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Design and Synthesis of Simple Macrocycles Active Against Vancomycin-Resistant *Enterococci* (VRE)

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Abstract: 16-membered *meta*,*para*-cyclophanes mimicking the vancomycin binding pocket (D–O–E ring) were designed and synthesized. The structural key features of these biaryl ether containing macrocycles are (1) the presence of β-amino-α-hydroxy acid or α,β-diamino acid as the *C*-terminal component of the cyclopeptide and (2) the presence of a hydrophobic chain or lipidated aminoglucose at the appropriate position. Cycloetherification by an intramolecular nucleophilic aromatic substitution reaction (S_NAr) is used as the key step for the construction of the macrocycle. The atropselectivity of this ring-closure reaction is found to be sensitive to the peptide backbone and chemoselective cyclization (phenol versus primary amine) is achievable. Glycosylation of phenol was realized with freshly prepared 3,4,6-tri-*O*-acetyl-2-*N*-lauroyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide under phase-transfer conditions. Minimum inhibitory concentrations for all of the derivatives are measured by using a standard microdilution assay, and potent bioactivities against both sensitive and resistant strains are found for some of these compounds (MIC (minimum inhibitory concentration) = 4 μg mL^{-1} against VRE). From these preliminary SAR studies, it was anticipated that both the presence of a hydrophobic substituent and an appropriate structure of the macrocycle were required for this series of compounds to be active against VRE.

Keywords: antibiotics · biaryl ether · glycopeptides · macrocycles · S_NAr · vancomycin

Introduction

Staphylococcus aureus, a major cause of potentially life-threating infections acquired in health care settings and in the community, developed resistance to most classes of antimicrobial agents soon after their introduction into clinical use. As the prevalence of antibiotic resistance spread during the 1980's, vancomycin became one of the few antibiotics used as a 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 was recognized in the late 1980's and the frequency of resistance has increased significantly over the past decades, reaching 30% among hospitalized patients in 2002 in the USA. As vancomycin-resistant *enterococci* (VRE) also carry resistance to virtually all other known antibiotics, it represents a serious threat to public health.[2]

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 of the peptidoglycan termini from D-Ala-D-Ala dipeptide to D-Ala-D-Lac (D-alanyl-D-lactate) depsipeptide, which binds only weakly to the drug.[3] 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

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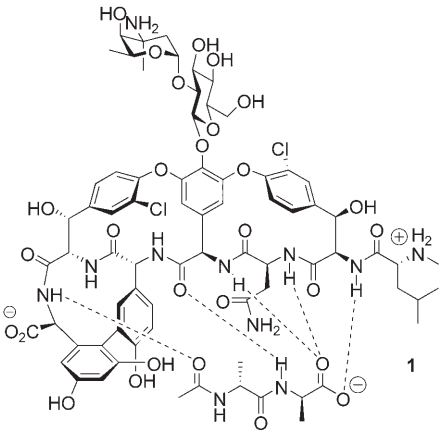
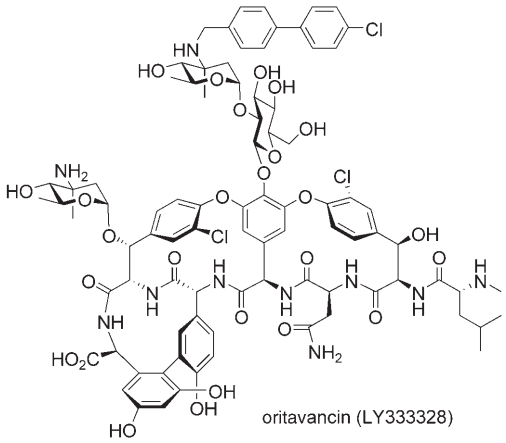
into about a 1000-fold reduced sensitivity of vancomycin-resistant bacteria to this drug (Scheme 1).[4,5]

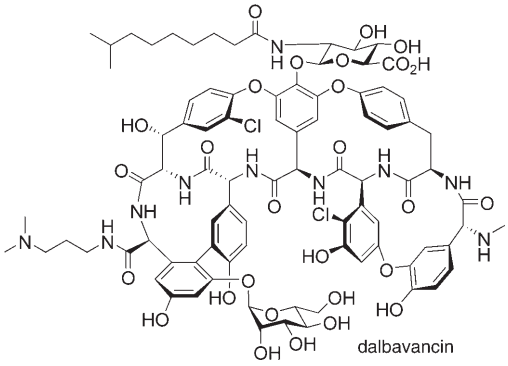


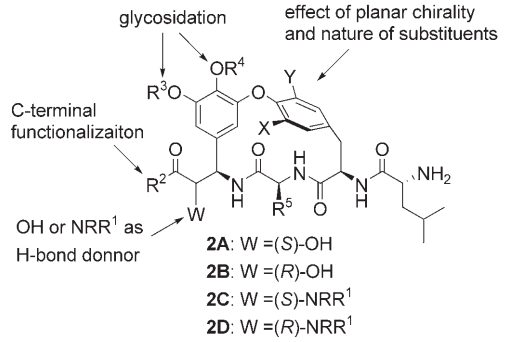
Scheme 1. Hydrogen-bonded network of the complex vancomycin (**1**) and *N*-Ac-D-Ala-D-Ala.

The emergence of vancomycin resistance provided an incentive for the discovery and development of new antibiotics that would be active against both sensitive and resistant strains of *enterococci*. One working direction has been the search for new classes of antibiotics and three drugs, namely synercid,[6] linezolid,[7] and daptomycin,[8] have been commercialized so far. On the other hand, efforts dedicated to the modification of natural glycopeptides to create new semisynthetic derivatives were also fruitful. Extensive structure-activity relationship (SAR) studies 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.[9] Indeed both oritavancin (LY333328)[10] and dalbavancin,[11] which entered into late-stage clinical trials, contain a hydrophobic group. The fact that a modification in the sugar part of vancomycin and teicoplanin can reverse the drug-resistance is surprising, as this subunit is not directly involved in substrate binding. Indeed, in vitro activity of oritavancin did not parallel with its binding affinity with D-Ala-D-Lac. Two theories have been proposed to account for oritavancin's bioactivity against VRE.[12] 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.[13] More recently, Kahne advanced that oritavancin acts against VRE by direct interaction with the transglycosylase without substrate binding[14] and evidence that supports this view has been accumulated.[15,16]

Guided by these two hypotheses, we designed molecules of a general structure (**2**, Scheme 2) in which the carboxylate-binding pocket of vancomycin is modified to keep the required hydrogen-bonding network with the modified peptidoglycan termini. We hypothesized that replacing the carbonyl group of AA4 (AA = amino acid) of vancomycin by a





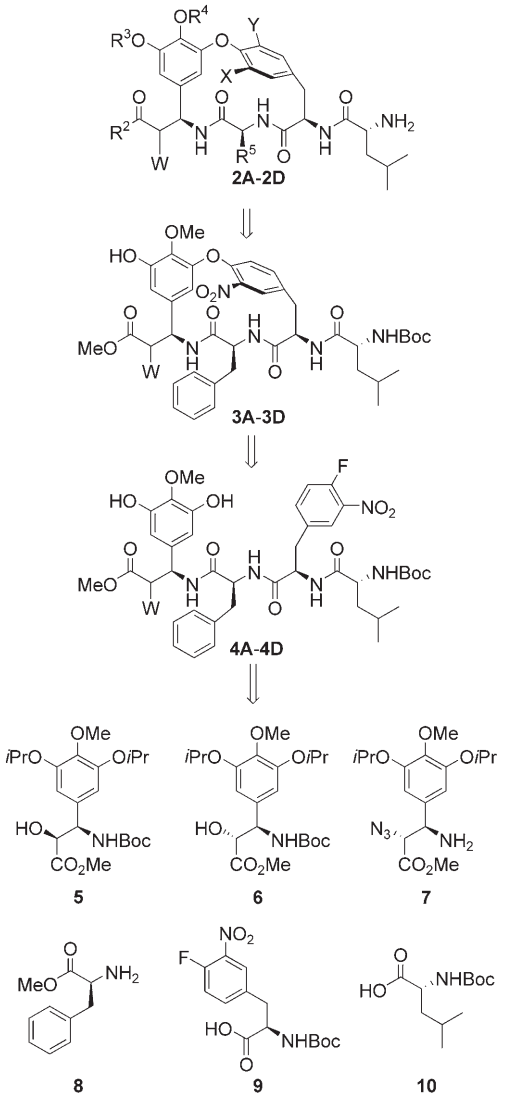


Scheme 2. Generic structure of the modified carboxylate-binding pocket of vancomycin.

CH*OH*COR or CH*NH*COR function can, a priori, lead to a compound with increased affinity towards *N*-Ac-D-Ala-D-Lac by restoring the missing hydrogen bond and by avoiding the unfavorable electronic repulsion found in the vancomycin/D-Ala-D-Lac complex.[17] A hydrophobic chain will be incorporated at the appropriate position to direct the molecule to interact with transglycosylase. In line with this work, but with a different design principle, Ellman and co-workers synthesized a combinatorial library of 16-membered macrocycles containing different tripeptide appendages at the *C*-terminal and identified synthetic receptors that bind to the *N*-Ac_2-L-Lys-D-Ala-D-Ala.[18] On the other hand, Pieters and co-workers have accomplished a solid-phase synthesis of the

C–O–D ring with different amino acid residues at the *i*+*2*-position and studied their binding properties.[19] It is worth noting that structural modification of the vancomycin-type glycopeptide is particularly challenging due to the molecular complexity.[20,21] Therefore, most of the chemical transformations reported to date have been localized on the periphery of the macrocycles relying on simple chemical reactions. Indeed, it would be extremely difficult, if it was not impossible, to reengineer the carboxylate-binding pocket (D–O–E ring) of natural glycopeptides to include new hydrogen-bond contacts with the modified peptidoglycan termini.[22] Therefore, the minimum structure required to carry the hydrophobic substituent remained unknown.[22,23]

In this paper, we report in detail the synthesis of the modified carboxylate-binding pocket of vancomycin featuring a key intramolecular S_NAr reaction according to the retrosynthetic analysis depicted in Scheme 3.[24,25] We demonstrate that both the structure of the macrocycle including stereochemistry and the presence of a hydrophobic chain are important for anti-VRE activity for this series of compounds. We also document that the presence of a lipidated aminosugar is not required if a lauroyl amide is incorporated at the appropriate position of the peptide backbone. Compounds **2Be** and **2Dc** could serve as useful templates, to a certain extent even more effectively than the entire glycopeptide framework, in searching for the active compounds against both vancomycin-sensitive and -resistant strains.



Scheme 3. Retrosynthetic analysis of the modified carboxylate-binding pocket of vancomycin. W = OH or NRR^1; X, Y = NO_2, NHCOR, or H; R^2 = OH, OR, or NHR; R^3, R^4 = H, alkyl, aryl, or amino sugar.

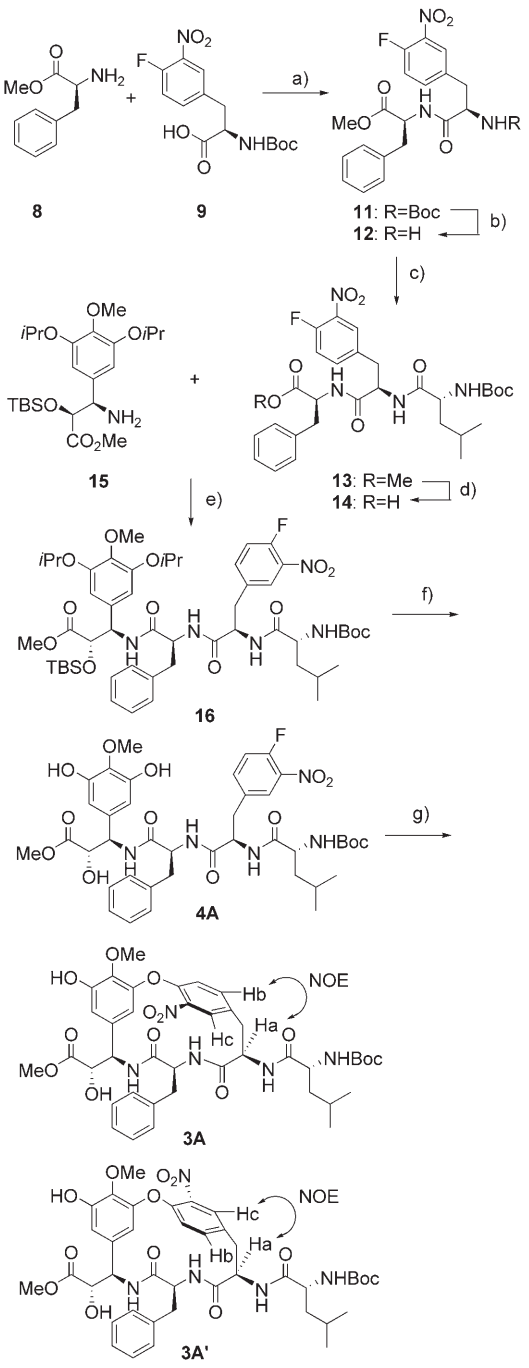
Results and Discussion

Synthesis of the modified carboxylate-binding pocket containing an external secondary hydroxy group: Synthesis of the 16-membered macrocycles **3A** and **3A′** was accomplished as depicted in Scheme 4. Coupling of L-phenylalanine methyl ester (**8**) with L-*N*-Boc-4-fluoro-3-nitrophenyl alanine (**9**)[26] (EDC, HOBt) afforded dipeptide **11** in 99% yield. Removal of the Boc group under acidic conditions followed by coupling with D-*N*-Boc-leucine (**10**) provided tripeptide **13**, which was subsequently converted to its carboxylic acid **14** upon hydrolysis (K_2CO_3, MeOH/H_2O). Coupling of the suitably protected (2*S*,3*R*)-α-hydroxy-β-amino acid **15**[27] with tripeptide **14** (EDC, HOBt) afforded tetrapeptide **16** in excellent yield. Treatment of **16** with BCl_3 led to the simultaneous deprotection of the isopropyl ether, the *tert*-butyldimethylsilyl ether, and the *N*-Boc function. Reintroduction of the Boc group furnished phenol **4A** in 81% yield over two steps.

The key intramolecular S_NAr-based cycloetherification of **4A** was performed in DMSO (concentration of substrate = 0.01 M) in the presence of CsF at room temperature. Two separable atropisomers **3A** and **3A′** were isolated in 72% overall yield (ratio **3A**/**3A′** 3:1). The absolute configuration of the planar chirality of **3A** and **3A′** was deduced by NOE studies.[28] Thus, the NOE correlation between protons Ha/Hb was observed in the NOESY spectrum of **3A**, indicative of the *P* configuration of this atropstereoisomer. On the other hand, a Ha/Hc correlation, a characteristic of the *M*-atropstereoisomer, was observed for compound **3A′**.

The tetrapeptide **4B** containing a (2*R*,3*R*)-α-hydroxy-β-amino acid unit was synthesized by following the same synthetic route as described for **4A**. Interestingly, cyclization of **4B** under identical conditions as described for **4A** afforded only one atropdiastereoisomer **3B** in 65% yield (Scheme 5). The high diastereoselectivity observed in the cycloetherification of **4B** relative to **4A** was difficult to rationalize, but was in accord with the previous observation that the atropdiastereoselectivity is highly substrate dependent.[20,24,29–31]

From compounds **3A** and **3A′**, a series of derivatives were synthesized (Scheme 6). Compound **2Aa** was synthesized in one step by heating a solution of **3A** in MeCN/conc. HCl (v/v 10:1, 40 °C). Under these conditions, both the methyl ester and *N*-Boc functions were hydrolyzed to provide **2Aa** in 86% yield. The synthesis of **2Ab** containing a



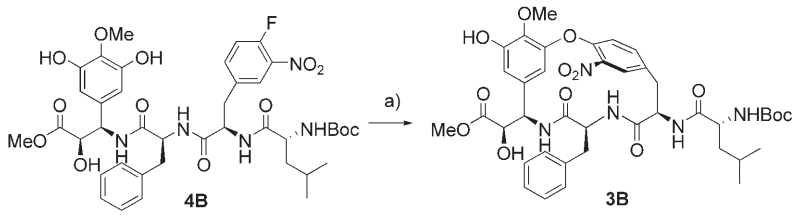
Scheme 4. Synthesis of 16-membered macrocycles **3A** and **3A′**: a) EDC, HOBt, CH_2Cl_2, 25 °C, 12 h, 99 %; b) conc. HCl, CH_3CN, 25 °C, 1.5 h; c) D-*N*-Boc leucine (**10**), EDC, HOBt, CH_2Cl_2, 25 °C, 12 h, 76 % (2 steps); d) K_2CO_3, MeOH/H_2O 10:1, 25 °C, 36 h, 96 %; e) EDC, HOBt, CH_2Cl_2, 25 °C, 12 h, 89 %; f) (i) BCl_3, CH_2Cl_2, 0 °C, 1 h; then MeOH. (ii) Boc_2O, $NaHCO_3$, dioxane/H_2O 2:1, 25 °C, 12 h, 81 % (2 steps); g) CsF, DMSO, 25 °C, 16 h, 72 %. Boc = *tert*-butoxycarbonyl; EDC = *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride; HOBt = 1-hydroxybenzotriazole.

hydrophobic chain is summarized in Scheme 7. Hydrogenation of the nitro group (H_2, 1 atm, Pd/C, MeOH) afforded aniline **17**, which was directly acylated with an excess of lauroyl chloride to give, after chemoselective saponification, the *N*-acylated compound **18** in 45 % yield. Saponification of the methyl ester (K_2CO_3, MeOH/H_2O) followed by removal of the *N*-Boc function (conc. HCl in MeCN, v/v 10:1, RT) provided compound **2Ab** in 85 % yield. Compound **2Ab** was synthesized in order to study the hydrophobic effect on the biological activity of this series of compounds.

