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Novel Azalides Derived from Sixteen-Membered Macrolides

I. Isolation of the Mobile Dialdehyde and Its One-Pot Macrocyclization with an Amine

Tomoaki Miura, Satomi Natsume, Kenichi Kanemoto, Kunio Atsumi, Hideki Fushimi, Hiroaki Sasai, Takayoshi Arai, Takuji Yoshida, Keiichi Ajito

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Abstract The design and synthesis of novel 15-membered 11-azalides and 16-membered 11,12-diazalide starting from 16-membered macrolides are reported. A mobile linear dialdehyde was isolated *via* a cyclic tetraol which was prepared by osmium oxidation of a conjugated diene. One-pot macrocyclization of this dialdehyde with an amine or a diamine afforded corresponding 15-membered azalides or 11,12-diazalide. Fundamental SAR studies of 15-membered 11-azalides disclosed their potentiality as a lead molecule for further chemical modifications. For environmental preservation, sustainable chemistry for synthesis of these azalides is also discussed.

Keywords azalide, 16-membered macrolide, one-pot macrocyclization, dialdehyde, leucomycin

Introduction

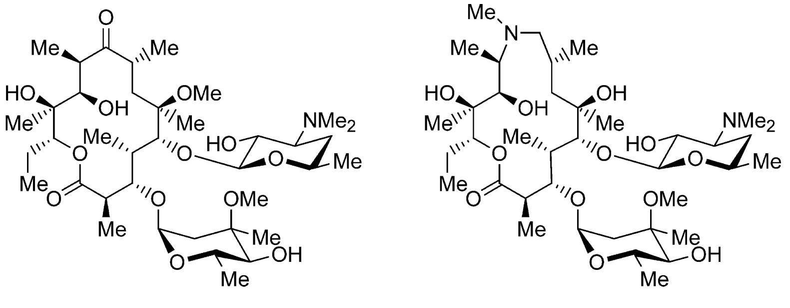
Macrolide antibiotics [1] are active against Gram-positive bacteria (especially *Streptococcus pneumoniae*), *Moraxella catarrhalis*, *Haemophillus influenzae*, and *Mycoplasma pneumoniae*, and regarded as very important chemotherapeutics from a clinical viewpoint. Clarithromycin [2] (CAM) and azithromycin [3] (AZM) (Fig. 1), which are representatives of widely used macrolides and are derived from 14-membered erythromycin, exhibited enhanced antibacterial activities and characteristic pharmacokinetics, respectively. As one of the next generation macrolides, *i.e.* ketolides, telithromycin [4] (TEL) has recently been launched as an efficient antibiotic which is effective against clinically important pathogens including erythromycin-resistant *Streptococcus pneumoniae* (ERSP). Moreover, the novel ketolide, S-013420 [5] is under the clinical trials in 2006.

Although telithromycin exhibits improved antibacterial activities against resistant bacteria of *S. pneumoniae* with an *erm* gene, it is not always sufficient. Specifically, it is affected by efflux pump function of resistant bacteria in *S. pneumoniae*, and its safety [6] seriously concerns clinical site especially in US. In 2001, we started a novel drug discovery program applying 16-membered macrolide antibiotics which have been proved to be safe and effective against resistant bacteria of *S. pneumoniae* with efflux pump.

Before we started this research program, we had already established two major pharmacological approaches by medicinal chemistry using 16-membered macrolides. Owing to these approaches, (i) biological stability in 16-membered macrolides was dramatically improved [7] by chemical modification of a neutral sugar moiety, and (ii) antibacterial activities against resistant pathogens

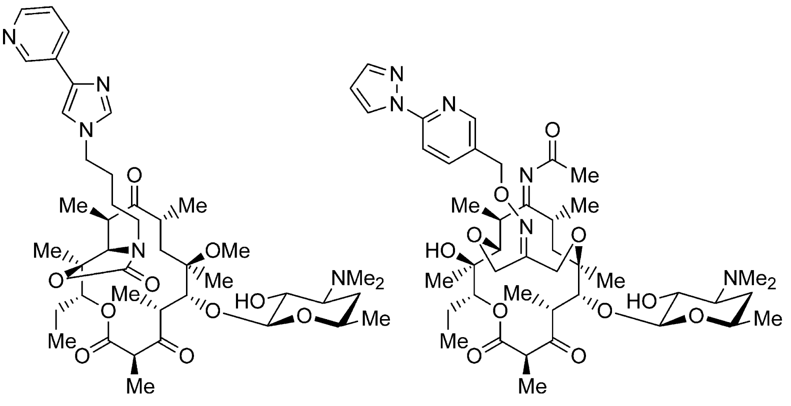
K. Ajito (Corresponding author), **T. Miura, S. Natsume, K. Kanemoto, K. Atsumi, H. Fushimi, T. Yoshida:** Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd., 760 Morooka-cho, Kohoku-ku, Yokohama, 222-8567 Japan,
E-mail: keiichi_ajito@meiji.co.jp

H. Sasai, T. Arai: The Institute of Scientific and Industrial Research (ISIR), Osaka University, 8-1 Mihogaoka, Ibaraki, Osaka, 567-0047 Japan



Clarithromycin(CAM)

Azithromycin(AZM)



Telithromycin(TEL)

S-013420

Fig. 1 Structures of representative macrolides.

in 16-membered macrolides was clearly enhanced [8] by introducing an appropriate aromatic ring with an adjusted length of an alkyl spacer into the lactone ring. There is, however, limitation in molecular design and synthesis of novel compounds, as long as we utilize known pharmacophores. We had to explore a novel pharmacophore.

Since the synthesis of azithromycin [9] was reported by Pliva in 1981, many novel azalides were reported in 1990's as shown in Fig. 2 [10∼15] and so on [16]. These examples include 13-membered to 17-membered azalides, but the position of the nitrogen atom in all derivatives is C-9 or C-10 (lactone carbonyl: designated to be C-1). On the other hand, several azalide-based new pharmacophores have been reported in the 21st century. Pliva disclosed an azalide-ketolide hybrid molecule [17] with an arylalkyl side chain at the C-6 position. Enanta reported a bicycle azalide [18] which had a bridge between the C-3 and C-6 positions. Pliva introduced *N*,*O*-carbonate [19] using azithromycin framework. But all of them had the nitrogen atom at the same position as in the derivatives reported in 1990's.

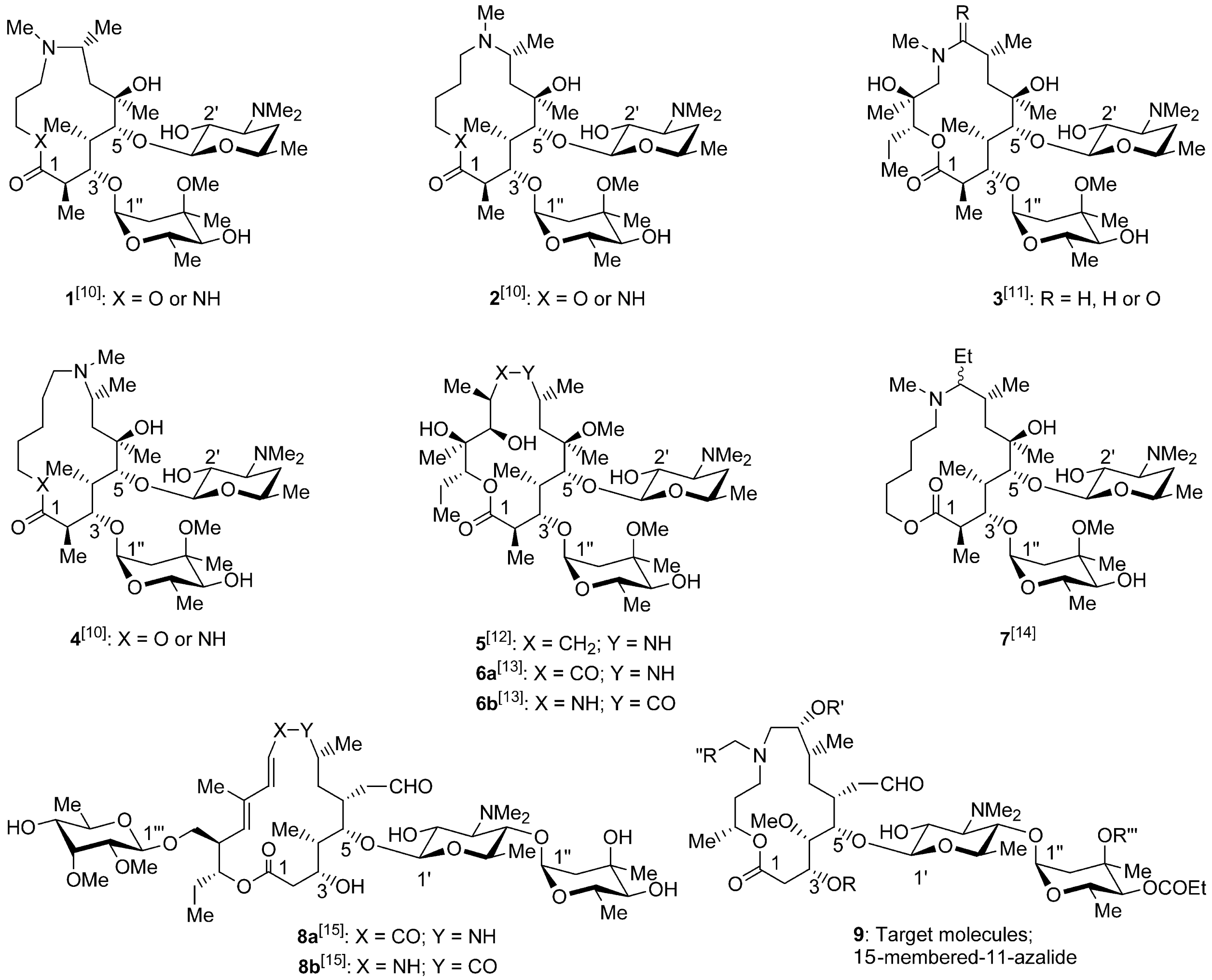
In this paper, we report the design and synthesis of novel 15-membered 11-azalides (**9**) and 16-membered 11,12-diazalide starting from 16-membered macrolides. Meanwhile, 12-azalide can be introduced as one of attractive novel azalides disclosed by Taisho in the 21st century [20].

Results and Discussion

Isolation of the Mobile Dialdehyde and Its One-Pot Macrocyclization

Before discussion of synthetic route for 15-membered azalides, an attractive example was reported by Ōmura in 1982 that two large molecules possessing an aldehyde group could reductively react with an amine one by one to afford a dialkylamine, 18,18′-dideoxo-18,18′-iminoleucomycin A_3 (**10**) [21] as shown in Fig. 3. Retrosynthetic analysis of 15-membered 11-azalides easily presented a linear dialdehyde (**12**) as shown in Fig. 4 or its structurally related molecule as a key intermediate. Then, we decided to isolate **12** and perform its macrocyclization with an amine.

We decided to use an aldehyde as a key intermediate for macrocyclization, and chose dimethoxy acetal protection for the original aldehyde at the C-18 position. Because we had to use difluoroacetic acid [22] to remove this protecting



1[10]: X = O or NH

2[10]: X = O or NH

3[11]: R = H, H or O

4[10]: X = O or NH

5[12]: X = CH$_2$; Y = NH
6a[13]: X = CO; Y = NH
6b[13]: X = NH; Y = CO

7[14]

8a[15]: X = CO; Y = NH
8b[15]: X = NH; Y = CO

9: Target molecules;
15-membered-11-azalide

Fig. 2 Structures of azalides reported in the 20th century as a novel macrolide framework and target molecules.

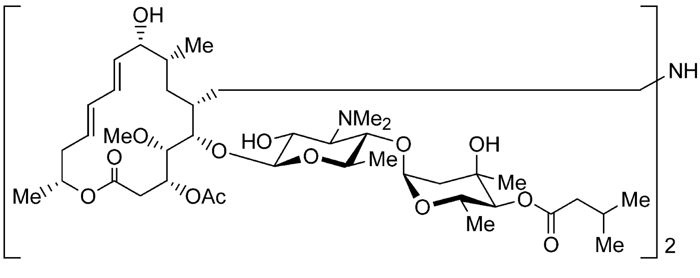


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Fig. 3 Dialkylamine (**10**) derived from leucomycin A$_3$.

group, we chose miokamycin (MOM [23]) as a starting material (not midecamycin (MDM [24])) (Scheme 1). A neutral sugar moiety in MOM with the 3″-acetoxy group is more stable against cleavage of a glycoside bond under acidic conditions because of its 1,3-diaxial steric hindrance than that in MDM with the 3″-hydroxyl group. On the other hand, an acetyl group at the C-9 position in MOM is necessary when we utilize a tetraol under oxidation conditions.

Sequential protections of MOM gave **15**, which was converted into the tetraol (**13**) in a moderate yield by osmium tetroxide with *N*-methylmorpholine *N*-oxide in

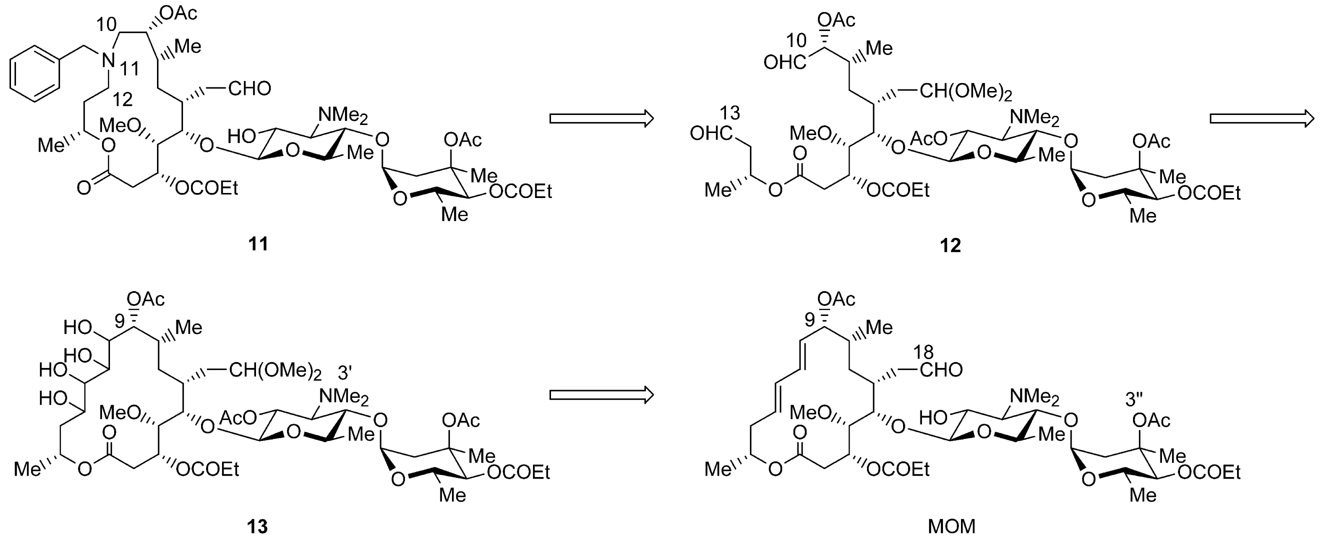
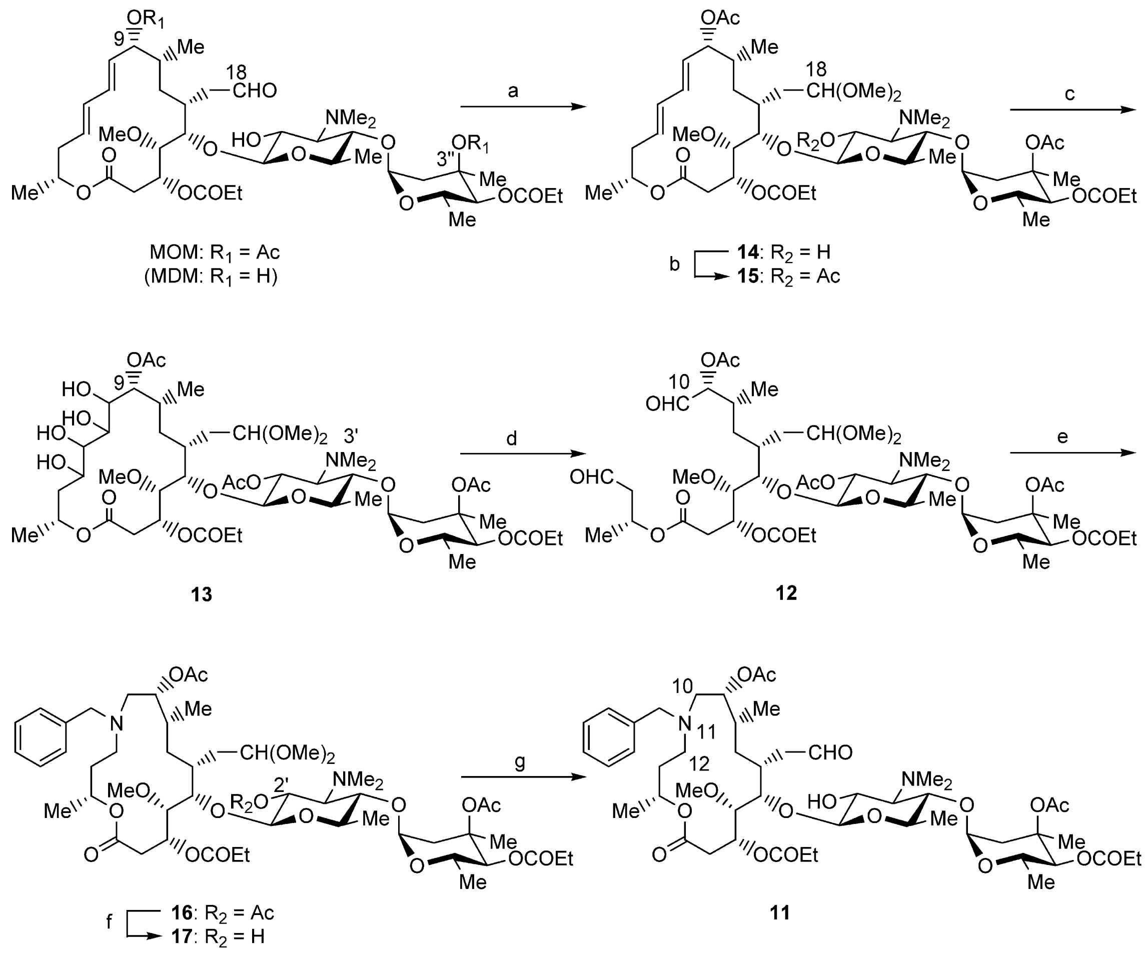
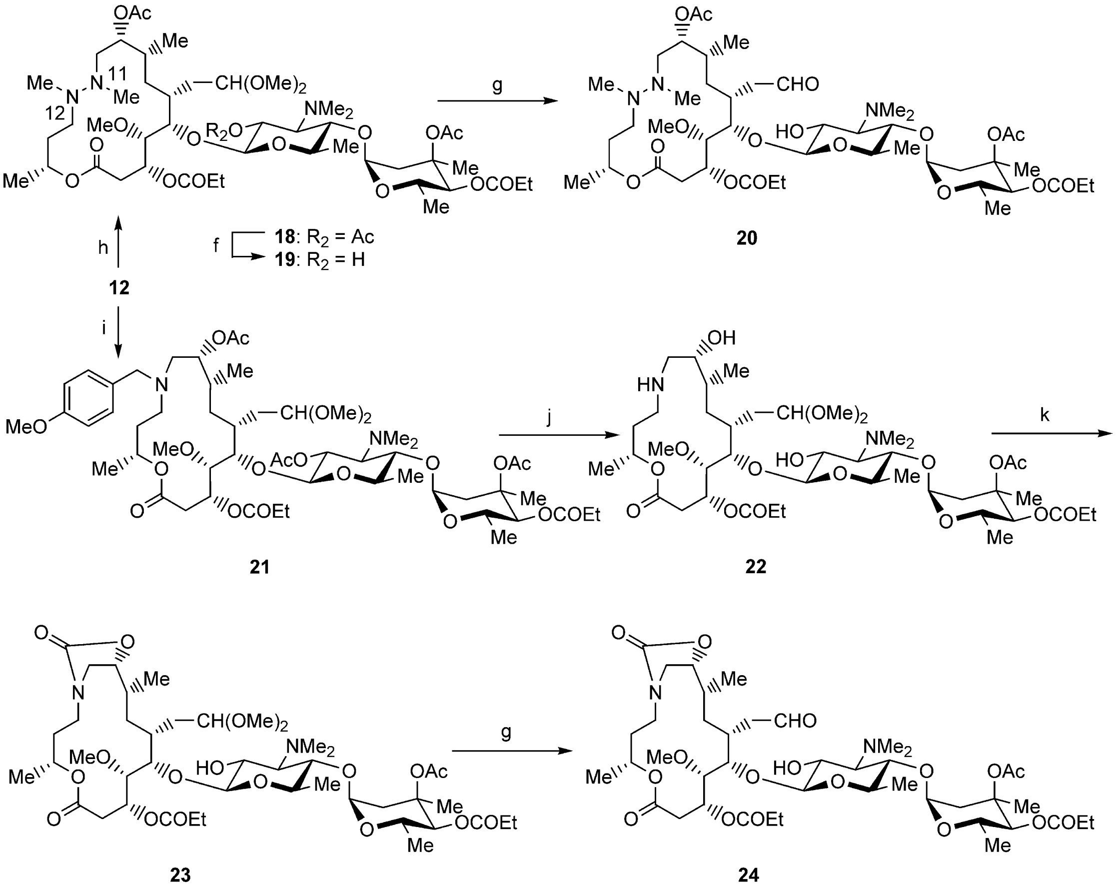


Fig. 4 Retrosynthetic analysis of compound (**11**), a prototype of 15-membered azalides.



