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Novel 16-membered macrolides modified at C-12 and C-13 positions of midecamycin A_1 and miokamycin. Part 1: Synthesis and evaluation of 12,13-carbamate and 12-arylalkylamino-13-hydroxy analogues

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Abstract—Design and synthesis of 16-membered macrolides modified at the C-12 and 13 positions are described. The compounds we report here have an arylalkylamino group attached to the C-12 position of the macrolactone. Both types of derivatives, 12,13-cyclic carbamates and non-carbamate analogues, were synthesized via 12-amino-13-hydroxy intermediates derived from 12,13-epoxide that was prepared by selective epoxidation at the C-12 and C-13 positions. 4′-Hydroxyl analogues were also prepared by acidic hydrolysis of a neutral sugar. These compounds were evaluated for in vitro antibacterial activity against respiratory tract pathogens. Some of these analogues exhibited an improved activity compared with the corresponding parent compound.
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1. Introduction

Macrolide antibiotics generally have low toxicity and are orally available. Therefore they play an important role in therapeutic treatments of bacterial infectious diseases. In particular, clinically representative macrolides such as clarithromycin (CAM)[1–6] and azithromycin (AZM)[7,8] derived from 14-membered erythromycin exhibit strong antibacterial activities against respiratory tract pathogens and have characteristic pharmacokinetics. An extensive use of these macrolides has, however, allowed an increase in emergence of erythromycin-resistant gram-positive bacteria, especially *Streptococcus pneumoniae*. Macrolide-resistant *S. pneumoniae* are roughly classified into ribosome methylation by an *erm* gene and efflux of macrolides by a *mef* gene. Recently, several researches have been made to overcome macrolide resistance, which resulted in the discovery of ketolides such as telithromycin (TEL)[9] and cethromycin (ABT-773)[10,11] (Fig. 1). These ketolides synthesized from 14-membered erythromycin showed strong potency against the *erm*- and *mef*-resistant *S. pneumoniae*.

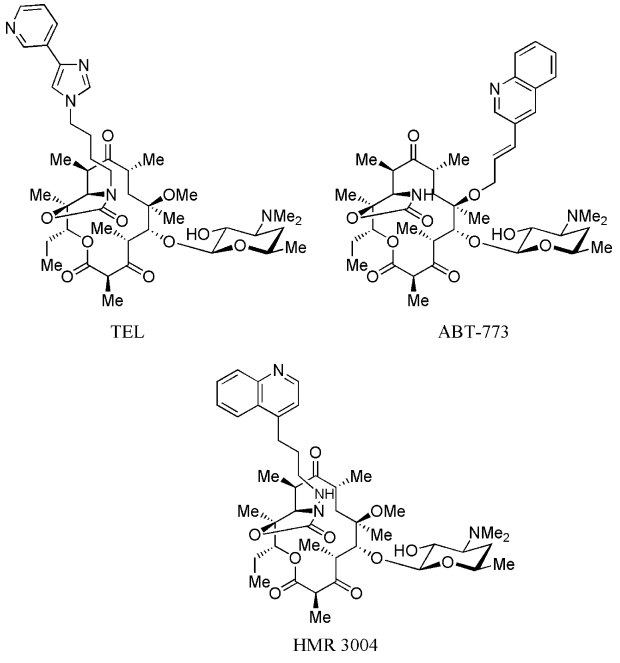

Figure 1. Structures of ketolides.

On the other hand, 16-membered macrolides that possess enough effects against resistant pathogens are rarely known. Some derivatives of leucomycin-type

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16-membered macrolides such as miokamycin (MOM)[12] and rokitamycin (RKM)[13,14] (Fig. 2) are not affected by efflux pumps. If we can discover the 16-membered macrolides possessing an activity against the *erm*-resistant *S. pneumoniae*, it would be very beneficial for chemotherapy against infectious diseases.

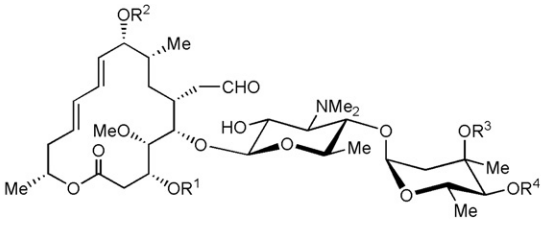
There is an aryl group in the ketolide molecule in general. The ketolide class compounds, such as TEL and HMR 3004[15] (Fig. 1), possess an arylalkyl-type side chain attached to the 11,12-cyclic carbamate in the western hemisphere of the macrolactone. It was reported that the arylalkyl group protected A752 residue in domain II of ribosomal RNA against chemical modification.[16] These observations suggested that the aryl side chain might interact with the second binding site in rRNA. Further, X-ray crystallographic analysis on ketolide–ribosome complex indicated that the aryl group of TEL or ABT-773 bound to domain II through stacking or hydrogen bonding.[17,18] Thus, the aryl side chain is significantly important for antibacterial activities against erythromycin-resistant pathogens. We recently exemplified novel azalides synthesized from leucomycin-type 16-membered macrolide.[19,20] To our knowledge, this is information on the introduction of an arylalkyl side chain in the western hemisphere as far as leucomycin analogues are concerned.

In this paper, we would like to disclose preparation and potency of 12,13-carbamate and 12-arylalkylamino-13-hydroxy analogues of midecamycin A_1.

2. Results and discussion

2.1. Preparation of 12,13-cyclic carbamates and their antibacterial activities

For introduction of an aryl moiety onto a macrolactone, we focused on the conjugated diene at the C-10 to 13 positions in leucomycin-type 16-membered macrolide. Muroi et al. described stereoselective and non-regioselective epoxidation at the C-10 to 13 positions in leucomycin A_3 (josamycin). They first peroxidized leucomycin



	R^1	R^2	R^3	R^4
Miokamycin (MOM)	COEt	Ac	Ac	COEt
Rokitamycin (RKM)	H	H	COEt	CO^{n}Pr
Midecamycin A_1 (MDM)	COEt	H	H	COEt

Figure 2. Natural antibiotic, midecamycin A_1 and representative semisynthetic 16-membered macrolides, miokamycin and rokitamycin.

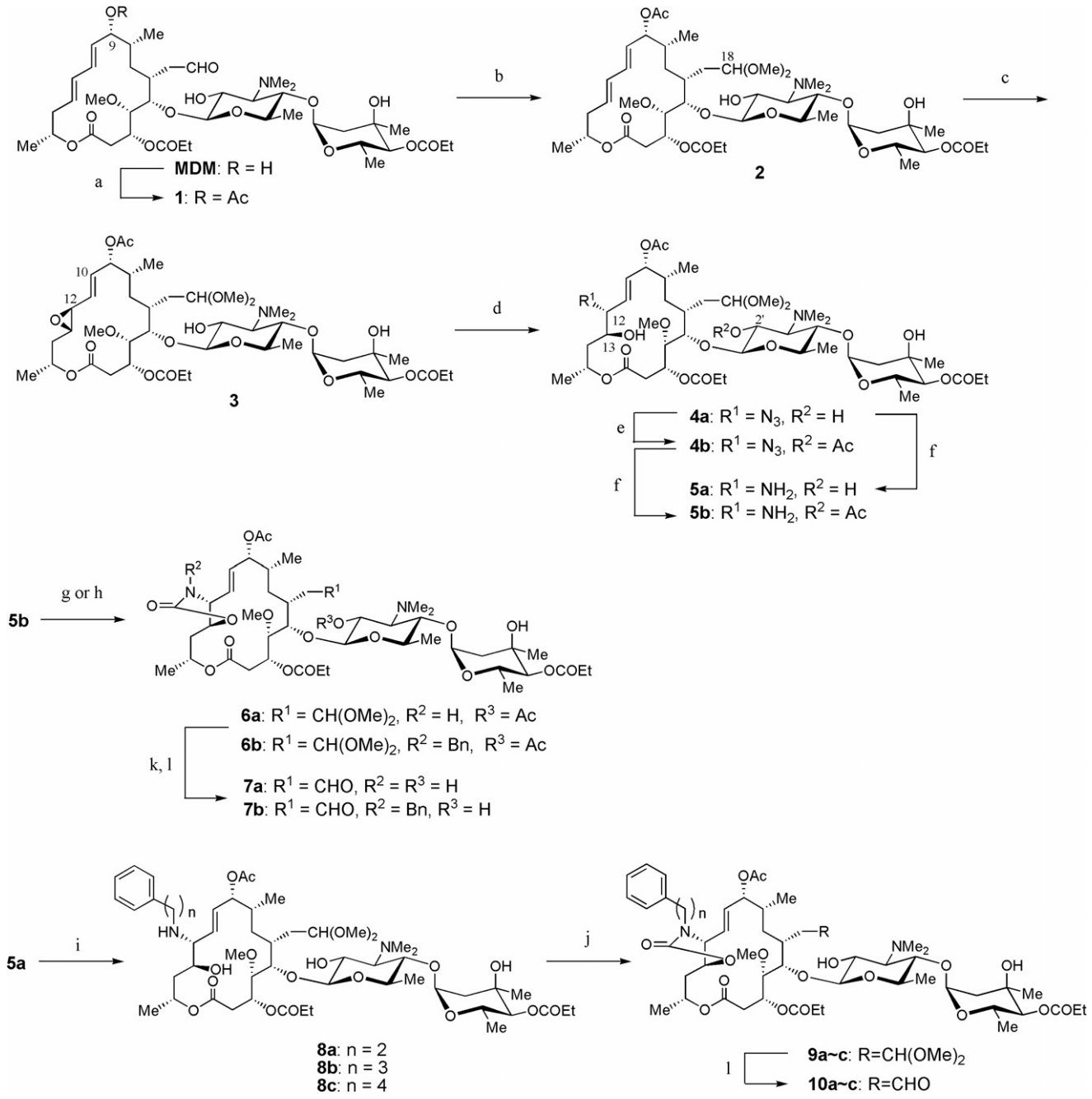
A_3 with *m*-chloroperbenzoic acid (*m*-CPBA) to afford the epoxy-*N*-oxide, and then reduced the *N*-oxide moiety with $Na_2S_2O_4$ to give the epoxide.[21] On the basis of this knowledge, we decided to synthesize an epoxide (**3**) by regio- and stereoselective reaction of **2** with *m*-CPBA. We planned to perform a ring-opening reaction of the epoxide (**3**) at an allylic position, which would afford an azide (**4**). It would then be converted into an amine intermediate (**5**).

In order to analyze fundamental structure–activity relationships (SAR), we chose midecamycin A_1 (MDM) as a starting material. Then, we decided to use 9-*O*-acetyl derivative (**2**) for accomplishment of regioselective epoxidation at the C-12,13 positions.

The synthetic methods of 12,13-cyclic carbamates are shown in Scheme 1. Protection at the C-18 position of 9-*O*-acetylmidecamycin A_1 (**1**)[22] afforded dimethyl acetal (**2**). Epoxidation of **2** with *m*-CPBA followed by reduction of a 3′-*N*-oxide using $Na_2S_2O_4$ gave the epoxide (**3**) regio- and stereoselectively. The structure of the epoxide (**3**) was determined by X-ray crystallographic analysis. Ring-opening reaction of the epoxide with sodium azide proceeded at the allylic position to generate the azide (**4a**), which was converted to **4b** by acetic anhydride without a base. Then, treatment of **4a** or **4b** with triphenylphosphine gave the corresponding 12-amino analogues (**5a** or **5b**). Conversion of **5b** to the cyclic carbamate (**6a**) was achieved with 1,1′-carbonyldiimidazole (CDI) at room temperature. Although the benzyl analogue (**6b**) was also obtained by reductive alkylation of **5b** with benzaldehyde followed by cyclization with CDI, higher reaction temperature and longer reaction time were required in this cyclization step. The phenylalkyl analogues (**9a**–**c**) were therefore prepared by treatment of the secondary amines (**8a**–**c**) derived from **5a** with triphosgene and triethylamine. Deprotection of **6a**, **b** and **9a**–**c** afforded the final products (**7a**, **b** and **10a**–**c**).

In compound **10b**, NOEs were observed between the proton at C-11 and the methylene proton at C-14, and also between the methine proton at C-12 and the methine proton at C-13. This result suggested that **10b** adopted 12*R* and 13*S* configuration (A in Fig. 3). On the other hand, in case of 12*S* and 13*S* configuration, NOE was not observed between the protons at the C-11 and C-14 positions or between the protons at the C-12 and C-13 positions (B in Fig. 3). We thus finally concluded that substitution by azide anion of the epoxide (**3**) proceeded through trans ring-opening reaction.

As shown in Table 1, antibacterial activities of these compounds against gram-positive bacteria were generally comparable with that of compound **1** or MDM. All compounds maintained antibacterial activities against efflux-resistant *S. pneumoniae* and characteristics of 16-membered macrolides as we had expected. An increase in the spacer length, however, led to a decrease in the activities against *Haemophilus influenzae*. On the other hand, **7b**, **10a**, and **10c** having phenylalkyl groups showed weak antibacterial activities against inducible-



Scheme 1. Synthesis of 12,13-cyclic carbamates of MDM. Reagents and conditions: (a) AcCl, pyridine, CH_2Cl_2, 0 °C, 45 min, quant; (b) pyridinium *p*-toluenesulfonate, $CH(OMe)_3$, MeOH, 50 °C, 33 h, 80%; (c) 1—*m*-CPBA, $CHCl_3$, rt, 14 h; 2—aq $Na_2S_2O_4$, EtOH, 0 °C, 30 min, 62% overall two steps; (d) NaN_3, NH_4Cl, EtOH/H_2O (8:1), 80 °C, 21 h, 73%; (e) Ac_2O, MeCN, 50 °C, 8 h, 90%; (f) Ph_3P, MeCN, rt, 23 h then H_2O, rt, 6 h, 67–68%; (g) CDI, THF, rt, 3 h, 88%; (h) 1—PhCHO, $NaBH(OAc)_3$, AcOH, $Cl(CH_2)_2Cl$, rt, 2 h, 80%; 2—CDI, THF, reflux, 26 h, 81%; (i) $Ph(CH_2)_{n-1}CHO$, $NaBH_3CN$, AcOH, MeOH, rt, 1–1.5 h, 33–59%; (j) triphosgene, Et_3N, CH_2Cl_2, 0 °C, 45 min–1.5 h, 42–90%; (k) MeOH/H_2O (9:1), 50 °C, 24–27 h, 97%; (l) CHF_2COOH, MeCN/H_2O (1:1), rt–35 °C, 26.5–41 h, 61–69%.

resistant *S. pneumoniae*. Although improved antibacterial activities were expected by converting the phenyl group to a certain heterocycle shown in ketolides (Fig. 1), for example, the quinolinyl group, we supposed that the construction of cyclic carbamate at the western hemisphere in 16-membered macrolide was not always an appropriate approach for seeking strong antimicrobial activities. We therefore decided to investigate fundamental SAR of compounds without the ring structure in the western hemisphere.

2.2. Preparation of 12-arylalkylamino-13-hydroxy analogues and their antibacterial activities

Scheme 2 describes the synthesis of 12-arylalkylamino-13-hydroxy analogues starting from the amine, **5a**. Reductive methylation of **5a** and **8a**–**c** with formaldehyde gave the corresponding 12-dialkylamino analogues (**11a** and **11c**–**e**). Moreover, other analogues (**11b** and **11f**–**h**) with a phenyl group attached to a different methylene linker or **11i**–**m** with a variety of aryl groups at-

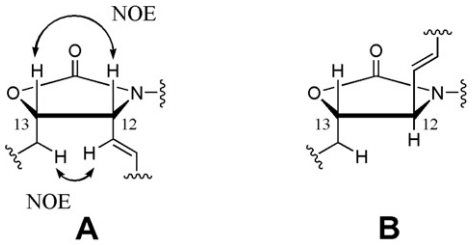


Figure 3. Possible configuration at the C-12 and C-13 positions in cyclic carbamates.

tached to a propyl group were prepared from **5a** by sequential reductive alkylations. Deprotection of **11a–m** with difluoroacetic acid furnished the desired products (**12a–m**) in 24–64% yield accompanied with the monosaccharide analogues (**13d** and **13i–m**) in which the neutral sugar was removed.

