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Parallel Synthesis and Biological Evaluation of Destruxin E Analogs Modified with a Side Chain in the α-Hydroxycarboxylic Acid Moiety

Masahito Yoshida,[a, §] Kenta Adachi, [a] Hayato Murase, [b] Hiroshi Nakagawa, [b] and Takayuki Doi*[a]

Abstract: This study demonstrates the synthesis and biological evaluation of destruxin E analogs possessing various functional groups in the α-hydroxycarboxylic acid moiety. Parallel synthesis of eleven analogs was successfully achieved through solution-phase peptide synthesis and macrolactonization. Biological evaluation of the synthetic analogs using osteoclast-like multi nuclear cells (OCLs) revealed that the epoxide group in the side chain of α-hydroxycarboxylic acid and the orientation of the oxygen atom are essential factors in the desired potent activity that induces morphological changes in OCLs for the inhibition of bone-resorbing activity.

Introduction

19-Membered cyclodepsipeptide destruxin E (**1**) was isolated from *Metarhidium anisopliae* by Päis *et al.* in 1981 and is composed of five amino acids (β-Ala, MeAla, MeVal, Ile, and Pro), and an α-hydroxycarboxylic acid with a terminal epoxide-containing a C3 side chain.[1] Thus far, various natural and synthetic analogs have been reported[2]; in particular, **1** exhibits the most potent vacuolar (H^+)-ATPase (V-ATPase) inhibitory activity.[3] We recently achieved the total synthesis of **1** and have determined that the (*S*)-epoxide moiety is important for inducing the potent V-ATPase inhibitory activity, whereas the presence of (*R*)-epoxide significantly decreases the activity of analog **2**.[4] In addition, destruxin E (**1**) reversibly inhibits the bone-resorbing activity by inducing morphological changes in osteoclasts-like multinuclear cells (OCLs) at an even lower dose level without affecting cell viability,[5] indicating that **1** and its analogs could be promising candidates for the development of novel anti-resorptive agents for therapeutics used to treat osteoporosis. Although the structure-activity relationships (SARs) have been studied by altering the amino acid moieties, a SAR study focusing on the epoxide-containing C3 side chain in the α-hydroxycarboxylic acid moiety has not yet been carried out, except for a study on the hydrophobic allyl and isobutyl groups shown in destruxins A (**3a**) and B (**3b**), which exhibit a potent activity that is 20-fold less than that found in destruxin E (**1**). In addition, destruxin E diol (**3c**) is inactive against OCLs, indicating that a hydrophilic moiety such as a hydroxy group could be prohibited for the biological activity (Figure 1).[6] In this study, we achieved the synthesis of destruxin E analogs with modification of the epoxide side chain on the α-hydroxycarboxylic acid and evaluated their biological activity to elucidate the effect of the epoxide moiety.

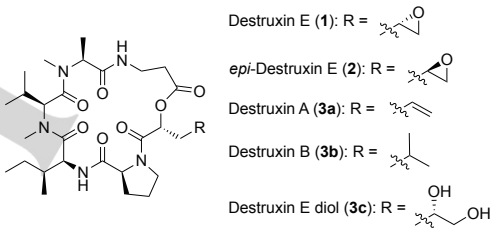

Figure 1. Destruxin E (**1**), *epi*-destruxin E (**2**), destruxin A (**3a**), B (**3b**), and diol derivative **3c**.

Results and Discussion

To explain the structure–activity relationship of the α-hydroxycarboxylic acid moiety, we designed various analogs possessing different functional groups on the side chain, such as a methyl ether **4a**, methyl ketone **4b**, difluoromethylene **4c**, cyclopropanes **4d**–**4f**, and oxetanes **4g**–**4i**. In addition, we also designed the synthesis of epoxide homologs **4j**–**4k** to determine the role of the epoxide moiety in the biological activity. Retrosynthesis of the analogs is shown in Scheme 1. According to the total synthesis of destruxin E (**1**),[4, 7] the desired analogs **4** would be afforded through macrolactonization of the linear precursors **5**, this can be prepared by amidation of acid **6,** containing various functional groups in the side chain and the known tetrapeptide **7** that we reported previously.

