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Synthesis and structure–activity relationship of a novel class of 15-membered macrolide antibiotics known as '11a-azalides'

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ABSTRACT

Macrolide antibiotics are widely prescribed for the treatment of respiratory tract infections; however, the increasing prevalence of macrolide-resistant pathogens is a public health concern. Therefore, the development of new macrolide scaffolds with activities against resistant pathogens is urgently needed. An efficient method for reconstructing the erythromycin A macrolactone skeleton has been established. Based on this methodology, novel 15-membered macrolides, known as '11a-azalides', with substituents at the C12, C13, or C4″ positions were synthesized and their antibacterial activities were evaluated. These derivatives showed promising antibacterial activities against erythromycin-resistant *Streptococcus pneumoniae*. Among them, the C4″ substituted derivatives had the most potent activity against erythromycin-resistant *S. pneumoniae*.

1. Introduction

Macrolide antibiotics[1–4] (see Fig. 1 for some structures) are a safe and effective class of drugs for the treatment of respiratory tract infections. Erythromycin A (EM-A) **1**, a 14-membered macrolide antibiotic, has been widely prescribed for more than five decades. Since EM-A decomposes to antibacterially inactive spiroketal products[5] under acidic conditions in the stomach, its bioavailability is relatively low and varies interindividually.[6] To improve the pharmacokinetic profile of EM-A caused by its instability, an enteric coating is applied to EM-A tablets and further chemical modifications of EM-A have been performed.[1–4] Second-generation macrolides, such as clarithromycin[7] (CAM) **2** and azithromycin[8] (AZM) **3**, were investigated in the 1980s and were eventually launched in the 1990s as a result of these chemical modification efforts. These macrolide antibiotics have been widely prescribed for more than three decades. Because of their widespread use, the increasing prevalence of macrolide-resistant pathogens among clinical isolates has become a public health concern.[9–12] The major mechanisms of resistance against Gram-positive pathogens are ribosome methylation by *erm* methyltransferase and efflux by macrolide efflux pumps (mediated by the *mef*-gene product).[13–15] The third generation macrolide, such as telithromycin **4** and cethromycin **5**, are known to be effective against erythromycin-resistant strains.[16,17] These two ketolides have similar structural features, such as a 3-keto group and a heteroaryl–alkyl side chain. The heteroaryl–alkyl side chain is believed to play a key role in overcoming resistance caused by ribosome methylation.[18–22] To overcome these resistance problems, numerous chemical modifications of EM-A have been attempted continuously.[23–25]

In a chemobiosynthesis report seeking novel scaffolds by transforming the macrolactone skeleton, the C13 position of EM-A was suggested to play a key role in improving the antibacterial activity against resistant pathogens.[26,27] However, chemical modification at the C13 position has been underexplored because of its lack of chemical reactivity. During the mid 1990s, Waddell[28,29] and Nishida[30] independently reported C9–C13 modified EM-A derivatives, synthesized from the original C1–8 or 9 fragment of EM-A and a newly-prepared C9 or 10–13 fragment. Although this 'cut and paste' methodology seemed to be a universal procedure for providing structural diversity in the C13 region, the reported compounds were limited to simple and primitive derivatives. Alternatively, a related ring reconstruction methodology using 16-membered macrolide as the starting material has been reported.[31]

In our previous paper,[32] we presented an efficient method for reconstructing of the 9-dihydroerythromycin A macrolactone skeleton. Based on this methodology, we synthesized a novel class of 15-membered macrolides, known as '11a-azalides', and demonstrated that their C-12/13 substituents were important for their antibacterial activities (Fig. 2). These 11a-azalides showed a potent antibacterial activity against erythromycin-susceptible *Streptococcus pnuemoniae* and an improved antibacterial activity against erythromycin-resistant strains. These results encouraged us to explore the structure–activity relationship of the 11a-azalide skeleton. Herein, we report the synthesis of 11a-azalides with a substituent

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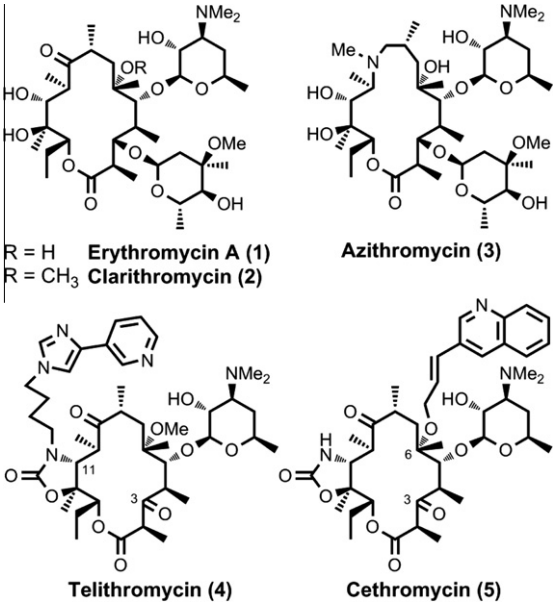


Figure 1. Structures of macrolide antibiotics.

having aromatic group at the C12, C13, or C4″ positions and the resulting antibacterial activities against erythromycin-resistant *S. pnuemo- niae*.

2. Results and discussion

2.1. Synthesis of 11a-azalides

The synthetic strategy for producing an 11a-azalide skeleton is shown in Scheme 1. The 11,12-diol moiety of the EM-A macrolactone skeleton was cleaved oxidatively. After the insertion of an appropriate functionalized amino alcohol and successive saponification of the remaining original C12–13 residue, the resulting acyclic skeleton was intramolecularly cyclized by a macrolactonization reaction.

2.1.1. Synthesis of C12/13 substituted derivatives

Following this synthetic route, C12/13 substituted 11a-azalides **15a–j** were synthesized from 9-dihydro-6-*O*-methylerythromycin A **8** (Scheme 2). The 9,2′,4″-hydroxyl groups of **8** were selectively protected by triethylsilyl (TES) groups to produce 11,12-diol **9**, which was then treated with lead tetraacetate to yield an acyclic aldehyde intermediate **10**. Reductive amination of aldehyde **10** with various aminoalcohols **11a–j** and subsequent methylation of the resulting secondary amine at the 11a-position with formaldehyde produced the desired seco-ester **12a–j**. The above three sequential reactions were performed in a one-pot manner. Saponification of seco-ester

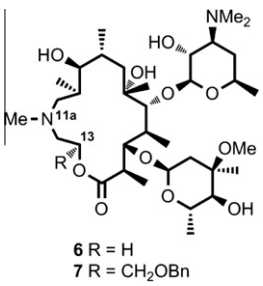
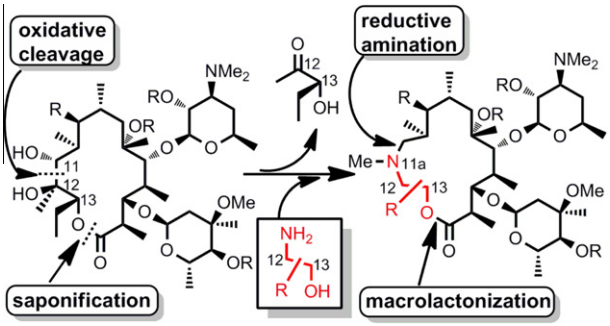


Figure 2. Structure of 11a-azalides.



Scheme 1. Synthetic strategy for producing an 11a-azalide skeleton.

12a–j with LiOH produced seco-acid **13a–j**. A macrolactonization reaction of seco-acids **13a–j** yielded the desired 15-membered products **14a–j**. When a 6-OH seco-acid was used, a seven-membered byproduct caused this macrolactonization reaction to have a low yield.[32] This seven-membered byproduct was avoided by using 6-O-methylated seco-acids for this reaction. The deprotection of the TES groups of **14a–j** was achieved using an HF-pyridine treatment to produce the desired C12/13-substituted 11a-azalides **15a–j.** A $Pd(OH)_2$-catalyzed hydrogenation step was applied to deprotect the benzyl group at the C13 position of **14e**. A Mitsunobu reaction[33] of the resulting hydroxyl derivative **16** and phenylphenols produced the biphenyl derivatives **15k–m**. Stille coupling of the iodophenoxy group at the C13 position of **15j** and pyridylstannane produced pyridylphenyl derivatives **15 n–o**.

2.1.2. Synthesis of 9-keto or 3-keto derivatives

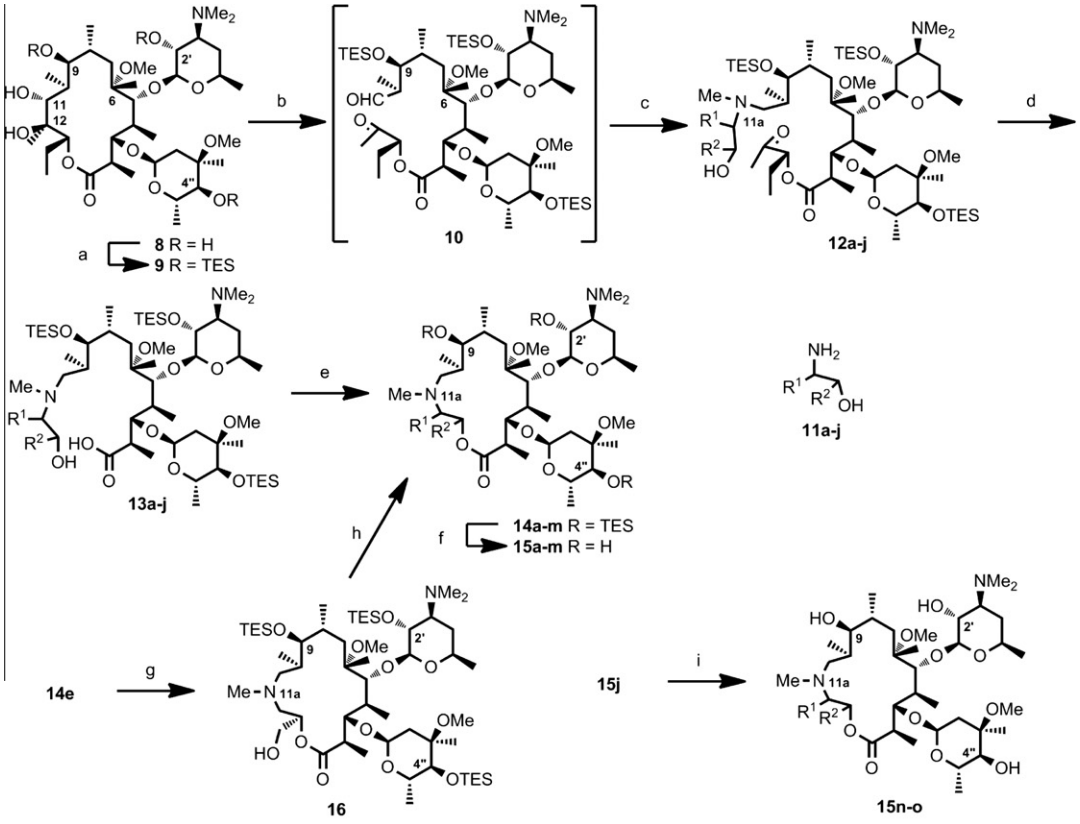
The synthesis of 9-keto or 3-keto derivatives is shown in Scheme 3. Selective deprotection of the 2′ and 4″-hydroxyl groups of **14a** was achieved by treatment with 2 equiv of tetra-*n*-butylammonium fluoride. Protection with an acetyl group and a carboxybenzyl group and the subsequent deprotection of the TES group yielded 9-OH derivative **17**. Acid hydrolysis of **14a** and subsequent carboxybenzylation of 9,2′-hydroxyl groups produced 3-OH derivative **18**. Oxidation with Dess–Martin reagent and deprotection of compounds **17** and **18** yielded keto derivatives **19** and **20**. The 3-keto derivative **20** could not be isolated as a single diastereomer because of the epimerization of the C2 methyl group. There is a previous report about C2 epimerization.[34] Although C2 epimer was not obtained in case most of 3-keto derivative including telithromycin, C2 epimerization was observed in case of the C6 carbamate ketolides. The ease of epimerization is probably dependent on the structure of ketolide.

2.1.3. Synthesis of 9-amino derivatives

The synthesis of 9-amino derivatives is shown in Scheme 4. Carboxybenzylation of the 9-amino and 2′-hydroxyl groups of 9-aminoerythromycin **21**[35,36] and subsequent deprotection of the 2′-hydroxyl groups by heating in methanol produced 9-*N*-carbobenzyloxy product. The 3′-dimethylamino group behaves as an intramolecular catalyst making possible the facile hydrolysis of the 2′-*O*-carbobenzyloxy group under neutral condition.[37] Then the 2′,4″-hydroxyl groups were protected by TES groups to produce 11,12-diol derivative **22**, and subsequent application of the ring reconstruction procedure used for **9** yielded the 9-carboxybenzylamino derivative **23a/e**. The deprotection of the carboxybenzyl group produced the 9-amino derivative **24a/e**.

2.1.4. Synthesis of C12 substituted derivatives

The transformation of the C12 substituent of **14b** is shown in Scheme 5. The benzyl group of **14b** was deprotected using Pd-catalyzed hydrogenation. The resulting hydroxyl derivative **25** was



Product	R^1	R^2
15a	H	H
15b	CH_2OCH_2Ph	H
15c	CH_2OCH_2Ph	H
15d	H	CH_2OCH_2Ph
15e	H	CH_2OCH_2Ph
15f	$CH_2CH_2OCH_2Ph$	H
15g	H	Ph
15h	H	$CH_2CH_2OCH_2Ph$
15i	H	CH_2OPh

Product	R^1	R^2
15j	H	CH_2O-(4-I-Ph)
15k	H	CH_2O-(2-Ph-Ph)
15l	H	CH_2O-(3-Ph-Ph)
15m	H	CH_2O-(4-Ph-Ph)
15n	H	CH_2O-(3-pyridyl)
15o	H	CH_2O-(2-pyridyl)

Scheme 2. Synthesis of **15a–o**. Reagents and conditions: (a) TESCl, imidazole, DMF; (b) $Pb(OAc)_4$, CH_2Cl_2; (c) **11a–j**, $NaBH(OAc)_3$, then HCHO(aq), $NaBH(OAc)_3$; (d) LiOH, THF–EtOH–H_2O; (e) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF then DMAP, CH_3CN, and reflux; (f) HF–pyridine, THF; (g) H_2, $Pd(OH)_2$, THF; (h) phenylphenol derivatives **k–m**, DEAD, PPh_3, THF; (i) pyridylstannane derivatives **n–o**, $Pd(PPh_3)_4$, toluene, reflux.

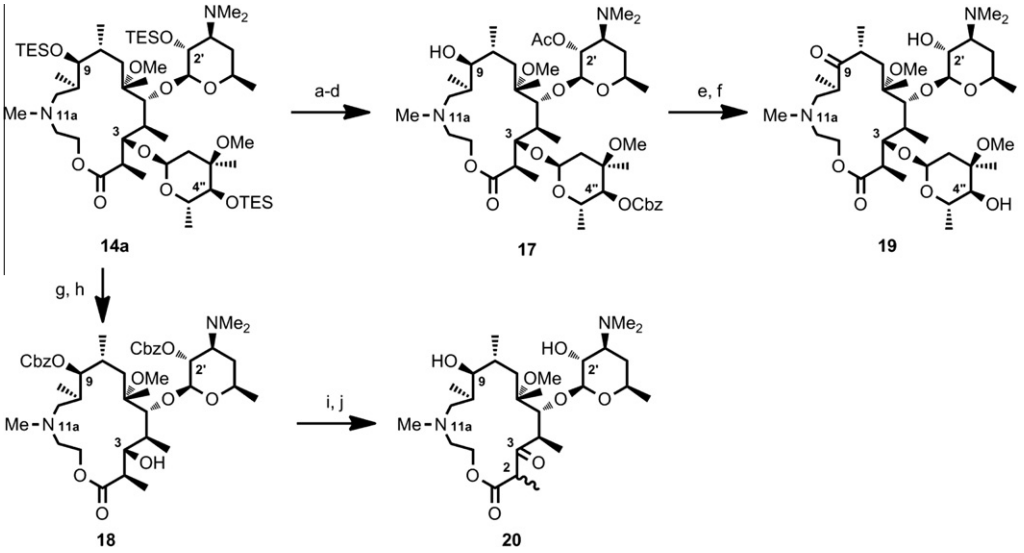
converted to azido derivative **26** with bis(*p*-nitrophenyl)phosphorazidate (*p*-NO_2DPPA).[38] The reduction of the azido group with triphenylphosphine and the subsequent reductive amination of **28** produced alkyl or arylmethyl-substituted amino derivatives **29–32**.

