

Importance of the Structure of Vancomycin Binding Pocket in Designing Compounds Active Against Vancomycin-resistant Enterococci (VRE)

Yanxing Jia, Michèle Bois-Choussy, Adriano Malabarba, Cristina Brunati, Jieping Zhu

In memory of Professor Kenneth L. Rinehart

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Abstract 16-Membered *meta*, *para*-cyclophanes mimicking the vancomycin binding pocket (D–O–E ring) are designed and synthesized. The structural features of these biaryl ether containing macrocycles are: a) the deletion of the carboxyl group of vancomycin's central amino acid (amino acid D); b) the elongation of the *N*-terminal; c) the presence of lipidated aminoglucose at the D-ring. Cycloetherification by way of an intramolecular nucleophilic aromatic substitution reaction (S_NAr) is used as a key step for the construction of the macrocycle. Minimum inhibitory concentrations for all of the derivatives are measured using a standard microdilution assay. Compounds **2a**–**2c** and **3a**–**3c** displayed weak activities against resistant strain *Enterococcus faecalis* L560 and were inactive against *Enterococcus faecium* resistant strain L2215.

Keywords antibiotic, glycopeptide, intramolecular nucleophilic aromatic substitution, macrocycle, vancomycin, vancomycin-resistant enterococci (VRE)

Introduction

For over a quarter of century, vancomycin (Fig. 1) was one of the few antibiotics of the last resort for the treatment of infections due to methicillin-resistant *Staphylococcus aureus* and other Gram-positive organisms in patients

allergic to β -lactam antibiotics [1]. Unfortunately, resistance to drugs of the vancomycin family has been recognized in the late 1980s and the frequency of resistance has increased significantly over the past decades, reaching 30% among hospitalized patients in 2002 in the USA. Since vancomycin-resistant enterococci (VRE) also carry resistance to virtually all other known antibiotics, it represents a serious threat to public health [2, 3].

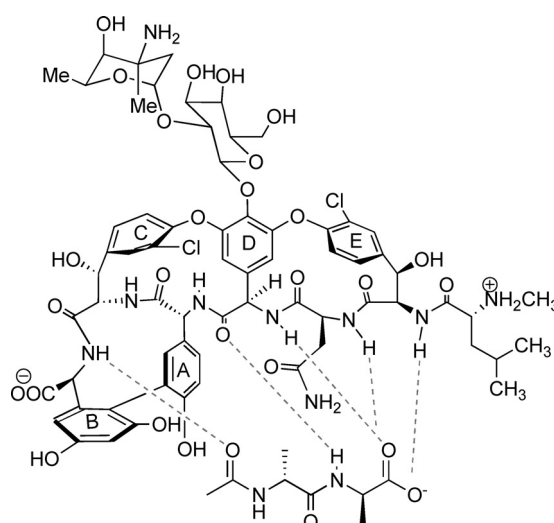


Fig. 1 Hydrogen bonding network of the vancomycin (**1**) and *N*-Ac-D-Ala-D-Ala complex.

J. Zhu (Corresponding author), **Y. Jia**, **M. Bois-Choussy**: Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France, E-mail: zhu@icsn.cnrs-gif.fr

A. Malabarba, **C. Brunati**: Vicuron Pharmaceuticals, Italy Research Center, via R. Lepetit, 34, I-21040 Gerenzano (VA), Italy

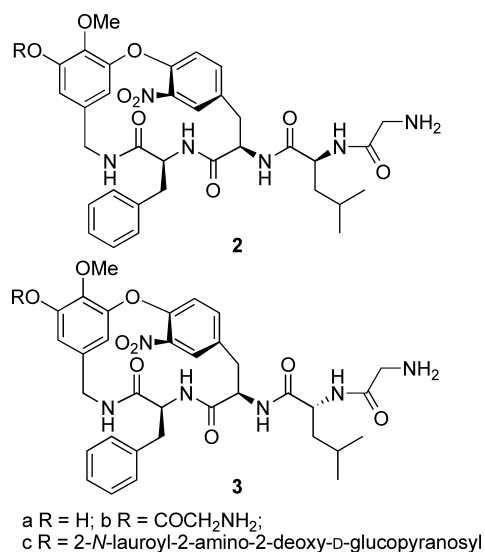
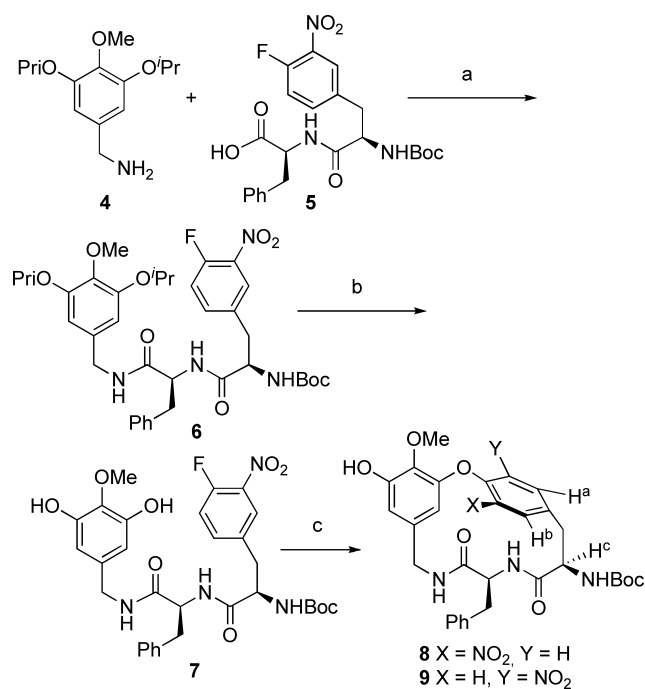


Fig. 2 Modified D–O–E ring of vancomycin.

Vancomycin acts by binding to the terminal D-alanyl-D-alanine (D-Ala-D-Ala) of the peptidoglycan precursors, thus blocking the final stages of the peptidoglycan synthesis. Bacteria become resistant to vancomycin by reprogramming the peptidoglycan termini from D-Ala-D-Ala dipeptide to D-Ala-D-Lac (D-alanyl-D-lactate) depsipeptide that binds only weakly to the drug. In fact, *in vitro* binding studies have shown that the affinity of vancomycin for *N*-Ac-D-Ala-D-Lac is about 1000 times less than its affinity for *N*-Ac-D-Ala-D-Ala, due to one missing hydrogen bond and the ground state repulsion between the two oxygen lone-pairs in the former complex. The reduced binding affinity translated into about 1000-fold reduced sensitivity of vancomycin-resistant bacteria to this drug (Fig. 1) [4].