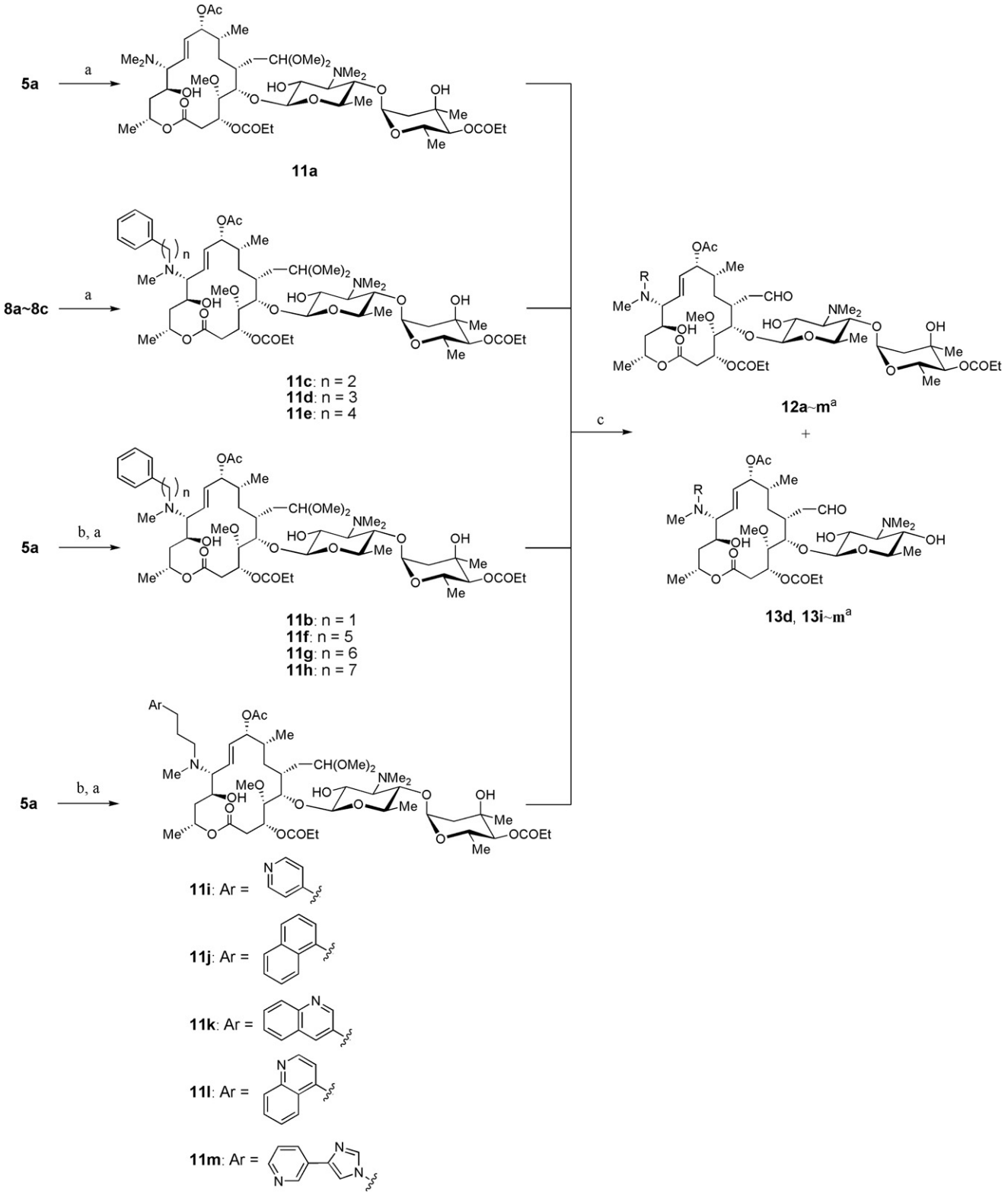
By the way, MOM, 3″-*O*-acetyl analogue of **1**, was much more active than **1** against inducible-resistant *S. pneumoniae*. Then, we decided to prepare the 3″-*O*-acetyl analogue of **12d**, compound **18**, as a model study focusing on antibacterial activities against *erm*-resistant *S. pneumoniae*. As shown in Scheme 3, compound **18** was synthesized by a similar method to **12d** starting from MOM. In this case, hydrolysis of the neutral sugar in the final deprotection step was not observed at all, unlike in the case of deprotection of **11**. The chemical stability of compound **18** under acidic conditions could be explained by 1, 3-diaxial relationship between the 4′-oxygen atom and the 3″-*O*-acetyl group. This phenomenon is often observed and acidic hydrolysis at the neutral sugar is believed to be spatially disturbed by the acetyl group.

The 12-dimethylamino analogue (**12a**) without a phenyl group was a little less active than **1** as shown in Table 2. The 12-phenylalkylamino analogues (**12f–h**) that have the spacer length of C5–C7 exhibited weak antibacterial activities against not only inducible-resistant *S. pneumoniae* but also constitutive ones. The activities of the 12-phenylpropylamino analogue (**12d**), however, seemed to exhibit the best-balanced antibacterial spectrum except against constitutive-resistant *S. pneumoniae*. We prepared some compounds with a variety of substituents, for example, methoxy, dimethylamino, fluoro, nitro etc., on the benzene ring of **12d**, but antibacterial activities of these compounds were not enhanced compared with those of **12d** (data not shown). Thus, the phenyl group of **12d** was converted into various aryl groups. The antibacterial activities against inducible-resistant *S. pneumoniae* were decreased, when a nitrogen atom was introduced into the benzene ring in **12d** (see **12i** in Table 3). On the other hand, introduction of a nitrogen atom into the naphthalene ring of **12j** was effective, namely, **12l** generally exhibited enhanced antibacterial activities and had the strongest activities among 3″-OH analogues. Antibacterial activities of **12l** against resistant *S. pneumoniae* were stronger than those of CAM. Compound **12l** was also effective against constitutive-resistant *S. pneumoniae*. We expected that the activity of the compound **12m** having the side chain of TEL would be enhanced, but its activity was not remarkable.

Table 1. Antibacterial activities of 12,13-cyclic carbamates

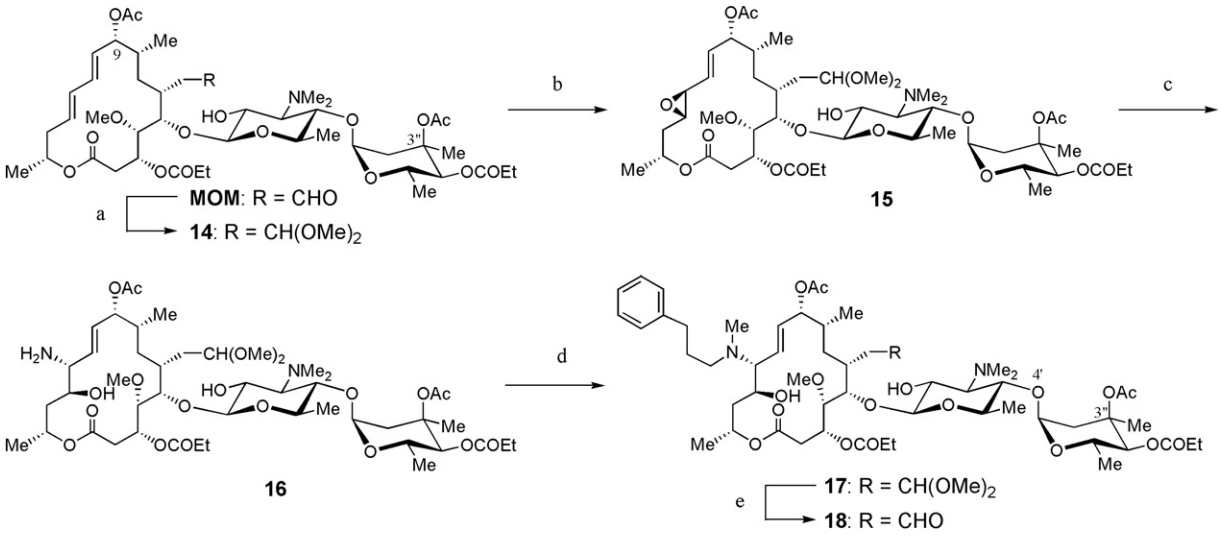
Test organism[a]	Characteristics	(MIC, μg/ml)						
		7a	**7b**	**10a**	**10b**	**10c**	**1**	MDM
S. aureus	Standard	0.39	0.39	0.78	0.78	0.78	0.39	0.39
S. aureus	Susceptible	0.78	0.78	0.78	0.78	0.78	0.78	0.78
S. aureus	Susceptible	0.39	0.39	0.39	0.78	0.39	0.39	0.78
S. aureus	*ermA* (c)[b]	>100	>100	>100	>100	>100	>100	>100
S. aureus	*ermB* (i)[c]	0.39	0.39	6.25	1.56	0.39	0.39	0.78
S. aureus	*ermC* (i)[c]	0.78	0.78	1.56	0.78	0.78	0.78	0.78
S. pneumoniae	Susceptible	0.2	0.2	0.2	0.2	0.2	0.2	0.39
S. pneumoniae	Susceptible	0.39	0.39	0.39	0.39	0.2	0.39	0.78
S. pneumoniae	*ermB* (c)[b]	>100	>100	>100	>100	>100	>100	>100
S. pneumoniae	*ermB* (i)[c]	>100	100	50	>100	100	100	>100
S. pneumoniae	*ermB* (i)[c]	>100	100	>100	>100	100	>100	>100
S. pneumoniae	*mefE* efflux	0.2	0.2	0.2	0.39	0.2	0.2	0.2
S. pneumoniae	*mefE* efflux	0.2	0.2	0.2	0.2	0.2	0.2	0.2
S. pyogenes	Standard	N.T.[d]	N.T.[d]	N.T.[d]	N.T.[d]	N.T.[d]	N.T.[d]	0.2
S. pyogenes	*ermB* (c)[b]	>100	>100	>100	>100	>100	>100	>100
S. pyogenes	*mefE* efflux	0.2	0.2	0.1	0.2	0.39	0.39	0.78
M. catarrhalis	Standard	0.39	1.56	0.78	1.56	3.13	0.78	1.56
M. catarrhalis	Standard	0.78	1.56	1.56	3.13	3.13	1.56	1.56
H. influenzae	Standard	0.78	3.13	3.13	6.25	6.25	3.13	3.13
H. influenzae	Standard	6.25	12.5	25	50	>100	12.5	12.5
H. influenzae	Susceptible	6.25	25	25	100	>100	25	12.5

[a] *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*; *S. pyogenes*, *Streptococcus pyogenes*; *M. catarrhalis*, *Moraxella catarrhalis*; *H. influenzae*, *Haemophilus influenzae*.
[b] Constitutive resistant.
[c] Inducible resistant.
[d] Not tested.



Scheme 2. Synthesis of 12-arylalkylamino analogues of MDM. Reagents and conditions: (a) HCHO, AcOH, $NaBH_3CN$, MeCN or MeOH, 0 °C–rt, 0.5–3 h, 60–97%; (b) the corresponding aldehyde, AcOH, $NaBH(OAc)_3$ or $NaBH_3CN$, AcOH, $Cl(CH_2)_2Cl$ or MeOH, rt, 1–4 h, 36–81%; (c) CHF_2COOH, MeCN/H_2O (1:1), rt, 4–75 h, 24–64% for **12**, 16–44% for **13**. [a]R: (a) Me; (b) benzyl; (c) 2-phenylethyl; (d) 3-phenylpropyl; (e) 4-phenylbutyl; (f) 5-phenylpentyl; (g) 6-phenylhexyl; (h) 7-phenylheptyl; (i) 3-(pyridin-4-yl)propyl; (j) 3-(naphthalen-1-yl)propyl; (k) 3-(quinolin-3-yl)propyl; (l) 3-(quinolin-4-yl)propyl; (m) 3-[4-(pyridin-3-yl)-imidazol-1-yl]propyl.

As a result, introduction of an acetyl group at the C-3″ position was shown to be important for enhancement of antibacterial activities against inducible-resistant *S. pneumoniae* in comparison between **12d** and **18** in Table 3. In general, a neutral sugar enhances its antibacterial activities, and the above-mentioned result was



Scheme 3. Synthesis of 12-(3-phenylpropyl)amino analogue of MOM. Reagents and conditions: (a) pyridinium *p*-toluenesulfonate, $CH(OMe)_3$, MeOH, 45 °C, 3 days, 79%; (b) 1—*m*-CPBA, $CHCl_3$, rt, 14 h; 2—aq $Na_2S_2O_4$, EtOH, 0 °C, 30 min, 53% overall two steps; (c) 1—NaN_3, NH_4Cl, EtOH/H_2O (8:1), 80 °C, 32 h; 2—Ph_3P, MeCN, rt, 21 h then H_2O, rt, 6 h, 69% overall two steps; (d) 1—$Ph(CH_2)_2CHO$, $NaBH_3CN$, AcOH, MeOH, rt, 2 h; 2—HCHO, $NaBH_3CN$, AcOH, MeOH, 0 °C, 1 h, 40% overall two steps; (e) CHF_2COOH, MeCN/H_2O (1:1), rt, 24 h, 87%.

Table 2. Antibacterial activities of 12-phenylalkylamino analogues with a variety of spacer length

Test organism[a]	Characteristics	(MIC, μg/ml)									
		12a	**12b**	**12c**	**12d**	**12e**	**12f**	**12g**	**12h**	**1**	MDM
S. aureus	Standard	0.78	0.39	0.39	0.2	0.39	0.39	0.39	1.56	0.39	0.39
S. aureus	Susceptible	1.56	0.78	0.78	0.39	0.78	0.78	0.78	3.13	0.78	0.78
S. aureus	Susceptible	0.78	0.39	0.39	0.2	0.39	0.39	0.39	0.78	0.39	0.78
S. aureus	*ermA* (c)[b]	>100	>100	>100	>100	>100	>100	100	100	>100	>100
S. aureus	*ermB* (i)[c]	1.56	0.2	0.78	0.2	1.56	0.78	0.2	0.78	0.39	0.78
S. aureus	*ermC* (i)[c]	0.78	0.39	0.39	0.2	0.78	0.39	0.39	1.56	0.78	0.78
S. pneumoniae	Susceptible	0.2	0.1	0.1	0.05	0.05	0.1	0.1	0.39	0.2	0.39
S. pneumoniae	Susceptible	0.39	0.2	0.2	0.1	0.1	0.2	0.2	0.78	0.39	0.78
S. pneumoniae	*ermB* (c)[b]	>100	>100	>100	>100	>100	100	50	25	>100	>100
S. pneumoniae	*ermB* (i)[c]	>100	100	50	12.5	25	12.5	6.25	12.5	100	>100
S. pneumoniae	*ermB* (i)[c]	>100	100	25	12.5	12.5	12.5	12.5	25	>100	>100
S. pneumoniae	*mefE* efflux	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.78	0.2	0.2
S. pneumoniae	*mefE* efflux	0.2	0.1	0.1	0.1	0.2	0.2	0.2	0.39	0.2	0.2
S. pyogenes	standard	0.2	0.1	N.T.[d]	N.T.[d]	N.T.[d]	N.T.[d]	0.2	0.39	N.T.[d]	0.2
S. pyogenes	*ermB* (c)[b]	>100	>100	>100	100	100	25	25	25	>100	>100
S. pyogenes	*mefE* efflux	0.39	0.39	0.2	0.1	0.2	0.2	0.2	0.78	0.39	0.78
M. catarrhalis	Standard	1.56	0.39	0.39	0.39	0.78	0.39	0.78	3.13	0.78	1.56
M. catarrhalis	Standard	1.56	1.56	0.78	0.78	1.56	0.78	1.56	3.13	1.56	1.56
H. influenzae	Standard	1.56	3.13	1.56	1.56	3.13	3.13	6.25	12.5	3.13	3.13
H. influenzae	Standard	12.5	12.5	12.5	6.25	12.5	12.5	12.5	25	12.5	12.5
H. influenzae	Susceptible	25	25	25	25	25	25	25	25	25	12.5

[a] *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*; *S. pyogenes*, *Streptococcus pyogenes*; *M. catarrhalis*, *Moraxella catarrhalis*; *H. influenzae*, *Haemophilus influenzae*.
[b] Constitutive resistant.
[c] Inducible resistant.
[d] Not tested.

corresponding to the report saying modification of the neutral sugar was useful for an improvement in activities against resistant bacteria.[13] In order to clarify the role of a neutral sugar in this series, we also evaluated antibacterial activities of monosaccharide analogues (**13d** and **13i–m**) as shown in Table 4. Beyond our expectation, **13j** and **13l** had comparatively excellent potency, and we found that activities of all monosaccharide analogues against gram-negative bacteria were stronger than those of the corresponding disaccharide analogues. To our regret, however, their activities against *erm*-resistant *S. pneumoniae* decreased, and it was revealed that the existence of the neutral sugar was necessary for an improvement in activities against resistant bacteria in this series.