Reagents and conditions: (a): $(MeO)_3CH$ (80 eq), PPTS (1.2 eq), MeOH, 40~50°C, 4 days; (b): Ac_2O (5 eq), MeCN, 40°C, 16 hours; (c): OsO_4 (0.15 eq), NMO (2 eq), aq. acetone, r.t., 24 hours, 30% in 3 steps; (d): $Pb(OAc)_4$ (2.1 eq), PhH, Na_2CO_3 (8 eq), r.t., 1 hour; (e): $BnNH_2$ (1.1 eq), $NaB(CN)H_3$ (3.9 eq), AcOH (15 eq), EtOH, 0°C to r.t., 15~20 hours, 10% in 2 steps; (f): aq MeOH, 55°C, 24 hours, 79~90%, (g): difluoroacetic acid (20 eq), MeCN - H_2O, r.t., 25 hours, 84~94%.

Scheme 1 Isolation of mobile dialdehyde (**12**) and its macrocyclization with amine or diamine.



Reagents and conditions: (h): 1,2-dimethylhydrazine hydrochloride (1.1 eq), others are same as (e), 13%; (i): *p*-methoxybenzylamine (1.1 eq), others are same as (e), 8.8%; (j): aq MeOH, 55°C, 96 hours, then, H_2, Pd/C, dioxane-EtOH, 30% in 2 steps; (k): triphosgene (1.2 eq), Et_3N (10 eq), CH_2Cl_2, 0°C, 90 minutes, 74%.

Scheme 1 Isolation of mobile dialdehyde (**12**) and its macrocyclization with amine or diamine. (continued)

aqueous acetone. In the osmium oxidation step, 3′-de-*N*-methyl derivative can be detected as a minor byproduct, but this can be converted to **13** by reductive methylation using aqueous formaldehyde and sodium cyanoborohydride in ethanol in the presence of acetic acid. Then, the oxidation of the tetraol using lead (IV) acetate with sodium carbonate in benzene afforded the mobile dialdehyde (**12**) in a low yield. This aldehyde can be purified with silica gel column chromatography to prepare desired pure product which shows one doublet (δ 9.59, H-10) and one triplet (δ 9.75, so called H-13) in ^{1}H-NMR spectroscopy. We did not, however, always purify this dialdehyde for further analogue synthesis. Macrocyclization between **12** and benzylamine with sodium cyanoborohydride in ethanol in the presence of acetic acid gave 15-membered 11-azalide (**16**) as the first example [25]. The two-step yield was around 10% from **13**. Deprotection of an acetyl group and dimethylacetal gave a novel macrolide, *i.e.* 15-membered azalide (**11**) as a prototype. The acetyl group at the C-2′ is exceptionally mobile because of the neighboring effect due to basicity of the 3′-dimethylamino group. In compound **11**, NOEs were observed between methylene protons in the benzyl group and the protons at C-10 and 12, respectively. Moreover, interactions between the alpha protons and C-10, and those between the alpha protons and C-12 were observed in the HMBC experiment. The structure of **11** was then confirmed. Structure of our 15-membered azalides was later proved by single crystallographic analysis of **31a** crystallized by chloroform and hexane (chemistry of **31a**: *vide infra*).

A novel lactone was continuously generated by the application of the key intermediate (**12**). Macrocyclization between **12** and 1,2-dimethylhydrazine hydrochloride under the same conditions for **16** gave 16-membered 11,12-diazalide (**18**) which was then converted to an active form **20** as the first example. In order to provide distortion to the 15-membered azalactone, we synthesized a fused azalide (**24**). Macrocyclization between **12** and *p*-

Table 1 Antibacterial activities of 15-membered azalides (**11** and **24**), 16-membered diazalide (**20**), and MOM

No.	Test organism[a]	Characteristics	(MIC, μg/ml)			
			11	**20**	**24**	MOM
1	*Staphylococcus aureus* 209P JC-1	standard	0.5	0.5	0.5	0.25
2	*S. aureus* #2	susceptible	1	1	1	1
3	*S. aureus* #3	susceptible	1	0.5	0.5	0.5
4	*S. aureus* #4	*ermA* methylase(c)	>128	>128	>128	>128
5	*S. aureus* #5	*ermB* methylase(i)	1	0.5	0.5	0.5
6	*S. aureus* #6	*ermC* methylase(i)	2	1	1	1
7	*Enterococcus faecalis* W-73	standard	4	4	N.T.	2
8	*Klebsiella pneumoniae* PCI602	standard	>128	>128	N.T.	>128
9	*Streptococcus pneumoniae* DP1 TypeI	standard	0.25	0.25	0.5	0.13
10	*S. pneumoniae* #2	susceptible	0.5	0.25	0.5	0.25
11	*S. pneumoniae* #3	*ermAM* methylase(c)	>128	>128	>128	>128
12	*S. pneumoniae* #4	*ermAM* methylase(c)	>128	>128	>128	>128
13	*S. pneumoniae* #5	*ermAM* methylase(i)	8	8	128	4
14	*S. pneumoniae* #6	*ermAM* methylase(i)	16	32	128	8
15	*S. pneumoniae* #7	*mefE* efflux	0.5	0.25	0.25	0.25
16	*S. pneumoniae* #8	*mefE* efflux	0.25	0.25	0.25	0.13
17	*Streptococcus pyogenes* Cook	standard	0.13	0.13	0.13	0.13
18	*S. pyogenes* #2	*ermAM* methylase(c)	>128	>128	>128	>128
19	*S. pyogenes* #3	*mefE* efflux	0.25	0.25	0.5	0.13
20	*Moraxella catarrhalis* #1	susceptible	0.5	0.5	0.5	0.5
21	*M. catarrhalis* #2	susceptible	1	1	1	1
22	*Haemophilus influenzae* #3	susceptible	4	4	4	4
23	*H. influenzae* #4	susceptible	32	16	16	16
24	*H. influenzae* #5	susceptible	32	16	16	16

[a] All strains except standard organisms were clinically isolated. N.T.: Not tested.

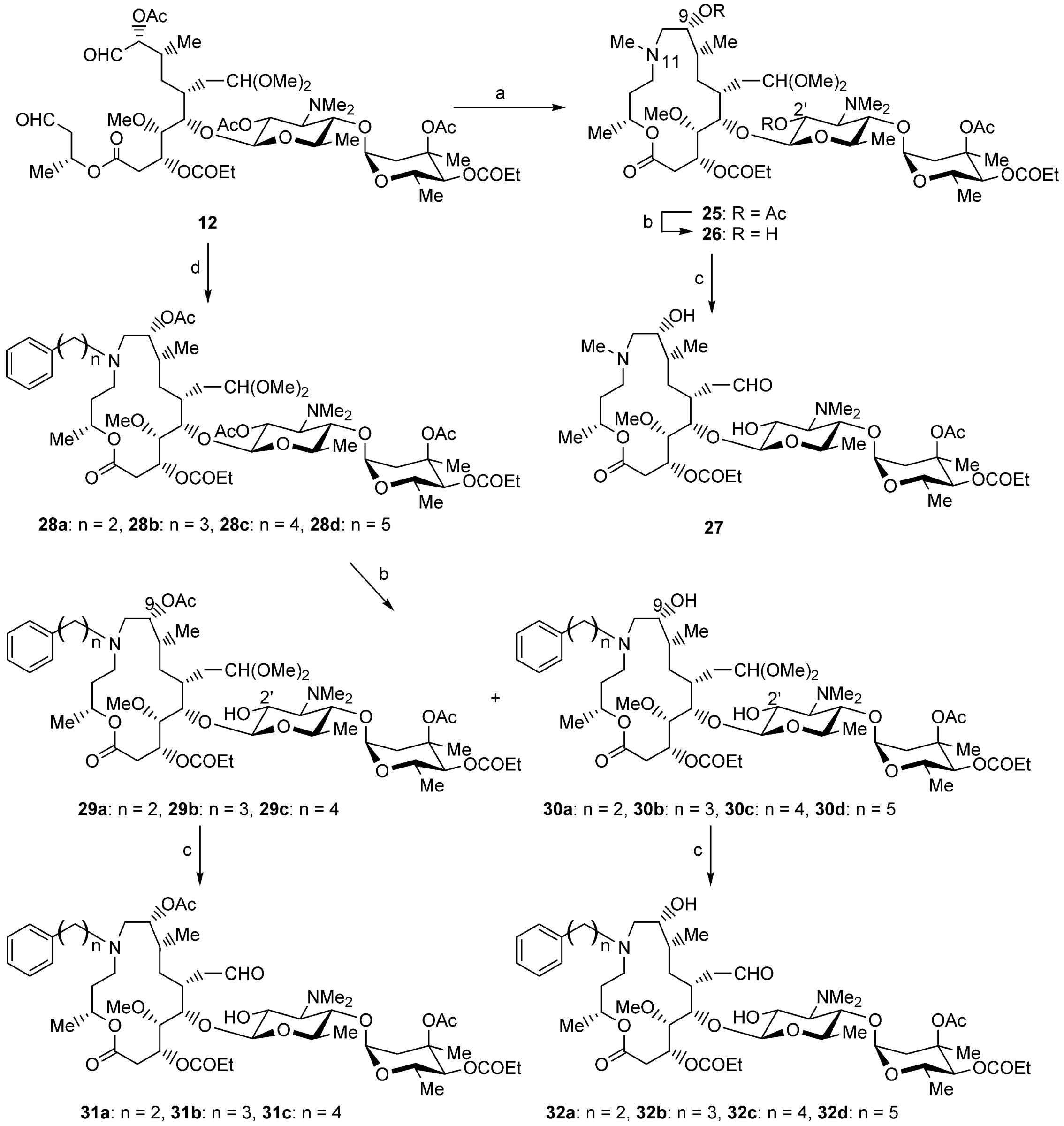
methoxybenzylamine gave methoxybenzyl azalide (**21**) which was consequently converted to aminodiol (**22**) by complete methanolysis and then hydrogenolysis in dioxane-ethanol. Reaction of **22** with triphosgene in the presence of triethylamine in dichloromethane gave a fused azalide (**23**) which was finally transformed to an alternative 15-membered azalide (**24**).

When antibacterial activities of these three prototypes were compared with those of MOM as shown in Table 1, **11** and **20** exhibited almost the same activities as those of MOM. Although we were interested in both pharmacophores of **11** and **20**, we chose 15-membered azalide as a preliminary lead. It was impossible to isolate regioisomers when we used an unsymmetrical hydrazine, for example 1-benzyl-2-methylhydrazine, instead of a symmetrical hydrazine like 1,2-dimethylhydrazine, and we recognized that further chemical modification of 16-membered diazalide (**20**) would not be efficient. Moreover, deprotection of 11,12-diazalide prepared by **12** with unsubstituted hydrazine gave complicated results. Then we analyzed relationships between the methylene length in the spacer and antimicrobial activities in 15-membered azalides.

Relationships between Spacer Length and Activities

Cyclization of **12** with methylamine gave the simplest framework in this series, **25**, as shown in Scheme 2, which was consequently converted to **27**. Methanolysis at the C-2′ position of **25** involves deacetylation at C-9 because of low steric hindrance of the *N*-methyl group at the 11-position. Next, a variety of phenylalkyl derivatives of 15-membered azalides were synthesized. Compounds **28a**∼**28d** were respectively prepared in approximately 10% yield from **12**. Methanolysis of **28a**∼**d** gave 2′-hydroxyl derivatives (**29a**∼**29c**) and 9,2′-dihydroxyl derivatives (**30a**∼**30d**), which were converted into desired **31a**∼**31c** and **32a**∼**32d**, respectively, by treatment with difluoroacetic acid.

As shown in Table 2, antibacterial activities of 9-



Reagents and conditions: (a): methylamine hydrochloride (1.1 eq), NaB(CN)H_3 (3.9 eq), AcOH (15 eq), EtOH, 0°C to r.t., 16 hours, 11%; (b): MeOH, r.t., 72 hours, 59% for **26**, see experimental for **29** and **30**, As an exception, **29c** and **30c** were separately prepared from **28c**; (c): difluoroacetic acid (20 eq), MeCN-H_2O, r.t., 24 hours, 70% for **27**, see experimental for **31** and **32**; (d): 2-phenylethylamine (1.1 eq), NaB(CN)H_3 (3.9 eq), AcOH (15 eq), EtOH, 0°C to r.t., 16 hours, 7.3% for **28a**, see experimental for **28b**~**28d**.

Scheme 2 Synthesis of *N*-phenylalkyl-azalides with a variety of spacer length.

hydroxyl analogues **32a**~**32d** are generally stronger than those of 9-acetoxy analogues **31a**~**31c**. In addition, it was found that the spacer length was optimized to C_3 or C_4 among these phenylalkyl analogues. We thus decided to confirm an appropriate template for further medicinal chemistry before fundamental optimization of 15-membered 11-azalide.

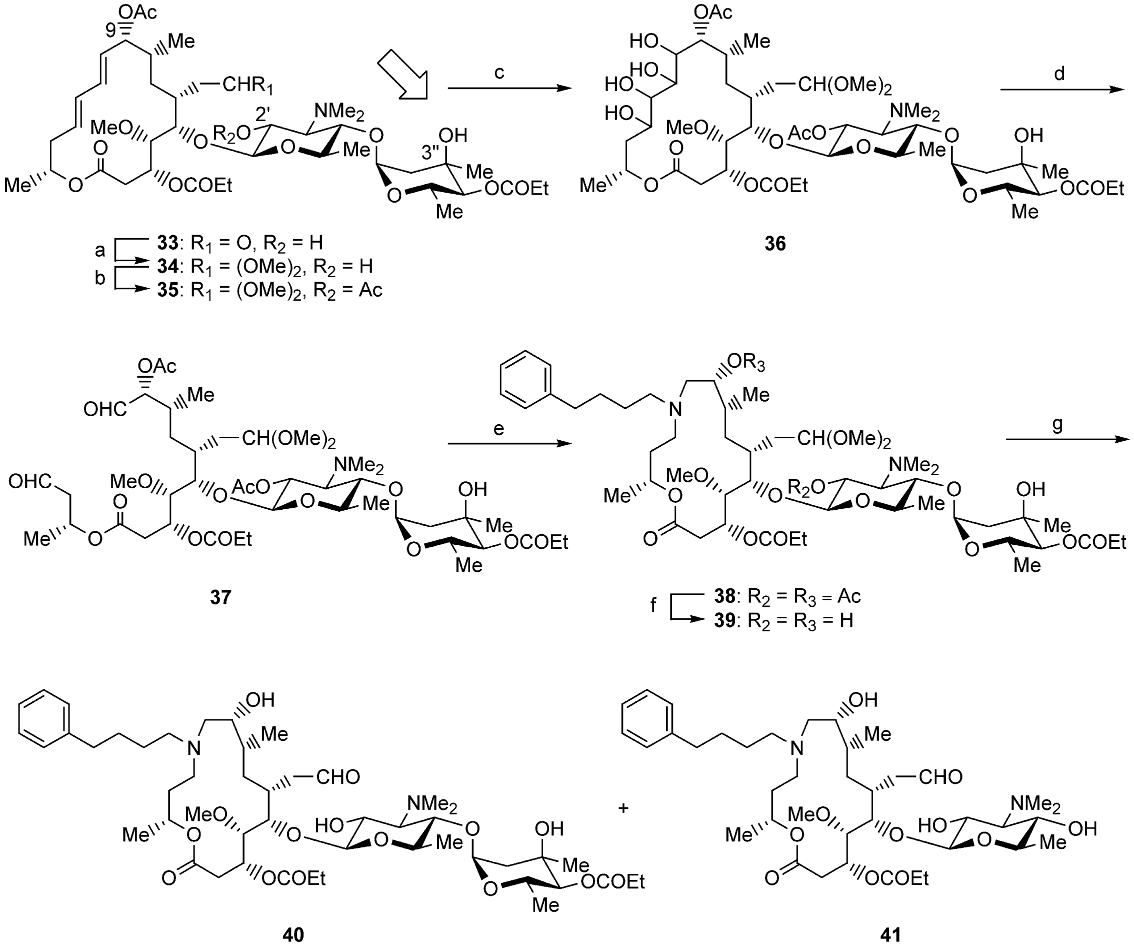
Appropriate Template and Fundamental Optimization

At this stage, we had to confirm antibacterial activities of 15-membered azalide which did not possess a neutral sugar, **41**, as shown in Scheme 3. In general, a neutral sugar enhances its antibacterial activities and sometimes plays an important role to exhibit activities against resistant bacteria as several examples reported [26]. But recent ketolides do not have a neutral sugar, so we had to prepare 15-membered azalide without a neutral sugar and measure

Table 2 Antibacterial activities of 15-membered azalides with a variety of phenyl alkyl moiety

No.	Test organism[a]	Characteristics	(MIC, μg/ml)							
			27	**31a**	**31b**	**31c**	**32a**	**32b**	**32c**	**32d**
1	*Staphylococcus aureus* 209P JC-1	standard	0.13	0.25	0.25	4	0.25	0.13	0.13	0.25
2	*S. aureus* #2	susceptible	0.5	1	1	>128	0.5	0.5	0.5	1
3	*S. aureus* #3	susceptible	0.25	0.5	0.5	4	0.25	0.25	0.25	0.5
4	*S. aureus* #4	*ermA* methylase(c)	>128	>128	>128	>128	>128	>128	>128	>128
5	*S. aureus* #5	*ermB* methylase(i)	0.25	0.5	1	4	0.25	0.25	0.5	0.5
6	*S. aureus* #6	*ermC* methylase(i)	0.5	1	1	8	0.5	0.5	0.5	1
7	*Streptococcus pneumoniae* DP1 TypeI	standard	0.06	0.25	0.25	1	0.13	0.06	0.06	0.13
8	*S. pneumoniae* #2	susceptible	0.13	0.25	0.25	2	0.13	0.13	0.13	0.13
9	*S. pneumoniae* #3	*ermAM* methylase(c)	>128	>128	>128	>128[b]	>128	128	128	64
10	*S. pneumoniae* #4	*ermAM* methylase(c)	>128	>128	>128	>128	>128	>128	>128	>128
11	*S. pneumoniae* #5	*ermAM* methylase(i)	64	>128	64	>128	32	32	8	4
12	*S. pneumoniae* #6	*ermAM* methylase(i)	8	32	8	>128	16	8	8	8
13	*S. pneumoniae* #7	*mefE* efflux	0.13	0.25	0.25	2	0.13	0.13	0.06	0.13
14	*S. pneumoniae* #8	*mefE* efflux	0.13	0.25	0.25	1	0.13	0.13	0.06	0.13
15	*Streptococcus pyogenes* Cook	standard	0.03	0.13	0.13	1	0.06	0.06	0.06	0.13
16	*S. pyogenes* #2	*ermAM* methylase(c)	>128	>128	>128	>128	>128	>128	>128	>128
17	*S. pyogenes* #3	*mefE* efflux	0.06	0.25	0.25	4	0.13	0.13	0.13	0.25
18	*Moraxella catarrhalis* #1	susceptible	0.13	0.25	0.25	16	0.13	0.13	0.13	0.25
19	*M. catarrhalis* #2	susceptible	0.25	0.5	0.5	>128	0.25	0.25	0.25	0.5
20	*Haemophilus influenzae* #1	*Δacr*	0.5	1	1	>128	0.5	0.5	0.5	0.5
21	*H. influenzae* #2	susceptible	16	>128	>128	>128	32	32	32	32
22	*H. influenzae* #3	susceptible	0.5	2	2	>128	1	1	1	2
23	*H. influenzae* #4	susceptible	4	8	8	>128	4	4	4	8
24	*H. influenzae* #5	susceptible	8	8	8	>128	8	8	8	8

[a] All strains except standard organisms were clinically isolated. [b] Test organism: *S. pneumoniae* #3a.



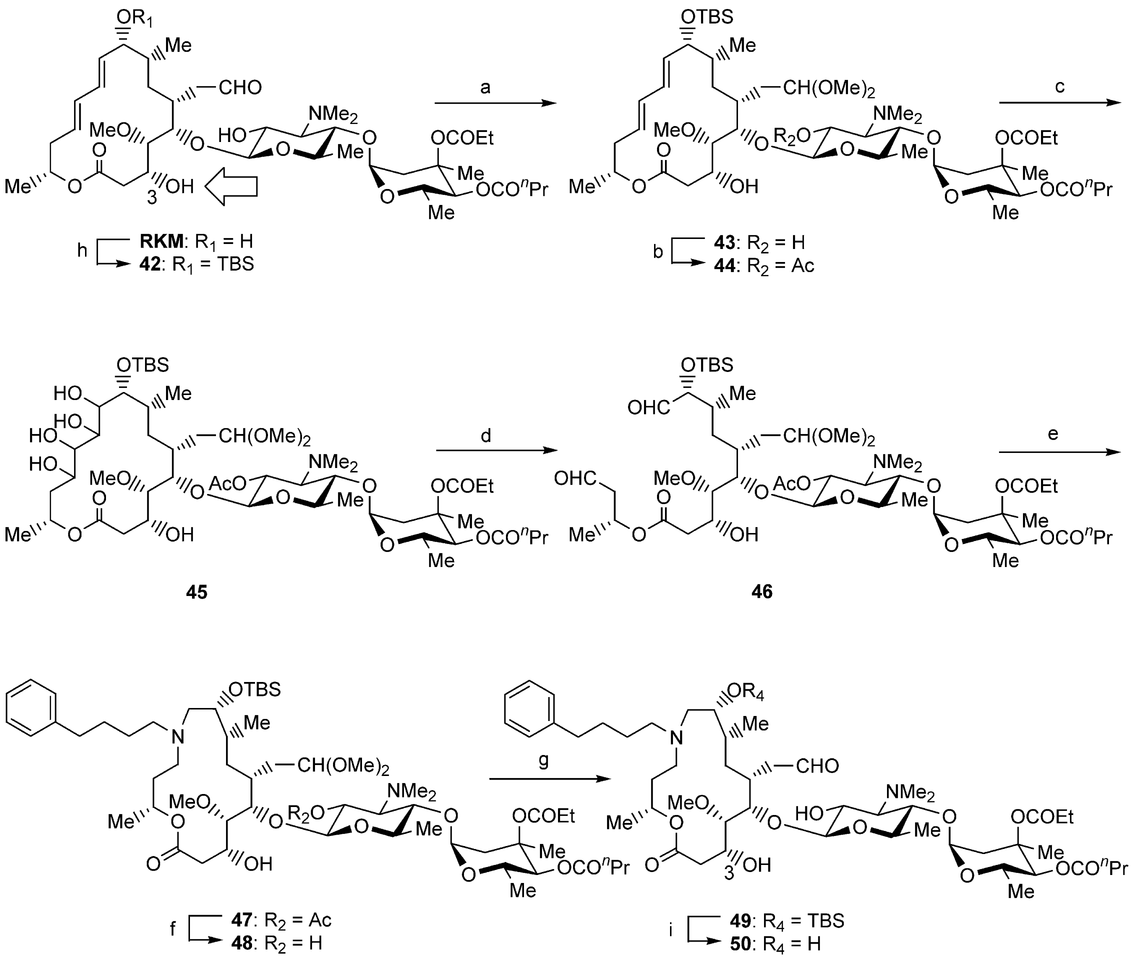
Reagents and conditions: (a): $(MeO)_3CH$ (80 eq), PPTS (1.2 eq), MeOH, 40~50°C, 4 days; (b): Ac_2O (5 eq), MeCN, 40°C, 16 hours; (c): OsO_4 (0.15 eq), NMO (2 eq), aq. acetone, r.t., 24 hours, 41% for **36**, 30% in 3 steps based on **33**, 34% for **45**; (d): $Pb(OAc)_4$ (2.1 eq), PhH, Na_2CO_3 (8 eq), r.t., 10 minutes; (e): 4-phenylbutylamine (1.1 eq), $NaB(CN)H_3$ (3.9 eq), AcOH (15 eq), EtOH, 0°C to r.t., 15~20 hours, 8.4% for **38** in 2 steps, 9.8% for **47** in 2 steps; (f): MeOH, r.t., 48 hours, 88% for **39** and 74% for **48**, (g): difluoroacetic acid (20 eq), MeCN - H_2O, r.t., 24 hours, 37% for **40** and 43% for **41**, 98% for **49**.

