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Structure–Activity Relationships

Solid-Phase Combinatorial Synthesis and Biological Evaluation of Destruxin E Analogues

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Abstract: The solid-phase combinatorial synthesis of cyclodepsipeptide destruxin E has been demonstrated. The combinatorial synthesis of cyclization precursors **8** was achieved by using a split and pool method on SynPhase Lanterns. The products were successfully macrolactonized in parallel in the solution phase by using 2-methyl-6-nitrobenzoic anhydride and 4-(dimethylamino)pyridine *N*-oxide to afford macrolactones **9**, and the subsequent formation of an epoxide in the side chain gave 18 member destruxin E analogues **6**. Biological evaluation of analogues **6** indicated that the *N*-MeAla residue was crucial to the induction of morphological changes in osteoclast-like multinuclear cells (OCLs). Based on structure–activity relationships, azido-containing analogues **15** were then designed for use as a molecular probe. The synthesis and biological evaluation of analogues **15** revealed that **15b**, in which the Ile residue was replaced with a Lys(N_3) residue, induced morphological changes in OCLs at a sufficient concentration, and modification around the Ile residue would be tolerated for attachment of a chemical tag toward the target identification of destruxin E (**1**).

Introduction

Cyclic peptides are novel compounds for use in the development of drugs because they more easily permeate cells and are more bioavailable than linear peptides.[1] Peptides such as FK228,[2] cyclosporine A,[3] and daptomycin[4] that can be used as drugs, not only have cyclic structures, but contain non-proteinogenic amino acids, such as *N*-methylated or D-amino acids. These features can give a drug unique pharmacological properties.[5] This makes cyclic peptides containing non-proteinogenic amino acids attractive candidates for both the lead discovery and lead optimization phases of drug development. Destruxin E (**1**) was isolated from *Metarhidium anisopliae* by Païs et al. in 1981.[6a] Compound **1** has a 19-membered cyclodepsipeptide structure that consists of five proteinogenic and non-proteinogenic amino acids (L-proline, L-isoleucine, *N*-Me-L-valine, *N*-Me-L-alanine, and β-alanine) and an epoxide-containing derivative of a hydroxy acid.[6] It has recently been found that **1** has several unique biological activities,[7] including antiproliferative activity against P388 leukemic cells,[8] the inhibition of the accumulation of lipid droplets in J774 macrophages,[9] and the ability to decrease the amount of amyloid-β (Aβ) generated without affecting the β-amyloid-cleaving enzyme (BACE) or presenilin (PS)/γ-secretase activity.[10] In particular, compound **1** is a more potent V-ATPase inhibitor than any other member of the destruxin family[11] and could therefore be a promising candidate drug for use in cancer therapies because V-ATPase plays an important role in allowing cancer cells to behave invasively.[12] Intriguingly, it has recently been reported that **1** induces morphological changes in osteoclast-like multinuclear cells (OCLs) reversibly at a lower concentration than that required to affect V-ATPase activity in the OCLs, resulting in inhibition of bone resorption without causing cell death.[13] Most anti-resorption agents induce cell death at the same time as inhibiting bone resorption; therefore **1** can be considered as a new type of anti-resorption agent for use in osteoporosis therapies. We wished to synthesize **1** because of its structural features and unique biological activity, and we recently achieved the first total synthesis of **1** and fully determined its structure. In particular, we found that the potency of the V-ATPase inhibitory activity of **1** depends on the stereochemistry of the epoxide moiety.[14] We therefore wished to elucidate the mode of action of **1** in OCLs. Studying the structure–activity relationships of the analogues of **1** would be worthwhile because the information provided could allow novel drug candidates for osteoporosis therapies to be developed.[15] Herein, we describe the combinatorial synthesis of analogues of **1** and present the results of biological evaluations of the analogues in terms of the morphological changes the analogues bring about in OCLs.

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Results and Discussion

Synthesis and biological evaluation of destruxin E analogues 6

It is already known that **1** and destruxin B (**2**) induce morphological changes in OCLs (Figure 1).[13] We assumed that the biological activities of destruxins would depend on the macrocyclic structures of the molecules. We also assumed that similar structures, such as pseudodestruxin A (**3**) and pseudodestruxin B (**4**),[16] would also act as negative regulators of the morphologies of osteoclasts (Figure 1).

We concluded that an epoxide moiety in the side chain would be required to give a potent biological activity to the molecule because **1** strongly affected the osteoclast morphology, whereas **2**, which contained an isobutyl side chain, would be less affected.[13] It seems, therefore, that the epoxide moiety was fixed in the analogues presented. We first evaluated the effect of the stereochemistry of the epoxide on osteoclast morphology (Figure 2). Intriguingly, we found that **1**, which contained an (*S*)-epoxide moiety in the side chain, strongly induced morphological changes in OCLs (0.04 μM), whereas *epi*-destruxin E (**5**), previously reported,[14] which contains an (*R*)-epoxide, affected the OCLs at a higher concentration (5 μM). We concluded that an (*S*)-epoxide moiety in the side chain was required to allow the molecule to affect the osteoclast morphology at low concentrations.

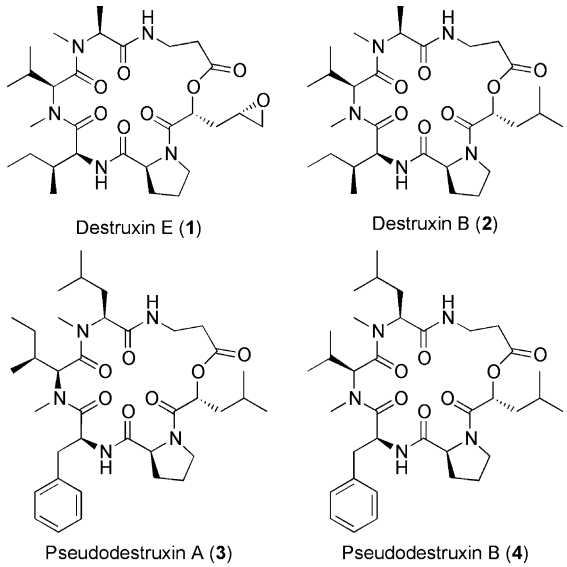


Figure 1. Structures of destruxin E (**1**), destruxin B (**2**), pseudodestruxin A (**3**), and pseudodestruxin B (**4**).

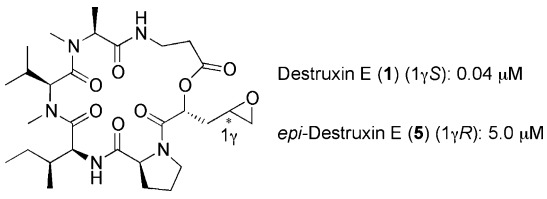


Figure 2. Minimum concentration of **1** and *epi*-destruxin E (**5**) for morphological changes in OCLs.

Using the structural information presented above, we designed destruxin E analogues composed of amino acid residues present in destruxins and pseudodestruxins. The synthetic strategy used to prepare the destruxin analogues **6** is shown in Figure 3. Cyclization precursors **8** were synthesized in the solid phase by using a split and pool method similar to the method we previously used for the total synthesis of **1**.[14] Macrolactones **9** were formed through macrolactonization mediated by MNBA[17] in the solution phase after the reactants had been cleaved from the polymer support. The formation of epoxide moieties in parallel then gave the 18 member destruxin analogues **6**. Each of the analogues consisted of the amino acids ***A*** (three), ***B*** (three), and ***C*** (two), as shown in Figure 3.

In brief, cyclization precursors **8** were synthesized in the solid-phase by using the split and pool method[18] outlined in Scheme 1. The 18 member β-Ala-OH-attached SynPhase Lanterns **10**,[14,19] which were visualized by using colored stems with cogs, were divided into three portions, and the first acylation was performed on each portion with a different amino acid, ***A1*** (*N*-Me-Ala), ***A2*** (*N*-Me-Val), or ***A3*** (*N*-Me-Leu), by using DIC/HOBt (Scheme 1, step 1). The lanterns were then mixed and washed with organic solvents to remove excess reagents. The Fmoc group was removed with 20% piperidine in DMF, and this left the polymer-supported amines **11**, which were split into three portions. The second coupling reaction was performed on each portion with a different amino acid, ***B1*** (*N*-Me-Val), ***B2*** (*N*-Me-Ile), or ***B3*** (*N*-Me-Phe), by using PyBroP[20]/DIEA. The lanterns were mixed and washed, and the Fmoc group was removed to afford the polymer-supported amines **12**. Acylation of **12** to give tetrapeptide **13** was difficult to achieve because of the presence of hindered *N*-Me-amines, as we have previously reported;[14] therefore, amines **12** had to be double coupled with Fmoc-Ile-OH ***C1*** and Fmoc-Phe-OH ***C2*** to give the tetrapeptides **13**. Once the Fmoc group in **13** had been removed, all of the polymer supports were acylated with acid **7**[21] to give hexapeptides **14**. The TBS group was removed with TBAF and then the products were cleaved in parallel from the lanterns (with 30% HFIP/CH_2Cl_2 at room temperature for 1 h)[22] to give the 18 member cyclization precursors **8**.[23]

The 18 member cyclization precursors **8** were macrolactonized and then epoxide moieties were formed to produce destruxin E analogues **6**, as shown in Scheme 2. Compound **8** was subsequently macrolactonized with MNBA and DMAPO[17] to provide the desired macrolactones **9** in 7–49% yields. Epoxide moieties in the side chains were formed through three steps, which have been described previously,[14] to give the 18 member destruxin E analogues **6** in moderate yields.

We evaluated the effects of destruxin E analogues **6** on the morphologies of polarized OCLs, and the results are summarized in Table 1. Among the analogues **6a**–**i**, which contain an isoleucine moiety in the R^3 group, only analogues **6a**–**c**, which contain an *N*-Me-alanine residue in the R^1 group, induced the desired morphological changes without cell death (Table 1, entries 1–3). Substitution of the R^2 group with a more bulky or hydrophobic group did not strongly negatively affect the bio-

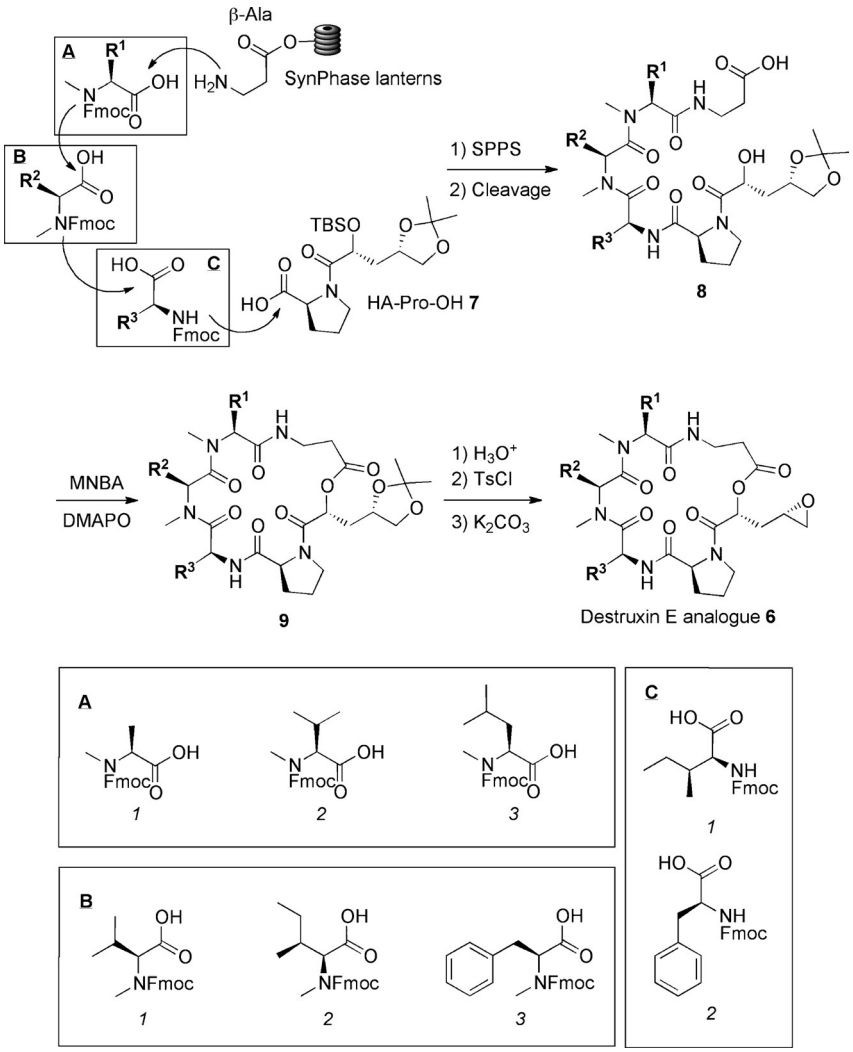


Figure 3. Synthetic strategy for producing the 18 member destruxin E analogues **6** and compositions of the analogues in terms of amino acids ***A***, ***B***, and ***C***. Fmoc = 9-fluorenylmethoxycarbonyl, TBS = *tert*-butyldimethylsilyl, SPPS = solid-phase peptide synthesis, MNBA = 2-methyl-6-nitrobenzoic anhydride, DMAPO = 4-(dimethylamino)-pyridine *N*-oxide, TsCl = 4-toluenesulfonyl chloride.

might allow the desired biological activity to be retained, even though introducing a phenylmethyl group into the R^3 group decreased the biological activity.

Design, synthesis, and biological evaluation of a molecular probe 15 based on 1

Having recorded the structure–activity relationships for morphological changes in OCLs, we next attempted the synthesis of a molecular probe based on the structure of **1**. According to the structure–activity relationships, modification of the side chain on the *N*-Me-Val or Ile residues would be tolerant for inducing morphological changes; thus we designed molecular probes **15a** and **15b**, which contained an alkyl azido moiety to connect a chemical tag, such as biotin or FLAG tags, by copper-catalyzed [3+2] cycloaddition.[24] In addition, we also planned to prepare **15c** as a negative control because replacement of the Ala residue diminished the desired biological activity (Figure 4).

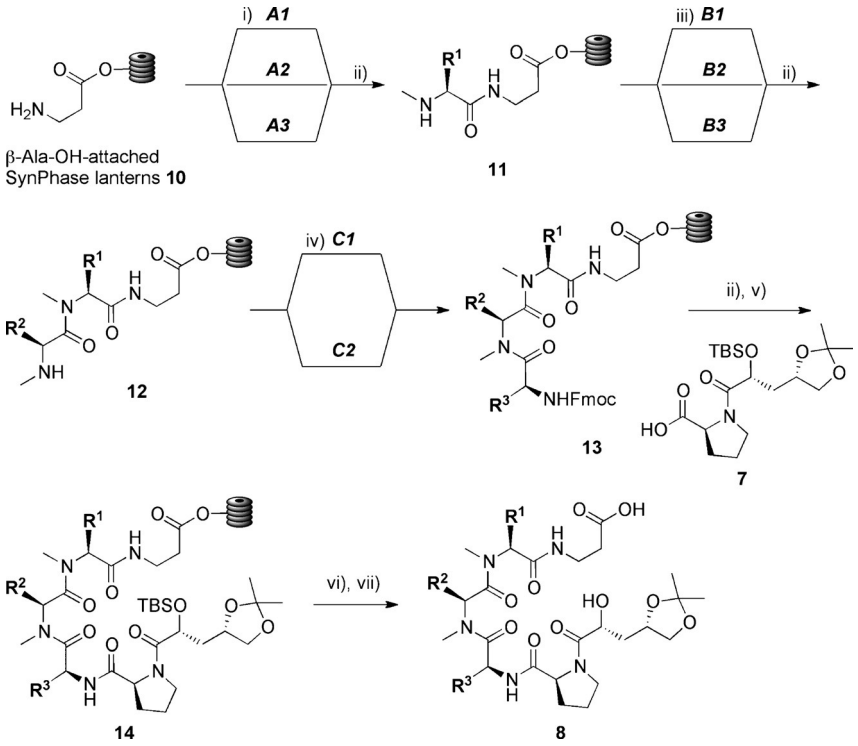
The synthesis of **15** was then performed in the same manner as that outlined above to prepare cyclization precursors **16a–c** (Scheme 3), which contained *N*-Me-Lys(N_3)[25] or Lys(N_3)[26], followed by macrolactonization with MNBA/DMAPO to produce macrolactones **17a–c**. Finally, the formation of the epoxide in the side chain gave derivatives **15a–c** in moderate yields.