3. Conclusion

On the basis of the structure of ketolides, the 12,13-cyclic carbamates were designed and synthesized starting

Table 3. Antibacterial activities of 12-arylpropylamino analogues

Test organism[a]	Characteristics	(MIC, μg/ml)									
		12i	**12j**	**12k**	**12l**	**12m**	**18**	**1**	MDM	MOM	CAM
S. aureus	Standard	0.2	0.39	0.39	0.1	0.39	0.39	0.39	0.39	0.2	0.1
S. aureus	Susceptible	0.39	0.78	0.78	0.39	0.78	0.78	0.78	0.78	0.78	0.1
S. aureus	Susceptible	0.2	0.39	0.39	0.1	0.2	0.39	0.39	0.78	0.78	0.1
S. aureus	*ermA* (c)[b]	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
S. aureus	*ermB* (i)[c]	0.2	3.13	0.2	0.1	0.39	0.2	0.39	0.78	1.56	>100
S. aureus	*ermC* (i)[c]	0.39	0.78	0.39	0.2	0.39	0.39	0.78	0.78	0.78	1.56
S. pneumoniae	Susceptible	0.05	0.1	0.05	0.013	0.06	0.05	0.2	0.39	0.1	0.025
S. pneumoniae	Susceptible	0.1	0.1	0.1	0.025	0.1	0.1	0.39	0.78	0.2	0.025
S. pneumoniae	*ermB* (c)[b]	>100	50	>100	50	>100	>100	>100	>100	>100	>100
S. pneumoniae	*ermB* (i)[c]	>100	6.25	12.5	3.13	>100	1.56	100	>100	6.25	>100
S. pneumoniae	*ermB* (i)[c]	>100	25	50	0.78	100	1.56	>100	>100	6.25	>100
S. pneumoniae	*mefE* efflux	0.1	0.1	0.1	0.025	0.1	0.2	0.2	0.2	0.39	0.78
S. pneumoniae	*mefE* efflux	0.1	0.1	0.1	0.05	0.1	0.1	0.2	0.2	0.2	0.78
S. pyogenes	Standard	N.T.[d]	0.1	0.1	0.05	0.1	0.05	N.T.[d]	0.2	0.1	N.T.[d]
S. pyogenes	*ermB* (c)[b]	>100	50	>100	>100	>100	50	>100	>100	>100	>100
S. pyogenes	*mefE* efflux	0.1	0.2	0.2	0.1	0.2	0.1	0.39	0.78	0.2	3.13
M. catarrhalis	Standard	0.78	0.78	0.78	0.39	1.56	0.39	0.78	1.56	0.78	0.1
M. catarrhalis	Standard	0.78	1.56	1.56	0.78	1.56	0.78	1.56	1.56	1.56	0.1
H. influenzae	Standard	1.56	6.25	3.13	1.56	1.56	3.13	3.13	3.13	3.13	1.56
H. influenzae	Standard	6.25	25	12.5	12.5	12.5	12.5	12.5	12.5	12.5	6.25
H. influenzae	Susceptible	12.5	25	25	12.5	25	25	25	12.5	25	6.25

[a] *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*; *S. pyogenes*, *Streptococcus pyogenes*; *M. catarrhalis*, *Moraxella catarrhalis*; *H. influenzae*, *Haemophilus influenzae*.
[b] Constitutive resistant.
[c] Inducible resistant.
[d] Not tested.

Table 4. Antibacterial activities of monosaccharide analogues with a variety of aryl groups

Test organism[a]	Characteristics	(MIC, μg/ml)							
		13d	**13i**	**13j**	**13k**	**13l**	**13m**	**1**	MDM
S. aureus	Standard	0.39	0.78	0.39	1.56	0.2	3.13	0.39	0.39
S. aureus	Susceptible	0.78	1.56	0.78	1.56	0.39	3.13	0.78	0.78
S. aureus	Susceptible	0.78	1.56	0.78	1.56	0.39	3.13	0.39	0.78
S. aureus	*ermA* (c)[b]	>100	>100	>100	>100	>50	>100	>100	>100
S. aureus	*ermB* (i)[c]	1.56	1.56	0.78	1.56	0.39	6.25	0.39	0.78
S. aureus	*ermC* (i)[c]	1.56	1.56	0.78	1.56	0.39	6.25	0.78	0.78
S. pneumoniae	Susceptible	0.2	0.39	0.025	0.2	0.025	0.2	0.2	0.39
S. pneumoniae	Susceptible	0.2	0.39	0.05	0.2	0.025	0.2	0.39	0.78
S. pneumoniae	*ermB* (c)[b]	>100	>100	>100	>100	>50	>100	>100	>100
S. pneumoniae	*ermB* (i)[c]	>100	>100	100	>100	12.5	>100	100	>100
S. pneumoniae	*ermB* (i)[c]	>100	>100	100	>100	12.5	>100	>100	>100
S. pneumoniae	*mefE* efflux	0.39	1.56	0.1	0.39	0.1	1.56	0.2	0.2
S. pneumoniae	*mefE* efflux	0.39	1.56	0.1	0.78	0.1	0.78	0.2	0.2
S. pyogenes	Standard	0.39	N.T.[d]	0.1	0.78	0.1	1.56	N.T.[d]	0.2
S. pyogenes	*ermB* (c)[b]	>100	>100	>100	>100	>50	>100	>100	>100
S. pyogenes	*mefE* efflux	0.78	6.25	0.39	3.13	1.56	25	0.39	0.78
M. catarrhalis	Standard	0.025	0.1	0.025	0.2	0.05	0.39	0.78	1.56
M. catarrhalis	Standard	0.025	0.1	0.05	0.2	0.05	0.39	1.56	1.56
H. influenzae	Standard	0.39	0.39	0.78	1.56	0.39	0.78	3.13	3.13
H. influenzae	Standard	0.78	1.56	1.56	3.13	0.78	6.25	12.5	12.5
H. influenzae	Susceptible	3.13	3.13	3.13	6.25	1.56	12.5	25	12.5

[a] *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*; *S. pyogenes*, *Streptococcus pyogenes*; *M. catarrhalis*, *Moraxella catarrhalis*; *H. influenzae*, *Haemophilus influenzae*.
[b] Constitutive resistant.
[c] Inducible resistant.
[d] Not tested.

from 16-membered macrolide. Epoxidation of a sequentially protected intermediate (**2**) followed by reduction afforded the epoxide (**3**) regioselectively and stereoselectively. The cyclic carbamates (**7b**, **10a**–**c**) possessing a phenylalkyl group were prepared from **3** via trans ring-opening reaction, but they did not show significant improvement in antibacterial activities compared to the parent compound (MDM) or compound **1**. Next, we

investigated the potential of non-cyclic 12-arylalkylamino-13-hydroxy 16-membered macrolides. After determination of the spacer length, we optimized an aryl group at the C-12 position. As a result, the 4-quinolinyl analogue (**12l**) exhibited the most potent antibacterial activities in 3″-OH series, and was especially effective against both inducible- and efflux-resistant *S. pneumoniae*. Furthermore, we synthesized the 3″-*O*-acetyl analogue of **12d**, compound **18**, from MOM in order to examine the effect of an acyl group at the C-3″ position on antibacterial activities against *erm*-resistant strains. Finally, **18** was 8-fold more active than **12d** against inducible-resistant *S. pneumoniae*.

This work suggests the possibility of 16-membered macrolides for overcoming resistant *S. pneumoniae*. SAR indicated here would be useful for the exploration of a new class of 16-membered macrolides in the future.

4. Experimental

4.1. Chemistry

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. ^{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.

4.1.1. 9-*O*-Acetylmidecamycin 18-dimethylacetal (2). To a solution of crude 9-*O*-acetyl midecamycin (**1**)[22] (2.0 g, 2.34 mmol) in MeOH (30 ml), trimethyl orthoformate (26 ml) and pyridinium *p*-toluenesulfonate (1.17 g, 2.34 mmol) were added and the reaction mixture was stirred for 33 h at 50 °C. Saturated aqueous $NaHCO_3$ was added and the mixture was evaporated. The aqueous layer was extracted with $CHCl_3$ 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 [$CHCl_3$/MeOH/NH_4OH (120:1:0.1)] to give 2 (1.68 g, 80%) as a colorless solid; $[\alpha]_D^{24}$ −32° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 902 $(M+H)^+$; ^{1}H NMR δ 0.92 (br t, 7-H), 0.97 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.24 (d, 16-H), 1.27 (d, 6′-H), 1.49 (br t, 7-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.00 (s, 9-$OCOCH_3$), 2.13 (ddd, 14-H), 2.25 (dd, 2-H), 2.49 (s, 3′-$N(CH_3)_2$), 2.69 (dd, 2-H), 3.22 (br d, 4-H), 3.24 (s, 18-OCH_3), 3.28 (s, 18-OCH_3), 3.52 (s, 4-OCH_3), 3.56 (dd, 2′-H), 3.89 (br d, 5-H), 4.47 (dq, 5″-H), 4.48 (d, 1′-H), 4.52 (dd, 18-H), 4.61 (d, 4″-H), 4.96 (ddq, 15-H), 5.05 (br dd, 3-H), 5.07 (d, 1″-H), 5.29 (dd, 9-H), 5.56 (dd, 10-H), 5.82 (ddd, 13-H), 6.05 (dd, 12-H), 6.64 (dd, 11-H).

4.1.2. 9-*O*-Acetyl-12,13-dihydro-12,13-epoxymidecamycin 18-dimethylacetal (3). To a solution of **2** (4.51 g, 5.0 mmol) in $CHCl_3$ (70 ml), 3-chloroperbenzoic acid (3.08 g, 12.5 mmol) was added and the reaction mixture was stirred for 14 h at room temperature. After EtOH (140 ml) was added, 5% aqueous $Na_2S_2O_4$ (50 ml) was added dropwise under ice cooling, and the mixture was stirred for 15 min. The reaction mixture was evaporated, and saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with $CHCl_3$ and the extract was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried and concentrated. The residue was purified by silica gel chromatography [$CHCl_3$/MeOH (70:1)] to give **3** (2.84 g, 62%) as a colorless solid. Recrystallization from $CHCl_3$/hexane afforded an analytically pure sample as colorless plate crystals; $[\alpha]_D^{20}$ −41° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 918 $(M+H)^+$; ^{1}H NMR δ 0.89 (br t, 7-H), 1.01 (d, 19-H), 1.09 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 16-H), 1.27 (d, 6′-H), 1.43 (ddd, 14-H), 1.55 (br t, 7-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.00 (s, 9-$OCOCH_3$), 2.22 (br d, 14-H), 2.35 (dd, 2-H), 2.50 (s, 3′-$N(CH_3)_2$), 2.72 (dd, 2-H), 3.14 (dd, 12-H), 3.17 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.54 (s, 4-OCH_3), 3.57 (dd, 2′-H), 3.97 (br d, 5-H), 4.48 (dq, 5″-H), 4.53 (d, 1′-H), 4.58 (dd, 18-H), 4.62 (d, 4″-H), 4.91 (ddq, 15-H), 5.07 (d, 1″-H), 5.11 (br dd, 3-H), 5.32 (dd, 9-H), 5.75 (dd, 11-H), 6.01 (dd, 10-H).

4.1.3. 9-*O*-Acetyl-12-azide-12,13-dihydro-13-hydroxymidecamycin 18-dimethylacetal (4a). To a solution of **3** (1.00 g, 1.09 mmol) and ammonium chloride (292 mg, 5.46 mmol) in EtOH/H_2O (8:1) (30 ml) was added sodium azide (709 mg, 10.9 mmol), and the reaction mixture was stirred for 21 h at 85 °C. Water was added and the mixture was evaporated. The aqueous layer was extracted with $CHCl_3$ 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 [$CHCl_3$/MeOH/NH_4OH (90:1:0.1–80:1:0.1)] to give **4a** (763 mg, 73%) as a colorless solid; $[\alpha]_D^{20}$ −54° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 961 $(M+H)^+$; ^{1}H NMR δ 0.95 (d, 19-H), 1.04 (br t, 7-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.31 (d, 16-H), 1.50 (br t, 7-H), 1.63 (br dd, 14-H), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.05 (s, 9-$OCOCH_3$), 2.50 (s, 3′-$N(CH_3)_2$), 2.60 (dd, 2-H), 2.84 (dd, 2-H), 3.16 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.48 (dd, 4-H), 3.53 (s, 4-OCH_3), 3.57 (dd, 2′-H), 3.95 (br dd, 13-H), 3.99 (br d, 5-H), 4.25 (br s, 12-H), 4.47 (dq, 5″-H), 4.51 (d, 1′-H), 4.58 (t, 18-H), 4.61 (d, 4″-H), 5.07 (d, 1″-H), 5.11 (ddq, 15-H), 5.12 (br dd, 3-H), 5.32 (br s, 9-H), 5.77 (br d, 10-H), 5.81 (br d, 11-H).

4.1.4. 9,2′-Di-*O*-acetyl-12-azide-12,13-dihydro-13-hydroxymidecamycin 18-dimethylacetal (4b). To a solution of **4a** (30 mg, 31.2 μmol) in CH_3CN (0.9 ml) was added acetic anhydride (6 μl, 63.5 μmol). After the reaction mixture was stirred for 27 h at 50 °C, acetic anhydride (6 μl, 63.5 μmol) was added and the reaction mixture was stirred for another 5 h at 50 °C. Saturated aqueous NaH-

CO_3 and water were added and the aqueous layer was extracted twice with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated to give a residue which was purified by preparative TLC [$CHCl_3$/MeOH/NH_4OH (30:1:0.1)] to afford **4b** (28.0 mg, 90%) as a colorless solid; $[\alpha]_D^{24}$ −74° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 1003 $(M+H)^+$; ^1H NMR δ 0.93 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.11 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.29 (d, 16-H), 1.48 (br dd, 7-H), 1.63 (br dd, 14-H), 1.70 (br dd, 17-H), 1.83 (dd, 2″-Hax), 1.86 (br dd, 14-H), 1.99 (s, 2′-$OCOCH_3$), 2.00 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.39 (s, 3′-$N(CH_3)_2$), 2.60 (dd, 2-H), 2.70 (t, 3′-H), 2.79 (dd, 2-H), 3.11 (s, 18-OCH_3), 3.24 (s, 18-OCH_3), 3.32 (m, 4′-H), 3.32 (m, 5′-H), 3.35 (dd, 4-H), 3.48 (s, 4-OCH_3), 3.93 (br d, 5-H), 3.93 (br dd, 13-H), 4.25 (br s, 12-H), 4.37 (dq, 5″-H), 4.60 (d, 4″-H), 4.63 (dd, 18-H), 4.75 (d, 1′-H), 4.99 (dd, 2′-H), 5.06 (d, 1″-H), 5.10 (br dd, 3-H), 5.11 (ddq, 15-H), 5.30 (br s, 9-H), 5.76 (br d, 11-H), 5.79 (br d, 10-H).

4.1.5. 9-*O*-Acetyl-12-amino-12,13-dihydro-13-hydroxymidecamycin 18-dimethylacetal (5a). To a solution of **4a** (154 mg, 156 μmol) in CH_3CN (4.6 ml) was added triphenylphosphine (63 mg, 240 μmol). After the reaction mixture was stirred for 23 h at room temperature, water (0.5 ml) was added and the reaction mixture was stirred for another 6 h at room temperature. Evaporation gave a residue which was purified by silica gel chromatography [$CHCl_3$/MeOH/NH_4OH (30:1:0.1)] to give **5a** (101 mg, 68%) as a colorless solid; $[\alpha]_D^{24}$ −32° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 935 $(M+H)^+$; ^1H NMR δ 0.94 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.29 (d, 16-H), 1.47 (br t, 7-H), 1.59 (br dd, 14-H), 1.75 (br dd, 14-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.50 (s, 3′-$N(CH_3)_2$), 2.63 (dd, 2-H), 2.87 (dd, 2-H), 3.16 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.52 (s, 4-OCH_3), 3.57 (dd, 2′-H), 3.72 (br s, 12-H), 3.81 (br dd, 13-H), 3.99 (br d, 5-H), 4.46 (dq, 5″-H), 4.51 (d, 1′-H), 4.58 (t, 18-H), 4.61 (d, 4″-H), 5.07 (d, 1″-H), 5.13 (ddq, 15-H), 5.16 (br dd, 3-H), 5.28 (dd, 9-H), 5.67 (dd, 10-H), 5.82 (dd, 11-H).

4.1.6. 9,2′-Di-*O*-acetyl-12-amino-12,13-dihydro-13-hydroxymidecamycin 18-dimethylacetal (5b). Reaction of **4b** with triphenylphosphine gave **5b** as a colorless solid in 68% yield by a similar procedure to **5a**; $[\alpha]_D^{25}$ −50° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 977 $(M+H)^+$; ^1H NMR δ 0.93 (d, 19-H), 0.96 (br t, 7-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.28 (d, 16-H), 1.28 (d, 6′-H), 1.49 (br t, 7-H), 1.55 (br dd, 14-H), 1.73 (br dd, 14-H), 1.84 (dd, 2″-Hax), 1.99 (s, 2′-$OCOCH_3$), 2.00 (d, 2″-Heq), 2.02 (s, 9-$OCOCH_3$), 2.40 (s, 3′-$N(CH_3)_2$), 2.64 (dd, 2-H), 2.71 (t, 3′-H), 2.83 (dd, 2-H), 3.12 (s, 18-OCH_3), 3.24 (s, 18-OCH_3), 3.32 (t, 4′-H), 3.35 (dq, 5′-H), 3.41 (br d, 4-H), 3.48 (s, 4-OCH_3), 3.69 (br s, 12-H), 3.78 (br d, 13-H), 3.95 (br d, 5-H), 4.37 (dq, 5″-H), 4.61 (d, 4″-H), 4.65 (dd, 18-H), 4.76 (d, 1′-H), 5.00 (dd, 2′-H), 5.07 (d, 1″-H), 5.14 (ddq, 15-H), 5.15 (br dd, 3-H), 5.28 (br dd, 9-H), 5.65 (br dd, 11-H), 5.80 (br dd, 10-H).

