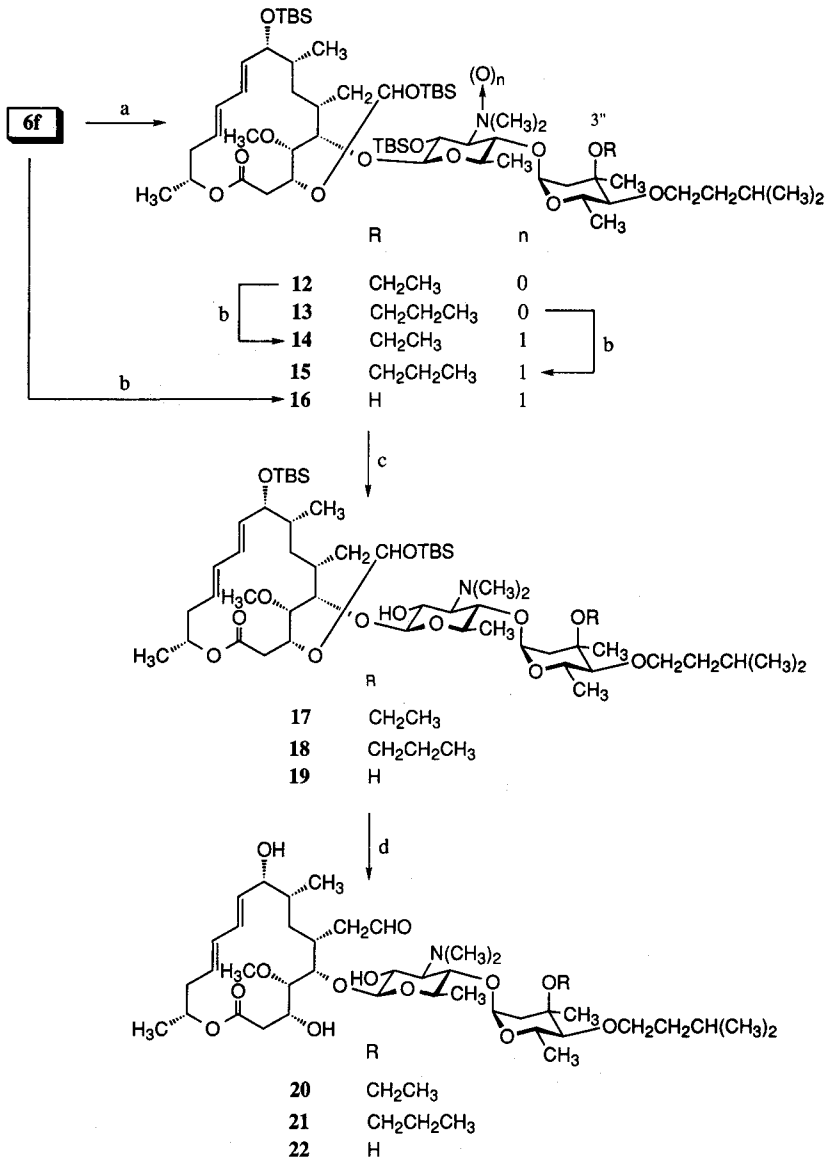
††† A large amount of LM-A_7 was produced from midecamycin A_1 *via* biotransformation using PF1083. See ref. 16. We are grateful to Drs. O. HARA, K. UOTANI, S. GOMI and Mr. A. SHIMIZU for their useful suggestions and supports.

Fig. 3. Midecamycin A_3 and its derivative (**11**).



	R	n
11	TBS	1
Midecamycin A_3	H	0

Scheme 2. Synthesis of compounds **20**~**22**[a].



[a]Reagents and conditions: (a) 30 equiv of alkyl iodide, 5.0 equiv of NaH, DMF, 45°C, 3-4 h; (b) 1.0 equiv of *m*CPBA, $CHCl_3$, 25°C, 5 min; (c) silica gel, 25°C, 3 days, 26, 25% overall 3 steps; (d) 2.0 M of TBAF in THF, 45°C, 1 h, 45-58%.

derivatives, compounds (**6b**～**6g**). A methyl group was then introduced at the tertiary hydroxyl group at the C-3″ position (Scheme 1). First, direct methylation of **6** gave poor results because of the presence of a free dimethylamino group. Thus, an *N*-oxide intermediate of the dimethylamino group was used as follows: Oxidation of the dimethylamino group of **6** with *m*CPBA gave unstable *N*-oxides, compounds (**7b**～**7g**), quantitatively. Without purification at this stage, subsequent methylation exclusively proceeded at the 3″-alcohol to form 4-*O*-alkyl-L-cladinose moiety as a neutral sugar, accompanied with slight decomposition. In the case of introducing two methyl groups, the dimethylamino group of **5** was oxidized followed by dimethylation to give the compound (**8a**).

Fully protected unstable intermediates (**8a**～**8g**) were successively treated with gently acidic conditions (*i.e.* silica gel or diluted hydrochloric acid) to generate the free dimethylamino alcohol of the mycaminose moiety. Evidence of structure on compound (**9f**) was demonstrated by acetylation of **9f** without any additional base to give its 2′-*O*-acetyl derivative (**10**) in a quantitative yield. Finally, deprotection of two TBS groups with exact 2.0 M of TBAF completed titled compounds (**3a**～**3g**) *via* acidic workups (see experimental). The above mentioned useful deprotection (compound (**8**) to (**9**)) could be observed in other substrates also. When unstable 2′-*O*-TBS midecamycin A_3 *N*-oxide (**11**) (Fig. 3) was treated with a mild acidic condition, midecamycin A_3 (a free dimethylamino alcohol) was mainly recovered as expected.

To investigate SAR of these molecules, especially at the neutral sugar moiety, we prepared another class of derivatives, **20** and **21** (Scheme 2). Alkylation (ethyl or *n*-propyl) at the 3″-OH group of **6f** proceeded in a moderate yield. Oxidation of the dimethylamino group allowed for chemoselective 2′-*O*-deprotection to generate the free dimethylamino alcohols, **17** and **18**. Finally, deprotection afforded compounds **20** and **21** possessing a totally unnatural neutral sugar. As a control material, 4-*O*-alkyl-L-mycarose analogue, compound (**22**), was also prepared by sequential deprotections of **6f** *via* **19** (Scheme 2).

Structures of these resulting antibiotic analogues (**3a**～**3g**) and (**20**～**22**) were confirmed by ^{1}H NMR spectra (see experimental). The compounds (**3f**, **3g**) were fully identified with those prepared *via* glycosylation and biotransformations previously[9]. The structure of the resulted neutral sugar was confirmed by acid hydrolysis. For example, treatment of **3f** with *p*-toluenesulfonic acid and ethanol smoothly gave ethyl 4-*O*-(3-methylbutyl)-β-L-cladinoside[5] with trace of its α-anomer.

Biological Evaluation

The antibacterial activities *in vitro* of novel 4-*O*-alkyl-α-L-cladinosyl derivatives (**3a**～**3g**) and the structurally related analogues (**20**～**22**), compared with corresponding antibiotics which possess a free hydroxyl group at the C-3 position, are shown in Table 1. In the class of cladinose analogues (3″-OCH_3), the activities of selected novel derivatives with suitable alkyl chain length (C_3～C_5 and benzyl) were clearly improved based on that of

Table 1. Antibacterial activities of leucomycin derivatives and LM-A_7 (MIC, μg/ml).

Test organisms	3a	3b	3c	3d	3e	3f	3g	20	21	22	LM-A7	RKM
Staphylococcus aureus 209P JC-1	1.56	0.78	0.20	0.10	0.10	0.10	0.10	0.20	0.20	0.10	0.20	0.10
S. aureus M133	6.26	3.13	0.39	0.39	0.39	0.39	0.39	0.78	0.78	0.39	0.39	0.39
S. aureus M126	>100	>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	>100
S. aureus MS15027	12.5	6.25	0.39	0.39	0.39	0.39	0.20	0.39	0.39	0.39	0.39	0.78
S. epidermidis ATCC14990	12.5	6.25	0.39	0.39	0.39	0.39	0.20	0.78	0.78	0.39	0.39	0.78
Micrococcus luteus ATCC9341	0.78	0.20	0.05	0.05	0.05	0.05	0.05	0.05	0.10	0.05	0.05	0.05
Enterococcus faecalis W-73	3.13	3.13	0.78	0.78	0.39	0.39	0.39	0.78	0.78	0.39	0.78	0.39
Streptococcus pneumoniae IP692	1.56	0.78	0.20	0.10	0.05	0.10	0.10	0.20	0.20	0.10	0.20	0.10
S. pneumoniae Type I	1.56	0.78	0.20	0.20	0.20	0.10	0.10	0.20	0.20	0.10	0.20	0.10
S. pyogenes Cook	1.56	0.78	0.10	0.10	0.10	0.05	0.10	0.10	0.10	0.10	0.10	0.05
Escherichia coli NIHJ JC-2	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
Klebsiella pneumoniae PCI602	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
Branhamella catarrhalis W-0500	12.5	3.13	1.56	0.78	0.39	0.39	0.78	0.39	0.78	0.78	0.78	0.20
B. catarrhalis W-0506	25	12.5	3.13	1.56	0.78	0.39	0.78	0.78	0.78	0.78	1.56	0.20
Haemophilus influenzae 9334	50	50	6.25	3.13	3.13	1.56	3.13	6.25	6.25	3.13	1.56	1.56

LM-V having a diol structure in the neutral sugar. The compound (**3d**～**3g**) were more effective than natural LM-A_7. Compound (**3f**) having 3-methylbutyl side chain showed the most potent activity *in vitro* which was comparable to that of RKM (Table 1). These new compounds having 3-OH were about two times more active *in vitro* than corresponding to 3-*O*-propionyl analogues.