Extensive structure-activity relationship (SAR) studies on vancomycin and teicoplanin type glycopeptide performed by both academic and industrial researchers indicated that the incorporation of a hydrophobic chain into the natural product is highly beneficial for activities against VRE [5, 6]. Indeed both oritavancin (LY333328) [7] and dalbavancin [8], that entered into late-stage clinical trials, contain a hydrophobic group. Two theories have been proposed to account for oritavancin's bioactivity against VRE [1–4]. Williams hypothesized that the presence of a lipid chain in the disaccharide part of vancomycin enhanced avidity for D-Ala-D-Lac by facilitating membrane anchoring and/or by promoting dimerization [9]. On the other hand, Kahne has recently advanced that oritavancin acts against VRE by direct interaction with the transglycosylase without substrate binding [10, 11] and



Scheme 1

Reagents and conditions: (a) HATU, DIPEA, DMF, 25°C, 12 hours, 89%; (b) i. BCl₃, CH₂Cl₂, 0°C, 1 hour; then MeOH; ii. Boc₂O, NaHCO₃, dioxane/H₂O (2:1), 25°C, 12 hours, 73% (2 steps); (c) CsF, DMSO, 25°C, 16 hours, 65%. HATU = *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, DIPEA = diisopropylethylamine.

evidences supportive to this view have been accumulated. We have been working on the design and synthesis of modified D–O–E ring of vancomycin and found that both the structure of the 16-membered macrocycle including the absolute configuration of the exo-cyclic stereocenter and the presence of a hydrophobic substituent (or a lipidated aminosugar) are important for the observed anti-VRE activities of our synthetic compounds [12–14]. As a continuation of this research project, we report herein the synthesis and biological activity evaluation of compound series 2, 3. The characteristic structural feature of these compounds are as follows: a) the deletion of the carboxyl group of vancomycin's central amino acid (amino acid D); b) the elongation of the *N*-terminal; c) the presence of lipidated aminoglucose at the D-ring.

Results and Discussion

Synthesis of Macrocycles 2 and 3

Synthesis of the 16-membered *meta*, *para*-cyclophane 8 was accomplished as shown in Scheme 1. Coupling of 3,5-

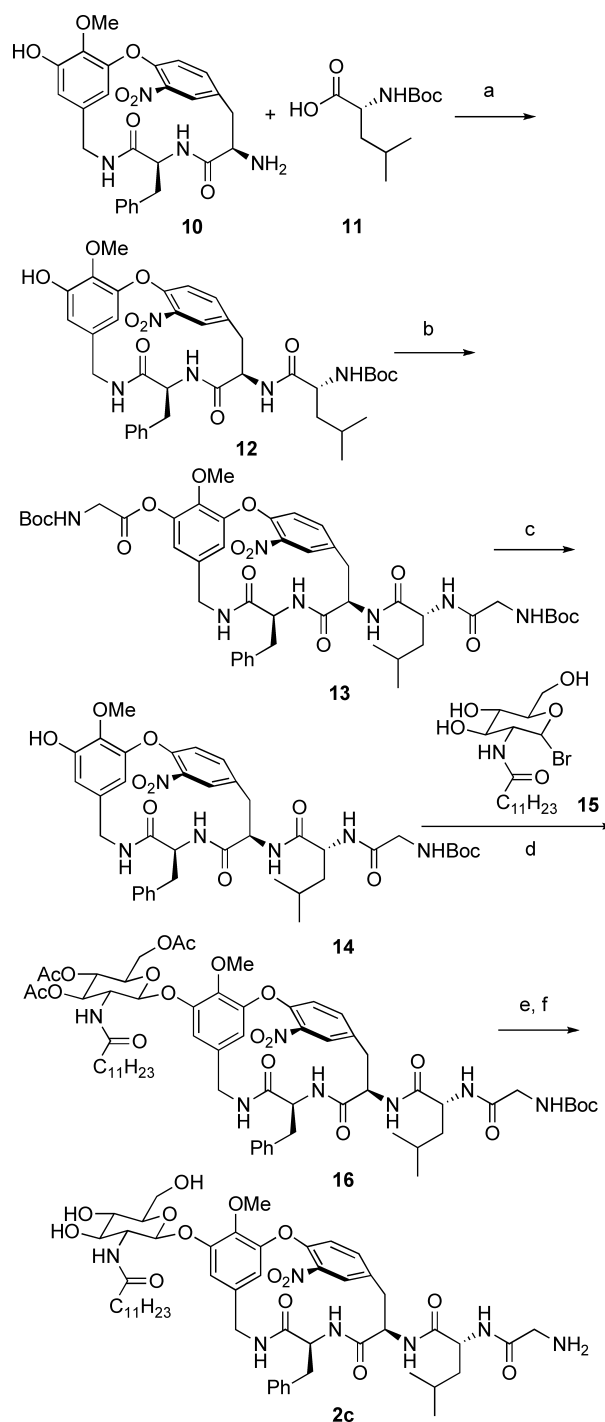
diisopropoxy-4-methoxybenzylamine (**4**) with *N*-Boc-*D*-(4-fluoro-3-nitro)phenylalanyl-*L*-phenylalanine (**5**) [14] afforded dipeptide **6** in 89% yield. Treatment of **6** with BCl_3 led to the simultaneous deprotection of the isopropyl ether and the *N*-Boc function. Re-introduction of the Boc group furnished phenol **7** in 73% overall yield. The key intramolecular $\text{S}_{\text{N}}\text{Ar}$ -based cycloetherification of **7** was performed in DMSO (concentration of substrate: 0.01 M) in the presence of CsF at room temperature [15, 16]. Two separable atropisomers **8** and **9** were isolated in 65% overall yield (ratio **8/9**=3/2). The absolute configuration of the planar chirality of **8** and **9** was deduced from detailed NOE studies. Thus, the NOE correlation between protons H^d/H^e was observed in the NOESY spectrum of **8**, indicative of the *P*-configuration of this atropstereoisomer. On the other hand, a H^b/H^c correlation, a characteristic of the *M*-atropstereoisomer, was observed for compound **9** [17].

Conversion of **8** to **2c** was shown in Scheme 2. Removal of *N*-Boc function under mild acidic conditions afforded the free amine **10** that was coupled directly with *D*-*N*-Boc Leu (**11**) to furnish, after saponification, the tripeptide **12** in 63% yield. The *N*-deprotection followed by coupling with 2 equivalents of *N*-Boc glycine provided compound **13** in 83% yield. Saponification of ester (LiOH, THF/ H_2O =3/1) afforded then the free phenol **14** in 98% yield. Koenigs-Knorr reaction [18] of **14** with freshly prepared 3,4,6-tri-*O*-acetyl-2-*N*-lauroyl-2-amino-2-deoxy-*D*-glucopyranosyl bromide (**15**) under phase transfer conditions (10% aqueous Na_2CO_3 , *n* Bu_4NHSO_4 , CH_2Cl_2 , rt) [19] afforded the desired β -glucoside **16** as the only isolable stereoisomer in 76% yield. Hydrolysis of acetate followed *N*-deprotection afforded compound **2c** in 80% yield. Compounds **2a** and **2b** (Fig. 2) were obtained by cleavage of *N*-protecting groups from **14** and **13**, respectively, under mild acidic conditions (TFA, CH_2Cl_2 , rt).

Since we have previously demonstrated that the stereochemistry of the exo-cyclic chiral center has great influence of macrocycle's bioactivities [12~14], compounds **3a**~**3c** (Fig. 2) have also been synthesized following the same synthetic scheme using *L*-leucine as coupling partner.