With the analogues **15a–c** in hand, we evaluated the biological activity and the results are summarized in Table 2. As expected, compound **15c** as a negative control did not exhibit the desired biological activity and cytotoxicity was observed at a concentration of higher than 10 μM. Intriguingly, analogue **15b** induced morphological changes in OCLs at 2.5 μM, whereas analogue **15a** required a higher concentration (10 μM) to exhibit the activity, which indicated that modification around the Ile residue would be tolerant for attaching a chemical tag, and analogue **15b** could be a good candidate as a molecular probe toward target identification of **1**.

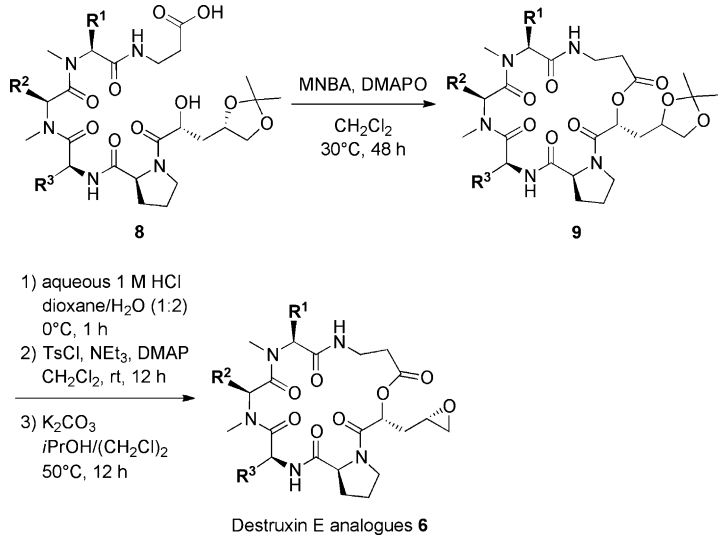
Conclusion

We performed the combinatorial synthesis of 18 member destruxin E analogues **6** and evaluated the biological activities of

logical activity, although a slightly higher concentration was required to induce the desired morphological changes in the OCLs. Analogues **6d–i** were not effective at the concentrations indicated in Table 1, but they were cytotoxic and induced cell death (Table 1, entries 4–9). Therefore, we conclude that replacing the R^1 group with a bulky or hydrophobic moiety removed the functionality we desire. We also conclude that the *N*-Me-alanine residue plays a crucial role in inducing morphological changes in OCLs. However, the desired biological activities were lower for analogues **6j–r**, in which R^3 was a phenylmethyl group, than those for analogues **6a–i** (Table 1, entries 10–18). Among analogues **6j–r**, only **6j** and **6k** exhibited the desired biological activity (Table 1, entries 10 and 11), and no effects on the osteoclasts were observed for analogues **6l–r**, which exhibited cytotoxicity over the concentrations indicated in Table 1, entries 12–18. Interestingly, analogue **6k**, in which the R^2 was a bulky *sec*-butyl group, induced the desired morphological changes at a lower concentration than that of analogue **6j**, which indicated that a bulky or hydrophobic R^2 group



Scheme 1. Solid-phase synthesis of cyclization precursors **8** by using a split and pool method. a) Fmoc-AA-OH (***A1***, ***A2***, and ***A3***) (0.1 M), diisopropylcarbodiimide (DIC; 0.1 M), 1-hydroxybenzotriazole (HOBt; 0.15 M), DMF, RT, 12 h; b) 20% piperidine/DMF, RT, 1 h; c) Fmoc-AA-OH (***B1***, ***B2***, and ***B3***) (0.1 M), bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP; 0.1 M), ethyldiisopropylamine (DIEA; 0.15 M), DMF, RT, 12 h; d) Fmoc-AA-OH (***C1*** and ***C2***) (0.1 M), PyBroP (0.1 M), DIEA (0.15 M), DMF, RT, 12 h, repeated; e) **7** (0.1 M), PyBroP (0.1 M), DIEA (0.15 M), DMF, RT, 12 h; f) tetrabutylammonium fluoride (TBAF), THF, 0 °C, 4 h; g) 30% hexafluoroisopropanol (HFIP)/CH_2Cl_2, RT, 1 h.



Scheme 2. Synthesis of destruxin analogues **6** from cyclization precursors **8**. a) MNBA, DMAPO, CH_2Cl_2, RT, 30 °C, 48 h; b) aqueous 1 M HCl, dioxane·H_2O (1:2), 0 °C, 1 h; c) TsCl, NEt_3, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, RT, 12 h; d) K_2CO_3, *i*PrOH·$(CH_2Cl)_2$, 50 °C, 12 h.

the analogues in terms of the effects they had on the morphologies of OCLs. The 18 member cyclization precursors **8** were efficiently synthesized with good purities in the solid phase by using a split and pool method. The macrolactonization of **8** with MNBA and DMAPO, followed by the formation of epoxide moieties in the side chains in parallel, gave the 18 member destruxin analogues **6** in moderate yields. Biological evaluations of the analogues showed that modifying the *N*-Me-valine residue allowed the molecule to induce morphological changes, but the *N*-Me-alanine residue was essential for an analogue to have the desired biological activity. This is the first time that the relationship between the structures of destruxins and morphological changes induced has been elucidated. In addition, based on the above structure–activity study, analogues **15** were designed as molecular probes, and synthesized in an analogous manner to that for the synthesis of **6**. Biological evaluation of analogues **15a–c** indicated that **15b** could be a good candidate as a molecular probe toward target identification of **1**. The results obtained will allow novel lead structures for anti-resorption agents based on cyclodepsipeptide scaffolds to be developed.

Experimental Section

General

All commercially available reagents were used as received. Dry THF and CH_2Cl_2 (Kanto Chemical Co.) were obtained by passing commercially available predried, oxygen-free formulations through activated alumina columns. MeOH was distilled from iodide and magnesium turnings. DMF was purchased from Wako Chemical Ind., Ltd. (for peptide synthesis, grade: 99.5%). Trityl alcohol lantern was purchased from Mimotopes (surface: polystyrene, loading: 35 μmol). Fmoc-protected amino acids (Fmoc-βAla-OH, Fmoc-MeAla-OH, Fmoc-Ala-OH·H_2O, Fmoc-MeVal-OH, Fmoc-MeLeu-OH, Fmoc-MeIle-OH, Fmoc-MePhe-OH, Fmoc-Ile-OH, and Fmoc-Phe-OH) were purchased from Watanabe Chemical Ind., Ltd. All reactions in solution were monitored by TLC carried out on 0.2 mm Merck silica gel plates (60F-254) and visualized with UV light, anisaldehyde, or 10% phosphomolybdic acid in ethanol. Silica gel 60N (Kanto Chemical Co. 100~210 μm) was used for column chromatography. ^1H (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on JEOL JNM-AL400 spectrometers. ^1H (600 MHz) and ^{13}C NMR spectra (150 MHz) were

Table 1. Evaluation of the effects of destruxin E analogues **6** on osteoclast morphology.

Entry	Analogue	{*A*, *B*, *C*}	Yield [%][a]	[μM][b]
1	**6a**[c]	{*1*, *1*, *1*}	13	0.04
2	**6b**	{*1*, *2*, *1*}	12	0.1
3	**6c**	{*1*, *3*, *1*}	8	10
4	**6d**	{*2*, *1*, *1*}	3	(5.0)
5	**6e**	{*2*, *2*, *1*}	2	(10)
6	**6f**	{*2*, *3*, *1*}	7	(2.5)
7	**6g**	{*3*, *1*, *1*}	4	(6.3)
8	**6h**	{*3*, *2*, *1*}	8	(2.5)
9	**6i**	{*3*, *3*, *1*}	5	(0.06)
10	**6j**	{*1*, *1*, *2*}	9	12.5
11	**6k**	{*1*, *2*, *2*}	13	3.1
12	**6l**	{*1*, *3*, *2*}	7	(25)
13	**6m**	{*2*, *1*, *2*}	3	(12.5)
14	**6n**	{*2*, *2*, *2*}	3	(25)
15	**6o**	{*2*, *3*, *2*}	7	(25)
16	**6p**	{*3*, *1*, *2*}	2	(12.5)
17	**6q**	{*3*, *2*, *2*}	5	(3.5)
18	**6r**	{*3*, *3*, *2*}	10	(25)

[a] Yield of product isolated, as calculated from β-Ala-OH-attached lantern **10**. [b] Minimum concentration required to induce morphological changes. Values in parentheses are maximum concentrations for cell survival. [c] Destruxin E (**1**).

Table 2. Evaluation of the effects of **15** on osteoclast morphology.

Entry	Analogue	Yield [%][a]	[μM][b]
1	**15a**	8	10
2	**15b**	9	2.5
3	**15c**	6	(10)[c]

[a] Yield of product isolated, as calculated from β-Ala-OH-attached lantern **10**. [b] Minimum concentration required to induce morphological changes. [c] The value in parentheses is the maximum concentration for cell survival.

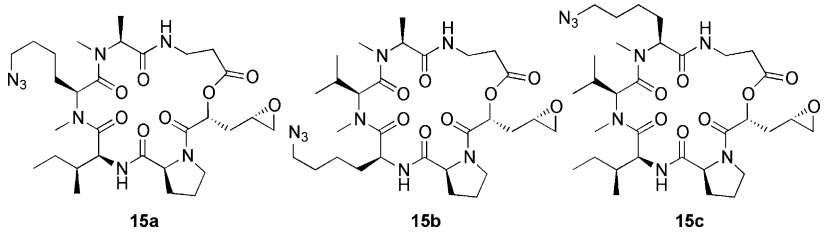
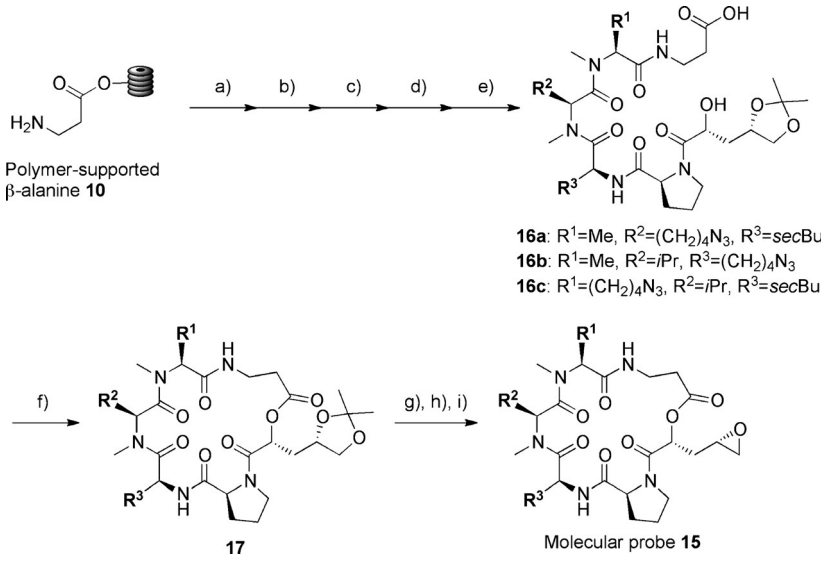


Figure 4. Design of a molecular probe containing an alkyl azido moiety.



Scheme 3. Synthesis of molecular probes **15**. a) i) Fmoc-Ala-OH (for **15a** and **15b**) or Fmoc-*N*-Me-Lys(N_3)-OH (for **15c**) (0.1 M), DIC (0.1 M), HOBt (0.15 M), DMF, RT, 12 h; ii) 20% piperidine/DMF, RT, 1 h; b) i) Fmoc-Me-Val-OH (for **15b** and **15c**) or Fmoc-*N*-Me-Lys(N_3)-OH (for **15a**), PyBroP (0.1 M), DIEA (0.15 M), DMF, RT, 12 h; ii) 20% piperidine/DMF, RT, 1 h; c) i) Fmoc-Ile-OH (for **15a** and **15c**) or Fmoc-Lys(N_3)-OH (for **15b**), PyBroP (0.1 M), DIEA (0.15 M), DMF, RT, 12 h, repeated; ii) 20% piperidine/DMF, RT, 1 h; d) **7** (0.1 M), PyBroP (0.1 M), DIEA (0.15 M), DMF, RT, 12 h; e) i) TBAF, THF, 0 °C, 4 h; ii) 30% HFIP/CH_2Cl_2, RT, 1 h; f) MNBA, DMAPO, CH_2Cl_2, RT, 30 °C, 48 h; g) aqueous 1 M HCl, dioxane/H_2O (1:2), 0 °C, 1 h; h) TsCl, NEt_3, DMAP, CH_2Cl_2, RT, 12 h; i) K_2CO_3, *i*PrOH/$(CH_2Cl)_2$, 50 °C, 12 h.

recorded on JEOL JNM-ECA600 spectrometers in the indicated solvent. Chemical shifts (δ) are reported in ppm relative to the signal for internal tetramethylsilane (TMS; $\delta = 0$ ppm for ^{1}H) for solutions in $CDCl_3$ or residual protonated solvent: $CDCl_3$ (7.26 ppm for ^{1}H or $\delta = 77.0$ ppm for ^{13}C) or [D_6]DMSO ($\delta = 2.49$ ppm for ^{1}H). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet) dd (doublet of doublet), dt (doublet of triplet), dquin (doublet of quintet), ddd (doublet of doublet of doublet), brt (broad triplet); coupling constants, *J*, are given in Hz. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. Only the strongest and/or structurally important absorptions are recorded in cm^{-1}. Optical rotations were measured on a JASCO P-1000 polarimeter. Melting points were recorded on a Round Science RFS-10 instrument and are uncorrected. Mass spectra (FAB) and high-resolution mass spectra (FAB) were measured on JEOL JMS-DX303 and JMS-700 instruments. Preparative HPLC purification was performed on reversed-phase HPLC (Waters HPLC system), and the purity was determined with peak area at $\lambda = 214$ nm. The column used was an X Bridge C18 5 μm, 10×150 mm (Waters) column. The gradient method was as follows: 10% B (0.00–1.00 min) 10–90% B (1.00–13.0 min), 90% B (13.0–18.0 min), 95–10% B (18.0–19.0 min), 10% B (19.0–22.0 min) (A: 0.100% $HCOOH/H_2O$, B: 0.100% HCOOH/MeOH).

General procedure I: Macrolactonization of 8

DMAPO (2.00 equiv) and MNBA (3.00 equiv) were added to a solution of crude cyclization precursor **8** (1 equiv) in dry CH_2Cl_2 (3.00 mM) at room temperature under an argon atmosphere. After being stirred at 30 °C for 48 h, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$. The or-

ganic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with $CHCl_3$/MeOH = 40:1) and preparative HPLC to afford macrolatone **9** as a colorless oil.

Compound 9a {*1*, *1*, *1*}: Yield: 38% from polymer-supported H-βAla-OH **10** (26.0 mg, 39.9 μmol); $[\alpha]_D^{24} = -216$ ($c = 0.606$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.19$ (d, $J = 7.8$ Hz, 1H), 7.14 (d, $J = 9.3$ Hz, 1H), 5.15 (q, $J = 6.8$ Hz, 1H), 5.05 (dd, $J = 5.9$, 8.0 Hz, 1H), 4.96 (d, $J = 11.0$ Hz, 1H), 4.89 (dd, $J = 6.3$, 9.0 Hz, 1H), 4.68 (d, $J = 6.8$ Hz, 1H), 4.00–4.11 (m, 3H), 3.90 (brt, $J = 7.6$ Hz, 1H), 3.75–3.81 (m, 1H), 3.62 (t, $J = 6.3$ Hz, 1H), 3.22 (s, 3H), 3.08 (brt, $J = 12.7$ Hz, 1H), 2.72 (s, 3H), 2.47–2.67 (m, 3H), 2.27–2.37 (m, 1H), 1.88–2.19 (m, 5H), 1.42 (s, 3H), 1.32 (s, 3H), 1.30 (d, $J = 6.8$ Hz, 3H), 1.25–1.42 (m, 2H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H), 0.85 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.5$, 173.4, 171.0, 170.8, 169.7, 168.9, 109.2, 71.6, 70.8, 69.1, 60.8, 58.0, 55.5, 53.4, 46.4, 37.5, 34.5, 34.4, 33.2, 30.8, 29.2, 28.1, 27.2, 26.8, 25.5, 24.3, 23.9, 20.0, 19.6, 15.4, 15.1, 11.4 ppm; IR (neat): $\tilde{\nu} = 2966$, 1732, 1668, 1627, 1520, 1446, 1379, 1180 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{32}H_{54}N_5O_9$ $[M+H]^+$: 652.3916; found: 652.3898.