Introducing other alkyl group in place of methyl into the 3″-OH position slightly reduced the activity. Although mycarose analogue, compound (**22**), showed excellent antibacterial activities, its chemical stability was obviously lower than those of cladinose analogues under acidic conditions (data not shown). Thus, introducing a methyl group onto the 3″-OH position increased a stability of the glycosyl bond of the neutral sugar, probably because of a 1,3-diaxial steric factor.

The most potent analogue, **3f**, was incubated in rat plasma to clarify its metabolic stability against esterase. Fig. 4 shows changes in the relative antibacterial activities against *Micrococcus luteus*, expressed by referring the initial activity of each compound in the plasma to 100%. The metabolic stability of **3f** was relatively improved compared with a structurally related 4-*O*-acyl-α-L-mycarosyl compound, LM-A_7 or 3,4-di-*O*-acyl-α-L-mycarosyl compound, RKM, since the neutral sugar moiety of **3f** could not be attacked by esterase. It must also be pointed out that the half-life ($T_{1/2}$) of **3f** was 3～4 times longer than those of RKM and LM-A_7. Thus, a greater stability has been achieved *in vitro* by introducing 4-*O*-alkyl-L-cladinose instead of 4-*O*-acyl-L-mycarose in sixteen-membered macrolides.

Preliminary pharmacokinetics of **3f** were examined with three antibiotics in mice. Serum concentrations after 200 mg/kg oral administration are shown in Fig. 5. A time course pattern of **3f** was very close to that of RKM, however, absolute concentrations of **3f** were clearly higher than that of RKM. A serum level of LM-A_7 was less than RKM, undoubtedly (data not shown). The maximum concentration of **3f** in serum was comparable to that of clarithromycin (CAM)[17] despite the free C-3 hydroxyl group of compound (**3f**). These excellent results led us to clarify further pharmacokinetic study of **3f** using hamsters as rather large test animals. In the field of sixteen-membered macrolides, pharmacokinetics are sometimes strongly affected with animal species[7]. Fig. 6 shows concentrations of antibiotics in serum of hamsters after 500 mg/kg oral administration. The maximum concentration of **3f** is higher than that of RKM or CAM.

Extremely high efficacy of synthesized **3f** *in vivo* may be promising with both its potent antibacterial activities *in vitro* and its splendidly high serum concentrations *in vivo*. The described chemistry is efficient considering the

Fig. 5. Concentration in serum.

200 mg/kg, mouse, n=2, p.o., ○ **3f**, ● RKM, ■ CAM.

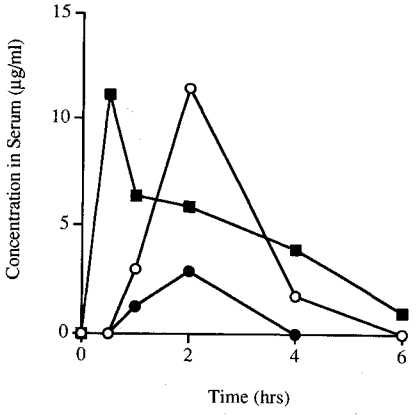


Fig. 4. Time course of relative potency.

Rat plasma (t=0; 100%, 37°C), ○ **3f**, ● RKM, ◆ LM-A_7.

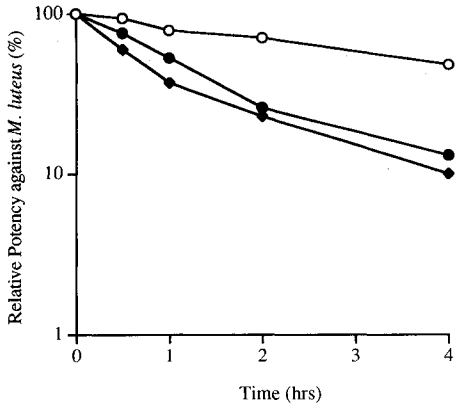
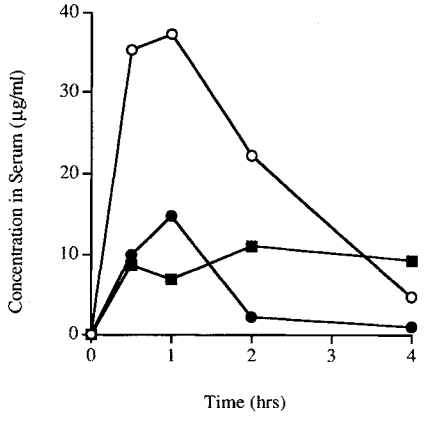


Fig. 6. Concentration in serum.

500 mg/kg, hamster, n=1, p.o., ○ **3f**, ● RKM, ■ CAM.



complexity of the designed molecules, and opens the way for eventually new chemical modifications of naturally occurring sixteen-membered macrolides. In addition, discovery of a quite potent analogue (**3f**) might allow the sixteen-membered macrolide antibiotics to exhibit closer efficacy to the second generation fourteen-membered macrolides, so-called *new* macrolides such as CAM.

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 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 concentration (MIC) was determined by the agar plate dilution method. Test strains were subjected to seed culture using Sensitivity test broth (STB, Nissui Pharmaceutical) except that the strains belonging to the genus *Streptococcus*, *Branhamella* and *Haemophilus* 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 and incubated at 37°C for 20 hours. Then, MIC was measured.

Metabolic Stability in Rat Plasma *In Vitro*

A solution of each test compound (500 μg) in CH_3OH (50 μl) were added to thawed rat plasma (950 μl) and the mixture was incubated at 37°C. A 20 μl portion of the mixture was sampled after 0, 0.5, 1, 2, and 4 hours and added to 0.05 M phosphate buffer (pH 7.6, 980 μl) including small amount of DFP. A 20 μl portion of the sample solution was used to measure antibacterial activity against *M. luteus* ATCC9341. The starting activity of each compound in rat plasma was reffered to as 100%.

Pharmacokinetics (Serum Level) Tests in Mice *In Vivo*

A test compound was mixed with a 0.2% aqueous solution of CMC to give a concentration of 4.0 mg/ml and a 1.0 ml portion of the resulting emulsion was orally administrated to 4 weeks old male Jcl : ICR mice. Blood was collected from armpit of the mice 0.5, 1, 2, 4 and 6 hours after the administration of the test compound (n = 2). The collected blood was allowed to stand at 0°C for 2 hours and centrifuged at 3000 rpm for 20 minutes to obtain serum. To the serum was added an equivalent volume of 50% CH_3CN - 0.05 M phosphate buffer (pH 7.0). The resulting mixture served as a serum sample. The concentration of the test compound in the serum sample was measured by a bioassay method using *M. luteus* ATCC9341.

Pharmacokinetics (Serum Level) Tests in Hamsters *In Vivo*

A test compound was mixed with a 0.2% aqueous solution of CMC to give a concentration of 40 mg/ml and a 1.0 ml portion of the resulting emulsion was orally administrated to 5 weeks old female Std : Syrian hamsters (*ca.* 80 g body weight). Blood was collected from armpit of the hamsters 0.5, 1, 2 and 4 hours after the administration of the test compound (n = 1). The collected blood was allowed to stand at 0°C for 2 hours and centrifuged at 3000 rpm for 20 minutes to obtain serum. To the serum was added an equivalent volume of 50% CH_3CN - 0.05 M phosphate buffer (pH 7.0). The resulting mixture served as a serum sample. The concentration of the test compound in the serum sample was measured by a bioassay method using *M. luteus* ATCC9341.

9,18,2′-Tri-*O*-*tert*-butyldimethylsilylleucomycin A_7 3,18-Acetal (**4**)

To 1.00 g (1.32 mmol) of leucomycin A_7 was added dry DMF (12 ml), and 1.18 g (7.82 mmol) of *t*-butyldimethylsilyl chloride 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 CH_3OH (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 **4**. A 60 mg portion of this crude compound was purified by preparative TLC [$CHCl_3$ - MeOH (50 : 1)] to give 35 mg (83%) of **4**.

MP 105~107°C; $[\alpha]_D$ −17° (*c* 1.0, CH_3OH); 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″-$OCOCH_2CH_3$), 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 V 3,18-Acetal (**5**)

One hundred thirty ml of benzene was added to 1.16 g (1.05 mmol) of crude **4**, 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 **5**.

MP 98~100°C; $[\alpha]_D$ −12° (*c* 1.0, CH_3OH); SI-MS *m/z* 1044 $(M+H)^+$; ^1H NMR δ 0.41 (1H, br dd, 7-H), 1.22 (3H, s, 3″-CH_3), 1.25 (3H, d, 6′-H), 1.30 (3H, d, 6″-H), 1.30 (3H, d, 16-H), 1.38 (1H, dt, 17-H), 1.66 (1H, br d, 17-H), 1.77 (1H, dd, 2″-Hax), 2.02 (1H, d, 2″-Heq), 2.37 (1H, br dd, 2-H), 2.51 (6H, s, 3′-$N(CH_3)_2$), 2.53 (1H, t, 3′-H), 2.61 (1H, dd, 2-H), 2.94 (1H, t, 4″-H), 3.13 (1H, br s, 4-H), 3.32 (1H, t, 4′-H), 3.37 (3H, s, 4-OCH_3), 3.42 (1H, br dd, 5-H), 3.57 (1H, dd, 2′-H), 3.99 (1H, dq, 5″-H), 4.20 (1H, d, 1′-H), 4.21 (1H, m, 3-H), 4.23 (1H, m, 9-H), 4.63 (1H, br dd, 18-H), 4.85 (1H, ddq, 15-H), 5.08 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.74 (1H, dd, 10-H), 6.11 (1H, m, 11-H), 6.11 (1H, m, 12-H).