Scheme 3 Synthesis of monosaccharide (**41**) and rokitamycin-type azalide (**50**).

its biological activities. As we previously mentioned in this article, a glycosidic bond at the neutral sugar can be cleaved under acidic conditions, if the C-3″ position is a free hydroxyl group. Thus, we used 9-*O*-acetylmidecamycin A_1 (**33**) [27] possessing a hydroxyl group at the C-3" position as a starting material. **33** was sequentially converted to a key intermediate, dialdehyde (**37**) which was macrocyclized with 4-phenylbutylamine to afford **38**. Complete methanolysis of **38** followed by treatment with difluoroacetic acid gave monosaccharide (**41**) accompanied with disaccharide (**40**).

Generally speaking, antibacterial activities of a 3-hydroxyl derivative tend to be stronger than those of corresponding 3-acyloxy analogue in 16-membered macrolides. We therefore designed a synthetic route for the 3-hydroxyl analogue of 15-membered azalide (**50**) as shown in Scheme 3. We usually apply the 3,18-*O*-silyl-hemiacetal protection [7b, 28, 29] for compounds which possess a free aldehyde group at C-18 and a free hydroxyl group at C-3. We decided, however, to apply dimethyl acetal protection at C-18 and no protection at C-3, because there seemed to be interference by a seven-membered ring of 3,18-*O*-silyl-hemiacetal toward the formation of 15-membered azalide. Sequentially protected rokitamycin [26] (**44**) [22b, 32] was oxidized to give a key intermediate (**46**), which was cyclized and then sequentially deprotected to afford the 3-hydroxyl analogue (**50**).

Preliminarily expected, **41** did not exhibit strong antibacterial activities as shown in Table 3. On the other hand, **50** showed strong activities, but there was not any big improvement compared to **32c** in spite of more reaction steps required. Then we performed fundamental



Reagents and conditions: (h): 1) *t*-butyldimethylsilyl chloride (1.5 eq), imidazole (3.3 eq), DMF, 45°C, 17 hours, 2) TBAF (1.4 eq), THF, r.t, 3 hours, 90%; (i): TBAF (5 eq), AcOH-THF (1 : 1), 60°C, 48 hours, 54%.

Scheme 3 Synthesis of monosaccharide (**41**) and rokitamycin-type azalide (**50**). (continued)

optimization of 15-membered azalide focusing on the chemical structure of **32b** as a lead compound as shown in Fig. 5. Synthesis of **52** was performed as in the case of **32b**. Compound **54**, an alternative hydrazine-based 15-membered azalide, was prepared *via* macrocyclization of **12** and 1-methyl-1-(3-phenylpropyl)hydrazine. The acetoxy group at the C-9 position was, however, unexpectedly reduced in the course of macrocyclization. Syntheses of **51**, **53**, and **55** to **58** were completed by *N*-alkylation of **22** (Scheme 1) or *N*-acylation (for **57**) and deprotection. Among these partially optimized derivatives, quinoline analogues with a saturated alkyl chain (**52** and **53**) exhibited the strongest antibacterial activities in this series as shown in Table 4, and were especially effective against resistant bacteria of *S. pneumoniae* which had the *erm* gene controlling inducible methylation of bacterial ribosome. Moreover, it is notable that these novel azalides are almost not affected by efflux pump function in *S. pneumoniae*.

Sustainable Chemistry for Synthesis of Azalides

So far we described the synthesis of novel 15-membered azalides starting from 16-memberd macrolides, leucomycin analogues including MOM, MDM, and rokitamycin (RKM). We, however, used osmium tetroxide and lead (IV) acetate in order to synthesize the key intermediates, dialdehydes (**12**, **37**, and **46**). We have to pay attention to human health and environmental preservation when we use these reagents in a large scale.

Thus, we applied direct oxidation method using ozone to afford the dialdehyde from the diene, **14** or **15**. Because the dialdehyde was very mobile as we have already mentioned, we confirmed the completion of this approach by detection of **30c** [30] as shown in Scheme 4. **30c** prepared with this ozone route was fully identified with that synthesized by the original route shown in Scheme 2 by FAB-MS and ^{1}H-NMR. As a result, we could omit the isolation process of the tetraol. In addition, we could reduce the number of total

Table 3 Antibacterial activities of 15-membered azalides with a variety of template

No.	Test organism[a]	Characteristics	(MIC, μg/ml)				
			40	**41**	MDM	**50**	RKM
1	*Staphylococcus aureus* 209P JC-1	standard	0.25	1	0.25	0.25	0.06
2	*S. aureus* #2	susceptible	0.5	2	0.5	0.5	0.25
3	*S. aureus* #3	susceptible	0.25	1	0.25	0.25	0.13
4	*S. aureus* #4	*ermA* methylase(c)	>128	>128	>128	>128	>128
5	*S. aureus* #5	*ermB* methylase(i)	0.25	2	0.25	0.25	0.13
6	*S. aureus* #6	*ermC* methylase(i)	0.5	2	0.5	0.5	0.25
7	*Streptococcus pneumoniae* DP1 TypeI	standard	0.06	0.5	0.06	0.06	0.03
8	*S. pneumoniae* #2	susceptible	0.13	0.5	0.13	0.06	0.03
9	*S. pneumoniae* #3a	*ermAM* methylase(c)+*mefE*	>128	>128	>128	>128	>128
10	*S. pneumoniae* #4	*ermAM* methylase(c)	>128	>128	>128	64	>128
11	*S. pneumoniae* #6	*ermAM* methylase(i)	32	>128	128	1	0.5
12	*S. pneumoniae* #7	*mefE* efflux	0.06	0.5	0.06	0.06	0.03
13	*S. pneumoniae* #8	*mefE* efflux	0.06	0.5	0.13	0.13	0.06
14	*Streptococcus pyogenes* Cook	standard	N.T.	N.T.	N.T.	N.T.	N.T.
15	*S. pyogenes* #2	*ermAM* methylase(c)	N.T.	N.T.	N.T.	N.T.	N.T.
16	*S. pyogenes* #3	*mefE* efflux	0.13	1	0.13	0.06	0.03
17	*Moraxella catarrhalis* #1	susceptible	0.5	2	2	0.25	0.06
18	*M. catarrhalis* #2	susceptible	0.5	2	2	0.25	0.13
19	*Haemophilus influenzae* #1	*Δacr*	0.5	1	0.5	0.5	0.25
20	*H. influenzae* #2	susceptible	32	64	32	16	8
21	*H. influenzae* #3	susceptible	1	8	2	1	1
22	*H. influenzae* #4	susceptible	8	32	16	4	4
23	*H. influenzae* #5	susceptible	16	128	16	8	4

[a] All strains except standard organisms were clinically isolated. N.T.: Not tested.

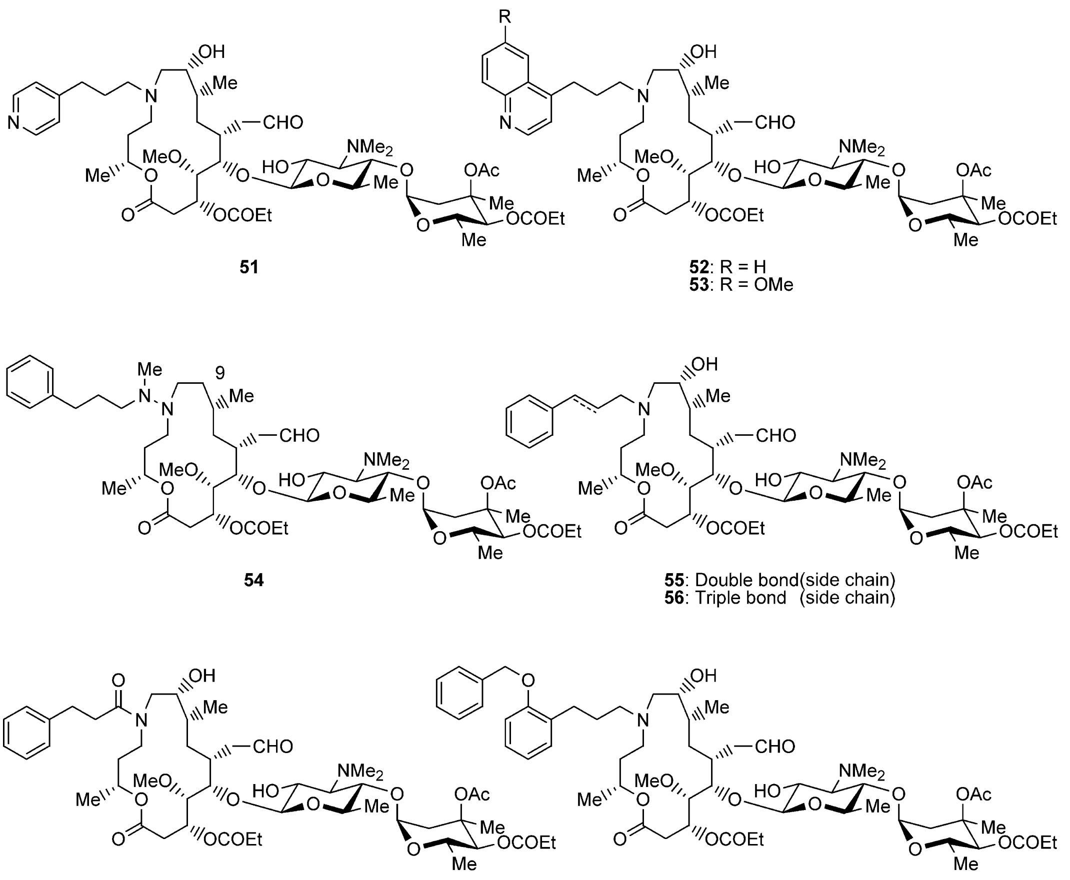
reaction steps, since this methodology did not require protection of the 2′-hydroxyl group. Our original synthetic route required five steps for **30c** based on **14** *via* **15**, **13**, **12** and **28c**, and a five-step yield was 0.43%. However, this ozone route can provide **30c** in 8.0% based on **14** in two steps. On the other hand, ozone oxidation can be applicable in "ton scale", [31] so these preliminary results regarding sustainable chemistry might be an acceptable solution for further experiments focusing on our azalide chemistry.

Conclusions

Novel 15-membered 11-azalides and 16-membered 11,12-diazalide starting from 16-membered macrolides were designed and synthesized. **12** was isolated *via* **13** which was prepared by osmium oxidation of a conjugated diene. One-pot macrocyclization of **12** with benzylamine or 1,2-dimethylhydrazine followed by deprotections afforded corresponding **11** or **20**, although the reaction conditions could not be optimized. When we used an unsymmetrical hydrazine as a diamine for macrocyclization with the dialdehyde, it was impossible to readily isolate regioisomers. We thus focused on chemical modification of 15-membered azalide.

In optimization of the spacer length, it became clear that C_3 to C_4 methylene exhibited strong antibacterial activities. As for a template for further medicinal chemistry, we chose the MOM framework which possessed 3″-*O*-acetyl-3-*O*-propionyl-pharmacophore. As a result of fundamental optimization of an aryl moiety at the 11-position, **52** and **53** exhibited the strongest antibacterial activities in this series, and were especially effective against resistant bacteria of *S. pneumoniae* which had the *erm* gene controlled inducible methylation of bacterial ribosome. Fifteen-membered 11-azalides disclosed their potentiality as a lead molecule for further drug discovery research.

For environmental preservation, the sustainable chemistry



51

52: R = H
53: R = OMe

54

55: Double bond(side chain)
56: Triple bond (side chain)

57

58

Fig. 5 Fundamental optimization of 15-membered azalides.

in application of ozone oxidation for synthesis of the key intermediate, dialdehyde, was also introduced as a preliminary solution for process chemistry of 15-membered 11-azalides. This approach practically decreased reaction steps and remarkably improved the synthetic yield.

Experimental

General Methods

Optical rotations were measured on a Perkin-Elmer 241 Polarimeter or Jasco P-1030 Polarimeter. Fast-atom bombardment (FAB) mass spectra were recorded on a JEOL JMS-700 instrument. ^{1}H-NMR spectra were recorded on Varian Gemini-300 spectrometers with chemical shifts reported in ppm relative to internal tetramethylsilane. ^{13}C-NMR spectra were measured with a Jeol JNM-GSX 400 NMR spectrometer for 100 MHz. Silica gel chromatography and preparative TLC were performed on Waco C-200 or C-300 and Merck TLC 60F$_{254}$ Art. 5744, respectively and visualized with a UV lamp or 10% H_2SO_4 containing 2.0% sodium molybdate and 2.0% phosphoric acid. Evaporation was carried out under reduced pressure below 35°C, unless otherwise noted.

9,2′,3″-Tri-*O*-acetyl-10,11,12,13-tetrahydro-10,11,12,13-tetrahydroxymidecamycin A$_1$ 18-dimethylacetal (**13**)

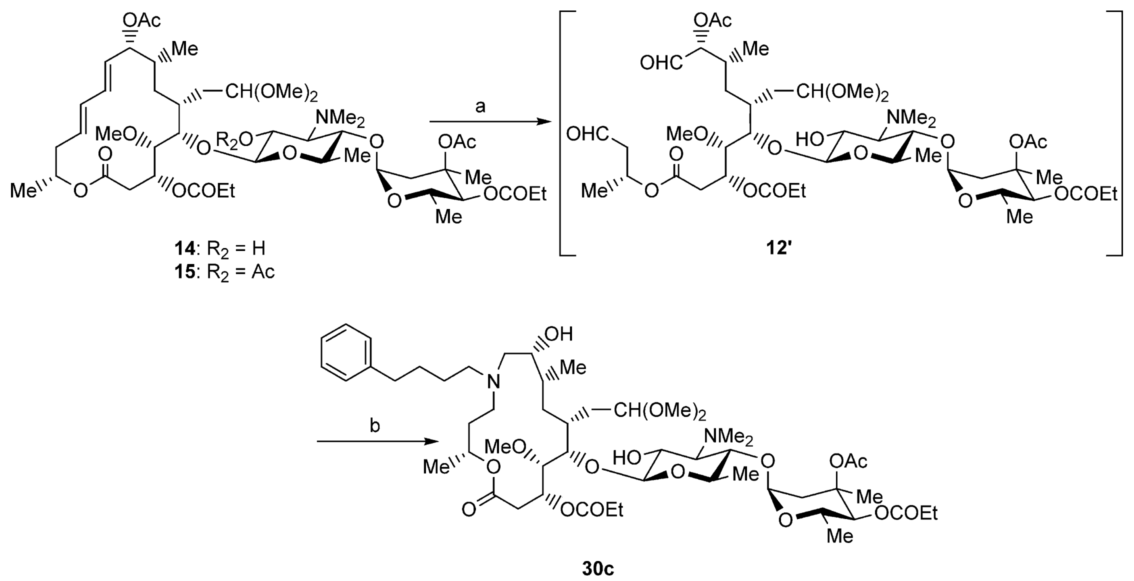
To a solution of 9,3″-di-*O*-acetylmidecamycin A$_1$ 18-dimethylacetal (**14**) [8b] (64.2 g) in acetonitrile (610 ml) was added acetic anhydride (7.8 ml), and the mixture was stirred at 40°C for 16 hours. After the reaction mixture was concentrated under reduced pressure, ethyl acetate (660 ml) was added, and the organic layer was successively washed twice with saturated aqueous sodium hydrogencarbonate solution (300 ml), and saturated brine (300 ml). The organic layer was dried over anhydrous sodium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure to obtain 9,2′,3″-tri-*O*-acetylmidecamycin A$_1$ 18-dimethylacetal (**15**) (67.0 g).

To a solution of **15** (20.0 g) in acetone (500 ml) and water (77 ml), *N*-methylmorpholine-*N*-oxide (9.5 ml) and 4.0% aqueous osmium tetraoxide (19.5 ml) were added and the mixture was stirred at room temperature. After 20 hours, *N*-methylmorpholine-*N*-oxide (2.4 ml) was added,

Table 4 Antibacterial activities of 15-membered azalides with a variety of *N*-substituent

No.	Test organism	Characteristics	(MIC, μg/ml)									
			32b	**51**	**52**	**53**	**54**	**55**	**56**	**57**	**58**	MOM
1	*Staphylococcus aureus* 209P JC-1	standard	0.13	0.25	0.13	0.13	4	0.5	0.5	0.25	1	0.5
2	*S. aureus* #2	susceptible	0.5	0.5	0.5	0.5	N.T.	1	2	0.5	2	1
3	*S. aureus* #3	susceptible	0.25	0.25	0.25	0.25	8	0.5	1	0.25	1	0.5
4	*S. aureus* #4	*ermA* methylase(c)	>32	>128	>128	>128	>128	>128	>128	>128	>128	>128
5	*S. aureus* #5	*ermB* methylase(i)	0.25	0.25	0.13	0.25	8	0.5	1	0.25	1	0.5
6	*S. aureus* #6	*ermC* methylase(i)	0.5	0.5	0.25	0.5	N.T.	1	2	0.5	2	1
7	*Streptococcus pneumoniae* DP1 Type I	standard	0.06	0.06	0.06	0.03	2	0.13	0.5	0.13	0.25	0.25
8	*S. pneumoniae* #2	susceptible	0.13	0.06	0.06	0.06	2	0.13	0.5	0.25	0.25	0.5
9	*S. pneumoniae* #3a	*ermAM* methylase(c)+*mefE*	>32	>128	>128[a]	>128	>128[b]	>128	>128	>128	>128	>128
10	*S. pneumoniae* #4	*ermAM* methylase(c)	>32	>128	>128	>128	>128	>128	>128	>128	>128	>128
11	*S. pneumoniae* #5	*ermAM* methylase(i)	8	4	4	2	>128	16	>128	32	8	64
12	*S. pneumoniae* #6	*ermAM* methylase(i)	8	4	8	2	>128	16	>128	64	8	128
13	*S. pneumoniae* #7	*mefE* efflux	0.13	0.13	0.13	0.13	1	0.25	1	0.25	0.5	0.5
14	*S. pneumoniae* #8	*mefE* efflux	0.13	0.13	0.13	0.06	2	0.13	0.5	0.25	0.5	0.5
15	*Streptococcus pyogenes* Cook	standard	0.03	0.06	0.06	0.06	1	0.06	0.13	0.06	0.25	0.25
16	*S. pyogenes* #2	*ermAM* methylase(c)	>32	>128	>128	>128	>128	>128	>128	>128	>128	>128
17	*S. pyogenes* #3	*mefE* efflux	0.25	0.13	0.13	0.25	4	0.25	1	0.5	1	0.5
18	*Moraxella catarrhalis* #1	susceptible	0.13	0.25	0.25	0.25	16	0.5	2	0.5	2	1
19	*M. catarrhalis* #2	susceptible	0.25	0.5	0.25	0.5	>128	0.5	2	0.5	2	2
20	*Haemophilus influenzae* #1	*Δacr*	0.5	1	0.5	1	>128	1	2	0.5	4	1
21	*H. influenzae* #2	susceptible	8	32	16	32	>128	32	>128	32	>128	64
22	*H. influenzae* #3	susceptible	1	1	1	1	>128	4	16	1	16	2
23	*H. influenzae* #4	susceptible	4	8	8	8	>128	8	>128	16	>128	32
24	*H. influenzae* #5	susceptible	8	8	8	8	>128	8	>128	8	>128	16

[a] All strains except standard organisms were clinically isolated. [b] Test organism: *S. pneumoniae* #3. N.T.: Not tested.



Reagents and conditions: (a): O_3, abs. MeOH, −78°C, 15 minutes, then, O_2 bubbling for 5~10 minutes, Me_2S, −78°C, 30 minutes; (b): 4-phenylbutylamine (1.1 eq), $NaB(OAc)_3H$ (3.0 eq), AcOH, r.t. Two-step yield is 8.0% from 14 to 30c.

Scheme 4 Sustainable chemistry for construction of 15-membered azalide.

and the mixture was further stirred for 4 hours. After the reaction mixture was concentrated under reduced pressure, ethyl acetate (600 ml) was added, and the organic layer was successively washed with water (200 ml), 5.0% aqueous sodium thiosulfate solution (300 ml) and saturated brine (300 ml). The organic layer was dried over anhydrous sodium sulfate, and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was roughly purified by flash silica gel column chromatography (chloroform/methanol (25 : 1~15 : 1)) and further purified by flash silica gel column chromatography (chloroform/ethyl acetate/methanol (30 : 30 : 1~25 : 25 : 1)) to obtain **13** (8.46 g, 40% based on **14**) as a colorless solid.

In the case of sequential reactions without purification of **14**, three-step yield of **13** based on MOM was 30%.