Compound 9b {*1*, *2*, *1*}: Yield: 27% from polymer-supported H-βAla-OH **10** (18.9 mg, 28.4 μmol); $[\alpha]_D^{24} = -187$ ($c = 0.350$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.21$ (d, $J = 8.8$ Hz, 1H), 7.14 (d, $J = 8.8$ Hz, 1H), 5.14 (q, $J = 6.8$ Hz, 1H), 5.06 (t, $J = 6.8$ Hz, 1H), 5.04 (d, $J = 11.2$ Hz, 1H), 4.89 (dd, $J = 6.8$, 8.8 Hz, 1H), 4.68 (d, $J = 6.8$ Hz, 1H), 4.00–4.12 (m, 3H), 3.91 (t, $J = 8.0$ Hz, 1H), 3.75–3.82 (m, 1H), 3.62 (t, $J = 6.8$ Hz, 1H), 3.20 (s, 3H), 3.08 (brt, $J = 13.2$ Hz, 1H), 2.72 (s, 3H), 2.50–2.65 (m, 2H), 2.46 (d, $J = 6.0$ Hz, 1H), 2.11–2.20 (m, 2H), 2.03–2.10 (m, 2H), 1.84–2.00 (m, 5H), 1.42 (s, 3H), 1.32 (s, 3H), 1.30 (d, $J = 6.8$ Hz, 3H), 1.25–1.32 (m, 2H), 0.92 (d, $J = 5.6$ Hz, 3H), 0.87 (t, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.85 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.5$, 173.4, 171.1, 170.9, 169.7, 168.9, 109.2, 71.6, 70.8, 69.1, 60.8, 56.7, 55.5, 53.6, 46.4, 37.5, 34.6, 34.5, 33.5, 33.2, 31.0, 29.3, 28.1, 26.9, 25.7, 25.5, 24.4, 23.9, 16.2, 15.4, 15.2, 11.4, 11.0 ppm; IR (neat): $\tilde{\nu} = 3383$, 3295, 2965, 2934, 2878, 1731, 1667, 1629, 1518, 1445, 1413, 1380, 1230, 1179, 1106, 1059 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{33}H_{55}N_5O_9$ $[M+H]^+$: 666.4078; found: 666.4091.

Compound 9c {*1*, *3*, *1*}: Yield: 26% from polymer-supported H-βAla-OH **10** (19.1 mg, 27.3 μmol); $[\alpha]_D^{24} = -146$ ($c = 0.560$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.25$ (d, $J = 7.2$ Hz, 1H), 7.14–7.30 (m, 5H), 7.11 (d, $J = 9.2$ Hz, 1H), 5.39 (dd, $J = 4.0$, 12.0 Hz, 1H), 5.04 (dd, $J = 6.0$, 8.0 Hz, 1H), 4.98 (dd, $J = 6.4$, 9.2 Hz, 1H), 4.70 (d, $J = 6.8$ Hz, 1H), 4.66 (q, $J = 6.8$ Hz, 1H), 4.02–4.12 (m, 2H), 3.88–3.98 (m, 2H), 3.75–3.84 (m, 1H), 3.62 (t, $J = 6.4$ Hz, 1H), 3.35 (s, 3H), 3.22–3.38 (m, 1H), 3.05 (brt, $J = 13.2$ Hz, 1H), 2.92 (dd, $J = 4.0$, 12.0 Hz, 1H), 2.56 (s, 3H), 2.51–2.66 (m, 2H), 2.46 (d, $J = 6.8$ Hz, 1H), 2.11–2.18 (m, 2H), 2.05–2.10 (m, 2H), 1.93–2.01 (m, 1H), 1.81–1.90 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 1.22–1.30 (m, 2H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.86 (t, $J = 6.8$ Hz, 3H), 0.18 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.3$, 172.6, 170.9, 170.7, 169.8, 168.9, 136.0, 129.5, 128.9, 127.3, 109.2, 71.6, 70.6, 69.1, 60.8, 55.6, 53.9, 53.2, 46.4, 37.7, 36.5, 34.5, 34.4, 33.2, 31.5, 29.5, 28.0, 26.8, 25.5, 24.3, 23.9, 15.6, 13.1, 11.3 ppm; IR (neat): $\tilde{\nu} = 3383$, 3305, 2965, 2935, 2878, 1731, 1664, 1636, 1518, 1493, 1448, 1412, 1379, 1337, 1228, 1191, 1109, 1060, 752, 702, 679 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{36}H_{54}N_5O_9$ $[M+H]^+$: 700.3922; found: 700.3911.

Compound 9d {*2*, *1*, *1*}: Yield: 15% from polymer-supported H-βAla-OH **10** (10.6 mg, 15.6 μmol); $[\alpha]_D^{24} = -133$ ($c = 0.230$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.10$ (d, $J = 10.0$ Hz, 1H), 7.15 (d, $J = 8.8$ Hz, 1H), 5.24 (d, $J = 10.8$ Hz, 1H), 5.10 (dd, $J = 6.0$, 8.8 Hz, 1H), 4.63–4.70 (m, 2H), 4.37 (d, $J = 10.4$ Hz, 1H), 4.05–4.13 (m, 2H), 3.97–4.04 (m, 1H), 3.95 (t, $J = 8.0$ Hz, 1H), 3.75–3.83 (m, 1H), 3.62 (t, $J = 6.8$ Hz, 1H), 3.15 (s, 3H), 3.12 (brt, $J = 12.4$ Hz, 1H), 2.94 (s, 3H), 2.67 (dd, $J = 5.6$, 18.4 Hz, 1H), 2.53 (dd, $J = 10.0$, 18.4 Hz, 1H), 2.40–2.47 (m, 2H), 2.33–2.38 (m, 1H), 2.15–2.24 (m, 1H), 2.05–2.13 (m, 1H), 1.93–2.04 (m, 4H), 1.47–1.54 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 1.24–1.32 (m, 1H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.90 (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 3H), 0.84 (d, $J = 7.2$ Hz, 3H), 0.78 ppm (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.6$, 173.2, 171.3, 170.6, 169.3, 168.5, 109.3, 71.5, 71.3, 69.2, 65.9, 60.8, 56.8, 53.7, 46.4, 37.3, 34.5, 34.1, 32.9, 30.5, 29.2, 29.1, 28.6, 27.2, 26.9, 25.7, 25.5, 24.0, 20.4, 19.8, 19.3, 18.7, 14.4, 11.0 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3386$, 3276, 2966, 2933, 2879, 1727, 1672, 1626, 1519, 1446, 1414, 1380, 1224, 1181, 1059, 751 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{34}H_{58}N_5O_9$ $[M+H]^+$: 680.4235; found: 680.4242.

Compound 9e {*2*, *2*, *1*}: Yield: 7.0% from polymer-supported H-βAla-OH **10** (5.1 mg, 7.35 μmol); $[\alpha]_D^{24} = -160$ ($c = 0.230$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.11$ (d, $J = 10.0$ Hz, 1H), 7.15 (d, $J = 8.8$ Hz, 1H), 5.29 (d, $J = 10.8$ Hz, 1H), 5.10 (dd, $J = 6.0$, 8.4 Hz, 1H), 4.69 (d, $J = 6.4$ Hz, 1H), 4.66 (t, $J = 8.8$ Hz, 1H), 4.36 (d, $J = 10.4$ Hz, 1H), 3.97–4.12 (m, 3H), 3.93 (t, $J = 8.4$ Hz, 1H), 3.75–3.83 (m, 1H), 3.62 (t, $J = 6.4$ Hz, 1H), 3.13 (s, 3H), 3.04–3.17 (m, 1H), 2.94 (s, 3H), 2.67 (dd, $J = 5.6$, 18.0 Hz, 1H), 2.53 (dd, $J = 10.0$, 18.0 Hz, 1H), 2.33–2.47 (m, 2H), 2.15–2.24 (m, 3H), 2.06–2.15 (m, 2H), 1.93–2.05 (m, 2H), 1.46–1.54 (m, 1H), 1.42 (s, 3H), 1.33–1.41 (m, 1H), 1.33 (s, 3H), 1.24–1.32 (m, 1H), 0.96–1.07 (m, 1H), 0.94 (d, $J = 6.8$ Hz, 3H), 0.89 (t, $J = 7.2$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H), 0.86 (t, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.4$ Hz, 3H), 0.78 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.7$, 173.1, 171.4, 170.7, 169.4, 168.7, 109.3, 71.5, 71.3, 69.2, 65.9, 60.8, 55.5, 53.7, 46.5, 37.3, 34.5, 34.1, 33.4, 33.0, 30.6, 29.3, 29.2, 28.6, 26.9, 25.7, 25.5, 24.7, 24.0, 19.8, 19.3, 16.6, 14.4, 11.1, 11.0 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3383$, 3271, 2966, 2933, 2877, 1727, 1671, 1625, 1522, 1449, 1413, 1380, 1225, 1180, 1077, 1059, 848, 751 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{35}H_{60}N_5O_9$ $[M+H]^+$: 694.4391; found: 694.4388.

Compound 9f {*2*, *3*, *1*}: Yield: 26% from polymer-supported H-βAla-OH **10** (19.9 mg, 27.3 μmol); $[\alpha]_D^{25} = -163$ ($c = 0.650$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.36$ (d, $J = 9.2$ Hz, 1H), 7.17–7.31 (m, 5H), 7.14 (d, $J = 9.2$ Hz, 1H), 5.81 (dd, $J = 6.8$, 8.4 Hz, 1H), 5.08 (dd, $J = 6.0$, 8.0 Hz, 1H), 4.84 (dd, $J = 6.4$, 9.2 Hz, 1H), 4.72 (d, $J = 6.8$ Hz, 1H), 4.35 (d, $J = 10.4$ Hz, 1H), 4.03–4.14 (m, 3H), 3.90 (t, $J = 8.0$ Hz, 1H), 3.76–3.84 (m, 1H), 3.63 (t, $J = 6.8$ Hz, 1H), 3.21–3.27 (m, 2H), 3.20 (s, 3H), 3.08–3.19 (m, 1H), 2.80 (s, 3H), 2.55–2.67 (m, 2H), 2.46 (d, $J = 6.4$ Hz, 1H), 2.23–2.31 (m, 1H), 2.08–2.21 (m, 2H), 2.01–2.08 (m, 1H), 1.91–1.99 (m, 2H), 1.83–1.90 (m, 1H), 1.43 (s, 3H), 1.36–1.47 (m, 1H), 1.33 (s, 3H), 1.20–1.32 (m, 1H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H), 0.84 (t, $J = 7.2$ Hz, 3H), 0.49 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.4$, 172.8, 171.4, 170.5, 168.9, 168.6, 136.0, 128.9, 128.5, 127.0, 109.2, 71.5, 70.9, 69.1, 66.3, 60.7, 53.4, 51.3, 46.3, 37.6, 35.0, 34.5, 34.4, 32.8, 31.7, 29.3, 29.0, 27.1, 26.8, 25.5, 24.3, 23.8, 19.6, 18.4, 15.4, 11.3 ppm; IR (neat): $\tilde{\nu} = 3386$, 3299, 2964, 2934, 2876, 1731, 1671, 1629, 1519, 1499, 1446, 1412, 1381, 1370, 1337, 1222, 1181, 1103, 1059, 754, 701 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{38}H_{58}N_5O_9$ $[M+H]^+$: 728.4235; found: 728.4213.

Compound 9g {*3*, *1*, *1*}: Yield: 23% from polymer-supported H-βAla-OH **10** (16.9 mg, 24.4 μmol); $[\alpha]_D^{24} = -195$ ($c = 0.845$, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, J = 9.6 Hz, 1H), 7.17 (d, J = 9.2 Hz, 1H), 5.06 (dd, J = 6.0, 8.0 Hz, 1H), 5.00 (d, J = 10.8 Hz, 1H), 4.94 (dd, J = 6.0, 9.2 Hz, 1H), 4.89 (dd, J = 2.0, 11.6 Hz, 1H), 4.72 (d, J = 6.8 Hz, 1H), 4.03–4.16 (m, 3H), 3.89 (t, J = 8.0 Hz, 1H), 3.76–3.84 (m, 1H), 3.63 (t, J = 6.8 Hz, 1H), 3.22 (s, 3H), 3.09 (brt, J = 12.0 Hz, 1H), 2.76 (s, 3H), 2.56–2.64 (m, 2H), 2.50 (d, J = 6.4 Hz, 1H), 2.36–2.41 (m, 1H), 2.29–2.36 (m, 1H), 2.09–2.21 (m, 2H), 2.01–2.08 (m, 1H), 1.93–2.00 (m, 2H), 1.85–1.90 (m, 1H), 1.47–1.58 (m, 1H), 1.42 (s, 3H), 1.33–1.42 (m, 1H), 1.33 (s, 3H), 1.25–1.32 (m, 1H), 0.99–1.05 (m, 1H), 0.97 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 6H), 0.90 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.83 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 173.1, 170.7, 170.6, 168.8, 168.6, 109.2, 71.6, 70.8, 69.1, 60.7, 58.6, 57.7, 53.5, 46.3, 39.2, 37.5, 34.5, 34.4, 32.8, 30.8, 29.3, 28.7, 27.4, 26.8, 25.6, 25.5, 24.2, 23.8, 23.6, 22.5, 20.0, 19.7, 15.5, 11.4 ppm; IR (neat): $\tilde{\nu}$ = 3387, 3299, 2962, 2936, 2875, 1732, 1673, 1634, 1516, 1446, 1414, 1380, 1370, 1343, 1218, 1181, 1061, 751 cm^{-1}; HRMS (FAB): m/z calcd for $C_{35}H_{60}N_5O_9$ $[M+H]^+$: 694.4391; found: 694.4376.

Compound 9h {***3***, ***2***, ***1***}: Yield: 32% from polymer-supported H-βAla-OH **10** (23.5 mg, 33.2 μmol); $[\alpha]_D^{25}$ = −162 (c = 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, J = 10.0 Hz, 1H), 7.16 (d, J = 9.2 Hz, 1H), 5.09 (d, J = 10.8 Hz, 1H), 5.07 (dd, J = 6.0, 8.0 Hz, 1H), 4.93 (dd, J = 6.4, 9.2 Hz, 1H), 4.89 (d, J = 12.0 Hz, 1H), 4.72 (d, J = 6.8 Hz, 1H), 4.03–4.17 (m, 3H), 3.89 (t, J = 8.0 Hz, 1H), 3.76–3.84 (m, 1H), 3.62 (t, J = 6.4 Hz, 1H), 3.20 (s, 3H), 3.09 (brt, J = 12.0 Hz, 1H), 2.76 (s, 3H), 2.57–2.64 (m, 2H), 2.47 (d, J = 6.0 Hz, 1H), 2.38 (dt, J = 4.0, 12.8 Hz, 1H), 2.11–2.22 (m, 3H), 2.04–2.11 (m, 2H), 1.92–2.00 (m, 1H), 1.83–1.91 (m, 1H), 1.47–1.58 (m, 1H), 1.42 (s, 3H), 1.38–1.47 (m, 2H), 1.33 (s, 3H), 1.25–1.32 (m, 1H), 0.97–1.05 (m, 2H), 0.97 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 0.91 (t, J = 7.6 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.83 ppm (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 173.1, 170.7, 170.6, 168.8, 168.6, 109.2, 71.6, 70.8, 69.1, 60.7, 58.6, 56.1, 53.5, 46.3, 39.2, 37.5, 34.5, 34.4, 33.4, 32.9, 30.9, 29.3, 28.7, 26.9, 25.7, 25.6, 25.5, 24.3, 23.8, 23.6, 22.5, 16.7, 15.4, 11.4, 10.7 ppm; IR (neat): $\tilde{\nu}$ = 3385, 3299, 2962, 2934, 2875, 1731, 1672, 1630, 1515, 1446, 1413, 1380, 1370, 1347, 1219, 1181, 1061, 752 cm^{-1}; HRMS (FAB): m/z calcd for $C_{36}H_{62}N_5O_9$ $[M+H]^+$: 708.4548; found: 708.4543.