Antibiotic Activity Evaluation

Minimum inhibitory concentrations for these compounds as well as reference compounds (vancomycin, teicoplanin) are measured using a standard microdilution assay. The selected results are summarized in Table 1. For the sake of comparison, the anti VRE activities of previously synthesized compounds **17** and **18** (Fig. 3) were also enlisted in the same table [14]. As it is seen, compounds **2a**~**2c** and **3a**~**3c** displayed poor activities against resistant



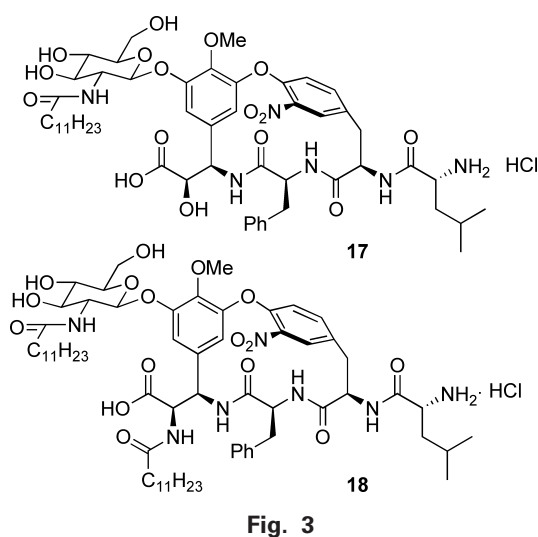
Scheme 2

Reagents and conditions: (a) i. HATU, DIPEA, DMF, 25°C, 12 hours; ii. LiOH, THF/ H_2O (3:1), 0°C, 1 hour, 63% (2 steps); (b) i. TFA, CH_2Cl_2 , 0°C, 1 hour; ii. HATU, DIPEA, DMF, 25°C, 12 hours, 83%; (c) LiOH, THF/ H_2O (3:1), 0°C, 1 hour, 98%; (d) **15**, (*n* Bu) $_4\text{NHSO}_4$, 10% aqueous $\text{Na}_2\text{CO}_3/\text{CH}_2\text{Cl}_2$ (1:1), 25°C, 4 hours, 76%; (e) LiOH, THF/ H_2O (3:1), 0°C, 1 hour; (f) TFA, CH_2Cl_2 , 0°C, 1 hour, 80% (2 steps).

Table 1 MICs ($\mu\text{g/ml}$) of selected macrocycles and reference compounds.^a

Entry	Cmpd.	<i>E. faecium</i>		<i>E. faecalis</i>	
		sensitive ^b	resistant ^c	sensitive ^d	resistant ^e
1	2a	>128	>128	128	128
2	2b	>128	>128	>128	128
3	2c	>128	>128	>128	128
4	3a	>128	>128	>128	128
5	3b	>128	>128	>128	128
6	3c	>128	>128	>128	128
7	17	64	32	8	8
8	18	128	32	8	8
9	Vancomycin	2	>128	1	>128
10	Teicoplanin	0.5	>128	0.125	64

^a MICs=Minimum Inhibitory Concentrations; ^b Bacterial strain L568 (isogenic of L569); ^c Bacterial strain L2215 clinical isolate Van-A; ^d Bacterial strain L559 (isogenic of L560); ^e Bacterial strain L560.



strain *Enterococcus faecalis* L560 and were inactive against clinically more relevant *E. faecium* resistant strain L2215.

Compounds **2** and **3** were designed based on following reasoning: a) the deletion of the carboxyl group of the vancomycin's central amino acid D (*cf.* Fig. 1) to avoid the unfavorable electrostatic interaction with the modified peptidoglycan terminal D-Ala-D-Lac [20, 21]; b) the N-terminal was elongated in order to introduce an additional hydrogen-bonding with D-Ala-D-Lac [22]. In order to explore the possible conformational effect, hence the relative three-dimensional orientation of NHs, compound **2** and **3** having D-Leucine (found in vancomycin), and D-leucine, respectively, were synthesized; the glycine was attached to leucine terminal in order to incorporate

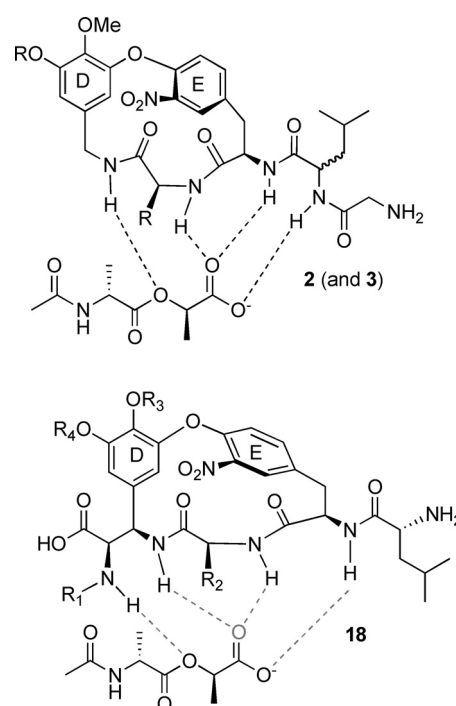


Fig. 4 Hypothetical complexes of **2(3)**/D-Ala-D-Lac and **18**/D-Ala-D-Lac.

potentially a fourth NH group that could interact with the carboxyl group of the D-Ala-D-Lac. Overall a hypothetical interaction between compound **2** (or **3**) and N-Ac-D-Ala-D-Lac was depicted in Fig. 4; c) a lipidated aminoglucose was incorporated at the D-ring in order to explore the hydrophobic effect. For the sake of clarity, the hypothetical binding between **18** and N-Ac-D-Ala-D-Lac was also

depicted in the Fig. 4.

In contrast to compounds **17** and **18** (Fig. 3) that displayed potent activities against VRE (entry 7, 8), both **2** and **3** were relatively impotent against the same resistant strains. Since both **2c** (**3c**) and **17** (**18**) contained the same lipidated aminoglucose at the same position and they differed only in the structure of the central amino acid (segment D), the present results reinforced our previous conclusion regarding the importance of the structure of the macrocycle in searching for compounds active against VRE.

Conclusion

In summary, we have designed and synthesized molecules of a general structure (**2** and **3**) in which the carboxylic acid group of vancomycin's central amino acid D was deleted and the *N*-terminal was elongated. These compounds including **2c** and **3c** with a lipidated aminoglucose at the D-ring displayed only weak activity against *E. faecalis* resistant strain and were inactive against clinically more relevant *E. faecium* resistant strain. We have previously demonstrated, by detailed SAR studies, the importance of the hydrophobic chain in the active compounds, we shown here that the structure of macrocycle is equally important in searching for compounds active against VRE.

Experimental

General Methods

Melting points were recorded using Reichert melting point apparatus. Infrared spectra were recorded on a Nicolet 205 FT-IR spectrometer. NMR spectra were performed on a Bruker AC-300 (300 MHz) spectrometer. Mass spectra were obtained from an AEI MS-9 using electron spray (ES). Optical rotation was measured on a Jasco P-100 polarimetre.

Compound 4

To a solution of 3,5-diisopropoxy-4-methoxy benzyl alcohol (1.21 g, 4.76 mmol) [17] in toluene/CH₂Cl₂ (3 : 1, 24 ml) was added PBr₃ (0.48 ml, 4.76 mmol) at 0°C, and the mixture was stirred at r.t. for overnight. The reaction was quenched with water, and extracted with ether. The ether layer was washed with sat. NaHCO₃ and brine successively, dried over Na₂SO₄. The solvent was concentrated and the residue was purified by column chromatograph (SiO₂, eluant: heptane/EtOAc=15/1) to give the bromide (1.38 g, 92%). IR (CHCl₃) 3426, 3025, 2929, 2856, 1746, 1685,

1584, 1521, 1492, 1434, 1369, 1345, 1234, 1165, 1112, 1034, 849 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.59 (s, 2H), 4.52 (hept, *J*=6.2 Hz, 2H), 4.42 (s, 2H), 3.81 (s, 3H), 1.35 (d, *J*=6.2 Hz, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 152.0, 141.5, 132.8, 110.4, 71.9, 60.6, 34.5, 22.4; MS (ESI): *m/z* 237 (M-Br)⁺.

