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Novel azalides derived from 16-membered macrolides. Part II: Isolation of the linear 9-formylcarboxylic acid and its sequential macrocyclization with an amino alcohol or an azidoamine

Tomoaki Miura *, Kenichi Kanemoto, Satomi Natsume, Kunio Atsumi, Hideki Fushimi, Takuji Yoshida, Keiichi Ajito *

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

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ABSTRACT

The design and synthesis of novel 14- to 16-membered 11-azalides starting from 16-membered macrolides are reported. A linear 9-formylcarboxylic acid was isolated via a mobile dialdehyde previously reported. Sequential macrocyclization of the formylcarboxylic acid with amino alcohol followed by deprotection afforded corresponding 14- to 16-membered azalides. On the other hand, reductive amination of the formylcarboxylic acid with an azidoamine followed by macrolactam formation with an amine generated from the azide gave 14- to 16-membered azalactams. Among these derivatives, 15-membered azalactams and 16-membered azalides exhibited characteristic in vitro antibacterial activities. Although optimization of 15-membered azalactams including demycarosyl analogues did not provide remarkably promising molecules, SAR studies of 16-membered azalides disclosed that substitution at the 15 position was very important for identification of a clinical candidate.

1. 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, that is, ketolides, telithromycin[4] (TEL) has recently been launched as an efficient antibiotic which is effective against clinically important pathogens including erythromycin-resistant *S. pneumoniae* (ERSP). Moreover, a novel ketolide, S-013420[5] is under clinical trials.

Although TEL 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] is seriously concerned in clinical site especially in the 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

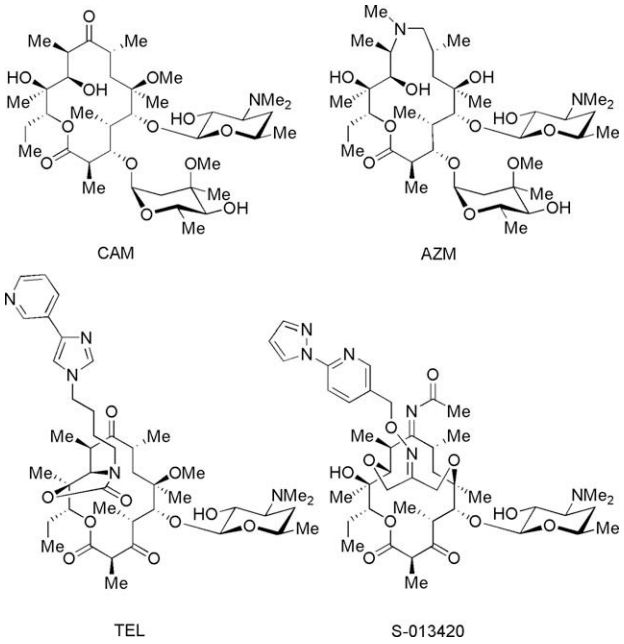

Figure 1. Structures of representative macrolide antibiotics.

* Corresponding authors. Tel.: +81 45 545 3131; fax: +81 45 543 9771.
E-mail addresses: tomoaki_miura@meiji.co.jp (T. Miura), keiichi_ajito@meiji.co.jp (K. Ajito).

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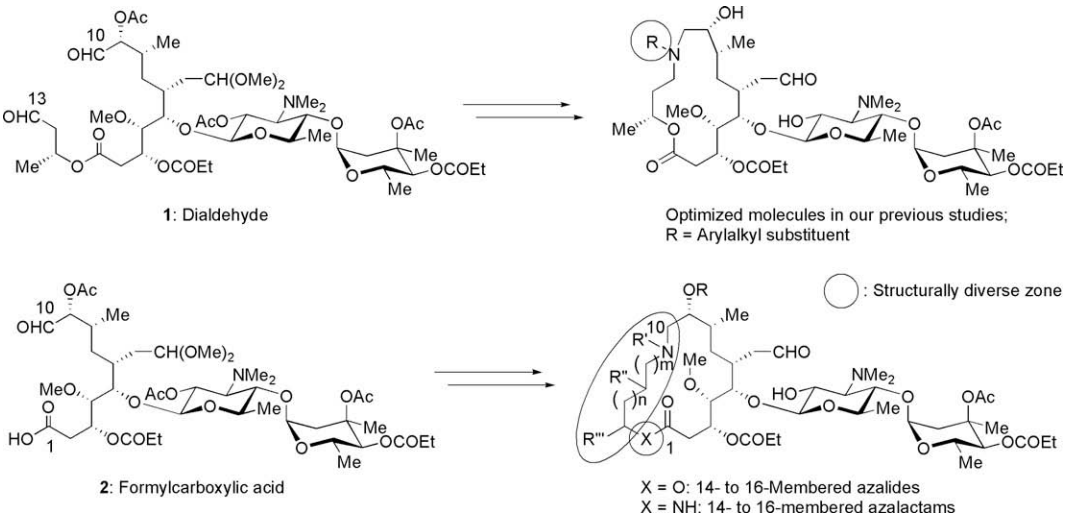


Figure 2. Research concept using formylcarboxylic acid (**2**).

resistant bacteria of *S. pneumoniae* with efflux pump, so called 'a *mef* gene'.

Before we started this research program, we had partially established a practical approach to overcome resistant bacteria by medicinal chemistry using 16-membered macrolides. Owing to this approach, antibacterial activities against resistant pathogens in 16-membered macrolides were clearly enhanced[7] by the introduction of 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. Therefore, we proposed synthesis of 15-membered 11-azalides and 16-membered diazalide as a novel template, and figured out their antibacterial activities.[8]

Our first approach using dialdehyde (**1**) (Fig. 2), however, enabled us to structurally diversify only a small area in an original lactone moiety as in the case of other related approaches.[9–14] Then, we practically utilized 9-formylcarboxylic acid (**2**) as a key intermediate for sequential macrocyclization in order to provide a variety of novel templates. In this paper, we report the design and synthesis of novel 14- to 16-membered 11-azalides and 14- to 16-membered azalactams starting from 16-membered macrolides. Although related medicinal chemistry using erythromycin has been reported,[15,16] no derivatives that are active against resistant *S. pneumoniae* possessing the *erm* gene or the *mef* gene have been identified.

2. Results and discussion

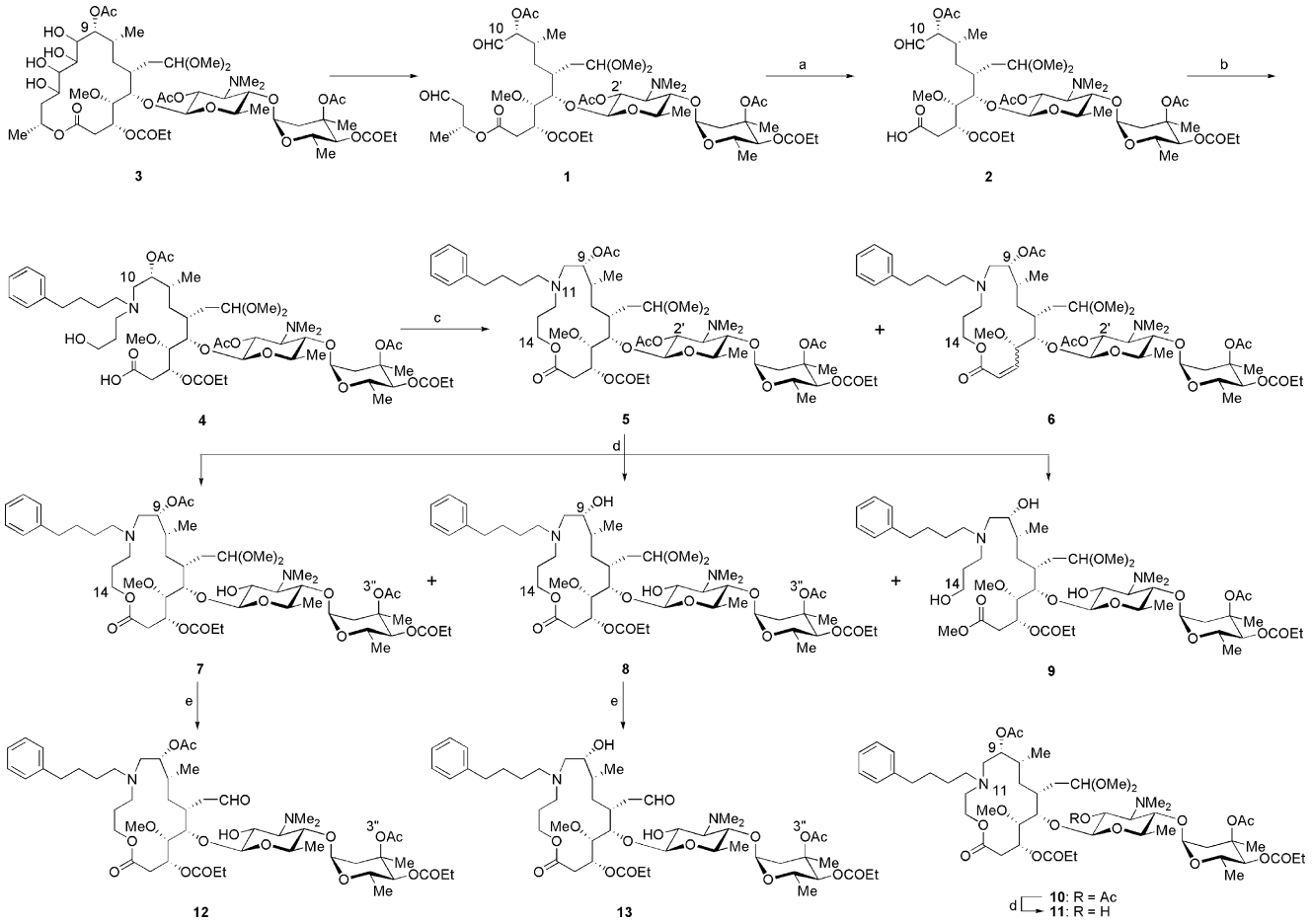
2.1. Synthesis of 15-membered azalides

An outline of the synthesis of 15-membered azalides is shown in Scheme 1. A key intermediate, 9-formylcarboxylic acid (**2**), was prepared under organic basic condition in 35% yield as dimethylacetal[17] from mobile 2′-acetylated dialdehyde (**1**).[8] On the other hand, compound **2** was isolated with 52% yield via two steps starting from tetraol (**3**)[8] without purification of dialdehyde (**1**) (see Section 4).

As the second step, an amino alcohol had to be introduced onto an aldehyde group. Because we were planning to explore a new template, which is active against resistant *S. pneumoniae*, we introduced an arylalkyl moiety (e.g., the 4-phenylbutyl group) into an amino alcohol. In Scheme 1,3-(4-phenylbutylamino)propanol (1.5 equiv) was reacted with formylcarboxylic acid (**2**) in 65% by optimized reductive amination protocol. As the first step, an amino alcohol and formylcarboxylic acid were kept in anhydrous dimethylformamide with molecular sieves 3A for 4 h in order to form a reactive intermediate, and then excess sodium borohydride was added to give compound **4**. In the case without the intermediate formation step, desired compound **4** could not be detected and an aldehyde was partially converted to a primary alcohol.

Macrolactonization of compound **4** was performed following Yamaguchi protocol. 2,4,6-Trichlorobenzoyl chloride (1.2 equiv) and 2 equiv of triethylamine were reacted in tetrahydrofuran at room temperature for 2 h. Then 6 equiv of 4-dimethylaminopyridine (DMAP) in highly diluted benzene solution were slowly added at room temperature taking 2 h. This reaction condition suppressed the formation of dimer and the yield of desired **5** was 43%. Fast addition of DMAP resulted in 29% yield of **5** and 22% of undesired dimer. In this macrolactonization, the higher reaction temperature tends to provide better reaction yield. The reaction condition at 80 °C, however, gave a mixture of compound **5** and its 2-eno derivative (**6**) (FAB-MS *m*/*z* 1021 $(M+H)^+$), which could not be easily separated from compound **5**. Then, we performed this lactonization at room temperature.

At the end of a synthetic route, deprotection had to be done. First, the 2′-*O*-acetyl group was removed by methanolysis. Compound **5** was kept in methanol solution at room temperature for 76 h, and compounds **7** and **8** were isolated in 32% and 24%, respectively. When the reaction period became longer, methanolysis excessively proceeded and the lactone moiety was affected, which gave more undesired methylester (**9**) (FAB-MS *m*/*z* 1043 $(M+H)^+$). The lactone ring possessing a substituent at the C-14 position, however, did not provide a corresponding methyl ester.[20] We will shortly mention reaction mechanism of these methanolysis. The 2′-*O*-acetyl group is removed by neighboring effect of the dimethylamino group at the C-3′ and the 9-*O*-acetyl group is also removed by the same effects of tertiary amine at the N-11. Because the amino sugar portion is always rigid, neighboring effect is constant. 15-Membered azalactone does not provide an appropriate distance between the 11-nitrogen atom and the 9-*O*-acetyl group, so this effect is not enough to remove the 9-*O*-acetyl group completely for compound **5**. As a matter of fact, methanolysis at the C-9 position could not be observed in 14-membered azalides. Thus, long-term methanolysis (5 days) of compound **10**[20] selectively provided the 9-*O*-acetyl derivative (**11**) in 89% yield. It is presumed that the tertiary amine at the N-11 did not spatially approach to the 9-*O*-acetyl group in 14-membered azalides. Deprotection of dimethyl acetals



Scheme 1. Synthesis of 15-membered 11-azalides (**12** and **13**). Reagents and conditions: (a) DBU (1.5 equiv), MeCN, rt, 6 h, 35% (52% via two steps based on **3**, see Section 4); (b) i—3-(4-phenylbutylamino)propanol (1.5 equiv), AcOH (10 equiv), molecular sieves 3A, DMF, rt, 4 h; ii—$NaBH_4$ (1.0 equiv), rt, 1.5 h, 65%; (c) i—2,4,6-$Cl_3C_6H_2COCl$ (1.2 equiv), TEA (2.0 equiv), THF, rt, 2 h; ii—DMAP (6 equiv) in PhH, slowly added, rt, 2 h, 43%; (d) MeOH, rt, 76 h, 32% for **7**, 24% for **8**, trace of **9**; MeOH, rt, 5 days, 89% for **11**; (e) difluoroacetic acid (30 equiv), MeCN–H_2O, rt, 25 h, 78% for **12**, 73% for **13**.

(**7** and **8**) by difluoroacetic acid[17] proceeded to provide desired 15-membered azalides (**12** and **13**), respectively. In the case of miokamycin[18] (MOM) derivatives whose 3″-position is an acetoxyl group (see Fig. 5, for miokamycin), a neutral sugar is stable under these acidic conditions because of its 1,3-diaxial hindrance. On the other hand, a neutral sugar moiety of midecamycin[19] derivatives whose 3″-position is a hydroxyl group is unstable under acidic conditions, so the neutral sugar is partially removed during this deprotection step (see compound **44** in Scheme 3).

2.2. Synthesis of 14-membered azalactams

Utilization of the formylcarboxylic acid (**2**) enabled us to theoretically generate any structures of the Western hemisphere (framework between the aldehyde at C-10 and the carboxylic acid at C-1) of the macrolactone ring (Fig. 2), and thus we applied azidoamine instead of amino alcohol in order to construct azalactam.

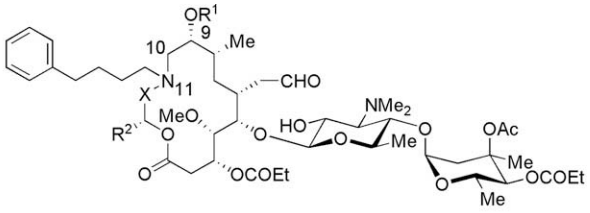
We used *N*-(2-azidoethyl)-4-phenylbutylamine to afford the desired coupling product (**14**) in moderate yield as shown in Scheme 2. Although the coupling reaction of amino alcohol with aldehyde required the intermediate (iminium ion, tentatively) formation step, application of azidoamine did not necessarily require this step. As a matter of fact, a yield of a coupling reaction in application of azidoamine accompanied with the intermediate formation step, was further increased to about 80% (see compound **37** in Scheme 3). Reduction of the azide by triphenylphosphine smoothly provided aminoacid (**15**), and its macrocyclization with diphenylphosphoryl azide quantitatively gave 14-membered azalactam (**16**).

Partial methanolysis mainly gave the 2′-hydroxyl derivative (**17**) and the 9-*O*-acetyl group was not affected under this methanolysis condition in the case of 14-membered azalactam as previously mentioned. On the other hand, 9-*O*-acetyl group was partially or dominantly removed in the same condition in the case of 15- or 16-membered azalactams. Final acidic hydrolysis afforded 14-membered 11-azalactam (**18**).

2.3. SAR analysis of 14- to 16-membered azalides and azalactams

According to the synthesis of **12** and **13** shown in Scheme 1, azalides **19**–**25** were synthesized (Fig. 3). Azalactams **26**–**33** (Fig. 4) were also synthesized by a similar procedure to **18** as shown in Scheme 2. Preparation procedures of amino alcohols and azidoamines applied to the synthesis of azalides or azalactams are disclosed in our patent.[20]

Antibacterial activities of 14- to 16-membered azalides are shown in Table 1 and those of 14- to 16-azalactams are shown in Table 2. Although both 15-membered compounds and 16-membered compounds exhibited remarkable antibacterial activities, 14-membered azalides and azalactams did not show strong potency. In general, 15-membered compounds exhibited strong activities against *H. influenzae* compared to MOM (Table 3), and their strong tendency was more clearly observed in 15-membered



Compd	R^1	R^2	X	Azalactone
19	Ac	Me	CH_2	14-membered
20[*a]	Ac	Me	CH_2CH_2	15-membered
21[*a]	H	Me	CH_2CH_2	15-
12	Ac	H	CH_2CH_2	15-
13	H	H	CH_2CH_2	15-
22	Ac	Me	$CH_2CH_2CH_2$	16-membered
23	H	Me	$CH_2CH_2CH_2$	16-
24[*b]	H	Me	$CH_2CH{=}CH$[*c]	16-
25[*b]	H	Me	$CH_2CH{=}CH$[*c]	16-

[*a]: These compounds were synthesized by our previous scheme. See reference #8;
[*b]: These compounds are diastereoisomers at the C-15 position (R^2). Each sterochemistry is not defined;
[*c]: The methylene is the C-12 position and the double bond is trans geometry.

Figure 3. Eleven-substituted 14- to 16-membered 11-azalides.

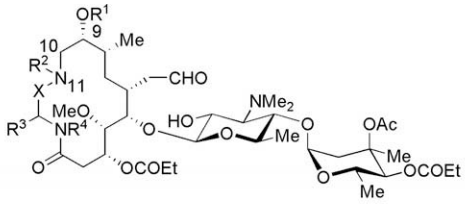
azalactams compared to 15-membered azalides (**20**, **21**, **12**, and **13** vs **29**–**32**). On the other hand, 16-membered analogues exhibited rather strong activities against *S. pneumoniae* including the *erm*-type resistant bacteria, and their positive phenomena were detected in 16-membered azalide (azalactone) as shown in compounds **23** and **24**.

2.4. Chemical modification of 15-membered azalactams

In the above SAR studies, we could find several attractive templates. Fifteen-membered molecules exhibited strong activities against *H. influenzae* strains, and 15-membered lactam was somehow stronger than 15-membered lactone. We first introduced a characteristic side chain, 3-(quinolin-4-yl)propyl group (Fig. 5) to 11-position of 15-membered lactam, which was proved to be one of the most effective substituents at 11-position for enhancing antibacterial activities in our previous studies.[8]

As shown in Scheme 3, we synthesized midecamycin type 15-membered azalactam (**43**) and its demycarosyl analogue (**44**) starting from the tetraol intermediate (**34**)[8] (see Fig. 5 for midecamycin A_1[19] (MDM)). Although a neutral sugar moiety is not believed to be essential for antibacterial activity in erythromycin derivatives,[4,21] we had to clarify antibacterial activities of demycarosyl analogues. Although the synthetic route is fundamentally same as in the preparation of **18** shown in Scheme 2, acidic hydrolysis of **42** gave demycarosyl derivative (**44**) accompanied with **43** because of poor 1,3-diaxial steric hindrance between the 1″- and 3″-position compared to that in **8**. Being different from lactone synthesis, complete methanolysis in heating condition is applicable to the deprotection of the 9-*O*-acetyl group in lactam synthesis (**41** to **42**). Moreover, considering of efficiency in the chemical screening of 11-substituted 15-membered azalactam, we modified the synthetic scheme in application of the common synthetic intermediate (**40**) as shown in Scheme 3. An efficient chemical screening using **40** will be reported elsewhere. Because 15-membered azalactams with a substituent at 11-position exhibited stronger antibacterial activity against *H. influenzae* (vide infra, Table 3), we pursued further optimization utilizing the 15-membered azalactam template.

Next, we investigated the design, synthesis, and evaluation of novel 15-membered azalactams with an appropriate side chain at the 14-position, in order to explore possibilities of optimization of 15-membered azalactam as shown in Scheme 4. There are a variety of strategies to construct meaningful and applicable 'small molecule focused library' derived from structurally complicated natural substances, like anticancer natural products or antibiotics. As characteristic examples, one-by-one synthesis and its perfect structure determination by conventional research, or split-and-pool methodology for peptide synthesis are well known. On the other hand, attractive strategies such as 'chemical biology studies'[22] and 'click chemistry'[23] were subsequently introduced as a novel approach to construct a qualified library. We chose (±)-*N*-(3-azido-5-hexenyl)-*N*-methylamine[20,24] as an important building



Compd	R^1	R^2	R^3	R^4	X	Azalactam
26[*a]	Ac	$CH_2(CH_2)_3Ph$	Me	H	CH_2	14-membered
18	Ac	$CH_2(CH_2)_3Ph$	H	H	CH_2	14-
27	Ac	$CH_2(CH_2)_3Ph$	H	Me	CH_2	14-
28	Ac	Me	H	$CH_2(CH_2)_3Ph$	CH_2	14-
29[*b]	H	$CH_2(CH_2)_3Ph$	Me	H	CH_2CH_2	15-membered
30[*b]	H	$CH_2(CH_2)_3Ph$	Me	H	CH_2CH_2	15-
31	Ac	$CH_2(CH_2)_3Ph$	H	H	CH_2CH_2	15-
32	H	$CH_2(CH_2)_3Ph$	H	H	CH_2CH_2	15-
33	H	$CH_2(CH_2)_3Ph$	H	H	$CH_2CH_2CH_2$	16-membered

[*a]: Stereochemistry of the C-13 is natural (the methyl group as R^3 is alpha configuration);
[*b]: These compounds are diastereoisomers at the C-14 position (R^3). Each sterochemistry is not defined;

Figure 4. Eleven-substituted 14- to 16-membered 11-azalactams.

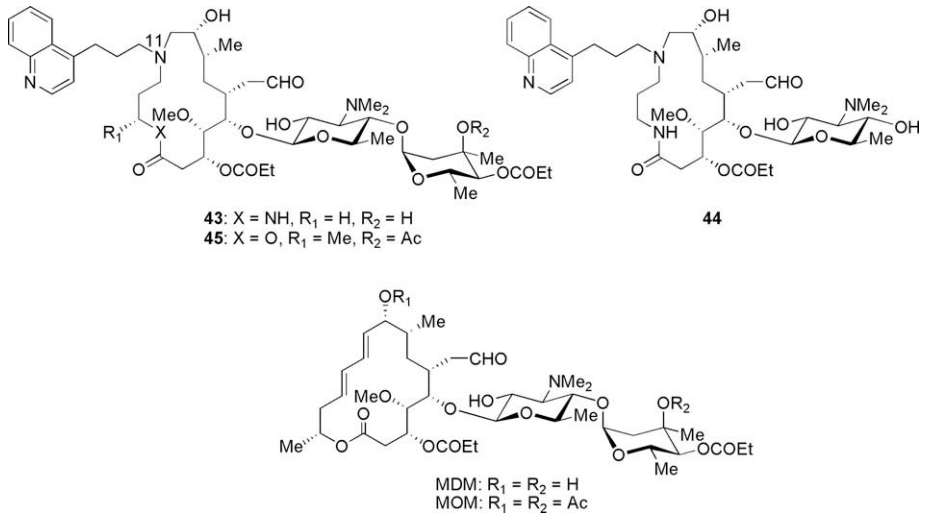
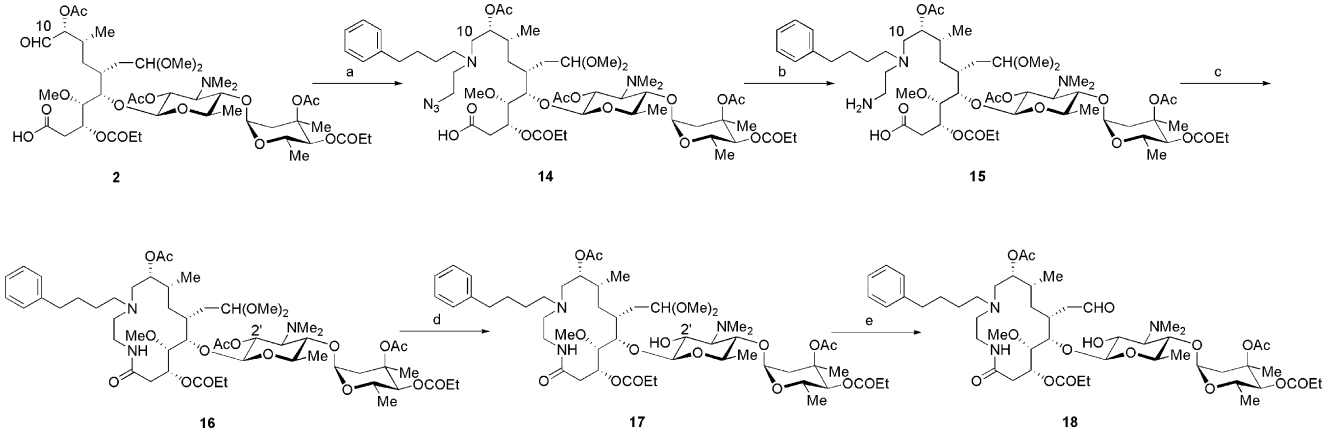


Figure 5. Fifteen-membered azalactams (**43** and **44**) and structurally related azalide (**45**).



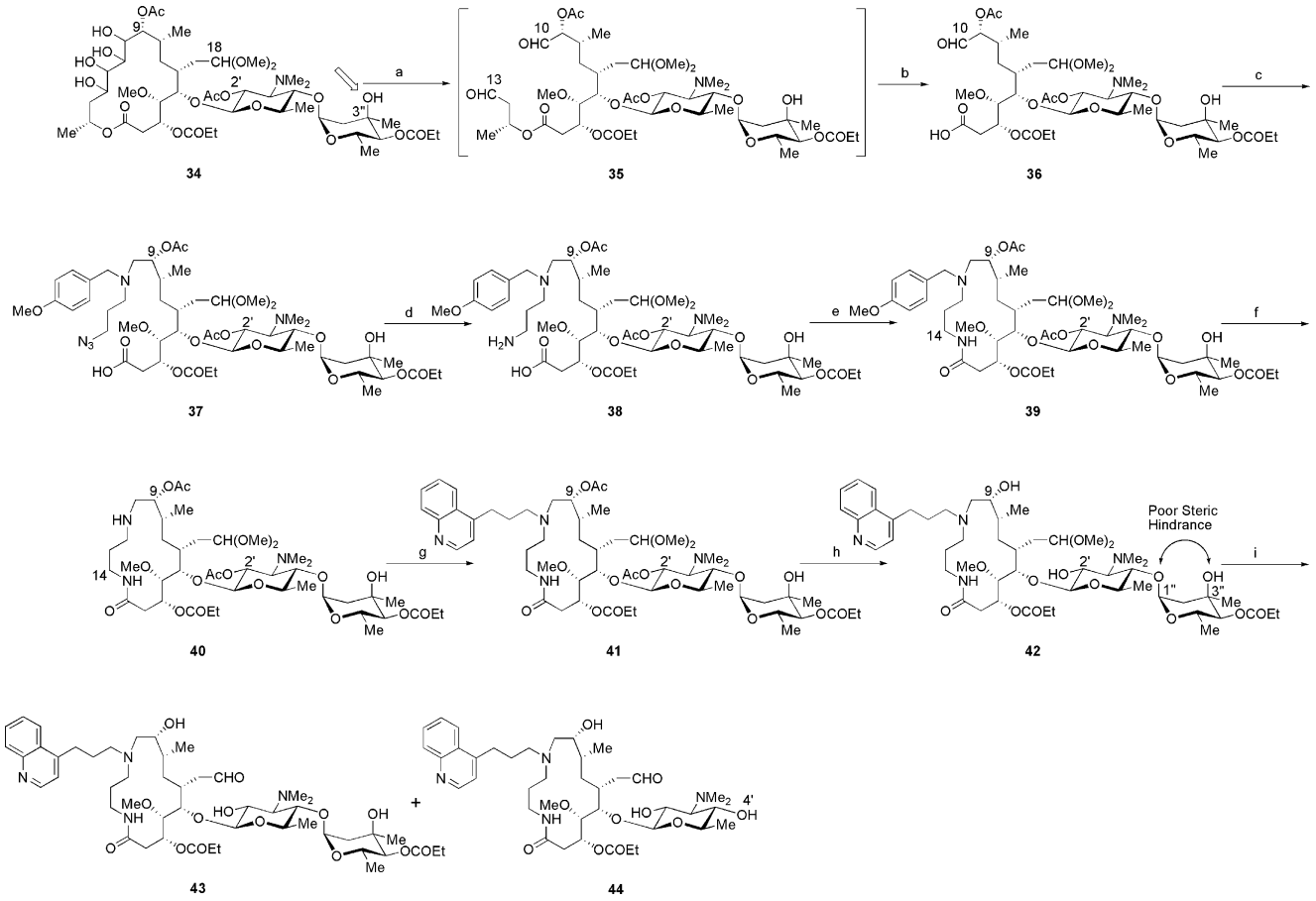
Scheme 2. Synthesis of 14-membered 11-azalactam (**18**). Reagents and conditions: (a) *N*-(2-azidoethyl)-4-phenylbutylamine (1.5 equiv), $NaBH_3CN$ (0.45 equiv), AcOH (8.4 equiv), EtOH, rt, 21 h, 52%; (b) PPh_3 (5.0 eq), 10% H_2O/THF, 60 °C, 36 h, 64%; (c) $(PhO)_2PON_3$ (3.4 equiv), $NaHCO_3$ (18 equiv), DMF, rt, 19 h, 96%; (d) MeOH, rt, 5 h, 70%; (e) difluoroacetic acid (30 equiv), MeCN/H_2O (1:1), rt, 25 h, 85%.

block including a tether part for preparation of the common intermediates (**48** and **49**), and isolated each diastereoisomer **48**/**49**. These intermediates were quite productive for expanding diversity of the library and rapid synthesis. After separation of these isomers, medicinal chemistry has been performed with a single stereochemistry at the C-14, but its configuration could not be figured out. Because we could not find an excellent lead compound for further modification from the compounds shown in Figure 6 or Figure 7, we did not define stereochemistry at the C-14 in Figure 6 and the C-13 in Figure 7. But we defined stereochemistry at the C-15 for more promising compounds shown in Figure 8. Heck reactions of **48**/**49** with 4-bromoquinoline as shown in Scheme 4 afforded 3-(quinolin-4-yl)allyl derivatives (**50**/**51**), and subsequent deprotections of them gave desired **54**/**55** and their demycarosyl analogues. In this series (14-substituted 15-membered azalactams), palladium acetate and tri-*o*-tolylphosphine[25] were used for Heck reaction. Even though we used a similar protocol, rearrangement of the double bond occurred depending on its side chain structure (Fig. 6) during Heck reaction. For example, the reaction with 3-bromoquinoline did not provide rearrangement products, but the reaction with 4-bromoquinoline led to rearrangement and generated an isomer as by-product (**58** and **59** in Fig. 6).

2.5. SAR analysis of optimized 15-membered azalactams

Antibacterial activities of 11-substituted 15-membered azalactam **43** and **44**,[8] and those of several reference compounds are shown in Table 3. Antibacterial activities of azalactam (**43**) were slightly weaker than those of 15-membered azalide (**45**) except for the activities against *H. influenzae*, even though **43** possessed an optimized side chain, the 3-(quinolin-4-yl)propyl group, in SAR studies of 11-substituted 15-membered azalides.[8] Thus, we did not pursue further optimization of substituents at the N-11 and we started SAR studies of 14-substituted 15-membered azalactams as novel pharmacophore. As a matter of fact, antibacterial activities of **44** against *M. catarrhalis* or *H. influenzae* were stronger than those of the demycarosyl analogue of midecamycin A_3 (data are not shown), so we decided to isolate and evaluate each demycarosyl analogue in this series.

