CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200700412

Three-Residue Turns in α/β-Peptides and Their Application in the Design of Tertiary Structures**

Gangavaram V. M. Sharma,*[a] Pendem Nagendar,[a] Kallaganti V. S. Ramakrishna,[b] Nagula Chandramouli,[a] Madavi Choudhary,[b] and Ajit C. Kunwar*[b]

Abstract: A new three-residue turn was serendipitously discovered in α/β hybrid peptides derived from alternating C-linked carbo-β-amino acids (β-Caa) and L-Ala residues. The three-residue β-α-β turn at the C termini, nucleated by a helix at the N termini, resulted in helix-turn (HT) supersecondary structures in these peptides. The turn in the HT motif is stabilized by two H bonds—CO(*i*−2)–NH(*i*), with a seven-membered pseudoring (γ turn) in the backward direction, and NH(*i*−2)–CO(*i*), with a 13-membered pseudoring in the forward direction (*i* being the last residue)—at the C termini. The study was extended to generalize the new three-residue turn (β-α-β) by using different α- and β-amino acids. Furthermore, the HT motifs were efficiently converted, by an extension with helical oligomers at the C termini, into peptides with novel helix-turn-helix (HTH) tertiary structures. However, this resulted in the destabilization of the β-α-β turn with the concomitant nucleation of another three-residue turn, α-β-β, which is stabilized by 11- and 15-membered bifurcated H bonds. Extensive NMR spectroscopic studies were carried out to delineate the secondary and tertiary structures in these peptides, which are further supported by molecular dynamics (MD) investigations.

Keywords: conformation analysis · helical structures · hydrogen bonds · peptides · tyligomers

Introduction

Proteins and peptides adopt compact three-dimensional structures to play myriad roles in biological processes. Details of the complex tertiary and quaternary structures in proteins, which are assembled from a limited number of secondary structures such as helices, strands, and turns, permit the understanding of their functions at the molecular level. Reverse turns[1] are often located at protein surfaces, where their structural compactness as well as the desirable orientation of the side chains permit them to participate actively in protein folding. β-Turns, the simplest defined loops, are the most frequently found reverse turns; their design principles are well-understood. On the other hand, reports on three-residue loops are scanty, thus providing the desired impetus to design such structural elements. Recently, Balaram and co-workers[2] designed a three-residue loop comprising D-Pro–L-Pro–D-Ala in a β-hairpin. Herein we describe the synthesis and discovery of novel three-residue turns as well as helix-turn (HT) and helix-turn-helix (HTH) motifs in α/β hybrid peptides **2**–**11** (Scheme 1).

α/β Hybrid peptides[3,4] have been extensively studied in the recent past, and Gellman and co-workers[3d,e] has amply emphasized their biological implications and self-assembly into quaternary helix bundles.[3h,i] In our studies, α/β-peptides containing alternating L-Ala and C-linked β-Caa, with the L-Ala–β-Caa–L-Ala (α-β-α) sequence at the C terminus, formed very robust 11/9 mixed helices.[3c] To understand the inherent features of α/β-peptides with the β-Caa–L-Ala–β-Caa (β-α-β) sequence at the C termini further, several peptides (**1**, **2**, **3a**, **5**, **6a**, and **7**) were synthesized, and extensive NMR spectroscopic (in $CDCl_3$), molecular dynamics (MD), and CD investigations were undertaken to obtain their

[a] Dr. G. V. M. Sharma, P. Nagendar, N. Chandramouli
D-211, Discovery Laboratory
Organic Chemistry Division III
Indian Institute of Chemical Technology
Hyderabad 500 007 (India)
Fax: (+91) 40-27160387
E-mail: esmvee@iict.res.in

[b] K. V. S. Ramakrishna, M. Choudhary, Dr. A. C. Kunwar
Centre for Nuclear Magnetic Resonance
Indian Institute of Chemical Technology
Hyderabad 500 007 (India)
Fax: (+91) 40-27193108
E-mail: kunwar@iict.res.in

[**] IICT Communication No. 070118

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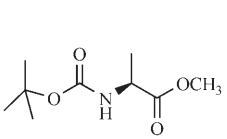
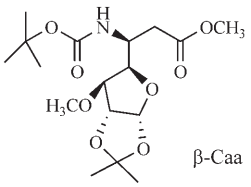


L-Ala



β-Caa

1 Boc-β-Caa-L-Ala-β-Caa-OMe
2 Boc-L-Ala-β-Caa-L-Ala-β-Caa-OMe
3 Boc-L-Ala-β-Caa-L-Ala-β-Caa-Xxx-β-Caa-OMe
3a Xxx = L-Ala; **3b** Xxx = L-Pro; **3c** Xxx = D-Pro
4 Boc-L-Ala-β-Caa-L-Ala-β-D-hAla-L-Ala-β-D-hAla-OMe
5 Boc-L-Ala-(β-Caa-L-Ala)$_2$-β-Caa-L-Ala-β-Caa-OMe
6 Boc-β-Caa-L-Ala-β-Caa-Xxx-β-Caa-OMe
6a Xxx = L-Ala; **6b** Xxx = L-Val; **6c** Xxx = Aib
7 Boc-(β-Caa-L-Ala)$_2$-β-Caa-L-Ala-β-Caa-OMe
8 Boc-β-Caa-L-Ala-β-Caa-Xxx-β-Caa-(β-Caa-L-Ala)$_2$-OMe
8a Xxx = L-Ala; **8b** Xxx = L-Val; **8c** Xxx = Aib
9 Boc-L-Ala-(β-Caa-L-Ala)$_2$-β-Caa-(β-Caa-L-Ala)$_2$-OMe
10 Boc-(β-Caa-L-Ala)$_2$-β-Caa-L-Ala-β-Caa-(β-Caa-L-Ala)$_2$-OMe
11 Boc-L-Ala-β-Caa-L-Ala-β-hGly-Xxx-β-hGly-OMe
11a Xxx = L-Ala; **11b** Xxx = L-Pro; **11c** Xxx = D-Pro

Scheme 1. Structures of peptides **1**–**11**. β-Caa = carbo-β-amino acid, h = helical.

structures.[5] Unlike our earlier study, an unusual and novel three-residue β-α-β turn was generated at the C termini,[3c] nucleated by an 11/9-helix at the N termini, thus resulting in a rather well-defined HT motif in these peptides in this study To generalize the above results, oligomers **3b**, **3c**, **4**, **6b, 6c**, and **11** were prepared in which the α- and β-amino acids in the C-terminal β-α-β fragment have been replaced with L-Val, L-Pro, D-Pro, Aib, β-D-hAla, and β-hGly, respectively. Several of these peptides resulted in the HT motifs. These motifs were further exploited by attaching helically folded peptides at the C termini in the design of novel HTH scaffolds. Interestingly, these folds nucleated yet another novel three-residue α-β-β turn. Detailed structural studies of peptides **1**–**11** are presented in this article.[5]

Results and Discussion

Synthesis of Peptides 1–11

The α/β-peptides **1**–**3**, **5**, **6**, **8**, and **9** (Scheme 2) and **4**, **7**, **10**, and **11** (Scheme 3) were prepared from α-amino acids (L-Ala, L-Val, L-Pro, D-Pro, and Aib) and β-Caa **12**,[6] β-D-hAla, and β-hGly by standard peptide coupling (EDCI/HOBt and DIPEA) in solution.

Accordingly, Boc-β-Caa-OMe (**12**; Scheme 2), upon base hydrolysis with 4N aqueous NaOH, gave the acid **12a**, which upon exposure to CF_3COOH in CH_2Cl_2 was converted into the salt **12b**. Condensation of **12a** in the presence of EDCI, HOBt, and DIPEA in CH_2Cl_2 with the HCl salt of L-Ala-OMe (**13**) afforded the dipeptide **15**. Base hydrolysis of ester **15** resulted in the corresponding acid **16a**, which upon exposure to CF_3COOH gave the salt **16b**. Furthermore, peptide coupling of **16a** independently with **12b** and **16b** resulted in the tripeptide **1** and the tetrapeptide **17**, respectively. Ester **17** upon base (NaOH) and acid (CF_3COOH) hydrolysis independently gave the acid **18a** and the salt **18b**, respectively.

Acids **14a–e** were coupled with amine salt **12b** to give the dipeptides **19a–e** (Scheme 2), which upon exposure to CF_3COOH in CH_2Cl_2 afforded **20a–e**. Coupling of salt **20a** with acid **21** (prepared from **19a** by reaction with 4N NaOH) in the presence of EDCI, HOBt, and DIPEA in CH_2Cl_2 gave the tetrapeptide **2**, which upon base hydrolysis and peptide coupling of the corresponding acid **22** with the salts **20a**, **20d**, and **20e** furnished hexapeptides **3a–c**, respectively. Peptide **3a** was converted into acid **23** by base hydrolysis and coupled with amine salts **20a** and **18b** to furnish the peptides **5** and **9**, respectively.

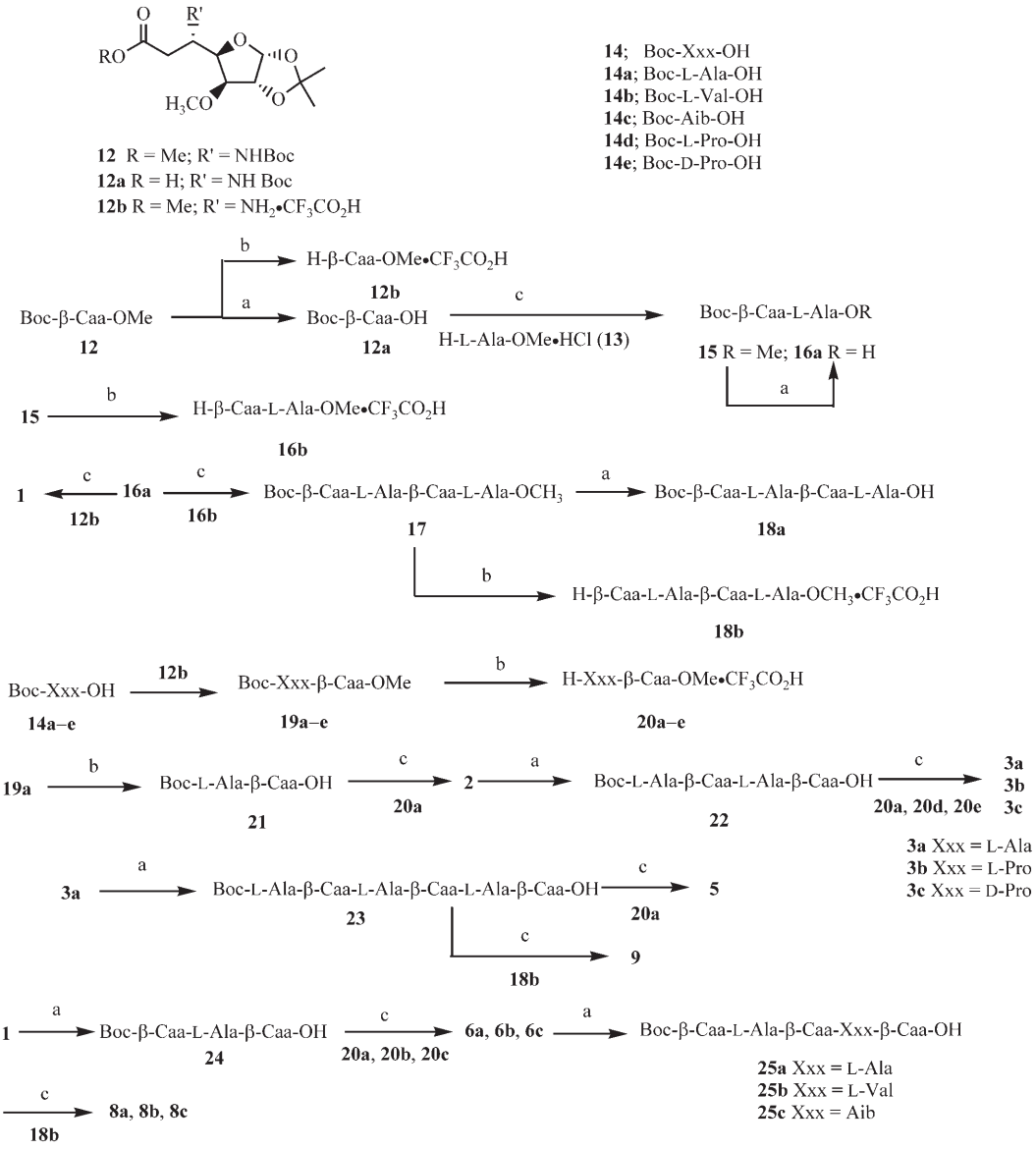
Treatment of acid **24**, prepared from tripeptide **1** (by reaction with 4N NaOH), with the salts **20a–c** afforded pentapeptides **6a–c**, respectively. Esters **6a–c** were subjected to base hydrolysis to give the acids **25a–c**, which upon further coupling with **18b** furnished the nonapeptides **8a–c**, respectively.

Peptide coupling of acid **25a** with the salt **20a** resulted in the heptapeptide **7** (Scheme 3), which upon base hydrolysis afforded acid **26**. Condensation of acid **26** with salt **18b** gave the undecapeptide **10**. Likewise, reaction of **14a** with salt **28**, obtained from **27** (prepared by the homologation of Boc-D-Ala-OH) by Boc deprotection (CF_3COOH in CH_2Cl_2), resulted in dipeptide **29**. Base hydrolysis (4N NaOH) of **29** and coupling of the resulting acid **30b** with salt **30a** (prepared by Boc deprotection of **29**) gave the tetrapeptide **31**. Salt **32** (prepared from **31**), upon coupling with the acid **21**, afforded hexapapeptide **4**.

Similarly, acids **14a**, **14d**, and **14e**, upon coupling with **33**, gave dipeptides **34a–c**, respectively, which upon reaction with CF_3COOH in CH_2Cl_2 afforded **35a–c**. Coupling of acid **21** with the salt **35a** furnished tetrapeptide **36**, which upon base hydrolysis gave the acid **37**. Furthermore, condensation of acid **37** with salts **35a–c** gave the peptides **11a–c**, respectively.

Conformational Analysis

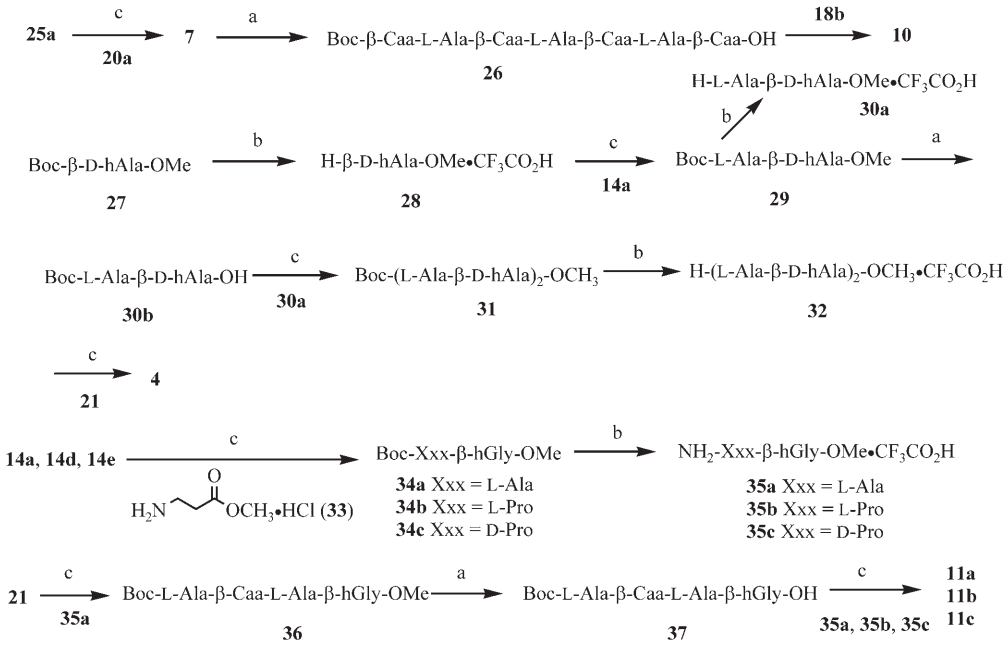
NMR spectroscopic studies of the peptides were carried out in 3–10 mM solutions in $CDCl_3$ usually at 278–303 K. The ^{1}H NMR spectrum of tripeptide **1** showed no signature peaks for any secondary structure.[5] For the tetrapeptide **2**, the amide protons NH2 and NH3 displayed large chemical shifts (δ) of >7 ppm; however, solvent titration studies performed by adding up to 33% (v/v) [D_6]DMSO (dimethyl sulfoxide) showed that the change in their chemical shifts ($\Delta\delta$) was smaller than 0.89 ppm, thus implying their participation in H bonding.[5] Furthermore, for β residues, the coupling constant $^3J_{C\alpha H,C\beta H} < 5.9$ Hz, which suggests a predominance of a single rotamer population about the Cα–Cβ bond, with N–Cβ–Cα–CO $\approx 60°$. However, $^3J_{NH,C\alpha H}$ (α residues) and $^3J_{NH,C\beta H}$ (β-residues), which had values between 6.5 and 7.7 Hz, differed considerably from those observed



Scheme 2. Synthesis of α/β-peptides **1**–**3**, **5**, **6**, **8**, and **9**. Reagents and conditions: a) aqueous NaOH (4 N), MeOH, 0 °C→room temperature, 2 h; b) CF_3COOH, dry CH_2Cl_2, 2 h; c) HOBt (1.2 equiv), EDCI (1.2 equiv), DIPEA (1.5 equiv), dry CH_2Cl_2, 0 °C→room temperature, 4 h. Boc = *tert*-butoxycarbonyl, DIPEA = diisopropylethylamine, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = 1-hydroxybenzotriazole.

for an 11/9-helix in α/β-peptides with the α-β-α sequence at the C termini.[3c,g] Although the medium-range NOE enhancements for CαH(1)/NH(3) and NH(2)/NH(3) are characteristic of a putative 11/9-helix at the N terminus, the presence of distinct NOE enhancements for C4H(2)/NH(4) and CαH(1)/NH(4) suggests some variation from a regular 11/9-helix at the C terminus. To obtain more definitive information on the underlying structure, larger oligomers **3a**, **5**, **6a**, and **7** were investigated.

For hexapeptide **3a**, all amide protons except NH(1) resonated at $\delta > 7$ ppm, thus suggesting their involvement in H bonding. Further confirmation of their participation in H bonding was obtained from the solvent titration studies (Figure 2a),[3c,5] in which, by adding up to 33% (*v*/*v*) [D_6]DMSO, it was found that these amide protons display small $\Delta\delta$ values (maximum $\Delta\delta < 0.80$ ppm). The distinguishing features of an 11/9-helical pattern,[3c,5] which encompasses residues 2–4, are supported by $^3J_{NH,C\alpha H} = 5.3$ Hz for the α residue and $^3J_{NH,C\beta H} > 9.0$ Hz and $^3J_{C\alpha H,C\beta H} < 5.3$ Hz for the β residues, as well as by the CαH(1)/NH(3), CαH(3)/NH(5), and NH(2)/NH(3) NOE cross-peaks. However, the NOE correlations C4H(4)/NH(6), CαH(3)/NH(6), NH(4)/NH(5), NH(4)/NH(6), and NH(5)/NH(6) (Figure 1 and Figure 2b), which involve the C-terminal residues, confirm the structural difference from those for 11/9-helices reported earlier. The proximity of CαH(3) to NH(6) as well as the short distance between the three amide protons at the C terminal suggests the presence of an unusual turn. The hexapeptide seems to display a novel HT motif.



Scheme 3. Synthesis of α/β-peptides **4**, **7**, **10**, and **11**. Reagents and conditions: a) aqueous NaOH (4 N), MeOH, 0 °C→room temperature, 2 h; b) CF_3COOH, dry CH_2Cl_2, 2 h; c) HOBt (1.2 equiv), EDCI (1.2 equiv), DIPEA (1.5 equiv), dry CH_2Cl_2, 0 °C→room temperature, 4 h.