To a solution of the above bromide in anhydrous DMSO (5.0 ml) was added NaN₃ (464 mg, 7.14 mmol). After stirred at 30°C for 24 hours under Ar, the reaction was cooled to room temperature and diluted with H₂O and extracted with EtOAc. The organic phase was washed with H₂O and brine, dried over anhydrous Na₂SO₄. The solvent was removed and the residue was purified by flash chromatography (SiO₂, eluant: heptane/EtOAc=35 : 1) to afford azide (1.08 g, 88%). IR (CHCl₃) 3526, 3025, 3018, 2980, 2937, 2101, 1590, 1499, 1435, 1385, 1374, 1363, 1333, 1321, 1209, 1137, 1115, 1080, 1005, 905 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.51 (s, 2H), 4.53 (hept, *J*=6.2 Hz, 2H), 4.22 (s, 2H), 3.82 (s, 3H), 1.35 (d, *J*=6.2 Hz, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 152.2, 141.4, 130.5, 109.7, 72.0, 60.6, 55.1, 22.4; HRMS (ESI): *m/z* calcd for C₁₄H₂₁N₃O₃Na (M+Na)⁺ 302.1481; found 302.1476.

To a solution of azide (300 mg, 1.08 mmol) in THF (10 ml) was added Ph₃P (423 mg, 1.61 mmol) and H₂O (194 μl, 10.8 mmol) at room temperature. After being stirred for 20 hours at the same temperature, The solvent was removed under vacuum and the residue was purified by flash column chromatography (SiO₂, eluant: CH₂Cl₂/MeOH=60/1 to 10/1) to afford 3,5-diisopropoxy-4-methoxy benzyl amine (**4**, 235 mg, 86%). ¹H NMR (300 MHz, CDCl₃) δ 6.50 (s, 2H), 4.50 (hept, *J*=6.2 Hz, 2H), 3.77 (s, 3H), 3.73 (s, 2H), 1.82 (s, 2H), 1.31 (d, *J*=6.2 Hz, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 152.0, 140.2, 138.3, 108.5, 71.7, 60.5, 46.5, 22.3; MS (ESI): *m/z* 507 (2M+H)⁺; 237 (M+H-NH₃)⁺.

Compound 6

To a solution of amine **4** (330 mg, 1.30 mmol) and acid **5** [23] (500 mg, 1.05 mmol) in DMF (15 ml) was added DIPEA (368 μl, 2.1 mmol) and HATU (599 mg, 1.58 mmol). The reaction mixture was stirred at room temperature for 12 hours before it was extracted with EtOAc. The organic phase was washed with 5% aqueous HCl, saturated NaHCO₃, brine, dried over Na₂SO₄, and concentrated under vacuum. The residue was purified by flash column chromatography (SiO₂, eluant: CH₂Cl₂/MeOH=80/1) to afford **6** (663 mg, 89%). [α]_D²³ +2.3 (*c* 1.0, CHCl₃); IR (CHCl₃) 3427, 3029, 2981, 1669, 1590, 1498, 1437, 1352, 1231, 1211, 1160, 1115, 1082, 1006, 906 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.77

(d, $J=5.9$ Hz, 1H), 7.27~7.06 (m, 8H), 6.72 (br s, 1H), 6.38 (s, 2H), 5.48 (br s, 1H), 4.66 (q, $J=7.4$ Hz, 1H), 4.46 (hept, $J=6.2$ Hz, 2H), 4.38 (m, 1H), 4.22 (d, $J=4.4$ Hz, 2H), 3.76 (s, 3H), 3.11~3.03 (m, 3H), 2.85~2.78 (m, 1H), 1.34~1.29 (m, 21H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.0, 170.8, 155.4, 154.4 (d, $J=263$ Hz), 151.9, 140.5, 136.6, 136.5, 134.1, 133.5, 132.9, 129.3 (2C), 128.6 (2C), 127.0, 126.8, 118.1 (d, $J=20$ Hz), 109.2, 109.0 (2C), 80.2, 71.6 (2C), 60.4, 55.1, 54.7, 43.9, 43.7, 38.6, 28.2 (3C), 22.2 (4C); HRMS (ESI): m/z calcd for $\text{C}_{37}\text{H}_{47}\text{N}_4\text{O}_9\text{FNa}$ ($\text{M}+\text{Na}$) $^+$ 733.3225; found 733.3223.

Compound 7

To a solution of **6** (790 mg, 1.11 mmol) in CH_2Cl_2 (22 ml) was added BCl_3 (1 M in CH_2Cl_2 , 22.2 ml, 22.2 mmol) at 0°C . After being stirred for 1 hour at 0°C , the reaction was quenched by slow addition of anhydrous MeOH. The volatile was evaporated and the residue was dissolved in dioxane/ H_2O (2 : 1, 45 ml), and then NaHCO_3 (932 mg, 11.1 mmol) and Boc_2O (271 mg, 1.22 mmol) was added. After being stirred at room temperature for overnight, the mixture was diluted with H_2O and acidified with 5% HCl to pH 3~4, and extracted with EtOAc. The combined organic layer was washed with H_2O , brine, dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by flash column chromatography (SiO_2 , eluant: $\text{CH}_2\text{Cl}_2/\text{MeOH}=50/1$) to afford **7** (510 mg, 73%). Mp 122~124 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{23} +15.4$ (c 0.70, CHCl_3); IR (CHCl_3) 3526, 3297, 3024, 1670, 1603, 1539, 1499, 1458, 1353, 1252, 1167, 1061, 996, 835 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.68 (m, 1H), 7.65 (d, $J=9.4$ Hz, 1H), 7.46 (br s, 1H), 7.27~7.03 (m, 9H), 6.22 (s, 2H), 5.51 (d, $J=7.9$ Hz, 1H), 4.91 (q, $J=7.2$ Hz, 1H), 4.44 (m, 1H), 4.37 (dd, $J=6.4$, 15.1 Hz, 1H), 3.98 (dd, $J=4.1$, 15.1 Hz, 1H), 3.83 (s, 3H), 3.14~2.93 (m, 3H), 2.43 (dd, $J=8.7$, 13.6 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.9, 171.5, 155.7, 154.4 (d, $J=265$ Hz), 149.5 (3C), 136.9 (d, $J=6.6$ Hz), 136.4 (d, $J=7.7$ Hz), 136.0, 133.9, 133.4, 129.3 (2C), 128.7 (2C), 127.2, 126.7, 118.3 (d, $J=21$ Hz), 107.0 (2C), 80.9, 67.1, 60.8, 54.7, 43.5, 38.7, 36.8, 28.1 (3C); HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{35}\text{N}_4\text{O}_9\text{FNa}$ ($\text{M}+\text{Na}$) $^+$ 649.2286; found 649.2304.