Compound 9i {***3***, ***3***, ***1***}: Yield: 49% from polymer-supported H-βAla-OH **10** (37.9 mg, 51.1 μmol); $[\alpha]_D^{24}$ = −143 (c = 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, J = 9.2 Hz, 1H), 7.15–7.31 (m, 5H), 7.14 (d, J = 9.2 Hz, 1H), 5.48 (dd, J = 5.6, 10.8 Hz, 1H), 5.06 (t, J = 8.0 Hz, 1H), 4.97 (dd, J = 6.0, 9.2 Hz, 1H), 4.73 (d, J = 6.4 Hz, 1H), 4.65 (dd, J = 3.6, 6.8 Hz, 1H), 3.99–4.12 (m, 4H), 3.89 (t, J = 7.6 Hz, 1H), 3.76–3.85 (m, 1H), 3.62 (t, J = 6.4 Hz, 1H), 3.33–3.41 (m, 1H), 3.30 (s, 3H), 3.05 (brt, J = 12.0 Hz, 1H), 2.92 (dd, J = 4.0, 14.0 Hz, 1H), 2.67 (s, 3H), 2.48–2.57 (m, 3H), 2.10–2.22 (m, 2H), 2.05–2.10 (m, 1H), 1.92–1.98 (m, 2H), 1.81–1.91 (m, 1H), 1.72 (dt, J = 5.2, 12.8 Hz, 1H), 1.42 (s, 3H), 1.41–1.45 (m, 1H), 1.33 (s, 3H), 1.30–1.37 (m, 1H), 1.21–1.30 (m, 1H), 0.88 (d, J = 6.8 Hz, 3H), 0.84 (t, J = 7.2 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H), 0.65 (d, J = 6.4 Hz, 3H), −0.31 ppm (ddd, J = 3.6, 8.8, 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 172.5, 170.6, 170.5, 168.8, 168.6, 136.0, 129.3, 128.9, 127.2, 109.2, 71.6, 70.7, 69.0, 60.6, 58.4, 53.4, 53.1, 46.3, 37.6, 37.2, 36.2, 34.5, 34.3, 32.8, 31.4, 29.4, 28.7, 26.8, 25.5, 24.7, 24.1, 23.8, 23.0, 21.8, 15.6, 11.4 ppm; IR (neat): $\tilde{\nu}$ = 3384, 3307, 2960, 2936, 2875, 1731, 1670, 1636, 1518, 1448, 1412, 1380, 1370, 1338, 1218, 1182, 1061, 753, 702 cm^{-1}; HRMS (FAB): m/z calcd for $C_{39}H_{60}N_5O_9$ $[M+H]^+$: 742.4391; found: 742.4374.

Compound 9j {***1***, ***1***, ***2***}: Yield: 34% from polymer-supported H-βAla-OH **10** (24.5 mg, 35.7 μmol); $[\alpha]_D^{29}$ = −132 (c = 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 9.2 Hz, 1H), 7.18–7.30 (m, 5H), 5.30 (q, J = 6.8 Hz, 1H), 5.08–5.15 (m, 1H), 5.07 (t, J = 6.8 Hz, 1H), 5.03 (d, J = 11.2 Hz, 1H), 4.61 (d, J = 7.6 Hz, 1H), 4.03–4.15 (m, 3H), 3.58–3.70 (m, 3H), 3.23 (s, 3H), 3.12–3.19 (m, 1H), 3.01–3.07 (m, 1H), 2.81–2.86 (m, 1H), 2.81 (s, 3H), 2.63–2.69 (m, 2H), 2.28–2.40 (m, 1H), 2.16–2.21 (m, 1H), 2.10–2.16 (m, 2H), 1.70–1.82 (m, 2H), 1.43 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H), 1.32 (s, 3H), 1.22–1.30 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H), 0.88 ppm (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 173.5, 170.7, 170.1, 169.7, 168.5, 136.5, 129.1, 128.4, 126.9, 109.1, 71.6, 70.9, 69.1, 60.3 58.0, 55.3, 51.1, 46.3, 37.5, 34.6, 34.3, 33.2, 30.3, 28.5, 28.1, 27.4, 26.8, 25.5, 23.2, 19.8, 19.3, 15.1 ppm; IR (neat): $\tilde{\nu}$ = 3385, 3307, 2980, 2936, 2879, 1728, 1668, 1634, 1531, 1446, 1414, 1380, 1338, 1228, 1182, 1061, 753, 701 cm^{-1}; HRMS (FAB): m/z calcd for $C_{35}H_{52}N_5O_9$ $[M+H]^+$: 686.3765; found: 686.3765.

Compound 9k {***1***, ***2***, ***2***}: Yield: 33% from polymer-supported H-βAla-OH **10** (24.2 mg, 34.7 μmol); $[\alpha]_D^{29}$ = −152 (c = 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 9.6 Hz, 1H), 7.19–7.30 (m, 5H), 5.29 (q, J = 6.8 Hz, 1H), 5.10–5.15 (m, 1H), 5.10 (d, J = 11.2 Hz, 1H), 5.07 (t, J = 6.8 Hz, 1H), 4.61 (d, J = 7.6 Hz, 1H), 4.05–4.13 (m, 3H), 3.59–3.70 (m, 3H), 3.21 (s, 3H), 3.12–3.20 (m, 1H), 3.03 (dd, J = 4.4, 13.6 Hz, 1H), 2.82 (dd, J = 11.2, 13.6 Hz, 1H), 2.81 (s, 3H), 2.62–2.69 (m, 2H), 2.05–2.21 (m, 3H), 1.71–1.83 (m, 2H), 1.43–1.51 (m, 1H), 1.43 (s, 3H), 1.32 (d, J = 7.2 Hz, 3H), 1.31 (s, 3H), 1.17–1.28 (m, 1H), 0.95–1.05 (m, 1H), 0.92 (t, J = 7.2 Hz, 3H), 0.84 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 173.4, 170.7, 170.2, 169.7, 168.5, 136.6, 129.1, 128.5, 126.9, 109.1, 71.6, 70.9, 69.1, 60.3, 56.6, 55.3, 51.2, 46.3, 37.5, 34.6, 34.3, 33.6, 33.2, 30.4, 28.6, 28.1, 26.8, 25.5, 25.4, 23.2, 16.0, 15.1, 11.0 ppm; IR (neat): $\tilde{\nu}$ = 3388, 3299, 2967, 2936, 2877, 1728, 1670, 1634, 1532, 1445, 1414, 1379, 1340, 1228, 1183, 1061, 753, 701, 665 cm^{-1}; HRMS (FAB): m/z calcd for $C_{36}H_{54}N_5O_9$ $[M+H]^+$: 700.3922; found: 700.3929.

Compound 9l {***1***, ***3***, ***2***}: Yield: 41% from polymer-supported H-βAla-OH **10** (31.6 mg, 43.1 μmol); $[\alpha]_D^{25}$ = −109 (c = 0.825, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.0 Hz, 1H), 7.10–7.30 (m, 11H), 5.47 (dd, J = 4.0, 12.0 Hz, 1H), 5.22 (dt, J = 4.4, 10.0 Hz, 1H), 5.04 (t, J = 6.8 Hz, 1H), 4.84 (q, J = 6.8 Hz, 1H), 4.63 (d, J = 7.2 Hz, 1H), 4.06–4.15 (m, 2H), 3.93–4.01 (m, 1H), 3.58–3.71 (m, 3H), 3.41 (t, J = 12.0 Hz, 1H), 3.35 (s, 3H), 3.07–3.13 (m, 1H), 3.04–3.07 (m, 1H), 2.89 (dd, J = 3.6, 12.0 Hz, 1H), 2.81–2.86 (m, 1H), 2.64 (s, 3H), 2.51–2.63 (m, 2H), 2.15–2.22 (m, 1H), 2.08–2.14 (m, 2H), 1.70–1.83 (m, 2H), 1.42 (s, 3H), 1.32 (s, 3H), 1.17–1.28 (m, 1H), 0.25 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 172.5, 170.5, 170.0, 169.7, 168.7, 136.3, 136.0, 129.4, 129.2, 128.8, 128.5, 127.3, 126.9, 109.1, 71.6, 70.7, 69.0, 60.4, 55.4, 53.8, 50.7, 46.3, 38.0, 36.6, 34.5, 34.3, 33.2, 31.0, 28.8, 28.0, 26.8, 25.4, 23.2, 13.2 ppm; IR (neat): $\tilde{\nu}$ = 3383, 3312, 2985, 2935, 2883, 1728, 1666, 1636, 1532, 1447, 1413, 1379, 1342, 1229, 1182, 1060, 752, 701 cm^{-1}; HRMS (FAB): m/z calcd for $C_{39}H_{52}N_5O_9$ $[M+H]^+$: 734.3765; found: 734.3768.

Compound 9m {***2***, ***1***, ***2***}: Yield: 16% from polymer-supported H-βAla-OH **10** (12.0 mg, 16.8 μmol); $[\alpha]_D^{25}$ = −154 (c = 0.525, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 10.0 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.13–7.30 (m, 5H), 5.25 (d, J = 10.8 Hz, 1H), 5.11 (dd, J = 5.6, 8.8 Hz, 1H), 4.93 (ddd, J = 4.4, 8.8, 11.2 Hz, 1H), 4.63 (d, J = 7.6 Hz, 1H), 4.46 (d, J = 10.8 Hz, 1H), 4.05–4.18 (m, 3H), 3.59–3.75 (m, 3H), 3.24 (brt, J = 12.8 Hz, 1H), 3.17 (s, 3H), 3.01 (s, 3H), 2.90–2.97 (m, 2H), 2.75 (dd, J = 5.6, 18.4 Hz, 1H), 2.56 (dd, J = 10.0,

18.4 Hz, 1H), 2.38–2.50 (m, 2H), 2.14–2.23 (m, 1H), 2.07–2.14 (m, 2H), 1.81–1.87 (m, 1H), 1.70–1.78 (m, 1H), 1.44 (s, 3H), 1.32 (s, 3H), 1.19–1.28 (m, 1H), 0.96 (d, J=6.4 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.87 (d, J=6.4 Hz, 3H), 0.85 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.0, 172.8, 170.6, 170.2, 169.4, 168.2, 136.9, 128.8, 128.5, 126.9, 109.2, 71.5, 71.4, 69.2, 65.6, 60.4, 56.9, 51.8, 46.3, 36.4, 34.4, 34.2, 32.8, 29.7, 29.2, 28.8, 28.2, 27.5, 26.9, 25.5, 23.2, 20.2, 19.6, 19.2, 18.4 ppm; IR ($CHCl_3$): $\tilde{\nu}$=3389, 3301, 2960, 2936, 2873, 1727, 1673, 1635, 1530, 1446, 1413, 1380, 1370, 1221, 1190, 1062, 753, 700 cm^{-1}; HRMS (FAB): m/z calcd for $C_{37}H_{56}N_5O_9$ $[M+H]^+$: 714.4078; found: 714.4078.

Compound 9n {*2*, *2*, *2*}: Yield: 10% from polymer-supported H-βAla-OH **10** (7.6 mg, 10.5 μmol); $[\alpha]_D^{24}$=−168 (c=0.210, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.75 (d, J=10.0 Hz, 1H), 7.36 (d, J=8.8 Hz, 1H), 7.22–7.30 (m, 5H), 5.29 (d, J=10.4 Hz, 1H), 5.11 (dd, J=5.6, 8.0 Hz, 1H), 4.90–4.97 (m, 1H), 4.63 (d, J=8.0 Hz, 1H), 4.46 (d, J=10.8 Hz, 1H), 4.05–4.18 (m, 3H), 3.67–3.74 (m, 1H), 3.59–3.67 (m, 2H), 3.23 (brt, J=12.0 Hz, 1H), 3.16 (s, 3H), 3.01 (s, 3H), 2.85–2.96 (m, 2H), 2.75 (dd, J=5.6, 18.8 Hz, 1H), 2.56 (dd, J=11.2, 18.8 Hz, 1H), 2.37–2.50 (m, 1H), 2.14–2.25 (m, 2H), 2.07–2.14 (m, 2H), 1.79–1.87 (m, 1H), 1.71–1.79 (m, 1H), 1.43 (s, 3H), 1.34–1.41 (m, 1H), 1.32 (s, 3H), 1.17–1.29 (m, 1H), 1.00–1.07 (m, 1H), 0.96 (d, J=6.4 Hz, 3H), 0.90 (t, J=7.2 Hz, 3H), 0.86 (d, J=7.2 Hz, 3H), 0.84 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.0, 172.8, 170.6, 170.3, 169.4, 168.3, 136.9, 128.9, 128.5, 126.9, 109.3, 71.5, 71.4, 69.2, 65.6, 60.4, 55.8, 51.8, 46.3, 36.5, 34.5, 34.3, 33.8, 32.8, 29.8, 29.2, 28.8, 28.3, 26.9, 25.5, 24.6, 23.2, 19.7, 19.2, 16.4, 11.2 ppm; IR (neat): $\tilde{\nu}$=3392, 3286, 2967, 2934, 2877, 1725, 1675, 1629, 1532, 1446, 1414, 1380, 1223, 1184, 1119, 1061, 752, 700 cm^{-1}; HRMS (FAB): m/z calcd for $C_{38}H_{58}N_5O_9$ $[M+H]^+$: 728.4235; found: 728.4255.

Compound 9o {*2*, *3*, *2*}: Yield: 24% from polymer-supported H-βAla-OH **10** (19.2 mg, 25.2 μmol); $[\alpha]_D^{28}$=−118 (c=0.845, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.94 (d, J=9.2 Hz, 1H), 7.36 (d, J=9.2 Hz, 1H), 7.18–7.28 (m, 10H), 5.83 (d, J=7.6 Hz, 1H), 5.07 (dd, J=6.0, 7.6 Hz, 1H), 5.01–5.07 (m, 1H), 4.64 (d, J=7.2 Hz, 1H), 4.41 (d, J=10.8 Hz, 1H), 4.05–4.18 (m, 3H), 3.60–3.68 (m, 3H), 3.34 (dd, J=7.6, 14.4 Hz, 1H), 3.23 (s, 3H), 3.07 (brt, J=14.0 Hz, 1H), 3.07 (dd, J=7.6, 14.4 Hz, 1H), 2.98–3.02 (m, 1H), 2.88 (s, 3H), 2.82–2.88 (m, 1H), 2.70 (dd, J=4.4, 18.8 Hz, 1H), 2.59 (dd, J=11.2, 18.8 Hz, 1H), 2.21–2.28 (m, 1H), 2.07–2.20 (m, 3H), 1.68–1.81 (m, 2H), 1.43 (s, 3H), 1.32 (s, 3H), 1.07–1.20 (m, 1H), 0.84 (d, J=6.4 Hz, 3H), 0.25 ppm (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.8, 172.6, 170.5, 169.8, 168.9, 168.6, 136.6, 136.0, 129.1, 129.0, 128.8, 128.4, 127.1, 126.9, 109.2, 71.5, 71.2, 69.1, 66.0, 60.3, 51.7, 51.2, 46.2, 37.5, 35.7, 34.5, 34.3, 32.8, 30.5, 29.1, 28.6, 27.1, 26.8, 25.5, 23.1, 19.3, 17.7 ppm; IR (neat): $\tilde{\nu}$=3388, 3299, 2963, 2932, 2875, 1726, 1672, 1631, 1530, 1446, 1413, 1380, 1337, 1221, 1189, 1055, 750, 700 cm^{-1}; HRMS (FAB): m/z calcd for $C_{41}H_{56}N_5O_9$ $[M+H]^+$: 762.4078; found: 762.4089.