Antibacterial activities of 14-substituted 15-membered azalactams with mycarose are shown in Table 4. As we expected, the activities against *H. influenzae* of these analogues were generally stronger than those of MDM, but their activities against the *erm*-type resistant bacteria of *S. pneumoniae* were none or weak as a lead compound for further modifications. Then we moved to investigation of 16-membered azalides. On the other hand, the demy-



Scheme 3. Synthesis of midecamycin type 15-membered 11-azalactam (**43**) and its demycarosyl analogue (**44**) by a convergent approach. Reagents and conditions: (a) $Pb(OAc)_4$ (2.5 equiv), Na_2CO_3 (8.0 equiv), PhH, rt, 30 min; (b) DBU (1.5 equiv), MeCN, rt, 5 h, 70% via two steps; (c) i—*N*-(3-azidopropyl)-4-methoxybenzylamine (1.5 equiv), AcOH (10 equiv), molecular sieves 3A, DMF, rt, 4 h; ii—$NaBH_4$ (1.0 equiv), rt, 1.5 h, 79%; (d) PPh_3 (5.0 equiv), 10% H_2O/THF, 60 °C, 36 h, 76%; (e) $(PhO)_2PON_3$ (3.4 equiv), $NaHCO_3$ (18 equiv), DMF, rt, 19 h, 72%; (f) 10% Pd/C, 1, 4-dioxane, rt, 24 h, 91%; (g) i—3-(quinolin-4-yl)propionaldehyde (1.2 equiv), AcOH (5.0 equiv), EtOH, 0 °C, 30 min; ii—$NaBH_3CN$ (3.0 equiv), 0 °C to rt, 3.5 h, 66%; (h) MeOH, 50 °C, 150 h, 83%; (i) difluoroacetic acid (30 equiv), MeCN/H_2O (1:1), rt, 25 h, 45% for **43** and 24% for **44** (total yield: 69%).

Table 1
Antibacterial activities of 14- to 16-membered 11-azalides with a 4-phenylbutyl group at the N-11 position.

	Test organism	Characteristics	(MIC, μg/ml)								
			19	**20**	**21**	**12**	**13**	**22**	**23**	**24**	**25**
1	*Staphylococcus aureus* 209P JC-1	Susceptible	4	0.5	0.13	0.5	0.25	0.5	0.25	0.13	0.25
2	*S. aureus* #2	Susceptible	>128	1	0.5	1	1	2	1	0.5	0.5
3	*S. aureus* #3	Susceptible	4	0.5	0.25	0.5	0.25	1	0.25	0.25	0.25
4	*S. aureus* #4	*ermA* (c)*	>128	>128	>128	>128	>128	>128	>128	>128	>128
5	*S. aureus* #5	*ermB* (i)**	4	0.5	0.5	0.5	0.25	1	0.25	0.13	0.25
6	*S. aureus* #6	*ermC* (i)	8	1	0.5	1	0.5	2	0.5	0.5	0.5
7	*Streptococcus pneumoniae* DP1 TypeI	Susceptible	1	0.25	0.06	0.25	0.13	0.25	0.06	0.03	0.03
8	*S. pneumoniae* #2	Susceptible	2	0.25	0.13	0.25	0.13	0.25	0.06	0.06	0.06
9	*S. pneumoniae* #5	*ermB* + *mefA* (c)	>128	>128	128***	>128	>128	>128	>128	>128	>128
10	*S. pneumoniae* #6	*ermB* (c)	>128	>128	>128	N.T.	N.T.	>128	64	>128	>128
11	*S. pneumoniae* #7	*ermB* (i)	>128	>128	8	8	4	4	1	2	8
12	*S. pneumoniae* #8	*ermB* (i)	>128	>128	8	32	16	4	1	2	4
13	*S. pneumoniae* #9	*mefA* efflux	2	0.5	0.06	0.5	0.25	0.25	0.13	0.06	0.06
14	*S. pneumoniae* #10	*mefA* efflux	2	0.25	0.06	0.25	0.13	0.13	0.06	0.06	0.06
15	*Streptococcus pyogenes* #1	Susceptible	2	0.25	0.06	0.25	0.06	0.25	0.13	0.06	0.06
16	*S. pyogenes* #2	*ermB* (c)	>128	>128	>128	>128	>128	>128	64	32	>128
17	*S. pyogenes* #3	*mefA* efflux	4	0.5	0.13	0.25	0.13	1	0.25	0.25	0.25
18	*Moraxella catarrhalis* #1	Susceptible	8	0.25	0.13	0.25	0.13	1	0.25	0.13	0.13
19	*M. catarrhalis* #2	Susceptible	>128	0.5	0.25	0.5	0.25	2	0.5	0.5	0.5
20	*Haemophilus influenzae* #1	Susceptible	>128	>128	32	>128	16	>128	32	32	64
21	*H. influenzae* #2	Susceptible	>128	2	1	2	1	4	0.5	2	4
22	*H. influenzae* #3	Susceptible	>128	16	4	4	4	>128	8	8	16
23	*H. influenzae* #4	Susceptible	>128	16	8	8	8	>128	16	8	8

NT, not tested.
* Constitutive.
** Inducible.
*** Test organism: *S. pneumoniae* #11 (*ermB* methylase(c)).

Table 2
Antibacterial activities of 14- to 16-membered 11-azalactams with a 4-phenylbutyl group at the N-11 position and compound **28**.

	Test organism	Characteristics	(MIC, μg/ml)								
			26	**18**	**27**	**28**	**29**	**30**	**31**	**32**	**33**
1	*Staphylococcus aureus* 209P JC-1	Susceptible	1	0.5	1	1	0.25	0.25	0.25	0.25	0.25
2	*S. aureus* #2	Susceptible	4	2	2	2	1	1	1	1	1
3	*S. aureus* #3	Susceptible	2	1	1	1	0.25	0.25	0.5	0.25	0.5
4	*S. aureus* #4	*ermA* (c)*	>128	>128	>128	>128	>128	>128	>128	>128	>128
5	*S. aureus* #5	*ermB* (i)**	1	1	1	0.5	0.25	0.25	0.25	0.25	0.25
6	*S. aureus* #6	*ermC* (i)	2	2	2	1	0.5	0.5	1	0.5	1
7	*Streptococcus pneumoniae* DP1 TypeI	susceptible	0.5	0.5	0.5	0.13	0.06	0.13	0.25	0.13	0.13
8	*S. pneumoniae* #2	Susceptible	1	0.5	1	0.5	0.13	0.25	0.5	0.25	0.25
9	*S. pneumoniae* #5	*ermB* + *mefA* (c)	>128	>128	>128	>128	>128	>128	>128	>128	>128
10	*S. pneumoniae* #6	*ermB* (c)	>128	>128	>128	>128	>128	>128	>128	>128	>128
11	*S. pneumoniae* #7	*ermB* (i)	32	>128	>128	16	128	32	32	16	8
12	*S. pneumoniae* #8	*ermB* (i)	32	>128	>128	16	128	32	32	16	8
13	*S. pneumoniae* #9	*mefA* efflux	1	1	1	0.5	0.25	0.25	0.25	0.25	0.13
14	*S. pneumoniae* #10	*mefA* efflux	1	0.5	1	0.5	0.25	0.25	0.25	0.25	0.13
15	*Streptococcus pyogenes* #1	Susceptible	0.5	0.5	0.5	0.5	0.06	0.06	0.13	0.13	0.06
16	*S. pyogenes* #2	*ermB* (c)	>128	>128	>128	>128	>128	>128	>128	>128	>128
17	*S. pyogenes* #3	*mefA* efflux	1	1	1	2	0.25	0.25	0.5	0.5	0.25
18	*Moraxella catarrhalis* #1	Susceptible	1	0.5	1	1	0.13	0.13	0.25	0.13	0.13
19	*M. catarrhalis* #2	Susceptible	1	1	1	2	0.13	0.25	0.25	0.25	0.25
20	*Haemophilus influenzae* #1	Susceptible	>128	>128	>128	>128	16	32	16	8	16
21	*H. influenzae* #2	Susceptible	4	2	4	8	1	1	0.5	0.5	1
22	*H. influenzae* #3	Susceptible	16	8	16	>128	4	8	2	2	4
23	*H. influenzae* #4	Susceptible	16	8	16	16	4	8	4	4	8

* Constitutive.
** Inducible.

Table 3
Antibacterial activities of 15-membered azalactams (**43** and **44**) and structurally related azalide (**45**).

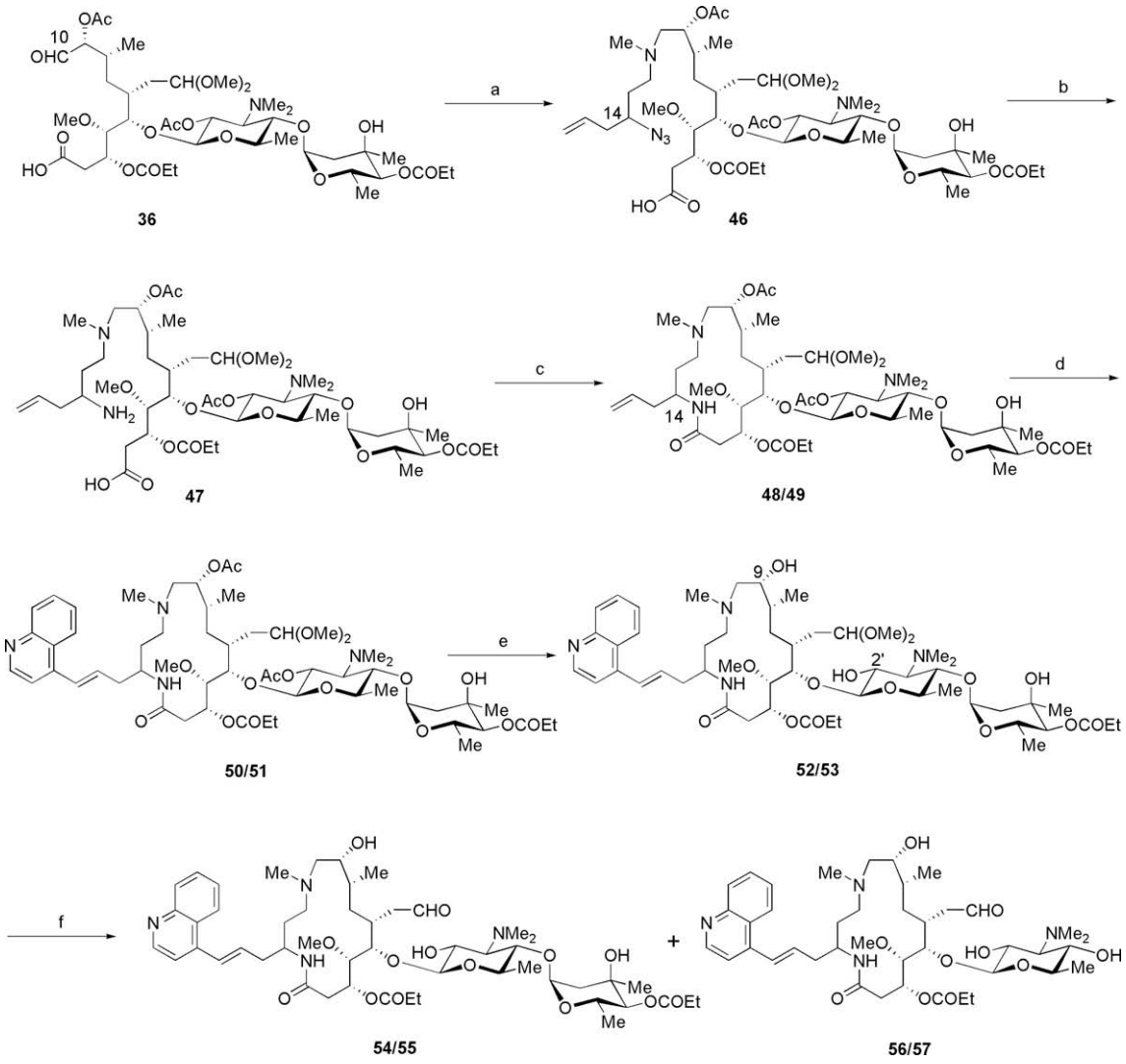
	Test organism	Characteristics	(MIC, μg/ml)				
			43	**44**	MDM	**45**	MOM
1	*Staphylococcus aureus* 209P JC-1	Susceptible	0.5	64	0.5	0.13	0.5
2	*S. aureus* #2	Susceptible	1	32	0.5	0.5	1
3	*S. aureus* #3	Susceptible	0.5	64	0.5	0.25	0.5
4	*S. aureus* #4	*ermA* (c)*	>128	>128	>128	>128	>128
5	*S. aureus* #5	*ermB* (i)**	0.5	64	0.5	0.13	0.5
6	*S. aureus* #6	*ermC* (i)	0.5	64	0.5	0.25	1
7	*Streptococcus pneumoniae* DP1 TypeI	Susceptible	0.06	16	0.13	0.06	0.25
8	*S. pneumoniae* #2	Susceptible	0.13	16	0.25	0.06	0.5
9	*S. pneumoniae* #5	*ermB* + *mefA* (c)	>128	>128	>128	>128***	>128
10	*S. pneumoniae* #6	*ermB* (c)	>128	>128	>128	>128	>128
11	*S. pneumoniae* #7	*ermB* (i)	16	>128	>128	4	64
12	*S. pneumoniae* #8	*ermB* (i)	16	>128	>128	8	128
13	*S. pneumoniae* #9	*mefA* efflux	0.13	32	0.5	0.13	0.5
14	*S. pneumoniae* #10	*mefA* efflux	0.13	32	0.25	0.13	0.5
15	*Streptococcus pyogenes* #1	susceptible	0.25	16	0.25	0.06	0.25
16	*S. pyogenes* #2	*ermB* (c)	>128	>128	>128	>128	>128
17	*S. pyogenes* #3	*mefA* efflux	1	128	1	0.13	0.5
18	*Moraxella catarrhalis* #1	Susceptible	2	8	2	0.25	1
19	*M. catarrhalis* #2	Susceptible	1	8	2	0.25	2
20	*Haemophilus influenzae* #1	Susceptible	16	64	64	16	64
21	*H. influenzae* #2	Susceptible	1	8	4	1	2
22	*H. influenzae* #3	Susceptible	4	64	16	8	32
23	*H. influenzae* #4	Susceptible	8	128	16	8	16

* Constitutive.
** Inducible.
*** Test organism: *S. pneumoniae* #11 (*ermB* methylase(c)).

carosyl analogues (**R = H** in Fig. 6) did not exhibit remarkable activities (data are not shown).

2.6. Chemical modification of 16-membered azalides

We next examined possibilities of 16-membered azalides as a clinical candidate. First, 13-substituted analogues were synthesized as shown in Scheme 5. Thirteen-substituted 16-membered azalides were synthesized with 3-(methylaminomethyl)-5-hexen-1-ol[26] by a basically similar method as a synthetic route for 14-substituted 15-membered azalactams shown in Scheme 4. Macrolactonization successfully proceeded with Shiina protocol[27] using the anhydride instead of the acid chloride. When we used a novel method[28] in application of tri-*tert*-butyl phosphine in Heck reaction, isomers generated by rearrangement of the double bond were only detected. Then, a small amount of *cis-isomers* were detected accompanied with major *trans-isomers* in some cases. In this series (Scheme 5), Heck reactions with other bromoquinolines, for example, 6-bromo-, 8-bromoquinoline, or 4-bromoisoquinoline, resulted in very low yield (15–25%, see Section 4). There might be



Scheme 4. Synthesis of 15-membered 11-azalactams with the quinolinylallyl group at the C-14 position. Reagents and conditions: (a) *N*-(3-azido-5-hexenyl)-*N*-methylamine (1.5 equiv), $NaBH_3CN$ (0.45 equiv), AcOH (8.4 equiv), EtOH, rt, 21 h, 54%; (b) PMe_3 (3.0 equiv), 10% H_2O/MeCN, 80 °C, 6.5 h, 53%; (c) $(PhO)_2PON_3$ (3.4 equiv), $NaHCO_3$ (18 equiv), DMF, rt, 19 h, 73% (38% + 35%); (d) palladium (II) acetate (0.21 equiv), tri-*o*-tolylphosphine (0.4 equiv), 4-bromoquinoline (2.3 equiv), Et_3N (2.0 equiv), 47% for **50** (plus 7% for rearrangement product of double bond) and 52% for **51** (plus 11% for rearrangement product of double bond); (e) MeOH, rt, 5 h, 86% for **52** and **53**; (f) difluoroacetic acid (30 equiv), MeCN/H_2O (1:1), rt, 25 h, 40% for **54** and 37% for **56** (total yield: 77%), 49% for **55** and 38% for **57** (total yield: 87%).

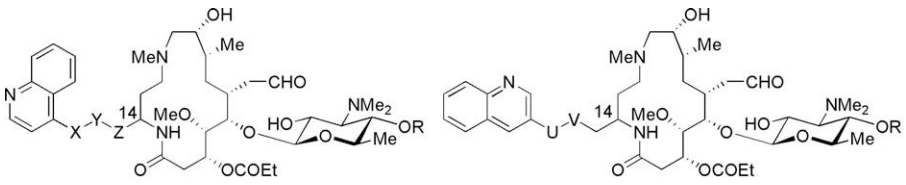
some relationships between these low yields and easy rearrangement of a double bond in the substituent at the C-13 position.

According to the synthetic method shown in Scheme 5, compounds **81**–**90** were prepared (Fig. 7). Because low yields and complicated rearrangement of the double bond of the 13-substituent during Heck reaction bothered us, we simultaneously performed synthetic studies of 15-substituted 16-membered azalides as shown in Scheme 6. Heck reaction of **92** or **93** with several kinds of bromoheterocycles afforded desired coupling products in rather higher yields compared to those of the reactions with **73** or **74**, and double bond rearrangement products could not be clearly detected (Fig. 8).

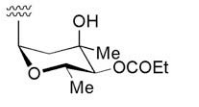
In this 15-substituted 16-membered azalides series, we first prepared both diastereoisomers at the C-15 position and did not define their stereochemistry. Antibacterial activities of these molecules (vide infra, Table 6), however, were good enough for further modifications, so we defined their stereochemistry at the C-15 and established the synthetic method for efficient preparation of single diastereoisomer of 15-substituted 16-membered azalides. As later mentioned, β-isomers exhibited stronger activities against the inducible *erm*-type resistant bacteria of *S. pneumoniae*. In order to synthesize only β-isomer (Fig. 8) at the C-15, we prepared compound **93** in the stereoselective manner. The coupling reaction of **36** with (*R*)-7-methylamino-1-hepten-4-ol[20] gave (15*R*)-**91** (seco acid of **93**) as a single diastereoisomer. Macrolactonization of this compound afforded a 16-membered azalide whose spectral data were consistent with those of compound **93**. (*R*)-7-Methylamino-1-hepten-4-ol was prepared from D-ornithine hydrochloride via eight steps.[20]

2.7. SAR analysis of optimized 16-membered azalides

Antibacterial activities of 13-substituted 16-membered azalides and 15-substituted 16-membered azalides are shown in Tables 5 and 6, respectively. Almost all 16-membered azalides possessing an arylalkyl substituent at the C-13 or C-15 exhibited well-balanced antibacterial activities for upper and lower respiratory pathogens (*S. pneumoniae, Streptococcus pyogenes, M. catarrhalis*, and *H. influenzae*) and very effective against the *mef*-type resistant bacteria of *S. pneiumoniae*. They are also somehow effective against the inducible *erm*-type resistant bacteria of *S. pneumoniae* (except compounds **80**, **83**, and **85**). Because several compounds synthe-



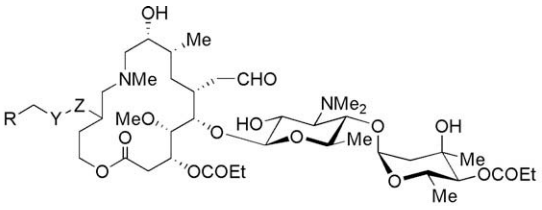
Compd	X-Y-Z*[a]	U-V*[a]	R
54*[b]	$CH=CHCH_2$		4-*O*-propionyl-α-L-mycarosyl
55*[b]	$CH=CHCH_2$		4-*O*-propionyl-α-L-mycarosyl
56*[c]	$CH=CHCH_2$		H
57*[c]	$CH=CHCH_2$		H
58*[d]	$CH_2CH=CH$		4-*O*-propionyl-α-L-mycarosyl
59*[d]	$CH_2CH=CH$		4-*O*-propionyl-α-L-mycarosyl
60*[e]	$CH_2CH_2CH_2$		4-*O*-propionyl-α-L-mycarosyl
61*[f]	$CH_2CH_2CH_2$		H
62*[e]	$CH_2CH_2CH_2$		4-*O*-propionyl-α-L-mycarosyl
63*[f]	$CH_2CH_2CH_2$		H
64*[g]		CH=CH	4-*O*-propionyl-α-L-mycarosyl
65		CH=CH	H
66*[g]		CH=CH	4-*O*-propionyl-α-L-mycarosyl
67*[h]		CH_2CH_2	4-*O*-propionyl-α-L-mycarosyl
68*[i]		CH_2CH_2	H
69*[h]		CH_2CH_2	4-*O*-propionyl-α-L-mycarosyl
70*[i]		CH_2CH_2	H



4-*O*-propionyl-α-L-mycarosyl

*[a]: All double bonds are "trans" geometry;
*[b-i]: These compounds are diastereoisomers at the C-14 position. Each sterochemistry is not defined;

Figure 6. Fourteen-substituted 15-membered azalactams.

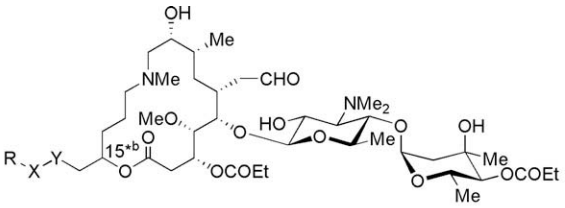


Compd	R	Y-Z
79*[a]	Quinolin-3-yl	CH=CH*[b]
80*[a]	Quinolin-3-yl	CH=CH*[b]
81	Quinolin-3-yl	CH=CH*[c]
82*[d]	Quinolin-4-yl	CH=CH*[b]
83*[d]	Quinolin-4-yl	CH=CH*[b]
84*[e]	Quinolin-4-yl	CH=CH*[c]
85*[e]	Quinolin-4-yl	CH=CH*[c]
86*[f]	Quinolin-4-yl	CH_2CH_2
87*[f]	Quinolin-4-yl	CH_2CH_2
88*[g]	Quinolin-6-yl	CH=CH*[b]
89*[g]	Quinolin-8-yl	CH=CH*[b]
90*[g]	Isoquinolin-4-yl	CH=CH*[b]

*[a, d-f]: These compounds are diastereoisomers at the C-13 position. Each sterochemistry is not defined;
*[b]: Double bonds are "trans" geometry; *[c]: Double bonds are "cis" geometry;
*[g]: Diastereoisomers at the C-13 of these compounds were not synthesized

Figure 7. Thirteen-substituted 16-membered azalides.

sized by Heck reaction using 4-bromoquinoline exhibited strong antibacterial activities, we defined their stereochemistry at the C-15. Comparing antibacterial activities of **98** and **100** with those of **99** and **101**, these analogues possessing β-configuration at the C-15 exhibited stronger activities against the inducible *erm*-type resistant bacteria of *S. pneumoniae* than the corresponding α-diastereoisomers. Thus, we prepared β-isomer only for other analogues. Among these compounds, **104** and **105** possessing the naphthalene ring exhibited weak response to the constitutive *erm*-type resistant bacteria of *S. pneumoniae*, although their activities against *H. influenzae* were decreased. For example, compounds **106** and **107** with the 3-quinolinyl moiety showed more potent antibacterial activities compared to MDM against almost all test organisms, and were active against the inducible *erm*-type and the *mef*-type resistant bacteria of *S. pneumoniae*. According to the above SAR studies, 15-substituted 16-membered azalides might



Compd*a	R	X-Y	Configuration*b
98	Quinolin-4-yl	CH=CH	α
99	Quinolin-4-yl	CH=CH	β
100	Quinolin-4-yl	CH_2CH_2	α
101	Quinolin-4-yl	CH_2CH_2	β
102	Phenyl	CH=CH	β
103	Pyridin-3-yl	CH=CH	β
104	α-Naphthyl	CH=CH	β
105	β-Naphthyl	CH=CH	β
106	Quinolin-3-yl	CH=CH	β
107	Quinolin-3-yl	CH_2CH_2	β
108	Quinolin-6-yl	CH=CH	β

*a: All double bonds are "trans" geometry; *b: Configuration at the C-15

Figure 8. Fifteen-substituted 16-membered azalides.

Table 4
Antibacterial activities of 14-substituted 15-membered azalactams.

	Test organism	Characteristics	(MIC, μg/ml)									
			54	**55**	**58**	**59**	**60**	**62**	**64**	**66**	**67**	**69**
1	*Staphylococcus aureus* 209P JC-1	Susceptible	1	4	0.5	2	1	4	0.5	1	0.5	1
2	*S. aureus* #2	Susceptible	2	8	1	4	1	8	1	2	1	2
3	*S. aureus* #3	Susceptible	0.5	2	0.5	1	0.5	2	0.25	0.5	0.25	0.5
4	*S. aureus* #4	*ermA* (c)*	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
5	*S. aureus* #5	*ermB* (i)**	0.5	2	0.5	2	1	4	0.5	1	0.5	0.5
6	*S. aureus* #6	*ermC* (i)	1	4	0.5	2	1	4	1	1	0.5	0.5
7	*Streptococcus pneumoniae* DP1 TypeI	Susceptible	0.13	0.25	0.03	0.13	0.06	0.13	0.06	0.13	0.03	0.03
8	*S. pneumoniae* #2	Susceptible	0.13	0.25	0.13	0.25	0.13	0.25	0.13	0.25	0.06	0.06
9	*S. pneumoniae* #3	Susceptible	0.25	0.25	0.06	0.25	0.13	0.25	0.13	0.25	0.06	0.06
10	*S. pneumoniae* #4	*ermB* (c)	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
11	*S. pneumoniae* #5	*ermB* + *mefA* (c)	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
12	*S. pneumoniae* #6	*ermB* (c)	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
13	*S. pneumoniae* #7	*ermB* (i)	>128	>128	8	64	32	64	32	>128	16	8
14	*S. pneumoniae* #8	*ermB* (i)	>128	>128	8	64	32	64	32	>128	64	8
15	*S. pneumoniae* #9	*mefA* efflux	0.25	0.5	0.13	0.25	0.13	0.25	0.13	0.5	0.06	0.06
16	*S. pneumoniae* #10	*mefA* efflux	0.25	0.25	0.13	0.25	0.13	0.25	0.13	0.25	0.06	0.06
17	*Streptococcus pyogenes* #1	susceptible	0.5	0.5	0.25	0.5	0.25	0.5	0.25	0.5	0.13	0.25
18	*S. pyogenes* #2	*ermB* (c)	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
19	*S. pyogenes* #3	*mefA* efflux	2	2	1	2	2	2	1	4	0.5	1
20	*Moraxella catarrhalis* #1	Susceptible	2	8	1	4	2	8	2	8	2	8
21	*M. catarrhalis* #2	Susceptible	1	4	2	4	2	8	2	4	2	4
22	*Haemophilus influenzae* #1	Susceptible	64	64	32	32	32	64	32	64	32	32
23	*H. influenzae* #2	Susceptible	2	4	1	1	2	2	2	4	1	2
24	*H. influenzae* #3	Susceptible	16	16	8	8	8	16	16	16	8	8
25	*H. influenzae* #4	Susceptible	32	16	8	16	8	8	16	32	16	16

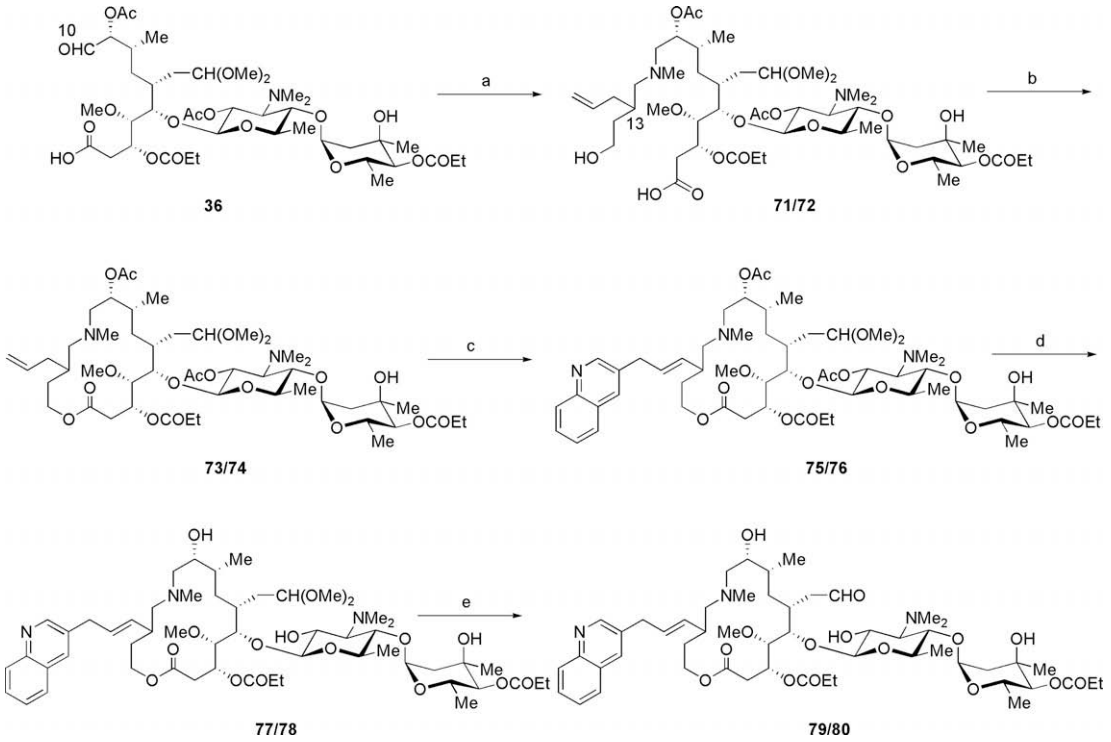
* Constitutive.
** Inducible.

be recognized as attractive lead compounds for further chemical modifications toward a clinical candidate.

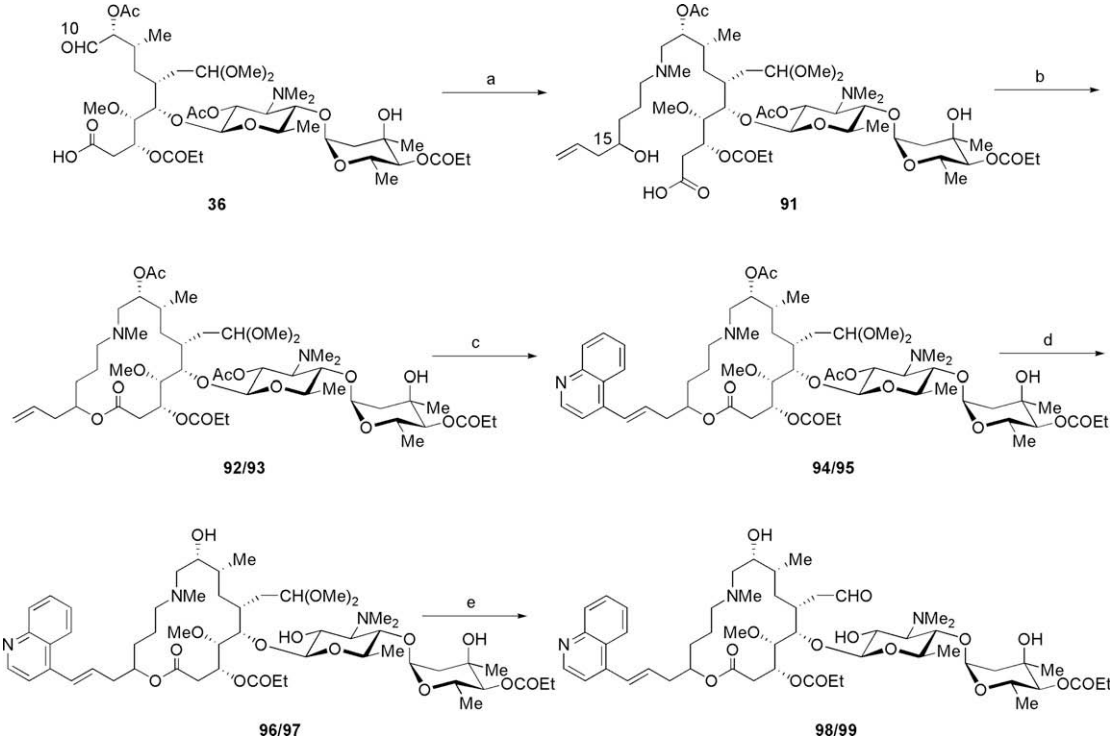
3. Conclusion

We have been studying new templates to explore novel semi-synthetic macrolide antibiotics that are effective against both resistant *S. pneumoniae* and *H. influenzae*. In order to discover a new efficient template, we chose 16-membered macloride as starting material, because it has been proven to be clinically safe and effective against the *mef*-type resistant bacteria of *S. pneumoniae*. As the first step of our research, we developed one-pot macrocyclization and synthesis of 15-membered azalides and 16-membered diazalide.[8] This approach, however, could only provide limited structural diversity (Fig. 2). Then, we utilized 9-formylcarboxylic acid (**2**) as a key intermediate for sequential macrocyclization to provide a variety of novel templates.

We prepared 14- to 16-membered azalides and 14- to 16-membered azalactams using this key intermediate (**2**). Among them, 15-membered azalactams and 16-membered azalides were chosen as



Scheme 5. Synthesis of 13-substituted 16-membered azalides. Reagents and conditions: (a) i—3-(methylaminomethyl)-5-hexen-1-ol (1.5 equiv), AcOH (10 equiv), molecular sieves 3A, DMF, rt, 4 h; ii—$NaBH_4$ (1.0 equiv), rt, 1.5 h, 40% for **71** and 30% for **72** (total yield: 70%); (b) 2-methy-6-nitrobenzoic anhydride (1.5 equiv), DMAP (3.0 equiv), CH_2Cl_2, 0 °C, 4.5 h, 63% for **73** and 54% for **74**; (c) 3-bromoquinoline (2.0 equiv), tris(dibenzylideneacetone)dipalladium (0) (0.3 equiv), $^tBu_3P$ (0.6 equiv), dicyclohexylmethylamine (2.0 equiv), 1,4-dioxane, 50 °C, 48 h, 5.8% for **75** accompanied with 2.8% for its *cis*-isomer, total yield of this Heck reaction was 8.6%, 28% for **76**; (d) MeOH, 40 °C, 48 h, 33% for **77** and 21% for **78**; (e) difluoroacetic acid (30 equiv), MeCN–H_2O, rt, 25 h, 51% for **79** and 45% for **80**.