4.1.7. 9,2′-Di-*O*-acetyl-12-amino-12,13-dihydro-13-hydroxymidecamycin 18-dimethylacetal 12-*N*,13-*O*-cyclic carbamate (6a). To a solution of **5b** (32 mg, 32.7 μmol) in THF (1.6 ml) was added CDI (10.6 mg, 65.4 μmol), and the reaction mixture was stirred for 3 h at room temperature. Saturated aqueous $NaHCO_3$ was added and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried, and concentrated to give a residue which was purified by preparative TLC [$CHCl_3$/MeOH/NH_4OH (30:1:0.1)] to afford **6a** (29.0 mg, 88%) as a colorless solid; $[\alpha]_D^{22}$ −16° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 1003 $(M+H)^+$; ^1H NMR δ 0.88 (br t, 7-H), 0.97 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.30 (d, 16-H), 1.45 (br t, 7-H), 1.70 (br s, 17-H), 1.83 (dd, 2″-Hax), 1.95 (s, 2′-$OCOCH_3$), 2.00 (d, 2″-Heq), 2.05 (s, 9-$OCOCH_3$), 2.39 (s, 3′-$N(CH_3)_2$), 2.70 (t, 3′-H), 2.75 (m, 2-H), 3.15 (br d, 4-H), 3.16 (s, 18-OCH_3), 3.25 (s, 18-OCH_3), 3.33 (m, 4′-H), 3.33 (m, 5′-H), 3.49 (s, 4-OCH_3), 3.91 (br d, 5-H), 4.36 (dq, 5″-H), 4.60 (d, 4″-H), 4.61 (t, 18-H), 4.72 (d, 1′-H), 5.00 (dd, 2′-H), 5.07 (d, 1″-H), 5.11 (ddq, 15-H), 5.38 (br s, 9-H), 5.72 (br dd, 11-H), 6.14 (dd, 10-H).

4.1.8. 9,2′-Di-*O*-acetyl-12-benzylamino-12,13-dihydro-13-hydroxymidecamycin 18-dimethylacetal 12-*N*,13-*O*-cyclic carbamate (6b). To a solution of **5b** (94 mg, 96.2 μmol) in 1,2-dichloroethane (1.9 ml), benzaldehyde (12 μl, 118 μmol), acetic acid (6 μl, 105 μmol), and sodium triacetoxyborohydride (31 mg, 144 μmol) were added and the reaction mixture was stirred for 2 h at room temperature. Saturated aqueous $NaHCO_3$ and water were added to the resulting mixture and the aqueous layer was extracted twice with $CHCl_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The resulting residue was purified by silica gel chromatography [$CHCl_3$/MeOH/NH_4OH (60:1:0.1)] and preparative TLC [$CHCl_3$/MeOH/NH_4OH (25:1:0.1)] to afford the 12-*N*-benzyl derivative of **5b** (82 mg, 80%) as a colorless solid; $[\alpha]_D^{22}$ −59° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 1067 $(M+H)^+$; ^1H NMR δ 0.93 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 6′-H), 1.27 (d, 16-H), 1.43 (br t, 7-H), 1.61 (br dd, 14-H), 1.83 (dd, 2″-Hax), 1.97 (s, 2′-$OCOCH_3$), 2.00 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.39 (s, 3′-$N(CH_3)_2$), 2.54 (dd, 2-H), 2.70 (t, 3′-H), 2.76 (dd, 2-H), 3.14 (s, 18-OCH_3), 3.24 (s, 18-OCH_3), 3.32 (m, 4′-H), 3.32 (m, 5′-H), 3.35 (br d, 4-H), 3.46 (s, 4-OCH_3), 3.71 (d, 12-$NCH_2C_6H_5$), 3.81 (br dd, 13-H), 3.85 (d, 12-$NCH_2C_6H_5$), 3.92 (br d, 5-H), 4.37 (dq, 5″-H), 4.60 (d, 4″-H), 4.64 (t, 18-H), 4.74 (d, 1′-H), 4.99 (dd, 2′-H), 5.06 (ddq, 15-H), 5.06 (d, 1″-H), 5.13 (br dd, 3-H), 5.32 (br dd, 9-H), 5.74 (br dd, 11-H), 5.83 (br dd, 10-H), 7.28 (m, C_6H_5).

Reaction of the 12-*N*-benzyl derivative of **5b** with CDI under reflux condition gave **6b** as a colorless solid in 81% yield by a similar procedure to **6a**; $[\alpha]_D^{22}$ −45° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 1093 $(M+H)^+$; ^1H NMR δ 0.97 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.15 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 16-H), 1.27 (d, 6′-H), 1.83 (dd, 2″-Hax), 1.94 (s, 2′-

$OCOCH_3$), 1.99 (d, 2″-Heq), 2.06 (s, 9-$OCOCH_3$), 2.38 (s, 3′-$N(CH_3)_2$), 2.57 (dd, 2-H), 2.66 (dd, 2-H), 3.10 (br d, 4-H), 3.19 (s, 18-OCH_3), 3.26 (s, 18-OCH_3), 3.32 (m, 4′-H), 3.32 (m, 5′-H), 3.46 (s, 4-OCH_3), 3.84 (d, 12-$NCH_2C_6H_5$), 3.89 (br d, 5-H), 4.11 (br t, 12-H), 4.36 (dq, 5″-H), 4.38 (br dd, 13-H), 4.60 (d, 4″-H), 4.67 (d, 12-$NCH_2C_6H_5$), 4.98 (dd, 2′-H), 5.03 (br dd, 3-H), 5.05 (d, 1″-H), 5.34 (br s, 9-H), 5.59 (br dd, 11-H), 6.22 (br dd, 10-H), 7.31 (m, C_6H_5).

4.1.9. 9-*O*-Acetyl-12-amino-12,13-dihydro-13-hydroxymidecamycin 12-*N*,13-*O*-cyclic carbamate (7a). A solution of **6a** (90 mg, 89.7 μmol) in MeOH and water (9:1) (3.6 ml) was stirred for 24 h at 50°C. The reaction mixture was concentrated to give the deacetylated derivative of **6a** (84 mg, 97%) as a colorless solid; $[\alpha]_D^{22}$ −3.2° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 961 $(M+H)^+$; ^1H NMR δ 0.97 (d, 19-H), 1.10 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.23 (d, 6′-H), 1.32 (d, 16-H), 1.46 (br t, 7-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.06 (s, 9-$OCOCH_3$), 2.49 (s, 3′-$N(CH_3)_2$), 2.72 (dd, 2-H), 2.79 (dd, 2-H), 3.20 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.53 (s, 4-OCH_3), 3.54 (dd, 2′-H), 3.96 (br d, 5-H), 4.36 (br t, 12-H), 4.47 (dq, 5″-H), 4.61 (d, 4″-H), 5.07 (br dd, 3-H), 5.11 (d, 1″-H), 5.37 (br t, 9-H), 5.72 (br dd, 11-H), 6.10 (dd, 10-H).

To a solution of deacetylated derivative of **6a** (83 mg, 86.4 μmol) in acetonitrile and water (1:1) (5 ml) was added difluoroacetic acid (35 μl, 509 μmol). After stirring at room temperature for 24 h, the reaction mixture was further stirred for 2.5 h at 35 °C. The resulting mixture was diluted with chloroform, and the extract was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The resulting residue was purified by preparative TLC [$CHCl_3$/MeOH/NH_4OH (20:1:0.1)] to give **7a** (50 mg, 63%) as a colorless solid; $[\alpha]_D^{23}$ −15° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 915 $(M+H)^+$; ^1H NMR δ 0.96 (d, 19-H), 1.10 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.17 (d, 6′-H), 1.33 (d, 16-H), 1.46 (dt, 7-H), 1.84 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.06 (s, 9-$OCOCH_3$), 2.50 (s, 3′-$N(CH_3)_2$), 2.77 (dd, 2-H), 2.84 (dd, 2-H), 2.92 (dd, 17-H), 3.24 (br d, 4-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.47 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.95 (br d, 5-H), 4.41 (d, 1′-H), 4.41 (dq, 5″-H), 4.61 (d, 4″-H), 4.62 (br dd, 13-H), 5.05 (d, 1″-H), 5.20 (br dd, 3-H), 5.80 (dd, 11-H), 6.13 (dd, 10-H), 9.65 (s, 18-H).

4.1.10. 9-*O*-Acetyl-12-benzylamino-12,13-dihydro-13-hydroxymidecamycin 12-*N*,13-*O*-cyclic carbamate (7b). Reaction of **6b** with aqueous MeOH gave deacetylated derivative of **6b** as a colorless solid in 97% yield by a similar procedure to the deacetylated derivative of **6a**; $[\alpha]_D^{22}$ −32° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1051 $(M+H)^+$; ^1H NMR δ 0.98 (d, 19-H), 1.11 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.29 (d, 16-H), 1.46 (br t, 7-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.07 (s, 9-$OCOCH_3$), 2.28 (br dd, 14-H), 2.54 (s, 3′-$N(CH_3)_2$), 2.57 (dd, 2-H), 2.72 (dd, 2-H), 3.23 (s, 18-OCH_3), 3.28 (s, 18-OCH_3), 3.31 (m, 4′-H), 3.31 (m, 5′-H), 3.50 (s, 4-OCH_3), 3.55 (dd, 2′-H), 3.87 (d, 12-$NCH_2C_6H_5$), 3.94 (br d, 5-H), 4.14 (br t, 12-H), 4.40 (br dd, 13-H), 4.40 (dq, 5″-H), 4.51 (d, 1′-H), 4.57 (t, 18-H), 4.61 (d, 4″-H), 4.69 (d, 12-$NCH_2C_6H_5$), 5.00 (br dd, 3-H), 5.00 (ddq, 15-H), 5.07 (d, 1″-H), 5.35 (br s, 9-H), 5.59 (br s, 11-H), 6.17 (br dd, 10-H), 7.31 (m, C_6H_5).

Reaction of the deacetylated derivative of **6a** with difluoroacetic acid gave **7b** as a colorless solid in 67% yield by a similar procedure to **7a**; $[\alpha]_D^{23}$ −42° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1005 $(M+H)^+$; ^1H NMR δ 0.96 (d, 19-H), 1.10 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.17 (d, 6′-H), 1.21 (t, 4″-$OCOCH_2CH_3$), 1.30 (d, 16-H), 1.46 (dt, 7-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.07 (s, 9-$OCOCH_3$), 2.29 (br dd, 14-H), 2.50 (s, 3′-$N(CH_3)_2$), 2.57 (dd, 2-H), 2.75 (dd, 2-H), 2.92 (dd, 17-H), 3.20 (br d, 4-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.48 (dd, 2′-H), 3.49 (s, 4-OCH_3), 3.88 (d, 12-$NCH_2C_6H_5$), 3.94 (dd, 5-H), 4.18 (dd, 12-H), 4.41 (d, 1′-H), 4.41 (dq, 5″-H), 4.61 (d, 4″-H), 4.70 (d, 12-$NCH_2C_6H_5$), 5.00 (ddq, 15-H), 5.05 (d, 1″-H), 5.14 (br dd, 3-H), 5.17 (dd, 9-H), 5.66 (dd, 11-H), 6.22 (dd, 10-H), 7.32 (m, C_6H_5), 9.67 (s, 18-H).

4.1.11. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-(2-phenylethyl)aminomidecamycin 18-dimethylacetal (8a). To a solution of **5a** (170 mg, 182 μmol) in MeOH (5.1 ml) were added phenylacetaldehyde (31 μl, 236 μmol) and acetic acid (42 μl, 727 μmol), and the reaction mixture was stirred for 40 min at room temperature. Sodium cyanoborohydride (34 mg, 545 μmol) was added to the resulting solution, and the mixture was stirred for 1.5 h at room temperature. Saturated aqueous $NaHCO_3$ was added to the resulting mixture and the aqueous layer was extracted twice with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The resulting residue was purified by silica gel chromatography [$CHCl_3$/MeOH/NH_4OH (60:1:0.1)] to afford **8a** (62 mg, 33%) as a colorless solid; $[\alpha]_D^{22}$ −42° (*c* 0.75, $CHCl_3$); FAB-MS *m*/*z* 1039 $(M+H)^+$; ^1H NMR δ 0.89 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 16-H), 1.27 (d, 6′-H), 1.45 (br t, 7-H), 1.52 (br dd, 14-H), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.50 (s, 3′-$N(CH_3)_2$), 2.63 (dd, 2-H), 3.18 (s, 18-OCH_3), 3.28 (s, 18-OCH_3), 3.31 (dq, 5′-H), 3.40 (br dd, 12-H), 3.48 (br d, 4-H), 3.51 (s, 4-OCH_3), 3.57 (dd, 2′-H), 3.73 (br dd, 13-H), 3.98 (br d, 5-H), 4.47 (dq, 5″-H), 4.50 (d, 1′-H), 4.58 (t, 18-H), 4.62 (d, 4″-H), 5.06 (ddq, 15-H), 5.07 (d, 1″-H), 5.16 (br dd, 3-H), 5.29 (br dd, 9-H), 5.61 (br dd, 11-H), 5.69 (br dd, 10-H), 7.20 (m, C_6H_5), 7.27 (m, C_6H_5).

4.1.12. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-(3-phenylpropyl)aminomidecamycin 18-dimethylacetal (8b). Reaction of **5a** with phenylpropionaldehyde gave **8b** as a colorless solid in 55% yield by a similar procedure to **8a**; $[\alpha]_D^{23}$ −39° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1053 $(M+H)^+$; ^1H NMR δ 0.94 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.28 (d, 16-H), 1.45 (dt,

7-H), 1.57 (br dd, 14-H), 1.80 (m, 12-N(CH_2)$_3$$C_6H_5$), 1.83 (dd, 2″-Hax), 1.92 (dt, 14-H), 2.00 (d, 2″-Heq), 2.02 (s, 9-OCOCH_3), 2.50 (s, 3′-N(CH_3)$_2$), 2.63 (dd, 2-H), 2.65 (t, 12-N(CH_2)$_3$$C_6H_5$), 2.84 (dd, 2-H), 3.18 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.31 (dq, 5′-H), 3.36 (br d, 12-H), 3.48 (br d, 4-H), 3.51 (s, 4-OCH_3), 3.57 (dd, 2′-H), 3.78 (br dd, 13-H), 3.98 (br d, 5-H), 4.47 (dq, 5″-H), 4.50 (d, 1′-H), 4.58 (t, 18-H), 4.61 (d, 4″-H), 5.06 (ddq, 15-H), 5.07 (d, 1″-H), 5.16 (br dd, 3-H), 5.30 (br s, 9-H), 5.69 (br dd, 11-H), 5.74 (br d, 10-H), 7.16 (m, C_6H_5), 7.26 (m, C_6H_5).

4.1.13. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-(4-phenylbutyl)aminomidecamycin 18-dimethylacetal (8c). Reaction of **5a** with 4-phenylbutanal gave **8c** as a colorless solid in 59% yield by a similar procedure to **8a**; $[\alpha]_D^{23}$ −36° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1067 $(M+H)^+$; ^1H NMR δ 0.94 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.12 (t, 3-OCOCH_2CH_3), 1.17 (t, 4″-OCOCH_2CH_3), 1.27 (d, 6′-H), 1.28 (d, 16-H), 1.51 (m, 12-N(CH_2)$_4$$C_6H_5$), 1.63 (m, 12-N($CH_2$)$_4$$C_6H_5$), 1.83 (dd, 2″-Hax), 1.93 (ddd, 14-H), 2.00 (d, 2″-Heq), 2.03 (s, 9-OCOCH_3), 2.50 (s, 3′-N(CH_3)$_2$), 2.61 (t, 12-N(CH_2)$_3$$C_6H_5$), 2.84 (dd, 2-H), 3.18 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.31 (m, 5′-H), 3.36 (br d, 12-H), 3.48 (br d, 4-H), 3.51 (s, 4-OCH_3), 3.57 (dd, 2′-H), 3.79 (br s, 13-H), 3.98 (br d, 5-H), 4.47 (dq, 5″-H), 4.50 (d, 1′-H), 4.58 (t, 18-H), 4.61 (d, 4″-H), 5.07 (ddq, 15-H), 5.07 (d, 1″-H), 5.16 (br dd, 3-H), 5.31 (br s, 9-H), 5.70 (dd, 11-H), 5.76 (dd, 10-H), 7.16 (m, C_6H_5), 7.25 (m, C_6H_5).