2.1.5. Synthesis of 4″-carbamate derivatives

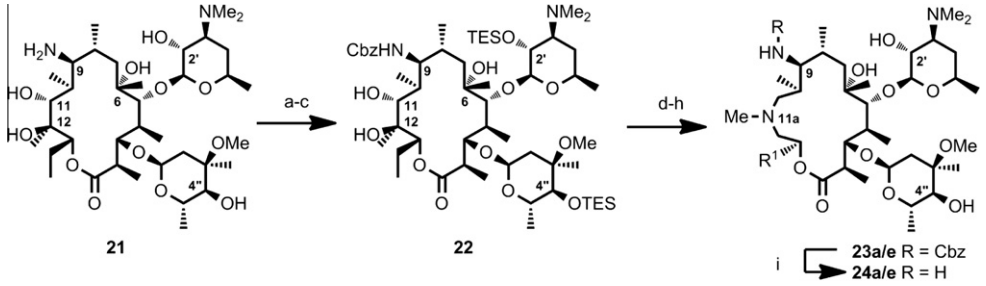
The synthesis of 4″-carbamate derivatives is shown in Scheme 6. Compound **23a/e** was treated with acetic anhydride to selectively acylate the 2′-hydroxyl groups. Subsequent treatment with CDI in the presence of NaH produced 4″-*O*-imidazocarbonyl intermediates **33a/e**. The intermediates **33a/e** were treated with amine **34** to install a 4″-carbamate side chain. The methanolysis of the 2′-*O*-acetyl groups and subsequent deprotection of the 9-*N*-caboxybenzyl groups with Pd-catalyzed hydrogenation yielded the 4″-carbamate **35a/e**.

2.2. In vitro antibacterial activity of 11a-azalides

The in vitro antibacterial activities of the prepared 11a-azalides were assessed against both erythromycin-susceptible and erythromycin-resistant strains of *Streptococcus pneumoniae*. Clarithromycin **2** was used for comparison in all the assays. The in vitro antibacterial activity was reported as the minimum inhibitory concentration (MIC) determined using the broth microdilution method



Scheme 3. Synthesis of 9-keto or 3-keto derivatives. Reagents and conditions : (a) *n*-Bu_4NF (2 equiv), THF; (b) Ac_2O, acetone; (c) triphosgene, pyridine, CH_2Cl_2 and then BnOH; (d) HF-pyridine, THF; (e) Dess–Martin periodinane, CH_2Cl_2; (f) H_2, Pd-C, MeOH; (g) 1 N HCl-EtOH; (h) CbzCl, $NaHCO_3$, CH_2Cl_2-H_2O; (i) Dess–Martin periodinane, CH_2Cl_2; (j) H_2, Pd-C, MeOH.



Scheme 4. Synthesis of 9-amino derivatives. Reagents and conditions : (a) CbzCl, $NaHCO_3$, CH_2Cl_2–H_2O; (b) MeOH; (c) TESCl, imidazole, DMF; (d) $Pb(OAc)_4$, CH_2Cl_2; (e) compound **11a/e**, $NaBH(OAc)_3$, then HCHO(aq), $NaBH(OAc)_3$; (f) LiOH, THF–EtOH–H_2O; (g) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, then DMAP, toluene, and reflux; (h) HF–pyridine, THF; (i) H_2, Pd-C, MeOH.

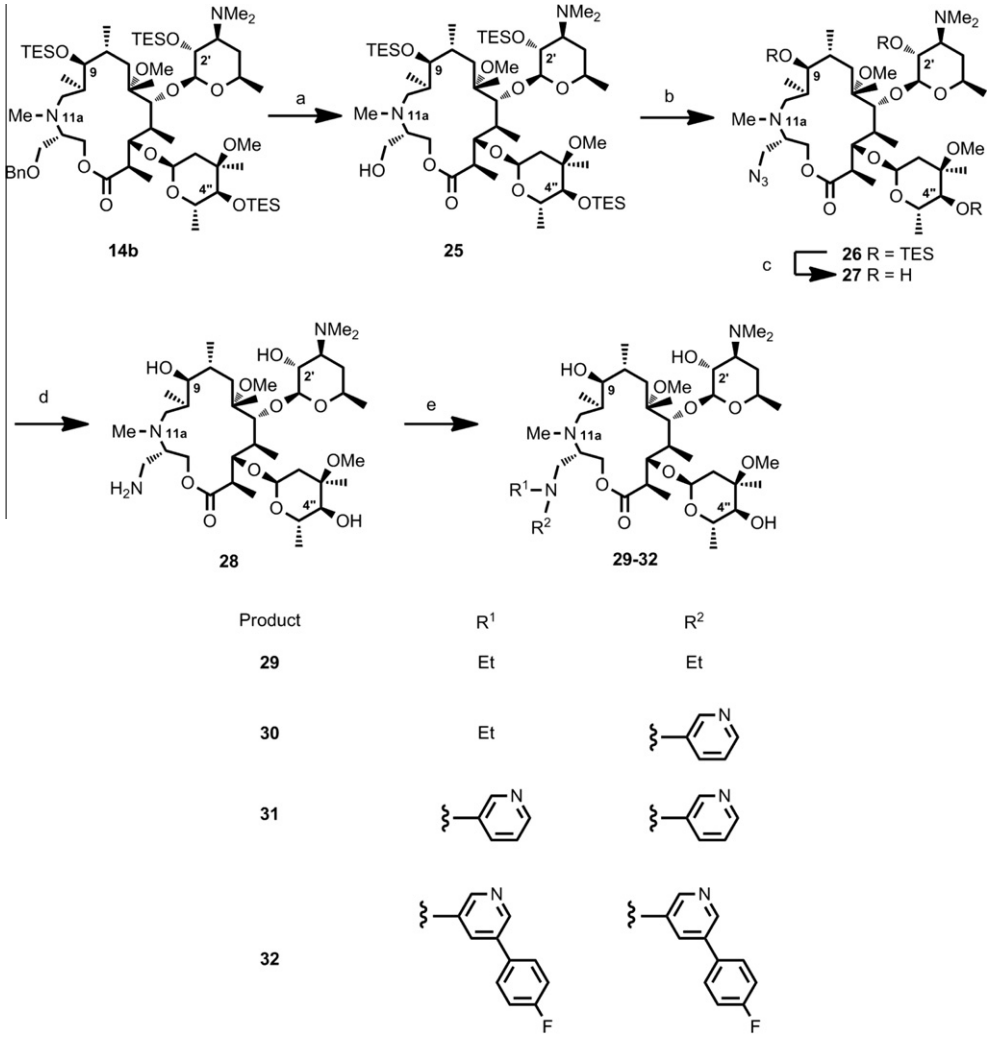
according to the guidelines of the Clinical and Laboratory Standards Institute (formerly the National Committee of Clinical Laboratory Standards) for *S. pneumoniae*. *S. pneumoniae* ATCC49619 is an erythromycin-susceptible strain, while *S. pneumoniae* 205 is an inducible MLSB-resistant strain encoded by the *erm*(B) gene.

First, we evaluated the effect of the 11a-azalide aglycon structure on antibacterial activity (Tables 1 and 2). The 6-*O*-methyl derivative **15a** (CAM type) had a better antibacterial activity than the 6-hydroxy derivative **4** (EM-A type). The 9-keto derivative **19** was 16–32-fold less potent than **15a**. The 3-keto derivative **20** completely lost its antibacterial activity. The 9-amino derivative **24a** showed a similar activity to that of **4**.

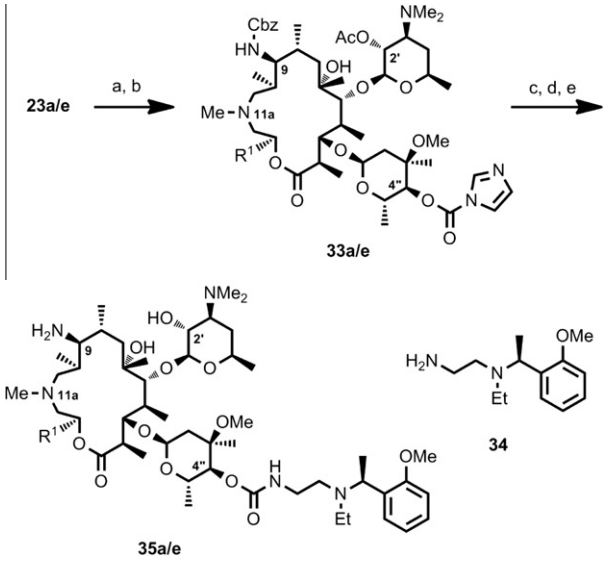
Next, we evaluated the effect of the introduction of a substituent to the C12 position of **15a** on antibacterial activity (Table 2). The 12-benzyloxymethyl derivative **15b** had a fourfold better activity against erythromycin-susceptible *S. pneumoniae* compared with **15c**, which has an opposite stereo chemical configuration at the 12-position. The 12-benzyloxyethyl derivative **15f** had the same antibacterial activity as **15b**. Although the amino derivative **28** and the dialkylamino derivative **29** had poor antibacterial activities, pyridylmethyl-substituted derivatives **30, 31** had the same activities as **15b**. Especially, the biaryl derivative **32** exhibited an improved activity against erythromycin-resistant *S. pneumoniae*, compared with CAM.

Next, we evaluated the effect of the introduction of a substituent introduction to the C13 position of **15a** on the antibacterial activity (Table 2). At the C13 position, the difference in the stereochemical configuration of the substituent had a significant impact on the antibacterial activity. The 13-benzyloxymethyl derivative **15e** showed a 16-fold better activity against erythromycin-susceptible *S. pneumoniae*, compared with **15d**. Next, we evaluated the effect of the distance of the phenyl group from aglycon on the activity against resistant *S. pneumoniae*. The most active compound was compound **15i**, which has a phenoxymethyl group at the 13-position. Furthermore, the introduction of a phenyl substituent at the phenoxymethyl group of **15i** increased the activity against resistant *S. pneumoniae*. Compound **15m**, which has a 4-phenylphenoxymethyl group, had a fourfold greater activity against resistant *S. pneumoniae* than **15i**. Compound **15o**, which has a 4-(2-pyridyl)phenylmethyl group, had an improved activity against erythromycin-susceptible *S. pneumoniae*.

Several reports have indicated that the introduction of an aromatic side chain at the C-4″ position enhances activity against erythromycin-resistant *S. pneumoniae*.[39,40] Especially, the 4″-carbamate derivative CP-544372 exhibited a significant in vitro activity against Gram-positive bacteria including erythromycin-resistant *S. pneumoniae*.[41] So, we applied a reported 4″-carbamate substituent to **24a/e**. The activities of **35a/e** against erythromycin-resistant *S. pneumoniae* were 256-fold stronger than those of the parent compound **24a/e** (Table 1). Although the benzyloxymethyl derivative **24e** showed a 16-fold better activity against erythromycin-susceptible *S. pneumoniae* than **24a**, the activities of **35a/e** against a resistant strain were almost the same.



Scheme 5. Synthesis of C12 substituted derivatives. Reagents and conditions : (a) H_2, $Pd(OH)_2$, THF; (b) *p*-NO_2-DPPA, DBU, toluene, 50 °C; (c) HF-Pyridine, THF; (d) Ph_3P, H_2O, THF; (e) aldehyde, $NaBH(OAc)_3$, $CHCl_3$.



Scheme 6. Synthesis of 4″-carbamate derivatives. Reagents and conditions : (a) Ac_2O, acetone; (b) CDI, NaH, THF–DMF, 0 °C; (c) amine **34**, THF; (d) MeOH; (e) H_2, Pd-C, MeOH.

3. Conclusion

A method of synthesizing structurally diverse 11a-azalides was established. Using this method, 11a-azalides with substituents at the C12, C13, and C4″ positions were synthesized and the antibacterial activities of the resulting compounds were evaluated. Among them, the C12-substituted derivative **32** and the C13-substituted derivative **15m** showed a 16-fold better activity against erythromycin-resistant *S. pneumoniae*, and their activities were comparable to that of CAM. The C4″-substituted derivative **35e** showed a significantly improved activity against an erythromycin-resistant strain and showed a potent activity against an erythromycin-susceptible strain, compared with the activities of CAM. These results reveal that the 11a-azalide scaffold is useful for improving the antibacterial activity against resistant pathogens.

4. Experimental section

All reactions sensitive to air or moisture were performed in a nitrogen atmosphere with anhydrous solvents. All the reagents and solvents were purchased commercially and were used without purification unless otherwise noted. Column chromatography was performed using a silica gel 60 with a particle size of 40–50 μm. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL Alpha

Table 1
Antibacterial activities of 11a-azalides

	MIC (μg/mL)												
	4	**19**	**20**	**24a**	**24e**	**28**	**29**	**30**	**31**	**32**	**35a**	**35e**	**2**
S. pneumoniae ATCC49619[a]	4	32	>128	2	0.12	64	128	4	1	0.5	0.12	0.12	0.03
S. pneumoniae 205[b]	>128	>128	>128	>128	>128	>128	>128	>128	>128	8	0.5	0.25	>128

[a] Erythromycin-susceptible strain.
[b] Erythromycin-resistant strain.

Table 2
Antibacterial activities of C12/C13-substituted 11a-azalides **15a–o**

	MIC (μg/mL)													
	15a	**15b**	**15c**	**15d**	**15e**	**15f**	**15g**	**15h**	**15i**	**15k**	**15l**	**15m**	**15n**	**15o**
S. pneumoniae ATCC49619[a]	2	1	4	1	0.06	1	0.5	0.12	0.25	0.5	1	1	0.5	0.25
S. pneumoniae 205[b]	>128	64	64	64	128	64	>128	128	32	16	16	8	64	16

[a] Erythromycin-susceptible strain.
[b] Erythromycin-resistant strain.

500 or JEOL Lambda 500 spectrometer. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Coupling constants (*J*) were given in hertz (Hz). Multiplicities were indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). All assignments were made using ^{1}H–^{1}H correlation spectroscopy (COSY), heteronuclear multiple-quantum coherence (HMQC), and heteronuclear multiple-bond correlation (HMBC) methods. Mass spectra (MS) were obtained with a Micromass Platform LC or a Micromass Q-Tof 2. The HRMS spectra were obtained with a Shimadzu LCMS-IT-TOF. The IR spectra were recorded using a PerkinElmer Paragon 1000 spectrometer as KBr pellets and were reported in reciprocal centimeters (cm^{-1}). Elemental analyses were performed using a PerkinElmer 2400 CHN analyzer.