Scheme 6. Synthesis of 15-substituted 16-membered azalides. Reagents and conditions: (a) i—7-methylamino-1-hepten-4-ol (1.5 equiv), AcOH (10 equiv), molecular sieves 3A, DMF, rt, 4 h; ii—$NaBH_4$ (1.0 equiv), rt, 1.5 h, 66%; (b) 2-methy-6-nitrobenzoic anhydride (1.5 equiv), DMAP (3.0 equiv), CH_2Cl_2, 0 °C, 2.5 h and rt, 2 h, 21% for **92** and 47% for **93** (total yield: 68%); (c) 4-bromoquinoline (2.0 equiv), tris(dibenzylideneacetone)dipalladium (0) (0.3 equiv), $^tBu_3P$ (0.6 equiv), dicyclohexylmethylamine (2.0 equiv), 1, 4-dioxane, 50 °C, 48 h, 25% for **94** and 42% for **95**; (d) MeOH, rt, 5 h, 61% for **96**, 41% for **97**; (e) difluoroacetic acid (30 equiv), MeCN–H_2O, rt, 25 h, 51% for **98**, 61% for **99**.

Table 5
Antibacterial activities of 13-substituted 16-membered azalides.

	Test organism	Characteristics	(MIC, μg/ml)											
			79	**80**	**81**	**82**	**83**	**84**	**85**	**86**	**87**	**88**	**89**	**90**
1	*Staphylococcus aureus* 209P JC-1	Susceptible	0.13	0.25	0.5	0.13	0.25	0.25	2	0.25	0.25	0.13	0.25	0.25
2	*S. aureus* #2	Susceptible	0.25	0.5	1	0.5	1	1	4	0.5	0.5	0.25	0.5	0.5
3	*S. aureus* #3	Susceptible	0.13	0.25	0.25	0.13	0.25	0.25	2	0.25	0.25	0.13	0.25	0.13
4	*S. aureus* #4	*ermA* (c)*	>128	>128	>64	>128	>128	>128	>128	>128	>128	>128	>128	>128
5	*S. aureus* #5	*ermB* (i)**	0.13	0.25	0.25	0.13	0.25	0.25	2	0.25	0.25	0.13	0.25	0.13
6	*S. aureus* #6	*ermC* (i)	0.25	0.5	1	0.25	0.5	0.5	4	0.5	0.5	0.25	0.5	0.25
7	*Streptococcus pneumoniae* DP1 TypeI	Susceptible	<0.008	0.015	0.06	0.015	0.03	0.03	0.5	0.015	0.015	0.015	0.015	0.015
8	*S. pneumoniae* #2	Susceptible	0.03	0.06	0.25	0.03	0.06	0.06	1	0.03	0.06	0.03	0.015	0.03
9	*S. pneumoniae* #3	Susceptible	0.015	0.03	0.13	0.03	0.03	0.06	0.5	0.03	0.03	0.015	0.015	0.015
10	*S. pneumoniae* #4	*ermB* (c)	128	>128	>64	>128	>128	>128	>128	>128	>128	>128	128	128
11	*S. pneumoniae* #5	*ermB* + *mefA* (c)	128	>128	>64	>128	>128	>128	>128	>128	>128	>128	128	128
12	*S. pneumoniae* #6	*ermB* (c)	128	>128	>64	>128	>128	>128	>128	>128	>128	128	128	128
13	*S. pneumoniae* #7	*ermB* (i)	1	128	8	8	128	8	>128	16	16	2	8	8
14	*S. pneumoniae* #8	*ermB* (i)	1	128	8	8	128	8	>128	16	16	2	8	8
15	*S. pneumoniae* #9	*mefA* efflux	0.015	0.06	0.13	0.03	0.06	0.06	1	0.03	0.06	0.015	0.03	0.015
16	*S. pneumoniae* #10	*mefA* efflux	0.015	0.06	0.13	0.03	0.06	0.06	1	0.03	0.06	0.015	0.03	0.03
17	*Streptococcus pyogenes* #1	Suseptible	0.03	0.13	0.13	0.03	0.13	0.13	1	0.06	0.06	0.03	0.06	0.03
18	*S. pyogenes* #2	*ermB* (c)	>128	>128	>64	>128	>128	>128	>128	>128	>128	>128	>128	>128
19	*S. pyogenes* #3	*mefA* efflux	0.13	0.5	0.5	0.13	0.25	0.5	4	0.25	0.25	0.25	0.25	0.25
20	*Moraxella catarrhalis* #1	Susceptible	1	2	2	1	2	2	16	1	1	1	1	1
21	*M. catarrhalis* #2	Susceptible	1	2	2	1	2	2	16	1	1	1	2	1
22	*Haemophilus influenzae* #1	Susceptible	32	64	>64	16	32	64	>128	32	16	32	32	32
23	*H. influenzae* #2	Susceptible	2	4	8	NT	4	NT	32	NT	2	2	2	2
24	*H. influenzae* #3	Susceptible	8	16	16	8	16	16	128	8	8	8	8	8
25	*H. influenzae* #4	Susceptible	4	16	16	8	16	16	128	8	8	8	8	8

NT, not tested.
* Constitutive.
** Inducible.

Table 6
Antibacterial activities of 15-substituted 16-membered azalides.

	Test organism	Characteristics	(MIC, μg/ml)										
			98	**99**	**100**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**
1	*Staphylococcus aureus* 209P JC-1	Susceptible	0.5	0.25	0.25	0.5	0.5	0.5	1	0.5	0.5	0.13	0.25
2	*S. aureus* #2	Susceptible	1	1	0.5	1	1	1	2	2	1	0.25	0.5
3	*S. aureus* #3	Susceptible	0.25	0.25	0.25	0.25	0.25	0.25	0.5	0.5	0.25	0.13	0.25
4	*S. aureus* #4	*ermA* (c)*	>128	>128	>128	>128	>128	>128	>128	64	>128	>128	>128
5	*S. aureus* #5	*ermB* (i)**	0.25	0.25	0.25	0.5	0.25	0.25	0.5	0.5	0.25	0.13	0.25
6	*S. aureus* #6	*ermC* (i)	0.5	0.5	0.5	0.5	0.5	0.5	1	1	0.5	0.25	0.25
7	*Streptococcus pneumoniae* DP1 TypeI	Susceptible	0.13	0.03	0.03	0.03	0.03	0.015	0.06	0.06	0.015	<0.008	0.015
8	*S. pneumoniae* #2	Susceptible	0.13	0.06	0.06	0.06	0.06	0.03	0.13	0.06	0.03	0.015	0.03
9	*S. pneumoniae* #3	Susceptible	0.06	0.015	0.06	0.06	0.06	0.03	0.06	0.13	0.03	<0.008	0.015
10	*S. pneumoniae* #4	*ermB* (c)	>128	>128	>128	>128	128	>128	64	32	128	128	>128
11	*S. pneumoniae* #5	*ermB* + *mefA* (c)	>128	>128	>128	>128	>128	>128	64	32	128	128	>128
12	*S. pneumoniae* #6	*ermB* (c)	>128	>128	>128	>128	>128	>128	64	32	128	128	>128
13	*S. pneumoniae* #7	*ermB* (i)	32	8	32	8	2	32	4	8	8	4	8
14	*S. pneumoniae* #8	*ermB* (i)	32	4	32	8	4	32	2	8	8	4	8
15	*S. pneumoniae* #9	*mefA* efflux	0.13	0.06	0.06	0.06	0.06	0.03	0.06	0.13	0.06	0.015	0.03
16	*S. pneumoniae* #10	*mefA* efflux	0.13	0.06	0.06	0.06	0.06	0.03	0.06	0.13	0.03	0.015	0.03
17	*Streptococcus pyogenes* #1	susceptible	0.25	0.13	0.13	0.06	0.13	0.06	0.25	0.25	0.06	0.015	0.06
18	*S. pyogenes* #2	*ermB* (c)	>128	>128	>128	>128	>128	>128	64	32	>128	>128	>128
19	*S. pyogenes* #3	*mefA* efflux	0.5	0.5	0.5	0.5	0.5	0.5	1	1	0.5	0.13	0.25
20	*Moraxella catarrhalis* #1	Susceptible	2	1	2	2	1	1	2	2	1	1	1
21	*M. catarrhalis* #2	Susceptible	4	1	2	2	1	1	2	2	1	1	1
22	*Haemophilus influenzae* #1	Susceptible	64	32	64	32	64	32	64	32	32	32	32
23	*H. influenzae* #2	Susceptible	8	2	4	4	8	2	16	8	2	2	4
24	*H. influenzae* #3	Susceptible	16	8	8	16	16	8	16	16	8	8	8
25	*H. influenzae* #4	Susceptible	16	8	8	16	8	16	16	16	8	8	8

* Constitutive.
** Inducible.

characteristic templates, and modified. As we expected, the activities against *H. influenzae* of 15-membered azalactams were generally stronger than those of MDM, but their activities against the *erm*-type resistant bacteria of *S. pneumoniae* were none or weak as a lead compound for further modifications. Although several optimized 14-substituted 15-membered azalactams exhibited stronger activities against *H. influenzae* than MDM and kept one of positive characters of 16-membered maclorides, that is, effectiveness against the *mef*-type resistant bacteria of *S. pneumoniae*, they are not enough as lead compounds for further modifications.

On the other hand, several optimized 13-substituted and 15-substituted 16-membered azalides exhibited well-balanced anti-

bacterial activities for upper and lower respiratory pathogens and very effective against the *mef*-type resistant bacteria of *S. pneumoniae*. They are also somehow effective against the inducible *erm*-type resistant bacteria of *S. pneumoniae*. Although there were not big differences between 13-substituted and 15-substituted analogues, we chose 15-substituted 16-membered azalides with β-configuration at the C-15 for further modifications toward a clinical candidate, because they have higher yields and less rearrangements of the double bond during Heck reaction. Optimization of structure of the arylalkyl moiety and modification at the neutral sugar moiety[29] for improvement of pharmacokinetics would be soon investigated.

4. Experimental

4.1. Chemistry

Optical rotations were measured on a Perkin-Elmer 241 Polarimeter or Jasco P-1030 Polarimeter. Fast-atom bombardment (FAB) mass spectra and high-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 instrument. ^{1}H NMR spectra were recorded on Varian Gemini-300 spectrometers for 300 MHz with chemical shifts reported in ppm relative to internal tetramethylsilane. Silica gel chromatography and preparative TLC were performed on Wako C-200 or C-300 and Merck TLC 60F_{254} Art. 5744, respectively. Evaporation was carried out under reduced pressure below 35 °C, unless otherwise noted.

4.1.1. Synthesis of 2

Compound **1**[8] (3.20 g, 3.23 mmol) was dissolved in acetonitrile (64 ml), and 1, 8-diazabicyclo[5.4.0]-7-undecene (0.72 ml, 4.82 mmol) was added. The solution was kept at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure, and then extracted with chloroform, and the organic layer was washed with saturated brine. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (chloroform/methanol (50:1 to 30:1)) to obtain 1.04 g (35%) of **2** as a colorless solid; FAB-MS *m*/*z* 922 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.03 (d, 8-CH_3), 1.07 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.42 (s, 3″-CH_3), 1.51 (m, 6-CH_2), 1.68 (dd, 2″-Hax), 1.86 (m, 6-CH_2), 2.03 (s, 3″-$OCOCH_3$), 2.06 (s, 2′-$OCOCH_3$), 2.15 (m, 8-H), 2.20 (s, 9-$OCOCH_3$), 2.43 (s, 3′-$N(CH_3)_2$), 2.62 (t, 3′-H), 2.69 (dd, 2-H), 2.83 (dd, 2-H), 3.13 (t, 4′-H), 3.18 (s, $CH(OCH_3)_2$), 3.19 (d, 2″-Heq), 3.26 (s, $CH(OCH_3)_2$), 3.48 (br d, 4-H), 3.55 (s, 4-OCH_3), 3.83 (br d, 5-H), 4.44 (dd, $CH(OCH_3)_2$), 4.49 (dq, 5″-H), 4.57 (d, 4″-H), 4.66 (d, 1′-H), 4.81 (d, 1″-H), 4.87 (d, 9-H), 5.24 (br dd, 3-H), 9.56 (s, 10-H).

Compound **3**[8] (4.00 g, 3.79 mmol) was dissolved in benzene (130 ml), and sodium carbonate (3.22 g, 30.4 mmol) was added. Moreover, lead tetraacetate (4.20 g, 9.47 mmol) was added with five portions for 20 min. The reaction mixture was stirred at room temperature for 1 h, and then the supernatant was transferred to a separating funnel. The residue was extracted with benzene, and the supernatant was transferred to the same funnel. The same procedure was repeated three times. The combined organic layer was washed with mixture of water and saturated aqueous sodium bicarbonate. The organic layer was further washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to obtain crude **1**. This was dissolved in acetonitrile (78 ml), and 1, 8-diazabicyclo[5.4.0]-7-undecene (0.85 ml, 5.70 mmol) was added. After the solution was kept at room temperature for 6 h, the reaction mixture was concentrated. The residue was extracted with chloroform and the organic layer was washed with saturated brine. The organic layer was separated, and then the aqueous layer was extracted with chloroform. The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (chloroform/methanol (50:1 to 30:1)) to obtain 1.82 g (52% via two steps) of **2** as a colorless solid.

4.1.2. Synthesis of 4

Compound **2** (400 mg, 0.434 mmol) and 3-(4-phenylbutylamino)propanol (135 mg, 0.651 mmol) were dissolved in dimethylformamide (1.0 ml). Molecular sieves 3A (800 mg) and acetic acid (0.25 ml, 4.37 mmol) were added and the reaction mixture was stirred at room temperature for 4 h. Then, sodium borohydride (17.1 mg, 0.452 mmol) was added, and further stirred at the same temperature for 1.5 h. The reaction mixture was filtered through Celite by using ethyl acetate (100 ml). The filtrate was successively washed twice with water (30 ml) and twice with saturated brine (30 ml). The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol (80:1 to 30:1)) to obtain 314 mg (65%) of **4** as a colorless solid; $[\alpha]_D^{23}$ −66° (*c* 0.65, $CHCl_3$); FAB-MS *m*/*z* 1113 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 0.87 (d, 8-CH_3), 1.03 (br dd, 7-H), 1.07 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.30 (m, 7-H), 1.42 (s, 3″-CH_3), 1.66 (dd, 2″-Hax), 1.85 (m, 8-H), 1.98 (s, 3″-$OCOCH_3$), 2.03 (s, 9-$OCOCH_3$), 2.03 (s, 2′-$OCOCH_3$), 2.43 (s, 3′-$N(CH_3)_2$), 2.62 (t, 3′-H), 2.88 (dd, 2-H), 3.12 (t, 4′-H), 3.19 (d, 2″-Heq), 3.20 (s, $CH(OCH_3)_2$), 3.26 (s, $CH(OCH_3)_2$), 3.54 (br d, 4-H), 3.57 (s, 4-OCH_3), 3.88 (br d, 5-H), 4.49 (dq, 5″-H), 4.53 (dd, $CH(OCH_3)_2$), 4.57 (d, 4″-H), 4.72 (d, 1′-H), 4.80 (d, 1″-H), 4.95 (dd, 2′-H), 5.24 (br dd, 9-H), 5.32 (br d, 3-H), 7.12–7.34 (m, C_6H_5).

4.1.3. Synthesis of 5

Compound **4** (132 mg, 0.119 mmol) was dissolved with tetrahydrofuran (3.5 ml), and triethylamine (0.032 ml, 0.223 mmol) and 2,4,6-trichlorobenzoyl chloride (0.022 ml, 0.141 mmol) were added. The solution was kept at room temperature for 2 h. The reaction mixture was poured into a solution of 4-dimethylaminopyridine (86.9 mg, 0.711 mmol) in anhydrous benzene (23 ml) in a dropwise manner over 30 min under ice cooling. The mixture was further stirred for 1 h at room temperature, and then water was added. Macrolactone was extracted with ethyl acetate, and the organic layer was successively washed with water, saturated aqueous sodium bicarbonate, and saturated brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (chloroform/ethyl acetate (15:1 to 5:1)), and further purified by preparative TLC (chloroform/ethyl acetate (2:1)) to obtain 55.9 mg (43%) of **5** as a colorless solid; $[\alpha]_D^{19}$ −85° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1095 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 8-CH_3), 1.07 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.42 (s, 3″-CH_3), 1.68 (dd, 2″-Hax), 1.99 (s, 3″-$OCOCH_3$), 2.02 (s, 9-$OCOCH_3$), 2.04 (s, 2′-$OCOCH_3$), 2.44 (s, 3′-$N(CH_3)_2$), 2.62 (t, 3′-H), 2.74 (dd, 2-H), 2.86 (dd, 2-H), 3.12 (s, $CH(OCH_3)_2$), 3.15 (t, 4′-H), 3.19 (d, 2″-Heq), 3.25 (s, $CH(OCH_3)_2$), 3.27 (m, 5′-H), 3.36 (br d, 4-H), 3.53 (s, 4-OCH_3), 3.95 (br d, 5-H), 4.08 (m, 14-H), 4.41 (m, 14-H), 4.48 (m, 5″-H), 4.57 (d, 4″-H), 4.67 (d, 1′-H), 4.77 (m, 9-H), 4.81 (d, 1″-H), 4.97 (dd, 2′-H), 5.17 (m, 3-H), 7.14–7.31 (m, C_6H_5).

4.1.4. Synthesis of 7 and 8

Compound **5** (84.0 mg, 0.0767 mmol) was dissolved in methanol (3.4 ml) and the solution was kept at room temperature for 76 h. The reaction mixture was concentrated, and the resulting residue was purified by preparative TLC (chloroform/methanol (30:1))

to obtain 25.8 mg (32%) of **7** as a colorless solid and 18.6 mg (24%) of **8** as a colorless solid. Total yield of this reaction was 56%. Compound **7**: $[\alpha]_D^{20}$ −60° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1053 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.92 (d, 8-CH_3), 1.09 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.21 (d, 6′-H), 1.42 (s, 3″-CH_3), 1.47 (quint, $C_6H_5(CH_2)_4$), 1.59 (quint, $C_6H_5(CH_2)_4$), 1.70 (dd, 2″-Hax), 2.00 (s, 3″-$OCOCH_3$), 2.02 (s, 9-$OCOCH_3$), 2.55 (s, 3′-$N(CH_3)_2$), 2.61 (t, $C_6H_5(CH_2)_4$), 2.75 (dd, 2-H), 2.89 (dd, 2-H), 3.15 (s, $CH(OCH_3)_2$), 3.23 (d, 2″-Heq), 3.27 (s, $CH(OCH_3)_2$), 3.42 (dd, 2′-H), 3.47 (br d, 4-H), 3.61 (s, 4-OCH_3), 3.94 (br d, 5-H), 4.09 (m, 14-H), 4.39 (m, 14-H), 4.47 (d, 1′-H), 4.48 (dd, $CH(OCH_3)_2$), 4.56 (m, 5″-H), 4.59 (d, 4″-H), 4.81 (m, 9-H), 4.86 (d, 1″-H), 5.21 (m, 3-H), 7.14–7.29 (m, C_6H_5). Compound **8**: $[\alpha]_D^{20}$ −51° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1011 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.93 (d, 8-CH_3), 1.07 (d, 6″-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.40 (s, 3″-CH_3), 1.68 (dd, 2″-Hax), 2.00 (s, 3″-$OCOCH_3$), 2.53 (s, 3′-$N(CH_3)_2$), 2.64 (dd, 2-H), 2.81 (dd, 2-H), 3.09 (s, $CH(OCH_3)_2$), 3.20 (m, 5′-H), 3.21 (d, 2″-Heq), 3.24 (m, 4′-H), 3.24 (s, $CH(OCH_3)_2$), 3.39 (dd, 2′-H), 3.50 (br d, 4-H), 3.62 (s, 4-OCH_3), 3.90 (br d, 5-H), 4.10 (m, 14-H), 4.28 (m, 14-H), 4.48 (dd, $CH(OCH_3)_2$), 4.48 (d, 1′-H), 4.54 (m, 5″-H), 4.57 (d, 4″-H), 4.84 (d, 1″-H), 5.23 (m, 3-H), 7.12–7.30 (m, C_6H_5).

4.1.5. Synthesis of 12

Compound **7** (30.0 mg, 0.0285 mmol) was dissolved in an equivolume mixed solvent of acetonitrile–water (1.2 ml), and difluoroacetic acid (0.054 ml, 0.859 mmol) was added. The solution was kept at room temperature for 25 h. The reaction mixture was diluted with chloroform, and washed with saturated aqueous sodium bicarbonate. The organic layer was further successively washed with saturated aqueous sodium bicarbonate, and saturated brine, dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated, and the resulting residue was purified by preparative TLC (chloroform/methanol (25:1)) to obtain 22.4 mg (78%) of **12** as a colorless solid; $[\alpha]_D^{19}$ −67° (*c* 0.67, $CHCl_3$); FAB-MS *m*/*z* 1007 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{82}N_2O_{17}$: 1007.5692. Found: 1007.5684 $(M+H)^+$; ^1H NMR $CDCl_3$) δ 0.91 (d, 8-CH_3), 1.08 (d, 6″-H), 1.13 (d, 6′-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.40 (s, 3″-CH_3), 1.69 (dd, 2″-Hax), 1.99 (s, 3″-$OCOCH_3$), 1.99 (s, 9-$OCOCH_3$), 2.04 (m, 6-H), 2.34 (dd, 6-CH_2), 2.54 (s, 3′-$N(CH_3)_2$), 2.70 (dd, 2-H), 2.87 (dd, 2-H), 2.93 (dd, 6-CH_2), 3.20 (m, 4′-H), 3.20 (m, 5′-H), 3.21 (d, 2″-Heq), 3.32 (dd, 2′-H), 3.51 (dd, 4-H), 3.61 (s, 4-OCH_3), 3.90 (br d, 5-H), 4.10 (m, 14-H), 4.32 (m, 14-H), 4.41 (d, 1′-H), 4.49 (dq, 5″-H), 4.57 (d, 4″-H), 4.79 (m, 9-H), 4.85 (d, 1″-H), 5.36 (m, 3-H), 7.14–7.29 (m, C_6H_5), 9.62 (s, CHO).

4.1.6. Preparation of 13

Reaction of **8** with difluoroacetic acid gave **13** in 73% yield by a similar procedure to **12**; $[\alpha]_D^{20}$ −65° (*c* 0.52, $CHCl_3$); FAB-MS *m*/*z* 965 $(M+H)^+$; HRMS: Calcd for $C_{50}H_{80}N_2O_{16}$: 965.5586. Found: 965.5587 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.96 (d, 8-CH_3), 0.98 (br dd, 7-H), 1.08 (d, 6″-H), 1.12 (d, 6′-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.40 (s, 3″-CH_3), 1.68 (dd, 2″-Hax), 1.99 (s, 3″-$OCOCH_3$), 2.54 (s, 3′-$N(CH_3)_2$), 2.82 (dd, 2-H), 2.96 (dd, 6-CH_2), 3.20 (m, 4′-H), 3.20 (m, 5′-H), 3.21 (d, 2″-Heq), 3.33 (dd, 2′-H), 3.45 (br d, 9-H), 3.53 (br d, 4-H), 3.62 (s, 4-OCH_3), 3.88 (br d, 5-H), 4.14 (m, 14-H), 4.25 (m, 14-H), 4.42 (d, 1′-H), 4.50 (dq, 5″-H), 4.57 (d, 4″-H), 4.84 (d, 1″-H), 5.37 (m, 3-H), 7.14–7.29 (m, C_6H_5), 9.63 (s, CHO).

4.1.7. Synthesis of 14

Compound **2** (134 mg, 0.145 mmol) was dissolved in ethanol (6.5 ml) under argon atmosphere, and 2-(4-phenylbutylamino)ethylazide (49.2 mg, 0.225 mmol) was added. Moreover, acetic acid (0.070 ml, 1.22 mmol) (8.4 equiv) and sodium borohydride (4.1 mg, 0.108 mmol) were added under ice cooling, and the mixture was stirred at room temperature for 21 h. The reaction mixture was diluted with ethyl acetate, and washed with 8% aqueous sodium bicarbonate. The aqueous layer was extracted twice with ethyl acetate. The organic layers were combined and washed with 25% brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (chloroform/methanol (30:1)) to obtain 85.0 mg (52%) of **14** as a colorless solid; $[\alpha]_D^{18}$ −64° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1124 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.87 (d, 8-CH_3), 1.07 (d, 6″-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.31 (m, 7-H), 1.41 (s, 3″-CH_3), 1.49 (m, 6-CH_2), 1.67 (dd, 2″-Hax), 1.90 (m, 6-CH_2), 2.00 (s, 3″-$OCOCH_3$), 2.03 (s, 9-$OCOCH_3$), 2.03 (s, 2′-$OCOCH_3$), 2.43 (s, 3′-$N(CH_3)_2$), 2.62 (t, 3′-H), 2.74 (dd, 2-H), 2.83 (m, 12-H), 3.13 (t, 4′-H), 3.19 (d, 2″-Heq), 3.22 (s, $CH(OCH_3)_2$), 3.26 (s, $CH(OCH_3)_2$), 3.53 (s, 4-OCH_3), 3.44 (br d, 4-H), 3.55 (m, 13-H), 3.88 (br d, 5-H), 4.50 (dq, 5″-H), 4.57 (d, 4″-H), 4.69 (d, 1′-H), 4.80 (d, 1″-H), 4.96 (dd, 2′-H), 7.12–7.33 (m, C_6H_5).

4.1.8. Synthesis of 15

Compound **14** (84.1 mg, 0.0748 mmol) was dissolved in tetrahydrofuran (5.0 ml) and water (0.5 ml), and triphenylphosphine (98.5 mg, 0.376 mmol) was added. The reaction mixture was stirred at 60 °C for 36 h, and then concentrated. The resulting residue was purified by silica gel column chromatography (chloroform/methanol (40:1 to 10:1)) to obtain 52.6 mg (64%) of **15** as a colorless solid; $[\alpha]_D^{20}$ −82° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1098 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.95 (d, 8-CH_3), 1.07 (d, 6″-H), 1.11 (t, 3-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.41 (s, 3″-CH_3), 1.67 (dd, 2″-Hax), 2.00 (s, 3″-$OCOCH_3$), 2.01 (s, 2′-$OCOCH_3$), 2.03 (s, 9-$OCOCH_3$), 2.43 (s, 3′-$N(CH_3)_2$), 2.61 (t, 3′-H), 3.13 (s, $CH(OCH_3)_2$), 3.19 (d, 2″-Heq), 3.24 (s, $CH(OCH_3)_2$), 3.55 (s, 4-OCH_3), 3.60 (br d, 4-H), 3.84 (br d, 5-H), 4.50 (dq, 5″-H), 4.57 (d, 4″-H), 4.71 (d, 1′-H), 4.80 (d, 1″-H), 4.96 (dd, 2′-H), 5.14 (br dd, 3-H), 7.12–7.33 (m, C_6H_5).

4.1.9. Synthesis of 16

Compound **15** (43.2 mg, 0.0393 mmol) was dissolved in dimethylformamide (9.0 ml) under argon atmosphere, and sodium bicarbonate (58.6 mg, 0.698 mmol) was added. Then, diphenylphosphoryl azide (0.030 ml, 0.133 mmol) was added under ice cooling, and the mixture was stirred at room temperature for 19 h. The reaction mixture was diluted with ethyl acetate, and washed twice with water, and once with 25% brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (ethyl acetate) to obtain 40.8 mg (96%) of **16** as a colorless solid; $[\alpha]_D^{20}$ −47° (*c* 0.43, $CHCl_3$); FAB-MS *m*/*z* 1080 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.88 (d, 8-CH_3), 1.07 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.42 (s, 3″-CH_3), 1.67 (dd, 2″-Hax), 1.77 (m, 8-H), 1.88 (m, 6-CH_2), 2.01 (s, 3″-$OCOCH_3$), 2.02 (s, 9-$OCOCH_3$), 2.02 (s, 2′-$OCOCH_3$), 2.43 (s, 3′-$N(CH_3)_2$), 2.93 (m, 13-H), 3.13 (s, $CH(OCH_3)_2$), 3.19 (d, 2″-Heq), 3.25 (s, $CH(OCH_3)_2$), 3.69 (s, 4-OCH_3), 3.93 (br d, 5-H), 4.50 (dq, 5″-H), 4.57 (d, 4″-H), 4.73 (d, 1′-H), 4.80 (d, 1″-H), 4.95 (dd, 2′-H), 5.05 (br dd, 3-H), 6.49 (br s,NH), 7.05–7.36 (m, C_6H_5).

4.1.10. Synthesis of 17

Compound **16** (40.0 mg, 0.0370 mmol) was dissolved in methanol (1.6 ml) and the solution was kept at room temperature for 5 h. The reaction mixture was concentrated, and the resulting residue was purified by preparative TLC (chloroform/methanol (30:1)) to obtain 27.0 mg (70%) of **17** as a colorless solid; $[\alpha]_D^{19}$ −38° (*c* 0.41, $CHCl_3$); FAB-MS *m*/*z* 1038 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.89 (d, 8-CH_3), 1.09 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-

$OCOCH_2CH_3$), 1.21 (d, 6′-H), 1.42 (s, 3″-CH_3), 1.69 (dd, 2″-Hax), 1.80 (m, 8-H), 2.02 (s, 9-$OCOCH_3$), 2.02 (s, 3″-$OCOCH_3$), 2.54 (s, 3′-$N(CH_3)_2$), 3.16 (s, $CH(OCH_3)_2$), 3.22 (d, 2″-Heq), 3.27 (s, $CH(OCH_3)_2$), 3.41 (dd, 2′-H), 3.46 (br d, 4-H), 3.67 (m, 13-H), 3.73 (s, 4-OCH_3), 3.95 (br d, 5-H), 4.59 (d, 4″-H), 4.80 (m, 9-H), 4.85 (d, 1″-H), 5.07 (br d, 3-H), 6.42 (br s, NH), 7.05–7.37 (m, C_6H_5).

4.1.11. Preparation of 18

Reaction of **17** with difluoroacetic acid gave **18** in 85% yield by a similar procedure to **12**; $[\alpha]_D^{18}$ −47° (*c* 0.34, $CHCl_3$); FAB-MS *m*/*z* 992 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{81}N_3O_{16}$: 992.5695. Found: 992.5705 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.86 (d, 8-CH_3), 1.09 (d, 6″-H), 1.14 (d, 6′-H), 1.19 (t, 3-$OCOCH_2CH_3$), 1.20 (t, 4″-$OCOCH_2CH_3$), 1.42 (s, 3″-CH_3), 1.69 (dd, 2″-Hax), 1.83 (m, 8-H), 2.01 (s, 9-$OCOCH_3$), 2.01 (s, 3″-$OCOCH_3$), 2.55 (s, 3′-$N(CH_3)_2$), 3.00 (m, 13-H), 3.07 (m, 6-CH_2), 3.22 (d, 2″-Heq), 3.34 (dd, 2′-H), 3.49 (br d, 4-H), 3.58 (m, 13-H), 3.73 (s, 4-OCH_3), 3.92 (br d, 5-H), 4.45 (d, 1′-H), 4.52 (dq, 5″-H), 4.59 (d, 4″-H), 4.78 (m, 9-H), 4.85 (d, 1″-H), 5.13 (br d, 3-H), 6.42 (br s, NH), 7.05–7.36 (m, C_6H_5), 9.63 (s, CHO).

4.1.12. According to synthesis of 12 and 13 shown in Scheme 1, azalides 19 and 22–25 were synthesized. Preparations of amino alcohols applied for synthesis of azalides were disclosed in our publication[20]

4.1.12.1 2′-O-Acetyl dimethylacetal of 19. $[\alpha]_D^{20}$ −66° (*c* 0.7, $CHCl_3$); FAB-MS *m*/*z* 1095 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.75 (m, 7-H), 0.92 (d, 8-CH_3), 1.07 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.21 (d, 6′-H), 1.22 (d, 13-CH_3), 1.42 (s, 3″-CH_3), 1.68 (dd, 2″-Hax), 2.02 (s, 3″-$OCOCH_3$), 2.04 (s, 9-$OCOCH_3$), 2.08 (s, 2′-$OCOCH_3$), 2.44 (s, 3′-$N(CH_3)_2$), 2.81 (dd, 12-H), 2.96 (dd, 2-H), 3.13 (m, 4′-H), 3.14 (s, $CH(OCH_3)_2$), 3.20 (d, 2″-Heq), 3.25 (s, $CH(OCH_3)_2$), 3.27 (m, 5′-H), 3.57 (s, 4-OCH_3), 3.71 (br d, 4-H), 3.86 (br d, 5-H), 4.45 (m, $CH(OCH_3)_2$), 4.47 (dq, 5″-H), 4.57 (d, 4″-H), 4.71 (d, 1′-H), 4.81 (d, 1″-H), 4.84 (m, 9-H), 4.98 (dd, 2′-H), 5.07 (m, 13-H), 5.18 (br d, 3-H), 7.05–7.36 (m, C_6H_5).