Compounds 8 and 9

A solution of **7** (475 mg, 0.76 mmol) and anhydrous CsF (238 g, 76 mmol) in dry DMSO (76 ml) was stirred at room temperature for 16 hours. The reaction mixture was diluted with saturated aqueous NH_4Cl , acidified with 5% HCl to pH 4, and extracted with EtOAc. The combined organic layer was washed with H_2O , brine, dried over Na_2SO_4 , and concentrated under vacuum. The residue was

purified by flash column chromatography (SiO_2 , eluant: $\text{CH}_2\text{Cl}_2/\text{MeOH}=100/1$ to 60/1) to afford **8** (180 mg, 39%) and **9** (120 mg, 27%). For compound **8**: Mp 163~165 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{23} +107$ (c 0.90, CHCl_3); IR (CHCl_3) 3525, 3434, 3020, 2937, 1717, 1664, 1595, 1536, 1513, 1456, 1437, 1353, 1242, 1167, 1088, 1044, 994, 856 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.78 (d, $J=2.3$ Hz, 1H), 7.35 (dd, $J=2.3$, 8.7 Hz, 1H), 7.24~7.07 (m, 6H), 6.87 (d, $J=8.7$ Hz, 1H), 6.77 (d, $J=8.7$ Hz, 1H), 6.27 (d, $J=1.9$ Hz, 1H), 5.53 (d, $J=7.2$ Hz, 1H), 5.40 (d, $J=1.9$ Hz, 1H), 5.23 (d, $J=7.5$ Hz, 1H), 4.71 (dd, $J=9.0$, 15.4 Hz, 1H), 4.66 (m, 1H), 4.26 (ddd, $J=5.3$, 8.7, 9.4 Hz, 1H), 3.95 (s, 3H), 3.52 (dd, $J=4.9$, 13.6 Hz, 1H), 3.25 (dd, $J=3.0$, 15.4 Hz, 1H), 2.91 (dd, $J=5.3$, 13.2 Hz, 1H), 2.80 (dd, $J=3.0$, 13.6 Hz, 1H), 2.71 (dd, $J=9.4$, 13.2 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.9, 169.2, 155.2, 152.1, 149.6, 148.7, 141.9, 137.0, 136.1, 135.5, 134.1, 133.7, 129.3 (2C), 128.7 (2C), 127.2, 125.9, 125.2, 108.7, 105.9, 81.5, 61.8, 60.6, 55.3, 41.9, 40.2, 37.3, 28.4 (3C); HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{34}\text{N}_4\text{O}_9\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 629.2223; found 629.2217. For compound **9**: Mp 160~163 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 7.86 (s, 1H), 7.49 (d, $J=7.5$ Hz, 1H), 7.32~7.20 (m, 7H), 6.89 (d, $J=7.8$ Hz, 1H), 6.33 (s, 1H), 5.59 (br s, 1H), 5.32 (s, 1H), 4.96 (br s, 1H), 4.75 (dd, $J=9.2$, 15.3 Hz, 1H), 4.74 (br s, 1H), 4.45 (m, 1H), 4.06 (s, 3H), 3.64 (dd, $J=4.1$, 13.7 Hz, 1H), 3.32 (d, $J=16.3$ Hz, 1H), 3.08 (dd, $J=3.9$, 12.8 Hz, 1H), 2.90 (d, $J=12.8$ Hz, 1H), 2.81 (dd, $J=10.3$, 12.7 Hz, 1H), 1.53 (s, 9H); HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{34}\text{N}_4\text{O}_9\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 629.2223; found 629.2213.

Compound 12

To a solution of compound **8** (60 mg, 0.1 mmol) in CH_2Cl_2 (4.0 ml) was added TFA (2.0 ml) at 0°C . After being stirred at the same temperature for 1.0 hour, the reaction mixture was concentrated to dryness under vacuum to afford compound **10** which was directly used for next reaction. To a solution of amine **10** and *D*-*N*-Boc Leucine **11** (55 mg, 0.24 mmol) in DMF (4 ml) was added DIPEA (174 μl , 1.0 mmol) and HATU (95 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 12 hours before it was extracted with EtOAc. The organic phase was washed with 5% aqueous HCl, saturated NaHCO_3 , brine, dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by flash column chromatography (SiO_2 , eluant: $\text{CH}_2\text{Cl}_2/\text{MeOH}=50/1$) to afford tripeptide (80 mg). To a solution of above tripeptide in THF/ H_2O (3/1, 6.0 ml) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (17 mg, 0.40 mmol) at 0°C . After being stirred for 1.0 hour at 0°C , the reaction mixture was acidified with 5% HCl to pH 3~4 and extracted with EtOAc. The combined organic phase was washed with

brine, dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by flash column chromatography (SiO_2 , eluant: $\text{CH}_2\text{Cl}_2/\text{MeOH}=40/1$) to afford **12** (45 mg, 63%). Mp 150~153°C; $[\alpha]_{\text{D}}^{23} +69.4$ (c 0.50, CHCl_3); IR (CHCl_3) cm^{-1} 3622, 3436, 3017, 2976, 1664 (brs), 1594, 1535, 1496, 1457, 1369, 1232, 1201, 1167, 1046, 877; ^1H NMR (300 MHz, CDCl_3) δ 8.28 (s, 1H), 7.67 (d, $J=8.7$ Hz, 1H), 7.45 (dd, $J=2.3, 8.7$ Hz, 1H), 7.32~7.13 (m, 5H), 6.98 (d, $J=8.7$ Hz, 1H), 6.80 (d, $J=8.3$ Hz, 1H), 6.39 (d, $J=1.5$ Hz, 1H), 5.65 (dd, $J=3.4, 9.4$ Hz, 1H), 5.47 (d, $J=1.5$ Hz, 1H), 5.00 (m, 1H), 4.97 (d, $J=7.2$ Hz, 1H), 4.80 (dd, $J=9.4, 15.8$ Hz, 1H), 4.37 (m, 1H), 4.25 (dd, $J=7.2, 14.3$ Hz, 1H), 4.04 (s, 3H), 3.57 (dd, $J=4.9, 13.6$ Hz, 1H), 3.41 (dd, $J=3.4, 15.8$ Hz, 1H), 2.95 (dd, $J=5.6, 13.6$ Hz, 1H), 2.84 (dd, $J=3.0, 13.6$ Hz, 1H), 2.78 (dd, $J=9.0, 13.6$ Hz, 1H), 1.84~1.54 (m, 3H), 1.49 (s, 9H), 0.99 (t, $J=6.8$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.0, 171.0, 168.5, 156.5, 152.2, 149.6, 148.1, 142.7, 137.0, 136.1, 135.3, 134.3, 134.1, 129.4 (2C), 128.8 (2C), 127.3, 125.8, 125.7, 108.2, 105.5, 81.0, 61.9, 55.3, 53.9, 53.4, 42.0, 40.3, 40.0, 37.1, 28.4 (3C), 25.1, 22.9, 22.4; HRMS (ESI): m/z calcd for $\text{C}_{37}\text{H}_{45}\text{N}_5\text{O}_{10}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 742.3064; found 742.3040.