9,18,2′-Tri-*O*-*tert*-butyldimethylsilyl-4″-*O*-(3-methylbutyl)leucomycin V 3,18-Acetal (**6f**)

To a stirred mixture of **5** (1.00 g, 0.95 mmol) and oily sodium hydride (192 mg as 60%, 4.8 mmol) in dry DMF (15 ml) was added 1-iodo-3-methylbutane (5.70 g, 28.8 mmol). The resulting mixture was stirred at 45°C for 1 hour, and it was cooled to room temperature. After slowly adding H_2O (250 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. Evaporation gave a residue which was purified by silica gel column chromatography [150 g, hexane-EtOAc (2:1)]. Thus, 715 mg (0.64 mmol, 68%) of **6f** was obtained.

MP 84~86°C; $[\alpha]_D$ −13° (*c* 1.0, CH_3OH); SI-MS *m/z* 1113 $(M)^+$; ^1H NMR δ 0.38 (1H, br dd, 7-H), 1.23 (3H, s, 3″-CH_3), 1.38 (1H, dt, 17-H), 1.49 (2H, m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.62 (1H, br d, 17-H), 1.68 (1H, m, 4″-OCH_2 $CH_2CH(CH_3)_2$), 1.74 (1H, dd, 2″-Hax), 1.95 (1H, br d, 2″-Heq), 2.37 (1H, br dd, 2-H), 2.50 (6H, s, 3′-$N(CH_3)_2$), 2.52 (1H, t, 3′-H), 2.59 (1H, dd, 2-H), 2.69 (1H, d, 4″-H), 3.34 (1H, t, 4′-H), 3.36 (3H, s, 4-OCH_3), 3.38 (1H, br dd, 5-H), 3.42 (1H, dd, 2′-H), 3.59 and 3.63 (each 1H, dt, 4″-$OCH_2CH_2CH(CH_3)_2$), 4.16 (1H, d, 1′-H), 4.20 (1H, m, 3-H), 4.20 (1H, m, 9-H), 4.20 (1H, dq, 5″-H), 4.60 (1H, br dd, 18-H), 4.81 (1H, ddq, 15-H), 5.01 (1H, d, 1″-H), 5.60 (1H, dt, 13-H), 5.73 (1H, dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18,2′-Tri-*O*-*tert*-butyldimethylsilyl-4″-*O*-ethylleucomycin V 3,18-Acetal (**6b**)

Reaction of **5** with iodoethane gave **6b** in 68% yield by a similar procedure to **6f**.

MP 92°C; $[\alpha]_D$ −17° (*c* 1.0, CH_3OH); SI-MS *m/z* 1072 $(M+H)^+$; ^1H NMR δ 0.39 (1H, br dd, 7-H), 1.23 (3H, s, 3″-CH_3), 1.38 (1H, dt, 17-H), 1.63 (1H, br d, 17-H), 1.75 (1H, dd, 2″-Hax), 1.96 (1H, br d, 2″-Heq), 2.37 (1H, br dd, 2-H), 2.50 (6H, s, 3′-$N(CH_3)_2$), 2.52 (1H, t, 3′-H), 2.60 (1H, dd, 2-H), 2.70 (1H, d, 4″-H), 3.34 (1H, t, 4′-H), 3.37 (3H, s, 4-OCH_3), 3.38 (1H, br dd, 5-H), 3.44 (1H, dd, 2′-H), 3.66 and 3.68 (each 1H, dq, 4″-OCH_2CH_3), 4.16 (1H, d, 1′-H), 4.21 (1H, m, 3-H), 4.21 (1H, m, 9-H), 4.22 (1H, dq, 5″-H), 4.61 (1H, br dd, 18-H), 4.82 (1H, ddq, 15-H), 5.02 (1H, d, 1″-H), 5.60 (1H, dt, 13-H), 5.73 (1H, dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18,2′-Tri-*O*-*tert*-butyldimethylsilyl-4″-*O*-*n*-propylleucomycin V 3,18-Acetal (**6c**)

Reaction of **5** with 1-iodopropane gave **6c** in 90% yield by a similar procedure to **6f**.

MP 88~90°C; $[\alpha]_D$ −11° (*c* 1.0, CH_3OH); FD-MS *m/z* 1085 $(M)^+$; ^1H NMR δ 0.39 (1H, br dd, 7-H), 0.92 (3H, t, 4″-$OCH_2CH_2CH_3$), 1.25 (3H, s, 3″-CH_3), 1.39 (1H, dt, 17-H), 1.76 (1H, dd, 2″-Hax), 1.97 (1H, br d, 2″-Heq), 2.38 (1H, br dd, 2-H), 2.51 (6H, s, 3′-$N(CH_3)_2$), 2.53 (1H, t, 3′-H), 2.60 (1H, dd, 2-H), 2.71 (1H, d, 4″-H), 3.35 (1H, t, 4′-H), 3.37 (3H, s, 4-OCH_3), 3.39 (1H, br dd, 5-H), 3.43 (1H, dd, 2′-H), 3.56 (2H, t, 4″-$OCH_2CH_2CH_3$), 4.17 (1H, d, 1′-H), 4.22 (1H, m, 3-H), 4.22 (1H, m, 9-H), 4.23 (1H, dq, 5″-H), 4.62 (1H, br dd, 18-H), 4.82 (1H, ddq, 15-H), 5.03 (1H, d, 1″-H), 5.61 (1H, dt, 13-H), 5.75 (1H, dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

4″-*O*-*n*-Butyl-9,18,2′-tri-*O*-*tert*-butyldimethylsilylleucomycin V 3,18-Acetal (**6d**)

Reaction of **5** with 1-bromobutane gave **6d** in 67% yield by a similar procedure to **6f**.

MP 82~83°C; $[\alpha]_D$ −13° (*c* 1.0, CH_3OH); FD-MS *m/z* 1099 $(M)^+$; ^1H NMR δ 0.40 (1H, br dd, 7-H), 0.90 (3H, t, 4″-$OCH_2CH_2CH_2CH_3$), 1.24 (3H, s, 3″-CH_3), 1.39 (1H, dt, 17-H), 1.64 (1H, br d, 17-H), 1.75 (1H, dd, 2″-Hax), 1.97 (1H, br d, 2″-Heq), 2.38 (1H, br dd, 2-H), 2.51 (6H, s, 3′-$N(CH_3)_2$), 2.53 (1H, t, 3′-H), 2.60 (1H, dd, 2-H), 2.70 (1H, d, 4″-H), 3.34 (1H, t, 4′-H), 3.37 (3H, s, 4-OCH_3), 3.39 (1H, br dd, 5-H), 3.43 (1H, dd, 2′-H), 3.60 (2H, dt, 4″-$OCH_2CH_2CH_2CH_3$), 4.17 (1H, d, 1′-H), 4.22 (1H, m, 3-H), 4.22 (1H, m, 9-H), 4.22 (1H, dq, 5″-H), 4.62 (1H, br dd, 18-H), 4.82 (1H, ddq, 15-H), 5.03 (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).

9,18,2′-Tri-*O*-*tert*-butyldimethylsilyl-4″-*O*-*n*-pentylleucomycin V 3,18-Acetal (**6e**)

Reaction of **5** with 1-iodopentane gave **6e** in 77% yield by a similar procedure to **6f**.

MP 77~78°C; $[\alpha]_D$ −13° (*c* 1.0, CH_3OH); FD-MS

m/z 1113 $(M)^+$; ^1H NMR δ 0.40 (1H, br dd, 7-H), 1.24 (3H, s, 3″-CH_3), 1.39 (1H, dt, 17-H), 1.76 (1H, dd, 2″-Hax), 1.97 (1H, br d, 2″-Heq), 2.38 (1H, br dd, 2-H), 2.51 (6H, s, 3′-$N(CH_3)_2$), 2.53 (1H, t, 3′-H), 2.61 (1H, dd, 2-H), 2.70 (1H, d, 4″-H), 3.35 (1H, t, 4′-H), 3.37 (3H, s, 4-OCH_3), 3.39 (1H, br dd, 5-H), 3.43 (1H, dd, 2′-H), 3.59 (2H, dt, 4″-$OCH_2CH_2CH_2CH_2CH_3$), 4.17 (1H, d, 1′-H), 4.22 (1H, m, 3-H), 4.22 (1H, m, 9-H), 4.22 (1H, dq, 5″-H), 4.62 (1H, br dd, 18-H), 4.83 (1H, ddq, 15-H), 5.03 (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).

4″-*O*-Benzyl-9,18,2′-tri-*O*-*tert*-butyldimethylsilyl-leucomycin V 3,18-Acetal (**6g**)

Reaction of **5** with benzyl bromide gave **6g** in 90% yield by a similar procedure to **6f**.

