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Design and synthesis of novel leucomycin analogues modified at the C-3 position. Part II: 3-*O*-(3-Aryl-2-propenyl)leucomycin analogues

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Abstract—The design and synthesis of 16-membered macrolides modified at the C-3 position are described. Starting from fully protected intermediate (**5**), appropriate modifications including Heck reaction were performed to furnish 3-*O*-(3-aryl-2-propenyl)leucomycin A_7 analogues (**9a**–**9m**). These leucomycin A_7 derivatives showed improved in vitro antibacterial activities against clinically important pathogens including erythromycin-resistant *Streptococcus pneumoniae* (ERSP). SAR analysis of derivatives modified at the C-3 and C-3″ positions suggested that single modification at C-3 or C-3″ was effective for in vitro antibacterial activity.

1. Introduction

Macrolide antibiotics have been used in the treatment of bacterial infections for many years. They inhibit protein biosynthesis by binding to ribosomal RNA (rRNA) of the bacterial ribosome to exhibit antibiotic activities. Clarithromycin[1–5] (Fig. 1) and azithromycin[6–8] (Fig. 1) are synthesized from 14-membered erythromycin. They are the representatives of widely used macrolides and have clinical importance. Ketolides have been developed as one of the next generation macrolides, and telithromycin[9] (Fig. 1) has been recently launched as a promising antibiotic. It is effective against important critical pathogens including MLS resistant *Streptococcus pneumoniae* and penicillin-resistant *S. pneumoniae* (PRSP). Enanta has found a new ketolide, S-013420[10] (Fig. 1) which is now under clinical trials. Although telithromycin exhibits strong potency against resistant bacteria of *S. pneumoniae*, it is still influenced by efflux pumps of resistant *S. pneumoniae*. Its clinical usage in pediatrics is not allowed because it has not been proven to be safe. On the other hand, some of the 16-membered macrolides, such as miokamycin (MOM)[11,12] and rokitamycin (RKM)[13,14] (Fig. 2) are not affected by efflux pumps. These two semisynthetic 16-membered macrolide antibiotics have been already proven to be safe in clinical use. Thus, drug discovery in the field of 16-membered macrolides is important for anti-infective chemotherapy in the future.

In the previous paper,[15] we synthesized 3-*O*-methyl analogues of three key 16-membered macrolides in our research (Fig. 3), and successfully improved both antibacterial activity and biological stability. We also found that a quinoline side chain in 3-*O*-[(2-quinolyl)carbonyl]leucomycin A_7 (Fig. 3) was effective to overcome resistants of *S. pneumoniae*. Being encouraged by these results and SAR studies in ketolides,[9,16,17] we decided to introduce a hetero aromatic ring which would coordinate with a new binding site of rRNA with an appropriate spacer. The spacer should be attached via ether bond, as we have already confirmed its stability under metabolic condition.

2. Results and discussion

2.1. Synthesis and evaluation of 3-*O*-[3-(3-quinolyl)-2-propenyl]rokitamycin

Since RKM is the most potent 16-membered macrolide in clinical use, we first synthesized 3-*O*-[3-(3-quinolyl)-

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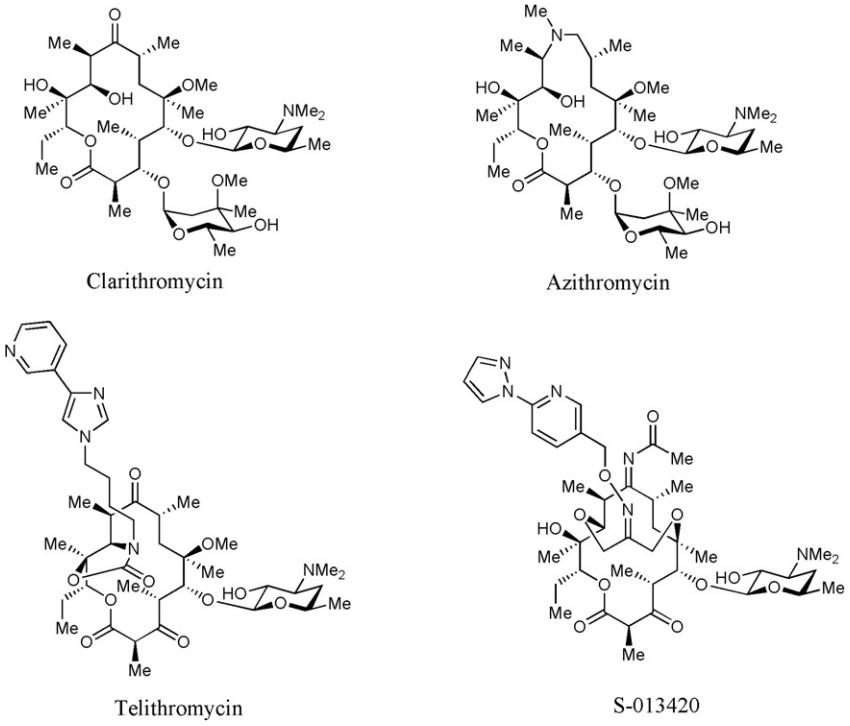
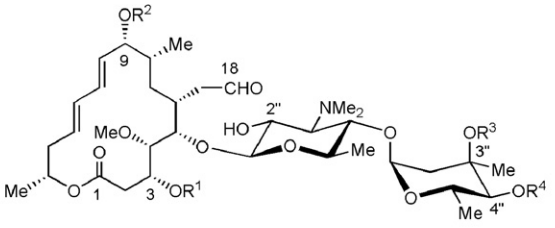


Figure 1. Structures of representative semisynthetic macrolides.



	R^1	R^2	R^3	R^4
Leucomycin A_7 (LM-A_7)	H	H	H	COEt
Miokamycin (MOM)	COEt	Ac	Ac	COEt
Rokitamycin (RKM)	H	H	COEt	CO^{n}Pr

Figure 2. Leucomycin A_7 and semisynthetic 16-membered macrolides, MOM and RKM.

2-propenyl]rokitamycin (**4**) from the previously reported intermediate (**1**)[15] as shown in Scheme 1. Fully protected RKM (**1**) was allylated using KOH and allyl iodide to give 3-*O*-allyl derivative (**2**) in 70% based on the recovery of the starting material. Heck reaction of **2** with 3-bromoquinoline was performed under Jeffery's condition[18] to introduce the quinoline side chain onto the allyl group at the C-3 position. After removal of the acetyl group on the C-2′ hydroxyl group, the TBS group and the dimethyl acetal were simultaneously deprotected[15] to furnish **4**.

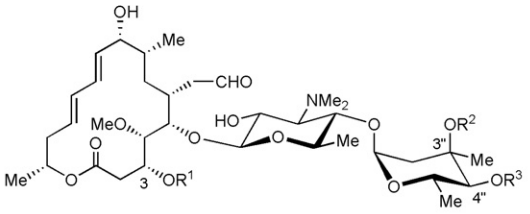
In vitro antibacterial activities of 3-*O*-[3-(3-quinolyl)-2-propenyl]rokitamycin (**4**) is shown in Table 1. Compound **4** was much less active than RKM against target microorganisms. Although methylation of the C-3 hydroxyl group of RKM resulted in enhancement of antibiotic activity,[15] the bulky quinoline moiety caused an inappropriate effect.

By the way, X-ray crystallographic analysis of RKM 18-methylhemiacetal implied that the propionyl group at the C-3″ position extended toward macrolide aglycon (Fig. 4).[19] This information led us to a hypothesis that a large substituent at the C-3 position caused steric repulsion between C-3 and C-3″ side chains. As a result, the quinolylpropenyl side chain at the C-3 hydroxyl group in the RKM analogue prevented the C-3″ propionyl group from coordinating with rRNA binding site to decrease its antibiotic activity.

This hypothesis prompted us to modify the C-3 position of leucomycin A_7 (LM-A_7, Fig. 2) which has a free hydroxyl group at the C-3″ position in order to evaluate substantial potency of a variety of arylalkyl side chains at the C-3 position.

2.2. Synthesis and evaluation of 3-*O*-(3-aryl-2-propenyl)leucomycin A_7 analogues

Synthesis of 3-*O*-(3-aryl-2-propenyl)leucomycin A_7 analogues (**9a**–**9m**) is shown in Scheme 2. All steps were conducted almost in the same way as in RKM derivatives shown in Scheme 1. Allyl ether (**6**) was obtained by using KOH and allyl iodide in 63% based on the recovery of the starting material (**5**). Palladium catalyzed allylation[20] turned out to be an alternative method for this allylation and we obtained **6** in 44% yield (71% based on the recovery of **5**). While we were introducing a variety of



3-*O*-Methylleucomycin A_7: R^1 = Me, R^2 = H, R^3 = COEt

3-*O*-Methylrokitamycin: R^1 = Me, R^2 = COEt, R^3 = CO^nPr

3, 3"- Di-*O*-methyl-4"-*O*-(3-methylbutyl)leucomycin V: R^1 = Me, R^2 = Me, R^3 = $CH_2CH_2CH(CH_3)_2$

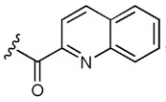
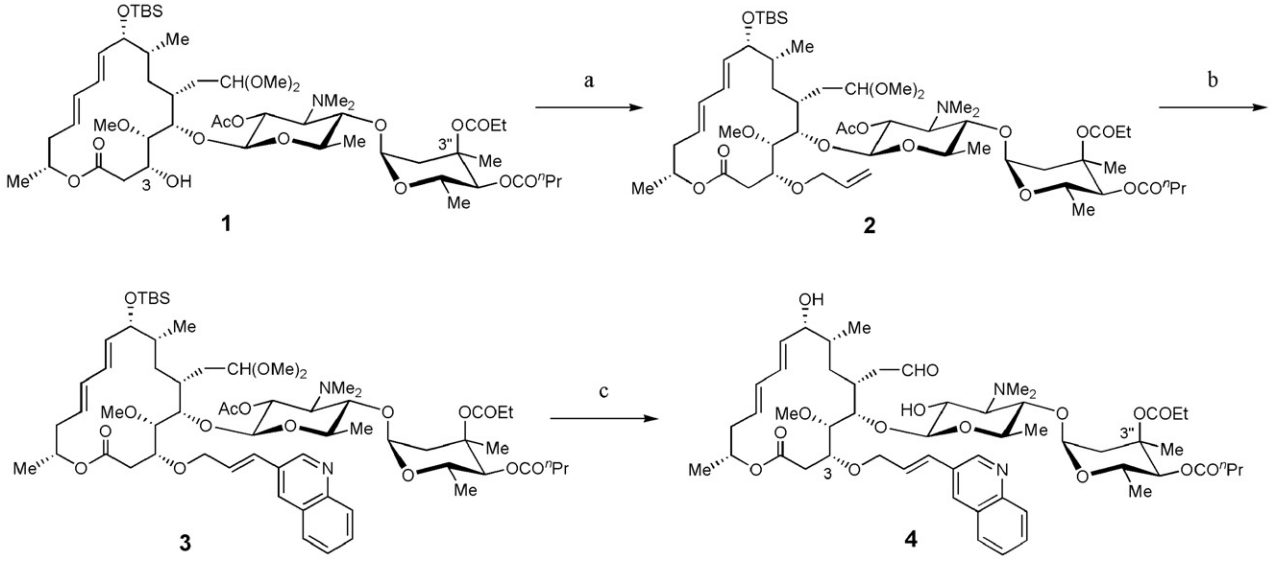
3-*O*-[(2-Quinolyl)carbonyl]leucomycin A_7: R^1 =  , R^2 = H, R^3 = COEt

Figure 3. Previously reported leucomycin analogues modified at the C-3 position.



Scheme 1. Synthesis of 3-*O*-[3-(3-quinolyl)-2-propenyl]rokitamycin (**4**). Reagents and conditions: (a) KOH, allyl iodide, DMSO, rt, 4 h, 35%, 70% based on the recovery of **1**; (b) $Pd(OAc)_2$, 3-bromoquinoline, K_2CO_3, *n*-Bu_4NCl, DMF, 50 °C, 4 d, 41%; (c) i—MeOH/H_2O (9:1), 50 °C, 22 h, 89%; ii—CHF_2COOH, MeCN/H_2O (1:1), rt, 2 d, 62%.

aromatic side chains to **6** by Heck reaction, we found that an allylic double bond was isomerized. After examining many reaction conditions, this isomerization was effectively prevented by using palladacycle[21] or $PdCl_2$. With fully modified intermediates (**7a**–**7m**) at hand, tandem removal of the acetyl group, the TBS group and the dimethyl acetal was conducted to furnish **9a**–**9m**.

Table 2 shows in vitro antibacterial activities of **9a**–**9m**. Most of the derivatives exhibited stronger antibiotic activities than LM-A_7 as we expected. Generally speaking, in vitro activity of LM-A_7 is half as strong as RKM because LM-A_7 lacks propionyl side chain at the C-3″ position (Fig. 2). However, introducing an appropriate arylalkyl group at the C-3 position resulted in enhancing in vitro activity against susceptible strains in *Staphylococcus aureus* and *S. pneumoniae* to overcome even RKM (see compounds **9a**–**9e**, **9h**, and **9m**). Some side chains at the C-3 position seemed to compensate for the propionyl group at C-3″ in RKM. Similar effects were observed when we focused on resistant strains. Although LM-A_7 is inactive against the inducible resistant strains, C-3 aromatic rings played a role to enhance antibacterial activities of LM-A_7 as the C-3″ propionyl moiety did in RKM (see compounds **9a**–**9c** and **9m**). As far as we know, compound **9m** was the first 16-membered leucomycin analogue that was active against constitutively resistant *S. pneumoniae* (**9a** was also somewhat active). Some potent ketolides also possess effective side chains containing imidazole[9,10] (Fig. 1) or quinoline[16,17] ring. Basic nitrogen atoms of these hetero aromatic rings seemed to enhance the rRNA binding abilities of **9m** and **9a**, and increased their antimicrobial activities. These results suggested that

Table 1. Antibacterial activities of 3-*O*-[3-(3-quinolyl)-2-propenyl]rokitamycin (**4**)

Test organisms	Characteristics	**4**	RKM	CAM
Staphylococcus aureus 209P JC-1	Standard	1	0.13	0.13
Staphylococcus aureus #2	Susceptible	2	0.25	0.13
Staphylococcus aureus #3	Susceptible	1	0.13	0.13
Staphylococcus aureus #4	*ermA* methylase(c*)	>128	>128	>128
Staphylococcus aureus #5	*ermB* methylase(i**)	1	0.13	>128
Staphylococcus aureus #6	*ermC* methylase(i**)	2	0.25	4
Streptococcus pneumoniae DP1 Type I	Standard	0.25	0.06	0.015
Streptococcus pneumoniae #2	Susceptible	0.25	0.13	0.03
Streptococcus pneumoniae #3	*ermB* methylase(c*)	>128	>128	>128
Streptococcus pneumoniae #4	*ermB* methylase(c*)	>128	>128	>128
Streptococcus pneumoniae #5	*ermB* methylase(i**)	8	4	>128
Streptococcus pneumoniae #6	*ermB* methylase(i**)	8	4	>128
Streptococcus pneumoniae #7	*mefA* efflux	0.25	0.13	0.5
Streptococcus pneumoniae #8	*mefA* efflux	0.25	0.06	0.5
Streptococcus pyogenes #1	Standard	0.25	0.06	0.015
Streptococcus pyogenes #2	*ermB* methylase(c*)	32	>128	>128
Streptococcus pyogenes #3	*mefA* efflux	0.25	0.06	4
Moraxella catarrhalis #1	Standard	2	0.13	0.13
Moraxella catarrhalis #2	Standard	4	0.13	0.13
Haemophilus influenzae #1	Standard	>128	2	2
Haemophilus influenzae #2	Standard	>128	4	8
Haemophilus influenzae #3	Susceptible	>128	8	8

c*, constitutive resistant; i**, inducible resistant.

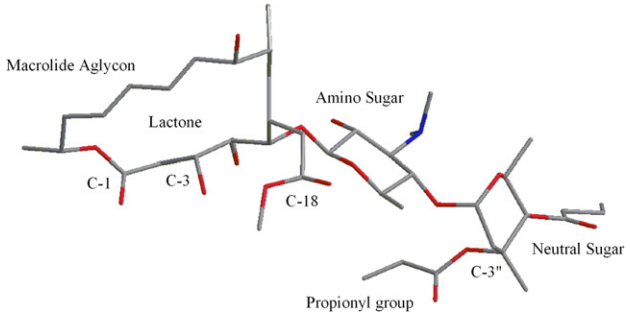


Figure 4. X-ray single crystallographic analysis of RKM (18-methylhemiacetal).

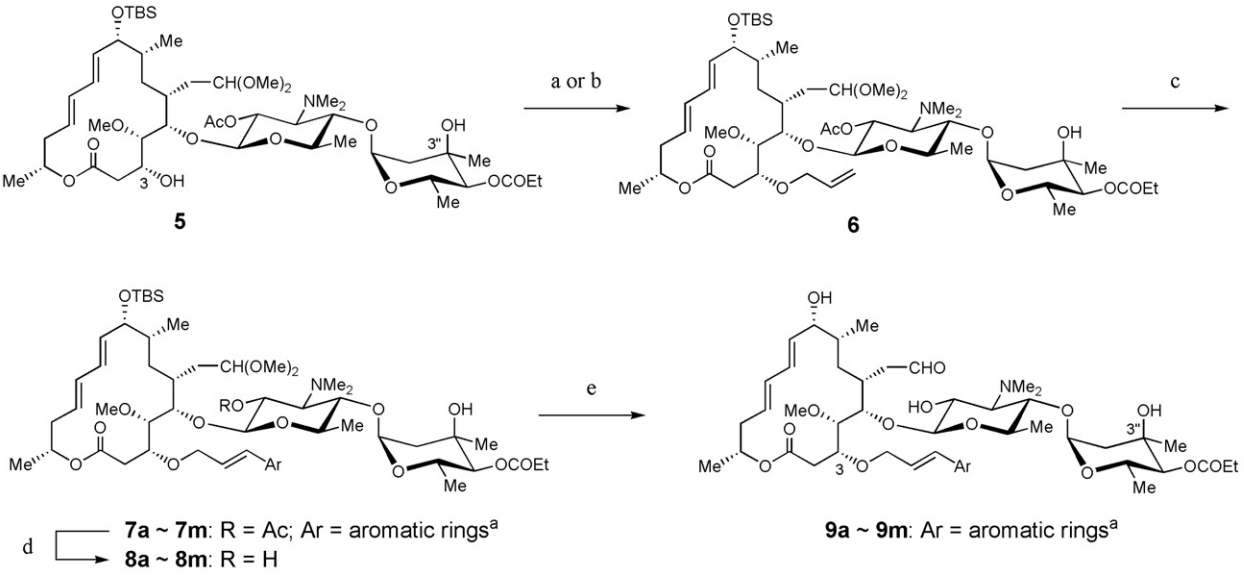
16-membered macrolides could also overcome resistant microorganisms, which encouraged us to explore new chemical modifications of 16-membered macrolide antibiotics.