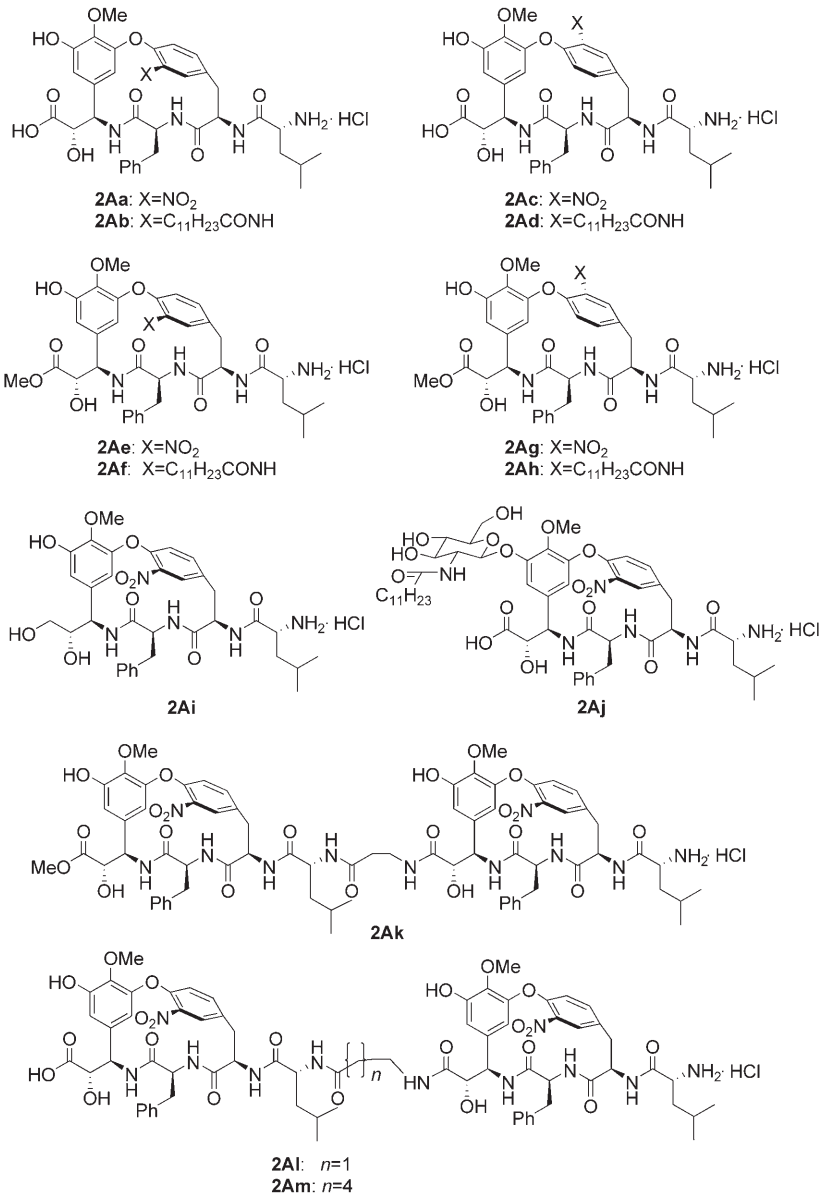
Williams and co-workers have shown, by elegant NMR spectroscopic studies, that vancomycin, ristocetin A, and eremomycin among others exist in solution as homo-dimers arranged in an antiparallel (head-to-tail) fashion.[13,32] This important observation has naturally provided incentive for the synthesis of covalently linked glycopeptide dimers.[33,34] To exploit the potential polyvalent interaction, dimers **2Al** and **Am** were prepared (Scheme 8). Saponification of compound **3A** (K_2CO_3, MeOH/H_2O) afforded the corresponding carboxylic acid **20** in quantitative yield. On the other hand, removal of the Boc group of compound **3A** to obtain **2Ae** was found to be more difficult than one may expect due to the lability of the methyl ester under aqueous acidic conditions. After considerable experimental trials, **2Ae** was finally obtained in quantitative yield by treatment of its methanol solution with thionyl chloride. Coupling of **2Ae** with *N*-Boc-3-amino propionic acid followed by chemoselective saponification of the aryl ester afforded **21**. *N*-deprotection under mild acidic conditions followed by coupling with **20** provided the head-to-tail dimer **23** in 41 % yield. Saponification of the methyl ester (LiOH, THF/H_2O) followed by acidic treatment (HCl in MeCN, RT) afforded the desired compound **2Al** in 79 % yield. Dimer **2Am** linked by 6-amino caproic acid was synthesized in a similar fashion via intermediate **22**.

The synthesis of compound **2Aj** containing an *N*-acylated aminoglucose unit was subsequently developed (Scheme 9). The commercially available aminoglucose **25** was transformed to glycosyl donor **28** in three steps. *N*-acylation of **25** with lauroyl chloride under Schotten–Baumann conditions ($C_{11}H_{23}COCl$, H_2O/dioxane, aqueous $NaHCO_3$), followed by *O*-acetylation gave the per-acylated compound **27**. Bromination of **27** was best performed with a solution of HBr in acetic acid[35] to afford 3,4,6-tri-*O*-acetyl-2-*N*-lauroyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide (**28**). This compound was stable only in solution and readily decomposed upon evaporation to dryness. Consequently after the usual workup, the organic extracts were used in the next step without further purification. Koenigs-Knorr reaction[36] of freshly prepared **28** with **3A** under phase-transfer conditions (10 % aqueous Na_2CO_3, nBu_4NHSO_4, CH_2Cl_2, RT)[37] afforded the desired β-glucoside **29** as the only isolable stereoisomer in 76 % yield. The neighboring-group participation (*N*-acyl) may explain the observed high β-selectivity. Finally, hydrolysis of acetate and methyl ester under basic conditions (LiOH, THF, H_2O) furnished acid **30** in 62 % yield. *N*-deprotection of **30** under acidic conditions provided **2Aj** in 57 % yield.

It is noteworthy that 2-acyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide is known to be unstable and readily un-



Scheme 5. Synthesis of 16-membered macrocycle **3B**: a) CsF, DMSO, 25 °C, 16 h, 65 %.



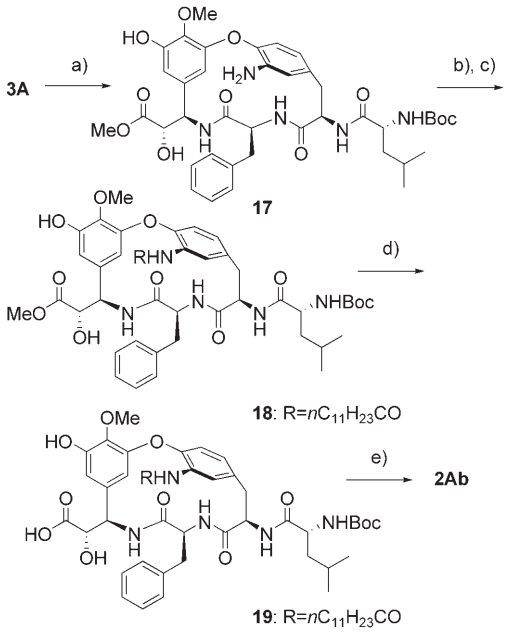
Scheme 6. Structures of macrocycles **2Aa**–**Am**.

dergoes the acyl migration probably via the oxazoline and ortho ester intermediates.[38,39] Thus we would like to stress that the procedure developed in the present study turned out to be quite general and reliable (seven examples, vide infra), and should find application in the synthesis of related glycosides.

Compounds **2Ac**, **Ad**, **Ag**, and **Ah** were prepared from **3A′** following the chemistry developed for the synthesis of **2Aa**, **Ab**, **Ae**, and **Af**. Compounds synthesized from **3B** are listed in Scheme 10.

Scheme 11 summarizes the synthesis of **2Bd**. Reaction of **3B** with 4-fluoro nitrobenzene (DMSO, CsF, RT) afforded aryl ether **31**. Subsequent treatment under push-pull conditions ($AlCl_3$, EtSH, CH_2Cl_2) provided a mixture of amino acid **32** and amino ester **33**, the ratio of which was found to be time-dependent. However, **32** can be converted quantitatively to **33** under standard conditions ($SOCl_2$, MeOH). *N-tert*-butoxycarbonylation of **33** provided **34**, which was glycosylated to **35**. Saponification followed by acidic treatment afforded the desired compound **2Bd** in good overall yield.

Compound **2Bf** was designed in the hope of introducing an additional hydrogen bond with the peptidoglycan termini (Scheme 12). Reaction of **3B** with freshly prepared 3,4,6-tri-*O*-acetyl-2-*N*-lauroyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide (**28**) under phase-transfer conditions (10 % aqueous Na_2CO_3, nBu_4NHSO_4, CH_2Cl_2, RT) afforded **36** in 72 % yield. Hydrolysis of the methyl ester under basic conditions (LiOH, THF/H_2O) removed the acetate function and provided the hydroxy acid **37**. Coupling of **37** with amine **38** (EDC, HOBt, CH_2Cl_2) provided **39**, which upon *N*-deprotection afforded the desired compound **2Bf** in 75 % yield.



Scheme 7. Synthesis of compound **2Ab**: a) 10% Pd/C, H_2, MeOH, 25°C, 2 h; b) lauroyl chloride, Et_3N, CH_2Cl_2, 25°C, 4 h; c) K_2CO_3, MeOH/H_2O 10:1, 25°C, 20 min, 45% (3 steps); d) K_2CO_3, MeOH/H_2O 10:1, 25°C, 20 h; e) conc. HCl, CH_3CN, 25°C, 2 h, 85% (2 steps).

Synthesis of the modified carboxylate-binding pocket of vancomycin containing an external secondary amide group: The synthesis of parent macrocycle **3D** incorporating an α,β-diamino acid at the *C*-terminal is shown in Scheme 13. Coupling of tripeptide **14** with azido amine **7** (EDC, HOBt) provided tetrapeptide **40**, which was converted into compound **41** as described for **4A**. Cyclization of azido derivative **41** under a set of conditions which varied the bases (CsF, K_2CO_3, Cs_2CO_3), temperature, and solvent (DMF, DMSO, THF) failed to produce the desired 16-membered macrocycle. We then turned our attention to amino compound **4D** which was obtained by reduction of the azide group under Staudinger conditions (Ph_3P, THF, H_2O). Gratifyingly, cycloetherification of **4D** (CsF, DMF) proceeded smoothly to provide a single atropisomer **3D**, the planar chirality of which was deduced from detailed NMR spectroscopic studies. Interestingly, the formation of 14-member *para*-cyclophane resulting from the nucleophilic addition of primary amine onto the fluoro-aromatic ring system was not observed under these conditions.[40]

A facile racemization process was discovered serendipitously during the course of this study (Scheme 14). Thus, saponification of methyl ester **42a** (R = Me) in THF/H_2O with lithium hydroxide at 0°C provided the desired carboxylic acid **43a** in almost quantitative yield. However, when the same reaction was performed at room temperature, a second product **44a** was isolated. A control experiment indicated that **43a** and **44a** were in equilibrium and a ratio of 1/1.5 was obtained after prolonged stirring at room temperature. The structure of **44a** was deduced to be a C_α-epimer. It is indeed reasonable to suppose that C_α is more prone to epimerization as its enolization would not introduce additional strain into the already strained macrocycle, in contrast to the enolization of internal amides of the macrocycle. Furthermore, in the absence of this external amide function, the macrocycle was found to be configurationally stable under saponification conditions as observed in the **2A** and **2B** series.

Starting from compounds **3D** and by taking advantage of this facile epimerization process, compounds **2Ca–Ce** and **2Da–Do** were synthesized. Their structures are shown in Schemes 15 and 16, respectively.

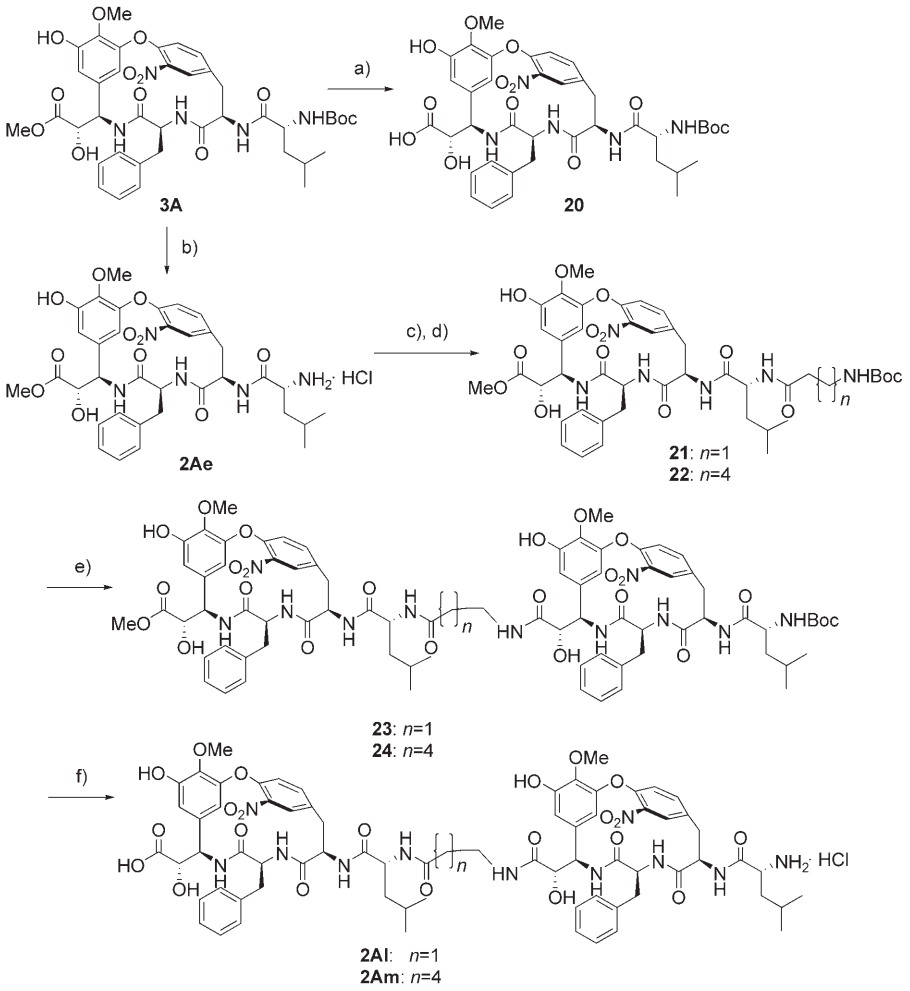
Compound **2De** was obtained by thermal atropisomerization of **42b** (150°C, DMSO, 1:1 ratio) subsequent saponification, and *N*-Boc deprotection. Compound **2Dg**, incorporating a L-asparagine unit at the *i*+*2*-position, and the desleucyl derivative **2Di** were synthesized by following the same synthetic strategy as described for **3D**. Compound **2Df**, devoid of planar chirality, was synthesized as shown in Scheme 17. Thus, acylation of **3D** with lauroyl chloride under Schotten–Baumann conditions afforded compound **45**. Catalytic hydrogenation of the nitro group (Pd/C, MeOH, H_2) provided the aniline intermediate, which was reductively deaminated (*t*BuONO, DMF, 75°C) to give compound **46**. The latter compound was then transformed into **2Df** by following a conventional two-step sequence.

Antibiotic activity evaluation: Minimum inhibitory concentrations for these compounds and reference compounds (vancomycin, teicoplanin, synercid®, and daptomycin) are measured by using a standard microdilution assay. The selected results are summarized in Table 1

Compounds **2Aa–Am** containing an external *S*-configured secondary hydroxy group were found to be inactive against both vancomycin-sensitive and resistant strains, regardless of the absolute configuration of the planar chirality (**2Aa** and **Ab** versus **2Ac** and **Ad**) of the cyclophane. The introduction of a hydrophobic chain at the E-ring (**2Ab** versus **2Aa**, **2Ad** versus **2Ac**), a lipidated aminoglucose at the D-ring (**2Aj**), or dimerization (**2Ak–m**) did not lead to the active compounds.

On the other hand, compounds derived from **3B** with an external *R*-configured secondary hydroxy group displayed interesting bioactivities. The parent compound **2Ba** was inactive, but its *O*-arylated derivatives **2Bb** and **Bc** were able to inhibit the growth of *E faecalis* Van A at reasonably low MIC values (Table 1, entries 3 and 4). More interestingly, *O*-glycosylated derivatives **2Bd** and especially **2Be** displayed potent activities against VRE (entries 5 and 6). Furthermore, compound **2Bf** containing an elongated peptide chain at the *C*-terminal was active not only against VRE, but also against vancomycin-sensitive *Staphylococcus aureus* (entry 7).

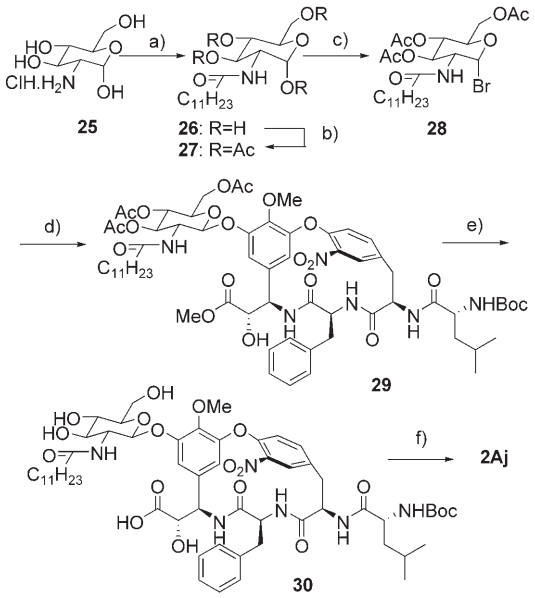
The activity of compounds **2Ca–Ce** and **2Da–Do** containing an α,β-diamino acid at the *C*-terminal was found to be less dependent on the stereochemistry of the C_α-carbon in contrast to the OH-series. However, the functionalization of the C_α-amino group has a large impact on the bioactivity of



Scheme 8. Synthesis of head-to-tail dimers **2Al** and **Am**: a) K_2CO_3, MeOH/H_2O 10:1, 25 °C, 24 h, 100 %; b) $SOCl_2$, MeOH, 25 °C, 1 h; c) *N*-Boc-3-amino propionic acid or *N*-Boc-6-amino caproic acid, EDC, HOBt, Et_3N, CH_2Cl_2, 25 °C, 12 h; d) K_2CO_3, MeOH/H_2O 10:1, 25 °C, 20 min, 60 % (3 steps); e) (i) $SOCl_2$, MeOH, 25 °C, 1 h; (ii) **20**, EDC, HOBt, Et_3N, CH_2Cl_2, 25 °C, 12 h; (iii) K_2CO_3, MeOH/H_2O 10:1, 25 °C, 20 min, 41 % (3 steps); f) (i) LiOH, THF/H_2O 3:1, 0 °C, 4 h; (ii) conc. HCl, CH_3CN, 25 °C, 2 h, 79 %.

these compounds. Thus, neither the parent compounds **2Da**, its *N,N*-dimethylated derivative **2Db**, or the *N*-acetyl derivatives **2Ca** and **2Dh** were active against VRE. On the other hand, the lauroyl (*N*-dodecanoyl) amides **2Cc** and **2Dc** produced interesting activities against VRE (entries 9 and 13), indicating the important role of a hydrophobic chain. Compound **2Dg** (entry 17), containing an asparagine unit instead of a phenylalanine in the *i*+*2*-position, was slightly less active than **2Dc** (entry 13). Planar chirality plays only a minor effect on the bioactivity as the potency of **2Dc** and **De** are comparable (entry 15). However, the presence of the nitro group at the E ring is beneficial as **2Df**, devoid of this group was much less active (entry 16). The activity against VRE remained essentially unchanged upon benzylation and glucosylation of the phenol function. Although **2Ce** missing the leucine-terminal is inactive, reasonable activities against VRE remained for des-leucyl derivative **2Di** (entry 19). As in the case of the OH series, compound **2Do** (entry 22) containing an elongated peptide chain at the *C*-terminal is active against a broad spectrum of both vancomycin-sensitive (*Staphylococcus aureus*) and resistant strains.