4.1. Synthesis of C12/13 substituted derivatives

4.1.1. Synthesis of 9

Chlorotriethylsilane (59.4 g, 394.4 mmol) and imidazole (80.6 g, 1183 mmol) were added to a solution of **8**[42] (84.5 g, 112.7 mmol) in DMF (1000 mL) at room temperature. After stirring at room temperature for 16 h, the reaction mixture was diluted with ethyl acetate (500 mL) and *n*-hexane (500 mL) and washed with distilled water (1000 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography (hexane/acetone = 100:1 to 5:1) to yield compound **9** (107.9 g, 88%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 5.06 (dd, J = 11.1, 2.5 Hz, 1H), 4.84 (d, J = 5.0 Hz, 1H), 4.46 (s, 1H), 4.30 (d, J = 6.6 Hz, 1H), 4.20–4.26 (m, 1H), 3.86 (d, J = 9.5 Hz, 1H), 3.79 (s, 1H), 3.62 (d, J = 9.1 Hz, 1H), 3.45–3.51 (m, 1H), 3.33 (dd, J = 9.7, 2.3 Hz, 1H), 3.30 (s, 3H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.20 (d, J = 9.1 Hz, 1H), 3.10 (dd, J = 9.9, 7.0 Hz, 1H), 2.81–2.89 (m, 1H), 2.48–2.54 (m, 1H), 2.36 (d, J = 14.9 Hz, 1H), 2.17 (s, 6H), 2.03–2.11 (m, 1H), 1.91–1.98 (m, 1H), 1.86–1.91 (m, 1H), 1.81 (s, 1H), 1.64–1.69 (m, 1H), 1.58–1.63 (m, 1H), 1.49 (dd, J = 14.9, 5.0 Hz, 1H), 1.22–1.30 (m, 4H), 0.92–1.19 (m, 44H), 0.84–0.91 (m, 12H), 0.80 (t, J = 7.4 Hz, 3H), 0.51–0.70 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 174.2, 103.5, 97.9, 85.9, 82.2, 81.0, 80.2, 78.3, 77.1, 74.4, 73.4, 73.3, 70.7, 67.7, 65.2, 51.0, 49.5, 45.5, 40.9, 39.9, 37.6, 36.5, 33.7, 32.9, 31.6, 29.4, 24.3, 22.6, 22.0, 21.7, 21.5, 19.2, 19.1, 16.3, 15.9, 14.1, 13.4, 10.4, 9.9, 7.2, 7.1, 7.0, 5.5, 5.4, 5.1; IR (KBr) 3456, 2958, 1738, 1459, 740 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 1092.7621, calcd for $C_{56}H_{113}NO_{13}Si_3$ 1092.7593.

4.1.2. Synthesis of aminoalcohols 11a–j

Compounds **11a** and **11g** were commercially available.

4.1.2.1. Preparation of (*R*)-2-amino-3-(benzyloxy)propan-1-ol 11b[43]. *O*-Benzyl-L-serine (15.0 g, 76.8 mmol) was added to a suspension of lithium aluminum hydride (4.37 g, 115.3 mmol) in THF (150 mL) under reflux. After stirring at this temperature for 1.5 h, the reaction mixture was cooled in an ice bath, and distilled water (4.4 mL), 10% aqueous NaOH (4.4 mL) and distilled water (4.4 mL) were added. After stirring at room temperature for 18 h, the resulting mixture was filtrated and washed with THF. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) yield amino alcohol **11b** (6.43 g, 69%) as a colorless foam: $[\alpha]_D^{27}$ −5.0 (*c* 0.760, methanol); ^{1}H NMR ($CDCl_3$) δ 7.27–7.41 (m, 5H), 4.53 (s, 2H), 3.39–3.67 (m, 4H), 3.03–3.17 (m, 1H), 1.85 (br s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.9, 128.2, 127.55, 127.50, 73.1, 72.5, 63.7, 52.3; MS (ESI) *m*/*z* 182.2 $[M+H]^+$; NMR data consistent with literature.[44]

4.1.2.2. Preparation of (*S*)-2-amino-3-(benzyloxy)propan-1-ol 11c[43]. *O*-Benzyl-D-serine (10.0 g, 51.2 mmol) was added to a suspension of lithium aluminum hydride (2.92 g, 76.8 mmol) in THF (200 mL) under reflux. After stirring at this temperature for 2 h, the reaction mixture was cooled in an ice bath, and distilled water (2.9 mL), 10% aqueous NaOH (2.9 mL) and distilled water (2.9 mL) were added. After stirring at room temperature for 18 h, the resulting mixture was filtrated and washed with THF. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) yield amino alcohol **11c** (6.43 g, 69%) as a colorless foam: $[\alpha]_D^{27}$ +4.2 (*c* 1.062, methanol); ^{1}H NMR ($CDCl_3$) δ 7.27–7.41 (m, 5H), 4.53 (s, 2H), 3.39–3.67 (m, 4H), 3.03–3.17 (m, 1H), 1.87 (br s, 3H); MS (ESI) *m*/*z* 182.2 $[M+H]^+$.

4.1.2.3. Preparation of (*S*)-1-amino-3-(benzyloxy)propan-2-ol 11d. (*S*)-Benzyl glycidyl ether (1.00 g, 6.09 mmol) was added

to 25% aqueous ammonia (10 mL) at room temperature. After stirring at room temperature for 18 h, the reaction mixture was extracted with $CHCl_3$ (20 ml × 3). The combined organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield amino alcohol d **11d** (810 mg, 73%) as a colorless solid: $[\alpha]_D^{27}$ +5.3 (*c* 1.06, $CHCl_3$) (Lit.[45] $[\alpha]_D$ −5.1); ^1H NMR ($CDCl_3$) δ 7.27–7.38 (m, 5H), 4.55 (s, 2H), 3.68–3.83 (m, 1H), 3.39–3.56 (m, 2H), 2.66–2.89 (m, 2H), 1.80 (br s, 2H); MS (ESI) *m*/*z* 182.0 $[M+H]^+$; NMR data consistent with literature.[45]

4.1.2.4. Preparation of (*R*)-1-amino-3-(benzyloxy)propan-2-ol 11e. (*R*)-Benzyl glycidyl ether (1.00 g, 6.09 mmol) was added to 25% aqueous ammonia (10 mL) at room temperature. After stirring at room temperature for 18 h, the reaction mixture was extracted with $CHCl_3$ (20 ml × 3). The combined organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield amino alcohol **11e** (670 mg, 61%) as a colorless solid: $[\alpha]_D^{27}$ +5.6 (*c* 1.03, $CHCl_3$) (Lit.[46] $[\alpha]_D^{27}$ +6.25); ^1H NMR ($CDCl_3$) δ 7.27–7.42 (m, 5H), 4.55 (s, 2H), 3.67–3.82 (m, 1H), 3.39–3.55 (m, 2H), 2.65–2.87 (m, 2H), 1.99 (br s, 3H); MS (ESI) *m*/*z* 182.0 $[M+H]^+$; NMR data consistent with literature.[45]

4.1.2.5. Preparation of (*S*)-2-amino-4-(benzyloxy)butan-1-ol 11f. Benzylbromide (1.05 g, 6.11 mmol) was added to *N*-Boc-(*S*)-2-(2,2-dimethyloxazolidin-4-yl)ethanol[47] (750 mg, 3.06 mmol) and 60% sodium hydride (244 mg, 6.11 mmol) in THF (10 mL) and DMF (0.5 mL) at room temperature. After stirring at room temperature for 18 h, the reaction was quenched by adding saturated NH_4Cl (20 mL), and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography (hexane/ethyl acetate = 10:1) to yield crude benzyl product (910 mg) as a colorless oil. This benzyl product (910 mg) was dissolved 1 M aqueous hydrochloric acid (10 mL). After stirring at room temperature for 2 days, the reaction mixture was neutralized with 10% sodium hydroxide and extracted with $CHCl_3$ (10 ml × 3). The combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield compound **11f** (500 mg, 84% for two steps) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.24–7.41 (m, 5H), 4.51 (s, 2H), 3.51–3.64 (m, 3H), 3.36 (dd, *J* = 10.7, 6.8 Hz, 1H), 3.04 (br s, 1H), 1.94 (br s, 2H), 1.54–1.82 (m, 2H); MS (ESI) *m*/*z* 195.1 $[M+H]^+$.

4.1.2.6. Preparation of (*S*)-1-amino-4-(benzyloxy)butan-2-ol 11h. (*S*)-(2-Benzyloxyethyl)oxirane[48] (2.60 g, 14.6 mmol) was added to 25% aqueous ammonia (100 mL) and methanol (5.0 mL) at room temperature. After stirring at room temperature for 6 h, the reaction mixture was extracted with ethyl acetate (50 ml × 3). The combined organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield amino alcohol **11h** (2.62 g, 92%) as a yellowish oil: ^1H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5H), 4.53 (s, 2H), 3.62–3.79 (m, 3H), 2.76–2.84 (m, 1H), 2.61 (dd, *J* = 12.6, 7.8 Hz, 1H), 2.00 (br s, 2H), 1.68–1.80 (m, 2H) ; MS (ESI) *m*/*z* 195.1 $[M+H]^+$.

4.1.2.7. Preparation of (*R*)-1-amino-3-phenoxypropan-2-ol 11i. (*R*)-2-(Phenoxymethyl)oxirane (1.35 g, 8.99 mmol) was added to 25% aqueous ammonia (15 mL) at room temperature. After stirring at room temperature for 18 h, the reaction mixture was extracted with $CHCl_3$ (20 ml × 3). The combined organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was recrystallized from diethyl ether to yield **11i** (794 mg, 53%) as a colorless powder: ^1H NMR ($CDCl_3$) δ 7.24–7.34 (m, 2H), 6.88–7.01 (m, 3H), 3.91–4.03 (m, 3H), 2.79–3.02 (m, 2H), 1.99 (br s, 2H); MS (ESI) *m*/*z* 168.0 $[M+H]^+$.

4.1.2.8. Preparation of (*R*)-1-amino-3-(4-iodophenoxy)propan-2-ol 11j. (*R*)-Glycidyl tosylate (1.35 g, 8.99 mmol) was added to 4-iodophenol (5.62 g, 25.5 mmol) and 60% sodium hydride (1.02 g, 25.5 mmol) in DMF (50 mL) at 0 °C. After stirring at 0 °C for 2 h, the reaction was quenched by adding saturated NH_4Cl (20 mL), and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was used in the next reaction without further purification. The residue was added to 25% aqueous ammonia (50 mL) and methanol (20 mL) at room temperature. After stirring at room temperature for 2 days, the reaction mixture was filtrated and washed with cold methanol to yield **11j** (7.15 g, 96%) as a colorless powder: ^1H NMR (DMSO-d_6) δ 7.56 (d, *J* = 9.1 Hz, 2H), 6.77 (d, *J* = 9.1 Hz, 2H), 4.99 (br s, 1H), 3.90–3.95 (m, 1H), 3.82–3.87 (m, 2H), 2.64–2.68 (m, 1H), 2.58–2.62 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 158.6, 137.9, 117.3, 82.9, 70.8, 68.0, 52.5; MS (ESI) *m*/*z* 294.0 $[M+H]^+$.

4.1.3. General procedure for the synthesis of C12/13 substituted azalides (15a–j)

Lead tetraacetate (90%, 2.37 g, 4.80 mmol) was added to a solution of compound **9** (5.00 g, 4.56 mmol) in $CHCl_3$ (80 mL) at 0 °C. After stirring for 15 minutes at 0 °C, 2-aminoethanol (558 mg, 9.15 mmol) and sodium triacetoxyborohydride (1.45 g, 6.86 mmol) were added to the reaction mixture. After stirring for 4 h at room temperature, 37% aqueous formaldehyde solution (1.81 g, 22.9 mmol) and sodium triacetoxyborohydride (1.45 g, 6.86 mmol) were added to the reaction mixture. After stirring at room temperature for 1 h, the reaction was quenched by adding saturated $NaHCO_3$ (80 mL), and the aqueous layer was extracted with $CHCl_3$ (40 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed in vacuo to yield crude seco-acid **12a** as a colorless oil. Ethanol (10 mL), distilled water (10 mL), and lithium hydroxide monohydrate (288 mg, 6.86 mmol) were added to a solution of crude seco-acid **12a** in THF (30 mL) at room temperature. After stirring at room temperature for 6 h, the reaction was quenched by addition of saturated NH_4Cl (20 mL). The organic solvent was removed in vacuo and the residual aqueous layer was extracted with $CHCl_3$ (20 ml × 3). The combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH = 50:1 to 5:1) to yield compound **13a** (2.28 g, 47%) as a colorless foam: ^1H NMR ($CDCl_3$) δ 4.85 (d, *J* = 4.6 Hz, 1H), 4.47 (d, *J* = 6.9 Hz, 1H), 4.23–4.30 (m, 1H), 3.91 (dd, *J* = 7.1, 1.7 Hz, 1H), 3.81–3.87 (m, 2H), 3.74 (d, *J* = 7.3 Hz, 1H), 3.59–3.65 (m, 1H), 3.31 (s, 3H), 3.24–3.27 (m, 4H), 3.14–3.21 (m, 2H), 3.06–3.11 (m, 1H), 2.97–3.03 (m, 1H), 2.88–2.94 (m, 1H), 2.66 (s, 3H), 2.60–2.65 (m, 1H), 2.42–2.57 (m, 3H), 2.36 (d, *J* = 14.9 Hz, 1H), 2.21–2.25 (m, 1H), 2.20 (s, 6H), 1.74–1.82 (m, 1H), 1.55–1.65 (m, 2H), 1.44 (dd, *J* = 14.9, 5.0 Hz, 1H), 1.30 (s, 3H), 1.27–1.29 (m, 1H), 1.23 (s, 3H), 1.15–1.20 (m, 10H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 7.3 Hz, 3H), 0.89–1.01 (m, 30H), 0.55–0.70 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 181.9, 102.8, 96.3, 83.0, 81.1, 80.3, 80.0, 77.9, 73.4, 73.2, 67.4, 65.6, 65.1, 61.4, 60.5, 57.2, 50.6, 49.5, 46.5, 43.1, 41.0, 39.8, 37.7, 36.1, 32.9, 31.2, 29.5, 22.3, 21.9, 21.5, 19.9, 19.5, 19.1, 14.2, 10.6, 7.2, 7.1, 7.1, 5.5, 5.5, 5.2.

Triethylamine (52 mg, 0.516 mmol) and 2,4,6-trichlorobenzoyl chloride (120 mg, 0.493 mmol) were added to a solution of compound **13a** (500 mg, 0.469 mmol) in THF (9.4 mL) at room temperature. After stirring at room temperature for 2 h, the reaction mixture was added to a refluxed solution of DMAP (1.20 g, 11.7 mmol) in

CH_3CN (94 mL) for 0.5 h. The reaction mixture was cooled and washed with saturated NH_4Cl (50 mL). The organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography (*n*-hexane/acetone = 20:1) to yield compound **14a** (254 mg, 52%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 4.74 (d, J = 5.0 Hz, 1H), 4.45 (s, 1H), 4.24–4.30 (m, 1H), 4.07–4.13 (m, 1H), 3.99–4.06 (m, 2H), 3.70 (d, J = 6.9 Hz, 1H), 3.58–3.64 (m, 1H), 3.45–3.50 (m, 1H), 3.30 (s, 3H), 3.13–3.21 (m, 5H), 2.79–2.86 (m, 1H), 2.69–2.75 (m, 1H), 2.42–2.51 (m, 3H), 2.33 (d, J = 14.9 Hz, 1H), 2.23 (s, 3H), 2.19 (s, 6H), 2.11–2.16 (m, 1H), 2.03–2.09 (m, 1H), 1.82–1.90 (m, 2H), 1.52–1.65 (m, 2H), 1.42–1.47 (m, 1H), 1.31 (s, 3H), 1.25–1.29 (m, 1H), 1.22 (d, J = 6.1 Hz, 3H), 1.10–1.18 (m, 10H), 1.07 (d, J = 7.3 Hz, 3H), 0.90–1.00 (m, 33H), 0.56–0.68 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 176.6, 102.8, 96.2, 81.0, 80.1, 78.0, 77.9, 77.3, 77.0, 76.8, 73.4, 73.1, 67.4, 65.8, 65.2, 62.9, 61.8, 57.1, 50.3, 49.4, 45.0, 43.4, 41.5, 41.0, 37.2, 35.9, 29.5, 22.3, 22.0, 21.9, 19.6, 18.9, 16.6, 12.6, 10.8, 7.1, 7.1, 7.0, 5.5, 5.4, 5.2; IR (KBr) 2957, 1734, 1460, 740 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 1047.7510, calcd for $C_{54}H_{110}N_2O_{11}Si_3$ 1047.7490.