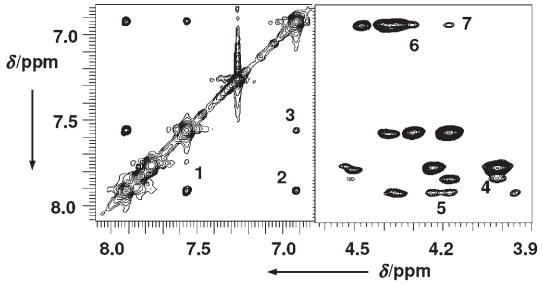


Figure 1. ROESY spectrum of **3a**. The NOE correlations NH(4)/NH(5), NH(5)/NH(6), NH(4)/NH(6), CαH(1)/NH(3), CαH(3)/NH(5), C4H/NH(6), and CαH(3)/NH(6) are marked as 1–7, respectively.

Restrained molecular dynamics (MD) calculations on **3a** reveal the presence of an unprecedented HT motif. Figure 3a depicts the stereo view of the superposition of 20 lowest-energy structures of **3a** with average pairwise heavy-atom and backbone RMSD (root-mean-square deviation) values of 0.50 and 0.47 Å, respectively.[5] The turn and helix are distinctly visible in another view of **3a** (Figure 3b). The 11/9-helix at the N terminal and the unusual pseudo α turn at the C terminal are distinctly visible in these novel structures. The turn in the β-α-β-fragment is stabilized by two H bonds: CO(4)–NH(6), a seven-membered pseudoring (γ turn) in the backward direction, and NH(4)–CO(6), a 13-membered pseudoring in the forward direction (Figure 2b). The backbone dihedral angles that characterize the turn are shown in Table 1. Furthermore, NMR spectroscopic studies of **3a** in the polar solvent[5] CD_3OH also showed the charac-

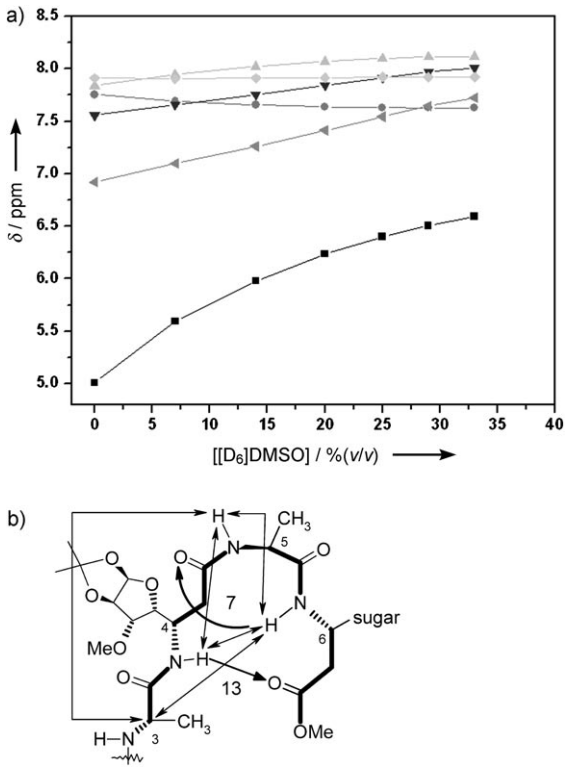


Figure 2. a) Solvent titration studies of **3a**. ■ = NH(1), ● = NH(2), ▲ = NH(3), ▼ = NH(4), ◆ = NH(5), ◀ = NH(6). b) Characteristic NOE correlations (dotted lines) and H bonds (smooth lines) defining the turn in **3a** (the numbers along the arrows (7 and 13) refer to the H-bonded pseudorings; the numbers in italics (*3–6*) represent the residues).

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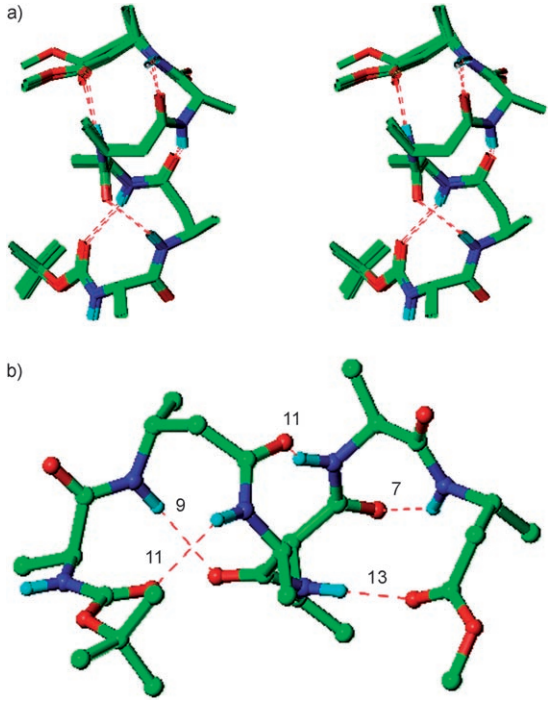

Figure 3. a) Stereoview of **3a**. b) View highlighting the turn and the helix in **3a** (the sugars were replaced with methyl groups after the calculations; the numbers represent the pseudorings of the H bonds).

Table 1. Backbone dihedral angles of **3a**, **5**, **6a**, and **7** in the turn region involving the β-α-β sequence.

	3a	5	6a	7
Residue $(i-2)$[a]				
ϕ [°]	79	77	75	81
θ [°]	57	57	56	52
ψ [°]	−103	−102	−104	−101
Residue $(i-1)$[a]				
ϕ [°]	−90	−89	−90	−92
ψ [°]	71	74	75	67
Residue i[a]				
ϕ [°]	86	81	88	97
θ [°]	68	66	66	66
ψ [°]	149	143	−156	−153

[a] i refers to the last residue.

teristic NOE enhancements observed in $CDCl_3$, albeit slightly weaker.

Peptides **5**, **6a**, and **7** display propagation of similar mixed helical structures at the N termini, with the last three residues having a distinct turn that results in HT supersecondary structures akin to that of **3a**.[5]

The new three-residue turn, β-Caa–L-Ala–β-Caa (Figure 4c), unlike the D-Pro–L-Pro–D-Ala (Figure 4b) turn reported by Balaram and co-workers,[2] contains no constrained amino acids and differs in the directionality of the 13-membered H bond. Furthermore, both turns differ from the α turns[7] observed in proteins. Pavone et al.[8] predicted such a turn (Figure 4c) through simple model building and realized it in a cyclic tetrapeptide derived from alternating L-Pro and β-hGly. Seebach et al.[4] recently observed two-residue turns in α/β-peptides involving β^2-Met–Lys and β^2-Leu–β^3-Val with nine- and 10-membered H bonds, respectively.

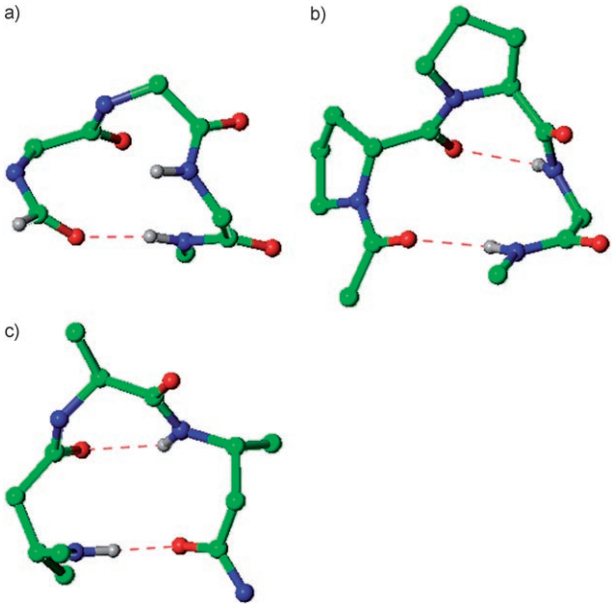

Figure 4. Ball-and-stick models of the turns: a) α-helix; b) D-Pro–L-Pro–D-Ala; c) β-Caa–L-Ala–β-Caa.

The CD spectra[5] of **2**, **3a**, **5**, **6a**, and **7** (Figure 5) in methanol (200 μM) show the signature peaks of the 11/9-helix,[3c] with maximum molar ellipticities per residue at around

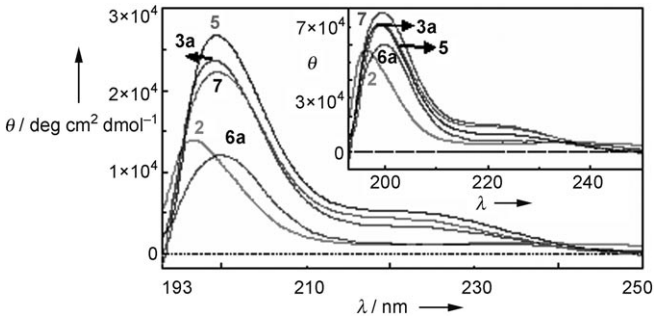

Figure 5. CD spectra of peptides **2**, **3a**, **5**, **6a**, and **7**. The vertical axis displays the molar ellipticities per residue, whereas the inset shows the molar ellipticities per 11-membered H bond.

200 nm. No separate features could be noticed from the turn loop. It was intriguing to observe a distinct correlation of molar ellipticities with the number of 11-membered H bonds in these peptides (Figure 5, inset). Compounds **2**, **3a**, **5**, **6a**, and **7** have maximum molar ellipticities of 56540, 142048, 213829, 60123, and 155682 deg cm^2 dmol^{-1} and one, two, three, one, and two 11-membered pseudo H bonds, respectively, which implies a molar ellipticity of about 70000 deg cm^2 dmol^{-1} per 11-membered H bond for the CD

absorption at around 200 nm. In 9/11-helices, the 11-membered H bond is almost parallel to the helix axis, whereas the nine-membered H bond is tilted away from the helix axis.[3c] It has been suggested[9] that the contribution to the molar ellipticities are decreased when the C=O bond is oriented away from the helix axis. Peptides **2** and **6a**, with smaller helices, show somewhat smaller molar ellipticities, possibly due to fraying in the termini, which compromises their robustness. Similarly, the largest value of about 77841 deg cm^2 dmol^{-1} for **7** may reflect the increased stability of the helix.

To establish the generality of the new three-residue β-α-β turn at the C terminus, oligomers **3b**, **3c**, **6b**, and **6c** were prepared by replacing L-Ala with L-Pro, D-Pro, L-Val, and Aib, respectively; peptides **4** and **11** were prepared by replacing β-Caa with β-D-hAla and β-hGly, respectively.

For pentapeptides **6b** and **6c**, which have L-Val and Aib, respectively, in the turn region, all the characteristic signals in the NMR spectra are very similar to those in **6a**, thus confirming an HT structure (see Supporting Information).[5] The Aib residue is generally used to induce constraints in peptides and has a high propensity to generate a 3_{10}/α-helix ($\phi \approx -60°$).[1a] This therefore implies that for **6c**, with $\phi \approx -86°$ for Aib, the turn is able to accommodate a considerable deviation from the allowed values in an HT peptide.

For peptides **3b** and **3c**, the presence of L-Pro and D-Pro, respectively, leads to two sets of peaks in the ^{1}H NMR spectra. The major isomer with a population of about 96% was identified as the *trans* isomer for **3b**, whereas, with a population of about 65%, the *cis* isomer dominated for **3c**. Detailed studies of these major isomers, despite supporting the presence of an 11/9-helix in the N termini, showed no sign of a turn at the C termini. This loss of structure could be attributed both to the lack of H bonds due to the absence of the amide protons in L- and D-Pro and to the rigidity of the Pro residues with $\phi \approx 60°$ for D-Pro and $-60°$ for L-Pro.

The structural information from the NMR spectroscopic data for the hexapeptides **4** and **11a** is very similar to that for **3a**, thus confirming an HT structure,[5] even though β-Caa was replaced by β-D-hAla or β-hGly in the turn region (Figure 6). However, the appearance of much weaker medium-range correlations in the NOE data for **4** indicates the weakening of the structure in the turn region.

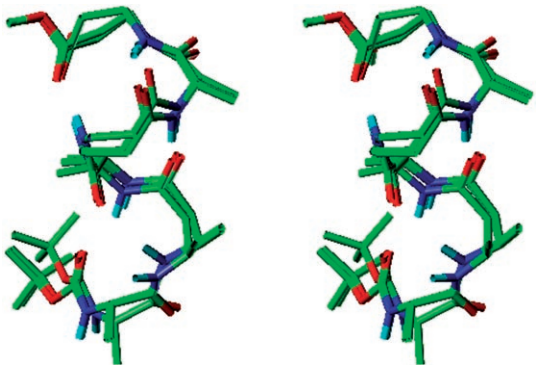

Figure 6. Stereoview of the MD structures of **11a** (the sugars were replaced with methyl groups after the calculations).

As discussed earlier, Pavone et al.[8] realized a β-α-β turn in a cyclic β-hGly–L-Pro–β-hGly–L-Pro tetrapeptide, which provided the impetus to prepare hexapeptides **11b** and **11c**, which have β-hGly–L-Pro–β-hGly and β-hGly–D-Pro–β-hGly at the C termini, and explore their structures. These peptides are very similar to **3b** and **3c** and consist of two isomers. The major isomer with a *trans* imide bond has a population of about 98% for **11b** and about 79% for **11c**. These two compounds, however, lack a side chain in the β residues of the turn region. NMR spectroscopic studies showed very similar structural features for all these peptides (**3b**, **3c**, **11b**, and **11c**), which display characteristics of α/β-helices[5] at the N termini involving residues 1–3, whereas the features for the turn at the C termini could not be noticed.

It is evident from the above studies that the β-α-β three-residue-turn region in the HT motif is well-accommodated with α and β residues such as L-Ala, L-Val, and Aib as well as β-D-hAla (with a proteinogenic side chain) and β-hGly (with no substitution), although both L- and D-Pro disrupted the turn structure. In view of these observations, the HT peptide motifs were envisaged as an attractive option for the design of helix-turn-helix (HTH) tertiary structures. However, the extension of **1** and **2** at the C termini with the smallest helix-forming α/β-peptide, Boc–L-Ala–β-Caa–L-Ala–OMe,[3c] resulted in peptides with an extended 11/9-helix. Therefore, to avoid such a helical continuity, peptides **8a–c**, **9**, and **10** were prepared by extending **6a–c**, **3a**, and **7**, respectively, at the C termini with Boc–NH–β-Caa–L-Ala–β-Caa–L-Ala–OMe.[3c]

The NMR spectrum of **8a** shows that, apart from NH(2), all amide proton resonances display a downfield shift. The involvement of these protons in H bonding was confirmed by the small values of $\Delta\delta$ (< 0.75 ppm) in the solvent titration studies.[5] Although the data indicate the presence of stable helices at the two termini, with characteristic H-bonding, coupling, and NOE patterns, the geometry of the turn region differed from that of the peptides with HT structures. The NOE enhancements for CαH(2)/NH(4), NH(1)/NH(2), and NH(3)/NH(4) and the couplings (involving the first few residues) $^3J_{NH,C\beta H} = 7.8$ (β-1 residue), $^3J_{NH,C\beta H} = 8.3$ (β-3 residue), $^3J_{NH,C\alpha H} = 5.0$ (α-2 residue), and $^3J_{NH,C\alpha H} = 5.6$ Hz (α-4 residue), as well as small values of $^3J_{C\alpha H,C\beta H}$ (due to overlap, not all coupling constants could be obtained) are those expected for an 11/9-helix at the N terminus. The turn region involving the residues 4–7 displayed new NOE correlations: NH(5)/C4H(6), NH(5)/C1H(6), NH(5)/NH(6), CαH(4)/NH(6), and CαH(4)/NH(7) (Figure 7a). The couplings $^3J_{NH,C\beta H}$ (β-8 residue) = 9.3, $^3J_{NH,C\alpha H}$ (α-7 residue) = 5.7, and $^3J_{C\alpha H(pro\text{-}R),C\beta H} = 4.8$ Hz (β-8 residue) and the NOE correlations CαH(7)/NH(9) and NH(8)/NH(9) provide emphatic support for an 11/9-helix at the C terminus. MD calculations[5] provide compelling evidence for an HTH structure for **8a**. Superposition of 20 lowest-energy structures resulted in average pairwise heavy-atom and backbone RMSD values of 0.56 and 0.49 Å, respectively. Interestingly, the

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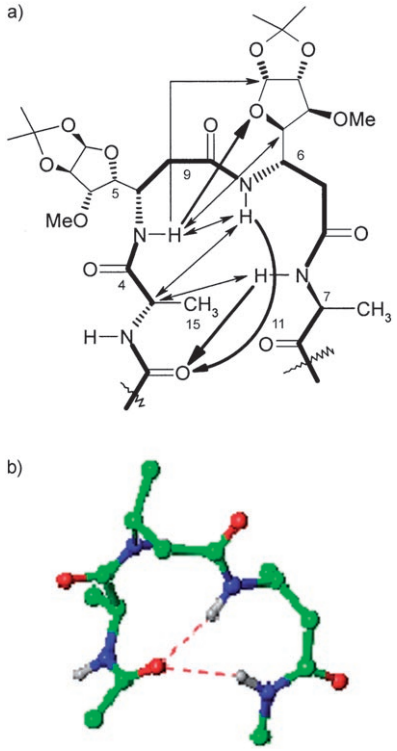

Figure 7. a) Characteristic NOE correlations (dotted lines) and H bonds (smooth lines) defining the turn in **9** (the numbers along the arrows (9, 11, and 15) refer to the H-bonded pseudorings; the numbers in italics (*4*–*7*) represent the residues); b) Ball-and-stick model of the turn L-Ala–β-Caa–β-Caa.

turn region shows the involvement of CO(3) in a three-center H bond with NH(6) and NH(7), which have 11- and 15-membered pseudorings, respectively. H bonding was also observed between NH(5) and O(6) of the furanose ring (Figure 7), which further aided the stabilization of the structure. The new three-residue turn imparts an angle of about 90° between the two helices. The backbone dihedral angles obtained from the MD studies are shown in Table 2. The 15-membered H bond in the turn is akin to those observed in a canonical α-helix. Such 11- and 14/15-membered pseudorings in α/β-peptides were first observed by Gellman and co-workers,[3a] whereas Balaram and co-workers[11] discussed a 15-helix from energetic considerations in peptides with α-β-β repeating units. However, the observed dihedral angles of the new turn (α-β-β) not only differ from those observed in 15-helices,[11] but also differ from those for the β-α-β turns observed for HT motifs (Tables 1 and 2).

The above characteristics of **8a** were also observed in **8b**, although the signature peaks in the NMR spectra were somewhat weakened, as seen from the NOE correlations and coupling constants. For peptide **8c**, although the involvement of a large number of amide protons in H bonding was observed,[5] severe overlap of signals in the amide region hampered the unambiguous assignment of the structure. Furthermore, the higher oligomers **9** and **10**, with

Table 2. Backbone dihedral angles of **8a**, **8b**, **9**, and **10** in the turn region involving the α-β-β sequence.

	8a	**8b**	**9**	**10**
Residue (*i*−5)[a]				
ϕ [°]	−73	−76	−59	−59
ψ [°]	138	120	132	135
Residue (*i*−4)				
ϕ [°]	81	83	93	85
θ [°]	65	72	67	68
ψ [°]	−85	−70	−86	−83
Residue (*i*−3)				
ϕ [°]	137	113	124	119
θ [°]	83	102	81	77
ψ [°]	−108	−61	−62	−57

[a] *i* refers to the last residue.

larger helical extensions at the N termini, reiterated the HTH structure elaborated above.[5] Figure 8 shows the stereo view of the superposition of 20 lowest-energy structures with average pairwise heavy-atom and backbone RMSD values of 0.50 and 0.45 Å, respectively. The extensive studies thus unambiguously establish the presence of the HTH motif in peptides **8**–**10** (Table 2), with bifurcated H bonding in the new α-β-β three-residue-turn region.