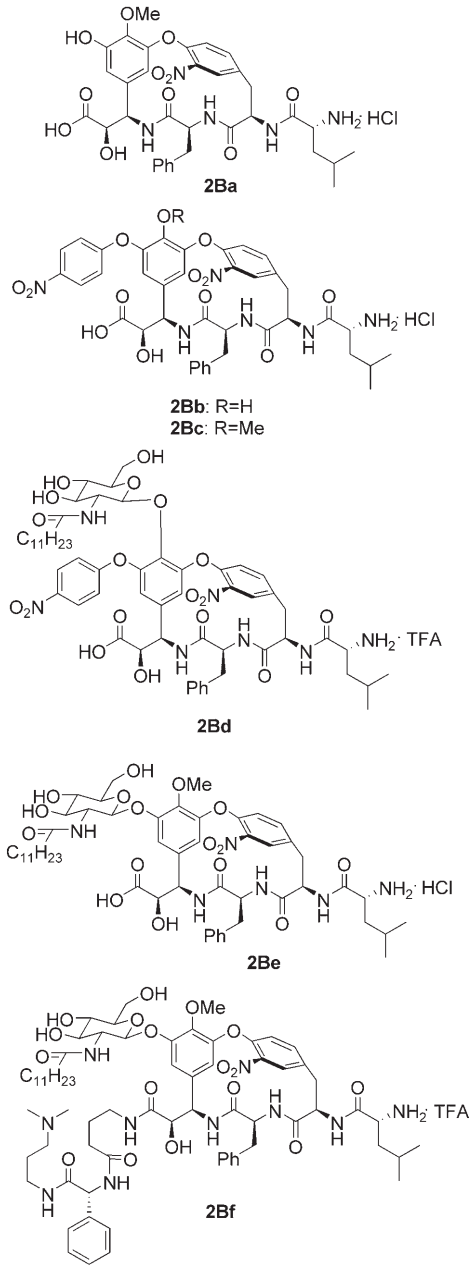
It is noteworthy that some of the macrocycles reported in this paper are more active, in vitro, against VRE than most of the vancomycin and teicoplanin derivatives reported in the literature and are almost as active as synercid®, a clinically used drug for combating VRE. The generic structure **2** was originally designed with the hope of restoring the missing hydrogen bond with the D-Ala-D-Lac depsipeptide by switching the amide carbonyl (hydrogen-bond acceptor) of vancomcyin's fourth amino acid into a hydroxy group (hydrogen-bond donor). Although interesting activities against VRE were indeed found for some of these derivatives, substrate binding cannot account for their antibiotic activities for the following reasons: (1) attempts to measure the binding affinity between **2Be** and *N*-Ac-D-Ala-D-Ala as well as **2Be** and *N*-Ac-D-Ala-D-Lac by either UV absorption techniques or by NMR titration (in DMSO) failed to provide any exploitable results, most probably due to the low receptor-substrate affinities, (2) although **2Ce** was inactive, **2Di** with a damaged binding pocket was able to inhibit the growth of *Enterococcus faecalis* Van A at a reasonably low MIC value, and (3) the observed hydrophobic effect is apparently not due to the simple increase of effective molarity resulting from membrane anchoring. Rather it was specific, as no beneficial effect was observed when the same aliphatic chain was introduced to E-ring of the molecule (**2Ab** and **Ad**). This result can be better explained on the basis of a specific interaction between the macrocycle and the target enzymes. Overall, and in accord with Kahne's observation,[14],[16] we hypothesize that these compounds might have a direct interaction with proteins critical for VRE cell-wall biosynthesis, although a detailed mechanism of action remains to be investigated.



Scheme 9. Synthesis of glycosylated macrocycle **2Aj**: a) lauroyl chloride, $NaHCO_3$, dioxane/H_2O 1:1, 0°C, 4 h, 61%; b) Ac_2O, pyridine, 0°C, 4 h, 94%; c) 30% HBr in HOAc, HOAc, 25°C, 3 h; d) **3A**, $(n\text{Bu})_4NHSO_4$, 10% aqueous Na_2CO_3/CH_2Cl_2 (1:1), 25°C, 4 h, 76%; e) LiOH, THF/H_2O 3:1, 0°C, 4 h, 62%; f) conc. HCl, CH_3CN, 25°C, 2 h, 57%.

Conclusion

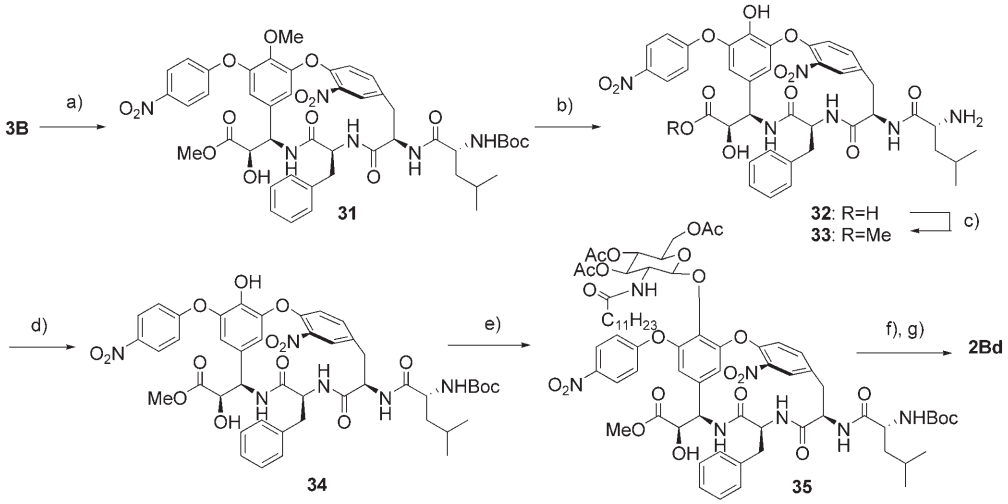
A modified vancomycin-binding pocket (D–O–E ring) has been designed and synthesized. The structural key features of this biaryl ether containing macrocycle are (1) the incorporation of β-amino-α-hydroxy acid or α,β-diamino acid as the *C*-terminal component of the cyclopeptide and (2) the presence of a hydrophobic chain or lipidated aminoglucose at the appropriate position. Cycloetherification by an intramolecular nucleophilic aromatic substitution reaction (S_NAr) is used as the key step for the construction of the macrocycle. We demonstrated in the present study that a combination of a modified binding pocket with a suitably positioned hydrophobic chain constitutes a viable approach in the search for compounds active against VRE. Furthermore, the presence of a lipidated aminosugar is not required if a lauroyl amide is incorporated at the appropriate position of the peptide backbone. Although substrate binding may not be the determinant factor for the anti-VRE activities of these compounds, we assume from these preliminary structure-activity relationship studies that the structure of the macrocycle is important for the observed activities and even a subtle change of one chiral center can perturb the potency of a given compound. Such an observation is of course understandable, if the enzyme-substrate interaction is considered to be the major mechanism of action of these cyclophanes.



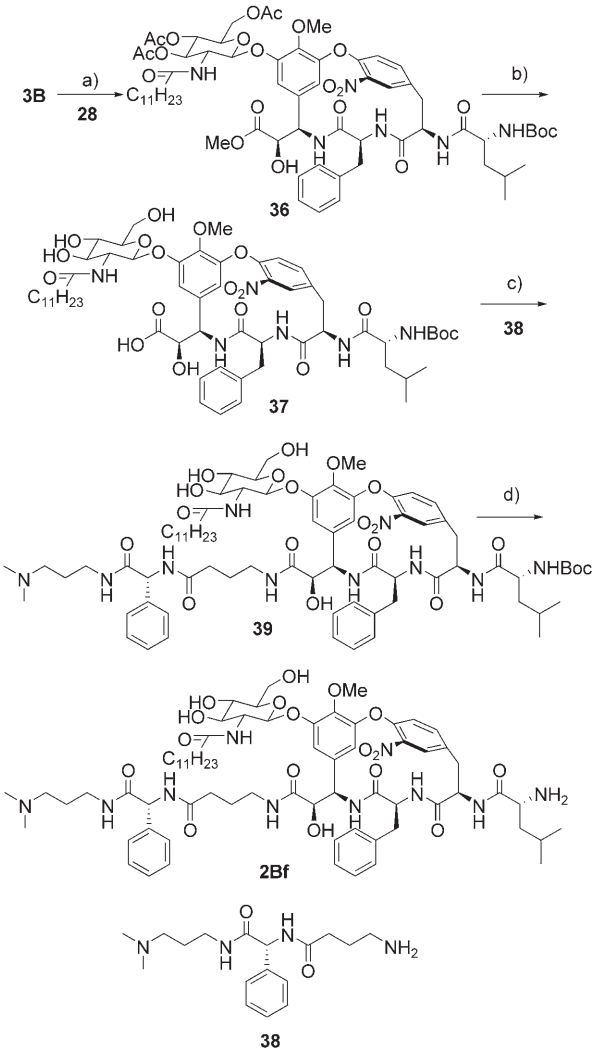
Scheme 10. Structures of macrocycles **2Ba–Bf**.

Experimental Section

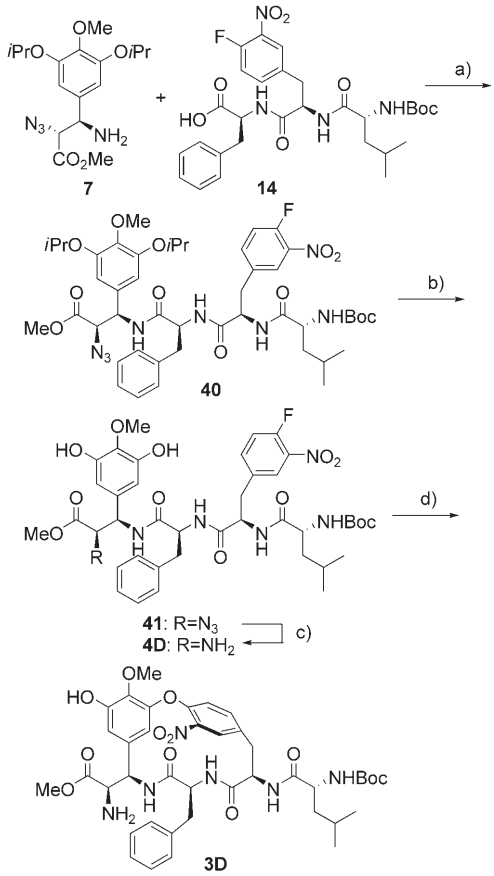
Compound 11: HOBt (1.44 g, 10.7 mmol) and EDC (2.39 g, 12.5 mmol) were added to a solution of amine **8** (1.75 g, 9.8 mmol) and acid **9** (2.92 g, 8.9 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred at room temperature for 12 h and then diluted with CH_2Cl_2 (100 mL). The resulting mixture was washed with 5% aqueous HCl, saturated $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash-column chromatography (silica gel, heptane/EtOAc 5:1) to afford **11** (4.31 g, 99%). M.p. 45–47°C; $[\alpha]_D = -8.9$ ($c = 0.15$ in MeOH); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.81$ (d, $J = 6.9$ Hz, 1H; ArH), 7.40–7.00 (m, 7H; ArH), 6.59 (d, $J = 7.7$ Hz, 1H; NH), 5.00 (d, $J = 8.6$ Hz, 1H; NH), 4.81 (dd, $J = 7.7$, 6.7 Hz, 1H; CH), 4.39 (m, 1H; CH), 3.73 (s, 3H; CO_2CH_3), 3.19–2.87 (m, 4H; $2 \times CH_2$), 1.38 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 171.4$, 170.1, 154.8, 153.9 ($J = 262$ Hz),



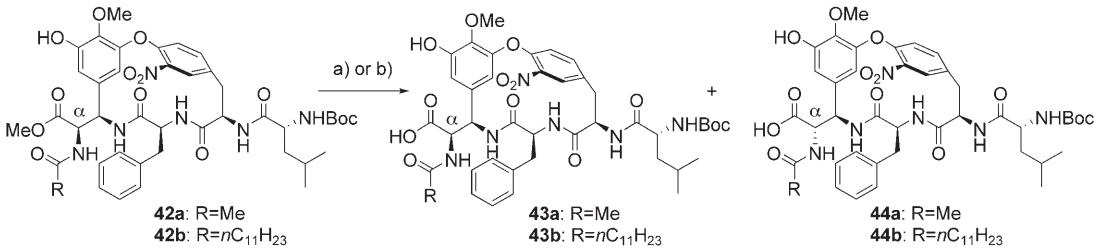
Scheme 11. Synthesis of glycosylated macrocycle **2Bd**: a) 1-fluoro-4-nitrobenzene, CsF, DMSO, 25 °C, 2 h, 100 %; b) $AlCl_3$, EtSH, CH_2Cl_2, 0 °C, 2.5 h, 53 %; c) $SOCl_2$, MeOH, 60 °C, 12 h; d) Boc_2O, $NaHCO_3$, dioxane/H_2O 2:1, 25 °C, 2 days, 60 %; e) **28**, $(n\text{Bu})_4NHSO_4$, 10 % aqueous Na_2CO_3/CH_2Cl_2 1:1, 25 °C, 4 h, 73 %; f) LiOH, THF/H_2O 3:1, 0 °C, 1.5 h; g) TFA, CH_2Cl_2, 0 °C, 1 h, 79 % (2 steps).



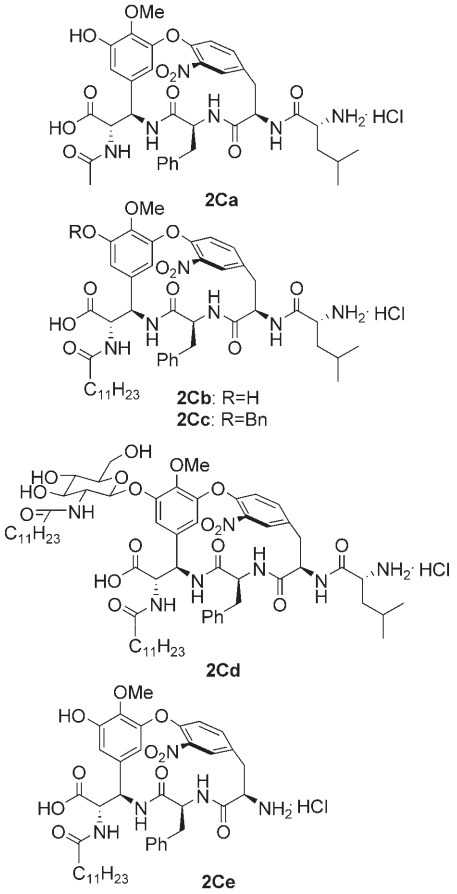
Scheme 12. Synthesis of *C*-terminal elongated macrocycle **2Bf**: a) **28**, $(n\text{Bu})_4NHSO_4$, 10 % aqueous Na_2CO_3/CH_2Cl_2 1:1, 25 °C, 4 h, 76 %; b) LiOH, THF/H_2O 3:1, 0 °C, 4 h, 62 %; c) **38**, EDC, HOBt, CH_2Cl_2, 25 °C, 12 h, 34 %; d) TFA, CH_2Cl_2, 0 °C, 1 h, 75 %.



Scheme 13. Synthesis of macrocycle **3D**: a) EDC, HOBt, CH_2Cl_2, 25 °C, 12 h, 93 %; b) (i) BCl_3, CH_2Cl_2, 0 °C, 1 h; then MeOH; (ii) Boc_2O, $NaHCO_3$, dioxane/H_2O 2:1, 25 °C, 12 h, 95 % (2 steps); c) Ph_3P, H_2O, THF, 25 °C, 12 h, 77 %; d) CsF, DMSO, 25 °C, 16 h, 85 %.



Scheme 14. Facile epimerization of macrocycle **42**: a) LiOH, THF/H_2O, 0 °C, **43**/**44** 1:0; b) LiOH, THF-H_2O, RT, **43**/**44** 1:1.5.