FD-MS *m/z* 1133 $(M)^+$; ^1H NMR δ 0.42 (1H, br dd, 7-H), 1.23 (3H, s, 3″-CH_3), 1.32 (3H, d, 16-H), 1.41 (1H, dt, 17-H), 1.66 (1H, br d, 17-H), 1.79 (1H, dd, 2″-Hax), 1.99 (1H, br d, 2″-Heq), 2.40 (1H, br dd, 2-H), 2.54 (6H, s, 3′-$N(CH_3)_2$), 2.56 (1H, t, 3′-H), 2.63 (1H, dd, 2-H), 2.95 (1H, d, 4″-H), 3.33 (1H, dq, 5′-H), 3.38 (1H, t, 4′-H), 3.40 (3H, s, 4-OCH_3), 3.42 (1H, br dd, 5-H), 3.48 (1H, dd, 2′-H), 4.20 (1H, d, 1′-H), 4.23 (1H, m, 3-H), 4.24 (1H, m, 9-H), 4.33 (1H, dq, 5″-H), 4.64 (1H, br dd, 18-H), 4.71 (2H, dd, 4″-$OCH_2C_6H_5$), 4.85 (1H, ddq, 15-H), 5.06 (1H, d, 1″-H), 5.64 (1H, dt, 13-H), 5.77 (1H, dd, 10-H), 6.13 (1H, m, 11-H), 6.13 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methyl-4″-*O*-(3-methylbutyl)leucomycin V 3,18-Acetal (**9f**)

To a solution of **6f** (1.42 g, 1.27 mmol) in $CHCl_3$ (71 ml) was added *m*CPBA (328 mg, 1.90 mmol). After stirring at room temperature for 5 minutes, the solution was dropped into 10% aqueous $Na_2S_2O_3$ (150 ml) and extracted with $CHCl_3$ (500 ml). The organic 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 1.42 g of *N*-oxide (**7f**). To a stirred mixture of crude **7f** (1.42 g) and oily sodium hydride (251 mg as 60%, 6.27 mmol) in dry DMF (14 ml) was added iodomethane (5.39 g, 37.9 mmol). The resulting mixture was stirred at 45°C for 1 hour, then cooled to room temperature. After slowly adding H_2O (500 ml), the mixture was extracted with $CHCl_3$ (500 ml) twice. The organic layers were combined and washed with brine (500 ml) twice, dried and concentrated to give 1.55 g of crude **8f**. A 190 mg portion of this oily product was dissolved in MeOH (12 ml) and adsorbed by 16.0 g of silica gel (Merck Kieselgel 60). After distilling off MeOH under reduced pressure, the residue was allowed to stand overnight. Then, the substance adsorbed by the silica gel was extracted with a mixture [$CHCl_3$-MeOH (5:1)]. The extract was purified by silica gel column chromatography [12 g, $CHCl_3$-MeOH (50:1)] to afford 103 mg (65% overall 3 steps) of **9f**.

MP 68~70°C; $[\alpha]_D$ −2° (*c* 1.0, CH_3OH); SI-MS *m/z* 1014 $(M+H)^+$; ^1H NMR δ 0.42 (1H, br dd, 7-H), 1.22 (3H, s, 3″-CH_3), 1.31 (3H, d, 16-H), 1.43 (1H, dt, 17-H), 1.54 (1H, dd, 2″-Hax), 1.66 (1H, br d, 17-H), 2.21 (1H, d, 2″-Heq), 2.42 (1H, dd, 2-H), 2.46 (1H, t, 3′-H), 2.55 (6H, s, 3′-$N(CH_3)_2$), 2.76 (1H, d, 4″-H), 3.25 (3H, s, 3″-OCH_3), 3.32 (1H, dd, 2′-H), 3.36 (1H, t, 4′-H), 3.44 (3H, s, 4-OCH_3), 3.46 (1H, dd, 5-H), 3.57 and 3.63 (each 1H, dt, 4″-$OCH_2CH_2CH(CH_3)_2$), 4.05 (1H, br dt, 3-H), 4.18 (1H, br d, 9-H), 4.30 (1H, d, 1′-H), 4.45 (1H, dq, 5″-H), 4.57 (1H, br dd, 18-H), 4.80 (1H, ddq, 15-H), 4.87 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.73 (1H, dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-4″-*O*-ethyl-3″-*O*-methylleucomycin V 3,18-Acetal (**9b**)

Reactions of **6b** gave **9b** *via* **7b** and **8b** in 63% yield (overall 3 steps) by similar procedures to **9f**.

MP 72~74°C; $[\alpha]_D$ −2° (*c* 1.0, CH_3OH); SI-MS *m/z* 971 $(M)^+$; ^1H NMR δ 0.41 (1H, br dd, 7-H), 1.21 (3H, s, 3″-CH_3), 1.30 (3H, d, 16-H), 1.43 (1H, dt, 17-H), 1.52 (1H, dd, 2″-Hax), 1.66 (1H, br d, 17-H), 2.23 (1H, d, 2″-Heq), 2.45 (1H, t, 3′-H), 2.55 (6H, s, 3′-$N(CH_3)_2$), 2.76 (1H, d, 4″-H), 3.25 (3H, s, 3″-OCH_3), 3.32 (1H, dd, 2′-H), 3.36 (1H, t, 4′-H), 3.43 (3H, s, 4-OCH_3), 3.45 (1H, br d, 5-H), 3.64 and 3.68 (each 1H, dq, 4″-OCH_2CH_3), 4.05 (1H, br dt, 3-H), 4.18 (1H, br d, 9-H), 4.29 (1H, d, 1′-H), 4.45 (1H, dq, 5″-H), 4.56 (1H, br dd, 18-H), 4.80 (1H, ddq, 15-H), 4.87 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.72 (1H, dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methyl-4″-*O*-*n*-propylleucomycin V 3,18-Acetal (**9c**)

Reactions of **6c** gave **9c** *via* **7c** and **8c** in 64% yield (overall 3 steps) by similar procedures to **9f**.

MP 67~69°C; $[\alpha]_D$ −3° (*c* 1.0, CH_3OH); SI-MS *m/z* 986 $(M+H)^+$; ^1H NMR δ 0.42 (1H, br dd, 7-H), 1.23 (3H, s, 3″-CH_3), 1.31 (3H, d, 16-H), 1.43 (1H, dt, 17-H), 1.54 (1H, dd, 2″-Hax), 1.63 (2H, m, 4″-$OCH_2CH_2CH_3$), 1.65 (1H, br d, 17-H), 2.22 (1H, d, 2″-Heq), 2.47 (1H, t, 3′-H), 2.56 (6H, s, 3′-$N(CH_3)_2$), 2.77 (1H, d, 4″-H), 3.25 (3H, s, 3″-OCH_3), 3.32 (1H, dd, 2′-H), 3.36 (1H, t, 4′-H), 3.43 (3H, s, 4-OCH_3), 3.54 and 3.57 (each 1H, dt, 4″-$OCH_2CH_2CH_3$), 4.05 (1H, br dt, 3-H), 4.18 (1H, br d, 9-H), 4.30 (1H, d, 1′-H), 4.45 (1H, dq, 5″-H), 4.57 (1H, br dd, 18-H), 4.80 (1H, ddq, 15-H), 4.87 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.73 (1H, dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

4″-*O*-*n*-Butyl-9,18-di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methylleucomycin V 3,18-Acetal (**9d**)

Reactions of **6d** gave **9d** *via* **7d** and **8d** in 63% yield (overall 3 steps) by similar procedures to **9f**.

MP 67~68°C; $[\alpha]_D$ −4° (*c* 1.0, CH_3OH); SI-MS *m/z* 999 $(M+H)^+$; ^1H NMR δ 0.42 (1H, br dd, 7-H), 0.99 (3H, t, 4″-$OCH_2CH_2CH_2CH_3$), 1.22 (3H, s, 3″-CH_3), 1.30 (3H, d, 16-H), 1.36 (2H, m, 4″-$OCH_2CH_2CH_2CH_3$), 1.43 (1H, dt, 17-H), 1.53 (1H, dd, 2″-Hax), 1.58 (2H, m,

4″-OCH$_2$CH_2CH$_2$CH$_3$), 1.66 (1H, br d, 17-H), 2.21 (1H, d, 2″-Heq), 2.46 (1H, t, 3′-H), 2.55 (6H, s, 3′-N(CH$_3$)$_2$), 2.76 (1H, d, 4″-H), 3.25 (3H, s, 3″-OCH$_3$), 3.32 (1H, dd, 2′-H), 3.36 (1H, t, 4′-H), 3.44 (3H, s, 4-OCH$_3$), 3.46 (1H, dd, 5-H), 3.57 and 3.61 (each 1H, dt, 4″-OCH_2CH$_2$CH$_2$CH$_3$), 4.05 (1H, br dt, 3-H), 4.18 (1H, br d, 9-H), 4.29 (1H, d, 1′-H), 4.45 (1H, dq, 5″-H), 4.56 (1H, br dd, 18-H), 4.80 (1H, ddq, 15-H), 4.87 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.73 (1H, dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methyl-4″-*O*-*n*-pentylleucomycin V 3,18-Acetal (**9e**)

Reactions of **6e** gave **9e** *via* **7e** and **8e** in 64% yield (overall 3 steps) by similar procedures to **9f**.