4.1.14. 9-*O*-Acetyl-12,13-dihydro-12-(2-phenylethyl)aminomidecamycin 18-dimethylacetal 12-*N*,13-*O*-cyclic carbamate (9a). To a solution of **8a** (62 mg, 59.7 μmol) and triethylamine (42 μl, 300 μmol) in CH_2Cl_2 (1.5 ml), a solution of triphosgene (10.6 mg, 35.8 μmol) in CH_2Cl_2 (1.5 ml) was added under ice cooling and the reaction mixture was stirred for 45 minutes at the same temperature. Chloroform and saturated aqueous $NaHCO_3$ were added to the reaction mixture. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated to give a residue which was purified by silica gel chromatography [$CHCl_3$/MeOH (60:1)] to give **9a** (57 mg, 90%) as a colorless/solid; $[\alpha]_D^{21}$ −18° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1065 $(M+H)^+$; ^1H NMR δ 0.96 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.13 (t, 3-OCOCH_2CH_3), 1.17 (t, 4″-OCOCH_2CH_3), 1.27 (d, 6′-H), 1.29 (d, 16-H), 1.49 (br dd, 7-H), 1.84 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.04 (s, 9-OCOCH_3), 2.22 (br t, 14-H), 2.50 (s, 3′-N(CH_3)$_2$), 2.67 (dd, 2-H), 3.04 (m, 12-N(CH_2)$_2$$C_6H_5$), 3.24 (s, 18-O$CH_3$), 3.29 (s, 18-O$CH_3$), 3.34 (m, 4′-H), 3.34 (m, 5′-H), 3.52 (s, 4-OCH_3), 3.58 (dd, 2′-H), 3.75 (m, 12-N(CH_2)$_2$$C_6H_5$), 4.28 (d, 1′-H), 4.30 (br dd, 13-H), 4.47 (dq, 5″-H), 4.59 (t, 18-H), 4.61 (d, 4″-H), 5.03 (ddq, 15-H), 5.07 (d, 1″-H), 5.11 (br dd, 3-H), 5.38 (br s, 9-H), 5.55 (br dd, 11-H), 6.19 (br dd, 10-H), 7.20 (m, C_6H_5).

4.1.15. 9-*O*-Acetyl-12,13-dihydro-12-(3-phenylpropyl)aminomidecamycin 18-dimethylacetal 12-*N*,13-*O*-cyclic carbamate (9b). Reaction of **8b** with triphosgene gave **9b** as a colorless solid in 42% yield by a similar procedure to **9a**; $[\alpha]_D^{21}$ −17° (*c* 0.60, $CHCl_3$); FAB-MS *m*/*z* 1079 $(M+H)^+$; ^1H NMR δ 0.99 (d, 19-H), 1.16 (s, 3″-CH_3), 1.17 (d, 6″-H), 1.17 (t, 3-OCOCH_2CH_3), 1.22 (t, 4″-OCOCH_2CH_3), 1.33 (d, 6′-H), 1.34 (d, 16-H), 1.54 (br t, 7-H), 1.88 (dd, 2″-Hax), 2.02 (d, 2″-Heq), 2.05 (s, 9-OCOCH_3), 2.27 (ddd, 14-H), 2.55 (s, 3′-N(CH_3)$_2$), 2.95 (dd, 2-H), 3.29 (s, 18-OCH_3), 3.34 (s, 18-OCH_3), 3.55 (dd, 2′-H), 3.58 (s, 4-OCH_3), 4.04 (br d, 5-H), 4.10 (br dd, 13-H), 4.22 (br t, 12-H), 4.52 (dq, 5″-H), 4.56 (d, 1′-H), 4.65 (t, 18-H), 4.66 (d, 4″-H), 5.06 (ddq, 15-H), 5.12 (d, 1″-H), 5.14 (br dd, 3-H), 5.39 (br s, 9-H), 5.54 (dd, 11-H), 6.22 (dd, 10-H), 7.24 (m, C_6H_5).

4.1.16. 9-*O*-Acetyl-12,13-dihydro-12-(4-phenylbutyl)aminomidecamycin 18-dimethylacetal 12-*N*,13-*O*-cyclic carbamate (9c). Reaction of **8c** with triphosgene gave **9c** as a colorless solid in 90% yield by a similar procedure to **9a**; $[\alpha]_D^{21}$ −18° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1093 $(M+H)^+$; ^1H NMR δ 0.97 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.13 (t, 3-OCOCH_2CH_3), 1.17 (t, 4″-OCOCH_2CH_3), 1.27 (d, 6′-H), 1.31 (d, 16-H), 1.49 (br dd, 7-H), 1.63 (m, 12-N(CH_2)$_4$$C_6H_5$), 1.84 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.04 (s, 9-OCOCH_3), 2.50 (s, 3′-N(CH_3)$_2$), 2.64 (m, 12-N(CH_2)$_4$$C_6H_5$), 2.69 (m, 2-H), 3.22 (s, 18-OCH_3), 3.28 (s, 18-OCH_3), 3.46 (dd, 2′-H), 3.53 (s, 4-OCH_3), 3.88 (br d, 5-H), 4.27 (br dd, 12-H), 4.44 (d, 1′-H), 4.44 (dq, 5″-H), 4.61 (d, 4″-H), 5.07 (br dd, 3-H), 5.07 (ddq, 15-H), 5.07 (d, 1″-H), 5.36 (br s, 9-H), 5.55 (br dd, 11-H), 6.16 (br dd, 10-H), 7.16 (m, C_6H_5), 7.25 (m, C_6H_5).

4.1.17. 9-*O*-Acetyl-12,13-dihydro-12-(2-phenylethyl)aminomidecamycin 12-*N*,13-*O*-cyclic carbamate (10a). Reaction of **9a** with difluoroacetic acid gave **10a** as a colorless solid in 62% yield by a similar procedure to **7a**; $[\alpha]_D^{23}$ −27° (*c* 0.80, $CHCl_3$); FAB-MS *m*/*z* 1019 $(M+H)^+$; ^1H NMR δ 0.94 (d, 19-H), 1.11 (s, 3″-CH_3), 1.17 (t, 4″-OCOCH_2CH_3), 1.30 (d, 16-H), 1.47 (br t, 7-H), 1.84 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.03 (s, 9-OCOCH_3), 2.25 (br dd, 14-H), 2.50 (s, 3′-N(CH_3)$_2$), 3.21 (br d, 4-H), 3.28 (m, 4′-H), 3.28 (m, 5′-H), 3.48 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.75 (m, 12-N(CH_2)$_2$$C_6H_5$), 3.97 (br d, 5-H), 4.15 (dd, 12-H), 4.30 (dd, 13-H), 4.41 (dq, 5″-H), 4.43 (d, 1′-H), 4.61 (d, 4″-H), 5.03 (ddq, 15-H), 5.05 (d, 1″-H), 5.18 (br dd, 3-H), 5.18 (br s, 9-H), 5.62 (dd, 11-H), 5.64 (dd, 10-H), 7.20 (m, C_6H_5), 9.72 (s, 18-H).

4.1.18. 9-*O*-Acetyl-12,13-dihydro-12-(3-phenylpropyl)aminomidecamycin 12-*N*,13-*O*-cyclic carbamate (10b). Reaction of **9b** with difluoroacetic acid gave **10b** as a colorless solid in 69% yield by a similar procedure to **7a**; $[\alpha]_D^{23}$ −27° (*c* 0.80, $CHCl_3$); FAB-MS *m*/*z* 1033 $(M+H)^+$; ^1H NMR δ 0.97 (d, 19-H), 1.16 (s, 3″-CH_3), 1.17 (d, 6″-H), 1.24 (t, 4″-OCOCH_2CH_3), 1.31 (d, 6′-H), 1.35 (d, 16-H), 1.53 (br t, 7-H), 1.89 (dd, 2″-Hax), 2.04 (s, 9-OCOCH_3), 2.06 (d, 2″-Heq), 2.26 (ddd, 14-H), 2.54 (s, 3′-N(CH_3)$_2$), 3.00 (dd, 17-H), 3.26 (br d, 4-H), 3.32 (m, 4′-H), 3.32 (m, 5′-H), 3.53 (dd, 2′-H), 3.57 (s, 4-OCH_3), 4.01 (br d, 5-H), 4.11 (dd, 13-H), 4.28 (dd, 12-H), 4.45 (dq, 5″-H), 4.48 (d, 1′-H), 4.66 (d, 4″-H), 5.07 (ddq, 15-H), 5.11 (d, 1″-H), 5.19 (dd, 9-H), 5.23 (br dd, 3-H), 5.60 (dd, 11-H), 6.23 (dd, 10-H), 7.18 (m, C_6H_5), 9.65 (s, 18-H).

4.1.19. 9-*O*-Acetyl-12,13-dihydro-12-(4-phenylbutyl)aminomidecamycin 12-*N*,13-*O*-cyclic carbamate (10c). Reaction of **9c** with difluoroacetic acid gave **10c** as a colorless solid in 61% yield by a similar procedure to **7a**; $[\alpha]_D^{22}$ −26° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1047 $(M+H)^+$; ^1H NMR δ 0.95 (d, 19-H), 1.00 (br t, 7-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.32 (d, 16-H), 1.48 (dt, 7-H), 1.84 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.29 (ddd, 14-H), 2.50 (s, 3′-$N(CH_3)_2$), 2.79 (dd, 2-H), 2.94 (dd, 17-H), 3.22 (br d, 4-H), 3.28 (m, 4′-H), 3.28 (m, 5′-H), 3.48 (dd, 2′-H), 3.53 (s, 4-OCH_3), 3.97 (br d, 5-H), 4.33 (dd, 12-H), 4.43 (br dd, 13-H), 4.43 (d, 1′-H), 4.44 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (ddq, 15-H), 5.06 (d, 1″-H), 5.17 (br dd, 3-H), 5.17 (br s, 9-H), 5.61 (dd, 11-H), 6.19 (dd, 10-H), 7.16 (m, C_6H_5), 7.24 (t, C_6H_5), 9.67 (s, 18-H).

4.1.20. 9-*O*-Acetyl-12,13-dihydro-12-(*N*,*N*-dimethylamino)-13-hydroxymidecamycin 18-dimethylacetal (11a). To a solution of **5a** (71 mg, 75.9 μmol) in MeCN (1.4 ml) were added 37% aqueous formaldehyde solution (62 μl, 759 μmol), acetic acid (40 μl, 759 μmol) and sodium cyanoborohydride (14 mg, 228 μmol). After stirring for 1 h at room temperature, saturated aqueous $NaHCO_3$ was added to the resulting mixture. The aqueous layer was extracted twice with EtOAc and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The resulting residue was purified by preparative TLC [$CHCl_3$/MeOH/NH_4OH (15:1:0.1)] to afford **11a** (44 mg, 60%) as a colorless solid; $[\alpha]_D^{23}$ −48° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 963 $(M+H)^+$; ^1H NMR δ 0.95 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.28 (d, 6′-H), 1.30 (d, 16-H), 1.48 (br t, 7-H), 1.74 (ddd, 14-H), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.07 (s, 9-$OCOCH_3$), 2.30 (s, 12-$N(CH_3)_2$), 2.50 (s, 3′-$N(CH_3)_2$), 2.70 (dd, 2-H), 2.79 (dd, 2-H), 3.20 (s, 18-OCH_3), 3.28 (s, 18-OCH_3), 3.31 (m, 4′-H), 3.31 (m, 5′-H), 3.44 (br d, 4-H), 3.53 (s, 4-OCH_3), 3.57 (dd, 2′-H), 4.00 (br d, 5-H), 4.00 (br dd, 13-H), 4.47 (dq, 5″-H), 4.52 (d, 1′-H), 4.58 (t, 18-H), 4.62 (d, 4″-H), 5.04 (ddq, 15-H), 5.07 (d, 1″-H), 5.21 (br dd, 3-H), 5.39 (br dd, 9-H), 5.71 (br dd, 11-H), 5.90 (br dd, 10-H).

4.1.21. 9-*O*-Acetyl-12-(*N*-benzyl-*N*-methylamino)-12,13-dihydro-13-hydroxymidecamycin 18-dimethylacetal (11b). Reaction of **5a** with benzaldehyde gave the 12-*N*-benzyl derivative of **5a** as a colorless solid in 81% yield by a similar procedure to the 12-*N*-benzyl derivative of **5b** (see **6b**). Then, reaction of this compound with 37% aqueous formaldehyde solution gave **11b** as a colorless solid in 62% yield by a similar procedure to **11a**; $[\alpha]_D^{20}$ −53° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1039 $(M+H)^+$; ^1H NMR δ 0.93 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.29 (d, 16-H), 1.49 (br t, 7-H), 1.70 (br dd, 14-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.05 (s, 9-$OCOCH_3$), 2.22 (s, 12-NCH_3), 2.49 (s, 3′-$N(CH_3)_2$), 2.65 (dd, 2-H), 2.75 (dd, 2-H), 3.18 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.45 (br d, 4-H), 3.52 (s, 4-OCH_3), 3.56 (dd, 2′-H), 3.58 (d, 12-$NCH_2C_6H_5$), 3.69 (d, 12-$NCH_2C_6H_5$), 3.99 (br d, 5-H), 4.07 (br dd, 13-H), 4.47 (dq, 5″-H), 4.51 (d, 1′-H), 4.61 (d, 4″-H), 5.04 (ddq, 15-H), 5.06 (d, 1″-H), 5.22 (br dd, 3-H), 5.42 (br s, 9-H), 5.79 (br d, 11-H), 5.85 (br d, 10-H), 7.29 (m, C_6H_5).

4.1.22. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(2-phenylethyl)amino] midecamycin 18-dimethylacetal (11c). Reaction of **8a** with 37% aqueous formaldehyde solution gave **11c** as a colorless solid in 63% yield by a similar procedure to **11a**; $[\alpha]_D^{21}$ −41° (*c* 0.85, $CHCl_3$); FAB-MS *m*/*z* 1053 $(M+H)^+$; ^1H NMR δ 0.91 (d, 19-H), 1.08 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 16-H), 1.26 (d, 6′-H), 1.49 (br t, 7-H), 1.53 (br dd, 14-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.39 (s, 12-NCH_3), 2.49 (s, 3′-$N(CH_3)_2$), 2.67 (dd, 2-H), 3.18 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.30 (m, 4′-H), 3.30 (m, 5′-H), 3.43 (br d, 4-H), 3.51 (s, 4-OCH_3), 3.55 (dd, 2′-H), 3.97 (br d, 5-H), 3.97 (br dd, 13-H), 4.47 (dq, 5″-H), 4.51 (d, 1′-H), 4.59 (t,18-H), 4.61 (d, 4″-H), 5.00 (ddq, 15-H), 5.06 (d, 1″-H), 5.20 (br dd, 3-H), 5.41 (br s, 9-H), 5.72 (br d, 11-H), 5.84 (br d, 10-H), 7.17 (m, C_6H_5), 7.26 (m, C_6H_5).

4.1.23. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-phenylpropyl)amino]midecamycin 18-dimethylacetal (11d). Reaction of **8b** with 37% aqueous formaldehyde solution gave **11d** as a colorless solid in 63% yield by a similar procedure to **11a**; $[\alpha]_D^{23}$ −45° (*c* 0.90, $CHCl_3$); FAB-MS *m*/*z* 1067 $(M+H)^+$; ^1H NMR δ 0.91 (d, 19-H), 1.11 (s, 3″-CH_3), 1.11 (t, 3-$OCOCH_2CH_3$), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 16-H), 1.27 (d, 6′-H), 1.49 (br t, 7-H), 1.58 (br dd, 14-H), 1.80 (m, 12-$N(CH_2)_3C_6H_5$), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.05 (s, 9-$OCOCH_3$), 2.30 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.58 (t, 12-$N(CH_2)_3C_6H_5$), 2.66 (dd, 2-H), 2.77 (dd, 2-H), 3.18 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.31 (m, 4′-H), 3.31 (m, 5′-H), 3.45 (br d, 4-H), 3.52 (s, 4-OCH_3), 3.56 (dd, 2′-H), 3.98 (br d, 5-H), 3.98 (br dd, 13-H), 4.47 (dq, 5″-H), 4.52 (d, 1′-H), 4.59 (t, 18-H), 4.61 (d, 4″-H), 5.04 (ddq, 15-H), 5.07 (d, 1″-H), 5.20 (br dd, 3-H), 5.38 (br s, 9-H), 5.72 (br d, 11-H), 5.80 (br d, 10-H), 7.16 (m, C_6H_5), 7.25 (m, C_6H_5).

4.1.24. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(4-phenylbutyl)amino]midecamycin 18-dimethylacetal (11e). Reaction of **8c** with 37% aqueous formaldehyde solution gave **11e** as a colorless solid in 69% yield by a similar procedure to **11a**; $[\alpha]_D^{23}$ −51° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1081 $(M+H)^+$; ^1H NMR δ 0.92 (d, 19-H), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.11 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.29 (d, 16-H), 1.56 (m, 12-$N(CH_2)_4C_6H_5$), 1.66 (br dd, 14-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.25 (s, 12-NCH_3), 2.49 (s, 3′-$N(CH_3)_2$), 2.60 (t, 12-$N(CH_2)_4C_6H_5$), 2.66 (dd, 2-H), 2.77 (dd, 2-H), 3.18 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.31 (m, 4′-H), 3.31 (m, 5′-H), 3.45 (br d, 4-H), 3.52 (s, 4-OCH_3), 3.55 (dd, 2′-H), 3.98 (br d, 5-H), 3.98 (br dd, 13-H), 4.47 (dq, 5″-H), 4.53 (d, 1′-H), 4.59 (t, 18-H), 4.61 (d, 4″-H), 5.06 (ddq, 15-H), 5.06 (d, 1″-H), 5.21 (br dd, 3-H), 5.39 (br s, 9-H), 5.72 (br d, 11-H), 5.82 (br d, 10-H), 7.15 (m, C_6H_5), 7.25 (m, C_6H_5).