2.3. Synthesis and biological evaluation of 3″-*O*-(3-phenylpropionyl)leucomycin A_7

To investigate the relationship between the C-3 and C-3″ position, we synthesized 3″-*O*-(3-phenylpropionyl)leucomycin A_7 (**12**) which had a bulky side chain at the C-3″ position and free hydroxyl group at the C-3 position (Scheme 3). Preparation of the starting material (**10**) was already reported by Kurihara et al.[22] Free hydroxyl group of **10** was acylated by 3-phenylpropionyl chloride to furnish **11** in application of the reported procedure for RKM synthesis.[3] After deprotection of the C-2′ acetyl group, the TBS acetal was successfully removed by diluted TBAF in THF without migration of C-10–C-12 double bonds. Acidic hydrolysis of the TBS group at the C-9 position was subsequently conducted to give **12**.

As shown in Table 3, the in vitro antibacterial profile of **12** was similar to that of RKM. Compound **12** exhibited strong activities against susceptible G (+) strains and was also effective against inducible resistant *S. pneumoniae*.

With the results observed above, we concluded that single modification at either C-3 or C-3″ position was promising, but modifying both of them caused reduction of antibacterial activities. Although we tried to determine the conformations of **4**, **9a**–**9m** and **12**, we did not succeed in crystallization or NMR analyses of these compounds. Then we carried out conformational analyses on newly introduced side chains at the C-3 and/or C-3″ positions of **4**, **9a**, and **12**.[23] Our calculation results implied that two sugar moieties of the minimized structure of **4** were dislocated upward from their original position (refer to the sugar moieties of RKM in Fig. 4), which presumably decreased its antibiotic activity. Furthermore, the C-3 quinoline ring and the C-3″ propionyl side chain of **4** seemed to be placed close indicating that there was a van der Waals interaction between these side chains. The minimized structures of **9a** and **12** were almost identical with that of RKM without any shift of the sugar moieties. More interestingly, the quinoline ring at the C-3 position of **9a** and the benzene ring at the C-3″ position of **12** seemed to be able to overlap three-dimensionally. Although the conformational analyses were performed only on the side chains at the C-3 and/or C-3″ positions, SARs of our leucomycin derivatives were efficiently explained by our molecular modeling studies.



Scheme 2. Synthesis of 3-*O*-(3-aryl-2-propenyl)leucomycin A_7 analogues (**9a**–**9m**). Reagents and conditions: (a) KOH, allyl iodide, DMSO, rt, 2 h, 27%, 63% based on the recovery of **5**; (b) $Pd_2(dba)_3$, 1,4-bis(diphenylphosphino)butane, allyl ethyl carbonate, THF, 90 °C, sealed tube, 25 h, 44%, 71% based on the recovery of **5**; (c) palladium catalysts, aryl halides (see Section 4), 22–66%; (d) MeOH/H_2O (10:1), 50 °C, 36 h–3 d; (e) CHF_2COOH, MeCN/H_2O (1:1), rt, 37 h–5 d, 53–78% overall two steps. [a]Aromatic rings: (a) 3-quinolyl; (b) 4-isoquinolyl; (c) phenyl; (d) 3-pyridyl; (e) 5-pyrimidinyl; (f) 1-naphthyl; (g) 2-naphthyl; (h) 4-nitrophenyl; (i) 4-methoxyphenyl; (j) 4-fluorophenyl; (k) 4-trifluoromethylphenyl; (l) 4-biphenylyl; (m) 4-(1-imidazolyl)phenyl.

3. Conclusion

On the basis of the SAR analysis of our reported in-house compounds and ketolides, we synthesized and evaluated a variety of 3-*O*-(3-aryl-2-propenyl)leucomycin A_7 analogues (**9a**–**9m**). As a result, we successfully improved antibacterial activity against clinically important microorganisms including resistant strains. We confirmed that the single modification at the C-3 position is promising for in vitro activity. Introduction of side chains only at the C-3″ position was also effective as we discussed in **2.3.** However, it was unsuccessful to modify both C-3 and C-3″ positions simultaneously. Together with the X-ray information of RKM and our results of conformational analyses on **4**, **9a**, and **12**, these experimental data suggested that side chains at the C-3 and C-3″ positions in leucomycin analogues would occupy three-dimensionally overlapped spaces.

To explore novel possibilities of macrolide antibiotics, other modifications of 16-membered macrolides (i.e. western hemisphere) are now undergoing. Using our information about the C-3 and C-3″ positions, we will continuously explore novel modification focusing on clinically promising 16-membered macrolides for the next generation.

4. Experimental

4.1. 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 and HRMS 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, the organic layer was dried with anhydrous Na_2SO_4, evaporation and concentration were carried out under reduced pressure below 35 °C, unless otherwise noted.

4.2. Antibacterial activity in vitro

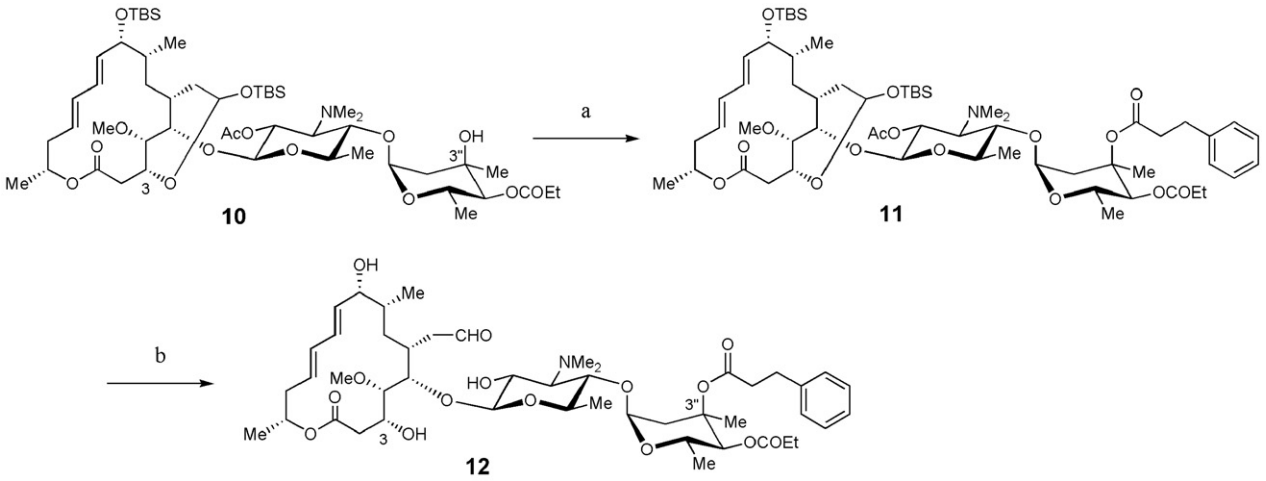
Minimum inhibitory concentration (MIC) was determined by the agar dilution method. Test strains were subjected to seed culture using sensitivity test broth (STB, Nissui Pharmaceutical) for *S. aureus*, or cultured on blood agar plate for *S. pneumoniae*, *Streptococcus pyogenes*, *Moraxella catarrhalis*, 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, 5 μg/ml hemin and 15 μg/ml nicotinamide adenine dinucleotide and incubated at 37 °C for 20 h. Then, MIC was measured.

4.2.1. 2′-*O*-Acetyl-3-*O*-allyl-9-*O*-(*tert*-butyldimethylsilyl)-rokitamycin 18-dimethylacetal (2). To a stirred solution of **1** (101 mg, 97.6 μmol) in 0.5 ml of DMSO, allyl iodide (0.100 ml, 1.09 mmol) and KOH (77.9 mg, 1.18 mmol) were added and the reaction mixture was stirred for 4 h at room temperature. Water was added to the reaction mixture and the aqueous layer was extracted with Et_2O. The extract was washed with 10% aqueous $Na_2S_2O_3$ solution, water, saturated aqueous $NaHCO_3$

Table 2. Antibacterial activities of 3-*O*-(3-aryl-2-propenyl)leucomycin A_7 analogues (**9a**–**9m**)

Test organisms	Characteristics	**9a**	**9b**	**9c**	**9d**	**9e**	**9f**	**9g**	**9h**	**9i**	**9j**	**9k**	**9l**	**9m**	LM-A_7	RKM	CAM
Staphylococcus aureus 209P JC-1	Standard	0.06	0.06	0.13	0.13	0.13	0.13	0.25	0.06	0.13	0.13	0.5	1	0.13	0.25	0.13	0.13
Staphylococcus aureus #2	Susceptible	0.13	0.13	0.25	0.25	0.25	0.25	0.25	0.13	0.25	0.25	1	2	0.25	0.5	0.25	0.13
Staphylococcus aureus #3	Susceptible	0.06	0.06	0.13	0.13	0.13	0.25	0.25	0.13	0.13	0.13	0.5	1	0.13	0.25	0.13	0.13
Staphylococcus aureus #4	*ermA* methylase(c*)	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
Staphylococcus aureus #5	*ermB* methylase(i**)	0.06	0.06	0.13	0.13	0.13	0.25	0.25	0.06	0.13	0.13	0.5	1	0.13	0.25	0.13	>128
Staphylococcus aureus #6	*ermC* methylase(i**)	0.13	0.13	0.13	0.25	0.25	0.25	0.5	0.13	0.25	0.25	1	2	0.25	0.5	0.25	4
Streptococcus pneumoniae DP1 Type I	Standard	0.03	0.015	0.03	0.03	0.03	0.03	0.06	0.06	0.06	0.06	0.25	0.25	0.03	0.13	0.06	0.015
Streptococcus pneumoniae #2	Susceptible	0.03	0.015	0.06	0.03	0.06	0.03	0.06	0.06	0.06	0.13	0.5	0.25	0.03	0.25	0.13	0.03
Streptococcus pneumoniae #3	*ermB* methylase(c*)	64	>128	128	>128	>128	>128	>128	>128	>128	>128	>128	>128	16	>128	>128	>128
Streptococcus pneumoniae #4	*ermB* methylase(c*)	64	>128	64	>128	>128	>128	>128	>128	>128	>128	>128	>128	32	>128	>128	>128
Streptococcus pneumoniae #5	*ermB* methylase(i**)	32	128	64	>128	>128	>128	>128	>128	>128	>128	>128	>128	0.5	>128	4	>128
Streptococcus pneumoniae #6	*ermB* methylase(i**)	16	32	64	>128	>128	8	8	128	16	>128	>128	>128	2	>128	4	>128
Streptococcus pneumoniae #7	*mefA* efflux	0.03	<0.008	0.03	0.03	0.06	0.03	0.06	0.06	0.06	0.13	0.5	0.25	0.06	0.13	0.13	0.5
Streptococcus pneumoniae #8	*mefA* efflux	0.015	0.015	0.015	0.015	0.03	0.03	0.06	0.06	0.06	0.25	1	2	0.03	0.13	0.06	0.5
Streptococcus pyogenes #1	Standard	0.03	0.015	0.03	0.03	0.06	0.06	0.06	0.03	0.06	0.06	0.25	0.25	0.06	0.13	0.06	0.015
Streptococcus pyogenes #2	*ermB* methylase(c*)	64	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
Streptococcus pyogenes #3	*mefA* efflux	0.06	0.06	0.06	0.03	0.13	0.25	0.25	0.13	0.13	0.13	0.5	0.5	0.13	0.25	0.06	4
Moraxella catarrhalis #1	Standard	0.5	0.5	0.5	0.5	0.5	1	1	0.5	1	1	4	8	1	1	0.13	0.13
Moraxella catarrhalis #2	Standard	0.5	0.5	1	1	1	1	2	1	1	1	4	8	1	1	0.13	0.13
Haemophilus influenzae #1	Standard	2	1	2	1	1	4	8	2	4	4	32	>128	2	2	2	2
Haemophilus influenzae #2	Standard	8	4	8	8	8	16	32	8	16	8	>128	>128	8	8	4	8
Haemophilus influenzae #3	Susceptible	4	4	8	4	8	16	16	8	8	16	>128	>128	8	8	8	8

c*, constitutive resistant; i**, inducible resistant.



Scheme 3. Synthesis of 3″-*O*-(3-phenylpropionyl)leucomycin A_7 (**12**). Reagents and conditions: (a) 3-phenylpropionyl chloride, tribenzylamine, 1,2-dichloroethane, 75 °C, 2 d, 56%; (b) i—MeOH/H_2O (10:1), 45 °C, overnight, 78%; ii—0.1 M TBAF, THF, rt, 15 min; iii—CHF_2COOH, MeCN/H_2O (1:1), rt, overnight, 82% overall three steps.

Table 3. Antibacterial activities of 3″-*O*-(3-phenylpropionyl)leucomycin A_7 (**12**)

Test organisms	Characteristics	**12**	RKM	CAM
Staphylococcus aureus 209P JC-1	Standard	0.10	0.10	0.10
Staphylococcus aureus #2	Susceptible	0.39	0.39	0.10
Staphylococcus aureus #3	Susceptible	0.20	0.20	0.10
Staphylococcus aureus #4	*ermA* methylase(c*)	>100	>100	>100
Staphylococcus aureus #5	*ermB* methylase(i**)	0.20	0.39	>100
Staphylococcus aureus #6	*ermC* methylase(i**)	0.20	0.20	3.13
Streptococcus pneumoniae DP1 Type I	Standard	0.05	0.05	0.025
Streptococcus pneumoniae #2	Susceptible	0.10	0.10	0.025
Streptococcus pneumoniae #3	*ermB* methylase(c*)	>100	100	>100
Streptococcus pneumoniae #4	*ermB* methylase(c*)	>100	>100	>100
Streptococcus pneumoniae #5	*ermB* methylase(i**)	1.56	0.78	>100
Streptococcus pneumoniae #6	*ermB* methylase(i**)	3.13	1.56	>100
Streptococcus pneumoniae #7	*mefA* efflux	0.10	0.10	0.78
Streptococcus pneumoniae #8	*mefA* efflux	0.10	0.10	0.78
Streptococcus pyogenes #1	Standard	0.025	0.05	0.013
Streptococcus pyogenes #2	*ermB* methylase(c*)	>100	100	>100
Streptococcus pyogenes #3	*mefA* efflux	0.025	0.05	1.56
Moraxella catarrhalis #1	Standard	0.05	0.10	0.10
Moraxella catarrhalis #2	Standard	0.20	0.20	0.10
Haemophilus influenzae #1	Standard	1.56	1.56	1.56
Haemophilus influenzae #2	Standard	6.25	3.13	3.13
Haemophilus influenzae #3	Susceptible	6.25	6.25	3.13

c*, constitutive resistant; i**, inducible resistant.

solution, and brine. After the organic layer was dried and concentrated, the residue was purified by silica gel chromatography [14 g, hexane/EtOAc (20:1–10:1–5:1–1:1)] to give **2** (37.0 mg, 35%, 70% based on the recovery of **1**).

$[\alpha]_D^{22}$ −103° (*c* 0.58, $CHCl_3$); FAB-MS *m*/*z* 1070 $(M+H)^+$; ^1H NMR δ −0.04 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.95 (d, 6.6 Hz, 3H, 19-H), 0.96 (t, 7.3 Hz, 3H, 4″-$OCOCH_2CH_2CH_3$), 1.04 (d, 6.0 Hz, 3H, 6″-H), 1.11 (t, 7.6 Hz, 3H, 3″-$OCOCH_2CH_3$), 1.17 (d, 5.8 Hz, 3H, 6′-H), 1.19–1.32 (m, 1H, 7-H), 1.27 (d, 6.3 Hz, 3H, 16-H), 1.39 (s, 3H, 3″-CH_3), 1.50–1.82 (m, 3H, 8-, 17-H), 1.65 (dd, 14.5, 3.9 Hz, 1H, 2″-Hax), 1.67 (sex, 7.4 Hz, 2H, 4″-$OCOCH_2CH_2CH_3$), 2.00 (s, 3H, 2′-$OCOCH_3$), 2.11 (dt, 14.3, 10.4 Hz, 1H, 14-H), 2.15–2.36 (m, 2H, 3″-$OCOCH_2CH_3$), 2.36 (t, 7.4 Hz, 2H, 4″-$OCOCH_2CH_2CH_3$), 2.36–2.47 (m, 1H, 2-H), 2.39 (s, 6H, 3′-$N(CH_3)_2$), 2.40–2.44 (m, 1H, 14-H), 2.59 (t, 10.0 Hz, 1H, 3′-H), 2.66 (dd, 16.7, 6.0 Hz, 1H, 2-H), 2.78 (dd, 3.8, 1.0 Hz, 1H, 4-H), 3.07 (t, 9.5 Hz, 1H, 4′-H), 3.16 (d, 14.5 Hz, 1H, 2″-Heq), 3.15–3.22 (m, 1H, 5′-H), 3.27 (s, 3H, 18-OCH_3), 3.30 (s, 3H, 18-OCH_3), 3.38 (s, 3H, 4-OCH_3), 3.48 (br, 1H, 3-H), 3.92 (br dd, 12.0, 5.9 Hz, 1H, 3-O–$CH_2CH{=}CH_2$), 3.98 (br dd, 12.0, 5.9 Hz, 1H, 3-O–$CH_2CH{=}CH_2$), 4.15 (dd, 7.4, 3.8 Hz, 1H, 9-H), 4.18 (br d, 5.8 Hz, 1H, 5-H), 4.45 (dq, 9.9, 6.0 Hz, 1H, 5″-H), 4.49 (dd, 8.4, 3.0 Hz, 1H, 18-H), 4.54 (d,

9.9 Hz, 1H, 4″-H), 4.62 (d, 7.7 Hz, 1H, 1′-H), 4.77 (d, 3.9 Hz, 1H, 1″-H), 4.94 (dd, 10.3, 7.7 Hz, 1H, 2′-H), 5.08–5.15 (m, 1H, 15-H), 5.16 (dd, 10.3, 1.3 Hz, 1H, 3-O–CH_2CH=CH_2), 5.25 (dd, 17.2, 1.5 Hz, 1H, 3-O–CH_2CH=CH_2), 5.52 (ddd, 14.5, 10.4, 3.8 Hz, 1H, 13-H), 5.59 (dd, 13.4, 7.4 Hz, 1H, 10-H), 5.89 (ddt, 17.0, 10.4, 5.9 Hz, 1H, 3-O–CH_2CH=CH_2), 5.97–6.10 (m 2H, 11-, 12-H).

