VOL. 56 NO. 4, APR. 2003 THE JOURNAL OF ANTIBIOTICS pp. 399 — 414

Synthesis and Biological Evaluation of Novel Leucomycin Analogues Modified at the C-3 Position

I. Epimerization and Methylation of the 3-Hydroxyl Group

TAKESHI FURUUCHI, KEN-ICHI KURIHARA,* TAKUJI YOSHIDA and KEIICHI AJITO

Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd., 760 Morooka-cho, Kohoku-ku, Yokohama 222-8567, Japan

(Received for publication December 17, 2002)

The synthesis and biological evaluation of sixteen-membered macrolides modified at the C-3 position are described. 3-*Epi*-leucomycin A_7 (**9**), 3-*O*-acyl-3-*epi*-leucomycin A_7 analogues (**11a**~**11e**), 3-*O*-acylleucomycin A_7 analogues (**13b**~**13e**) and 3-*O*-methylleucomycin analogues (**16a**, **16b** and **22**) were synthesized *via* fully protected intermediates (**7**, **5a**, **5b** and **20**). After appropriate modification, subsequent deprotections were performed to furnish a variety of leucomycin analogues. Methylation of the 3-hydroxyl group was found to improve the pharmacoprofile of leucomycin antibiotics. 3-*O*-Methylrokitamycin (**16b**) showed enhanced antibacterial activity *in vitro* and 3,3″-di-*O*-methyl-4″-*O*-(3-methylbutyl)leucomycin V (**22**) exhibited improved metabolic stability in rat plasma *in vitro*.

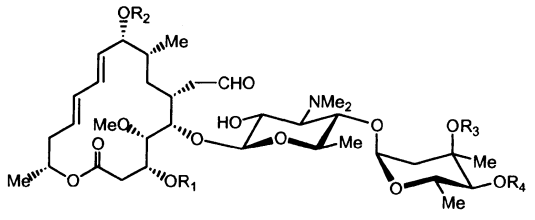
Macrolide antibiotics have been used in the treatment of bacterial infections for many years. Especially, the new macrolides represented by clarithromycin[1~5] and azithromycin[6~8] synthesized from fourteen-membered erythromycin are important chemotherapeutics from a clinical point of view. However, exploration of novel macrolides that could overcome the resistant strains has been an urgent issue, since macrolide-lincosamide-streptogramin B (MLS) cross-resistant organisms emerged. Ketolides have been developed as the next generation macrolides, and telithromycin[9] was recently launched as a promising antibiotic. It is effective against critical pathogens including MLS resistant *Streptococcus pneumoniae* and penicillin-resistant *Streptococcus pneumoniae* (PRSP). Moreover, a new ketolide, cethromycin (ABT-773)[10,11], is now at the late stage of clinical trial. Although these ketolides exhibit strong potency against not only *erm* inducible resistant strains of *S. pneumoniae* but also *erm* constitutive resistant strains, they are still exposed to the menace of resistant *S. pneumoniae* with efflux pump. On the other hand, some of the sixteen-membered macrolides, such as miokamycin (MOM)[12,13] and rokitamycin (RKM)[14,15] (Fig. 1) are not affected by efflux pumps. In addition, these two semisynthetic sixteen-membered macrolide antibiotics have been already proven to be safe in clinical use. Thus, drug discovery in the field of sixteen-membered macrolides is important for antiinfective chemotherapy in the future.

Background

In the leucomycin family, 3-OH type derivatives exhibit stronger antibiotic activities than corresponding 3-*O*-acyl analogues. However, the biological stability of these two groups has not been fully discussed because of complexity of their metabolism at the neutral sugar moiety. KURIHARA *et al.*[16] and AJITO *et al.*[17] synthesized 3″-*O*-methyl-4″-*O*-(3-methylbutyl)leucomycin V (Fig. 2, **1**) and its 3-*O*-propionyl derivative (**2**), respectively, and evaluated their metabolic stability in rat plasma. As a result, 3-OH type

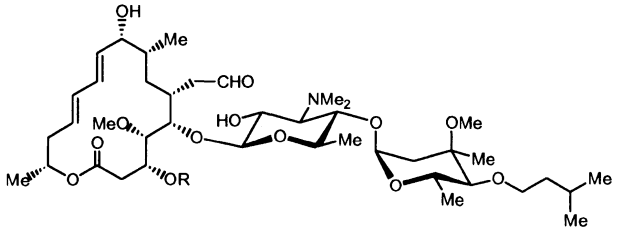
* Corresponding author: kenichi_kurihara@meiji.co.jp

Fig. 1. Representative natural leucomycins and their semisynthetic analogues, MOM and RKM.



	R_1	R_2	R_3	R_4
Midecamycin A_1 (MDM)	COEt	H	H	COEt
Leucomycin A_7 ($LM\text{-}A_7$)	H	H	H	COEt
Miokamycin (MOM)	COEt	Ac	Ac	COEt
Rokitamycin (RKM)	H	H	COEt	CO^nPr

Fig. 2. 3″-*O*-Methyl-4″-*O*-(3-methylbutyl) derivatives of leucomycin.



	R
1	H
2	COEt

derivative (**1**) was rather unstable in comparison with **2** under the experimental condition. In spiramycin I, undesirable 3,18-hemiacetal formation between the 3-hydroxyl group and the 18-formyl group was observed along with opening of the lactone ring[18]. This hemiacetal formation may be one of the reasons for instability of **1** under the metabolic condition.

Thus, we performed modification at the C-3 position to enhance antibacterial activity and improve the metabolic stability. In this paper we wish to disclose the synthesis and evaluation of novel 3-*epi*-, 3-*O*-acyl-3-*epi*-, 3-*O*-acyl- and 3-*O*-methylleucomycin analogues. The reported 3-*O*-methyl derivatives (**16a**, **16b** and **22**) exhibited enhanced antibiotic activity than corresponding 3-OH type analogues.

Results and Discussion

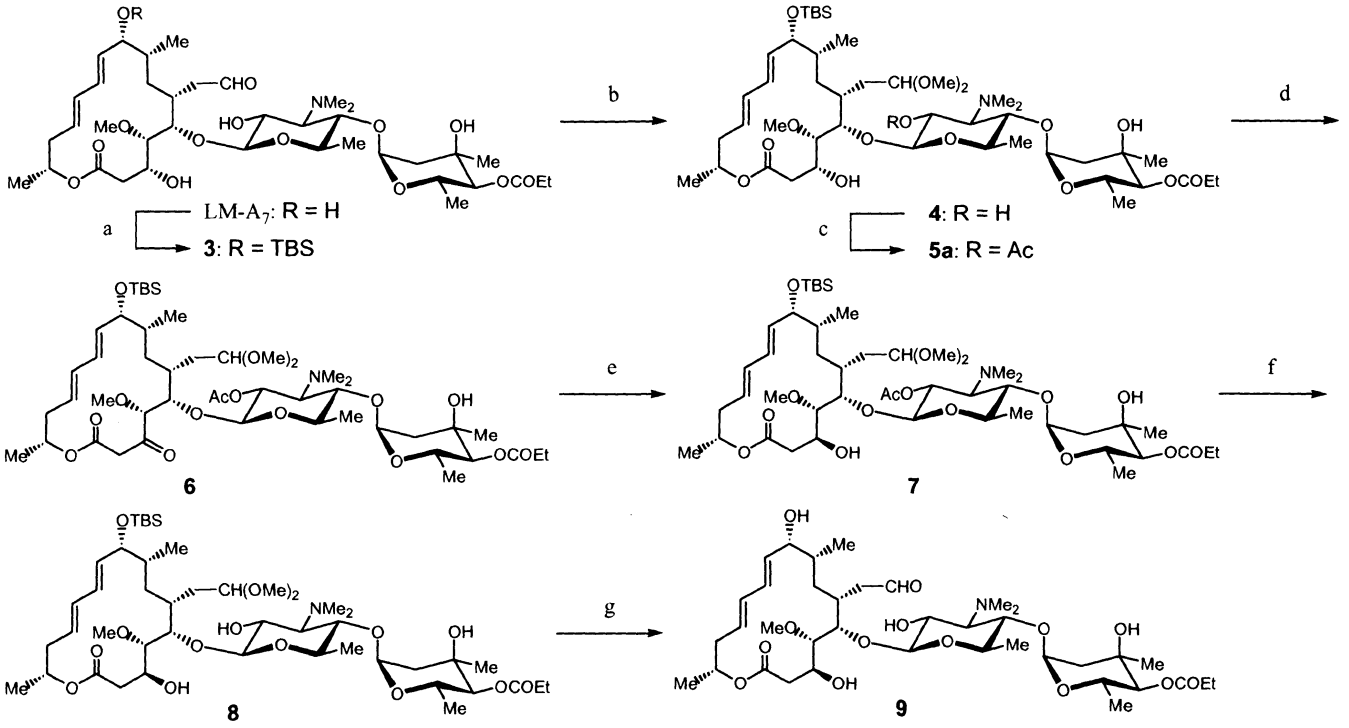
1. Synthesis of 3-*Epi*-leucomycin A_7, 3-*O*-Acyl-3-*epi*-leucomycins, and 3-*O*-Acylleucomycins

We first synthesized 3-*epi*-leucomycin A_7 (**9**) from leucomycin A_7 ($LM\text{-}A_7$, Fig. 1)[19] as shown in Scheme 1. $LM\text{-}A_7$ was prepared from midecamycin A_1 (MDM, Fig. 1)[20,21] *via* biotransformation using PF1083 on a large scale[21]. There were mainly two synthetic strategies for preparation of **9**. One of them was S_N2 substitution of the 3-hydroxyl group (including Mitsunobu reaction) and the other was stereoselective reduction of 3-dehydro (3-keto) compound (**6**). As far as we know, there are a few reports about oxidation of the 3-hydroxyl group in sixteen-membered macrolides. KIRST *et al.*[23] succeeded in preparation of 3-dehydro derivatives of tylosin. In the leucomycin family, oxidation of the 3-hydroxyl group using a lactone without a sugar moiety was reported by SUZUKI *et al.*[24] Thus, we selected the oxidation-reduction route for our synthetic goal.

The synthesis of **9** is shown in Scheme 1. Treatment of $LM\text{-}A_7$ with *t*-butyldimethylsilyl chloride afforded a *t*-butyldimethylsilyl (TBS) ether (**3**) along with 9,18-bis-*O*-TBS-$LM\text{-}A_7$ 3,18-acetal. This 3,18-silyl acetal was cleaved by tetrabutylammonium fluoride to afford a mono-TBS ether (**3**). Then, the 18-formyl group was protected as a dimethyl acetal to give **4** and selective acetylation of the 2′-hydroxyl group furnished fully protected $LM\text{-}A_7$ (**5a**). Although oxidation of **5a** using PDC or other mild oxidants (*i.e.* Dess-Martin periodinane or TPAP-NMO) was not successful, the desired ketone (**6**) was obtained up to 30% yield by DMSO oxidation with trifluoroacetic anhydride. ^1H NMR spectrum of **6** indicated this molecule existed as a keto-enol mixture with equilibrium. Treatment of **6** with $NaBH_4$ furnished the desired β-alcohol (**7**) exclusively. After removal of the acetyl group at the C-2′ position, both the TBS group and the dimethyl acetal were deprotected[25] to furnish **9**.

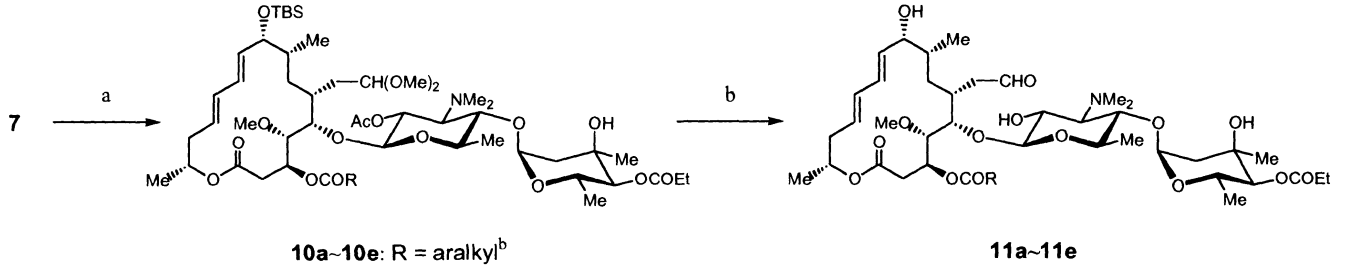
In the leucomycin family, 3-OH type derivatives exhibit stronger antibiotic activity than corresponding 3-*O*-acyl analogues. However, we did not have any information on structure-activity relationships (SAR) in the series of 3-*epi* derivatives. On the other hand, potent fourteen-membered macrolides, acylides (3-*O*-acylerythromycin derivatives), were reported by TANIKAWA *et al.*[26] Thus, we started

Scheme 1. Synthesis of 3-*epi*-leucomycin A_7 (**9**)[a].