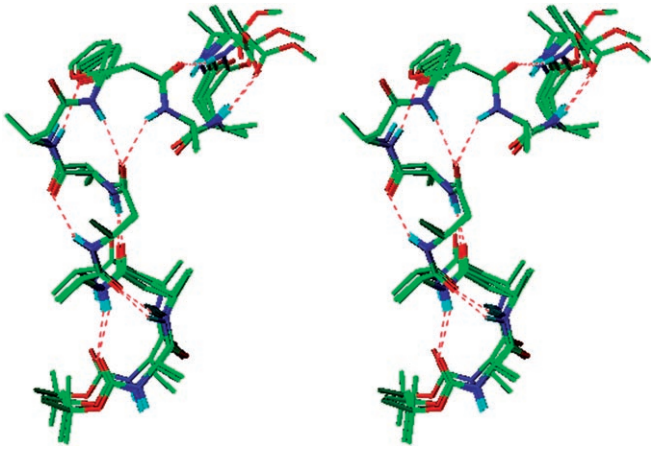

Figure 8. Stereoview of peptide **9** (the sugars were replaced with methyl groups after the calculations, except for that of residue 7; dotted lines indicate H bonds).

Conclusions

In this study, β-α-β and α-β-β tripeptides, devoid of any constrained amino acids, have emerged as novel three-residue-turn motifs. It was rather serendipitous that a helix turn in α/β-peptides with the β-α-β sequence at the C termini was obtained. Although the β-α-β turn in the HTH motif, designed from the HT motifs, was disturbed, nucleation of another turn, the α-β-β turn, generated the tertiary scaffolds. Furthermore, this study also established the generality of

the new turns with the incorporation of several α- and β-amino acid residues in the turn region to generate HT and HTH motifs. This report, along with our recent design of HTH motifs,[12] provides options to form a variety of tertiary structures, referred to as "tyligomers" by Moore and co-workers,[13] from hybrid peptides with a very large pool of helices, sheets, and turn motifs in the foldamer domain. We therefore cautiously and optimistically approach the moment when a glimpse in the wide horizon of designed artificial proteins is permitted, with various functional groups appropriately decorated in such scaffolds derived from foldamers and tyligomers.

Experimental Section

General

NMR spectra (1D and 2D experiments) for peptides **1**–**11** were obtained at 500 and 600 MHz for ^{1}H and at 75 and 150 MHz for ^{13}C. Chemical shifts are reported in ppm with respect to tetramethylsilane (TMS) as an internal reference. IR spectra were recorded with an FTIR spectrometer at 400–4000 cm^{-1} in KBr pellets. Melting points were determined in open capillaries and are not corrected.

CD spectra were obtained with a Jasco J-810 spectropolarimeter by using rectangular fused quartz cells of 0.2-cm path length with 200 μM solutions in methanol. The binomial method was used for smoothing the spectra. Molar ellipticities (θ) are expressed as deg cm^2 $dmol^{-1}$.

Restrained MD studies were carried out with the INSIGHT-II Discover module on an SGI workstation. The constraints were derived from the volume integrals obtained from ROESY spectra by using a two-spin approximation and a reference distance of 1.8 Å for the geminal protons. The upper and lower bound of the distance constraints were obtained by enhancing and decreasing the derived distance by 10%.

Syntheses

15: A cooled (0°C) solution of **12** (0.6 g, 1.6 mmol) in methanol (6.5 mL) was treated with aqueous NaOH (4 N, 6.5 mL), and the mixture was stirred at room temperature. After 2 h, methanol was removed, the pH was adjusted to pH 2–3 with aqueous HCl (1 N) at 0°C, and the mixture was extracted with ethyl acetate (2×10 mL). The organic layers were dried (Na_2SO_4) and concentrated to give **12a** (0.49 g, 85%) as a pale-yellow syrup, which was used without further purification in the next step. A suspension of **13** (0.517 g, 3.71 mmol; prepared from L-Ala in methanolic HCl) in CH_2Cl_2 (5 mL) was treated with DIPEA (0.96 mL, 5.56 mmol) at 0°C, and the mixture was stirred for 15 min to give free amine H-L-Ala-OCH_3. A solution of **12a** (1.34 g, 3.71 mmol), HOBt (0.6 g, 4.45 mmol), and EDCI (0.25 g, 1.34 mmol) in CH_2Cl_2 (15 mL) was stirred at 0°C under N_2 atmosphere for 15 min, and the mixture was treated with the above amine and stirred for 8 h. The reaction was quenched at 0°C with saturated aqueous NH_4Cl (10 mL). After 10 min, the reaction mixture was diluted with $CHCl_3$ (10 mL) and washed with HCl (1 N, 10 mL), water (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the residue was purified by column chromatography (silica gel, 50% ethyl acetate in petroleum ether) to afford **15** (1.2 g, 72.5%) as a white solid. M.p.: 69–72°C; $[\alpha]_D = -38.72$ ($c = 0.25$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3372$, 3351, 2985, 2940, 1733, 1701, 1653, 1523,1295, 1174, 1079, 997, 641 cm^{-1}; ^{1}H NMR ($CDCl_3$, 303 K, 300 MHz): $\delta = 6.62$ (d, $J = 6.8$ Hz, 1H, NH2), 5.89 (d, $J = 3.7$ Hz, 1H, C1H1), 5.14 (br s, 1H, NH1), 4.58 (d, $J = 3.9$ Hz, 1H, C2H1), 4.57–4.48 (m, 1H, CαH2), 4.28 (dd, $J = 3.3$, 7.7 Hz, 1H, C4H1), 4.21–4.12 (m, 1H, CβH1), 3.74 (d, $J = 3.3$ Hz, 1H, C3H1), 373 (s, 3H, COOMe), 3.37 (s, 3H, OMe), 2.57 (dd, $J = 5.7$, 14.9 Hz, 1H, $C\alpha H_{(pro\text{-}R)}1$), 2.52 (dd, $J = 6.2$, 14.9 Hz, 1H, $C\alpha H_{(pro\text{-}S)}$-1), 1.48 (s, 3H, CH_3), 1.44 (s, 9H, Boc), 1.40 (d, $J = 7.3$ Hz, 3H, $CH_3$2), 1.31 ppm (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.3$, 170.1, 156.1, 111.7, 104.7, 83.9, 81.3, 80.2, 79.6, 57.5, 52.4, 48.1, 47.8, 39.0, 28.3 (3C), 26.7, 26.3, 18.0 ppm; HRMS (ESI): m/z calcd for $C_{20}H_{34}N_2O_9$: 447.2439 $[M+H]^+$; found: 447.2462.

1: As described for **12a**, a solution of **15** (0.25 g, 0.56 mmol) gave **16a** (0.236 g, 97.5%) as a white solid, which was used without further purification in the next step. A solution of **12** (0.317 g, 0.845 mmol) and trifluoroacetic acid (TFA; 0.3 mL) in CH_2Cl_2 (3 mL) was stirred at room temperature for 1 h. After completion of the reaction, the solvent was evaporated under reduced pressure to give **12b**, which was dried under high vacuum and used without further purification in the next step. As described for the synthesis of **15**, a solution of **16a** (0.365 g, 0.845 mmol), HOBt (0.137 g, 1.014 mmol), and EDCI (0.194 g, 1.014 mmol) in CH_2Cl_2 (8 mL) was stirred at 0°C under N_2 atmosphere for 15 min. Compound **12b** and DIPEA (0.22 mL, 1.27 mmol) were added sequentially, and the mixture was stirred for 8 h. Workup and purification of the residue by column chromatography (silica gel, 70% ethyl acetate in petroleum ether) afforded **1** (0.495 g, 85%) as a white solid. M.p.: 125–127°C; $[\alpha]_D = -128.6$ ($c = 0.25$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3303$, 3269, 2984, 2936, 1738, 1700, 1697, 1647, 1534, 1373, 1252, 1169, 1081, 1019 cm^{-1}; ^{1}H NMR ($CDCl_3$, 303 K, 500 MHz): $\delta = 6.60$ (d, 1H, NH3), 6.54 (br s, 1H, NH2), 5.90 (d, $J = 3.7$ Hz, 1H, C1H3), 5.90 (d, $J = 3.9$ Hz, 1H, C1H1), 5.28 (br s, 1H, NH1), 4.57 (d, $J = 3.9$ Hz, 1H, C2H1), 4.55 (d, $J = 3.7$ Hz, 1H, C2H3), 4.54–4.50 (m, 1H, CβH1), 4.40–4.36 (m, 1H, CαH2), 4.35 (dd, $J =$ 3.4, 7.8 Hz, 1H, C4H1), 4.32 (dd, $J = 3.4$, 7.8 Hz, 1H, C4H3), 4.18–4.12 (m, 1H, CβH3), 3.74 (d, $J = 3.4$ Hz, 1H, C3H1), 3.68 (d, $J = 3.4$ Hz, 1H, C3H3), 3.68 (s, 3H, COOMe), 3.37 (s, 3H, OMe), 3.36 (s, 3H, OMe), 2.68 (dd, $J = 6.5$, 16.3 Hz, 1H, $C\alpha H_{(pro\text{-}R)}3$), 2.55 (dd, $J = 5.4$, 14.4 Hz, 1H, $C\alpha H_{(pro\text{-}R)}1$), 2.48 (dd, $J = 5.9$, 16.3 Hz, 1H, $C\alpha H_{(pro\text{-}S)}3$), 2.48 (dd, $J = 5.7$, 14.4 Hz, 1H, $C\alpha H_{(pro\text{-}S)}1$), 1.48 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.43 (s, 9H, Boc), 1.34 (d, $J = 7.2$ Hz, 3H, $CH_3$2), 1.31 (s, 3H, CH_3), 1.31 ppm (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 171.7$, 171.6, 170.3, 156.1, 111.6, 104.8, 104.7, 84.4, 83.9, 81.3, 80.2, 79.6, 79.3, 77.2, 57.5, 57.4, 51.8, 49.0, 48.9, 48.1, 45.7, 38.9, 36.1, 29.7, 28.4 (3C), 26.7, 26.3, 26.2, 17.8 ppm; HRMS (ESI): m/z calcd for $C_{31}H_{51}N_3O_{14}$: 712.3268 $[M+Na]^+$; found: 712.3266.

19a: As described for the synthesis of **1**, a mixture of **14a** (0.37 g, 1.96 mmol), HOBt (0.317 g, 2.35 mmol), and EDCI (0.45 g, 2.35 mmol) in CH_2Cl_2 (10 mL) was stirred at 0°C for 15 min and then treated with **12b** (prepared from **12** (0.735 g, 1.96 mmol) and TFA (0.7 mL) in CH_2Cl_2 (3 mL)) and DIPEA (0.51 mL, 2.94 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 40% ethyl acetate in petroleum ether) afforded **19a** (0.67 g, 76.6%) as a yellow syrup. $[\alpha]_D = -40.4$ ($c = 0.5$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3333$, 2982, 2937, 1716, 1673, 1517, 1370, 1169, 1167, 1080, 1023, 857 cm^{-1}; ^{1}H NMR ($CDCl_3$, 303 K, 500 MHz): $\delta = 6.50$ (d, $J = 8.5$ Hz, 1H, NH2), 5.89 (d, $J =$ 3.8 Hz, 1H, C1H2), 5.04 (br s, 1H, NH1), 4.59–4.56 (m, 1H, CβH2), 4.55 (d, $J = 3.9$ Hz, 1H, C2H2), 4.36 (dd, $J = 3.5$, 6.2 Hz, 1H, C4H2), 4.16–4.06 (m, 1H, CαH1), 3.69 (d, $J = 3.5$ Hz, 1H, C3H2), 3.66 (s, 3H, COOMe), 3.36 (s, 3H, OMe), 2.71 (dd, $J = 6.4$, 16.1 Hz, 1H, $C\alpha H_{(pro\text{-}R)}2$), 2.62 (dd, $J = 5.5$, 16.1 Hz, 1H, $C\alpha H_{(pro\text{-}S)}2$), 1.48 (s, 3H, CH_3), 1.44 (s, 9H, Boc), 1.33 (d, $J = 7.0$ Hz, 3H, $CH_3$1), 1.31 ppm (s, 3H, $CH_3$1); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 172.1$, 171.5, 155.2, 111.6, 104.6, 84.3, 81.2, 79.6, 79.1, 57.4, 51.6, 49.9, 45.4, 36.1, 28.2 (3C), 26.6, 26.1, 18.4 ppm; HRMS (ESI): m/z calcd for $C_{20}H_{34}N_2O_9$: 447.2345 $[M+H]^+$; found: 447.2363.

19b: As described for the synthesis of **1**, a mixture of **14b** (0.395 g, 1.818 mmol), HOBt (0.295 g, 2.18 mmol), and EDCI (0.418 g, 2.18 mmol) in CH_2Cl_2 (10 mL) was stirred at 0°C for 15 min and then treated with **12b** (prepared from 12 (0.5 g, 1.818 mmol) and TFA (0.5 mL) in CH_2Cl_2 (3 mL)) and DIPEA (0.47 mL, 2.73 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 50% ethyl acetate in petroleum ether) afforded **19b** (0.75 g, 87.0%) as a white solid. M.p.: 88–92°C; $[\alpha]_D = -105.84$ ($c = 0.5$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3333$, 2989, 2939, 1717, 1675, 1520, 1369, 1171, 1167, 1084, 1023, 857 cm^{-1}; ^{1}H NMR ($CDCl_3$, 303 K, 300 MHz): $\delta = 6.47$ (d, $J = 7.2$ Hz, 1H, NH2), 5.89 (d, $J = 3.8$ Hz, 1H, C1H2), 5.10 (d, $J = 8.1$ Hz 1H, NH1), 4.56 (d, $J =$ 3.8 Hz, 1H, C2H2), 4.59–4.50 (m, 1H, CαH1), 4.37 (dd, $J = 3.3$, 6.3 Hz, 1H, C4H2), 3.96–3.85 (m, 1H, CβH1), 3.68 (s, 3H, COOMe), 3.67 (dd, 1H, $J = 3.3$ Hz, C3H2), 3.36 (s, 3H, OMe), 2.72(dd, J=6.3, 16.5 Hz, 1H,

CαH$_{(pro\text{-}R)}$2), 2.64 (dd, J=5.2, 16.5 Hz, 1H, CαH$_{(pro\text{-}S)}$2), 2.20–2.03 (m, 1H, CβH1), 1.47 (s, 3H, CH$_3$), 1.43 (s, 9H, Boc), 1.31 ppm (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz): δ=171.7, 170.9, 155.7, 111.7, 104.7, 84 .4, 81.3, 79.2, 59.7, 57.4, 51.7, 45.5, 36.1, 31.0, 28.2 (3C), 26.7, 26.2, 19.1, 17.3 ppm; HRMS (ESI): m/z calcd for $C_{22}H_{38}N_2O_9$: 475.2345 $[M+H]^+$; found: 475.2363.

19c: As described for the synthesis of **1**, a mixture of **14c** (0.203 g, 1.0 mmol), HOBt (0.162 g, 1.2 mmol), and EDCI (0.23 g, 1.2 mmol) in CH_2Cl_2 (5 mL) was stirred at 0°C for 15 min and then treated with **12b** (prepared from **12** (0.375 g, 1.0 mmol) and TFA (0.3 mL) in CH_2Cl_2 (3 mL)) and DIPEA (0.26 mL, 1.5 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 35% ethyl acetate in petroleum ether) afforded **19c** (0.4 g, 86.9%) as a syrup. $[\alpha]_D$=−84.3 (c=0.5, CHCl$_3$); IR (KBr): $\tilde{\nu}$=3334, 2989, 2940, 1720, 1679, 1520, 1375, 1176, 1165, 1086, 1023, 857 cm^{-1}; ^{1}H NMR (CDCl$_3$, 303 K, 300 MHz): δ=6.91 (d, J=7.7 Hz, 1H, NH2), 5.88 (d, J=3.7 Hz, 1H, C1H2), 5.02 (s, 1H, NH1), 4.55 (d, J=3.9 Hz, 1H, C2H2), 4.55–4.50 (m, 1H, CβH2), 4.37 (dd, J=3.2, 6.4 Hz, 1H, C4H2), 3.68 (d, J=3.2 Hz, 1H, C3H2), 3.66 (s, 3H, COOMe), 3.35 (s, 3H, OMe), 2.72 (dd, J=6.3, 16.1 Hz, 1H, CαH$_{(pro\text{-}R)}$2), 2.61 (dd, J=4.9, 16.1 Hz, 1H, CαH$_{(pro\text{-}S)}$2), 1.47 (s, 3H, CH$_3$), 1.46 (d, J=7.2 Hz, 3H, CH$_3$1), 1.42 (s, 9H, Boc), 1.30 ppm (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz): δ=174.0, 171.8, 154.4, 111.5, 104.7, 84 .4, 81.3, 79.1, 57.4, 56.6, 51.6, 45.5, 35.8, 29.6, 28.3 (3C), 26.7, 26.2, 25.8, 24.9 ppm; HRMS (ESI): m/z calcd for $C_{21}H_{36}N_2O_9$: 461.2434 $[M+H]^+$; found: 461.2463.

19d: As described for the synthesis of **1**, a mixture of **14d** (0.5 g, 2.33 mmol), HOBt (0.377 g, 2.79 mmol), and EDCI (0.535 g, 2.79 mmol) in CH_2Cl_2 (10 mL) was stirred at 0°C for 15 min and then treated with **12b** (prepared from **12** (0.64 g, 2.33 mmol) and TFA (0.4 mL) in CH_2Cl_2 (3 mL)) and DIPEA (0.6 mL, 3.47 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 60% ethyl acetate in petroleum ether) afforded **19d** (0.96 g, 95%) as a yellow syrup. $[\alpha]_D$=−170.6 (c=0.5, CHCl$_3$); IR (KBr): $\tilde{\nu}$=3330, 2988, 2947, 1719, 1677, 1527, 1375, 1179, 1169, 1083, 1025, 857 cm^{-1}; ^{1}H NMR (CDCl$_3$, 303 K, 300 MHz): δ=7.17 (br s, 1H, NH1), 6.61 (br s, 1H, NH1), 5.89 (d, J=3.7 Hz, 1H, C1H2), 4.56 (d, J=3.7 Hz, 1H, C2H2 and CαH1), 4.34 (dd, J=3.3, 8.1 Hz, 1H, C4H2), 4.28–4.15 (m, 1H, CβH2), 3.69 (d, J=3.2 Hz, 1H, C3H2), 3.67 (s, 3H, COOMe), 3.54–3.40 (m, 2H, CδH2), 3.38 (s, 3H, OMe), 2.70 (dd, J=5.5, 15.8 Hz, 1H, CαH$_{(pro\text{-}R)}$2), 2.57 (dd, J=5.7, 15.8 Hz, 1H, CαH$_{(pro\text{-}S)}$2), 2.29–2.12 (m, 2H, CβH1), 1.94–1.80 (m, 2H, CγH1), 1.72 (s, 3H, CH$_3$), 1.46 (s, 9H, Boc), 1.31 ppm (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz): δ=171.6, 111.6, 104.8, 84.1, 81.2, 79.3, 61.2, 60.0, 57.4, 51.7, 46.8, 45.5, 35.8, 30.9, 28.3 (3C), 26.7, 26.2, 24.3, 23.4 ppm; HRMS (ESI): m/z calcd for $C_{22}H_{36}N_2O_9$: 473.2425 $[M+H]^+$; found: 473.2434.