4.2.2. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(3-quinolyl)-2-propenyl]rokitamycin 18-dimethylacetal (3). To a stirred solution of **2** (71.4 mg, 66.7 μmol), potassium carbonate (27.8 mg, 201 μmol), tetra-*n*-butylammonium chloride (77.9 mg, 281 μmol) and palladium(II) acetate (2.6 mg, 11.6 μmol) in 0.7 ml of DMF, 3-bromoquinoline (36.0 μl, 265 μmol) was added. After the reaction mixture was stirred for 4 days at 50 °C, EtOAc was added to the reaction mixture and filtrated. The organic layer was washed with water, saturated $NaHCO_3$ solution, and brine. After the organic layer was dried and concentrated, the residue was purified by silica gel chromatography [7 g, hexane/EtOAc (3:1)] to give **3** (32.5 mg, 41%).

$[\alpha]_D^{22}$ −68° (*c* 0.87, $CHCl_3$); FAB-MS *m*/*z* 1197 $(M+H)^+$; ^{1}H NMR δ −0.04 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.95 (d, 6.6 Hz, 3H, 19-H), 0.96 (t, 7.4 Hz, 3H, 4″-$OCOCH_2CH_2CH_3$), 1.04 (d, 6.0 Hz, 3H, 6″-H), 1.11 (t, 7.5 Hz, 3H, 3″-$OCOCH_2CH_3$), 1.12 (d, 6.6 Hz, 3H, 6′-H), 1.20–1.32 (m, 1H, 7-H), 1.28 (d, 6.3 Hz, 3H, 16-H), 1.39 (s, 3H, 3″-CH_3), 1.54–1.84 (m, 3H, 8-, 17-H), 1.61 (dd, 15.3, 4.2 Hz, 1H, 2″-Hax), 1.67 (sex, 7.4 Hz, 2H, 4″-$OCOCH_2CH_2CH_3$), 2.02 (s, 3H, 2′-$OCOCH_3$), 2.12 (dt, 13.7, 10.8 Hz, 1H, 14-H), 2.16–2.34 (m, 2H, 3″-$OCOCH_2CH_3$), 2.35 (t, 7.4 Hz, 2H, 4″-$OCOCH_2CH_2CH_3$), 2.35–2.47 (m, 2H, 2-, 14-H), 2.40 (s, 6H, 3′-$N(CH_3)_2$), 2.59 (t, 9.9 Hz, 1H, 3′-H), 2.75 (dd, 15.9, 7.2 Hz, 1H, 2-H), 2.91 (dd, 7.6, 2.3 Hz, 1H, 4-H), 3.09 (t, 9.5 Hz, 1H, 4′-H), 3.12 (d, 15.3 Hz, 1H, 2″-Heq), 3.16–3.28 (m, 1H, 5′-H), 3.20 (s, 3H, 18-OCH_3), 3.25 (s, 3H, 18-OCH_3), 3.44 (s, 3H, 4-OCH_3), 3.64 (br, 1H, 3-H), 4.02 (br, 1H, 5-H), 4.15 (dd, 8.1, 3.9 Hz, 1H, 9-H), 4.30 (br dd, 12.1, 5.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.37 (br dd, 12.1, 5.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.45 (dq, 9.9, 6.0 Hz, 1H, 5″-H), 4.53 (d, 9.9 Hz, 1H, 4″-H), 4.55 (m, 1H, 18-H), 4.68 (d, 7.5 Hz, 1H, 1′-H), 4.74 (d, 4.2 Hz, 1H, 1″-H), 4.96 (dd, 10.2, 7.8 Hz, 1H, 2′-H), 5.12 (m, 1H, 15-H), 5.52 (m, 1H, 13-H), 5.62 (dd, 13.9, 8.2 Hz, 1H, 10-H), 5.96–6.11 (m, 2H, 11-, 12-H), 6.54 (dt, 16.2, 5.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.75 (d, 16.2 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.52 (ddd, 7.9, 6.9, 1.2 Hz, 1H, quinoline), 7.65 (ddd, 8.4, 7.0, 1.3 Hz, 1H, quinoline), 7.83 (dd, 7.8, 0.9 Hz, 1H, quinoline), 8.04 (br d, 8.4 Hz, 1H, quinoline), 8.06 (s, 1H, quinoline), 8.98 (d, 2.4 Hz, 1H, quinoline).

4.2.3. 3-*O*-[3-(3-Quinolyl)-2-propenyl]rokitamycin (4). A solution of **3** (120 mg, 100 μmol) in 6 ml of MeOH/H_2O (9:1) was stirred for 22 h at 50 °C. The reaction mixture was concentrated and the residue was purified by silica gel chromatography [12 g, $CHCl_3$/MeOH (100:1–50:1)] to give 9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(3-quinolyl)-2-propenyl]rokitamycin 18-dimethylacetal (103 mg, 89%).

To a stirred solution of this compound (95.7 mg, 82.8 μmol) in 28 ml of MeCN/H_2O (1:1), difluoroacetic acid (27.0 μl, 429 μmol) was added and the reaction mixture was stirred for 2 days at room temperature. Saturated $NaHCO_3$ solution was added to the reaction mixture and the aqueous layer was extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated. The residue was purified by preparative TLC [$CHCl_3$/MeOH/NH_4OH (100:10:1)] to afford **4** (51.0 mg, 62%).

$[\alpha]_D^{24}$ −32° (*c* 0.59, $CHCl_3$); FAB-MS *m*/*z* 995 $(M+H)^+$; ^{1}H NMR δ 0.95 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_2CH_3$), 1.00 (d, 6.6 Hz, 3H, 19-H), 1.02 (d, 6.9 Hz, 3H, 6′-H), 1.03 (t, 7.4 Hz, 3H, 3″-$OCOCH_2CH_3$), 1.05 (d, 6.0 Hz, 3H, 6″-H), 1.10 (m, 1H, 7-H), 1.29 (d, 6.0 Hz, 3H, 16-H), 1.37 (s, 3H, 3″-CH_3), 1.39 (m, 1H, 7-H), 1.62 (dd, 15.2, 4.3 Hz, 1H, 2″-Hax), 1.66 (sex, 7.5 Hz, 2H, 4″-$OCOCH_2CH_2CH_3$), 1.83 (m, 1H, 8-H), 2.08–2.20 (m, 2H, 6-, 14-H), 2.12–2.25 (m, 2H, 3″-$OCOCH_2CH_3$), 2.28–2.46 (m, 4H, 2-, 14-, 17-, 3′-H), 2.34 (t, 7.1 Hz, 2H, 4″-$OCOCH_2CH_2CH_3$), 2.50 (s, 6H, 3′-$N(CH_3)_2$), 2.81 (dd, 15.6, 7.8 Hz, 1H, 2-H), 2.96 (dd, 18.0, 9.9 Hz, 1H, 17-H), 3.01 (dd, 7.8, 2.1 Hz, 1H, 4-H), 3.06–3.16 (m, 1H, 5′-H), 3.13 (t, 8.1 Hz, 1H, 4′-H), 3.13 (d, 15.2 Hz, 1H, 2″-Heq), 3.36 (dd, 10.1 Hz, 1H, 2′-H), 3.51 (s, 3H, 4-OCH_3), 3.73 (br, 1H, 3-H), 3.91 (br, 1H, 5-H), 4.09 (br dd, 8.4, 3.9 Hz, 1H, 9-H), 4.34 (dd, 12.0, 5.7 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.42 (d, 7.8 Hz, 1H, 1′-H), 4.44 (dd, 12.0, 5.7 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.46 (m, 1H, 5″-H), 4.53 (d, 9.9 Hz, 1H, 4″-H), 4.76 (d, 4.0 Hz, 1H, 1″-H), 5.11 (m, 1H, 15-H), 5.60 (ddd, 14.5, 10.5, 3.9 Hz, 1H, 13-H), 5.67 (dd, 14.8, 8.4 Hz, 1H, 10-H), 6.05 (br dd, 14.7, 10.7 Hz, 1H, 12-H), 6.24 (dd, 15.1, 10.4 Hz, 1H, 11-H), 6.63 (dt, 15.9, 6.0 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.78 (d, 15.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.49 (ddd, 7.8, 6.9, 1.2 Hz, 1H, quinoline), 7.63 (ddd, 8.4, 6.9, 1.3 Hz, 1H, quinoline), 7.81 (dd, 7.5, 1.0 Hz, 1H, quinoline), 8.04 (d, 8.4 Hz, 1H, quinoline), 8.10 (d, 1.8 Hz, 1H, quinoline), 9.02 (d, 2.4 Hz, 1H, quinoline), 9.75 (br s, 1 H, 18-H); HRMS: Calcd for $C_{54}H_{78}N_2O_{15}$: 995.5480. Found: 995.5478.

4.2.4. 2′-*O*-Acetyl-3-*O*-allyl-9-*O*-(*tert*-butyldimethylsilyl)leucomycin A_7 18-dimethylacetal (6). *Method a*. To a stirred solution of **5** (0.545 g, 0.567 mmol) in 5 ml of DMSO, allyl iodide (0.520 ml, 5.69 mmol) and KOH (0.519 g, 7.87 mmol) were added and the reaction mixture was stirred for 2 h at room temperature. Water was added to the reaction mixture and the aqueous layer was extracted with Et_2O. The extract was washed with 10% aqueous $Na_2S_2O_3$ solution, water, saturated aqueous $NaHCO_3$ solution, and brine. After the organic layer was dried and concentrated, the residue was purified by silica gel chromatography [40 g, hexane/EtOAc (2:1)] to give **6** (154 mg, 27%, 63% based on the recovery of **5**).

Method b. A solution of **5** (0.706 g, 0.735 mmol), tris(dibenzylideneacetone)dipalladium (16.3 mg, 17.8 μmol), 1,4-bis(diphenylphosphino)butane (31.3 mg, 73.4 μmol) and allyl ethyl carbonate (0.970 ml, 7.38 mmol) in 7 ml of THF was stirred at 90 °C for 25 h in sealed tube. The reaction mixture was concentrated and the residue was purified by silica gel chromatography [25 g, hexane/EtOAc (2:1)] to give **6** (326 mg, 44%, 71% based on the recovery of **5**).

$[\alpha]_D^{21}$ −103° (*c* 0.42, $CHCl_3$); FAB-MS *m*/*z* 1000 $(M+H)^+$; ^1H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.96 (d, 6.9 Hz, 3H, 19-H), 1.10 (s, 3H, 3″-CH_3), 1.10–1.15 (m, 1H, 7-H), 1.11 (d, 6.2 Hz, 3H, 6″-H), 1.16 (t, 7.7 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.20–1.33 (m, 1H, 7-H), 1.25 (d, 5.7 Hz, 3H, 6′-H), 1.27 (d, 6.3 Hz, 3H, 16-H), 1.53–1.63 (m, 1H, 17-H), 1.65–1.80 (m, 3H, 6-, 8-, 17-H), 1.82 (dd, 14.5, 3.9 Hz, 1H, 2″-Hax), 1.99 (br d, 14.5 Hz, 1H, 2″-Heq), 2.01 (s, 3H, 2′-$OCOCH_3$), 2.12 (dt, 13.8, 10.8 Hz, 1H, 14-H), 2.36–2.47 (m, 2H, 4″-$OCOCH_2CH_3$), 2.37–2.48 (m, 2H, 2-, 14-H), 2.38 (s, 6H, 3′-$N(CH_3)_2$), 2.67 (dd, 16.2, 6.3 Hz, 1H, 2-H), 2.71 (t, 10.6 Hz, 1H, 3′-H), 2.81 (dd, 7.6, 2.0 Hz, 1H, 4-H), 3.23–3.33 (m, 2H, 4′-, 5′-H), 3.27 (s, 3H, 18-OCH_3), 3.31 (s, 3H, 18-OCH_3), 3.38 (s, 3H, 4-OCH_3), 3.50 (br, 1H, 3-H), 3.97 (br dd, 12.3, 6.0 Hz, 1H, 3-O–$CH_2CH{=}CH_2$), 3.97 (br, 1H, 5-H), 4.16 (br dd, 12.3, 6.0 Hz, 1H, 3-O–$CH_2CH{=}CH_2$), 4.16 (dd, 7.5, 4.1 Hz, 1H, 9-H), 4.37 (dq, 10.2, 6.2 Hz, 1H, 5″-H), 4.49 (dd, 8.6, 2.9 Hz, 1H, 18-H), 4.60 (d, 10.2 Hz, 1H, 4″-H), 4.67 (d, 7.8 Hz, 1H, 1′-H), 4.99 (dd, 10.4, 7.7 Hz, 1H, 2′-H), 5.05 (d, 3.6 Hz, 1H, 1″-H), 5.13 (dq, 10.2, 1.8 Hz, 1H, 3-O–$CH_2CH{=}CH_2$), 5.13 (m, 15-H), 5.25 (dq, 17.1, 1.8 Hz, 1H, 3-O–$CH_2CH{=}CH_2$), 5.51 (m, 13-H), 5.60 (dd, 13.8, 7.5 Hz, 1H, 10-H), 5.90 (ddt, 17.1, 10.2, 6.0 Hz, 1H, 3-O–$CH_2CH{=}CH_2$), 5.98–6.10 (m, 2H, 11-, 12-H).

4.2.5. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(3-quinolyl)-2-propenyl]leucomycin A_7 18-dimethylacetal (7a).

To a stirred solution of **6** (268 mg, 268 μmol), sodium acetate (83.7 mg, 1.01 mmol), *trans*-di(μ-acetato)bis[*O*-(di-*O*-tolylphosphino)benzyl]dipalladium(II) (48.1 mg, 51.3 μmol) and tetra-*n*-butylammonium bromide (1.55 g, 4.81 mmol) in 6.0 ml of *N*,*N*-dimethylacetamide, 3-bromoquinoline (110 μl, 810 μmol) was added and the reaction mixture was stirred for 17 h at 100 °C. EtOAc was added to the reaction mixture and the organic layer was washed with 10% aqueous $KHSO_4$ solution, saturated $NaHCO_3$ solution, and brine. After the organic layer was dried and concentrated, the residue was purified by silica gel chromatography [35 g, hexane/EtOAc (2:1–1:1)] to give **7a** (142 mg, 47%).

$[\alpha]_D^{22}$ −62° (*c* 0.53, $CHCl_3$); FAB-MS *m*/*z* 1127 $(M+H)^+$; ^1H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, 6.6 Hz, 3H, 19-H), 1.04 (s, 3H, 3″-CH_3), 1.08 (d, 6.3 Hz, 3H, 6″-H), 1.15 (d, 6.0 Hz, 3H, 6′-H), 1.15 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.29 (d, 6.3 Hz, 3H, 16-H), 1.55–1.84 (m, 4H, 6-, 8-, 17-H), 1.68 (dd, 14.1, 3.9 Hz, 1H, 2″-Hax), 1.76 (br d, 14.1 Hz, 1H, 2″-Heq), 2.02 (s, 3H, 2′-$OCOCH_3$), 2.13 (dt, 13.9, 10.8 Hz, 1H, 14-H), 2.35–2.47 (m, 2H, 4″-$OCOCH_2CH_3$), 2.35–2.49 (m, 2H, 2-, 14-H), 2.37 (s, 6H, 3′-$N(CH_3)_2$), 2.71 (t, 10.0 Hz, 1H, 3′-H), 2.75 (dd, 15.9, 6.9 Hz, 1H, 2-H), 2.90 (dd, 7.8, 1.8 Hz, 1H, 4-H), 3.20–3.33 (m, 2H, 4′-, 5′-H), 3.24 (s, 3H, 18-OCH_3), 3.29 (s, 3H, 18-OCH_3), 3.43 (s, 3H, 4-OCH_3), 3.60 (br, 1H, 3-H), 4.04 (br, 1H, 5-H), 4.16 (dd, 8.0, 4.0 Hz, 1H, 9-H), 4.24 (br dd, 12.2, 5.8 Hz, 1H, 3-O–$CH_2CH{=}CH$–Ar), 4.34 (dq, 10.2, 6.3 Hz, 1H, 5″-H), 4.39 (br dd, 12.3, 5.7 Hz, 1H, 3-O–$CH_2CH{=}CH$–Ar), 4.55 (d, 10.2 Hz, 1H, 4″-H), 4.57 (m, 1H, 18-H), 4.72 (d, 7.8 Hz, 1H, 1′-H), 4.95 (d, 3.5 Hz, 1H, 1″-H), 5.00 (dd, 10.3, 7.7 Hz, 1H, 2′-H), 5.15 (m, 1H, 15-H), 5.54 (m, 1H, 13-H), 5.62 (dd, 14.6, 8.0 Hz, 1H, 10-H), 5.97–6.12 (m, 2H, 11-, 12-H), 6.55 (dt, 15.9, 5.9 Hz, 1H, 3-O–$CH_2CH{=}CH$–Ar), 6.76 (d, 16.2 Hz, 1H, 3-O–$CH_2CH{=}CH$–Ar), 7.51 (ddd, 8.0, 7.1, 0.9 Hz, 1H, quinoline), 7.65 (ddd, 8.2, 6.9, 1.2 Hz, 1H, quinoline), 7.77 (dd, 8.1, 1.2 Hz, 1H, quinoline), 8.03 (d, 1.5 Hz, 1H, quinoline), 8.04 (d, 8.1 Hz, 1H, quinoline), 8.97 (d, 1.8 Hz, 1H, quinoline).

4.2.6. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(4-isoquinolyl)-2-propenyl]leucomycin A_7 18-dimethylacetal (7b).