4.1.12.2. Compound 19. $[\alpha]_D^{20}$ −61° (*c* 0.6, $CHCl_3$); FAB-MS *m*/*z* 1007 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{82}N_2O_{17}$: 1007.5692. Found: 1007.5684 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.93 (d, 8-CH_3), 1.10 (d, 6″-H), 1.15 (d, 6′-H), 1.18 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.24 (d, 13-CH_3), 1.42 (s, 3″-CH_3), 1.55 (quint, $C_6H_5(CH_2)_4$), 1.71 (dd, 2″-Hax), 1.76 (m, 8-H), 2.01 (s, 3″-$OCOCH_3$), 2.04 (s, 9-$OCOCH_3$), 2.24 (dd, 6-CH_2), 2.37 (dd, 10-H), 2.56 (s, 3′-$N(CH_3)_2$), 2.61 (t, $C_6H_5(CH_2)_4$), 2.72 (dd, 12-H), 2.88 (dd, 10-H), 2.99 (dd, 2-H), 3.05 (dd, 6-CH_2), 3.23 (m, 4′-H), 3.23 (m, 5′-H), 3.23 (d, 2″-Heq), 3.35 (dd, 2′-H), 3.64 (s, 4-OCH_3), 3.87 (br s, 4-H), 3.87 (br s, 5-H), 4.43 (d, 1′-H), 4.50 (dq, 5″-H), 4.59 (d, 4″-H), 4.87 (d, 1″-H), 4.93 (m, 9-H), 5.07 (br dq, 13-H), 5.36 (br d, 3-H), 7.05–7.36 (m, C_6H_5), 9.63 (s, CHO).

4.1.12.3. 2′-O-Acetyl dimethylacetal of 22 (9,2′-di-*O*-acetyl dimethylacetal of 23). $[\alpha]_D^{21}$ −67° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 1123 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.89 (d, 8-CH_3), 1.07 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.23 (d, 15-CH_3), 1.36 (br dd, 7-H), 1.41 (s, 3″-CH_3), 1.67 (dd, 2″-Hax), 1.87 (br dd, 6-CH_2), 2.02 (s, 3″-$OCOCH_3$), 2.03 (s, 9-$OCOCH_3$), 2.05 (s, 2′-$OCOCH_3$), 2.43 (s, 3′-$N(CH_3)_2$), 2.80 (dd, 2-H), 3.13 (t, 4′-H), 3.15 (s, $CH(OCH_3)_2$), 3.19 (d, 2″-Heq), 3.24 (s, $CH(OCH_3)_2$), 3.33 (br d, 4-H), 3.52 (s, 4-OCH_3), 3.82 (br d, 5-H), 4.39 (dd, $CH(OCH_3)_2$), 4.48 (dq, 5″-H), 4.57 (d, 4″-H), 4.67 (d, 1′-H), 4.81 (d, 1″-H), 4.90 (m, 9-H), 4.90 (m, 15-H), 4.95 (dd, 2′-H), 5.32 (br t, 3-H), 7.13–7.32 (m, C_6H_5).

4.1.12.4. Compound 22. $[\alpha]_D^{23}$ −43° (*c* 0.54, $CHCl_3$); FAB-MS *m*/*z* 1035 $(M+H)^+$; HRMS: Calcd for $C_{54}H_{86}N_2O_{17}$: 1035.6005. Found: 1035.6007 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.89 (d, 8-CH_3), 1.04 (br dd, 7-H), 1.09 (d, 6″-H), 1.14 (d, 6′-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.24 (d, 15-CH_3), 1.42 (s, 3″-CH_3), 1.70 (dd, 2″-Hax), 1.98 (s, 9-$OCOCH_3$), 2.01 (s, 3″-$OCOCH_3$), 2.17 (m, 6-H), 2.26 (br d, 6-CH_2), 2.55 (s, 3′-$N(CH_3)_2$), 2.78 (dd, 2-H), 2.94 (dd, 6-CH_2), 3.22 (m, 4′-H), 3.22 (m, 5′-H), 3.22 (d, 2″-Heq), 3.34 (dd, 2′-H), 3.50 (dd, 4-H), 3.59 (s, 4-OCH_3), 3.85 (br d, 5-H), 4.42 (d, 1′-H), 4.51 (dq, 5″-H), 4.59 (d, 4″-H), 4.84 (m, 15-H), 4.85 (d, 1″-H), 4.95 (m, 9-H), 5.52 (m, 3-H), 7.16–7.27 (m, C_6H_5), 9.62 (s, CHO).

4.1.12.5. Compound 23. $[\alpha]_D^{24}$ −48° (*c* 0.64, $CHCl_3$); FAB-MS *m*/*z* 993 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{84}N_2O_{16}$: 993.5900. Found: 993.5896 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.85 (d, 8-CH_3), 1.04 (br dd, 7-H), 1.09 (d, 6″-H), 1.13 (d, 6′-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.23 (d, 15-CH_3), 1.31 (m, 8-H), 1.42 (s, 3″-CH_3), 1.69 (dd, 2″-Hax), 1.81 (br dd, 7-H), 2.01 (s, 3″-$OCOCH_3$), 2.15 (m, 6-H), 2.30 (br d, 6-CH_2), 2.55 (s, 3′-$N(CH_3)_2$), 2.94 (dd, 6-CH_2), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.22 (d, 2″-Heq), 3.36 (dd, 2′-H), 3.57 (br d, 4-H), 3.60 (s, 4-OCH_3), 3.80 (br dd, 9-H), 3.87 (br d, 5-H), 4.42 (d, 1′-H), 4.52 (dq, 5″-H), 4.59 (d, 4″-H), 4.77 (m, 15-H), 4.85 (d, 1″-H), 5.54 (br dd, 3-H), 7.14–7.32 (m, C_6H_5), 9.63 (s, CHO).

4.1.12.6. 9,2′-Di-O-acetyl dimethylacetal of 24 (polar than 9,2′-di-O-acetyl dimethylacetal of 25 in TLC developed by chloroform/ethyl acetate (1:2)). FAB-MS *m*/*z* 1121 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.91 (d, 8-CH_3), 1.07 (d, 6″-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.33 (d, 15-CH_3), 1.42 (s, 3″-CH_3), 1.67 (dd, 2″-Hax), 1.87 (br dd, 6-CH_2), 2.02 (s, 3″-$OCOCH_3$), 2.02 (s, 9-$OCOCH_3$), 2.05 (s, 2′-$OCOCH_3$), 2.44 (s, 3′-$N(CH_3)_2$), 2.78 (dd, 2-H), 3.14 (s, $CH(OCH_3)_2$), 3.19 (d, 2″-Heq), 3.24 (s, $CH(OCH_3)_2$), 3.55 (s, 4-OCH_3), 3.86 (br d, 5-H), 4.45 (dd, $CH(OCH_3)_2$), 4.49 (dq, 5″-H), 4.57 (d, 4″-H), 4.68 (d, 1′-H), 4.81 (d, 1″-H), 4.98 (dd, 2′-H), 5.06 (br d, 9-H), 5.17 (m, 3-H), 5.28 (dq, 15-H), 5.49 (dd, 14-H), 5.87 (m, 13-H), 7.13–7.31 (m, C_6H_5).

4.1.12.7. Compound 24. $[\alpha]_D^{23}$ −60° (*c* 0.35, $CHCl_3$); FAB-MS *m*/*z* 991 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{82}N_2O_{16}$: 991.5743. Found: 991.5739 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.87 (d, 8-CH_3), 1.09 (d, 6″-H), 1.14 (d, 6′-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.34 (d, 15-CH_3), 1.42 (s, 3″-CH_3), 1.48 (m, 8-H), 1.69 (dd, 2″-Hax), 2.01 (s, 3″-$OCOCH_3$), 2.55 (s, 3′-$N(CH_3)_2$), 2.66 (dd, 2-H), 2.79 (dd, 2-H), 2.96 (dd, 6-CH_2), 3.11 (m, 12-H), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.22 (d, 2″-Heq), 3.40 (m, 9-H), 3.40 (dd, 2′-H), 3.55 (dd, 4-H), 3.59 (s, 4-OCH_3), 3.93 (br d, 5-H), 4.44 (d, 1′-H), 4.54 (dq, 5″-H), 4.59 (d, 4″-H), 4.85 (d, 1″-H), 5.27 (dq, 15-H), 5.39 (br d, 3-H), 5.64 (dd, 14-H), 5.84 (m, 13-H), 7.14–7.31 (m, C_6H_5), 9.64 (s, CHO).

4.1.12.8. 9,2′-Di-*O*-acetyl dimethylacetal of 25 (less polar than 9,2′-di-*O*-acetyl dimethylacetal of 24 in TLC developed by chloroform/ethyl acetate (1:2)). $[\alpha]_D^{25}$ −55° (*c* 0.31, $CHCl_3$); FAB-MS *m*/*z* 1121 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.89 (d, 8-CH_3), 1.07 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.37 (d, 15-CH_3), 1.41 (s, 3″-CH_3), 1.67 (dd, 2″-Hax), 1.82 (br dd, 6-CH_2), 2.02 (s, 3″-$OCOCH_3$), 2.06 (s, 9-$OCOCH_3$), 2.08 (s, 2′-$OCOCH_3$), 2.43 (s, 3′-$N(CH_3)_2$), 2.86 (dd, 2-H), 2.98 (m, 12-H), 3.13 (s, $CH(OCH_3)_2$), 3.19 (d, 2″-Heq), 3.23 (s, $CH(OCH_3)_2$), 3.32 (br d, 4-H), 3.55 (s, 4-OCH_3), 3.88 (br d, 5-H), 4.43 (dd, $CH(OCH_3)_2$), 4.51 (dq, 5″-H), 4.57 (d, 4″-H), 4.67 (d, 1′-H), 4.80 (d, 1″-H), 4.96 (dd, 2′-H), 5.02 (m, 9-H), 5.15 (m, 3-H), 5.33 (dq, 15-H), 5.58 (dd, 14-H), 5.84 (m, 13-H), 7.15–7.29 (m, C_6H_5).

4.1.12.9. Compound 25. $[\alpha]_D^{23}$ −37° (*c* 0.39, $CHCl_3$); FAB-MS *m*/*z* 991 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{82}N_2O_{16}$: 991.5743. Found: 991.5747 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (m, 7-H), 0.97 (d, 8-CH_3), 1.09 (d, 6″-H), 1.13 (d, 6′-H), 1.18 (t, 3-

$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.33 (d, 15-CH_3), 1.42 (s, 3″-CH_3), 1.43 (m, 8-H), 1.55 (m, 7-H), 1.70 (dd, 2″-Hax), 2.01 (s, 3″-$OCOCH_3$), 2.05 (m, 6-H), 2.29 (dd, 6-CH_2), 2.55 (s, 3′-$N(CH_3)_2$), 2.80 (dd, 2-H), 2.87 (br dd, 12-H), 3.01 (dd, 6-CH_2), 3.21 (m, 5′-H), 3.22 (d, 2″-Heq), 3.23 (m, 4′-H), 3.33 (dd, 2′-H), 3.39 (dd, 4-H), 3.59 (s, 4-OCH_3), 3.91 (br d, 5-H), 4.40 (d, 1′-H), 4.52 (dq, 5″-H), 4.59 (d, 4″-H), 4.86 (d, 1″-H), 5.25 (dq, 15-H), 5.39 (br dd, 3-H), 5.49 (dd, 14-H), 5.86 (m, 13-H), 7.16–7.31 (m, C_6H_5), 9.62 (s, CHO).

4.1.13. Azalactams 26–33 were synthesized by a similar procedure to 18 as shown in Scheme 2. Preparations of azidoamines applied for synthesis of azalactams were disclosed in our publication[20]

4.1.13.1. Compound 26. $[\alpha]_D^{18}$ −58° (*c* 0.39, $CHCl_3$); FAB-MS *m*/*z* 1006 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{83}N_3O_{16}$: 1006.5852. Found: 1006.5848 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.89 (d, 8-CH_3), 1.09 (d, 6″-H), 1.14 (d, 6′-H), 1.19 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.24 (d, 13-CH_3), 1.42 (s, 3″-CH_3), 1.70 (dd, 2″-Hax), 1.85 (m, 8-H), 2.02 (s, 9-$OCOCH_3$), 2.02 (s, 3″-$OCOCH_3$), 2.30 (dd, 6-CH_2), 2.55 (s, 3′-$N(CH_3)_2$), 3.09 (dd, 6-CH_2), 3.22 (d, 2″-Heq), 3.38 (dd, 2′-H), 3.55 (ddq, 13-H), 3.64 (s, 4-OCH_3), 3.79 (br d, 4-H), 3.88 (br d, 5-H), 4.41 (d, 1′-H), 4.51 (dq, 5″-H), 4.59 (d, 4″-H), 4.85 (d, 1″-H), 5.26 (m, 3-H), 6.35 (br s, NH), 7.16–7.20 (m, C_6H_5), 7.23–7.30 (m, C_6H_5), 9.63 (s, CHO).

4.1.13.2. Compound 27. $[\alpha]_D^{24}$ −45° (*c* 0.25, $CHCl_3$); FAB-MS *m*/*z* 1006 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{83}N_3O_{16}$: 1006.5852. Found: 1006.5852 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.59 (m, 7-H), 0.82 (d, 8-CH_3), 1.02 (d, 6″-H), 1.05 (d, 6′-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.14 (t, 4″-$OCOCH_2CH_3$), 1.35 (s, 3″-CH_3), 1.62 (dd, 2″-Hax), 1.74 (m, 7-H), 1.94 (s, 9-$OCOCH_3$), 1.98 (s, 3″-$OCOCH_3$), 2.08 (d, 6-CH_2), 2.48 (s, 3′-$N(CH_3)_2$), 3.02 (dd, 6-CH_2), 3.15 (d, 2″-Heq), 3.24 (s, NCH_3), 3.28 (dd, 2′-H), 3.44 (br d, 4-H), 3.78 (s, 4-OCH_3), 3.86 (br d, 5-H), 4.17 (m, 13-H), 4.41 (d, 1′-H), 4.44 (dq, 5″-H), 4.52 (d, 4″-H), 4.61 (br dd, 9-H), 4.77 (d, 1″-H), 5.10 (br dd, 3-H), 7.08–7.11 (m, C_6H_5), 7.19–7.23 (m, C_6H_5), 9.53 (s, CHO).

4.1.13.3. Compound 28. $[\alpha]_D^{23}$ −50° (*c* 0.3, $CHCl_3$); FAB-MS *m*/*z* 1006 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{83}N_3O_{16}$: 1006.5852. Found: 1006.5854 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.72 (m, 7-H), 0.87 (d, 8-CH_3), 1.08 (d, 6″-H), 1.11 (d, 6′-H), 1.18 (t, 3-$OCOCH_2CH_3$), 1.19 (t, 4″-$OCOCH_2CH_3$), 1.41 (s, 3″-CH_3), 1.67 (dd, 2″-Hax), 1.78 (m, 8-H), 2.00 (s, 3″-$OCOCH_3$), 2.04 (s, 9-$OCOCH_3$), 2.22 (s, NCH_3), 2.41 (t, 3′-H), 2.54 (s, 3′-$N(CH_3)_2$), 2.65 (t, $C_6H_5(CH_2)_3CH_2$), 2.74 (dd, 2-H), 3.10 (dd, 6-CH_2), 3.15 (m, 4′-H), 3.20 (m, 5′-H), 3.55 (dd, 2′-H), 3.49 (br d, 4-H), 3.84 (s, 4-OCH_3), 3.92 (br d, 5-H), 4.47 (d, 1′-H), 4.51 (dq, 5″-H), 4.58 (d, 4″-H), 4.71 (br dd, 9-H), 4.83 (d, 1″-H), 5.09 (br dd, 3-H), 7.13–7.21 (m, C_6H_5), 7.22–7.30 (m, C_6H_5), 9.58 (s, CHO).

4.1.13.4. 9,2′-Di-*O*-acetyl dimethylacetal of 29 (polar than 9,2′-di-*O*-acetyl dimethylacetal of 30 in TLC developed by chloroform/methanol (20:1)). $[\alpha]_D^{26}$ −71° (*c* 0.52, $CHCl_3$); FAB-MS *m*/*z* 1108 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.82 (d, 8-CH_3), 0.99 (d, 6″-H), 1.06 (t, 3-$OCOCH_2CH_3$), 1.12 (d, 6′-H), 1.12 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 14-CH_3), 1.34 (s, 3″-CH_3), 1.59 (dd, 2″-Hax), 1.90 (s, 3″-$OCOCH_3$), 1.94 (s, 9-$OCOCH_3$), 1.94 (s, 2′-$OCOCH_3$), 2.36 (s, 3′-$N(CH_3)_2$), 2.53 (t, 3′-H), 3.00 (s, $CH(OCH_3)_2$), 3.05 (t, 4′-H), 3.12 (d, 2″-Heq), 3.17 (s, $CH(OCH_3)_2$), 3.20 (dq, 5′-H), 3.27 (br d, 4-H), 3.45 (m, 14-H), 3.51 (s, 4-OCH_3), 3.84 (br d, 5-H), 4.40 (dq, 5″-H), 4.49 (d, 4″-H), 4.61 (d, 1′-H), 4.68 (br d, 9-H), 4.73 (d, 1″-H), 4.88 (dd, 2′-H), 5.02 (br dd, 3-H), 7.06–7.11 (m, C_6H_5), 7.16–7.21 (m, C_6H_5), 7.30 (br s, NH).

4.1.13.5. Compound 29. $[\alpha]_D^{25}$ −61° (*c* 0.47, $CHCl_3$); FAB-MS *m*/*z* 978 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{83}N_3O_{15}$: 978.5902. Found: 978.5903 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.84 (d, 8-CH_3), 1.02 (d, 6″-H), 1.07 (d, 6′-H), 1.10 (t, 3-$OCOCH_2CH_3$), 1.12 (t, 4″-$OCOCH_2CH_3$), 1.21 (d, 14-CH_3), 1.35 (s, 3″-CH_3), 1.45 (m, 8-H), 1.62 (dd, 2″-Hax), 1.80 (m, 13-H), 1.93 (s, 3″-$OCOCH_3$), 2.48 (s, 3′-$N(CH_3)_2$), 2.92 (dd, 6-CH_2), 3.15 (d, 2″-Heq), 3.28 (dd, 2′-H), 3.50 (m, 14-H), 3.57 (s, 4-OCH_3), 3.80 (dd, 5-H), 4.36 (d, 1′-H), 4.43 (dq, 5″-H), 4.51 (d, 4″-H), 4.78 (d, 1″-H), 5.10 (m, 3-H), 6.65 (dd, NH), 7.08–7.12 (m, C_6H_5), 7.18–7.23 (m, C_6H_5), 9.58 (s, CHO).

4.1.13.6. 9,2′-Di-*O*-acetyl dimethylacetal of 30 (less polar than 9,2′-di-*O*-acetyl dimethylacetal of 29 in TLC developed by chloroform/methanol (20:1)). $[\alpha]_D^{24}$ −76° (*c* 0.67, $CHCl_3$); FAB-MS *m*/*z* 1108 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.80 (d, 8-CH_3), 1.00 (d, 6″-H), 1.06 (t, 3-$OCOCH_2CH_3$), 1.07 (d, 14-CH_3), 1.12 (d, 6′-H), 1.12 (t, 4″-$OCOCH_2CH_3$), 1.19 (br dd, 7-H), 1.34 (s, 3″-CH_3), 1.59 (dd, 2″-Hax), 1.88 (s, 3″-$OCOCH_3$), 1.95 (s, 9-$OCOCH_3$), 1.98 (s, 2′-$OCOCH_3$), 2.36 (s, 3′-$N(CH_3)_2$), 2.53 (t, $C_6H_5(CH_2)_4$), 2.54 (t, 3′-H), 2.67 (dd, 2-H), 2.95 (s, $CH(OCH_3)_2$), 3.05 (t, 4′-H), 3.12 (d, 2″-Heq), 3.16 (s, $CH(OCH_3)_2$), 3.21 (dq, 5′-H), 3.34 (br d, 4-H), 3.65 (s, 4-OCH_3), 3.91 (br d, 5-H), 3.97 (m, 14-H), 4.40 (dq, 5″-H), 4.49 (d, 4″-H), 4.65 (d, 1′-H), 4.73 (d, 1″-H), 4.75 (br d, 9-H), 4.86 (br d, 3-H), 4.88 (dd, 2′-H), 6.55 (d, NH), 7.07–7.11 (m, C_6H_5), 7.17–7.22 (m, C_6H_5).

4.1.13.7. Compound 30. $[\alpha]_D^{26}$ −77° (*c* 0.68, $CHCl_3$); FAB-MS *m*/*z* 978 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{83}N_3O_{15}$: 978.5902. Found: 978.5903 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.81 (d, 8-CH_3), 0.93 (br dd, 7-H), 1.02 (d, 6″-H), 1.07 (d, 14-CH_3), 1.07 (d, 6′-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.12 (t, 4″-$OCOCH_2CH_3$), 1.26 (br dd, 7-H), 1.34 (s, 3″-CH_3), 1.62 (dd, 2″-Hax), 1.78 (m, 13-H), 1.84 (m, 6-H), 1.93 (s, 3″-$OCOCH_3$), 2.48 (s, 3′-$N(CH_3)_2$), 2.55 (t, $C_6H_5(CH_2)_4$), 2.76 (dd, 2-H), 2.93 (dd, 6-CH_2), 3.14 (m, 4′-H), 3.14 (m, 5′-H), 3.15 (d, 2″-Heq), 3.30 (dd, 2′-H), 3.58 (dd, 4-H), 3.51 (s, 4-OCH_3), 3.83 (br d, 5-H), 3.98 (m, 14-H), 4.37 (d, 1′-H), 4.44 (dq, 5″-H), 4.51 (d, 4″-H), 4.78 (d, 1″-H), 4.90 (br d, 3-H), 6.13 (br d, NH), 7.08–7.12 (m, C_6H_5), 7.18–7.23 (m, C_6H_5), 9.58 (s, CHO).

4.1.13.8. Compound 31. FAB-MS *m*/*z* 1006 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{83}N_3O_{16}$: 1006.5852. Found: 1006.5848 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.81 (d, 8-CH_3), 1.02 (d, 6″-H), 1.07 (d, 6′-H), 1.10 (t, 3-$OCOCH_2CH_3$), 1.12 (t, 4″-$OCOCH_2CH_3$), 1.34 (s, 3″-CH_3), 1.62 (dd, 2″-Hax), 1.73 (m, 13-H), 1.91 (s, 9-$OCOCH_3$), 1.93 (s, 3″-$OCOCH_3$), 2.48 (s, 3′-$N(CH_3)_2$), 2.68 (dd, 2-H), 2.88 (dd, 6-CH_2), 3.15 (d, 2″-Heq), 3.25 (dd, 2′-H), 3.45 (dd, 4-H), 3.58 (m, 14-H), 3.63 (s, 4-OCH_3), 3.86 (br d, 5-H), 4.39 (d, 1′-H), 4.43 (dq, 5″-H), 4.51 (d, 4″-H), 4.69 (br d, 9-H), 4.78 (d, 1″-H), 5.05 (br d, 3-H), 7.07–7.13 (m, C_6H_5), 7.17–7.21 (m, C_6H_5), 9.57 (s, CHO).

4.1.13.9. Compound 32. $[\alpha]_D^{24}$ −81° (*c* 0.36, $CHCl_3$); FAB-MS *m*/*z* 964 $(M+H)^+$; HRMS: Calcd for $C_{50}H_{81}N_3O_{15}$: 964.5746. Found: 964.5750 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.81 (d, 8-CH_3), 0.93 (br dd, 7-H), 1.01 (d, 6″-H), 1.06 (d, 6′-H), 1.11 (t, 3-$OCOCH_2CH_3$), 1.12 (t, 4″-$OCOCH_2CH_3$), 1.23 (m, 7-H), 1.34 (s, 3″-CH_3), 1.62 (dd, 2″-Hax), 1.84 (m, 6-H), 1.93 (s, 3″-$OCOCH_3$), 2.16 (m, 10-H), 2.27 (dd, 2-H), 2.48 (s, 3′-$N(CH_3)_2$), 2.54 (t, $C_6H_5(CH_2)_4$), 2.74 (dd, 2-H), 2.93 (dd, 6-CH_2), 3.14 (d, 2″-Heq), 3.28 (dd, 2′-H), 3.39 (d, 9-H), 3.54 (dd, 4-H), 3.69 (s, 4-OCH_3), 3.83 (br d, 5-H), 4.38 (d, 1′-H), 4.43 (dq, 5″-H), 4.51 (d, 4″-H), 4.77 (d, 1″-H), 4.91 (br d, 3-H), 6.65 (dd, NH), 7.07–7.12 (m, C_6H_5), 7.17–7.22 (m, C_6H_5), 9.58 (s, CHO).

4.1.13.10. Compound 33. $[\alpha]_D^{24}$ −66° (*c* 0.45, $CHCl_3$); FAB-MS *m*/*z* 978 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{83}N_3O_{15}$: 978.5902. Found: 978.5903 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.78 (d, 8-CH_3), 1.01 (d, 6″-H), 1.07 (d, 6′-H), 1.11 (t, 3-$OCOCH_2CH_3$), 1.12 (t, 4″-$OCOCH_2CH_3$),

1.27 (m, 8-H), 1.34 (s, 3″-CH_3), 1.61 (dd, 2″-Hax), 1.94 (s, 3″-$OCOCH_3$), 2.47 (s, 3′-$N(CH_3)_2$), 2.55 (t, $C_6H_5(CH_2)_4$), 2.72 (dd, 2-H), 2.83 (dd, 6-CH_2), 3.10 (m, 4′-H), 3.13 (m, 5′-H), 3.14 (d, 2″-Heq), 3.33 (dd, 2′-H), 3.64 (s, 4-OCH_3), 3.71 (br d, 4-H), 3.81 (br d, 5-H), 4.33 (d, 1′-H), 4.45 (dq, 5″-H), 4.51 (d, 4″-H), 4.77 (d, 1″-H), 5.35 (br dd, 3-H), 6.35 (br d, NH), 7.08–7.12 (m, C_6H_5), 7.18–7.23 (m, C_6H_5), 9.59 (s, CHO).

4.1.14. Synthesis of 36

Compound **34**[8] (10.0 g, 9.88 mmol) was dissolved in benzene (300 ml), and sodium carbonate (8.38 g, 79.1 mmol) was added. Lead tetraacetate (11.0 g, 24.8 mmol) was added as three portions with intervals of 5 min. The reaction mixture was stirred at room temperature for 30 min, and then insoluble matter was removed by filtration through a Celite by using ethyl acetate (260 ml). After the filtrate was concentrated to about 80 ml, acetonitrile (100 ml) was added to the mixture. The resulting solution was concentrated to about 80 ml. The same substitution and concentration procedures were further repeated twice to obtain about 80 ml of a solution containing **35**. Without purification of **35**, acetonitrile (300 ml) and 1, 8-diazabicyclo[5.4.0]-7-undecene (2.2 ml, 14.7 mmol) were added to this solution, and the mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol (30:1 to 20:1)) to obtain 6.07 g (70%) of **36** as a colorless solid; $[\alpha]_D^{25}$ −53° (*c* 0.56, $CHCl_3$); FAB-MS *m*/*z* 880 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.95 (d, 8-CH_3), 1.04 (s, 3″-CH_3), 1.04 (t, 3-$OCOCH_2CH_3$), 1.05 (d, 6″-H), 1.10 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.43 (m, 6-CH_2), 1.56 (m, 7-H), 1.77 (dd, 2″-Hax), 1.94 (d, 2″-Heq), 1.99 (s, 2′-$OCOCH_3$), 2.11 (s, 9-$OCOCH_3$), 2.33 (s, 3′-$N(CH_3)_2$), 2.58 (dd, 2-H), 2.65 (t, 3′-H), 2.72 (dd, 2-H), 3.09 (s, $CH(OCH_3)_2$), 3.18 (s, $CH(OCH_3)_2$), 3.26 (t, 4′-H), 3.26 (t, 5′-H), 3.42 (br d, 4-H), 3.46 (s, 4-OCH_3), 3.76 (br d, 5-H), 4.31 (dq, 5″-H), 4.37 (dd, $CH(OCH_3)_2$), 4.54 (d, 4″-H), 4.62 (d, 1′-H), 4.80 (br d, 9-H), 4.91 (dd, 2′-H), 4.99 (d, 1″-H), 5.17 (br dd, 3-H), 9.48 (s, 10-H).

4.1.15. Preparation of 37

Reaction of **36** with 3-(4-methoxybenzylamino)propylazide gave **37** in 79% yield by a similar procedure to **4**; $[\alpha]_D^{23}$ −56° (*c* 0.30, $CHCl_3$); FAB-MS *m*/*z* 1084 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.84 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (t, 3-$OCOCH_2CH_3$), 1.14 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 6′-H), 1.47 (m, 6-CH_2), 1.62 (m, 7-H), 1.83 (dd, 2″-Hax), 1.86 (m,$(CH_2)_3N_3$), 2.01 (d, 2″-Heq), 2.01 (s, 9-$OCOCH_3$), 2.04 (s, 2′-$OCOCH_3$), 2.39 (s, 3′-$N(CH_3)_2$), 2.70 (m, $(CH_2)_3N_3$), 3.19 (s, $CH(OCH_3)_2$), 3.25 (s, $CH(OCH_3)_2$), 3.30 (m, 4′-H), 3.33 (m, 5′-H), 3.47 (br d, 4-H), 3.49 (s, 4-OCH_3), 3.78 (s, C_6H_4-OCH_3), 3.79 (s, $C_6H_4CH_2$), 3.87 (br d, 5-H), 4.37 (dq, 5″-H), 4.52 (dd, $CH(OCH_3)_2$), 4.60 (d, 4″-H), 4.71 (d, 1′-H), 4.97 (dd, 2′-H), 5.05 (d, 1″-H), 5.13 (br d, 9-H), 5.14 (br dd, 3-H), 6.86 (d, C_6H_4), 7.29 (d, C_6H_4).

4.1.16. Preparation of 38

Reaction of **37** with triphenylphosphine gave **38** in 76% yield by a similar procedure to **15**; $[\alpha]_D^{25}$ −64° (*c* 0.42, $CHCl_3$); FAB-MS *m*/*z* 1058 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.95 (d, 8-CH_3), 1.08 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.48 (m, 6-CH_2), 1.72 (m, 7-H), 1.83 (dd, 2″-Hax), 2.02 (d, 2″-Heq), 2.06 (s, 9-$OCOCH_3$), 2.21 (s, 2′-$OCOCH_3$), 2.40 (s, 3′-$N(CH_3)_2$), 2.71 (m, $(CH_2)_3NH_2$), 3.08 (s, $CH(OCH_3)_2$), 3.10 (br d, 4-H), 3.24 (s, $CH(OCH_3)_2$), 3.32 (m, 4′-H), 3.35 (m, 5′-H), 3.64 (s, 4-OCH_3), 3.69 (d, $C_6H_4CH_2$), 3.78 (s, C_6H_4-OCH_3), 3.88 (d, $C_6H_4CH_2$), 4.00 (br d, 5-H), 4.38 (dq, 5″-H), 4.49 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.81 (d, 1′-H), 5.01 (dd, 2′-H), 5.07 (d, 1″-H), 5.27 (br dd, 3-H), 5.44 (br d, 9-H), 6.82 (d, C_6H_4), 7.03 (d, C_6H_4).

4.1.17. Preparation of 39

Reaction of **38** with diphenylphosphoryl azide gave **39** in 72% yield by a similar procedure to **16**; $[\alpha]_D^{26}$ −90° (*c* 0.40, $CHCl_3$); FAB-MS *m*/*z* 1040 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.81 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (t, 3-$OCOCH_2CH_3$), 1.13 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 6′-H), 1.50 (m, 6-CH_2), 1.83 (dd, 2″-Hax), 1.98 (s, 9-$OCOCH_3$), 2.00 (d, 2″-Heq), 2.03 (s, 2′-$OCOCH_3$), 2.40 (s, 3′-$N(CH_3)_2$), 2.71 (t, 3′-H), 3.03 (s, $CH(OCH_3)_2$), 3.22 (s, $CH(OCH_3)_2$), 3.31 (m, 4′-H), 3.34 (m, 5′-H), 3.35 (br d, 4-H), 3.38 (d, $C_6H_4CH_2$), 3.56 (d, $C_6H_4CH_2$), 3.64 (s, 4-OCH_3), 3.78 (s, C_6H_4-OCH_3), 3.98 (br d, 5-H), 4.36 (dq, 5″-H), 4.50 (dd, $CH(OCH_3)_2$), 4.60 (d, 4″-H), 4.73 (d, 1′-H), 4.86 (br d, 9-H), 4.98 (dd, 2′-H), 5.04 (br dd, 3-H), 5.06 (d, 1″-H), 6.81 (d, C_6H_4), 6.96 (br d, NH), 7.18 (d, C_6H_4).

4.1.18. Synthesis of 40

Compound **39** (300 mg, 0.288 mmol) was dissolved in 1, 4-dioxane (12 ml), and 10% Pd/C (75 mg) was added. The reaction vessel was purged with hydrogen, and the reaction mixture was stirred at room temperature for 24 h. After the catalyst was removed by filtration, the filtrate was washed with ethyl acetate, and concentrated. The resulting residue was purified by preparative TLC (chloroform/methanol (10:1)) to obtain 241 mg of **40** (91%) as a colorless solid; FAB-MS *m*/*z* 920 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.90 (d, 8-CH_3), 1.10 (s, 3″-CH_3), 1.12 (t, 3-$OCOCH_2CH_3$), 1.13 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 6′-H), 1.50 (m, 6-CH_2), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.08 (s, 2′-$OCOCH_3$), 2.40 (s, 3′-$N(CH_3)_2$), 2.72 (t, 3′-H), 3.12 (s, $CH(OCH_3)_2$), 3.23 (s, $CH(OCH_3)_2$), 3.29 (dd, 4-H), 3.30 (m, 4′-H), 3.30 (m, 5′-H), 3.57 (s, 4-OCH_3), 3.92 (br d, 5-H), 4.36 (dq, 5″-H), 4.49 (dd, $CH(OCH_3)_2$), 4.60 (d, 4″-H), 4.69 (d, 1′-H), 4.98 (dd, 2′-H), 5.00 (br dd, 3-H), 5.05 (d, 1″-H), 7.92 (br d, NH).