19e: As described for the synthesis of **1**, a mixture of **14e** (0.287 g, 1.33 mmol), HOBt (0.216 g, 1.6 mmol), and EDCI (0.307 g, 1.6 mmol) in CH_2Cl_2 (8 mL) was stirred at 0°C for 15 min and then treated with **12b** (prepared from 12 (0.5 g, 1.33 mmol) and TFA (0.5 mL) in CH_2Cl_2 (3 mL)) and DIPEA (0.4 mL, 2.0 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 45% ethyl acetate in petroleum ether) afforded **19e** (0.6 g, 95.3%) as a white solid. M.p.: 153–157°C; $[\alpha]_D$=+39.16 (c=0.5, CHCl$_3$); IR (KBr): $\tilde{\nu}$= 3336, 2988, 2937, 1716, 1673, 1529, 1370, 1169, 1167, 1080, 1023, 857 cm^{-1}; ^{1}H NMR (CDCl$_3$, 303 K, 300 MHz): δ=7.24 (br s, 1H, NH1), 6.69 (br s, 1H, NH1), 5.58 (d, J=3.8 Hz, 1H, C1H2), 4.55 (d, J=3.8 Hz, 2H, C2H2 and CαH1), 4.35 (dd, J=3.3, 7.5 Hz, 1H, C4H2), 4.30–4.16 (m, 1H, CβH2), 3.68 (d, J=3.3 Hz, 1H, C3H2), 3.67 (s, 3H, COOMe), 3.52–3.30 (m, 2H, CδH1), 3.35 (s, 3H, OMe), 2.75–2.61 (m, 2H, CαH2), 2.27–2.12 (m, 2H, CβH1), 1.94–1.80 (m, 2H, CγH1), 1.46 (s, 3H, CH$_3$). 1.45 (s, 9H, Boc), 1.46 ppm (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz): δ=171.8, 171.5, 154.6, 111.5, 104.6, 84.5, 81.3, 79.1, 61.2, 60.2, 57.4, 51.6, 46.8, 45.2, 36.2, 30.9, 28.3 (3C), 26.7, 26.2, 24.3, 23.3 ppm; HRMS (ESI): m/z calcd for $C_{22}H_{36}N_2O_9$: 473.2463 $[M+H]^+$; found: 473.2459.

2: As described for the synthesis of **12a**, a solution of **19a** (0.22 g, 0.493 mmol) gave **21** (0.21 g, 98.5%) as a white solid, which was without further purification in the next step. As described for the synthesis of **1**, a mixture of **21** (0.185 g, 0.428 mmol), HOBt (0.069 g, 0.513 mmol), and EDCI (0.25 g, 0.513 mmol) in CH_2Cl_2 (5 mL) was stirred at 0°C for 15 min and then treated with **20a** (prepared from **19a** (0.191 g, 0.428 mmol) and TFA (0.2 mL) in CH_2Cl_2 (0.5 mL)) and DIPEA (0.11 mL, 0.64 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 1.9% methanol in CHCl$_3$) afforded **2** (0.243 g, 74.6%) as a white solid. M.p.: 112–115°C; $[\alpha]_D$=−6.7 (c=0.25, CHCl$_3$); IR (KBr): $\tilde{\nu}$=3329, 2986, 2933, 1663, 1528, 1377, 1250, 1216, 1167, 1080, 1022, 856 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ=7.50 (d, 1H, J=7.0 Hz, NH3), 7.36 (d, J=8.4 Hz, 1H, NH2), 6.75 (d, J= 7.8 Hz, 1H, NH4), 5.98 (d, J=3.9 Hz, 1H, C1H4), 5.88 (d, J=3.9 Hz, 1H, C1H2), 4.99 (d, J=6.2 Hz, 1H, NH1), 4.58 (d, J=3.9 Hz, 1H, C2H2), 4.56 (d, J=3.7 Hz, 1H, C2H4), 4.50–4.45 (m, 1H, CβH2), 4.44–4.40 (m, 1H, CβH4), 4.39–4.35 (m, 1H, CαH3), 4.26 (dd, J=3.4, 9.8 Hz, 1H, C4H2), 3.66 (d, J=3.4 Hz, 1H, C3H4), 4.02 (d, J=3.4 Hz, 1H, C3H2), 4.00–3.96 (m, 1H, CαH1), 3.69 (s, 3H, COOMe), 3.39 (s, 3H, OMe), 3.36 (s, 3H, OMe), 2.71 (dd, J=5.9, 16.0 Hz , 1H, CαH$_{(pro\text{-}R)}$4), 2.62 (dd, J=5.7, 16.0 Hz, 1H, CαH$_{(pro\text{-}S)}$4), 2.61 (dd, J=5.1, 13.5 Hz, 1H, CαH$_{(pro\text{-}R)}$2), 2.26 (dd, J=3.7, 13.5 Hz, 1H, CαH$_{(pro\text{-}S)}$2), 1.47 (s, 3H, CH$_3$), 1.45 (s, 3H, CH$_3$), 1.41 (s, 9H, Boc), 1.36 (d, J=7.4 Hz, 3H, CH$_3$3), 1.34 ppm (d, J=7.0 Hz, 3H, CH$_3$1); ^{13}C NMR (CDCl$_3$, 100 MHz): δ=173.3, 172.9, 171.9, 170.8, 155.9, 111.5, 111.5, 105.0, 104.8, 84.3, 83.6, 81.5, 81.3, 80.0, 79.7, 78.9, 57.4, 57.3, 51.8, 51.0, 49.7, 46.8, 46.0, 38.3, 35.8, 28.2 (3C), 26.7, 26.6, 26.2, 17.5, 16.5 ppm; HRMS (ESI): m/z calcd for $C_{34}H_{57}N_4O_{15}$: 761.3820 $[M+H]^+$; found: 761.3820.

3a: As described for the synthesis of **12a**, a solution of **2** (0.175 g, 0.23 mmol) gave **22** (0.17 g, 96.05%) as a white solid, which was used without further purification in the next step. As described for the synthesis of **1**, a mixture of **22** (0.12 g, 0.16 mmol), HOBt (0.026 g, 0.192 mmol), and EDCI (0.037 g, 0.192 mmol) in CH_2Cl_2 (3 mL) was stirred at 0°C for 15 min and then treated with **20a** (prepared from **19a** (0.071 g, 0.16 mmol) and TFA (0.1 mL) in CH_2Cl_2 (0.7 mL)) and DIPEA (0.041 mL, 0.24 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 2.5% methanol in CHCl$_3$) afforded **3a** (0.132 g, 76.4%) as a white solid. M.p.: 181–183°C; $[\alpha]_D$= 4.6 (c=0.15, CHCl$_3$); IR (KBr): $\tilde{\nu}$=3299, 2985, 2937, 1657, 1542, 1377, 1250, 1167, 1080, 1022, 856 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ=7.91 (d, J=7.2 Hz, 1H, NH5), 7.83 (d, J=5.3 Hz, 1H, NH3), 7.76 (d, J= 9.4 Hz, 1H, NH2), 7.56 (d, J=8.8 Hz, 1H, NH4), 6.92 (d, J=8.1 Hz, 1H, NH6), 5.99 (d, J=3.9 Hz, 1H, C1H4), 5.88 (d, J=3.9 Hz, 2H, C1H2 and C1H6), 5.02 (d, J=6.1 Hz, 1H, NH1), 4.58 (d, J=3.7 Hz, 1H, C2H4), 4.57 (d, J=3.7 Hz, 1H, C2H6), 4.56 (d, J=3.7 Hz, 1H, C2H2), 4.54–4.50 (m, 1H, CβH2), 4.48 (dd, J=3.4, 7.3 Hz, 1H, C4H6), 4.42–4.40 (m, 1H, CβH6), 4.39 (m, 1H, CβH4), 4.35 (m, 1H, CαH5), 4.30 (dd, J=3.2, 10.2 Hz, 1H, C4H4), 4.24 (dd, J=3.3, 9.7 Hz, 1H, C4H2), 4.21–4.15 (m, 1H, CαH3), 4.05 (d, J=3.2 Hz, 1H, C3H4), 4.03–3.99 (m, 1H, CαH1), 3.96 (d, J=3.3 Hz, 1H, C3H2), 3.68 (s, 3H, COOMe), 3.66 (d, J=3.4 Hz, 1H, C3H6), 3.38 (s, 3H, OMe), 3.36 (s, 6H, OMe), 271 (dd, J=6.8, 16.0 Hz, 1H, CαH$_{(pro\text{-}R)}$6), 2.69 (dd, J=5.0, 13.0 Hz, 1H, CαH$_{(pro\text{-}R)}$2), 2.67 (dd, J=5.3, 13.2 Hz, 1H, CαH$_{(pro\text{-}R)}$4), 2.56 (dd, J=3.0, 12.8 Hz, 1H, CαH$_{(pro\text{-}S)}$4), 2.19 (dd, J=3.3, 13.0 Hz, 1H, CαH$_{(pro\text{-}S)}$2), 2.13 (dd, J=3.2, 13.3 Hz, 1H, CαH$_{(pro\text{-}S)}$4), 1.46 (s, 3H, CH$_3$), 1.45 (s, 6H, CH$_3$), 1.40 (s, 9H, Boc), 1.39 (d, J=7.0 Hz, 3H, CH$_3$3), 1.38 (d, J=7.2 Hz, 3H, CH$_3$5), 1.35 (d, J=7.1 Hz, 3H, CH$_3$1), 1.30 (s, 6H, CH$_3$), 1.28 ppm (s, 3H, CH$_3$); ^{1}H NMR (500 MHz, CD$_3$OH): δ=8.58 (d, J=8.4 Hz, 1H, NH2), 8.51 (d, J=8.7 Hz, 1H, NH4), 8.20 (d, J=6.8 Hz, 1H, NH5), 8.18 (d, J=4.5 Hz, 1H, NH3), 8.04 (d, J=8.4 Hz, 1H, NH6), 6.85 (d, J=5.2 Hz, 1H, NH1), 5.96 (d, J=3.9 Hz, 1H, C1H6), 5.82 (d, J=3.9 Hz, 2H, C1H4), 5.81 (d, J=3.9 Hz, 1H, C1H2), 4.67 (d, J=3.9 Hz, 1H, C2H6), 4.66 (d, J=3.9 Hz, 2H, C2H4 and C2H2), 4.47–4.42 (m, 1H, CβH6), 4.38–4.35 (m, 1H, CβH4), 4.34 (dd, J=3.2, 8.4 Hz, 1H, C4H6), 4.32 (m, 1H, CβH2), 4.29 (m, 1H, CαH5), 4.25 (dd, J=3.1, 9.9 Hz, 1H, C4H4), 4.25 (dd, J=3.1, 9.9 Hz, 1H, C4H2), 4.23–4.19 (m, 1H, CαH3), 4.08–4.02 (m, 1H, CαH1), 3.95 (d, J=3.1 Hz, 1H, C3H4), 3.93 (d, J=3.1 Hz, 1H, C3H2), 3.68 (d, J=3.2 Hz, 1H, C3H6), 3.67 (s, 3H, COOMe), 3.40 (s, 3H, OMe), 3.39 (s, 3H, OMe), 3.36 (s, 3H, OMe), 2.65 (dd, J=6.8, 16.0 Hz, 1H, CαH$_{(pro\text{-}R)}$6), 2.63 (dd, J=5.4, 15.6 Hz, 1H, CαH$_{(pro\text{-}R)}$6), 2.58 (dd, J=4.5, 13.4 Hz, 1H, CαH$_{(pro\text{-}R)}$2), 2.53 (dd, J=6.6, 15.6 Hz, 1H, CαH$_{(pro\text{-}S)}$6), 2.24 (dd, J=4.5, 13.4 Hz, 1H, CαH$_{(pro\text{-}S)}$2), 2.17 (dd, J=3.8, 13.4 Hz, 1H, CαH$_{(pro\text{-}S)}$4), 1.46 (s, 3H, CH$_3$), 1.44 (s, 3H, CH$_3$), 1.43 (s, 3H, CH$_3$), 1.42 (s, 9H, Boc),

1.39 (d, J=7.1 Hz, 3H, $CH_3$1), 1.36 (d, J=7.1 Hz, 3H, $CH_3$3), 1.35 (d, J=7.4 Hz, 3H, $CH_3$5), 1.29 (s, 3H, CH_3), 1.28 ppm (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=174.7, 173.4, 173.2, 172.1, 172.0, 170.8, 155.8, 111.5, 111.4, 111.3, 105.1, 104.9, 104.9, 84.4, 83.4, 83.4, 81.4, 81.2, 80.1, 79.9, 79.5, 78.8, 57.4, 57.3, 57.2, 51.9, 51.7, 51.4, 50.9, 49.8, 47.3, 46.8, 46.2, 39.1, 35.8, 29.7, 28.2 (3C), 26.7, 26.6, 26.2, 26.2, 26.0, 17.3, 16.5 ppm; HRMS (ESI): m/z calcd for $C_{48}H_{78}N_6O_{21}$: 1097.5117 $[M+Na]^+$; found: 1097.5120.

3b: As described for the synthesis of **1**, a mixture of **22** (0.09 g, 0.12 mmol), HOBt (0.02 g, 0.145 mmol), and EDCI (0.028 g, 0.145 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 15 min and then treated with **20d** (prepared from **19d** (0.057 g, 0.12 mmol) and TFA (0.1 mL) in CH_2Cl_2 (0.5 mL)) and DIPEA (0.031 mL, 0.18 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 4.0% methanol in $CHCl_3$) afforded **3b** (0.08 g, 60.3%) as a white solid. M.p.: 130–133 °C; $[\alpha]_D$=−104.3 (c=0.1, $CHCl_3$); IR (KBr): $\tilde{\nu}$= 3283, 2970, 2948, 1670, 1549, 1380, 1263, 1136 1068, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 293 K, 600 MHz): δ=7.84 (d, J=7.6 Hz, 1H, NH2), 7.47 (d, J= 7.8 Hz, 1H, NH6), 7.40 (br s, 1H, NH3), 7.30 (d, J=8.7 Hz, 1H, NH4), 5.93 (d, J=3.8 Hz, 1H, C1H6), 5.90 (d, J=3.8 Hz, 1H, C1H4), 5.89(d, J=3.7 Hz, 1H, C1H2), 5.05 (d, J=6.3 Hz, 1H, NH1), 4.75 (dd, J=3.2, 9.3 Hz, 1H, C4H4), 4.59 (m, 1H, C2H4), 4.58 (m, 1H, C2H6), 4.57 (m, 2H, C2H2 and C4H6), 4.42 (m, 1H, CβH2), 4.41 (m, 1H, CβH4), 4.39 (m, 1H, CαH3), 4.38 (m, 1H, CαH5), 4.30 (dd, J=3.2, 9.6 Hz, 1H, C4H2), 4.23–4.17 (m, 1H, CβH6), 4.04–3.99 (m, 1H, CαH1), 3.92 (d, J= 3.4 Hz, 1H, C3H2), 3.80–3.76 (m, 1H, Cδ H5), 3.69 (s, 3H, COOMe), 3.64 (d, J=3.3 Hz, 1H, C3H6), 3.63 (d, J=3.3 Hz, 1H, C3H4), 3.38 (s, 6H, OMe), 3.37 (s, 3H, OMe), 3.36–3.33 (m, 1H, Cδ′H5), 2.90 (m, 1H, $C\alpha H_{(pro\text{-}R)}6$), 2.88 (m, 1H, $C\alpha H_{(pro\text{-}R)}4$), 2.55 (dd, J=5.1, 15.6 Hz, 1H, $C\alpha H_{(pro\text{-}S)}6$), 2.49 (dd, J=5.0, 13.4 Hz, 1H, $C\alpha H_{(pro\text{-}R)}2$), 2.41 (dd, J=4.5, 15.2 Hz, 1H, $C\alpha H_{(pro\text{-}S)}4$), 2.37–2.32 (m, 1H, $C\alpha H_{(pro\text{-}S)}2$), 2.21–2.17 (m, 1H, CβH5), 2.16–2.11 (m, 1H, Cβ′H5), 1.99–1.90 (m, 2H, CγH5), 1.48 (s, 3H, Me), 1.47 (s, 3H, Me), 1.46 (s, 3H, Me), 1.40 (s, 9H, Boc), 1.38 (d, J=6.8 Hz, 1H, $CH_3$3), 1.32 (d, J=7.5 Hz, 1H, $CH_3$1), 1.30 (s, 6H, Me), 1.28 ppm (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=174.0, 173.4, 172.1, 171.7, 171.1, 170.3, 155.7, 111.6, 111.3, 104.9, 104.8, 104.6, 84.1, 83.8, 83.4, 81.4, 81.3, 79.8, 79.7, 78.9, 60.6, 57.4, 57.3, 57.2, 51.9, 50.9, 50.3, 48.2, 47.0, 46.9, 46.7, 35.3, 35.0, 29.7, 29.7, 29.7, 29.7, 28.9, 28.2 (3C), 26.7, 26.6, 26.3, 26.2, 24.8, 17.8, 17.0 ppm; HRMS (ESI): m/z calcd for $C_{50}H_{80}N_6O_{21}$: 1123.5274 $[M+Na]^+$; found: 1123.5293.

3c: As described for the synthesis of **1**, a mixture of **22** (0.1 g, 0.134 mmol), HOBt (0.021 g, 0.161 mmol), and EDCI (0.031 g, 0.161 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 15 min and then treated with **20e** (prepared from **19e** (0.063 g, 0.134 mmol) TFA (0.1 mL) in CH_2Cl_2 (0.6 mL)) and DIPEA (0.034 mL, 0.201 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 3.0% methanol in $CHCl_3$) afforded **3c** (0.09 g, 61.03%) as a white solid. M.p.: 135–138 °C; $[\alpha]_D$=+4.7 (c=0.1, $CHCl_3$); IR (KBr): $\tilde{\nu}$= 3286, 2969, 2944, 1667, 1545, 1378, 1256, 1133, 1065, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 303 K, 500 MHz): (major isomer): δ=7.46 (m, 1H, NH-3), 7.44 (m, 1H, NH2), 7.39 (m, 1H, NH6), 7.29 (br s, 1H, NH4), 5.96–5.86 (m, 3H, C1H4), 5.05 (br s, 1H, NH1), 4.62 (m, 1H, CβH6), 4.56 (m, 2H, C2H2 and C2H6), 4.53 (m, 1H, C2H4), 4.51 (m, 1H, CβH2), 4.42 (m, 1H, CβH4), 4.38 (m, 1H, CαH3), 4.36 (m, 1H, CαH5), 4.34 (m, 1H, C4H6), 4.26 (m, 1H, C4H2), 4.04 (m, 1H, CαH1), 3.95 (m, 1H, C3H2), 3.68 (m, 1H, C3H4), 3.67 (s, 3H, COOMe), 3.66 (m, 1H, C3H6), 3.56 (m, 1H, Cδ H5), 3.50 (m, 1H, Cδ′H5), 3.38–3.36 (s, 9H, OMe), 2.60 (m, 2H, CαH6), 2.59 (m, 1H, $C\alpha H_{(pro\text{-}R)}1$), 2.52 (m, 2H, CαH4), 2.30 (m, 1H, $C\alpha H_{(pro\text{-}S)}1$), 2.21 (m, 1H, CβH5), 2.13 (m, 1H, Cβ′H5), 1.96 (m, 1H, CγH5), 1.86 (m, 1H, CγH5), 1.48–1.46 (s, 9H, Me), 1.41 (s, 9H, Boc), 1.34 (m, 6H, $CH_3$1 and $CH_3$3), 1.30–1.28 ppm (s, 9H, Me); (minor isomer): δ=7.75 (d, J=9.6 Hz, 1H, NH2), 7.54 (d, 1H, J=7.4 Hz, NH3), 7.16 (br s, 1H, NH6), 6.85 (br s, 1H, NH4), 5.96–5.86 (m, 3H, C1H4), 5.10 (d, J=6.4 Hz, 1H, NH1), 4.57 (m, 1H, C4H4), 4.58 (m, 1H, C2H6), 4.56 (m, 1H, C2H4), 4.55 (m, 1H, C2H1), 4.52 (m, 1H, CβH6), 4.51 (m, 1H, CβH4), 4.50 (m, 1H, CβH2), 4.47 (m, 1H, CαH5), 4.39 (m, 1H, CαH3), 4.36 (m, 1H, C4H6), 4.34 (m, 1H, C4H2), 4.12 (m, 1H, CαH1), 3.97 (m, 1H, C3H2), 3.73 (m, 1H, C3H4), 3.69 (m, 1H, C3H6), 3.67 (s, 3H, COOMe), 3.54 (m, 2H, Cδ H5), 3.37 (s, 9H, OMe), 2.65 (m, 2H, CαH6), 2.64 (m, 1H, $C\alpha H_{(pro\text{-}R)}1$), 2.64 (m, 2H, CαH4), 2.29 (m, 1H, $C\alpha H_{(pro\text{-}S)}1$), 2.27 (m, 1H, CβH5), 2.05 (m, 1H, Cβ′H5), 1.96 (m, 2H, CγH5), 1.47 (s, 9H, Me), 1.41 (s, 9H, Boc), 1.34 (m, 3H, $CH_3$1), 1.32 (m, 3H, $CH_3$3), 1.29 ppm (s, 9H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 173.3, 172.9, 171.8, 170.8, 170.7, 170.2, 155.7, 111.5, 111.4, 104.8, 104.7, 104.6, 84.1, 83.7, 83.5, 81.4, 81.4, 81.3, 79.8, 79.6, 79.4, 60.1, 57.7, 57.3, 51.8, 51.7, 50.8, 49.5, 47.5, 46.6, 46.5, 46.1, 45.4, 38.3, 36.1, 29.6, 28.4 (3C), 28.2, 26.7, 26.6, 26.6, 26.2, 26.1, 24.6, 17.7, 16.8 ppm; HRMS (ESI): m/z calcd for $C_{50}H_{80}N_6O_{21}$: 1123.5274 $[M+Na]^+$; found: 1123.5283.