To a stirred solution of **6** (439 mg, 439 μmol), sodium acetate (133 mg, 1.62 mmol), *trans*-di(μ-acetato)bis[*O*-(di-*O*-tolylphosphino)benzyl]dipalladium(II) (44.0 mg, 46.9 μmol), and tetra-*n*-butylammonium bromide (2.83 g, 8.78 mmol) in 5.0 ml of DMF, 4-bromoisoquinoline (276 mg, 1.33 mmol) was added and the reaction mixture was stirred for 3 days at 100 °C. EtOAc was added to the reaction mixture and the organic layer was washed with 10% aqueous $KHSO_4$ solution, saturated $NaHCO_3$ solution, and brine. After the organic layer was dried and concentrated, the residue was purified by silica gel chromatography [60 g, hexane/EtOAc (2:1)] to give **7b** (231 mg, 47%).

$[\alpha]_D^{21}$ −72° (*c* 0.68, $CHCl_3$); FAB-MS *m*/*z* 1127 $(M+H)^+$; ^1H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, 6.6 Hz, 3H, 19-H), 1.08 (d, 6.1 Hz, 3H, 6″-H), 1.09 (s, 3H, 3″-CH_3), 1.10 (d, 6.0 Hz, 3H, 6′-H), 1.16 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.20–1.33 (m, 1H, 7-H), 1.30 (d, 6.3 Hz, 3H, 16-H), 1.55–1.68 (m, 1H, 17-H), 1.68–1.88 (m, 3H, 6-, 8-, 17-H), 1.74 (dd, 14.2, 3.7 Hz, 1H, 2″-Hax), 1.84 (br d, 14.0 Hz, 1H, 2″-Heq), 2.02 (s, 3H, 2′-$OCOCH_3$), 2.14 (dt, 14.1 Hz, 1H, 14-H), 2.34–2.50 (m, 2H, 4″-$OCOCH_2CH_3$), 2.34–2.52 (m, 2H, 2-, 14-H), 2.37 (s, 6H, 3′-$N(CH_3)_2$), 2.68 (t, 9.8 Hz, 1H, 3′-H), 2.78 (dd, 16.0, 6.8 Hz, 1H, 2-H), 2.90 (dd, 7.8, 1.8 Hz, 1H, 4-H), 3.17–3.28 (m, 2H, 4′-, 5′-H), 3.21 (s, 3H, 18-OCH_3), 3.24 (s, 3H, 18-OCH_3), 3.44 (s, 3H, 4-OCH_3), 3.65 (br, 1H, 3-H), 4.05 (br, 1H, 5-H), 4.16 (dd, 7.9, 3.8 Hz, 1H, 9-H), 4.30 (br dd, 12.3, 6.0 Hz, 1H, 3-O–$CH_2CH{=}CH$–Ar), 4.34 (dq, 9.9, 6.1 Hz, 1H, 5″-H), 4.45 (br dd, 12.3, 6.0 Hz, 1H, 3-O–$CH_2CH{=}CH$–Ar), 4.55 (dd, 8.1, 3.3 Hz, 1H, 18-H), 4.57 (d, 9.9 Hz, 1H, 4″-H), 4.72 (d, 7.8 Hz, 1H, 1′-H), 4.91 (d, 3.3 Hz, 1H, 1″-H), 4.99 (dd, 10.3, 7.8 Hz, 1H, 2′-H), 5.17 (m, 1H, 15-H), 5.55 (m, 1H, 13-H), 5.63 (dd, 13.8, 8.1 Hz, 1H, 10-H), 5.96–6.12 (m, 2H, 11-, 12-H), 6.41 (dt, 15.8, 5.9 Hz, 1H, 3-O–$CH_2CH{=}CH$–Ar), 7.22 (d, 15.8 Hz,

1H, 3-O–CH_2CH=CH–Ar), 7.61 (br t, 7.5 Hz, 1H, isoquinoline), 7.72 (ddd, 8.1, 7.1, 1.2 Hz, 1H, isoquinoline), 7.96 (br d, 8.1 Hz, 1H, isoquinoline), 8.10 (br d, 8.1 Hz, 1H, isoquinoline), 8.60 (s, 1H, isoquinoline), 9.14 (s, 1H, isoquinoline).

4.2.7. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-(3-phenyl-2-propenyl)leucomycin A_7 18-dimethylacetal (7c). Reaction of **6** (198 mg, 198 μmol) with iodobenzene (67.0 μl, 601 μmol) gave **7c** (161 mg, 76%) by a similar procedure to **7b**.

$[\alpha]_D^{22}$ −75° (*c* 0.62, $CHCl_3$); FAB-MS *m*/*z* 1076 $(M+H)^+$; ^1H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.96 (d, 6.6 Hz, 3H, 19-H), 1.09 (s, 3H, 3″-CH_3), 1.09 (d, 6.3 Hz, 3H, 6″-H), 1.12 (d, 6.0 Hz, 3H, 6′-H), 1.16 (t, 7.6 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.18–1.32 (m, 1H, 7-H), 1.28 (d, 6.6 Hz, 3H, 16-H), 1.55–1.64 (m, 1H, 17-H), 1.65–1.86 (m, 3H, 6-, 8-, 17-H), 1.73 (dd, 14.2, 3.4 Hz, 1H, 2″-Hax), 1.82 (br d, 14.0 Hz, 1H, 2″-Heq), 2.01 (s, 3H, 2′-$OCOCH_3$), 2.13 (dt, 13.8, 10.3 Hz, 1H, 14-H), 2.36–2.47 (m, 2H, 4″-$OCOCH_2CH_3$), 2.36–2.52 (m, 2H, 2-, 14-H), 2.37 (s, 6H, 3′-$N(CH_3)_2$), 2.70 (t, 10.0 Hz, 1H, 3′-H), 2.72 (dd, 16.5, 6.6 Hz, 1H, 2-H), 2.83 (dd, 7.5, 1.8 Hz, 1H, 4-H), 3.18–3.32 (m, 2H, 4′-, 5′-H), 3.25 (s, 3H, 18-OCH_3), 3.29 (s, 3H, 18-OCH_3), 3.41 (s, 3H, 4-OCH_3), 3.55 (br, 1H, 3-H), 4.00 (br, 1H, 5-H), 4.13 (br dd, 12.0, 6.0 Hz, 1H, 3-O–CH_2CH=CH–Ph), 4.15 (dd, 7.5, 3.7 Hz, 1H, 9-H), 4.34 (br dd, 12.0, 6.0 Hz, 1H, 3-O–CH_2CH=CH–Ph), 4.35 (dq, 10.0, 6.3 Hz, 1H, 5″-H), 4.54 (m, 1H, 18-H), 4.57 (d, 9.9 Hz, 1H, 4″-H), 4.69 (d, 7.8 Hz, 1H, 1′-H), 4.91 (d, 3.0 Hz, 1H, 1″-H), 4.99 (dd, 10.5, 7.8 Hz, 1H, 2′-H), 5.16 (m, 1H, 15-H), 5.53 (m, 1H, 13-H), 5.60 (dd, 13.8, 7.5 Hz, 1H, 10-H), 5.96–6.10 (m, 2H, 11-, 12-H), 6.30 (dt, 15.9, 5.9 Hz, 1H, 3-O–CH_2CH=CH–Ph), 6.57 (d, 15.9 Hz, 1H, 3-O–CH_2CH=CH–Ph), 7.15–7.38 (m, 5H, Ph).

4.2.8. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(3-pyridyl)-2-propenyl]leucomycin A_7 18-dimethylacetal (7d). Reaction of **6** (215 mg, 215 μmol) with 3-bromopyridine (63.0 μl, 654 μmol) gave **7d** (56.1 mg, 24%) by a similar procedure to **7b**.

$[\alpha]_D^{22}$ −69° (*c* 0.52, $CHCl_3$); FAB-MS *m*/*z* 1077 $(M+H)^+$; ^1H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.96 (d, 6.6 Hz, 3H, 19-H), 1.00–1.12 (m, 1H, 7-H), 1.08 (d, 6.3 Hz, 3H, 6″-H), 1.09 (s, 3H, 3″-CH_3), 1.14 (d, 6.0 Hz, 3H, 6′-H), 1.16 (t, 7.6 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.20–1.32 (m, 1H, 7-H), 1.28 (d, 6.3 Hz, 3H, 16-H), 1.61 (m, 1H, 17-H), 1.68–1.82 (m, 3H, 6-, 8-, 17-H), 1.77 (dd, 14.1, 3.4 Hz, 1H, 2″-Hax), 1.88 (br d, 14.1 Hz, 1H, 2″-Heq), 2.01 (s, 3H, 2′-$OCOCH_3$), 2.13 (dt, 13.9, 10.8 Hz, 1H, 14-H), 2.36–2.47 (m, 2H, 4″-$OCOCH_2CH_3$), 2.36–2.49 (m, 2H, 2-, 14-H), 2.37 (s, 6H, 3′-$N(CH_3)_2$), 2.70 (t, 10.0 Hz, 1H, 3′-H), 2.72 (dd, 16.0, 6.9 Hz, 1H, 2-H), 2.88 (dd, 7.6, 1.5 Hz, 1H, 4-H), 3.19–3.31 (m, 2H, 4′-, 5′-H), 3.24 (s, 3H, 18-OCH_3), 3.28 (s, 3H, 18-OCH_3), 3.42 (s, 3H, 4-OCH_3), 3.57 (br, 1H, 3-H), 4.00 (br, 1H, 5-H), 4.15 (dd, 8.0, 4.0 Hz, 1H, 9-H), 4.18 (br dd, 12.6, 5.8 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.34 (br dd, 12.6, 5.8 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.35 (dq, 1H, 10.2, 6.3 Hz, 5″-H), 4.55 (m, 1H, 18-H), 4.58 (d, 10.2 Hz, 1H, 4″-H), 4.69 (d, 7.5 Hz, 1H, 1′-H), 4.96 (d, 3.0 Hz, 1H, 1″-H), 4.99 (dd, 10.3, 7.7 Hz, 1H, 2′-H), 5.13 (m, 1H, 15-H), 5.52 (m, 1H, 13-H), 5.62 (dd, 14.1, 8.0 Hz, 1H, 10-H), 5.97–6.10 (m, 2H, 11-, 12-H), 6.38 (dt, 16.1, 5.8 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.57 (d, 15.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.23 (dd, 7.8, 4.8 Hz, 1H, pyridine), 7.68 (dt, 7.8, 1.8 Hz, 1H, pyridine), 8.44 (dd, 4.5, 1.5 Hz, pyridine), 8.56 (d, 1.8 Hz, 1H, pyridine).

4.2.9. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(5-pyrimidinyl)-2-propenyl]leucomycin A_7 18-dimethylacetal (7e). Reaction of **6** (306 mg, 306 μmol) with 5-bromopyrimidine (148 mg, 933 μmol) gave **7e** (177 mg, 54%) by a similar procedure to **7b**.

$[\alpha]_D^{21}$ −66° (*c* 0.63, $CHCl_3$); FAB-MS *m*/*z* 1078 $(M+H)^+$; ^1H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, 6.6 Hz, 3H, 19-H), 1.06 (m, 1H, 7-H), 1.10 (s, 3H, 3″-CH_3), 1.10 (d, 6.0 Hz, 3H, 6″-H), 1.16 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.18 (d, 6.0 Hz, 3H, 6′-H), 1.26–1.34 (m, 1H, 7-H), 1.29 (d, 6.3 Hz, 3H, 16-H), 1.62 (m, 1H, 17-H), 1.70–1.86 (m, 3H, 6-, 8-, 17-H), 1.80 (dd, 14.1, 3.6 Hz, 1H, 2″-Hax), 1.96 (br d, 14.1 Hz, 1H, 2″-Heq), 2.02 (s, 3H, 2′-$OCOCH_3$), 2.13 (dt, 14.2, 10.8 Hz, 1H, 14-H), 2.36–2.50 (m, 2H, 2-, 14-H), 2.36–2.50 (m, 2H, 4″-$OCOCH_2CH_3$), 2.38 (s, 6H, 3′-$N(CH_3)_2$), 2.71 (t, 10.0 Hz, 1H, 3′-H), 2.73 (dd, 16.2, 7.2 Hz, 1H, 2-H), 2.92 (dd, 7.8, 2.4 Hz, 1H, 4-H), 3.20–3.33 (m, 2H, 4′-, 5′-H), 3.24 (s, 3H, 18-OCH_3), 3.26 (s, 3H, 18-OCH_3), 3.43 (s, 3H, 4-OCH_3), 3.61 (br, 1H, 3-H), 3.99 (br, 1H, 5-H), 4.15 (dd, 8.4, 3.9 Hz, 1H, 9-H), 4.25 (br dd, 12.7, 4.4 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.36 (br dd, 12.7, 4.4 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.36 (dq, 10.5, 6.0 Hz, 1H, 5″-H), 4.56 (m, 1H, 18-H), 4.59 (d, 10.5 Hz, 1H, 4″-H), 4.71 (d, 7.5 Hz, 1H, 1′-H), 5.00 (dd, 10.3, 7.5 Hz, 1H, 2′-H), 5.00 (d, 3.0 Hz, 1H, 1″-H), 5.11 (m, 1H, 15-H), 5.51 (m, 1H, 13-H), 5.63 (dd, 13.8, 8.4 Hz, 1H, 10-H), 5.97–6.10 (m, 2H, 11-, 12-H), 6.48 (dt, 16.2, 4.5 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.54 (d, 16.2 Hz, 1H, 3-O–CH_2CH=CH–Ar), 8.71 (s, 1H, pyrimidine), 9.05 (s, 1H, pyrimidine).

4.2.10. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(1-naphthyl)-2-propenyl]leucomycin A_7 18-dimethylacetal (7f). To a stirred solution of **6** (214 mg, 214 μmol), $PdCl_2$ (9.4 mg, 53 μmol), 1,3-bis(diphenylphosphino)propane (40.6 mg, 98.4 μmol), and $NaHCO_3$ (75.9 mg, 903 μmol) in 4.0 ml of DMF, 1-bromonaphthalene (90.0 μl, 643 μmol) was added and the reaction mixture was stirred for 3 days at 100 °C. EtOAc was added to the reaction mixture and the organic layer was washed with water and brine. After the organic layer was dried and concentrated, the residue was purified by silica gel chromatography [20 g, hexane/EtOAc (4:1–3:1)] to give **7f** (157 mg, 65%).

$[\alpha]_D^{21}$ −73° (*c* 0.63, $CHCl_3$); FAB-MS *m*/*z* 1126 $(M+H)^+$; ^1H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, 6.6 Hz, 3H, 19-H),

1.08 (d, 6.0 Hz, 3H, 6″-H), 1.09 (s, 3H, 3″-CH_3), 1.11 (d, 6.0 Hz, 3H, 6′-H), 1.16 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.29 (d, 6.3 Hz, 3H, 16-H), 1.54–1.64 (m, 1H, 17-H), 1.66–1.85 (m, 3H, 6-, 8-, 17-H), 1.70 (dd, 14.1, 3.8 Hz, 1H, 2″-Hax), 1.77 (br d, 14.1 Hz, 1H, 2″-Heq), 2.02 (s, 3H, 2′-$OCOCH_3$), 2.14 (dt, 13.8, 10.8 Hz, 1H, 14-H), 2.34–2.48 (m, 2H, 4″-$OCOCH_2CH_3$), 2.34–2.54 (m, 2H, 2-, 14-H), 2.37 (s, 6H, 3′-$N(CH_3)_2$), 2.69 (t, 10.0 Hz, 1H, 3′-H), 2.77 (dd, 15.9, 6.3 Hz, 1H, 2-H), 2.87 (dd, 7.6, 1.9 Hz, 1H, 4-H), 3.19–3.33 (m, 2H, 4′-, 5′-H), 3.21 (s, 3H, 18-OCH_3), 3.26 (s, 3H, 18-OCH_3), 3.43 (s, 3H, 4-OCH_3), 3.63 (br, 1H, 3-H), 4.05 (br, 1H, 5-H), 4.15 (dd, 7.8, 4.2 Hz, 1H, 9-H), 4.27 (br dd, 12.4, 5.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.33 (dq, 10.2, 6.0 Hz, 1H, 5″-H), 4.45 (br dd, 12.4, 5.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.54 (m, 1H, 18-H), 4.56 (d, 10.2 Hz, 1H, 4″-H), 4.72 (d, 7.5 Hz, 1H, 1′-H), 4.85 (d, 3.4 Hz, 1H, 1″-H), 4.99 (dd, 10.2, 7.8 Hz, 1H, 2′-H), 5.20 (m, 1H, 15-H), 5.56 (m, 1H, 13-H), 5.62 (dd, 14.2, 7.8 Hz, 1H, 10-H), 5.99–6.11 (m, 2H, 11-, 12-H), 6.34 (dt, 15.6, 6.2 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.34–7.54 (m, 3H, naphthalene), 7.36 (d, 15.6 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.59 (br d, 6.6 Hz, 1H, naphthalene), 7.75 (br d, 8.1 Hz, 1H, naphthalene), 7.83 (m, 1H, naphthalene), 8.12 (br d, 9.0 Hz, 1H, naphthalene).

4.2.11. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(2-naphthyl)-2-propenyl]leucomycin A_7 18-dimethylacetal (7g).

Reaction of **6** (167 mg, 167 μmol) with 2-bromonaphthalene (109 mg, 525 μmol) gave **7g** (164 mg, 87%) by a similar procedure to **7f**.