4.1.19. Synthesis of 41

Compound **40** (241 mg, 0.262 mmol) was dissolved in ethanol (12 ml), and 3-(quinolin-4-yl)propionaldehyde (58.2 mg, 0.314 mmol) and acetic acid (0.075 ml, 1.31 mmol) were added under ice cooling. After the reaction mixture was stirred at the same temperature for 30 min, sodium cyanoborohydride (49.4 mg, 0.786 mmol) was added under ice cooling. The reaction mixture was further stirred at room temperature for 3.5 h. The reaction mixture was diluted with ethyl acetate, successively washed with saturated aqueous sodium bicarbonate, and saturated brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by preparative TLC (chloroform/methanol (10:1)) to obtain 187 mg of **41** (66%) as a colorless solid; $[\alpha]_D^{26}$ −81° (*c* 0.22, $CHCl_3$); FAB-MS *m*/*z* 1089 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.90 (d, 8-CH_3), 1.11 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.13 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.54 (m, 6-CH_2), 1.83 (dd, 2″-Hax), 1.92 (s, 9-$OCOCH_3$), 2.01 (d, 2″-Heq), 2.04 (s, 2′-$OCOCH_3$), 2.40 (s, 3′-$N(CH_3)_2$), 2.72 (t, 3′-H), 3.03 (s, $CH(OCH_3)_2$), 3.23 (s, $CH(OCH_3)_2$), 3.32 (m, 4′-H), 3.35 (m, 5′-H), 3.39 (br d, 4-H), 3.66 (s, 4-OCH_3), 3.99 (br d, 5-H), 4.37 (dq, 5″-H), 4.51 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.74 (d, 1′-H), 4.85 (br d, 9-H), 4.99 (dd, 2′-H), 5.02 (br dd, 3-H), 5.06 (d, 1″-H), 6.97 (br d, NH), 7.24 (d, quinoline), 7.55 (ddd, quinoline), 7.69 (ddd, quinoline), 8.04 (dd, quinoline), 8.10 (dd, quinoline), 8.79 (d, quinoline).

4.1.20. Synthesis of 42

Compound **41** (90.0 mg, 0.0826 mmol) was dissolved in methanol (6.3 ml), and the reaction mixture was heated at 50 °C for 150 h. The reaction mixture was concentrated, and the resulting residue was purified by preparative TLC (chloroform/methanol/aqueous ammonia (10:1:0.1)) to obtain 69.0 mg of **42** (83%) as a color less solid; $[\alpha]_D^{21}$ −53° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 1005

(M+H)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (t, 3-$OCOCH_2CH_3$), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.64 (m, 6-CH_2), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.50 (s, 3′-$N(CH_3)_2$), 2.78 (dd, 2-H), 3.10 (s, $CH(OCH_3)_2$), 3.25 (s, $CH(OCH_3)_2$), 3.32 (m, 4′-H), 3.32 (m, 5′-H), 3.46 (br d, 9-H), 3.57 (dd, 2′-H), 3.59 (br d, 4-H), 3.75 (s, 4-OCH_3), 3.98 (br d, 5-H), 4.45 (dq, 5″-H), 4.48 (dd, $CH(OCH_3)_2$), 4.49 (d, 1′-H), 4.61 (d, 4″-H), 4.90 (br dd, 3-H), 5.07 (d, 1″-H), 6.48 (br d, NH), 7.23 (d, quinoline), 7.55 (ddd, quinoline), 7.70 (ddd, quinoline), 8.02 (dd, quinoline), 8.10 (dd, quinoline), 8.80 (d, quinoline).

4.1.21. Preparation of 43 and 44

Reaction of **42** with difluoroacetic acid gave **43** in 45% yield and **44** in 24% yield by a similar procedure to **12**. Total yield of this reaction was 69%. Compound **43**: $[\alpha]_D^{21}$ −78° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 959 (M+H)$^+$; HRMS: Calcd for $C_{50}H_{78}N_4O_{14}$: 959.5593. Found: 959.5581 (M+H)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 8-CH_3), 1.10 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.16 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.49 (br d, 8-H), 1.82 (dd, 2″-Hax), 1.91 (m, quinoline-$(CH_2)_3$), 2.00 (d, 2″-Heq), 2.50 (s, 3′-$N(CH_3)_2$), 2.64 (m, quinoline-$(CH_2)_3$), 2.97 (br dd, 6-CH_2), 3.08 (m, quinoline-$(CH_2)_3$), 3.27 (m, 4′-H), 3.28 (m, 5′-H), 3.48 (br d, 9-H), 3.52 (dd, 2′-H), 3.64 (dd, 4-H), 3.73 (s, 4-OCH_3), 3.91 (br d, 5-H), 4.44 (d, 1′-H), 4.45 (dq, 5″-H), 4.61 (d, 4″-H), 4.97 (br dd, 3-H), 5.06 (d, 1″-H), 6.63 (br d, NH), 7.23 (d, quinoline), 7.55 (ddd, quinoline), 7.69 (ddd, quinoline), 8.01 (dd, quinoline), 8.10 (dd, quinoline), 8.80 (d, quinoline), 9.64 (s, CHO). Compound **44**: $[\alpha]_D^{22}$ −48° (*c* 0.35, $CHCl_3$); FAB-MS *m*/*z* 759 (M+H)$^+$; HRMS: Calcd for $C_{40}H_{62}N_4O_{10}$: 747.4431. Found: 747.4433 (M+H)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 8-CH_3), 1.16 (t, 3-$OCOCH_2CH_3$), 1.23 (d, 6′-H), 1.50 (br d, 8-H), 1.92 (m, quinoline-$(CH_2)_3$), 2.51 (s, 3′-$N(CH_3)_2$), 2.63 (m, quinoline-$(CH_2)_3$), 3.02 (br dd, 6-CH_2), 3.08 (m, quinoline-$(CH_2)_3$), 3.29 (m, 5′-H), 3.47 (br d, 9-H), 3.51 (dd, 2′-H), 3.63 (dd, 4-H), 3.74 (s, 4-OCH_3), 3.92 (br d, 5-H), 24.46 (d, 1′-H), 4.97 (br dd, 3-H), 6.64 (br d, NH), 7.23 (d, quinoline), 7.55 (ddd, quinoline), 7.70 (ddd, quinoline), 8.01 (dd, quinoline), 8.10 (dd, quinoline), 8.79 (d, quinoline), 9.66 (s, CHO).

4.1.22. Preparation of 46

Reaction of **36** with *N*-(3-azido-5-hexenyl)-*N*-methylamine[24] gave **46** as an about 1:1 mixture of diastereoisomers at the C-14 position in 54% yield by a similar procedure to **14**; $[\alpha]_D^{24}$ −54° (*c* 0.84, $CHCl_3$); FAB-MS *m*/*z* 1018 (M+H)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.81 (d, 8-CH_3), 1.04 (s, 3″-CH_3), 1.05 (d, 6″-H), 1.06 (t, 3-$OCOCH_2CH_3$), 1.10 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-CH_3), 1.26 (m, 7-H), 1.47 (m, 6-CH_2), 1.76 (dd, 2″-Hax), 1.94 (d, 2″-Heq), 2.33 (s, 3′-$N(CH_3)_2$), 2.42 (s, NCH_3), 2.74 (br t, 12-H), 3.14 (s, $CH(OCH_3)_2$), 3.19 (s, $CH(OCH_3)_2$), 3.26 (m, 4′-H), 3.26 (m, 5′-H), 3.41 (br d, 4-H), 3.46 and 3.48 (each s, 4-OCH_3), 3.81 (br d, 5-H), 4.30 (dq, 5″-H), 4.47 (dd, $CH(OCH_3)_2$), 4.54 (d, 4″-H), 4.66 (d, 1′-H), 4.92 (dd, 2′-H), 4.99 (d, 1″-H), 5.06 (m, 3-H), 5.09 (m, CH_2=CH), 5.73 (ddt, CH_2=CH).

4.1.23. Synthesis of 47

Compound **46** (1.06 g, 1.04 mmol) was dissolved in acetonitrile (50 ml) and water (5.0 ml), and a 0.52 M solution of trimethylphosphine in toluene (6.0 ml, 3.12 mmol) was added. The reaction mixture was stirred at 80 °C for 6.5 h. The reaction mixture was concentrated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol (10:1 to 5:1)) to obtain 548 mg of compound **47** (53%) as a colorless solid. It was an about 1:1 mixture of diastereoisomers at the C-14 position; $[\alpha]_D^{20}$ −49° (*c* 0.86, $CHCl_3$); FAB-MS *m*/*z* 992 (M+H)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 8-CH_3), 1.02 and 1.03 (each t, 3-$OCOCH_2CH_3$), 1.05 (s, 3″-CH_3), 1.06 (d, 6″-H), 1.10 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-CH_3), 1.38 (m, 6-CH_2), 1.61 (m, 8-H), 1.77 (dd, 2″-Hax), 1.95 (d, 2″-Heq), 2.19 and 2.23 (each s, NCH_3), 2.34 (s, 3′-$N(CH_3)_2$), 3.06 (s, $CH(OCH_3)_2$), 3.18 and 3.18 (each s, $CH(OCH_3)_2$), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.43 and 3.59 (each br d, 4-H), 3.53 and 3.56 (each s, 4-OCH_3), 3.81 (br d, 5-H), 4.31 (dq, 5″-H), 4.41 (m, $CH(OCH_3)_2$), 4.54 (d, 4″-H), 4.72 and 4.75 (each d, 1′-H), 4.93 (dd, 2′-H), 5.00 (d, 1″-H), 5.03 (m, CH_2=CH), 5.58 (m, CH_2=CH).

4.1.24. Preparation of 48 and 49

Reaction of **47** with diphenylphosphoryl azide gave **48** in 38% yield and **49** in 35% yield, respectively, by a similar procedure to **16**. Total yield of this reaction was 73%. Compound **48**; Less polar; R_f value = 0.60, chloroform/methanol/aqueous. NH_4OH (10:1:0.1); $[\alpha]_D^{21}$ −57° (*c* 0.52, $CHCl_3$); FAB-MS *m*/*z* 974 (M+H)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.81 (d, 8-CH_3), 1.05 (s, 3″-CH_3), 1.05 (d, 6″-H), 1.06 (t, 3-$OCOCH_2CH_3$), 1.10 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.50 (br dd, 6-CH_2), 1.57 (m, 8-H), 1.77 (dd, 2″-Hax), 1.95 (d, 2″-Heq), 1.95 (s, 9-$OCOCH_3$), 1.99 (s, 2′-$OCOCH_3$), 2.19 (s, NCH_3), 2.34 (s, 3′-$N(CH_3)_2$), 2.65 (t, 3′-H), 2.69 (dd, 2-H), 2.99 (s, $CH(OCH_3)_2$), 3.17 (s, $CH(OCH_3)_2$), 3.26 (t, 5′-H), 3.39 (br d, 4-H), 3.65 (s, 4-OCH_3), 3.94 (br d, 5-H), 3.99 (m, 14-H), 4.30 (dq, 5″-H), 4.49 (dd, $CH(OCH_3)_2$), 4.55 (d, 4″-H), 4.69 (d, 1′-H), 4.84 (br dd, 3-H), 4.93 (dd, 2′-H), 4.99 (m, CH_2=CH), 5.00 (d, 1″-H), 5.66 (ddt, CH_2=CH), 6.45 (br d, NH). Compound **49**: polar; R_f value = 0.49, chloroform/methanol/aqueous NH_4OH (10:1:0.1); $[\alpha]_D^{24}$ −53° (*c* 0.40, $CHCl_3$); FAB-MS *m*/*z* 974 (M+H)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.85 (d, 8-CH_3), 1.05 (s, 3″-CH_3), 1.06 (d, 6″-H), 1.07 (t, 3-$OCOCH_2CH_3$), 1.10 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.43 (br dd, 6-CH_2), 1.77 (dd, 2″-Hax), 1.95 (d, 2″-Heq), 1.95 (s, 9-$OCOCH_3$), 1.95 (s, 2′-$OCOCH_3$), 2.10 (dd, 10-H), 2.19 (s, NCH_3), 2.34 (s, 3′-$N(CH_3)_2$), 2.65 (t, 3′-H), 3.06 (s, $CH(OCH_3)_2$), 3.06 (t, 4′-H), 3.18 (s, $CH(OCH_3)_2$), 3.27 (br d, 4-H), 3.29 (dq, 5′-H), 3.49 (s, 4-OCH_3), 3.87 (br d, 5-H), 4.31 (dq, 5″-H), 4.47 (m, $CH(OCH_3)_2$), 4.55 (d, 4″-H), 4.67 (d, 1′-H), 4.76 (m, 9-H), 4.94 (dd, 2′-H), 5.00 (d, 1″-H), 5.68 (ddt, CH_2=CH).

4.1.25. Synthesis of 50

Compound **48** (338 mg, 0.347 mmol) was dissolved in acetonitrile (20 ml) under argon atmosphere, and palladium (II) acetate (16.6 mg, 0.0739 mmol), tri-*o*-tolylphosphine (44.0 mg, 0.145 mmol), 4-bromoquinoline (165 mg, 0.793 mmol), and triethylamine (0.098 ml, 0.730 mmol) were added. The reaction mixture was stirred at 80 °C for 16 h. Then, the reaction mixture was diluted with ethyl acetate, and washed with 8% aqueous sodium hydrogencarbonate. After the aqueous layer was extracted twice with ethyl acetate, and the organic layers were combined, and washed with 25% brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (chloroform/methanol (50:1)), and further purified by preparative TLC (chloroform/methanol/aqueous ammonia (20:1:0.1)) to obtain 181 mg of **50** (47%) as a colorless solid accompanied with 28.0 mg (7%) of 9, 2′-di-*O*-acetyl dimethyacetal of **58** as a colorless solid. Total yield of this Heck reaction was 54%. Compound **50**; $[\alpha]_D^{20}$ −49° (*c* 0.78, $CHCl_3$); FAB-MS *m*/*z* 1101 (M+H)$^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, 8-CH_3), 1.03 (s, 3″-CH_3), 1.03 (t, 3-$OCOCH_2CH_3$), 1.04 (d, 6″-H), 1.08 (t, 4″-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.24 (m, 7-H), 1.48 (br dd, 6-CH_2), 1.57 (m, 8-H), 1.75 (dd, 2″-Hax), 1.92 (d, 2″-Heq), 1.94 (s, 9-$OCOCH_3$), 1.97 (s, 2′-$OCOCH_3$), 2.21 (s, NCH_3), 2.32 (s, 3′-$N(CH_3)_2$), 2.64 (t, 3′-H), 2.98 (s, $CH(OCH_3)_2$), 3.15 (s, $CH(OCH_3)_2$), 3.24 (m, 4′-H), 3.27 (m, 5′-H), 3.34 (br d, 4-H), 3.62 (s, 4-OCH_3), 3.93 (br d, 5-H), 4.14 (m, 14-H), 4.29 (dq, 5″-H), 4.47 (dd, $CH(OCH_3)_2$), 4.57 (d, 4″-H), 4.67 (d, 1′-H), 4.83 (m, 9-H), 4.85 (br dd, 3-H), 4.91 (dd, 2′-H), 4.98 (d, 1″-H), 6.32 (dt, *J* = 15.4, 7.4 Hz, quinoline-CH=CH), 6.80 (br d, NH), 7.05 (d, *J* = 15.4 Hz, quinoline-CH), 7.33 (d, quinoline), 7.45 (ddd, quinoline), 7.61 (ddd, quinoline), 8.00 (br d, quinoline), 8.00 (br d, quinoline), 8.74 (d,

quinoline). 9,2′-Di-*O*-acetyl dimethyacetal of **58**; FAB-MS *m*/*z* 1101 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.79 (d, 8-CH_3), 1.04 (s, 3″-CH_3), 1.05 (d, 6″-H), 1.05 (t, 3-$OCOCH_2CH_3$), 1.10 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.46 (br dd, 6-CH_2), 1.59 (m, 8-H), 1.70 (br dd, 6-CH_2), 1.77 (dd, 2″-Hax), 1.93 (s, 9-$OCOCH_3$), 1.97 (s, 2′-$OCOCH_3$), 2.15 (s, NCH_3), 2.33 (s, 3′-$N(CH_3)_2$), 2.65 (t, 3′-H), 2.69 (dd, 2-H), 2.99 (s, $CH(OCH_3)_2$), 3.16 (s, $CH(OCH_3)_2$), 3.22 (m, 4′-H), 3.25 (m, 5′-H), 3.32 (br d, 4-H), 3.61 (s, 4-OCH_3), 3.75 (br d, quinoline-CH_2), 3.92 (br d, 5-H), 4.30 (dq, 5″-H), 4.48 (dd, $CH(OCH_3)_2$), 4.54 (d, 4″-H), 4.68 (d, 1′-H), 4.80 (br d, 9-H), 4.85 (br d, 3-H), 4.92 (dd, 2′-H), 5.00 (d, 1″-H), 5.42 (dd, *J* = 15.7, 5.5 Hz, 14-CH), 5.77 (ddd, *J* = 15.7, 5.8, 1.2 Hz, 14-CH=CH), 6.98 (br d, NH), 7.16 (d, quinoline), 7.48 (ddd, quinoline), 7.63 (ddd, quinoline), 7.91 (dd, quinoline), 8.04 (dd, quinoline), 8.75 (d, quinoline).

4.1.26. Preparation of 51

Reaction of **49** with 4-bromoquinoline gave **51** in 52% yield and 9,2′-di-*O*-acetyl dimethyacetal of **59** in 11% yield by a similar procedure to **50**. Total yield of this Heck reaction was 63%. Compound **51**; $[\alpha]_D^{22}$ −46° (*c* 0.89, $CHCl_3$); FAB-MS *m*/*z* 1101 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.84 (d, 8-CH_3), 1.04 (s, 3″-CH_3), 1.05 (d, 6″-H), 1.09 (t, 3-$OCOCH_2CH_3$), 1.10 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.43 (br dd, 6-CH_2), 1.63 (m, 8-H), 1.76 (dd, 2″-Hax), 1.89 (d, 2″-Heq), 1.95 (s, 9-$OCOCH_3$), 1.95 (s, 2′-$OCOCH_3$), 2.20 (s, NCH_3), 2.32 (s, 3′-$N(CH_3)_2$), 2.64 (t, 3′-H), 3.05 (s, $CH(OCH_3)_2$), 3.17 (s, $CH(OCH_3)_2$), 3.49 (s, 4-OCH_3), 3.87 (br d, 5-H), 4.30 (dq, 5″-H), 4.45 (m, $CH(OCH_3)_2$), 4.54 (d, 4″-H), 4.65 (d, 1′-H), 4.77 (m, 9-H), 4.93 (dd, 2′-H), 4.99 (d, 1″-H), 5.03 (br dd, 3-H), 6.35 (dt, *J* = 15.7, 7.4 Hz, CH=CH), 7.08 (d, *J* = 15.7 Hz, quinoline-CH), 7.34 (d, quinoline), 7.48 (ddd, quinoline), 7.63 (ddd, quinoline), 8.01 (br d, quinoline), 8.01 (br d, quinoline), 8.70 (d, quinoline). 9,2′-Di-*O*-acetyl dimethylacetal of **59**; $[\alpha]_D^{20}$ −43° (*c* 0.64, $CHCl_3$); FAB-MS *m*/*z* 1101 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.75 (d, 8-CH_3), 1.04 (d, 6″-H), 1.04 (s, 3″-CH_3), 1.06 (t, 3-$OCOCH_2CH_3$), 1.10 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.38 (br dd, 6-CH_2), 1.62 (m, 8-H), 1.76 (dd, 2″-Hax), 1.93 (d, 2″-Heq), 1.93 (s, 9-$OCOCH_3$), 1.93 (s, 2′-$OCOCH_3$), 2.14 (s, NCH_3), 2.29 (s, 3′-$N(CH_3)_2$), 2.62 (t, 3′-H), 3.04 (s, $CH(OCH_3)_2$), 3.16 (s, $CH(OCH_3)_2$), 3.23 (m, 4′-H), 3.26 (m, 5′-H), 3.44 (s, 4-OCH_3), 3.74 (br d, quinoline-CH_2), 3.87 (br d, 5-H), 4.29 (dq, 5″-H), 4.45 (m, $CH(OCH_3)_2$), 4.53 (d, 4″-H), 4.63 (d, 1′-H), 4.74 (m, 9-H), 4.90 (dd, 2′-H), 4.99 (d, 1″-H), 5.54 (br d, 14-CH), 5.75 (br dd, 14-CH=CH), 7.22 (d, quinoline), 7.48 (br dd, quinoline), 7.63 (br dd, quinoline), 7.91 (br d, quinoline), 8.03 (br d, quinoline), 8.12 (br d, NH), 8.74 (d, quinoline).

4.1.27. Preparation of 52

Reaction of **50** with methanol gave **52** in 86% yield by a similar procedure to **8**; $[\alpha]_D^{20}$ −28° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 1017 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.87 (d, 8-CH_3), 1.04 (t, 3-$OCOCH_2CH_3$), 1.04 (s, 3″-CH_3), 1.05 (d, 6″-H), 1.10 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.39 (m, 13-H), 1.56 (br dd, 6-CH_2), 1.72 (br dd, 6-CH_2), 1.76 (dd, 2″-Hax), 1.93 (d, 2″-Heq), 2.18 (s, NCH_3), 2.44 (s, 3′-$N(CH_3)_2$), 2.76 (dd, 2-H), 3.06 (s, $CH(OCH_3)_2$), 3.19 (s, $CH(OCH_3)_2$), 3.22 (m, 4′-H), 3.22 (m, 5′-H), 3.36 (br dd, 9-H), 3.53 (dd, 2′-H), 3.70 (s, 4-OCH_3), 3.75 (br d, 4-H), 3.88 (br d, 5-H), 4.28 (m, 14-H), 4.37 (d, 1′-H), 4.40 (dq, 5″-H), 4.55 (d, 4″-H), 4.82 (br d, 3-H), 5.00 (d, 1″-H), 6.15 (br d, NH), 6.34 (dt, CH=CH), 7.07 (d, quinoline-CH), 7.34 (d, quinoline), 7.45 (ddd, quinoline), 7.63 (ddd, quinoline), 7.99 (br d, quinoline), 8.02 (br d, quinoline), 8.76 (d, quinoline).

4.1.28. Preparation of 53

Reaction of **51** with methanol gave **53** in 86% yield by a similar procedure to **8**; $[\alpha]_D^{17}$ −39° (*c* 0.69, $CHCl_3$); FAB-MS *m*/*z* 1017 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.84 (d, 8-CH_3), 0.96 (br dd, 7-H), 1.03 (t, 3-$OCOCH_2CH_3$), 1.04 (s, 3″-CH_3), 1.05 (d, 6″-H), 1.11 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.33 (br dd, 7-H), 1.51 (br dd, 6-CH_2), 1.54 (m, 8-H), 1.76 (dd, 2″-Hax), 1.94 (d, 2″-Heq), 2.29 (s, NCH_3), 2.42 (s, 3′-$N(CH_3)_2$), 2.71 (dd, 2-H), 3.12 (s, $CH(OCH_3)_2$), 3.20 (s, $CH(OCH_3)_2$), 3.21 (m, 4′-H), 3.24 (m, 5′-H), 3.37 (br d, 4-H), 3.48 (dd, 2′-H), 3.53 (s, 4-OCH_3), 3.56 (br d, 9-H), 3.81 (br d, 5-H), 3.96 (m, 14-H), 4.34 (d, 1′-H), 4.39 (m, 5″-H), 4.55 (d, 4″-H), 5.00 (d, 1″-H), 5.14 (br dd, 3-H), 6.35 (dt, CH=CH), 7.07 (d, quinoline-CH), 7.33 (d, quinoline), 7.48 (ddd, quinoline), 7.63 (ddd, quinoline), 8.00 (br d, quinoline), 8.02 (br d, quinoline), 8.76 (d, quinoline).

4.1.29. Preparation of 54 and 56

Reaction of **52** with difluoroacetic acid gave **54** in 40% yield and **56** in 37% yield by a similar procedure to **12**. Total yield of this reaction was 77%. Compound **54**; $[\alpha]_D^{20}$ −44° (*c* 0.78, $CHCl_3$); FAB-MS *m*/*z* 971 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{78}N_4O_{14}$: 971.5593. Found: 971.5587 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.88 (d, 8-CH_3), 1.04 (s, 3″-CH_3), 1.06 (d, 6″-H), 1.08 (t, 3-$OCOCH_2CH_3$), 1.11 (t, 4″-$OCOCH_2CH_3$), 1.13 (d, 6′-H), 1.28 (br t, 8-H), 1.54 (br dd, 7-H), 1.76 (dd, 2″-Hax), 1.93 (d, 2″-Heq), 2.20 (s, NCH_3), 2.44 (s, 3′-$N(CH_3)_2$), 2.78 (dd, 2-H), 2.90 (dd, 6-CH_2), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.38 (br dd, 9-H), 3.48 (dd, 2′-H), 3.68 (s, 4-OCH_3), 3.76 (br d, 4-H), 3.82 (br d, 5-H), 4.26 (m, 14-H), 4.34 (d, 1′-H), 4.39 (dq, 5″-H), 4.55 (d, 4″-H), 4.95 (br d, 3-H), 4.99 (d, 1″-H), 6.28 (br d, NH), 6.34 (dt, CH=CH), 7.08 (d, quinoline-CH), 7.35 (d, quinoline), 7.47 (ddd, quinoline), 7.63 (ddd, quinoline), 8.00 (br d, quinoline), 8.03 (br d, quinoline), 8.76 (d, quinoline), 9.59 (s, CHO).

Compound **56**: $[\alpha]_D^{21}$ −8.7° (*c* 0.57, $CHCl_3$); FAB-MS *m*/*z* 771 $(M+H)^+$; HRMS: Calcd for $C_{41}H_{62}N_4O_{10}$: 771.4544. Found: 771.4529 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ0.88 (d, 8-CH_3), 1.08 (t, 3-$OCOCH_2CH_3$), 1.17 (d, 6′-H), 1.30 (br t, 8-H), 1.45 (m, 13-H), 1.53 (br dd, 7-H), 1.89 (m, 6-H), 1.92 (m, 13-H), 2.22 (s, NCH_3), 2.46 (s, 3′-$N(CH_3)_2$), 2.78 (dd, 2-H), 2.92 (br dd, 6-CH_2), 2.97 (t, 4′-H), 3.22 (dq, 5′-H), 3.40 (br dd, 9-H), 3.47 (dd, 2′-H), 3.69 (s, 4-OCH_3), 3.76 (br d, 4-H), 3.83 (br d, 5-H), 4.26 (m, 14-H), 4.35 (d, 1′-H), 4.95 (br d, 3-H), 6.34 (dt, CH=CH), 7.18 (d, quinoline-CH), 7.35 (d, quinoline), 7.48 (br dd, quinoline), 7.64 (br dd, quinoline), 8.00 (br d, quinoline), 8.03 (br d, quinoline), 8.76 (d, quinoline), 9.61 (s, CHO).

4.1.30. Preparation of 55 and 57

Reaction of **53** with difluoroacetic acid gave **55** in 49% yield and **57** in 38% yield by a similar procedure to **12**. Total yield of this reaction was 87%. Compound **55**: $[\alpha]_D^{20}$ −49° (*c* 0.92, $CHCl_3$); FAB-MS *m*/*z* 971 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{78}N_4O_{14}$: 971.5593. Found: 971.5587 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.85 (d, 8-CH_3), 1.04 (s, 3″-CH_3), 1.05 (d, 6″-H), 1.07 (t, 3-$OCOCH_2CH_3$), 1.10 (t, 4″-$OCOCH_2CH_3$), 1.11 (d, 6′-H), 1.40 (br d, 8-H), 1.76 (dd, 2″-Hax), 1.80 (m, 13-H), 1.93 (d, 2″-Heq), 2.36 (s, NCH_3), 2.42 (s, 3′-$N(CH_3)_2$), 2.75 (dd, 10-H), 2.93 (dd, 6-CH_2), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.43 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.62 (br d, 9-H), 3.79 (br d, 5-H), 3.84 (m, 14-H), 4.34 (d, 1′-H), 4.38 (dq, 5″-H), 4.54 (d, 4″-H), 4.99 (d, 1″-H), 5.19 (br dd, 3-H), 6.36 (dt, quinoline –CH=CH), 7.07 (d, quinoline-CH), 7.35 (d, quinoline), 7.48 (ddd, quinoline), 7.63 (ddd, quinoline), 8.00 (br d, quinoline), 8.02 (br d, quinoline), 8.76 (d, quinoline), 9.57 (s, CHO). Compound **57**: $[\alpha]_D^{21}$ −20° (*c* 0.56, $CHCl_3$); FAB-MS *m*/*z* 771 $(M+H)^+$; HRMS: Calcd for $C_{41}H_{62}N_4O_{10}$: 771.4544. Found: 771.4529 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.85 (d, 8-CH_3), 0.95 (br dd, 7-H), 1.04 (s, 3″-CH_3), 1.07 (t, 3-$OCOCH_2CH_3$), 1.16 (d, 6′-H), 1.38 (br dd, 7-H), 1.42 (m, 8-H), 1.80 (m, 13-H), 2.35 (s, NCH_3), 2.41 (s, 3′-$N(CH_3)_2$), 2.76 (dd, 10-H), 2.95 (d, 6-CH_2), 3.00 (t, 4′-H), 3.21 (dq, 5′-H), 3.40 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.63 (br d, 9-H), 3.81 (br d, 5-H), 3.85 (m, 14-H), 4.36 (d, 1′-H), 5.19 (br dd, 3-H), 6.36 (dt, CH=CH), 7.08 (d, quinoline-CH), 7.36 (d, quinoline), 7.49 (ddd, quinoline), 7.64 (ddd, quinoline), 7.69 (br s, NH), 8.00 (br d, quinoline), 8.03 (br d, quinoline), 8.76 (d, quinoline), 9.59 (s, CHO).

4.1.31. Preparation of 58 and 59

Reaction of 9,2′-di-*O*-acetyl dimethyacetal of **58** and 9,2′-di-*O*-acetyl dimethyacetal of **59** with methanol gave dimethyacetal of **58** in 65% yield and dimethyacetal of **59** in 55% yield, respectively, by a similar procedure to **8**. Then, these compounds with difluoroacetic acid gave **58** in 38% yield and **59** in 55% yield, respectively, by a similar procedure to **12**. **58**; $[\alpha]_D^{19}$ −34° (*c* 0.31, $CHCl_3$); FAB-MS *m*/*z* 971 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{78}N_4O_{14}$: 971.5593. Found: 971.5587 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.87 (d, 8-CH_3), 1.05 (s, 3″-CH_3), 1.06 (d, 6″-H), 1.10 (t, 3-OCOCH$_2$CH$_3$), 1.11 (t, 4″-OCOCH$_2$CH$_3$), 1.13 (d, 6′-H), 1.26 (br dd, 7-H), 1.39 (m, 13-H), 1.52 (br dd, 8-H), 1.77 (dd, 2″-Hax), 1.94 (d, 2″-Heq), 2.18 (s, NCH_3), 2.45 (s, 3′-N$(CH_3)_2$), 2.79 (dd, 2-H), 2.90 (dd, 6-CH_2), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.38 (br dd, 9-H), 3.48 (dd, 2′-H), 3.68 (s, 4-OCH_3), 3.74 (br d, 4-H), 3.82 (br d, 5-H), 4.35 (d, 1′-H), 4.40 (dq, 5″-H), 4.55 (d, 4″-H), 4.60 (m, 14-H), 4.93 (br d, 3-H), 5.00 (d, 1″-H), 5.43 (dd, 14-CH), 5.80 (ddd, 14-CH═CH), 6.30 (br d,NH), 7.16 (d, quinoline), 7.50 (ddd, quinoline), 7.65 (ddd, quinoline), 7.92 (br d, quinoline), 8.05 (br d, quinoline), 8.77 (d, quinoline), 9.59 (s, CHO). Compound **59**: $[\alpha]_D^{18}$ −66° (*c* 0.39, $CHCl_3$); FAB-MS *m*/*z* 971 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{78}N_4O_{14}$: 971.5593. Found: 971.5587 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.74 (d, 8-CH_3), 1.05 (s, 3″-CH_3), 1.06 (d, 6″-H), 1.06 (t, 3-OCOCH$_2$CH$_3$), 1.10 (d, 6′-H), 1.11 (t, 4″-OCOCH$_2$CH$_3$), 1.30 (br dd, 8-H), 1.61 (m, 13-H), 1.77 (dd, 2″-Hax), 1.95 (d, 2″-Heq), 2.14 (dd, 6-CH_2), 2.28 (s, NCH_3), 2.50 (s, 3′-N$(CH_3)_2$), 2.97 (dd, 6-CH_2), 3.12 (br d, 4-H), 3.21 (m, 4′-H), 3.21 (m, 5′-H), 3.33 (s, 4-OCH_3), 3.52 (dd, 2′-H), 3.58 (br dd, 9-H), 4.34 (d, 1′-H), 4.42 (dq, 5″-H), 4.56 (d, 4″-H), 5.01 (m, 3-H), 5.01 (d, 1″-H), 5.29 (dd, 14-CH), 5.76 (ddd, 14-CH═CH), 7.20 (d, quinoline), 7.50 (ddd, quinoline), 7.63 (ddd, quinoline), 7.93 (dd, quinoline), 8.02 (dd, quinoline), 8.22 (br d, NH), 8.73 (d, quinoline), 9.55 (s, CHO).