Hydrogen fluoride–pyridine (70%, 37 mg, 1.29 mmol) was added to a solution of compound **14a** (450 mg, 0.429 mmol) in THF (10.0 mL) at room temperature. After stirring at room temperature for 18 h, the reaction was neutralized with saturated $NaHCO_3$ (10.0 mL). The resulting mixture was diluted with ethyl acetate (20 mL) and then separated. The organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield compound **15a** (300 mg, 99%) as a colorless foam: $[\alpha]_D^{26}$ −99.7 (c 0.108, $CHCl_3$); MASS (ESI) m/z 705.5 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 4.90 (d, J = 4.9 Hz, 1H), 4.41 (d, J = 7.3 Hz, 1H), 4.29–4.37 (m, 1H), 4.25 (d, J = 3.7 Hz, 1H), 4.03–4.12 (m, 1H), 3.91–3.99 (m, 1H), 3.74 (d, J = 7.3 Hz, 1H), 3.58–3.66 (m, 1H), 3.43–3.52 (m, 1H), 3.33 (s, 3H), 3.16–3.26 (m, 5H), 3.01 (t, J = 9.8 Hz, 1H), 2.88–2.96 (m, 1H), 2.74–2.84 (m, 1H), 2.33–2.51 (m, 5H), 2.32 (s, 3H), 2.30 (s, 6H), 2.18–2.28 (m, 2H), 2.11 (dd, J = 12.5, 4.6 Hz, 1H), 1.86–1.93 (m, 1H), 1.73–1.80 (m, 1H), 1.63–1.68 (m, 1H), 1.54 (dd, J = 15.3, 4.9 Hz, 1H), 1.34 (s, 3H), 1.29 (d, J = 6.1 Hz, 3H), 1.20–1.27 (m, 7H), 1.18 (d, J = 7.3 Hz, 3H), 1.10 (d, J = 7.3 Hz, 3H), 0.87 (d, J = 7.3 Hz, 3H), 0.77 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 177.5, 103.6, 96.2, 80.7, 79.4, 78.4, 78.3, 77.9, 72.8, 71.2, 69.0, 65.5, 65.4, 62.9, 61.0, 56.3, 50.1, 49.5, 45.2, 44.1, 42.0, 40.5, 37.0, 35.1, 34.0, 30.9, 29.3, 21.9, 21.7, 21.4, 18.3, 15.1, 13.7, 10.6, 6.6, 5.8; IR (KBr) 3469, 2974, 1733, 1461 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 705.4903, calcd for $C_{36}H_{68}N_2O_{11}$ 705.4896.

Using the general procedure described above, the following compounds (**15b–j**) were also prepared:

4.1.3.1. Compound 15b. MASS (ESI) m/z 825.5 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 7.25–7.38 (m, 5H), 4.81 (d, J = 4.2 Hz, 1H), 4.49 (s, 2H), 4.44 (d, J = 7.3 Hz, 1H), 4.24 (dd, J = 11.9, 3.0 Hz, 1H), 4.03–4.14 (m, 1H), 3.95 (dd, J = 12.0, 9.0 Hz, 1H), 3.83 (d, J = 7.5 Hz, 1H), 3.57–3.64 (m, 2H), 3.35–3.54 (m, 3H), 3.31 (s, 3H), 3.21 (s, 3H), 2.95 (s, 4H), 2.29 (s, 6H), 2.26 (s, 3H), 2.20–2.22 (m, 5H), 2.07–2.17 (m, 1H), 1.91–1.99 (m, 1H), 1.42–1.83 (m, 3H), 1.33 (s, 3H), 1.27 (d, J = 6.2 Hz, 3H), 1.24 (d, J = 6.1 Hz, 3H), 1.21 (s, 3H), 1.17 (d, J = 7.5 Hz, 3H), 1.13 (d, J = 7.3 Hz, 3H), 1.03–1.05 (m, 2H), 0.89 (d, J = 7.2 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.6, 138.1, 128.5, 127.8, 127.7, 104.0, 96.8, 80.9, 80.0, 78.6, 78.3, 78.2, 73.5, 72.8, 71.0, 69.2, 67.4, 65.7, 65.4, 63.4, 62.4, 50.0, 49.5, 45.0, 40.9, 40.4, 37.4, 35.7, 35.4, 34.4, 31.3, 29.1, 21.7, 21.4, 21.3, 18.1, 15.4, 14.8, 12.2, 11.9; HRMS (ESI/APCI-dual, $[M+H]^+$) found 825.5474, calcd for $C_{44}H_{76}N_2O_{12}$ 825.5471.

4.1.3.2. Compound 15c. $[\alpha]_D^{25}$ −89.1 (c 0.229, $CHCl_3$); MASS (ESI) m/z 825.5 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 7.26–7.38 (m, 5H), 4.91 (d, J = 4.7 Hz, 1H), 4.47 (d, J = 2.0 Hz, 2H), 4.41 (d, J = 7.2 Hz, 1H), 4.27–4.32 (m, 1H), 4.23 (d, J = 10.9 Hz, 1H), 4.16 (d, J = 3.9 Hz, 1H), 4.07–4.08 (m, 1H), 3.74 (d, J = 8.1 Hz, 1H), 3.63–3.68 (m, 1H), 3.58 (dd, J = 9.7, 4.4 Hz, 1H), 3.42–3.54 (m, 2H), 3.37 (dd, J = 9.5, 7.0 Hz, 1H), 3.32 (s, 3H), 3.19 (s, 3H), 3.07–3.11 (m, 1H), 2.88–3.05 (m, 2H), 2.48 (s, 3H), 2.29 (s, 6H), 2.17–2.22 (m, 6H), 1.58–1.93 (m, 3H), 1.53 (dd, J = 15.1, 4.9 Hz, 1H), 1.33 (s, 3H), 1.29 (d, J = 6.4 Hz, 3H), 1.23 (s, 3H), 1.17 (d, J = 7.5 Hz, 3H), 1.10 (d, J = 7.5 Hz, 3H), 0.99–1.03 (m, 5H), 0.85 (d, J = 7.0 Hz, 3H), 0.73 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 177.5, 138.0, 128.6, 127.9, 127.7, 103.7, 96.4, 80.8, 79.4, 78.6, 78.3, 77.8, 73.5, 72.8, 71.1, 69.0, 65.5, 65.4, 62.5, 62.1, 57.3, 50.1, 49.5, 45.5, 41.9, 41.6, 40.4, 37.1, 35.2, 32.7, 30.9, 30.4, 29.2, 21.8, 21.7, 21.4, 18.2, 15.9, 14.9, 13.7, 11.0; IR (KBr) 3437, 2973, 1733, 1457, 737 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 825.5496, calcd for $C_{44}H_{76}N_2O_{12}$ 825.5471.

4.1.3.3. Compound 15d. $[\alpha]_D^{25}$ −109.7 (c 0.275, $CHCl_3$); MASS (ESI) m/z 825.4 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 7.24–7.37 (m, 5H), 5.26–5.36 (m, 1H), 4.92 (d, J = 4.51 Hz, 1H), 4.54 (m, 1H), 4.47 (d, J = 12.12 Hz, 1H), 4.39 (d, J = 7.31 Hz, 1H), 4.35 (d, J = 6.37 Hz, 1H), 4.08 (m, 1H), 3.72 (d, J = 7.77 Hz, 1H), 3.59 (dd, J = 8.47, 2.41 Hz, 1H), 3.42–3.55 (m, 3H), 3.32 (s, 3H), 3.24 (s, 3H), 3.17–3.27 (m, 1H), 3.10 (s, 1H), 3.01 (t, J = 9.56 Hz, 1H), 2.81–2.96 (m, 2H), 2.30 (s, 6H), 2.18–2.61 (m, 9H), 1.97 (dd, J = 12.20, 3.50 Hz, 1H), 1.59–1.92 (m, 5H), 1.52 (dd, J = 14.92, 4.82 Hz, 1H), 1.31 (d, J = 6.37 Hz, 3H) 1.33 (s, 3H), 1.23 (d, J = 6.06 Hz, 3H), 1.23 (s, 3H), 1.17 (d, J = 7.46 Hz, 3H), 1.14–1.35 (m, 2H), 1.08 (d, J = 7.31 Hz, 3H), 0.82 (d, J = 6.99 Hz, 3H), 0.70 (d, J = 6.68 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.5, 137.9, 128.4, 127.7, 127.7, 103.5, 96.1, 80.0, 79.4, 78.4, 78.2, 73.4, 72.7, 71.3, 70.4, 68.7, 68.2, 65.4, 65.1, 62.9, 58.6, 50.0, 49.5, 45.4, 44.3, 41.7, 40.4, 37.1, 35.0, 32.7, 30.5, 29.5, 22.7, 21.6, 21.4, 18.3, 15.1, 10.4; IR (KBr) 3460, 2973, 1733, 1458, 737 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 825.5490, calcd for $C_{44}H_{76}N_2O_{12}$ 825.5471.

4.1.3.4. Compound 15e. $[\alpha]_D^{25}$ −40.0 (c 0.219, $CHCl_3$); MASS (ESI) m/z 825.5 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 7.24–7.37 (m, 5H), 4.91–5.01 (m, 1H), 4.80 (d, J = 4.35 Hz, 1H), 4.57 (d, J = 11.97 Hz, 1H), 4.41–4.48 (m, 2H), 4.03–4.14 (m, 1H), 3.88 (d, J = 6.84 Hz, 1H), 3.54–3.60 (m, 2H), 3.42–3.53 (m, 2H), 3.26 (s, 3H), 3.23 (s, 3H), 3.18–3.28 (m, 3H), 2.87–3.03 (m, 3H), 2.43–2.55 (m, 3H), 2.29 (s, 6H), 2.26 (s, 3H), 2.16–2.34 (m, 3H), 1.93 (m, 1H), 1.77–1.91 (m, 1H), 1.60–1.72 (m, 2H), 1.33 (s, 3H), 1.28 (d, J = 6.22 Hz, 3H), 1.24 (d, J = 6.22 Hz, 3H), 1.19 (d, J = 6.99 Hz, 3H), 1.16 (s, 3H), 1.14 (d, J = 7.31 Hz, 3H), 1.10–1.36 (m, 2H), 0.94 (d, J = 6.99 Hz, 3H), 0.93 (d, J = 6.53 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.7, 138.1, 128.5, 127.8, 104.1, 97.0, 80.8, 79.2, 78.8, 78.1, 73.3, 72.7, 71.9, 71.1, 70.2, 69.1, 65.8, 65.4, 59.1, 49.8, 49.5, 45.8, 44.6, 40.5, 39.4, 37.7, 35.4, 34.1, 31.0, 29.3, 21.6, 21.4, 21.1, 18.2, 16.9, 11.5; IR (KBr) 3469, 2973, 1730, 1457, 736 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 825.5483, calcd for $C_{44}H_{76}N_2O_{12}$ 825.5471.

4.1.3.5. Compound 15f. $[\alpha]_D^{25}$ −56.8 (c 0.359, $CHCl_3$); MASS (ESI) m/z 839.7 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 7.25–7.38 (m, 5H), 4.82 (d, J = 4.5 Hz, 1H), 4.50 (s, 2H), 4.46 (d, J = 7.3 Hz, 1H), 4.39–4.44 (m, 1H), 4.02–4.17 (m, 2H), 3.79–3.88 (m, 2H), 3.53 (t, J = 6.4 Hz, 2H), 3.39–3.40 (m, 3H), 3.31 (s, 3H), 3.22 (s, 3H), 2.95 (s, 4H), 2.44–2.64 (m, 3H), 2.29 (s, 6H), 2.19 (s, 3H), 2.05–2.07 (m, 3H), 1.93–2.02 (m, 1H), 1.43–1.90 (m, 5H), 1.33 (s, 3H), 1.28 (d, J = 6.4 Hz, 3H), 1.24 (d, J = 6.1 Hz, 3H), 1.21 (s, 3H), 1.18 (d,

J = 7.3 Hz, 3H), 1.13 (d, J = 7.3 Hz, 3H), 1.04 (s, 2H), 0.91 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.3, 138.4, 128.5, 127.8, 127.8, 103.9, 96.4, 81.0, 80.3, 78.5, 78.2, 77.4, 77.1, 76.8, 73.2, 72.8, 71.0, 69.2, 68.0, 65.6, 65.4, 64.0, 61.4, 50.0, 49.5, 44.6, 40.4, 37.4, 35.3, 34.1, 33.9, 30.4, 29.1, 27.2, 21.7, 21.4, 21.1, 18.1, 15.9, 12.3, 11.9; IR (KBr) 3392, 2977, 1726, 1464, 741 cm^{-1}; HRMS (ESI/APCI-dual, [M+H]$^+$) found 839.5643, calcd for $C_{45}H_{78}N_2O_{12}$ 839.5628.

4.1.3.6. Compound 15g. $[\alpha]_D^{25}$ −29.1 (c 0.102, $CHCl_3$); MASS (ESI) m/z 781.4 [M+H]$^+$; ^{1}H NMR ($CDCl_3$) δ 7.23–7.40 (m, 5H), 5.66 (dd, J = 9.40, 3.65 Hz, 1H), 4.61 (s, 1H), 4.51 (d, J = 4.04 Hz, 1H), 4.47 (d, J = 7.15 Hz, 2H), 3.91–4.10 (m, 2H), 3.63–3.73 (m, 1H), 3.41–3.55 (m, 2H), 3.32 (s, 3H), 3.17 (s, 3H), 3.14–3.36 (m, 2H), 2.99–3.08 (m, 1H), 2.85–2.94 (m, 1H), 2.43–2.59 (m, 3H), 2.30 (s, 6H), 2.27 (s, 3H), 2.22–2.34 (m, 2H), 1.84–2.09 (m, 3H), 1.72–1.82 (m, 1H), 1.62–1.71 (m, 1H), 1.36 (s, 3H), 1.27 (d, J = 5.75 Hz, 3H), 1.25 (d, J = 5.75 Hz, 3H), 1.17 (d, J = 7.15 Hz, 3H), 1.14 (d, J = 7.31 Hz, 3H), 1.07 (s, 3H), 1.05–1.40 (m, 2H), 0.90–1.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.4, 139.4, 128.6, 128.2, 127.0, 104.4, 97.0, 81.1, 79.6, 78.5, 78.1, 74.5, 72.5, 71.1, 69.2, 65.6, 65.4, 63.9, 49.9, 49.5, 45.5, 43.8, 40.5, 39.5, 38.1, 35.2, 34.3, 31.1, 29.4, 21.6, 21.4, 21.1, 18.1, 17.3, 12.1, 11.4; IR (KBr) 3462, 2973, 1734, 1458, 760 cm^{-1}; HRMS (ESI/APCI-dual, [M+H]$^+$) found 781.5230, calcd for $C_{42}H_{72}N_2O_{11}$ 781.5209.

4.1.3.7. Compound 15h. $[\alpha]_D^{31}$ −41.4 (c 0.149, $CHCl_3$); MASS (ESI) m/z 839.6 [M+H]$^+$; ^{1}H NMR ($CDCl_3$) δ 7.25–7.35 (m, 5H), 4.89–4.98 (m, 1H), 4.79 (d, J = 4.2 Hz, 1H), 4.48–4.54 (m, 1H), 4.45–4.47 (m, 1H), 4.43 (d, J = 7.3 Hz, 1H), 4.33–4.39 (m, 1H), 4.03–4.16 (m, 1H), 3.89 (d, J = 6.4 Hz, 1H), 3.41–3.55 (m, 6H), 3.28 (s, 3H), 3.26–3.27 (m, 1H), 3.25 (s, 3H), 2.90–3.06 (m, 3H), 2.85 (dd, J = 13.5, 7.8 Hz, 1H), 2.30 (s, 6H), 2.25 (s, 3H), 2.14–2.23 (m, 6H), 1.60–2.04 (m, 5H), 1.49 (dd, J = 14.7, 5.2 Hz, 1H), 1.32 (s, 3H), 1.28 (d, J = 6.1 Hz, 3H), 1.24 (d, J = 6.1 Hz, 3H), 1.20 (s, 3H), 1.10–1.16 (m, 6H), 0.89–0.97 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.6, 138.2, 128.4, 128.3, 127.7, 127.6, 127.6, 104.3, 96.5, 80.7, 78.9, 78.0, 73.1, 72.6, 71.0, 69.0, 66.8, 65.3, 62.5, 49.8, 49.5, 45.3, 40.5, 39.2, 37.5, 35.3, 33.8, 33.5, 30.9, 29.5, 21.7, 21.4, 21.0, 18.3, 11.1; IR (KBr) 3469, 2973, 1728, 1458, 737 cm^{-1}; HRMS (ESI/APCI-dual, [M+H]$^+$) found 839.5630, calcd for $C_{45}H_{78}N_2O_{12}$ 839.5628.