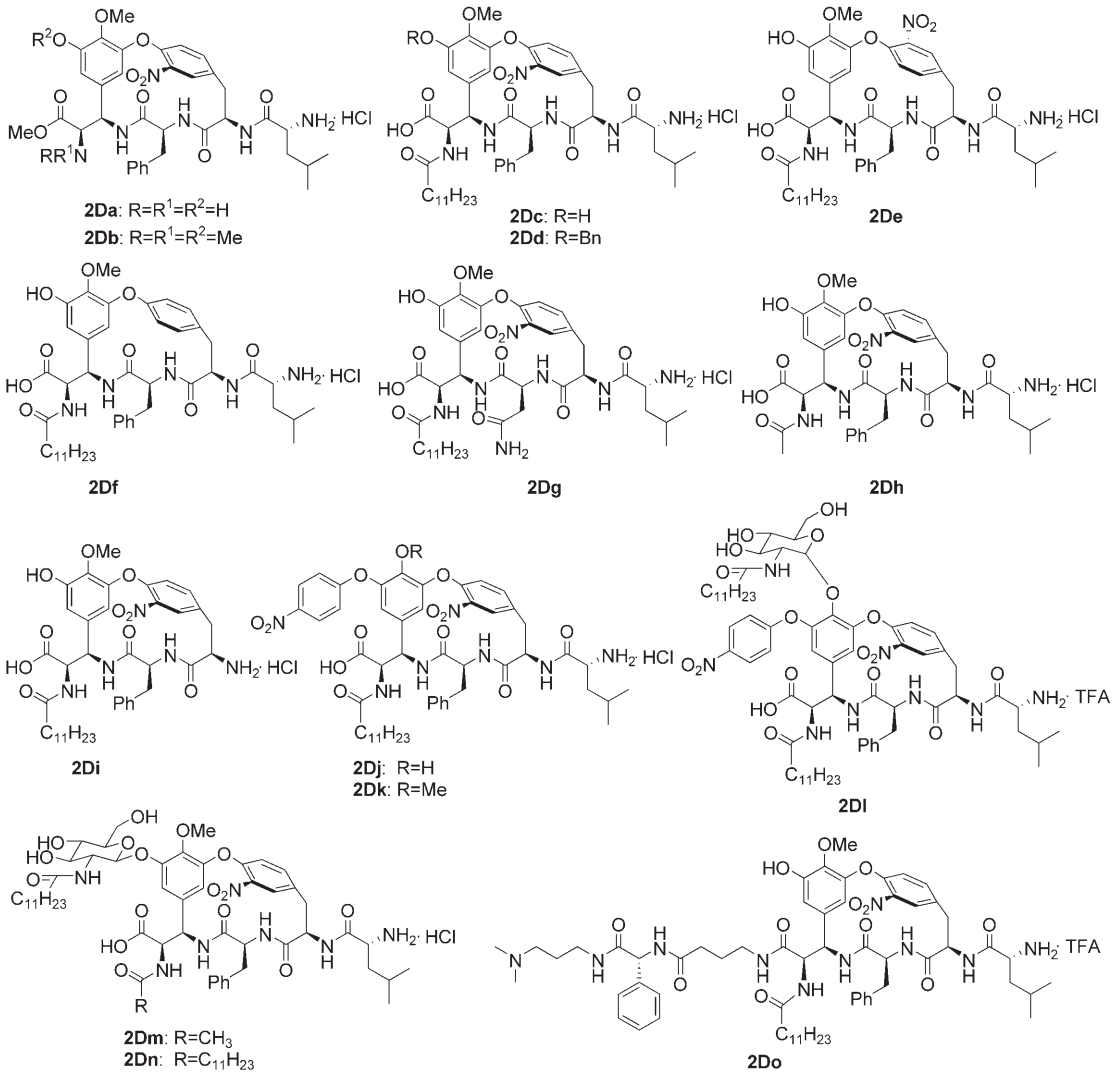
Scheme 15. Structures of macrocycles **2Ca**–**Ce**.

136.1, 135.9, 135.2, 133.4, 128.6, 128.1, 126.7, 126.1, 117.7 (J=29 Hz), 79.9, 54.2, 52.8, 51.9, 37.2, 36.6, 27.6 ppm; IR ($CHCl_3$): $\tilde{\nu}$=3425, 3032, 2983, 1742, 1683, 1622, 1540, 1497, 1352, 1253, 1163 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{24}H_{28}N_3O_7FNa$: 512.1809 $[M+Na]^+$; found: 512.1813.

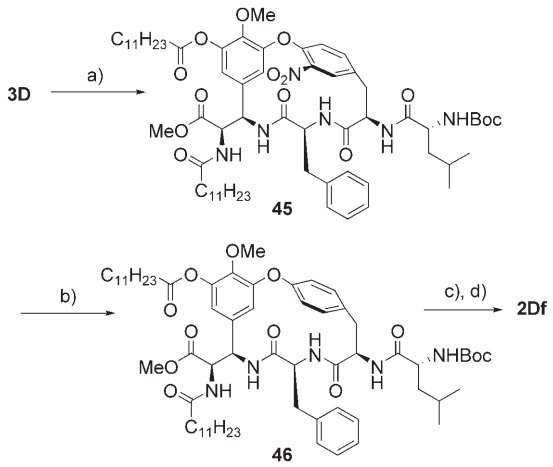
Compound 13: Concentrated HCl (6.0 mL) was added to a solution of **11** (5.13 g, 10.9 mmol) in CH_3CN (60 mL). After the reaction mixture had been stirred for 1.5 h at room temperature, it was diluted with EtOAc (100 mL), basified to pH 8–10 with saturated $NaHCO_3$, and then extracted with EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum to afford **12** which was used directly for next reaction. HOBt (1.29 g, 9.6 mmol) and EDC (2.33 g, 12.2 mmol) were added to a solution of amine **12** (3.38 g, 8.7 mmol) and acid **10** (2.21 g, 9.6 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred at room temperature for 12 h and then diluted with CH_2Cl_2 (100 mL). The resulting mixture was washed with 5% aqueous HCl, saturated $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash-column chromatography (silica gel, CH_2Cl_2/MeOH 100:1) to afford **13** (5.0 g, 76%). M.p. 175–177 °C; α_D=+15.3 (c=0.24 in MeOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.79 (dd, J=7.3, 2.3 Hz, 1H; ArH), 7.40–6.90 (m, 7H; ArH), 6.80–6.60 (m, 2H; 2×NH), 4.80–4.60 (m, 3H; NH, 2×CH), 3.99 (m, 1H; CH), 3.70 (s, 3H; CO_2CH_3), 3.20–2.95 (m, 4H; 2×CH_2), 1.70–1.40 (m, 3H; CH, CH_2), 1.41 (s, 9H; $C(CH_3)_3$), 0.91 (d, J=4.7 Hz, 3H; CH_3), 0.89 ppm (d, J=4.7 Hz, 3H; CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ= 172.4, 171.2, 169.3, 155.4, 153.8 (J=254 Hz), 136.2, 136.0, 135.4, 132.9, 128.6, 128.1, 126.7, 126.2, 117.8 (J=21 Hz), 80.0, 53.1, 53.0, 52.7, 51.9, 40.3, 37.2, 36.2, 27.6, 24.2, 22.4, 21.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$=3667, 3427, 3030, 3010, 2961, 2934, 2873, 1742, 1691, 1675, 1621, 1540, 1499, 1439, 1369, 1353, 1253, 1161, 1047 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{30}H_{39}N_4O_8FNa$: 625.2650 $[M+Na]^+$; found: 625.2664.

Compound 14: K_2CO_3 (552 mg, 4.0 mmol) was added to a solution of **13** (1.2 g, 2.0 mmol) in MeOH/H_2O (10:1, 55 mL). After the reaction mixture had been stirred for 36 h at room temperature, it was concentrated under vacuum. The resulting residue was acidified to pH 2–3 with 5% aqueous HCl and extracted with EtOAc. The 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 (silica gel, CH_2Cl_2/MeOH 40:1–20:1) to afford **14** (1.13 g, 96%). M.p. 94–97 °C; $[\alpha]_D$=+25.4 (c=0.28 in MeOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.83 (d, J=5.7 Hz, 1H; ArH), 7.42–6.90 (m, 8H; ArH, NH), 7.00 (m, 1H; NH), 5.09 (d, J=6.6 Hz, 1H; NH), 4.92 (m, 1H; CH), 4.72 (m, 1H; CH), 4.08 (m, 1H; CH), 3.30–2.80 (m, 4H; 2×CH_2), 1.39 (s, 9H; $C(CH_3)_3$), 1.70–1.20 (m, 3H; CH, CH_2), 0.82 (d, J=3.3 Hz, 3H; CH_3), 0.80 ppm (d, J=3.3 Hz, 3H; CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=175.9, 174.6, 172.5, 158.2, 155.9 (J=259 Hz), 138.8, 138.4, 138.2, 135.9, 130.7, 129.9, 128.2, 128.1, 119.5 (J=20 Hz), 81.1, 55.6, 55.2, 54.8, 42.5, 38.7, 38.3, 29.1, 26.2, 23.8, 22.2 ppm; IR ($CHCl_3$): $\tilde{\nu}$=3686, 3431, 3374, 3034, 3011, 2961, 2934, 2873, 1666, 1540, 1500, 1455, 1369, 1352, 1253, 1162, 1017 cm^{-1}; MS (EI): m/z: 587 $[M-H]^+$.

Compound 16: TBDSOTf (5.18 mL, 22.1 mmol) was added to a solution of **5** (3.25 g, 7.37 mmol) and 2,6-lutidine (2.19 mL, 18.4 mmol) in CH_2Cl_2 (20 mL) over 30 min. After the reaction mixture had been stirred for 30 min, it was acidified with HCl (2N) to pH 2 and stirring continued for an additional 30 min. The resulting reaction mixture was basified to pH 7–8 with saturated $NaHCO_3$. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum to give the desired amine **15**, which was of sufficient purity for direct use in the next step. ^{1}H NMR (200 MHz, CD_3CN): δ= 6.61 (s, 2H; ArH), 4.57 (m, 2H; CH(CH_3)$_2$), 4.32 (d, J=3.8 Hz, 1H; CH), 4.16 (d, J=3.8 Hz, 1H; CH), 3.68 (s, 3H; OCH_3), 3.66 (s, 3H; CO_2CH_3), 1.31 (d, J=4.4 Hz, 6H; CH(CH_3)$_2$), 1.28 (d, J=4.2 Hz, 6H; CH(CH_3)$_2$), 0.79 (s, 9H; Si(CH_3)$_3$), −0.08 (s, 3H; SiCH_3), −0.23 ppm (s, 3H; SiCH_3); MS (ESI): m/z: 456 $[M+H]^+$. HOBt (1.12 g, 8.1 mmol) and EDC (1.59 g, 8.1 mmol) were added to a solution of the above crude amine **15** and acid **14** (5.21 g, 8.85 mmol) in CH_2Cl_2 (80 mL). The reaction mixture was stirred at room temperature for 12 h before it was diluted with CH_2Cl_2 (100 mL). The resulting mixture was washed with 5% aqueous HCl, saturated $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash-column chromatography to afford **16** (6.7 g, 89%). M.p. 90–92 °C; $[\alpha]_D$=+11.6



Scheme 16. Structures of macrocycles **2 Da**–**Do**.



Scheme 17. Synthesis of macrocycle **2Df**: a) lauroyl chloride, $NaHCO_3$, dioxane/H_2O 2:1, 0 °C, 4 h, 74 %; b) (i) 10 % Pd/C, H_2, MeOH, 25 °C, 30 min; (ii) *t*BuONO, DMF, 75 °C, 15 min, 52 %; c) LiOH, THF/H_2O 3:1, 0 °C, 4 h, 52 %; d) TFA, CH_2Cl_2, 25 °C, 30 min, 80 %.

($c = 0.22$ in MeOH); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.73$ (dd, $J = 7.0$, 2.1 Hz, 1H; ArH), 7.30–7.14 (m, 7H; ArH), 7.12–7.10 (m, 2H; 2×NH), 6.85 (d, $J = 8.3$ Hz, 1H; NH), 6.44 (s, 2H; ArH), 5.26 (dd, $J = 8.8$, 1.7 Hz, 1H; CH), 4.84 (d, $J = 6.6$ Hz, 1H; NH), 4.80–4.64 (m, 2H; 2×CH), 4.54–4.44 (m, 2H; $CH(CH_3)_2$), 4.22 (d, $J = 8.8$ Hz, 1H; CH), 3.99 (m, 1H; CH), 3.79 (s, 3H; OCH_3), 3.69 (s, 3H; CO_2CH_3), 3.30 (dd, $J = 13.6$, 5.7 Hz, 1H; CH_2), 3.17 (dd, $J = 13.8$, 6.0 Hz, 1H; CH_2), 3.02–2.86 (m, 2H; CH_2), 1.64–1.34 (m, 3H; CH, CH_2), 1.42 (s, 9H; $C(CH_3)_3$), 1.34 (d, $J = 5.7$ Hz, 6H; $CH(CH_3)_2$), 1.32 (d, $J = 5.7$ Hz, 6H; $CH(CH_3)_2$), 0.90 (d, $J = 6.6$ Hz, 3H; CH_3), 0.87 (d, $J = 6.6$ Hz, 3H; CH_3), 0.76 (s, 9H; $Si(CH_3)_3$), −0.16 (s, 3H; $SiCH_3$), −0.24 ppm (s, 3H; $SiCH_3$); ^{13}C NMR (50.3 MHz, CD_3OD): $\delta = 175.5$, 173.5, 173.1, 172.5, 158.6, 156.0 (d, $J = 261$ Hz), 153.3, 138.7, 138.4, 138.2, 135.9, 135.7, 130.8, 130.6, 130.0, 128.3, 128.2, 119.5 (d, $J = 21$ Hz), 109.9, 109.7, 81.0, 77.5, 73.2, 73.1, 61.4, 57.8, 56.3, 54.9, 53.3, 53.1, 42.5, 39.5, 38.7, 29.2, 26.7, 26.6, 26.2, 24.0, 23.9, 23.4, 23.2, 23.1, 23.0, 22.2, 19.6, −4.6, −5.0 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3676$, 3420, 3022, 2957, 2933, 2859, 1746, 1683, 1590, 1497, 1369, 1352, 1254, 1212, 1139, 1116, 1006 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{52}H_{76}N_5O_{13}FSiNa$: 1048.5091 $[M+Na]^+$; found: 1048.5081.

Compound 4A: BCl_3 (1 M in CH_2Cl_2, 130 mL, 130 mmol) was added to a solution of **16** (6.67 g, 6.50 mmol) in CH_2Cl_2 (50 mL) at 0 °C. After the reaction mixture had been stirred for 1 h at 0 °C, the reaction was quenched by the slow addition of anhydrous MeOH. The volatile was evaporated

Table 1. MICs [mg mL^{-1}] of selected macrocycles and reference compounds.[a]

Entry		*E. faecium*		*E. faecalis*		*Staph. aureus*[f]
		Sensitive[b]	**Resistant**[c]	Sensitive[d]	**Resistant**[e]	
1	**2Aj**	>128	>128	>128	>128	>128
2	**2Ba**	>1024	>1024	>1024	>1024	>1024
3	**2Bb**	>128	>128	64	64	>128
4	**2Bc**	128	128	16	16	>128
5	**2Bd**	128	128	64	32	>128
6	**2Be**	64	32	8	8	128
7	**2Bf**	16	8	16	8	32
8	**2Cb**	1024	1024	32	32	>1024
9	**2Cc**	256	32	2	4	>256
10	**2Cd**	256	32	8	8	128
11	**2Ce**	>128	>128	>128	>128	>128
12	**2Da**	>1024	>1024	512	512	>1024
13	**2Dc**	128	8	4	4	64
14	**2Dd**	256	16	8	4	128
15	**2De**	128	16	8	8	>128
16	**2Df**	>128	128	128	128	>128
17	**2Dg**	>128	128	16	8	64
18	**2Dh**	>1024	>1024	>1024	>1024	>1024
19	**2Di**	128	>128	64	64	>128
20	**2Dj**	128	128	4	4	>128
21	**2Dk**	128	128	4	2	>128
22	**2Dl**	>128	>128	8	8	
20	**2Dm**	1024	1024	64	64	>1024
21	**2Dn**	128	32	8	8	>256
22	**2Do**	8	8	8	8	16
23	vancomycin	2	>128	1	>128	1
24	teicoplanin	0.5	>128	0.125	64	1
25	synercid	4	4	4	8	1
26	daptomycin	32	16	4	8	2

[a] MICs = minimum inhibitory concentrations. [b] Bacterial strain L568 (isogenic of L569). [c] Bacterial strain L2215 clin. isolate Van-A. [d] Bacterial strain L559 (isogenic of L560). [e] Bacterial strain L560. [f] Bacterial strain L613 clin. isolate Met-R.

and the resulting residue was dissolved in dioxane/H_2O (2:1, 450 mL), neutralized with Na_2CO_3 to pH 7, and then more Na_2CO_3 (2.06 g, 19.5 mmol) and Boc_2O (1.60 g, 7.11 mmol) were added. After the mixture had been stirred at room temperature overnight, the mixture was diluted with H_2O, acidified with 5% HCl to pH 3–4, and then extracted with EtOAc. The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash-column chromatography to afford **4A** (4.35 g, 81%). M.p. 123–126 °C; $[\alpha]_D = +2.3$ ($c = 0.31$ in MeOH); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 7.81$ (dd, $J = 7.2$, 2.0 Hz, 1H; ArH), 7.22 (m, 1H; ArH), 7.18–7.05 (m, 6H; ArH), 6.33 (s, 2H; ArH), 5.15 (d, $J = 4.2$ Hz, 1H; CH), 4.56–4.46 (m, 2H; CH), 4.43 (d, $J = 4.2$ Hz, 1H; CH), 4.01 (dd, $J = 9.2$, 5.6 Hz, 1H; CH), 3.75 (s, 3H; OCH_3), 3.68 (s, 3H; CO_2CH_3), 3.20 (dd, $J = 14.0$, 4.2 Hz, 1H; CH_2), 2.95–2.65 (m, 3H; CH_2), 1.65–1.50 (m, 1H; C*H*-$(CH_3)_2$), 1.40 (s, 9H; $C(CH_3)_3$), 1.35–1.25 (m, 2H; CH_2), 0.87 (d, $J = 6.0$ Hz, 3H; CH_3), 0.85 ppm (d, $J = 6.0$ Hz, 3H; CH_3); ^{13}C NMR (50.3 MHz, CD_3OD): $\delta = 176.6$, 174.4, 173.4, 173.2, 158.5, 154.6 (d, $J = 260$ Hz), 152.0, 138.7, 138.1, 137.9, 136.5, 135.9, 135.5, 130.6, 130.4, 129.8, 128.2, 127.9, 119.6 (d, $J = 21$ Hz), 107.8, 81.0, 75.4, 61.1, 57.4, 56.8, 56.1, 54.7, 53.2, 42.0, 38.9, 37.6, 29.0, 26.1, 23.8, 21.9 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3668$, 3460, 3329, 3021, 2958, 1738, 1682, 1606, 1540, 1456, 1353, 1254, 1222, 1166, 1013 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{40}H_{50}N_5O_{13}FNa$: 850.3287 $[M+Na]^+$; found: 850.3281.