Compound 13

To a solution of compound **12** (45 mg, 0.063 mmol) in CH_2Cl_2 (2.0 ml) was added TFA (1.0 ml) at 0°C. After being stirred at the same temperature for 1.0 hour, the reaction mixture was concentrated to dryness under vacuum to afford amine which was directly used for next reaction. To a solution of amine and *N*-Boc glycine (26 mg, 0.15 mmol) in DMF (3 ml) was added DIPEA (44 μl , 0.25 mmol) and HATU (60 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 12 hours before it was extracted with EtOAc. The organic phase was washed with 5% aqueous HCl, saturated NaHCO_3 , brine, dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by flash column chromatography (SiO_2 , eluant: $\text{CH}_2\text{Cl}_2/\text{MeOH}=40/1$) to afford **13** (48 mg, 83%). Mp 131~133°C; $[\alpha]_{\text{D}}^{23} +59.2$ (c 0.50, CHCl_3); IR (CHCl_3) 3434, 3352, 3028, 2932, 2854, 1773, 1666, 1509, 1436, 1368, 1315, 1281, 1156, 998, 857 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.03 (d, $J=1.5$ Hz, 1H), 7.43 (m, 2H), 7.27~7.19 (m, 4H), 7.08 (d, $J=6.8$ Hz, 2H), 6.98 (d, $J=8.3$ Hz, 1H), 6.90 (brs, 1H), 6.77~6.70 (m, 2H), 6.53 (s, 1H), 5.86 (s, 1H), 5.61 (brs, 1H), 5.24 (m, 1H), 4.89 (m, 1H), 4.60 (m, 1H), 4.52 (dd, $J=8.1, 15.1$ Hz, 1H), 4.28~4.19 (m, 3H), 3.93 (s, 3H), 3.79~3.60 (m, 3H), 3.54 (dd, $J=4.5, 13.6$ Hz, 1H), 2.95~2.79 (m, 3H), 1.80~1.65 (m, 3H), 1.46 (s, 9H), 1.40 (s, 9H), 0.99 (d, $J=6.4$ Hz, 3H), 0.94 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ

172.6, 171.6, 171.3, 168.9, 168.5, 156.5, 155.8, 153.4, 147.9, 143.9, 142.7, 140.3, 137.4, 136.0, 134.5, 134.1, 129.7 (2C), 128.7 (2C), 127.2, 126.1, 125.5, 115.2, 111.5, 80.8, 80.5, 61.7, 54.9, 54.6, 53.6, 42.5, 41.6, 40.0, 39.5, 36.5, 29.8, 28.4 (3C), 28.3 (3C), 25.1, 23.1, 21.7; HRMS (ESI): m/z calcd for $\text{C}_{46}\text{H}_{60}\text{N}_7\text{O}_{14}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 956.4018; found 956.4022.

Compound 14

To a solution of **13** (40 mg, 0.043 mmol) in $\text{THF}\cdot\text{H}_2\text{O}$ (3/1, 4.0 ml) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (18 mg, 0.43 mmol) at 0°C. After being stirred for 1.0 hour at 0°C, the reaction mixture was acidified with 5% HCl to pH 3~4 and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by flash column chromatography (SiO_2 , eluant: $\text{CH}_2\text{Cl}_2/\text{MeOH}=40/1$) to afford **14** (35 mg, 98%). Mp 158~160°C; $[\alpha]_{\text{D}}^{23} +52.3$ (c 1.00, CHCl_3); IR (CHCl_3) 3410, 3020, 2936, 1664 (br s), 1593, 1535, 1512, 1456, 1368, 1244, 1220, 1168, 1089, 1045, 994, 897, 857 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD) δ 8.25 (d, $J=2.1$ Hz, 1H), 7.38 (dd, $J=2.3, 8.5$ Hz, 1H), 7.24~7.07 (m, 5H), 7.06 (d, $J=8.5$ Hz, 1H), 6.37 (d, $J=1.9$ Hz, 1H), 5.47 (s, 1H), 4.67 (m, 1H), 4.64 (d, $J=15.8$ Hz, 1H), 4.50 (dd, $J=5.7, 8.9$ Hz, 1H), 4.42 (t, $J=7.0$ Hz, 1H), 3.90 (s, 3H), 3.79 (d, $J=4.7$ Hz, 2H), 3.46 (d, $J=15.8$ Hz, 1H), 3.43 (dd, $J=5.7, 14.3$ Hz, 1H), 3.03 (dd, $J=2.6, 14.3$ Hz, 1H), 2.83 (d, $J=7.0$ Hz, 2H), 1.75~1.58 (m, 3H), 1.41 (s, 9H), 0.97 (d, $J=6.2$ Hz, 3H), 0.94 (d, $J=6.2$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.6, 173.0, 172.6, 170.6, 158.5, 154.3, 152.2, 149.4, 144.2, 137.7, 137.4, 137.0, 135.7, 135.6, 130.7 (2C), 129.4 (2C), 127.9, 127.1, 127.0, 110.0, 105.9, 80.7, 61.7, 56.3, 55.7, 53.7, 44.6, 42.6, 41.2, 40.8, 36.8, 28.7 (3C), 26.1, 23.4, 22.2; HRMS (ESI): m/z calcd for $\text{C}_{39}\text{H}_{48}\text{N}_6\text{O}_{11}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 799.3279; found 799.3289.

Compound 16

To a solution of 1,3,4,6-*tetra-O*-acetyl-2-*N*-lauroyl-2-amino-2-deoxy-2-D-glucopyranose (85 mg, 0.16 mmol) in AcOH (2 ml) was added 33% HBr/AcOH (0.9 ml) at room temperature [14]. After being stirred for 3 hours at room temperature, the reaction mixture was diluted with ice-water and it was extracted with CH_2Cl_2 . The combined organic phases were washed with cooled aqueous NaHCO_3 and brine. The solvent was concentrated to about 1 ml under vacuum below 30°C and the resulting solution was immediately used for next reaction. To the above solution was added compound **14** (18 mg, 0.023 mmol), 10% aqueous Na_2CO_3 (1.0 ml) and catalytic amount of $(n\text{Bu})_4\text{NH}\text{SO}_4$. After being stirred at room temperature for 4 hours, the reaction mixture was acidified with citric

acid to pH 4~5 and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 . The combined organic phases were washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by flash column chromatography (SiO_2 , eluant: $\text{CH}_2\text{Cl}_2/\text{MeOH}=40/1$) to afford **16** (22 mg, 76%). Mp $>230^\circ\text{C}$; $[\alpha]_{\text{D}}^{23} +50.8$ (*c* 1.00, CHCl_3); IR (CHCl_3) 3431, 2928, 2855, 1747, 1667, 1537, 1508, 1435, 1368, 1258, 1161, 1049, 1045, 1040, 902, 857 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD) δ 8.27 (d, $J=2.3$ Hz, 1H), 7.40 (dd, $J=2.3, 8.7$ Hz, 1H), 7.24~7.06 (m, 6H), 6.71 (d, $J=1.9$ Hz, 1H), 5.71 (s, 1H), 5.35 (dd, $J=9.4, 10.6$ Hz, 1H), 5.28 (d, $J=8.7$ Hz, 1H), 5.06 (t, $J=9.8$ Hz, 1H), 4.67 (d, $J=15.8$ Hz, 1H), 4.67 (dd, $J=2.3, 5.7$ Hz, 1H), 4.51 (dd, $J=6.0, 9.0$ Hz, 1H), 4.41 (t, $J=6.8$ Hz, 1H), 4.30~4.14 (m, 3H), 3.98 (m, 1H), 3.84 (s, 3H), 3.78 (d, $J=6.4$ Hz, 2H), 3.51 (d, $J=15.8$ Hz, 1H), 3.44 (dd, $J=5.7, 14.0$ Hz, 1H), 3.05 (dd, $J=2.3, 14.0$ Hz, 1H), 2.83 (t, $J=6.8$ Hz, 2H), 2.17 (t, $J=7.5$ Hz, 2H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.75~1.50 (m, 5H), 1.42 (s, 9H), 1.35~1.20 (br s, 16H), 0.98 (d, $J=6.0$ Hz, 3H), 0.94 (d, $J=6.0$ Hz, 3H), 0.87 (t, $J=6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.6, 175.6, 173.1, 172.7, 172.3, 171.7, 171.3, 170.6, 158.5, 154.6, 152.2, 149.2, 144.1, 139.5, 137.9, 137.4, 135.9, 135.6, 130.7 (2C), 129.4 (2C), 127.9, 127.2, 126.9, 111.2, 109.5, 100.6, 80.8, 73.9, 73.2, 70.2, 63.3, 62.0, 56.3, 55.7, 55.3, 53.6, 44.6, 42.7, 41.2, 40.8, 37.5, 36.8, 33.1, 30.8 (2C), 30.6, 30.5 (3C), 30.3, 28.8 (3C), 27.0, 26.1, 23.8, 23.4, 22.2, 20.8, 20.7, 14.5; HRMS (ESI): m/z calcd for $\text{C}_{63}\text{H}_{87}\text{N}_7\text{O}_{19}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 1268.5954; found 1268.5955.