[a]Reagents and conditions: (a) (1) *t*-Butyldimethysilyl chloride, Imidazole, DMF, 45°C, 17 h; (2) Tetrabutylammonium fluoride, THF, r.t., 3 h; (b) Pyridinium *p*-toluenesulfonate, $CH(OMe)_3$, MeOH, 45°C, 36 h; (c) Ac_2O, MeCN, r.t., 24 h, 62% overall 4 steps; (d) DMSO, Trifluoroacetic anhydride, Et_3N, CH_2Cl_2, -78°C, 65 min, 30%; (e) $NaBH_4$, 1,4-Dioxane, r.t., overnight, 75%; (f) MeOH-H_2O (9:1), 50°C, overnight, 98%; (g) CHF_2COOH, MeCN-H_2O (1:1), r.t., overnight, 78%.

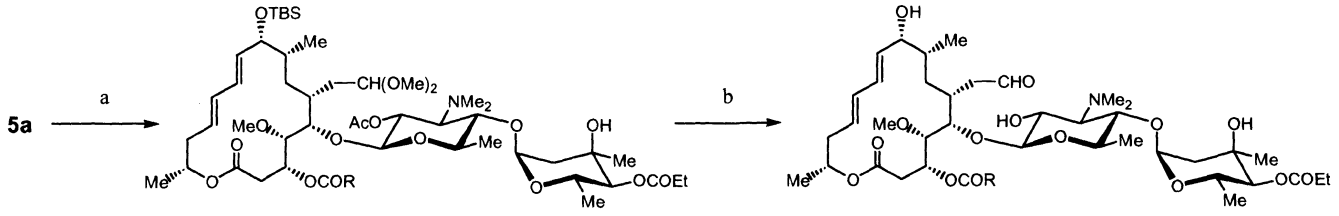
Scheme 2. Synthesis of 3-*O*-acyl derivatives of **9**[a].



[a]Reagents and conditions: (a) RCOCl, 4-(Dimethylamino)pyridine, Pyridine or Et_3N, CH_2Cl_2, r.t., 4 h~4 d, 52~93%; (b) (1) MeOH-H_2O (9:1), 40~50°C, 18~41 h; (2) CHF_2COOH, MeCN-H_2O (1:1), r.t., 2~4 d, 43~69% overall 2 steps.

[b]Aralkyl side chains: (a) ethyl; (b) phenyl; (c) cyclohexyl; (d) 5-phenylpentyl; (e) quinolin-2-yl.

Scheme 3. Synthesis of 3-*O*-acyl derivatives of LM-A_7[a].



[a]Reagents and conditions: (a) RCOCl, 4-(Dimethylamino)pyridine, Pyridine or Et_3N, CH_2Cl_2, r.t., 21 h~3 d, 64~85%; (b) (1) MeOH-H_2O (9:1), 40~50°C, 18 h~3 d; (2) CHF_2COOH, MeCN-H_2O (1:1), r.t., 23 h~4 d, 37~55% overall 2 steps.
[b]Aralkyl side chains: (b) phenyl; (c) cyclohexyl; (d) 5-phenylpentyl; (e) quinolin-2-yl.

Table 1. Antibacterial activities of 3-*O*-acylleucomycin derivatives and their 3-OH analogues (**9** and LM-A_7).

Test organisms	Characteristics	9	LM-A_7	11a	MDM	11b	13b	11c	13c	11d	13d	11e	13e
Staphylococcus aureus 209P JC-1	susceptible	0.78	0.39	1.56	0.78	0.39	0.39	3.13	0.78	6.25	0.78	1.56	0.20
Staphylococcus aureus MS15009	susceptible	0.78	0.39	0.78	0.78	0.39	0.39	3.13	0.39	6.25	0.78	0.78	0.20
Staphylococcus aureus MS15009/pMS99	*ermA* methylase (c*)	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
Staphylococcus aureus MS15009/pMS98	*ermB* methylase (i**)	0.78	0.20	0.78	0.78	0.39	3.13	3.13	0.39	6.25	0.78	0.78	0.20
Micrococcus luteus ATCC9341	susceptible	0.20	0.10	0.20	0.20	0.10	0.05	0.39	0.10	0.78	0.20	0.10	0.05
Streptococcus pneumoniae DP1 TypeI	susceptible	0.39	0.20	0.20	0.20	0.20	0.10	0.78	0.20	1.56	0.39	0.78	0.05
Streptococcus pneumoniae IP692	susceptible	0.78	0.20	0.39	0.39	0.20	0.39	3.13	0.78	3.13	0.39	1.56	0.10
Streptococcus pneumoniae TH-83	*ermAM* methylase (c*)	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
Streptococcus pneumoniae PRC-91	*ermAM* methylase (i**)	100	100	50	50	50	>100	>100	>100	>100	>100	>100	50
Streptococcus pneumoniae PRC-53	*mefE* efflux	0.39	0.20	0.20	0.20	0.20	0.39	1.56	0.39	3.13	0.39	1.56	0.10
Moraxella catarrhalis W-0500	susceptible	0.78	0.78	0.78	1.56	0.78	1.56	3.13	1.56	12.5	3.13	6.25	1.56
Haemophilus influenzae 9334	susceptible	0.78	1.56	3.13	6.25	6.25	6.25	12.5	12.5	>100	25	6.25	3.13
Haemophilus influenzae PRC-44	susceptible	6.25	6.25	12.5	25	12.5	25	50	50	>100	>100	50	12.5

c*: constitutive resisitant; i**: inducible resisitant

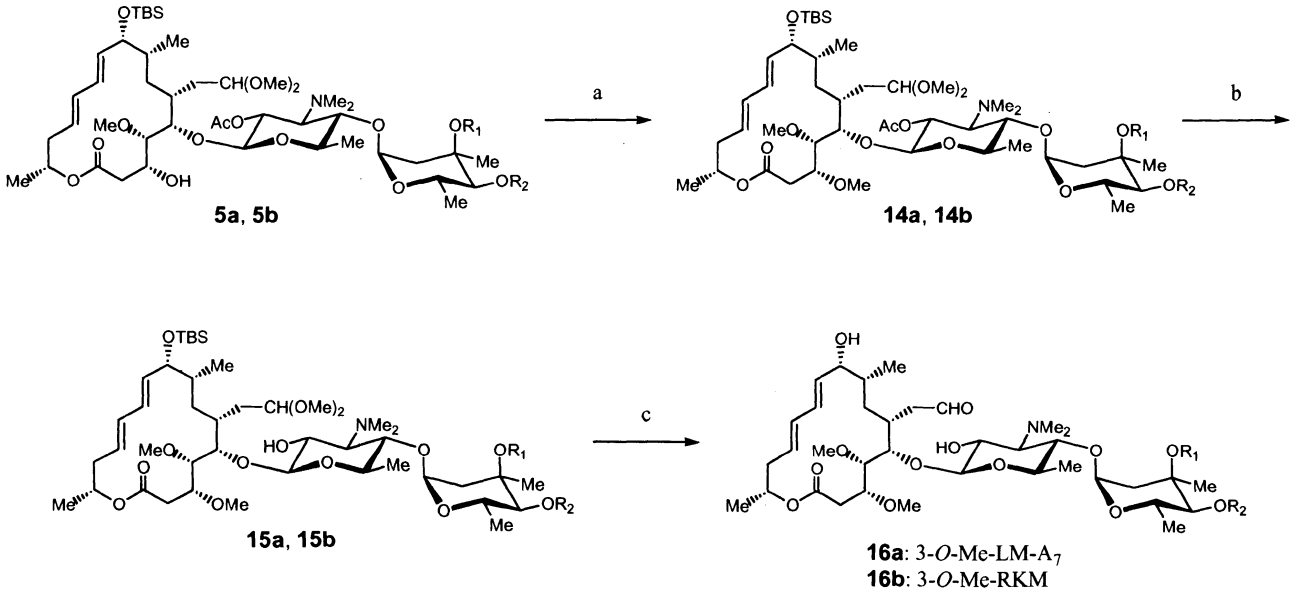
introducing acyl groups in an attempt to improve both antibacterial activity and biological stability. As illustrated in Scheme 2, acyl side chains were introduced to **7** to give **10a**~**10e**. Deprotections were carried out to furnish 3-*O*-acyl-3-*epi*-LM-A_7 derivatives (**11a**~**11e**).

As shown in Scheme 3, we also synthesized 3-*O*-acyl-LM-A_7 derivatives (**13b**~**13e**) with natural stereochemistry at the C-3 position.

2. Biological Evaluation of Novel 3-*O*-Acylleucomycins

In vitro antibacterial activities of 3-*epi*-LM-A_7 (**9**), 3-*O*-acyl-3-*epi*-LM-A_7 analogues (**11a**~**11e**) and their corresponding compounds (LM-A_7, MDM, **13b**~**13e**) with natural stereochemistry at the C-3 position are shown in Table 1. Compound **9** was less active than LM-A_7 against target microorganisms, and in most cases, acylation or epimerization at the C-3 position did not improve antibacterial activities compared with LM-A_7. However, a

Scheme 4. Synthesis of 3-*O*-methyl derivatives of LM-A_7 and RKM[a].



[a]Reagents and conditions: (a) KOH, MeI, DMSO, r.t., 1~4 h, 40~80%; (b) MeOH-H_2O (9:1), r.t.~50°C, overnight; (c) CHF_2COOH, MeCN-H_2O (1:1), r.t.~40°C, overnight~38 h, 22~66% overall 2 steps.

Leucomycin A_7 derivatives are represented as suffix "a" compounds: R_1 = H, R_2 = COEt

Rokitamycin derivatives are represented as suffix "b" compounds: R_1 = COEt, R_2 = CO^nPr

quinolyl analogue (**13e**) exceptionally exhibited improved activities against Gram-positive bacteria compared with LM-A_7. Compound **13e** was slightly active against inducible resistant *Streptococcus pneumoniae* PRC-91, implying possibility of the quinoline ring to overcome the methylase resistant strains.

Unfortunately, stability of **9** in rat plasma was significantly decreased compared with that of LM-A_7 even in the preliminary study. Thus, $T_{1/2}$ of **9** was approximately eight times shorter than that of LM-A_7 (data not shown).

With these results, however, we reconfirmed that modification at the C-3 position was practically important for both antibacterial activity and metabolic stability.

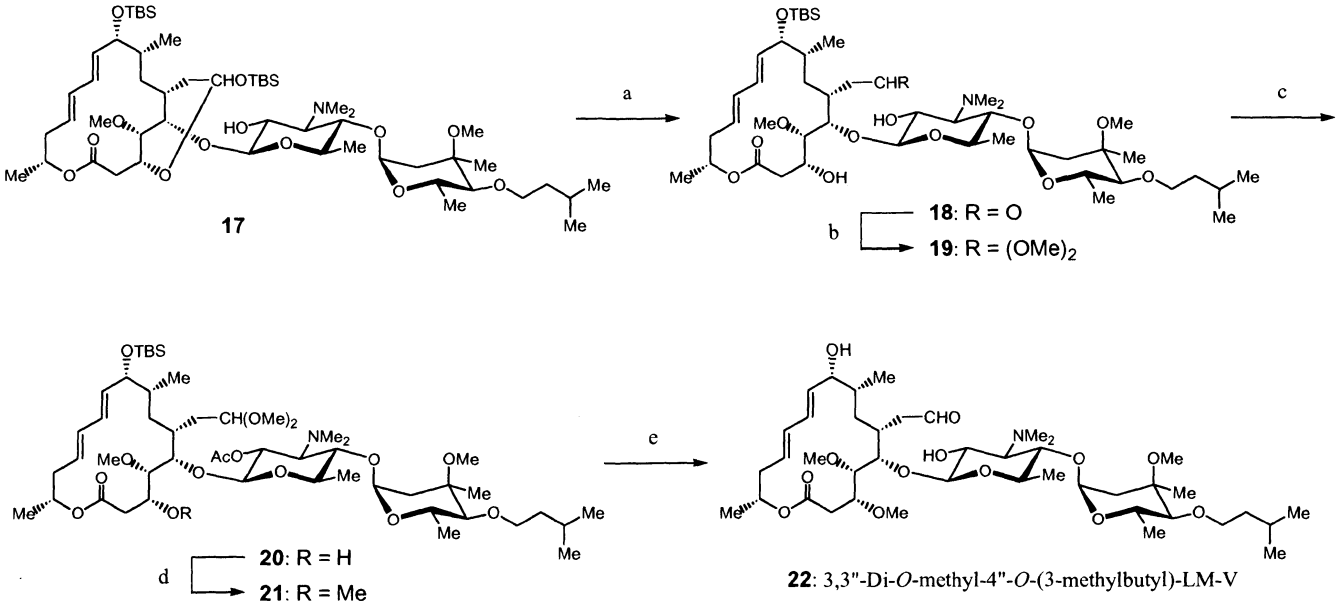
3. Synthesis of 3-*O*-Methylleucomycins

In 3-*O*-acyl derivatives, suppression of lactone opening by the C-3 side chain must be one of the reasons for their stability. Thus, we conducted methylation of the 3-hydroxyl group to donate the steric hindrance to the lactone ring. 3-*O*-methyl group can also electronically stabilize the lactone carbonyl more efficiently than an acyl group. Additionally, undesirable 3,18-hemiacetal formation can be avoided by masking the 3-hydroxyl group. Thus, this modification can be one of the most promising approaches in drug discovery of sixteen-membered macrolides. Although there is one example[27] of methylation of the 3-hydroxyl group in platenolide skeleton, precise SAR information has not been discussed so far.