Compound 9p {*3*, *1*, *2*}: Yield: 49% from polymer-supported H-βAla-OH **10** (38.3 mg, 51.6 μmol); $[\alpha]_D^{24}$=−149 (c=0.800, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.98 (d, J=9.6 Hz, 1H), 7.34 (d, J=9.2 Hz, 1H), 7.15–7.31 (m, 5H), 4.98–5.18 (m, 4H), 4.64 (d, J=7.6 Hz, 1H), 3.99–4.08 (m, 3H), 3.58–3.72 (m, 3H), 3.24 (s, 3H), 3.18 (brt, J=12.8 Hz, 1H), 2.93–3.08 (m, 1H), 2.85 (s, 3H), 2.78–2.85 (m, 1H), 2.58–2.75 (m, 2H), 2.28–2.43 (m, 2H), 2.08–2.20 (m, 3H), 1.66–1.80 (m, 2H), 1.48–1.61 (m, 1H), 1.43 (s, 3H), 1.32 (s, 3H), 1.05–1.20 (m, 1H), 0.99 (d, J=6.4 Hz, 3H), 0.95 (d, J=7.2 Hz, 3H), 0.93 (d, J=6.4 Hz, 3H), 0.90 ppm (d, J=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.7, 173.1, 170.4, 169.8, 168.8, 168.5, 136.6, 129.1, 128.4, 126.8, 109.2, 71.5, 71.0, 69.0, 60.2, 58.3, 57.7, 51.1, 46.1, 39.3, 37.5, 34.5, 34.2, 32.9, 30.3, 28.8, 28.5, 27.5, 26.8, 25.4, 25.3, 23.6, 23.0, 22.6, 19.8, 19.3 ppm; IR (neat): $\tilde{\nu}$=3391, 3291, 2967, 2936, 2878, 1725, 1674, 1630, 1532, 1446, 1414, 1380, 1371, 1345, 1308, 1222, 1185, 1061, 751, 701 cm^{-1}; HRMS (FAB): m/z calcd for $C_{38}H_{58}N_5O_9$ $[M+H]^+$: 728.4235; found: 728.4221.

Compound 9q {*3*, *2*, *2*}: Yield: 48% from polymer-supported H-βAla-OH **10** (37.4 mg, 50.4 μmol); $[\alpha]_D^{24}$=−158 (c=0.675, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.00 (d, J=9.6 Hz, 1H), 7.33 (d, J=8.8 Hz, 1H), 7.21–7.27 (m, 5H), 5.14 (d, J=11.2 Hz, 1H), 5.09–5.13 (m, 1H), 5.08 (t, J=6.8 Hz, 1H), 5.03 (dd, J=3.6, 11.2 Hz, 1H), 4.64 (d, J=7.2 Hz, 1H), 4.12–4.20 (m, 1H), 4.04–4.11 (m, 2H), 3.60–3.69 (m, 3H), 3.22 (s, 3H), 3.18 (brt, J=12.0 Hz, 1H), 2.96–3.03 (m, 1H), 2.85 (s, 3H), 2.81–2.89 (m, 1H), 2.64–2.70 (m, 2H), 2.33 (dt, J=3.6, 11.2 Hz, 1H), 2.15–2.21 (m, 2H), 2.08–2.14 (m, 2H), 1.68–1.82 (m, 3H), 1.45–1.57 (m, 1H), 1.43 (s, 3H), 1.32 (s, 3H), 1.02–1.17 (m, 2H), 0.99 (d, J=6.4 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H), 0.91 (t, J=7.2 Hz, 3H), 0.86 ppm (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.7, 173.1, 170.4, 170.0, 168.9, 168.5, 136.6, 129.1, 128.4, 126.9, 109.2, 71.6, 71.0, 69.0, 60.2, 58.3, 56.0, 51.1, 46.2, 39.3, 37.5, 34.5, 34.3, 33.5, 33.0, 30.4, 28.8, 28.5, 26.8, 25.5, 25.4, 25.3, 23.6, 23.1, 22.6, 16.0, 10.7 ppm; IR (neat): $\tilde{\nu}$=3389, 3302, 2962, 2936, 2875, 1785, 1726, 1676, 1631, 1530, 1449, 1413, 1381, 1370, 1228, 1193, 1110, 1062, 752, 700 cm^{-1}; HRMS (FAB): m/z calcd for $C_{39}H_{60}N_5O_9$ $[M+H]^+$: 742.4391; found: 742.4401.

Compound 9r {*3*, *3*, *2*}: Yield: 28% from polymer-supported H-βAla-OH **10** (23.0 mg, 29.6 μmol); $[\alpha]_D^{26}$=−124 (c=1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.02 (d, J=8.4 Hz, 1H), 7.14–7.32 (m, 11H), 5.56 (dd, J=5.2, 6.8 Hz, 1H), 5.20 (ddd, J=4.4, 9.2, 10.8 Hz, 1H), 5.06 (t, J=7.2 Hz, 1H), 4.76 (q, J=4.0, 10.8 Hz, 1H), 4.65 (d, J=7.2 Hz, 1H), 4.02–4.13 (m, 3H), 3.58–3.67 (m, 3H), 3.41 (t, J=11.6 Hz, 1H), 3.32 (s, 3H), 3.08–3.13 (m, 1H), 3.04 (dd, J=4.4, 14.4 Hz, 1H), 2.87–2.93 (m, 1H), 2.78–2.86 (m, 1H), 2.74 (s, 3H), 2.53–2.64 (m, 2H), 2.15–2.20 (m, 1H), 2.04–2.14 (m, 2H), 1.68–1.81 (m, 3H), 1.43 (s, 3H), 1.32 (s, 3H), 1.20–1.28 (m, 1H), 1.08–1.20 (m, 1H), 0.68 (d, J=6.8 Hz, 1H), 0.67 (d, J=6.4 Hz, 3H), −0.23 ppm (ddd, J=4.0, 8.8, 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.5, 172.5, 170.2, 169.8, 168.7, 168.6, 136.4, 136.1, 129.3, 129.1, 128.9, 128.5, 127.2, 126.9, 109.2, 71.6, 70.8, 69.0, 60.2, 58.4, 53.1, 50.8, 46.2, 37.9, 37.4, 36.4, 34.6, 34.3, 32.8, 30.9, 28.8, 28.7, 26.8, 25.5, 24.8, 23.1, 23.0, 22.0 ppm; IR (neat): $\tilde{\nu}$=3387, 3310, 2955, 2871, 1727, 1671, 1636, 1529, 1448, 1414, 1380, 1338, 1217, 1189, 1059, 753, 701 cm^{-1}; HRMS (FAB): m/z calcd for $C_{42}H_{58}N_5O_9$ $[M+H]^+$: 776.4235; found: 776.4227.

General procedure II: Synthesis of destruxin E analogues 6

A 3 M aqueous solution of HCl (0.500 mL) was added to a solution of macrolactone **9** (1 equiv) in 1,4-dioxane (0.500 mL) and H_2O (0.500 mL). After being stirred at 0 °C for 1 h, the reaction mixture was concentrated in vacuo, and the resulting residue was used in the next reaction without further purification.

TsCl (2.00 equiv) was added to a solution of the crude diol (1 equiv), triethylamine (5.00 equiv), and DMAP (0.100 equiv) in dry CH_2Cl_2 (1.00 mL) at 0 °C under an argon atmosphere. After being stirred at room temperature for 12 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and aqueous layer was extracted with $CHCl_3$. The organic layer was washed with a 1 M aqueous solution of HCl, a saturated aqueous solution of

$NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by flash column chromatography on silica gel (eluted with $CHCl_3$/MeOH = 40:1) to afford tosylate **S3** as a colorless oil. (Data for **S3** are shown in the Supporting Information.)

K_2CO_3 (4.00 equiv) was added to a solution of tosylate **S3** (1 equiv) in *i*PrOH/$(CH_2Cl)_2$ (10:1, 2.00 mL) at 0 °C under an argon atmosphere. After being stirred at 50 °C for 12 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and the aqueous layer was extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by flash column chromatography on silica gel (eluted with $CHCl_3$/MeOH = 40:1) to afford destruxin E derivatives **6** as a colorless oil.

Compound 6a {*1*, *1*, *1*} (destruxin E): Yield (3 steps): 34% (8.1 mg, 13.6 μmol); $[\alpha]_D^{28} = -224$ ($c = 0.200$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$ (d, $J = 8.0$ Hz, 1H), 7.15 (d, $J = 9.2$ Hz, 1H), 5.16 (q, $J = 6.6$ Hz, 1H), 4.99 (t, $J = 7.3$ Hz, 1H), 4.97 (d, $J = 10.9$ Hz, 1H), 4.90 (dd, $J = 6.6$, 9.1 Hz, 1H), 4.69 (d, $J = 7.0$ Hz, 1H), 4.01–4.07 (m, 1H), 3.95 (br t, $J = 8.3$ Hz, 1H), 3.60–3.67 (m, 1H), 3.23 (s, 3H), 3.07 (br t, $J = 12.8$ Hz, 1H), 2.93–2.97 (m, 1H), 2.83 (t, $J = 4.6$ Hz, 1H), 2.72 (s, 3H), 2.63–2.68 (m, 1H), 2.47–2.59 (m, 3H), 2.24–2.35 (m, 2H), 1.81–2.07 (m, 5H), 1.38–1.48 (m, 2H), 1.30 (d, $J = 6.8$ Hz, 3H), 1.27–1.31 (m, 1H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 7.2$ Hz, 3H), 0.85 ppm (t, $J = 7.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.5$, 173.4, 171.0, 170.8, 169.7, 168.6, 70.6, 60.9, 58.0, 55.5, 53.6, 47.8, 47.1, 46.6, 37.4, 34.5, 33.6, 33.1, 31.2, 30.8, 29.6, 29.1, 28.1, 27.2, 24.3, 24.0, 20.0, 19.6, 15.4, 15.1, 11.3 ppm; IR (neat): $\tilde{\nu} =$ 2965, 2929, 1734, 1670, 1629, 1518, 1444, 1179 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{29}H_{48}N_5O_8$ $[M+H]^+$: 594.3497; found: 594.3480.

Compound 6b {*1*, *2*, *1*}: Yield (3 steps): 45% (7.8 mg, 12.8 μmol); $[\alpha]_D^{25} = -211$ ($c = 0.110$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.22$ (d, $J = 8.8$ Hz, 1H), 7.14 (d, $J = 9.2$ Hz, 1H), 5.13 (q, $J = 6.8$ Hz, 1H), 5.04 (d, $J = 11.2$ Hz, 1H), 4.99 (t, $J = 6.8$ Hz, 1H), 4.88 (dd, $J = 6.8$, 10.0 Hz, 1H), 4.69 (d, $J = 6.8$ Hz, 1H), 4.00–4.08 (m, 1H), 3.95 (t, $J = 8.0$ Hz, 1H), 3.62–3.70 (m, 1H), 3.21 (s, 3H), 3.08 (br t, $J = 12.8$ Hz, 1H), 2.93–2.98 (m, 1H), 2.83 (t, $J = 4.8$ Hz, 1H), 2.72 (s, 3H), 2.63–2.68 (m, 1H), 2.51–2.59 (m, 2H), 2.43–2.49 (m, 1H), 2.24–2.32 (m, 1H), 2.03–2.13 (m, 2H), 1.91–2.01 (m, 3H), 1.86–1.91 (m, 1H), 1.50–1.76 (m, 2H), 1.38–1.48 (m, 2H), 1.31 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 5.6$ Hz, 3H), 0.87 (t, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.85 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.6$, 173.5, 171.1, 170.9, 169.7, 168.6, 70.7, 60.9, 56.8, 55.5, 53.7, 47.9, 47.1, 46.7, 37.5, 34.5, 33.7, 33.5, 33.2, 31.0, 29.2, 28.1, 25.8, 24.5, 24.0, 16.2, 15.4, 15.2, 11.4, 11.1 ppm; IR (neat): $\tilde{\nu} = 2964$, 2930, 2876, 1732, 1668, 1633, 1519, 1444, 1380, 1340, 1280, 1257, 1127, 1101 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{30}H_{50}N_5O_8$ $[M+H]^+$: 608.3659; found: 608.3657.

Compound 6c {*1*, *3*, *1*}: Yield (3 steps): 30% (5.2 mg, 8.18 μmol); $[\alpha]_D^{25} = -166$ ($c = 0.115$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.26$ (d, $J = 8.0$ Hz, 1H), 7.15–7.36 (m, 5H), 7.11 (d, $J = 9.2$ Hz, 1H), 5.39 (dd, $J = 4.0$, 12.0 Hz, 1H), 4.93–5.05 (m, 2H), 4.70 (d, $J = 7.6$ Hz, 1H), 4.68 (q, $J = 7.2$ Hz, 1H), 3.88–4.00 (m, 2H), 3.62–3.70 (m, 1H), 3.36 (s, 3H), 3.32–3.39 (m, 1H), 3.04 (br t, $J = 11.2$ Hz, 1H), 2.94–2.98 (m, 1H), 2.92 (dd, $J = 4.0$, 12.0 Hz, 1H), 2.83 (t, $J = 4.0$ Hz, 1H), 2.58–2.68 (m, 1H), 2.56 (s, 3H), 2.49–2.56 (m, 2H), 2.43–2.49 (m, 1H), 2.24–2.32 (m, 1H), 2.04–2.10 (m, 1H), 1.91–2.01 (m, 3H), 1.82–1.90 (m, 1H), 1.38–1.48 (m, 1H), 1.25–1.34 (m, 1H), 0.90 (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 7.2$ Hz, 3H), 0.18 ppm (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 173.3$, 172.6, 170.9, 170.7, 169.8, 168.7, 136.0, 129.5, 128.9, 127.3, 70.5, 60.9, 55.7, 54.0, 53.3, 47.9, 47.1, 46.7, 37.7, 36.6, 34.5, 33.7, 33.2, 31.6, 29.5, 28.1, 24.3, 24.0, 15.6, 13.1, 11.4 ppm; IR (neat): $\tilde{\nu} = 2961$, 2926, 2875, 2849, 1731, 1666, 1634, 1519, 1447, 1380, 1179, 1130, 1102 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{33}H_{48}N_5O_8$ $[M+H]^+$: 642.3503; found: 642.3511.

Compound 6d {*2*, *1*, *1*}: Yield (3 steps): 21% (2.0 mg, 3.22 μmol); $[\alpha]_D^{25} = -233$ ($c = 0.100$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.12$ (d, $J = 9.6$ Hz, 1H), 7.16 (d, $J = 8.8$ Hz, 1H), 5.24 (d, $J = 10.8$ Hz, 1H), 5.05 (t, $J = 7.2$ Hz, 1H), 4.69 (d, $J = 8.4$ Hz, 1H), 4.66 (t, $J = 8.8$ Hz, 1H), 4.38 (d, $J = 10.8$ Hz, 1H), 3.93–4.06 (m, 2H), 3.62–3.70 (m, 1H), 3.15 (s, 3H), 3.08–3.14 (m, 1H), 2.96–3.00 (m, 1H), 2.95 (s, 3H), 2.84 (t, $J = 4.0$ Hz, 1H), 2.61 (dd, $J = 5.2$, 18.0 Hz, 1H), 2.57–2.70 (m, 1H), 2.49–2.57 (m, 1H), 2.37–2.48 (m, 2H), 2.27–2.36 (m, 2H), 2.07–2.13 (m, 2H), 1.93–2.04 (m, 3H), 1.46–1.54 (m, 1H), 1.22–1.34 (m, 1H), 0.94 (d, $J = 6.4$ Hz, 3H), 0.90 (d, $J = 6.4$ Hz, 3H), 0.89 (d, $J = 5.6$ Hz, 3H), 0.88 (d, $J = 7.6$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H), 0.78 ppm (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 173.6$, 173.2, 171.2, 170.6, 169.4, 168.2, 71.2, 65.9, 60.8, 56.7, 53.7, 47.9, 47.2, 46.6, 37.3, 34.1, 33.6, 32.9, 30.5, 29.2, 29.1, 28.6, 27.2, 25.7, 24.1, 20.4, 19.8, 19.3, 18.7, 14.4, 11.0 ppm; IR (neat): $\tilde{\nu} = 2966$, 2930, 2877, 1729, 1671, 1625, 1523, 1448, 1383, 1350, 1224, 1180, 1119, 1077 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{31}H_{52}N_5O_8$ $[M+H]^+$: 622.3816; found: 622.3822.