Compounds 3A and 3A′: A solution of **4A** (1.24 g, 1.50 mmol) and anhydrous CsF (4.56 g, 30 mmol) in dry DMSO (150 mL) was stirred at room temperature for 16 h. After this time, the reaction mixture was diluted with saturated aqueous NH_4Cl, acidified with 5% HCl to pH 4, and extracted with EtOAc. The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash-column chromatography to afford **3A** and **3A′** (872 mg, 72%). For compound **3A**: m.p. 135–139 °C; $[\alpha]_D = -6.0$ ($c = 0.20$ in MeOH); ^{1}H NMR (200 MHz, CD_3CN): $\delta = 8.19$ (s, 1H; ArH), 7.37 (dd, $J = 8.4$, 1.9 Hz, 1H; ArH), 7.30–7.00 (m, 8H; ArH, 2×NH), 6.62 (m, 1H; NH), 6.57 (s, 1H; ArH), 5.79 (m, 1H; NH), 5.50 (s, 1H; ArH), 5.05 (m, 1H; CH), 4.60–4.40 (m, 3H; 3×CH), 4.16 (dd, $J = 7.6$, 4.9 Hz, 1H; CH), 3.92 (s, 3H; OCH_3), 3.60 (s, 3H; CO_2CH_3), 3.36 (dd, $J = 13.5$, 4.9 Hz, 1H; CH_2), 2.93–2.56 (m, 3H; CH_2), 1.66 (m, 1H; C*H*$(CH_3)_2$), 1.57–1.25 (m, 2H; CH_2), 1.44 (s, 9H; $C(CH_3)_3$), 0.97 (d, $J = 6.6$ Hz, 3H; CH_3), 0.94 ppm (d, $J = 6.6$ Hz, 3H; CH_3); ^{13}C NMR (75.0 MHz, CD_3OD): $\delta = 175.6$, 174.0, 173.3, 171.0, 158.1, 154.1, 152.4, 149.2, 144.1, 137.7, 137.2, 135.6, 135.1, 130.1, 129.4, 127.8, 127.2, 126.4, 109.4, 106.1, 81.0, 74.3, 61.5, 58.2, 56.8, 55.7, 54.2, 52.8, 41.0, 40.7, 37.2, 28.7, 25.7, 23.5, 22.0 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3692$, 3651, 3525, 3406, 3032, 3008, 2960, 2937, 2873, 1737, 1687, 1596, 1578, 1536, 1498, 1456, 1438, 1394, 1369, 1352, 1271, 1249, 1192, 1168, 1090 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{40}H_{49}N_5O_{13}Na$: 830.3225 $[M+Na]^+$; found: 830.3233. For compound **3A′**: m.p. 139–143 °C; $[\alpha]_D = +25.3$ ($c = 0.15$ in MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.87$ (s, 1H; ArH), 7.73 (d, $J = 7.6$ Hz, 1H; ArH), 7.36–7.30 (m, 2H; ArH, NH), 7.30–6.90 (m, 5H; ArH), 6.99 (d, $J = 7.1$ Hz, 1H; NH), 6.83 (s, 1H; ArO*H*), 6.57 (d, $J = 8.3$ Hz, 1H; NH), 6.47 (s, 1H; ArH), 5.27 (s, 1H; ArH), 5.20–5.05 (m, 2H; NH, OH), 4.89 (m, 1H; CH), 4.82 (m, 1H; CH), 4.66 (m, 1H; CH), 4.48 (dd, $J = 8.9$, 2.9 Hz, 1H; CH), 4.15 (m, 1H; CH), 4.04 (s, 3H; OCH_3), 3.73 (s, 3H; CO_2CH_3), 3.50 (dd, $J = 13.4$, 4.8 Hz, 1H; CH_2), 3.00–2.60 (m, 3H; CH_2), 1.80–1.50 (m, 3H; CH_2, C*H*$(CH_3)_2$), 1.47 (s, 9H; $C(CH_3)_3$), 0.97 (d, $J = 6.0$ Hz, 3H; CH_3), 0.90 ppm (d, $J = 6.0$ Hz, 3H; CH_3); ^{13}C NMR (62.5 MHz, CD_3OD): $\delta = 175.8$, 174.0, 173.6, 170.8, 158.4, 153.4, 152.7, 151.6, 148.6, 144.2, 137.2, 136.8, 136.1, 134.6, 130.5, 129.4, 128.9, 127.8, 126.8, 109.4, 104.1, 81.0, 74.5, 61.2, 58.4, 56.4, 55.7, 54.4, 52.8, 40.6, 37.2, 27.9, 25.9, 23.4, 21.9 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3686$, 3627, 3525, 3412, 3034, 3011, 2961, 2937, 2874, 1737, 1690, 1598, 1537, 1511, 1456, 1438, 1369, 1352, 1238, 1196, 1169, 1090, 1039 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{40}H_{49}N_5O_{13}Na$: 830.3225 $[M+Na]^+$; found: 830.3215.

Compound 3B: Following the procedure described for compound **3**, compound **3B** was prepared by starting from compound **4B**. M.p. 132–136 °C; $[\alpha]_D = -60.7$ ($c = 1.70$ in $CHCl_3$); ^{1}H NMR (250 MHz, CD_3OD): $\delta = 8.29$ (s, 1H; ArH), 7.38 (dd, $J = 8.5$, 2.0 Hz, 1H; ArH), 7.28–7.06 (m, 5H; ArH), 7.02 (d, $J = 8.5$ Hz, 1H; ArH), 6.32 (d, $J = 2.0$ Hz, 1H; ArH), 5.66 (d, $J = 2.0$ Hz, 1H; ArH), 4.64–4.50 (m, 4H; CH), 4.20 (dd, $J = 7.9$, 7.0 Hz, 1H; CH), 3.91 (s, 3H; OCH_3), 3.74 (s, 3H; CO_2CH_3), 3.42 (dd, $J = 14.1$, 5.3 Hz, 1H; CH_2), 3.02–2.75 (m, 3H; CH_2), 1.68 (m, 1H; CH), 1.55 (m, 2H; CH_2), 1.48 (s, 9H; $C(CH_3)_3$), 0.97 (d, $J = 6.5$ Hz, 3H; CH_3), 0.92 ppm (d, $J = 6.5$ Hz, 3H; CH_3); ^{13}C NMR (62.5 MHz, CD_3OD): $\delta = 173.0$, 172.9, 172.1, 166.7, 154.1, 152.5, 151.6, 149.4, 147.9, 144.0, 137.7, 137.3, 137.1, 135.2, 134.3, 130.4, 129.3, 127.7, 126.4, 111.1, 107.6, 80.8, 73.7, 61.4, 59.7, 56.0, 55.8, 54.3, 52.6, 40.9, 40.1, 36.8, 28.5, 25.8, 23.1, 21.9 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3424$, 3406, 3029, 3023, 3013, 2959, 2936, 2872, 1741, 1685, 1594, 1534, 1497, 1234, 1230, 1208, 1167, 1038 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{40}H_{49}N_5O_{13}Na$: 830.3225 $[M+Na]^+$; found: 830.3215.

Compound 18: Pd/C catalyst (10%, 5 mg) was added to a stirred solution of compound **3A** (30 mg, 0.037 mmol) in MeOH (1.0 mL). The mixture was then hydrogenated under a H_2 atmosphere (balloon) at room temperature for 2 h. After this time, the mixture was filtered through a short celite pad. The solvent was removed and the residue was directly used for next step. Et_3N (31 μL, 0.223 mmol) and Lauroyl chloride (35 μL, 0.149 mmol) were added to the solution of the above crude product in CH_2Cl_2 (2.0 mL). After the mixture had been stirred at room temperature for 4 h, the reaction was quenched by the addition of aqueous NH_4Cl. The two phases were separated and 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 mixture of the above crude product and K_2CO_3 (20 mg, 0.145 mmol) in MeOH/H_2O (10:1, 5.5 mL) was stirred at room temperature for 20 min. The resulting residue was acidified to pH 2–3 with citric acid and concentrated to remove the volatile. The residue was diluted with water and extracted with EtOAc. The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash-column chromatography (silica gel, heptane/EtOAc 1:2) to afford **18** (16 mg, 45%). M.p. 78–84 °C; $[\alpha]_D = -17.4$ ($c = 0.81$ in $CHCl_3$); ^{1}H NMR (250 MHz, CD_3OD): $\delta = 7.95$ (s, 1H; ArH), 7.25–7.17 (m, 5H; ArH), 7.07 (dd, $J = 7.8$, 1.9 Hz, 1H; ArH), 6.90 (d, $J = 7.8$ Hz, 1H; ArH), 6.48 (d, $J = 1.8$ Hz, 1H; ArH), 5.40 (d, $J = 1.8$ Hz, 1H; ArH), 5.07 (m, 1H; CH), 4.70–4.42 (m, 3H; CH), 4.30 (m, 1H; CH), 3.96 (s, 3H; OCH_3), 3.70 (s, 3H; CO_2CH_3), 3.30 (m, 1H; CH_2), 2.91 (dd, $J = 13.7$, 5.0 Hz, 1H; CH_2), 2.82–2.62 (m, 2H; CH_2), 2.19 (t, $J = 7.2$ Hz, 2H; CH_2), 1.86–1.50 (m, 5H; CH, CH_2), 1.46 (s, 9H; $C(CH_3)_3$), 1.29 (m, 16H; CH_2), 1.04 (d, $J = 6.5$ Hz, 3H; CH_3), 1.02 (d, $J = 6.5$ Hz, 3H; CH_3), 0.89 ppm (d, $J = 6.7$ Hz, 3H; CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 173.7$, 173.6, 172.7, 170.7, 169.7, 156.1, 151.7, 150.1, 145.8, 136.2, 134.2, 134.0, 129.8, 129.4, 129.2, 128.8, 127.2, 125.0, 123.6, 107.5, 105.4, 81.0, 73.7, 61.6, 55.2, 54.3, 53.6, 52.8, 41.5, 39.1, 37.2, 37.1, 36.0, 32.0, 29.7, 29.6, 29.4, 29.3, 29.2, 28.4, 25.4, 25.1, 23.3, 22.8, 21.6, 14.2 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3530$, 3416, 3032, 3013, 2929, 2856, 1739, 1683, 1597, 1509, 1368, 1265, 1167, 1121, 1038 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{52}H_{73}N_5O_{12}Na$: 982.5153 $[M+Na]^+$; found: 982.5149.

Compound 2Ab: The reaction conditions for preparing compound **19** were similar to those of compound **18**, except that the final hydrolysis with K_2CO_3 in MeOH/H_2O was conducted for 20 h. A solution of the above crude product was dissolved in CH_3CN (1.0 mL) and conc. HCl (0.1 mL). After being stirred at room temperature for 2 h, the reaction mixture was concentrated to dryness and the crude product obtained was purified by HPLC to afford compound **2Ab** (15 mg, 85%). M.p. 165–168 °C; $[\alpha]_D = -82.4$ ($c = 0.81$ in acetone); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 7.94$ (s, 1H; ArH), 7.24–7.06 (m, 7H; ArH), 6.51 (d, $J = 1.9$ Hz, 1H; ArH), 5.57 (d, $J = 1.9$ Hz, 1H; ArH), 5.11 (d, $J = 3.1$ Hz, 1H; CH), 4.65–4.55 (m, 2H; CH), 4.38 (d, $J = 3.1$ Hz, 1H; CH), 4.33 (m, 1H, CH), 3.95 (s, 3H; OCH_3), 3.23 (dd, $J = 13.7$, 5.2 Hz, 1H; CH_2), 3.05–2.70 (m, 3H; CH_2), 2.36 (t, $J = 7.6$ Hz, 2H; CH_2), 1.85–1.55 (m, 5H; CH, CH_2), 1.26 (m, 16H; CH_2), 1.07 (d, $J = 5.4$ Hz, 3H; CH_3), 1.05 (d, $J = 5.3$ Hz, 3H; CH_3), 0.88 ppm (d, $J = 6.8$ Hz, 3H; CH_3); ^{13}C NMR (50.3 MHz, CD_3OD): $\delta = 176.2$, 172.5, 170.5, 168.9, 167.4, 153.6, 151.0, 137.4, 135.8, 134.3, 133.2, 130.6, 129.8, 129.3, 129.2, 127.5, 125.0, 123.7, 110.0, 105.7, 74.1, 66.8, 63.0, 61.3, 58.6, 56.9, 54.6, 43.0, 43.0, 39.4, 37.3, 32.7, 28.8, 26.3, 26.3, 25.5, 23.4, 23.2, 22.7, 14.4 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3674$, 3529, 3285, 3035, 3009, 2976, 2929, 2856, 1677, 1598, 1531, 1455, 1435, 1345, 1262, 1193, 1121, 1035 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{46}H_{63}N_5O_{10}Na$: 868.4473 $[M+Na]^+$; found: 868.4510.

Compound 20: To a solution of **3A** (50 mg, 0.062 mmol) in MeOH/H_2O (10:1, 0.8 mL) was added K_2CO_3 (51 mg, 0.372 mmol). After the reaction mixture had been stirred at room temperature for 24 h, it was concentrated to remove the volatile. The resulting residue was diluted with H_2O and washed with heptane/ether (1:1). The aqueous phase was acidified to pH 2–3 with citric acid and extracted with EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum to afford **20** (47 mg, 96%), which was used without further purification. $[\alpha]_D = -31.0$ ($c = 0.20$ in acetone); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 8.34$ (s, 1H; ArH), 7.38 (dd, $J = 8.4$, 1.9 Hz, 1H; ArH), 7.29–7.11 (m, 5H; ArH), 7.08 (d, $J = 8.4$ Hz, 1H; ArH), 6.56 (d, $J = 1.6$ Hz, 1H; ArH), 5.48 (d, $J = 1.6$ Hz, 1H; ArH), 5.03 (m, 1H; CH), 4.60 (m, 2H; 2×CH), 4.51 (d, $J = 2.8$ Hz, 1H; ArH), 4.19 (dd, $J = 9.7$, 5.5 Hz, 1H; CH), 3.91 (s, 3H; OCH_3), 3.43 (dd, $J = 13.9$, 5.1 Hz, 1H; CH_2), 2.96–2.71 (m, 3H; CH_2), 1.71–1.49 (m, 3H; CH_2), 1.49 (s, 9H; $C(CH_3)_3$), 1.00 (d, $J = 6.5$ Hz, 3H; CH_3), 0.96 ppm (d, $J = 6.4$ Hz, 3H; CH_3); ^{13}C NMR (50.3 MHz, CD_3OD): $\delta = 175.4$, 175.2, 172.8, 170.6, 158.0, 153.8, 152.1, 148.9, 143.9, 138.3, 137.0, 136.7, 135.3, 135.2, 129.8, 129.0, 127.3, 126.9, 126.0, 109.0, 105.6, 80.6, 74.2, 68.6, 61.1, 57.5, 57.0, 55.4, 53.8, 40.4, 40.1, 36.9, 28.3, 25.3, 23.1, 21.6 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3668$, 3524, 3373, 3024, 2959, 2933, 2872, 1686, 1596, 1536, 1514, 1456, 1438, 1369, 1351, 1272, 1235, 1164, 1117, 1089, 1036 cm^{-1}.

Compound 2Ae: To a solution of **3A** (30 mg, 0.037 mmol) in MeOH (1.0 mL) was added $SOCl_2$ (0.1 mL). After the reaction mixture had been stirred at room temperature for 1 h, it was concentrated to dryness to afford quantitatively compound **2Ae**, which was used without further purification. $[\alpha]_D = -14.4$ ($c = 0.25$ in MeOH); ^{1}H NMR (200 MHz, CD_3OD): $\delta = 8.11$ (d, $J = 1.8$ Hz, 1H; ArH), 7.47 (dd, $J = 8.6$, 1.8 Hz, 1H; ArH), 7.20–7.06 (m, 6H; ArH), 6.49 (d, $J = 1.9$ Hz, 1H; ArH), 5.64 (d, $J = 1.9$ Hz, 1H; ArH), 4.86 (m, 1H; CH), 4.60–4.42 (m, 3H; 3×CH), 4.07 (m, 1H; CH), 3.93 (s, 3H; OCH_3), 3.69 (s, 3H; CO_2CH_3), 3.45 (dd, $J = 14.1$, 5.3 Hz, 1H; CH_2), 3.20–2.80 (m, 3H; CH_2), 1.80–1.60 (m, 3H; CH, CH_2), 1.05 (d, $J = 5.5$ Hz, 3H; CH_3), 0.98 ppm (d, $J = 5.4$ Hz, 3H; CH_3); ^{13}C NMR (75.0 MHz, CD_3COCD_3): $\delta = 173.1$, 170.8, 168.3, 170.0, 154.5, 151.3, 150.6, 143.8, 138.5, 136.0, 135.9, 130.0, 128.9, 127.2, 109.0, 75.6, 61.6, 61.4, 57.1, 55.8, 55.0, 51.9, 41.4, 41.0, 37.2, 25.6, 23.1, 23.0 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3691$, 3530, 3039, 3024, 2995, 2954, 2852, 1742, 1677, 1601, 1534, 1437, 1348, 1262, 1232, 1226, 1216, 1202, 1103 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{35}H_{42}N_5O_{11}$: 708.2881 $[M+H]^+$; found: 708.2876.

Compound 21: HOBt (11 mg, 0.081 mmol) and EDC (16 mg, 0.081 mmol) were added to a solution of the above crude amine **2Ae** and *N*-Boc-3-amino-propionic acid (14 mg, 0.070 mmol) in CH_2Cl_2 (3.0 mL). The reaction mixture was stirred at room temperature for 12 h and was then diluted with CH_2Cl_2 (100 mL). The resulting mixture was washed with 5% aqueous HCl, saturated $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum. The mixture of the above crude product and K_2CO_3 (14 mg, 0.10 mmol) in MeOH/H_2O (10:1, 5.5 mL) was stirred at room temperature for 20 min. The resulting residue was acidified to pH 2–3 with citric acid and concentrated to remove the volatile. The residue was diluted with water and extracted with EtOAc. The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash-column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) to afford **21** (19 mg, 60%). $[\alpha]_D = -7.1$ ($c = 0.41$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 1.9$ Hz, 1H; ArH), 7.51 (dd, $J = 8.6$, 1.9 Hz, 1H; ArH), 7.30–7.16 (m, 5H; ArH), 7.11 (d, $J = 8.6$ Hz, 1H; ArH), 7.10 (d, $J = 6.5$ Hz, 1H; NH), 7.01 (d, $J = 10.2$ Hz, 1H; NH), 6.62 (d, $J = 1.9$ Hz, 1H; ArH), 6.24 (m, 2H; NH), 5.43 (d, $J = 9.1$ Hz, 1H; NH), 5.24 (d, $J = 1.9$ Hz, 1H; ArH), 5.07 (m, 1H; CH), 4.95–4.75 (m, 3H; 3×CH), 4.10 (m, 1H; CH), 4.04 (s, 3H; OCH_3), 3.75 (s, 3H; CO_2CH_3), 3.69 (dd, $J = 13.7$, 3.8 Hz, 1H; CH_2), 3.30 (m, 2H; CH_2), 2.99 (dd, $J = 13.7$, 5.3 Hz, 1H; CH_2), 2.76 (m, 2H), 2.32 (t, $J = 5.6$ Hz, 2H; CH_2), 1.86 (m, 3H; CH, CH_2), 1.46 (s, 9H; $C(CH_3)_3$), 1.04 (d, $J = 6.5$ Hz, 3H; CH_3), 1.01 ppm (d, $J = 6.5$ Hz, 3H; CH_3); IR ($CHCl_3$): $\tilde{\nu} = 3686$, 3627, 3332, 3030, 3014, 2977, 1742, 1684, 1534, 1515, 1436, 1349, 1232, 1202, 1088, 1038 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{43}H_{54}N_6O_{14}Na$: 901.3596 $[M+Na]^+$; found: 901.3608.