29: As described for the synthesis of **1**, a mixture of **14a** (0.435 g, 2.3 mmol), HOBt (0.373 g, 2.76 mmol), and EDCI (0.53 g, 2.76 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 15 min and then treated with **28** (prepared from commercially available **27** (0.5 g, 2.3 mmol) and TFA (0.4 mL) in CH_2Cl_2 (1 mL)) and DIPEA (0.6 mL, 3.46 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 50% ethyl acetate in petroleum ether) afforded **29** (0.65 g, 98.0%) as a white solid. M.p.: 65–67 °C; $[\alpha]_D$=−48.52 (c=0.5, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3332, 2986, 2939, 1720, 1676, 1516, 1372, 1169, 1172, 1082, 1023 cm^{-1}; ^{1}H NMR ($CDCl_3$, 303 K, 300 MHz): δ=6.59 (d, J=7.3 Hz, 1H, NH2), 4.99 (br s, 1H, NH1), 4.39–4.26 (m, 1H, CβH2), 4.14–4.04 (m, 1H, CαH1), 3.70 (s, 3H, COOMe), 2.52 (d, J=5.4 Hz, 2H, CαH2), 1.45 (s, 9H, Boc), 1.34 (d, J=7.0 Hz, 3H, $CH_3$1), 1.22 ppm (d, J=7.0 Hz, 3H, $CH_3$2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=171.9, 155.4, 79.9, 51.6, 50.1, 41.9, 39.8, 28.2 (3C), 19.9, 18.4 ppm; HRMS (ESI): m/z calcd for $C_{13}H_{24}N_2O_5$: 289.3417 $[M+H]^+$; found: 289.3463.

31: As described for the synthesis of **12a**, a solution of **29** (0.15 g, 0.52 mmol) gave **30b** (0.138 g, 96.7%) as a white solid, which was used without further purification in the next step. As described for the synthesis of **1**, a mixture of **30b** (0.1 g, 0.36 mmol), HOBt (0.06 g, 0.44 mmol), and EDCI (0.083 g, 0.44 mmol) in CH_2Cl_2 (4 mL) was stirred at 0 °C for 15 min and then treated with **30a** (prepared from **29** (0.105 g, 0.36 mmol) and TFA (0.1 mL) in CH_2Cl_2 (1 mL)) and DIPEA (0.1 mL, 0.55 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 2.0% methanol in $CHCl_3$) afforded **31** (0.13 g, 80.2%) as a white solid. M.p.: 185–186 °C; $[\alpha]_D$=+154.5 (c=0.5, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3330, 2988, 2935, 1664, 1529, 1377, 1252, 1218, 1169, 1080, 1027, 856 cm^{-1}; ^{1}H NMR ($CDCl_3$, 303 K, 500 MHz): δ=7.47 (d, J=9.0 Hz, 1H, NH2), 7.27 (br s, 1H, NH3), 6.68 (d, J=9.0 Hz, 1H, NH4), 5.10 (d, J=6.5 Hz, 1H, NH1), 4.44–4.38 (m, 1H, CαH3), 4.35–4.33 (m, 1H, CβH2 and CβH4), 4.10–4.03 (m, 1H, CαH1), 3.70 (s, 3H, COOMe), 2.57 (dd, J=5.3, 12.9 Hz, 1H, $C\alpha H_{(pro\text{-}R)}2$), 2.53 (dd, J=5.2, 15.4 Hz, 1H, $C\alpha H_{(pro\text{-}R)}4$), 2.50 (dd, J=6.0, 15.4 Hz, 1H, $C\alpha H_{(pro\text{-}R)}2$), 2.22 (dd, J=3.9, 12.9 Hz, 1H, $C\alpha H_{(pro\text{-}S)}2$), 1.42 (s, 9H, Boc), 1.37 (d, J= 7.1 Hz, 3H, $CH_3$3), 1.35 (d, J=7.0 Hz, 3H, $CH_3$1), 1.24 (d, J=6.7 Hz, 3H, $CH_3$4), 1.22 ppm (d, J=6.7 Hz, 3H, $CH_3$2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=172.9, 172.8, 172.3, 171.0, 155.8, 79.9, 51.8, 50.9, 49.4, 42.4, 42.3, 42.2, 40.0, 28.2 (3C), 20.0, 18.8, 17.6, 17.2 ppm; HRMS (ESI): m/z calcd for $C_{20}H_{36}N_4O_7$: 445.2695 $[M+H]^+$; found: 445.2685.

4: As described for the synthesis of **1**, a mixture of **21** (0.05 g, 0.115 mmol), HOBt (0.019 g, 0.138 mmol), and EDCI (0.027 g, 0.138 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 15 min and then treated with **32** (prepared from **31** (0.051 g, 0.115 mmol) and TFA (0.1 mL) in CH_2Cl_2 (0.5 mL)) and DIPEA (0.03 mL, 0.17 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 4.0% methanol in $CHCl_3$) afforded **4** (0.045 g, 51.2%) as a white solid. M.p.: 200–203 °C; $[\alpha]_D$=+193.1 (c=0.1, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3333, 2983, 2939, 1665, 1523, 1377, 1258, 1228, 1169, 1082, 1029, 856 cm^{-1}; ^{1}H NMR ($CDCl_3$, 283 K, 600 MHz): δ=8.02 (d, J=5.6 Hz, 1H, NH3), 7.92 (d, J=7.3 Hz, 1H, NH5), 7.86 (d, J=8.8, 1H, NH4), 7.81 (d, J=9.5 Hz, 1H, NH2), 6.85 (d, J=8.8 Hz, 1H, NH6), 5.88 (d, J=3.7 Hz, 1H, C1H2), 5.03 (d, J=5.8 Hz, 1H, NH1), 4.56 (d, J=3.7 Hz, 1H, C2H2), 4.56–4.50 (m, 1H, CβH2), 4.45–4.39 (m, 1H, CαH5), 4.37–4.31 (m, 1H, CβH6), 4.30–4.24 (m, 1H, CβH4), 4.22 (dd, J=3.3, 9.7 Hz, 1H, C4H2), 4.20–4.16 (m, 1H, CαH3), 4.03–3.99 (m, 1H, CαH1), 3.98 (d, J= 3.3 Hz, 1H, C3H3), 3.70 (s, 3H, COOMe), 3.37 (s, 3H, OMe), 2.71 (dd, J=4.8, 15.2, 1H, $C\alpha H_{(pro\text{-}R)}6$), 2.69 (dd, J=6.4, 15.2, 1H, $C\alpha H_{(pro\text{-}S)}6$), 2.68 (dd, J=4.6, 12.4, 1H, $C\alpha H_{(pro\text{-}R)}4$), 2.56 (dd, J=5.1, 13.0 Hz, 1H, $C\alpha H_{(pro\text{-}R)}2$), 2.19 (dd, J=2.8, 13.0 Hz, 1H, $C\alpha H_{(pro\text{-}S)}2$), 2.11 (dd, J=3.4,

12.4 Hz, 1H, CαH$_{(pro\text{-}S)}$2), 1.45 (s, 3H, Me), 1.40 (s, 9H, Me), 1.40 (d, J= 7.0 Hz, 3H, CH$_3$3), 1.39 (d, J=7.1 Hz, 3H, CH$_3$1), 1.30 (s, 3H, Me), 1.25 (d, 3H, J=7.2 Hz, CH$_3$4), 1.24 ppm (d, J=7.0 Hz, 3H, CH$_3$6); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=174.2, 173.3, 173.2, 172.6, 171.8, 171.0, 155.9, 111.3, 105.0, 83.5, 81.2, 80.2, 80.0, 57.3, 51.9, 51.4, 49.6, 46.9, 42.9, 42.4, 42.1, 40.3, 38.1, 28.2, 26.6, 26.0, 20.2, 18.3, 17.3, 16.5 ppm; HRMS (ESI): m/z calcd for $C_{34}H_{58}N_6O_{13}$: 781.3959 [M+Na]$^+$; found: 781.3965.

5: As described for the synthesis of **12a**, a solution of **3a** (0.05 g, 0.046 mmol) gave **23** (0.048 g, 97.3%) as a white solid, which was used without further purification in the next step. As described for the synthesis of **1**, a mixture of **23** (0.040 g, 0.038 mmol), HOBt (0.006 g, 0.045 mmol), and EDCI (0.008 g, 0.045 mmol) in CH_2Cl_2 (1.5 mL) was stirred at 0°C for 15 min and then treated with **20a** (0.017 g, 0.038 mmol) and DIPEA (0.009 mL, 0.057 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 2.9% methanol in $CHCl_3$) afforded **5** (0.04 g,76.4%) as a white solid. M.p.: 175–177°C; $[\alpha]_D$=+26 (c=0.25, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3397, 3080, 2988, 2938, 1673, 1641, 1553, 1380, 1249, 1079, 1022, 857 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.33 (d, J=5.8 Hz, 1H, NH5), 8.02 (d, J=9.6 Hz, 1H, NH4), 7.96 (d, J=7.3 Hz, 1H, NH7), 7.90 (d, J=5.2 Hz, 1H, NH3), 7.87 (d, J=9.9 Hz, 1H, NH2), 7.58 (d, J=8.4 Hz, 1H, NH6), 6.95 (d, J= 8.1 Hz, 1H, NH8), 6.0 (d, J=4.0 Hz, 1H, C1H6), 5.88 (d, J=3.9 Hz, 3H, C1H8, C1H4, and C1H2), 4.98 (d, J=5.9 Hz, 1H, NH1), 4.58 (d, J= 4.0 Hz, 1H, C2H6), 4.58 (d, J=3.9 Hz, 1H, C2H8), 4.57 (d, J=3.9 Hz, 1H, C2H2), 4.56 (d, J=3.9 Hz, 1H, C2H4), 4.52 (m, 1H, CβH2), 4.50 (m, 1H, C4H8), 4.49 (m, 1H, CβH4), 4.40 (m, 1H, CβH8), 4.39 (m, 1H, CβH6), 4.35 (m, 1H, CαH7), 4.32 (dd, J=3.3, 10.3 Hz, 1H, C4H6), 4.26 (m, 1H, CαH2), 4.25 (m, 2H, C4H4 and C4H2), 4.21–4.16 (m, 1H, CαH5), 4.06 (d, J=3.3 Hz, 1H, C3H6), 4.01 (d, J=3.0 Hz, 1H, C3H2), 4.01–3.97 (m, 1H, CαH1), 3.95 (d, J=3.3 Hz, 1H, C3H4), 3.69 (s, 3H, COOMe), 3.67 (d, J=3.5 Hz, 1H, C3H8), 3.40 (s, 3H, OMe), 3.39 (s, 3H, OMe), 3.38 (s, 3H, OMe), 3.36 (s, 3H, OMe), 271 (dd, J=7.0, 15.8 Hz, 1H, CαH$_{(pro\text{-}R)}$8), 2.67 (dd, J=4.9, 12.9 Hz, 1H, CαH$_{(pro\text{-}R)}$6), 2.65 (dd, J= 5.3, 15.8 Hz, 1H, CαH$_{(pro\text{-}S)}$8), 2.55 (dd, J=5.2, 13.0 Hz, 1H, CαH$_{(pro\text{-}R)}$2), 2.53 (dd, J=5.7, 13.1 Hz, 1H, CαH$_{(pro\text{-}R)}$4), 2.19 (dd, J=3.2, 13.0 Hz, 1H, CαH$_{(pro\text{-}S)}$2), 2.13 (dd, J=3.1, 12.9 Hz, 1H, CαH$_{(pro\text{-}S)}$6), 2.07 (dd, J=2.9, 13.1 Hz, 1H, CαH$_{(pro\text{-}S)}$4), 1.49 (s, 6H, CH$_3$), 1.46 (s, 3H, CH$_3$), 1.45 (s, 3H, CH$_3$), 1.42 (d, J=7.2 Hz, 3H, CH$_3$3), 1.41 (s, 9H, Boc), 1.39 (d, J= 7.2 Hz, 3H, CH$_3$5), 1.38 (d, J=7.0 Hz, 3H, CH$_3$7), 1.36 (d, J=7.0 Hz, 3H, CH$_3$1), 1.32 (s, 3H, CH$_3$), 1.31 (s, 6H, CH$_3$), 1.30 ppm (s, 3H, CH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=175.1, 173.3, 173.1, 172.1. 172.0, 171.9, 170.8, 155.8, 111.6, 111.5, 111.4, 111.3, 105.1, 104.9, 84.4, 83.4, 81.5, 81.3, 80.2, 80.1, 79.5, 78.8, 57.3, 57.2, 52.1, 51.9, 51.8, 51.5, 49.8, 47.4, 47.2, 46.9, 46.2, 38.3, 38.1, 38.1, 35.8, 28.2 (3C), 26.7, 26.6, 26.3, 26.2, 26.0, 17.3, 16.5, 16.4, 15.8 ppm; HRMS (ESI): m/z calcd for $C_{62}H_{100}N_8O_{27}$: 1411.6595 [M+ Na]$^+$; found: 1411.6580.

6a: As described for the synthesis of **12a**, a solution of **1** (0.4 g, 0.58 mmol) gave **24** (0.39 g, 99.5%) as a white solid, which was used without further purification in the next step. As described for the synthesis of **1**, a mixture of **24** (0.385 g, 0.570 mmol), HOBt (0.092 g, 0.684 mmol), and EDCI (0.131 g, 0.684 mmol) in CH_2Cl_2 (7 mL) was stirred at 0°C for 15 min and then treated with **20a** (prepared from **19a** (0.255 g, 0.570 mmol)a and TFA (0.2 mL) in CH_2Cl_2 (2 mL)) and DIPEA (0.148 mL, 0.855 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 2.0% methanol in $CHCl_3$) afforded **6a** (0.382 g, 66.7%) as a white solid. M.p.: 149–151°C; $[\alpha]_D$= −70.6 (c=0.25, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3335, 3269, 2991, 2938, 1730, 1700, 1650, 1526, 1167, 1074, 1013 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.43 (d, J=7.6 Hz, 1H, NH4), 7.32 (d, J=8.2 Hz, 1H, NH3), 7.05 (d, J= 8.0 Hz, 1H, NH5), 6.41 (d, J=4.4 Hz, 1H, NH2), 6.06 (d, J=4.0 Hz, 1H, C1H5), 5.89 (d, J=4.0 Hz, 1H, C1H1), 5.87 (d, J=3.8 Hz, 1H, C1H3) 5.55 (d, J=8.1 Hz, 1H, NH1), 4.57 (d, J=4.0 Hz, 1H, C2H5), 4.57 (d, J= 3.8 Hz, 1H, C2H3), 4.56 (d, J=4.0 Hz, 1H, C2H1), 4.51 (dd, J=3.3, 8.0 Hz, 1H, C4H5), 4.38 (m, 1H, CβH5), 4.37 (m, 1H, CβH3), 4.36 (m, 1H, CαH4), 4.34 (dd, J=3.3, 8.2 Hz, 1H, C4H1), 4.27 (dd, J=3.4, 10.0 Hz, 1H, C4H3), 4.23–4.16 (m, 1H, CαH2), 4.15–4.09 (m, 1H, CβH1), 4.04 (d, J=3.4 Hz, 1H, C3H3), 3.72 (d, J=3.3 Hz, 1H, C3H1), 3.68 (s, 3H, COOMe), 3.65 (d, J=3.3 Hz, 1H, C3H5), 3.39 (s, 3H, OMe), 3.36 (s, 6H, OMe), 2.73 (dd, J=5.4, 16.0 Hz, 1H, CαH$_{(pro\text{-}R)}$5), 2.71 (dd, J=5.0, 13.7 Hz, 1H, CαH$_{(pro\text{-}R)}$3), 2.61 (dd, J=5.8, 16.0 Hz, 1H, CαH$_{(pro\text{-}S)}$5), 2.54–2.49 (m, 2H, CαH$_{(pro\text{-}R)}$1, CαH$_{(pro\text{-}S)}$1), 2.21 (dd, J=3.7, 13.7 Hz, 1H, CαH$_{(pro\text{-}S)}$3), 1.64 (s, 6H, CH$_3$), 1.47 (s, 3H, CH$_3$), 1.43 (s, 9H, Boc), 1.37 (d, J=7.2 Hz, 3H, CH$_3$4), 1.36 (d, J=6.9 Hz, 3H, CH$_3$2), 1.31 (s, 3H, CH$_3$), 1.30 ppm (s, 6H, CH$_3$); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=173.4, 172.7, 172.0, 171.3, 170.5, 156.0, 111.6, 111.5, 111.2, 105.0, 104.9, 104.7, 84.1, 83.7, 83.3, 81.3, 81.1, 81.0, 79.8, 79.6, 79.4, 78.7, 57.4, 57.3, 57.2, 51.9, 50.5, 50.2, 48.1, 47.3, 45.8, 38.1, 37.5, 35.1, 28.3 (3C), 26.6, 26.5, 26.2, 26.1, 17.2, 16.4 ppm; HRMS (ESI): m/z calcd for $C_{45}H_{73}N_5O_{20}$: 1026.4746 [M+ Na]$^+$; found: 1026.4725.