MP 63~64°C; $[\alpha]_D$ −2° (*c* 1.0, CH$_3$OH); SI-MS *m/z* 1014 (M+H)$^+$; ^{1}H NMR δ 0.42 (1H, br dd, 7-H), 1.22 (3H, s, 3″-CH$_3$), 1.31 (3H, d, 16-H), 1.43 (1H, dt, 17-H), 1.54 (1H, dd, 2″-Hax), 1.66 (1H, br d, 17-H), 2.22 (1H, d, 2″-Heq), 2.47 (1H, t, 3′-H), 2.55 (6H, s, 3′-N(CH$_3$)$_2$), 2.76 (1H, d, 4″-H), 3.25 (3H, s, 3″-OCH$_3$), 3.32 (1H, dd, 2′-H), 3.36 (1H, t, 4′-H), 3.44 (3H, s, 4-OCH$_3$), 3.45 (1H, dd, 5-H), 3.54 and 3.60 (each 1H, dt, 4″-OCH_2CH$_2$CH$_2$CH$_2$CH$_3$), 4.06 (1H, br dt, 3-H), 4.18 (1H, br d, 9-H), 4.29 (1H, d, 1′-H), 4.45 (1H, dq, 5″-H), 4.57 (1H, br dd, 18-H), 4.80 (1H, ddq, 15-H), 4.87 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.73 (1H, dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

4″-*O*-Benzyl-9,18-di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methylleucomycin V 3,18-Acetal (**9g**)

Reactions of **6g** gave **9g** *via* **7g** and **8g** in 51% yield (overall 3 steps) by similar procedures to **9f**.

MP 61~63°C; $[\alpha]_D$ −2° (*c* 1.0, CH$_3$OH); FD-MS *m/z* 1033 (M)$^+$; ^{1}H NMR δ 0.44 (1H, br dd, 7-H), 1.24 (3H, s, 3″-CH$_3$), 1.33 (3H, d, 16-H), 1.45 (1H, dt, 17-H), 1.56 (1H, dd, 2″-Hax), 1.68 (1H, br d, 17-H), 2.22 (1H, d, 2″-Heq), 2.57 (6H, s, 3′-N(CH$_3$)$_2$), 3.00 (1H, d, 4″-H), 3.27 (3H, s, 3″-OCH$_3$), 3.35 (1H, dd, 2′-H), 3.38 (1H, t, 4′-H), 3.46 (3H, s, 4-OCH$_3$), 3.48 (1H, dd, 5-H), 4.08 (1H, br dt, 3-H), 4.21 (1H, br d, 9-H), 4.32 (1H, d, 1′-H), 4.54 (1H, dq, 5″-H), 4.59 (1H, br dd, 18-H), 4.67 (2H, dd, 4″-OCH_2C$_6$H$_5$), 4.82 (1H, ddq, 15-H), 4.90 (1H, d, 1″-H), 5.64 (1H, dt, 13-H), 5.74 (1H, dd, 10-H), 6.12 (1H, m, 11-H), 6.12 (1H, m, 12-H), 7.3~7.4 (5H, m, 4″-OCH$_2$C$_6$$H_5$).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3″,4″-di-*O*-methylleucomycin V 3,18-Acetal (**9a**)

To a solution of **5** (200 mg, 0.19 mmol) in CHCl$_3$ (10 ml) was added *m*CPBA (50 mg, 0.28 mmol). After stirring at room temperature for 5 minutes, the solution was dropped into 10% aqueous Na$_2$S$_2$O$_3$ (100 ml) and extracted with CHCl$_3$ (100 ml). The organic layer was successively washed with saturated aqueous NaHCO$_3$ (100 ml) twice and brine (100 ml) twice. Then, the organic layer was dried and concentrated to afford 200 mg of *N*-oxide of **5**. To a stirred mixture of this crude *N*-oxide (200 mg) and oily sodium hydride (60 mg as 60%, 1.5 mmol) in dry DMF (2.0 ml) was added iodomethane (1.2 g, 8.4 mmol). The resulting mixture was stirred at 45°C for 1 hour, then cooled to room temperature. After slowly adding H$_2$O (100 ml), the mixture was extracted with CHCl$_3$ (100 ml) twice. The organic layers were combined and washed with brine (100 ml) twice, dried and concentrated to give 170 mg of crude **8a**. This oily product was charged on preparative TLC plates (Merck TLC 60F$_{254}$). After allowing the plates stand for 2 days, and then development was carried out for purification [CHCl$_3$ - MeOH (20:1)] to afford 93 mg (0.10 mmol, 51% overall 3 steps) of **9a**.

MP 76°C; $[\alpha]_D$ −4° (*c* 1.0, CH$_3$OH); FD-MS *m/z* 958 (M+H)$^+$; ^{1}H NMR δ 0.41 (1H, br dd, 7-H), 1.23 (3H, s, 3″-CH$_3$), 1.30 (3H, d, 16-H), 1.43 (1H, dt, 17-H), 1.52 (1H, dd, 2″-Hax), 1.66 (1H, br d, 17-H), 2.22 (1H, d, 2″-Heq), 2.46 (1H, t, 3′-H), 2.55 (6H, s, 3′-N(CH$_3$)$_2$), 2.66 (1H, d, 4″-H), 3.24 (3H, s, 3″-OCH$_3$), 3.33 (1H, dd, 2′-H), 3.36 (1H, t, 4′-H), 3.44 (3H, s, 4-OCH$_3$), 3.46 (1H, br d, 5-H), 3.53 (3H, s, 4″-OCH$_3$), 4.05 (1H, br dt, 3-H), 4.18 (1H, br d, 9-H), 4.30 (1H, d, 1′-H), 4.44 (1H, dq, 5″-H), 4.57 (1H, br dd, 18-H), 4.80 (1H, ddq, 15-H), 4.87 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.72 (1H, dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

2′-*O*-Acetyl-9,18-di-*O*-*tert*-butyldimethylsilyl-3″-*O*-methyl-4″-*O*-(3-methylbutyl)leucomycin V 3,18-Acetal (**10**)

To a stirred solution of **9f** (30 mg, 0.03 mmol) in dry CH$_3$CN (0.90 ml) was added at room temperature acetic anhydride (6.0 μl, 0.06 mmol). After stirring at 30°C for 16 hours, 1.0 M NH$_4$OH (0.90 ml, 0.09 mmol) was added to the resulting solution, which was allowed to stand at room temperature for 20 minutes. Evaporation gave a residue which was extracted with CHCl$_3$ (30 ml) and the organic layer was washed with saturated aqueous NaHCO$_3$ (30 ml) and brine (30 ml). This was concentrated and purified by preparative TLC [hexane - acetone (2:1)] to afford 29 mg (92%) of **10**.

MP 66~71°C; $[\alpha]_D$ −15° (*c* 1.0, CH$_3$OH); EI-MS *m/z* 1055 (M)$^+$; ^{1}H NMR δ 0.42 (1H, br dd, 7-H), 1.23 (3H, s, 3″-CH$_3$), 1.30 (3H, d, 16-H), 2.10 (3H, s, 2′-OCOCH$_3$), 2.22 (1H, d, 2″-Heq), 2.43 (6H, s, 3′-N(CH$_3$)$_2$), 2.75 (1H, d, 4″-H), 3.17 (1H, t, 4′-H), 3.28 (3H, s, 3″-OCH$_3$), 3.42 (3H, s, 4-OCH$_3$), 3.62 (2H, m, 4″-OCH_2CH$_2$CH(CH$_3$)$_2$), 4.14 (1H, br dd, 3-H), 4.19 (1H, br dd, 9-H), 4.27 (1H, d, 1′-H), 4.45 (1H, dq, 5″-H), 4.54 (1H, br dd, 18-H), 4.64 (1H, ddq, 15-H), 4.80 (1H, d, 1″-H), 5.06 (1H, dd, 2′-H), 5.47 (1H, dt, 13-H), 5.96 (1H, m, 10-H), 5.96 (1H, m, 11-H), 6.32 (1H, dd, 12-H).

3″-*O*-Methyl-4″-*O*-(3-methylbutyl)leucomycin V (**3f**)

To 1.07 g (1.05 mmol) of **9f** was added 8.4 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, concentrated and the resulting residue was purified by silica gel column chromatography [100 g, $CHCl_3$ - MeOH (50 : 1)]. Thus, 565 mg (0.72 mmol, 69%) of **3f** was obtained.

MP 87~91°C; $[\alpha]_D$ −64° (*c* 0.8, CH_3OH); EI-MS *m/z* 785 $(M)^+$; ^1H NMR δ 0.89 (6H, d, 4″-OCH_2CH_2-$CH(CH_3)_2$), 0.99 (3H, d, 19-H), 1.18 (3H, d, 6′-H), 1.23 (3H, d, 6″-H), 1.25 (3H, s, 3″-CH_3), 1.31 (3H, d, 16-H), 1.52 (2H, m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.57 (1H, dd, 2″-Hax), 1.70 (1H, m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.91 (1H, m, 8-H), 2.13 (1H, dt, 14-H), 2.22 (1H, br d, 2-H), 2.23 (1H, d, 2″-Heq), 2.34 (1H, br dd, 17-H), 2.41 (1H, t, 3′-H), 2.52 (1H, br d, 14-H), 2.57 (6H, s, 3′-$N(CH_3)_2$), 2.71 (1H, dd, 2-H), 2.79 (1H, d, 4″-H), 2.88 (1H, br dd, 17-H), 3.10 (1H, br d, 4-H), 3.18 (1H, dd, 2′-H), 3.26 (3H, s, 3″-OCH_3), 3.28 (1H, dq, 5′-H), 3.48 (1H, t, 4′-H), 3.55 (3H, s, 4-OCH_3), 3.60 and 3.64 (each 1H, dt, 4″-$OCH_2CH_2CH(CH_3)_2$), 3.80 (1H, br d, 3-H), 4.11 (1H, dd, 9-H), 4.12 (1H, br dd, 5-H), 4.43 (1H, dq, 5″-H), 4.60 (1H, d, 1′-H), 4.90 (1H, d, 1″-H), 5.30 (1H, ddq, 15-H), 5.62 (1H, ddd, 13-H), 5.69 (1H, dd, 10-H), 6.04 (1H, br dd, 12-H), 6.27 (1H, dd, 11-H), 9.81 (1H, br s, 18-H).