Compound 23: $SOCl_2$ (0.1 mL) was added to a solution of **21** (18 mg, 0.021 mmol) in MeOH (1.0 mL). After the reaction mixture had been stirred at room temperature for 1 h, it was concentrated to dryness to afford the amine quantitatively, which was used without further purification. Et_3N (5.6 uL, 0.04 mmol), HOBt (7 mg, 0.049 mmol), and EDC (10 mg, 0.049 mmol) were added to a solution of the above crude amine and acid **20** (36 mg, 0.045 mmol) in CH_2Cl_2 (3.0 mL). The reaction mixture was stirred at room temperature for 12 h and was then diluted with CH_2Cl_2 (100 mL). The resulting mixture was washed with 5% aqueous HCl, saturated $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum. The mixture of the above crude product and K_2CO_3 (18 mg, 0.13 mmol) in MeOH/H_2O (10:1, 5.5 mL) was stirred at room

temperature for 20 min. The resulting residue was acidified to pH 2–3 with citric acid and concentrated to remove the volatile. The residue was diluted with water and extracted with EtOAc. The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash-column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) to afford **23** (13 mg, 41%). $[\alpha]_D = -28.3$ ($c = 0.63$ in MeOH); ^{1}H NMR (300 MHz, CD_3CD): $\delta = 8.32$ (s, 1H), 8.19 (d, $J = 1.9$ Hz, 1H; ArH), 7.43 (dd, $J = 8.1$, 1.4 Hz, 1H; ArH), 7.37 (dd, $J = 8.4$, 1.9 Hz, 1H; ArH), 7.23–7.00 (m, 12H; ArH), 6.60 (d, $J = 1.8$ Hz, 1H; ArH), 6.51 (d, $J = 1.9$ Hz, 1H; ArH), 5.48 (d, $J = 1.9$ Hz, 1H; ArH), 5.38 (d, $J = 1.8$ Hz, 1H; ArH), 5.02 (d, $J = 2.4$ Hz, 1H; CH), 4.93 (d, $J = 3.4$ Hz, 1H; CH), 4.62–4.52 (m, 5H; 5×CH), 4.37 (d, $J = 2.4$ Hz, 1H; CH), 4.25 (dd, $J = 9.7$, 5.4 Hz, 1H; CH), 4.18 (dd, $J = 9.8$, 5.4 Hz, 1H; CH), 3.91 (s, 3H; OCH_3), 3.92 (s, 3H; OCH_3), 3.67 (s, 3H; CO_2CH_3), 3.50–3.34 (m, 10H; CH_2), 2.43 (t, $J = 7.0$ Hz, 2H; CH_2), 1.80–1.50 (m, 6H; CH, CH_2), 1.48 (s, 9H; $C(CH_3)_3$), 0.98 (d, $J = 5.1$ Hz, 3H; CH_3), 0.96 (d, $J = 5.9$ Hz, 3H; CH_3), 0.91 ppm (d, $J = 6.3$ Hz, 6H; CH_3); ^{13}C NMR (50.3 MHz, CD_3OD): $\delta = 175.8$, 175.2, 174.7, 174.1, 174.0, 173.4, 173.1, 171.2, 171.1, 158.4, 154.3, 152.7, 152.5, 149.6, 149.4, 114.4, 137.9, 137.5, 135.9, 135.7, 135.4, 130.3, 129.6, 129.5, 128.0, 127.8, 127.4, 126.7, 126.4, 110.0, 109.6, 106.1, 106.0, 81.0, 75.1, 74.5, 61.6, 61.5, 58.3, 57.7, 57.2, 56.0, 55.7, 54.4, 52.9, 50.6, 41.0, 40.6, 40.5, 37.3, 36.9, 36.7, 36.2, 28.7, 25.9, 25.8, 23.6, 23.5, 22.1, 21.9 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3713$, 3671, 3524, 3335, 3021, 2991, 2930, 2853, 1736, 1685, 1597, 1534, 1498, 1458, 1350, 1217, 1142 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{77}H_{91}N_{11}O_{24}Na$: 1576.6136 $[M+Na]^+$; found: 1576.6108.

Compound 2Al: LiOH·H_2O (2.2 mg, 0.05 mmol) was added to a solution of **23** (16 mg, 0.010 mmol) in THF/H_2O (3:1, 2 mL) at room temperature. After the reaction mixture had been stirred for 4 h, it was acidified with citric acid to pH 3–4 and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under vacuum to dryness. To a solution of the above crude product was dissolved in CH_3CN (1.0 mL) and conc. HCl (0.1 mL), and the resulting mixture stirred at room temperature for 2 h. After this time, the reaction mixture was concentrated to dryness and the crude product obtained was purified by HPLC to afford compound **2Al** (12 mg, 79%). M.p. >220 °C; $[\alpha]_D = -62.4$ ($c = 0.58$ in acetone); ^{1}H NMR (250 MHz, CD_3CD): $\delta = 8.23$ (s, 1H; ArH), 8.02 (s, 1H; ArH), 7.44 (d, $J = 6.0$ Hz, 1H; ArH), 7.35 (dd, $J = 8.0$ Hz, 1H; ArH), 7.26–7.00 (m, 12H; ArH), 6.59 (s, 1H; ArH), 6.55 (d, $J = 1.9$ Hz, 1H; ArH), 5.49 (s, 1H; ArH), 5.47 (d, $J = 1.9$ Hz, 1H; ArH), 5.19 (m, 1H; CH), 5.02 (m, 1H; CH), 4.68–4.52 (m, 4H; 4×CH), 4.50 (d, $J = 2.7$ Hz, 1H; CH), 4.32 (d, $J = 1.7$ Hz, 1H; CH), 4.26 (m, 1H; CH), 4.16 (m, 1H; CH), 3.93 (s, 3H; OCH_3), 3.91 (s, 3H; OCH_3), 3.70–3.32 (m, 4H; CH_2), 3.10–2.70 (m, 6H; CH_2), 2.47 (t, $J = 7.4$ Hz, 2H; CH_2), 1.96–1.40 (m, 6H; CH, CH_2), 1.06 (d, $J = 6.5$ Hz, 3H; CH_3), 1.01 (d, $J = 6.7$ Hz, 3H; CH_3), 0.98 (d, $J = 6.3$ Hz, 3H; CH_3), 0.92 ppm (d, $J = 5.9$ Hz, 3H; CH_3); IR (KBr): $\tilde{\nu} = 3658$, 3548, 3020, 2997, 2854, 1781, 1710, 1463, 1419, 1364, 1223, 1172 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{71}H_{82}N_{11}O_{22}$: 1440.5635 $[M+H]^+$; found: 1440.5635.

Compound 29: HBr/AcOH (33%, 400 μL) was added to a solution of 1,3,4,6-*tetra*-*O*-acetyl-2-deoxy-2-lauric amido-D-glucopyranose **27** (70 mg, 0.13 mmol) in AcOH (2 mL) at room temperature. After the reaction mixture had been stirred for 3 h at room temperature, it was diluted with ice-water and 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 the next reaction. Compound **3A** (35 mg, 0.043 mmol), 10% aqueous Na_2CO_3 (1.0 mL), and catalytic amount of $(n\mathrm{Bu})_4NHSO_4$ were added to the above solution. After the reaction mixture had been stirred at room temperature for 4 h, it was acidified with citric acid to pH 4–5 and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 and 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 to afford **29** (42 mg, 76%). M.p. 116–118 °C; $[\alpha]_D = -19.4$ ($c = 1.6$ in $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 8.32$ (s, 1H; ArH), 7.39 (dd, $J = 8.6$, 2.0 Hz, 1H; ArH), 7.32–7.14 (m, 5H; ArH), 7.11 (d, $J = 8.6$ Hz, 1H; ArH), 6.82 (d, $J = 1.8$ Hz, 1H; ArH), 5.79 (d, $J = 1.8$ Hz, 1H; ArH), 5.38 (t, $J = 9.6$ Hz, 1H; CH), 5.32 (d, $J = 9.0$ Hz, 1H; CH), 5.07 (m, 1H; CH), 4.97 (m, 1H; CH), 4.67 (d, $J = 3.8$ Hz, 1H; CH), 4.60 (m, 2H; CH), 4.35–4.10 (m, 4H; CH, CH, CH_2), 4.04 (m, 1H; CH), 3.85 (s, 3H; OCH_3), 3.71 (s, 3H; CO_2CH_3), 3.24 (dd, $J = 13.7$, 5.0 Hz, 1H; CH_2), 3.00–2.58 (m, 3H; CH_2), 2.17 (t, $J = 7.8$ Hz, 2H; CH_2), 2.07 (s, 3H; $COCH_3$), 2.02 (s, 3H; $COCH_3$), 2.00 (s, 3H; $COCH_3$), 1.80–1.45 (m, 5H), 1.48 (s, 9H; $C(CH_3)_3$), 1.27 (m, 16H; CH_2), 1.00 (d, $J = 6.5$ Hz, 3H; CH_3), 0.95 (d, $J = 6.4$ Hz, 3H; CH_3), 0.88 ppm (t, $J = 4.4$ Hz, 3H; CH_3); IR ($CHCl_3$): $\tilde{\nu} = 3658$, 3432, 3028, 2929, 1744, 1686, 1593, 1536, 1499, 1438, 1369, 1237, 1218, 1159, 1047 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{64}H_{88}N_6O_{21}Na$: 1299.5900 $[M+Na]^+$; found: 1299.5911.

Compound 30: LiOH·H_2O (7 mg, 0.16 mmol) was added to a solution of compound **29** (20 mg, 0.016 mmol) in THF/H_2O (3:1, 4 mL) at 0 °C. After the reaction mixture had been stirred for 4 h at 0 °C, it was acidified with citric acid to pH 3–4 and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under vacuum to afford compound acid **30** (11 mg, 62%), which proved to be of sufficient purity for direct use in the next step. M.p. 164–168 °C; $[\alpha]_D = +4.2$ ($c = 0.53$ in MeOH); ^{1}H NMR (200 MHz, CD_3OD): $\delta = 8.34$ (s, 1H; ArH), 7.39 (dd, $J = 8.5$, 1.8 Hz, 1H; ArH), 7.28–7.12 (m, 6H; ArH), 6.96 (d, $J = 1.5$ Hz, 1H; ArH), 5.71 (d, $J = 1.5$ Hz, 1H; ArH), 5.07 (d, $J = 8.4$ Hz, 1H; CH), 5.05 (m, 1H; CH), 4.60 (m, 3H; CH), 4.18 (dd, $J = 8.9$, 5.9 Hz, 1H; CH), 3.85 (s, 3H; OCH_3), 4.06–3.90, 3.78–3.40 (m, 7H), 3.00–2.70 (m, 3H; CH_2), 2.25 (t, $J = 8.3$ Hz, 2H; CH_2), 1.80–1.54 (m, 5H), 1.49 (s, 9H; $C(CH_3)_3$), 1.27 (m, 16H; CH_2), 1.00 (d, $J = 6.4$ Hz, 3H; CH_3), 0.95 (d, $J = 6.3$ Hz, 3H; CH_3), 0.86 ppm (t, $J = 4.4$ Hz, 3H; CH_3); ^{13}C NMR (50.3 MHz, CD_3OD): $\delta = 176.9$, 175.9, 175.6, 173.6, 171.1, 158.6, 154.4, 153.3, 149.1, 144.4, 137.9, 137.5, 136.1, 135.5, 130.5, 129.6, 128.7, 127.9, 127.3, 127.1, 126.8, 126.2, 110.9, 109.2, 101.2, 81.2, 78.5, 76.1, 74.6, 72.2, 62.7, 62.0, 58.6, 57.3, 54.8, 54.4, 44.0, 41.0, 40.7, 40.5, 38.1, 37.7, 37.5, 35.0, 33.1, 31.0, 30.6, 30.6, 30.6, 30.4, 29.9, 29.8, 28.8, 27.0, 26.2, 25.9, 23.8, 23.6, 22.2, 14.5 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3648$, 3317, 3018, 2991, 2956, 2929, 2856, 1712, 1651, 1598, 1558, 1536, 1513, 1497, 1456, 1435, 1368, 1352, 1283, 1239, 1160, 1105, 1009 cm^{-1}; MS (ESI): *m/z*: 1135 $[M-H]^+$.

Compound 2Aj: Following the procedure described for compound **2Ab**, compound **2Aj** (8 mg, 57%) was prepared by starting from compound **30** (15 mg, 0.013 mmol). M.p. 220 °C; $[\alpha]_D = -100$ ($c = 0.25$ in acetone); ^{1}H NMR (200 MHz, CD_3OD): $\delta = 8.13$ (d, $J = 1.8$ Hz, 1H; ArH), 7.45 (dd, $J = 8.4$, 1.8 Hz, 1H; ArH), 7.30–7.15 (m, 5H; ArH), 7.12 (d, $J = 8.4$, 1H; ArH), 6.91 (s, 1H; ArH), 5.72 (s, 1H; ArH), 5.05 (d, $J = 8.5$ Hz, 1H; CH), 4.94 (m, 1H; CH), 4.60–4.40 (m, 3H; CH), 4.18 (dd, $J = 8.9$, 5.9 Hz, 1H; CH), 3.85 (s, 3H; OCH_3), 4.06–3.90, 3.78–3.40 (m, 6H), 3.69 (dd, $J = 11.8$, 5.7 Hz, 1H; CH), 3.25–3.00 (m, 3H; CH_2), 2.89 (t, $J = 6.2$ Hz, 2H; CH_2), 1.90–1.50 (m, 5H), 1.26 (m, 16H; CH_2), 1.03 (d, $J = 5.3$ Hz, 3H; CH_3), 0.95 (d, $J = 5.8$ Hz, 3H; CH_3), 0.86 ppm (t, $J = 5.7$ Hz, 3H; CH_3); IR ($CHCl_3$): $\tilde{\nu} = 3692$, 3519, 3028, 3006, 2984, 2934, 2855, 1731, 1706, 1673, 1464, 1395, 1376, 1327, 1250, 1176, 1146, 1046 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{52}H_{72}N_6O_{16}Na$: 1059.4903 $[M+Na]^+$; found: 1059.4883.

Compound 31: 1-Fluoro-4-nitrobenzene (80 μL, 0.76 mmol) and CsF (303 mg, 1.94 mmol) were added to a solution of compound **3B** (104 mg, 0.129 mmol) in DMSO (4.0 mL). After the reaction mixture had been stirred at room temperature for 2 h, it was extracted with EtOAc. 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 (silica gel, CH_2Cl_2/MeOH 100:1) to afford compound **31** (120 mg, 100%). M.p. 124–126 °C; $[\alpha]_D = -41.5$ ($c = 0.68$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.20$ (d, $J = 9.0$ Hz, 2H; ArH), 8.18 (s, 1H; ArH), 7.58 (dd, $J = 8.7$, 1.9 Hz, 1H; ArH), 7.34 (m, 1H; NH), 7.28–7.06 (m, 5H; ArH), 7.05 (d, $J = 8.7$ Hz, 1H; ArH), 6.96 (d, $J = 9.0$ Hz, 2H; ArH), 6.95 (m, 1H; NH), 6.50 (d, $J = 9.1$ Hz, 1H; NH), 6.42 (d, $J = 2.3$ Hz, 1H; ArH), 5.69 (d, $J = 2.1$ Hz, 1H; ArH), 5.17 (m, 2H; NH, CH), 4.84 (m, 2H; CH), 4.23 (d, $J = 2.6$ Hz, 1H; CH), 4.10 (m, 1H; CH), 3.87 (s, 3H; OCH_3), 3.62 (s, 3H; CO_2CH_3), 3.60 (m, 1H; CH_2), 3.08 (dd, $J = 13.6$, 6.4 Hz, 1H; CH_2), 2.94 (dd, $J = 13.6$, 5.3 Hz, 1H; CH_2), 2.84 (dd, $J = 13.6$, 3.4 Hz, 1H; CH_2), 1.62 (m, 3H; CH, CH_2), 1.46 (s, 9H; C-$(CH_3)_3$), 0.96 (d, 3H, $J = 6.4$ Hz; CH_3), 0.90 ppm (d, 3H, $J = 6.4$ Hz; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.3$, 171.8, 170.6, 169.0, 163.0, 156.6, 154.3, 148.5, 147.5, 143.2, 142.9, 141.3, 138.2, 135.8, 135.1, 131.6, 129.4 (2C), 128.9 (2C), 127.4, 126.1 (2C), 126.0, 125.7, 116.4 (2C), 114.9,

112.6, 81.2, 73.6, 61.8, 55.6, 54.3, 54.1, 53.4, 53.0, 40.1, 38.8, 36.6, 28.4 (3C), 24.8, 23.1, 21.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3405, 3026, 2957, 2854, 1693, 1582, 1490, 1432, 1345, 1236, 1165, 1112, 1025, 898, 849 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{46}H_{52}N_6O_{15}Na$: 951.3318 $[M+Na]^+$; found: 951.3370.