13: $[\alpha]_D^{21}$ −81° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 1054 $(M+H)^+$ as $C_{49}H_{83}NO_{23}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.96 (d, 19-H), 1.07 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.27 (d, 16-H), 1.41 (s, 3″-CH_3), 1.50 (br dd, 14-H), 1.68 (dd, 2″-Hax), 1.88 (br dd, 17-H), 2.03 (s, 9-$OCOCH_3$), 2.04 (s, 3″-$OCOCH_3$), 2.17 (s, 2′-$OCOCH_3$), 2.35 (m, 8-H), 2.44 (s, 3′-$N(CH_3)_2$), 2.60 (t, 3′-H), 2.73 (dd, 2-H), 3.15 (t, 4′-H), 3.18 (s, 18-OCH_3), 3.20 (d, 2″-Heq), 3.22 (s, 18-OCH_3), 3.27 (dq, 5′-H), 3.39 (br d, 4-H), 3.57 (s, 4-OCH_3), 3.63 (m, 12-H), 3.83 (br d, 5-H), 3.91 (dd, 10-H), 4.09 (br t, 13-H), 4.38 (dd, 18-H), 4.48 (dq, 5″-H), 4.57 (d, 4″-H), 4.70 (d, 1′-H), 4.82 (d, 1″-H), 4.96 (dd, 2′-H), 5.02 (m, 9-H), 5.04 (m, 15-H), 5.34 (br d, 3-H).

(−)-(1*R*)-1-Methyl-3-oxopropyl(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*)-9-acetoxy-5-[2-*O*-acetyl-4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-4-methoxy-8-methyl-10-oxo-3-propionyloxydecanoate (**12**)

To a solution of **13** (30 mg) in benzene (1.0 ml) was added sodium carbonate (18 mg), and then lead tetraacetate (29 mg) divided into 5 portions were added over 20 minutes. After the reaction mixture was stirred at room temperature for 1 hour, the supernatant was transferred into a separatory funnel. To the residue was added benzene (5.0 ml), and the supernatant was transferred into the separatory funnel, and then the same operations were repeated three times. Water (10 ml) and saturated aqueous sodium hydrogencarbonate solution (15 ml) were added to the separatory funnel to wash the organic layer. The organic layer was further washed with saturated brine (15 ml), dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by preparative TLC (hexane/acetone (2 : 3)) to obtain **12** (6.5 mg, 23%) as a colorless solid.

12: FAB-MS *m/z* 992 $(M+H)^+$ as $C_{47}H_{77}NO_{21}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.05 (d, 8-CH_3), 1.08 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.21 (d, 6′-H), 1.33 (d, $OCH(CH_3)CH_2CHO$), 1.42 (s, 3″-CH_3), 1.68 (dd, 2″-Hax), 1.85 (m, 6-H), 2.03 (s, 3″-$OCOCH_3$), 2.07 (s, 2′-$OCOCH_3$), 2.20 (s, 9-$OCOCH_3$), 2.36, 2.37 (2×q, 4″-

OCOCH$_2$CH$_3$), 2.44 (s, 3′-N(CH$_3$)$_2$), 2.62 (t, 3′-H), 2.64 (br d, 2-H), 2.76 (dd, 2-H), 3.17 (t, 4′-H), 3.19 (s, 6-CH$_2$CH(OCH$_3$)$_2$), 3.23 (d, 2″-Heq), 3.26 (s, 6-CH$_2$CH(OCH$_3$)$_2$), 3.46 (dd, 4-H), 3.52 (s, 4-OCH$_3$), 3.82 (br d, 5-H), 4.48 (dq, 5″-H), 4.58 (d, 4″-H), 4.66 (d, 1′-H), 4.81 (d, 1″-H), 4.92 (br d, 9-H), 4.96 (dd, 2′-H), 5.27 (br dd, 3-H), 5.39 (ddq, OCH(CH$_3$)CH$_2$CHO), 9.59 (d, 10-H), 9.75 (t, OCH(CH$_3$)CH$_2$CHO).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[2-*O*-acetyl-4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-11-benzyl-6-(2,2-dimethoxyethyl)-4-methoxy-8-methyl-3-propionyloxy-11-aza-pentadecan-14-olide (**16**)

To a solution of **12** (457 mg) in ethanol (46 ml) were added acetic acid (395 ml), benzylamine (32 mg) and sodium cyanoborohydride (75 mg) under ice cooling, and the mixture was stirred for 18 hours. Then sodium cyanoborohydride (75 mg) was added, and the mixture was stirred at room temperature for 15 hours. The reaction mixture was diluted with ethyl acetate (180 ml), washed successively with water (50 ml), saturated aqueous sodium hydrogencarbonate solution (50 ml) and saturated brine (50 ml). The organic layer was dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol (60 : 1∼50 : 1)) to obtain **16** (98.3 mg, 20%) as a colorless solid.

In the case of sequential reactions without purification of **12**, two-step yield of **16** based on **13** was 10%.

16: $[\alpha]_{\mathrm{D}}^{22}$ −79° (*c* 0.64, CHCl$_3$); FAB-MS *m/z* 1067 (M+H)$^+$ as C$_{54}$H$_{86}$N$_2$O$_{19}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.90 (d, 18-H), 1.08 (d, 6″-H), 1.16 (t, 3-OCOCH$_2$CH$_3$), 1.19 (d, 15-H), 1.20 (t, 4″-OCOCH$_2$CH$_3$), 1.25 (d, 6′-H), 1.43 (s, 3″-CH$_3$), 1.59 (m, 16-H), 1.69 (dd, 2″-Hax), 1.85 (m, 16-H), 2.02 (s, 9-OCOCH$_3$), 2.03 (s, 3″-OCOCH$_3$), 2.06 (s, 2′-OCOCH$_3$), 2.45 (s, 3′-N(CH$_3$)$_2$), 2.84 (dd, 2-H), 3.16 (s, 17-OCH$_3$), 3.21 (d, 2″-Heq), 3.27 (s, 17-OCH$_3$), 3.48 (br d, 4-H), 3.56 (s, 4-OCH$_3$), 3.59 (d, C$_6$H$_5$CH$_2$), 3.71 (d, C$_6$H$_5$CH$_2$), 3.91 (br d, 5-H), 4.52 (dq, 5″-H), 4.58 (d, 4″-H), 4.69 (d, 1′-H), 4.82 (d, 1″-H), 4.90 (m, 9-H), 4.90 (m, 14-H), 4.99 (dd, 2′-H), 5.19 (br dd, 3-H), 7.29 (m, C$_6$H$_5$); ^{13}C-NMR (100 MHz, CDCl$_3$) δ: 17.0 (18-C), 17.3 (6″-C), 18.0 (6′-C), 20.2 (15-C), 22.1 (3″-CH$_3$), 30.4 (7-C), 31.7 (16-C), 32.0 (13-C), 33.6 (8-C), 34.0 (6-C), 36.2 (2″-C), 36.8 (2-C), 49.2 (12-C), 53.8 (10-C), 58.6 (11-CH$_2$), 61.3 (4-OCH$_3$), 63.0 (5″-C), 68.0 (3′-C), 69.9 (3-C), 70.4 (14-C), 70.8 (2′-C), 72.7 (5′-C), 75.1 (9-C), 75.8 (5-C), 77.7 (4″-C), 78.1 (3″-C), 79.2 (4′-C), 97.8 (1″-C), 100.6 (1′-C), 101.5 (17-C), 169.4 (1-C).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-11-benzyl-6-(2,2-dimethoxyethyl)-4-methoxy-8-methyl-3-propionyloxy-11-aza-pentadecan-14-olide (**17**)

16 (20.0 mg) was dissolved in methanol and water (9 : 1) (2.0 ml), and the mixture was stirred at 55°C for 24 hours. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by preparative TLC (chloroform/methanol (20 : 1)) to obtain **17** (17.3 mg, 90%) as a colorless solid.

17: $[\alpha]_{\mathrm{D}}^{21}$ −60° (*c* 0.61, CHCl$_3$); FAB-MS *m/z* 1025 (M+H)$^+$ as C$_{52}$H$_{84}$N$_2$O$_{18}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.90 (d, 18-H), 1.10 (d, 6″-H), 1.15 (t, 3-OCOCH$_2$CH$_3$), 1.16 (d, 15-H), 1.20 (t, 4″-OCOCH$_2$CH$_3$),1.24 (d, 6′-H), 1.43 (s, 3″-CH$_3$), 1.56 (m, 16-H), 1.69 (dd, 2″-Hax), 2.03 (s, 9-OCOCH$_3$), 2.03 (s, 3″-OCOCH$_3$), 2.56 (s, 3′-N(CH$_3$)$_2$), 2.87 (dd, 2-H), 3.17 (s, 17-OCH$_3$), 3.27 (s, 17-OCH$_3$), 3.44 (dd, 2′-H), 3.54 (d, C$_6$H$_5$CH$_2$), 3.57 (br d, 4-H), 3.62 (s, 4-OCH$_3$), 3.72 (d, C$_6$H$_5$CH$_2$), 3.92 (br d, 5-H), 4.51 (d, 1′-H), 4.54 (dq, 5″-H), 4.60 (d, 4″-H), 4.87 (d, 1″-H), 4.87 (m, 14-H), 4.91 (m, 9-H), 5.24 (br dd, 3-H), 7.24 (m, C$_6$H$_5$), 7.29 (m, C$_6$H$_5$).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-11-benzyl-6-formylmethyl-4-methoxy-8-methyl-3-propionyloxy-11-aza-pentadecan-14-olide (**11**)

To a solution of **17** (25 mg) in acetonitrile and water (1 : 1) (0.75 ml) was added difluoroacetic acid (35 μl), and the mixture was stirred at room temperature for 25 hours. The reaction mixture was diluted with chloroform (40 ml), and washed with saturated aqueous sodium hydrogencarbonate solution (25 ml). Further, the organic layer was successively washed with saturated aqueous sodium hydrogencarbonate solution (35 ml) and saturated brine (35 ml), dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by preparative TLC (chloroform/methanol/aqueous ammonia (15 : 1 : 0.1)) to obtain **11** (20 mg, 84%).

11: $[\alpha]_{\mathrm{D}}^{21}$ −70° (*c* 0.47, CHCl$_3$); FAB-MS *m/z* 979 (M+H)$^+$ as C$_{50}$H$_{78}$N$_2$O$_{17}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.90 (d, 18-H), 1.10 (d, 6″-H), 1.16 (d, 6′-H), 1.17 (t, 3-OCOCH$_2$CH$_3$), 1.19 (d, 15-H), 1.20 (t, 4″-OCOCH$_2$CH$_3$), 1.43 (s, 3″-CH$_3$), 1.48 (br dd, 7-H), 1.70 (dd, 2″-Hax), 2.02 (s, 9-OCOCH$_3$), 2.03 (s, 3″-OCOCH$_3$), 2.15 (m, 6-H), 2.58 (s, 3′-N(CH$_3$)$_2$), 2.85 (dd, 2-H), 2.95 (dd, 16-H), 3.24 (d, 2″-

Heq), 3.25 (m, 4′-H), 3.25 (m, 5′-H), 3.38 (dd, 2′-H), 3.55 (d, $C_6H_5CH_2$), 3.61 (s, 4-OCH_3), 3.64 (br d, 4-H), 3.73 (d, $C_6H_5CH_2$), 3.94 (br d, 5-H), 4.48 (d, 1′-H), 4.48 (dq, 5″-H), 4.60 (d, 4″-H), 4.78 (br q, 14-H), 4.89 (d, 1″-H), 4.89 (m, 9-H), 5.38 (br dd, 3-H), 7.25 (m, C_6H_5), 7.29 (m, C_6H_5), 9.65 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,15*R*)-9-Acetoxy-5-[2-*O*-acetyl-4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-4-methoxy-8,11,12-trimethyl-3-propionyloxy-11,12-diaza-hexadecan-15-olide (**18**)

Reaction of **12** with 1,2-dimethylhydrazine dihydrochloride gave **18** in 13% yield by a similar procedure to **16**.

18: $[\alpha]_D^{24}$ −71° (*c* 0.76, $CHCl_3$); FAB-MS *m/z* 1019 $(M)^+$ as $C_{49}H_{85}N_3O_{19}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (d, 19-H), 1.07 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.26 (d, 16-H), 1.41 (s, 3″-CH_3), 1.52 (m, 17-H), 1.67 (dd, 2″-Hax), 1.71 (m, 8-H), 2.03 (s, 9-$OCOCH_3$), 2.03 (s, 3″-$OCOCH_3$), 2.05 (s, 2′-$OCOCH_3$), 2.22 (s, 11-NCH_3), 2.22 (s, 12-NCH_3), 2.43 (s, 3′-$N(CH_3)_2$), 2.61 (t, 3′-H), 2.75 (dd, 2-H), 3.14 (t, 4′-H), 3.19 (d, 2″-Heq), 3.20 (s, 18-OCH_3), 3.25 (s, 18-OCH_3), 3.43 (br d, 4-H), 3.57 (s, 4-OCH_3), 3.85 (br d, 5-H), 4.45 (t, 18-H), 4.48 (dq, 5″-H), 4.57 (d, 4″-H), 4.67 (d, 1′-H), 4.81 (d, 1″-H), 4.90 (m, 15-H), 4.98 (dd, 2′-H), 5.05 (br dd, 9-H), 5.22 (m, 3-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,15*R*)-9-Acetoxy-5-[4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-4-methoxy-8,11,12-trimethyl-3-propionyloxy-11,12-diaza-hexadecan-15-olide (**19**)

Reaction of **18** with aqueous methanol gave **19** in 79% yield by a similar procedure to **17**.

19: $[\alpha]_D^{22}$ −52° (*c* 0.77, $CHCl_3$); FAB-MS *m/z* 978 $(M+H)^+$ as $C_{47}H_{83}N_3O_{18}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.95 (d, 19-H), 1.09 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.21 (d, 6′-H), 1.26 (d, 16-H), 1.42 (s, 3″-CH_3), 1.59 (m, 17-H), 1.70 (dd, 2″-Hax), 2.02 (s, 9-$OCOCH_3$), 2.05 (s, 3″-$OCOCH_3$), 2.37, 2.38 (each q, 4″-$OCOCH_2CH_3$), 2.42 (s, 11-NCH_3), 2.42 (s, 12-NCH_3), 2.43 (br q, 3-$OCOCH_2CH_3$), 2.54 (s, 3′-$N(CH_3)_2$), 2.78 (dd, 2-H), 3.22 (s, 18-OCH_3), 3.24 (d, 2″-Heq), 3.27 (s, 18-OCH_3), 3.46 (dd, 2′-H), 3.50 (br d, 4-H), 3.63 (s, 4-OCH_3), 3.88 (br d, 5-H), 4.45 (t, 18-H), 4.46 (d, 1′-H), 4.56 (m, 5″-H), 4.59 (d, 4″-H), 4.85 (d, 1″-H), 4.94 (m, 15-H), 5.05 (m, 9-H), 5.31 (m, 3-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,15*R*)-9-Acetoxy-5-[4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-formylmethyl-4-methoxy-8,11,12-trimethyl-3-propionyloxy-11,12-diaza-hexadecan-15-olide (**20**)

Reaction of **19** with aqueous difluoroacetic acid gave **20** in 94% yield by a similar procedure to **11**.

20: $[\alpha]_D^{22}$ −74° (*c* 0.42, $CHCl_3$); FAB-MS *m/z* 932 $(M+H)^+$ as $C_{45}H_{77}N_3O_{17}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.97 (d, 19-H), 1.09 (d, 6″-H), 1.15 (d, 6′-H), 1.17 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 16-H), 1.42 (s, 3″-CH_3), 1.70 (dd, 2″-Hax), 1.76 (m, 8-H), 2.02 (s, 9-$OCOCH_3$), 2.05 (s, 3″-$OCOCH_3$), 2.22 (s, 11-NCH_3), 2.25 (s, 12-NCH_3), 2.56 (s, 3′-$N(CH_3)_2$), 3.04 (dd, 17-H), 3.23 (m, 4′-H), 3.23 (m, 5′-H), 3.23 (d, 2″-Heq), 3.40 (dd, 2′-H), 3.58 (s, 4-OCH_3), 3.99 (br d, 5-H), 4.42 (d, 1′-H), 4.50 (dq, 5″-H), 4.59 (d, 4″-H), 4.86 (d, 1″-H), 4.90 (m, 15-H), 5.00 (m, 9-H), 5.38 (br dd, 3-H), 9.64 (s, 18-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[2-*O*-acetyl-4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-4-methoxy-11-(4-methoxybenzyl)-8-methyl-3-propionyloxy-11-aza-pentadecan-14-olide (**21**)

Reaction of **12** with 4-methoxybenzylamine gave **21** in 8.8% yield by a similar procedure to **16**.

21: $[\alpha]_D^{25}$ −87° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 1097 $(M+H)^+$ as $C_{55}H_{88}N_2O_{20}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (d, 18-H), 1.07 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.17 (d, 15-H), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.21 (d, 6′-H), 1.42 (s, 3″-CH_3), 1.54 (br dd, 16-H), 1.68 (dd, 2″-Hax), 2.02 (s, 9-$OCOCH_3$), 2.02 (s, 3″-$OCOCH_3$), 2.05 (s, 2′-$OCOCH_3$), 2.44 (s, 3′-$N(CH_3)_2$), 2.83 (dd, 2-H), 3.14 (s, 17-OCH_3), 3.15 (m, 4′-H), 3.15 (m, 5′-H), 3.19 (d, 2″-Heq), 3.26 (s, 17-OCH_3), 3.48 (br d, 4-H), 3.50 (d, $C_6H_4CH_2$), 3.55 (s, 4-OCH_3), 3.64 (d, $C_6H_4CH_2$), 3.79 (s, $CH_3OC_6H_4$), 3.90 (br d, 5-H), 4.49 (dq, 5″-H), 4.57 (d, 4″-H), 4.68 (d, 1′-H), 4.81 (d, 1″-H), 4.89 (m, 9-H), 4.89 (m, 14-H), 4.98 (dd, 2′-H), 5.19 (m, 3-H), 6.8 3(d, C_6H_4), 7.19 (d, C_6H_4).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-9-hydroxy-4-methoxy-8-methyl-3-propionyloxy-11-aza-pentadecan-14-olide (**22**)

Reaction of **21** with aqueous methanol gave *N*-(4-methoxybenzyl) derivative of **22** in 52% yield by a similar procedure to **17**.

N-(4-Methoxybenzyl) derivative of **22**: $[\alpha]_D^{26}$ −68° (*c* 0.60, $CHCl_3$); FAB-MS *m/z* 1013 $(M+H)^+$ as $C_{51}H_{84}N_2O_{18}$;

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.93 (d, 18-H), 1.10 (d, 6″-H), 1.14 (t, 3-OCOCH$_2$CH$_3$), 1.20 (t, 4″-OCOCH$_2$CH$_3$), 1.21 (d, 6′-H), 1.22 (d, 15-H), 1.43 (s, 3″-CH$_3$), 1.61 (br dd, 16-H), 1.70 (dd, 2″-Hax), 2.02 (s, 3″-OCOCH$_3$), 2.56 (s, 3′-N(CH$_3$)$_2$), 2.60 (dd, 2-H), 2.84 (dd, 2-H), 3.13 (s, 17-OCH$_3$), 3.22 (m, 4′-H), 3.22 (m, 5′-H), 3.23 (d, 2″-Heq), 3.27 (s, 17-OCH$_3$), 3.41 (dd, 2′-H), 3.43 (d, C$_6$H$_4$CH$_2$), 3.61 (s, 4-OCH$_3$), 3.63 (dd, 4-H), 3.73 (d, C$_6$H$_4$CH$_2$), 3.81 (s, C$_6$H$_4$OMe), 3.90 (br d, 5-H), 4.49 (d, 1′-H), 4.50 (t, 17-H), 4.55 (dq, 5″-H), 4.59 (d, 4″-H), 4.82 (m, 14-H), 4.86 (d, 1″-H), 5.24 (br dd, 3-H), 6.86 (d, C$_6$H$_4$), 7.20 (d, C$_6$H$_4$).

To a solution of *N*-(4-methoxybenzyl) derivative of **22** (63.0 mg) in 1,4-dioxane (1.5 ml) was added 10% Pd-C catalyst (6.3 mg) suspended in ethanol (1.0 ml). The atmosphere in the reaction vessel was replaced with hydrogen, and the mixture was stirred at room temperature for 135 minutes. 10% Pd-C catalyst (12.6 mg) suspended in ethanol (0.5 ml) was added, and the reaction mixture was stirred for 165 minutes. Then, 10% Pd-C catalyst (6.3 mg) suspended in ethanol (0.5 ml) was added, and the mixture was stirred for 1 hour, and the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by preparative TLC (chloroform/methanol/aqueous ammonia (10 : 1 : 0.1)) to obtain **22** (32.0 mg, 58%).

Two-step yield of **22** based on **21** was 30%.

22: $[\alpha]_D^{25}$ −67° (*c* 0.80, CHCl$_3$); FAB-MS *m/z* 893 (M+H)$^+$ as C$_{43}$H$_{76}$N$_2$O$_{17}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.91 (d, 18-H), 1.08 (d, 6″-H), 1.14 (t, 3-OCOCH$_2$CH$_3$), 1.19 (t, 4″-OCOCH$_2$CH$_3$), 1.21 (d, 6′-H), 1.27 (d, 15-H), 1.41 (s, 3″-CH$_3$), 1.69 (dd, 2″-Hax), 2.01 (s, 3″-OCOCH$_3$), 2.54 (s, 3′-N(CH$_3$)$_2$), 2.60 (dd, 2-H), 2.72 (dd, 2-H), 2.80 (br d, 10-H), 2.91 (m, 12-H), 3.15 (s, 17-OCH$_3$), 3.22 (d, 2″-Heq), 3.25 (s, 17-OCH$_3$), 3.41 (dd, 2′-H), 3.62 (s, 4-OCH$_3$), 3.86 (br d, 5-H), 4.46 (br t, 17-H), 4.46 (d, 1′-H), 4.52 (dq, 5″-H), 4.58 (d, 4″-H), 4.85 (d, 1″-H), 4.96 (m, 14-H), 5.17 (br dd, 3-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-9-*O*,11-carbonyl-6-(2,2-dimethoxyethyl)-4-methoxy-8-methyl-3-propionyloxy-11-aza-pentadecan-14-olide (**23**)

To a solution of **22** (30.0 mg) in dichloromethane (1.0 ml) were added triethylamine (42 μl) and a solution of triphosgene (11 mg) in dichloromethane (0.50 ml) under ice cooling, and the mixture was stirred for 1.5 hours at the same temperature. Chloroform (20 ml) and saturated aqueous sodium hydrogencarbonate solution (15 ml) were added to the resulting mixture, and the organic layer was separated. The organic layer was washed with saturated brine (15 ml), and dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by preparative TLC (ethyl acetate/methanol/aqueous ammonia (35 : 1 : 0.1)) to obtain **23** (23.0 mg, 74%).