Compound 6e {*2*, *2*, *1*}: Yield (3 steps): 28% (1.3 mg, 2.04 μmol); $[\alpha]_D^{25} = -250$ ($c = 0.0500$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.14$ (d, $J = 10.0$ Hz, 1H), 7.16 (d, $J = 8.8$ Hz, 1H), 5.29 (d, $J = 10.8$ Hz, 1H), 5.04 (dd, $J = 6.4$, 7.6 Hz, 1H), 4.70 (d, $J = 7.2$ Hz, 1H), 4.66 (t, $J = 8.8$ Hz, 1H), 4.37 (d, $J = 10.4$ Hz, 1H), 3.93–4.06 (m, 2H), 3.62–3.70 (m, 1H), 3.13 (s, 3H), 3.06–3.12 (m, 1H), 2.96–3.00 (m, 1H), 2.95 (s, 3H), 2.84 (t, $J = 4.4$ Hz, 1H), 2.61 (dd, $J = 4.4$, 18.4 Hz, 1H), 2.51–2.60 (m, 2H), 2.35–2.47 (m, 2H), 2.29–2.34 (m, 1H), 2.12–2.21 (m, 1H), 2.03–2.10 (m, 2H), 1.92–2.02 (m, 3H), 1.44–1.54 (m, 1H), 1.22–1.43 (m, 2H), 0.97–1.08 (m, 1H), 0.94 (d, $J = 6.4$ Hz, 3H), 0.90 (t, $J = 7.6$ Hz, 3H), 0.87 (d, $J = 7.6$ Hz, 3H), 0.86 (t, $J = 7.6$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H), 0.78 ppm (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 173.6$, 173.2, 171.2, 170.7, 169.4, 168.3, 71.2, 65.9, 60.8, 55.6, 53.7, 47.9, 47.1, 46.6, 37.4, 34.1, 33.6, 33.5, 32.9, 30.6, 29.2, 29.1, 28.7, 25.7, 24.8, 24.1, 19.9, 19.4, 16.7, 14.4, 11.1, 11.0 ppm; IR (neat): $\tilde{\nu} = 2964$, 2929, 2879, 1728, 1671, 1625, 1523, 1445, 1382, 1225, 1179, 1077 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{32}H_{54}N_5O_8$ $[M+H]^+$: 636.3972; found: 636.3965.

Compound 6f {*2*, *3*, *1*}: Yield (3 steps): 26% (4.7 mg, 7.07 μmol); $[\alpha]_D^{24} = -202$ ($c = 0.155$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.35$ (d, $J = 9.6$ Hz, 1H), 7.16–7.31 (m, 5H), 7.16 (d, $J = 9.2$ Hz, 1H), 5.81 (dd, $J = 6.8$, 8.8 Hz, 1H), 5.01 (d, $J = 6.8$ Hz, 1H), 4.84 (dd, $J = 6.4$, 9.2 Hz, 1H), 4.72 (d, $J = 6.8$ Hz, 1H), 4.36 (d, $J = 10.4$ Hz, 1H), 4.06–4.17 (m, 1H), 3.94 (t, $J = 8.0$ Hz, 1H), 3.62–3.70 (m, 1H), 3.20–3.29 (m, 2H), 3.19 (s, 3H), 3.08–3.16 (m, 1H), 2.94–3.02 (m, 1H), 2.84 (t, $J = 4.4$ Hz, 1H), 2.80 (s, 3H), 2.60–2.68 (m, 2H), 2.57–2.60 (m, 1H), 2.43–2.53 (m, 1H), 2.22–2.36 (m, 2H), 2.03–2.12 (m, 1H), 1.93–2.02 (m, 3H), 1.82–1.91 (m, 1H), 1.36–1.47 (m, 1H), 1.20–1.34 (m, 1H), 0.88 (d, $J = 6.4$ Hz, 3H), 0.84 (t, $J = 7.2$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H), 0.49 ppm (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta =$ 173.4, 172.9, 171.5, 170.5, 168.7, 168.6, 136.1, 128.9, 128.6, 127.1, 70.8, 66.3, 60.8, 53.5, 51.4, 47.9, 47.1, 46.6, 37.6, 35.0, 34.5, 33.6, 32.8, 31.2, 29.2, 29.0, 27.2, 24.4, 24.0, 19.7, 18.5, 15.4, 11.3 ppm; IR (neat): $\tilde{\nu} = 2964$, 2929, 2876, 1731, 1668, 1630, 1519, 1446, 1383, 1180, 1078 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{35}H_{52}N_5O_8$ $[M+H]^+$: 670.3816; found: 670.3815.

Compound 6g {*3*, *1*, *1*}: Yield (3 steps): 15% (2.4 mg, 3.70 μmol); $[\alpha]_D^{25} = -236$ ($c = 0.0950$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.33$ (d, $J = 9.6$ Hz, 1H), 7.18 (d, $J = 9.6$ Hz, 1H), 5.01 (dd, $J = 4.4$, 6.8 Hz, 1H), 4.99 (d, $J = 8.0$ Hz, 1H), 4.93 (dd, $J = 6.4$, 9.6 Hz, 1H), 4.90 (d, $J = 10.0$ Hz, 1H), 4.73 (d, $J = 6.8$ Hz, 1H), 4.09–4.18 (m, 1H), 3.92 (t, $J = 8.8$ Hz, 1H), 3.62–3.70 (m, 1H), 3.22 (s, 3H), 3.05–3.13 (m, 1H), 2.94–3.00 (m, 1H), 2.84 (t, $J = 4.0$ Hz, 1H), 2.76 (s, 3H), 2.59–2.64 (m, 2H), 2.57–2.70 (m, 1H), 2.49–2.57 (m, 1H), 2.57 (dd, $J = 2.4$, 4.0 Hz, 1H), 2.51 (d, $J = 6.4$ Hz, 1H), 2.26–2.42 (m, 2H), 2.04–2.12 (m, 1H), 1.98–2.02 (m, 2H), 1.93–1.98 (m, 2H), 1.83–1.92 (m, 1H), 1.47–1.58 (m, 1H), 1.35–1.43 (m, 1H), 1.22–1.33 (m, 1H), 1.00–1.06 (m, 1H), 0.97 (d, $J = 6.4$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 6H), 0.91 (d, $J = 6.4$ Hz, 3H), 0.84 (d, $J = 7.2$ Hz, 3H), 0.83 ppm (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 173.4$, 173.2, 170.7, 170.6, 168.7, 168.6, 70.8, 60.8, 58.7, 57.8, 53.6, 47.9, 47.0, 46.6, 39.3, 37.6, 34.5, 33.6, 32.9, 30.9, 29.2, 28.7, 27.4, 25.6, 24.3, 23.9, 23.6, 22.6, 20.1, 19.7, 15.5, 11.4 ppm; IR (neat): $\tilde{\nu} = 2962$, 2932, 2875, 1731, 1671, 1630, 1518, 1445, 1382, 1345, 1217, 1181, 1111, 1082 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{32}H_{54}N_5O_8$ $[M+H]^+$: 636.3972; found: 636.3963.

Compound 6h {*3*, *2*, *1*}: Yield (3 steps): 26% (5.6 mg, 8.64 μmol); $[\alpha]_D^{26} = -223$ ($c = 0.185$, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.35$ (d, $J = 10.2$ Hz, 1H), 7.16 (d, $J = 9.6$ Hz, 1H), 5.09 (d, $J = 11.4$ Hz, 1H), 5.01 (t, $J = 7.2$ Hz, 1H), 4.92 (dd, $J = 6.6$, 9.6 Hz, 1H), 4.90 (d, $J = 9.0$ Hz, 1H), 4.73 (d, $J = 6.6$ Hz, 1H), 4.07–4.16 (m, 1H), 3.94 (t, $J = 8.4$ Hz, 1H), 3.60–3.72 (m, 1H), 3.20 (s, 3H), 3.08 (brt, $J = 12.0$ Hz, 1H), 2.94–3.00 (m, 1H), 2.84 (t, $J = 4.8$ Hz, 1H), 2.77 (s, 3H), 2.59–2.64 (m, 2H), 2.57 (dd, $J = 3.6$, 4.8 Hz, 1H), 2.50 (d, $J = 5.4$ Hz, 1H), 2.38 (dt, $J = 4.2$, 12.6 Hz, 1H), 2.27–2.33 (m, 1H), 2.03–2.15 (m, 2H), 1.96–2.00 (m, 1H), 1.92–1.96 (m, 2H), 1.85–1.92 (m, 1H), 1.47–1.55 (m, 1H), 1.35–1.47 (m, 2H), 1.22–1.33 (m, 1H), 0.97–1.05 (m, 2H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.91 (t, $J = 7.2$ Hz, 3H), 0.87 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.6$ Hz, 3H), 0.84 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 173.4$, 173.1, 170.7, 170.6, 168.7, 168.6, 70.7, 60.8, 58.7, 56.2, 53.6, 47.9, 47.0, 46.5, 39.3, 37.6, 34.5, 33.6, 33.5, 32.9, 31.0, 29.2, 28.7, 25.7, 25.6, 24.3, 23.9, 23.6, 22.5, 16.2, 15.4, 11.4, 10.8 ppm; IR (neat): $\tilde{\nu} = 2962$, 2932, 2875, 1731, 1671, 1629, 1517, 1445, 1382, 1180, 1083 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{33}H_{56}N_5O_8$ $[M+H]^+$: 650.4129; found: 650.4141.

Compound 6i {*3*, *3*, *1*}: Yield (3 steps): 11% (3.9 mg, 5.66 μmol); $[\alpha]_D^{23} = -251$ ($c = 0.110$, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.32$ (d, $J = 9.0$ Hz, 1H), 7.15–7.30 (m, 5H), 7.14 (d, $J = 9.0$ Hz, 1H), 5.47 (dd, $J = 5.4$, 10.2 Hz, 1H), 4.99 (t, $J = 7.2$ Hz, 1H), 4.96 (dd, $J = 6.6$, 9.0 Hz, 1H), 4.74 (d, $J = 6.6$ Hz, 1H), 4.66 (dd, $J = 3.6$, 10.8 Hz, 1H), 4.02–4.07 (m, 1H), 3.93 (t, $J = 9.0$ Hz, 1H), 3.62–3.68 (m, 1H), 3.37 (t, $J = 11.4$ Hz, 1H), 3.30 (s, 3H), 3.03 (brt, $J = 10.8$ Hz, 1H), 2.91–3.00 (m, 2H), 2.83 (t, $J = 4.2$ Hz, 1H), 2.67 (s, 3H), 2.49–2.58 (m, 3H), 2.27–2.32 (m, 1H), 2.03–2.13 (m, 2H), 1.96–2.00 (m, 1H), 1.91–1.96 (m, 2H), 1.83–1.90 (m, 1H), 1.73 (dt, $J = 5.4$, 12.6 Hz, 1H), 1.38–1.46 (m, 1H), 1.21–1.32 (m, 2H), 0.88 (d, $J = 6.6$ Hz, 3H), 0.84 (t, $J = 7.2$ Hz, 3H), 0.67 (d, $J = 6.0$ Hz, 3H), 0.65 (d, $J = 6.0$ Hz, 3H), −0.31 ppm (ddd, $J = 3.6$, 9.0, 12.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 173.3$, 172.6, 170.6, 170.5, 168.7, 168.6, 136.1, 129.3, 128.9, 127.2, 70.6, 60.8, 58.5, 53.5, 53.2, 47.9, 47.0, 46.6, 37.7, 37.3, 36.3, 34.6, 33.5, 32.8, 31.5, 29.4, 28.7, 24.8, 24.2, 23.9, 23.0, 21.8, 15.6, 11.4 ppm; IR (neat): $\tilde{\nu} = 2958$, 2925, 2875, 1731, 1670, 1630, 1518, 1448, 1382, 1341, 1180, 1076 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{36}H_{54}N_5O_8$ $[M+H]^+$: 684.3972; found: 684.3964.

Compound 6j {*1*, *1*, *2*}: Yield (3 steps): 27% (6.1 mg, 9.66 μmol); $[\alpha]_D^{27} = -126$ ($c = 0.185$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.86$ (d, $J = 7.6$ Hz, 1H), 7.35 (d, $J = 8.8$ Hz, 1H), 7.21–7.30 (m, 5H), 5.31 (q, $J = 6.8$ Hz, 1H), 5.10 (dt, $J = 4.0$, 8.8 Hz, 1H), 5.02 (d, $J = 12.0$ Hz, 1H), 5.01 (t, $J = 6.8$ Hz, 1H), 4.63 (d, $J = 8.0$ Hz, 1H), 4.05–4.13 (m, 1H), 3.72 (t, $J = 8.8$ Hz, 1H), 3.45–3.53 (m, 1H), 3.23 (s, 3H), 3.16 (brt, $J = 12.4$ Hz, 1H), 3.04 (dd, $J = 4.0$, 13.6 Hz, 1H), 2.96–3.01 (m, 1H), 2.81 (s, 3H), 2.81–2.87 (m, 2H), 2.57 (dd, $J = 2.4$, 4.8 Hz, 1H), 2.30–2.40 (m, 1H), 2.21–2.27 (m, 1H), 2.16–2.21 (m, 1H), 1.98–2.07 (m, 1H), 1.73–1.83 (m, 2H), 1.32 (d, $J = 6.8$ Hz, 3H), 1.17–1.25 (m, 1H), 0.93 (d, $J = 6.4$ Hz, 3H), 0.88 ppm (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 173.6$, 173.5, 170.7, 170.1, 169.7, 168.4, 136.6, 129.1, 128.5, 126.9, 70.8, 60.4, 58.0, 55.3, 51.2, 47.9, 47.1, 46.5, 37.6, 34.6, 33.5, 33.2, 30.3, 28.5, 28.1, 27.4, 23.3, 19.8, 19.3, 15.2 ppm; IR (neat): $\tilde{\nu} = 2965$, 2931, 2875, 1728, 1671, 1631, 1529, 1444, 1379, 1342, 1274, 1227, 1181, 1100 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{32}H_{46}N_5O_8$ $[M+H]^+$: 628.3346; found: 628.3348.

Compound 6k {*1*, *2*, *2*}: Yield (3 steps): 39% (8.6 mg, 13.4 μmol); $[\alpha]_D^{29} = -211$ ($c = 0.225$, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.86$ (d, $J = 8.4$ Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 1H), 7.21–7.30 (m, 5H), 5.30 (q, $J = 7.2$ Hz, 1H), 5.09 (d, $J = 10.8$ Hz, 1H), 5.06–5.12 (m, 1H), 5.01 (t, $J = 7.2$ Hz, 1H), 4.62 (d, $J = 8.4$ Hz, 1H), 4.06–4.13 (m, 1H), 3.72 (t, $J = 7.8$ Hz, 1H), 3.45–3.51 (m, 1H), 3.21 (s, 3H), 3.15 (brt, $J = 12.6$ Hz, 1H), 3.02 (dd, $J = 4.2$, 13.8 Hz, 1H), 2.99 (dt, $J = 4.2$, 7.2 Hz, 1H), 2.81–2.86 (m, 2H), 2.81 (s, 3H), 2.71 (ddd, $J = 1.8$, 12.0, 19.2 Hz, 1H), 2.62 (dd, $J = 2.4$, 19.2 Hz, 1H), 2.57 (dd, $J = 2.4$, 4.8 Hz, 1H), 2.23 (ddd, $J = 4.2$, 7.2, 14.4 Hz, 1H), 2.16–2.21 (m, 1H), 2.07–2.13 (m, 1H), 2.02 (dt, $J = 7.2$, 14.4 Hz, 1H), 1.74–1.82 (m, 2H), 1.43–1.49 (m, 1H), 1.32 (d, $J = 7.2$ Hz, 3H), 1.18–1.27 (m, 1H), 0.96–1.04 (m, 1H), 0.92 (t, $J = 7.2$ Hz, 3H), 0.85 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 173.7$, 173.5, 170.7, 170.1, 169.7, 168.4, 136.6, 129.1, 128.5, 126.9, 70.8, 60.4, 56.6, 55.3, 51.2, 47.9, 47.1, 46.5, 37.5, 34.5, 33.6, 33.5, 33.2, 30.4, 28.5, 28.1, 25.5, 25.3, 16.0, 15.2, 11.0 ppm; IR (neat): $\tilde{\nu} = 2965$, 2933, 2879, 1728, 1671, 1631, 1529, 1444, 1380, 1227, 1181 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{33}H_{48}N_5O_8$ $[M+H]^+$: 642.3503; found: 642.3519.