Compound 32 and 33: EtSH (1.5 mL) and $AlCl_3$ (100 mg, 0.72 mmol) were added to a solution of compound **31** (77 mg, 0.083 mmol) in CH_2Cl_2 (5 mL) at 0°C. After the reaction mixture had been stirred at the same temperature for 2.5 h, the volatile was removed under vacuum and the residue was diluted with EtOAc and H_2O. The mixture was then stirred for a further 10 min, after which time, the reaction mixture was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by preparative TLC (silica gel, CH_2Cl_2/MeOH 15:1) to afford compound **32** (9 mg, 13%) and **33** (27 mg, 40%). For compound **32**: M.p. >260°C; HRMS (ESI): *m/z*: calcd for $C_{39}H_{40}N_6O_{13}Na$: 823.2506 $[M+Na]^+$; found: 823.2514. For compound **33**: M.p. 138–140°C; $[\alpha]_D = -135$ (*c* = 0.54 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 9.2 Hz, 2H; ArH), 7.83 (d, *J* = 1.8 Hz, 1H; ArH), 7.75 (brs, 1H; NH), 7.58 (dd, *J* = 8.5, 1.8 Hz, 1H; ArH), 7.25–7.04 (m, 5H; ArH), 7.01 (d, *J* = 8.5 Hz, 1H; ArH), 6.96 (d, *J* = 9.2 Hz, 2H; ArH), 6.66 (d, 1H, *J* = 8.1 Hz; NH), 6.45 (d, 1H, *J* = 9.6 Hz; NH), 6.38 (d, *J* = 1.5 Hz, 1H; ArH), 5.55 (s, 1H; ArH), 5.26 (dd, *J* = 8.8, 1.8 Hz, 1H; CH), 5.00 (s, 1H; CH), 4.88 (m, 1H; CH), 4.09 (d, *J* = 2.6 Hz, 1H; CH), 3.70 (dd, *J* = 13.6, 5.1 Hz, 1H; CH_2), 3.57 (s, 3H), 3.44 (dd, *J* = 10.3, 4.0 Hz, 1H; CH), 3.36 (brs, 3H; NH_2 and OH), 3.21 (dd, 1H, *J* = 14.0, 4.4 Hz, 1H; CH_2), 2.87–2.77 (m, 2H; CH_2), 1.77 (m, 2H; CH_2), 1.47 (m, 1H; CH), 1.01 (d, *J* = 6.3 Hz, 3H; CH_3), 0.97 ppm (d, *J* = 6.3 Hz, 3H; CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 175.4, 171.8, 169.8, 169.4, 162.7, 149.6, 149.2, 143.1, 142.3, 138.6, 138.4, 135.7, 135.2, 129.9 (2C), 128.8 (2C), 127.5, 127.4, 126.8, 126.1 (3C), 125.5, 116.6 (2C), 115.1, 111.9, 73.4, 54.0, 53.9, 53.0, 52.9, 43.7, 38.5, 36.5, 29.8, 25.1, 23.4, 21.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3544, 3410, 3024, 2958, 2930, 2854, 1743, 1682, 1607, 1588, 1518, 1490, 1345, 1234, 1199, 1112, 1007, 906, 850 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{40}H_{43}N_6O_{13}$: 815.2888 $[M+H]^+$; found: 815.2899.

Compound 33: $SOCl_2$ (0.20 mL) was added to a solution of compound **32** (9 mg, 0.011 mmol) in MeOH (1.0 mL). After the reaction mixture had been stirred at 60°C for 12 h, the volatile was removed under vacuum and the residue was basified with aqueous $NaHCO_3$ to pH 7–8 and extracted with EtOAc. The combined organic phases were washed with H_2O and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by preparative TLC to afford compound **33** (9 mg, 90%).

Compound 34: $NaHCO_3$ (13 mg, 0.148 mmol) and Boc_2O (9.6 mg, 0.044 mmol) were added to a solution of compound **33** (30 mg, 0.037 mmol) in dixoane/H_2O (2:1, 2.0 mL). After the reaction mixture had been stirred at room temperature for 2 d, the reaction mixture was extracted with EtOAc. The combined organic phases were washed with H_2O and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by preparative TLC (silica gel, CH_2Cl_2/MeOH = 30/1) to afford compound **34** (20 mg, 60%). M.p. 144–146°C; $[\alpha]_D = -77.9$ (*c* = 0.76 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 9.2 Hz, 2H; ArH), 8.11 (s, 1H; ArH), 7.60 (d, *J* = 8.5 Hz, 1H; ArH), 7.28–7.08 (m, 6H; one NH, ArH), 7.03 (d, *J* = 8.5 Hz, 1H; ArH), 6.99 (d, *J* = 9.2 Hz, 2H; ArH), 6.69 (d, *J* = 8.1 Hz, 1H; NH), 6.42 (d, *J* = 8.8 Hz, 1H; NH), 6.40 (s, 1H; ArH), 5.64 (s, 1H; ArH), 5.18 (dd, *J* = 8.8, 1.5 Hz, 1H; CH), 5.01 (d, *J* = 7.4 Hz, 1H; NH), 4.90 (m, 1H; CH), 4.83 (dt, *J* = 9.6, 5.9 Hz, 1H; CH), 4.18 (d, *J* = 2.6 Hz, 1H; CH), 4.11 (m, 1H; CH), 3.64 (dd, *J* = 14.0, 5.5 Hz, 1H; CH_2), 3.58 (s, 3H), 3.12 (dd, *J* = 14.0, 6.6 Hz, 1H; CH_2), 2.94 (dd, *J* = 14.0, 5.5 Hz, 1H; CH_2), 2.83 (dd, *J* = 14.0, 4.0 Hz, 1H; CH_2), 1.61 (m, 3H; CH, CH_2), 1.45 (s, 9H; $C(CH_3)_3$), 0.97 (d, *J* = 6.3 Hz, 3H; CH_3), 0.90 ppm (d, *J* = 6.3 Hz, 3H; CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 173.1, 171.7, 170.3, 168.9, 162.5, 156.5, 149.3, 148.6, 143.2, 142.9, 141.9, 138.3, 138.0, 135.7, 135.1, 129.3 (2C), 128.8 (2C), 127.3 (2C), 125.9 (2C), 125.8, 125.5, 116.5 (2C), 114.8, 112.1, 81.0, 73.3, 55.2, 54.3, 54.0, 53.3, 52.9, 39.9, 38.5, 36.5, 28.3 (3C), 24.7, 23.0, 21.6 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3547, 3421, 3023, 2929, 2854, 1689, 1588, 1518, 1491, 1440, 1345, 1232, 1219, 1201, 1165, 1112, 1006, 896, 861 cm^{-1}; HRMS (ESI): *m/z*: 937 $[M+Na]^+$.

Compound 35: Following the procedure described for compound **29**, **35** (42 mg, 73%) was prepared by starting from **34** (38 mg, 0.046 mmol). Compound **35** was purified by preparative TLC (silica gel, CH_2Cl_2/MeOH 30:1). M.p. 128–130°C; $[\alpha]_D = -70.2$ (*c* = 0.82 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 2.2 Hz, 1H; ArH), 8.18 (d, *J* = 9.2 Hz, 2H; ArH), 7.59 (dd, *J* = 8.5, 2.2 Hz, 1H; ArH), 7.38 (d, *J* = 7.7 Hz, 1H; NH), 7.29–7.07 (m, 6H; one NH, ArH), 7.01 (d, *J* = 8.5 Hz, 1H; ArH), 6.97 (d, *J* = 9.2 Hz, 2H; ArH), 6.54 (d, *J* = 9.2 Hz, 1H; NH), 6.33 (d, *J* = 1.8 Hz, 1H; ArH), 5.84 (d, *J* = 9.2 Hz, 1H; NH), 5.76 (d, *J* = 1.5 Hz, 1H; ArH), 5.23–5.01 (m, 5H; one NH, CH), 4.82 (m, 2H; CH), 4.25 (m, 1H), 4.23 (s, 1H), 4.12 (m, 1H), 4.02 (dd, *J* = 12.5, 3.7 Hz, 1H; CH_2), 3.79 (m, 1H), 3.69–3.58 (m, 2H), 3.57 (s, 3H), 3.05 (dd, *J* = 13.6, 6.6 Hz, 1H; CH_2), 2.96 (dd, *J* = 13.6, 5.9 Hz, 1H; CH_2), 2.85 (dd, *J* = 14.0, 3.3 Hz, 1H; CH_2), 2.67 (brs, 1H; OH), 1.97 (s, 3H; $COCH_3$), 1.96 (s, 3H; $COCH_3$), 1.94 (s, 3H; $COCH_3$), 2.00–1.05 (m, 23H), 1.46 (s, 9H; $C(CH_3)_3$), 0.97 (d, *J* = 5.9 Hz, 3H; CH_3), 0.93 (d, *J* = 5.9 Hz, 3H; CH_3), 0.85 ppm (t, *J* = 7.4 Hz, 3H; CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 173.3, 173.2, 171.3, 170.8, 170.7, 170.6, 169.4, 168.7, 162.7, 156.7, 153.7, 148.6, 148.4, 143.2, 143.1, 138.5, 137.8, 135.9, 135.4, 133.5, 129.4 (2C), 128.9 (2C), 127.5, 125.9, 125.8 (2C), 125.5, 117.3 (2C), 115.0, 112.2, 102.3, 81.3, 77.4, 73.7, 72.8, 72.3, 68.1, 61.6, 56.2, 54.3, 54.2, 53.6, 53.0, 40.0, 38.9, 36.9, 36.8, 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 28.4 (3C), 25.6, 24.9, 23.1, 22.8, 21.9, 20.7 (2C), 20.6, 14.2 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3426, 3025, 2929, 2856, 1746, 1685, 1584, 1521, 1492, 1434, 1369, 1345, 1234, 1165, 1112, 1034, 849 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{69}H_{89}N_7O_{23}Na$: 1406.5898 $[M+Na]^+$; found: 1406.5907.

Compound 2Bd: $LiOH{\cdot}H_2O$ (24 mg, 0.58 mmol) was added to a solution of compound **35** (40 mg, 2.9 μmol) in THF/H_2O (3:1, 4.0 mL) at 0°C. After the reaction mixture had been stirred for 2.0 h at 0°C, the reaction mixture was acidified with 5% HCl to pH 3–4 and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under vacuum to afford the corresponding acid, which proved to be of sufficient purity for direct use in the next step. TFA (0.5 mL) was added to a solution of above acid in CH_2Cl_2 (1.0 mL) at 0°C. After the reaction mixture had been stirred at the same temperature for 1.0 h, it was concentrated to dryness under vacuum. The residue was purified by preparative TLC (silica gel, CH_2Cl_2/MeOH 6:1) to afford compound **2Bd** (26 mg, 79%). M.p. 175–177°C; ^1H NMR (300 MHz, CD_3SOCD_3): δ = 9.08 (d, *J* = 7.4 Hz, 1H; NH), 8.79 (d, *J* = 6.6 Hz, 1H; NH), 8.29–8.22 (m, 4H; one NH, ArH), 7.56 (d, *J* = 9.2 Hz, 1H; NH), 7.32–7.02 (m, 9H), 6.77 (d, *J* = 1.8 Hz, 1H), 6.58 (d, *J* = 1.8 Hz, 1H), 4.97 (d, *J* = 8.5 Hz, 1H), 4.65 (brs, 6H; OH, NH_2), 4.52 (m, 1H), 4.40 (m, 1H), 4.28 (m, 1H), 3.99 (m, 1H), 3.70 (m, 1H), 3.61 (m, 1H), 3.51 (m, 1H), 3.41 (m, 1H), 3.23 (m, 2H), 3.07 (m, 1H), 2.97 (m, 2H), 2.81 (m, 1H), 2.58 (m, 1H), 1.78–1.00 (m, 23H), 0.88–0.84 ppm (m, 9H); ^{13}C NMR (75.0 MHz, CD_3OD): δ = 173.1, 171.7, 171.1, 169.8, 167.0, 162.8, 154.3, 149.4, 145.8, 142.1, 141.9, 137.6, 137.4, 136.6, 134.0, 129.2 (2C), 127.9 (2C), 126.3, 125.9, 125.7 (2C), 125.1, 124.9, 117.7, 117.1 (2C), 116.2, 102.8, 77.8, 73.5, 71.0, 70.7, 61.2, 57.6, 55.4, 54.7, 53.6, 51.1, 35.6, 34.4, 31.3, 30.4, 29.0 (2C), 28.9, 28.8 (2C), 28.7 (2C), 24.9, 23.9, 22.3, 22.2, 22.1, 13.9 ppm; HRMS (ESI): *m/z*: calcd for $C_{39}H_{40}N_6O_{13}Na$: 823.2551 $[M-sugar]^+$; found: 823.2514.

Compound 36: Following the procedure described for compound **29**, **36** (24 mg, 76%) was prepared by starting from compound **3B** (20 mg, 0.025 mmol). M.p. 102–105°C; $[\alpha]_D = -33.8$ (*c* = 1.2 in $CHCl_3$); ^1H NMR (250 MHz, CD_3OD): δ = 8.30 (s, 1H; ArH), 7.39 (dd, *J* = 8.5, 2.0 Hz, 1H; ArH), 7.28–7.07 (m, 5H; ArH), 7.04 (d, *J* = 8.5 Hz, 1H; ArH), 6.63 (d, *J* = 2.0 Hz, 1H; ArH), 5.93 (d, *J* = 2.0 Hz, 1H; ArH), 5.32 (dd, *J* = 10.1, 10.1 Hz, 1H; CH), 5.15 (d, *J* = 8.5 Hz, 1H; CH), 5.06 (m, 1H; CH), 4.89 (m, 1H; CH), 4.58 (m, 2H; CH), 4.46 (t, *J* = 6.9 Hz, 1H; CH), 4.30–4.10 (m, 4H; CH, CH_2), 3.93 (m, 1H; CH), 3.85 (s, 3H; OCH_3), 3.76 (s, 3H; CO_2CH_3), 3.41 (dd, *J* = 14.1, 5.5 Hz, 1H; CH_2), 3.04–2.78 (m, 3H; CH_2), 2.17 (t, *J* = 7.5 Hz, 2H; CH_2), 2.03 (s, 3H; $COCH_3$), 2.03 (s, 3H; $COCH_3$), 2.00 (s, 3H; $COCH_3$), 1.74–1.50 (m, 5H), 1.48 (s, 9H; $C(CH_3)_3$), 1.27 (m, 16H; CH_2), 0.96 (d, *J* = 6.4 Hz, 3H; CH_3), 0.92 (d, *J* = 6.4 Hz, 3H; CH_3), 0.87 ppm (t, *J* = 4.1 Hz, 3H; CH_3); ^{13}C NMR (62.5 MHz,

CD_3OD): δ = 176.5, 176.3, 175.4, 173.3, 172.4, 172.2, 171.6, 171.2, 154.4, 151.9, 149.7, 144.2, 138.1, 137.3, 135.8, 134.5, 130.5, 129.4, 127.9, 126.8, 126.5, 112.7, 111.4, 101.0, 81.0, 73.9, 73.6, 73.3, 70.6, 70.0, 63.6, 63.3, 61.9, 60.1, 56.3, 55.8, 55.0, 54.5, 53.0, 41.3, 40.4, 37.4, 37.0, 33.0, 30.7, 30.5, 30.4, 30.3, 30.2, 28.7, 26.8, 25.9, 23.7, 23.2, 22.2, 20.8, 20.7, 20.6, 14.4 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3658, 3468, 3435, 3020, 2990, 2957, 2929, 2856, 1744, 1676, 1594, 1535, 1508, 1499, 1369, 1237, 1223, 1214, 1258, 1207, 1114, 1088, 1048 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{64}H_{88}N_6O_{21}Na$: 1299.5900 $[M+Na]^+$; found: 1299.5906.

Compound 39: $LiOH{\cdot}H_2O$ (26 mg, 0.63 mmol) was added to a solution of compound **36** (80 mg, 0.063 mmol) in THF/H_2O (3:1, 4 mL) at 0 °C. After the reaction mixture had been stirred for 4 h at 0 °C, it was acidified with citric acid to pH 3–4 and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under vacuum to afford compound acid **37** (44 mg, 62 %), which proved to be of sufficient purity for direct use in the next step. HOBt (11 mg, 0.078 mmol) and EDC (15 mg, 0.078 mmol) were added to a solution of the above crude acid **37** (44 mg, 0.039 mmol) and amine **38** (53 mg, 0.156 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 12 h, and was then diluted with CH_2Cl_2 (100 mL). The resulting mixture was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash-column chromatography to afford **39** (19 mg, 34 %). M.p. 165–168 °C; $[\alpha]_D$ = +51.4 (*c* = 0.14 in MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.32 (s, 1H; ArH), 7.47–7.32 (m, 6H; ArH), 7.28–7.19 (m, 3H; ArH), 7.13 (d, *J* = 7.6 Hz, 2H; ArH), 7.03 (d, *J* = 8.9 Hz, 1H; ArH), 6.54 (s, 1H; ArH), 5.79 (d, *J* = 1.2 Hz, 1H; ArH), 5.39 (s, 1H; CH), 4.96 (d, *J* = 9.1 Hz, 1H; CH), 4.76 (br s, 1H; CH), 4.60–4.58 (m, 2H; CH), 4.23 (t, *J* = 7.5 Hz, 2H; CH), 4.01 (t, *J* = 8.5 Hz, 1H; CH), 3.93 (t, *J* = 13.2 Hz, 2H; CH_2), 3.84 (s, 3H; OCH_3), 3.76 (dd, *J* = 12.7, 5.1 Hz, 1H; CH_2), 3.63 (dd, *J* = 10.0, 8.4 Hz, 1H; CH_2), 3.54–3.40 (m, 3H; CH, CH, CH_2), 3.28–3.05 (m, 6H; CH, CH_2, CH_2, CH_2), 2.37–2.17 (m, 6H; 3 × CH_2), 2.15 (s, 6H; $N(CH_3)_2$), 1.85–1.51 (m, 9H; CH, 4 × CH_2), 1.49 (s, 9H; $C(CH_3)_3$), 1.33–1.25 (m, 16H), 0.90 (d, *J* = 6.8 Hz, 3H; CH_3), 0.87 ppm (t, *J* = 6.0 Hz, 6H; CH_3); ^{13}C NMR (75.0 MHz, CD_3OD): δ = 176.9, 176.8, 174.9, 173.8, 173.0, 172.7, 170.8, 170.0, 154.1, 152.5, 152.4, 149.7, 144.4, 139.6, 139.1, 138.0, 137.2, 135.9, 134.0, 130.7, 129.9, 129.6, 129.4, 128.9, 128.8, 128.7, 128.1, 126.9, 126.6, 111.0, 110.9, 101.3, 81.0, 78.4, 75.8, 75.4, 71.9, 62.5, 62.0, 59.2, 58.0, 57.0, 56.8, 55.7, 54.6, 54.5, 45.4, 41.8, 40.6, 39.9, 38.8, 37.7, 33.7, 33.1, 30.9, 30.8, 30.7, 30.6, 30.5, 29.6, 29.1, 28.8, 27.9, 27.0, 26.6, 26.1, 23.8, 23.2, 22.4, 14.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3300, 3021, 2929, 2856, 1708, 1660, 1579, 1508, 1438, 1368, 1235, 1162, 1090, 1014 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{74}H_{107}N_{10}O_{19}N$: 1439.7714 $[M+H]^+$; found: 1439.7737.