23: $[\alpha]_D^{26}$ −48° (*c* 0.61, CHCl$_3$); FAB-MS *m/z* 919 (M+H)$^+$ as C$_{44}$H$_{74}$N$_2$O$_{18}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 1.02 (d, 18-H), 1.08 (d, 6″-H), 1.13 (t, 3-OCOCH$_2$CH$_3$), 1.19 (t, 4″-OCOCH$_2$CH$_3$), 1.20 (d, 6′-H), 1.32 (d, 15-H), 1.41 (s, 3″-CH$_3$), 1.48 (m, 16-H), 1.68 (dd, 2″-Hax), 1.82 (m, 13-H), 2.01 (s, 3″-OCOCH$_3$), 2.08 (m, 13-H), 2.37 (q, 4″-OCOCH$_2$CH$_3$), 2.40 (t, 3′-H), 2.42 (q, 3-OCOCH$_2$CH$_3$), 2.54 (s, 3′-N(CH$_3$)$_2$), 2.62 (dd, 2-H), 2.79 (dd, 2-H), 3.04 (br dd, 12-H), 3.15 (t, 4′-H), 3.20 (d, 2″-Heq), 3.21 (s, 17-OCH$_3$), 3.25 (s, 17-OCH$_3$), 3.39 (dd, 4-H), 3.46 (dd, 10-H), 3.54 (dd, 2′-H), 3.56 (s, 4-OCH$_3$), 3.81 (br d, 5-H), 3.83 (m, 12-H), 4.26 (br dd, 9-H), 4.46 (t, 17-H), 4.47 (d, 1′-H), 4.57 (m, 4″-H), 4.57 (m, 5″-H), 4.83 (d, 1″-H), 5.04 (br dq, 14-H), 5.35 (br dd, 3-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-9-*O*,11-carbonyl-6-formylmethyl-4-methoxy-8-methyl-3-propionyloxy-11-aza-pentadecan-14-olide (**24**)

Reaction of **23** with aqueous difluoroacetic acid gave **24** in 86% yield by a similar procedure to **11**.

24: $[\alpha]_D^{26}$ −55° (*c* 0.51, CHCl$_3$); FAB-MS *m/z* 873 (M+H)$^+$ as C$_{42}$H$_{68}$N$_2$O$_{17}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 1.03 (d, 18-H), 1.08 (d, 6″-H), 1.14 (d, 6′-H), 1.17 (t, 3-OCOCH$_2$CH$_3$), 1.19 (t, 4″-OCOCH$_2$CH$_3$), 1.33 (d, 15-H), 1.41 (s, 3″-CH$_3$), 1.63 (m, 8-H), 1.68 (dd, 2″-Hax), 1.81 (m, 6-H), 1.85 (m, 13-H), 2.01 (s, 3″-OCOCH$_3$), 2.09 (m, 13-H), 2.24 (dd, 16-H), 2.40 (q, 3-OCOCH$_2$CH$_3$), 2.40 (t, 3′-H), 2.45 (q, 4″-OCOCH$_2$CH$_3$), 2.55 (s, 3′-N(CH$_3$)$_2$), 2.67 (dd, 2-H), 2.80 (dd, 2-H), 3.02 (m, 12-H), 3.09 (dd, 16-H), 3.14 (t, 4′-H), 3.21 (d, 2″-Heq), 3.38 (dd, 4-H), 3.49 (dd, 2′-H), 3.51 (m, 10-H), 3.57 (s, 4-OCH$_3$), 3.90 (m, 12-H), 3.92 (br d, 5-H), 4.21 (br dd, 9-H), 4.44 (d, 1′-H), 4.55 (m, 5″-H), 4.57 (m, 4″-H), 4.83 (d, 1″-H), 5.03 (m, 14-H), 5.43 (br dd, 3-H), 9.64 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[2-*O*-acetyl-4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-4-methoxy-8,11-dimethyl-3-propionyloxy-11-aza-pentadecan-14-olide (**25**)

Reaction of **12** with methylamine hydrochloride gave **25** in 11% yield by a similar procedure to **16**.

25: $[\alpha]_D^{22}$ −72° (*c* 1.0, CHCl$_3$); FAB-MS *m/z* 991

$(M+H)^+$ as $C_{48}H_{82}N_2O_{19}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.94 (d, 18-H), 1.07 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.24 (d, 15-H), 1.41 (s, 3″-CH_3), 1.53 (br dd, 16-H), 1.67 (dd, 2″-Hax), 1.82 (br s, 16-H), 2.02 (s, 9-$OCOCH_3$), 2.03 (s, 3″-$OCOCH_3$), 2.04 (s, 2′-$OCOCH_3$), 2.26 (s, 11-NCH_3), 2.43 (s, 3′-$N(CH_3)_2$), 2.58 (dd, 2-H), 2.62 (t, 3′-H), 2.82 (dd, 2-H), 3.14 (t, 4′-H), 3.17 (s, 17-OCH_3), 3.19 (d, 2″-Heq), 3.25 (s, 17-OCH_3), 3.35 (br d, 4-H), 3.57 (s, 4-OCH_3), 3.86 (br d, 5-H), 4.48 (dq, 5″-H), 4.56 (d, 4″-H), 4.68 (d, 1′-H), 4.81 (d, 1″-H), 4.98 (dd, 2′-H), 5.12 (m, 14-H), 5.16 (m, 3-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-9-hydroxy-4-methoxy-8,11-dimethyl-3-propionyloxy-11-aza-pentadecan-14-olide (**26**)

25 (50.0 mg) was dissolved in methanol (2.0 ml), and the mixture was stirred at room temperature for 72 hours. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by preparative TLC (chloroform/methanol/aqueous ammonia (10 : 1 : 0.1)) to obtain **26** (27.2 mg, 59%).

26: $[\alpha]_D^{23}$ −60° (*c* 0.4, $CHCl_3$); FAB-MS *m/z* 907 $(M+H)^+$ as $C_{44}H_{78}N_2O_{17}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.97 (d, 18-H), 1.09 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.21 (d, 6′-H), 1.27 (d, 15-H), 1.42 (s, 3″-CH_3), 1.53 (m, 8-H), 1.60 (m, 16-H), 1.69 (dd, 2″-Hax), 1.90 (br dd, 16-H), 2.02 (s, 3″-$OCOCH_3$), 2.39 (s, 11-NCH_3), 2.55 (s, 3′-$N(CH_3)_2$), 2.62 (dd, 2-H), 2.79 (dd, 2-H), 3.16 (s, 17-OCH_3), 3.23 (d, 2″-Heq), 3.27 (s, 17-OCH_3), 3.43 (dd, 2′-H), 3.54 (br d, 4-H), 3.60 (s, 4-OCH_3), 3.87 (br d, 5-H), 4.47 (d, 1′-H), 4.57 (d, 4″-H), 4.85 (d, 1″-H), 4.90 (m, 14-H), 5.27 (br dd, 3-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-8,11-dimethyl-3-propionyloxy-11-aza-pentadecan-14-olide (**27**)

Reaction of **26** with aqueous difluoroacetic acid gave **27** in 70% yield by a similar procedure to **11**.

27: $[\alpha]_D^{25}$ −72° (*c* 0.48, $CHCl_3$); FAB-MS *m/z* 861 $(M+H)^+$ as $C_{42}H_{72}N_2O_{16}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.99 (d, 18-H), 1.10 (d, 6″-H), 1.15 (d, 6′-H), 1.17 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.28 (d, 15-H), 1.42 (s, 3″-CH_3), 1.56 (br dd, 7-H), 1.70 (dd, 2″-Hax), 1.88 (m, 13-H), 2.01 (s, 3″-$OCOCH_3$), 2.07 (br t, 6-H), 2.34 (s, 11-NCH_3), 2.56 (s, 3′-$N(CH_3)_2$), 2.80 (dd, 2-H), 2.96 (dd, 16-H), 3.22 (m, 4′-H), 3.22 (m, 5′-H), 3.23 (d, 2″-Heq), 3.37 (dd, 2′-H), 3.60 (s, 4-OCH_3), 3.62 (dd, 4-H), 3.87 (br d, 5-H), 4.43 (d, 1′-H), 4.53 (dq, 5″-H), 4.59 (d, 4″-H), 4.86 (d, 1″-H), 4.88 (m, 14-H), 5.40 (br dd, 3-H), 9.66 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[2-*O*-acetyl-4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-4-methoxy-8-methyl-11-(2-phenylethyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**28a**)

Reaction of **12** with 2-phenylethylamine gave **28a** in 7.3% yield by a similar procedure to **16**.

28a: $[\alpha]_D^{25}$ −86° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 1081 $(M+H)^+$ as $C_{55}H_{88}N_2O_{19}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (d, 18-H), 1.08 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.21 (d, 6′-H), 1.23 (d, 15-H), 1.42 (s, 3″-CH_3), 1.55 (br dd, 16-H), 1.68 (dd, 2″-Hax), 1.82 (m, 16-H), 2.02 (s, 9-$OCOCH_3$), 2.03 (s, 3″-$OCOCH_3$), 2.05 (s, 2′-$OCOCH_3$), 2.44 (s, 3′-$N(CH_3)_2$), 2.83 (dd, 2-H), 3.15 (s, 17-OCH_3), 3.20 (d, 2″-Heq), 3.26 (s, 17-OCH_3), 3.43 (br d, 4-H), 3.56 (s, 4-OCH_3), 3.90 (br d, 5-H), 4.50 (dq, 5″-H), 4.57 (d, 4″-H), 4.68 (d, 1′-H), 4.78 (m, 9-H), 4.82 (d, 1″-H), 4.94 (ddq, 14-H), 4.99 (dd, 2′-H), 5.17 (m, 3-H), 7.19 (m, C_6H_5), 7.27 (m, C_6H_5).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-4-methoxy-8-methyl-11-(2-phenylethyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**29a**) and (−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-9-hydroxy-4-methoxy-8-methyl-11-(2-phenylethyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**30a**)

Reaction of **28a** with methanol gave **29a** in 54% yield and **30a** in 32% yield, respectively, by a similar procedure to **26**. Total recovery was 86% in this reaction.

29a: $[\alpha]_D^{24}$ −65° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 1039 $(M+H)^+$ as $C_{53}H_{86}N_2O_{18}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (d, 18-H), 1.10 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.22 (d, 6′-H), 1.24 (d, 15-H), 1.42 (s, 3″-CH_3), 1.55 (m, 16-H), 1.70 (dd, 2″-Hax), 2.03 (s, 9-$OCOCH_3$), 2.03 (s, 3″-$OCOCH_3$), 2.56 (s, 3′-$N(CH_3)_2$), 2.85 (dd, 2-H), 3.18 (s, 17-OCH_3), 3.20 (m, 4′-H), 3.20 (m, 5′-H), 3.23 (d, 2″-Heq), 3.27 (s, 17-OCH_3), 3.44 (dd, 2′-H), 3.50 (br d, 4-H), 3.62 (s, 4-OCH_3), 3.91 (br d, 5-H), 4.50 (d, 1′-H), 4.54 (dq, 5″-H), 4.59 (d, 4″-H), 4.81 (m, 9-H), 4.86 (d, 1″-H), 4.95 (m, 14-H), 5.23 (m, 3-H), 7.19 (m, C_6H_5), 7.27 (m, C_6H_5).

30a: $[\alpha]_D^{24}$ −67° (*c* 0.71, $CHCl_3$); FAB-MS *m/z* 997 $(M+H)^+$ as $C_{51}H_{84}N_2O_{17}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.95 (d, 18-H), 1.10 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.22 (d, 6′-H), 1.24 (d, 15-H), 1.40 (br dd, 7-H), 1.43 (s, 3″-CH_3), 1.61 (m, 8-H), 1.61 (m, 16-H), 1.70 (dd, 2″-Hax), 1.89 (ddd, 16-H), 2.02 (s, 3″-$OCOCH_3$), 2.40 (t, 3′-H), 2.55 (s, 3′-$N(CH_3)_2$), 2.59 (dd, 2-H), 2.82 (dd, 2-H), 3.14 (s, 17-OCH_3), 3.22 (m, 4′-H), 3.22 (m, 5′-H), 3.23 (d, 2″-Heq), 3.27 (s, 17-OCH_3), 3.41 (dd, 2′-H), 3.55 (dd, 4-H), 3.60 (s, 4-OCH_3), 3.90 (br d, 5-H), 4.48 (d, 1′-H), 4.50 (dd, 17-H), 4.55 (dq, 5″-H), 4.59 (d, 4″-H), 4.77 (ddq, 14-H), 4.86 (d, 1″-H), 5.20 (br dd, 3-H), 7.20 (m, C_6H_5), 7.30 (m, C_6H_5).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-formylmethyl-4-methoxy-8-methyl-11-(2-phenylethyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**31a**)

Reaction of **29a** with aqueous difluoroacetic acid gave **31a** in 95% yield by a similar procedure to **11**.

31a: $[\alpha]_D^{23}$ −65° (*c* 0.98, $CHCl_3$); FAB-MS *m/z* 993 $(M+H)^+$ as $C_{51}H_{80}N_2O_{17}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (d, 18-H), 1.10 (d, 6″-H), 1.15 (d, 6′-H), 1.18 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 15-H), 1.42 (s, 3″-CH_3), 1.48 (br dd, 7-H), 1.70 (dd, 2″-Hax), 2.02 (s, 9-$OCOCH_3$), 2.02 (s, 3″-$OCOCH_3$), 2.20 (m, 6-H), 2.57 (s, 3′-$N(CH_3)_2$), 2.95 (dd, 16-H), 3.23 (m, 4′-H), 3.23 (m, 5′-H), 3.23 (d, 2″-Heq), 3.27 (dd, 2′-H), 3.58 (br d, 4-H), 3.60 (s, 4-OCH_3), 3.94 (br d, 5-H), 4.46 (d, 1′-H), 4.52 (dq, 5″-H), 4.59 (d, 4″-H), 4.79 (m, 9-H), 4.87 (d, 1″-H), 4.87 (m, 14-H), 5.37 (m, 3-H), 7.19 (m, C_6H_5), 7.27 (m, C_6H_5), 9.65 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-8-methyl-11-(2-phenylethyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**32a**)

Reaction of **30a** with aqueous difluoroacetic acid gave **32a** in 90% yield by a similar procedure to **11**.

32a: $[\alpha]_D^{22}$ −73° (*c* 0.60, $CHCl_3$); FAB-MS *m/z* 951 $(M+H)^+$ as $C_{49}H_{78}N_2O_{16}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.96 (d, 18-H), 1.10 (d, 6″-H), 1.15 (d, 6′-H), 1.17 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 15-H), 1.42 (s, 3″-CH_3), 1.46 (br dd, 7-H), 1.71 (dd, 2″-Hax), 2.01 (s, 3″-$OCOCH_3$), 2.01 (m, 6-H), 2.56 (s, 3′-$N(CH_3)_2$), 2.60 (dd, 2-H), 2.81 (dd, 2-H), 2.96 (dd, 16-H), 3.23 (m, 4′-H), 3.23 (m, 5′-H), 3.23 (d, 2″-Heq), 3.34 (dd, 2′-H), 3.60 (s, 4-OCH_3), 3.64 (br d, 4-H), 3.89 (br d, 5-H), 4.44 (d, 1′-H), 4.51 (dq, 5″-H), 4.59 (d, 4″-H), 4.76 (ddq, 14-H), 4.86 (d, 1″-H), 5.33 (br dd, 3-H), 7.20 (m, C_6H_5), 7.30 (m, C_6H_5), 9.65 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[2-*O*-acetyl-4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-4-methoxy-8-methyl-11-(3-phenylpropyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**28b**)

Reaction of **12** with 3-phenylpropylamine gave **28b** in 7.3% yield by a similar procedure to **16**.

28b: $[\alpha]_D^{26}$ −86° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 1095 $(M+H)^+$ as $C_{56}H_{90}N_2O_{19}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (d, 18-H), 1.07 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.24 (d, 15-H), 1.42 (s, 3″-CH_3), 1.54 (br dd, 16-H), 1.67 (dd, 2″-Hax), 1.70 (m, $Ph(CH_2)_3$), 1.85 (m, 16-H), 1.99 (s, 9-$OCOCH_3$), 2.02 (s, 3″-$OCOCH_3$), 2.04 (s, 2′-$OCOCH_3$), 2.44 (s, 3′-$N(CH_3)_2$), 2.84 (dd, 2-H), 3.14 (s, 17-OCH_3), 3.14 (m, 4′-H), 3.15 (d, 2″-Heq), 3.25 (s, 17-OCH_3), 3.46 (br d, 4-H), 3.55 (s, 4-OCH_3), 3.90 (br d, 5-H), 4.49 (dq, 5″-H), 4.57 (d, 4″-H), 4.68 (d, 1′-H), 4.79 (m, 9-H), 4.81 (d, 1″-H), 4.93 (m, 14-H), 4.98 (dd, 2′-H), 5.16 (m, 3-H), 7.17 (m, C_6H_5), 7.27 (m, C_6H_5).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-4-methoxy-8-methyl-11-(3-phenylpropyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**29b**) and (−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-9-hydroxy-4-methoxy-8-methyl-11-(3-phenylpropyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**30b**)

Reaction of **28b** with methanol gave **29b** in 38% yield and **30b** in 33% yield, respectively, by a similar procedure to **26**. Total recovery was 71% in this reaction.

29b: $[\alpha]_D^{24}$ −58° (*c* 0.90, $CHCl_3$); FAB-MS *m/z* 1053 $(M+H)^+$ as $C_{54}H_{88}N_2O_{18}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.96 (d, 18-H), 1.10 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.22 (d, 6′-H), 1.26 (d, 15-H), 1.43 (s, 3″-CH_3), 1.44 (br dd, 7-H), 1.60 (m, 8-H), 1.60 (m, 16-H), 1.70 (dd, 2″-Hax), 1.86 (m, $Ph(CH_2)_3$), 1.90 (m, 16-H), 2.02 (s, 3″-$OCOCH_3$), 2.55 (s, 3′-$N(CH_3)_2$), 2.83 (dd, 2-H), 3.13 (s, 17-OCH_3), 3.22 (m, 4′-H), 3.22 (m, 5′-H), 3.23 (d, 2″-Heq), 3.27 (s, 17-OCH_3), 3.41 (dd, 2′-H), 3.58 (br d, 4-H), 3.60 (s, 4-OCH_3), 3.90 (br d, 5-H), 4.49 (d, 1′-H), 4.52 (dq, 5″-H), 4.59 (d, 4″-H), 4.83 (ddq, 14-H), 4.86 (d, 1″-H), 5.22 (br dd, 3-H), 7.19 (m, C_6H_5), 7.29 (m, C_6H_5).

30b: $[\alpha]_D^{26}$ $-60°$ (*c* 0.76, $CHCl_3$); FAB-MS *m*/*z* 1011 $(M+H)^+$ as $C_{52}H_{86}N_2O_{17}$; ^1H-NMR (300 MHz, $CDCl_3$) δ: 0.96 (d, 18-H), 1.10 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.22 (d, 6′-H), 1.26 (d, 15-H), 1.43 (s, 3″-CH_3), 1.44 (br dd, 7-H), 1.60 (m, 8-H), 1.60 (m, 16-H), 1.70 (dd, 2″-Hax), 1.86 (m, $Ph(CH_2)_3$), 1.90 (m, 16-H), 2.02 (s, 3″-$OCOCH_3$), 2.55 (s, 3′-$N(CH_3)_2$), 2.83 (dd, 2-H), 3.13 (s, 17-OCH_3), 3.22 (m, 4′-H), 3.22 (m, 5′-H), 3.23 (d, 2″-Heq), 3.27 (s, 17-OCH_3), 3.41 (dd, 2′-H), 3.58 (br d, 4-H), 3.60 (s, 4-OCH_3), 3.90 (br d, 5-H), 4.49 (d, 1′-H), 4.52 (dq, 5″-H), 4.59 (d, 4″-H), 4.83 (ddq, 14-H), 4.86 (d, 1″-H), 5.22 (br dd, 3-H), 7.19 (m, C_6H_5), 7.29 (m, C_6H_5).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-formylmethyl-4-methoxy-8-methyl-11-(3-phenylpropyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**31b**)

Reaction of **29b** with aqueous difluoroacetic acid gave **31b** in 70% yield by a similar procedure to **11**.

31b: $[\alpha]_D^{25}$ $-70°$ (*c* 0.61, $CHCl_3$); FAB-MS *m*/*z* 1007 $(M+H)^+$ as $C_{52}H_{82}N_2O_{17}$; ^1H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (d, 18-H), 1.10 (d, 6″-H), 1.16 (d, 6′-H), 1.18 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 15-H), 1.43 (s, 3″-CH_3), 1.45 (br dd, 7-H), 1.71 (dd, 2″-Hax), 2.00 (s, 9-$OCOCH_3$), 2.02 (s, 3″-$OCOCH_3$), 2.20 (m, 6-H), 2.57 (s, 3′-$N(CH_3)_2$), 2.84 (dd, 2-H), 2.95 (dd, 16-H), 3.23 (m, 4′-H), 3.23 (m, 5′-H), 3.23 (d, 2″-Heq), 3.26 (dd, 2′-H), 3.59 (s, 4-OCH_3), 3.94 (dd, 5-H), 4.46 (d, 1′-H), 4.49 (dq, 5″-H), 4.60 (d, 4″-H), 4.79 (m, 14-H), 4.82 (m, 9-H), 4.87 (d, 1″-H), 5.36 (m, 3-H), 7.18 (m, C_6H_5), 7.28 (m, C_6H_5), 9.64 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-8-methyl-11-(3-phenylpropyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**32b**)

Reaction of **30b** with aqueous difluoroacetic acid gave **32b** in 84% yield by a similar procedure to **11**.