4.1.3.8. Compound 15i. MASS (ESI) m/z 811.4 [M+H]$^+$; ^{1}H NMR ($CDCl_3$) δ 7.23–7.30 (m, 2H), 6.95 (t, J = 7.3 Hz, 2H), 6.87 (d, J = 7.9 Hz, 1H), 5.04 (d, J = 3.7 Hz, 1H), 4.77 (d, J = 4.3 Hz, 1H), 4.47 (d, J = 7.3 Hz, 1H), 4.18 (dd, J = 10.4, 3.7 Hz, 1H), 4.00–4.07 (m, 2H), 3.91 (d, J = 7.3 Hz, 1H), 3.45–3.57 (m, 2H), 3.35 (d, J = 9.2 Hz, 1H), 3.30 (s, 3H), 3.25–3.27 (m, 1H), 3.22 (s, 3H), 2.92–3.17 (m, 3H), 2.84 (t, J = 8.9 Hz, 1H), 2.59 (dd, J = 14.0, 3.7 Hz, 1H), 2.42–2.56 (m, 3H), 2.30 (s, 3H), 2.29 (s, 6H), 1.81–2.15 (m, 5H), 1.54–1.70 (m, 2H), 1.35 (s, 3H), 1.18 (d, J = 6.7 Hz, 3H), 1.14 (d, J = 7.3 Hz, 3H), 0.93–1.38 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 174.0, 158.7, 129.6, 121.2, 114.6, 104.1, 97.5, 81.0, 79.9, 78.0, 72.6, 71.7, 71.0, 69.1, 68.7, 67.6, 65.7, 65.4, 49.9, 49.5, 46.2, 40.5, 39.4, 37.8, 35.5, 34.3, 30.9, 29.1, 21.4, 21.4, 21.0, 18.1, 16.8, 11.8, 7.2, 5.6; HRMS (ESI/APCI-dual, [M+H]$^+$) found 811.5314, calcd for $C_{43}H_{74}N_2O_{12}$ 811.5315.

4.1.3.9. Compound 15j. $[\alpha]_D^{25}$ −32.8 (c 0.121, $CHCl_3$); MASS (ESI) m/z 937.4 [M+H]$^+$; ^{1}H NMR ($CDCl_3$) δ 7.54 (d, J = 8.9 Hz, 2H), 6.67 (d, J = 8.6 Hz, 2H), 4.98–5.04 (m, 1H), 4.73–4.77 (m, 1H), 4.45 (d, J = 7.2 Hz, 1H), 3.99–4.18 (m, 4H), 3.88 (d, J = 7.2 Hz, 1H), 3.44–3.56 (m, 2H), 3.29 (s, 3H), 3.20–3.26 (m, 4H), 2.95–3.15 (m, 2H), 2.90 (d, J = 9.3 Hz, 1H), 2.45–2.61 (m, 4H), 2.31 (s, 6H), 2.29 (s, 3H), 2.17–2.25 (m, 1H), 2.12 (d, J = 15.1 Hz, 1H), 1.95–2.03 (m, 1H), 1.79–1.89 (m, 1H), 1.65–1.73 (m, 1H), 1.35 (s, 3H), 1.04–1.33 (m, 17H), 0.94–0.99 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.5, 158.5, 138.3, 117.0, 103.8, 97.2, 83.2, 80.8, 79.7, 79.0, 77.9, 72.5, 71.5, 70.9, 69.0, 67.8, 65.7, 65.3, 49.9, 49.4, 46.0, 44.8, 40.4, 39.2, 37.6, 36.6, 35.4, 34.0, 30.9, 29.2, 21.5, 21.4, 21.4, 21.0, 18.2, 16.9, 12.0, 11.5; IR (KBr) 3468, 2973, 1732, 1588, 1488, 820 cm^{-1}; HRMS (ESI/APCI-dual, [M+H]$^+$) found 937.4305, calcd for $C_{43}H_{73}IN_2O_{12}$ 937.4281.

4.1.4. General procedure for the synthesis of compound 15k–m

A mixture of **14e** (12.9 g, 11.0 mmol) and 20% $Pd(OH)_2$ (25.0 g) in THF (130 mL) was stirred in a hydrogen atmosphere at room temperature for 18 h. After the removal of insoluble particles using filtration, the solvent was removed in vacuo and the residue was purified using silica gel chromatography (hexane/acetone = 5:1) to yield compound **16** (6.24 g, 53%) as a colorless foam: MASS (ESI) m/z 1077.7 [M+H]$^+$; ^{1}H NMR ($CDCl_3$) δ 4.97–5.11 (m, 1H), 4.76 (d, J = 4.1 Hz, 1H), 4.43 (d, J = 7.0 Hz, 1H), 4.22–4.30 (m, 1H), 3.65–3.77 (m, 3H), 3.57–3.64 (m, 1H), 3.34–3.43 (m, 1H), 3.29 (s, 3H), 3.25 (s, 3H), 3.14–3.22 (m, 3H), 2.74–2.83 (m, 1H), 2.27–2.64 (m, 9H), 2.21 (br s, 6H), 2.02–2.11 (m, 1H), 1.90–1.99 (m, 1H), 1.77–1.85 (m, 1H), 1.58–1.70 (m, 1H), 1.40–1.50 (m, 2H), 1.32 (s, 3H), 1.04–1.26 (m, 23H), 0.90–1.01 (m, 27H), 0.54–0.71 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 174.4, 103.1, 96.0, 80.9, 80.7, 77.8, 73.3, 73.2, 67.5, 65.6, 65.4, 64.0, 63.0, 58.9, 49.9, 49.5, 46.0, 41.0, 39.6, 36.1, 29.6, 22.2, 21.7, 20.1, 18.9, 11.4, 7.1, 7.0, 5.5, 5.4, 5.2; HRMS (ESI/APCI-dual, [M+H]$^+$) found 1077.7626, calcd for $C_{55}H_{112}N_2O_{12}Si_3$ 1077.7596.

Diethyl azodicarboxylate (0.19 g, 1.10 mmol) was added to a solution of compound **16** (396 mg, 0.367 mmol), triphenylphosphine (0.29 g, 1.10 mmol) and o-phenylphenol (0.19 g, 1.10 mmol) in THF (8 mL) at room temperature. After stirring at room temperature for 18 h, the solvent was removed in vacuo and the residue was diluted with diethyl ether (60 mL) and washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$. The solvent was removed in vacuo to yield a crude product as yellow oil. Hydrogen fluoride–pyridine (70%, 105 mg, 3.67 mmol) was added to a solution of the crude product in THF (10 mL) at room temperature. After stirring at room temperature for 18 h, the reaction was neutralized with saturated $NaHCO_3$ (20 mL). The resulting mixture was diluted with ethyl acetate (60 mL) and then separated. The organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield compound **15k** (39 mg, 12% for two steps) as a colorless foam: $[\alpha]_D^{31}$ −17.3 (c 0.208, $CHCl_3$); MASS (ESI) m/z 887.4 [M+H]$^+$; ^{1}H NMR ($CDCl_3$) δ 7.46–7.56 (m, 2H), 7.22–7.44 (m, 5H), 6.92–7.10 (m, 2H), 4.91–5.02 (m, 1H), 4.72 (d, J = 4.40 Hz, 1H), 4.43 (d, J = 7.03 Hz, 1H), 4.24–4.34 (m, 1H), 3.98–4.22 (m, 3H), 3.83 (d, J = 7.91 Hz, 1H), 3.25 (s, 3H), 3.15 (s, 3H), 3.11–3.57 (m, 5H), 2.80–3.00 (m, 3H), 2.28 (s, 6H), 2.19 (s, 3H), 2.08–2.66 (m, 8H), 1.58–2.00 (m, 4H), 0.89–1.40 (m, 26H); ^{13}C NMR ($CDCl_3$) δ 174.3, 155.4, 138.3, 131.1, 130.9, 129.7, 128.6, 127.8, 126.9, 121.4, 112.5, 103.8, 97.1, 80.6, 80.0, 79.3, 78.0, 77.3, 77.0, 76.8, 72.5, 72.0, 71.0, 69.0, 67.9, 65.6, 65.4, 58.2, 49.8, 49.4, 45.9, 44.8, 40.4, 39.0, 37.4, 35.5, 33.8, 30.7, 29.7, 29.1, 21.4, 21.4, 21.1, 18.3, 16.8, 12.4, 11.4; IR (KBr) 3468, 2972, 1730, 1600, 1459, 754 cm^{-1}; HRMS (ESI/APCI-dual, [M+H]$^+$) found 887.5657, calcd for $C_{49}H_{78}N_2O_{12}$ 887.5628.

4.1.4.1. Compound 15l. Compound **15l** (87 mg, 22% for two steps) was prepared from compound **16** (473 mg, 0.439 mmol) according to the procedure used to prepare **15k**: $[\alpha]_D^{25}$ −24.1 (c 0.123, $CHCl_3$); MASS (ESI) m/z 887.3 [M+H]$^+$; ^{1}H NMR ($CDCl_3$) δ 7.52–7.60 (m, 2H), 7.39–7.46 (m, 2H), 7.29–7.38 (m, 2H), 7.15–7.21 (m, 1H), 7.09 (m, 1H), 6.85 (dd, J = 7.77, 2.18 Hz, 1H), 5.02–5.10 (m, 1H), 4.78 (d, J = 4.66 Hz, 1H), 4.58–4.67 (m, 1H), 4.46 (d,

J = 7.31 Hz, 1H), 4.25 (dd, J = 10.49, 3.34 Hz, 1H), 4.10 (dd, J = 10.26, 3.57 Hz, 1H), 4.03 (dd, J = 9.56, 6.14 Hz, 1H), 3.91 (d, J = 7.62 Hz, 1H), 3.42–3.62 (m, 3H), 3.32 (s, 3H), 3.21 (s, 3H), 3.12–3.27 (m, 2H), 2.97–3.07 (m, 1H), 2.73–2.83 (m, 1H), 2.61 (dd, J = 13.99, 4.20 Hz, 1H), 2.42–2.66 (m, 2H), 2.31 (s, 3H), 2.29 (s, 6H), 2.17–2.35 (m, 2H), 1.97–2.10 (m, 2H), 1.82–1.93 (m, 2H), 1.62–1.71 (m, 1H), 1.36 (s, 3H), 1.25 (d, J = 6.22 Hz, 3H), 1.23 (s, 3H), 1.22 (d, J = 6.22 Hz, 3H), 1.19 (d, J = 6.99 Hz, 3H), 1.15 (d, J = 7.15 Hz, 3H), 1.11–1.40 (m, 2H), 0.91–1.01 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.9, 159.1, 143.0, 141.0, 129.9, 128.9, 127.7, 127.3, 120.2, 113.8, 113.1, 104.1, 97.6, 81.0, 79.7, 78.8, 78.0, 72.6, 71.7, 71.0, 69.1, 67.8, 65.7, 65.5, 49.9, 49.5, 46.3, 40.4, 39.5, 37.9, 35.5, 34.4, 31.0, 29.2, 21.4, 21.4, 21.0, 18.0, 16.8, 11.9; IR (KBr) 3469, 2973, 1732, 1599, 1460, 759 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 887.5654, calcd for $C_{49}H_{78}N_2O_{12}$ 887.5628.

4.1.4.2. Compound 15m. Compound **15m** (101 mg, 36% for two steps) was prepared from compound **16** (340 mg, 0.315 mmol) according to the procedure used to prepare **15k**: $[\alpha]_D^{25}$ −24.0 (c 0.053, $CHCl_3$); MASS (ESI) m/z 887.5 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 7.46–7.56 (m, 4H), 7.37–7.45 (m, 2H), 7.27–7.34 (m, 1H), 6.90–6.98 (m, 2H), 5.01–5.10 (m, 1H), 4.79 (d, J = 4.20 Hz, 1H), 4.50–4.61 (m, 1H), 4.47 (d, J = 7.15 Hz, 1H), 4.23 (dd, J = 10.57, 3.57 Hz, 1H), 4.01–4.13 (m, 2H), 3.91 (d, J = 6.99 Hz, 1H), 3.42–3.61 (m, 3H), 3.32 (s, 3H), 3.23 (s, 3H), 3.09–3.36 (m, 2H), 2.97–3.07 (m, 1H), 2.79–2.90 (m, 1H), 2.61 (dd, J = 14.22, 4.27 Hz, 1H), 2.42–2.67 (m, 3H), 2.31 (s, 3H), 2.29 (s, 6H), 2.19–2.36 (m, 2H), 1.81–2.14 (m, 4H), 1.62–1.72 (m, 1H), 1.36 (s, 3H), 1.27 (d, J = 4.66 Hz, 3H), 1.25 (d, J = 4.66 Hz, 3H), 1.19 (d, J = 7.15 Hz, 3H), 1.15 (d, J = 7.15 Hz, 3H), 1.08–1.40 (m, 2H), 1.01 (s, 3H), 0.97 (d, J = 6.37 Hz, 3H), 0.96 (d, J = 6.53 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.9, 158.3, 140.8, 134.5, 128.9, 128.3, 126.9, 115.0, 104.0, 97.5, 81.0, 79.9, 78.0, 72.6, 71.0, 69.1, 67.9, 65.9, 65.7, 65.5, 49.9, 49.5, 46.2, 40.4, 39.4, 37.8, 35.5, 34.3, 31.0, 29.1, 21.4, 21.0, 18.2, 16.9, 15.3, 11.8; IR (KBr) 3469, 2973, 1731, 1611, 1459, 764 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 887.5656, calcd for $C_{49}H_{78}N_2O_{12}$ 887.5628.

4.1.4.3. Compound 15n. Tetrakis(triphenylphosphine)palladium (12 mg, 0.0107 mmol) was added to a solution of compound **15j** (100 mg, 0.107 mmol) and 3-(tributylstannyl)pyridine (0.059 mg, 0.160 mmol) and in toluene (5 mL) at room temperature. After stirring at reflux temperature for 18 h, the reaction mixture was cooled to room temperature. The solvent was removed in vacuo. The residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield compound **15n** (33 mg, 34%) as a colorless foam: MASS (ESI) m/z 888.6 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 8.81 (d, J = 1.9 Hz, 1H), 8.55 (dd, J = 4.6, 1.5 Hz, 1H), 7.83 (dt, J = 7.9, 2.0 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.33 (dd, J = 7.5, 5.2 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 4.69 (d, J = 4.6 Hz, 1H), 4.45 (d, J = 7.3 Hz, 1H), 4.12–4.21 (m, 1H), 3.99–4.07 (m, 5H), 3.68–3.72 (m, 1H), 3.44–3.54 (m, 2H), 3.29 (s, 3H), 3.22 (s, 3H), 3.18–3.21 (m, 1H), 2.96–3.03 (m, 1H), 2.71–2.81 (m, 2H), 2.60–2.67 (m, 1H), 2.46–2.55 (m, 1H), 2.24–2.43 (m, 12H), 1.81–1.93 (m, 2H), 1.62–1.74 (m, 2H), 1.47–1.55 (m, 2H), 1.19–1.36 (m, 19H), 1.14 (d, J = 6.9 Hz, 3H), 1.10 (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.2, 158.9, 148.0, 147.9, 136.2, 133.9, 130.6, 128.2, 123.5, 115.2, 102.7, 95.4, 80.4, 80.0, 78.8, 78.1, 72.8, 71.0, 70.5, 69.1, 67.1, 65.4, 64.7, 63.1, 60.9, 51.7, 50.0, 49.4, 41.8, 40.4, 37.4, 37.2, 35.2, 32.8, 30.6, 21.7, 21.3, 20.6, 18.1, 14.7, 14.1, 11.3, 10.9; HRMS (ESI/APCI-dual, $[M+H]^+$) found 888.5596, calcd for $C_{48}H_{77}N_3O_{12}$ 888.5580.