4.1.25. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(5-phenylpentyl)amino]midecamycin 18-dimethylacetal (11f). Reaction of **5a** with 5-phenylpentanal gave the 12-*N*-(5-phenylpentyl) derivative of **5a** as a colorless solid in 51% yield by a similar procedure to **8a**. Then, reaction of this compound with 37% aqueous formaldehyde solution gave **11f** as a colorless solid in 70% yield by a similar procedure to **11a**; $[\alpha]_D^{23}$ −47° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1095 $(M+H)^+$; ^1H NMR δ 0.92 (d, 19-H), 1.10 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.29 (d, 16-H), 1.51 (m, 12-$N(CH_2)_5C_6H_5$), 1.62 (m, 12-$N(CH_2)_5C_6H_5$), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.27 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.59 (t, 12-$N(CH_2)_4C_6H_5$), 2.68 (dd, 2-H), 2.78 (dd, 2-H), 3.18 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.31 (m, 4′-H), 3.31 (m, 5′-H), 3.45 (br d, 4-H), 3.52 (s, 4-OCH_3), 3.55 (dd, 2′-H), 3.99 (br d, 5-H), 3.99 (br dd, 13-H), 4.47 (dq, 5″-H), 4.51 (d, 1′-H), 4.58 (t, 18-H), 4.61 (d, 4″-H), 5.06 (ddq, 15-H), 5.07 (d, 1″-H), 5.20 (br dd, 3-H), 5.39 (br s, 9-H), 5.72 (br d, 11-H), 5.83 (br d, 10-H), 7.15 (m, C_6H_5), 7.25 (m, C_6H_5).

4.1.26. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(6-phenylhexyl)amino]midecamycin 18-dimethylacetal (11g). Reaction of **5a** with 6-phenylhexanal gave the 12-*N*-(6-phenylhexyl) derivative of **5a** as a colorless solid in 41% yield by a similar procedure to **8a**. Then, reaction of this compound with 37% aqueous formaldehyde solution gave **11g** as a colorless solid in 79% yield by a similar procedure to **11a**; $[\alpha]_D^{22}$ −51° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1109 $(M+H)^+$; ^1H NMR δ 0.92 (d, 19-H), 1.11 (s, 3″-CH_3), 1.11 (t, 3-$OCOCH_2CH_3$), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.29 (d, 16-H), 1.46 (m, 12-$N(CH_2)_6C_6H_5$), 1.60 (m, 12-$N(CH_2)_6C_6H_5$), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.05 (s, 9-$OCOCH_3$), 2.25 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.58 (t, 12-$N(CH_2)_6C_6H_5$), 2.69 (dd, 2-H), 2.78 (dd, 2-H), 3.18 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.31 (m, 4′-H), 3.31 (m, 5′-H), 3.46 (br d, 4-H), 3.52 (s, 4-OCH_3), 3.55 (dd, 2′-H), 3.97 (br d, 5-H), 3.97 (br dd, 13-H), 4.47 (dq, 5″-H), 4.51 (d, 1′-H), 4.59 (t, 18-H), 4.61 (d, 4″-H), 5.07 (ddq, 15-H), 5.07 (d, 1″-H), 5.21 (br dd, 3-H), 5.39 (br s, 9-H), 5.72 (dd, 11-H), 5.80 (dd, 10-H), 7.15 (m, C_6H_5), 7.25 (t, C_6H_5).

4.1.27. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(7-phenylheptyl)amino]midecamycin 18-dimethylacetal (11h). Reaction of **5a** with 7-phenylheptanal gave the 12-*N*-(7-phenylheptyl) derivative of **5a** as a colorless solid in 42% yield by a similar procedure to **8a**. Then, reaction of this compound with 37% aqueous formaldehyde solution gave **11h** as a colorless solid in 71% yield by a similar procedure to **11a**; $[\alpha]_D^{22}$ −46° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1123 $(M+H)^+$; ^1H NMR δ 0.92 (d, 19-H), 1.11 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.30 (d, 16-H), 1.46 (m, 12-$N(CH_2)_7C_6H_5$), 1.59 (m, 12-$N(CH_2)_7C_6H_5$), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.06 (s, 9-$OCOCH_3$), 2.26 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.58 (t, 12-$N(CH_2)_7C_6H_5$), 2.69 (dd, 2-H), 2.78 (dd, 2-H), 3.18 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.31 (m, 4′-H), 3.31 (m, 5′-H), 3.46 (br d, 4-H), 3.52 (s, 4-OCH_3), 3.56 (dd, 2′-H), 3.98 (br d, 5-H), 3.98 (br dd, 13-H), 4.47 (dq, 5″-H), 4.52 (d, 1′-H), 4.58 (t, 18-H), 4.59 (d, 4″-H), 5.07 (ddq, 15-H), 5.07 (d, 1″-H), 5.21 (br dd, 3-H), 5.39 (br s, 9-H), 5.72 (br d, 11-H), 5.81 (br d, 10-H), 7.16 (m, C_6H_5), 7.25 (m, C_6H_5).

4.1.28. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(pyridin-4-yl)propyl)amino]midecamycin 18-dimethylacetal (11i). Reaction of **5a** with 3-(pyridin-4-yl)propionaldehyde gave the 12-*N*-(3-(pyridin-4-yl)propyl) derivative of **5a** as a colorless solid in 36% yield by a similar procedure to **8a**. Then, reaction of this compound with 37% aqueous formaldehyde solution gave **11i** as a colorless solid in 97% yield by a similar procedure to **11a**; $[\alpha]_D^{19}$ −47° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 1068 $(M+H)^+$; ^1H NMR δ 0.91 (d, 19-H), 1.09 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 6′-H), 1.27 (d, 16-H), 1.47 (br t, 7-H), 1.59 (br dd, 14-H), 1.78 (m, 12-$N(CH_2)_3$-pyridine), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.05 (s, 9-$OCOCH_3$), 2.29 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.61 (dd, 2-H), 2.69 (t, 12-$N(CH_2)_3$-pyridine), 3.17 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.29 (br d, 12-H), 3.31 (m, 4′-H), 3.31 (m, 5′-H), 3.45 (br d, 4-H), 3.53 (s, 4-OCH_3), 3.57 (dd, 2′-H), 3.93 (br d, 5-H), 3.98 (br dd, 13-H), 4.46 (dq, 5″-H), 4.53 (d, 1′-H), 4.59 (t, 18-H), 4.61 (d, 4″-H), 5.06 (ddq, 15-H), 5.07 (d, 1″-H), 5.19 (br dd, 3-H), 5.38 (br s, 9-H), 5.68 (dd, 11-H), 5.81 (dd, 10-H), 7.11 (dd, pyridine), 8.46 (dd, pyridine).

4.1.29. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(naphthalen-1-yl)propyl) amino]midecamycin 18-dimethylacetal (11j). Reaction of **5a** with 3-(naphthalen-1-yl)propionaldehyde gave the 12-*N*-(3-(naphthalen-1-yl)propyl) derivative of **5a** as a colorless solid in 55% yield by a similar procedure to **8a**. Then, reaction of this compound with 37% aqueous formaldehyde solution gave **11j** as a colorless solid in 94% yield by a similar procedure to **11a**; $[\alpha]_D^{20}$ −46° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 1117 $(M+H)^+$; ^1H NMR δ 0.91 (d, 19-H), 1.09 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.23 (d, 16-H), 1.28 (d, 6′-H), 1.48 (br t, 7-H), 1.55 (br dd, 14-H), 1.80 (m, 12-$N(CH_2)_3$-naphthalene), 1.83 (dd, 2″-Hax), 1.91 (br dt, 14-H), 2.01 (d, 2″-Heq), 2.05 (s, 9-$OCOCH_3$), 2.29 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.61 (br t, 12-$N(CH_2)_3$-naphthalene), 2.71 (m, 2-H), 3.06 (m, 12-$N(CH_2)_3$-naphthalene), 3.18 (s, 18-OCH_3), 3.28 (s, 18-OCH_3), 3.31 (t, 4′-H), 3.32 (dq, 5′-H), 3.45 (br d, 4-H), 3.52 (s, 4-OCH_3), 3.57 (dd, 2′-H), 3.97 (br d, 5-H), 3.98 (br dd, 13-H), 4.46 (dq, 5″-H), 4.52 (d, 1′-H), 4.60 (t, 18-H), 4.62 (d, 4″-H), 5.04 (ddq, 15-H), 5.07 (d, 1″-H), 5.21 (br dd, 3-H), 5.40 (br s, 9-H), 5.76 (br s, 10-H), 5.76 (br s, 11-H), 7.30 (d, naphthalene), 7.37 (t, naphthalene), 7.47 (m, naphthalene), 7.69 (d, naphthalene), 7.83 (dd, naphthalene), 8.01 (d, naphthalene).

4.1.30. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(quinolin-3-yl)propyl)amino]midecamycin 18-dimethylacetal (11k). Reaction of **5a** with 3-(quinolin-3-yl)propionaldehyde gave the 12-*N*-(3-(quinolin-3-yl)propyl) derivative of **5a** as a colorless solid in 63%

yield by a similar procedure to **8a**. Then, reaction of this compound with 37% aqueous formaldehyde solution gave **11k** as a colorless solid in 89% yield by a similar procedure to **11a**; $[\alpha]_D^{22}$ −46° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1118 $(M+H)^+$; ^1H NMR δ 0.90 (d, 19-H), 1.05 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 16-H), 1.27 (d, 6′-H), 1.51 (br t, 7-H), 1.62 (br dd, 14-H), 1.83 (dd, 2″-Hax), 1.92 (m, 12-N$(CH_2)_3$-quinoline), 2.00 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.30 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.59 (m, 12-N$(CH_2)_3$-quinoline), 2.70 (dd, 2-H), 2.78 (m, 12-N$(CH_2)_3$-quinoline), 3.18 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.31 (m, 4′-H), 3.31 (m, 5′-H), 3.44 (br d, 4-H), 3.52 (s, 4-OCH_3), 3.56 (dd, 2′-H), 3.98 (br d, 5-H), 3.98 (br dd, 13-H), 4.45 (dq, 5″-H), 4.52 (d, 1′-H), 4.58 (t, 18-H), 4.61 (d, 4″-H), 5.04 (ddq, 15-H), 5.06 (d, 1″-H), 5.20 (br dd, 3-H), 5.39 (br s, 9-H), 5.72 (dd, 11-H), 5.83 (dd, 10-H), 7.50 (br dd, quinoline), 7.64 (br dd, quinoline), 7.75 (br dd, quinoline), 7.92 (br d, quinoline), 8.05 (d, quinoline), 8.77 (d, quinoline).

4.1.31. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(quinolin-4-yl)propyl)amino]midecamycin 18-dimethylacetal (11l). Reaction of **5a** with 3-(quinolin-4-yl)propionaldehyde gave the 12-*N*-(3-(quinolin-4-yl) propyl) derivative of **5a** as a colorless solid in 45% yield by a similar procedure to **8a**. Then, reaction of this compound with 37% aqueous formaldehyde solution gave **11l** as a colorless solid in 84% yield by a similar procedure to **11a**; $[\alpha]_D^{22}$ −43° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1118 $(M+H)^+$; ^1H NMR δ 0.92 (d, 19-H), 1.06 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.28 (d, 16-H), 1.28 (d, 6′-H), 1.51 (br t, 7-H), 1.51 (br dd, 14-H), 1.83 (dd, 2″-Hax), 2.02 (d, 2″-Heq), 2.05 (s, 9-$OCOCH_3$), 2.35 (s, 12-NCH_3), 2.51 (s, 3′-$N(CH_3)_2$), 2.65 (m, 12-N$(CH_2)_3$-quinoline), 2.74 (dd, 2-H), 3.17 (s, 18-OCH_3), 3.27 (s, 18-OCH_3), 3.32 (m, 4′-H), 3.32 (m, 5′-H), 3.43 (br d, 4-H), 3.53 (s, 4-OCH_3), 3.59 (dd, 2′-H), 3.98 (br d, 5-H), 3.98 (br dd, 13-H), 4.48 (dq, 5″-H), 4.54 (d, 1′-H), 4.58 (t, 18-H), 4.61 (d, 4″-H), 5.00 (ddq, 15-H), 5.07 (d, 1″-H), 5.16 (br dd, 3-H), 5.38 (br s, 9-H), 5.72 (br d, 11-H), 5.81 (br d, 10-H), 7.24 (d, quinoline), 7.56 (ddd, quinoline), 7.69 (ddd, quinoline), 8.03 (br d, quinoline), 8.09 (br d, quinoline), 8.78 (d, quinoline).

4.1.32. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(4-(pyridin-3-yl)-imidazol-1-yl)propyl)amino]-midecamycin 18-dimethylacetal (11m). Reaction of **5a** with 3-(4-(pyridin-3-yl)-imidazol-1-yl)propionaldehyde gave the 12-*N*-(3-(4-(pyridin-3-yl)-imidazol-1-yl)propyl) derivative of **5a** as a colorless solid in 47% yield by a similar procedure to **8a**. Then, reaction of this compound with 37% aqueous formaldehyde solution gave **11m** as a colorless solid in 89% yield by a similar procedure to **11a**; $[\alpha]_D^{22}$ −75° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 1134 $(M+H)^+$; ^1H NMR δ 0.66 (d, 19-H), 1.07 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.24 (d, 16-H), 1.26 (d, 6′-H), 1.48 (br t, 7-H), 1.58 (br dd, 14-H), 1.73 (m, pyridinylimidazole), 1.82 (dd, 2″-Hax), 1.96 (br dt, 14-H), 2.01 (d, 2″-Heq), 2.02 (s, 9-$OCOCH_3$), 2.36 (s, 12-NCH_3), 2.54 (s, 3′-$N(CH_3)_2$), 2.70 (dd, 2-H), 2.83 (dd, 2-H), 3.12 (s, 18-OCH_3), 3.23 (s, 18-OCH_3), 3.28 (br s, 12-H), 3.29 (t, 4′-H), 3.31 (dq, 5′-H), 3.61 (s, 4-OCH_3), 3.61 (dd, 2′-H), 3.74 (br d, 4-H), 3.96 (br d, 5-H), 4.02 (m, pyridinylimidazole), 4.07 (br dd, 13-H), 4.47 (dq, 5″-H), 4.59 (d, 1′-H), 4.61 (d, 4″-H), 4.62 (t, 18-H), 5.02 (ddq, 15-H), 5.07 (d, 1″-H), 5.23 (br dd, 3-H), 5.37 (br t, 9-H), 5.68 (dd, 11-H), 5.78 (dd, 10-H), 7.25 (d, imidazole), 7.27 (dd, pyridine), 7.61 (d, imidazole), 7.96 (dt, pyridine), 8.41 (dd, pyridine), 9.04 (d, pyridine).

4.1.33. 9-*O*-Acetyl-12,13-dihydro-12-(*N*,*N*-dimethylamino)-13-hydroxymidecamycin (12a). Reaction of **11a** with difluoroacetic acid gave **12a** as a colorless solid in 27% yield by a similar procedure to **7a**; $[\alpha]_D^{23}$ −67° (*c* 0.53, $CHCl_3$); FAB-MS *m*/*z* 917 $(M+H)^+$; ^1H NMR δ 0.93 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.31 (d, 16-H), 1.47 (dt, 7-H), 1.74 (ddd, 14-H), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.06 (s, 9-$OCOCH_3$), 2.29 (s, 12-$N(CH_3)_2$), 2.50 (s, 3′-$N(CH_3)_2$), 2.71 (dd, 2-H), 2.80 (dd, 2-H), 2.92 (dd, 17-H), 3.28 (m, 4′-H), 3.28 (m, 5′-H), 3.40 (br d, 4-H), 3.49 (dd, 2′-H), 3.53 (s, 4-OCH_3), 3.97 (br d, 5-H), 4.02 (ddd, 13-H), 4.42 (d, 1′-H), 4.44 (dq, 5″-H), 4.61 (d, 4″-H), 5.03 (ddq, 15-H), 5.06 (d, 1″-H), 5.22 (br t, 9-H), 5.30 (br dd, 3-H), 5.75 (br dd, 11-H), 5.91 (br dd, 10-H), 9.67 (s, 18-H).

4.1.34. 9-*O*-Acetyl-12-(*N*-benzyl-*N*-methylamino)-12,13-dihydro-13-hydroxymidecamycin (12b). Reaction of **11b** with difluoroacetic acid gave **12b** as a colorless solid in 59% yield by a similar procedure to **7a**; $[\alpha]_D^{23}$ −68° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 993 $(M+H)^+$; ^1H NMR δ 0.93 (d, 19-H), 1.01 (dt, 7-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.31 (d, 16-H), 1.50 (dt, 7-H), 1.65 (br dd, 14-H), 1.84 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.05 (s, 9-$OCOCH_3$), 2.51 (s, 3′-$N(CH_3)_2$), 2.60 (dd, 2-H), 2.70 (dd, 17-H), 3.28 (m, 4′-H), 3.28 (m, 5′-H), 3.52 (s, 4-OCH_3), 3.96 (br d, 5-H), 3.96 (br dd, 13-H), 4.24 (br dd, 12-H), 4.43 (d, 1′-H), 4.43 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (d, 1″-H), 5.11 (ddq, 15-H), 5.13 (br dd, 9-H), 5.21 (br dd, 3-H), 5.81 (br dd, 11-H), 5.86 (br dd, 10-H), 9.65 (s, 18-H).