3″,4″-Di-*O*-methylleucomycin V (**3a**)

Reaction of **9a** gave **3a** in 54% yield by a similar procedure to **3f**.

MP 99~101°C; $[\alpha]_D$ −53° (*c* 1.0, CH_3OH); SI-MS *m/z* 730 $(M+H)^+$; ^1H NMR δ 1.16 (3H, d, 6′-H), 1.21 (3H, d, 6″-H), 1.22 (3H, s, 3″-CH_3), 1.29 (3H, d, 16-H), 1.53 (1H, dd, 2″-Hax), 1.87 (1H, m, 8-H), 2.10 (1H, dt, 14-H), 2.20 (1H, br d, 2-H), 2.22 (1H, d, 2″-Heq), 2.31 (1H, br dd, 17-H), 2.40 (1H, t, 3′-H), 2.49 (1H, br d, 14-H), 2.57 (6H, s, 3′-$N(CH_3)_2$), 2.66 (1H, d, 4″-H), 2.68 (1H, dd, 2-H), 2.85 (1H, br dd, 17-H), 3.08 (1H, br d, 4-H), 3.22 (3H, s, 3″-OCH_3), 3.24 (1H, dq, 5′-H), 3.46 (1H, t, 4′-H), 3.52 (3H, s, 4-OCH_3), 3.52 (3H, s, 4″-OCH_3), 3.77 (1H, br d, 3-H), 4.08 (1H, dd, 9-H), 4.09 (1H, br dd, 5-H), 4.37 (1H, dq, 5″-H), 4.57 (1H, d, 1′-H), 4.88 (1H, d, 1″-H), 5.27 (1H, ddq, 15-H), 5.59 (1H, ddd, 13-H), 5.66 (1H, dd, 10-H), 6.02 (1H, br dd, 12-H), 6.25 (1H, dd, 11-H), 9.80 (1H, br s, 18-H).

4″-*O*-Ethyl-3″-*O*-methylleucomycin V (**3b**)

Reaction of **9b** gave **3b** in 71% yield by a similar procedure to **3f**.

MP 89~92°C; $[\alpha]_D$ −60° (*c* 1.0, CH_3OH); SI-MS *m/z* 744 $(M+H)^+$; ^1H NMR δ 0.99 (3H, d, 19-H), 1.15 (3H, d, 6′-H), 1.21 (3H, s, 3″-CH_3), 1.21 (3H, d, 6″-H), 1.28 (3H, d, 16-H), 1.53 (1H, dd, 2″-Hax), 1.88 (1H, m, 8-H), 2.10 (1H, dt, 14-H), 2.20 (1H, br d, 2-H), 2.22 (1H, d, 2″-Heq), 2.31 (1H, br dd, 17-H), 2.40 (1H, t, 3′-H), 2.48 (1H, br d, 14-H), 2.57 (6H, s, 3′-$N(CH_3)_2$), 2.68 (1H, dd, 2-H), 2.76 (1H, d, 4″-H), 2.85 (1H, br dd, 17-H), 3.07 (1H, br d, 4-H), 3.22 (3H, s, 3″-OCH_3), 3.24 (1H, dq, 5′-H), 3.45 (1H, t, 4′-H), 3.52 (3H, s, 4-OCH_3), 3.63 and 3.67 (each 1H, dq, 4″-OCH_2CH_3), 3.76 (1H, br d, 3-H), 4.07 (1H, dd, 9-H), 4.08 (1H, br dd, 5-H), 4.39 (1H, dq, 5″-H), 4.56 (1H, d, 1′-H), 4.87 (1H, d, 1″-H), 5.26 (1H, ddq, 15-H), 5.58 (1H, ddd, 13-H), 5.66 (1H, dd, 10-H), 6.01 (1H, br dd, 12-H), 6.24 (1H, dd, 11-H), 9.80 (1H, br s, 18-H).

3″-*O*-Methyl-4″-*O*-*n*-propylleucomycin V (**3c**)

Reaction of **9c** gave **3c** in 94% yield by a similar procedure to **3f**.

MP 79~81°C; $[\alpha]_D$ −55° (*c* 1.0, CH_3OH); SI-MS *m/z* 758 $(M+H)^+$; ^1H NMR δ 0.90 (3H, t, 4″-OCH_2-CH_2CH_3), 0.99 (3H, d, 19-H), 1.15 (3H, d, 6′-H), 1.21 (3H, d, 6″-H), 1.22 (3H, s, 3″-CH_3), 1.28 (3H, d, 16-H), 1.54 (1H, dd, 2″-Hax), 1.60 (2H, m, 4″-$OCH_2CH_2CH_3$), 1.88 (1H, m, 8-H), 2.10 (1H, dt, 14-H), 2.20 (1H, br d, 2-H), 2.21 (1H, d, 2″-Heq), 2.31 (1H, br dd, 17-H), 2.39 (1H, t, 3′-H), 2.48 (1H, br d, 14-H), 2.55 (6H, s, 3′-$N(CH_3)_2$), 2.68 (1H, dd, 2-H), 2.76 (1H, d, 4″-H), 2.85 (1H, br dd, 17-H), 3.07 (1H, br d, 4-H), 3.16 (1H, dd, 2′-H), 3.23 (3H, s, 3″-OCH_3), 3.25 (1H, dq, 5′-H), 3.45 (1H, t, 4′-H), 3.52 (3H, s, 4-OCH_3), 3.52 and 3.56 (each 1H, dt, 4″-$OCH_2CH_2CH_3$), 3.77 (1H, br d, 3-H), 4.07 (1H, dd, 9-H), 4.08 (1H, br dd, 5-H), 4.40 (1H, dq, 5″-H), 4.56 (1H, d, 1′-H), 4.87 (1H, d, 1″-H), 5.26 (1H, ddq, 15-H), 5.58 (1H, ddd, 13-H), 5.66 (1H, dd, 10-H), 6.01 (1H, br dd, 12-H), 6.24 (1H, dd, 11-H), 9.80 (1H, br s, 18-H).

4″-*O*-*n*-Butyl-3″-*O*-methylleucomycin V (**3d**)

Reaction of **9d** gave **3d** in 72% yield by a similar procedure to **3f**.

MP 80~84°C; $[\alpha]_D$ −54° (*c* 1.0, CH_3OH); SI-MS *m/z* 772 $(M+H)^+$; ^1H NMR δ 0.89 (3H, t, 4″-OCH_2-$CH_2CH_2CH_3$), 1.16 (3H, d, 6′-H), 1.21 (3H, d, 6″-H), 1.22 (3H, s, 3″-CH_3), 1.29 (3H, d, 16-H), 1.36 (2H, m, 4″-$OCH_2CH_2CH_2CH_3$), 1.54 (1H, dd, 2″-Hax), 1.60 (2H, m, 4″-$OCH_2CH_2CH_2CH_3$), 1.89 (1H, m, 8-H), 2.10 (1H, dt, 14-H), 2.20 (1H, br d, 2-H), 2.21 (1H, d, 2″-Heq), 2.31 (1H, br dd, 17-H), 2.39 (1H, t, 3′-H), 2.49 (1H, br d, 14-H), 2.55 (6H, s, 3′-$N(CH_3)_2$), 2.68 (1H, dd, 2-H), 2.76 (1H, d, 4″-H), 2.86 (1H, br dd, 17-H), 3.08 (1H, br d, 4-H), 3.16 (1H, dd, 2′-H), 3.23 (3H, s, 3″-OCH_3), 3.25 (1H, dq, 5′-H), 3.45 (1H, t, 4′-H), 3.53 (3H, s, 4-OCH_3), 3.55 and 3.60 (each 1H, dt, 4″-OCH_2-$CH_2CH_2CH_3$), 3.77 (1H, br d, 3-H), 4.08 (1H, dd, 9-H), 4.09 (1H, br dd, 5-H), 4.40 (1H, dq, 5″-H), 4.57 (1H, d, 1′-H), 4.87 (1H, d, 1″-H), 5.27 (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), 9.80 (1H, br s, 18-H).

3″-*O*-Methyl-4″-*O*-*n*-pentylleucomycin V (**3e**)

Reaction of **9e** gave **3e** in 77% yield by a similar procedure to **3f**.