4.1.4.4. Compound 15o. Compound **15o** (27 mg, 28%) was prepared from compound **15j** (100 mg, 0.107 mmol) according to the procedure used to prepare **15k**: $[\alpha]_D^{31}$ −42.8 (c 0.057, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.63–8.66 (m, 1H), 7.94 (d, J = 9.1 Hz, 2H), 7.69–7.73 (m, 1H), 7.67 (s, 1H), 7.16–7.19 (m, 1H), 7.01 (d, J = 9.1 Hz, 2H), 4.69 (d, J = 5.0 Hz, 1H), 4.45 (d, J = 7.0 Hz, 1H), 4.13–4.18 (m, 1H), 4.01–4.07 (m, 3H), 3.71 (d, J = 5.0 Hz, 1H), 3.67 (s, 3H), 3.45–3.53 (m, 2H), 3.30 (s, 3H), 3.23–3.28 (m, 2H), 3.22 (s, 3H), 2.96–3.02 (m, 1H), 2.72–2.79 (m, 2H), 2.60–2.66 (m, 1H), 2.47–2.54 (m, 1H), 2.38 (br s, 3H), 2.24–2.35 (m, 8H), 1.81–1.93 (m, 2H), 1.64–1.75 (m, 2H), 1.46–1.54 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.23 (d, J = 5.8 Hz, 3H), 1.22 (s, 3H), 1.20–1.29 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 7.4 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.2, 159.5, 157.1, 149.6, 136.7, 132.4, 128.2, 121.5, 119.8, 114.8, 102.7, 95.4, 80.5, 80.0, 78.9, 78.6, 78.1, 72.8, 71.0, 70.5, 69.1, 67.0, 65.4, 64.9, 61.0, 51.7, 50.0, 49.4, 43.6, 41.8, 40.4, 37.5, 37.2, 35.2, 32.8, 30.6, 29.1, 21.7, 21.3, 20.7, 18.1, 14.7, 14.1, 11.3, 10.9; HRMS (ESI/APCI-dual, $[M+H]^+$) found 888.5620, calcd for $C_{48}H_{77}N_3O_{12}$ 888.5580.

4.2. Synthesis of 9-keto or 3-keto derivatives

4.2.1. Synthesis of compound 19

Tetra-*n*-butylammonium fluoride (1.0 M THF solution, 6.68 ml, 6.68 mmol) was added to a solution of compound **14a** (3.50 g, 3.34 mmol) in THF (50 mL) at room temperature. After stirring at room temperature for 18 h, the reaction was diluted with ethyl acetate (50 mL) and washed with brine (100 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 30:1:0.1) to yield the 2′,4″-hydroxy product (1.44 g, 53%), resembling a colorless foam. Acetic anhydride (349 mg, 3.42 mmol) was added to a solution of this 2′,4″-hydroxy product (1.40 g, 1.71 mmol) in acetone (10 mL) at room temperature. After stirring at room temperature for 18 h, the reaction was diluted with ethyl acetate (20 mL) and saturated $NaHCO_3$ (20 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was removed in vacuo to yield crude 2′-*O*-acetyl product as a colorless foam. Benzyl alcohol (1.56 ml, 15.1 mmol) was added to a solution of this 2′-*O*-acetyl product, pyridine (1.10 ml, 13.6 mmol) and triphosgene (671 mg, 2.26 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After stirring for 15 minutes at 0 °C, the reaction was quenched by adding distilled water (20 mL), and the aqueous layer was extracted with $CHCl_3$ (20 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield a 4″-*O*-benzyloxycarbonyl product (1.60 g, 94% from 2′,4″-hydroxy product) , resembling a yellowish foam. Hydrogen fluoride-pyridine (70%, 89.0 mg, 3.11 mmol) was added to a solution of this 4″-*O*-benzyloxycarbonyl product (1.55 g, 1.56 mmol) in THF (20 mL) at room temperature. After stirring at room temperature for 18 h, the reaction was neutralized with saturated $NaHCO_3$ (2.0 mL). The resulting mixture was diluted with ethyl acetate (10 mL) and then separated. The organic layer was dried over $MgSO_4$. The solvent was removed in vacuo to yield compound **17** (1.16 g, 84%), resembling a colorless foam.

Dess–Martin periodinane (818 mg, 1.92 mmol) was added to a solution of compound **17** (1.13 g, 1.28 mmol) in CH_2Cl_2 (20 mL) at room temperature. After stirring at room temperature for 1.0 h, the reaction was quenched with saturated $NaHCO_3$ (2.0 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography (*n*-hexane/acetone/Et_3N = 10:10:0.2) to yield a 9-keto product, resembling a brownish foam (810 mg, 72% yield). This material was dissolved in methanol (5 mL). After stirring at reflux temperature for 1 h, the reaction mixture was cooled to room temperature. After the addition of

5% palladium carbon (100 mg), the suspension was stirred in a hydrogen atmosphere at room temperature. After the removal of insoluble particles using filtration, the solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield compound **19** (280 mg, 44%) as a colorless foam: $[\alpha]_D^{25}$ −86.6 (*c* 0.139, $CHCl_3$); MASS (ESI) *m*/*z* 703.6 $[M+H]^+$; ^1H NMR ($CDCl_3$) δ 4.78 (d, *J* = 4.3 Hz, 1H), 4.46 (d, *J* = 7.3 Hz, 1H), 4.18 (ddd, *J* = 11.6, 5.5, 2.4 Hz, 1H), 4.01–4.08 (m, 1H), 3.92–3.98 (m, 2H), 3.77 (d, *J* = 7.3 Hz, 1H), 3.45–3.54 (m, 1H), 3.34 (s, 3H), 3.17–3.25 (m, 4H), 2.98–3.10 (m, 2H), 2.65–2.80 (m, 4H), 2.52–2.59 (m, 1H), 2.41–2.48 (m, 1H), 2.39 (d, *J* = 15.3 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 6H), 2.17–2.27 (m, 2H), 2.07 (dd, *J* = 14.3, 5.8 Hz, 1H), 1.66 (d, *J* = 13.4 Hz, 1H), 1.56 (dd, *J* = 15.3, 4.9 Hz, 1H), 1.48 (dd, *J* = 15.0, 4.6 Hz, 1H), 1.34 (s, 3H), 1.29 (d, *J* = 6.7 Hz, 3H), 1.24 (d, *J* = 6.1 Hz, 6H), 1.06–1.18 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 218.2, 176.5, 103.0, 96.0, 79.5, 78.9, 78.2, 72.9, 71.0, 68.9, 65.7, 63.2, 61.6, 56.7, 50.7, 49.5, 44.5, 44.3, 41.8, 41.4, 41.3, 40.8, 40.4, 36.8, 35.0, 28.8, 21.6, 21.5, 20.6, 18.7, 18.4, 16.7, 13.0, 9.6; IR (KBr) 3461, 2974, 1733, 1459, 730 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 703.4731, calcd for $C_{36}H_{66}N_2O_{11}$ 703.4739.

4.2.2. Synthesis of compound 20

Compound **14a** (10.0 g, 9.54 mmol) was dissolved in 1 M aqueous hydrochloric acid (50 mL) and EtOH (100 mL) at room temperature. After stirring at 60 °C for 2 h, the EtOH was removed in vacuo and the residue was washed with ethyl acetate (50 ml × 2) and then adjusted to pH 11 with 2 M NaOH solution and extracted with ethyl acetate (50 ml × 2). The organic layer was dried over $MgSO_4$, and removed in vacuo. The residue was used in the next reaction without further purification. Benzyl chloroformate (5.02 g, 29.4 mmol) was added to a solution of the residue in CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ (40 mL) at 0 °C. After stirring at room temperature for 0.5 h, the reaction was extracted with $CHCl_3$ (50 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 30:1:0.1) to yield compound **18** (4.81 g, 62% for two steps) as a colorless foam: MASS (ESI) *m*/*z* 815.4 $[M+H]^+$; ^1H NMR ($CDCl_3$) δ 7.30–7.41 (m, 10H), 5.13–5.21 (m, 4H), 4.66 (d, *J* = 7.4 Hz, 1H), 4.56 (dd, *J* = 10.3, 7.4 Hz, 1H), 4.50 (d, *J* = 9.9 Hz, 1H), 4.26–4.31 (m, 1H), 4.00–4.06 (m, 1H), 3.74 (d, *J* = 2.1 Hz, 1H), 3.41–3.52 (m, 2H), 3.08 (s, 3H), 2.70–2.83 (m, 2H), 2.59–2.66 (m, 1H), 2.45–2.58 (m, 3H), 2.26 (s, 6H), 2.23 (s, 3H), 2.13–2.19 (m, 1H), 2.05–2.13 (m, 1H), 1.97 (d, *J* = 7.0 Hz, 2H), 1.69–1.74 (m, 1H), 1.30–1.41 (m, 2H), 1.26 (s, 3H), 1.19–1.24 (m, 6H), 1.10 (dd, *J* = 14.2, 8.5 Hz, 1H), 1.02–1.05 (m, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.9, 155.8, 154.5, 135.7, 135.5, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 100.4, 87.5, 82.7, 78.8, 78.6, 75.7, 69.5, 69.4, 68.9, 63.3, 63.2, 58.8, 56.2, 49.7, 46.2, 44.4, 44.0, 40.7, 36.2, 35.5, 33.8, 30.9, 28.6, 21.2, 21.1, 19.4, 17.1, 14.6, 7.3; HRMS (ESI/APCI-dual, $[M+H]^+$) found 815.4709, calcd for $C_{44}H_{66}N_2O_{12}$ 815.4689.

Dess–Martin periodinane (3.72 mg, 8.74 mmol) was added to a solution of compound **18** (4.75 g, 5.83 mmol) in CH_2Cl_2 (30 mL) at room temperature. After stirring at room temperature for 1.0 h, the reaction was quenched with saturated $NaHCO_3$ (20 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 30:1:0.1) to yield a crude 3-keto product (5.00 g) as a colorless foam. After the addition of 5% palladium carbon (1.67 g), the suspension was stirred in a hydrogen atmosphere at room temperature for 18 h. After the removal of the insoluble particles using filtration, the solvent was removed in vacuo. The residue was dissolved in 1 M aqueous hydrochloric acid (20 mL) and washed with ethyl acetate (20 mL), then adjusted to pH 11 with 2 M NaOH solution, and extracted with ethyl acetate (50 ml × 2). The organic layer was separated and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 20:1:0.1) to yield compound **20** (1.06 g, 32% for two steps) as a colorless foam: MASS (ESI) *m*/*z* 545.3 $[M+H]^+$; ^1H NMR ($CDCl_3$) δ 3.86–4.50 (m, 4H for both diastereomers and 1H for one diastereomer), 3.18–3.56 (m, 4H for both diastereomers and 1H for one diastereomer), 2.91–2.99 (m, 4H for one diastereomer), 2.85 (s, 3H for one diastereomer), 2.13–2.76 (m, 14H for both diastereomers and 1H for one diastereomer), 1.59–2.01 (m, 3H for both diastereomers), 1.36 (m, 3H for both diastereomers), 1.16–1.31 (m, 11H for both diastereomers), 1.00 (d, *J* = 7.2 Hz, 3H for one diastereomer), 0.86 (d, *J* = 7.2 Hz, 3H for one diastereomer), 0.83 (d, *J* = 6.9 Hz, 3H for one diastereomer), 0.71 (d, *J* = 6.9 Hz, 3H for one diastereomer); ^{13}C NMR ($CDCl_3$) δ 206.6, 205.9, 172.5, 170.4, 104.8, 104.5, 84.9, 83.2, 81.4, 80.6, 79.0, 77.9, 70.4, 69.8, 69.5, 69.4, 66.4, 65.7, 65.3, 64.3, 61.2, 56.6, 55.7, 54.5, 52.8, 50.3, 50.0, 48.8, 48.1, 45.4, 44.1, 42.9, 42.0, 40.5, 40.3, 37.8, 37.0, 35.8, 34.9, 33.1, 30.7, 29.8, 29.6, 28.5, 21.3, 21.2, 20.2, 17.2, 15.9, 15.2, 14.9, 14.1, 12.3; HRMS (ESI/APCI-dual, $[M+H]^+$) found 545.3806, calcd for $C_{28}H_{52}N_2O_8$ 545.3796.

4.3. Synthesis of 9-amino derivatives

4.3.1. Synthesis of compound 22

Benzyl chloroformate (66.8 g, 392 mmol) was added to a suspention of compound **21** (131 g, 178 mmol) in $CHCl_3$ (630 mL) and $NaHCO_3$ (33.8 g, 402 mmol) in distilled water (630 mL) at 0 °C. After stirring at 0 °C for 1.0 h, the reaction was extracted. The organic layer was washed with brine (500 mL) and dried over $MgSO_4$. The solvent was removed in vacuo. The residue was recrystallized from diisopropyl ether (1050 mL) to yield 9-*N*-Cbz, 2′-*O*-Cbz product (135 g, 75%), resembling a colorless powder. 9-*N*-Cbz, 2′-*O*-Cbz product (10.0 g, 9.97 mmol) was dissolved in methanol (50 mL). After stirring at reflux temperature for 18 h, the reaction mixture was cooling to room temperature. The solvent was removed in vacuo. The residue was dissolved in DMF (50 mL). Chlorotriethylsilane (3.76 g, 24.9 mmol) and imidazole (5.09 g, 74.8 mmol) were added to the solution at room temperature. After stirring at room temperature for 18 h, the reaction mixture was diluted with ethyl acetate (50 mL) and *n*-hexane (50 mL) and washed with distilled water (200 ml × 3). The organic layer was separated and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography (hexane/acetone = 20:1) to yield compound **22** (8.53 g, 78%) as a colorless foam: ^1H NMR ($CDCl_3$) δ 7.25–7.37 (m, 5H), 6.06 (d, *J* = 9.9 Hz, 1H), 5.00–5.16 (m, 3H), 4.66–4.75 (m, 1H), 4.64 (d, *J* = 9.9 Hz, 1H), 4.06–4.22 (m, 2H), 3.60–3.82 (m, 3H), 3.46 (br s, 1H), 3.32 (s, 3H), 3.29–3.32 (m, 1H), 3.16–3.25 (m, 2H), 2.77–2.84 (m, 1H), 2.46–2.55 (m, 2H), 2.37 (d, *J* = 14.9 Hz, 1H), 2.21–2.31 (m, 1H), 2.18 (s, 6H), 2.12–2.16 (m, 1H), 1.88–1.98 (m, 1H), 1.74–1.82 (m, 1H), 1.58–1.71 (m, 2H), 1.43–1.55 (m, 2H), 0.85–1.31 (m, 49H), 0.53–0.70 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 179.1, 157.4, 137.4, 128.5, 128.3, 128.1, 127.7, 101.7, 95.7, 80.9, 77.4, 75.3, 74.7, 73.1, 72.9, 69.5, 67.9, 66.1, 65.9, 65.3, 63.4, 49.0, 45.0, 43.5, 40.9, 35.2, 34.1, 32.1, 29.2, 22.4, 21.6, 21.5, 21.2, 19.2, 18.6, 16.1, 13.9, 12.8, 11.2, 9.7, 7.0, 7.0, 5.5, 5.4, 5.1; IR (KBr) 3526, 2954, 1733, 1511, 1124, 741 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 1097.7110, calcd for $C_{57}H_{104}N_2O_{14}Si_2$ 1097.7099.