6b: As described for the synthesis of **1**, a mixture of **24** (0.15 g, 0.222 mmol), HOBt (0.036 g, 0.266 mmol), and EDCI (0.051 g, 0.266 mmol) in CH_2Cl_2 (5 mL) was stirred at 0°C for 15 min and then treated with **20b** (prepared from **19b** (0.105 g, 0.222 mmol) and TFA (0.1 mL) in CH_2Cl_2 (1 mL)) and DIPEA (0.06 mL, 0.332 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 3.1% methanol in $CHCl_3$) afforded **6b** (0.115 g, 50.19%) as a white solid. M.p.: 233–236°C; $[\alpha]_D$= −115.1 (c=0.1, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3345, 3271, 2983, 2924, 1751, 1716, 1643, 1526, 1153, 1033, 1013 cm^{-1}; ^{1}H NMR ($CDCl_3$, 308 K, 500 MHz): δ=7.23 (d, J=8.0 Hz, 1H, NH4), 7.19 (d, J=8.1 Hz, 1H, NH3), 6.97 (d, J=7.8 Hz, 1H, NH5), 6.40 (d, J= 5.2 Hz, 1H, NH2), 6.02 (d, J=4.1 Hz, 1H, C1H5), 5.88 (d, J=3.8 Hz, 1H, C1H1), 5.87 (d, J=3.8 Hz, 1H, C1H3**)**, 5.58 (d, J=8.6 Hz, 1H, NH1), 4.57–4.54 (m, 3H, C2H1, C2H3, and C2H5), 4.52 (dd, J=3.7, 8.8 Hz, 1H, C4H5), 4.39 (m, 1H, CβH3), 4.36 (m, 1H, CβH5), 4.37 (m, 1H, C4H1), 4.29–4.24 (m, 1H, CαH3), 4.10 (m, 1H, CαH4), 4.08 (m, 1H, CβH1), 4.0 (d, J=3.8 Hz, 1H, C3H2), 3.72 (d, J=3.6 Hz, 1H, C3H1), 3.68 (s, 3H, COOMe), 3.63 (d, J=3.7 Hz, 1H, C3H5), 3.38 (s, 3H, OMe), 3.36 (s, 6H, OMe), 2.71 (dd, J=4.7, 13.9, 1H, CαH$_{(pro\text{-}R)}$3), 2.68–2.65 (m, 2H, CαH5), 2.55 (dd, J=6.9, 13.9 Hz, 1H, CαH$_{(pro\text{-}R)}$1), 2.49 (dd, J=5.2, 13.9 Hz, 1H, CαH$_{(pro\text{-}S)}$1), 2.28 (dd, J=4.1, 13.9, 1H, CαH$_{(pro\text{-}S)}$3), 2.18–2.10 (m, 1H, CβH4) 1.47 (s, 3H, Me), 1.46 (s, 3H, Me), 1.44 (s, 3H, Me), 1.44 (s, 9H, Boc), 1.36 (d, J=7.0 Hz, 1H, CH$_3$2), 1.30 (s, 3H, Me), 1.30 (s, 3H, Me), 1.29 (s, 3H, Me), 0.97 (d, J=5.0 Hz, 3H, CH$_3$4), 0.95 ppm (d, J=4.9 Hz, 3H, CH$_3$4); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.7, 172.2, 171.8, 171.4, 170.7, 156.1, 111.7, 111.5, 111.3, 105.0, 104.9, 104.7, 84.1, 83.8, 83.5, 81.4, 81.2, 81.1, 79.8, 79.7, 79.5, 78.8, 60.5, 57.5, 57.3, 51.9, 50.4, 48.4, 47.2, 45.8, 38.0, 37.8, 35.2, 29.7, 29.5, 28.4 (3C), 26.7, 16.6, 26.3, 26.2, 19.3, 18.8, 17.3 ppm; HRMS (ESI): m/z calcd for $C_{47}H_{77}N_5O_{20}$: 1054.5059 [M+Na]$^+$; found: 1054.5069.

6c: As described for the synthesis of **1**, a mixture of **24** (0.15 g, 0.222 mmol), HOBt (0.036 g, 0.266 mmol), and EDCI (0.051 g, 0.266 mmol) in CH_2Cl_2 (5 mL) was stirred at 0°C for 15 min and then treated with **20c** (prepared from **19c** (0.102 g, 0.222 mmol) and TFA (0.1 mL) in CH_2Cl_2 (1 mL)) and DIPEA (0.06 mL, 0.332 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 3.2% methanol in $CHCl_3$) afforded **6c** (0.125 g, 54.6%) as a white solid. M.p.: 118–121°C; $[\alpha]_D$= −64.2 (c=0.1, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3343, 3263, 2963, 2933, 1745, 1721, 1638, 1521, 1162, 1023, 1013 cm^{-1}; ^{1}H NMR ($CDCl_3$, 278 K, 600 MHz): δ=7.59 (d, J=8.3 Hz, 1H, NH3), 7.39 (d, J=8.0 Hz, 1H, NH5), 7.21 (br s, 1H, NH4), 6.41 (d, J=5.9 Hz, 1H, NH2), 6.13 (d, J=4.2 Hz, 1H, C1H5), 5.92 (d, J=3.7 Hz, 1H, C1H1), 5.89 (d, J=3.7 Hz, 1H, C1H3), 5.66 (d, J=8.2 Hz, 1H, NH1), 4.60–4.57 (m, 3H, C2H1, C2H3, and C2H5), 4.55 (dd, J=5.4, 9.4 Hz, 1H, C4H5), 4.41 (dd, J=3.0, 9.8 Hz, 1H, C4H3), 4.39–4.35 (m, 1H, CβH5), 4.34 (dd, J=3.3, 8.2 Hz, 1H, C4H1), 4.32–4.28 (m, 1H, CβH3), 4.25 (q, J=6.5 Hz, 1H, CαH2), 4.20–4.14 (m, 1H, CβH1), 4.04 (d, J=3.0 Hz, 1H, C3H3), 3.72 (d, J=3.3 Hz, 1H, C3H3), 3.69 (s, 3H, COOMe), 3.66 (d, J=3.3 Hz, 1H, C3H5), 3.37 (s, 6H, OMe), 3.36 (s, 3H, OMe), 2.92 (dd, J=5.6, 16.4 Hz, 1H, CαH$_{(pro\text{-}R)}$5), 2.63 (dd, J=4.8, 13.6 Hz, 1H, CαH$_{(pro\text{-}R)}$3), 2.51 (m, 2H, CαH1), 2.50 (m, 1H, CαH$_{(pro\text{-}S)}$1), 2.16 (dd, J=3.6, 13.6 Hz, 1H, CαH$_{(pro\text{-}S)}$3), 1.55 (s, 3H, CH$_3$4), 1.48 (s, 3H, Me), 1.47 (s, 3H, Me), 1.45 (s, 3H, Me), 1.42 (s, 3H, CH$_3$4), 1.42 (s, 9H, Boc), 1.36 (d, J= 7.0 Hz, 1H, CH$_3$2), 1.32 (s, 3H, Me), 1.31 (s, 3H, Me), 1.30 ppm (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.7, 172.2, 171.8, 171.4, 170.7, 156.1, 111.7, 111.5, 111.3, 105.0, 104.9, 104.7, 84.1, 83.8, 83.5, 81.4, 81.2, 81.1, 79.8, 79.7, 79.5, 78.8, 60.5, 57.5, 57.3, 51.9, 50.4, 48.4, 47.2, 45.8, 38.0, 37.8, 35.2, 29.7, 29.5, 28.4 (3C), 26.7, 16.6, 26.3, 26.2, 19.3, 18.8, 17.3 ppm;

HRMS (ESI): *m/z* calcd for $C_{46}H_{75}N_5O_{20}$: 1040.4903 $[M+Na]^+$; found: 1040.4912.

7: As described for the synthesis of **12a**, a solution of **6a** (0.29 g, 0.289 mmol) gave **25a** (0.281 g, 98.3%) as a white solid, which was used without further purification in the next step. As described for the synthesis of **1**, a mixture of **25a** (0.245 g, 0.247 mmol), HOBt (0.04 g, 0.296 mmol), and EDCI (0.057 g, 0.296 mmol) in CH_2Cl_2 (5 mL) was stirred at 0°C for 15 min and then treated with **20a** (pepared from **19a** (0.110 g, 0.247 mmol) and TFA (0.1 mL) in CH_2Cl_2 (1 mL)) and DIPEA (0.064 mL, 0.37 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 2.4% methanol in $CHCl_3$) afforded **7** (0.165 g, 50.6%) as a white solid. M.p.: 177–179°C; $[\alpha]_D = -7.5$ ($c=0.5$, $CHCl_3$); IR (KBr): $\tilde{\nu}=3296$, 2986, 2937, 1647, 1543, 1379, 1218, 1168, 1081, 1021 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.99$ (d, $J=5.3$ Hz, 1H, NH4), 7.90 (d, $J=7.3$ Hz, 1H, NH6), 7.78 (d, $J=9.4$ Hz, 1H, NH3), 7.59 (d, $J=8.4$ Hz, 1H, NH5), 6.92 (d, $J=8.1$ Hz, 1H, NH7), 6.43 (d, $J=4.3$ Hz, 1H, NH2), 5.99 (d, $J=3.8$ Hz, 1H, C1H7), 5.89 (d, $J=3.9$ Hz, 1H, C1H3), 5.88 (d, $J=3.9$ Hz, 1H, C1H5), 5.87 (d, $J=3.9$ Hz, 1H, C1H1), 5.49 (d, $J=8.2$ Hz, 1H, NH1), 4.58 (d, $J=3.9$ Hz, 1H, C2H5), 4.57 (d, $J=3.8$ Hz, 1H, C2H7), 4.56 (d, $J=3.9$ Hz, 1H, C2H1), 4.55 (d, $J=3.9$ Hz, 1H, C2H3), 4.49 (m, 1H, CβH3), 4.48 (dd, $J=3.0$, 7.3 Hz, 1H, C4H7), 4.39 (m, 1H, CβH7), 4.38 (m, 1H, CβH5), 4.34 (m, 1H, CαH6), 4.31 (dd, $J=3.3$, 10.2 Hz, 1H, C4H5), 4.27 (dd, $J=3.3$, 7.8 Hz, 1H, C4H1), 4.23 (dd, $J=3.3$, 9.8 Hz, 1H, C4H3), 4.20 (m, 1H, CαH2), 4.17 (m, 1H, CαH4), 4.16 (m, 1H, CβH1), 4.04 (d, $J=3.4$ Hz, 1H, C3H5), 3.94 (d, $J=3.3$ Hz, 1H, C3H3), 3.75 (d, $J=3.3$ Hz, 1H, C3H1), 3.68 (s, 3H, COOMe), 3.66 (d, $J=3.3$ Hz, 1H, C3H7), 3.39 (s, 3H, OMe), 3.37 (s, 6H, OMe), 3.36 (s, 3H, OMe), 2.69 (dd, $J=6.8$, 15.9 Hz, 1H, $C\alpha H_{(pro\text{-}R)}7$), 2.66 (dd, $J=5.0$, 13.1 Hz, 1H, $C\alpha H_{(pro\text{-}R)}5$), 2.63 (dd, $J=5.5$, 15.9 Hz, 1H, $C\alpha H_{(pro\text{-}S)}7$), 2.55 (dd, $J=5.1$, 13.1 Hz, 1H, $C\alpha H_{(pro\text{-}R)}3$), 2.54 (dd, $J=4.8$, 14.5 Hz, 1H, $C\alpha H_{(pro\text{-}R)}1$), 2.45 (dd, $J=6.2$, 14.5 Hz, 1H, $C\alpha H_{(pro\text{-}S)}1$), 2.14 (dd, $J=2.9$, 13.1 Hz, 1H, $C\alpha H_{(pro\text{-}S)}5$), 2.14 (dd, $J=3.2$, 13.1 Hz, 1H, $C\alpha H_{(pro\text{-}S)}3$), 1.48 (s, 3H, CH_3), 1.44 (s, 9H, Boc), 1.44 (s, 6H, CH_3), 1.43 (s, 3H, CH_3), 1.40 (d, $J=7.0$ Hz, 3H, $CH_3$2), 1.38 (d, $J=7.0$ Hz, 3H, $CH_3$4), 1.37 (d, $J=7.0$ Hz, 3H, $CH_3$6), 1.31 (s, 3H, CH_3), 1.30 (s, 6H, CH_3), 1.29 ppm (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=174.8$, 173.1, 172.8, 172.0, 171.9, 171.3, 170.7, 156.0, 111.7, 111.6, 111.4, 111.3, 105.1, 105.0, 104.9, 104.8, 84.5, 84.0, 83.6, 83.5, 81.5, 81.3, 80.2, 80.2, 79.6, 78.8, 57.5, 57.4, 57.2, 51.8, 51.7, 51.1, 49.8, 47.9, 47.4, 46.9, 46.2, 38.7, 38.1,35.9, 28.4 (3C), 26.7, 26.7, 26.3, 26.0, 17.1, 16.6, 16.0 ppm; HRMS (ESI): *m/z* calcd for $C_{59}H_{95}N_7O_{26}$: 1340.6224 $[M+Na^+]$; found: 1340.6280.

17: As described for the synthesis of **1**, a mixture of **16a** (0.2 g, 0.463 mmol), HOBt (0.075 g, 0.555 mmol), and EDCI (0.106 g, 0.555 mmol) in CH_2Cl_2 (5 mL) was stirred at 0°C for 15 min and then treated with **16b** (prepared from **15** (0.2 g, 0.463 mmol) and TFA (0.2 mL) in CH_2Cl_2 (2 mL)) and DIPEA (0.12 mL, 0.69 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 2.0% $CHCl_3$ in MeOH) afforded **17** (0.29 g, 82.42%) as a white solid. M.p.: 210–212°C; $[\alpha]_D=-14.0$ ($c=0.25$, $CHCl_3$); IR (KBr): $\tilde{\nu}=3329$, 2984, 2938, 1760, 1694, 1650, 1534, 1374, 1252, 1167, 1078, 1023, 854 cm^{-1}; ^1H NMR ($CDCl_3$, 303 K, 500 MHz): $\delta=7.71$ (d, $J=7.7$ Hz, 1H, NH4), 7.17 (d, $J=9.2$ Hz, 1H, NH3), 6.50 (d, $J=4.8$ Hz, 1H, NH2), 5.33 (d, $J=8.4$ Hz, 1H, NH1), 5.89 (d, $J=4.0$ Hz, 1H, C1H1), 5.88 (d, $J=4.0$ Hz, 1H, C1H3), 4.58 (d, $J=4.0$ Hz, 1H, C2H3), 4.56 (m, 1H, CαH4), 4.55 (d, $J=4.0$ Hz, 1H, C2H1), 4.51–4.44 (m, 1H, CβH3), 4.23 (dd, $J=3.2$, 7.4 Hz, 1H, C4H1), 4.19 (dd, $J=3.3$, 9.9 Hz, 1H, C4H3), 4.18–4.14 (m, 1H, CβH1), 4.11–4.04 (m, 1H, CαH2), 4.00 (d, $J=3.3$ Hz, 1H, C3H3), 3.72 (d, $J=3.2$ Hz, 1H, C3H1), 3.71 (s, 3H, COOMe), 3.39 (s, 3H, OMe), 3.36 (s, 3H, OMe), 2.58 (dd, $J=5.0$, 13.4 Hz, 1H, $C\alpha H_{(pro\text{-}R)}3$), 2.56 (dd, $J=5.2$, 14.7 Hz, 1H, $C\alpha H_{(pro\text{-}R)}1$), 2.44 (dd, $J=6.4$, 14.7 Hz, 1H, $C\alpha H_{(pro\text{-}S)}1$), 2.25 (dd, $J=3.9$, 13.4 Hz, 1H, $C\alpha H_{(pro\text{-}S)}3$), 1.47 (s, 6H, CH_3), 1.44 (s, 9H, Boc), 1.43 (d, $J=7.2$ Hz, 3H, $CH_3$4), 1.40 (d, $J=6.9$ Hz, 3H, $CH_3$2), 1.31 (s, 3H, CH_3), 1.30 ppm (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=175.4$, 172.4, 171.3, 170.8, 156.1, 111.6, 104.9, 104.7, 84.1, 83.4, 81.4, 81.2, 80.1, 79.9, 79.6, 57.5, 57.3, 52.4, 50.9, 48.5, 47.8, 46.5, 38.9, 38.3, 28.4 (3C), 26.7, 26.6, 26.4, 26.2, 17.0, 16.3 ppm; HRMS (ESI): *m/z* calcd for $C_{34}H_{57}N_4O_{15}$: 761.3731 $[M+H]^+$; found: 761.3742.

8a: As described for the synthesis of **1**, a mixture of **25a** (0.03 g, 0.03 mmol), HOBt (0.004 g, 0.036 mmol), and EDCI (0.007 g, 0.036 mmol) in CH_2Cl_2 (1.5 mL) was stirred at 0°C for 15 min and then treated with **18b** (prepared from **17** (0.023 g, 0.03 mmol) and TFA (0.1 mL) in CH_2Cl_2 (0.5 mL)) and DIPEA (0.007 mL, 0.045 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 3.5% methanol in $CHCl_3$) afforded **8a** (0.029 g, 56.6%) as a white solid. M.p.: 200–202°C; $[\alpha]_D=+2.84$ ($c=0.17$, $CHCl_3$); IR (KBr): $\tilde{\nu}=3309$, 2985, 2931, 1653, 1541, 1379, 1218, 1165, 1081, 1022, 856 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=8.10$ (d, $J=7.4$ Hz, 1H, NH9), 7.93 (d, $J=8.2$ Hz, 1H, NH4), 7.80 (d, $J=7.8$ Hz, 1H, NH3), 7.74 (d, $J=8.5$ Hz, 1H, NH6), 7.61 (d, $J=5.7$ Hz, 1H, NH7), 7.39 (d, $J=9.3$ Hz, 1H, NH8), 7.05 (d, $J=7.6$ Hz, 1H, NH5), 6.89 (d, $J=5.0$ Hz, 1H, NH2), 5.90 (d, $J=3.8$ Hz, 1H, C1H8), 5.89 (d, $J=3.9$ Hz, 1H, C1H3), 5.88 (d, $J=3.8$ Hz, 1H, C1H6 and C1H1), 5.88 (d, $J=3.5$ Hz, 1H, C1H5), 5.55 (d, $J=8.3$ Hz, 1H, NH1), 4.63 (d, $J=3.8$ Hz, 1H, C2H1), 4.62 (d, $J=3.8$ Hz, 2H, C2H8 and C2H1), 4.62 (d, $J=3.8$ Hz, 2H, C2H6), 4.59 (d, $J=3.5$ Hz, 1H, C2H5), 4.59 (m, 1H, CβH6), 4.59 (d, $J=3.9$ Hz, 1H, C2H3), 4.54 (m, 1H, CαH9), 4.51–4.49 (m, 1H, CβH3), 4.48–4.44 (m, 1H, CβH8), 4.43–4.39 (m, 1H, CβH5), 4.34 (dd, $J=3.0$, 9.6 Hz, 1H, C4H6), 4.28 (m, 1H, CαH4), 4.25 (m, 1H, CβH1), 4.24 (m, 2H, C4H5 and CαH2), 4.22 (m, 1H, C4H3), 4.17 (dd, $J=3.0$, 10.0 Hz, 1H, C4H8 and C4H1), 4.05 (d, $J=3.0$ Hz, 1H, C3H7), 4.03–3.98 (m, 1H, CαH7), 3.89 (m, 1H, C3H5), 3.88 (m, 1H, C3H3), 3.73 (d, $J=3.0$ Hz, 1H, C3H6), 3.72 (d, $J=3.0$ Hz, 1H, C3H1), 3.71 (s, 3H, COOMe), 3.40 (s, 3H, OMe), 3.39 (s, 3H, OMe), 3.38 (s, 6H, OMe), 3.36 (s, 3H, OMe), 2.60 (dd, $J=4.8$, 13.0 Hz, 1H, $C\alpha H_{(pro\text{-}R)}8$), 2.58–2.56 (m, 1H, $C\alpha H_{(pro\text{-}R)}3$), 2.54 (dd, $J=4.8$, 14.5 Hz, 1H, $C\alpha H_{(pro\text{-}R)}1$), 2.51 (dd, $J=4.8$, 14.5 Hz, 1H, $C\alpha H_{(pro\text{-}R)}5$), 2.48 (m, 1H, $C\alpha H_{(pro\text{-}S)}1$), 2.47 (m, 1H, $C\alpha H_{(pro\text{-}R)}6$), 2.37 (dd, $J=6.2$, 14.5 Hz, 2H, $C\alpha H_{(pro\text{-}S)}6$ and $C\alpha H_{(pro\text{-}S)}5$), 2.23 (m, 1H, $C\alpha H_{(pro\text{-}S)}3$), 2.21 (m, 1H, $C\alpha H_{(pro\text{-}S)}8$), 1.48 (s, 9H, CH_3), 1.43 (m, 6H, $CH_3$9 and $CH_3$7), 1.43 (s, 9H, Boc), 1.40 (d, $J=7.0$ Hz, 3H, $CH_3$2), 1.34 (d, $J=7.2$ Hz, 3H, $CH_3$4), 1.31 (s, 3H, CH_3), 1.30 (s, 9H, CH_3), 1.25 ppm (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 298 K, 150 MHz,): $\delta=175.5$, 173.7, 173.0, 172.8, 171.6, 171.4, 171.1, 170.9, 170.2, 156.1, 156.0, 111.7, 111.6, 104.9, 104.9, 104.8, 104.7, 96.1, 84.0, 83.8, 83.5, 83.4, 81.4, 81.4, 81.4, 81.4, 81.2, 80.3, 79.9, 79.8, 79.5, 57.5, 57.4, 57.4, 57.3, 53.6, 52.4, 51.3, 50.9, 50.5, 48.6, 47.8, 46.9, 46.7, 46.5, 46.1, 41.9, 38.7, 38.6, 38.4, 38.3, 38.1, 31.9, 29.7, 29.4, 28.4 (3C), 26.8, 26.8, 26.7, 26.7, 26.5, 26.4, 26.3, 26.1, 26.1, 22.7, 19.2, 18.6, 17.4, 17.1, 17.0, 16.8, 16.2, 14.1 ppm; HRMS (ESI): *m/z* calcd for $C_{73}H_{117}N_9O_{32}$: 838.8794 $[M+Na2]^+$; found: 838.8766.