Compound 6l {*1*, *3*, *2*}: Yield (3 steps): 18% (5.2 mg, 7.64 μmol); $[\alpha]_D^{29} = -197$ ($c = 0.115$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.91$ (d, $J = 7.2$ Hz, 1H), 7.14–7.30 (m, 11H), 5.46 (dd, $J = 4.0$, 12.0 Hz, 1H), 5.21 (dt, $J = 4.4$, 10.0 Hz, 1H), 4.98 (t, $J = 6.8$ Hz, 1H), 4.85 (q, $J = 6.8$ Hz, 1H), 4.63 (d, $J = 8.0$ Hz, 1H), 3.94–4.04 (m, 1H), 3.72 (t, $J = 8.8$ Hz, 1H), 3.48–3.55 (m, 1H), 3.40 (t, $J = 12.0$ Hz, 1H), 3.34 (s, 3H), 3.04–3.13 (m, 2H), 2.95–3.01 (m, 1H), 2.89 (dd, $J = 3.6$, 12.0 Hz, 1H), 2.79–2.86 (m, 3H), 2.64 (s, 3H), 2.52–2.60 (m, 2H), 2.17–2.26 (m, 2H), 2.00 (dt, $J = 3.2$, 14.0 Hz, 1H), 1.73–1.85 (m, 2H), 1.16–1.25 (m, 1H), 0.25 ppm (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 173.5$, 172.6, 170.5, 169.9, 169.7, 168.5, 136.3, 136.1, 129.4, 129.2, 128.9, 128.5, 127.3, 127.0, 70.6, 60.5, 55.4, 53.8, 50.7, 47.9, 47.0, 46.5, 38.0, 36.7, 34.5, 33.5, 33.2, 31.0, 28.7, 28.1, 23.3, 13.2 ppm; IR (neat): $\tilde{\nu} = 2928$, 1729, 1668, 1636, 1529, 1446, 1378, 1345, 1179, 1108, 1079 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{36}H_{46}N_5O_8$ $[M+H]^+$: 676.3346; found: 676.3364.

Compound 6m {*2*, *1*, *2*}: Yield (3 steps): 18% (2.0 mg, 3.06 μmol); $[\alpha]_D^{27} = -211$ ($c = 0.0900$, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.74$ (d, $J = 9.6$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.18–7.30 (m, 5H), 5.24 (d, $J = 10.2$ Hz, 1H), 5.06 (t, $J = 7.2$ Hz, 1H), 4.91–4.96 (m, 1H), 4.64 (d, $J = 7.8$ Hz, 1H), 4.47 (d, $J = 10.8$ Hz, 1H), 4.10–4.18 (m, 1H), 3.76 (t, $J = 9.0$ Hz, 1H), 3.45–3.54 (m, 1H), 3.24 (brt, $J = 11.4$ Hz, 1H), 3.16 (s, 3H), 3.01 (s, 3H), 2.93–3.01 (m, 2H), 2.84 (t, $J = 4.2$ Hz, 1H), 2.75 (dd, $J = 5.4$, 18.6 Hz, 1H), 2.56–2.62 (m, 2H), 2.37–2.47 (m, 2H), 2.27–2.33 (m, 1H), 2.08–2.14 (m, 1H), 1.98–2.04 (m, 1H), 1.81–1.86 (m, 1H), 1.72–1.81 (m, 1H), 1.21–1.29 (m, 1H), 0.97 (d, $J = 6.6$ Hz,

3H), 0.90 (d, $J=6.6$ Hz, 3H), 0.87 (d, $J=7.2$ Hz, 3H), 0.86 ppm (d, $J=8.4$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=174.0$, 172.8, 170.5, 170.3, 169.4, 168.0, 136.9, 128.9, 128.5, 127.0, 71.4, 65.6, 60.5, 57.0, 51.9, 47.9, 47.1, 46.5, 36.5, 34.2, 33.5, 32.8, 29.7, 29.2, 28.7, 28.3, 27.5, 23.3, 20.2, 19.7, 19.2, 18.5 ppm; IR (neat): $\tilde{\nu}=2967$, 2931, 2879, 1725, 1673, 1628, 1531, 1445, 1384, 1338, 1260, 1223, 1184, 1079 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{34}H_{50}N_5O_8$ $[M+H]^+$: 656.3659; found: 656.3655.

Compound 6n {*2*, *2*, *2*}: Yield (3 steps): 28% (2.0 mg, 2.99 μmol); $[\alpha]_D^{28}=-171$ ($c=0.080$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.76$ (d, $J=10.2$ Hz, 1H), 7.37 (d, $J=8.4$ Hz, 1H), 7.21–7.30 (m, 5H), 5.29 (d, $J=10.8$ Hz, 1H), 5.06 (t, $J=7.2$ Hz, 1H), 4.94 (ddd, $J=4.2$, 8.4, 11.4 Hz, 1H), 4.64 (d, $J=7.8$ Hz, 1H), 4.47 (d, $J=10.2$ Hz, 1H), 4.12–4.17 (m, 1H), 3.75 (t, $J=9.0$ Hz, 1H), 3.48–3.55 (m, 1H), 3.23 (brt, $J=12.6$ Hz, 1H), 3.15 (s, 3H), 3.01 (s, 3H), 2.97–3.00 (m, 1H), 2.88–2.96 (m, 2H), 2.84 (t, $J=4.8$ Hz, 1H), 2.74 (dd, $J=5.4$, 18.6 Hz, 1H), 2.59 (ddd, $J=1.8$, 12.0, 18.6 Hz, 1H), 2.58 (dd, $J=3.0$, 4.8 Hz, 1H), 2.38–2.45 (m, 1H), 2.30 (ddd, $J=4.2$, 7.2, 12.0 Hz, 1H), 2.17–2.22 (m, 1H), 2.12 (dd, $J=6.6$, 12.0 Hz, 1H), 2.00 (quin, $J=7.2$ Hz, 1H), 1.80–1.86 (m, 1H), 1.75–1.80 (m, 1H), 1.35–1.42 (m, 1H), 1.22–1.32 (m, 1H), 1.02–1.07 (m, 1H), 0.96 (d, $J=6.0$ Hz, 3H), 0.90 (t, $J=7.2$ Hz, 3H), 0.87 (d, $J=7.2$ Hz, 3H), 0.84 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=174.0$, 172.8, 170.5, 170.3, 169.4, 168.1, 136.9, 128.9, 128.5, 127.0, 71.4, 65.7, 60.5, 55.8, 51.9, 47.9, 47.1, 46.5, 36.5, 34.2, 33.9, 33.5, 32.8, 29.8, 29.2, 28.7, 28.3, 24.7, 23.3, 19.7, 19.3, 16.5, 11.2 ppm; IR (neat): $\tilde{\nu}=2966$, 2931, 2877, 1725, 1671, 1628, 1533, 1445, 1383, 1183, 1077 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{35}H_{52}N_5O_8$ $[M+H]^+$: 670.3816; found: 670.3820.

Compound 6o {*2*, *3*, *2*}: Yield (3 steps): 28% (4.9 mg, 6.97 μmol); $[\alpha]_D^{23}=-155$ ($c=0.140$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.94$ (d, $J=9.6$ Hz, 1H), 7.36 (d, $J=9.2$ Hz, 1H), 7.18–7.29 (m, 10H), 5.83 (t, $J=7.6$ Hz, 1H), 5.02–5.08 (m, 1H), 5.02 (t, $J=6.8$ Hz, 1H), 4.65 (d, $J=7.6$ Hz, 1H), 4.44 (d, $J=10.8$ Hz, 1H), 4.10–4.18 (m, 1H), 3.69 (t, $J=9.6$ Hz, 1H), 3.44–3.52 (m, 1H), 3.33 (dd, $J=7.6$, 14.4 Hz, 1H), 3.21 (s, 3H), 3.20 (brt, $J=14.8$ Hz, 1H), 3.08 (dd, $J=8.0$, 14.4 Hz, 1H), 2.97–3.04 (m, 2H), 2.88 (s, 3H), 2.84–2.88 (m, 1H), 2.84 (t, $J=4.8$ Hz, 1H), 2.62–2.75 (m, 2H), 2.58 (dd, $J=2.4$, 4.8 Hz, 1H), 2.26–2.30 (m, 1H), 2.22–2.26 (m, 1H), 2.15–2.22 (m, 1H), 2.02 (dt, $J=6.8$, 14.8 Hz, 1H), 1.71–1.80 (m, 2H), 1.12–1.21 (m, 1H), 0.85 (d, $J=6.4$ Hz, 3H), 0.27 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=173.8$, 172.7, 170.5, 169.7, 168.9, 168.4, 136.6, 136.1, 129.1, 129.0, 128.8, 128.5, 127.1, 126.9, 71.0, 66.0, 60.4, 51.7, 51.3, 47.9, 47.0, 46.4, 37.5, 35.7, 34.5, 33.4, 32.8, 30.5, 29.1, 28.5, 27.1, 23.2, 19.4, 17.8 ppm; IR (neat): $\tilde{\nu}=2964$, 2927, 2879, 1726, 1671, 1630, 1532, 1446, 1384, 1222, 1182, 1077 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{38}H_{50}N_5O_8$ $[M+H]^+$: 704.3659; found: 704.3648.

Compound 6p {*3*, *1*, *2*}: Yield (3 steps): 5% (1.6 mg, 2.32 μmol); $[\alpha]_D^{25}=-186$ ($c=0.0450$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.98$ (d, $J=9.0$ Hz, 1H), 7.34 (d, $J=9.0$ Hz, 1H), 7.18–7.32 (m, 5H), 5.11–5.16 (m, 1H), 5.05 (d, $J=10.8$ Hz, 1H), 5.04 (d, $J=11.4$ Hz, 1H), 5.02 (t, $J=7.2$ Hz, 1H), 4.65 (d, $J=6.6$ Hz, 1H), 4.13–4.18 (m, 1H), 3.68 (t, $J=9.6$ Hz, 1H), 3.45–3.53 (m, 1H), 3.23 (s, 3H), 3.18 (brt, $J=12.0$ Hz, 1H), 2.97–3.03 (m, 2H), 2.85 (s, 3H), 2.84 (t, $J=4.2$ Hz, 1H), 2.82–2.85 (m, 1H), 2.62–2.70 (m, 1H), 2.56–2.59 (m, 1H), 2.41–2.47 (m, 1H), 2.29–2.41 (m, 1H), 2.22–2.28 (m, 1H), 2.17–2.22 (m, 1H), 2.00–2.06 (m, 1H), 1.72–1.78 (m, 2H), 1.51–1.57 (m, 1H), 1.08–1.18 (m, 2H), 0.99 (d, $J=6.0$ Hz, 3H), 0.95 (d, $J=5.4$ Hz, 3H), 0.94 (d, $J=6.6$ Hz, 3H), 0.90 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=173.7$, 173.2, 170.4, 169.8, 168.9, 168.4, 136.7, 129.1, 128.5, 126.9, 70.9, 60.3, 58.4, 57.8, 51.2, 48.0, 47.0, 46.4, 39.3, 37.6, 34.5, 33.4, 33.0, 30.3, 28.8, 28.4, 27.5, 25.4, 23.6, 23.2, 22.7, 19.9, 19.4 ppm; IR (neat): $\tilde{\nu}=2959$, 2924, 2873, 1727, 1674, 1634, 1531, 1446, 1383, 1343, 1275, 1182, 1081 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{35}H_{52}N_5O_8$ $[M+H]^+$: 670.3816; found: 670.3818.

Compound 6q {*3*, *2*, *2*}: Yield (3 steps): 10% (3.6 mg, 5.20 μmol); $[\alpha]_D^{23}=-194$ ($c=0.0900$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.99$ (d, $J=9.6$ Hz, 1H), 7.33 (d, $J=8.4$ Hz, 1H), 7.21–7.30 (m, 5H), 5.14 (d, $J=10.8$ Hz, 1H), 5.10–5.14 (m, 1H), 5.05 (dd, $J=3.6$, 11.4 Hz, 1H), 5.02 (t, $J=5.4$ Hz, 1H), 4.65 (d, $J=7.8$ Hz, 1H), 4.12–4.17 (m, 1H), 3.66 (t, $J=9.6$ Hz, 1H), 3.44–3.50 (m, 1H), 3.21 (s, 3H), 3.19 (brt, $J=12.6$ Hz, 1H), 2.97–3.04 (m, 2H), 2.85 (s, 3H), 2.84 (t, $J=4.8$ Hz, 1H), 2.80–2.84 (m, 1H), 2.62–2.75 (m, 2H), 2.57 (dd, $J=2.4$, 4.8 Hz, 1H), 2.33 (dt, $J=4.8$, 12.0 Hz, 1H), 2.23–2.28 (m, 1H), 2.13–2.21 (m, 2H), 1.99–2.05 (m, 1H), 1.71–1.79 (m, 2H), 1.48–1.55 (m, 1H), 1.42–1.47 (m, 1H), 1.20–1.27 (m, 1H), 1.00–1.17 (m, 2H), 0.99 (d, $J=6.6$ Hz, 3H), 0.95 (d, $J=6.6$ Hz, 3H), 0.91 (t, $J=7.2$ Hz, 3H), 0.86 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=173.7$, 173.1, 170.4, 170.0, 168.9, 168.4, 136.7, 129.1, 128.5, 126.9, 70.9, 60.3, 58.4, 56.1, 51.2, 48.0, 47.0, 46.4, 39.3, 37.5, 34.5, 33.5, 33.4, 33.0, 30.4, 28.8, 28.4, 25.4, 25.3, 23.6, 23.2, 22.6, 16.0, 10.7 ppm; IR (neat): $\tilde{\nu}=2960$, 2929, 2875, 1727, 1674, 1633, 1531, 1446, 1383, 1188, 1081 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{36}H_{54}N_5O_8$ $[M+H]^+$: 684.3972; found: 684.3984.

Compound 6r {*3*, *3*, *2*}: Yield (3 steps): 34% (7.3 mg, 10.1 μmol); $[\alpha]_D^{23}=-96.9$ ($c=0.235$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.02$ (d, $J=9.2$ Hz, 1H), 7.16–7.34 (m, 11H), 5.55 (dd, $J=4.8$, 10.4 Hz, 1H), 5.19 (dt, $J=4.0$, 10.0 Hz, 1H), 4.99 (t, $J=7.2$ Hz, 1H), 4.77 (dd, $J=4.0$, 10.8 Hz, 1H), 4.66 (d, $J=7.6$ Hz, 1H), 4.02–4.13 (m, 1H), 3.66 (t, $J=9.2$ Hz, 1H), 3.42–3.52 (m, 1H), 3.42 (t, $J=11.6$ Hz, 1H), 3.32 (s, 3H), 3.12 (brt, $J=12.0$ Hz, 1H), 3.03 (dd, $J=4.0$, 14.0 Hz, 1H), 2.96–3.03 (m, 1H), 2.88–2.93 (m, 1H), 2.83 (t, $J=4.4$ Hz, 1H), 2.79–2.83 (m, 1H), 2.74 (s, 3H), 2.58–2.64 (m, 2H), 2.57 (dd, $J=2.8$, 4.4 Hz, 1H), 2.17–2.28 (m, 2H), 2.02 (dt, $J=7.2$, 14.4 Hz, 1H), 1.68–1.82 (m, 3H), 1.17–1.25 (m, 1H), 1.07–1.25 (m, 1H), 0.67 (d, $J=6.8$ Hz, 3H), 0.66 (d, $J=6.4$ Hz, 3H), −0.25 ppm (ddd, $J=4.0$, 8.4, 13.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=173.6$, 172.5, 170.2, 169.8, 168.8, 168.4, 136.5, 136.1, 129.4, 129.2, 128.9, 128.5, 127.2, 126.9, 70.7, 60.3, 58.4, 53.1, 50.9, 48.0, 47.0, 46.4, 37.9, 37.4, 36.5, 34.6, 33.4, 32.9, 30.9, 28.8, 28.6, 24.8, 23.1, 23.0, 22.0 ppm; IR (neat): $\tilde{\nu}=2955$, 2928, 2871, 1728, 1671, 1633, 1530, 1445, 1382, 1181, 1078 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{39}H_{52}N_5O_8$ $[M+H]^+$: 718.3816; found: 718.3819.