As shown in Scheme 4, 3-*O*-Me-LM-A_7 (**16a**) was synthesized from **5a**. Methylation of the 3-hydroxyl group was achieved using KOH as a base in DMSO[2]. Subsequent removal of three protecting groups furnished **16a**. Completion of synthesis of **16a** encouraged us to expand this route to the synthesis of 3-*O*-Me-RKM (Scheme 4, **16b**), which was expected to exhibit strong antibacterial activity. Fully protected RKM (**5b**) was prepared in the same way as described in the synthesis of **5a** (Scheme 1). Methylation of the 3-hydroxyl group followed by two-step deprotection furnished **16b**.

We further explored 3-*O*-methylation of 3″-*O*-methyl-4″-*O*-(3-methylbutyl)leucomycin V (Fig. 2, **1**) as shown in Scheme 5. Compound **1** is one of the most potent semisynthetic sixteen-membered macrolides showing long

Scheme 5. Synthesis of 3,3″-di-*O*-methyl-4″-*O*-(3-methylbutyl)-LM-V[a].



[a]Reagents and conditions: (a) Tetrabutylammonium fluoride, THF, r.t., 15 min; (b) Pyridinium *p*-toluenesulfonate, $CH(OMe)_3$, MeOH, 30°C, overnight; (c) Ac_2O, MeCN, 30°C, overnight, 90% overall 3 steps; (d) KOH, MeI, DMSO, r.t., 5 h, 55%; (e) (1) MeOH-H_2O (9:1), r.t., overnight; (2) CHF_2COOH, MeCN-H_2O (1:1), 40°C, overnight (20% overall 2 steps)

duration time. Selective desilylation of bis-TBS ether (**17**)[16] liberated the 18-formyl group which was protected as a dimethyl acetal to furnish **19**. Acetylation at the C-2′ position gave fully protected **20**, which was subjected to the methylation condition to yield **21**. After two-step deprotection, 3,3″-di-*O*-methyl-4″-*O*-(3-methylbutyl) leucomycin V (**22**) was obtained.

4. Biological Evaluation of 3-*O*-Methylleucomycins

Table 2 shows *in vitro* antibacterial activities of 3-*O*-methylleucomycin analogues (**16a**, **16b** and **22**) and their corresponding 3-OH type analogues (LM-A_7, RKM and **1**). For both natural LM-A_7 and semisynthetic RKM, introducing of the methyl group to the C-3 position resulted in enhancement of antibacterial activity *in vitro*. From MIC values, **16a** and **16b** are more potent than LM-A_7 and RKM against Gram-positive organisms. Moreover, **16b** exhibited somehow improved biological stability in rat plasma. After incubation for 2 hours at 37°C, **16b** was two to three times more stable than RKM in preliminary experiments. Although **22** and **1** exhibited almost the same antibacterial activities (Table 2), biological stability of **22** was improved. Actually, **22** was almost intact in rat plasma as we first expected. Even after incubation for 6 hours at 37°C, **22** was approximately two times more stable than **1** in preliminary experiments. Thus, **22** was proposed to be one of the most biologically stable sixteen-membered macrolides with strong antibacterial activities. From these results, we can conclude that methylation of the 3-hydroxyl group is one of the most promising modification of sixteen-membered macrolides for the improvement of their pharmacoprofiles.

Conclusion

On the basis of the reported structure of a metabolite of spiramycin I and biological properties of our in-house compounds (Fig. 2, **1** and **2**), we synthesized and evaluated a variety of 3-*epi*-leucomycin analogues (**9**, **11a**~**11e**) along with 3-*O*-acyl compounds with a natural stereo center at the C-3 position (**13b**~**13e**). As a result, we reconfirmed that the C-3 position is important for pharmacoprofiles in the leucomycin family. Thus, we synthesized 3-*O*-methyl

Table 2. Antibacterial activities of 3-*O*-methylleucomycin derivatives and their 3-OH analogues (LM-A_7, RKM and **1**).

Test organisms	Characteristics	**16a**	LM-A_7	**16b**	RKM	**22**	**1**
Staphylococcus aureus 209P JC-1	susceptible	0.20	0.39	0.10	0.20	0.20	0.20
Staphylococcus aureus MS15009	susceptible	0.20	0.39	0.10	0.20	0.39	0.39
Staphylococcus aureus MS15009/pMS99	*ermA* methylase (c*)	>100	>100	>100	>100	>100	>100
Staphylococcus aureus MS15009/pMS98	*ermB* methylase (i**)	0.10	0.20	0.20	0.20	0.20	0.20
Micrococcus luteus ATCC9341	susceptible	0.05	0.10	0.03	0.05	0.05	0.05
Streptococcus pneumoniae DP1 TypeI	susceptible	0.10	0.20	0.05	0.10	0.10	0.10
Streptococcus pneumoniae IP692	susceptible	0.20	0.20	0.10	0.10	0.10	0.10
Streptococcus pneumoniae TH-83	*ermAM* methylase (c*)	>100	>100	100	100	>100	>100
Streptococcus pneumoniae PRC-91	*ermAM* methylase (i**)	100	100	0.78	1.56	3.13	6.25
Streptococcus pneumoniae PRC-53	*mefE* efflux	0.10	0.20	0.10	0.20	0.10	0.10
Moraxella catarrhalis W-0500	susceptible	0.78	0.78	0.20	0.20	0.39	0.20
Haemophilus influenzae 9334	susceptible	1.56	1.56	3.13	1.56	1.56	1.56
Haemophilus influenzae PRC-44	susceptible	6.25	6.25	6.25	6.25	12.5	6.25

c*: constitutive resisitant; i**: inducible resisitant

analogues of three representative leucomycin derivatives (**16a**, **16b** and **22**), and successfully improved both antibacterial activity and biological stability. Recently, we have achieved the synthesis of 3-*O*-allyl type compounds, which would widen the diversity of leucomycin derivatives.

To explore a new aspect of macrolide antibiotics, other modification of sixteen-membered macrolides, except at the C-3 position, is now undergoing. Involved with these new explorations, our successful improvement of pharmacoproperties in the leucomycin family by modifying the C-3 position and the neutral sugar moiety must be promising for drug discovery in the future.

Experimental

General Methods

Optical rotations were measured on a Perkin-Elmer 241 polarimeter or JASCO DIP-370. Mass spectra were obtained on a JEOL JMS-700 for FAB-MS or Agilent HP5989A for TSP-MS or HITACHI M-80B for EI-MS. ^{1}H NMR spectra were measured with a Varian Gemini-300 for 300 MHz in $CDCl_3$ using $CHCl_3$ as internal standard. Silica gel chromatography and preparative TLC were performed on Wako C-300 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 35°C, unless otherwise noted.

Antibacterial Activity *In Vitro*

Minimum inhibitory concentration (MIC) was determined by the agar dilution method. Test strains were subjected to seed culture using Sensitivity test broth (STB, Nissui Pharmaceutical) for *Staphylococcus aureus* and *Micrococcus luteus*, or cultured on blood agar plate for *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae*. 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.

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)leucomycin A_7 18-Dimethylacetal (**5a**)

To a stirred solution of LM-A_7 (12.0 g, 15.9 mmol) in DMF (200 ml), imidazole (3.52 g, 51.7 mmol) and *t*-butyldimethylsilyl chloride (3.51 g, 23.3 mmol) were added and the reaction mixture was stirred for 17 hours at 45°C. To this solution was added MeOH (50 ml) and the mixture was stirred for 1.5 hours at room temperature. Evaporation gave a residue which was diluted with $CHCl_3$ and the organic layer was washed with 5% aqueous $KHSO_4$ and

brine. Then the organic layer was dried and concentrated to afford crude **3** along with 9,18-bis-*O*-TBS-LM-A_7 3,18-acetal. This mixture was used for the next step without purification.

To a stirred solution of **3** and 9,18-bis-*O*-TBS-LM-A_7 3,18-acetal in THF (300 ml) was added tetrabutylammonium fluoride (1.0 M in THF, 22.9 ml, 22.9 mmol). After stirring for 3 hours at room temperature, 5% aqueous $KHSO_4$ was added and the aqueous layer was extracted with EtOAc. The extract was washed with water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried and concentrated to give crude **3** (14.3 g) which was used for the next step without purification.

To a stirred solution of crude **3** (14.3 g) in MeOH (120 ml), trimethyl orthoformate (120 ml) and pyridinium *p*-toluenesulfonate (5.94 g, 23.6 mmol) were added and the reaction mixture was stirred for 36 hours at 45°C. Evaporation gave a residue which was diluted with EtOAc and the extract was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and concentrated to afford crude **4** (37.1 g) which was used for the next step without purification.

To a stirred solution of crude **4** (37.1 g) in MeCN (200 ml) was added acetic anhydride (7.50 ml, 79.5 mmol) and the reaction mixture was stirred for 24 hours at room temperature. Saturated aqueous $NaHCO_3$ were added and the mixture was evaporated. The aqueous layer was extracted with EtOAc and the extract was washed with saturated aqueous $NaHCO_3$ and brine. After the organic layer was dried and concentrated, the residue was purified by silica gel chromatography [750 g, hexane - EtOAc (1 : 1)] to afford **5a** (8.23 g, 62% overall 4 steps).

$[\alpha]_D^{25}$ −103° (*c* 1.0, MeOH); FAB-MS *m/z* 960 $(M+H)^+$; ^1H NMR δ 0.68 (br t, 7-H), 0.93 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.29 (d, 16-H), 1.44 (br dt, 7-H), 1.69 (br t, 6-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.01 (s, 2′-$OCOCH_3$), 2.07 (dt, 14-H), 2.19 (br d, 2-H), 2.39 (s, 3′-$N(CH_3)_2$), 2.42 (m, 4″-$OCOCH_2CH_3$), 2.62 (dd, 2-H), 2.70 (t, 3′-H), 2.95 (d, 4-H), 3.25 (s, 18-OCH_3), 3.30 (t, 4′-H), 3.32 (dq, 5′-H), 3.38 (s, 18-OCH_3), 3.44 (s, 4-OCH_3), 3.72 (br d, 3-H), 4.04 (d, 5-H), 4.22 (dd, 9-H), 4.37 (dq, 5″-H), 4.49 (dd, 18-H), 4.60 (d, 4″-H), 4.73 (d, 1′-H), 4.98 (dd, 2′-H), 5.07 (d, 1″-H), 5.27 (ddq, 15-H), 5.49 (ddd, 13-H), 5.62 (dd, 10-H), 5.95 (br dd, 12-H), 6.02 (dd, 11-H)

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-dehydroleucomycin A_7 18-Dimethylacetal (**6**)

To a stirred and cooled solution of DMSO (630 μl, 8.88 mmol) in CH_2Cl_2 (20 ml), trifluoroacetic anhydride (840 μl, 5.95 mmol) was added and the reaction mixture was stirred for 20 minutes at −78°C. To this solution was added **5a** (1.51 g, 1.57 mmol) in CH_2Cl_2 (8.0 ml). After stirring for 45 minutes at −78°C, Et_3N (2.20 ml, 15.8 mmol) was added and the mixture was gradually warmed to room temperature. Saturated aqueous $NaHCO_3$ was added and the aqueous layer was extracted with $CHCl_3$. The extract was washed with brine, dried and concentrated. The residue was purified by silica gel chromatography [300 g, benzene - acetone (20 : 1∼15 : 1)] to give **6** (448 mg, 30%). This was a equilibrium mixture of keto and *trans* enol tautomer (*ca.* 1 : 1).

$[\alpha]_D^{24}$ −59° (*c* 1.0, MeOH); TSP-MS *m/z* 958 $(M+H)^+$; ^1H NMR (for 3-keto tautomer) δ 0.68 (br t, 7-H), 0.92 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.32 (d, 16-H), 1.52 (m, 6-H), 1.59 (m, 7-H), 1.61 (m, 17-H), 1.83 (m, 8-H), 1.83 (dd, 2″-Hax), 1.84 (m, 17-H), 1.99 (d, 2″-Heq), 2.04 (s, 2′-$OCOCH_3$), 2.39 (s, 3′-$N(CH_3)_2$), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.71 (t, 3′-H), 3.25 (s, 18-OCH_3), 3.27 (s, 4-OCH_3), 3.37 (s, 18-OCH_3), 4.01 (br d, 5-H), 4.18 (dd, 9-H), 4.38 (dq, 5″-H), 4.47 (dd, 18-H), 4.60 (d, 4″-H), 4.79 (d, 1′-H), 4.99 (dd, 2′-H), 5.07 (d, 1″-H), 5.28 (ddq, 15-H), 5.40 (ddd, 13-H), 5.65 (dd, 10-H), 5.89 (br dd, 12-H), 5.94 (dd, 11-H).