32b: $[\alpha]_D^{26}$ $-72°$ (*c* 0.61, $CHCl_3$); FAB-MS *m*/*z* 965 $(M+H)^+$ as $C_{50}H_{80}N_2O_{16}$; ^1H-NMR (300 MHz, $CDCl_3$) δ: 0.98 (d, 18-H), 1.10 (d, 6″-H), 1.15 (d, 6′-H), 1.17 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 15-H), 1.43 (s, 3″-CH_3), 1.47 (m, 8-H), 1.71 (dd, 2″-Hax), 2.01 (s, 3″-$OCOCH_3$), 2.56 (s, 3′-$N(CH_3)_2$), 2.63 (t, $Ph(CH_2)_3$), 2.82 (dd, 2-H), 2.97 (dd, 16-H), 3.23 (m, 4′-H), 3.23 (m, 5′-H), 3.27 (d, 2″-Heq), 3.53 (dd, 2′-H), 3.60 (s, 4-OCH_3), 3.65 (dd, 4-H), 3.89 (br d, 5-H), 4.44 (d, 1′-H), 4.50 (dq, 5″-H), 4.60 (d, 4″-H), 4.79 (ddq, 14-H), 4.86 (d, 1″-H), 5.34 (br dd, 3-H), 7.19 (m, C_6H_5), 7.29 (m, C_6H_5), 9.66 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[2-*O*-acetyl-4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-4-methoxy-8-methyl-11-(4-phenylbutyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**28c**)

Reaction of **12** with 4-phenylbutylamine gave **28c** in 7.7% yield by a similar procedure to **16**.

28c: $[\alpha]_D^{23}$ $-69°$ (*c* 0.53, $CHCl_3$); FAB-MS *m*/*z* 1109 $(M+H)^+$ as $C_{57}H_{92}N_2O_{19}$; ^1H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (d, 18-H), 1.08 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.21 (d, 6′-H), 1.25 (d, 15-H), 1.42 (s, 3″-CH_3), 1.58 (m, 16-H), 1.68 (dd, 2″-Hax), 1.81 (m, 16-H), 1.99 (s, 9-$OCOCH_3$), 2.02 (s, 3″-$OCOCH_3$), 2.05 (s, 2′-$OCOCH_3$), 2.44 (s, 3′-$N(CH_3)_2$), 2.83 (dd, 2-H), 3.14 (s, 17-OCH_3), 3.20 (d, 2″-Heq), 3.26 (s, 17-OCH_3), 3.45 (br d, 4-H), 3.55 (s, 4-OCH_3), 3.89 (br d, 5-H), 4.50 (dq, 5″-H), 4.57 (d, 4″-H), 4.68 (d, 1′-H), 4.78 (m, 9-H), 4.81 (d, 1″-H), 4.94 (m, 14-H), 4.98 (dd, 2′-H), 5.16 (m, 3-H), 7.18 (m, C_6H_5), 7.27 (m, C_6H_5).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyl]-6-(2,2-dimethoxyethyl)-4-methoxy-8-methyl-11-(4-phenylbutyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**29c**)

Reaction of **28c** with methanol gave **29c** in 14% yield by a similar procedure to **26**.

29c: $[\alpha]_D^{27}$ $-65°$ (*c* 0.61, $CHCl_3$); FAB-MS *m*/*z* 1067 $(M+H)^+$ as $C_{55}H_{90}N_2O_{18}$; ^1H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (d, 18-H), 1.07 (d, 6″-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.23 (d, 15-H), 1.40 (s, 3″-CH_3), 1.68 (dd, 2″-Hax), 1.97 (s, 9-$OCOCH_3$), 2.00 (s, 3″-$OCOCH_3$), 2.53 (s, 3′-$N(CH_3)_2$), 2.59 (t, $Ph(CH_2)_4$), 2.83 (dd, 2-H), 3.15 (s, 17-OCH_3), 3.21 (d, 2″-Heq), 3.25 (s, 17-OCH_3), 3.41 (dd, 2′-H), 3.51 (br d, 4-H), 3.59 (s, 4-OCH_3), 3.88 (br d, 5-H), 4.47 (d, 1′-H), 4.57 (d, 4″-H), 4.77 (m, 9-H), 4.84 (d, 1″-H), 4.91 (m, 14-H), 5.20 (m, 3-H), 7.15 (m, C_6H_5), 7.25 (m, C_6H_5).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-formylmethyl-4-methoxy-8-methyl-11-(4-phenylbutyl)-3-propionyloxy-11-aza-pentadecan-14-

olide (**31c**)

Reaction of **29c** with aqueous difluoroacetic acid gave **31c** in 51% yield by a similar procedure to **11**.

31c: $[\alpha]_D^{26}$ −60° (*c* 1.55, CHCl$_3$); FAB-MS *m/z* 1021 $(M+H)^+$ as $C_{53}H_{84}N_2O_{17}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.91 (d, 18-H), 1.08 (d, 6″-H), 1.13 (d, 6′-H), 1.16 (t, 3-OCOCH$_2$CH$_3$), 1.18 (t, 4″-OCOCH$_2$CH$_3$), 1.25 (d, 15-H), 1.40 (s, 3″-CH$_3$), 1.69 (dd, 2″-Hax), 1.93 (s, 9-OCOCH$_3$), 2.00 (s, 3″-OCOCH$_3$), 2.16 (m, 6-H), 2.54 (s, 3′-N(CH$_3$)$_2$), 2.81 (dd, 2-H), 2.93 (dd, 16-H), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.21 (d, 2″-Heq), 3.34 (dd, 2′-H), 3.58 (s, 4-OCH$_3$), 3.91 (br d, 5-H), 4.44 (d, 1′-H), 4.49 (dq, 5″-H), 4.57 (d, 4″-H), 4.75 (br dd, 9-H), 4.82 (m, 14-H), 4.84 (d, 1″-H), 5.34 (m, 3-H), 7.16 (m, C$_6$H$_5$), 7.25 (m, C$_6$H$_5$), 9.62 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-9-hydroxy-4-methoxy-8-methyl-11-(4-phenylbutyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**30c**)

Reaction of **28c** with methanol gave **30c** in 62% yield by a similar procedure to **26**.

30c: $[\alpha]_D^{21}$ −68° (*c* 0.60, CHCl$_3$); FAB-MS *m/z* 1025 $(M+H)^+$ as $C_{53}H_{88}N_2O_{17}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.95 (d, 18-H), 1.07 (d, 6″-H), 1.11 (t, 3-OCOCH$_2$CH$_3$), 1.18 (t, 4″-OCOCH$_2$CH$_3$), 1.19 (d, 6′-H), 1.24 (d, 15-H), 1.40 (s, 3″-CH$_3$), 1.68 (dd, 2″-Hax), 1.87 (br dd, 16-H), 2.00 (s, 3″-OCOCH$_3$), 2.53 (s, 3′-N(CH$_3$)$_2$), 2.79 (dd, 2-H), 3.11 (s, 17-OCH$_3$), 3.21 (d, 2″-Heq), 3.24 (s, 17-OCH$_3$), 3.38 (dd, 2′-H), 3.54 (br d, 4-H), 3.58 (s, 4-OCH$_3$), 3.87 (br d, 5-H), 4.47 (d, 1′-H), 4.51 (dq, 5″-H), 4.57 (d,4″-H), 4.78 (m, 14-H), 4.84 (d, 1″-H), 5.20 (br dd, 3-H), 7.16 (m, C$_6$H$_5$), 7.26 (m, C$_6$H$_5$).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-8-methyl-11-(4-phenylbutyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**32c**)

Reaction of **30c** with aqueous difluoroacetic acid gave **32c** in 87% yield by a similar procedure to **11**.

32c: $[\alpha]_D^{22}$ −72° (*c* 0.75, CHCl$_3$); FAB-MS *m/z* 979 $(M+H)^+$ as $C_{51}H_{82}N_2O_{16}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.98 (d, 18-H), 1.10 (d, 6″-H), 1.15 (d, 6′-H), 1.17 (t, 3-OCOCH$_2$CH$_3$), 1.20 (t, 4″-OCOCH$_2$CH$_3$), 1.27 (d, 15-H), 1.42 (s, 3″-CH$_3$), 1.49 (m, Ph(CH$_2$)$_4$), 1.64 (quint, Ph(CH$_2$)$_4$), 1.70 (dd, 2″-Hax), 2.01 (s, 3″-OCOCH$_3$), 2.36 (dd, 16-H), 2.56 (s, 3′-N(CH$_3$)$_2$), 2.63 (t, Ph(CH$_2$)$_4$), 2.81 (dd, 2-H), 2.97 (dd, 16-H), 3.22 (m, 4′-H), 3.22 (m, 5′-H), 3.23 (d, 2″-Heq), 3.34 (dd, 2′-H), 3.60 (s, 4-OCH$_3$), 3.65 (dd, 4-H), 3.89 (br d, 5-H), 4.44 (d, 1′-H), 4.51 (dq, 5″-H), 4.59 (d, 4″-H), 4.78 (br dq, 14-H), 4.86 (d, 1″-H), 5.34 (br dd, 3-H), 7.19 (m, C$_6$H$_5$), 7.28 (m, C$_6$H$_5$), 9.65 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[2-*O*-acetyl-4-*O*-(3-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-4-methoxy-8-methyl-11-(5-phenylpentyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**28d**)

Reaction of **12** with 5-phenylpentylamine gave **28d** in 4.6% yield by a similar procedure to **16**.

28d: $[\alpha]_D^{26}$ −87° (*c* 0.50, CHCl$_3$); FAB-MS *m/z* 1123 $(M+H)^+$ as $C_{58}H_{94}N_2O_{19}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.92 (d, 18-H), 1.07 (d, 6″-H), 1.14 (t, 3-OCOCH$_2$CH$_3$), 1.19 (t, 4″-OCOCH$_2$CH$_3$), 1.20 (d, 6′-H), 1.26 (d, 15-H), 1.42 (s, 3″-CH$_3$), 1.54 (br dd, 16-H), 1.74 (dd, 2″-Hax), 1.82 (m, 16-H), 2.00 (s, 9-OCOCH$_3$), 2.02 (s, 3″-OCOCH$_3$), 2.05 (s, 2′-OCOCH$_3$), 2.44 (s, 3′-N(CH$_3$)$_2$), 2.60 (t, Ph(CH$_2$)$_5$), 2.83 (dd, 2-H), 3.14 (s, 17-OCH$_3$), 3.16 (m, 4′-H), 3.19 (d, 2″-Heq), 3.25 (m, 5′-H), 3.25 (s, 17-OCH$_3$), 3.45 (br d, 4-H), 3.55 (s, 4-OCH$_3$), 3.89 (br d, 5-H), 4.49 (dq, 5″-H), 4.57 (d, 4″-H), 4.68 (d, 1′-H), 4.76 (m, 9-H), 4.81 (d, 1″-H), 4.95 (m, 14-H), 4.98 (dd, 2′-H), 5.16 (m, 3-H), 7.17 (m, C$_6$H$_5$), 7.27 (m, C$_6$H$_5$).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyransyloxy]-6-(2,2-dimethoxyethyl)-9-hydroxy-4-methoxy-8-methyl-11-(5-phenylpentyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**30d**)

Reaction of **28d** with methanol gave **30d** in 43% yield by a similar procedure to **26**.

30d: $[\alpha]_D^{26}$ −66° (*c* 1.30, CHCl$_3$); FAB-MS *m/z* 1039 $(M+H)^+$ as $C_{54}H_{90}N_2O_{17}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.96 (d, 18-H), 1.09 (d, 6″-H), 1.13 (t, 3-OCOCH$_2$CH$_3$), 1.20 (t, 4″-OCOCH$_2$CH$_3$), 1.21 (d, 6′-H), 1.27 (d, 15-H), 1.42 (s, 3″-CH$_3$), 1.63 (m, Ph(CH$_2$)$_5$), 1.70 (dd, 2″-Hax), 1.89 (br dd, 16-H), 2.02 (s, 3″-OCOCH$_3$), 2.55 (s, 3′-N(CH$_3$)$_2$), 2.61 (m, Ph(CH$_2$)$_5$), 2.82 (dd, 2-H), 3.14 (s, 17-OCH$_3$), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.23 (d, 2″-Heq), 3.27 (s, 17-OCH$_3$), 3.41 (dd, 2′-H), 3.45 (br d, 9-H), 3.57 (dd, 4-H), 3.60 (s, 4-OCH$_3$), 3.90 (br d, 5-H), 4.48 (d, 1′-H), 4.50 (dd, 17-H), 4.53 (dq, 5″-H), 4.59 (d, 4″-H), 4.83 (m, 14-H), 4.86 (d, 1″-H), 5.22 (br dd, 3-H), 7.17 (m, C$_6$H$_5$), 7.28 (m, C$_6$H$_5$).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-

dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-8-methyl-11-(5-phenylpentyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**32d**)

Reaction of **30d** with aqueous difluoroacetic acid gave **32d** in 85% yield by a similar procedure to **11**.

32d: $[\alpha]_D^{25}$ −79° (*c* 0.51, $CHCl_3$); FAB-MS *m/z* 993 $(M+H)^+$ as $C_{52}H_{84}N_2O_{16}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.98 (d, 18-H), 1.10 (d, 6″-H), 1.15 (d, 6′-H), 1.17 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 15-H), 1.33 (quint, $Ph(CH_2)_5$), 1.42 (s, 3″-CH_3), 1.45 (m, 8-H), 1.48 (m, 7-H), 1.63 (m, $Ph(CH_2)_5$), 1.70 (dd, 2″-Hax), 2.00 (s, 3″-$OCOCH_3$), 2.56 (s, 3′-$N(CH_3)_2$), 2.81 (dd, 2-H), 2.96 (dd, 16-H), 3.23 (m, 4′-H), 3.23 (m, 5′-H), 3.23 (d, 2″-Heq), 3.35 (dd, 2′-H), 3.60 (s, 4-OCH_3), 3.65 (dd, 4-H), 3.89 (br d, 5-H), 4.79 (m, 14-H), 4.86 (d, 1″-H), 5.34 (br dd, 3-H), 7.18 (m, C_6H_5), 7.28 (m, C_6H_5), 9.66 (s, 17-H).

9,2′-Di-*O*-acetyl-10,11,12,13-tetrahydro-10,11,12,13-tetrahydroxymidecamycin A_1 18-Dimethylacetal (**36**)

Reaction of 9-*O*-acetylmidecamycin A_1 18-dimethylacetal (**34**) [8b] with acetic anhydride gave **35** quantitatively by a similar procedure to **15**.

Reaction of 9,2′-di-*O*-acetylmidecamycin A_1 18-dimethylacetal (**35**) with osmium tetraoxide gave **36** in 41% yield by a similar procedure to **13**.

36: $[\alpha]_D^{21}$ −74° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 1012 $(M+H)^+$ as $C_{47}H_{81}NO_{21}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.96 (d, 19-H), 1.12 (s, 3″-CH_3), 1.13 (t, 3-$OCOCH_2CH_3$), 1.14 (d, 6″-H), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 16-H), 1.27 (d, 6′-H), 1.43 (br dd, 7-H), 1.53 (br dd, 14-H), 1.63 (m, 6-H), 1.69 (br dd, 14-H), 1.72 (m, 17-H), 1.85 (dd, 2″-Hax), 2.02 (d, 2″-Heq), 2.05 (s, 9-$OCOCH_3$), 2.17 (s, 2′-$OCOCH_3$), 2.35 (m, 8-H), 2.42 (s, 3′-$N(CH_3)_2$), 2.49 (dd, 2-H), 2.73 (dd, 2-H), 2.73 (t, 3′-H), 3.18 (s, 18-OCH_3), 3.23 (s, 18-OCH_3), 3.34 (t, 4′-H), 3.57 (s, 4-OCH_3), 3.62 (br d, 12-H), 3.86 (br d, 5-H), 3.90 (dd, 10-H), 4.10 (m, 13-H), 4.38 (dq, 5″-H), 4.40 (dd, 18-H), 4.63 (d, 4″-H), 4.74 (d, 1′-H), 5.01 (dd, 2′-H), 5.02 (br d, 9-H), 5.07 (m, 15-H), 5.08 (d, 1″-H), 5.35 (br d, 3-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-Acetoxy-5-[2-*O*-acetyl-4-*O*-(2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-4-methoxy-8-methyl-11-(4-phenylbutyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**38**)

Reaction of **36** (714 mg) with lead tetraacetate gave crude **37** (680 mg) by a similar procedure to **12**.

Reaction of crude **37** (680 mg) with 4-phenylbutylamine gave **38** (63 mg, 8.4% *via* two steps based on **36**) by a similar procedure to **16**.

38: $[\alpha]_D^{21}$ −61° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 1067 $(M+H)^+$ as $C_{55}H_{90}N_2O_{18}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (d, 18-H), 1.13 (s, 3″-CH_3), 1.14 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.18 (t, 4″-O $COCH_2CH_3$), 1.25 (d, 15-H), 1.28 (d, 6′-H), 1.40 (br dd, 7-H), 1.44 (quint, $Ph(CH_2)_4$), 1.61 (m, $Ph(CH_2)_4$), 1.85 (dd, 2″-Hax), 1.99 (s, 9-$OCOCH_3$), 2.02 (d, 2″-Heq), 2.06 (s, 2′-$OCOCH_3$), 2.42 (s, 3′-$N(CH_3)_2$), 2.74 (t, 3′-H), 2.83 (dd, 2-H), 3.14 (s, 17-OCH_3), 3.26 (s, 17-OCH_3), 3.34 (m, 4′-H), 3.36 (m, 5′-H), 3.47 (br d, 4-H), 3.55 (s, 4-OCH_3), 3.91 (br d, 5-H), 4.39 (dq, 5″-H), 4.54 (dd, 17-H), 4.63 (d, 4″-H), 4.72 (d, 1′-H), 4.77 (m, 9-H), 4.92 (br q, 14-H), 5.03 (dd, 2′-H), 5.08 (d, 1″-H), 5.17 (m, 3-H), 7.17 (m, C_6H_5), 7.27 (m, C_6H_5).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(2,6-Dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-9-hydroxy-4-methoxy-8-methyl-11-(4-phenylbutyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**39**)

Reaction of **38** with methanol gave **39** in 88% yield by a similar procedure to **26**.

39: $[\alpha]_D^{21}$ −58° (*c* 0.56, $CHCl_3$); FAB-MS *m/z* 983 $(M+H)^+$ as $C_{51}H_{86}N_2O_{16}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.97 (d, 18-H), 1.06 (br dd, 7-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.13 (s, 3″-CH_3), 1.14 (d, 6″-H), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 15-H), 1.28 (d, 6′-H), 1.44 (br dd, 7-H), 1.48 (m, $Ph(CH_2)_4$), 1.64 (m, $Ph(CH_2)_4$), 1.84 (dd, 2″-Hax), 2.02 (d, 2″-Heq), 2.51 (s, 3′-$N(CH_3)_2$), 2.60 (dd, 2-H), 2.63 (t, $Ph(CH_2)_4$), 2.80 (dd, 2-H), 3.16 (s, 17-OCH_3), 3.28 (s, 17-OCH_3), 3.54 (br d, 4-H), 3.56 (dd, 2′-H), 3.58 (s, 4-OCH_3), 3.93 (br d, 5-H), 4.45 (d, 1′-H), 4.47 (dq, 5″-H), 4.63 (d, 4″-H), 4.85 (m, 14-H), 5.09 (d, 1″-H), 5.24 (br dd, 3-H), 7.19 (m, C_6H_5), 7.28 (m, C_6H_5).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(2,6-Dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-8-methyl-11-(4-phenylbutyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**40**) and (−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-(3,6-Dideoxy-3-dimethylamino-β-D-glucopyranosyloxy)-6-formylmethyl-9-hydroxy-4-methoxy-8-methyl-11-(4-phenylbutyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**41**)

Reaction of **39** with aqueous difluoroacetic acid gave **40** in 37% yield and **41** in 43% yield by a similar procedure to **11**.

40: $[\alpha]_D^{21}$ −68° (*c* 0.40, $CHCl_3$); FAB-MS *m/z* 937 $(M+H)^+$ as $C_{49}H_{80}N_2O_{15}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ:

1.00 (d, 18-H), 1.13 (s, 3″-CH$_3$), 1.16 (d, 6″-H), 1.16 (t, 3-OCOCH$_2$CH$_3$), 1.19 (t, 4″-OCOCH$_2$CH$_3$), 1.21 (d, 6′-H), 1.26 (d, 15-H), 1.48 (m, Ph(CH$_2$)$_4$), 1.64 (quint, Ph(CH$_2$)$_4$), 1.79 (m, 13-H), 1.84 (dd, 2″-Hax), 2.02 (d, 2″-Heq), 2.05 (m, 6-H), 2.3 8(br d, 16-H), 2.52 (s, 3′-N(CH$_3$)$_2$), 2.64 (t, Ph(CH$_2$)$_4$), 2.79 (dd, 2-H), 2.94 (dd, 16-H), 3.28 (m, 4′-H), 3.30 (m, 5′-H), 3.54 (dd, 2′-H), 3.57 (s, 4-OCH$_3$), 3.64 (dd, 4-H), 3.90 (br d, 5-H), 4.42 (d, 1′-H), 4.48 (dq, 5″-H), 4.63 (d, 4″-H), 4.80 (m, 14-H), 5.08 (d, 1″-H), 5.36 (br dd, 3-H), 7.18 (m, C$_6$H$_5$), 7.28 (m, C$_6$H$_5$), 9.66 (s, 17-H).