Compound 2Bf: TFA (0.5 mL) was added to a solution of compound **39** (15 mg, 0.010 mmol) in CH_2Cl_2 (1.0 mL). After the reaction mixture had been stirred at room temperature for 30 min, it was concentrated to dryness under vacuum. The crude product was then purified by HPLC to afford amine **2Bf** (10 mg, 75 %). M.p. > 240 °C; $[\alpha]_D$ = +19.8 (*c* = 0.06 in MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.48–8.44 (br s, 2H; NH), 8.13 (s, 1H; ArH), 7.48–7.36 (m, 6H; ArH), 7.26–7.10 (m, 5H; ArH), 7.02 (d, *J* = 8.5 Hz, 1H; ArH), 6.54 (d, *J* = 1.7 Hz, 1H; ArH), 5.78 (d, *J* = 1.2 Hz, 1H; ArH), 5.27 (s, 1H; CH), 5.00 (d, *J* = 8.5 Hz, 1H; CH), 4.90 (d, *J* = 10.2 Hz, 1H; CH), 4.89–4.78 (m, 2H; CH), 4.65 (br s, 1H; CH), 4.50 (t, *J* = 6.2 Hz, 1H; CH), 4.22 (br s, 1H; CH), 4.04–3.88 (m, 3H; CH, CH_2), 3.85 (s, 3H; OCH_3), 3.75 (dd, *J* = 12.4, 4.6 Hz, 1H; CH_2), 3.65 (dd, *J* = 10.2, 7.9 Hz, 1H; CH), 3.51–3.39 (m, 3H; 2 × CH, CH_2), 3.12–2.91 (m, 6H), 2.78 (br s, 8H; CH_2, $N(CH_3)_2$), 2.28 (t, *J* = 7.0 Hz, 2H; CH_2), 2.20 (t, *J* = 7.6 Hz, 2H; CH_2), 1.96–1.80 (m, 3H; CH, CH_2), 1.78–1.54 (m, 6H; 2 × CH_2), 1.38–1.21 (m, 16H), 0.98 (d, *J* = 5.3 Hz, 3H; CH_3), 0.87 (t, *J* = 6.5 Hz, 3H; CH_3), 0.85 ppm (d, *J* = 5.3 Hz, 3H; CH_3); IR ($CHCl_3$): $\tilde{\nu}$ = 3300, 3028, 3021, 3018, 2928, 2855, 1659, 1596, 1533, 1467, 1439, 1351, 1237, 1222, 1214, 1204, 1087 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{69}H_{99}N_{10}O_{17}$: 1339.7190 $[M+H]^+$; found: 1339.7202.

Compound 40: HOBt (538 mg, 3.89 mmol) and EDC (834 mg, 4.25 mmol) were added to a solution of amine **7** (1.30 g, 3.54 mmol) and acid **14** (2.08 g, 3.54 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 12 h, and was then diluted with CH_2Cl_2 (100 mL). The resulting mixture was washed with 5 % aqueous HCl, saturated $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash-column chromatography to afford **40** (3.08 g, 93 %). M.p. 133–135 °C; $[\alpha]_D$ = +18.9 (*c* = 0.55 in $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD): δ = 7.82 (dd, *J* = 7.0, 1.8 Hz, 1H; ArH), 7.34 (m, 1H; ArH), 7.23 (dd, *J* = 11.0, 8.5 Hz, 1H; ArH), 7.30–7.05 (m, 5H; ArH), 6.58 (s, 2H; ArH), 5.28 (d, *J* = 6.3 Hz, 1H; CH), 4.74–4.65 (m, 4H; CH, $CH(CH_3)_2$), 4.46 (d, *J* = 6.3 Hz, 1H; CH), 3.94 (dd, *J* = 10.0, 5.0 Hz, 1H; CH), 3.77 (s, 3H; OCH_3), 3.74 (s, 3H; CO_2CH_3), 3.07–2.85 (m, 4H; CH_2), 1.60–1.40 (m, 3H; CH, CH_2), 1.42 (s, 9H; $C(CH_3)_3$), 1.34 (d, *J* = 6.0 Hz, 6H; $CH(CH_3)_2$), 1.33 (d, *J* = 6.0 Hz, 6H; $CH(CH_3)_2$), 0.88 (d, *J* = 6.7 Hz, 3H; CH_3), 0.85 ppm (d, *J* = 6.7 Hz, 3H; CH_3); ^{13}C NMR (50.3 MHz, CD_3OD): δ = 175.7, 172.4, 172.2, 170.2, 158.1, 155.5 (d, *J* = 261 Hz), 152.8, 138.0, 137.9, 137.8, 135.7, 133.4, 130.2, 129.6, 129.4, 127.9, 127.8, 119.2 (d, *J* = 21 Hz), 110.1, 80.7, 72.7, 66.6, 60.9, 56.1, 55.4, 55.1, 54.7, 53.4, 42.0, 38.9, 37.6, 28.8, 25.8, 23.4, 22.6, 22.5, 21.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3627, 3417, 3011, 3024, 2978, 2936, 2115, 1745, 1686, 1623, 1590, 1540, 1498, 1438, 1370, 1351, 1319, 1203, 1159, 1116, 1087 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{46}H_{61}N_8O_{12}FNa$: 959.4291 $[M+Na]^+$; found: 959.4289.

Compound 41: Following the procedure described for compound **4A**, compound **41** was prepared in 95 % yield by starting from compound **40**. M.p. 102–106 °C; $[\alpha]_D$ = +8.3 (*c* = 1.48 in $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD): δ = 7.80 (dd, *J* = 7.0, 1.8 Hz, 1H; ArH), 7.27 (m, 1H; ArH), 7.24–7.10 (m, 6H; ArH), 6.35 (s, 2H; ArH), 5.16 (d, *J* = 7.0 Hz, 1H; CH), 4.57 (m, 2H; CH), 4.37 (d, *J* = 7.0 Hz, 1H; CH), 3.95 (dd, *J* = 9.5, 5.4 Hz, 1H; CH), 3.77 (s, 3H; OCH_3), 3.73 (s, 3H; CO_2CH_3), 3.15–2.74 (m, 4H; CH_2), 1.62–1.42 (m, 3H; CH, CH_2), 1.40 (s, 9H; $C(CH_3)_3$), 0.87 (d, *J* = 6.7 Hz, 3H; CH_3), 0.84 ppm (d, *J* = 6.7 Hz, 3H; CH_3); ^{13}C NMR (62.5 MHz, CD_3OD): δ = 175.7, 172.7, 172.3, 170.2, 158.2, 155.5 (d, *J* = 260 Hz), 151.7, 138.1, 137.9, 137.7, 136.8, 135.5, 133.8, 130.2, 129.4, 127.8, 127.7, 119.1 (d, *J* = 21 Hz), 108.3, 80.6, 66.0, 60.8, 56.0, 55.1, 54.6, 53.4, 41.9, 38.7, 37.5, 28.9, 28.7, 25.8, 23.4, 21.7 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3652, 3530, 3442, 3020, 2961, 2114, 1736, 1627, 1541, 1508, 1454, 1368, 1353, 1266, 1222, 1209, 1167, 1062 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{40}H_{49}N_8O_{12}FNa$: 875.3352 $[M+Na]^+$; found: 875.3369.

Compound 4D: Ph_3P (1.45 g, 5.5 mmol) and H_2O (100 μL, 5.5 mmol) were added to a solution of azide **41** (470 mg, 0.55 mmol) in THF (20 mL) at room temperature. After the reaction mixture had been stirred for 36 h at room temperature, the solvent was removed under vacuum and the residue was purified by flash-column chromatography (silica gel, CH_2Cl_2/MeOH 35:1) to afford amine **4D** (352 mg, 77 %). M.p. 136–139 °C; $[\alpha]_D$ = −20.8 (*c* = 0.13 in $CHCl_3$); ^{1}H NMR (250 MHz, CD_3OD): δ = 7.82 (dd, *J* = 6.9, 2.0 Hz, 1H; ArH), 7.35 (m, 1H; ArH), 7.26–7.10 (m, 6H; ArH), 6.27 (s, 2H; ArH), 5.10 (d, *J* = 5.4 Hz, 1H; CH), 4.63 (dd, *J* = 9.9, 4.7 Hz, 1H; CH), 4.50 (dd, *J* = 7.8, 6.2 Hz, 1H; CH), 3.96 (dd, *J* = 10.2, 5.0 Hz, 1H; CH), 3.78 (s, 3H; OCH_3), 3.75 (m, 1H; CH_2), 3.71 (s, 3H; OCH_3), 3.19 (dd, *J* = 14.0, 4.9 Hz, 1H; CH_2), 3.07 (dd, *J* = 14.0, 4.9 Hz, 1H; CH_2), 2.95–2.80 (m, 2H; CH_2), 1.63–1.30 (m, 3H; CH, CH_2), 1.42 (s, 9H; $C(CH_3)_3$), 0.87 (d, *J* = 7.0 Hz, 3H; CH_3), 0.85 ppm (d, *J* = 7.0 Hz, 3H; CH_3); ^{13}C NMR (62.5 MHz, CD_3OD): δ = 175.4, 172.4, 172.3, 170.3, 157.2, 155.4 (d, *J* = 260 Hz), 151.7, 138.7, 137.8, 137.7, 136.7, 135.5, 133.5, 130.5, 130.2, 129.4, 127.8, 127.7, 119.0 (d, *J* = 21 Hz), 107.4, 80.8, 60.7, 60.3, 58.1, 55.5, 54.9, 54.3, 52.5, 42.0, 38.4, 37.6, 28.7, 25.8, 23.3, 21.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3628, 3526, 3435, 3342, 3026, 2961, 2932, 2873, 1750, 1694, 1670, 1539, 1498, 1457, 1368, 1357, 1252, 1221, 1208, 1164, 1048 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{40}H_{51}N_6O_{12}FNa$: 849.4291 $[M+Na]^+$; found: 849.4289.

Compound 3D: Following the procedure described for compound **3A**, compound **3D** was prepared in 85 % yield by starting from compound **4D**. M.p. 131–134 °C; $[\alpha]_D$ = −66.4 (*c* = 0.22 in $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.33 (s, 1H; ArH), 7.42 (dd, *J* = 8.5, 2.0 Hz, 1H; ArH), 7.30–7.12 (m, 5H; ArH), 7.07 (d, *J* = 8.5 Hz, 1H; ArH), 6.19 (d, *J* = 1.9 Hz, 1H; ArH), 5.76 (s, 1H; ArH), 5.11 (s, 1H; CH), 4.67–4.60 (m, 2H; CH), 4.25 (t, *J* = 7.0 Hz, 1H; CH), 4.07 (s, 1H; CH), 3.96 (s, 6H; OCH_3, CO_2CH_3), 3.42 (dd, *J* = 14.0, 5.5 Hz, 1H; CH_2), 3.06–2.89 (m, 3H; CH_2), 1.75 (m, 1H; CH), 1.63 (m, 2H; CH_2), 1.49 (s, 9H; $C(CH_3)_3$), 1.01 (d, *J* = 6.5 Hz, 3H; CH_3), 0.96 ppm (d, *J* = 6.5 Hz, 3H; CH_3); ^{13}C NMR (75.0 MHz, CD_3OD): δ = 176.4, 174.3, 173.7, 172.5, 156.7, 154.7, 150.1,

145.7, 144.4, 138.5, 137.9, 137.9, 134.0, 130.5, 129.6, 128.0, 127.3, 126.6, 110.9, 107.4, 81.2, 76.7, 61.7, 59.6, 59.0, 56.6, 54.5, 42.9, 41.1, 39.9, 37.5, 28.9, 26.0, 23.5, 22.2 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3628, 3573, 3404, 3028, 3014, 2961, 2935, 2837, 1740, 1684, 1595, 1536, 1497, 1369, 1354, 1234, 1200, 1168, 1116, 1040 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{40}H_{50}N_6O_{12}Na$: 829.3384 $[M+Na]^+$; found: 829.3395.

Compound 45: Lauroyl chloride (680 μL, 2.5 mmol) and $NaHCO_3$ (420 mg, 4.96 mmol) were added to a solution of compound **3D** (500 mg, 0.62 mmol) in dioxane/H_2O (2:1, 45 mL). After the reaction mixture had been stirred at room temperature for 4 h, it was extracted with EtOAc. 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 to afford compound **45** (540 mg, 74%). HRMS (ESI): *m/z*: calcd for $C_{64}H_{94}N_6O_{14}Na$: 1193.6726 $[M+Na]^+$; found: 1193.6737.

Compound 46: The mixture of compound **45** (20 mg, 0.017 mmol) and a catalytic amount of Pd/C (10%) in MeOH (2.0 mL) was stirred under hydrogen at atmospheric pressure at room temperature for 30 min. After this time, the reaction mixture was filtrated through a pad of Celite and the filtrate was concentrated to dryness. A solution of *t*BuONO (0.015 mL) in anhydrous degassed DMF (0.5 mL) was then warmed at 75°C under argon. A solution of the above amino compound in anhydrous degassed DMF (1.0 mL) was added and the resulting mixture was stirred at 75°C for 15 min. After this time, the reaction mixture was cooled to room temperature and extracted with EtOAc. 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 to afford compound **46** (10 mg, 52%). M.p. 231–232°C; $[\alpha]_D$ = −140 (*c* = 0.19 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.3 Hz, 1H; NH), 7.62 (d, *J* = 7.7 Hz, 1H; ArH), 7.48 (d, *J* = 10.1 Hz, 1H; NH), 7.37 (dd, *J* = 8.6, 2.8 Hz, 1H; ArH), 7.21 (t, *J* = 7.6 Hz, 3H; ArH), 7.09 (dd, *J* = 7.6, 1.6 Hz, 2H; ArH), 6.92 (dd, *J* = 8.3, 2.4 Hz, 1H; ArH), 6.89 (dd, *J* = 8.6, 2.4 Hz, 1H; ArH), 6.11 (d, *J* = 8.3 Hz, 1H; NH), 6.10 (d, *J* = 2.1 Hz, 1H; ArH), 6.09 (d, *J* = 5.5 Hz, 1H; NH), 5.46 (d, *J* = 8.4 Hz, 1H; CH), 5.20–5.12 (m, 1H; CH), 5.03 (m, 2H, ArH; CH), 4.88 (d, *J* = 8.8 Hz, 1H; NH), 4.24–4.13 (m, 1H; CH), 3.95 (s, 3H; CO_2CH_3), 3.93 (s, 3H; OCH_3), 3.75 (d, *J* = 5.5 Hz, 1H; CH), 3.62 (dd, *J* = 13.4, 4.2 Hz, 1H; CH_2), 3.31 (dd, *J* = 13.8, 4.8 Hz, 1H; CH_2), 2.85 (dd, *J* = 13.8, 4.8 Hz, 1H; CH_2), 2.78 (dd, *J* = 13.4, 3.6 Hz, 1H; CH_2), 2.56 (t, *J* = 7.4 Hz, 2H; CH_2), 2.51–2.40 (m, 1H; CH_2), 2.32–2.18 (m, 1H; CH_2), 1.81–1.71 (m, 2H), 1.69–1.58 (m, 2H), 1.50–1.40 (m, 3H), 1.45 (s, 9H; $C(CH_3)_3$), 1.31–1.22 (m, 32H), 0.93 (d, *J* = 6.3 Hz, 3H; CH_3), 0.89 (t, *J* = 6.7 Hz, 3H; CH_3), 0.87 (t, *J* = 6.7 Hz, 3H; CH_3), 0.76 ppm (d, *J* = 6.3 Hz, 3H; CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 176.2, 174.1, 171.7, 169.2, 168.8, 168.7, 155.8, 155.3, 154.8, 144.4, 140.0, 136.0, 134.3, 134.0, 131.2, 130.5, 129.7, 128.8, 127.3, 123.8, 122.4, 113.1, 111.7, 80.0, 61.0, 59.5, 54.9, 53.8, 53.1, 52.8, 40.6, 38.6, 37.1, 37.0, 34.3, 32.0, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 28.5, 26.5, 25.2, 24.7, 23.3, 22.8, 22.0, 14.2 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3402, 3314, 3018, 2957, 2929, 2856, 1747, 1708, 1683, 1642, 1587, 1505, 1468, 1439, 1367, 1311, 1222, 1217, 1204, 1163, 1139, 1107, 1031 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{64}H_{95}N_5O_{12}Na$: 1148.6875 $[M+Na]^+$; found: 1148.6855.

Compound 2Df: Following the procedure described for compound **2Ab**, compound **2Df** (4.0 mg, 64%) was prepared by starting from compound **46** (8.6 mg, 7.6 μmmol). $[\alpha]_D$ = +7.8 (*c* = 0.08 in MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 7.74 (dd, *J* = 8.4, 1.6 Hz, 1H; ArH), 7.45 (dd, *J* = 8.3, 2.1 Hz, 1H; ArH), 7.27–7.15 (m, 3H; ArH), 7.13–7.05 (m, 3H; ArH), 6.72 (dd, *J* = 8.4, 2.5 Hz, 1H; ArH), 6.33 (d, *J* = 2.0 Hz, 1H; ArH), 5.27 (d, *J* = 2.0 Hz, 1H; ArH), 5.11 (d, *J* = 8.0 Hz, 1H; CH), 4.73 (dd, *J* = 5.3, 3.8 Hz, 1H; CH), 4.69 (d, *J* = 8.0 Hz, 1H; CH), 4.37 (t, *J* = 6.1 Hz, 1H; CH), 4.12 (t, *J* = 7.2 Hz, 1H; CH), 3.90 (s, 3H; OCH_3), 3.35 (dd, *J* = 14.1, 5.3 Hz, 1H; CH_2), 2.99 (dd, *J* = 14.1, 4.8 Hz, 1H; CH_2), 2.92 (dd, *J* = 14.1, 3.8 Hz, 1H; CH_2), 2.86 (dd, *J* = 14.1, 6.7 Hz, 1H; CH_2), 2.12 (t, *J* = 7.8 Hz, 2H; CH_2), 1.65–1.57 (m, 3H; CH, CH_2), 1.31–1.20 (m, 18H), 0.99 (d, *J* = 5.9 Hz, 3H; CH_3), 0.91 (d, *J* = 5.9 Hz, 3H; CH_3), 0.88 ppm (t, *J* = 6.8 Hz, 3H; CH_3); HRMS (ESI): *m/z*: calcd for $C_{46}H_{63}N_5O_9Na$: 852.4523 $[M+Na]^+$; found: 852.4528.

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