Compound 2c

To a solution of compound **16** (20 mg, $1.6\ \mu\text{mol}$) in $\text{THF}/\text{H}_2\text{O}$ (3/1, 2.0 ml) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (16 mg, 0.38 mmol) at 0°C . After being stirred for 1.0 hour at 0°C , the reaction mixture was acidified with 5% HCl to pH 3~4 and extracted with EtOAc . The combined organic phase was washed with brine, dried over Na_2SO_4 , and concentrated under vacuum to afford compound acid, which proved to be of sufficient purity and was used directly for next step. To a solution of above acid in CH_2Cl_2 (1.0 ml) was added TFA (0.5 ml) at 0°C . After being stirred at the same temperature for 1.0 hour, the reaction mixture was concentrated to dryness under vacuum to afford compound **2c** (13 mg, 80%). Mp $>230^\circ\text{C}$; $[\alpha]_{\text{D}}^{23} +57.6$ (*c* 0.30, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 8.30 (d, $J=2.3$ Hz, 1H), 7.42 (dd, $J=2.3, 8.7$ Hz, 1H), 7.26~7.10 (m, 5H), 7.09 (d, $J=8.7$ Hz, 1H), 6.72 (d, $J=1.9$ Hz, 1H), 5.59 (s, 1H), 5.08 (d, $J=8.3$ Hz, 1H), 4.69 (dd, $J=2.3, 5.7$ Hz, 1H), 4.58 (d, $J=15.8$ Hz, 1H), 4.46 (t, $J=6.8$ Hz, 1H), 4.42 (dd, $J=5.7, 9.0$ Hz, 1H), 3.93 (dd, $J=8.3,$

10.2 Hz, 1H), 3.89 (m, 1H), 3.86 (s, 3H), 3.71~3.57 (m, 3H), 3.56 (d, $J=15.8$ Hz, 1H), 3.46~3.38 (m, 4H), 3.07 (dd, $J=2.3, 14.3$ Hz, 1H), 2.87 (d, $J=7.2$ Hz, 2H), 2.24 (t, $J=7.5$ Hz, 2H), 1.80~1.55 (m, 5H), 1.39~1.20 (m, 16H), 1.01 (d, $J=6.0$ Hz, 3H), 0.97 (d, $J=6.0$ Hz, 3H), 0.87 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.9, 175.7, 173.2, 170.3, 168.6, 154.2, 152.9, 149.1, 144.2, 139.1, 138.6, 137.5, 136.1, 135.3, 130.6 (2C), 129.4 (2C), 127.9, 127.1, 127.0, 110.7, 108.1, 101.2, 78.5, 75.8, 72.2, 62.7, 62.0, 57.4, 56.0, 55.5, 55.1, 42.7, 41.5, 41.0 (2C), 37.7, 36.6, 33.1, 30.8 (2C), 30.7, 30.6, 30.5, 30.4, 27.0, 26.1, 23.8, 23.3, 22.1, 14.5; HRMS (ESI): m/z calcd for $\text{C}_{52}\text{H}_{73}\text{N}_7\text{O}_{14}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 1042.5113; found 1042.5106.

Compound 2a

Mp $155\sim 157^\circ\text{C}$; $[\alpha]_{\text{D}}^{23} +58.4$ (*c* 0.25, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 8.27 (d, $J=2.1$ Hz, 1H), 7.41 (dd, $J=2.3, 8.5$ Hz, 1H), 7.26~7.12 (m, 5H), 7.11 (d, $J=8.5$ Hz, 1H), 6.35 (d, $J=2.1$ Hz, 1H), 5.38 (d, $J=2.1$ Hz, 1H), 4.69 (dd, $J=2.4, 6.0$ Hz, 1H), 4.57 (d, $J=15.8$ Hz, 1H), 4.46 (t, $J=7.2$ Hz, 1H), 4.40 (dd, $J=5.5, 9.1$ Hz, 1H), 3.91 (s, 3H), 3.87 (s, 2H), 3.47 (d, $J=15.8$ Hz, 1H), 3.43 (dd, $J=6.0, 14.3$ Hz, 1H), 3.06 (dd, $J=2.4, 14.3$ Hz, 1H), 2.87 (d, $J=7.2$ Hz, 1H), 2.86 (d, $J=7.2$ Hz, 1H), 1.80~1.65 (m, 3H), 1.02 (d, $J=6.0$ Hz, 3H), 0.98 (d, $J=6.0$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.6, 173.2, 170.2, 168.8, 154.1, 152.4, 149.1, 144.4, 138.5, 137.5, 136.9, 136.0, 135.3, 130.6 (2C), 129.4 (2C), 127.9, 127.1, 126.8, 109.7, 105.0, 61.6, 55.9, 55.6, 55.4, 42.6, 41.5, 41.0, 40.9, 36.6, 26.1, 23.3, 22.0; HRMS (ESI): m/z calcd for $\text{C}_{34}\text{H}_{41}\text{N}_6\text{O}_9$ ($\text{M}+\text{H}$) $^+$ 677.2935; found 677.2932.

Compound 2b

Mp $173\sim 175^\circ\text{C}$; $[\alpha]_{\text{D}}^{23} +68.9$ (*c* 0.35, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 8.36 (d, $J=2.3$ Hz, 1H), 7.46 (dd, $J=2.3, 8.5$ Hz, 1H), 7.26~7.12 (m, 6H), 6.70 (d, $J=2.0$ Hz, 1H), 5.88 (d, $J=2.0$ Hz, 1H), 4.69 (dd, $J=2.5, 6.0$ Hz, 1H), 4.61 (d, $J=16.1$ Hz, 1H), 4.48 (t, $J=7.0$ Hz, 1H), 4.42 (dd, $J=5.3, 9.0$ Hz, 1H), 4.20 (s, 2H), 3.96 (s, 3H), 3.87 (s, 2H), 3.60 (d, $J=16.1$ Hz, 1H), 3.45 (dd, $J=6.0, 14.3$ Hz, 1H), 3.10 (dd, $J=2.5, 14.3$ Hz, 1H), 2.88 (d, $J=7.0$ Hz, 2H), 1.81~1.62 (m, 3H), 1.01 (d, $J=6.2$ Hz, 3H), 0.97 (d, $J=6.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.7, 173.4, 170.3, 168.7, 167.2, 154.2, 148.3, 144.7, 144.1, 140.9, 138.9, 137.5, 136.8, 135.5, 130.6 (2C), 129.5 (2C), 127.9, 127.3, 126.8, 115.6, 112.5, 62.0, 56.1, 55.5, 55.2, 42.2, 41.5, 41.0 (2C), 36.6, 30.8, 26.1, 23.3, 22.1; HRMS (ESI): m/z calcd for $\text{C}_{36}\text{H}_{44}\text{N}_7\text{O}_{10}$ ($\text{M}+\text{H}$) $^+$ 734.3150; found 734.3160.