41: $[\alpha]_{\mathrm{D}}^{23}$ $-35°$ (*c* 0.44, CHCl$_3$); FAB-MS *m/z* 737 (M+H)$^+$ as C$_{39}$H$_{64}$N$_2$O$_{11}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 1.00 (d, 18-H), 1.06 (br t, 7-H), 1.17 (t, 3-OCOCH$_2$CH$_3$), 1.25 (d, 6′-H), 1.27 (d, 15-H), 1.49 (m, Ph(CH$_2$)$_4$), 1.64 (quint, Ph(CH$_2$)$_4$), 1.68 (m, 13-H), 1.79 (m, 13-H), 2.05 (br t, 6-H), 2.35 (t, 3′-H), 2.51 (s, 3′-N(CH$_3$)$_2$), 2.63 (t, Ph(CH$_2$)$_4$), 2.80 (dd, 2-H), 2.99 (dd, 16-H), 3.04 (t, 4′-H), 3.30 (dq, 5′-H), 3.52 (dd, 2′-H), 3.58 (s, 4-OCH$_3$), 3.65 (dd, 4-H), 3.92 (br d, 5-H), 4.44 (d, 1′-H), 4.81 (m, 14-H), 5.37 (br dd, 3-H), 7.19 (m, C$_6$H$_5$), 7.29 (m, C$_6$H$_5$), 9.68 (s, 17-H).

2′-*O*-Acetyl-9-*O*-*tert*-butyldimethylsilyl-10,11,12,13-tetrahydro-10,11,12,13-tetrahydroxyrokitamycin 18-dimethylacetal (**45**)

To a mixture of 2′-*O*-Acetyl-9-*O*-*tert*-butyldimethylsilylrokitamycin 18-dimethylacetal (**44**) [22b, 32] (1.08 g) in acetone (27 ml) and water (4.2 ml) were added *N*-methylmorpholine-*N*-oxide (0.49 ml) and 4% aqueous osmium tetraoxide (1.0 ml), and the mixture was stirred at room temperature for 24 hours. After the reaction mixture was concentrated under reduced pressure, the concentrate was extracted with ethyl acetate (40 ml), and then the organic layer was washed with saturated brine (30 ml). The organic layer was dried over anhydrous sodium sulfate and filtered. Then, the filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash silica gel column chromatography (chloroform/methanol (40 : 1~30 : 1)) to obtain **45** (394 mg, 34%) as a colorless solid.

45: $[\alpha]_{\mathrm{D}}^{22}$ $-81°$ (*c* 1.0, CHCl$_3$); FAB-MS *m/z* 1098 (M+H)$^+$ as C$_{52}$H$_{95}$NO$_{21}$Si; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.04 (s, 9-OSi(CH$_3$)$_2{}^t$Bu), 0.07 (s, 9-OSi(CH$_3$)$_2{}^t$Bu), 0.93 (d, 19-H), 0.93 (s, 9-OSi(CH$_3$)$_2{}^t$Bu), 0.98 (t, 4″-OCO(CH$_2$)$_2$CH$_3$), 1.07 (d, 6″-H), 1.16 (t, 3″-OCOCH$_2$CH$_3$), 1.22 (d, 6′-H), 1.29 (d, 16-H), 1.42 (s, 3″-CH$_3$), 1.55 (br dd, 14-H), 1.69 (dd, 2″-Hax), 1.70 (sext, 4″-OCO(CH$_2$)$_2$CH$_3$), 2.02 (s, 2′-OCOCH$_3$), 2.29, 2.32 (each q, 3″-OCOCH$_2$CH$_3$), 2.38 (t, 4″-OCO(CH$_2$)$_2$CH$_3$), 2.43 (s, 3′-N(CH$_3$)$_2$), 2.59 (t, 3′-H), 3.15 (t, 4′-H), 3.21 (d, 2″-Heq), 3.31 (s, 18-OCH$_3$), 3.35 (s, 18-OCH$_3$), 3.48 (s, 4-OCH$_3$), 3.63 (m, 12-H), 3.89 (br d, 5-H), 4.49 (dq, 5″-H), 4.58 (d, 4″-H), 4.82 (d, 1″-H), 4.97 (dd, 2′-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[2-*O*-Acetyl-4-*O*-(4-*O*-butyryl-2,6-dideoxy-3-*C*-methyl-3-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-9-*O*-*tert*-butyldimethylsilyl-6-(2,2-dimethoxyethyl)-3-hydroxy-4-methoxy-8-methyl-11-(4-phenylbutyl)-11-aza-pentadecan-14-olide (**47**)

Reaction of **45** (389 mg) with lead tetraacetate gave crude **46** (370 mg) by a similar procedure to **12**.

Reaction of crude **46** (370 mg) with 4-phenylbutylamine gave **47** (40.0 mg, 9.8% *via* two steps based on **45**) by a similar procedure to **16**.

47: $[\alpha]_{\mathrm{D}}^{21}$ $-76°$ (*c* 1.0, CHCl$_3$); FAB-MS *m/z* 1153 (M+H)$^+$ as C$_{60}$H$_{104}$N$_2$O$_{17}$Si; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.03 (s, 9-OSi(CH$_3$)$_2{}^t$Bu), 0.87 (s, 9-OSi(CH$_3$)$_2{}^t$Bu), 0.90 (d, 18-H), 0.98 (t, 4″-OCO(CH$_2$)$_2$CH$_3$), 1.07 (d, 6″-H), 1.15 (t, 3″-OCOCH$_2$CH$_3$), 1.20 (d, 6′-H), 1.22 (d, 15-H), 1.42 (s, 3″-CH$_3$), 1.55 (m, Ph(CH$_2$)$_4$), 1.67 (dd, 2″-Hax), 1.70 (sext, 4″-OCO(CH$_2$)$_2$CH$_3$), 2.04 (s, 2′-OCOCH$_3$), 2.29, 2.32 (each q, 3″-OCOCH$_2$CH$_3$), 2.38 (t, 4″-OCO(CH$_2$)$_2$CH$_3$), 2.42 (s, 3′-N(CH$_3$)$_2$), 3.01 (br d, 4-H), 3.14 (t, 4′-H), 3.20 (d, 2″-Heq), 3.32 (s, 17-OCH$_3$), 3.49 (s, 4-OCH$_3$), 3.96 (br d, 5-H), 4.48 (dq, 5″-H), 4.49 (d, 1′-H), 4.57 (d, 4″-H), 4.81 (d, 1″-H), 4.97 (dd, 2′-H), 5.12 (m, 14-H), 7.17 (m, Ph), 7.28 (m, Ph).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-*O*-*tert*-Butyldimethylsilyl-5-[4-*O*-(4-*O*-butyryl-2,6-dideoxy-3-*C*-methyl-3-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-3-hydroxy-4-methoxy-8-methyl-11-(4-phenylbutyl)-11-aza-pentadecan-14-olide (**48**)

Reaction of **47** with methanol gave **48** in 74% yield by a similar procedure to **26**.

48: $[\alpha]_{\mathrm{D}}^{22}$ $-70°$ (*c* 0.85, CHCl$_3$); FAB-MS *m/z* 1111 (M+H)$^+$ as C$_{58}$H$_{102}$N$_2$O$_{16}$Si; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.06 (s, 9-OSi(CH$_3$)$_2{}^t$Bu), 0.89 (s, 9-OSi(CH$_3$)$_2{}^t$Bu), 0.90 (d, 18-H), 0.99 (t, 4″-OCO(CH$_2$)$_2$CH$_3$), 1.09 (d, 6″-H), 1.14 (t, 3″-OCOCH$_2$CH$_3$), 1.22 (d, 15-H), 1.22 (d, 6′-H), 1.42 (s, 3″-CH$_3$), 1.57 (m, Ph(CH$_2$)$_4$), 1.70 (dd, 2″-Hax), 1.70 (sext, 4″-OCO(CH$_2$)$_2$CH$_3$), 2.30, 2.32 (each q, 3″-OCOCH$_2$CH$_3$), 2.39 (t, 4″-OCO(CH$_2$)$_2$CH$_3$), 2.53 (s, 3′-N(CH$_3$)$_2$), 2.61 (t, Ph(CH$_2$)$_4$), 3.10 (m, 4-H), 3.12 (d, 2″-Heq), 3.32 (s, 17-OCH$_3$), 3.33 (s, 17-OCH$_3$), 3.49 (dd, 2′-H), 3.61 (s, 4-OCH$_3$), 3.92 (m, 5-H), 4.34 (d, 1′-H), 4.47 (t, 17-H), 4.55 (m, 5″-H), 4.59 (d, 4″-H), 4.83 (d, 1″-H), 5.19 (m, 14-H), 7.17 (m, Ph), 7.28 (m, Ph).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-9-*O*-*tert*-Butyldimethylsilyl-

5-[4-*O*-(4-*O*-butyryl-2,6-dideoxy-3-*C*-methyl-3-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-formylmethyl-3-hydroxy-4-methoxy-8-methyl-11-(4-phenylbutyl)-11-aza-pentadecan-14-olide (**49**)

Reaction of **48** with aqueous difluoroacetic acid gave **49** in 98% yield by a similar procedure to **11**.

49: $[\alpha]_D^{20}$ −61° (*c* 0.60, $CHCl_3$); FAB-MS *m/z* 1065 $(M+H)^+$ as $C_{56}H_{96}N_2O_{15}Si$; ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 0.02 (s, 9-$OSi(CH_3)_2{}^tBu$), 0.03 (s, 9-$OSi(CH_3)_2{}^tBu$), 0.87 (s, 9-$OSi(CH_3)_2{}^tBu$), 0.93 (d, 18-H), 0.99 (t, 4″-$OCO(CH_2)_2CH_3$), 1.09 (d, 6″-H), 1.14 (t, 3″-$OCOCH_2CH_3$), 1.19 (d,6′-H), 1.22 (d, 15-H), 1.42 (s, 3″-CH_3), 1.57 (m, $Ph(CH_2)_4$), 1.65 (dd, 2″-Hax), 1.70 (sext, 4″-$OCO(CH_2)_2CH_3$), 2.39 (t, 4″-$OCO(CH_2)_2CH_3$), 2.53 (s, 3′-$N(CH_3)_2$), 2.62 (t, $Ph(CH_2)_4$), 2.74 (dd, 2-H), 2.97 (dd, 16-H), 3.23 (d, 2″-Heq), 3.43 (dd, 2′-H), 3.59 (s, 4-OCH_3), 3.81 (br d, 5-H), 4.17 (m, 3-H), 4.34 (d, 1′-H), 4.53 (dq, 5″-H), 4.59 (d, 4″-H), 4.84 (d, 1″-H), 5.14 (m, 14-H), 7.18 (m, Ph), 7.28 (m, Ph), 9.70 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(4-*O*-Butyryl-2,6-dideoxy-3-*C*-methyl-3-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-formylmethyl-3,9-dihydroxy-4-methoxy-8-methyl-11-(4-phenylbutyl)-11-aza-pentadecan-14-olide (**50**)

To a solution of **49** (13.0 mg) in tetrahydrofuran (0.5 ml) and acetic acid (0.5 ml) was added 1 M tetrabutylammonium fluoride tetrahydrofuran solution (60 *μ*l), and the mixture was stirred at 60°C for 48 hours. The reaction mixture was slowly poured into saturated aqueous sodium hydrogencarbonate solution (10 ml), and extracted with ethyl acetate (25 ml). The organic layer was washed successively with water (15 ml), saturated aqueous sodium hydrogencarbonate solution (15 ml) and saturated brine (15 ml), dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by preparative TLC (chloroform/methanol/aqueous ammonia (20 : 1 : 0.1)) to obtain **50** (6.3 mg, 54%).

50: $[\alpha]_D^{22}$ −95° (*c* 0.38, $CHCl_3$); FAB-MS *m/z* 951 $(M+H)^+$ as $C_{50}H_{82}N_2O_{15}$; ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 0.91 (d, 18-H), 0.98 (t, 4″-$OCO(CH_2)_2CH_3$), 1.09 (d, 6″-H), 1.13 (t, 3″-$OCOCH_2CH_3$), 1.17 (d, 6′-H), 1.26 (d, 15-H), 1.42 (s, 3″-CH_3), 1.46 (m, $Ph(CH_2)_4$), 1.63 (m, $Ph(CH_2)_4$), 1.69 (sext, 4″-$OCO(CH_2)_2CH_3$), 2.38 (t, 4″-$OCO(CH_2)_2CH_3$), 2.54 (s, 3′-$N(CH_3)_2$), 2.62 (t, $Ph(CH_2)_4$), 2.80 (dd, 2-H), 3.02 (dd, 16-H), 3.19 (m, 4′-H), 3.19 (m, 5′-H), 3.23 (d, 2″-Heq), 3.35 (dd, 2′-H), 3.59 (s, 4-OCH_3), 3.82 (br d, 5-H), 4.28 (br dd, 3-H), 4.34 (d, 1′-H), 4.52 (dq, 5″-H), 4.59 (d, 4″-H), 4.85 (d, 1″-H), 4.94 (m, 14-H), 7.18 (m, Ph), 7.28 (m, Ph), 9.75 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-8-methyl-3-propionyloxy-11-(3-(pyridin-4-yl)propyl)-11-aza-pentadecan-14-olide (**51**)

To a solution of **22** (30.0 mg) in methanol (0.60 ml) were added acetic acid (9.6 *μ*l) and 3-(pyridin-4-yl)propanal (6.3 *μ*l) under ice cooling, and the mixture was stirred for 30 minutes. To the resulting solution was added sodium cyanoborohydride (6.3 mg), and the mixture was stirred for 12 hours with gradually warming to room temperature. Ethyl acetate (3.0 ml) and saturated aqueous sodium hydrogencarbonate solutiom (3.0 ml) were added, and the mixture was stirred at room temperature for 30 minutes. The organic layer was separated, and then the aqueous layer was twice extracted with ethyl acetate (5.0 ml). The organic layers were combined and washed successively with saturated aqueous sodium hydrogencarbonate solution (10 ml) and saturated brine (10 ml), dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by preparative TLC (chloroform/methanol/aqueous ammonia (20 : 1 : 0.1)) to obtain 18-dimethylacetal of **51** (30.0 mg, 88%).

18-Dimethylacetal of **51**: $[\alpha]_D^{22}$ −70° (*c* 0.50, $CHCl_3$); FAB-MS *m/z* 1012 $(M+H)^+$ as $C_{51}H_{85}N_3O_{17}$; ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 0.94 (d, 18-H), 1.07 (d, 6″-H), 1.11 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.24 (d, 15-H), 1.40 (s, 3″-CH_3), 1.58 (m, 8-H), 1.58 (m, 16-H), 1.68 (dd, 2″-Hax), 2.00 (s, 3″-$OCOCH_3$), 2.53 (s, 3′-$N(CH_3)_2$), 2.81 (dd, 2-H), 3.10 (s, 17-OCH_3), 3.21 (d, 2″-Heq), 3.23 (m, 4′-H), 3.23 (m, 5′-H), 3.24 (s, 17-OCH_3), 3.38 (dd, 2′-H), 3.56 (br d, 4-H), 3.58 (s, 4-OCH_3), 3.88 (br d, 5-H), 4.47 (d, 1′-H), 4.49 (dq, 5″-H), 4.57 (d, 4″-H), 4.81 (ddq, 14-H), 4.84 (d, 1″-H), 5.19 (br dd, 3-H), 7.10 (dd, pyridine), 8.48 (dd, pyridine).

Reaction of 18-dimethylacetal of **51** with aqueous difluoroacetic acid gave **51** in 84% yield by a similar procedure to **11**.

51: $[\alpha]_D^{20}$ −84° (*c* 0.50, $CHCl_3$); FAB-MS *m/z* 966 $(M+H)^+$ as $C_{49}H_{79}N_3O_{16}$; ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 0.95 (d, 18-H), 1.07 (d, 6″-H), 1.13 (d, 6′-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.24 (d, 15-H), 1.40 (s, 3″-CH_3), 1.43 (m, 8-H), 1.68 (dd, 2″-Hax), 1.98 (s, 3″-$OCOCH_3$), 2.54 (s, 3′-$N(CH_3)_2$), 2.79 (dd, 2-H), 2.95 (dd, 16-H), 3.21 (d, 2″-Heq), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.31 (dd, 2′-H), 3.58 (s, 4-OCH_3), 3.62 (dd, 4-H), 3.87 (br d, 5-H), 4.42 (d, 1′-H), 4.48 (dq, 5″-H), 4.57 (d, 4″-H), 4.77 (ddq, 14-H), 4.84 (d, 1″-H), 5.31 (br dd, 3-H), 7.10 (dd, pyridine), 8.48 (dd, pyridine), 9.63 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-8-methyl-3-propionyloxy-11-(3-(quinolin-4-yl)propyl)-11-aza-pentadecan-14-olide (**52**)

Reaction of **12** with 3-(quinolin-4-yl)propylamine gave 9,2′-diacetate 18-dimethylacetal of **52** in 9.4% yield by a similar procedure to **16**.

9,2′-Diacetate 18-dimethylacetal of **52**: $[\alpha]_{\mathrm{D}}^{26}$ −79° (*c* 1.0, CHCl$_3$); FAB-MS *m/z* 1146 $(\mathrm{M+H})^+$ as $\mathrm{C_{59}H_{91}N_3O_{19}}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.93 (d, 18-H), 1.06 (d, 6″-H), 1.13 (t, 3-OCOCH$_2$CH$_3$), 1.18 (t, 4″-OCOCH$_2$CH$_3$), 1.22 (d, 6′-H), 1.23 (d, 15-H), 1.40 (s, 3″-CH$_3$), 1.54 (m, 16-H), 1.67 (dd, 2″-Hax), 1.86 (m, quinoline-(CH$_2$)$_3$), 1.96 (s, 9-OCOCH$_3$), 2.01 (s, 3″-OCOCH$_3$), 2.03 (s, 2′-OCOCH$_3$), 2.43 (s, 3′-N(CH$_3$)$_2$), 2.84 (dd, 2-H), 3.07 (t, quinoline-(CH$_2$)$_3$), 3.12 (s, 17-OCH$_3$), 3.19 (d, 2″-Heq), 3.24 (s, 17-OCH$_3$), 3.48 (dd, 4-H), 3.54 (s, 4-OCH$_3$), 3.89 (br d, 5-H), 4.47 (dq, 5″-H), 4.56 (d, 4″-H), 4.67 (d, 1′-H), 4.80 (d, 1″-H), 4.84 (m, 9-H), 4.93 (m, 14-H), 4.97 (dd, 2′-H), 5.17 (m, 3-H), 7.25 (d, quinoline), 7.56 (ddd, quinoline), 7.70 (ddd, quinoline), 8.06 (br d, quinoline), 8.09 (br d, quinoline), 8.79 (d, quinoline).

9,2′-Diacetate 18-dimethylacetal of **52** (135 mg) was dissolved in methanol (5.4 ml), and the reaction mixture was stirred at 45°C for 44 hours, and then concentrated under reduced pressure. The resulting residue was purified by preparative TLC (chloroform/methanol (10 : 1)) to obtain 18-dimethyacetal of **52** (58.0 mg, 46%).

18-Dimethyacetal of **52**: $[\alpha]_{\mathrm{D}}^{26}$ −64° (*c* 1.30, CHCl$_3$); FAB-MS *m/z* 1062 $(\mathrm{M+H})^+$ as $\mathrm{C_{55}H_{87}N_3O_{17}}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.96 (d, 18-H), 1.09 (d, 6″-H), 1.13 (t, 3-OCOCH$_2$CH$_3$), 1.19 (t, 4″-OCOCH$_2$CH$_3$), 1.21 (d, 6′-H), 1.25 (d, 15-H), 1.42 (s, 3″-CH$_3$), 1.69 (dd, 2″-Hax), 1.91 (m, 16-H), 1.94 (quint, quinoline-(CH$_2$)$_3$), 2.01 (s, 3″-OCOCH$_3$), 2.55 (s, 3′-N(CH$_3$)$_2$), 2.59 (dd, 2-H), 2.83 (dd, 2-H), 3.09 (t, quinoline-(CH$_2$)$_3$), 3.13 (s, 17-OCH$_3$), 3.22 (d, 2″-Heq), 3.23 (m, 4′-H), 3.23 (m, 5′-H), 3.26 (s, 17-OCH$_3$), 3.40 (dd, 2′-H), 3.59 (dd, 4-H), 3.60 (s, 4-OCH$_3$), 3.90 (br d, 5-H), 4.48 (d, 1′-H), 4.52 (dq, 5″-H), 4.59 (d, 4″-H), 4.83 (m, 14-H), 4.86 (d, 1″-H), 5.24 (br dd, 3-H), 7.25 (d, quinoline), 7.58 (ddd, quinoline), 7.71 (ddd, quinoline), 8.03 (br d, quinoline), 8.12 (br d, quinoline), 8.81 (d, quinoline).

Reaction of 18-dimethylacetal of **52** with aqueous difluoroacetic acid gave **52** in 86% yield by a similar procedure to **11**.

52: $[\alpha]_{\mathrm{D}}^{26}$ −71° (*c* 0.58, CHCl$_3$); FAB-MS *m/z* 1016 $(\mathrm{M+H})^+$ as $\mathrm{C_{53}H_{81}N_3O_{16}}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.98 (d, 18-H), 1.09 (d, 6″-H), 1.15 (d, 6′-H), 1.16 (t, 3-OCOCH$_2$CH$_3$), 1.19 (t, 4″-OCOCH$_2$CH$_3$), 1.25 (d, 15-H), 1.42 (s, 3″-CH$_3$), 1.48 (br s, 8-H), 1.70 (dd, 2″-Hax), 1.94 (m, quinoline-(CH$_2$)$_3$), 2.00 (s, 3″-OCOCH$_3$), 2.56 (s, 3′-N(CH$_3$)$_2$), 2.82 (dd, 2-H), 2.98 (dd, 16-H), 3.01 (dt, quinoline-(CH$_2$)$_3$), 3.22 (m, 4′-H), 3.22 (m, 5′-H), 3.22 (d, 2″-Heq), 3.34 (dd, 2′-H), 3.60 (s, 4-OCH$_3$), 3.65 (dd, 4-H), 3.89 (br d, 5-H), 4.45 (d, 1′-H), 4.51 (dq, 5″-H), 4.59 (d, 4″-H), 4.79 (m, 14-H), 4.86 (d, 1″-H), 5.34 (br dd, 3-H), 7.25 (d, quinoline), 7.57 (ddd, quinoline), 7.71 (ddd, quinoline), 8.03 (dd, quinoline), 8.12 (dd, quinoline), 8.81 (d, quinoline), 9.65 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-*α*-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-*β*-D-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-11-(3-(6-methoxyquinolin-4-yl)propyl)-8-methyl-3-propionyloxy-11-aza-pentadecan-14-olide (**53**)

Reaction of **22** with 3-(6-methoxyquinolin-4-yl)propanal gave 18-dimethylacetal of **53** in 90% yield by a similar procedure to 18-dimethylacetal of **51**.