$[\alpha]_D^{21}$ −67° (*c* 0.27, $CHCl_3$); FAB-MS *m*/*z* 1126 $(M+H)^+$; ^1H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, 6.6 Hz, 3H, 19-H), 1.02 (s, 3H, 3″-CH_3), 1.07 (d, 6.3 Hz, 3H, 6″-H), 1.10 (d, 6.0 Hz, 3H, 6′-H), 1.15 (t, 7.6 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.29 (d, 6.3 Hz, 3H, 16-H), 1.54–1.64 (m, 1H, 17-H), 1.67–1.86 (m, 3H, 6-, 8-, 17-H), 1.74 (dd, 14.1, 3.6 Hz, 1H, 2″-Hax), 1.82 (br d, 14.1 Hz, 1H, 2″-Heq), 2.02 (s, 3H, 2′-$OCOCH_3$), 2.13 (dt, 14.1, 10.8 Hz, 1H, 14-H), 2.34–2.46 (m, 2H, 4″-$OCOCH_2CH_3$), 2.34–2.53 (m, 2H, 2-, 14-H), 2.37 (s, 6H, 3′-$N(CH_3)_2$), 2.71 (t, 10.0 Hz, 1H, 3′-H), 2.75 (dd, 15.9, 6.6 Hz, 1H, 2-H), 2.86 (dd, 7.5, 1.5 Hz, 1H, 4-H), 3.14–3.33 (m, 2H, 4′-, 5′-H), 3.26 (s, 3H, 18-OCH_3), 3.31 (s, 3H, 18-OCH_3), 3.42 (s, 3H, 4-OCH_3), 3.58 (br, 1H, 3-H), 4.02 (br, 1H, 5-H), 4.16 (dd, 7.7, 4.0 Hz, 1H, 9-H), 4.19 (br dd, 11.4, 5.4 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.32 (dq, 10.2, 6.2 Hz, 1H, 5″-H), 4.40 (br dd, 11.4, 5.4 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.52 (d, 10.5 Hz, 1H, 4″-H), 4.57 (m, 1H, 18-H), 4.71 (d, 7.8 Hz, 1H, 1′-H), 4.82 (br s, 1H, 1″-H), 4.99 (dd, 10.5, 8.1 Hz, 1H, 2′-H), 5.18 (m, 1H, 15-H), 5.54 (m, 1H, 13-H), 5.61 (dd, 14.4, 7.9 Hz, 1H, 10-H), 5.96–6.12 (m, 2H, 11-, 12-H), 6.44 (dt, 15.9, 6.0 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.74 (d, 16.2 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.37–7.47 (m, 2H, naphthalene), 7.58 (dd, 8.4, 1.5 Hz, 1H, naphthalene), 7.69 (br s, 1H, naphthalene), 7.76 (br d, 7.5 Hz, 1H, naphthalene), 7.76 (br d, 7.5 Hz, 1H, naphthalene), 7.76 (br d, 7.4 Hz, 1H, naphthalene).

4.2.12. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(4-nitrophenyl)-2-propenyl]leucomycin A_7 18-dimethylacetal (7h).

Reaction of **6** (203 mg, 203 μmol) with 4-iodonitrobenzene (167 mg, 670 μmol) gave **7h** (153 mg, 67%) by a similar procedure to **7b**.

$[\alpha]_D^{22}$ −63° (*c* 0.65, $CHCl_3$); FAB-MS *m*/*z* 1121 $(M+H)^+$; ^1H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, 6.6 Hz, 3H, 19-H), 1.04–1.16 (m, 1H, 7-H), 1.09 (s, 3H, 3″-CH_3), 1.10 (d, 6.0 Hz, 3H, 6″-H), 1.12 (d, 6.0 Hz, 3H, 6′-H), 1.16 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.20–1.32 (m, 1H, 7-H), 1.29 (d, 6.3 Hz, 3H, 16-H), 1.57–1.66 (m, 1H, 17-H), 1.68–1.86 (m, 3H, 6-, 8-, 17-H), 1.78 (dd, 14.4, 3.9 Hz, 1H, 2″-Hax), 1.86 (br d, 14.0 Hz, 1H, 2″-Heq), 2.02 (s, 3H, 2′-$OCOCH_3$), 2.13 (dt, 14.1, 10.9 Hz, 1H, 14-H), 2.36–2.47 (m, 2H, 4″-$OCOCH_2CH_3$), 2.36–2.50 (m, 2H, 2-, 14-H), 2.38 (s, 6H, 3′-$N(CH_3)_2$), 2.70 (t, 10.0 Hz, 1H, 3′-H), 2.73 (dd, 15.9, 6.9 Hz, 1H, 2-H), 2.90 (dd, 7.8, 2.1 Hz, 1H, 4-H), 3.18–3.33 (m, 2H, 4′-, 5′-H), 3.24 (s, 3H, 18-OCH_3), 3.28 (s, 3H, 18-OCH_3), 3.43 (s, 3H, 4-OCH_3), 3.58 (br, 1H, 3-H), 4.00 (br, 1H, 5-H), 4.15 (dd, 8.4, 3.9 Hz, 1H, 9-H), 4.23 (br dd, 12.3, 5.4 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.36 (dq, 10.2, 6.0 Hz, 1H, 5″-H), 4.37 (br dd, 12.3, 5.4 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.55 (m, 1H, 18-H), 4.58 (d, 10.2 Hz, 1H, 4″-H), 4.70 (d, 7.8 Hz, 1H, 1′-H), 4.96 (d, 3.6 Hz, 1H, 1″-H), 5.00 (dd, 10.5, 7.8 Hz, 1H, 2′-H), 5.12 (m, 1H, 15-H), 5.51 (m, 1H, 13-H), 5.63 (dd, 13.7, 8.0 Hz, 1H, 10-H), 5.98–6.10 (m, 1H, 11-, 12-H), 6.50 (dt, 15.9, 5.4 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.65 (d, 15.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.48 (d, 8.7 Hz, 2H, C_6H_4–NO_2), 8.16 (d, 8.7 Hz, 2H, C_6H_4–NO_2).

4.2.13. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(4-methoxyphenyl)-2-propenyl]leucomycin A_7 18-dimethylacetal (7i).

Reaction of **6** (254 mg, 254 μmol) with 4-iodoanisole (190 mg, 814 μmol) gave **7i** (203 mg, 72%) by a similar procedure to **7b**.

$[\alpha]_D^{24}$ −79° (*c* 0.61, $CHCl_3$); FAB-MS *m*/*z* 1106 $(M+H)^+$; ^1H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.96 (d, 6.9 Hz, 3H, 19-H), 1.09 (s, 3H, 3″-CH_3), 1.09 (d, 6.3 Hz, 3H, 6″-H), 1.11 (d, 6.0 Hz, 3H, 6′-H), 1.16 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.16–1.31 (m, 1H, 7-H), 1.28 (d, 6.3 Hz, 3H, 16-H), 1.56–1.64 (m, 1H, 17-H), 1.66–1.82 (m, 3H, 6-, 8-, 17-H), 1.74 (dd, 14.2, 3.7 Hz, 1H, 2″-Hax), 1.82 (br d, 13.8 Hz, 1H, 2″-Heq), 2.01 (s, 3H, 2′-$OCOCH_3$), 2.13 (dt, 14.4, 10.7 Hz, 1H, 14-H), 2.36–2.46 (m, 2H, 4″-$OCOCH_2CH_3$), 2.36–2.52 (m, 2H, 2-, 14-H), 2.37 (s, 6H, 3′-$N(CH_3)_2$), 2.70 (t, 10.0 Hz, 1H, 3′-H), 2.72 (dd, 16.2, 5.7 Hz, 1H, 2-H), 2.82 (dd, 7.2, 1.9 Hz, 1H, 4-H), 3.16-3.33 (m, 2H, 4′-, 5′-H), 3.25 (s, 3H, 18-OCH_3), 3.30 (s, 3H, 18-OCH_3), 3.40 (s, 3H, 4-OCH_3), 3.54 (br, 1H, 3-H), 3.78 (s, 3H, C_6H_4–OCH_3), 3.99 (br, 1H, 5-H), 4.09 (br dd, 12.6, 6.8 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.15 (dd, 7.5, 3.9 Hz, 1H, 9-H), 4.30 (br dd, 12.6, 6.0 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.34 (dq, 10.2, 6.3 Hz, 1H, 5″-H), 4.54 (m, 1H, 18-H), 4.57 (d, 10.2 Hz, 1H, 4″-H), 4.68 (d, 7.5 Hz, 1H, 1′-H), 4.92 (d, 1H, 3.0 Hz, 1″-H), 4.98 (dd, 10.5, 7.5 Hz, 1H, 2′-H), 5.16 (m, 1H, 15-H), 5.52 (m, 1H, 13-H), 5.60

(dd, 13.8, 7.5 Hz, 1H, 10-H), 5.97–6.10 (m, 2H, 11-, 12-H), 6.16 (dt, 16.0, 6.3 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.51 (d, 15.7 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.82 (d, 8.7 Hz, 2H, C_6H_4–OCH_3), 7.28 (d, 8.7 Hz, 2H, C_6H_4–OCH_3).

4.2.14. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(4-fluorophenyl)-2-propenyl]leucomycin A_7 18-dimethylacetal (7j). Reaction of **6** (206 mg, 206 μmol) with 4-fluoroiodobenzene (72.0 μl, 623 μmol) gave **7j** (168 mg, 74%) by a similar procedure to **7b**.

$[\alpha]_D^{23}$ −79° (*c* 0.34, $CHCl_3$); FAB-MS *m*/*z* 1094 $(M+H)^+$; ^{1}H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.96 (d, 6.6 Hz, 3H, 19-H), 1.09 (d, 6.0 Hz, 3H, 6″-H), 1.10 (s, 3H, 3″-CH_3), 1.11 (d, 6.0 Hz, 3H, 6′-H), 1.16 (t, 7.6 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.20–1.32 (m, 1H, 7-H), 1.28 (d, 6.3 Hz, 3H, 16-H), 1.61 (m, 1H, 17-H), 1.66–1.85 (m, 3H, 6-, 8-, 17-H), 1.75 (dd, 14.2, 3.4 Hz, 1H, 2″-Hax), 1.82 (br d, 13.8 Hz, 1H, 2″-Heq), 2.01 (s, 3H, 2′-$OCOCH_3$), 2.13 (dt, 14.4, 10.8 Hz, 1H, 14-H), 2.36–2.47 (m, 2H, 4″-$OCOCH_2CH_3$), 2.36–2.51 (m, 2H, 2-, 14-H), 2.37 (s, 6H, 3′-$N(CH_3)_2$), 2.69 (t, 10.5 Hz, 1H, 3′-H), 2.71 (dd, 15.9, 6.0 Hz, 1H, 2-H), 2.84 (dd, 7.8, 1.8 Hz, 1H, 4-H), 3.16-3.33 (m, 2H, 4′-, 5′-H), 3.25 (s, 3H, 18-OCH_3), 3.29 (s, 3H, 18-OCH_3), 3.41 (s, 3H, 4-OCH_3), 3.54 (br, 1H, 3-H), 3.99 (br, 1H, 5-H), 4.11 (br dd, 12.4, 6.6 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.15 (dd, 7.7, 4.3 Hz, 1H, 9-H), 4.32 (br dd, 12.4, 6.0 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.35 (dq, 10.2, 6.3 Hz, 1H, 5″-H), 4.54 (m, 1H, 18-H), 4.57 (d, 10.2 Hz, 1H, 4″-H), 4.68 (d, 8.1 Hz, 1H, 1′-H), 4.92 (d, 3.0 Hz, 1H, 1″-H), 4.99 (dd, 10.2, 7.8 Hz, 1H, 2′-H), 5.16 (m, 1H, 15-H), 5.52 (m, 1H, 13-H), 5.61 (dd, 13.8, 7.8 Hz, 1H, 10-H), 5.96–6.10 (m, 2H, 11-, 12-H), 6.22 (dt, 15.9, 5.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.53 (d, 15.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.99 (t, 8.7 Hz, 2H, C_6H_4–F), 7.31 (dd, 8.7, 5.4 Hz, 2H, C_6H_4–F).

4.2.15. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(4-trifluoromethylphenyl)-2-propenyl]leucomycin A_7 18-dimethylacetal (7k). Reaction of **6** (204 mg, 204 μmol) with 4-iodobenzotrifluoride (90.0 μl, 612 μmol) gave **7k** (150 mg, 64%) by a similar procedure to **7b**.

$[\alpha]_D^{23}$ −72° (*c* 0.34, $CHCl_3$); FAB-MS *m*/*z* 1144 $(M+H)^+$; ^{1}H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, 6.6 Hz, 3H, 19-H), 1.09 (s, 3H, 3″-CH_3), 1.10 (d, 6.0 Hz, 3H, 6′-H), 1.10 (d, 6.0 Hz, 3H, 6″-H), 1.16 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.20–1.31 (m, 1H, 7-H), 1.28 (d, 6.3 Hz, 3H, 16-H), 1.62 (m, 1H, 17-H), 1.67–1.86 (m, 3H, 6-, 8-, 17-H), 1.76 (dd, 14.4, 3.6 Hz, 1H, 2″-Hax), 1.83 (br d, 14.0 Hz, 1H, 2″-Heq), 2.02 (s, 3H, 2′-$OCOCH_3$), 2.13 (dt, 14.0, 10.8 Hz, 1H, 14-H), 2.36–2.48 (m, 2H, 4″-$OCOCH_2CH_3$), 2.36–2.50 (m, 2H, 2-, 14-H), 2.38 (s, 6H, 3′-$N(CH_3)_2$), 2.71 (t, 10.0 Hz, 1H, 3′-H), 2.72 (dd, 16.0, 6.8 Hz, 1H, 2-H), 2.87 (dd, 7.8, 1.8 Hz, 1H, 4-H), 3.16–3.33 (m, 2H, 4′-, 5′-H), 3.24 (s, 3H, 18-OCH_3), 3.28 (s, 3H, 18-OCH_3), 3.42 (s, 3H, 4-OCH_3), 3.56 (br, 1H, 3-H), 4.00 (br, 1H, 5-H), 4.15 (dd, 7.7, 3.7 Hz, 1H, 9-H), 4.18 (br dd, 12.3, 6.6 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.35 (dq, 10.2, 6.0 Hz, 1H, 5″-H), 4.36 (br dd, 12.3, 6.3 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.54 (m, 1H, 18-H), 4.58 (d, 10.2 Hz, 1H, 4″-H), 4.70 (d, 7.5 Hz, 1H, 1′-H), 4.93 (d, 3.3 Hz, 1H, 1″-H), 4.99 (dd, 10.5, 7.5 Hz, 1H, 2′-H), 5.15 (m, 1H, 15-H), 5.52 (m, 1H, 13-H), 5.62 (dd, 13.9, 7.8 Hz, 1H, 10-H), 5.98–6.11 (m, 2H, 11-, 12-H), 6.41 (dt, 15.9, 5.7 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.61 (d, 15.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.44 (d, 8.1 Hz, 2H, C_6H_4–CF_3), 7.55 (d, 8.1 Hz, 2H, C_6H_4–CF_3).

4.2.16. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-[3-(4-biphenylyl)-2-propenyl]leucomycin A_7 18-dimethylacetal (7l). Reaction of **6** (220 mg, 220 μmol) with 4-bromobiphenyl (156 mg, 670 μmol) gave **7l** (193 mg, 76%) by a similar procedure to **7b**.

$[\alpha]_D^{22}$ −68° (*c* 0.59, $CHCl_3$); FAB-MS *m*/*z* 1152 $(M+H)^+$; ^{1}H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, 6.6 Hz, 3H, 19-H), 0.98 (s, 3H, 3″-CH_3), 1.08 (d, 6.3 Hz, 3H, 6″-H), 1.12 (d, 6.0 Hz, 3H, 6′-H), 1.15 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.18–1.32 (m, 1H, 7-H), 1.29 (d, 6.3 Hz, 3H, 16-H), 1.54–1.65 (m, 1H, 17-H), 1.65–1.82 (m, 3H, 6-, 8-, 17-H), 1.66 (dd, 14.1, 3.7 Hz, 1H, 2″-Hax), 1.77 (br d, 14.0 Hz, 1H, 2″-Heq), 2.02 (s, 3H, 2′-$OCOCH_3$), 2.14 (dt, 13.8, 10.7 Hz, 1H, 14-H), 2.36–2.48 (m, 1H, 2-H), 2.36–2.48 (m, 2H, 4″-$OCOCH_2CH_3$), 2.37 (s, 6H, 3′-$N(CH_3)_2$), 2.48 (br d, 13.8 Hz, 1H, 14-H), 2.72 (t, 10.0 Hz, 1H, 3′-H), 2.73 (dd, 16.0, 6.6 Hz, 1H, 2-H), 2.85 (dd, 7.7, 2.0 Hz, 1H, 4-H), 3.20–3.33 (m, 2H, 4′-, 5′-H), 3.27 (s, 3H, 18-OCH_3), 3.31 (s, 3H, 18-OCH_3), 3.42 (s, 3H, 4-OCH_3), 3.56 (br, 1H, 3-H), 4.02 (br, 1H, 5-H), 4.15 (br dd, 11.4, 6.8 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.16 (dd, 7.2, 4.2 Hz, 1H, 9-H), 4.33 (dq, 10.7, 6.3 Hz, 1H, 5″-H), 4.36 (br dd, 11.4, 6.3 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.53 (d, 10.7 Hz, 1H, 4″-H), 4.56 (dd, 9.0, 2.1 Hz, 1H, 18-H), 4.70 (d, 7.8 Hz, 1H, 1′-H), 4.90 (d, 3.3 Hz, 1H, 1″-H), 4.99 (dd, 10.3, 7.7 Hz, 1H, 2′-H), 5.18 (m, 1H, 15-H), 5.54 (m, 1H, 13-H), 5.61 (dd, 14.0, 7.2 Hz, 1H, 10-H), 5.98–6.12 (m, 2H, 11-, 12-H), 6.36 (dt, 15.9, 6.2 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.61 (d, 15.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.26–7.34 (m, 1H, C_6H_4-Ph), 7.37–7.46 (m, 2H, C_6H_4–Ph), 7.42 (br d, 8.5 Hz, 2H, C_6H_4–Ph), 7.54 (br d, 8.7 Hz, 2H, C_6H_4–Ph), 7.52–7.62 (m, 2H, C_6H_4–Ph).

4.2.17. 2′-*O*-Acetyl-9-*O*-(*tert*-butyldimethylsilyl)-3-*O*-{3-[4-(1-imidazolyl)phenyl]-2-propenyl}leucomycin A_7 18-dimethylacetal (7m). Reaction of **6** (244 mg, 244 μmol) with 4-(1-imidazolyl)bromobenzene (146 mg, 655 μmol) gave **7m** (187 mg, 67%) by a similar procedure to **7f**.