8b: As described for the synthesis of **12a**, a solution of **6b** (0.13 g, 0.126 mmol) gave **25b** (0.127 g, 99.0%) as a white solid, which was used without further purification in the next step. As described for the synthesis of **1**, a mixture of **25b** (0.12 g, 0.117 mmol), HOBt (0.019 g, 0.142 mmol), and EDCI (0.027 g, 0.142 mmol) in CH_2Cl_2 (3 mL) was stirred at 0°C for 15 min and then treated with **18b** (prepared from **17** (0.089 g, 0.117 mmol) and TFA (0.1 mL) in CH_2Cl_2 (0.5 mL)) and DIPEA (0.03 mL, 0.175 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 4.0% methanol in $CHCl_3$) afforded **8b** (0.08 g, 35%) as a white solid. M.p.: 215–217°C; $[\alpha]_D=-72.5$ ($c=0.1$, $CHCl_3$); IR (KBr): $\tilde{\nu}=3315$, 2978, 2941, 1644, 1543, 1381, 1221, 1153, 1089, 1063 cm^{-1}; ^1H NMR ($CDCl_3$, 288 K, 600 MHz): $\delta=8.08$ (d, $J=7.4$ Hz, 1H, NH9), 7.77 (br s, 1H, NH7), 7.66 (d, $J=5.6$ Hz, 1H, NH6), 7.59 (d, $J=5.3$ Hz, 1H, NH4), 7.42 (d, $J=8.9$ Hz, 1H, NH3), 7.33 (d, $J=9.3$ Hz, 1H, NH8), 7.17 (d, $J=6.3$ Hz, 1H, NH5), 7.02 (d, $J=8.1$ Hz, 1H, NH2), 5.89 (d, $J=3.8$ Hz, 1H, C1H8), 5.88 (m, 3H, C1H1, C1H3, and C1H6), 5.87 (d, $J=3.8$ Hz, 1H, C1H5), 5.67 (d, $J=8.6$ Hz, 1H, NH1), 4.60 (d, $J=3.8$ Hz, 1H, C2H8), 4.59 (m, 1H, C2H1 and C2H5), 4.57 (m, 1H, C2H1 and C2H5), 4.57 (m, 1H, C4H6), 4.56 (m, 2H, C2H1 and C2H5), 4.55 (m, 1H, CαH9), 4.53 (m, 1H, CβH3), 4.45 (tt, $J=4.2$, 9.5 Hz, 1H, CβH8), 4.36 (dd, $J=3.1$, 9.4 Hz, 1H, C4H6), 4.35 (m, 1H, CαH2), 4.33 (m, 1H, CβH5), 4.33 (m, 1H, C4H5), 4.29 (m, 1H, C4H3), 4.27 (dd, $J=3.1$, 8.6 Hz, 1H, C4H1), 4.17 (dd, $J=3.0$, 9.5 Hz, 1H, C4H8), 4.15–4.11 (m, 1H, CβH1), 4.04 (d, $J=3.0$ Hz, 1H, C3H8), 4.03–4.00 (m, 1H, CαH7), 3.87 (t, $J=7.5$ Hz, 1H, CαH4), 3.84 (d, $J=3.2$ Hz, 1H, C3H3), 3.83–3.80 (m, 1H, C3H5), 3.76 (d, $J=3.1$ Hz, 1H, C3H6), 3.72 (m, 1H, C3H1), 3.71 (s, 3H, COOMe), 3.39 (s, 6H, OMe), 3.38 (s, 6H, OMe), 3.35 (s, 3H, OMe), 2.63 (dd, $J=4.2$, 14.5 Hz, 1H,

CαH$_{(pro\text{-}R)}$3), 2.59 (dd, J=4.7, 13.0 Hz, 1H, CαH$_{(pro\text{-}R)}$8), 2.52 (m, 2H, CαH1), 2.51 (m, 2H, CαH5), 2.49 (m, 1H, CαH$_{(pro\text{-}R)}$6), 2.38 (dd, J=5.2, 14.3 Hz, 1H, CαH$_{(pro\text{-}S)}$6), 2.31 (dd, J=6.2, 14.8 Hz, 1H, CαH$_{(pro\text{-}S)}$3), 2.21 (dd, J=2.9, 13 Hz, 1H, CαH$_{(pro\text{-}S)}$8), 2.02–1.96 (m, 1H, CβH4), 1.48 (s, 6H, Me), 1.47 (s, 3H, Me), 1.46 (m, 3H, CH$_3$7), 1.45 (s, 6H, Me), 1.43 (s, 9H, Boc), 1.43 (m, 3H, CH$_3$9), 1.39 (d, J=6.8 Hz, 3H, CH$_3$2), 1.31 (s, 3H, Me), 1.30 (s, 6H, Me), 1.29 (s, 6H, Me), 0.99 (d, J=6.7 Hz, 3H, CH$_3$4), 0.98 ppm (d, J=6.7 Hz, 3H, CH$_3$4); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 175.4, 173.3, 173.1, 172.0, 171.6, 171.2, 170.9, 170.3, 156.0, 111.6. 111.5, 111.4, 104.9, 104.8, 104.7,83.9, 83.7, 83.4, 81.4, 81.3, 81.0, 80.3, 79.9, 79.4, 77.3, 77.0, 76.7, 61.3, 57.4, 57.3, 52.4, 51.4, 50.1, 48.6, 48.0, 46.7, 46.7, 46.4, 46.2, 38.7, 38.5, 38.2, 38.1, 37.9, 29.7, 28.4 (3C), 26.7,26.4, 26.3, 26.3, 26.1, 19.2, 19.0, 17.1, 16.7, 16.2 ppm; HRMS (ESI): m/z calcd for $C_{75}H_{121}N_9O_{32}$: 1682.8015 $[M+Na]^+$; found: 1682.8008.

8c: As described for the synthesis of **12a**, a solution of **6c** (0.065 g, 0.064 mmol) gave **25c** (0.063 g, 98.2%) as a white solid, which was used without further purification in the next step. As described for the synthesis of **1**, a mixture of **25c** (0.06 g, 0.059 mmol), HOBt (0.01 g, 0.072 mmol), and EDCI (0.014 g, 0.072 mmol) in CH_2Cl_2 (3 mL) was stirred at 0°C for 15 min and then treated with **18b** (prepared from **17** (0.045 g, 0.059 mmol) and TFA (0.1 mL) in CH_2Cl_2 (0.5 mL)) and DIPEA (0.02 mL, 0.107 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 4.0% methanol in $CHCl_3$) afforded **8c** (0.04 g, 40.2%) as a white solid. M.p.: 135–137°C; $[\alpha]_D$=−50.4 (c=0.05, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3325, 2963, 2933, 1661, 1523, 1327, 1256, 1136, 1076, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$, 288 K, 600 MHz): δ=8.20 (d, J=6.7 Hz, 1H, NH), 8.01 (br s, 1H, NH), 7.80 (d, J=7.5 Hz, 1H, NH), 7.36–7.23 (m, 5H, NH), 5.90–5.88 (m, 5H, C1H), 4.61–4.51 (m, 8H), 4.47–4.42 (m, 1H), 4.32–4.10 (m, 7H), 4.05 (d, J=3.4 Hz, 1H), 4.01–3.99 (m, 1H), 3.86–3.84 (m, 1H), 3.79–3.72 (m, 4H, C3H), 3.70 (s, 3H, COOMe), 3.39 (m, 6H, OMe), 3.38 (s, 3H, OMe), 3.37 (s, 3H, OMe), 3.35 (s, 3H, OMe), 2.65–2.55 (m, 3H, CαH), 2.50–2.27 (m, 6H, CαH), 2.15 (dd, J=2.3, 13.1 Hz, 1H, CαH), 1.49 (s, 3H, Me), 1.48 (s, 6H, Me), 1.48 (m, 3H, CH$_3$7), 1.44 (s, 3H, Me), 1.43 (s, 9H, Boc), 1.43 (m, 3H, CH$_3$), 1.36 (m, 6H, CH$_3$), 1.31 (m, 6H, CH$_3$), 1.29 (s, 6H, Me), 1.25 ppm (s, 12H, Me); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=175.4, 174.4, 173.6, 173.4, 171.7, 170.9, 170.4, 169.9, 156.1, 111.6, 111.6, 111.6, 111.3, 105.0, 104.9, 104.9, 104.8, 104.7, 96.1, 84.3, 83.8, 83.5, 83.4, 81.4, 81.3, 80.9, 80.5, 80.0, 79.8, 79.5, 78.0, 57.5, 57.4, 57.3, 57.3, 57.1, 52.4, 51.9, 48.6, 47.5, 46.9, 46.2, 46.1, 45.8, 39.8, 38.6, 38.5, 38.1, 31.9, 29.7, 29.3, 28.4, 26.8, 26.8, 26.7, 26.4, 26.3, 26.2, 26.1, 26.1, 22.7, 17.2, 16.6, 16.1, 14.1, 8.6 ppm; HRMS (ESI): m/z calcd for $C_{74}H_{119}N_9O_{32}$: 1668.7858 $[M+Na]^+$; found: 1668.7922.

9: As described for the synthesis of **1**, a mixture of **23** (0.103 g, 0.097 mmol), HOBt (0.016 g, 0.116 mmol), and EDCI (0.022 g, 0.116 mmol) in CH_2Cl_2 (2.5 mL) was stirred at 0°C for 15 min and then treated with **18b** (prepared from **17** (0.074 g, 0.097 mmol) and TFA (0.1 mL) in CH_2Cl_2 (0.3 mL)) and DIPEA (0.025 mL, 0.145 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 2.5% methanol in $CHCl_3$) afforded **9** (0.052 g, 31.4%) as a white solid. M.p.: 172–174°C; $[\alpha]_D$=+65.7 (c=0.25, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3320, 2987, 2937, 1652, 1540, 1456, 1380, 1218, 1166, 1080, 1022, 856 cm^{-1}; 500 MHz (^{1}H NMR, $CDCl_3$): δ=8.22 (d, J=6.4 Hz, 1H, NH5), 7.94 (d, J=7.7 Hz, 1H, NH10), 7.91 (d, J=9.0 Hz, 1H, NH4), 7.89 (d, J=5.2 Hz, 1H, NH3), 7.81 (d, J=9.4 Hz, 1H, NH2), 7.48 (d, J=9.5 Hz, 1H, NH7), 7.40 (d, J=4.9 Hz, 1H, NH8), 7.27 (d, J=9.6 Hz, 1H, NH9), 6.95 (d, J=8.8 Hz, 1H, NH6), 5.88 (d, J=3.8 Hz, 1H, C1H6), 5.88 (d, J=3.8 Hz, 1H, C1H4), 5.88 (d, J=3.4 Hz, 1H, C1H2), 5.87 (d, J=4.1 Hz, 1H, C1H9), 5.87 (d, J=3.9 Hz, 1H, C1H7), 5.0 (d, J=5.9 Hz, 1H, NH1), 4.64 (m, 1H, CβH7), 4.61 (d, J=3.9 Hz, 1H, C2H7), 4.59 (d, J=4.1 Hz, 1H, C2H9), 4.57 (d, J=3.8 Hz, 2H, C2H6 and C2H4), 4.55 (d, J=3.4 Hz, 1H, C2H2), 4.55 (m, 1H, CβH2), 4.55 (m, 1H, CαH10), 4.49 (m, 1H, CβH9), 4.47 (m, 1H, CβH6), 4.46 (m, 1H, CβH4),), 4.37 (dd, J=3.0, 9.5 Hz, 1H, C4H7), 4.35–4.33 (m, 1H, CαH5), 4.24 (m, 1H, C4H2), 4.23 (dd, J=3.4, 9.9 Hz 1H, C4H4), 4.23 (m, 1H, CαH3), 4.19 (m, 1H, C4H6), 4.18 (m, 1H, C4H9), 4.05 (m, 1H, CαH8), 4.04 (d, J=3.3 Hz, 1H, C3H9), 4.02 (m, 1H, CαH1), 3.96 (m, 1H, C3H7 and C3H2), 3.94 (d, J=3.4 Hz, 1H, C3H4), 3.92 (d, J=3.4 Hz, 1H, C3H6), 3.71 (d, J=3.0 Hz, 1H, C3H7), 3.71 (s, 3H, COOMe), 3.40 (s, 3H, OMe), 3.39 (s, 3H, OMe), 3.38 (s, 9H, OMe), 2.59 (dd, J=4.8, 13.0 Hz, 1H, CαH$_{(pro\text{-}R)}$9), 2.57 (m, 1H, CαH$_{(pro\text{-}R)}$4), 2.56 (m, 2H, CαH$_{(pro\text{-}R)}$6 and CαH$_{(pro\text{-}R)}$2), 2.43 (m, 1H, CαH$_{(pro\text{-}S)}$7), 2.43 (m, 1H, CαH$_{(pro\text{-}R)}$7), 2.28 (dd, J=5.3, 13.1 Hz, 1H, CαH$_{(pro\text{-}S)}$6), 2.25 (dd, J=3.6, 13.0 Hz, 1H, CαH$_{(pro\text{-}S)}$9), 2.19 (dd, J=3.5, 12.9 Hz, 1H, CαH$_{(pro\text{-}S)}$2), 2.11 (dd, J=3.0, 12.9 Hz, 1H, CαH$_{(pro\text{-}S)}$4), 1.49 (s, 3H, CH$_3$), 1.47 (s, 6H, CH$_3$), 1.46 (s, 3H, CH$_3$), 1.44 (s, 3H, CH$_3$), 1.43 (d, J=7.1 Hz, 3H, CH$_3$10), 1.41 (d, J=7.3 Hz, 6H, CH$_3$8 and CH$_3$3), 1.41 (s, 9H, Boc), 1.36 (d, J=7.2 Hz, 3H, CH$_3$1), 1.35 (d, J=7.0 Hz, 3H, CH$_3$5), 1.31 (s, 9H, CH$_3$), 1.30 ppm (s, 6H, CH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=175.8, 175.0, 174.4, 173.6, 172.9, 172.2, 172.1, 171.3, 171.2, 170.5, 156.0, 111.9, 111.8, 111.5, 105.2, 104.9, 83.6, 81.7, 81.5, 81.4, 80.4, 80.2, 80.1, 80.0, 57.6, 57.6, 57.5, 52.7, 52.1, 51.6, 51.5, 51.3, 48.9, 47.3, 47.0, 46.8, 46.4, 39.1, 38.7, 38.5, 38.4, 29.9, 28.5 (3C), 27.0, 29.9, 26.7, 26.6, 26.4, 26.3, 17.6, 17.1, 16.7, 16.4 ppm; HRMS (ESI): m/z calcd for $C_{76}H_{122}N_{10}O_{33}$: 1725.8073 $[M+Na]^+$; found: 1725.8088.

10: As described for the synthesis of **12a**, a solution of **7** (0.086 g, 0.065 mmol) gave **26** (0.078 g, 91.7%) as a white solid, which was used without further purification in the next step. As described for the synthesis of **1**, a mixture of **26** (0.078 g, 0.06 mmol), HOBt (0.009 g, 0.072 mmol), and EDCI (0.013 g, 0.072 mmol) in CH_2Cl_2 (1.5 mL) was stirred at 0°C for 15 min and treated with **18b** (prepared from **17** (0.046 g, 0.06 mmol) and TFA (0.1 mL) in CH_2Cl_2 (0.5 mL)) and DIPEA (0.015 mL, 0.09 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 4.0% methanol in $CHCl_3$) afforded **10** (0.03 g, 25.8%) as a white solid. M.p.: 220–222°C; $[\alpha]_D$=+63.73 (c=0.25, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3309, 2985, 2931, 1653, 1541, 1379, 1218, 1165, 1081, 1022, 856 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.18 (d, J=5.5 Hz, 1H, NH6), 7.98 (d, J=5.2 Hz, 1H, NH4), 7.88 (d, J=7.8 Hz, 1H, NH11), 7.85 (d, J=9.6 Hz, 1H, NH5), 7.76 (d, J=9.3 Hz, 1H, NH3), 7.42 (d, J=8.3 Hz, 1H, NH8), 7.38 (d, J=5.2 Hz, 1H, NH9), 7.22 (d, J=9.3 Hz, 1H, NH10), 6.93 (d, J=9.0 Hz, 1H, NH7), 6.47 (d, J=5.4 Hz, 1H, NH2), 5.88 (d, J=3.7 Hz, 1H, C1H7), 5.88 (d, J=3.9 Hz, 1H, C1H1), 5.87 (d, J=3.8 Hz, 1H, C1H10), 5.87 (d, J=3.4 Hz, 2H, C1H5 and C1H3), 5.86 (d, J=3.9 Hz, 1H, C1H8), 5.50 (d, J=8.3 Hz, 1H, NH1), 4.64–4.61 (m, 1H, CβH8), 4.59 (d, J=3.9 Hz, 2H, C2H8), 4.58 (d, J=3.8 Hz, 1H, C2H10), 4.57 (d, J=3.7 Hz, 1H, C2H7), 4.56 (d, J=3.4 Hz, 2H, C2H5 and C2H3), 4.55 (m, 1H, CαH11), 4.55 (d, J=3.9 Hz, 1H, C2H1), 4.49 (m, 1H, CβH3), 4.47 (m, 1H, CβH10), 4.45 (m, 1H, CβH5), 4.44 (m, 1H, CβH7), 4.36 (dd, J=3.0, 9.5 Hz, 1H, C4H8), 4.35–4.28 (m, 1H, CαH6), 4.27 (m, 1H, CβH1), 4.25 (m, 1H, CαH4), 4.24 (m, 1H, C4H3), 4.23 (m, 1H, C4H5), 4.20 (m, 1H, CαH2), 4.19 (m, 1H, C4H7), 4.07–4.03 (m, 1H, CαH9), 4.02 (d, J=3.2 Hz, 1H, C3H10), 3.93–3.90 (m, 2H, C3H7 and C3H5), 3.74 (d, J=3.2 Hz, 1H, C3H1), 3.70 (d, J=3.0 Hz, 1H, C3H8), 3.71 (s, 3H, COOMe), 3.39 (s, 3H, OMe), 3.38 (s, 6H, OMe), 3.37 (s, 3H, OMe), 3.36 (s, 6H, OMe), 2.58 (dd, J=5.0, 13.2 Hz, 1H, CαH$_{(pro\text{-}R)}$10), 2.55 (m, 1H, CαH$_{(pro\text{-}R)}$3), 2.54 (dd, J=5.5, 14.1 Hz, 2H, CαH$_{(pro\text{-}R)}$7 and CαH$_{(pro\text{-}R)}$1), 2.53 (m, 1H, CαH$_{(pro\text{-}R)}$5), 2.44 (dd, J=6.0, 14.1 Hz, 1H, CαH$_{(pro\text{-}S)}$1), 2.43 (dd, J=6.7, 14.9 Hz, 1H, CαH$_{(pro\text{-}R)}$8), 2.39 (dd, J=6.4, 14.9 Hz, 1H, CαH$_{(pro\text{-}S)}$8), 2.27 (dd, J=5.2, 14.1 Hz, 1H, CαH$_{(pro\text{-}S)}$7), 2.24 (dd, J=3.8, 13.2 Hz, 1H, CαH$_{(pro\text{-}S)}$10), 2.15 (dd, J=3.6, 13.4 Hz, 1H, CαH$_{(pro\text{-}S)}$3), 2.13 (dd, J=2.6, 13.3 Hz, 1H, CαH$_{(pro\text{-}S)}$5), 1.48 (s, 3H, CH$_3$), 1.47 (s, 9H, CH$_3$), 1.45 (s, 3H, CH$_3$), 1.44 (s, 9H, Boc), 1.43 (d, J=6.5 Hz, 3H, CH$_3$11), 1.41 (d, J=7.0 Hz, 3H, CH$_3$9), 1.38 (d, J=7.0 Hz, 6H, CH$_3$2 and CH$_3$4), 1.35 (d, J=7.0 Hz, 3H, CH$_3$6), 1.31 (s, 9H, CH$_3$), 1.30 (s, 3H, CH$_3$), 1.29 (s, 6H, CH$_3$), 1.25 ppm (s, 3H, CH$_3$); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=175.6, 174.8, 174.1, 172.8, 172.7, 171.8, 171.2, 171.0, 170.3, 111.7, 111.6, 111.3, 104.9, 104.9, 104.7, 104.6, 96.2, 96.1, 83.8, 83.4, 83.4, 83.3, 81.3, 81.2, 81.1, 81.0, 80.2, 80.0, 79.8, 79.7, 79.5, 57.5, 57.4, 57.3, 57.3, 52.5, 51.3, 51.1, 48.6, 46.7, 46.7, 46.5, 38.6, 38.3, 38.1, 29.7, 28.4 (3C), 26.8, 26.7, 26.6, 26.4, 26.3, 26.2, 26.1, 26.0, 17.0, 16.8, 16.5, 16.2, 16.1, 15.7, 15.0, 14.8, 14.6, 14.1, 13.5, 13.1, 12.9, 12.7, 12.6, 12.4, 12.2, 11.9, 11.8, 11.6, 11.4, 11.0, 10.8, 10.7, 10.4 ppm; HRMS (ESI): m/z calcd for $C_8H_{139}N_{11}O_{38}$: 995.9533 $[M+Na2]^+$; found: 995.9490.