4.1.32. Synthesis of dimethylacetal of 60

Compound **52** (104 mg, 0.102 mmol) was dissolved in ethanol (10 ml), and acetic acid (0.12 ml, 2.10 mmol) and 10% Pd/C catalyst (52.3 mg) were added. The reaction vessel was purged with hydrogen, and the reaction mixture was stirred for 5 h. The reaction mixture was filtered through a Celite layer, and washed with methanol. The filtrate was concentrated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol (25:1)) to obtain 49.2 mg of dimethylacetal of **60** (47%) as a colorless solid; FAB-MS *m*/*z* 1019 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.85 (d, 8-CH_3), 1.05 (d, 6″-H), 1.05 (t, 3-OCOCH$_2$CH$_3$), 1.05 (s, 3″-CH_3), 1.10 (t, 4″-OCOCH$_2$CH$_3$), 1.20 (d, 6′-H), 1.76 (dd, 2″-Hax), 1.94 (d, 2″-Heq), 2.45 (s, 3′-N$(CH_3)_2$), 2.76 (dd, 2-H), 3.00 (m, quinoline-CH_2), 3.04 (s, CH$(OCH_3)_2$), 3.18 (s, CH$(OCH_3)_2$), 3.25 (m, 4′-H), 3.25 (m, 5′-H), 3.51 (dd, 2′-H), 3.70 (s, 4-OCH_3), 3.89 (br d, 5-H), 4.02 (m, 14-H), 4.40 (d, 1′-H), 4.38 (dq, 5″-H), 4.55 (d, 4″-H), 4.80 (br d, 3-H), 5.01 (d, 1″-H), 7.14 (d, quinoline), 7.47 (br dd, quinoline), 7.62 (br dd, quinoline), 7.93 (br d, quinoline), 8.03 (br d, quinoline), 8.72 (d, quinoline).

4.1.33. Preparation of 60 and 61

Reaction of 9, 2′-di-*O*-acetyl dimethyacetal of **60** with difluoroacetic acid gave **60** in 38% yield and **61** in 40% yield by a similar procedure to **12**. Total yield of this reaction was 78%. Compound **60**; $[\alpha]_D^{20}$ −51° (*c* 0.53, $CHCl_3$); FAB-MS *m*/*z* 973 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{80}N_4O_{14}$: 973.5749. Found: 973.5754 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.87 (d, 8-CH_3), 1.05 (s, 3″-CH_3), 1.06 (d, 6″-H), 1.07 (t, 3-OCOCH$_2$CH$_3$), 1.11 (t, 4″-OCOCH$_2$CH$_3$), 1.13 (d, 6′-H), 1.29 (br dd, 7-H), 1.36 (m, 13-H), 1.76 (dd, 2″-Hax), 1.94 (d, 2″-Heq), 2.21 (s, NCH_3), 2.44 (s, 3′-N$(CH_3)_2$), 2.79 (dd, 2-H), 2.89 (dd, 6-CH_2), 3.01 (ddd, quinoline-CH_2), 3.20 (m, 4′-H), 3.22 (m, 5′-H), 3.39 (br d, 9-H), 3.48 (dd, 2′-H), 3.70 (s, 4-OCH_3), 3.76 (br d, 4-H), 3.82 (br d, 5-H), 4.06 (m, 14-H), 4.35 (d, 1′-H), 4.40 (dq, 5″-H), 4.55 (d, 4″-H), 4.91 (br d, 3-H), 5.00 (d, 1″-H), 7.15 (d, quinoline), 7.48 (ddd, quinoline), 7.63 (ddd, quinoline), 7.94 (br d, quinoline), 8.03 (br d, quinoline), 8.73 (d, quinoline), 9.58 (s, CHO). Compound **61**: $[\alpha]_D^{26}$ −21° (*c* 0.44, $CHCl_3$); FAB-MS *m*/*z* 773 $(M+H)^+$; HRMS: Calcd for $C_{41}H_{64}N_4O_{10}$: 773.4701. Found: 773.4716 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.87 (d, 8-CH_3), 1.10 (t, 3-OCOCH$_2$CH$_3$), 1.18 (d, 6′-H), 1.29 (br dd, 7-H), 1.35 (m, 13-H), 1.74 (m, quinoline-CH_2CH_2), 1.86 (br t, 6-H), 2.20 (s, NCH_3), 2.46 (s, 3′-N$(CH_3)_2$), 2.79 (dd, 2-H), 2.94 (dd, 6-CH_2), 2.98 (t, 4′-H), 3.02 (ddd, quinoline-CH_2), 3.23 (dq, 5′-H), 3.38 (br dd, 9-H), 3.47 (dd, 2′-H), 3.70 (s, 4-OCH_3), 3.76 (br d, 4-H), 3.83 (br d, 5-H), 4.07 (m, 14-H), 4.36 (d, 1′-H), 4.92 (br d, 3-H), 6.02 (br d, NH), 7.15 (d, quinoline), 7.48 (ddd, quinoline), 7.63 (ddd, quinoline), 7.94 (br d, quinoline), 8.04 (br d, quinoline), 8.73 (d, quinoline), 9.60 (s, CHO).

4.1.34. Preparation of dimethylacetal of 62

Hydrogenolysis of **53** gave dimethylacetal of **62** in 71% yield by a similar procedure to dimethylacetal of **60**; $[\alpha]_D^{22}$ −36° (*c* 0.43, $CHCl_3$); FAB-MS *m*/*z* 1019 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.84 (d, 8-CH_3), 0.92 (br dd, 7-H), 1.04 (s, 3″-CH_3), 1.05 (t, 3-OCOCH$_2$CH$_3$), 1.05 (d, 6″-H), 1.10 (t, 4″-OCOCH$_2$CH$_3$), 1.20 (d, 6′-H), 1.32 (br dd, 7-H), 1.76 (dd, 2″-Hax), 1.83 (br dd, 6-CH_2), 1.93 (d, 2″-Heq), 2.27 (s, NCH_3), 2.43 (s, 3′-N$(CH_3)_2$), 2.54 (br t, 13-H), 3.01 (ddd, quinoline-CH_2), 3.12 (s, CH$(OCH_3)_2$), 3.19 (s, CH$(OCH_3)_2$), 3.21 (m, 4′-H), 3.24 (m, 5′-H), 3.28 (br d, 4-H), 3.51 (s, 4-OCH_3), 3.79 (br d, 5-H), 3.84 (m, 14-H), 4.32 (d, 1′-H), 4.37 (dd, CH$(OCH_3)_2$), 4.39 (dq, 5″-H), 4.54 (d, 4″-H), 5.00 (d, 1″-H), 5.11 (br dd, 3-H), 6.73 (br s, NH), 7.13 (d, quinoline), 7.48 (br dd, quinoline), 7.62 (br dd, quinoline), 7.94 (br d, quinoline), 8.02 (br d, quinoline), 8.71 (d, quinoline).

4.1.35. Preparation of 62 and 63

Reaction of 9,2′-di-*O*-acetyl dimethyacetal of **62** with difluoroacetic acid gave **62** in 51% yield and **63** in 40% yield by a similar procedure to **12**. Total yield of this reaction was 91%. Compound **62**; $[\alpha]_D^{23}$ −43° (*c* 0.85, $CHCl_3$); FAB-MS *m*/*z* 973 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{80}N_4O_{14}$: 973.5749. Found: 973.5754 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.87 (d, 8-CH_3), 0.91 (br dd, 7-H), 1.04 (s, 3″-CH_3), 1.06 (d, 6″-H), 1.08 (t, 3-OCOCH$_2$CH$_3$), 1.10 (t, 4″-OCOCH$_2$CH$_3$), 1.11 (d, 6′-H), 1.38 (m, 8-H), 1.48 (br dd, 13-H), 1.76 (dd, 2″-Hax), 1.94 (d, 2″-Heq), 2.23 (dd, 6-CH_2), 2.33 (s, NCH_3), 2.45 (s, 3′-N$(CH_3)_2$), 2.91 (dd, 6-CH_2), 3.02 (br dd, quinoline-CH_2), 3.20 (m, 4′-H), 3.21 (m, 5′-H), 3.43 (br d, 4-H), 3.49 (s, 4-OCH_3), 3.56 (br d, 9-H), 3.71 (m, 14-H), 3.77 (br d, 5-H), 4.34 (d, 1′-H), 4.39 (dq, 5″-H), 4.55 (d, 4″-H), 4.99 (d, 1″-H), 5.15 (br dd, 3-H), 7.14 (d, quinoline), 7.26 (br s, NH), 7.48 (ddd, quinoline), 7.62 (ddd, quinoline), 7.94 (br d, quinoline), 8.02 (br d, quinoline), 8.71 (d, quinoline), 9.56 (s, CHO). Compound **63**; $[\alpha]_D^{23}$ −14° (*c* 0.53, $CHCl_3$); FAB-MS *m*/*z* 773 $(M+H)^+$; HRMS: Calcd for $C_{41}H_{64}N_4O_{10}$: 773.4701. Found: 773.4716 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.86 (d, 8-CH_3), 0.93 (br dd, 7-H), 1.08 (t, 3-OCOCH$_2$CH$_3$), 1.16 (d, 6′-H), 1.96 (br t, 6-H), 2.31 (s, NCH_3), 2.43 (s, 3′-N$(CH_3)_2$), 2.96 (dd, 6-CH_2), 2.96 (t, 4′-H), 3.21 (dq, 5′-H), 3.42 (br d, 4-H), 3.44 (dd, 2′-H), 3.50 (s, 4-OCH_3), 3.57 (br d, 9-H), 3.72 (m, 14-H), 3.79 (br d, 5-H), 4.36 (d, 1′-H), 5.16 (br dd, 3-H), 7.15 (d, quinoline), 7.25 (br s, NH), 7.49 (ddd, quinoline), 7.63 (ddd, quinoline), 7.94 (br d, quinoline), 8.03 (br d, quinoline), 8.72 (d, quinoline), 9.59 (s, CHO).

4.1.36. Preparation of 9,2′-di-*O*-acetyl dimethylacetal of 64

Reaction of **48** with 3-bromoquinoline gave 9,2′-di-*O*-acetyl dimethylacetal of **64** in 59% yield by a similar procedure to **50**; $[\alpha]_D^{28}$ −55° (*c* 0.65, $CHCl_3$); FAB-MS *m*/*z* 1101 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.81 (d, 8-CH_3), 1.04 (t, 3-OCOCH$_2$CH$_3$), 1.04 (s, 3″-CH_3), 1.05 (d, 6″-H), 1.10 (t, 4″-OCOCH$_2$CH$_3$), 1.19 (d, 6′-H), 1.24 (br dd, 7-H), 1.36 (m, 13-H), 1.50 (br dd, 6-CH_2), 1.58 (m, 8-H), 1.68 (br

dd, 6-CH_2), 1.76 (dd, 2″-Hax), 1.94 (d, 2″-Heq), 1.95 (s, 9-$OCOCH_3$), 1.98 (s, 2′-$OCOCH_3$), 2.21 (s, NCH_3), 2.33 (s, 3′-$N(CH_3)_2$), 2.65 (t, 3′-H), 2.68 (dd, 2-H), 2.99 (s, $CH(OCH_3)_2$), 3.16 (s, $CH(OCH_3)_2$), 3.25 (m, 4′-H), 3.28 (m, 5′-H), 3.36 (br d, 4-H), 3.63 (s, 4-OCH_3), 3.93 (br d, 5-H), 4.14 (m, 14-H), 4.30 (dq, 5″-H), 4.48 (dd, $CH(OCH_3)_2$), 4.54 (d, 4″-H), 4.68 (d, 1′-H), 4.83 (m, 9-H), 4.85 (br d, 3-H), 4.92 (dd, 2′-H), 4.99 (d, 1″-H), 6.30 (dt, CH=CH), 6.50 (d, quinoline-CH), 6.62 (br d, NH), 7.44 (ddd, quinoline), 7.57 (ddd, quinoline), 7.70 (br d, quinoline), 7.93 (d, quinoline), 7.87 (br d, quinoline), 8.86 (d, quinoline).

4.1.37. Preparation of 64 and 65

Reaction of 9,2′-Di-*O*-acetyl dimethyacetal of **64** with methanol gave dimethyacetal of **64** in 92% yield by a similar procedure to **8**. Then, dimethyacetal of **64** with difluoroacetic acid gave **64** in 43% yield and **65** in 32% yield by a similar procedure to **12**. Total yield of this reaction was 75%. Compound **64**; $[\alpha]_D^{23}$ −48° (*c* 0.83, $CHCl_3$); FAB-MS *m*/*z* 971 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{78}N_4O_{14}$: 971.5593. Found: 971.5591 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.83 (br dd, 7-H), 0.87 (d, 8-CH_3), 1.04 (s, 3″-CH_3), 1.05 (d, 6″-H), 1.09 (t, 3-$OCOCH_2CH_3$), 1.11 (t, 4″-$OCOCH_2CH_3$), 1.12 (d, 6′-H), 1.29 (m, 8-H), 1.41 (m, 13-H), 1.52 (br dd, 7-H), 1.76 (dd, 2″-Hax), 1.93 (d, 2″-Heq), 2.21 (s, NCH_3), 2.44 (s, 3′-$N(CH_3)_2$), 2.78 (dd, 2-H), 2.90 (dd, 6-CH_2), 3.20 (m, 4′-H), 3.20 (m, 5′-H), 3.38 (br dd, 9-H), 3.48 (dd, 2′-H), 3.69 (s, 4-OCH_3), 3.76 (br d, 4-H), 3.82 (br d, 5-H), 4.22 (m, 14-H), 4.34 (d, 1′-H), 4.40 (dq, 5″-H), 4.55 (d, 4″-H), 4.94 (br d, 3-H), 5.00 (d, 1″-H), 6.21 (br d, NH), 6.31 (dt, CH=CH), 6.52 (d, quinoline-CH_2), 7.45 (ddd, quinoline), 7.59 (ddd, quinoline), 7.71 (br d, quinoline), 7.94 (br s, quinoline), 7.98 (br d, quinoline), 8.87 (d, quinoline), 9.59 (s, CHO). Compound **65**; $[\alpha]_D^{23}$ −14° (*c* 0.50, $CHCl_3$); FAB-MS *m*/*z* 771 $(M+H)^+$; HRMS: Calcd for $C_{41}H_{62}N_4O_{10}$: 771.4544. Found: 771.4529 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.88 (d, 8-CH_3), 1.09 (t, 3-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.30 (m, 8-H), 1.43 (m, 13-H), 1.53 (br dd, 7-H), 1.85 (m, 6-H), 1.91 (m, 13-H), 2.22 (s, NCH_3), 2.46 (s, 3′-$N(CH_3)_2$), 2.78 (dd, 2-H), 2.95 (dd, 6-CH_2), 2.98 (t, 4′-H), 3.23 (dq, 5′-H), 3.39 (br dd, 9-H), 3.47 (dd, 2′-H), 3.69 (s, 4-OCH_3), 3.77 (br d, 4-H), 3.83 (brd, 5-H), 4.22 (m, 14-H), 4.36 (d, 1′-H), 4.95 (br d, 3-H), 6.22 (br d, NH), 6.32 (dt, CH=CH), 6.53 (d, quinoline-CH_2), 7.45 (ddd, quinoline), 7.59 (ddd, quinoline), 7.72 (br d, quinoline), 7.95 (br s, quinoline), 7.99 (br d, quinoline), 8.87 (d, quinoline), 9.61 (s, CHO).

4.1.38. Preparation of 9,2′-di-*O*-acetyl dimethylacetal of 66

Reaction of **49** with 3-bromoquinoline gave 9, 2′-di-*O*-acetyl dimethylacetal of **66** in 42% yield by a similar procedure to **50**; $[\alpha]_D^{18}$ −37° (*c* 0.70, $CHCl_3$); FAB-MS *m*/*z* 1,101 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.83 (d, 8-CH_3), 1.04 (d, 6″-H), 1.04 (s, 3″-CH_3), 1.05 (t, 3-$OCOCH_2CH_3$), 1.09 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.41 (br dd, 6-CH_2), 1.65 (m, 8-H), 1.76 (dd, 2″-Hax), 1.93 (s, 9-$OCOCH_3$), 1.95 (s, 2′-$OCOCH_3$), 2.18 (s, NCH_3), 2.32 (s, 3′-$N(CH_3)_2$), 2.65 (t, 3′-H), 3.04 (s, $CH(OCH_3)_2$), 3.17 (s, $CH(OCH_3)_2$), 3.24 (m, 4′-H), 3.27 (m, 5′-H), 3.50 (s, 4-OCH_3), 3.87 (br d, 5-H), 4.30 (dq, 5″-H), 4.46 (m, $CH(OCH_3)_2$), 4.54 (d, 4″-H), 4.66 (d, 1′-H), 4.76 (m, 3-H), 4.94 (dd, 2′-H), 4.99 (d, 1″-H), 5.00 (m, 9-H), 6.32 (dt, CH=CH), 6.52 (d, quinoline-CH), 7.44 (ddd, quinoline), 7.58 (ddd, quinoline), 7.71 (br d, quinoline), 7.93 (br s, quinoline), 7.97 (br d, quinoline), 8.86 (d, quinoline).

4.1.39. Preparation of 66

Reaction of 9,2′-di-*O*-acetyl dimethylacetal of **66** with methanol gave dimethylacetal of **66** in 80% yield by a similar procedure to **8**. Then, dimethylacetal of **66** with difluoroacetic acid gave **66** in 41% yield by a similar procedure to **12**; $[\alpha]_D^{18}$ −119° (*c* 0.41, $CHCl_3$); FAB-MS *m*/*z* 971 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{78}N_4O_{14}$: 971.5593. Found: 971.5587 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.43 (d, 8-CH_3), 1.07 (s, 3″-CH_3), 1.09 (t, 3-$OCOCH_2CH_3$), 1.11 (d, 6′-H), 1.11 (d, 6″-H), 1.13 (t, 4″-$OCOCH_2CH_3$), 1.77 (dd, 2″-Hax), 1.97 (d, 2″-Heq), 2.10 (s, NCH_3), 2.61 (s, 3′-$N(CH_3)_2$), 2.72 (dd, 2-H), 2.81 (dd, 6-CH_2), 3.23 (m, 4′-H), 3.25 (m, 5′-H), 3.59 (br d, 4-H), 3.72 (s, 4-OCH_3), 3.91 (br d, 5-H), 3.93 (m, 14-H), 4.47 (dq, 5″-H), 4.51 (d, 1′-H), 4.57 (d, 4″-H), 5.03 (d, 1″-H), 5.05 (m, 3-H), 6.42 (br dd, CH=CH), 6.53 (d, quinoline-CH), 7.49 (ddd, quinoline), 7.62 (ddd, quinoline), 7.72 (br d, quinoline), 7.88 (br s, quinoline), 8.02 (br d, quinoline), 8.77 (br d, NH), 9.04 (br s, quinoline), 9.53 (s, CHO).

4.1.40. Preparation of 67 and 68

Hydrogenolysis of dimethylacetal of **64** gave dimethylacetal of **67** in 64% yield by a similar procedure to dimethylacetal of **60**. Reaction of dimethylacetal of **67** with difluoroacetic acid gave **67** in 51% yield and **68** in 30% yield by a similar procedure to **12**. Total yield of this reaction was 81%. Compound **67**; $[\alpha]_D^{22}$ −54° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 973 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{80}N_4O_{14}$: 973.5749. Found: 973.5754 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.86 (d, 8-CH_3), 1.04 (s, 3″-CH_3), 1.06 (d, 6″-H), 1.09 (t, 3-$OCOCH_2CH_3$), 1.10 (t, 4″-$OCOCH_2CH_3$), 1.12 (d, 6′-H), 1.28 (m, 8-H), 1.33 (m, 13-H), 1.69 (m, quinoline-CH_2CH_2), 1.69 (m, 6-H), 1.76 (dd, 2″-Hax), 1.93 (d, 2″-Heq), 2.19 (s, NCH_3), 2.44 (s, 3′-$N(CH_3)_2$), 2.73 (m, quinoline-CH_2), 2.79 (dd, 2-H), 2.89 (dd, 6-CH_2), 3.20 (m, 4′-H), 3.21 (m, 5′-H), 3.37 (br dd, 9-H), 3.48 (dd, 2′-H), 3.69 (s, 4-OCH_3), 3.76 (br d, 4-H), 3.82 (br d, 5-H), 4.04 (m, 14-H), 4.34 (d, 1′-H), 4.39 (dq, 5″-H), 4.55 (d, 4″-H), 4.91 (br d, 3-H), 4.99 (d, 1″-H), 6.00 (br d, NH), 7.45 (ddd, quinoline), 7.58 (ddd, quinoline), 7.69 (br d, quinoline), 7.83 (d, quinoline), 8.00 (br d, quinoline), 8.68 (d, quinoline), 9.58 (s, CHO). Compound **68**: $[\alpha]_D^{22}$ −21° (*c* 0.47, $CHCl_3$); FAB-MS *m*/*z* 773 $(M+H)^+$; HRMS: Calcd for $C_{41}H_{64}N_4O_{10}$: 773.4701. Found: 773.4716 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.87 (d, 8-CH_3), 1.10 (t, 3-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.29 (m, 8-H), 1.36 (m, 13-H), 1.70 (m, quinoline-CH_2CH_2), 1.78 (m, 13-H), 1.86 (br t, 6-H), 2.20 (s, NCH_3), 2.47 (s, 3′-$N(CH_3)_2$), 2.75 (m, quinoline-CH_2), 2.80 (dd, 2-H), 2.94 (dd, 6-CH_2), 2.98 (t, 4′-H), 3.23 (dq, 5′-H), 3.38 (br dd, 9-H), 3.47 (dd, 2′-H), 3.70 (s, 4-OCH_3), 3.76 (br d, 4-H), 3.83 (br d, 5-H), 4.05 (m, 14-H), 4.36 (d, 1′-H), 4.91 (br d, 3-H), 5.99 (br d, NH), 7.45 (ddd, quinoline), 7.59 (ddd, quinoline), 7.70 (br d, quinoline), 7.84 (d, quinoline), 8.00 (br d, quinoline), 8.68 (d, quinoline), 9.60 (s, CHO).

4.1.41. Preparation of 69 and 70

Hydrogenolysis of dimethylacetal of **66** gave dimethylacetal of **69** in 85% yield by a similar procedure to dimethylacetal of **60**. Reaction of dimethylacetal of **69** with difluoroacetic acid gave **69** in 24% yield and **70** in 59% yield by a similar procedure to **12**. Total yield of this reaction was 83%. Compound **69**; $[\alpha]_D^{16}$ −75° (*c* 0.39, $CHCl_3$); FAB-MS *m*/*z* 973 $(M+H)^+$; HRMS: Calcd for $C_{51}H_{80}N_4O_{14}$: 973.5749. Found: 973.5760 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.18 (d, 8-CH_3), 1.04 (s, 3″-CH_3), 1.06 (t, 3-$OCOCH_2CH_3$), 1.08 (d, 6″-H), 1.12 (d, 6′-H), 1.12 (t, 4″-$OCOCH_2CH_3$), 1.78 (dd, 2″-Hax), 1.97 (d, 2″-Heq), 2.89 (br d, 6-CH_2), 2.55 (s, 3′-$N(CH_3)_2$), 2.88 (m, quinoline-CH_2), 2.93 (dd, 6-CH_2), 3.26 (m, 4′-H), 3.26 (m, 5′-H), 3.52 (m, 9-H), 3.69 (s, 4-OCH_3), 3.79 (br d, 5-H), 4.02 (m, 14-H), 4.49 (dq, 5″-H), 4.50 (d, 1′-H), 4.57 (d, 4″-H), 4.88 (br d, 3-H), 5.05 (d, 1″-H), 7.48 (ddd, quinoline), 7.63 (ddd, quinoline), 7.74 (br d, quinoline), 7.87 (d, quinoline), 7.96 (br d, quinoline), 8.24 (br s, NH), 8.65 (d, quinoline), 9.54 (s, CHO). Compound **70**; $[\alpha]_D^{17}$ −54° (*c* 0.77, $CHCl_3$); FAB-MS *m*/*z* 773 $(M+H)^+$; HRMS: Calcd for $C_{41}H_{64}N_4O_{10}$: 773.4701. Found: 773.4716 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.14 (d, 8-CH_3), 0.31 (m, 7-H), 1.06 (t, 3-$OCOCH_2CH_3$), 1.16 (d, 6′-H), 1.26 (m, 14-CH_2), 1.42 (m, 13-H), 1.78 (m, 13-H), 1.93 (m, 10-H), 2.01 (br d, 6-CH_2), 2.17 (br d, 10-H), 2.25 (s, NCH_3), 2.41 (t, 3′-H), 2.56 (s, 3′-$N(CH_3)_2$), 2.90 (br dd, quinoline-CH_2), 2.97 (dd, 6-CH_2), 3.00 (t, 4′-H), 3.12 (br d, 4-H), 3.27 (dq, 5′-H), 3.49 (m, 9-H), 3.68 (s, 4-OCH_3), 3.78 (dd, 2′-H), 3.81 (br d,

5-H), 4.03 (m, 14-H), 4.53 (d, 1′-H), 4.84 (br dd, 3-H), 7.48 (ddd, quinoline), 7.63 (ddd, quinoline), 7.74 (br d, quinoline), 7.87 (d, quinoline), 7.94 (br d, quinoline), 8.22 (br d, NH), 8.64 (d, quinoline), 9.55 (s, CHO).

4.1.42. Preparation of 71 and 72

Reaction of **36** with 3-(methylaminomethyl)-5-hexen-1-ol[26] gave **71** in 40% yield and **72** in 30% yield by a similar procedure to **4**. Total yield of this reaction was 70%. Compound **71**: less polar; R_f value = 0.34, chloroform/methanol (5:1); $[\alpha]_D^{17}$ −56° (*c* 0.80, $CHCl_3$); FAB-MS *m*/*z* 1007 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.90 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.17 (d, 6′-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.05 (s, 2′-$OCOCH_3$), 2.39 (s, 3′-$N(CH_3)_2$), 2.48 (s, NCH_3), 2.58 (dd, 10-H), 2.71 (t, 3′-H), 3.16 (s, $CH(OCH_3)_2$), 3.24 (s, $CH(OCH_3)_2$), 3.30 (m, 4′-H), 3.33 (m, 5′-H), 3.55 (s, 4-OCH_3), 3.76 (m, 15-H), 3.86 (br d, 5-H), 4.37 (dq, 5″-H), 4.50 (dd, $CH(OCH_3)_2$), 4.60 (d, 4″-H), 4.73 (d, 1′-H), 4.98 (dd, 2′-H), 5.03 (m, CH=CH_2), 5.06 (dd, 1″-H), 5.15 (m, 9-H), 5.16 (m, 3-H), 5.70 (ddt, CH=CH_2). Compound **72**: polar; R_f value = 0.14, chloroform/methanol (5:1); $[\alpha]_D^{17}$ −42° (*c* 1.5, $CHCl_3$); FAB-MS *m*/*z* 1007 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.91 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.15 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 6′-H), 1.83 (dd, 2″-Hax), 1.94 (m, 13-H), 1.99 (d, 2″-Heq), 2.00 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.06 (s, 2′-$OCOCH_3$), 2.40 (s, 3′-$N(CH_3)_2$), 2.51 (s, NCH_3), 2.71 (t, 3′-H), 3.19 (s, $CH(OCH_3)_2$), 3.25 (s, $CH(OCH_3)_2$), 3.30 (m, 4′-H), 3.33 (m, 5′-H), 3.54 (s, 4-OCH_3), 3.56 (br d, 4-H), 3.77 (m, 15-H), 3.86 (br d, 5-H), 4.37 (dq, 5″-H), 4.61 (d, 4″-H), 4.72 (d, 1′-H), 4.80 (dd, $CH(OCH_3)_2$), 4.98 (dd, 2′-H), 5.03 (m, CH=CH_2), 5.07 (d, 1″-H), 5.19 (m, 9-H), 5.21 (m, 3-H), 5.71 (ddt, CH=CH_2).

4.1.43. Synthesis of 73

2-Methyl-6-nitrobenzoic anhydride[27] (374 mg, 0.773 mmol) and 4-dimethylaminopyridine (266 mg, 2.18 mmol) were dissolved in methylene chloride (200 ml). A solution of **71** (730 mg, 0.725 mmol) in methylene chloride (200 ml) was dropwised over 2.5 h under ice cooling, and then stirred for 2 h. Saturated aqueous ammonium chloride was added to the reaction mixture, and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (diethyl ether/acetone/aqueous ammonia (100:5:0.1)) to obtain 339 mg (63%) of **73** as a colorless solid; $[\alpha]_D^{19}$ −70° (*c* 0.3, $CHCl_3$); FAB-MS *m*/*z* 989 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.94 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.58 (m, 14-H), 1.84 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.04 (s, 2′-$OCOCH_3$), 2.40 (s, NCH_3), 2.40 (s, 3′-$N(CH_3)_2$), 2.61 (dd, 10-H), 2.71 (t, 3′-H), 3.16 (s, $CH(OCH_3)_2$), 3.24 (s, $CH(OCH_3)_2$), 3.26 (br d, 4-H), 3.28 (t, 4′-H), 3.33 (dq, 5′-H), 3.53 (s, 4-OCH_3), 3.90 (br d, 5-H), 4.20 (m, 15-H), 4.38 (dq, 5″-H), 4.50 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.70 (d, 1′-H), 5.07 (d, 1″-H), 5.19 (br dd, 3-H), 5.75 (ddt, CH=CH_2).

4.1.44. Preparation of 74

Macrolactonization of **72** gave **74** in 54% yield by a similar procedure to **73**; $[\alpha]_D^{19}$ −68° (*c* 0.3, $CHCl_3$); FAB-MS *m*/*z* 989 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.94 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.84 (dd, 2″-Hax), 1.95 (br dd, 13-H), 2.01 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.05 (s, 2′-$OCOCH_3$), 2.25 (s, NCH_3), 2.41 (s, 3′-$N(CH_3)_2$), 2.53 (dd, 10-H), 2.69 (m, 2-H), 2.72 (t, 3′-H), 3.13 (s, $CH(OCH_3)_2$), 3.24 (s, $CH(OCH_3)_2$), 3.33 (m, 4′-H), 3.34 (br d, 4-H), 3.35 (m, 5′-H), 3.54 (s, 4-OCH_3), 3.89 (br d, 5-H), 4.16 (m, 15-H), 4.38 (dq, 5″-H), 4.49 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.72 (d, 1′-H), 5.07 (d, 1″-H), 5.23 (br dd, 3-H), 5.72 (ddd, CH=CH_2).

4.1.45. Synthesis of 75 and its *cis*-isomer, 9,2′-di-*O*-acetyl dimethylacetal of 81

Compound **73** (485 mg, 0.493 mmol) and 3-bromoquinoline (204 mg, 0.981 mmol) were dissolved in 1,4-dioxane (4.9 ml), and tris(dibenzylideneacetone)dipalladium (0) (135 mg, 0.147 mmol) and dicyclohexylmethylamine (0.21 ml, 0.989 mmol) were added. The reaction vessel was purged with argon, and then a 0.174 M solution of tri-*tert*-butylphosphine in 1,4-dioxane (1.69 ml, 0.294 mmol) was added to the reaction mixture. After the reaction mixture was stirred at 50 °C for 48 h, the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/acetone (2:1) and chloroform/methanol (20:1)) to obtain 31.7 mg (5.8%) of **75** as a colorless solid and 15.3 mg (2.8%) of its *cis*-isomer, 9,2′-di-*O*-acetyl dimethylacetal of **81** as a colorless solid. Total yield of this Heck reaction was 8.6%. Compound **75**; $[\alpha]_D^{25}$ −64° (*c* 0.35, $CHCl_3$); FAB-MS *m*/*z* 1116 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.95 (d, 8-CH_3), 1.02 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.39 (m, 14-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.05 (s, 2′-$OCOCH_3$), 2.12 (m, 14-H), 2.28 (s, NCH_3), 2.40 (s, 3′-$N(CH_3)_2$), 3.12 (s, $CH(OCH_3)_2$), 3.22 (s, $CH(OCH_3)_2$), 3.52 (d, quinoline-CH_2), 3.53 (s, 4-OCH_3), 3.88 (d, 5-H), 4.16 (m, 15-H), 4.37 (dq, 5″-H), 4.45 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.70 (d, 1′-H), 5.00 (dd, 2′-H), 5.06 (d, 1″-H), 5.23 (m, 3-H), 5.29 (dd, *J* = 15.4, 8.2 Hz, 13-CH), 5.84 (dt, *J* = 15.4, 5.9 Hz, CH=CH), 7.51 (ddd, quinoline), 7.65 (ddd, quinoline), 7.77 (br d, quinoline), 7.96 (d, quinoline), 8.06 (br d, quinoline), 8.74 (d, quinoline). **75**′s *cis*-isomer, 9,2′-di-*O*-acetyl dimethylacetal of **81**; $[\alpha]_D^{24}$ −61° (*c* 0.77, $CHCl_3$); FAB: *m*/*z* 1116 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.96 (d, 8-CH_3), 1.01 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.84 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.06 (s, 2′-$OCOCH_3$), 2.31 (s, NCH_3), 2.40 (s, 3′-$N(CH_3)_2$), 2.49 (dd, 2-H), 3.08 (s, $CH(OCH_3)_2$), 3.21 (s, $CH(OCH_3)_2$), 3.55 (s, 4-OCH_3), 3.69 (d, *J* = 7.7 Hz, quinoline-CH_2), 3.89 (d, 5-H), 4.07 (m, 15-H), 4.37 (dq, 5″-H), 4.50 (m, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.71 (d, 1′-H), 5.06 (d, 1″-H), 5.23 (m, 3-H), 5.31 (m, 13-CH), 5.70 (dt, *J* = 10.4, 7.7 Hz, CH=CH), 7.51 (ddd, quinoline), 7.65 (ddd,quinoline), 7.77 (br d, quinoline), 7.94 (d, quinoline), 8.05 (br d, quinoline), 8.80 (d, quinoline).