MP 76~78°C; $[\alpha]_D$ −55° (*c* 1.0, CH_3OH); SI-MS *m/z* 786 $(M+H)^+$; ^1H NMR δ 0.87 (3H, br t, 4″-$OCH_2CH_2CH_2CH_2CH_3$), 0.99 (3H, d, 19-H), 1.15 (3H, d, 6′-H), 1.20 (3H, d, 6″-H), 1.22 (3H, s, 3″-CH_3), 1.28

(3H, d, 16-H), 1.54 (1H, dd, 2″-Hax), 1.88 (1H, m, 8-H), 2.10 (1H, dt, 14-H), 2.19 (1H, br d, 2-H), 2.20 (1H, d, 2″-Heq), 2.31 (1H, br dd, 17-H), 2.40 (1H, t, 3′-H), 2.48 (1H, br d, 14-H), 2.56 (6H, s, 3′-N(CH_3)$_2$), 2.68 (1H, dd, 2-H), 2.75 (1H, d, 4″-H), 3.07 (1H, br d, 4-H), 3.16 (1H, dd, 2′-H), 3.23 (3H, s, 3″-OCH_3), 3.25 (1H, dq, 5′-H), 3.45 (1H, t, 4′-H), 3.52 (3H, s, 4-OCH_3), 3.54 and 3.58 (each 1H, dt, 4″-O$CH_2CH_2CH_2CH_2CH_3$), 3.77 (1H, br d, 3-H), 4.07 (1H, dd, 9-H), 4.08 (1H, br dd, 5-H), 4.39 (1H, dq, 5″-H), 4.57 (1H, d, 1′-H), 4.86 (1H, d, 1″-H), 5.27 (1H, ddq, 15-H), 5.58 (1H, ddd, 13-H), 5.66 (1H, dd, 10-H), 6.01 (1H, br dd, 12-H), 6.24 (1H, dd, 11-H), 9.80 (1H, br s, 18-H).

4″-*O*-Benzyl-3″-*O*-methylleucomycin V (**3g**)

Reaction of **9g** gave **3g** in 68% yield by a similar procedure to **3f**.

MP 104~108°C; $[\alpha]_D$ −67° (*c* 1.0, CH_3OH); FD-MS *m/z* 805 $(M)^+$; ^1H NMR δ 0.99 (3H, d, 19-H), 1.14 (3H, s, 3″-CH_3), 1.18 (3H, d, 6′-H), 1.23 (3H, d, 6″-H), 1.30 (3H, d, 16-H), 1.56 (1H, dd, 2″-Hax), 1.60 (1H, br dt, 7-H), 1.90 (1H, m, 8-H), 2.12 (1H, dt, 14-H), 2.22 (1H, br d, 2-H), 2.22 (1H, d, 2″-Heq), 2.33 (1H, br dd, 17-H), 2.43 (1H, t, 3′-H), 2.50 (1H, br d, 14-H), 2.58 (6H, s, 3′-N(CH_3)$_2$), 2.70 (1H, dd, 2-H), 2.86 (1H, br dd, 17-H), 2.99 (1H, d, 4″-H), 3.09 (1H, br d, 4-H), 3.20 (1H, dd, 2′-H), 3.25 (3H, s, 3″-OCH_3), 3.27 (1H, dq, 5′-H), 3.48 (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 dd, 5-H), 4.47 (1H, dq, 5″-H), 4.59 (1H, d, 1′-H), 4.62 and 4.70 (each 1H, d, 4″-O$CH_2C_6H_5$), 4.90 (1H, d, 1″-H), 5.29 (1H, ddq, 15-H), 5.60 (1H, ddd, 13-H), 5.68 (1H, dd, 10-H), 6.03 (1H, br dd, 12-H), 6.26 (1H, dd, 11-H), 7.3~7.4 (5H, m, 4″-$OCH_2C_6H_5$), 9.80 (1H, s, 18-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-3″-*O*-ethyl-4″-*O*-(3-methylbutyl)leucomycin V 3,18-Acetal (**17**)

To a stirred mixture of **6f** (190 mg, 0.17 mmol) and oily sodium hydride (34 mg as 60%, 0.85 mmol) in dry DMF (1.0 ml) was added iodoethane (796 mg, 5.1 mmol). The resulting mixture was stirred at 45°C for 3 hours, then cooled to room temperature. After slowly adding H_2O (100 ml), the mixture was extracted with $CHCl_3$ (100 ml) twice. The organic layers were combined and washed with brine (100 ml) twice, dried and concentrated to give 114 mg of crude **12**. To a solution of crude **12** in $CHCl_3$ (5.7 ml) was added *m*CPBA (26 mg, 0.15 mmol). After stirring at room temperature for 5 minutes, the solution was dropped into 10% aqueous $Na_2S_2O_3$ (30 ml) and extracted with $CHCl_3$ (60 ml). The organic layer was successively washed with saturated aqueous $NaHCO_3$ (60 ml) twice and brine (60 ml) twice. Then, the organic layer was dried and concentrated to prepare 120 mg of crude **14**. This oily product was charged on preparative TLC plates (Merck TLC $60F_{254}$). After allowing the plates stand for 3 days, and then development was carried out for purification [$CHCl_3$ - MeOH (20 : 1)] to afford 45 mg (0.04 mmol, 26% overall 3 steps) of **17**.

MP 66~67°C; $[\alpha]_D$ −11° (*c* 1.0, CH_3OH); FD-MS *m/z* 1028 $(M+H)^+$; ^1H NMR δ 0.42 (1H, br dd, 7-H), 1.14 (3H, t, 3″-OCH_2CH_3), 1.23 (3H, s, 3″-CH_3), 1.31 (3H, d, 16-H), 1.44 (1H, dt, 17-H), 1.54 (1H, dd, 2″-Hax), 1.66 (1H, br d, 17-H), 2.21 (1H, d, 2″-Heq), 2.41 (1H, dd, 2-H), 2.45 (1H, t, 3′-H), 2.55 (6H, s, 3′-N(CH_3)$_2$), 2.74 (1H, d, 4″-H), 3.24 (1H, dq, 5′-H), 3.31 (1H, t, 4′-H), 3.33 (1H, dd, 2′-H), 3.44 (3H, s, 4-OCH_3), 3.45 and 3.50 (each 1H, dq, 3″-OCH_2CH_3), 3.54 and 3.66 (each 1H, dt, 4″-O$CH_2CH_2CH(CH_3)_2$), 4.05 (1H, br dt, 3-H), 4.19 (1H, dd, 9-H), 4.29 (1H, d, 1′-H), 4.46 (1H, dq, 5″-H), 4.57 (1H, br dd, 18-H), 4.80 (1H, ddq, 15-H), 4.84 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.73 (1H, dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18,2′-Tri-*O*-*tert*-butyldimethylsilyl-4″-*O*-(3-methylbutyl)-3″-*O*-*n*-propylleucomycin V 3,18-Acetal (**13**)

To a stirred mixture of **6f** (410 mg, 0.37 mmol) and oily sodium hydride (74 mg as 60%, 1.85 mmol) in dry DMF (820 μl) was added 1-iodopropane (1.88 g, 11.0 mmol). The resulting mixture was stirred at 45°C for 4 hours, then cooled to room temperature. After slowly adding H_2O (200 ml), the mixture was extracted with $CHCl_3$ (200 ml) twice. The organic layers were combined and washed with brine (400 ml) twice, dried and concentrated to give 420 mg of crude **13**. This was purified by preparative TLC [$CHCl_3$ - MeOH (20 : 1)] to afford 260 mg (0.23 mmol, 61%) of **13**.

MP 146~153°C; $[\alpha]_D$ −21° (*c* 1.0, $CHCl_3$); FD-MS *m/z* 1156 $(M+H)^+$; ^1H NMR δ 0.40 (1H, br dd, 7-H), 1.24 (3H, t, 3″-OCH_2CH_3), 1.33 (3H, d, 16-H), 2.22 (1H, d, 2″-Heq), 2.44 (1H, dd, 2-H), 2.62 (1H, dd, 2-H), 2.50 (6H, s, 3′-N(CH_3)$_2$), 2.77 (1H, d, 4″-H), 3.42 (3H, s, 4-OCH_3), 4.18 (1H, d, 1′-H), 4.22 (1H, br d, 3-H), 4.22 (1H, dd, 9-H), 4.44 (1H, dq, 5″-H), 4.62 (1H, br dd, 18-H), 4.80 (1H, ddq, 15-H), 4.92 (1H, d, 1″-H), 5.62 (1H, dt, 13-H), 5.76 (1H, dd, 10-H), 6.10 (1H, m, 11-H), 6.10 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-4″-*O*-(3-methylbutyl)-3″-*O*-*n*-propylleucomycin V 3,18-Acetal (**18**)

To a solution of **13** (147 mg, 0.13 mmol) in $CHCl_3$ (6.5 ml) was added *m*CPBA (24 mg, 0.14 mmol). After stirring at room temperature for 5 minutes, the solution was dropped into 10% aqueous $Na_2S_2O_3$ (30 ml) and extracted with $CHCl_3$ (60 ml). The organic layer was successively washed with saturated aqueous $NaHCO_3$ (60 ml) twice and brine (60 ml) twice. Then, the organic layer was dried and concentrated to afford 155 mg of crude **15**. This oily product was charged on preparative TLC plates (Merck TLC $60F_{254}$). After allowing the plates stand for 3 days, and then development was carried out for purification [$CHCl_3$ - MeOH (20 : 1)] to afford 60 mg (0.06 mmol, 41% overall 2 steps) of **18**.