34a: As described for the synthesis of **1**, a mixture of **14a** (0.5 g, 2.65 mmol), HOBt (0.429 g, 3.17 mmol), and EDCI (0.61 g, 3.17 mmol) in CH_2Cl_2 (10 mL) was stirred at 0°C for 15 min and then treated with **33** (0.37 g, 2.65 mmol) and DIPEA (0.69 mL, 3.96 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 60% ethyl acetate in petroleum ether) afforded **34a** (0.68 g, 93.8%)

as a white solid. M.p.: 62–65 °C; $[\alpha]_D = -50.5$ ($c = 0.5$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3323$, 2972, 2937, 1716, 1673, 1517, 1370, 1169, 1157, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 303 K, 300 MHz): $\delta = 6.66$ (br s, 1H, NH2), 5.01 (br s, 1H, NH1), 4.14–4.09 (m, 1H, CαH1), 3.69 (s, 3H, COOMe), 3.57–3.47 (m, 2H, CβH2), 2.54 (t, $J = 5.9$ Hz, 2H, CαH2), 1.44 (s, 9H, Boc), 1.34 (d, $J = 7.0$ Hz, 3H, $CH_3$1), 1.34 ppm (d, $J = 7.0$ Hz, 3H, $CH_3$2); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 172.6$, 155.4, 79.9, 51.6, 50.3, 34.7, 33.7, 28.2 (3C), 18.4 ppm; HRMS (ESI): m/z calcd for $C_{12}H_{22}N_2O_5$: 275.1548 $[M+H]^+$; found: 275.1531.

34b: As described for the synthesis of **1**, a mixture of **14d** (0.5 g, 2.33 mmol), HOBt (0.38 g, 2.79 mmol), and EDCI (0.54 g, 2.79 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 15 min and then treated with **33** (0.324 g, 2.33 mmol) and DIPEA (0.604 mL, 3.72 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 35% ethyl acetate in petroleum ether) afforded **34b** (0.68 g, 97.5%) as a yellow syrup. $[\alpha]_D = -287.36$ ($c = 0.5$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3325$, 2962, 2935, 1715, 1678, 1525, 1365, 1171, 1157, 1082 cm^{-1}; ^1H NMR ($CDCl_3$, 303 K, 300 MHz): $\delta = 7.13$ (br s, 1H, NH1), 6.61 (br s, 1H, NH1), 4.22 (br s, 1H, CαH1), 3.69 (s, 3H, COOMe), 3.59–3.45 (m, 4H, CδH1 and CβH2), 2.57–2.51 (m, 2H, CαH2), 2.27–2.11 (m, 2H, CβH1), 1.98–1.89 (m, 2H, CγH1), 1.45 ppm (s, 9H, Boc); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 172.6$, 172.2, 80.2, 61.1, 60.0, 51.7, 46.8, 34.7, 33.7, 30.9, 28.5, 28.2 (3C), 24.7, 23.5 ppm; HRMS (ESI): m/z calcd for $C_{14}H_{24}N_2O_5$: 301.1786 $[M+H]^+$, found: 301.1735.

34c: As described for the synthesis of **1**, a mixture of **14e** (0.5 g, 2.33 mmol), HOBt (0.38 g, 2.79 mmol), and EDCI (0.54 g, 2.79 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 15 min and then treated with **33** (0.324 g, 2.33 mmol) and DIPEA (0.604 mL, 3.72 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 40% ethyl acetate in petroleum ether) afforded **34c** (0.65 g, 93.2%) as a yellow syrup. $[\alpha]_D = +224.9$ ($c = 0.5$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3329$, 2967, 2945, 1719, 1680, 1523, 1365, 1171, 1159, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 303 K, 300 MHz): $\delta = 7.14$ (br s, 1H, NH1), 6.60 (br s, 1H, NH1), 4.22 (br s, 1H, CαH1), 3.68 (s, 3H, COOMe), 3.59–3.45 (m, 4H, CδH1 and CβH2), 2.57–2.51 (m, 2H, CαH2), 2.27–2.11 (m, 2H, CβH1), 1.95–1.78 (m, 2H, CγH1), 1.45 ppm (s, 9H, Boc); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 172.6$, 172.2, 80.2, 61.1, 60.0, 51.6, 46.9, 46.8, 35.6, 34.6, 33.6, 29.6, 28.3 (3C), 24.4, 23.5 ppm; HRMS (ESI): m/z calcd for $C_{14}H_{24}N_2O_5$: 301.1770 $[M+H]^+$; found: 301.1788.

36: As described for the synthesis of **1**, a mixture of **21** (0.35 g, 0.81 mmol), HOBt (0.131 g, 0.972 mmol), and EDCI (0.186 g, 0.972 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C for 15 min and then treated with **35a** (prepared from 34a (0.222 g, 0.81 mmol) and TFA (0.2 mL) in CH_2Cl_2 (2 mL)) and DIPEA (0.21 mL, 1.121 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 2.0% methanol in $CHCl_3$) afforded **36** (0.38 g, 77.9%) as a white solid. M.p.: 175–178 °C; $[\alpha]_D = -59.6$ ($c = 0.5$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3330$, 2986, 2940, 1762, 1693, 1645, 1539, 1364, 1256, 1167, 1078, 1026, 856 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.49$ (d, $J = 9.0$ Hz, 1H, NH2), 7.32 (d, $J = 7.7$ Hz, 1H, NH3), 6.66 (d, $J = 6.3$ Hz, 1H, NH4), 5.87 (d, $J = 3.8$ Hz, 1H, C1H2), 5.08 (d, $J = 6.5$ Hz, 1H, NH1), 4.57 (d, $J = 3.7$ Hz, 1H, C2H2), 4.49–4.44 (m, 1H, CβH3), 4.44–4.35 (m, 1H, CαH3), 4.20 (dd, $J = 3.2$, 9.3 Hz, 1H, C4H2), 4.09–4.03 (m, 1H, CαH1), 3.97 (d, $J = 3.2$ Hz, 1H, C3H2), 3.71 (s, 3H, COOMe), 3.59–3.53 (m, 1H, CβH4), 3.48–3.41 (m, 1H, Cβ′H4), 3.39 (s, 3H, OMe), 2.62 (dd, $J = 5.0$, 13.4 Hz, 1H, $CαH_{(pro\text{-}R)}2$), 2.56–2.51 (m, 1H, CαH4), 2.29 (dd, $J = 6.4$, 14.7 Hz, 1H, $CαH_{(pro\text{-}S)}2$), 1.45 (s, 3H, CH_3), 1.41 (s, 9H, Boc), 1.39 (d, $J = 7.5$ Hz, 3H, $CH_3$3), 1.36 (d, $J = 6.9$ Hz, 3H, $CH_3$1), 1.30 ppm (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 173.5$, 173.4, 173.2, 170.9, 155.9, 111.6, 104.9, 83.6, 81.4, 79.9, 79.7, 57.4, 52.0, 50.9, 49.9, 46.5, 38.5, 34.9, 33.6, 28.2 (3C), 26.8, 26.4 ppm; HRMS (ESI): m/z calcd for $C_{26}H_{44}N_4O_{11}$: 611.7865 $[M+Na]^+$, found: 611.7835.

11a: As described for the synthesis of **12a**, a solution of **36** (0.1 g, 0.166 mmol) gave **37** (0.095 g, 97.2%) as a white solid, which was used without further purification in the next step. As described for the synthesis of **1**, a mixture of **37** (0.035 g, 0.081 mmol), HOBt (0.013 g, 0.097 mmol), and EDCI (0.019 g, 0.097 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C for 15 min and then treated with **35a** (prepared from **34a** (0.034 g, 0.081 mmol) and TFA (0.1 mL) in CH_2Cl_2 (0.3 mL)) and DIPEA (0.02 mL, 0.122 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 4.2% methanol in $CHCl_3$) afforded **11a** (0.035 g, 59.2%) as a white solid. M.p.: 205–208 °C; $[\alpha]_D = +146$ ($c = 0.1$, $CHCl_3$);); IR (KBr): $\tilde{\nu} = 3277$, 2966, 2956, 1665, 1559, 1379, 1241, 1199, 1075, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 283 K, 600 MHz): $\delta = 8.08$ (d, $J = 5.5$ Hz, 1H, NH3), 7.82 (d, $J = 9.5$ Hz, 1H, NH2), 7.75 (dd, $J = 4.5$, 7.5 Hz, 1H, NH6), 7.24 (t, $J = 5.5$ Hz, 1H, NH4), 7.15 (d, $J = 6.6$ Hz, 1H, NH5), 5.91 (d, $J = 3.7$ Hz, 1H, C1H2), 5.02 (d, $J = 5.5$ Hz, 1H, NH1), 4.60 (d, $J = 3.7$ Hz, 1H, C2H2), 4.56–4.52 (m, 1H, CβH2), 4.34–4.29 (m, 2H, CαH3 and CαH5), 4.18 (dd, $J = 3.0$, 9.7 Hz, 1H, C4H2), 4.04 (d, $J = 3.0$ Hz, 1H, C3H2), 4.01–3.97 (m, 1H, CαH1), 3.80–3.73 (m, 1H, CβH6), 3.74 (s, 3H, COOMe), 3.61–3.56 (m, 1H, CβH4), 3.38 (s, 3H, OMe), 3.36–3.29 (m, 1H, Cβ′H4), 3.23–3.16 (m, 1H, Cβ′H6), 2.80 (ddd, $J = 4.3$, 9.2, 17.1 Hz, 1H, $CαH_{(pro\text{-}R)}4$), 2.57 (dd, $J = 5.2$, 13.0 Hz, 1H, $CαH_{(pro\text{-}R)}2$), 2.52 (m, 1H, $CαH_{(pro\text{-}R)}6$), 2.50 (m, 1H, $CαH_{(pro\text{-}S)}4$), 2.22 (dd, $J = 2.8$, 13.0 Hz, 1H, $CαH_{(pro\text{-}S)}2$), 2.19–2.16 (m, 1H, $CαH_{(pro\text{-}S)}6$), 1.51 (s, 3H, Me), 1.41 (s, 9H, Me), 1.41 (m, 3H, $CH_3$5), 1.40 (m, 3H, $CH_3$3), 1.39 (d, $J = 6.8$ Hz, 3H, $CH_3$1), 1.32 ppm (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.2, 173.6, 173.5, 173.3, 172.2, 171.9, 155.9, 111.5, 105.0, 83.4, 81.2, 80.5, 80.1, 57.4, 51.9, 51.5, 51.3, 50.3, 47.0, 38.2, 36.9, 36.6, 35.2, 33.5, 28.3 (3C), 26.9, 25.9, 17.6, 17.4, 16.7 ppm; HRMS (ESI): m/z calcd for $C_{32}H_{52}N_5O_{14}$: 753.3408 $[M+Na]^+$; found: 753.3416.

11b: As described for the synthesis of **1**, a mixture of **37** (0.13 g, 0.221 mmol), HOBt (0.036 g, 0.221 mmol), and EDCI (0.051 g, 0.265 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 15 min and then treated with **35b** (prepared from **34b** (0.066 g, 0.221 mmol) and TFA (0.1 mL) in CH_2Cl_2 (0.3 mL)) and DIPEA (0.057 mL, 0.329 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 4.0% methanol in $CHCl_3$) afforded **11b** (0.09 g, 52.8%) as a white solid. M.p.: 100–104 °C; $[\alpha]_D = -163.6$ ($c = 0.1$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3276$, 2968, 2946, 1667, 1545, 1373, 1257, 1199, 1065, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 303 K, 600 MHz): $\delta = 8.25$ (d, $J = 8.0$ Hz, 1H, NH2), 7.42 (d, $J = 6.0$ Hz, 1H, NH4), 7.35 (d, $J = 7.7$, 1H, NH3), 7.10 (t, $J = 5.6$ Hz, 1H, NH6), 5.96 (d, $J = 4.0$ Hz, 1H, C1H2), 4.98 (d, $J = 6.2$ Hz, 1H, NH1), 4.60 (d, $J = 4.0$ Hz, 1H, C2H2), 4.47 (m, 1H, CβH2), 4.46 (m, 1H, CαH3), 4.38–4.35 (m, 1H, CαH5), 4.14–4.09 (m, 1H, CαH1), 4.03 (d, $J = 3.3$ Hz, 1H, C3H2), 3.67 (s, 3H, COOMe), 3.66–3.62 (m, 1H, CδH5), 3.58 (m, 1H, CβH4), 3.56 (m, 1H, CβH6), 3.41 (m, 1H, Cδ′H5), 3.38 (s, 3H, OMe), 3.36 (m, 1H, CδH6), 3.34 (m, 1H, CδH4), 2.71 (dd, $J = 4.9$, 13.5 Hz, 1H, $CαH_{(pro\text{-}R)}2$), 2.58 (m, 1H, $CαH_{(pro\text{-}R)}6$), 2.57 (m, 1H, $CαH_{(pro\text{-}R)}4$), 2.53 (m, 1H, $CαH_{(pro\text{-}S)}4$), 2.49 (m, 1H, $CαH_{(pro\text{-}S)}6$), 2.24 (dd, $J = 3.2$, 13.5 Hz, 1H, $CαH_{(pro\text{-}S)}2$), 2.10 (m, 1H, CγH5), 2.06 (m, 1H, Cβ′H5), 2.02 (m, 1H, CβH5), 1.95–1.89 (m, 1H, Cγ′H5), 1.47 (s, 3H, Me), 1.40 (s, 9H, Me), 1.39 (d, $J = 7.2$ Hz, 3H, $CH_3$3), 1.30 (d, $J = 6.8$ Hz, 3H, $CH_3$1), 1.32 ppm (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.7, 173.1, 172.3, 172.0, 171.2, 170.7, 156.0, 111.1, 105.0, 83.5, 81.3, 79.9, 79.7, 60.2, 57.2, ,51.7, 50.7, 49.9, 47.6, 46.7, 38.0, 35.0, 35.0, 33.6, 33.6, 29.5, 28.2 (3C), 26.6, 25.8, 24.5, 17.4, 17.3 ppm; HRMS (ESI): m/z calcd for $C_{34}H_{56}N_6O_{13}$: 779.3803 $[M+Na]^+$; found: 779.3821.

11c: As described for the synthesis of **1**, a mixture of **37** (0.095 g, 0.162 mmol), HOBt (0.026 g, 0.194 mmol), and EDCI (0.037 g, 0.194 mmol) in CH_2Cl_2 (4 mL) was stirred at 0 °C for 15 min and then treated with **35c** (prepared from **34c** (0.048 g, 0.162 mmol) and TFA (0.1 mL) in CH_2Cl_2 (0.3 mL)) and DIPEA (0.042 mL, 0.242 mmol) under N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 3.0% methanol in $CHCl_3$) afforded **11c** (0.075 g, 60.3%) as a white solid. M.p.: 105–108 °C; $[\alpha]_D = +90.17$ ($c = 0.1$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3278$, 2966, 2956, 1666, 1549, 1379, 1251, 1189, 1075, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 303 K, 500 MHz): $\delta = 7.67$ (d, $J = 9.0$ Hz, 1H, NH2), 7.41 (d, $J = 8.0$ Hz, 1H, NH3), 7.15 (t, $J = 6.1$ Hz, 1H, NH6), 6.87 (t, $J = 6.2$ Hz, 1H, NH4), 5.88 (d, $J = 4.0$ Hz, 1H, C1H2), 5.13 (d, $J = 7.0$ Hz, 1H, NH1), 4.57 (d, $J = 4.0$ Hz, 1H, C2H2), 4.53–4.48 (m, 2H, CβH2 and CαH5), 4.38–4.35 (m, 1H, CαH3), 4.25–4.16 (m, 1H, C4H2), 4.07–4.01 (m, 1H, CαH1), 3.96 (d, $J = 2.7$ Hz, 1H, C3H2), 3.71 (s, 3H, COOMe), 3.57 (m, 2H, CβH4), 3.54 (m, 1H, CβH6), 3.53 (m, 1H, CδH5), 3.48 (m, 1H, Cβ′H6), 3.42 (m, 1H, Cδ′H5), 3.39 (s, 3H, OMe), 2.56 (m, 3H, $CαH_{(pro\text{-}R)}2$ and CαH6), 2.55 (m, 1H, $CαH_{(pro\text{-}R)}4$), 2.51–2.44

(m, 1H, $C\alpha H_{(pro\text{-}S)}4$), 2.38–2.27 (m, 1H, $C\alpha H_{(pro\text{-}S)}2$), 2.12–2.03 (m, 2H, Cβ*H*5), 2.01–1.88 (m, 2H, Cγ*H*5), 1.46 (s, 3H, Me), 1.41 (s, 9H, Me), 1.38 (d, $J=7.0$ Hz, 3H, $CH_3$3), 1.36 (d, $J=6.9$ Hz, 3H, $CH_3$1), 1.30 ppm (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=173.6$, 173.3, 173.0, 171.8, 171.4, 170.9, 155.8, 111.5, 104.8, 83.5, 81.3, 79.9, 79.7, 60.0, 57.3, 51.9, 51.0, 49.9, 47.4, 46.2, 38.4, 35.0, 34.0, 33.7, 33.5, 28.2 (3C), 26.7, 26.2, 26.1, 24.7, 17.5, 17.4 ppm; HRMS (ESI): *m*/*z* calcd for $C_{34}H_{56}N_6O_{13}$: 779.3803 $[M+Na]^+$; found: 779.3831.

Acknowledgements

P.N., N.C., and M.C. are grateful to CSIR, New Delhi for financial support.

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Received: December 14, 2007
Published online: April 8, 2008