$[\alpha]_D^{21}$ −52° (*c* 0.40, $CHCl_3$); FAB-MS *m*/*z* 1142 $(M+H)^+$; ^{1}H NMR δ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, 6.6 Hz, 3H, 19-H), 1.03 (s, 3H, 3″-CH_3), 1.09 (d, 6.0 Hz, 3H, 6″-H), 1.11 (d, 6.0 Hz, 3H, 6′-H), 1.15 (t, 7.6 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.20–1.32 (m, 1H, 7-H), 1.29 (d, 6.3 Hz, 3H, 16-H), 1.61 (m, 1H, 17-H), 1.67–1.87 (m, 3H, 6-, 8-, 17-H), 1.75 (dd, 13.8, 3.6 Hz, 1H, 2″-Hax), 1.83 (br d, 13.8 Hz, 1H, 2″-Heq), 2.02 (s, 3H, 2′-

$OCOCH_3$), 2.13 (dt, 14.1, 10.8 Hz, 1H, 14-H), 2.34–2.48 (m, 2H, 4″-$OCOCH_2CH_3$), 2.36–2.50 (m, 2H, 2-, 14-H), 2.38 (s, 6H, 3′-$N(CH_3)_2$), 2.70 (t, 10.0 Hz, 1H, 3′-H), 2.73 (dd, 15.9, 7.0 Hz, 1H, 2-H), 2.88 (dd, 7.8, 1.8 Hz, 1H, 4-H), 3.15–3.35 (m, 2H, 4′-, 5′-H), 3.26 (s, 3H, 18-OCH_3), 3.29 (s, 3H, 18-OCH_3), 3.42 (s, 3H, 4-OCH_3), 3.57 (br, 1H, 3-H), 4.00 (br, 1H, 5-H), 4.16 (dd, 7.7, 4.0 Hz, 1H, 9-H), 4.18 (m, 1H, 3-O–CH_2CH═CH–Ar), 4.34 (m, 1H, 3-O–CH_2CH═CH–Ar), 4.35 (dq, 10.2, 6.0 Hz, 1H, 5″-H), 4.56 (m, 1H, 18-H), 4.57 (d, 10.2 Hz, 1H, 4″-H), 4.71 (d, 7.5 Hz, 1H, 1′-H), 4.96 (d, 3.3 Hz, 1H, 1″-H), 5.00 (dd, 10.2, 7.5 Hz, 1H, 2′-H), 5.13 (m, 1H, 15-H), 5.52 (m, 1H, 13-H), 5.62 (dd, 14.1, 7.8 Hz, 1H, 10-H), 5.98–6.11 (m, 2H, 11-, 12-H), 6.34 (dt, 15.9, 6.0 Hz, 1H, 3-O–CH_2CH═CH–Ar), 6.59 (d, 15.9 Hz, 1H, 3-O–CH_2CH═CH–Ar), 7.19 (br s, 1H, imidazole), 7.22–7.34 (br, 1H, imidazole), 7.31 (d, 8.7 Hz, 2H, C_6H_4–imidazole), 7.44 (d, 8.4 Hz, 2H, C_6H_4–imidazole), 7.72–7.84 (br, 1H, imidazole).

4.2.18. 3-*O*-[3-(3-Quinolyl)-2-propenyl]leucomycin A_7 (9a). A solution of **7a** (196 mg, 174 μmol) in 7.7 ml of MeOH/H_2O (10:1) was stirred for 46 h at 50 °C. The reaction mixture was concentrated and the residue was purified by silica gel chromatography [10 g, $CHCl_3$/MeOH (50:1)] to give **8a** (183 mg, 97%).

To a stirred solution of **8a** (177 mg, 163 μmol) in 54 ml of MeCN/H_2O (1:1), difluoroacetic acid (62.0 μl, 985 μmol) was added and the reaction mixture was stirred for 5 days at room temperature. Saturated $NaHCO_3$ solution 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 [30 g, $CHCl_3$/MeOH/NH_4OH (200:10:1)] to give 137 mg of **9a**. A portion of **9a** (24.0 mg) was again purified by preparative TLC [$CHCl_3$/MeOH/NH_4OH (100:10:1)] to afford **9a** (18.9 mg, 80%).

$[\alpha]_D^{24}$ −39° (*c* 0.82, $CHCl_3$); FAB-MS *m*/*z* 925 $(M+H)^+$; ^1H NMR δ 0.02 (d, 6.6 Hz, 3H, 19-H), 1.05 (s, 3H, 3″-CH_3), 1.06 (d, 6.3 Hz, 3H, 6′-H), 1.08 (d, 6.0 Hz, 3H, 6″-H), 1.15 (t, 7.6 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.29 (d, 6.3 Hz, 3H, 16-H), 1.33 (m, 1H, 7-H), 1.70 (dd, 14.4, 3.6 Hz, 1H, 2″-Hax), 1.74–1.86 (m, 1H, 8-H), 1.78 (br d, 14.1 Hz, 1H, 2″-Heq), 2.01–2.16 (m, 1H, 6-H), 2.16 (dt, 14.1 Hz, 1H, 14-H), 2.36–2.48 (m, 2H, 4″-$OCOCH_2CH_3$), 2.36–2.52 (m, 4H, 2-, 14-, 17-, 3′-H), 2.47 (s, 3′-$N(CH_3)_2$), 2.79 (dd, 16.2, 6.6 Hz, 1H, 2-H), 2.95 (m, 1H, 17-H), 2.98 (dd, 7.2, 2.4 Hz, 1H, 4-H), 3.11–3.22 (m, 1H, 5′-H), 3.20 (t, 9.3 Hz, 1H, 4′-H), 3.50 (s, 3H, 4-OCH_3), 3.53 (dd, 10.5, 7.8 Hz, 1H, 2′-H), 3.76 (br, 1H, 3-H), 3.88 (br, 1H, 5-H), 4.13 (dd, 7.9, 4.0 Hz, 1H, 9-H), 4.32–4.47 (m, 2H, 3-O–CH_2CH═CH–Ar), 4.40 (m, 1H, 5″-H), 4.41 (d, 7.8 Hz, 1H, 1′-H), 4.55 (d, 10.2 Hz, 1H, 4″-H), 4.91 (d, 3.2 Hz, 1H, 1″-H), 5.19 (m, 1H, 15-H), 5.63 (m, 1H, 13-H), 5.67 (dd, 14.9, 7.9 Hz, 1H, 10-H), 6.07 (br dd, 15.1, 10.5 Hz, 1H, 12-H), 6.24 (dd, 14.9, 10.5 Hz, 1H, 11-H), 6.59 (dt, 15.9, 5.9 Hz, 1H, 3-O–CH_2CH═CH–Ar), 6.78 (d, 15.9 Hz, 1H, 3-O–CH_2CH═CH–Ar), 7.51 (ddd, 8.0, 6.8, 1.2 Hz, 1H, quinoline), 7.64 (ddd, 8.4, 7.0, 1.3 Hz, 1H, quinoline), 7.78 (dd, 7.2, 1.0 Hz, 1H, quinoline), 8.04 (d, 8.4 Hz, 1H, quinoline), 8.07 (d, 1.9 Hz, 1H, quinoline), 9.00 (d, 2.1 Hz, 1H, quinoline), 9.77 (br s, 1H, 18-H); HRMS: Calcd for $C_{50}H_{72}N_2O_{14}$: 925.5062. Found: 925.5072.

4.2.19. 3-*O*-[3-(4-Isoquinolyl)-2-propenyl]leucomycin A_7 (9b). By a similar procedure to **9a**, **7b** (215 mg, 191 μmol) was deacetylated to give **8b** (193 mg, 93%). Subsequently, **8b** (187 mg, 177 μmol) was deprotected to furnish 147 mg of **9b**. A portion of **9b** (34.2 mg) was purified by preparative TLC to afford **9b** (29.7 mg, 80%).

$[\alpha]_D^{20}$ −44° (*c* 0.57, $CHCl_3$); FAB-MS *m*/*z* 925 $(M+H)^+$; ^1H NMR δ 0.01 (d, 6.3 Hz, 3H, 19-H), 1.08 (d, 6.3 Hz, 3H, 6′-H), 1.08 (s, 3H, 3″-CH_3), 1.10 (d, 6.0 Hz, 3H, 6″-H), 1.15 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.28 (d, 6.3 Hz, 3H, 16-H), 1.32 (m, 1H, 7-H), 1.74 (dd, 14.4, 3.9 Hz, 1H, 2″-Hax), 1.76–1.85 (m, 1H, 8-H), 1.84 (br d, 14.4 Hz, 1H, 2″-Heq), 2.05–2.15 (m, 1H, 6-H), 2.15 (dt, 14.1, 10.8 Hz, 1H, 14-H), 2.30–2.51 (m, 4H, 2-, 14-, 17-, 3′-H), 2.36–2.49 (m, 2H, 4″-$OCOCH_2CH_3$), 2.43 (s, 6H, 3′-$N(CH_3)_2$), 2.81 (dd, 16.3, 6.5 Hz, 1H, 2-H), 2.95 (dd, 16.8, 9.6 Hz, 1H, 17-H), 2.99 (m, 1H, 4-H), 3.09 (m, 1H, 5′-H), 3.17 (t, 9.4 Hz, 1H, 4′-H), 3.51 (s, 3H, 4-OCH_3), 3.51 (m, 1H, 2′-H), 3.80 (br, 1H, 3-H), 3.86 (br, 1H, 5-H), 4.13 (dd, 8.1, 3.9 Hz, 1H, 9-H), 4.34–4.49 (m, 2H, 3-O–CH_2CH═CH–Ar), 4.39 (d, 7.5 Hz, 1H, 1′-H), 4.43 (m, 1H, 5″-H), 4.56 (d, 1H, 9.9 Hz, 4″-H), 4.91 (d, 1H, 3.6 Hz, 1″-H), 5.19 (m, 1H, 15-H), 5.63 (m, 1H, 13-H), 5.67 (dd, 15.0, 8.1 Hz, 1H, 10-H), 6.06 (br dd, 14.6, 10.6 Hz, 1H, 12-H), 6.24 (dd, 15.0, 10.5 Hz, 1H, 11-H), 6.44 (dt, 15.7, 5.8 Hz, 1H, 3-O–CH_2CH═CH–Ar), 7.25 (d, 15.9 Hz, 1H, 3-O–CH_2CH═CH–Ar), 7.59 (br t, 7.4 Hz, 1H, isoquinoline), 7.70 (br t, 7.5 Hz, 1H, isoquinoline), 7.94 (br d, 8.1 Hz, 1H, isoquinoline), 8.11 (br d, 8.4 Hz, 1H, isoquinoline), 8.62 (s, 1H, isoquinoline), 9.12 (s, 1H, isoquinoline), 9.76 (br s, 1H, 18-H); HRMS: Calcd for $C_{50}H_{72}N_2O_{14}$: 925.5062. Found: 925.5052.

4.2.20. 3-*O*-(3-Phenyl-2-propenyl)leucomycin A_7 (9c). By a similar procedure to **9a**, **7c** (160 mg, 149 μmol) was deacetylated to give **8c** (137 mg, 89%). Subsequently, **8c** (83.0 mg, 80.2 μmol) was deprotected to furnish **9c** (46.2 mg, 66%).

$[\alpha]_D^{22}$ −63° (*c* 0.58, $CHCl_3$); FAB-MS *m*/*z* 874 $(M+H)^+$; ^1H NMR δ 0.01 (d, 6.6 Hz, 3H, 19-H), 1.04 (d, 6.3 Hz, 3H, 6′-H), 1.09 (s, 3H, 3″-CH_3), 1.09 (d, 6.0 Hz, 3H, 6″-H), 1.16 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.26–1.36 (m, 1H, 7-H), 1.28 (d, 6.3 Hz, 3H, 16-H), 1.75 (dd, 14.2, 3.6 Hz, 1H, 2″-Hax), 1.72–1.84 (m, 1H, 8-H), 1.86 (br d, 14.2 Hz, 1H, 2″-Heq), 1.94–2.06 (m, 1H, 6-H), 2.16 (dt, 14.4, 10.8 Hz, 1H, 14-H), 2.32–2.60 (m, 2H, 4″-$OCOCH_2CH_3$), 2.32–2.62 (m, 4H, 2-, 14-, 17-, 3′-H), 2.46 (s, 6H, 3′-$N(CH_3)_2$), 2.75 (dd, 16.2, 5.7 Hz, 1H, 2-H), 2.91 (dd, 16.9, 9.6 Hz, 1H, 17-H), 2.92 (dd, 7.2, 2.4 Hz, 1H, 4-H), 3.09 (m, 1H, 5′-H), 3.17 (t, 9.3 Hz, 1H, 4′-H), 3.48 (s, 3H, 4-OCH_3), 3.52 (m, 1H, 2′-H), 3.72 (br, 1H, 3-H), 3.81 (br, 1H, 5-H), 4.12 (dd, 8.1, 3.7 Hz, 1H, 9-H), 4.21 (br dd, 11.5, 6.7 Hz, 3-O–CH_2CH═CH–Ph), 4.35 (br dd, 11.5,

6.0 Hz, 1H, 3-O–CH_2CH=CH–Ph), 4.38 (d, 7.5 Hz, 1H, 1′-H), 4.42 (dq, 10.2, 6.0 Hz, 1H, 5″-H), 4.57 (d, 10.2 Hz, 1H, 4″-H), 4.93 (d, 3.3 Hz, 1H, 1″-H), 5.21 (m, 1H, 15-H), 5.63 (m, 1H, 13-H), 5.64 (dd, 15.0, 8.1 Hz, 1H, 10-H), 6.06 (br dd, 15.3, 10.3 Hz, 1H, 12-H), 6.22 (dd, 15.0, 10.3 Hz, 1H, 11-H), 6.32 (dt, 15.9, 6.3 Hz, 1H, 3-O–CH_2CH=CH–Ph), 6.59 (d, 15.9 Hz, 1H, 3-O–CH_2CH=CH–Ph), 6.98–7.24 (m, 5H, Ph), 9.76 (br s, 1H, 18-H); HRMS: Calcd for $C_{47}H_{71}NO_{14}$: 874.4953. Found: 874.4943.

4.2.21. 3-*O*-[3-(3-Pyridyl)-2-propenyl]leucomycin A_7 (9d). By a similar procedure to **9a**, **7d** (72.9 mg, 67.7 μmol) was deacetylated to give **8d** (65.0 mg, 93%). Subsequently, **8d** (65.0 mg, 62.8 μmol) was deprotected to furnish **9d** (39.9 mg, 73%).

$[\alpha]_D^{23}$ −56° (*c* 0.53, $CHCl_3$); FAB-MS *m*/*z* 875 $(M+H)^+$; ^{1}H NMR δ 0.01 (d, 6.6 Hz, 3H, 19-H), 1.09 (d, 6.0 Hz, 3H, 6′-H), 1.09 (s, 3H, 3″-CH_3), 1.09 (d, 6.0 Hz, 3H, 6″-H), 1.15 (t, 7.6 Hz, 3H, 4″-OCOCH_2CH_3), 1.28 (d, 6.0 Hz, 3H, 16-H), 1.32 (m, 1H, 7-H), 1.75–1.86 (m, 1H, 8-H), 1.78 (dd, 14.1, 3.7 Hz, 1H, 2″-Hax), 1.89 (br d, 14.1 Hz, 1H, 2″-Heq), 1.99–2.09 (m, 1H, 6-H), 2.15 (dt, 14.1, 10.8 Hz, 1H, 14-H), 2.34–2.48 (m, 2H, 4″-OCOCH_2CH_3), 2.34–2.51 (m, 4H, 2-, 14-, 17-, 3′-H), 2.46 (s, 6H, 3′-N$(CH_3)_2$), 2.76 (dd, 16.0, 6.4 Hz, 1H, 2-H), 2.94 (dd, 17.4, 10.2 Hz, 1H, 17-H), 2.95 (dd, 7.2, 2.4 Hz, 1H, 4-H), 3.12 (dq, 9.6, 6.0 Hz, 1H, 5′-H), 3.20 (t, 9.6 Hz, 1H, 4′-H), 3.48 (s, 3H, 4-OCH_3), 3.52 (dd, 9.9, 7.5 Hz, 1H, 2′-H), 3.72 (br, 1H, 3-H), 3.84 (br, 1H, 5-H), 4.11 (dd, 8.4, 3.9 Hz, 1H, 9-H), 4.30 (br dd, 12.6, 6.5 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.34 (m, 1H, 3-O–CH_2CH=CH–Ar), 4.37 (d, 7.5 Hz, 1H, 1′-H), 4.43 (dq, 10.5, 6.0 Hz, 1H, 5″-H), 4.58 (d, 10.5 Hz, 1H, 4″-H), 4.96 (d, 3.3 Hz, 1H, 1″-H), 5.17 (m, 1H, 15-H), 5.62 (m, 1H, 13-H), 5.66 (dd, 14.7, 8.4 Hz, 1H, 10-H), 6.05 (br dd, 15.0, 10.5 Hz, 1H, 12-H), 6.22 (dd, 14.7, 10.4 Hz, 1H, 11-H), 6.42 (dt, 16.0, 5.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.60 (d, 16.2 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.23 (dd, 7.5, 4.6 Hz, 1H, pyridine), 7.72 (dt, 7.8, 1.9 Hz, 1H, pyridine), 8.42 (dd, 4.8, 1.5 Hz, 1H, pyridine), 8.56 (d, 2.1 Hz, 1H, pyridine), 9.75 (br s, 1H, 18-H); HRMS: Calcd for $C_{46}H_{70}N_2O_{14}$: 875.4905. Found: 875.4905.

4.2.22. 3-*O*-[3-(5-Pyrimidinyl)-2-propenyl]leucomycin A_7 (9e). By a similar procedure to **9a**, **7e** (166 mg, 154 μmol) was deacetylated to give **8e** (131 mg, 82%). Subsequently, **8e** (125 mg, 121 μmol) was deprotected to furnish 93.3 mg of **9e**. A portion of **9e** (30.9 mg) was purified by preparative TLC to afford **9e** (29.2 mg, 84%).