Compound 3a

Mp 165~167°C; $[\alpha]_D^{23} +161.8$ (*c* 0.30, MeOH); $^1\text{H NMR}$ (300 MHz, CD_3OD) δ 8.31 (d, $J=2.3$ Hz, 1H), 7.41 (dd, $J=2.3, 8.3$ Hz, 1H), 7.26~7.09 (m, 6H), 6.37 (d, $J=2.2$ Hz, 1H), 5.46 (d, $J=2.1$ Hz, 1H), 4.68 (dd, $J=2.6, 5.2$ Hz, 1H), 4.62 (d, $J=15.8$ Hz, 1H), 4.50 (t, $J=7.4$ Hz, 1H), 4.43 (dd, $J=5.7, 8.3$ Hz, 1H), 3.89 (s, 3H), 3.68 (d, $J=15.8$ Hz, 1H), 3.48 (d, $J=15.8$ Hz, 1H), 3.45 (d, $J=15.8$ Hz, 1H), 3.47~3.42 (m, 1H), 3.07 (dd, $J=2.6, 14.3$ Hz, 1H), 2.86 (dd, $J=5.6, 13.2$ Hz, 1H), 2.76 (dd, $J=8.3, 13.2$ Hz, 1H), 1.79~1.63 (m, 3H), 1.05 (d, $J=6.4$ Hz, 3H), 1.00 (d, $J=6.0$ Hz, 3H); $^{13}\text{C NMR}$ (75 MHz, CD_3OD) δ 173.9, 172.9, 170.8, 168.1, 154.4, 152.5, 149.1, 144.4, 137.7, 137.6, 137.0, 135.7, 135.1, 130.6 (2C), 129.5 (2C), 128.0, 127.2, 127.1, 109.9, 105.3, 61.7, 56.4, 56.0, 53.7, 42.4, 41.5, 40.7, 39.8, 36.6, 26.0, 23.3, 22.5; HRMS (ESI): m/z calcd for $\text{C}_{34}\text{H}_{41}\text{N}_6\text{O}_9$ (M+H)⁺ 677.2935; found 677.2938.

Compound 3b

Mp 167~169°C; $[\alpha]_D^{23} +139.1$ (*c* 0.40, MeOH); $^1\text{H NMR}$ (300 MHz, CD_3OD) δ 8.37 (d, $J=2.3$ Hz, 1H), 7.46 (dd, $J=2.3, 8.5$ Hz, 1H), 7.26~7.09 (m, 6H), 6.72 (d, $J=2.1$ Hz, 1H), 5.96 (d, $J=2.0$ Hz, 1H), 4.69 (dd, $J=2.8, 5.4$ Hz, 1H), 4.67 (d, $J=16.2$ Hz, 1H), 4.49 (t, $J=8.1$ Hz, 1H), 4.46 (dd, $J=5.7, 8.1$ Hz, 1H), 4.20 (s, 2H), 3.94 (s, 3H), 3.69 (d, $J=16.1$ Hz, 1H), 3.56 (d, $J=16.1$ Hz, 1H), 3.51~3.45 (m, 1H), 3.48 (d, $J=16.2$ Hz, 1H), 3.09 (dd, $J=2.8, 14.3$ Hz, 1H), 2.87 (dd, $J=5.7, 13.3$ Hz, 1H), 2.77 (dd, $J=8.1, 13.3$ Hz, 1H), 1.79~1.64 (m, 3H), 1.05 (d, $J=6.0$ Hz, 3H), 1.00 (d, $J=6.0$ Hz, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 174.1, 173.1, 170.7, 168.1, 167.2, 154.5, 148.3, 144.7, 144.2, 141.0, 138.2, 137.5, 136.5, 135.3, 130.6 (2C), 129.5 (2C), 128.0, 127.5, 126.8, 115.7, 112.8, 62.0, 56.4, 56.0, 53.8, 42.0, 41.4, 41.0, 40.7, 40.0, 36.6, 26.0, 23.3, 22.5; HRMS (ESI): m/z calcd for $\text{C}_{36}\text{H}_{44}\text{N}_7\text{O}_{10}$ (M+H)⁺ 734.3150; found 734.3163.

Compound 3c

Mp >230°C; $[\alpha]_D^{23} +124.2$ (*c* 0.40, MeOH); $^1\text{H NMR}$ (300 MHz, CD_3OD) δ 8.30 (d, $J=2.3$ Hz, 1H), 7.42 (dd, $J=2.3, 8.7$ Hz, 1H), 7.26~7.08 (m, 6H), 6.74 (s, 1H), 5.66 (s, 1H), 5.10 (d, $J=8.7$ Hz, 1H), 4.69 (dd, $J=2.6, 5.3$ Hz, 1H), 4.63 (d, $J=15.8$ Hz, 1H), 4.49 (t, $J=7.9$ Hz, 1H), 4.45 (dd, $J=5.7, 8.3$ Hz, 1H), 3.93~3.87 (m, 2H), 3.84 (s, 3H), 3.72~3.37 (m, 8H), 3.06 (dd, $J=2.3, 13.9$ Hz, 1H), 2.86 (dd, $J=5.7, 13.6$ Hz, 1H), 2.76 (dd, $J=8.3, 13.6$ Hz, 1H), 2.24 (t, $J=7.5$ Hz, 2H), 1.78~1.53 (m, 5H), 1.38~1.20 (m, 16H), 1.06 (d, $J=5.7$ Hz, 3H), 1.03 (d, $J=5.7$ Hz, 3H), 0.87 (t, $J=6.8$ Hz, 3H); $^{13}\text{C NMR}$ (75 MHz, CD_3OD) δ 176.9, 174.1, 173.0, 170.7, 168.1, 154.5, 152.9, 149.1, 144.2, 139.3, 138.0, 137.6, 135.9, 135.1, 130.6 (2C), 129.5 (2C),

128.0, 127.3, 127.0, 111.0, 108.5, 101.2, 78.5, 75.7, 72.2, 62.8, 62.0, 57.4, 56.3, 56.0, 53.8, 42.5, 41.5, 40.7, 40.0, 37.7, 36.6, 33.1, 30.8 (2C), 30.6, 30.5 (2C), 30.4, 26.9, 26.0, 23.8, 23.3, 22.5, 14.5; HRMS (ESI): m/z calcd for $\text{C}_{52}\text{H}_{74}\text{N}_7\text{O}_{14}$ (M+H)⁺ 1020.5294; found 1020.5276.

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