MP 57~63°C; $[\alpha]_D$ −17° (*c* 1.0, $CHCl_3$); FD-MS *m/z* 1042 $(M+H)^+$; ^1H NMR δ 0.88 (3H, t, 3″-$OCH_2CH_2CH_3$), 0.90 (6H, d, 4″-$OCH_2CH_2CH(CH_3)_2$),

1.22 (3H, d, 6″-H), 1.24 (3H, s, 3″-CH_3), 1.33 (3H, d, 16-H), 1.49 (1H, br dd, 17-H), 1.57 (1H, dd, 2″-Hax), 2.21 (1H, d, 2″-Heq), 2.43 (1H, dd, 2-H), 2.48 (1H, t, 3′-H), 2.58 (6H, s, 3′-$N(CH_3)_2$), 2.77 (1H, d, 4″-H), 3.25 (1H, dq, 5′-H), 3.27 (1H, br d, 4-H), 3.36 (1H, dd, 2′-H), 3.42 (2H, dt, 3″-$OCH_2CH_2CH_3$), 3.46 (3H, s, 4-OCH_3), 3.48 (1H, br dd, 5-H), 3.59 and 3.68 (each 1H, dt, 4″-$OCH_2CH_2CH(CH_3)_2$), 4.07 (1H, br d, 3-H), 4.21 (1H, dd, 9-H), 4.31 (1H, d, 1′-H), 4.46 (1H, dq, 5″-H), 4.59 (1H, br s, 18-H), 4.83 (1H, ddq, 15-H), 4.85 (1H, d, 1″-H), 5.64 (1H, ddd, 13-H), 5.75 (1H, dd, 10-H), 6.12 (1H, m, 11-H), 6.12 (1H, m, 12-H).

9,18-Di-*O*-*tert*-butyldimethylsilyl-4″-*O*-(3-methylbutyl)leucomycin V 3,18-Acetal (**19**)

To a solution of **6f** (1.00 g, 0.89 mmol) in $CHCl_3$ (50 ml) was added *m*CPBA (187 mg, 1.00 mmol). After stirring at room temperature for 5 minutes, the solution was dropped into 10% aqueous $Na_2S_2O_3$ (25 ml) and extracted with $CHCl_3$ (500 ml). The organic 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 1.01 g of crude **16**. A 220 mg portion of this oily product was charged on preparative TLC plate (Merck TLC $60F_{254}$). After allowing the plates stand for 3 days, and then development was carried out for purification [$CHCl_3$-MeOH (20:1)] to afford 118 mg (67% overall 2 steps) of **19**.

MP 70~73°C; $[\alpha]_D$ −6° (*c* 1.0, CH_3OH); EI-MS *m/z* 999 $(M)^+$; ^1H NMR δ 0.44 (1H, br dd, 7-H), 0.99 (6H, d, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.26 (3H, s, 3″-CH_3), 1.31 (3H, d, 16-H), 1.45 (1H, dt, 17-H), 1.53 (2H, m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.69 (1H, br d, 17-H), 1.70 (1H, m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.74 (1H, dd, 2″-Hax), 1.97 (1H, d, 2″-Heq), 2.53 (6H, s, 3′-$N(CH_3)_2$), 2.72 (1H, d, 4″-H), 3.44 (3H, s, 4-OCH_3), 3.64 (2H, m, 4″-$OCH_2CH_2CH(CH_3)_2$), 4.04 (1H, br dt, 3-H), 4.22 (1H, br d, 9-H), 4.26 (1H, d, 1′-H), 4.33 (1H, dq, 5″-H), 4.59 (1H, br dd, 18-H), 4.87 (1H, ddq, 15-H), 5.02 (1H, d, 1″-H), 5.63 (1H, dt, 13-H), 5.71 (1H, dd, 10-H), 6.11 (1H, m, 11-H), 6.11 (1H, m, 12-H).

3″-*O*-Ethyl-4″-*O*-(3-methylbutyl)leucomycin V (**20**)

Reaction of **17** gave **20** in 58% yield by a similar procedure to **3f**.

MP 98~100°C; $[\alpha]_D$ −70° (*c* 1.0, CH_3OH); EI-MS *m/z* 799 $(M)^+$; ^1H NMR δ 0.87 (6H, d, 4″-$OCH_2CH_2CH(CH_3)_2$), 0.97 (3H, d, 19-H), 1.11 (3H, t, 3″-OCH_2CH_3), 1.15 (3H, d, 6′-H), 1.21 (3H, d, 6″-H), 1.22 (3H, s, 3″-CH_3), 1.29 (3H, d, 16-H), 1.49 (2H, m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.55 (1H, dd, 2″-Hax), 1.65 (1H, m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.88 (1H, m, 8-H), 2.10 (1H, dt, 14-H), 2.20 (1H, br d, 2-H), 2.20 (1H, d, 2″-Heq), 2.31 (1H, br dd, 17-H), 2.38 (1H, t, 3′-H), 2.49 (1H, br d, 14-H), 2.55 (6H, s, 3′-$N(CH_3)_2$), 2.69 (1H, dd, 2-H), 2.73 (1H, d, 4″-H), 2.86 (1H, br dd, 17-H), 3.08 (1H, br d, 4-H), 3.16 (1H, dd, 2′-H), 3.24 (1H, dq, 5′-H), 3.40 (1H, t, 4′-H), 3.42 and 3.47 (each 1H, dq, 3″-OCH_2CH_3), 3.53 (3H, s, 4-OCH_3), 3.56 and 3.64 (each 1H, dt, 4″-$OCH_2CH_2CH(CH_3)_2$), 3.77 (1H, br d, 3-H), 4.08 (1H, dd, 9-H), 4.09 (1H, br dd, 5-H), 4.41 (1H, dq, 5″-H), 4.56 (1H, d, 1′-H), 4.83 (1H, d, 1″-H), 5.27 (1H, ddq, 15-H), 5.59 (1H, ddd, 13-H), 5.66 (1H, dd, 10-H), 6.01 (1H, br dd, 12-H), 6.25 (1H, dd, 11-H), 9.80 (1H, br s, 18-H).

4″-*O*-(3-Methylbutyl)-3″-*O*-*n*-propylleucomycin V (**21**)

Reaction of **18** gave **21** in 58% yield by a similar procedure to **3f**.

MP 88~93°C; $[\alpha]_D$ −73° (*c* 1.0, CH_3OH); SI-MS *m/z* 814 $(M+H)^+$; ^1H NMR δ 0.87 (3H, t, 3″-$OCH_2CH_2CH_3$), 0.89 (6H, d, 4″-$OCH_2CH_2CH(CH_3)_2$), 0.98 (3H, d, 19-H), 1.17 (3H, d, 6′-H), 1.22 (3H, d, 6″-H), 1.23 (3H, s, 3″-CH_3), 1.30 (3H, d, 16-H), 1.57 (1H, dd, 2″-Hax), 1.68 (1H, m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.91 (1H, m, 8-H), 2.12 (1H, dt, 14-H), 2.21 (1H, d, 2″-Heq), 2.22 (1H, br d, 2-H), 2.33 (1H, br dd, 17-H), 2.40 (1H, t, 3′-H), 2.51 (1H, br d, 14-H), 2.56 (6H, s, 3′-$N(CH_3)_2$), 2.70 (1H, dd, 2-H), 2.76 (1H, d, 4″-H), 2.88 (1H, br dd, 17-H), 3.10 (1H, br d, 4-H), 3.18 (1H, dd, 2′-H), 3.26 (1H, dq, 5′-H), 3.28 and 3.39 (each 1H, dt, 3″-$OCH_2CH_2CH_3$), 3.41 (1H, t, 4′-H), 3.55 (3H, s, 4-OCH_3), 3.58 and 3.66 (each 1H, dt, 4″-$OCH_2CH_2CH(CH_3)_2$), 3.79 (1H, br d, 3-H), 4.10 (1H, br dd, 5-H), 4.11 (1H, dd, 9-H), 4.41 (1H, dq, 5″-H), 4.58 (1H, d, 1′-H), 4.84 (1H, d, 1″-H), 5.29 (1H, ddq, 15-H), 5.61 (1H, ddd, 13-H), 5.68 (1H, dd, 10-H), 6.04 (1H, br dd, 12-H), 6.26 (1H, dd, 11-H), 9.80 (1H, br s, 18-H).

4″-*O*-(3-Methylbutyl)leucomycin V (**22**)

Reaction of **19** gave **22** in 45% yield by a similar procedure to **3f**.

MP 94~97°C; $[\alpha]_D$ −69° (*c* 1.0, CH_3OH); EI-MS *m/z* 771 $(M)^+$; ^1H NMR δ 0.90 (6H, d, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.01 (3H, d, 19-H), 1.20 (3H, d, 6′-H), 1.25 (3H, s, 3″-CH_3), 1.28 (3H, d, 6″-H), 1.31 (3H, d, 16-H), 1.52 (2H, m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.71 (1H, m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.75 (1H, dd, 2″-Hax), 1.91 (1H, m, 8-H), 1.98 (1H, d, 2″-Heq), 2.12 (1H, dt, 14-H), 2.23 (1H, br d, 2-H), 2.35 (1H, br dd, 17-H), 2.54 (6H, s, 3′-$N(CH_3)_2$), 2.70 (1H, dd, 2-H), 2.71 (1H, d, 4″-H), 2.83 (1H, br dd, 17-H), 3.08 (1H, br d, 4-H), 3.32 (1H, dq, 5′-H), 3.44 (1H, t, 4′-H), 3.51 (3H, s, 4-OCH_3), 3.63 (2H, dt, 4″-$OCH_2CH_2CH(CH_3)_2$), 3.79 (1H, br d, 3-H), 4.12 (1H, br dd, 5-H), 4.12 (1H, dd, 9-H), 4.27 (1H, dq, 5″-H), 4.51 (1H, d, 1″-H), 5.00 (1H, d, 1″-H), 5.29 (1H, ddq, 15-H), 5.62 (1H, ddd, 13-H), 5.69 (1H, dd, 10-H), 6.03 (1H, br dd, 12-H), 6.27 (1H, dd, 11-H), 9.81 (1H, br s, 18-H).

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