General procedure III: Macrolactonization of 16

The synthesis of macrolactone **17** from **16** was performed in the same manner as that used for the synthesis of **9**; see general procedure I.

Compound 17a: Yield: 33% from polymer-supported H-βAla-OH **10** (8.2 mg, 11.6 μmol); $[\alpha]_D^{25}=-124$ ($c=0.388$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.32$ (d, $J=7.2$ Hz, 1H), 7.06 (d, $J=10$ Hz, 1H), 5.21 (t, $J=7.6$ Hz, 1H), 5.03–5.08 (m, 2H), 4.93 (dd, $J=6.0$, 9.2 Hz, 1H), 4.65 (d, $J=6.4$ Hz, 1H), 3.95–4.15 (m, 3H), 3.91 (brt, $J=8.8$ Hz, 1H), 3.80 (q, $J=8.8$ Hz, 1H), 3.62 (t, $J=6.8$ Hz, 1H), 3.29 (t, $J=6.8$ Hz, 2H), 3.23 (s, 3H), 3.04–3.15 (m, 1H), 2.69 (s, 3H), 2.52–2.67 (m, 2H), 2.45–2.50 (m, 1H), 2.12–2.18 (m, 2H), 2.00–2.10 (m, 1H), 1.94–1.98 (m, 2H), 1.80–1.91 (m, 2H), 1.71–1.80 (m, 2H), 1.58–1.68 (m, 2H), 1.42 (s, 3H), 1.32 (s, 3H), 1.31 (d, $J=6.8$ Hz, 3H), 1.25–1.30 (m, 4H), 0.89 (d, $J=7.2$ Hz, 3H), 0.85 ppm (d, $J=7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=173.3$, 173.0, 171.6, 170.8, 169.6,

169.0, 109.2, 77.2, 71.6, 70.6, 69.1, 60.9, 55.6, 53.3, 52.3, 51.0, 46.5, 37.6, 34.6, 34.5, 33.5, 31.1, 29.5, 29.4, 28.8, 28.3, 26.9, 25.5, 24.3, 23.9, 15.6, 15.2, 11.3 ppm; IR (neat): $\tilde{\nu}$ = 3383, 3302, 2958, 2929, 2875, 2097, 1732, 1665, 1640, 1519, 1446, 1408, 1379, 1345, 1303, 1258, 1231, 1180, 1102, 1061 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{33}H_{55}N_8O_9$ $[M+H]^+$: 707.4092; found: 707.4073.

Compound 17b: Yield: 31% from polymer-supported H-βAla-OH **10** (7.6 mg, 11.0 μmol); $[\alpha]_D^{26} = -221$ (*c* = 0.225, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 10 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 5.23 (q, *J* = 6.8 Hz, 1H), 5.05 (t, *J* = 6.8 Hz, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.87 (dt, *J* = 4.0, 9.6 Hz, 1H), 4.74 (d, *J* = 7.2 Hz, 1H), 4.07–4.15 (m, 2H), 4.03 (m, 1H), 3.87 (t, *J* = 10 Hz, 1H), 3.75 (q, *J* = 10 Hz, 1H), 3.64 (t, *J* = 9.6 Hz, 1H), 3.29 (dt, *J* = 2.8, 10 Hz, 2H), 3.20 (s, 3H), 3.02–3.09 (m, 1H), 2.77 (s, 3H), 2.59–2.70 (m, 2H), 2.48–2.53 (m, 1H), 2.29–2.37 (m, 1H), 2.11–2.17 (m, 2H), 2.05–2.10 (m, 1H), 1.88–1.97 (m, 2H), 1.62–1.73 (m, 1H), 1.54–1.59 (m, 2H), 1.46–1.54 (m, 2H), 1.42 (s, 3H), 1.33 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.87 ppm (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 173.5, 171.0, 170.7, 169.7, 168.8, 109.1, 77.2, 71.6, 70.8, 69.1, 60.5, 57.9, 55.3, 51.0, 49.7, 46.3, 34.5, 34.3, 33.2, 31.1, 30.4, 28.5, 28.2, 28.1, 27.4, 26.8, 25.5, 23.0, 19.8, 19.4, 15.0 ppm; IR (neat): $\tilde{\nu}$ = 3383, 3306, 2961, 2932, 2875, 2097, 1730, 1671, 1632, 1529, 1446, 1413, 1379, 1344, 1261, 1229, 1180, 1101, 1061 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{32}H_{52}N_8O_9$ $[M+H]^+$: 693.3936; found: 693.3964.

Compound 17c: Yield: 20% from polymer-supported H-βAla-OH **10** (5.1 mg, 6.94 μmol); $[\alpha]_D^{25} = -142$ (*c* = 0.240, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 9.2 Hz, 1H), 7.15 (d, *J* = 9.2 Hz, 1H), 5.06 (dd, *J* = 6.0, 8.0 Hz, 1H), 5.05 (d, *J* = 11.2 Hz, 1H), 4.91 (dd, *J* = 6.4, 9.2 Hz, 1H), 4.80 (dd, *J* = 2.8, 11.2 Hz, 1H), 4.70 (d, *J* = 7.2 Hz, 1H), 4.04–4.13 (m, 3H), 3.90 (brt, *J* = 9.6 Hz, 1H), 3.80 (m, 1H), 3.62 (dd, *J* = 6.0, 7.2 Hz, 1H), 3.28 (t, *J* = 6.8 Hz, 2H), 3.22 (s, 3H), 3.07–3.13 (m, 1H), 2.75 (s, 3H), 2.61 (t, *J* = 4.0 Hz, 2H), 2.47 (d, *J* = 5.6 Hz, 1H), 2.27–2.37 (m, 4H), 2.09–2.17 (m, 2H), 2.03–2.08 (m, 1H), 1.92–1.97 (m, 2H), 1.88–1.90 (m, 1H), 1.57–1.68 (m, 2H), 1.42 (s, 3H), 1.33 (s, 3H), 1.24–1.32 (m, 2H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 7.2 Hz, 3H), 0.84 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 173.4, 170.9, 170.8, 168.9, 168.4, 109.2, 77.2, 71.6, 70.9, 69.1, 60.8, 60.1, 57.7, 53.5, 51.1, 46.4, 37.5, 34.6, 34.5, 30.9, 30.2, 29.3, 29.0, 28.7, 27.3, 26.9, 25.5, 24.4, 23.9, 23.7, 20.0, 19.5, 15.4, 11.4 ppm; IR (neat): $\tilde{\nu}$ = 3387, 3298, 2962, 2924, 2879, 2853, 2097, 1731, 1672, 1632, 1530, 1450, 1405, 1380, 1260, 1181 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{35}H_{59}N_8O_9$ $[M+H]^+$: 735.4405; found: 735.4407.

General procedure IV: Synthesis of molecular probe 15

The synthesis of molecular probe **15** from **17** was performed in the same manner as that used for the synthesis of **6**; see general procedure II.

Compound 15a: Yield (3 steps): 24% (1.8 mg, 2.77 μmol); $[\alpha]_D^{22} = -172$ (*c* = 0.0900, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 9.2 Hz, 1H), 5.20 (t, *J* = 7.2 Hz, 1H), 5.08 (q, *J* = 6.8 Hz, 1H), 4.98 (t, *J* = 7.2 Hz, 1H), 4.92 (dd, *J* = 6.0, 9.2 Hz, 1H), 4.66 (d, *J* = 7.2 Hz, 1H), 3.93–4.05 (m, 2H), 3.58–3.69 (m, 1H), 3.29 (t, *J* = 6.8 Hz, 1H), 3.23 (s, 3H), 3.11 (brt, *J* = 12.0 Hz, 1H), 2.92–2.97 (m, 1H), 2.83 (t, *J* = 4.4 Hz, 1H), 2.70 (s, 3H), 2.63–2.69 (m, 1H), 2.50–2.58 (m, 2H), 2.29–2.43 (m, 1H), 2.23–2.31 (m, 1H), 1.99–2.10 (m, 1H), 1.92–1.99 (m, 3H), 1.83–1.92 (m, 2H), 1.55–1.68 (m, 2H), 1.30 (d, *J* = 6.8 Hz, 3H) 1.23–1.37 (m, 4H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.86 ppm (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 173.0, 171.5, 170.7, 169.6, 168.7, 77.2, 70.5, 60.9, 55.6, 53.4, 52.3, 51.0, 47.9, 47.1, 46.7, 38.1, 37.6, 34.5, 33.6, 33.4, 31.1, 28.8, 28.3, 25.7, 24.3, 23.9, 15.6, 15.2, 11.4 ppm; IR (neat): $\tilde{\nu}$ = 3383, 3308, 2958, 2925, 2875, 2853, 2097, 1734, 1665, 1636, 1540, 1517, 1447, 1412, 1378, 1345, 1260, 1232, 1178, 1130, 1101, 1029 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{30}H_{49}N_8O_8$ $[M+H]^+$: 649.3673; found: 649.3654.

Compound 15b: Yield (3 steps): 29% (2.0 mg, 3.15 μmol); $[\alpha]_D^{27} = -237$ (*c* = 0.100, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 5.25 (q, *J* = 6.8 Hz, 1H), 4.99 (t, *J* = 6.8 Hz, 1H), 4.98 (d, *J* = 10.4 Hz, 1H), 4.87 (dt, *J* = 3.6, 10.0 Hz, 1H), 4.75 (d, *J* = 7.6 Hz, 1H), 3.98–4.07 (m, 1H), 3.91 (brt, *J* = 8.8 Hz, 1H), 3.57–3.68 (m, 1H), 3.30 (dt, *J* = 2.8, 6.4 Hz, 2H), 3.20 (s, 3H), 3.06 (brt, *J* = 11.6 Hz, 1H), 2.98–3.03 (m, 1H), 2.84 (t, *J* = 4.4 Hz, 1H), 2.77 (s, 3H), 2.62–2.72 (m, 1H), 2.55–2.60 (m, 2H), 2.49–2.59 (m, 1H), 2.27–2.37 (m, 1H), 2.19–2.27 (m, 1H), 2.06–2.15 (m, 1H), 1.95–2.06 (m, 1H), 1.88–1.95 (m, 2H), 1.53–1.73 (m, 4H), 1.44–1.52 (m, 2H), 1.31 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.87 ppm (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 173.5, 170.9, 170.7, 169.7, 168.6, 70.7, 60.6, 57.9, 55.2, 51.0, 49.7, 47.9, 47.1, 46.5, 34.5, 33.4, 33.2, 31.1, 30.4, 28.4, 28.3, 28.1, 27.5, 24.1, 23.0, 19.8, 19.4, 15.1 ppm; IR (neat): $\tilde{\nu}$ = 3384, 3305, 3062, 2961, 2925, 2875, 2849, 2097, 1729, 1669, 1631, 1528, 1446, 1414, 1379, 1344, 1260, 1228, 1178, 1119, 1100 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{29}H_{47}N_8O_8$ $[M+H]^+$: 635.3517; found: 635.3518.

Compound 15c: Yield (3 steps): 31% (1.5 mg, 2.16 μmol); $[\alpha]_D^{25} = -227$ (*c* = 0.0750, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 9.2 Hz, 1H), 4.96–5.04 (m, 2H), 4.91 (dd, *J* = 6.8, 9.2 Hz, 1H), 4.81 (dd, *J* = 2.4, 10.8 Hz, 1H), 4.71 (d, *J* = 7.2 Hz, 1H), 4.06–4.16 (m, 1H), 3.95 (brt, *J* = 8.8 Hz, 1H), 3.61–3.68 (m, 1H), 3.29 (t, *J* = 6.8 Hz, 2H), 3.22 (s, 3H), 3.05–3.13 (m, 1H), 2.94–3.00 (m, 1H), 2.84 (t, *J* = 4.8 Hz, 1H), 2.76 (s, 3H), 2.60–2.64 (m, 2H), 2.57 (dd, *J* = 2.4, 4.8 Hz, 1H), 2.47–2.53 (m, 1H), 2.25–2.39 (m, 4H), 2.07–2.10 (m, 1H), 1.92–2.03 (m, 4H), 1.88–1.92 (m, 1H), 1.57–1.68 (m, 2H), 1.32–1.38 (m, 2H), 1.27–1.31 (m, 2H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.84 ppm (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 173.3, 170.8, 170.7, 168.6, 168.4, 77.2, 70.8, 60.9, 60.1, 57.7, 53.5, 51.1, 47.9, 47.1, 46.6, 37.5, 34.6, 33.6, 33.0, 30.9, 30.2, 29.0, 28.7, 27.3, 24.4, 24.0, 23.7, 20.0, 19.5, 15.4, 11.4 ppm; IR (neat): $\tilde{\nu}$ = 3386, 3297, 2961, 2925, 2875, 2849, 2096, 1733, 1669, 1628, 1540, 1517, 1444, 1413, 1381, 1345, 1260, 1178, 1115, 1089, 1025 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{32}H_{53}N_8O_8$ $[M+H]^+$: 677.3986; found: 677.3989.

General procedure V: Preparation of mouse osteoclasts from bone marrow cells

For the preparation and culture of mouse osteoclasts, α-MEM supplemented with 10% (v/v) heat-inactivated fetal calf serum (ICN Biomedicals, Inc., Aurora, OH, USA), L-glutamine (4 mM), penicillin (100 U mL^{-1}), streptomycin (100 μg mL^{-1}), and amphotericin B (250 ng mL^{-1}) was used in this study, and the cells were cultured at 37 °C in a humidified atmosphere of 5% (v/v) CO_2 in air. Mouse osteoclasts were prepared from mouse bone marrow cells of six- to nine-week-old male ddY mice (SLC Inc., Shizuoka, Japan). In brief, mouse bone marrow cells ($1.0–1.5\times10^7$ cells/dish/6 mL) were cultured for the first 3 days in the presence of 4000 U mL^{-1} recombinant human M-CSF (M-CSF), 1 ng mL^{-1} recombinant human TGF-β_1 (TGF-β_1), and 100 ng mL^{-1} GST-human sRANKL (GST-RANKL) in 100 mm diameter type I collagen-coated culture dishes (AGC

Techno Glass Co., Ltd., Chiba, Japan), in which GST-RANKL and Leukoprol were used for the preparation of mouse osteoclasts instead of RANKL and M-CSF, respectively, according to previous reports.[27–29] TGF-β_1 was added to the culture medium together with M-CSF and GST-RANKL, according to previous reports to promote the efficiency of osteoclast differentiation.[30–33] After 3 days of culture, adherent cells were harvested by treatment with trypsin–ethylenediaminetetraacetic acid (EDTA), and the resulting harvested cells (3×10^4 cells/well/100 μL) were placed on 96-well half-area culture plates (Corning Inc., Corning, NY, USA) to promote the efficiency of osteoclastic fusion and maturation. This study with experimental animals was approved by and conducted in accordance with the guidelines of the Animal Experiment Committee of Chubu University.

General procedure VI: TRAP staining

Osteoclasts cultured with 0.5% (v/v) vehicle (DMSO) or test compounds for 24 h were stained for tartrate-resistant acid phosphatase (TRAP), a typical marker enzyme of osteoclasts, as previously described[13,34,35] to visualize osteoclasts. In brief, the cells were fixed with 3.7% formaldehyde in phosphate-buffered saline (PBS) for 15 min. After treatment with ethanol/acetone (1:1) for 1 min, the well surface was dried and treated with the TRAP staining solution (0.1 M sodium acetate buffer (pH 5.0) containing 50 mM sodium tartrate, 0.1 mg mL^{-1} naphthol AS-MX phosphate, and 1 mg mL^{-1} fast red violet LB salt) for 30 min. The resulting visualized osteoclasts were detected under an all-in-one fluorescence microscope (BZ-8100 BIOZERO; KEYENCE Corp., Osaka, Japan), with which the number of osteoclasts with more than five nuclei were also counted. Similar results were obtained in more than two other experiments.

General procedure VII: Assay for OCL morphology

Osteoclasts prepared from bone marrow cells were further cultured in 96-well culture plates for 24 h after the culture medium was replaced with fresh medium that contained 4000 U mL^{-1} M-CSF, 100 ng mL^{-1} sRANKL, and 0.5% (v/v) vehicle (DMSO) or test compounds. After culturing, cells were fixed and stained for TRAP and then the number of osteoclasts with more than five nuclei with a clear cytoplasm and smooth periphery were counted. Similar results were obtained in more than two other experiments.

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