^1H NMR (for *trans* enol tautomer) δ 0.98 (d, 19-H), 1.10 (s, 3″-CH_3), 1.10 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.83 (dd, 2″-Hax), 1.98 (d, 2″-Heq), 2.06 (s, 2′-$OCOCH_3$), 2.35 (s, 3′-$N(CH_3)_2$), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.68 (t, 3′-H), 3.27 (s, 18-OCH_3), 3.32 (s, 18-OCH_3), 3.48 (s, 4-OCH_3), 3.62 (m, 4-H), 4.18 (dd, 9-H), 4.27 (br d, 1′-H), 4.60 (d, 4″-H), 4.79 (d, 1′-H), 4.92 (s, 2-H), 4.94 (dd, 2′-H), 5.04 (d, 1″-H), 5.61 (dd, 10-H), 6.04 (dd, 11-H).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*epi*-leucomycin A_7 18-Dimethylacetal (**7**)

To a stirred solution of **6** (346 mg, 361 μmol) in 1,4-dioxane (8.0 ml), $NaBH_4$ (65.0 mg, 1.72 mmol) was added and the mixture was stirred overnight at room temperature. Water was added and the aqueous layer was extracted with $CHCl_3$. The organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel chromatography [50 g, hexane - EtOAc (2 : 1∼1 : 1)] to give **7** (259 mg, 75%).

$[\alpha]_D^{23}$ −91° (*c* 1.0, MeOH); FAB-MS *m/z* 960 $(M+H)^+$; ^1H NMR δ 0.95 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.30 (d, 16-H), 1.49 (m, 17-H), 1.62 (m, 8-H), 1.83 (dd, 2″-Hax), 1.98 (d, 2″-Heq), 2.03 (s, 2′-$OCOCH_3$), 2.15 (dt, 14-H), 2.27 (br d,

2-H), 2.39 (s, 3′-N(CH_3)$_2$), 2.42 (q, 4″-OCOCH_2CH_3), 2.43 (q, 4″-OCOCH_2CH_3), 2.50 (m, 14-H), 2.59 (dd, 2-H), 2.71 (t, 3′-H), 3.28 (s, 18-OCH_3), 3.32 (s, 18-OCH_3), 3.46 (s, 4-OCH_3), 3.60 (br d, 5-H), 3.77 (m, 3-H), 4.16 (dd, 9-H), 4.39 (dq, 5″-H), 4.49 (dd, 18-H), 4.60 (d, 4″-H), 4.66 (d, 1′-H), 4.98 (dd, 2′-H), 5.06 (d, 1″-H), 5.23 (ddq, 15-H), 5.53 (ddd, 13-H), 5.66 (dd, 10-H), 6.01 (br dd, 12-H), 6.06 (dd, 11-H).

3-*Epi*-leucomycin A_7 (**9**)

A solution of **7** (73.4 mg, 76.4 μmol) in 10 ml of MeOH - H_2O (9 : 1) was stirred overnight at 50°C. The reaction mixture was concentrated and the residue was purified by silica gel chromatography [6.0 g, $CHCl_3$ - MeOH (20 : 1～10 : 1)] to give **8** (68.7 mg).

To a stirred solution of **8** (68.7 mg, 74.8 μmol) in 26 ml of MeCN - H_2O (1 : 1), difluoroacetic acid (24.0 μl, 381 μmol) was added and the reaction mixture was stirred overnight at room temperature. Saturated aqueous $NaHCO_3$ was added and the aqueous layer was extracted with $CHCl_3$. The organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel chromatography [15 g, $CHCl_3$ - MeOH - NH_4OH (450 : 3 : 0.1～600 : 6 : 1)] to give **9** (44.4 mg, 76% overall 2 steps).

$[\alpha]_D^{23}$ −57° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 758 $(M+H)^+$; ^{1}H NMR δ 1.10 (s, 3″-CH_3), 1.10 (d, 6″-H), 1.11 (d, 19-H), 1.16 (t, 4″-OCOCH_2CH_3), 1.19 (d, 6′-H), 1.30 (d, 16-H), 1.37 (m, 7-H), 1.61 (m, 8-H), 1.81 (dd, 2″-Hax), 1.98 (d, 2″-Heq) 2.19 (dt, 14-H), 2.42 (q, 4″-OCOCH_2CH_3), 2.43 (q, 4″-OCOCH_2CH_3), 2.47 (s, 3′-N(CH_3)$_2$), 2.61 (d, 2-H), 3.14 (m, 4-H), 3.21 (t, 4′-H), 3.28 (dq, 5′-H), 3.42 (s, 4-OCH_3), 3.57 (dd, 2′-H), 3.86 (br t, 5-H), 3.92 (br t, 3-H), 4.18 (m, 9-H), 4.20 (d, 1′-H), 4.47 (dq, 5″-H), 4.60 (d, 4″-H), 5.04 (d, 1″-H), 5.34 (ddq, 15-H), 5.65 (dd, 10-H), 5.65 (ddd, 13-H), 6.05 (br dd, 12-H), 6.18 (dd, 11-H), 9.72 (br s, 18-H).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*epi*-3-*O*-propionylleucomycin A_7 18-Dimethylacetal (**10a**)

To a stirred solution of **7** (101 mg, 105 μmol), pyridine (130 μl, 1.61 mmol) and 4-(dimethylamino)pyridine (12.7 mg, 104 μmol) in CH_2Cl2 (1.2 ml), was added propionyl chloride (50.0 μl, 575 μmol) and the reaction mixture was stirred for 4 hours at room temperature. Saturated aqueous $NaHCO_3$ was added and the aqueous layer was extracted with $CHCl_3$. The organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel chromatography [15 g, hexane - EtOAc (5 : 1～2 : 1～1 : 1)] to give **10a** (55.1 mg, 52%).

$[\alpha]_D^{23}$ −127° (*c* 1.0, MeOH); FAB-MS *m/z* 1016 $(M+H)^+$; ^{1}H NMR δ 0.99 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.16 (t, 4″-OCOCH_2CH_3), 1.22 (t, 3-OCOCH_2CH_3), 1.24 (d, 16-H), 1.28 (d, 6′-H), 1.55 (m, 17-H), 1.78 (m, 8-H), 1.84 (dd, 2″-Hax), 1.98 (dt, 14-H), 2.00 (d, 2″-Heq), 2.03 (s, 2′-OCOCH_3), 2.20 (br d, 2-H), 2.36 (q, 3-OCOCH_2CH_3), 2.39 (s, 3′-N(CH_3)$_2$), 2.42 (q, 4″-OCOCH_2CH_3), 2.43 (q, 4″-OCOCH_2CH_3), 2.69 (t, 3′-H), 2.81 (dd, 2-H), 3.28 (s, 18-OCH_3), 3.34 (s, 18-OCH_3), 3.40 (dd, 4-H), 3.41 (s, 4-OCH_3), 3.46 (br d, 5-H), 4.21 (dd, 9-H), 4.38 (dq, 5″-H), 4.52 (dd, 18-H), 4.61 (d, 4″-H), 4.68 (d, 1′-H), 4.87 (br d, 3-H), 4.96 (dd, 2′-H), 5.07 (d, 1″-H), 5.10 (ddq, 15-H), 5.41 (ddd, 13-H), 5.89 (dd, 10-H), 6.95 (br dd, 12-H), 6.06 (dd, 11-H).

2′-*O*-Acetyl-3-*O*-benzoyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*epi*-leucomycin A_7 18-Dimethylacetal (**10b**)

By a similar procedure to **10a**, reaction of **7** and benzoyl chloride gave crude **10b**. This was purified by silica gel chromatography [hexane - EtOAc (5 : 1～3 : 1～2 : 1～1 : 1)] to give **10b** (93%).

$[\alpha]_D^{20}$ −128° (*c* 0.53, $CHCl_3$); FAB-MS *m/z* 1064 $(M+H)^+$; ^{1}H NMR δ 0.98 (d, 16-H), 1.03 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.15 (t, 4″-OCOCH_2CH_3), 1.29 (d, 6′-H), 1.56 (m, 17-H), 1.69 (dt, 14-H), 1.83 (m, 8-H), 1.83 (m, 17-H), 1.83 (dd, 2″-Hax), 1.98 (d, 2″-Heq), 1.98 (s, 2′-OCOCH_3), 2.27 (br d, 2-H), 2.27 (br d, 14-H), 2.37 (s, 3′-N(CH_3)$_2$), 2.41 (q, 4″-OCOCH_2CH_3), 2.42 (q, 4″-OCOCH_2CH_3), 2.68 (t, 3′-H), 3.00 (dd, 2-H), 3.29 (s, 18-OCH_3), 3.35 (s, 18-OCH_3), 3.39 (s, 4-OCH_3), 3.52 (br d, 5-H), 3.61 (dd, 4-H), 4.24 (dd, 9-H), 4.38 (dq, 5″-H), 4.57 (dd, 18-H), 4.60 (d, 4″-H), 4.73 (d, 1′-H), 4.97 (dd, 2′-H), 5.05 (ddq, 15-H), 5.06 (d, 1″-H), 5.08 (br d, 3-H), 5.38 (ddd, 13-H), 5.91 (br dd, 12-H), 5.98 (dd, 10-H), 6.08 (dd, 11-H), 7.46 (br t, 3-OCOC_6H_5), 7.58 (tt, 3-OCOC_6H_5), 8.11 (dd, 3-OCOC_6H_5).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-(cyclohxylcarbonyl)-3-*epi*-leucomycin A_7 18-Dimethylacetal (**10c**)

By a similar procedure to **10a**, reaction of **7** and cyclohexylcarbonyl chloride gave crude **10c**. This was purified by silica gel chromatography [hexane - EtOAc (3 : 1)] to give **10c** (59%).

$[\alpha]_D^{24}$ −100° (*c* 1.8, $CHCl_3$); TSP-MS *m/z* 1070 $(M+H)^+$; ^{1}H NMR δ 0.99 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.16 (t, 4″-OCOCH_2CH_3), 1.24 (d, 16-H), 1.28 (d, 6′-H), 1.49 (br q, 3-OCOC_6H_{11}), 1.50 (m, 17-H), 1.70 (m, 3-OCOC_6H_{11}), 1.81 (m, 3-OCOC_6H_{11}), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.02 (s, 2′-OCOCH_3), 2.20 (br d, 2-H), 2.31 (tt, 3-OCOC_6H_{11}), 2.38 (s, 3′-N(CH_3)$_2$), 2.42 (q, 4″-OCOCH_2CH_3), 2.43 (q, 4″-OCOCH_2CH_3), 2.69 (t, 3′-H),

2.81 (dd, 2-H), 3.27 (s, 18-OCH_3), 3.33 (s, 18-OCH_3), 3.41 (s, 4-OCH_3), 3.46 (br d, 5-H), 4.21 (dd, 9-H), 4.38 (dq, 5″-H), 4.51 (dd, 18-H), 4.61 (d, 4″-H), 4.67 (d, 1′-H), 4.81 (br d, 3-H), 4.96 (dd, 2′-H), 5.06 (d, 1″-H), 5.09 (ddq, 15-H), 5.41 (ddd, 13-H), 5.91 (br dd, 12-H), 5.91 (dd, 10-H), 6.04 (dd, 11-H).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*epi*-3-*O*-(6-phenylhexanoyl)leucomycin A_7 18-Dimethylacetal (**10d**)

By a similar procedure to **10a**, reaction of **7** and 6-phenylhexanoyl chloride gave crude **10d**. This was purified by silica gel chromatography [hexane - EtOAc (5 : 1～3 : 1～1 : 1)] to give **10d** (59%).

$[\alpha]_D^{23}$ −87° (*c* 1.9, $CHCl_3$); TSP-MS *m/z* 1134 $(M+H)^+$; ^1H NMR δ 0.99 (d, 19-H), 1.10 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.22 (d, 16-H), 1.28 (d, 6′-H), 1.67 (quint, 3-$OCO(CH_2)_5C_6H_5$), 1.83 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.02 (s, 2′-$OCOCH_3$), 2.20 (br d, 2-H), 2.32 (t, 3-$OCO(CH_2)_5C_6H_5$), 2.39 (s, 3′-$N(CH_3)_2$), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.63 (t, 3-$OCO(CH_2)_5C_6H_5$), 2.69 (t, 3′-H), 2.80 (dd, 2-H), 3.27 (s, 18-OCH_3), 3.33 (s, 18-OCH_3), 3.40 (s, 4-OCH_3), 3.46 (br d, 5-H), 4.21 (dd, 9-H), 4.39 (dq, 5″-H), 4.52 (dd, 18-H), 4.61 (d, 4″-H), 4.68 (d, 1′-H), 4.86 (br d, 3-H), 4.96 (dd, 2′-H), 5.06 (d, 1″-H), 5.08 (ddq, 15-H), 5.40 (ddd, 13-H), 5.90 (dd, 10-H),) 5.93 (br dd, 12-H), 6.06 (dd, 11-H), 7.15 (m, 3-$OCO(CH_2)_5C_6H_5$), 7.25 (m, 3-$OCO(CH_2)_5C_6H_5$).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*epi*-3-*O*-[(quinolin-2-yl)carbonyl]leucomycin A_7 18-Dimethylacetal (**10e**)

To a stirred solution of **7** (104 mg, 108 μmol), Et_3N (499 μl, 3.58 mmol) and 4-(dimethylamino)pyridine (51.0 mg, 417 μmol) in CH_2Cl_2 (1.5 ml), was added (quinolin-2-yl)carbonyl chloride (264 mg, 1.16 mmol) and the reaction mixture was stirred for 3 days at room temperature. Saturated aqueous $NaHCO_3$ was added and the aqueous layer was extracted with $CHCl_3$. The organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel chromatography [15 g, hexane - EtOAc (4 : 1～3 : 1～2 : 1)] to give **10e** (71.2 mg, 59%).