$[\alpha]_D^{20}$ −47° (*c* 0.54, $CHCl_3$); FAB-MS *m*/*z* 876 $(M+H)^+$; ^{1}H NMR δ 0.01 (d, 6.6 Hz, 3H, 19-H), 1.08 (s, 3H, 3″-CH_3), 1.09 (d, 6.0 Hz, 3H, 6″-H), 1.13 (d, 6.0 Hz, 3H, 6′-H), 1.15 (t, 7.5 Hz, 3H, 4″-OCOCH_2CH_3), 1.28 (d, 6.3 Hz, 3H, 16-H), 1.34 (m, 1H, 7-H), 1.79 (dd, 14.4, 3.9 Hz, 1H, 2″-Hax), 1.77–1.87 (m, 1H, 8-H), 1.94 (br d, 14.2 Hz, 1H, 2″-Heq), 2.03–2.13 (m, 1H, 6-H), 2.14 (dt, 13.9, 12.0 Hz, 1H, 14-H), 2.36–2.46 (m, 2H, 4″-OCOCH_2CH_3), 2.36–2.50 (m, 4H, 2-, 14-, 17-, 3′-H), 2.47 (s, 6H, 3′-N$(CH_3)_2$), 2.77 (dd, 15.9, 6.9 Hz, 1H, 2-H), 2.96 (m, 1H, 17-H), 2.98 (dd, 7.2, 2.4 Hz, 1H, 4-H), 3.14–3.23 (m, 1H, 5′-H), 3.23 (t, 9.0 Hz, 1H, 4′-H), 3.48 (s, 3H, 4-OCH_3), 3.52 (dd, 10.2, 7.5 Hz, 1H, 2′-H), 3.72 (br, 1H, 3-H), 3.86 (br, 1H, 5-H), 4.10 (dd, 8.4, 3.9 Hz, 1H, 9-H), 4.29–4.43 (m, 2H, 3-O–CH_2CH=CH–Ar), 4.37 (d, 7.5 Hz, 1H, 1′-H), 4.42 (dq, 10.2, 6.0 Hz, 1H, 5″-H), 4.58 (d, 10.2 Hz, 1H, 4″-H), 5.00 (d, 3.6 Hz, 1H, 1″-H), 5.14 (m, 1H, 15-H), 5.60 (m, 1H, 13-H), 5.66 (dd, 15.0, 8.5 Hz, 1H, 10-H), 6.05 (br dd, 15.0, 10.8 Hz, 1H, 12-H), 6.22 (dd, 14.7, 10.5 Hz, 1H, 11-H), 6.53 (dt, 16.0, 4.5 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.57 (d, 16.0 Hz, 1H, 3-O–CH_2CH=CH–Ar), 8.74 (s, 1H, pyrimidine), 9.03 (s, 1H, pyrimidine), 9.74 (br s, 1H, 18-H); HRMS: Calcd for $C_{45}H_{69}N_3O_{14}$: 876.4858. Found: 876.4856.

4.2.23. 3-*O*-[3-(1-Naphthyl)-2-propenyl]leucomycin A_7 (9f). By a similar procedure to **9a**, **7f** (122 mg, 109 μmol) was deacetylated to give **8f** (104 mg, 88%). Subsequently, **8f** (74.6 mg, 68.8 μmol) was deprotected to furnish **9f** (40.0 mg, 63%).

$[\alpha]_D^{23}$ −46° (*c* 0.51, $CHCl_3$); FAB-MS *m*/*z* 924 $(M+H)^+$; ^{1}H NMR δ 0.89 (d, 6.0 Hz, 3H, 6′-H), 1.01 (d, 6.6 Hz, 3H, 19-H), 1.08 (d, 6.0 Hz, 3H, 6″-H), 1.10 (s, 3H, 3″-CH_3), 1.16 (t, 7.5 Hz, 3H, 4″-OCOCH_2CH_3), 1.28 (d, 6.3 Hz, 3H, 16-H), 1.30 (m, 1H, 7-H), 1.71–1.85 (m, 1H, 8-H), 1.71 (dd, 14.4, 3.6 Hz, 1H, 2″-Hax), 1.79 (br d, 14.0 Hz, 1H, 2″-Heq), 2.00-2.13 (m, 1H, 6-H), 2.16 (dt, 14.1, 10.6 Hz, 1H, 14-H), 2.33–2.48 (m, 2H, 4″-OCOCH_2CH_3), 2.33–2.55 (m, 3H, 2-, 14-, 17-H), 2.34 (t, 10.2 Hz, 1H, 3′-H), 2.44 (s, 6H, 3′-N$(CH_3)_2$), 2.80 (dd, 16.3, 5.9 Hz, 1H, 2-H), 2.90–3.02 (m, 1H, 5′-H), 2.92 (m, 1H, 17-H), 2.96 (dd, 7.2, 2.7 Hz, 1H, 4-H), 3.12 (t, 9.5 Hz, 1H, 4′-H), 3.50 (dd, 10.2, 7.8 Hz, 1H, 2′-H), 3.51 (s, 3H, 4-OCH_3), 3.81 (br, 1H, 3-H), 3.84 (br, 1H, 5-H), 4.12 (dd, 8.0, 3.9 Hz, 1H, 9-H), 4.34 (br dd, 12.1, 6.0 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.38 (d, 7.8 Hz, 1H, 1′-H), 4.42 (dq, 10.2, 6.0 Hz, 1H, 5″-H), 4.47 (br dd, 12.1, 5.7 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.55 (d, 10.2 Hz, 1H, 4″-H), 4.84 (d, 3.3 Hz, 1H, 1″-H), 5.22 (m, 1H, 15-H), 5.64 (m, 1H, 13-H), 5.66 (dd, 15.0, 8.4 Hz, 1H, 10-H), 6.06 (br dd, 15.3, 10.4 Hz, 1H, 12-H), 6.23 (dd, 14.9, 10.5 Hz, 1H, 11-H), 6.37 (dt, 15.5, 6.1 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.39 (d, 15.2 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.35–7.53 (m, 3H, naphthalene), 7.63 (br d, 6.9 Hz, 1H, naphthalene), 7.75 (br d, 8.1 Hz, 1H, naphthalene), 7.81 (m, 1H, naphthalene), 8.15 (br d, 9.0 Hz, 1H, naphthalene), 9.76 (br s, 1H, 18-H); HRMS: Calcd for $C_{51}H_{73}NO_{14}$: 924.5109. Found: 924.5109.

4.2.24. 3-*O*-[3-(2-Naphthyl)-2-propenyl]leucomycin A_7 (9g). By a similar procedure to **9a**, **7g** (130 mg, 115 μmol) was deacetylated to give **8g** (114 mg, 91%). Subsequently, **8g** (82.8 mg, 76.4 μmol) was deprotected to furnish **9g** (41.7 mg, 59%).

$[\alpha]_D^{23}$ −39° (*c* 0.49, $CHCl_3$); FAB-MS *m*/*z* 924 $(M+H)^+$; ^{1}H NMR δ 0.98 (d, 6.0 Hz, 3H, 6′-H), 1.02 (d, 6.9 Hz, 3H, 19-H), 1.05 (s, 3H, 3″-CH_3), 1.07 (d, 6.0 Hz, 3H, 6″-H), 1.16 (t, 7.6 Hz, 3H, 4″-OCOCH_2CH_3), 1.26–

1.36 (m, 1H, 7-H), 1.29 (d, 6.0 Hz, 3H, 16-H), 1.63 (br s, 2H, 2″-H), 1.74–1.85 (m, 1H, 8-H), 1.96–2.10 (m, 1H, 6-H), 2.16 (dt, 13.8, 10.5 Hz, 1H, 14-H), 2.36–2.48 (m, 2H, 4″-$OCOCH_2CH_3$), 2.36–2.56 (m, 4H, 2-, 14-, 17-, 3′-H), 2.46 (s, 6H, 3′-$N(CH_3)_2$), 2.77 (dd, 16.2, 5.7 Hz, 1H, 2-H), 2.93 (m, 1H, 17-H), 2.94 (dd, 7.0, 2.7 Hz, 1H, 4-H), 3.05 (dq, 9.5, 6.0 Hz, 1H, 5′-H), 3.14 (t, 9.5 Hz, 1H, 4′-H), 3.50 (s, 3H, 4-OCH_3), 3.52 (dd, 10.5, 7.6 Hz, 1H, 2′-H), 3.75 (br, 1H, 3-H), 3.84 (br, 1H, 5-H), 4.12 (dd, 8.1, 3.9 Hz, 1H, 9-H), 4.27 (br dd, 12.0, 6.6 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.32–4.48 (m, 2H, 3-O–CH_2CH=CH–Ar, 5″-H), 4.40 (d, 7.8 Hz, 1H, 1′-H), 4.53 (d, 10.2 Hz, 1H, 4″-H), 4.82 (br s, 1H, 1″-H), 5.22 (m, 1H, 15-H), 5.64 (m, 1H, 13-H), 5.65 (dd, 14.9, 8.0 Hz, 1H, 10-H), 6.06 (br dd, 15.1, 10.4 Hz, 1H, 12-H), 6.23 (dd, 14.9, 10.6 Hz, 1H, 11-H), 6.46 (dt, 7.8, 6.3 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.76 (d, 8.0 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.34–7.47 (m, 2H, naphthalene), 7.61 (dd, 8.4, 1.5 Hz, 1H, naphthalene), 7.71 (br s, 1H, naphthalene), 7.77 (br d, 9.0 Hz, 1H, naphthalene), 7.77 (br d, 9.0 Hz, 1H, naphthalene), 7.77 (br d, 9.0 Hz, 1H, naphthalene), 9.78 (br s, 1H, 18-H); HRMS: Calcd for $C_{51}H_{73}NO_{14}$: 924.5109. Found: 924.5119.

4.2.25. 3-*O*-[3-(4-Nitrophenyl)-2-propenyl]leucomycin A_7 (9h). By a similar procedure to **9a**, **7h** (102 mg, 91.0 μmol) was deacetylated to give crude **8h**, which was deprotected to furnish **9h** (48.5 mg, 58% in two steps).

$[\alpha]_D^{23}$ −40° (*c* 0.48, $CHCl_3$); FAB-MS *m*/*z* 919 $(M+H)^+$; ^1H NMR δ 0.01 (d, 6.6 Hz, 3H, 19-H), 1.07 (d, 6.0 Hz, 3H, 6′-H), 1.08 (s, 3H, 3″-CH_3), 1.09 (d, 6.3 Hz, 3H, 6″-H), 1.15 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.28 (d, 6.3 Hz, 3H, 16-H), 1.30 (m, 1H, 7-H), 1.76–1.86 (m, 1H, 8-H), 1.77 (dd, 14.2, 3.7 Hz, 1H, 2″-Hax), 1.86 (br d, 14.2 Hz, 1H, 2″-Heq), 2.00–2.14 (m, 1H, 6-H), 2.15 (dt, 14.0, 10.8 Hz, 1H, 14-H), 2.33–2.48 (m, 2H, 4″-$OCOCH_2CH_3$), 2.33–2.50 (m, 4H, 2-, 14-, 17-, 3′-H), 2.46 (s, 6H, 3′-$N(CH_3)_2$), 2.76 (dd, 16.2, 6.6 Hz, 1H, 2-H), 2.93 (m, 1H, 17-H), 2.96 (dd, 7.5, 2.1 Hz, 1H, 4-H), 3.11 (dq, 9.0, 6.0 Hz, 1H, 5′-H), 3.19 (t, 9.3 Hz, 1H, 4′-H), 3.48 (s, 3H, 4-OCH_3), 3.52 (dd, 10.0, 7.2 Hz, 1H, 2′-H), 3.71 (br, 1H, 3-H), 3.83 (br, 1H, 5-H), 4.10 (dd, 8.3, 4.0 Hz, 1H, 9-H), 4.28–4.43 (m, 2H, 3-O–CH_2CH=CH–Ar), 4.36 (d, 7.2 Hz, 1H, 1′-H), 4.42 (dq, 10.2, 6.3 Hz, 1H, 5″-H), 4.57 (d, 10.2 Hz, 1H, 4″-H), 4.95 (d, 3.3 Hz, 1H, 1″-H), 5.16 (m, 1H, 15-H), 5.61 (m, 1H, 13-H), 5.65 (dd, 15.0, 8.4 Hz, 1H, 10-H), 6.04 (br dd, 15.2, 10.5 Hz, 1H, 12-H), 6.21 (dd, 15.0, 10.6 Hz, 1H, 11-H), 6.53 (dt, 15.9, 5.7 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.68 (d, 16.1 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.50 (d, 9.0 Hz, 2H, C_6H_4–NO_2), 8.15 (d, 9.3 Hz, 2H, C_6H_4–NO_2), 9.74 (br s, 1H, 18-H); HRMS: Calcd for $C_{47}H_{70}N_2O_{16}$: 919.4804. Found: 919.4819.

4.2.26. 3-*O*-[3-(4-Methoxyphenyl)-2-propenyl]leucomycin A_7 (9i). By a similar procedure to **9a**, **7i** (112 mg, 101 μmol) was deacetylated to give crude **8i**, which was deprotected to furnish **9i** (55.4 mg, 60% in two steps).

$[\alpha]_D^{23}$ −56° (*c* 0.60, $CHCl_3$); FAB-MS *m*/*z* 904 $(M+H)^+$; ^1H NMR δ 0.01 (d, 6.6 Hz, 3H, 19-H), 1.06 (d, 5.7 Hz, 3H, 6′-H), 1.09 (s, 3H, 3″-CH_3), 1.09 (d, 6.1 Hz, 3H, 6″-H), 1.16 (t, 7.6 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.25–1.35 (m, 1H, 7-H), 1.28 (d, 6.3 Hz, 3H, 16-H), 1.73–1.85 (m, 1H, 8-H), 1.75 (dd, 14.2, 3.7 Hz, 1H, 2″-Hax), 1.86 (br d, 14.1 Hz, 1H, 2″-Heq), 1.96–2.05 (m, 1H, 6-H), 2.15 (dt, 14.4, 10.8 Hz, 1H, 14-H), 2.32–2.53 (m, 4H, 2-, 14-, 17-, 3′-H), 2.35–2.48 (m, 2H, 4″-$OCOCH_2CH_3$), 2.46 (s, 6H, 3′-$N(CH_3)_2$), 2.73 (dd, 16.2, 5.4 Hz, 1H, 2-H), 2.90 (dd, 6.6, 2.4 Hz, 1H, 4-H), 2.90 (dd, 16.0, 10.0 Hz, 1H, 17-H), 3.10 (dq, 9.3, 5.7 Hz, 1H, 5′-H), 3.17 (t, 9.3 Hz, 1H, 4′-H), 3.48 (s, 3H, 4-OCH_3), 3.52 (dd, 9.9, 7.5 Hz, 1H, 2′-H), 3.71 (br, 1H, 3-H), 3.74–3.83 (m, 1H, 5-H), 3.78 (s, 3H, C_6H_4-OCH_3), 4.12 (m, 1H, 9-H), 4.16 (br dd, 11.1, 7.2 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.31 (br dd, 11.1, 6.1 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.39 (d, 7.8 Hz, 1H, 1′-H), 4.42 (dq, 9.9, 6.1 Hz, 1H, 5″-H), 4.57 (d, 9.9 Hz, 1H, 4″-H), 4.94 (d, 3.4 Hz, 1H, 1″-H), 5.20 (m, 1H, 15-H), 5.63 (m, 1H, 13-H), 5.64 (dd, 14.7, 8.4 Hz, 1H, 10-H), 6.04 (br dd, 14.9, 10.1 Hz, 1H, 12-H), 6.17 (dt, 15.9, 6.4 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.21 (dd, 14.7, 10.5 Hz, 1H, 11-H), 6.53 (d, 15.6 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.83 (d, 8.7 Hz, 2H, C_6H_4–OCH_3), 7.30 (d, 8.7 Hz, 2H, C_6H_4–OCH_3), 9.76 (br s, 1H, 18-H); HRMS: Calcd for $C_{48}H_{73}NO_{15}$: 904.5058. Found: 904.5052.

4.2.27. 3-*O*-[3-(4-Fluorophenyl)-2-propenyl]leucomycin A_7 (9j). By a similar procedure to **9a**, **7j** (113 mg, 103 μmol) was deacetylated to give crude **8j**, which was deprotected to furnish **9j** (48.6 mg, 53% in two steps).

$[\alpha]_D^{21}$ −58° (*c* 0.68, $CHCl_3$); FAB-MS *m*/*z* 892 $(M+H)^+$; ^1H NMR δ 0.00 (d, 6.9 Hz, 3H, 19-H), 1.03 (d, 6.0 Hz, 3H, 6′-H), 1.08 (d, 6.0 Hz, 3H, 6″-H), 1.09 (s, 3H, 3″-CH_3), 1.15 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.24–1.35 (m, 1H, 7-H), 1.27 (d, 6.3 Hz, 3H, 16-H), 1.72–1.85 (m, 1H, 8-H), 1.76 (dd, 13.8, 3.7 Hz, 1H, 2″-Hax), 1.84 (br d, 13.8 Hz, 1H, 2″-Heq), 1.95–2.06 (m, 1H, 6-H), 2.14 (dt, 14.1, 10.9 Hz, 1H, 14-H), 2.34–2.48 (m, 2H, 4″-$OCOCH_2CH_3$), 2.34–2.52 (m, 4H, 2-, 14-, 17-, 3′-H), 2.45 (s, 6H, 3′-$N(CH_3)_2$), 2.73 (dd, 16.2, 5.7 Hz, 1H, 2-H), 2.90 (dd, 6.6, 2.7 Hz, 1H, 4-H), 2.90 (m, 1H, 17-H), 3.06 (dq, 9.3, 6.0 Hz, 1H, 5′-H), 3.16 (t, 9.3 Hz, 1H, 4′-H), 3.47 (s, 3H, 4-OCH_3), 3.51 (dd, 10.5, 8.1 Hz, 1H, 2′-H), 3.70 (br, 1H, 3-H), 3.79 (br, 1H, 5-H), 4.11 (dd, 8.0, 3.9 Hz, 1H, 9-H), 4.18 (br dd, 11.1, 6.6 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.32 (br dd, 11.1, 5.7 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.37 (d, 7.8 Hz, 1H, 1′-H), 4.42 (dq, 10.2, 6.0 Hz, 1H, 5″-H), 4.57 (d, 10.2 Hz, 1H, 4″-H), 4.93 (d, 3.3 Hz, 1H, 1″-H), 5.19 (m, 1H, 15-H), 5.62 (m, 1H, 13-H), 5.64 (dd, 15.0, 7.8 Hz, 1H, 10-H), 6.04 (br dd, 15.0, 10.8 Hz, 1H, 12-H), 6.21 (dd, 15.0, 10.6 Hz, 1H, 11-H), 6.23 (dt, 15.9, 6.1 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.55 (d, 15.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.98 (t, 8.7 Hz, 2H, C_6H_4-F), 7.33 (dd, 8.7, 5.4 Hz, 2H, C_6H_4-F), 9.75 (br s, 1H, 18-H); HRMS: Calcd for $C_{47}H_{70}FNO_{14}$: 892.4859. Found: 892.4860.

4.2.28. 3-*O*-[3-(4-Trifluoromethylphenyl)-2-propenyl]leucomycin A_7 (9k). By a similar procedure to **9a**, **7k** (108 mg, 94.4 μmol) was deacetylated to give crude **8k**, which was deprotected to furnish **9k** (58.3 mg, 66% in two steps).