4.1.46. Preparation of 76

Reaction of **74** with 3-bromoquinoline gave **76** in 28% yield by a similar procedure to **75**; $[\alpha]_D^{25}$ −34° (*c* 0.66, $CHCl_3$); FAB-MS *m*/*z* 1116 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.93 (d, 8-CH_3), 1.08 (t, 3-$OCOCH_2CH_3$), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.83 (dd, 2″-Hax), 1.95 (s, 9-$OCOCH_3$), 1.97 (s, 2′-$OCOCH_3$), 2.27 (s, NCH_3), 2.38 (s, 3′-$N(CH_3)_2$), 2.70 (t, 3′-H), 3.11 (s, $CH(OCH_3)_2$), 3.23 (s, $CH(OCH_3)_2$), 3.31 (t, 4′-H), 3.51 (s, 4-OCH_3), 3.51 (d, *J* = 6.3 Hz, quinoline-CH_2), 3.89 (d, 5-H), 4.22 (m, 15-H), 4.36 (dq, 5″-H), 4.49 (dd, $CH(OCH_3)_2$), 4.60 (d, 4″-H), 4.70 (d, 1′-H), 4.98 (dd, 2′-H), 5.05 (d, 1″-H), 5.24 (t, 3-H), 5.48 (dd, *J* = 15.1, 6.0 Hz, 13-CH), 5.62 (dt, *J* = 15.1, 6.3 Hz, CH=CH), 7.51 (t, quinoline), 7.65 (m, quinoline), 7.76 (d, quinoline), 7.90 (d, quinoline), 8.05 (d, quinoline), 8.73 (d, quinoline).

4.1.47. Preparation of 79, 80, and 81

Reaction of **75** with methanol at 40 °C for 48 h gave **77** in 33% yield. Reaction of **77** with difluoroacetic acid gave **79** in 51% yield by a similar procedure to **12**. Compounds **80** and **81** were prepared from **76** and 9,2′-di-*O*-acetyl dimethylacetal of **81**, respectively, by a similar procedure to **79**. Compound **79**; $[\alpha]_D^{25}$ −61° (*c* 0.24, $CHCl_3$); FAB-MS *m*/*z* 986 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5586 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.90 (d, 8-CH_3), 1.00 (t, 3-$OCOCH_2CH_3$), 1.12 (s, 3″-CH_3), 1.13 (d, 6″-H), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.44 (m, 14-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.11 (m, 14-H), 2.32 (s, NCH_3), 2.50 (s, 3′-

$N(CH_3)_2$), 2.60 (m, 2-H), 2.85 (dd, 6-CH_2), 3.25 (t, 4′-H), 3.53 (d, quinoline-CH_2), 3.59 (s, 4-OCH_3), 3.62 (d, 4-H), 3.82 (d, 5-H), 4.07 (m, 15-H), 4.33 (d, 1′-H), 4.46 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (d, 1″-H), 5.24 (dd, 13-CH), 5.85 (t, 3-H), 5.95 (dt, CH=CH), 7.53 (ddd, quinoline), 7.66 (ddd, quinoline), 7.78 (dd, quinoline), 7.91 (d, quinoline), 8.07 (br d, quinoline), 8.75 (d, quinoline), 9.62 (s, CHO). Compound **80**; $[\alpha]_D^{26}$ −50° (*c* 0.25, $CHCl_3$); FAB-MS *m*/*z* 986 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5586 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.94 (d, 8-CH_3), 1.13 (d, 6″-H), 1.16 (s, 3″-CH_3), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.84 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.36 (s, NCH_3), 2.53 (s, 3′-$N(CH_3)_2$), 2.91 (dd, 6-CH_2), 3.59 (s, 4-OCH_3), 3.90 (d, 5-H), 4.09 (m, 15-H), 4.26 (m, 15-H), 4.44 (d, 1′-H), 4.62 (d, 4″-H), 5.07 (d, 1″-H), 5.44 (m, 3-H), 5.47 (dd, 13-CH), 5.75 (dt, CH=CH), 7.52 (t, quinoline), 7.66 (t, quinoline), 7.78 (d, quinoline), 7.94 (s, quinoline), 8.08 (d, quinoline), 8.77 (d, quinoline), 9.64 (s, CHO). Compound **81**; $[\alpha]_D^{26}$ −32° (*c* 0.35, $CHCl_3$); FAB-MS *m*/*z* 986 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5586 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.83 (d, 8-CH_3), 1.04 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.13 (d, 6″-H), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.30 (s, NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.69 (dd, 2-H), 2.88 (dd, 6-CH_2), 2.94 (m, 13-H), 3.55 (dd, 2′-H), 3.59 (s, 4-OCH_3), 3.83 (m, quinoline-CH_2), 4.01 (m, 15-H), 4.27 (m, 15-H), 4.35 (d, 1′-H), 4.46 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (d, 1″-H), 5.31 (t, 13-CH), 5.74 (m, 3-H), 5.79 (dt, CH=CH), 7.51 (ddd, quinoline), 7.65 (ddd, quinoline), 7.75 (dd, quinoline), 7.93 (d, quinoline), 8.05 (br d, quinoline), 8.78 (d, quinoline), 9.63 (s, CHO).

4.1.48. Preparation of 9,2′-di-*O*-acetyl dimethylacetal of 82 and its *cis*-isomer, 9,2′-di-*O*-acetyl dimethylacetal of 84

Reaction of **73** with 4-bromoquinoline gave 9,2′-di-*O*-acetyl dimethylacetal of **82** in 45% yield and its *cis*-isomer, 9,2′-di-*O*-acetyl dimethylacetal of **84** in 4.4% yield by a similar procedure to **75**. Total yield of this reaction was 49%. 9,2′-Di-*O*-acetyl dimethylacetal of **82**; $[\alpha]_D^{20}$ −64° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1116 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.94 (d, 8-CH_3), 1.02 (t, 3-$OCOCH_2CH_3$), 1.12 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.19 (s, 3″-CH_3), 1.24 (d, 6′-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.02 (s, 9-$OCOCH_3$), 2.03 (s, 2′-$OCOCH_3$), 2.25 (s, NCH_3), 2.39 (s, 3′-$N(CH_3)_2$), 3.08 (s, $CH(OCH_3)_2$), 3.21 (s, $CH(OCH_3)_2$), 3.32 (m, 4′-H), 3.32 (m, 5′-H), 3.52 (s, 4-OCH_3), 3.78 (d, *J* = 6.4 Hz, quinoline-CH_2), 3.87 (br d, 5-H), 4.12 (m, 15-H), 4.26 (br s, 3″-OH), 4.36 (dq, 5″-H), 4.44 (dd, $CH(OCH_3)_2$), 4.60 (d, 4″-H), 4.69 (d, 1′-H), 4.99 (dd, 2′-H), 5.05 (d, 1″-H), 5.22 (m, 3-H), 5.25 (dd, *J* = 15.2, 8.7 Hz, 13-CH), 5.88 (dt, *J* = 15.2, 6.4 Hz, CH=CH), 7.23 (d, quinoline), 7.53 (ddd, quinoline), 7.69 (ddd, quinoline), 8.00 (br d, quinoline), 8.09 (br d, quinoline), 8.80 (d, quinoline). 9,2′-Di-*O*-acetyl dimethylacetal of **84**; $[\alpha]_D^{20}$ −65° (*c* 0.9, $CHCl_3$); FAB-MS *m*/*z* 1116 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3-$OCOCH_2CH_3$), 0.95 (d, 8-CH_3), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.24 (d, 6′-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.05 (s, 2′-$OCOCH_3$), 2.31 (s, NCH_3), 2.39 (s, 3′-$N(CH_3)_2$), 3.05 (s, $CH(OCH_3)_2$), 3.20 (s, $CH(OCH_3)_2$), 3.33 (m, 4′-H), 3.33 (m, 5′-H), 3.35 (br d, 4-H), 3.54 (s, 4-OCH_3), 3.87 (br d, 5-H), 3.93 (d, *J* = 6.9 Hz, quinoline-CH_2), 4.07 (dd, 15-H), 4.26 (br s, 3″-OH), 4.36 (dd, 15-H), 4.37 (m, 5″-H), 4.49 (dd, $CH(OCH_3)_2$), 4.60 (d, 4″-H), 4.69 (d, 1′-H), 4.99 (dd, 2′-H), 5.05 (d, 1″-H), 5.21 (m, 3-H), 5.33 (dd, *J* = 10.7, 1.0 Hz, 13-CH), 5.69 (dt, *J* = 10.7, 6.9 Hz, CH=CH), 7.27 (d, quinoline), 7.53 (ddd,quinoline), 7.69 (ddd, quinoline), 8.06 (br d, quinoline), 8.10 (br d, quinoline), 8.80 (d, quinoline).

4.1.49. Preparation of 9, 2′-di-*O*-acetyl dimethylacetal of 83 and its *cis*-isomer, 9,2′-di-*O*-acetyl dimethylacetal of 85

Reaction of **74** with 4-bromoquinoline gave 9,2′-di-*O*-acetyl dimethylacetal of **83** in 40% yield and its *cis*-isomer, 9,2′-di-*O*-acetyl dimethylacetal of **85** in 5.1% yield by a similar procedure to **75**. Total yield of this reaction was 45%. 9,2′-Di-*O*-acetyl dimethylacetal of **83**; $[\alpha]_D^{17}$ −29° (*c* 1.3, $CHCl_3$); FAB-MS *m*/*z* 1116 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.93 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.11 (t, 3-$OCOCH_2CH_3$), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.83 (dd, 2″-Hax), 1.92 (s, 9-$OCOCH_3$), 1.99 (s, 2′-$OCOCH_3$), 2.01 (d, 2″-Heq), 2.25 (s, NCH_3), 2.39 (s, 3′-$N(CH_3)_2$), 2.66 (m, 2-H), 2.70 (t, 3′-H), 3.11 (s, $CH(OCH_3)_2$), 3.23 (s, $CH(OCH_3)_2$), 3.32 (m, 4′-H), 3.34 (m, 5′-H), 3.51 (s, 4-OCH_3), 3.80 (br d, quinoline-CH_2), 3.90 (br d, 5-H), 4.10 (m, 15-H), 4.17 (m, 15-H), 4.26 (br s, 3″-OH), 4.37 (dq, 5″-H), 4.49 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.70 (d, 1′-H), 4.96 (m, 9-H), 4.99 (dd, 2′-H), 5.06 (d, 1″-H), 5.24 (br dd, 3-H), 5.50 (dd, *J* = 15.7, 6.2 Hz, 13-CH), 5.65 (dt, *J* = 15.7, 6.3 Hz, CH=CH), 7.24 (d, quinoline), 7.55 (ddd, quinoline), 7.70 (ddd, quinoline), 8.02 (br d, quinoline), 8.09 (br d, quinoline), 8.81 (d, quinoline). 9,2′-Di-*O*-acetyl dimethylacetal of **85**; $[\alpha]_D^{18}$ −32° (*c* 0.3, $CHCl_3$); FAB-MS *m*/*z* 1116 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.95 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.11 (t, 3-$OCOCH_2CH_3$), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.83 (dd, 2″-Hax), 1.93 (s, 9-$OCOCH_3$), 1.96 (d, 2″-Heq), 2.00 (s, 2′-$OCOCH_3$), 2.23 (s, NCH_3), 2.38 (s, 3′-$N(CH_3)_2$), 2.52 (dd, 10-H), 2.59 (dd, 2-H), 2.70 (t, 3′-H), 2.82 (m, 13-H), 3.13 (s, $CH(OCH_3)_2$), 3.23 (s, $CH(OCH_3)_2$), 3.25 (br d, 4-H), 3.31 (m, 4′-H), 3.33 (m, 5′-H), 3.87 (m, quinoline-CH_2), 4.11 (m, 15-H), 4.24 (m, 15-H), 4.36 (dq, 5″-H), 4.50 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.69 (d, 1′-H), 4.98 (dd, 2′-H), 5.06 (d, 1″-H), 5.25 (br dd, 3-H), 5.53 (dd, *J* = 10.4, 1.2 Hz, 13-CH), 5.70 (dt, *J* = 10.4, 6.9 Hz, CH=CH), 7.27 (d, quinoline), 7.56 (ddd, quinoline), 7.71 (ddd, quinoline), 8.04 (br d, quinoline), 8.11 (br d, quinoline), 8.81 (d, quinoline).

4.1.50. Preparation of 82 and 83

Reaction of 9,2′-Di-*O*-acetyl dimethyacetal of **82** and 9,2′-Di-*O*-acetyl dimethyacetal of **83** with methanol gave dimethyacetal of **82** in 41% yield and dimethyacetal of **83** in 31% yield, respectively, by a similar procedure to **42**. Then, these compounds with difluoroacetic acid gave **82** in 57% yield and **83** in 27% yield, respectively, by a similar procedure to **12**. Compound **82**; $[\alpha]_D^{20}$ −48° (*c* 0.9, $CHCl_3$); FAB-MS *m*/*z* 986 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5583 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.88 (d, 8-CH_3), 0.93 (m, 7-H), 1.01 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.38 (m, 14-H), 1.82 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.06 (m, 14-H), 2.28 (s, NCH_3), 2.49 (s, 3′-$N(CH_3)_2$), 2.84 (dd, 6-CH_2), 3.25 (m, 4′-H), 3.25 (m, 5′-H), 3.53 (dd, 2′-H), 3.60 (br d, 4-H), 3.57 (s, 4-OCH_3), 3.78 (br d, quinoline-CH_2), 3.81 (br d, 5-H), 4.33 (d, 1′-H), 4.46 (dq, 5″-H), 4.60 (d, 4″-H), 5.05 (d, 1″-H), 5.18 (dd, 13-CH), 5.82 (br dd, 3-H), 5.97 (dt, CH=CH), 7.24 (d, quinoline), 7.54 (ddd, quinoline), 7.69 (ddd, quinoline), 8.00 (dd, quinoline), 8.10 (dd, quinoline), 8.81 (d, quinoline), 9.61 (s, CHO). Compound **83**; $[\alpha]_D^{19}$ −46° (*c* 0.3, $CHCl_3$); FAB-MS *m*/*z* 986 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5583 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.02 (d, 8-CH_3), 1.08 (d, 6″-H), 1.11 (s, 3″-CH_3), 1.14 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.24 (d, 6′-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.51 (s, 3′-$N(CH_3)_2$), 3.28 (m, 4′-H), 3.28 (m, 5′-H), 3.55 (s, 4-OCH_3), 4.43 (d, 1′-H), 4.45 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (d, 1″-H), 5.41 (m, 3-H), 5.51 (dd, 13-CH), 5.79 (dt, CH=CH), 7.25 (d, quinoline), 7.54 (ddd, quinoline), 7.69 (ddd, quinoline), 8.04 (br d, quinoline), 8.04 (br d, quinoline), 8.10 (d, quinoline), 9.63 (s, CHO).

4.1.51. Preparation of 84 and 85

Reaction of 9,2′-di-*O*-acetyl dimethyacetal of **84** and 9,2′-di-*O*-acetyl dimethyacetal of **85** with methanol gave dimethyacetal of **84** in 52% yield and dimethyacetal of **85** in 33% yield, respectively, by a similar procedure to **42**. Then, these compounds with difluoroacetic acid gave **84** in 55% yield and **85** in 40% yield, respectively, by a

similar procedure to **12**. Compound **84**; $[\alpha]_D^{20}$ −37° (*c* 0.2, $CHCl_3$); FAB-MS *m*/*z* 986 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5593 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.92 (d, 8-CH_3), 0.93 (t, 3-$OCOCH_2CH_3$), 1.13 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.24 (d, 6′-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.50 (s, 3′-$N(CH_3)_2$), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.57 (s, 4-OCH_3), 4.33 (d, 1′-H), 4.46 (m, 5″-H), 4.60 (d, 4″-H), 5.05 (d, 1″-H), 7.24 (d, quinoline), 7.54 (ddd, quinoline), 7.69 (ddd, quinoline), 8.00 (br d, quinoline), 8.10 (br d, quinoline), 8.81 (d, quinoline), 9.61 (s, CHO). Compound **85**; $[\alpha]_D^{19}$ −23° (*c* 0.3, $CHCl_3$); FAB-MS *m*/*z* 1028 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5584 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.98 (d, 8-CH_3), 1.12 (s, 3″-CH_3), 1.13 (d, 6″-H), 1.17 (t, 3-$OCOCH_2CH_3$), 1.23 (t, 4″-$OCOCH_2CH_3$), 1.24 (d, 6′-H), 1.84 (dd, 2″-Hax), 1.96 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.75 (m, 2-H), 3.60 (s, 4-OCH_3), 3.93 (m, 15-H), 4.20 (m, 15-H), 4.41 (dq, 5″-H), 4.62 (d, 4″-H), 5.07 (d, 1″-H), 5.43 (m, 3-H), 5.61 (dd, 13-CH), 5.99 (dt, CH=CH), 7.18 (d, quinoline), 7.52 (ddd, quinoline), 7.69 (ddd, quinoline), 8.10 (br d, quinoline), 8.10 (br d, quinoline), 8.82 (d, quinoline), 9.62 (s, CHO).

4.1.52. Preparation of 86 and 87

Compounds **86** and **87** were sequentially prepared from dimethylacetal of **82** and dimethylacetal of **83**, respectively, by a similar procedure to **60**. Reaction yield in hydrogenolysis step is 24% and 62%, respectively. The double bond in dimethylacetal of **82** was not easily reduced, and a quinoline moiety was partially reduced as a result. Compound **86**; $[\alpha]_D^{19}$ −47° (*c* 0.3, $CHCl_3$); FAB-MS *m*/*z* 988 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{81}N_3O_{15}$: 988.5746. Found: 988.5737 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.88 (d, 8-CH_3), 1.07 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 6′-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.50 (s, 3′-$N(CH_3)_2$), 2.65 (m, 2-H), 3.26 (m, 4′-H), 3.26 (m, 5′-H), 3.56 (dd, 2′-H), 3.61 (s, 4-OCH_3), 3.80 (br d, 5-H), 4.34 (d, 1′-H), 4.46 (m, 5″-H), 4.61 (d, 4″-H), 5.07 (d, 1″-H), 5.82 (m, 3-H), 7.23 (d, quinoline), 7.55 (ddd, quinoline), 7.70 (ddd, quinoline), 8.02 (br d, quinoline), 8.11 (br d, quinoline), 8.79 (d, quinoline), 9.60 (s, CHO). Compound **87**; $[\alpha]_D^{21}$ −48° (*c* 0.4, $CHCl_3$); FAB-MS *m*/*z* 988 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{81}N_3O_{15}$: 988.5746. Found: 988.5739 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3″-H), 1.14 (d, 6″-H), 1.16 (d, 8-CH_3), 1.17 (d, 6′-H), 1.17 (t, 3-$OCOCH_2CH_3$), 1.24 (t, 4″-$OCOCH_2CH_3$), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.52 (s, 3′-$N(CH_3)_2$), 2.64 (dd, 2-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.50 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.82 (br d, 5-H), 4.03 (m, 15-H), 4.22 (m, 15-H), 4.43 (d, 1′-H), 4.44 (dq, 5″-H), 4.62 (d, 4″-H), 5.06 (d, 1″-H), 5.27 (m, 3-H), 7.32 (d, quinoline), 7.57 (ddd, quinoline), 7.69 (ddd, quinoline), 8.10 (br d, quinoline), 8.10 (br d, quinoline), 8.80 (d, quinoline), 9.63 (s, CHO).

4.1.53. Preparation of 9,2′-di-*O*-acetyl dimethylacetal of 88, 9,2′-di-*O*-acetyl dimethylacetal of 89, and 9,2′-di-*O*-acetyl dimethylacetal of 90

Reaction of **73** with 6-bromoquinoline, 8-bromoquinoline and 4-bromoisoquinoline gave the corresponding 9, 2′-di-*O*-acetyl dimethylacetals in 25%, 15%, and 19% yield, respectively, by a similar procedure to **75**. 9,2′-Di-*O*-acetyl dimethylacetal of **88**; $[\alpha]_D^{26}$ −60° (*c* 0.73, $CHCl_3$); FAB-MS *m*/*z* 1116 $(M+H)^+$; ^1H NMR ($CDCl_3$) 0.95 (d, 8-CH_3), 1.02 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 6′-H), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.02 (s, 9-$OCOCH_3$), 2.05 (s, 2′-$OCOCH_3$), 2.28 (s, NCH_3), 2.40 (s, 3′-$N(CH_3)_2$), 3.11 (s, $CH(OCH_3)_2$), 3.21 (s, $CH(OCH_3)_2$), 3.52 (d, quinoline-CH_2), 3.53 (s, 4-OCH_3), 3.87 (d, 5-H), 4.37 (dq, 5″-H), 4.45 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.69 (d, 1′-H), 4.99 (dd, 2′-H), 5.06 (d, 1″-H), 5.24 (m, 3-H), 5.28 (dd, 13-CH), 5.84 (dt, CH=CH), 7.36 (dd, quinoline), 7.54 (d, quinoline), 7.56 (s, quinoline), 8.00 (d, quinoline), 8.10 (d, quinoline), 8.85 (d, quinoline). 9, 2′-Di-*O*-acetyl dimethylacetal of **89**; $[\alpha]_D^{26}$ −59° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1116 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.95 (d, 8-CH_3), 1.04 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.84 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.04 (s, 2′-$OCOCH_3$), 2.10 (m, 14-H), 2.26 (s, NCH_3), 2.32 (dq, 3-$OCOCH_2CH_3$), 2.40 (s, 3′-$N(CH_3)_2$), 2.43 (dq, $OCOCH_2CH_3$), 2.72 (t, 3′-H), 3.13 (s, $CH(OCH_3)_2$), 3.23 (s, $CH(OCH_3)_2$), 3.32 (t, 4′-H), 3.53 (s, 4-OCH_3), 3.87 (d, 5-H), 4.01 (d, quinoine-CH_2), 4.10 (dt, 15-H), 4.19 (dt, 15-H), 4.37 (dq, 5″-H), 4.46 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.70 (d, 1′-H), 4.94 (dd, 9-H), 5.00 (dd, 2′-H), 5.06 (d, 1″-H), 5.23 (m, 3-H), 5.31 (dd, 13-CH), 5.92 (dt, CH=CH), 7.39 (dd, quinoline), 7.46 (t, quinoline), 7.54 (d, quinoline), 7.67 (d, quinoline), 8.13 (dd, quinoline), 8.92 (dd, quinoline). 9,2′-Di-*O*-acetyl dimethylacetal of **90**; $[\alpha]_D^{25}$ −49° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1116 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.92 (d, 8-CH_3), 1.06 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.10 (s, 3″-CH_3), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 6′-H), 1.55 (m, 6-CH_2), 1.76 (m, 8-H), 1.83 (dd, 2″-Hax), 2.00 (s, 9-$OCOCH_3$), 2.01 (s, 2″-$OCOCH_3$), 2.24 (s, NCH_3), 2.30 (m, 10-H), 2.39 (s, 3′-$N(CH_3)_2$), 2.68 (m, 3′-H), 3.08 (s, $CH(OCH_3)_2$), 3.20 (s, $CH(OCH_3)_2$), 3.32 (m, 4′-H), 3.32 (m, 5′-H), 3.52 (dd, 4-OCH_3), 3.72 (d, isoquinoline-CH_2), 3.86 (m, 5-H), 4.36 (d, 5″-H), 4.42 (dd, $CH(OCH_3)_2$), 4.60 (d, 4″-H), 4.68 (d, 1′-H), 4.96 (m, 9-H), 4.98 (dd, 2′-H), 5.06 (d, 1″-H), 5.21 (dd, CH=CH), 5.85 (dt, CH=CH), 7.58 (t, isoquinoline), 7.69 (t, isoquinoline), 7.96 (d, isoquinoline), 8.00 (m, isoquinoline), 8.34 (s, isoquinoline), 9.11 (d, isoquinoline).

4.1.54. Preparation of 88, 89, and 90

Reaction of the corresponding 9,2′-di-*O*-acetyl dimethylacetals with methanol gave the corresponding dimethyacetals in 49%, 55%, and 53% yield, respectively, by a similar procedure to **42**. Then, these compounds with difluoroacetic acid gave **88** in 55% yield, **89** in 56% yield and **90** in 56% yield, respectively, by a similar procedure to **12**. Compound **88**: $[\alpha]_D^{24}$ −51° (*c* 0.39, $CHCl_3$); FAB-MS *m*/*z* 986 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5586 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.90 (d, 8-CH_3), 0.99 (t, 3-$OCOCH_2CH_3$), 1.12 (s, 3″-CH_3), 1.13 (d, 6″-H), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.45 (m, 14-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.32 (s, NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.66 (d, 2-H), 2.85 (dd, 6-CH_2), 3.53 (d, quinoline-CH_2), 3.59 (s, 4-OCH_3), 3.62 (d, 4-H), 3.82 (d, 5-H), 4.08 (m, 15-H), 4.33 (d, 1′-H), 4.46 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (d, 1″-H), 5.23 (dd, 13-CH), 5.84 (t, 3-H), 5.94 (dt, CH=CH), 7.38 (dd, quinoline), 7.54 (dd, quinoline), 7.57 (s, quinoline), 8.02 (d, quinoline), 8.12 (d, quinoline), 8.86 (d, quinoline), 9.62 (s, CHO). Compound **89**; $[\alpha]_D^{25}$ −61° (*c* 0.23, $CHCl_3$); FAB-MS *m*/*z* 986 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5586 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.89 (d, 8-CH_3), 0.99 (t, 3-$OCOCH_2CH_3$), 1.12 (s, 3″-CH_3), 1.13 (d, 6″-H), 1.18 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.30 (m, 8-H), 1.46 (m, 14-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.07 (m, 14-H), 2.26 (dd, 6-CH_2), 2.30 (s, NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.65 (d, 2-H), 2.85 (dd, 6-CH_2), 3.25 (t, 4′-H), 3.55 (dd, 2′-H), 3.59 (s, 4-OCH_3), 3.63 (d, 4-H), 3.81 (d, 5-H), 4.02 (d, quinoline-CH_2), 4.10 (m, 15-H), 4.32 (d, 1′-H), 4.47 (dq, 5″-H), 4.62 (d, 4″-H), 5.06 (d, 1″-H), 5.27 (dd, 13-CH), 5.79 (t, 3-H), 6.00 (dt, CH=CH), 7.40 (dd, quinoline), 7.48 (t, quinoline), 7.55 (d, quinoline), 7.68 (dd, quinoline), 8.14 (dd, quinoline), 8.93 (dd, quinoline), 9.63 (s, CHO). Compound **90**; $[\alpha]_D^{60}$ −44° (*c* 0.9, $CHCl_3$); FAB-MS *m*/*z* 986 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5583 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.89 (d, 8-CH_3), 1.00 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.14 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.29 (m, 8-H), 1.82 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.24 (m, 6-CH_2), 2.30 (s, NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.64 (m, 2-H), 3.25 (m, 4′ -H), 3.25 (m, 5′ -H), 3.54 (dd, 2′-H), 3.58 (s, 4-OCH_3), 3.60 (m, 4-H), 3.72 (d, isoquinoline-CH_2), 3.80 (br d, 5-H), 4.32 (d, 1′-H), 4.45 (m, 5″-H), 4.60 (d, 4″-H), 5.06 (d, 1″-H), 5.16 (m, CH=CH), 5.79 (m, 3-H), 5.96 (m, CH=CH), 7.58 (t, isoquinoline), 7.69 (t, isoquinoline), 7.98 (m, isoquinoline), 8.36 (s, isoquinoline), 9.15 (s, isoquinoline), 9.64 (s, CHO).

4.1.55. Synthesis of 92 and 93

Reaction of **36** with 7-methylamino-1-hepten-4-ol[20] gave **91** in 66% yield by a similar procedure to **4**. Macrolactonization of **91** gave **92** in 21% yield and **93** in 47% yield by a similar procedure to **73**. Compound **92**: $[\alpha]_D^{17}$ −58° (*c* 3.3, $CHCl_3$); FAB-MS *m*/*z* 989 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.94 (d, 8-CH_3), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.56 (br dd, 6-CH_2), 1.65 (m, 14-H), 1.83 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.03 (s, 2′-$OCOCH_3$), 2.20 (s, NCH_3), 2.29 (m, 15-CH2), 2.39 (s, 3′-$N(CH_3)_2$), 2.50 (m, 10-H), 2.62 (br d, 2-H), 2.71 (t, 3′-H), 2.73 (dd, 2-H), 3.16 (s, $CH(OCH_3)_2$), 3.24 (s, $CH(OCH_3)_2$), 3.34 (m, 4′-H), 3.39 (m, 5′-H), 3.40 (br d, 4-H), 3.52 (s, 4-OCH_3), 3.89 (br d, 5-H), 4.25 (s, 3″-OH), 4.36 (dq, 5″-H), 4.49 (dd, $CH(OCH_3)_2$), 4.60 (d, 4″-H), 4.69 (d, 1′-H), 5.05 (dd, 2′-H), 5.05 (m, 9-H), 5.06 (m, 15-H), 5.10 (d, 1″-H), 5.10 (d, CH=CH_2), 5.23 (br dd, 3-H), 5.71 (m, CH=CH_2). **93**; $[\alpha]_D^{15}$ −47° (*c* 2.0, $CHCl_3$); FAB-MS *m*/*z* 989 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.91 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.27 (d, 6′-H), 1.83 (dd, 2″-Hax), 2.01 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.04 (s, 2′-$OCOCH_3$), 2.21 (s, NCH_3), 2.25 (m, 15-CH_2), 2.37 (m, 10-H), 2.40 (s, 3′-$N(CH_3)_2$), 2.57 (dd, 2-H), 2.72 (t, 3′-H), 2.86 (dd, 2-H), 3.14 (s, $CH(OCH_3)_2$), 3.25 (s, $CH(OCH_3)_2$), 3.29 (m, 4′-H), 3.31 (m, 5′-H), 3.61 (s, 4-OCH_3), 3.66 (br d, 4-H), 3.93 (br d, 5-H), 4.28 (s, 3″-OH), 4.38 ((dq, 5″-H), 4.55 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.73 (d, 1′-H), 4.90 (m, 9-H), 4.97 (dd, 2″-H), 4.99 (br dd, 3-H), 4.99 (m, 15-H), 5.01 (d, 1″-H), 5.02 (d, CH=CH_2), 5.71 (m, CH=CH_2).

4.1.56. Synthesis of 94

Heck reaction of **92** gave **94** in 25% yield by a similar procedure to **75**; $[\alpha]_D^{18}$ −59° (*c* 1.1, $CHCl_3$); FAB-MS *m*/*z* 1116 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.94 (d, 8-CH_3), 1.10 (s, 3″-CH_3), 1.11 (d, 6″-H), 1.12 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.82 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.00 (s, 9-$OCOCH_3$), 2.03 (s, 2′-$OCOCH_3$), 2.23 (s, NCH_3), 2.39 (s, 3′-$N(CH_3)_2$), 2.70 (t, 3′-H), 3.16 (s, $CH(OCH_3)_2$), 3.24 (s, $CH(OCH_3)_2$), 3.31 (m, 4′-H), 3.33 (m, 5′-H), 3.39 (br d, 4-H), 3.52 (s, 4-OCH_3), 3.88 (br d, 5-H), 4.24 (s, 3″-OH), 4.36 (dq, 5″-H), 4.49 (dd, $CH(OCH_3)_2$), 4.60 (d, 4″-H), 4.69 (d, 1′-H), 4.99 (dd, 2′-H), 5.05 (d, 1″-H), 5.14 (m, 15-H), 5.25 (br dd, 3-H), 6.36 (dt, *J* = 15.7, 7.1 Hz, CH=CH), 7.12 (d, *J* = 15.7 Hz, CH=CH), 7.38 (d, quinoline), 7.54 (ddd, quinoline), 7.69 (ddd, quinoline), 8.05 (br d, quinoline), 8.08 (br d, quinoline), 8.83 (d, quinoline).

4.1.57. Synthesis of 95

Reaction of **93** with 4-bromoquinoline gave **95** in 42% yield by a similar procedure to **75**; $[\alpha]_D^{20}$ −21° (*c* 1.1, $CHCl_3$); FAB-MS *m*/*z* 1116 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.91 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.11 (t, 3-$OCOCH_2CH_3$), 1.12 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.83 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.04 (s, 2′-$OCOCH_3$), 2.23 (s, NCH_3), 2.40 (s, 3′-$N(CH_3)_2$), 2.45 (m, 10-H), 2.59 (dd, 2-H), 2.61 (m, 15-CH_2), 2.71 (t, 3′-H), 2.84 (dd, 2-H), 3.14 (s, $CH(OCH_3)_2$), 3.24 (s, $CH(OCH_3)_2$), 3.32 (m, 4′-H), 3.37 (m, 5′-H), 3.55 (s, 4-OCH_3), 3.61 (br d, 4-H), 3.93 (br d, 5-H), 4.26 (br s, 3″-OH), 4.37 (dq, 5″-H), 4.55 (dd, $CH(OCH_3)_2$), 4.60 (d, 4″-H), 4.71 (d, 1′-H), 4.91 (m, 9-H), 5.00 (dd, 2′-H), 5.06 (d, 1″-H), 5.06 (br dd, 3-H), 5.18 (m, 15-H), 6.36 (dt, *J* = 15.9, 7.1 Hz, CH=CH), 7.14 (d, *J* = 15.9 Hz, CH=CH), 7.39 (d, quinoline), 7.54 (ddd, quinoline), 7.70 (ddd, quinoline), 8.07 (br d, quinoline), 8.09 (br d, quinoline), 8.82 (d, quinoline).