$[\alpha]_D^{24}$ −136° (*c* 0.62, $CHCl_3$); FAB-MS *m/z* 1115 $(M+H)^+$; ^1H NMR δ 1.02 (d, 19-H), 1.04 (d, 16-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.15 (t, 4″-$OCOCH_2CH_3$), 1.30 (d, 6′-H), 1.56 (m, 17-H), 1.78 (m, 14-H), 1.83 (dd, 2″-Hax), 1.84 (m, 8-H), 1.98 (d, 2″-Heq), 1.98 (s, 2′-$OCOCH_3$), 2.30 (br d, 14-H), 2.33 (br d, 2-H), 2.37 (s, 3′-$N(CH_3)_2$), 2.41 (q, 4″-$OCOCH_2CH_3$), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.67 (t, 3′-H), 3.12 (dd, 2-H), 3.30 (s, 18-OCH_3), 3.37 (s, 18-OCH_3), 3.40 (s, 4-OCH_3), 3.57 (br d, 5-H), 3.68 (dd, 4-H), 4.25 (dd, 9-H), 4.38 (dq, 5″-H), 4.59 (m, 18-H), 4.60 (d, 4″-H), 4.74 (d, 1′-H), 4.97 (dd, 2′-H), 5.07 (d, 1″-H), 5.12 (ddq, 15-H), 5.25 (br d, 3-H), 5.42 (ddd, 13-H), 6.06 (br dd, 12-H), 6.07 (dd, 10-H), 6.12 (dd, 11-H), 7.67 (ddd, 3-OCO-quinoline), 7.81 (ddd, 3-OCO-quinoline), 7.90 (br d, 3-OCO-quinoline), 8.20 (d, 3-OCO-quinoline), 8.33 (d, 3-OCO-quinoline), 8.37 (br d, 3-OCO-quinoline).

3-*Epi*-3-*O*-propionylleucomycin A_7 (**11a**)

By similar procedures to **9**, reactions of **10a** gave crude **11a**. This was purified by preparative TLC [$CHCl_3$ - MeOH - NH_4OH (400 : 20 : 1)] to afford **11a** (69% overall 2 steps).

$[\alpha]_D^{24}$ −99° (*c* 0.38, $CHCl_3$); FAB-MS *m/z* 814 $(M+H)^+$; ^1H NMR δ 1.07 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.20 (t, 3-$OCOCH_2CH_3$), 1.22 (d, 6′-H), 1.25 (ddd, 7-H), 1.25 (d, 16-H), 1.54 (ddd, 7-H), 1.58 (m, 8-H), 1.82 (dd, 2″-Hax), 1.98 (d, 2″-Heq) 2.09 (dt, 14-H), 2.16 (m, 6-H), 2.35 (t, 3-$OCOCH_2CH_3$), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.48 (s, 3′-$N(CH_3)_2$), 2.84 (dd, 2-H), 2.99 (dd, 17-H), 3.44 (s, 4-OCH_3), 3.48 (dd, 2′-H), 3.53 (d, 5-H), 4.11 (m, 9-H), 4.28 (d, 1′-H), 4.46 (dq, 5″-H), 4.61 (d, 4″-H), 5.03 (br d, 3-H), 5.05 (d, 1″-H), 5.06 (ddq, 15-H), 5.54 (ddd, 13-H), 5.77 (dd, 10-H), 5.99 (br dd, 12-H), 6.24 (dd, 11-H), 9.74 (br s, 18-H).

3-*O*-Benzoyl-3-*epi*-leucomycin A_7 (**11b**)

By similar procedures to **9**, reactions of **10b** gave crude **11b**. This was purified by preparative TLC [$CHCl_3$ - MeOH - NH_4OH (150 : 1 : 1)] to afford **11b** (55% overall 2 steps).

$[\alpha]_D^{26}$ −112° (*c* 1.3, $CHCl_3$); TSP-MS *m/z* 862 $(M+H)^+$; ^1H NMR α 0.99 (d, 16-H), 1.10 (s, 3″-CH_3), 1.12 (d, 19-H), 1.12 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.22 (d, 6′-H), 1.31 (br t, 7-H), 1.69 (ddd, 7-H), 1.82 (dd, 2″-Hax), 1.86 (m, 8-H), 1.90 (dt, 14-H), 1.99 (d, 2″-Heq) 2.20 (m, 6-H), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.44 (q, 4″-$OCOCH_2CH_3$), 2.47 (s, 3′-$N(CH_3)_2$), 2.62 (dd, 2-H), 3.03 (dd, 2-H), 3.03 (dd, 17-H), 3.24 (m, 5′-H), 3.25 (m, 4′-H), 3.42 (s, 4-OCH_3), 3.52 (dd, 2′-H), 3.54 (br d, 4-H), 3.81 (br d, 5-H), 4.15 (m, 9-H), 4.30 (d, 1′-H), 4.46 (dq, 5″-H), 4.61 (d, 4″-H), 5.00 (ddq, 15-H), 5.06 (d, 1″-H), 5.21 (br d, 3-H), 5.46 (ddd, 13-H), 5.83 (dd, 10-H), 5.98 (br dd, 12-H), 6.29 (dd, 11-H), 7.47 (br t, 3-$OCOC_6H_5$), 7.60 (br t, 3-$OCOC_6H_5$), 8.10 (br d, 3-$OCOC_6H_5$), 9.76 (s, 18-H).

3-*O*-(Cyclohxylcarbonyl)-3-*epi*-leucomycin A_7 (**11c**)

By similar procedures to **9**, reactions of **10c** gave crude **11c**. This was purified by preparative TLC [$CHCl_3$-MeOH (10:1)] to afford **11c** (43% overall 2 steps).

$[\alpha]_D^{21}$ −87° (*c* 1.4, $CHCl_3$); FAB-MS *m/z* 868 $(M+H)^+$; ^1H NMR δ 1.06 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.26 (d, 16-H), 1.49 (m, 3-$OCOC_6H_{11}$), 1.55 (ddd, 7-H), 1.68 (m, 3-$OCOC_6H_{11}$), 1.79 (m, 3-$OCOC_6H_{11}$), 1.81 (dd, 2″-Hax), 1.93 (m, 3-$OCOC_6H_{11}$), 1.98 (d, 2″-Heq) 2.09 (dt, 14-H), 2.16 (m, 6-H), 2.30 (tt, 3-$OCOC_6H_{11}$), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.47 (s, 3′-$N(CH_3)_2$), 2.83 (dd, 2-H), 2.98 (dd, 17-H), 3.44 (s, 4-OCH_3), 3.48 (br d, 4-H), 3.50 (dd, 2′-H), 3.57 (br d, 5-H), 4.10 (br dd, 9-H), 4.24 (d, 1′-H), 4.45 (dq, 5″-H), 4.60 (d, 4″-H), 4.96 (br d, 3-H), 5.04 (ddq, 15-H), 5.05 (d, 1″-H), 5.52 (ddd, 13-H), 5.78 (dd, 10-H), 5.96 (br dd, 12-H), 6.20 (dd, 11-H), 9.73 (br s, 18-H).

3-*Epi*-3-*O*-(6-phenylhexanoyl)leucomycin A_7 (**11d**)

By similar procedures to **9**, reactions of **10d** gave crude **11d**. This was purified by preparative TLC [$CHCl_3$-MeOH-NH_4OH (100:10:1)] to afford **11d** (46% in 2 steps).

$[\alpha]_D^{24}$ −92° (*c* 1.2, $CHCl_3$); TSP-MS *m/z* 932 $(M+H)^+$; ^1H NMR δ 1.06 (d, 19-H), 1.09 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.23 (d, 16-H), 1.39 (m, 3-$OCO(CH_2)_5C_6H_5$), 1.52 (ddd, 7-H), 1.65 (quint, 3-$OCO(CH_2)_5C_6H_5$), 1.67 (quint, 3-$OCO(CH_2)_5C_6H_5$), 1.78 (m, 8-H), 1.81 (dd, 2″-Hax), 1.98 (d, 2″-Heq) 2.07 (dt, 14-H), 2.31 (t, 3-$OCO(CH_2)_5C_6H_5$), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.48 (s, 3′-$N(CH_3)_2$), 2.61 (t, 3-$OCO(CH_2)_5C_6H_5$), 2.81 (dd, 2-H), 2.99 (dd, 17-H), 3.41 (s, 4-OCH_3), 3.51 (dd, 2′-H), 4.10 (br t, 9-H), 4.27 (d, 1′-H), 4.45 (dq, 5″-H), 4.59 (d, 4″-H), 5.00 (br d, 3-H), 5.02 (m, 15-H), 5.05 (d, 1″-H), 5.52 (ddd, 13-H), 5.76 (dd, 10-H), 5.97 (br dd, 12-H), 6.22 (dd, 11-H), 7.16 (m, 3-$OCO(CH_2)_5C_6H_5$), 7.26 (m, 3-$OCO(CH_2)_5C_6H_5$), 9.72 (br s, 18-H).

3-*Epi*-3-*O*-[(quinolin-2-yl)carbonyl]leucomycin A_7 (**11e**)

By similar procedures to **9**, reactions of **10e** gave crude **11e**. This was purified by preparative TLC [$CHCl_3$-MeOH-NH_4OH (100:10:1)] to afford **11e** (45% overall 2 steps).

$[\alpha]_D^{23}$ −132° (*c* 0.27, $CHCl_3$); TSP-MS *m/z* 913 $(M+H)^+$; ^1H NMR δ 1.09 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 16-H), 1.11 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.21 (d, 6′-H), 1.33 (m, 7-H), 1.82 (dd, 2″-Hax), 1.84 (m, 8-H), 1.96 (m, 14-H), 1.98 (d, 2″-Heq), 2.23 (m, 6-H), 2.37 (br d, 14-H), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.49 (s, 3′-$N(CH_3)_2$), 2.67 (br d, 2-H), 2.99 (dd, 17-H), 3.11 (dd, 2-H), 3.42 (s, 4-OCH_3), 3.53 (dd, 2′-H), 3.66 (br d, 5-H), 3.78 (br d, 4-H), 4.09 (dd, 9-H), 4.33 (d, 1′-H), 4.45 (dq, 5″-H), 4.60 (d, 4″-H), 5.00 (m, 15-H), 5.05 (d, 1″-H), 5.35 (br d, 3-H), 5.53 (ddd, 13-H), 5.94 (dd, 10-H), 6.14 (br dd, 12-H), 6.30 (dd, 11-H), 7.67 (ddd, 3-OCO-quinoline), 7.80 (ddd, 3-OCO-quinoline), 7.90 (br d, 3-OCO-quinoline), 8.19 (d, 3-OCO-quinoline), 8.32 (d, 3-OCO-quinoline), 8.41 (br d, 3-OCO-quinoline), 9.75 (br s, 18-H).

2′-*O*-Acetyl-3-*O*-benzoyl-9-*O*-(*tert*-butyldimethyl-silyl)-leucomycin A_7 18-Dimethylacetal (**12b**)

By a similar procedure to **10a**, reaction of **5a** and benzoyl chloride gave crude **12b**. This was purified by silica gel chromatography [hexane-EtOAc (3:1~2:1)] to give **12b** (85%).

$[\alpha]_D^{23}$ −68° (*c* 0.62, $CHCl_3$); FAB-MS *m/z* 1064 $(M+H)^+$; ^1H NMR δ 0.86 (m, 7-H), 0.95 (d, 19-H), 1.06 (d, 6′-H), 1.10 (d, 6″-H), 1.11 (s, 3″-CH_3), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.23 (d, 16-H), 1.37 (ddd, 7-H), 1.50 (br t, 17-H), 1.66 (br t, 17-H), 1.81 (dd, 2″-Hax), 1.82 (m, 8-H), 1.95 (d, 2″-Heq), 2.03 (s, 2′-$OCOCH_3$), 2.13 (dt, 14-H), 2.36 (dd, 2-H), 2.39 (s, 3′-$N(CH_3)_2$), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.66 (t, 3′-H), 2.83 (dd, 2-H), 3.05 (s, 18-OCH_3), 3.09 (s, 18-OCH_3), 3.20 (dd, 4-H), 3.24 (t, 4′-H), 3.47 (s, 4-OCH_3), 3.83 (br d, 5-H), 4.17 (br d, 18-H), 4.25 (dd, 9-H), 4.37 (dq, 5″-H), 4.59 (d, 4″-H), 4.72 (d, 1′-H), 4.97 (dd, 2′-H), 4.99 (d, 1″-H), 4.99 (ddq, 15-H), 5.25 (br d, 3-H), 5.61 (dd, 10-H), 5.76 (ddd, 13-H), 6.06 (br dd, 12-H), 6.38 (dd, 11-H), 7.41 (br t, 3-$OCOC_6H_5$), 7.53 (tt, 3-$OCOC_6H_5$), 8.06 (br d, 3-$OCOC_6H_5$).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-(cyclohxylcarbonyl)leucomycin A_7 18-Dimethylacetal (**12c**)

By a similar procedure to **10a**, reaction of **5a** and cyclohexylcarbonyl chloride gave crude **12c**. This was purified by silica gel chromatography [hexane-EtOAc (5:1~3:1)] to give **12c** (72%).