$[\alpha]_D^{21}$ −49° (*c* 0.55, $CHCl_3$); FAB-MS *m*/*z* 942 $(M+H)^+$; ^1H NMR δ 0.00 (d, 6.6 Hz, 3H, 19-H), 1.03 (d, 6.0 Hz, 3H, 6′-H), 1.07 (s, Hz, 3H, 3″-CH_3), 1.08 (d, 6.0 Hz, 3H, 6″-H), 1.15 (t, 7.6 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.25–1.36 (m, 1H, 7-H), 1.27 (d, 6.3 Hz, 3H, 16-H), 1.74–1.85 (m, 1H, 8-H), 1.75 (dd, 14.4, 3.9 Hz, 1H, 2″-Hax), 1.85 (br d, 14.4 Hz, 1H, 2″-Heq), 1.97–2.09 (m, 1H, 6-H), 2.14 (dt, 14.1, 10.8 Hz, 1H, 14-H), 2.34–2.46 (m, 2H, 4″-$OCOCH_2CH_3$), 2.34–2.51 (m, 4H, 2-, 14-, 17-, 3′-H), 2.46 (s, 6H, 3′-$N(CH_3)_2$), 2.74 (dd, 16.2, 6.0 Hz, 1H, 2-H), 2.91 (m, 1H, 17-H), 2.93 (dd, 6.9, 2.7 Hz, 1H, 4-H), 3.08 (dq, 9.6, 6.0 Hz, 1H, 5′-H), 3.18 (t, 9.6 Hz, 1H, 4′-H), 3.47 (s, 3H, 4-OCH_3), 3.52 (dd, 10.3, 8.1 Hz, 1H, 2′-H), 3.71 (br, 1H, 3-H), 3.80 (br, 1H, 5-H), 4.11 (dd, 8.1, 3.6 Hz, 1H, 9-H), 4.26 (br dd, 12.6, 6.3 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.36 (br dd, 12.6, 6.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.36 (d, 7.8 Hz, 1H, 1′-H), 4.42 (dq, 10.2, 6.0 Hz, 1H, 5″-H), 4.56 (d, 10.2 Hz, 1H, 4″-H), 4.93 (d, 3.5 Hz, 1H, 1″-H), 5.17 (m, 1H, 15-H), 5.60 (m, 1H, 13-H), 5.64 (dd, 14.9, 8.1 Hz, 1H, 10-H), 6.04 (br dd, 15.0, 10.3 Hz, 1H, 12-H), 6.20 (dd, 15.1, 10.3 Hz, 1H, 11-H), 6.42 (dt, 15.9, 6.0 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.62 (d, 15.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.45 (d, 8.4 Hz, 2H, C_6H_4–CF_3), 7.53 (d, 8.4 Hz, 2H, C_6H_4–CF_3), 9.74 (br s, 1H, 18-H); HRMS: Calcd for $C_{48}H_{70}F_3NO_{14}$: 942.4827. Found: 942.4810.

4.2.29. 3-*O*-[3-(4-Biphenylyl)-2-propenyl]leucomycin A_7 (9l). By a similar procedure to **9a**, **7l** (162 mg, 141 μmol) was deacetylated to give crude **8l**, which was deprotected to furnish **9l** (74.6 mg, 59% in two steps).

$[\alpha]_D^{20}$ −40° (*c* 0.52, $CHCl_3$); FAB-MS *m*/*z* 950 $(M+H)^+$; ^1H NMR δ 0.98 (s, 3H, 3″-CH_3), 1.02 (d, 6.9, Hz, 3H, 19-H), 1.06 (d, 6.0 Hz, 3H, 6′-H), 1.08 (d, 6.0 Hz, 3H, 6″-H), 1.15 (t, 7.6 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.24–1.36 (m, 1H, 7-H), 1.29 (d, 6.3 Hz, 3H, 16-H), 1.60–1.80 (m, 1H, 8-H), 1.66 (dd, 14.4, 3.9 Hz, 1H, 2″-Hax), 1.77 (br d, 14.4 Hz, 1H, 2″-Heq), 1.97–2.10 (m, 1H, 6-H), 2.16 (dt, 14.1, 10.8 Hz, 1H, 14-H), 2.33–2.48 (m, 2H, 4″-$OCOCH_2CH_3$), 2.33–2.55 (m, 4H, 2-, 14-, 17-, 3′-H), 2.47 (s, 6H, 3′-$N(CH_3)_2$), 2.76 (dd, 16.5, 5.4 Hz, 1H, 2-H), 2.94 (dd, 7.0, 2.0 Hz, 1H, 4-H), 2.94 (m, 1H, 17-H), 3.11 (dq, 9.3, 6.0 Hz, 1H, 5′-H), 3.18 (t, 9.3 Hz, 1H, 4′-H), 3.50 (s, 3H, 4-OCH_3), 3.54 (dd, 10.0, 7.6 Hz, 1H, 2′-H), 3.74 (br, 1H, 3-H), 3.83 (br, 1H, 5-H), 4.14 (dd, 8.1, 3.2 Hz, 1H, 9-H), 4.24 (br dd, 12.3, 6.6 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.38 (br dd, 12.3, 5.8 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.40 (d, 7.5 Hz, 1H, 1′-H), 4.42 (dq, 10.2, 6.0 Hz, 1H, 5″-H), 4.54 (d, 10.2 Hz, 1H, 4″-H), 4.91 (d, 3.3 Hz, 1H, 1″-H), 5.22 (m, 1H, 15-H), 5.65 (m, 1H, 13-H), 5.66 (dd, 14.7, 8.4 Hz, 1H, 10-H), 6.06 (br dd, 15.3, 10.5 Hz, 1H, 12-H), 6.23 (dd, 15.0, 10.5 Hz, 1H, 11-H), 6.37 (dt, 15.9, 6.3 Hz, 1H, 3-O–CH_2CH=CH–Ar), 6.63 (d, 15.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.31 (m, 1H, C_6H_4-Ph), 7.39 (br d, 7.8 Hz, 2H, C_6H_4–Ph), 7.45 (br d, 8.8 Hz, 2H, C_6H_4–Ph), 7.53–7.61 (m, 2H, C_6H_4–Ph), 7.55 (br d, 9.0 Hz, 2H, C_6H_4–Ph), 9.78 (br s, 1H, 18-H); HRMS: Calcd for $C_{53}H_{75}NO_{14}$: 950.5266. Found: 950.5264.

4.2.30. 3-*O*-{3-[4-(1-Imidazolyl)phenyl]-2-propenyl}leucomycin A_7 (9m). By a similar procedure to **9a**, **7m** (167 mg, 146 μmol) was deacetylated to give crude **8m**, which was deprotected to furnish 100 mg of **9m**. A portion of **9m** (49.6 mg) was purified by preparative TLC to afford **9m** (39.9 mg, 56% in two steps).

$[\alpha]_D^{23}$ −40° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 940 $(M+H)^+$; ^1H NMR δ 0.02 (d, 6.6 Hz, 3H, 19-H), 1.03 (s, 3H, 3″-CH_3), 1.08 (d, 6.0 Hz, 3H, 6″-H), 1.10 (d, 6.0 Hz, 3H, 6′-H), 1.15 (t, 7.5 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.16–1.39 (m, 2H, 7-H), 1.28 (d, 6.3 Hz, 3H, 16-H), 1.72–1.84 (m, 1H, 8-H), 1.74 (dd, 14.2, 3.4 Hz, 1H, 2″-Hax), 1.82 (br d, 14.2 Hz, 1H, 2″-Heq), 1.96–2.10 (m, 1H, 6-H), 2.15 (dt, 14.4, 10.8 Hz, 1H, 14-H), 2.36–2.52 (m, 4H, 2-, 14-, 17-, 3′-H), 2.37–2.48 (m, 2H, 4″-$OCOCH_2CH_3$), 2.46 (s, 6H, 3′-$N(CH_3)_2$), 2.76 (dd, 16.2, 6.3 Hz, 1H, 2-H), 2.93 (dd, 18.0, 10.2 Hz, 1H, 17-H), 2.95 (dd, 6.5, 2.3 Hz, 1H, 4-H), 3.12 (dq, 9.6, 6.0 Hz, 1H, 5′-H), 3.19 (t, 9.6 Hz, 1H, 4′-H), 3.49 (s, 3H, 4-OCH_3), 3.53 (dd, 9.6, 7.5 Hz, 1H, 2′-H), 3.72 (br, Hz, 1H, 3-H), 3.83 (br, 1H, 5-H), 4.12 (dd, 8.1, 4.0 Hz, 1H, 9-H), 4.27 (br dd, 12.3, 6.3 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.35 (br dd, 12.3, 6.3 Hz, 1H, 3-O–CH_2CH=CH–Ar), 4.38 (d, 7.5 Hz, 1H, 1′-H), 4.42 (dq, 9.6, 6.0 Hz, 1H, 5″-H), 4.56 (d, 9.6 Hz, 1H, 4″-H), 4.95 (d, 3.1 Hz, 1H, 1″-H), 5.18 (m, 1H, 15-H), 5.62 (m, 1H, 13-H), 5.66 (dd, 15.0, 8.4 Hz, 1H, 10-H), 6.06 (br dd, 14.9, 10.1 Hz, 1H, 12-H), 6.22 (dd, 15.0, 10.4 Hz, 1H, 11-H), 6.36 (dt, 15.9, 6.1 Hz, 1H, 3-O–CH_2CH=CHAr), 6.62 (d, 15.9 Hz, 1H, 3-O–CH_2CH=CH–Ar), 7.16 (br s, 1H, imidazole), 7.27 (br s, 1H, imidazole), 7.32 (d, 8.4 Hz, 2H, C_6H_4–imidazole), 7.47 (d, 8.4 Hz, 2H, C_6H_4–imidazole), 7.85 (br s, 1H, imidazole), 9.76 (br s, 1H, 18-H); HRMS: Calcd for $C_{50}H_{73}N_3O_{14}$: 940.5171. Found: 940.5185.

4.2.31. 2′-*O*-Acetyl-9,18-di-*O*-(*tert*-butyldimethylsilyl)-3″-*O*-(3-phenylpropionyl)leucomycin A_7 3,18-acetal (11). To a stirred solution of **10** (0.300 g, 0.292 mmol) and tribenzylamine (0.516 g, 1.80 mmol) in 1 ml of 1,2-dichloroethane, 3-phenylpropionyl chloride (0.125 ml, 0.841 mmol) was added and the reaction mixture was stirred for 2 days at 75 °C. Saturated aqueous $NaHCO_3$ solution was added to the reaction mixture and the aqueous layer was extracted with $CHCl_3$. The extract was washed with 5% aqueous $KHSO_4$ solution, saturated aqueous $NaHCO_3$ solution, and brine. After the organic layer was dried and concentrated, the residue was purified by silica gel chromatography [30 g, hexane/EtOAc (5:1–4:1)] to give **11** (191 mg, 56%).

$[\alpha]_D^{25}$ −32° (*c* 0.51, $CHCl_3$); FAB-MS *m*/*z* 1160 $(M+H)^+$; ^1H NMR δ 0.00 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.42 (br t, 12.7 Hz, 1H, 7-H), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.92 (d, 7.6 Hz, 3H, 19-H), 0.94 (s, 9H, $SiC(CH_3)_3$), 1.09 (d, 6.0 Hz, 3H, 6″-H), 1.19 (t, 7.6 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.21 (d, 6.4 Hz, 3H, 6′-H), 1.31 (d,

6.0 Hz, 3H, 16-H), 1.40 (s, 3H, 3″-CH_3), 1.45 (br d, 14.4 Hz, 1H, 17-H), 1.52 (m, 1H, 8-H), 1.59–1.69 (m, 1H, 17-H), 1.71 (dd, 14.8, 4.0 Hz, 1H, 2″-Hax), 2.11 (s, 3H, 2′-$OCOCH_3$), 2.21 (dd, 13.2, 1.6 Hz, 1H, 2-H), 2.21 (m, 1H, 6-H), 2.28–2.46 (m, 3H, 7-, 14-H), 2.34–2.44 (m, 2H, 4″-$OCOCH_2CH_3$), 2.43 (s, 6H, 3′-$N(CH_3)_2$), 2.52–2.70 (m, 2H, 3″-$OCOCH_2CH_2Ph$), 2.68 (t, 10.2 Hz, 1H, 3′-H), 2.66–2.72 (m, 1H, 2-H), 2.92 (br s, 1H, 4-H), 2.93–2.99 (m, 2H, 3″-$OCOCH_2CH_2Ph$), 3.06–3.17 (m, 2H, 4′-, 5′-H), 3.23 (d, 14.8 Hz, 1H, 2″-Heq), 3.28 (br d, 10.0 Hz, 1H, 5-H), 3.34 (s, 3H, 4-OCH_3), 4.13 (br d, 12.5 Hz, 1H, 3-H), 4.19 (m, 1H, 9-H), 4.20 (d, 7.6 Hz, 1H, 1′-H), 4.52 (m, 1H, 5″-H), 4.53 (br d, 12.4 Hz, 1H, 18-H), 4.58 (d, 9.6 Hz, 1H, 4″-H), 4.65 (m, 1H, 15-H), 4.83 (d, 4.0 Hz, 1H, 1″-H), 5.07 (dd, 10.2, 7.8 Hz, 1H, 2′-H), 5.47 (ddd, 15.2, 9.6, 5.8 Hz, 1H, 13-H), 5.93 (dd, 16.1, 8.6 Hz, 1H, 11-H), 5.96 (dd, 16.1, 5.6 Hz, 1H, 10-H), 6.31 (br dd, 15.0, 8.6 Hz, 1H, 12-H), 7.19–7.32 (m, 5H, 3″-$OCOCH_2CH_2Ph$).

4.2.32. 3″-*O*-(3-Phenylpropionyl)leucomycin A_7 (12). A solution of **11** (215 mg, 0.185 mmol) in 12 ml of MeOH/H_2O (10:1) was stirred overnight at 45 °C. The reaction mixture was concentrated and the residue was purified by silica gel chromatography [20 g, hexane/EtOAc (5:1)] to give 9,18-di-*O*-(*tert*-butyldimethylsilyl)-3″-*O*-(3-phenylpropionyl)leucomycin A_7 3,18-acetal (162 mg, 78%).

To a stirred solution of this compound (89.5 mg, 80.0 μmol) in 1.5 ml of THF, 0.1 M solution of TBAF (1.60 ml, 160 μmol) was added and the reaction mixture was stirred for 15 min at room temperature. Five percentage aqueous $KHSO_4$ solution was added to the reaction mixture and the aqueous layer was extracted with $CHCl_3$. After the extract was washed with brine, the organic layer was dried and concentrated to give crude 9-*O*-(*tert*-butyldimethylsilyl)-3″-*O*-(3-phenylpropionyl)leucomycin A_7.

To a stirred solution of this crude product in 26 ml of MeCN/H_2O (1:1), difluoroacetic acid (25.0 μl, 397 μmol) was added and the reaction mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ solution 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 preparative TLC [$CHCl_3$/MeOH/NH_4OH (100:10:1)] to afford **12** (58.1 mg, 82%).

$[\alpha]_D^{25}$ −58° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 890 $(M+H)^+$; ^1H NMR δ 0.92 (m, 1H, 7-H), 0.99 (d, 6.4 Hz, 3H, 19-H), 1.08 (d, 6.2 Hz, 3H, 6″-H), 1.15 (d, 6.0 Hz, 3H, 6′-H), 1.17 (t, 7.6 Hz, 3H, 4″-$OCOCH_2CH_3$), 1.31 (d, 6.4 Hz, 3H, 16-H), 1.38 (s, 3H, 3″-CH_3), 1.55 (br dt, 2.4, 13.3, Hz, 1H, 7-H), 1.71 (dd, 14.7, 4.4 Hz, 1H, 2″-Hax), 1.91 (m, 1H, 8-H), 2.12 (dt, 13.2, 11.2 Hz, 1H, 14-H), 2.23 (br d, 14.8 Hz, 1H, 2-H), 2.25–2.42 (m, 2H, 6-, 17-H), 2.33 (t, 9.8 Hz, 1H, 3′-H), 2.39 (q, 7.6 Hz, 2H, 4″-$OCOCH_2CH_3$), 2.48–2.56 (m, 1H, 14-H), 2.52 (s, 6H, 3′-$N(CH_3)_2$), 2.54–2.68 (m, 2H, 3″-$OCOCH_2CH_2Ph$), 2.70 (dd, 14.8, 10.8 Hz, 1H, 2-H), 2.86 (br dd, 16.8, 9.6 Hz, 1H, 17-H), 2.92 (br t, 7.8 Hz, 2H, 3″-$OCOCH_2CH_2Ph$), 3.08 (br d, 4.2 Hz, 1H, 4-H), 3.11 (dq, 9.4, 6.0 Hz, 1H, 5′-H), 3.21 (t, 9.4 Hz, 1H, 4′-H), 3.23 (d, 14.7 Hz, 1H, 2″-Heq), 3.31 (dd, 10.0, 7.6 Hz, 1H, 2′-H), 3.52 (s, 3H, 4-OCH_3), 3.79 (br d, 10.8 Hz, 1H, 3-H), 4.07–4.13 (m, 1H, 5-H), 4.11 (br dd, 9.6, 4.0 Hz, 1H, 9-H), 4.47 (dq, 9.6, 6.2 Hz, 1H, 5″-H), 4.49 (d, 7.6 Hz, 1H, 1′-H), 4.58 (d, 9.6 Hz, 1H, 4″-H), 4.86 (d, 4.4 Hz, 1H, 1″-H), 5.29 (m, 1H, 15-H), 5.62 (ddd, 15.2, 11.2, 4.4 Hz, 1H, 13-H), 5.68 (dd, 15.0, 9.6 Hz, 1H, 10-H), 6.03 (br dd, 15.2, 10.4 Hz, 1H, 12-H), 6.27 (dd, 15.0, 10.6 Hz, 1H, 11-H), 7.18–7.31 (m, 5H, 3″-$OCOCH_2CH_2Ph$), 9.80 (s, 1H, 18-H); HRMS: Calcd for $C_{47}H_{71}NO_{15}$: 890.4902, Found: 890.4910.

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23. Molecular modeling software, Quanta/CHARMm (Accelrys Software Inc.) was used for our studies. Initial structures and conformations of **4**, **9a**, and **12** were constructed by referring the X-ray single crystallographic data of RKM.[19] Systematic search was carried out on the torsional angles of the side chains at the C-3 and/or C-3″ positions for conformational analyses.