18-Dimethylacetal of **53**: $[\alpha]_{\mathrm{D}}^{21}$ −60° (*c* 0.50, CHCl$_3$); FAB-MS *m/z* 1092 $(\mathrm{M+H})^+$ as $\mathrm{C_{56}H_{89}N_3O_{18}}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.94 (d, 18-H), 1.07 (d, 6″-H), 1.11 (t, 3-OCOCH$_2$CH$_3$), 1.18 (t, 4″-OCOCH$_2$CH$_3$), 1.19 (d, 6′-H), 1.23 (d, 15-H), 1.40 (s, 3″-CH$_3$), 1.42 (br dd, 7-H), 1.59 (m, 8-H), 1.68 (dd, 2″-Hax), 1.94 (m, quinoline-(CH$_2$)$_3$), 2.00 (s, 3″-OCOCH$_3$), 2.53 (s, 3′-N(CH$_3$)$_2$), 2.81 (dd, 2-H), 3.04 (m, quinoline-(CH$_2$)$_3$), 3.10 (s, 17-OCH$_3$), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.21 (d, 2″-Heq), 3.24 (s, 17-OCH$_3$), 3.38 (dd, 2′-H), 3.57 (br d, 4-H), 3.59 (s, 4-OCH$_3$), 3.89 (br d, 5-H), 3.94 (s, quinoline-OCH$_3$), 4.48 (d, 1′-H), 4.50 (dq, 5″-H), 4.57 (d, 4″-H), 4.80 (ddq, 14-H), 4.84 (d, 1″-H), 5.19 (br dd, 3-H), 7.18 (d, quinoline), 7.21 (d, quinoline), 7.35 (dd, quinoline), 8.00 (d, quinoline), 8.65 (d, quinoline).

Reaction of 18-dimethylacetal of **53** with aqueous difluoroacetic acid gave **53** in 76% yield by a similar procedure to **11**.

53: $[\alpha]_{\mathrm{D}}^{18}$ −76° (*c* 0.50, CHCl$_3$); FAB-MS *m/z* 1046 $(\mathrm{M+H})^+$ as $\mathrm{C_{54}H_{83}N_3O_{17}}$; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.95 (d, 18-H), 1.08 (d, 6″-H), 1.13 (d, 6′-H), 1.15 (t, 3-OCOCH$_2$CH$_3$), 1.18 (t, 4″-OCOCH$_2$CH$_3$), 1.24 (d, 15-H), 1.40 (s, 3″-CH$_3$), 1.44 (m, 8-H), 1.69 (dd, 2″-Hax), 1.95 (m, quinoline-(CH$_2$)$_3$), 1.99 (s, 3″-OCOCH$_3$), 2.54 (s, 3′-N(CH$_3$)$_2$), 2.80 (dd, 2-H), 2.96 (dd, 16-H), 3.03 (m, quinoline-(CH$_2$)$_3$), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.21 (d, 2″-Heq), 3.31 (dd, 2′-H), 3.51 (br d, 9-H), 3.58 (s, 4-OCH$_3$), 3.63 (dd, 4-H), 3.87 (br d, 5-H), 3.94 (s, quinoline-OCH$_3$), 4.43 (d, 1′-H), 4.48 (dq, 5″-H), 4.57 (d, 4″-H), 4.77 (ddq, 14-H), 4.85 (d, 1″-H), 5.31 (br dd, 3-H), 7.18 (d, quinoline), 7.21 (d, quinoline), 7.35 (dd, quinoline), 8.00 (d, quinoline), 8.65 (d, quinoline), 9.63 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-formylmethyl-4-methoxy-8-methyl-11-(*N*-methyl-*N*-(3-phenylpropyl)amino)-3-propionyloxy-11-aza-pentadecan-14-olide (**54**)

Reaction of **12** with 1-methyl-1-(3-phenylpropyl)hydrazine gave 2′-acetate 18-dimethylacetal of **54** in 8.6% yield by a similar procedure to **16**. In the course of this macrocyclization reaction, the acetoxy group at the C-9 position was unexpectedly reduced.

2′-Acetate 18-dimethylacetal of **54**: $[\alpha]_D^{25}$ −71° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1066 $(M+H)^+$ as $C_{55}H_{91}N_3O_{17}$; ^1H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (d, 18-H), 1.07 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.24 (d, 15-H), 1.42 (s, 3″-CH_3), 1.46 (br dd, 16-H), 1.67 (dd, 2″-Hax), 1.81 (m, $Ph(CH_2)_3$), 2.02 (s, 3″-$OCOCH_3$), 2.04 (s, 2′-$OCOCH_3$), 2.25 (s, 11-NCH_3), 2.44 (s, 3′-$N(CH_3)_2$), 3.12 (s, 17-OCH_3), 3.19 (d, 2″-Heq), 3.25 (s, 17-OCH_3), 3.27 (br d, 4-H), 3.55 (s, 4-OCH_3), 3.81 (br s, 5-H), 4.44 (dd, 17-H), 4.49 (dq, 5″-H), 4.57 (d, 4″-H), 4.66 (d, 1′-H), 4.81 (d, 1″-H), 4.88 (m,14-H), 4.96 (dd, 2′-H), 5.36 (br dd, 3-H), 7.19 (m, C_6H_5), 7.27 (m, C_6H_5).

Reaction of 2′-acetate 18-dimethylacetal of **54** with methanol gave 18-dimethylacetal of **54** in 69% yield by a similar procedure to **26**.

18-Dimethylacetal of **54**: $[\alpha]_D^{26}$ −58° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1024 $(M+H)^+$ as $C_{53}H_{89}N_3O_{16}$; ^1H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (d, 18-H), 1.09 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.23 (d, 6′-H), 1.24 (d, 15-H), 1.42 (s, 3″-CH_3), 1.59 (m, 7-H), 1.69 (dd, 2″-Hax), 1.80 (quint, $Ph(CH_2)_3$), 2.03 (s, 3″-$OCOCH_3$), 2.25 (s, 11-NCH_3), 2.55 (s, 3′-$N(CH_3)_2$), 3.18 (s, 17-OCH_3), 3.22 (d, 2″-Heq), 3.27 (s, 17-OCH_3), 3.47 (dd, 2′-H), 3.58 (s, 4-OCH_3), 3.83 (br d, 5-H), 4.43 (d, 1′-H), 4.56 (m, 5″-H), 4.57 (d, 4″-H), 4.85 (d, 1″-H), 4.94 (m, 14-H), 5.40 (m, 3-H), 7.19 (m, C_6H_5), 7.27 (m, C_6H_5).

Reaction of 18-dimethylacetal of **54** with aqueous difluoroacetic acid gave **54** in 76% yield by a similar procedure to **11**.

54: $[\alpha]_D^{25}$ −70° (*c* 0.61, $CHCl_3$); FAB-MS *m*/*z* 978 $(M+H)^+$ as $C_{51}H_{83}N_3O_{15}$; ^1H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (d, 18-H), 1.09 (d, 6″-H), 1.15 (d, 6′-H), 1.18 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 15-H), 1.31 (m, 8-H), 1.42 (s, 3″-CH_3), 1.69 (dd, 2″-Hax), 1.80 (quint, $Ph(CH_2)_3$), 2.02 (s, 3″-$OCOCH_3$), 2.22 (br d, 16-H), 2.26 (s, 11-NCH_3), 2.55 (s, 3′-$N(CH_3)_2$), 3.02 (dd, 17-H), 3.22 (m, 4′-H), 3.22 (d, 2″-Heq), 3.23 (m, 5′-H), 3.39 (br d, 4-H), 3.43 (dd, 2′-H), 3.57 (s, 4-OCH_3), 3.87 (br d, 5-H), 4.46 (d, 1′-H), 4.54 (dq, 5″-H), 4.59 (d, 4″-H), 4.85 (d, 1″-H), 4.90 (m, 14-H), 5.54 (br dd, 3-H), 7.19 (m, C_6H_5), 7.28 (m, C_6H_5), 9.63 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-8-methyl-11-(*trans*-3-phenyl-2-propenyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**55**)

Reaction of **22** with *trans*-cinnamaldehyde gave 18-dimethylacetal of **55** in 71% yield by a similar procedure to 18-dimethylacetal of **51**.

18-Dimethylacetal of **55**: $[\alpha]_D^{21}$ −66° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 1009 $(M+H)^+$ as $C_{52}H_{84}N_2O_{17}$; ^1H-NMR (300 MHz, $CDCl_3$) δ: 0.94 (d, 18-H), 1.07 (d, 6″-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.25 (d, 15-H), 1.40 (s, 3″-CH_3), 1.44 (br dd, 7-H), 1.56 (m, 8-H), 1.68 (dd, 2″-Hax), 2.00 (s, 3″-$OCOCH_3$), 2.53 (s, 3′-$N(CH_3)_2$), 2.81 (dd, 2-H), 3.12 (s, 17-OCH_3), 3.20 (m, 4′-H), 3.20 (m, 5′-H), 3.21 (d, 2″-Heq), 3.25 (s, 17-OCH_3), 3.40 (dd, 2′-H), 3.59 (s, 4-OCH_3), 3.60 (br d, 4-H), 3.88 (br d, 5-H), 4.47 (d, 1′-H), 4.50 (dq, 5″-H), 4.57 (d, 4″-H), 4.82 (ddq, 14-H), 4.84 (d, 1″-H), 5.23 (br dd, 3-H), 6.20 (dt, PhCH=CH), 6.50 (d, PhCH=CH), 7.26 (m, C_6H_5).

Reaction of 18-dimethylacetal of **55** with aqueous difluoroacetic acid gave **55** in 87% yield by a similar procedure to **11**.

55: $[\alpha]_D^{20}$ −78° (*c* 0.40, $CHCl_3$); FAB-MS *m*/*z* 963 $(M+H)^+$ as $C_{50}H_{78}N_2O_{16}$; ^1H-NMR (300 MHz, $CDCl_3$) δ: 0.96 (d, 18-H), 1.08 (d, 6″-H), 1.13 (d, 6′-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 15-H), 1.40 (s, 3″-CH_3), 1.44 (m, 8-H), 1.68 (dd, 2″-Hax), 1.99 (s, 3″-$OCOCH_3$), 2.54 (s, 3′-$N(CH_3)_2$), 2.80 (dd, 2-H), 2.95 (dd, 16-H), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.21 (d, 2″-Heq), 3.30 (dd, 2′-H), 3.52 (br d, 9-H), 3.58 (s, 4-OCH_3), 3.66 (dd, 4-H), 3.87 (br d, 5-H), 4.42 (d, 1′-H), 4.49 (dq, 5″-H), 4.57 (d, 4″-H), 4.79 (ddq, 14-H), 4.84 (d, 1″-H), 5.36 (br dd, 3-H), 6.19 (dt, PhCH=CH), 6.50 (d, PhCH=CH), 7.26 (m, C_6H_5), 9.63 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-8-methyl-11-(3-phenyl-2-propynyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**56**)

Reaction of **22** with phenylpropargyl aldehyde gave 18-

dimethylacetal of **56** in 59% yield by a similar procedure to 18-dimethylacetal of **51**.

18-Dimethylacetal of **56**: $[\alpha]_D^{20}$ −67° (*c* 0.40, $CHCl_3$); FAB-MS *m/z* 1007 $(M+H)^+$ as $C_{52}H_{82}N_2O_{17}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.95 (d, 18-H), 1.07 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.27 (d, 15-H), 1.40 (s, 3″-CH_3), 1.47 (br dd, 7-H), 1.57 (m, 8-H), 1.57 (m, 16-H), 1.68 (dd, 2″-Hax), 1.88 (m, 16-H), 2.00 (s, 3″-$OCOCH_3$), 2.53 (s, 3′-$N(CH_3)_2$), 2.79 (dd, 2-H), 3.16 (s, 17-OCH_3), 3.20 (d, 2″-Heq), 3.22 (m, 4′-H), 3.23 (m, 5′-H), 3.25 (s, 17-OCH_3), 3.42 (dd, 2′-H), 3.59 (s, 4-OCH_3), 3.62 (br d, 4-H), 3.86 (br d, 5-H), 4.44 (d, 1′-H), 4.50 (dq, 5″-H), 4.57 (d, 4″-H), 4.83 (d, 1″-H), 4.97 (ddq, 14-H), 5.27 (br dd, 3-H), 7.29 (m, C_6H_5), 7.42 (m, C_6H_5).

Reaction of 18-dimethylacetal of **56** with aqueous difluoroacetic acid gave **56** in 73% yield by a similar procedure to **11**.

56: $[\alpha]_D^{23}$ −71° (*c* 0.25, $CHCl_3$); FAB-MS *m/z* 961 $(M+H)^+$ as $C_{50}H_{76}N_2O_{16}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.98 (d, 18-H), 1.08 (d, 6″-H), 1.13 (d, 6′-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 15-H), 1.40 (s, 3″-CH_3), 1.51 (m, 8-H), 1.68 (dd, 2″-Hax), 1.99 (s, 3″-$OCOCH_3$), 2.54 (s, 3′-$N(CH_3)_2$), 2.79 (dd, 2-H), 2.94 (dd, 16-H), 3.21 (d, 2″-Heq), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.35 (dd, 2′-H), 3.58 (s, 4-OCH_3), 3.61 (br d, 4-H), 3.87 (br d, 5-H), 4.41 (d, 1′-H), 4.49 (dq, 5″-H), 4.57 (d, 4″-H), 4.84 (d, 1″-H), 4.90 (ddq, 14-H), 5.41 (br dd, 3-H), 7.29 (m, C_6H_5), 7.42 (m, C_6H_5), 9.64 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-8-methyl-11-(3-phenylpropionyl)-3-propionyloxy-11-aza-pentadecan-14-olide (57)

To a solution of **22** (30.0 mg) in dichloromethane (0.60 ml), triethylamine (17 μl) and 3-phenylpropionyl chloride (6 μl) were added under ice cooling, and the mixture was stirred for 1 hour. Chloroform (5.0 ml) and water (5.0 ml) were added to the reaction mixture, and the organic layer was separated. Then the aqueous layer was extracted twice with chloroform (10 ml). The organic layers were combined, washed successively with saturated aqueous sodium hydrogencarbonate solution (10 ml) and saturated brine (10 ml), dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by preparative TLC (ethyl acetate/methanol/aqueous ammonia (30 : 1 : 0.1) and chloroform/methanol/aqueous ammonia (20 : 1 : 0.1)) to obtain 18-dimethylacetal of **57** (20.0 mg, 58%).

18-Dimethylacetal of **57**: $[\alpha]_D^{21}$ −26° (*c* 0.40, $CHCl_3$); FAB-MS *m/z* 1025 $(M+H)^+$ as $C_{52}H_{84}N_2O_{18}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.99 (d, 18-H), 1.08 (d, 6″-H), 1.09 (t, 3-$OCOCH_2CH_3$), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.21 (d, 15-H), 1.41 (s, 3″-CH_3), 1.50 (br dd, 7-H), 1.69 (dd, 2″-Hax), 1.74 (m, 8-H), 1.99 (s, 3″-$OCOCH_3$), 2.54 (s, 3′-$N(CH_3)_2$), 2.78 (dd, 2-H), 3.07 (s, 17-OCH_3), 3.21 (s, 17-OCH_3), 3.22 (d, 2″-Heq), 3.23 (m, 4′-H), 3.24 (m, 5′-H), 3.34 (dd, 2′-H), 3.50 (br d, 4-H), 3.61 (s, 4-OCH_3), 3.78 (br d, 9-H), 3.89 (br d, 5-H), 4.51 (dq, 5″-H), 4.54 (ddq, 14-H), 4.55 (d, 1′-H), 4.58 (d, 4″-H), 4.85 (d, 1″-H), 5.14 (br dd, 3-H), 7.20 (m, C_6H_5), 7.28 (m, C_6H_5).

Reaction of 18-dimethylacetal of **57** with aqueous difluoroacetic acid gave **57** in 79% yield by a similar procedure to **11**.

57: $[\alpha]_D^{20}$ −37° (*c* 0.40, $CHCl_3$); FAB-MS *m/z* 979 $(M+H)^+$ as $C_{50}H_{78}N_2O_{17;}$ ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.99 (d, 18-H), 1.08 (d, 6″-H), 1.11 (d, 6′-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.22 (d, 15-H), 1.40 (s, 3″-CH_3), 1.53 (m, 8-H), 1.69 (dd, 2″-Hax), 1.98 (s, 3″-$OCOCH_3$), 2.55 (s, 3′-$N(CH_3)_2$), 2.76 (dd, 2-H), 2.89 (dd, 16-H), 3.21 (d, 2″-Heq), 3.22 (m, 4′-H), 3.22 (m, 5′-H), 3.28 (dd, 2′-H), 3.46 (dd, 4-H), 3.61 (s, 4-OCH_3), 3.73 (br d, 9-H), 3.89 (br d, 5-H), 4.44 (d, 1′-H), 4.47 (dq, 5″-H), 4.50 (ddq, 14-H), 4.58 (d, 4″-H), 4.85 (d, 1″-H), 5.22 (br dd, 3-H), 7.20 (m, C_6H_5), 7.28 (m, C_6H_5), 9.59 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-11-(3-(2-benzyloxyphenyl)propyl)-6-formylmethyl-9-hydroxy-4-methoxy-8-methyl-3-propionyloxy-11-aza-pentadecan-14-olide (58)

Reaction of **22** with 3-(2-benzyloxyphenyl)propanal gave 18-dimethylacetal of **58** in 80% yield by a similar procedure to 18-dimethylacetal of **51**.

18-Dimethylacetal of **58**: $[\alpha]_D^{22}$ −57° (*c* 0.50, $CHCl_3$); FAB-MS *m/z* 1117 $(M+H)^+$ as $C_{59}H_{92}N_2O_{18}$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (d, 18-H), 1.08 (d, 6″-H), 1.11 (t, 3-$OCOCH_2CH_3$), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.20 (d, 15-H), 1.41 (s, 3″-CH_3), 1.64 (m, 16-H), 1.68 (dd, 2″-Hax), 1.86 (m, $C_6H_4(CH_2)_3$), 1.90 (m, 16-H), 2.00 (s, 3″-$OCOCH_3$), 2.53 (s, 3′-$N(CH_3)_2$), 2.81 (dd, 2-H), 3.11 (s, 17-OCH_3), 3.20 (m, 4′-H), 3.20 (m, 5′-H), 3.21 (d, 2″-Heq), 3.25 (s, 17-OCH_3), 3.40 (dd, 2′-H), 3.56 (br d, 4-H), 3.58 (s, 4-OCH_3), 3.88 (br d, 5-H), 4.47 (d, 1′-H), 4.51 (dq, 5″-H), 4.58 (d, 4″-H), 4.75 (ddq, 14-H), 4.84 (d, 1″-H), 5.07 (s, $C_6H_5CH_2$), 5.19 (br dd, 3-H), 6.90 (m, C_6H_4), 7.15 (m, C_6H_4), 7.36 (m, C_6H_5).

Reaction of 18-dimethylacetal of **58** with aqueous difluoroacetic acid gave **58** in 76% yield by a similar procedure to **11**.

58: $[\alpha]_{\mathrm{D}}^{19}$ $-73°$ (*c* 0.50, $\mathrm{CHCl_3}$); FAB-MS *m/z* 1071 $(\mathrm{M+H})^+$ as $\mathrm{C_{57}H_{86}N_2O_{17}}$; ^{1}H-NMR (300 MHz, $\mathrm{CDCl_3}$) δ: 0.95 (d, 18-H), 1.08 (d, 6″-H), 1.13 (d, 6′-H), 1.15 (t, 3-$\mathrm{OCOCH_2CH_3}$), 1.18 (t, 4″-$\mathrm{OCOCH_2CH_3}$), 1.20 (d, 15-H), 1.41 (s, 3″-$\mathrm{CH_3}$), 1.46 (m, 8-H), 1.69 (dd, 2″-Hax), 1.77 (m, $\mathrm{C_6H_4(CH_2)_3}$), 1.99 (s, 3″-$\mathrm{OCOCH_3}$), 2.54 (s, 3′-$\mathrm{N(CH_3)_2}$), 2.66 (m, $\mathrm{C_6H_4(CH_2)_3}$), 2.79 (dd, 2-H), 2.95 (dd, 16-H), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.21 (d, 2″-Heq), 3.33 (dd, 2′-H), 3.57 (s, 4-$\mathrm{OCH_3}$), 3.63 (dd, 4-H), 3.87 (br d, 5-H), 4.42 (d, 1′-H), 4.48 (dq, 5″-H), 4.58 (d, 4″-H), 4.71 (ddq, 14-H), 4.84 (d, 1″-H), 5.07 (s, $\mathrm{C_6H_5CH_2}$), 5.31 (br dd, 3-H), 6.88 (m, $\mathrm{C_6H_4}$), 7.15 (m, $\mathrm{C_6H_4}$), 7.36 (m, $\mathrm{C_6H_5}$), 9.63 (s, 17-H).

(−)-(3*R*,4*S*,5*S*,6*R*,8*R*,9*R*,14*R*)-5-[4-*O*-(3-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-4-*O*-propionyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyloxy]-6-(2,2-dimethoxyethyl)-9-hydroxy-4-methoxy-8-methyl-11-(4-phenylbutyl)-3-propionyloxy-11-aza-pentadecan-14-olide (**30c**)

14 (150 mg) was dissolved in anhydrous methanol (5.0 ml), and ozone was introduced into this solution at −78°C for 15 minutes until getting blue color solution of reaction mixture. Then, oxygen was bubbled for 5 minutes in order to remove excess ozone at the same temperature. Dimethylsulfide (1.0 ml) was added at −78°C and the reaction mixture was kept at the same temperature for 30 minutes. Next, 4-phenylbutyl amine (28 μl) and sodium triacetoxyborohydride (100 mg) were added, and the mixture was gradually warmed up to room temperature. About half volume of methanol was evaporated under the reduced pressure, and the resulting solution was neutralized with saturated aqueous sodium bicarbonate solution. Then, the aqueous layer was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate (5 : 1 to 1 : 1)) to obtain **30c** (13.0 mg, 8.0%).

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