$[\alpha]_D^{24}$ −57° (*c* 0.90, $CHCl_3$); TSP-MS *m/z* 1070 $(M+H)^+$; ^1H NMR δ 0.92 (d, 19-H), 0.98 (br t, 7-H), 1.10 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.23 (d, 16-H), 1.24 (d, 6′-H), 1.44 (dq, 3-$OCOC_6H_{11}$), 1.64 (m, 3-$OCOC_6H_{11}$), 1.74 (m, 3-$OCOC_6H_{11}$), 1.83 (dd, 2″-Hax), 1.92 (br d, 3-$OCOC_6H_{11}$), 2.00 (d, 2″-Heq), 2.00 (s, 2′-$OCOCH_3$), 2.10 (dt, 14-H), 2.22 (br d, 2-H), 2.31 (tt, 3-$OCOC_6H_{11}$), 2.39 (s, 3′-$N(CH_3)_2$), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.68 (dd, 2-H), 2.70 (t, 3′-H), 3.13 (br d, 4-H), 3.22 (s, 18-OCH_3), 3.27 (s,

18-OCH_3), 3.44 (s, 4-OCH_3), 3.72 (br d, 5-H), 4.24 (dd, 9-H), 4.17 (dd, 18-H), 4.38 (dq, 5″-H), 4.61 (d, 4″-H), 4.73 (d, 1′-H), 4.92 (ddq, 15-H), 4.98 (dd, 2′-H), 5.02 (br d, 3-H), 5.06 (d, 1″-H), 5.56 (dd, 10-H), 5.67 (ddd, 13-H), 6.01 (br dd, 12-H), 6.31 (dd, 11-H).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-(6-phenylhexanoyl)leucomycin A_7 18-Dimethylacetal (**12d**)

By a similar procedure to **10a**, reaction of **5a** and 6-phenylhexanoyl chloride gave crude **12d**. This was purified by silica gel chromatography [hexane - EtOAc (5 : 1～3 : 1～1 : 1)] to give **12d** (64%).

$[\alpha]_D^{23}$ −54° (*c* 0.79, $CHCl_3$); TSP-MS *m/z* 1134 $(M+H)^+$; ^1H NMR δ 0.93 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.23 (d, 16-H), 1.24 (d, 6′-H), 1.39 (m, 3-$OCO(CH_2)_5C_6H_5$), 1.64 (m, 3-$OCO(CH_2)_5C_6H_5$), 1.64 (quint, 3-$OCO(CH_2)_5C_6H_5$), 1.83 (m, 8-H), 1.83 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.00 (s, 2′-$OCOCH_3$), 2.10 (dt, 14-H), 2.23 (br d, 2-H), 2.35 (t, 3-$OCO(CH_2)_5C_6H_5$), 2.39 (s, 3′-$N(CH_3)_2$), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.61 (t, 3-$OCO(CH_2)_5C_6H_5$), 2.65 (dd, 2-H), 2.69 (t, 3′-H), 3.14 (dd, 4-H), 3.18 (s, 18-OCH_3), 3.20 (s, 18-OCH_3), 3.46 (s, 4-OCH_3), 3.78 (br d, 5-H), 4.16 (dd, 9-H), 4.38 (dq, 5″-H), 4.47 (dd, 18-H), 4.61 (d, 4″-H), 4.73 (d, 1′-H), 4.92 (ddq, 15-H), 4.98 (dd, 2′-H), 5.04 (br d, 3-H), 5.06 (d, 1″-H), 5.55 (dd, 10-H), 5.69 (ddd, 13-H), 6.01 (br dd, 12-H), 6.36 (dd, 11-H), 7.15 (m, 3-$OCO(CH_2)_5C_6H_5$), 7.25 (m, 3-$OCO(CH_2)_5C_6H_5$).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[(quinolin-2-yl)carbonyl]leucomycin A_7 18-Dimethylacetal (**12e**)

By a similar procedure to **10e**, reaction of **5a** and (quinolin-2-yl)carbonyl chloride gave crude **12e**. This was purified by silica gel chromatography [hexane - EtOAc (3 : 1～2 : 1～1 : 1)] to give **12e** (82%).

$[\alpha]_D^{21}$ −50° (*c* 0.64, $CHCl_3$); TSP-MS *m/z* 1115 $(M+H)^+$; ^1H NMR δ 0.95 (d, 19-H), 0.95 (d, 6′-H), 1.08 (d, 6″-H), 1.10 (s, 3″-CH_3), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.23 (d, 16-H), 1.40 (ddd, 7-H), 1.47 (dd, 17-H), 1.65 (m, 17-H), 1.74 (dd, 2″-Hax), 1.82 (br d, 2″-Heq), 2.04 (s, 2′-$OCOCH_3$), 2.13 (dt, 14-H), 2.38 (s, 3′-$N(CH_3)_2$), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.68 (t, 3′-H), 2.95 (s, 18-OCH_3), 3.04 (s, 18-OCH_3), 3.28 (br d, 4-H), 3.53 (s, 4-OCH_3), 3.78 (br d, 5-H), 4.22 (dd, 9-H), 4.23 (dd, 18-H), 4.35 (dq, 5″-H), 4.57 (d, 4″-H), 4.80 (d, 1′-H), 4.90 (d, 1″-H), 4.97 (dd, 2′-H), 5.04 (ddq, 15-H), 5.37 (br d, 3-H), 5.63 (dd, 10-H), 5.83 (ddd, 13-H), 6.08 (br dd, 12-H), 6.46 (dd, 11-H), 7.63 (ddd, 3-OCO-quinoline), 7.78 (ddd, 3-OCO-quinoline), 7.87 (br d, 3-OCO-quinoline), 8.20 (d, 3-OCO-quinoline), 8.28 (d, 3-OCO-quinoline), 8.31 (br d, 3-OCO-quinoline).

3-*O*-Benzoylleucomycin A_7 (**13b**)

By similar procedures to **9**, reactions of **12b** gave crude **13b**. This was purified by preparative TLC [$CHCl_3$ - MeOH (20 : 1)] to afford **13b** (42% overall 2 steps).

$[\alpha]_D^{23}$ −21° (*c* 0.37, $CHCl_3$); FAB-MS *m/z* 862 $(M+H)^+$; ^1H NMR δ 1.01 (d, 19-H), 1.09 (s, 3″-CH_3), 1.10 (d, 6′-H), 1.10 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.23 (d, 16-H), 1.45 (br ddd, 17-H), 1.80 (dd, 2″-Hax), 1.91 (m, 8-H), 1.95 (d, 2″-Heq), 2.13 (dt, 14-H), 2.34 (br dd, 17-H), 2.38 (br d, 2-H), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.49 (s, 3′-$N(CH_3)_2$), 2.74 (br dd, 17-H), 2.91 (dd, 2-H), 3.19 (m, 5′-H), 3.22 (t, 4′-H), 3.31 (dd, 4-H), 3.52 (dd, 2′-H), 3.56 (s, 4-OCH_3), 3.81 (br d, 5-H), 4.17 (dd, 9-H), 4.32 (d, 1′-H), 4.43 (dq, 5″-H), 4.59 (d, 4″-H), 5.01 (d, 1″-H), 5.06 (ddq, 15-H), 5.37 (br d, 3-H), 5.67 (dd, 10-H), 5.78 (ddd, 13-H), 6.09 (br dd, 12-H), 6.67 (dd, 11-H), 7.43 (br t, 3-$OCOC_6H_5$), 7.54 (tt, 3-$OCOC_6H_5$), 8.06 (br d, 3-$OCOC_6H_5$), 9.52 (br s, 18-H).

3-*O*-(Cyclohxylcarbonyl)leucomycin A_7 (**13c**)

By similar procedures to **9**, reactions of **12c** gave crude **13c**. This was purified by preparative TLC [$CHCl_3$ - MeOH - NH_4OH (100 : 10 : 1)] to afford **13c** (55% in 2 steps).

$[\alpha]_D^{21}$ −34° (*c* 1.2, $CHCl_3$); TSP-MS *m/z* 868 $(M+H)^+$; ^1H NMR δ 0.95 (br t, 7-H), 0.98 (d, 19-H), 1.10 (s, 7″-H), 1.11 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.24 (d, 16-H), 1.45 (br dq, 3-$OCOC_6H_{11}$), 1.45 (m, 7-H), 1.63 (m, 3-$OCOC_6H_{11}$), 1.74 (m, 3-$OCOC_6H_{11}$), 1.82 (dd, 2″-Hax), 1.90 (m, 8-H), 1.99 (d, 2″-Heq), 2.03 (m, 3-$OCOC_6H_{11}$), 2.12 (dt, 14-H), 2.24 (br d, 2-H), 2.33 (br dd, 17-H), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.49 (s, 3′-$N(CH_3)_2$), 2.74 (dd, 2-H), 2.76 (br dd, 17-H), 3.22 (dd, 4-H), 3.25 (t, 4′-H), 3.51 (dd, 2′-H), 3.51 (s, 4-OCH_3), 3.79 (br d, 5-H), 4.09 (dd, 9-H), 4.38 (d, 1′-H), 4.44 (dq, 5″-H), 4.60 (d, 4″-H), 5.01 (ddq, 15-H), 5.05 (d, 1″-H), 5.10 (br d, 3-H), 5.61 (dd, 10-H), 5.74 (ddd, 13-H), 6.05 (br dd, 12-H), 6.59 (dd, 11-H), 9.64 (br s, 18-H).

3-*O*-(6-Phenylhexanoyl)leucomycin A_7 (**13d**)

By similar procedures to **9**, reactions of **12d** gave crude **13d**. This was purified by preparative TLC [$CHCl_3$ - MeOH - NH_4OH (100 : 10 : 1)] to afford **13d** (37% overall 2 steps).

$[\alpha]_D^{24}$ −36° (*c* 0.81, $CHCl_3$); TSP-MS *m/z* 932 $(M+H)^+$;

^{1}H NMR δ 0.91 (br ddd, 7-H), 0.98 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.17 (d, 6′-H), 1.24 (d, 16-H), 1.42 (quint, 3-$OCO(CH_2)_5C_6H_5$), 1.66 (quint, 3-$OCO(CH_2)_5C_6H_5$), 1.71 (quint, 3-$OCO(CH_2)_5C_6H_5$), 1.82 (dd, 2″-Hax), 1.88 (m, 8-H), 1.99 (d, 2″-Heq), 2.12 (dt, 14-H), 2.24 (br d, 2-H), 2.33 (br dd, 17-H), 2.42 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.50 (s, 3′-$N(CH_3)_2$), 2.61 (t, 3-$OCO(CH_2)_5C_6H_5$), 2.72 (dd, 2-H), 2.79 (dd, 17-H), 3.22 (dd, 4-H), 3.25 (t, 4′-H), 3.51 (dd, 2′-H), 3.51 (s, 4-OCH_3), 3.84 (br d, 5-H), 4.07 (br dd, 9-H), 4.39 (d, 1′-H), 4.43 (dq, 5″-H), 4.61 (d, 4″-H), 4.99 (ddq, 15-H), 5.05 (d, 1″-H), 5.11 (br d, 3-H), 5.60 (dd, 10-H), 5.74 (ddd, 13-H), 6.05 (br dd, 12-H), 6.62 (dd, 11-H), 7.16 (m, 3-$OCO(CH_2)_5C_6H_5$), 7.25 (m, 3-$OCO(CH_2)_5C_6H_5$), 9.61 (br s, 18-H).

3-*O*-[(Quinolin-2-yl)carbonyl]leucomycin A_7 (**13e**)

By similar procedures to **9**, reactions of **12e** gave crude **13e**. This was purified by preparative TLC [$CHCl_3$-MeOH-NH_4OH (100 : 10 : 1)] to afford **13e** (39% overall 2 steps).

$[\alpha]_D^{23}$ +4.2° (*c* 0.34, $CHCl_3$); TSP-MS *m/z* 913 $(M+H)^+$; ^{1}H NMR δ 1.01 (d, 19-H), 1.01 (d, 6′-H), 1.09 (s, 3″-H), 1.09 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.22 (d, 16-H), 1.46 (br ddd, 7-H), 1.78 (dd, 2″-Hax), 1.90 (m, 8-H), 1.91 (d, 2″-Heq), 2.14 (dt, 14-H), 2.32 (br d, 17-H), 2.41 (br d, 2-H), 2.41 (q, 4″-$OCOCH_2CH_3$), 2.43 (q, 4″-$OCOCH_2CH_3$), 2.49 (s, 3′-$N(CH_3)_2$), 2.75 (dd, 17-H), 3.02 (dd, 2-H), 3.22 (t, 4′-H), 3.39 (br d, 4-H), 3.51 (dd, 2′-H), 3.61 (s, 4-OCH_3), 3.79 (br d, 5-H), 4.17 (dd, 9-H), 4.41 (d, 1′-H), 4.42 (dq, 5″-H), 4.58 (d, 4″-H), 4.97 (d, 1″-H), 5.08 (ddq, 15-H), 5.49 (br d, 3-H), 5.68 (dd, 10-H), 5.86 (ddd, 13-H), 6.11 (br dd, 12-H), 6.78 (dd, 11-H), 7.61 (ddd, 3-OCO-quinoline), 7.75 (ddd, 3-OCO-quinoline), 7.86 (br d, 3-OCO-quinoline), 8.24 (d, 3-OCO-quinoline), 8.26 (d, 3-OCO-quinoline), 8.34 (br d, 3-OCO-quinoline), 9.64 (br s, 18-H).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)rokitamycin 18-Dimethylacetal (**5b**)

Reactions of RKM gave **5b** in 32% yield (overall 4 steps) by similar procedures to **5a**.