4.3.2. Synthesis of compound 23a

Compound **23a** (3.0 g, 16%) was prepared from compound **22** (25.0 g, 22.8 mmol) according to the procedure used to prepare **15a**: MASS (ESI) *m*/*z* 824.4 $[M+H]^+$; ^1H NMR ($CDCl_3$) δ 7.28–7.40 (m, 5H), 5.76 (br s, 1H), 5.03–5.15 (m, 2H), 4.69 (d, *J* = 4.3 Hz,

1H), 4.45 (d, J = 7.3 Hz, 1H), 4.19–4.30 (m, 2H), 4.00–4.13 (m, 2H), 3.65–3.71 (m, 1H), 3.48–3.59 (m, 3H), 3.23–3.33 (m, 4H), 2.97–3.05 (m, 1H), 2.76–2.85 (m, 1H), 2.71–2.76 (m, 1H), 2.39–2.55 (m, 3H), 2.28–2.31 (m, 6H), 2.23–2.36 (m, 1H), 2.20 (s, 3H), 1.89–2.17 (m, 4H), 1.71–1.79 (m, 1H), 1.63–1.69 (m, 1H), 1.50 (dd, J = 15.0, 4.6 Hz, 1H), 1.02–1.36 (m, 23H), 0.98 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.2, 156.8, 137.2, 128.5, 128.2, 128.0, 103.7, 96.4, 85.1, 79.2, 77.9, 75.1, 72.8, 70.9, 69.3, 66.4, 65.9, 65.3, 62.6, 61.8, 59.3, 56.1, 49.4, 45.2, 42.2, 41.3, 40.5, 39.3, 35.1, 33.1, 29.1, 25.6, 21.6, 21.2, 20.0, 18.0, 13.7, 10.1; HRMS (ESI/APCI-dual, $[M+H]^+$) found 824.5294, calcd for $C_{43}H_{73}N_3O_{12}$ 824.5267.

4.3.3. Synthesis of compound 23e

Compound **23e** (1.39 g, 16%) was prepared from compound **22** (10.0 g, 9.11 mmol) according to the procedure used to prepare **15a**: MASS (ESI/APCI-dual) m/z 944.6 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 7.27–7.38 (m, 10H), 5.80–5.90 (m, 1H), 5.22–5.28 (m, 1H), 5.10 (d, J = 12.4 Hz, 1H), 5.00–5.05 (m, 1H), 4.71–4.76 (m, 1H), 4.43–4.56 (m, 3H), 4.24–4.29 (m, 1H), 3.98–4.06 (m, 1H), 3.84–3.92 (m, 1H), 3.57–3.70 (m, 2H), 3.48–3.56 (m, 1H), 3.44 (d, J = 5.0 Hz, 1H), 3.33–3.37 (m, 1H), 3.27–3.30 (m, 1H), 3.26 (s, 3H), 2.90–3.01 (m, 2H), 2.82–2.89 (m, 1H), 2.75–2.82 (m, 1H), 2.44–2.53 (m, 1H), 2.20–2.42 (m, 11H), 2.18 (s, 3H), 2.07–2.13 (m, 1H), 1.85–2.02 (m, 3H), 1.61–1.68 (m, 1H), 1.32–1.45 (m, 2H), 1.16–1.30 (m, 13H), 1.04–1.15 (m, 9H), 0.97 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.0, 156.7, 138.0, 137.1, 128.4, 128.2, 127.9, 127.7, 127.5, 103.7, 96.7, 84.3, 79.9, 77.7, 77.3, 77.0, 76.8, 75.2, 73.2, 72.6, 70.9, 70.5, 69.6, 69.3, 66.3, 66.1, 65.2, 63.3, 60.3, 59.7, 49.3, 46.1, 40.9, 40.4, 39.9, 35.3, 31.9, 29.1, 26.2, 21.6, 21.2, 20.5, 19.6, 18.1, 14.4, 10.2; HRMS (ESI/APCI-dual, $[M+H]^+$) found 944.5873, calcd for $C_{51}H_{81}N_3O_{13}$ 944.5842.

4.3.4. Synthesis of compound 24a

A mixture of **23a** (3.0 g, 3.64 mmol) and 5% palladium carbon (1.0 g) was stirred in a hydrogen atmosphere at room temperature for 18 h. After the removal of the insoluble particles using filtration, the solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield compound **24a** (1.20 g, 48%) as a colorless foam: $[\alpha]_D^{26}$ −59.0 (c 0.248, $CHCl_3$); MASS (ESI) m/z 690.3 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 4.77 (d, J = 4.9 Hz, 1H), 4.43 (d, J = 6.7 Hz, 1H), 4.24 (dd, J = 6.1, 1.8 Hz, 1H), 4.13–4.18 (m, 2H), 4.03–4.09 (m, 1H), 3.50–3.60 (m, 3H), 3.31 (s, 3H), 3.27 (dd, J = 9.8, 7.3 Hz, 1H), 3.02 (t, J = 9.8 Hz, 1H), 2.70–2.90 (m, 3H), 2.30 (s, 6H), 2.26 (s, 3H), 2.05–2.54 (m, 6H), 1.82–1.89 (m, 1H), 1.61–1.70 (m, 2H), 1.57 (dd, J = 15.3, 4.9 Hz, 1H), 1.40 (dd, J = *14.6,* 5.5 Hz, 1H), 1.31 (d, J = 6.1 Hz, 3H), 1.28 (s, 3H), 1.24 (s, 3H), 1.19 (d, J = 7.3 Hz, 3H), 1.12–1.25 (m, 4H), 1.06–1.11 (m, 6H), 0.99 (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.7, 103.3, 95.5, 84.7, 79.2, 78.0, 74.9, 72.8, 71.0, 69.1, 65.6, 65.4, 62.1, 61.6, 59.8, 56.3, 49.4, 44.3, 42.5, 40.6, 40.4, 35.0, 30.9, 28.9, 26.1, 21.6, 21.3, 20.0, 18.9, 18.1, 13.8, 10.0; IR (KBr) 3444, 2976, 1734, 1460 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 690.4913, calcd for $C_{35}H_{67}N_3O_{10}$ 690.4899.

4.3.5. Synthesis of compound 24e

Compound **24e** (810 mg, 68%) was prepared from compound **23e** (2.40 g, 1.47 mmol) according to the procedure used to prepare **24a**: $[\alpha]_D^{25}$ −35.0 (c 0.221, $CHCl_3$); MASS (ESI) m/z 811.5 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 7.25–7.38 (m, 5H), 4.74 (m, 1H), 4.43–4.54 (m, 3H), 4.14–4.24 (m, 3H), 4.04 (m, 1H), 3.50–3.63 (m, 3H), 3.45 (m, 1H), 3.31 (s, 3H), 3.14–3.35 (m, 2H), 3.02 (m, 1H), 2.67–2.82 (m, 3H), 2.42–2.56 (m, 2H), 2.29 (s, 6H), 2.23 (s, 3H), 2.06–2.37 (m, 4H), 1.74–1.88 (m, 2H), 1.66 (m, 1H), 1.55 (dd, J = 15.23, 4.82 Hz, 1H), 1.30 (d, J = 6.22 Hz, 3H), 1.23 (s, 3H), 1.21 (s, 3H), 1.15–1.31 (m, 8H), 1.05 (m, 6H), 0.95 (d, J = 6.84 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.2, 137.9, 128.4, 127.7, 127.6, 103.8, 96.2, 84.3, 80.1, 78.0, 75.2, 73.2, 72.6, 71.0, 70.6, 69.6, 69.3, 65.8, 65.3, 62.6, 59.9, 59.5, 49.4, 45.7, 42.7, 40.4, 39.3, 35.2, 31.4, 29.0, 26.5, 21.6, 21.3, 19.9, 18.8, 18.3, 14.6, 10.2; IR (KBr) 3448, 2973, 1728, 1457, 737 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 810.5493, calcd for $C_{43}H_{75}N_3O_{11}$ 810.5474.

4.4. Synthesis of C12 substituted derivatives

4.4.1. Synthesis of compound 28

A mixture of **14b** (25.3 g, 21.7 mmol) and 20% $Pd(OH)_2$ (15.0 g) in THF (300 mL) was stirred in a hydrogen atmosphere at room temperature for 72 h. After the removal of the insoluble particles using filtration, the solvent was removed in vacuo to yield compound **25** (23.3 g, 100%) as a brownish foam: MASS (ESI) m/z 1077.7 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 4.81 (d, J = 4.1 Hz, 1H), 4.48–4.57 (m, 1H), 4.25–4.34 (m, 1H), 3.94–4.13 (m, 3H), 3.67 (d, J = 5.4 Hz, 1H), 3.58–3.64 (m, 1H), 3.38–3.52 (m, 2H), 3.29 (s, 3H), 3.23 (s, 3H), 3.10–3.26 (m, 3H), 2.80–2.88 (m, 1H), 2.60–2.77 (m, 3H), 2.44–2.53 (m, 1H), 2.31 (d, J = 14.9 Hz, 1H), 2.19 (br s, 9H), 2.03–2.09 (m, 1H), 1.83–1.95 (m, 2H), 1.60–1.67 (m, 1H), 1.45–1.52 (m, 2H), 1.27 (s, 3H), 1.23 (d, J = 6.6 Hz, 3H), 1.05–1.21 (m, 14H), 0.87–1.00 (m, 33H), 0.54–0.69 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 176.1, 125.5, 102.0, 95.6, 81.0, 80.2, 77.8, 73.5, 73.1, 67.7, 65.9, 65.2, 64.7, 61.8, 58.3, 50.0, 49.5, 44.6, 41.0, 40.2, 39.2, 36.0, 32.0, 30.3, 29.4, 29.3, 22.3, 21.9, 19.9, 18.8, 13.5, 12.6, 11.3, 7.1, 7.1, 7.0, 5.5, 5.5, 5.3, 5.2; HRMS (ESI/APCI-dual, $[M+H]^+$) found 1077.7609, calcd for $C_{55}H_{112}N_2O_{12}Si_3$ 1077.7596.

DBU (510 mg, 3.35 mmol) was added to a solution of compound **25** (3.01 g, 2.79 mmol) and bis(p-nitrophenyl)phosphorazidate (1.78 g, 5.59 mmol) in toluene (30 mL) at room temperature. After stirring at 50 °C for 3.0 h, the solvent was removed in vacuo and the residue was purified using silica gel chromatography (n-hexane/acetone/Et_3N = 50:1:0.1) to yield crude compound **26** (2.86 g) as a yellow foam. Hydrogen fluoride-pyridine (70%, 371 mg, 13.0 mmol) was added to a solution of compound **26** (2.86 g, 2.59 mmol) in THF (5.0 mL) at room temperature. After stirring at room temperature for 18 h, the reaction was neutralized with saturated $NaHCO_3$ (20 mL). The resulting mixture was diluted with ethyl acetate (20 mL) and then separated. The organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield compound **27** (1.89 g, 89% for two steps) as a colorless foam: HRMS (ESI/APCI-dual, $[M+H]^+$) found 760.5077, calcd for $C_{37}H_{69}N_5O_{11}$ 760.5066.

Triphenylphosphine (5.95 g, 22.7 mmol) was added to a solution of compound **27** (20.4 g, 18.9 mmol) and distilled water (408 mg, 22.7 mmol) in THF (200 mL) at room temperature. After stirring at room temperature for 24 h, the solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield compound **28** (10.4 g, 53%) as a colorless foam: $[\alpha]_D^{31}$ −49.7 (c 0.193, $CHCl_3$); MASS (ESI) m/z 734.5 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 4.84 (d, J = 4.2 Hz, 1H), 4.47 (d, J = 7.2 Hz, 1H), 4.23–4.29 (m, 1H), 4.18 (m, J = 9.9 Hz, 1H), 4.04–4.11 (m, 1H), 3.98 (dd, J = 11.7, 7.8 Hz, 1H), 3.80 (d, J = 6.8 Hz, 1H), 3.44–3.58 (m, 2H), 3.32 (s, 3H), 3.25 (s, 3H), 3.18–3.23 (m, 1H), 3.01 (d, J = 9.5 Hz, 1H), 2.95 (dd, J = 7.3, 3.0 Hz, 1H), 2.77–2.92 (m, 3H), 2.43–2.67 (m, 3H), 2.31 (s, 6H), 2.26–2.38 (m, 1H), 2.22 (s, 3H), 1.93–2.15 (m, 3H), 1.78–1.88 (m, 1H), 1.65–1.73 (m, 1H), 1.55 (dd, J = 15.1, 4.9 Hz, 1H), 1.34 (s, 3H), 1.28 (d, J = 6.4 Hz, 3H), 1.23 (s, 3H), 1.19 (d, J = 7.3 Hz, 3H), 1.13–1.26 (m, 5H), 1.10 (d, J = 7.3 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.9, 103.4, 95.7, 80.8, 80.0, 79.0, 78.6, 78.1, 72.8, 70.9, 69.0, 66.1, 65.5, 65.4, 62.8, 50.3, 49.5, 44.2, 40.4, 40.1, 39.7, 37.2, 35.2, 34.3, 33.6, 32.1, 29.0, 21.7, 21.4, 20.9, 18.1, 16.4, 13.0, 11.5; HRMS (ESI/APCI-dual, $[M+H]^+$) found 734.5188, calcd for $C_{37}H_{71}N_3O_{11}$ 734.5161.

4.4.2. General procedure for the synthesis of compounds 29, 31, 32

Sodium triacetoxyborohydride (132 mg, 0.625 mmol) was added to a solution of compound **28** (90 mg, 0.125 mmol) and acetaldehyde (28 mg, 0.625 mmol) in CH_2Cl_2 (1.0 mL). After stirring at room temperature for 1 h, the reaction was quenched by adding saturated $NaHCO_3$ (5 mL), and the aqueous layer was extracted using $CHCl_3$ (5 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield compound **29** (14 mg, 14%) as a colorless foam: $[\alpha]_D^{25}$ −31.0 (*c* 0.125, $CHCl_3$); MASS (ESI) *m*/*z* 790.4 $[M+H]^+$; ^1H NMR ($CDCl_3$) δ 4.86 (m, *J* = 3.9 Hz, 1H), 4.45 (d, *J* = 7.3 Hz, 1H), 4.39 (dd, *J* = 11.7, 2.8 Hz, 1H), 4.04–4.15 (m, 1H), 3.95 (dd, *J* = 11.7, 7.9 Hz, 1H), 3.83 (d, *J* = 7.3 Hz, 1H), 3.42–3.63 (m, 3H), 3.31 (s, 3H), 3.22 (s, 3H), 3.19–3.26 (m, 1H), 2.68–3.04 (m, 4H), 2.30 (s, 6H), 2.24 (s, 3H), 2.05–2.62 (m, 11H), 1.91–2.03 (m, 1H), 1.62–1.83 (m, 2H), 1.52 (dd, *J* = 14.9, 5.0 Hz, 1H), 1.33 (s, 3H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 7.3 Hz, 3H), 1.09–1.26 (m, 14H), 0.87–1.02 (m, 9H), 0.80 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.5, 103.9, 96.5, 80.8, 80.2, 78.6, 78.3, 78.1, 72.8, 70.9, 69.1, 65.6, 65.3, 63.0, 62.7, 50.1, 49.9, 49.5, 47.5, 46.5, 45.0, 44.2, 40.8, 40.4, 37.3, 35.4, 35.3, 34.0, 31.3, 29.3, 21.7, 21.4, 19.8, 18.1, 16.3, 14.5, 12.4, 11.7; HRMS (ESI/APCI-dual, $[M+H]^+$) found 790.5787, calcd for $C_{41}H_{79}N_3O_{11}$ 790.5787.