4.1.58. Preparation of 96

Reaction of **94** with methanol gave **96** in 61% yield by a similar procedure to **17**; $[\alpha]_D^{16}$ −53° (*c* 2.2, $CHCl_3$); FAB-MS *m*/*z* 1032 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.99 (d, 8-CH_3), 1.10 (s, 3″-CH_3), 1.10 (t, 3-$OCOCH_2CH_3$), 1.11 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.24 (d, 6′-H), 1.81 (dd, 2″-Hax), 1.98 (d, 2″-Heq), 2.34 (s, NCH_3), 2.46 (s, 3′-$N(CH_3)_2$), 3.15 (s, $CH(OCH_3)_2$), 3.24 (s, $CH(OCH_3)_2$), 3.49 (br d, 4-H), 3.51 (s, 4-OCH_3), 3.56 (dd, 2′-H), 3.82 (br d, 5-H), 4.43 (d, 1′-H), 4.46 (dd, $CH(OCH_3)_2$), 4.49 (dq, 5″-H), 4.60 (d, 4″-H), 4.99 (m, 15-H), 5.05 (d, 1″-H), 5.36 (br dd, 3-H), 6.36 (dt, CH=CH), 7.11 (d, CH=CH), 7.42 (d, quinoline), 7.53 (ddd, quinoline), 7.69 (ddd, quinoline), 8.04 (br d, quinoline), 8.08 (br d, quinoline), 8.83 (d, quinoline).

4.1.59. Preparation of 97

Reaction of **95** with methanol gave **97** in 41% yield by a similar procedure to **17**; $[\alpha]_D^{18}$ −35° (*c* 0.71, $CHCl_3$); FAB-MS *m*/*z* 1032 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.87 (d, 8-CH_3), 1.08 (t, 3-$OCOCH_2CH_3$), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.82 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.33 (s, NCH_3), 2.49 (s, 3′-$N(CH_3)_2$), 2.61 (dd, 2-H), 2.61 (m, 15-CH_2), 2.79 (dd, 2-H), 3.15 (s, $CH(OCH_3)_2$), 3.24 (s, $CH(OCH_3)_2$), 3.35 (m, 9-H), 3.58 (s, 4-OCH_3), 3.89 (br d, 5-H), 4.31 (d, 1′-H), 4.45 (dq, 5″-H), 4.46 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 5.07 (d, 1″-H), 5.17 (m, 15-H), 5.47 (m, 3-H), 6.35 (dt, CH=CH), 7.12 (d, CH=CH), 7.37 (d, quinoline), 7.54 (ddd, quinoline), 7.70 (ddd, quinoline), 8.07 (br d, quinoline), 8.09 (br d, quinoline), 8.81 (d, quinoline).

4.1.60. Preparation of 98

Reaction of **96** with difluoroacetic acid gave **98** in 51% yield by a similar procedure to **12**; $[\alpha]_D^{17}$ −49° (*c* 0.53, $CHCl_3$); FAB-MS *m*/*z* 986 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5586 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.04 (d, 8-CH_3), 1.10 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.16 (d, 6′-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.81 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.35 (s, NCH_3), 2.47 (s, 3′-$N(CH_3)_2$), 2.91 (dd, 6-CH_2), 3.24 (m, 4′-H), 3.24 (m, 5′-H), 3.47 (dd, 2′-H), 3.48 (s, 4-OCH_3), 3.56 (br d, 4-H), 3.84 (br d, 5-H), 4.29 (br s, 3″-OH), 4.35 (d, 1′-H), 4.44 (dq, 5″-H), 4.61 (d, 4″-H), 5.01 (m, 15-H), 5.05 (d, 1″-H), 5.48 (br dd, 3-H), 6.42 (dt, CH=CH), 7.14 (d, CH=CH), 7.48 (d, quinoline), 7.55 (ddd, quinoline), 7.70 (ddd, quinoline), 8.05 (br d, quinoline), 8.09 (br d, quinoline), 8.85 (d, quinoline), 9.63 (s, CHO).

4.1.61. Preparation of 99

Reaction of **97** with difluoroacetic acid gave **99** in 61% yield by a similar procedure to **12**; $[\alpha]_D^{18}$ −38° (*c* 0.41, $CHCl_3$); FAB-MS *m*/*z* 986 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5583 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.91 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.20 (d, 6′-H), 1.82 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.33 (s, NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.63 (dd, 2-H), 3.24 (m, 4′-H), 3.27 (m, 5′-H), 3.36 (m, 9-H), 3.54 (dd, 2′-H), 3.58 (s, 4-OCH_3), 3.85 (br d, 4-H), 3.99 (br d, 5-H), 4.36 (d, 1′-H), 4.47 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (d, 1″-H), 5.17 (m, 15-H), 5.54 (m, 3-H), 6.35 (dt, CH=CH), 7.13 (d, CH=CH), 7.38 (d, quinoline), 7.55 (ddd, quinoline), 7.71 (ddd, quinoline), 8.06 (br d, quinoline), 8.09 (br d, quinoline), 8.82 (d, quinoline), 9.64 (s, CHO).

4.1.62. Preparation of 100

Hydrogenolysis of **96** in 1, 4-dioxane-H_2O (2:1) gave dimethylacetal of **100** in 95% yield by a similar procedure to **40**. Reaction of dimethylacetal of **100** with difluoroacetic acid gave **100** in 41% yield by a similar procedure to **12**; $[\alpha]_D^{15}$ −45° (*c* 0.40, $CHCl_3$); FAB-MS *m*/*z* 988 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{81}N_3O_{15}$: 988.5746. Found: 988.5757 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.00 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.15 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.34 (s, NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.91 (dd, 6-CH_2), 3.07 (br t, quinoline-CH_2), 3.26 (m, 4′-H), 3.26 (m, 5′-H), 3.51 (dd, 2′-H), 3.52 (s, 4-OCH_3), 3.86 (br d, 5-H), 4.38 (d, 1′-H), 4.46 (dq, 5″-H), 4.61 (d, 4″-H), 4.90 (m, 15-H), 5.06 (d, 1″-H), 5.42 (br dd,

3-H), 7.21 (d, quinoline), 7.56 (ddd, quinoline), 7.70 (ddd, quinoline), 7.99 (br d, quinoline), 8.11 (br d, quinoline), 8.80 (d, quinoline), 9.63 (s, CHO).

4.1.63. Preparation of 101

Hydrogenolysis of **97** in 1, 4-dioxane/H_2O (2:1) gave dimethylacetal of **101** in 61% yield by a similar procedure to **40**. Reaction of dimethylacetal of **101** with difluoroacetic acid gave **101** in 60% yield by a similar procedure to **12**; $[\alpha]_D^{15}$ −34° (*c* 0.44, $CHCl_3$); FAB-MS *m*/*z* 988 $(M+H)^+$; HRMS: Calcd for $C_{52}H_{81}N_3O_{15}$: 988.5746. Found: 988.5757 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.93 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 6′-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.33 (s, NCH_3), 2.50 (s, 3′-$N(CH_3)_2$), 2.58 (dd, 2-H), 3.07 (t, quinoline-CH_2), 3.26 (m, 4′-H), 3.29 (m, 5′-H), 3.56 (dd, 2′-H), 3.65 (s, 4-OCH_3), 3.86 (br d, 4-H), 3.99 (br d, 5-H), 4.38 (d, 1′-H), 4.46 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (d, 1″-H), 5.09 (m, 15-H), 5.45 (m, 3-H), 7.21 (d, quinoline), 7.55 (ddd, quinoline), 7.70 (ddd, quinoline), 8.01 (br d, quinoline), 8.11 (dd, quinoline), 8.79 (d, quinoline), 9.64 (s, CHO).

4.1.64. Stereoselective preparation of seco acid of 93

Reaction of **36** with (*R*)-7-methylamino-1-hepten-4-ol[30] gave seco acid of **93** in 75% yield by a similar procedure to **4**; $[\alpha]_D^{22}$ −57° (*c* 1.12, $CHCl_3$); FAB-MS: *m*/*z* 1007 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.88 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.04 (s, 2′-$OCOCH_3$), 2.23 (m, 15-CH2), 2.40 (s, 3′-$N(CH_3)_2$), 2.48 (s, NCH_3), 2.72 (dd, 3′-H), 2.74 (dd, 2-H), 2.87 (dd, 2-H), 3.21 (s, $CH(OCH_3)_2$), 3.25 (s, $CH(OCH_3)_2$), 3.31 (dd, 4′-H), 3.32 (m, 5′-H), 3.46 (d, 4-H), 3.55 (s, 4-OCH_3), 3.65 (m, 15-H), 3.88 (d, 5-H), 4.25 (br s, 3″-OH), 4.37 (dq, 5″-H), 4.54 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.73 (d, 1′-H), 4.98 (dd, 2′-H), 5.04 (d, 1″-H), 5.07 (m, 15-CH_2CH═CH), 5.14 (br t, 3-H), 5.14 (m, 9-H), 5.81 (m, 15-CH_2CH═CH).

4.1.64. Preparation of 9,2′-di-*O*-acetyl dimethylacetal of 102

Reaction of seco acid of **93** with 2-methyl-6-nitrobenzoic anhydride gave **93** in 53% yield by a similar procedure to **92** and **93** starting from **91**.Reaction of **93** with bromobenzene gave the corresponding 9,2′-di-*O*-acetyl dimethylacetal in 81% yield by a similar procedure to **95**; FAB-MS *m*/*z* 1065 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.90 (d, 8-CH_3), 1.10 (s, 3″-CH_3), 1.11 (t, 3-$OCOCH_2CH_3$), 1.12 (d, 6″-H), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 6′-H), 1.72 (m, 8-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.04 (s, 9-$OCOCH_3$), 2.04 (s, 2′-$OCOCH_3$), 2.20 (s, NCH_3), 2.40 (s, 3′-$N(CH_3)_2$), 2.42 (m, 10-H), 2.44 (dd, 15-CH_2), 2.57 (m, 2-H), 2.71 (t, 3′-H), 2.84 (dd, 2′-H), 3.13 (s, $CH(OCH_3)_2$), 3.23 (s, $CH(OCH_3)_2$), 3.34 (m, 4′-H), 3.34 (m, 5′-H), 3.58 (s, 4-OCH_3), 3.65 (br d, 4-H), 3.92 (br d, 5-H), 4.37 (dq, 5″-H), 4.55 (dd, $CH(OCH_3)_2$), 4.60 (d, 4″-H), 4.72 (d, 1′-H), 4.88 (m, 9-H), 5.00 (dd, 2′-H), 5.06 (d, 1″-H), 6.09 (dt, CH═CH), 6.42 (d, CH═CH), 7.25–7.35 (m, C_6H_5).

4.1.66. Preparation of 102

Reaction of 9, 2′-di-*O*-acetyl dimethylacetal of **102** with methanol gave dimethylacetal of **102** in 59% yield by a similar procedure to **17**. Reaction of dimethylacetal of **102** with difluoroacetic acid gave **102** in 53% yield by a similar procedure to **12**; $[\alpha]_D^{16}$ −55° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 935 $(M+H)^+$; HRMS: Calcd for $C_{49}H_{78}N_2O_{15}$: 935.548. Found: 935.5466 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.90 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.19 (d, 6′-H), 1.30 (m, 8-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.30 (s, NCH_3), 2.45 (m, 3′-H), 2.49 (s, 3′-$N(CH_3)_2$), 2.61 (dd, 2-H), 2.82 (dd, 2-H), 2.88 (dd, 6-CH_2), 3.28 (m, 4′-H), 3.28 (m, 5′-H), 3.36 (m, 9-H), 3.55 (dd, 2′-H), 3.60 (s, 4-OCH_3), 3.84 (br d, 4-H), 4.00 (br d, 5-H), 4.36 (d, 1′-H), 4.46 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (d, 1″-H), 5.09 (m, 15-H), 5.52 (m, 3-H), 7.25–7.34 (m, C_6H_5), 9.64 (s, CHO).

4.1.67. Preparation of 9, 2′-di-*O*-acetyl dimethylacetal of 103

Reaction of **93** with 3-bromopyridine gave the corresponding 9,2′-di-*O*-acetyl dimethylacetal in 81% yield by a similar procedure to **95**; $[\alpha]_D^{27}$ −43° (*c* 1.00, $CHCl_3$); FAB-MS *m*/*z* 1066 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.89 (d, 8-CH_3), 1.09 (s, 3″-CH_3), 1.10 (d, 6″-H), 1.11 (t, 3-$OCOCH_2CH_3$), 1.15 (t, 4″-$OCOCH_2CH_3$), 1.25 (d, 6′-H), 1.82 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.02 (s, 9-$OCOCH_3$), 2.02 (s, 2′-$OCOCH_3$), 2.20 (s, NCH_3), 2.39 (s, 3′-$N(CH_3)_2$), 2.47 (m, 15-CH_2), 2.56 (dd, 2-H), 2.71 (t, 3′-H), 2.83 (dd, 2-H), 3.13 (s, $CH(OCH_3)_2$), 3.23 (s, $CH(OCH_3)_2$), 3.32 (m, 4′-H), 3.32 (m, 5′-H), 3.56 (s, 4-OCH_3), 3.59 (d, 4-H), 3.92 (d, 5-H), 4.25 (br s, 3″-OH), 4.36 (dq, 5″-H), 4.53 (dd, $CH(OCH_3)_2$), 4.59 (d, 4″-H), 4.70 (d, 1′-H), 4.88 (m, 9-H), 4.99 (dd, 2′-H), 5.05 (d, 1″-H), 6.17 (dt, 15-CH_2CH═CH), 6.40 (d, 15-CH_2CH═CH), 7.19 (dd, pyridine), 7.63 (dt, pyridine), 8.41 (dd, pyridine), 8.52 (d, pyridine).

4.1.68. Preparation of 103

Reaction of 9,2′-di-*O*-acetyl dimethylacetal of **103** with methanol gave dimethylacetal of **103** in 53% yield by a similar procedure to **17**. Reaction of dimethylacetal of **103** with difluoroacetic acid gave **103** in 54% yield by a similar procedure to **12**; $[\alpha]_D^{26}$ −52° (*c* 0.90, $CHCl_3$); FAB-MS *m*/*z* 936 $(M+H)^+$; HRMS: Calcd for $C_{48}H_{77}N_3O_{15}$: 936.5433. Found: 936.5431 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.90 (d, 8-CH_3), 1.10 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.14 (t, 3-$OCOCH_2CH_3$), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.82 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.30 (d, 10-H), 2.30 (s, NCH_3), 2.43 (q, 3-$OCOCH_2CH_3$), 2.44 (q, 4″-$OCOCH_2CH_3$), 2.49 (s, 3′-$N(CH_3)_2$), 2.60 (dd, 2-H), 2.86 (dd, 2-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.32 (m, 9-H), 3.55 (dd, 2′-H), 3.62 (s, 4-OCH_3), 3.85 (d, 4-H), 3.99 (d, 5-H), 4.36 (d, 1′-H), 4.47 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (d, 1″-H), 5.08 (m, 15-H), 5.53 (m, 3-H), 6.17 (dt, 15-CH_2CH═CH), 6.40 (d, 15-CH_2CH═CH), 7.20 (dd, pyridine), 7.62 (dt, pyridine), 8.43 (dd, pyridine), 8.52 (d, pyridine), 9.64 (s, CHO).

4.1.69. Preparation of 9,2′-di-*O*-acetyl dimethylacetal of 104

Reaction of **93** with 1-bromonaphthalene gave the corresponding 9,2′-di-*O*-acetyl dimethylacetal in 58% yield by a similar procedure to **95**; $[\alpha]_D^{22}$ −43° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 1115 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.91 (d, 8-CH_3), 1.11 (s, 3″-CH_3), 1.11 (t, 3-$OCOCH_2CH_3$), 1.12 (d, 6″-H), 1.17 (t, 4″-$OCOCH_2CH_3$), 1.26 (d, 6′-H), 1.83 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.03 (s, 9-$OCOCH_3$), 2.05 (s, 2′-$OCOCH_3$), 2.23 (s, NCH_3), 2.40 (s, 3′-$N(CH_3)_2$), 2.55 (m, 15-CH_2), 2.60 (dd, 2-H), 2.71 (t, 3′-H), 2.85 (dd, 2-H), 3.14 (s, $CH(OCH_3)_2$), 3.24 (s, $CH(OCH_3)_2$), 3.32 (m, 4′-H), 3.32 (m, 5′-H), 3.56 (s, 4-OCH_3), 3.68 (d, 4-H), 3.93 (d, 5-H), 4.28 (br s, 3″-OH), 4.38 (dq, 5″-H), 4.56 (dd, $CH(OCH_3)_2$), 4.61 (d, 4″-H), 4.72 (d, 1′-H), 4.91 (m, 9-H), 5.00 (dd, 2′-H), 5.06 (d, 1″-H), 5.17 (m, 15-H), 6.11 (dt, 15-CH_2CH═CH), 7.15 (d, 15-CH_2CH═CH), 7.40 (t, naphthalene), 7.48 (m, naphthalene), 7.74 (d, naphthalene), 7.83 (m, naphthalene), 7.86 (m, naphthalene).

4.1.70. Preparation of 104

Reaction of 9,2′-di-*O*-acetyl dimethylacetal of **104** with methanol gave dimethylacetal of **104** in 86% yield by a similar procedure to **17**. Reaction of dimethylacetal of **104** with difluoroacetic acid gave **104** in 54% yield by a similar procedure to **12**; $[\alpha]_D^{22}$ −44° (*c* 1.0, $CHCl_3$); FAB-MS *m*/*z* 985 $(M+H)^+$; HRMS: Calcd for $C_{53}H_{80}N_2O_{15}$: 985.5637. Found: 985.5634 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.90 (d, 8-CH_3), 1.10 (s, 3″-CH_3), 1.12 (d, 6″-H), 1.13 (t, 3-$OCOCH_2CH_3$), 1.16 (t, 4″-$OCOCH_2CH_3$), 1.18 (d, 6′-H), 1.82 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.31 (d, 10-H), 2.31 (s, NCH_3), 2.41 (q,

3-OCOCH$_2$CH$_3$), 2.43 (q, 4″-OCOCH$_2$CH$_3$), 2.49 (s, 3′-N(CH$_3$)$_2$), 2.58 (dd, 2-H), 2.82 (dd, 2-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.34 (m, 9-H), 3.54 (dd, 2′-H), 3.57 (s, 4-OCH$_3$), 3.84 (d, 4-H), 4.02 (d, 5-H), 4.36 (d, 1′-H), 4.47 (dq, 5″-H), 4.60 (d, 4″-H), 5.05 (d, 1″-H), 5.16 (m, 15-H), 5.53 (m, 3-H), 6.10 (dt, 15-CH$_2$CH=CH), 7.14 (d, 15-CH$_2$CH=CH), 7.39 (dt, naphthalene), 7.47 (dt, naphthalene), 7.73 (dd, naphthalene), 7.82 (d, naphthalene), 8.04 (d, naphthalene), 9.63 (s, CHO).

4.1.71. Preparation of 9,2′-di-*O*-acetyl dimethylacetal of 105

Reaction of **93** with 2-bromonaphthalene gave the corresponding 9,2′-di-*O*-acetyl dimethylacetal in 45% yield by a similar procedure to **95**; $[\alpha]_D^{27}$ −48° (*c* 1.0, CHCl$_3$); FAB-MS *m*/*z* 1115 (M+H)$^+$; ^{1}H NMR (CDCl$_3$) δ 0.90 (d, 8-CH$_3$), 1.10 (s, 3″-CH$_3$), 1.11 (d, 6″-H), 1.11 (t, 3-OCOCH$_2$CH$_3$), 1.16 (t, 4″-OCOCH$_2$CH$_3$), 1.26 (d, 6′-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.03 (s, 9-OCOCH$_3$), 2.04 (s, 2′-OCOCH$_3$), 2.22 (s, NCH$_3$), 2.39 (s, 3′-N(CH$_3$)$_2$), 2.51 (m, 15-CH$_2$), 2.59 (dd, 2-H), 2.71 (t, 3′-H), 2.84 (dd, 2-H), 3.14 (s, CH(OCH$_3$)$_2$), 3.24 (s, CH(OCH$_3$)$_2$), 3.32 (m, 4′-H), 3.32 (m, 5′-H), 3.56 (s, 4-OCH$_3$), 3.64 (d, 4-H), 3.92 (d, 5-H), 4.26 (br s, 3″-OH), 4.37 (dq, 5″-H), 4.54 (dd, CH(OCH$_3$)$_2$), 4.60 (d, 4″-H), 4.71 (d, 1′-H), 4.90 (m, 9-H), 5.00 (dd, 2′-H), 5.05 (d, 1″-H), 5.05 (br t, 3-H), 5.12 (m, 15-H), 6.22 (dt, 15-CH$_2$CH=CH), 6.58 (d, 15-CH$_2$CH=CH), 7.41 (m, naphthalene), 7.53 (dd, naphthalene), 7.65 (s, naphthalene), 7.75 (m, naphthalene).

4.1.72. Preparation of 105

Reaction of 9,2′-di-*O*-acetyl dimethylacetal of **105** with methanol gave dimethylacetal of **105** in 54% yield by a similar procedure to **17**. Reaction of dimethylacetal of **105** with difluoroacetic acid gave **105** in 61% yield by a similar procedure to **12**; $[\alpha]_D^{26}$ −41° (*c* 1.07, CHCl$_3$); FAB-MS *m*/*z* 985 (M+H)$^+$; HRMS: Calcd for $C_{53}H_{80}N_2O_{15}$: 985.5637. Found: 985.5630 (M+H)$^+$; ^{1}H NMR (CDCl$_3$) δ 0.91 (d, 8-CH$_3$), 1.11 (s, 3″-CH$_3$), 1.12 (d, 6″-H), 1.14 (t, 3-OCOCH$_2$CH$_3$), 1.17 (t, 4″-OCOCH$_2$CH$_3$), 1.18 (d, 6′-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.30 (d, 10-H), 2.31 (s, NCH$_3$), 2.43 (q, 3-OCOCH$_2$CH$_3$), 2.44 (q, 4″-OCOCH$_2$CH$_3$), 2.49 (s, 3′-N(CH$_3$)$_2$), 2.62 (dd, 2-H), 2.84 (dd, 2-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.35 (m, 9-H), 3.55 (dd, 2′-H), 3.60 (s, 4-OCH$_3$), 3.85 (d, 4-H), 4.01 (d, 5-H), 4.36 (d, 1′-H), 4.47 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (d, 1″-H), 5.13 (m, 15-H), 5.53 (m, 3-H), 6.21 (dt, 15-CH$_2$CH=CH), 6.58 (d, 15-CH$_2$CH=CH), 7.43 (m, naphthalene), 7.53 (dd, naphthalene), 7.65 (s, naphthalene), 7.76 (dt, naphthalene), 9.64 (s, CHO).

4.1.73. Preparation of 9,2′-di-*O*-acetyl dimethylacetal of 106

Reaction of **93** with 3-bromoquinoline gave the corresponding 9,2′-di-*O*-acetyl dimethylacetal in 25% yield by a similar procedure to **95**; $[\alpha]_D^{21}$ −42° (*c* 1.5, CHCl$_3$); FAB-MS *m*/*z* 1116 (M+H)$^+$; ^{1}H NMR (CDCl$_3$) δ 0.90 (d, 8-CH$_3$), 1.10 (s, 3″-CH$_3$), 1.11 (d, 6″-H), 1.11 (t, 3-OCOCH$_2$CH$_3$), 1.16 (t, 4″-OCOCH$_2$CH$_3$), 1.25 (d, 6′-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.02 (s, 9-OCOCH$_3$), 2.04 (s, 2′-OCOCH$_3$), 2.22 (s, NCH$_3$), 2.39 (s, 3′-N(CH$_3$)$_2$), 2.54 (m, 15-CH2), 2.71 (t, 3′-H), 2.84 (dd, 2-H), 3.13 (s, CH(OCH$_3$)$_2$), 3.23 (s, CH(OCH$_3$)$_2$), 3.31 (m, 4′-H), 3.34 (m, 5′-H), 3.56 (s, 4-OCH$_3$), 3.93 (br d, 5-H), 4.27 (br s, 3″-OH), 4.36 (dq, 5″-H), 4.54 (dd, CH(OCH$_3$)$_2$), 4.60 (d, 4″-H), 4.71 (d, 1′-H), 4.89 (m, 9-H), 4.99 (dd, 2′-H), 5.05 (d, 1″-H), 5.13 (m, 15-H), 6.34 (dt, CH=CH), 6.59 (d, CH=CH), 7.50 (br t, quinoline), 7.64 (ddd, quinoline), 7.76 (br d, quinoline), 7.99 (d, quinoline), 8.03 (d, quinoline), 8.92 (d,quinoline).

4.1.74. Preparation of 106

Reaction of 9,2′-di-*O*-acetyl dimethylacetal of **106** with methanol gave dimethylacetal of **106** in 61% yield by a similar procedure to **17**. Reaction of dimethylacetal of **106** with difluoroacetic acid gave **106** in 45% yield by a similar procedure to **12**; $[\alpha]_D^{20}$ −51° (*c* 0.36, CHCl$_3$); FAB-MS *m*/*z* 986 (M+H)$^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5601 (M+H)$^+$; ^{1}H NMR (CDCl$_3$) δ 0.91 (d, 8-CH$_3$), 1.11 (s, 3″-CH$_3$), 1.12 (d, 6″-H), 1.14 (t, 3-OCOCH$_2$CH$_3$), 1.17 (t, 4″-OCOCH$_2$CH$_3$), 1.18 (d, 6′-H), 1.32 (m, 8-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.33 (s, NCH$_3$), 2.49 (s, 3′-N(CH$_3$)$_2$), 2.62 (dd, 2-H), 2.84 (dd, 2-H), 2.87 (dd, 6-CH$_2$), 3.25 (m, 4′-H), 3.25 (m, 5′-H), 3.38 (m, 9-H), 3.55 (dd, 2′-H), 3.62 (s, 4-OCH$_3$), 3.85 (br d, 4-H), 3.99 (br d, 5-H), 4.37 (d, 1′-H), 4.46 (dq, 5″-H), 4.61 (d, 4″-H), 5.06 (d, 1″-H), 5.13 (m, 15-H), 5.53 (m, 3-H), 6.34 (dt, CH=CH), 6.58 (d, CH=CH), 7.52 (ddd, quinoline), 7.65 (ddd, quinoline), 7.76 (dd, quinoline), 7.98 (d, quinoline), 8.05 (br d, quinoline), 8.92 (d, quinoline), 9.64 (s, CHO).

4.1.75. Preparation of 107

Hydrogenolysis of dimethylacetal of **106** in 1, 4-dioxane/H$_2$O (2:1) gave dimethylacetal of **107** in 63% yield by a similar procedure to **40**. Reaction of dimethylacetal of **107** with difluoroacetic acid gave **107** in 36% yield by a similar procedure to **12**. $[\alpha]_D^{24}$ −57° (*c* 0.43, CHCl$_3$); FAB-MS *m*/*z* 988 (M+H)$^+$; HRMS: Calcd for $C_{52}H_{81}N_3O_{15}$: 988.5746. Found: 988.5751 (M+H)$^+$; ^{1}H NMR (CDCl$_3$) δ 0.91 (d, 8-CH$_3$), 1.11 (s, 3″-CH$_3$), 1.12 (d, 6″-H), 1.13 (t, 3-OCOCH$_2$CH$_3$), 1.17 (t, 4″-OCOCH$_2$CH$_3$), 1.21 (d, 6′-H), 1.81 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.29 (s, NCH$_3$), 2.29 (d, 10-H), 2.43 (q, 3-OCOCH$_2$CH$_3$), 2.44 (q, 4″-OCOCH$_2$CH$_3$), 2.50 (s, 3′-N(CH$_3$)$_2$), 2.60 (dd, 2-H), 2.84 (dd, 2-H), 3.27 (m, 4′-H), 3.27 (m, 5′-H), 3.36 (m, 9-H), 3.56 (dd, 2′-H), 3.66 (s, 4-OCH$_3$), 3.85 (d, 4-H), 4.00 (d, 5-H), 4.37 (d, 1′-H), 4.46 (dq, 5″-H), 4.62 (d, 4″-H), 5.04 (m, 15-H), 5.06 (d, 1″-H), 5.47 (m, 3-H), 7.52 (ddd, quinoline), 7.65 (ddd, quinoline), 7.75 (dd, quinoline), 7.89 (d, quinoline), 8.06 (br d, quinoline), 8.74 (d, quinoline), 9.64 (s, CHO).

4.1.76. Preparation of 9, 2′-di-*O*-acetyl dimethylacetal of 108

Reaction of **93** with 6-bromoquinoline gave the corresponding 9,2′-di-*O*-acetyl dimethylacetal in 43% yield by a similar procedure to **95**; $[\alpha]_D^{27}$ −45° (*c* 1.0, CHCl$_3$); FAB-MS *m*/*z* 1116 (M+H)$^+$; ^{1}H NMR (CDCl$_3$) δ 0.90 (d, 8-CH$_3$), 1.10 (s, 3″-CH$_3$), 1.10 (t, 3-OCOCH$_2$CH$_3$), 1.11 (d, 6″-H), 1.15 (t, 4″-OCOCH$_2$CH$_3$), 1.25 (d, 6′-H), 1.82 (dd, 2″-Hax), 2.00 (d, 2″-Heq), 2.02 (s, 9-OCOCH$_3$), 2.03 (s, 2′-OCOCH$_3$), 2.21 (s, NCH$_3$), 2.39 (s, 3′-N(CH$_3$)$_2$), 2.52 (m, 15-CH$_2$), 2.58 (dd, 2-H), 2.70 (t, 3′-H), 2.83 (dd, 2-H), 3.13 (s, CH(OCH$_3$)$_2$), 3.23 (s, CH(OCH$_3$)$_2$), 3.32 (dd, 4′-H), 3.32 (m, 5′-H), 3.55 (s, 4-OCH$_3$), 3.61 (d, 4-H), 3.92 (d, 5-H), 4.26 (br s, 3″-OH), 4.36 (dq, 5″-H), 4.53 (dd, CH(OCH$_3$)$_2$), 4.59 (d, 4″-H), 4.70 (d, 1′-H), 4.89 (m, 9-H), 4.99 (dd, 2′-H), 5.05 (d, 1″-H), 5.05 (br t, 3-H), 5.12 (m, 15-H), 6.27 (dt, 15-CH$_2$CH=CH), 6.58 (d, 15-CH$_2$CH=CH), 7.35 (dd, quinoline), 7.63 (d, quinoline), 7.77 (dd, quinoline), 7.99 (d, quinoline), 8.08 (dd, quinoline), 8.82 (dd, quinoline).

4.1.77. Preparation of 108

Reaction of 9,2′-di-*O*-acetyl dimethylacetal of **108** with methanol gave dimethylacetal of **108** in 66% yield by a similar procedure to **17**. Reaction of dimethylacetal of **108** with difluoroacetic acid gave **108** in 65% yield by a similar procedure to **12**; $[\alpha]_D^{24}$ −34° (*c* 1.0, CHCl$_3$); FAB-MS *m*/*z* 986 (M+H)$^+$; HRMS: Calcd for $C_{52}H_{79}N_3O_{15}$: 986.5589. Found: 986.5583 (M+H)$^+$; ^{1}H NMR (CDCl$_3$) δ 0.90 (d, 8-CH$_3$), 1.10 (s, 3″-CH$_3$), 1.12 (d, 6″-H), 1.14 (t, 3-OCOCH$_2$CH$_3$), 1.17 (t, 4″-OCOCH$_2$CH$_3$), 1.20 (d, 6′-H), 1.82 (dd, 2″-Hax), 1.99 (d, 2″-Heq), 2.30 (d, 10-H), 2.30 (s, NCH$_3$), 2.42 (q, 3-OCOCH$_2$CH$_3$), 2.44 (q, 4″-OCOCH$_2$CH$_3$), 2.49 (s, 3′-N(CH$_3$)$_2$), 2.61 (dd, 2-H), 2.86 (dd, 2-H), 3.26 (t, 4′-H), 3.27 (m, 5′-H), 3.38 (m, 9-H), 3.54 (dd, 2′-H), 3.60 (s, 4-OCH$_3$), 3.86 (d, 4-H), 4.00 (d, 5-H), 4.35 (d, 1′-H), 4.46 (dq, 5″-H), 4.60 (d, 4″-H), 5.05 (d, 1″-H), 5.13 (m, 15-H), 5.54 (m, 3-H), 6.26 (dt, 15-CH$_2$CH=CH), 6.58 (d, 15-CH$_2$CH=CH), 7.37 (dd, quinoline), 7.62 (d, quinoline), 7.76 (dd, quinoline), 8.01 (d, quinoline), 8.09 (dd, quinoline), 8.83 (dd, quinoline), 9.64 (s, CHO).

4.2. Biology

4.2.1. In vitro antibacterial activity

Minimum inhibitory concentration (MIC) was determined by the agar dilution method. Test strains were subjected to seed culture using Sensitivity test broth (STB, Nissui Pharmaceutical) for *Staphylococcus aureus*, or cultured on blood agar plate for *S. pneumoniae, S. pyogenes, M. catarrhalis*, and *H. influenzae*. A 5 μl portion of cell suspension of the test strains having about 10^6 CFU/ml was inoculated into Sensitivity disk agar (SDA, Nissui Pharmaceutical) supplemented with 5% horse blood and incubated at 37 °C for 20 h. Then, MIC was defined as the lowest drug concentration that prevented visible growth.

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