$[\alpha]_D^{23}$ −98° (*c* 1.1, $CHCl_3$); TSP-MS *m/z* 1030 $(M+H)^+$; ^{1}H NMR δ 0.69 (br t, 7-H), 0.93 (d, 19-H), 0.96 (t, 4″-$OCOCH_2CH_2CH_3$), 1.05 (d, 6″-H), 1.11 (t, 3″-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.29 (d, 16-H), 1.40 (s, 3″-CH_3), 1.45 (br dt, 7-H), 1.66 (dd, 2″-Hax), 1.68 (sex, 4″-$OCOCH_2CH_2CH_3$), 2.00 (s, 2′-$OCOCH_3$), 2.07 (dt, 14-H), 2.18 (br d, 2-H), 2.25 (q, 3″-$OCOCH_2CH_3$), 2.27 (q, 3″-$OCOCH_2CH_3$), 2.36 (t, 4″-$OCOCH_2CH_2CH_3$), 2.40 (s, 3′-$N(CH_3)_2$), 2.47 (m, 14-H), 2.55 (t, 3′-H), 2.63 (dd, 2-H), 2.94 (br d, 4-H), 3.09 (t, 4′-H), 3.17 (d, 2″-Heq), 3.18 (m, 5′-H), 3.25 (s, 18-OCH_3), 3.38 (s, 18-OCH_3), 3.44 (s, 4-OCH_3), 3.71 (br d, 3-H), 3.88 (br s, 3-OH), 4.02 (d, 5-H), 4.22 (dd, 9-H), 4.46 (dq, 5″-H), 4.47 (dd, 18-H), 4.55 (d, 4″-H), 4.67 (d, 1′-H), 4.79 (d, 1″-H), 4.93 (dd, 2′-H), 5.27 (ddq, 15-H), 5.49 (ddd, 13-H), 5.62 (dd, 10-H), 5.95 (br dd, 12-H), 6.02 (dd, 11-H).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-methylleucomycin A_7 18-Dimethylacetal (**14a**)

To a stirred solution of **5a** (40.0 mg, 41.7 μmol) in DMSO (800 μl), MeI (13.0 μl, 201 μmol) and KOH (41.0 mg, 618 μmol) were added and the reaction mixture was stirred for 1 hour at room temperature. Water was added and the aqueous layer was extracted with Et_2O. The extract was washed with brine, dried and concentrated. The residue was purified by preparative TLC [hexane-EtOAc (1 : 1)] to afford **14a** (16.4 mg, 40%).

$[\alpha]_D^{23}$ −106° (*c* 0.82, $CHCl_3$); TSP-MS *m/z* 974 $(M+H)^+$; ^{1}H NMR δ 0.96 (d, 19-H), 0.97 (br t, 7-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.28 (d, 16-H), 1.30 (br dt, 7-H), 1.77 (m, 8-H), 1.82 (dd, 2″-Hax), 1.99 (s, 2′-$OCOCH_3$), 1.99 (br d, 2-H), 2.01 (d, 2″-Heq), 2.14 (dt, 14-H), 2.38 (s, 3′-$N(CH_3)_2$), 2.42 (m, 4″-$OCOCH_2CH_3$), 2.43 (br d, 14-H), 2.66 (dd, 2-H), 2.71 (t, 3′-H), 2.87 (dd, 4-H), 3.26 (s, 18-OCH_3), 3.31 (s, 18-OCH_3), 3.38 (s, 4-OCH_3), 3.39 (s, 3-OCH_3), 3.96 (br d, 5-H), 4.18 (dd, 9-H), 4.38 (dq, 5″-H), 4.53 (dd, 18-H), 4.60 (d, 4″-H), 4.70 (d, 1′-H), 4.99 (dd, 2′-H), 5.06 (d, 1″-H), 5.30 (ddq, 15-H), 5.50 (ddd, 13-H), 5.62 (dd, 10-H), 6.03 (br dd, 12-H), 6.08 (dd, 11-H).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-methylrokitamycin 18-Dimethylacetal (**14b**)

By a similar procedure to **14a**, reaction of **5b** gave crude **14b**. This was purified by silica gel chromatography [hexane-EtOAc (5 : 1)] to give **14b** (80%).

$[\alpha]_D^{24}$ −105° (*c* 0.53, $CHCl_3$); TSP-MS *m/z* 1044 $(M+H)^+$; ^{1}H NMR δ 0.96 (d, 19-H), 0.97 (t, 4″-$OCOCH_2CH_2CH_3$), 1.05 (d, 6″-H), 1.12 (t, 3″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.28 (d, 16-H), 1.40 (s, 3″-CH_3), 1.66 (dd, 2″-Hax), 1.68 (sex, 4″-$OCOCH_2CH_2CH_3$), 2.00 (s, 2′-$OCOCH_3$), 2.14 (dt, 14-H), 2.26 (q, 3″-$OCOCH_2CH_3$), 2.28 (q, 3″-$OCOCH_2CH_3$), 2.37 (t, 4″-$OCOCH_2CH_2CH_3$), 2.40 (s, 3′-$N(CH_3)_2$), 2.59 (t, 3′-H), 2.65 (dd, 2-H), 2.84 (dd, 4-H), 3.09 (t, 4′-H), 3.17 (d, 2″-Heq), 3.19 (m, 5′-H), 3.27 (s, 18-OCH_3), 3.31 (s, 18-OCH_3), 3.39 (s, 4-OCH_3), 3.40 (s, 3-OCH_3), 3.94 (br d, 5-H), 4.17 (dd, 9-H), 4.46 (dq, 5″-H), 4.53 (dd, 18-H), 4.55 (d,

4″-H), 4.65 (d, 1′-H), 4.79 (d, 1″-H), 4.95 (dd, 2′-H), 5.08 (ddq, 15-H), 5.51 (ddd, 13-H), 5.62 (dd, 10-H), 6.02 (br dd, 12-H), 6.07 (dd, 11-H).

3-*O*-Methylleucomycin A_7 (**16a**)

A solution of **14a** (23.0 mg, 23.6 μmol) in 2.3 ml of MeOH - H_2O (9 : 1) was stirred overnight at room temperature. The reaction mixture was concentrated and the crude **15a** was diluted in 4.0 ml of MeCN - H_2O (1 : 1). To this solution difluoroacetic acid (8.3 μl, 132 μmol) was added and the reaction mixture was stirred overnight at 40°C. The solution was diluted with CH_2Cl_2, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried and concentrated. The residue was purified by preparative TLC [hexane - EtOAc (1 : 1)] to afford **16a** (4.0 mg, 22% overall 2 steps).

$[\alpha]_D^{24}$ −167° (*c* 0.40, MeOH); EI-MS *m/z* 771 $(M)^+$; ^1H NMR δ 1.05 (d, 19-H), 1.11 (d, 6′-H), 1.14 (t, 4″-$OCOCH_2CH_3$), 1.22 (d, 6″-H), 1.33 (ddd, 7-H), 1.81 (dd, 2″-Hax), 1.98 (br d, 2″-Heq), 2.15 (br d, 14-H), 2.42 (m, 4″-$OCOCH_2CH_3$), 2.47 (s, 3′-$N(CH_3)_2$), 2.70 (dd, 2-H), 2.93 (dd, 4-H), 2.93 (dq, 17-H), 3.25 (dq, 5′-H), 3.43 (s, 4-OCH_3), 3.45 (s, 3-OCH_3), 3.54 (t, 4′-H), 3.79 (br dd, 5-H), 4.11 (dd, 9-H), 4.36 (d, 1′-H), 4.45 (dq, 5″-H), 4.59 (d, 4″-H), 5.05 (d, 1″-H), 5.13 (ddq, 15-H), 5.63 (dd, 10-H), 5.63 (ddd, 13-H), 6.05 (br dd, 12-H), 6.23 (dd, 11-H), 9.77 (br s, 18-H).

3-*O*-Methylrokitamycin (**16b**)

By similar procedures to **9**, reactions of **14b** gave crude **16b** *via* **15b**. The crude **16b** was purified by preparative TLC [$CHCl_3$ - MeOH - NH_4OH (200 : 10 : 1)] to afford **16b** (66% overall 2 steps).

$[\alpha]_D^{24}$ −89° (*c* 0.51, $CHCl_3$); TSP-MS *m/z* 842 $(M+H)^+$; ^1H NMR δ 0.97 (t, 4″-$OCOCH_2CH_2CH_3$), 1.01 (d, 19-H), 1.07 (d, 6″-H), 1.10 (t, 3″-$OCOCH_2CH_3$), 1.15 (d, 6′-H), 1.29 (d, 16-H), 1.40 (s, 3″-CH_3), 1.42 (br dt, 7-H), 1.68 (sex, 4″-$OCOCH_2CH_2CH_3$), 1.68 (dd, 2″-Hax), 1.83 (m, 8-H), 2.04 (m, 6-H), 2.16 (dt, 14-H), 2.25 (q, 3″-$OCOCH_2CH_3$), 2.27 (q, 3″-$OCOCH_2CH_3$), 2.35 (t, 4″-$OCOCH_2CH_2CH_3$), 2.36 (dd, 2-H), 2.51 (s, 3′-$N(CH_3)_2$), 2.73 (dd, 2-H), 2.96 (dd, 4-H), 2.96 (dd, 17-H), 3.14 (t, 4′-H), 3.18 (m, 5′-H), 3.20 (d, 2″-Heq), 3.38 (dd, 2′-H), 3.46 (s, 4-OCH_3), 3.48 (s, 3-OCH_3), 3.86 (br d, 5-H), 4.09 (dd, 9-H), 4.38 (d, 1′-H), 4.50 (dq, 5″-H), 4.57 (d, 4″-H), 4.82 (d, 1″-H), 5.12 (ddq, 15-H), 5.62 (ddd, 13-H), 5.67 (dd, 10-H), 6.07 (br dd, 12-H), 6.26 (dd, 11-H), 9.77 (br s, 18-H).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3″-*O*-methyl-4″-*O*-(3-methylbutyl)leucomycin V 18-Dimethylacetal (**20**)

To **17** (510 mg, 0.503 mmol) was added tetrabutylammonium fluoride (1.0 M in THF, 2.5 ml, 2.5 mmol) and the reaction mixture was stirred for 15 minutes at room temperature. The reaction mixture was diluted with CH_2Cl_2 and the organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel chromatography [30 g, $CHCl_3$ - MeOH (10 : 1)] to give crude **18** (440 mg) which was used for the next step without further purification.

To a stirred solution of **18** (50.0 mg) in MeOH (1.0 ml), trimethyl orthoformate (1.0 ml) and pyridinium *p*-toluenesulfonate (30.0 mg, 119 μmol) were added and the mixture was stirred overnight at 30°C. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. The organic layer was dried and concentrated to give **19** which was used for the next step without purification.

To a stirred solution of **19** in MeCN (1.0 ml), acetic anhydride (25.0 μl, 265 μmol) was added and the mixture was stirred overnight at 30°C. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. After the organic layer was dried and concentrated, the residue was purified by silica gel chromatography [5.0 g, hexane - EtOAc (1 : 1)] to give **20** (51.0 mg, 90% overall 3 steps).

$[\alpha]_D^{24}$ −88° (*c* 1.0, $CHCl_3$); EI-MS *m/z* 987 $(M)^+$; ^1H NMR δ 0.86 (d, 4″-$OCH_2CH_2CH(CH_3)_2$), 0.91 (d, 19-H), 1.17 (d, 6-H), 1.20 (s, 3″-CH_3), 1.20 (d, 6″-H), 1.28 (d, 6-H), 1.48 (m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.98 (s, 2′-$OCOCH_3$), 2.18 (br d, 2-H), 2.18 (br d, 2″-Hax), 2.40 (s, 3′-$N(CH_3)_2$), 2.43 (br d, 14-H), 2.72 (d, 4″-H), 2.86 (dd, 4-H), 3.59 (dt, 4″-$OCH_2CH_2CH(CH_3)_2$), 3.96 (br d, 18-H), 4.18 (dd, 9-H), 4.43 (dq, 5″-H), 4.54 (br dd, 5-H), 4.68 (d, 1′-H), 4.76 (d, 1″-H), 4.91 (dd, 2′-H), 5.05 (ddq, 15-H), 5.50 (ddd, 13-H), 5.63 (dd, 10-H), 6.05 (dd, 11-H), 6.05 (br dd, 12-H).