4.4.2.1. Compound 31. The general procedure used for compound **28** (90 mg, 0.125 mmol) was also used for compound **31** (22 mg, 20%), which resembled as a colorless foam: $[\alpha]_D^{25}$ −29.2 (*c* 0.200, $CHCl_3$); MASS (ESI) *m*/*z* 916.5 $[M+H]^+$; ^1H NMR ($CDCl_3$) δ 8.54 (d, *J* = 2.0 Hz, 2H), 8.52 (dd, *J* = 4.8, 1.5 Hz, 2H), 7.69–7.74 (m, 2H), 7.25–7.30 (m, 2H), 4.91 (m, *J* = 4.3 Hz, 1H), 4.41–4.47 (m, 2H), 4.29–4.35 (m, 1H), 4.22 (dd, *J* = 5.9, 3.7 Hz, 1H), 4.02–4.12 (m, 1H), 3.57–3.85 (m, 4H), 3.38–3.54 (m, 5H), 3.32 (s, 3H), 3.16 (s, 3H), 2.89–3.24 (m, 4H), 2.27 (s, 6H), 2.15–2.65 (m, 7H), 2.07 (s, 3H), 1.88–2.05 (m, 2H), 1.58–1.79 (m, 2H), 1.54 (dd, *J* = 15.1, 4.8 Hz, 1H), 1.31 (s, 3H), 1.27 (d, *J* = 6.1 Hz, 3H), 1.23 (s, 3H), 1.19 (d, *J* = 7.3 Hz, 3H), 1.10 (d, *J* = 7.2 Hz, 3H), 1.07–1.34 (m, 5H), 0.82–0.95 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 176.3, 150.3, 148.9, 136.7, 134.0, 130.9, 128.8, 123.5, 103.5, 96.2, 80.5, 80.1, 78.8, 78.1, 77.8, 72.8, 70.9, 69.0, 68.2, 65.6, 65.4, 62.7, 61.6, 56.2, 51.1, 50.2, 49.5, 44.7, 40.5, 40.4, 38.8, 37.1, 35.2, 34.7, 34.3, 30.4, 29.1, 28.9, 23.8, 23.0, 21.7, 21.3, 21.2, 18.2, 14.1, 13.0, 11.4, 11.0; HRMS (ESI/APCI-dual, $[M+H]^+$) found 916.6002, calcd for $C_{49}H_{81}N_5O_{11}$ 916.6005.

4.4.2.2. Compound 32. The general procedure used for compound **28** (100 mg, 0.136 mmol) was also used for compound **32** (55 mg, 36%), which resembled a colorless foam: $[\alpha]_D^{25}$ −34.1 (*c* 0.042, $CHCl_3$); MASS (ESI) *m*/*z* 1104.7 $[M+H]^+$; ^1H NMR ($CDCl_3$) δ 8.70 (d, *J* = 2.2 Hz, 2H), 8.51 (d, *J* = 2.0 Hz, 2H), 7.94 (t, *J* = 1.8 Hz, 2H), 7.51–7.59 (m, 4H), 7.14 (t, *J* = 8.6 Hz, 4H), 4.85 (d, *J* = 4.2 Hz, 1H), 4.57 (dd, *J* = 11.6, 1.9 Hz, 1H), 4.43 (d, *J* = 7.3 Hz, 1H), 4.18–4.26 (m, 1H), 3.98–4.07 (m, 1H), 3.85 (d, *J* = 14.8 Hz, 2H), 3.76 (d, *J* = 6.2 Hz, 1H), 3.58–3.67 (m, 1H), 3.52 (d, *J* = 13.7 Hz, 2H), 3.35–3.48 (m, 2H), 3.28 (s, 3H), 3.13–3.24 (m, 2H), 3.11 (s, 3H), 2.83–3.02 (m, 2H), 2.31 (s, 6H), 2.11 (s, 3H), 1.89–2.74 (m, 8H), 1.42–1.75 (m, 4H), 1.28 (s, 3H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.19 (s, 3H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.12–1.26 (m, 5H), 1.07 (d, *J* = 7.3 Hz, 1H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.6, 164.0, 162.0, 148.9, 147.2, 135.5, 134.9, 134.2, 133.6, 128.9, 128.8, 116.2, 116.0, 103.3, 95.7, 80.4, 79.9, 78.6, 78.0, 77.6, 72.7, 70.9, 68.9, 65.6, 65.4, 62.8, 56.1, 51.3, 50.3, 49.4, 44.6, 40.6, 40.3, 35.0, 35.0, 29.0, 21.6, 21.4, 21.1, 18.2, 13.5, 10.9; IR (KBr) 3437, 2973, 1728, 1608, 1515, 836, 724 cm^{-1}; HRMS (ESI/APCI-dual, $[M+H]^+$) found 1104.6442, calcd for $C_{61}H_{87}F_2N_5O_{11}$ 1104.6443.

4.4.3. Synthesis of compound 30

Sodium triacetoxyborohydride (132 mg, 0.625 mmol) was added to a solution of compound **28** (90 mg, 0.125 mmol) and acetaldehyde (5.5 mg, 0.125 mmol) in CH_2Cl_2 (1.0 mL). After stirring at room temperature for 0.5 h, nicotine aldehyde (20 mg, 0.189 mmol) was added to the reaction and stirred for 0.5 h. The reaction was quenched by adding saturated $NaHCO_3$ (5 mL), and the aqueous layer was extracted with $CHCl_3$ (5 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield compound **30** (36 mg, 35%) as a colorless foam: $[\alpha]_D^{25}$ −36.1 (*c* 0.398, $CHCl_3$); MASS (ESI) *m*/*z* 853.4 $[M+H]^+$; ^1H NMR ($CDCl_3$) δ 8.47–8.53 (m, 2H), 7.65–7.73 (m, 1H), 7.22–7.28 (m, 1H), 4.84–4.89 (m, 1H), 4.34–4.47 (m, 3H), 4.03–4.14 (m, 1H), 3.78–3.87 (m, 2H), 3.39–3.71 (m, 5H), 3.31 (s, 3H), 3.20–3.26 (m, 1H), 3.19 (s, 3H), 2.89–3.09 (m, 3H), 2.28 (s, 6H), 2.19 (s, 3H), 1.89–2.66 (m, 11H), 1.59–1.84 (m, 2H), 1.53 (dd, *J* = 15.0, 4.7 Hz, 1H), 1.32 (s, 3H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.22 (s, 3H), 1.18 (d, *J* = 7.5 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.98–1.31 (m, 8H), 0.91 (d, *J* = 7.5 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.4, 150.1, 148.5, 136.5, 134.9, 123.4, 103.7, 96.4, 80.7, 80.3, 78.7, 78.1, 72.8, 70.9, 69.0, 65.7, 65.3, 62.9, 62.8, 62.0, 56.1, 54.7, 50.6, 50.0, 49.5, 47.7, 44.8, 40.4, 37.2, 35.2, 34.8, 34.2, 34.1, 31.5, 30.4, 29.3, 21.7, 21.3, 21.3, 18.1, 16.8, 15.6, 12.7, 11.6, 11.0; HRMS (ESI/APCI-dual, $[M+H]^+$) found 853.5888, calcd for $C_{45}H_{80}N_4O_{11}$ 853.5896.

4.5. Synthesis of 4″-carbamate derivatives

4.5.1. Synthesis of compound 33a/e

Acetic anhydride (67 mg, 0.657 mmol) was added to a solution of compound **23a** (190 mg, 0.219 mmol) in acetone (5 mL) at room temperature. After stirring at room temperature for 6 h, the reaction was diluted with ethyl acetate (10 mL) and saturated $NaHCO_3$ (5 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was removed in vacuo to yield crude 2′-*O*-acetyl product resembling a colorless foam. 1,1′-Carbonyldiimidazole (107 mg, 0.657 mmol) was added to a suspension of the crude 2′-*O*-acetyl product in THF (5 mL)-DMF (1 mL) at room temperature. After stirring at room temperature for 2 h, the reaction was diluted with ethyl acetate (10 mL) and saturated NH_4Cl (5 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified using silica gel chromatography (*n*-hexane/acetone/Et_3N = 10:10:0.2) to yield compound **33a** (189 mg, 90%) as a colorless foam: ^1H NMR ($CDCl_3$) δ 8.08 (s, 1H), 7.27–7.40 (m, 5H), 7.11 (s, 1H), 5.50 (br s, 1H), 5.05–5.13 (m, 2H), 4.80–4.85 (m, 1H), 4.71–4.79 (m, 3H), 4.41–4.50 (m, 1H), 4.20–4.30 (m, 2H), 3.99–4.06 (m, 1H), 3.82 (br s, 1H), 3.57–3.70 (m, 2H), 3.53 (d, *J* = 5.8 Hz, 1H), 3.38 (s, 3H), 2.69–2.88 (m, 3H), 2.39–2.50 (m, 4H), 2.29 (s, 3H), 2.19 (s, 3H), 2.01–2.09 (m, 7H), 1.94–2.00 (m, 1H), 1.85–1.92 (m, 1H), 1.59–1.78 (m, 3H), 1.25–1.40 (m, 2H), 1.03–1.23 (m, 18H), 0.93–1.00 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 175.9, 169.8, 156.7, 148.7, 136.9, 130.9, 128.4, 128.2, 128.0, 117.0, 100.1, 95.7, 83.2, 83.0, 78.8, 77.2, 75.1, 72.8, 71.7, 68.3, 66.4, 63.4, 62.8, 62.4, 61.8, 59.3, 56.4, 49.4, 46.1, 44.2, 42.1, 41.4, 40.7, 38.8, 35.3, 33.3, 30.7, 29.3, 25.1, 21.4, 21.3, 21.1, 19.6, 17.6, 13.4, 9.7; HRMS (ESI/APCI-dual, $[M+H]^+$) found 960.5546, calcd for $C_{49}H_{77}N_5O_{14}$ 960.5540.

Compound **33e** (304 mg, 83% for two steps) was prepared from compound **23e** (325 mg, 0.344 mmol) according to the procedure used to prepare **33a**: MASS (ESI) *m*/*z* 1080.7 $[M+H]^+$; ^1H NMR ($CDCl_3$) δ 8.09 (s, 1H), 7.25–7.41 (m, 11H), 7.11 (s, 1H), 5.82–5.90 (m, 1H), 5.21–5.27 (m, 1H), 5.02–5.09 (m, 2H), 4.80–4.85 (m, 2H), 4.74 (d, *J* = 7.4 Hz, 1H), 4.70 (d, *J* = 9.9 Hz, 1H), 4.38–4.54 (m, 3H), 4.22 (d, *J* = 5.8 Hz, 1H), 3.42–3.67 (m, 5H), 3.32 (s, 3H), 2.92 (d,

J = 12.0 Hz, 1H), 2.78–2.84 (m, 1H), 2.69–2.76 (m, 1H), 2.33–2.44 (m, 2H), 2.29 (s, 6H), 2.27 (d, J = 6.6 Hz, 1H), 2.13–2.19 (m, 3H), 2.01–2.10 (m, 5H), 1.92 (d, J = 6.6 Hz, 1H), 1.79–1.85 (m, 1H), 1.74 (d, J = 12.4 Hz, 1H), 1.53 (d, J = 14.4 Hz, 1H), 1.26–1.42 (m, 3H), 1.16–1.22 (m, 3H), 0.95–1.15 (m, 21H); ^{13}C NMR ($CDCl_3$) δ 173.9, 169.8, 156.6, 148.7, 138.0, 137.1, 137.0, 131.0, 128.4, 128.4, 128.4, 127.9, 127.8, 127.5, 117.0, 100.2, 96.0, 83.0, 82.7, 75.1, 73.3, 72.7, 71.7, 70.4, 69.7, 68.4, 66.4, 63.2, 62.8, 60.2, 59.7, 49.3, 45.8, 40.7, 40.0, 38.7, 35.3, 31.7, 30.7, 25.4, 21.4, 21.3, 21.0, 20.1, 19.5, 17.7, 14.6, 9.9; HRMS (ESI/APCI-dual, $[M+H]^+$) found 1080.6130, calcd for $C_{57}H_{85}N_5O_{15}$ 1080.6115.

4.5.2. Synthesis of compound 35a

A mixture of **33a** (90 mg, 0.094 mmol) and amine **34** (17 mg, 0.077) was stirred at room temperature for 6 days. The solvent was removed in vacuo and the residue was purified using silica gel chromatography (n-hexane/acetone/Et_3N = 10:10:0.2) to yield a crude carbamate product resembling a colorless foam. This material was dissolved in methanol (5 mL). After stirring at reflux temperature for 1 h, the reaction mixture was cooling to room temperature. After the addition of 5% palladium carbon (50 mg), the suspension was stirred in a hydrogen atmosphere at room temperature for 18 h. After the removal of the insoluble particles using filtration, the solvent was removed in vacuo and the residue was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_4OH = 10:1:0.1) to yield compound **35a** (20 mg, 23% for two steps) as a colorless foam: $[\alpha]_D^{31}$ −72.6 (c 0.357, $CHCl_3$); MASS (ESI) m/z 938.9 $[M+H]^+$; ^{1}H NMR ($CDCl_3$) δ 7.20–7.46 (m, 2H), 6.93–6.99 (m, 1H), 6.90 (d, J = 8.6 Hz, 1H), 4.85 (d, J = 4.3 Hz, 1H), 4.52–4.58 (m, 1H), 3.99–4.51 (m, 4H), 3.85 (s, 3H), 3.28 (s, 3H), 2.92–3.70 (m, 7H), 2.39 (s, 6H), 2.37 (s, 3H), 2.16–2.90 (m, 14H), 1.33 (s, 3H), 1.23 (d, J = 6.8 Hz, 3H), 1.15 (s, 3H), 1.04 (d, J = 6.7 Hz, 3H), 0.86–2.15 (m, 24H); ^{13}C NMR ($CDCl_3$) δ 175.8, 157.2, 156.5, 131.6, 127.9, 127.7, 120.3, 110.6, 102.8, 96.1, 84.2, 78.9, 74.9, 73.2, 71.1, 68.4, 65.2, 63.5, 61.8, 61.5, 59.9, 56.4, 55.3, 51.0, 49.4, 48.9, 44.5, 42.8, 42.6, 40.7, 40.4, 38.9, 38.4, 35.6, 34.4, 30.8, 29.0, 26.2, 21.6, 21.0, 20.0, 18.9, 17.7, 16.7, 13.7, 12.6, 10.1; HRMS (ESI/APCI-dual, $[M+H]^+$) found 938.6417, calcd for $C_{49}H_{87}N_5O_{12}$ 938.6424.

4.5.3. Synthesis of compound 35e

Compound **35e** (65 mg, 71%) was prepared from compound **33e** (106 mg, 0.0859 mmol) according to the procedure used to prepare **35a**. Compound **35e** : $[\alpha]_D^{31}$ −26.3 (c 0.160, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.25–7.37 (m, 6H), 7.18–7.23 (m, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 5.57 (t, J = 4.6 Hz, 1H), 5.23–5.30 (m, 1H), 4.87 (d, J = 4.8 Hz, 1H), 4.44–4.55 (m, 5H), 4.34–4.42 (m, 4H), 3.84 (s, 3H), 3.63–3.69 (m, 2H), 3.54–3.60 (m, 1H), 3.47–3.52 (m, 2H), 3.38 (br s, 1H), 3.29 (s, 3H), 3.21–3.27 (m, 3H), 2.91–2.99 (m, 1H), 2.82–2.89 (m, 1H), 2.46–2.66 (m, 6H), 2.31–2.46 (m, 4H), 2.15–2.30 (m, 11H), 2.02–2.10 (m, 1H), 1.92–2.01 (m, 1H), 1.84–1.91 (m, 1H), 1.65–1.72 (m, 1H), 1.48–1.59 (m, 2H), 1.33–1.40 (m, 1H), 1.06–1.32 (m, 19H), 1.03 (d, J = 6.5 Hz, 3H), 0.90–0.99 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 157.2, 156.5, 137.9, 131.3, 128.4, 127.8, 127.7, 127.6, 120.2, 110.6, 103.6, 78.9, 75.1, 73.2, 70.9, 70.6, 69.6, 68.8, 65.1, 63.5, 62.7, 59.9, 55.3, 51.4, 49.5, 49.2, 45.7, 43.1, 40.3, 39.4, 35.7, 31.3, 29.0, 26.9, 21.4, 21.0, 20.1, 18.6, 17.7, 16.4, 14.2, 13.2, 10.4; HRMS (ESI/APCI-dual, $[M+H]^+$) found 1058.6998, calcd for $C_{57}H_{95}N_5O_{13}$ 1058.6999.

4.6. Biological experiments

The minimal inhibitory concentration (MIC) was determined using the broth microdilution method according to the Clinical and Laboratory Standards Institute's guidelines for *S. pnuemoniae*.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.08.007.

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