4.1.35. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(2-phenylethyl)amino]midecamycin (12c). Reaction of **11c** with difluoroacetic acid gave **12c** as a colorless solid in 48% yield by a similar procedure to **7a**; $[\alpha]_D^{23}$ −53° (*c* 0.89, $CHCl_3$); FAB-MS *m*/*z* 1007 $(M+H)^+$; ^1H NMR δ 0.89 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.28 (d, 16-H), 1.48 (dt, 7-H), 1.55 (br dd, 14-H), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.05 (s, 9-$OCOCH_3$), 2.41 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.67 (dd, 2-H), 2.92 (dd, 17-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.37 (br d, 4-H), 3.48 (dd, 2′-H), 3.51 (s, 4-OCH_3), 3.96 (br d, 5-H), 4.01 (br s, 13-H), 4.42 (d, 1′-H), 4.43 (dq, 5″-H), 4.61 (d, 4″-H), 4.99 (ddq, 15-H), 5.05 (d, 1″-H), 5.22 (br s, 9-H), 5.28 (br dd, 3-H), 5.79 (dd, 11-H), 5.87 (br d, 10-H), 7.18 (m, C_6H_5), 7.27 (m, C_6H_5), 9.65 (s, 18-H).

4.1.36. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-phenylpropyl)amino]midecamycin (12d) and 9-*O*-acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-phenylpropyl)amino]demycarosylplatenomycin (13d). Reaction of **11d** with difluoroacetic acid gave **12d** as a colorless solid in 26% yield and **13d** as a colorless solid in 16%, respectively, by a similar procedure to **7a**. Total recovery was 42% in this reaction; **12d**; $[\alpha]_D^{22}$ −62° (*c* 0.50, $CHCl_3$); FAB-MS *m/z* 1021 $(M+H)^+$; ^1H NMR δ 0.88 (d, 19-H), 1.10 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.28 (d, 16-H), 1.48 (dt, 7-H), 1.58 (br dd, 14-H), 1.78 (m, 12-$N(CH_2)_3C_6H_5$), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.29 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.59 (t, 12-$N(CH_2)_3C_6H_5$), 2.92 (dd, 17-H), 3.24 (br s, 12-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.39 (br d, 4-H), 3.49 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.96 (dd, 5-H), 4.02 (br dd, 13-H), 4.42 (d, 1′-H), 4.43 (dq, 5″-H), 4.61 (d, 4″-H), 5.03 (ddq, 15-H), 5.05 (d, 1″-H), 5.20 (br d, 9-H), 5.28 (br dd, 3-H), 5.77 (br d, 11-H), 5.81 (br d, 10-H), 7.16 (m, C_6H_5), 7.25 (m, C_6H_5), 9.65 (s, 18-H). **13d**; $[\alpha]_D^{23}$ −38° (*c* 0.75, $CHCl_3$); FAB-MS *m/z* 821 $(M+H)^+$; ^1H NMR δ 0.89 (d, 19-H), 1.09 (br t, 7-H), 1.17 (t, 3-$OCOCH_2CH_3$), 1.23 (d, 6′-H), 1.29 (d, 16-H), 1.51 (dt, 7-H), 1.59 (br dd, 14-H), 1.83 (m, 12-$N(CH_2)_3C_6H_5$), 2.06 (s, 9-$OCOCH_3$), 2.30 (s, 12-NCH_3), 2.34 (t, 3′-H), 2.50 (s, 3′-$N(CH_3)_2$), 2.61 (t, 12-$N(CH_2)_3C_6H_5$), 2.99 (dd, 17-H), 3.07 (t, 4′-H), 3.24 (br s, 12-H), 3.28 (dq, 5′-H), 3.42 (br d, 4-H), 3.48 (dd, 2′-H), 3.55 (s, 4-OCH_3), 4.00 (br d, 5-H), 4.03 (br dd, 13-H), 4.45 (d, 1′-H), 5.05 (ddq, 15-H), 5.22 (br d, 9-H), 5.31 (br dd, 3-H), 5.78 (br d, 11-H), 5.82 (br d, 10-H), 7.17 (m, C_6H_5), 7.27 (m, C_6H_5), 9.65 (s, 18-H).

4.1.37. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-(*N*-methyl-*N*-(4-phenylbutyl)amino)midecamycin (12e). Reaction of **11e** with difluoroacetic acid gave **12e** as a colorless solid in 53% yield by a similar procedure to **7a**; $[\alpha]_D^{21}$ −59° (*c* 0.90, $CHCl_3$); FAB-MS *m/z* 1035 $(M+H)^+$; ^1H NMR δ 0.90 (d, 19-H), 1.10 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.17 (d, 6′-H), 1.30 (d, 16-H), 1.57 (m, 12-$N(CH_2)_4C_6H_5$), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.25 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.92 (dd, 17-H), 3.20 (br s, 12-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.40 (br d, 4-H), 3.49 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.97 (br d, 5-H), 4.04 (br dd, 13-H), 4.42 (d, 1′-H), 4.42 (dq, 5″-H), 4.61 (d, 4″-H), 5.04 (ddq, 15-H), 5.05 (d, 1″-H), 5.21 (br s, 9-H), 5.28 (br dd, 3-H), 5.78 (dd, 11-H), 5.84 (br d, 10-H), 7.16 (m, C_6H_5), 7.25 (m, C_6H_5), 9.66 (s, 18-H).

4.1.38. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-(*N*-methyl-*N*-(5-phenylpentyl)amino)midecamycin (12f). Reaction of **11f** with difluoroacetic acid gave **12f** as a colorless solid in 59% yield by a similar procedure to **7a**; $[\alpha]_D^{21}$ −60° (*c* 0.85, $CHCl_3$); FAB-MS *m/z* 1049 $(M+H)^+$; ^1H NMR δ 0.90 (d, 19-H), 1.10 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.30 (d, 16-H), 1.30 (d, 6′-H), 1.49 (m, 12-$N(CH_2)_5C_6H_5$), 1.62 (m, 12-$N(CH_2)_5C_6H_5$), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.25 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.91 (dd, 17-H), 3.19 (br d, 12-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.40 (br d, 4-H), 3.49 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.97 (br d, 5-H), 4.03 (br dd, 13-H), 4.42 (d, 1′-H), 4.43 (dq, 5″-H), 4.61 (d, 4″-H), 5.02 (ddq, 15-H), 5.05 (d, 1″-H), 5.22 (br s, 9-H), 5.29 (br dd, 3-H), 5.76 (br d, 11-H), 5.83 (br d, 10-H), 7.15 (m, C_6H_5), 7.25 (m, C_6H_5), 9.66 (s, 18-H).

4.1.39. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-(*N*-methyl-*N*-(6-phenylhexyl)amino)midecamycin (12g). Reaction of **11g** with difluoroacetic acid gave **12g** as a colorless solid in 59% yield by a similar procedure to **7a**; $[\alpha]_D^{22}$ −64° (*c* 0.66, $CHCl_3$); FAB-MS *m/z* 1063 $(M+H)^+$; ^1H NMR δ 0.90 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.30 (d, 16-H), 1.30 (d, 6′-H), 1.45 (m, 12-$N(CH_2)_6C_6H_5$), 1.60 (m, 12-$N(CH_2)_6C_6H_5$), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.06 (s, 9-$OCOCH_3$), 2.25 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.58 (t, 12-$N(CH_2)_6C_6H_5$), 2.91 (dd, 17-H), 3.19 (br s, 12-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.41 (br d, 4-H), 3.49 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.97 (br d, 5-H), 4.02 (br dd, 13-H), 4.42 (d, 1′-H), 4.42 (dq, 5″-H), 4.61 (d, 4″-H), 5.05 (ddq, 15-H), 5.05 (d, 1″-H), 5.22 (br s, 9-H), 5.29 (br dd, 3-H), 5.77 (dd, 11-H), 5.82 (dd, 10-H), 7.15 (m, C_6H_5), 7.25 (m, C_6H_5), 9.65 (s, 18-H).

4.1.40. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(7-phenylheptyl)amino]midecamycin (12h). Reaction of **11h** with difluoroacetic acid gave **12h** as a colorless solid in 53% yield by a similar procedure to **7a**; $[\alpha]_D^{22}$ −62° (*c* 0.55, $CHCl_3$); FAB-MS *m/z* 1077 $(M+H)^+$; ^1H NMR δ 0.90 (d, 19-H), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.30 (d, 16-H), 1.30 (d, 6′-H), 1.45 (m, 12-$N(CH_2)_7C_6H_5$), 1.59 (m, 12-$N(CH_2)_7C_6H_5$), 1.65 (br dd, 14-H), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.06 (s, 9-$OCOCH_3$), 2.26 (s, 12-NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.58 (t, 12-$N(CH_2)_7C_6H_5$), 2.92 (dd, 17-H), 3.19 (br s, 12-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.41 (br d, 4-H), 3.49 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.97 (br d, 5-H), 4.03 (br dd, 13-H), 4.42 (d, 1′-H), 4.42 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (ddq, 15-H), 5.06 (d, 1″-H), 5.22 (br s, 9-H), 5.30 (br dd, 3-H), 5.77 (br d, 11-H), 5.83 (br d, 10-H), 7.15 (m, C_6H_5), 7.25 (m, C_6H_5), 9.66 (s, 18-H).

4.1.41. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(pyridin-4-yl)propyl)amino]midecamycin (12i) and 9-*O*-acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(pyridin-4-yl)propyl)amino]demycarosylplatenomycin (13i). Reaction of **11i** with difluoroacetic acid gave **12i** as a colorless solid in 24% yield and **13i** as a colorless solid in 41%, respectively, by a similar procedure to **7a**. Total recovery was 65% in this reaction. **12i**; $[\alpha]_D^{20}$ −67° (*c* 0.49, $CHCl_3$); FAB-MS *m/z* 1022 $(M+H)^+$; ^1H NMR δ 0.89 (d, 19-H), 1.03 (br t, 7-H), 1.11 (s, 3″-CH_3), 1.13 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.29 (d, 16-H), 1.49 (br t, 7-H), 1.62 (br dd, 14-H), 1.84 (dd, 2″-Hax), 1.85 (m, 12-$N(CH_2)_3$-pyridine), 2.01 (d, 2″-Heq), 2.05 (s, 9-$OCOCH_3$), 2.09 (br dt, 14-H), 2.33 (s, 12-NCH_3), 2.51 (s, 3′-$N(CH_3)_2$), 2.61 (dd, 2-H), 2.75 (t, 12-$N(CH_2)_3$-pyridine), 2.93 (dd, 17-H), 3.24 (m, 4′-H), 3.27 (m, 5′-H), 3.28 (br d, 12-H), 3.38 (br d, 4-H), 3.51 (dd, 2′-H), 3.53 (s, 4-OCH_3), 3.96 (br d, 5-H), 4.05 (br dd, 13-H),

4.43 (d, 1′-H), 4.44 (dq, 5″-H), 4.62 (d, 4″-H), 5.02 (ddq, 15-H), 5.06 (d, 1″-H), 5.19 (br t, 9-H), 5.27 (br t, 3-H), 5.76 (dd, 11-H), 5.86 (dd, 10-H), 7.11 (d, pyridine), 8.47 (d, pyridine), 9.65 (s, 18-H). **13i**; $[\alpha]_D^{19}$ −43° (*c* 0.50, $CHCl_3$); FAB-MS *m/z* 822 $(M+H)^+$; ^1H NMR δ 0.88 (d, 19-H), 1.08 (br t, 7-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.22 (d, 6′-H), 1.29 (d, 16-H), 1.50 (br t, 7-H), 1.60 (br dd, 14-H), 1.83 (m, 12-$N(CH_2)_3$-pyridine), 2.05 (s, 9-$OCOCH_3$), 2.10 (br dt, 14-H), 2.29 (s, 12-NCH_3), 2.33 (t, 3′-H), 2.50 (s, 3′-$N(CH_3)_2$), 2.75 (dt, 12-$N(CH_2)_3$-pyridine), 2.98 (dd, 17-H), 3.06 (t, 4′-H), 3.20 (br t, 12-H), 3.27 (dq, 5′-H), 3.40 (br d, 4-H), 3.47 (dd, 2′-H), 3.54 (s, 4-OCH_3), 3.97 (br d, 5-H), 4.01 (br dd, 13-H), 4.45 (d, 1′-H), 5.04 (ddq, 15-H), 5.21 (br t, 9-H), 5.28 (br t, 3-H), 5.74 (dd, 11-H), 5.83 (dd, 10-H), 7.11 (dd, pyridine), 8.46 (dd, pyridine), 9.67 (s, 18-H).

4.1.42. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(naphthalen-1-yl)propyl)amino]midecamycin (12j) and 9-*O*-acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(naphthalen-1-yl)propyl)amino]demycarosylplatenomycin (13j). Reaction of **11j** with difluoroacetic acid gave **12j** as a colorless solid in 46% yield and **13j** as a colorless solid in 25%, respectively, by a similar procedure to **7a**. Total recovery was 71% in this reaction. **12j**; $[\alpha]_D^{19}$ −61° (*c* 0.50, $CHCl_3$); FAB-MS *m/z* 1071 $(M+H)^+$; ^1H NMR δ 0.89 (d, 19-H), 1.11 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.15 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.23 (d, 16-H), 1.24 (d, 6′-H), 1.49 (br t, 7-H), 1.58 (br dd, 14-H), 1.84 (dd, 2″-Hax), 1.93 (br dt, 14-H), 2.01 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.06 (m, 12-$N(CH_2)_3$-naphthalene), 2.32 (s, 12-NCH_3), 2.51 (s, 3′-$N(CH_3)_2$), 2.64 (t, 12-$N(CH_2)_3$-naphthalene), 2.75 (m, 2-H), 2.92 (dd, 17-H), 3.07 (dq, 5′-H), 3.26 (br d, 12-H), 3.28 (t, 4′-H), 3.39 (br d, 4-H), 3.50 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.97 (br d, 5-H), 4.05 (br dd, 13-H), 4.43 (d, 1′-H), 4.45 (dq, 5″-H), 4.62 (d, 4″-H), 5.01 (ddq, 15-H), 5.06 (d, 1″-H), 5.18 (br d, 9-H), 5.28 (br dd, 3-H), 5.80 (br s, 11-H), 5.81 (br s, 10-H), 7.30 (d, naphthalene), 7.37 (t, naphthalene), 7.47 (m, naphthalene), 7.69 (d, naphthalene), 7.83 (dd, naphthalene), 8.02 (d, naphthalene), 9.66 (s, 18-H). **13j**; $[\alpha]_D^{20}$ −433° (*c* 0.74, $CHCl_3$); FAB-MS *m/z* 871 $(M+H)^+$; ^1H NMR δ 0.88 (d, 19-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.22 (d, 16-H), 1.24 (d, 6′-H), 1.46 (br t, 7-H), 1.54 (br dd, 14-H), 1.95 (m, 12-$N(CH_2)_3$-naphthalene), 2.04 (s, 9-$OCOCH_3$), 2.10 (br dt, 14-H), 2.32 (s, 12-NCH_3), 2.51 (s, 3′-$N(CH_3)_2$), 2.73 (dt, 12-$N(CH_2)_3$-naphthalene), 2.76 (m, 2-H), 2.98 (dd, 17-H), 3.06 (t, 4′-H), 3.25 (br d, 12-H), 3.28 (dq, 5′-H), 3.40 (br d, 4-H), 3.47 (dd, 2′-H), 3.53 (s, 4-OCH_3), 3.98 (br d, 5-H), 4.04 (br dd, 13-H), 4.44 (d, 1′-H), 5.01 (ddq, 15-H), 5.18 (br d, 9-H), 5.29 (br dd, 3-H), 5.79 (br s, 11-H), 5.80 (br s, 10-H), 7.30 (d, naphthalene), 7.37 (t, naphthalene), 7.47 (m, naphthalene), 7.69 (d, naphthalene), 7.83 (dd, naphthalene), 8.02 (d, naphthalene), 9.68 (s, 18-H).