2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3,3″-di-*O*-methyl-4″-*O*-(3-methylbutyl)leucomycin V 18-Dimethylacetal (**21**)

To a stirred solution of **20** (45.0 mg, 45.5 μmol) in DMSO (450 μl), MeI (11.0 μl, 177 μmol) and KOH (40.0 mg, 606 μmol) were added and the mixture stirred for 5 hours at room temperature. The reaction mixture was diluted with CH_2Cl_2 and the organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel chromatography [hexane - EtOAc (1 : 1)] to afford **21** (25.0 mg, 55%).

$[\alpha]_D^{24}$ −98° (*c* 1.0, $CHCl_3$); EI-MS *m/z* 1001 $(M)^+$; ^1H

NMR δ 0.86 (d, 4″-$OCH_2CH_2CH(CH_3)_2$), 0.92 (d, 19-H), 1.18 (d, 6′-H), 1.20 (s, 3″-CH_3), 1.20 (d, 6″-H), 1.28 (d, 16-H), 1.48 (m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.67 (m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.82 (m, 8-H), 1.98 (s, 2′-$OCOCH_3$), 2.07 (dt, 14-H), 2.18 (br d, 2-H), 2.18 (br d, 2″-Hax), 2.40 (s, 3′-$N(CH_3)_2$), 2.46 (br d, 14-H), 2.72 (d, 4″-H), 2.93 (br d, 4-H), 3.37 (s, 4-OCH_3), 3.44 (s, 3-OCH_3), 3.59 (dt, 4″-$OCH_2CH_2CH(CH_3)_2$), 3.71 (br d, 3-H), 4.01 (br d, 18-H), 4.21 (dd, 9-H), 4.41 (dq, 5″-H), 4.48 (br dd, 5-H), 4.70 (d, 1′-H), 4.77 (d, 1″-H), 4.88 (dd, 2′-H), 5.26 (ddq, 15-H), 5.48 (ddd, 13-H), 5.61 (dd, 10-H), 5.98 (dd, 11-H), 5.98 (br dd, 12-H).

3,3″-Di-*O*-methyl-4″-*O*-(3-methylbutyl)leucomycin V (**22**)

By similar procedures to **16a**, reactions of **21** gave crude **22**. This was purified by preparative TLC [$CHCl_3$ - MeOH - NH_4OH (400 : 20 : 1)] to afford **22** (20% overall 2 steps).

$[\alpha]_D^{24}$ −65° (*c* 0.40, MeOH); EI-MS *m/z* 799 $(M)^+$; ^1H NMR δ 0.87 (d, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.00 (d, 19-H), 1.17 (d, 6′-H), 1.21 (d, 6″-H), 1.22 (s, 3″-CH_3), 1.30 (d, 16-H), 1.55 (m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.67 (m, 4″-$OCH_2CH_2CH(CH_3)_2$), 1.88 (m, 8-H), 2.13 (dt, 14-H), 2.21 (br d, 2-H), 2.21 (br d, 2″-Hax), 2.29 (t, 3′-H), 2.32 (br dd, 17-H), 2.47 (br d, 14-H), 2.55 (s, 3′-$N(CH_3)_2$), 2.76 (dd, 2-H), 2.76 (d, 4″-H), 2.90 (br dd, 17-H), 3.23 (s, 3″-OCH_3), 3.48 (s, 4-OCH_3), 3.49 (s, 3-OCH_3), 3.60 (dt, 4″-$OCH_2CH_2CH(CH_3)_2$), 3.95 (br dd, 5-H), 4.08 (dd, 9-H), 4.41 (dq, 5″-H), 4.52 (d, 1′-H), 4.87 (d, 1″-H), 5.01 (ddq, 15-H), 5.60 (ddd, 13-H), 5.69 (dd, 10-H), 6.09 (br dd, 12-H), 6.28 (dd, 11-H), 9.76 (br s, 18-H).

Acknowledgements

We wish to thank Drs. S. HOSHIKO, H. WATABE and Mrs. M. TABATA for biological studies, and Drs. T. OKONOGI, K. ATSUMI and Mr. MIURA for valuable scientific discussion. We are also grateful to Dr. N. AMAN for providing a large amount of LM-A_7, and Drs. T. ASAKA and T. AKASHI for useful scientific discussion on macrolide antibiotics, and Mrs. TAKAGI for manuscript.

References

1) MORIMOTO, S.; Y. TAKAHASHI, Y. WATANABE & S. ŌMURA: Chemical modification of erythromycins. I. Synthesis and antibacterial activity of 6-*O*-methylerythromycins A. J. Antibiotics 37: 187~189, 1984
2) WATANABE, Y.; T. ADACHI, T. ASAKA, M. KASHIMURA & S. MORIMOTO: Chemical modification of erythromycins. VIII. A new effective route to clarithromycin (6-*O*-methylerythromycin A). Heterocycles 31: 2121~2124, 1990
3) MORIMOTO, S.; T. NAGATE, K. SUGITA, T. ONO, K. NUMATA, J. MIYACHI, Y. MISAWA, K. YAMADA & S. OMURA: Chemical modification of erythromycins. III. *In vitro* and *in vivo* antibacterial activities of new semisynthetic 6-*O*-methylerythromycins A, TE-031 (clarithromycin) and TE-032. J. Antibiotics 43: 295~305, 1990
4) KOHNO, Y.; H. YOSHIDA, T. SUWA & T. SUGA: Comparative pharmacokinetics of clarithromycin (TE-031), a new macrolide antibiotic, and erythromycin in rats. Antimicrob. Agents Chemother. 33: 751~756, 1989
5) ADACHI, T.; S. MORIMOTO, H. KONDOH, T. NAGATE, Y. WATANABE & K. SOTA: 14-Hydroxy-6-*O*-methylerythromycins A, active metabolites of 6-*O*-methylerythromycin A in human. J. Antibiotics 41: 966~975, 1988
6) DJOKIÆ, S.; G. KOBREHEL, G. LAZAREVSKI, N. LOPOTAR & Z. TAMBURASEV: Erythromycin series. Part 11. Ring expansion of erythromycin A oxime by the Beckmann rearrangement. J. Chem. Soc. Perkin Trans. I 1986: 188~1890, 1986
7) BRIGHT, G. M.; A. A. NAGEL, J. BORDNER, K. A. DESAI, J. N. DIBRINO, J. NOWAKOWSKA, L. VINCENT, R. M. WATROUS, F. C. SCIAVOLINO, A. R. ENGLISH, J. A. RETSEMA, M. R. ANDERSON, L. A. BRENNAN, R. J. BOROVOY, C. R. CIMOCHOWSKI, J. A. FAIELLA, A. E. GIRARD, D. GIRARD, C. HERBERT, M. MANOUSOS & R. MASON: Synthesis, *in vitro* and *in vivo* activity of novel 9-deoxo-9a-aza-9a-homoerythromycin A derivatives; A new class of macrolide antibiotics, the azalides. J. Antibiotics 41: 1029~1047, 1988
8) RETSEMA, J.; A. GIRARD, W. SCHELKLY, M. MANOUSOS, M. ANDERSON, G. BRIGHT, R. BOROVOY, L. BRENNAN & R. MASON: Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against Gram-negative oraganisms. Antimicrob. Agents Chemother. 31: 1939~1947, 1987
9) DENIS, A.; C. AGOURIDAS, J-M. AUGER, Y. BENEDETTI, A. BONNEFOY, F. BRETIN, J-F. CHANTOT, A. DUSSARAT, C. FROMENTIN, S. G. D'AMBRIERES, S. LACHAUD, P. LAURIN, O. L. MARTRET, V. LOYAU, N. TESSOT, J-M. PEJAC & S. PERRON: Synthesis and antibacterial activity of HMR 3647. A new ketolide highly potent against erythromycin-resistant and susceptible pathogens. Bioorg. Med. Chem. Lett. 44: 3075~3080, 1999
10) OR, Y. S.; R. F. CLARK, S. WANG, D. T. W. CHU, A. M. NILIUS, R. K. FLAMM, M. MITTEN, P. EWING, J. ALDER & Z. MA: Design, synthesis, and antimicrobial activity of 6-*O*-substituted ketolides active against resistant respiratory tract pathogens. J. Med. Chem. 43: 1045~1049, 2000
11) MA, Z.; R. F. CLARK, A. BRAZZALE, S. WANG, M. J. RUPP, L. LI, G. GRIESGRABER, S. ZHANG, H. YONG, L. T. PHAN, P. A. NEMOTO, D. T. W. CHU, J. J. PLATTNER, X. ZHANG, P. ZHONG, Z. CAO, A. M. NILIUS, V. D. SHORTRIDGE, R. FLAMM, M. MITTEN, J. MEULBROEK, P. EWING, J. ALDER & Y. S. OR: Novel Erythromycin Derivatives with Aryl Groups Tethered to the C-6 Position are Potent Protein Synthesis Inhibitors and Active against Multidrug-Resistant Respiratory Pathogens. J. Med. Chem. 44: 4137~4156, 2001

12) OMOTO, S.; K. IWAMATSU, S. INOUYE & T. NIIDA: Modifications of a macrolide antibiotic midecamycin (SF-837) I. Synthesis and structure of 9,3″-diacetylmidecamycin. J. Antibiotics 29: 536~548, 1976
13) KAWAHARAJO, K.; Y. SEKIZAWA & M. INOUE: *In vitro* and *in vivo* antibacterial activity of 9,3″-di-*O*-acetyl midecamycin (MOM), a new macrolide antibiotic. J. Antibiotics 34: 436~442, 1981
14) SAKAKIBARA, H.; O. OKEKAWA, T. FUJIWARA, M. OTANI & S. ŌMURA: Acyl derivatives of 16-membered macrolides I. Synthesis and biological properties of 3″-*O*-propionylleucomycin A_5 (TMS-19-Q). J. Antibiotics 34: 1001~1010, 1981
15) SAKAKIBARA, H.; O. OKEKAWA, T. FUJIWARA, M. AIZAWA & S. ŌMURA: Acyl derivatives of 16-membered macrolides II. Antibacterial activities and serum levels of 3″-*O*-acyl derivatives of leucomycin. J. Antibiotics 34: 1011~1018, 1981
16) KURIHARA, K.; N. KIKUCHI & K. AJITO: Cladinose analogues of sixteen-membered macrolide antibiotics III. Efficient synthesis of 4-*O*-alkyl-L-cladinose analogues: Improved antibacterial activities compatible with pharmacokinetics. J. Antibiotics 50: 32~44, 1997
17) AJITO, K.; K. KURIHARA, S. SHIBAHARA, O. HARA, A. SHIMIZU, M. ARAAKE & S. OMOTO: Cladinose analogues of sixteen-membered macrolide antibiotics II. Preparation of pharmacokinetically improved analogues *via* biotransformation. J. Antibiotics 50: 92~95, 1997
18) INOUE, A.; T. DEGUCHI, M. YOSHIDA & K. SHIRAHATA: Biosynthesis and the metabolic fate of carbon-14 labeled spiramycin I. J. Antibiotics 36: 442~444, 1983
19) ŌMURA, S. & A. NAKAGAWA: Chemical and biological studies on 16-membered macrolide antibiotics. J. Antibiotics 28: 401~433, 1975
20) TSURUOKA, T.; T. SHOMURA, N. EZAKI, H. WATANABE, E. AKITA, S. INOUYE & T. NIIDA: Studies on antibiotic SF-837, a new antibiotic. I. The producing microorganism and isolation and characterization of the antibiotic. J. Antibiotics 24: 452~459, 1971
21) INOUYE, S.; T. TSURUOKA, T. SHOMURA, S. OMOTO & T. NIIDA: Studies on antibiotic SF-837, a new antibiotic. II. Chemical structure of antibiotic SF-837. J. Antibiotics 24: 460~475, 1971
22) SHIMIZU, A.; S. GOMI, K. AJITO, T. YAGUCHI, E. TANAKA, O. HARA & S. MIYADOH (Meiji Seika Kaisha, LTD.): Process for producing 3-deacylated derivative of 16-membered macrolide antibiotic. U.S. 5,219,736, Jun. 15, 1993
23) CREEMER, L. C.; J. E. TOTH & H. A. KIRST: Synthesis and *in vitro* antimicrobial activity of 3-keto 16-membered macrolides derived from tylosin. J. Antibiotics 55: 427~436, 2002
24) KINUMAKI, A.; K. HARADA, T. FURUMAI & M. SUZUKI: Mass spectrometry of platenolides and their derivatives in connection with structure elucidation. J. Antibiotics 29: 1209~1217, 1976
25) FREIBERG, L. A.; R. S. EGAN & W. H. WASHBURN: The synthesis of 9-*epi*-leucomycin A_3. The revised configurational assignment of C-9 in natural leucomycin A_3. J. Org. Chem. 39: 2474~2475, 1974
26) TANIKAWA, T.; T. ASAKA, M. KASHIMURA, Y. MISAWA, K. SUZUKI, M. SATO, K. KAMEO, S. MORIMOTO & A. NISHIDA: Synthesis and antibacterial activity of acylides (3-*O*-acyl-erythromycin derivatives): A novel class of macrolide antibiotics. J. Med. Chem. 44: 4027~4030, 2001
27) ŌMURA, S.; H. SANO, K. YAMASHITA & M. OKAJI (Kyowa Hakko Co., Ltd., Japan): 3-*O*-Alkyl-3″,4″-di-*O*-acylspiramycin I. JP 61126096 , Jun. 13, 1986