4.1.43. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(quinolin-3-yl)propyl)amino]midecamycin (12k) and 9-*O*-acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(quinolin-3-yl)propyl)amino]demycarosylplatenomycin (13k). Reaction of **11k** with difluoroacetic acid gave **12k** as a colorless solid in 28% yield and **13k** as a colorless solid in 40%, respectively, by a similar procedure to **7a**. Total recovery was 68% in this reaction. **12k**; $[\alpha]_D^{21}$ −63° (*c* 0.55, $CHCl_3$); FAB-MS *m/z* 1072 $(M+H)^+$; ^1H NMR δ 0.88 (d, 19-H), 1.08 (br t, 7-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.13 (s, 3″-CH_3), 1.14 (d, 6″-H), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.28 (d, 16-H), 1.48 (dt, 7-H), 1.64 (br dd, 14-H), 1.85 (dd, 2″-Hax), 1.98 (m, 12-$N(CH_2)_3$-quinoline), 2.02 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.32 (s, 12-NCH_3), 2.53 (s, 3′-$N(CH_3)_2$), 2.60 (m, 12-$N(CH_2)_3$-quinoline), 2.82 (m, 12-$N(CH_2)_3$-quinoline), 2.94 (dd, 17-H), 3.24 (m, 12-H), 3.29 (m, 4′-H), 3.29 (m, 5′-H), 3.31 (br d, 4-H), 3.52 (dd, 2′-H), 3.54 (s, 4-OCH_3), 3.98 (br d, 5-H), 4.07 (br dd, 13-H), 4.45 (d, 1′-H), 4.46 (dq, 5″-H), 4.63 (d, 4″-H), 5.04 (ddq, 15-H), 5.08 (d, 1″-H), 5.20 (br s, 9-H), 5.30 (br t, 3-H), 5.79 (dd, 11-H), 5.85 (dd, 10-H), 7.52 (br dd, quinoline), 7.66 (br dd, quinoline), 7.77 (br d, quinoline), 7.95 (br d, quinoline), 8.06 (d, quinoline), 8.78 (d, quinoline), 9.67 (s, 18-H). **13k**; $[\alpha]_D^{22}$ −34° (*c* 0.51, $CHCl_3$); FAB-MS *m/z* 872 $(M+H)^+$; ^1H NMR δ 0.88 (d, 19-H), 1.08 (br t, 7-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.23 (d, 6′-H), 1.28 (d, 16-H), 1.51 (dt, 7-H), 1.64 (br dd, 14-H), 1.95 (m, 12-$N(CH_2)_3$-quinoline), 2.03 (s, 9-$OCOCH_3$), 2.31 (s, 12-NCH_3), 2.35 (t, 3′-H), 2.51 (s, 3′-$N(CH_3)_2$), 2.60 (m, 12-$N(CH_2)_3$-quinoline), 3.00 (dd, 17-H), 3.08 (t, 4′-H), 3.24 (m, 12-H), 3.28 (dq, 5′-H), 3.43 (dd, 4-H), 3.49 (dd, 2′-H), 3.55 (s, 4-OCH_3), 4.00 (br d, 5-H), 4.06 (br dd, 13-H), 4.46 (d, 1′-H), 5.05 (ddq, 15-H), 5.21 (br s, 9-H), 5.31 (br t, 3-H), 5.79 (dd, 11-H), 5.85 (dd, 10-H), 7.52 (br dd, quinoline), 7.66 (br dd, quinoline), 7.70 (br d, quinoline), 7.96 (br d, quinoline), 8.07 (d, quinoline), 8.79 (d, quinoline), 9.69 (s, 18-H).

4.1.44. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(quinolin-4-yl)propyl)amino] midecamycin (12l) and 9-*O*-acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(quinolin-4-yl)propyl)amino]demycarosylplatenomycin (13l). Reaction of **11l** with difluoroacetic acid gave **12l** as a colorless solid in 39% yield and **13l** as a colorless solid in 33%, respectively, by a similar procedure to **7a**. Total recovery was 72% in this reaction. **12l**; $[\alpha]_D^{24}$ −58° (*c* 0.70, $CHCl_3$); FAB-MS *m/z* 1072 $(M+H)^+$; ^1H NMR δ 0.88 (d, 19-H), 1.11 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.17 (d, 6′-H), 1.20 (d, 16-H), 1.47 (br t, 7-H), 1.54 (br dd, 14-H), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.32 (s, 12-NCH_3), 2.51 (s, 3′-$N(CH_3)_2$), 2.93 (dd, 17-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.37 (br t, 4-H), 3.51 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.95 (br d, 5-H), 4.01 (br dd, 13-H), 4.43 (d, 1′-H), 4.44 (dq, 5″-H), 4.61 (d, 4″-H), 5.00 (ddq, 15-H), 5.05 (d, 1″-H), 5.16 (br s, 9-H), 5.25 (br t, 3-H), 5.75 (br d, 11-H), 5.81 (br d, 10-H), 7.22 (d, quinoline), 7.54 (ddd, quinoline), 7.68 (ddd, quinoline), 8.03 (br d, quinoline), 8.08 (br d, quinoline), 8.77 (d, quinoline), 9.65 (s, 18-H). **13l**; $[\alpha]_D^{24}$ −34° (*c* 0.50, $CHCl_3$); FAB-MS *m/z* 872 $(M+H)^+$; ^1H NMR δ 0.88 (d, 19-H), 1.05 (br t, 7-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.21 (d, 6′-H), 1.22 (d, 16-H), 1.50 (dt, 7-H), 1.55 (br dd, 14-H), 2.02 (m, 12-$N(CH_2)_3$-quinoline), 2.04 (s, 9-$OCOCH_3$), 2.32 (s, 12-NCH_3), 2.34 (t, 3′-H), 2.50 (s, 3′-$N(CH_3)_2$), 2.99 (dd, 17-H), 3.06 (t, 4′-H), 3.27 (dq, 5′-H), 3.39 (br d, 4-H),

3.48 (dd, 2′-H), 3.54 (s, 4-OCH$_3$), 3.97 (br d, 5-H), 4.02 (br dd, 13-H), 4.45 (d, 1′-H), 5.00 (ddq, 15-H), 5.17 (br s, 9-H), 5.26 (br t, 3-H), 5.76 (dd, 11-H), 5.82 (br d, 10-H), 7.23 (d, quinoline), 7.54 (dd, quinoline), 7.68 (dd, quinoline), 8.04 (d, quinoline), 8.09 (d, quinoline), 8.78 (d, quinoline), 9.67 (s, 18-H).

4.1.45. 9-*O*-Acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(4-pyridin-3-yl-imidazol-1-yl)propyl)amino]midecamycin (12m) and 9-*O*-acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-(4-pyridin-3-yl-imidazol-1-yl)propyl)-amino]demycarosylplatenomycin (13m). Reaction of **11m** with difluoroacetic acid gave **12m** as a colorless solid in 38% yield and **13m** as a colorless solid in 44%, respectively, by a similar procedure to **7a**. Total recovery was 82% in this reaction. **12m**; $[\alpha]_D^{22}$ −123° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 1088 $(M+H)^+$; ^{1}H NMR δ 0.41 (d, 19-H), 1.12 (s, 3″-CH$_3$), 1.13 (t, 3-OCOCH$_2$CH$_3$), 1.14 (d, 6″-H), 1.17 (t, 4″-OCOCH$_2$CH$_3$), 1.25 (d, 6′-H), 1.32 (d, 16-H), 1.64 (br dd, 14-H), 1.82 (dd, 2″-Hax), 1.99 (s, 9-OCOCH$_3$), 2.01 (d, 2″-Heq), 2.13 (br dt, 14-H), 2.41 (s, 12-NCH$_3$), 2.60 (s, 3′-N(CH$_3$)$_2$), 2.78 (dd, 2-H), 2.85 (m, 12-N(CH$_2$)$_3$-imidazole), 2.89 (dd, 17-H), 3.12 (br t, 12-H), 3.25 (br d, 4-H), 3.26 (t, 4′-H), 3.27 (dq, 5′-H), 3.60 (dd, 2′-H), 3.75 (s, 4-OCH$_3$), 3.95 (br d, 5-H), 4.06 (m, 12-N(CH$_2$)$_3$-imidazole), 4.20 (br dd, 13-H), 4.47 (dq, 5″-H), 4.54 (d, 1′-H), 4.62 (d, 4″-H), 5.05 (ddq, 15-H), 5.07 (d, 1″-H), 5.12 (br s, 9-H), 5.32 (br dd, 3-H), 5.69 (dd, 11-H), 5.79 (dd, 10-H), 7.25 (d, imidazole), 7.28 (dd, pyridine), 7.67 (d, imidazole), 7.90 (dt, pyridine), 8.39 (dd, pyridine), 9.19 (d, pyridine), 9.60 (s, 18-H). **13m**; $[\alpha]_D^{23}$ −109° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 888 $(M+H)^+$; ^{1}H NMR δ 0.42 (d, 19-H), 1.13 (t, 3-OCOCH$_2$CH$_3$), 1.19 (d, 6′-H), 1.32 (d, 16-H), 1.63 (br dd, 14-H), 2.00 (s, 9-OCOCH$_3$), 2.10 (br dt, 14-H), 2.38 (s, 12-NCH$_3$), 2.60 (s, 3′-N(CH$_3$)$_2$), 2.78 (dd, 2-H), 2.87 (m, 12-N(CH$_2$)$_3$-imidazole), 2.91 (dd, 17-H), 3.09 (br t, 12-H), 3.27 (br d, 4-H), 3.28 (t, 4′-H), 3.31 (dq, 5′-H), 3.57 (dd, 2′-H), 3.74 (s, 4-OCH$_3$), 3.96 (br d, 5-H), 4.04 (m, 12-N(CH$_2$)$_3$-imidazole), 4.17 (br dd, 13-H), 4.55 (d, 1′-H), 5.06 (ddq, 15-H), 5.13 (br s, 9-H), 5.33 (br dd, 3-H), 5.67 (dd, 11-H), 5.78 (dd, 10-H), 7.25 (d, imidazole), 7.28 (dd, pyridine), 7.66 (d, imidazole), 7.91 (dt, pyridine), 8.38 (dd, pyridine), 9.18 (d, pyridine), 9.62 (s, 18-H).

4.1.46. 9,3″-Di-*O*-acetyl-12,13-dihydro-12,13-epoxymidecamycin 18-dimethylacetal (15). Reaction of 9,3″-di-*O*-acetylmidecamycin in MeOH with pyridinium *p*-toluenesulfonate gave **14** as a colorless solid in 79% yield by a similar procedure to **2**. Then, reaction of **14** with 3-chroloperbenzoic acid gave **15** as a colorless solid in 42% yield by a similar procedure to **3**; $[\alpha]_D^{23}$ −45° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 960 $(M+H)^+$; ^{1}H NMR δ 0.89 (dt, 7-H), 1.01 (d, 19-H), 1.09 (d, 6″-H), 1.10 (t, 3-OCOCH$_2$CH$_3$), 1.19 (t, 4″-OCOCH$_2$CH$_3$), 1.22 (d, 6′-H), 1.27 (d, 16-H), 1.42 (s, 3″-CH$_3$), 1.47 (br dd, 14-H), 1.63 (dt, 7-H), 1.70 (dd, 2″-Hax), 2.00 (s, 3″-OCOCH$_3$), 2.01 (s, 9-OCOCH$_3$), 2.23 (br d, 14-H), 2.38 (q, 3-OCOCH$_2$CH$_3$), 2.43 (q, 4″-OCOCH$_2$CH$_3$), 2.57 (s, 3′-N(CH$_3$)$_2$), 2.74 (dd, 2-H), 3.16 (s, 18-OCH$_3$), 3.22 (d, 2″-Heq), 3.26 (s, 18-OCH$_3$), 3.30 (br d, 4-H), 3.57 (s, 4-OCH$_3$), 3.94 (br d, 5-H), 4.51 (dq, 5″-H), 4.60 (d, 1′-H), 4.60 (d, 4″-H), 4.62 (t, 18-H), 4.88 (d, 1″-H), 4.91 (ddq, 15-H), 5.10 (br d, 3-H), 5.35 (dd, 9-H), 5.76 (dd, 11-H), 6.02 (dd, 10-H).

4.1.47. 9,3″-Di-*O*-acetyl-12-amino-12,13-dihydro-13-hydroxymidecamycin 18-dimethylacetal (16). Reaction of **15** in MeOH with sodium azide gave 9,3″-di-*O*-acetyl-12-azide-12,13-dihydro-13-hydroxymidecamycin 18-dimethylacetal by a similar procedure to **4a**. Then, reaction of this compound with triphenylphosphine gave **16** as a colorless solid in 69% yield (overall two steps) by a similar procedure to **5a**; $[\alpha]_D^{23}$ −41° (*c* 1.5, $CHCl_3$); FAB-MS *m*/*z* 977 $(M+H)^+$; ^{1}H NMR δ 0.95 (d, 19-H), 1.09 (d, 6″-H), 1.13 (t, 3-OCOCH$_2$CH$_3$), 1.19 (t, 4″-OCOCH$_2$CH$_3$), 1.22 (d, 6′-H), 1.31 (d, 16-H), 1.42 (s, 3″-CH$_3$), 1.54 (br t, 7-H), 1.59 (br dd, 14-H), 1.70 (dd, 2″-Hax), 2.01 (s, 3″-OCOCH$_3$), 2.04 (s, 9-OCOCH$_3$), 2.36 (t, 3′-H), 2.56 (s, 3′-N(CH$_3$)$_2$), 2.64 (dd, 2-H), 2.90 (dd, 2-H), 3.16 (s, 18-OCH$_3$), 3.23 (d, 2″-Heq), 3.27 (s, 18-OCH$_3$), 3.38 (dd, 2′-H), 3.53 (br d, 4-H), 3.55 (s, 4-OCH$_3$), 3.75 (br s, 12-H), 3.86 (br dd, 13-H), 3.95 (br d, 5-H), 4.52 (dq, 5″-H), 4.56 (d, 1′-H), 4.59 (d, 4″-H), 4.61 (t, 18-H), 4.86 (d, 1″-H), 5.12 (ddq, 15-H), 5.18 (br dd, 3-H), 5.30 (dd, 9-H), 5.70 (br d, 10-H), 5.82 (dd, 11-H).

4.1.48. 9,3″-Di-*O*-acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-phenylpropyl)amino]midecamycin 18-dimethylacetal (17). Reaction of **16** with phenylpropionaldehyde gave the crude 12-*N*-(3-phenylpropyl) derivative of **16** as a colorless solid by a similar procedure to **8a**. Then, reaction of this compound with 37% aqueous formaldehyde solution gave **17** as a colorless solid in 37% yield (overall two steps) by a similar procedure to **11a**; $[\alpha]_D^{22}$ −59° (*c* 1.0, $CHCl_3$); TSP-MS *m*/*z* 1109 $(M+H)^+$; ^{1}H NMR δ 0.92 (d, 19-H), 1.10 (d, 6″-H), 1.12 (t, 3-OCOCH$_2$CH$_3$), 1.20 (t, 4″-OCOCH$_2$CH$_3$), 1.23 (d, 6′-H), 1.29 (d, 16-H), 1.43 (s, 3″-CH$_3$), 1.55 (br t, 7-H), 1.62 (br dd, 14-H), 2.02 (s, 3″-OCOCH$_3$), 2.07 (s, 9-OCOCH$_3$), 2.36 (s, 12-NCH$_3$), 2.56 (s, 3′-N(CH$_3$)$_2$), 2.61 (t, 12-N(CH$_2$)$_3$C$_6$H$_5$), 2.64 (dd, 2-H), 2.80 (dd, 2-H), 3.19 (s, 18-OCH$_3$), 3.24 (d, 2″-Heq), 3.28 (s, 18-OCH$_3$), 3.38 (dd, 2′-H), 3.47 (br d, 4-H), 3.56 (s, 4-OCH$_3$), 3.96 (br d, 5-H), 4.05 (br dd, 13-H), 4.52 (dq, 5″-H), 4.57 (d, 1′-H), 4.59 (d, 4″-H), 4.63 (t, 18-H), 4.87 (d, 1″-H), 5.05 (ddq, 15-H), 5.21 (br dd, 3-H), 5.41 (br s, 9-H), 5.74 (dd, 11-H), 5.87 (br d, 10-H), 7.18 (m, C$_6$H$_5$), 7.27 (m, C$_6$H$_5$).

4.1.49. 9,3″-Di-*O*-acetyl-12,13-dihydro-13-hydroxy-12-[*N*-methyl-*N*-(3-phenylpropyl)amino]midecamycin (18). Reaction of **17** with difluoroacetic acid gave **18** as a colorless solid in 87% yield by a similar procedure to **7a**; $[\alpha]_D^{23}$ −73° (*c* 1.0, $CHCl_3$); TSP-MS *m*/*z* 1063 $(M+H)^+$; ^{1}H NMR δ 0.89 (d, 19-H), 1.10 (d, 6″-H), 1.14 (d, 6′-H), 1.17 (t, 3-OCOCH$_2$CH$_3$), 1.20 (t, 4″-OCOCH$_2$CH$_3$), 1.29 (d, 16-H), 1.43 (s, 3″-CH$_3$), 1.56 (dt, 7-H), 1.59 (br dd, 14-H), 1.72 (dd, 2″-Hax), 1.85 (m, 12-N(CH$_2$)$_3$C$_6$H$_5$), 2.01 (s, 3″-OCOCH$_3$), 2.07 (s, 9-OCOCH$_3$), 2.33 (s, 12-NCH$_3$), 2.57 (s, 3′-N(CH$_3$)$_2$), 2.80 (dd, 2-H), 2.97 (dd, 17-H), 3.43 (br d, 4-H), 3.57 (s, 4-OCH$_3$), 3.96 (br d, 5-H), 4.06 (br dd, 13-H), 4.47

(d, 1′-H), 4.48 (dq, 5″-H), 4.60 (d, 4″-H), 4.88 (d, 1″-H), 5.04 (ddq, 15-H), 5.22 (br d, 9-H), 5.30 (br dd, 3-H), 5.79 (br d, 11-H), 5.83 (br d, 10-H), 7.18 (m, C_6H_5), 7.27 (m, C_6H_5), 9.67 (s, 18-H).

4.2. Biology

4.2.1. 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*, or cultured on blood agar plate for *S. pneumoniae*, *Streptococcus pyogenes*, *Moraxella catarrhalis* and *H. 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 h. Then, MIC was measured.

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