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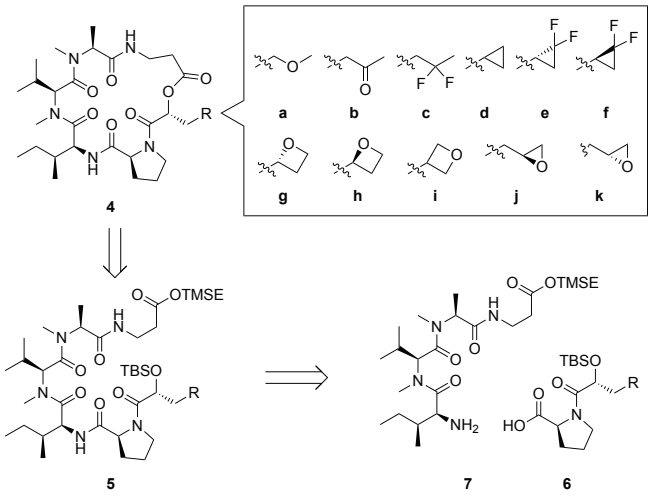
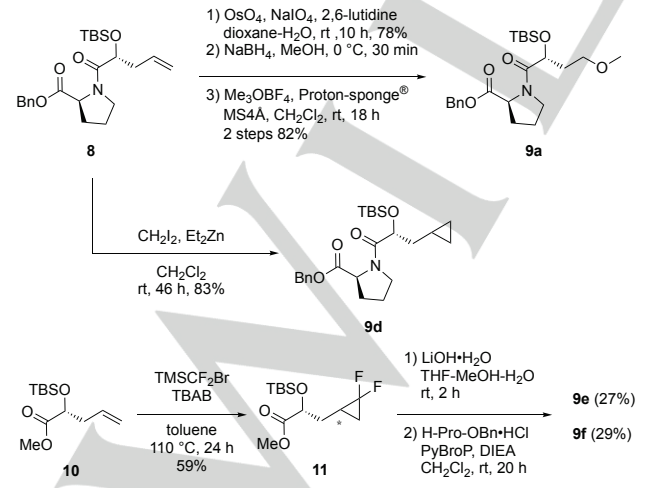


Scheme 1. Retrosynthesis of destruxin E analogs.

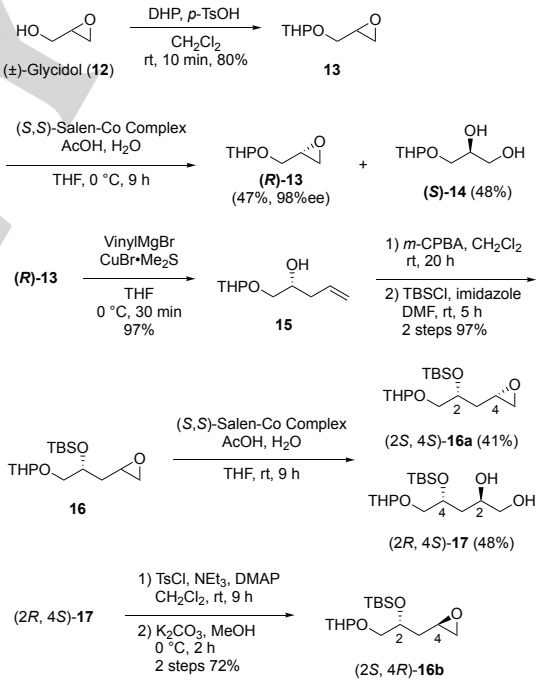
As detailed in the retrosynthesis described above, we initially attempted the preparation of the methyl ether **9a** and the cyclopropyl derivatives **9d**–**9f** (Scheme 2). The oxidative cleavage of the alkene moiety in **8**[7] afforded aldehyde and reduction of the resulting aldehyde followed by *O*-methylation using Me_3OBF_4 provided the desired methyl ether **9a** in 82% yield. The cyclopropyl derivatives **9d**–**9f** were prepared as follows: the Simmons–Smith reaction of **8** using CH_2I_2/Et_2Zn afforded **9d** in 83% yield. However, the preparation of difluorocyclopropane moiety in dipeptide **8** using difluorocarbene generated from trimethylsilyl fluorosulfonyldifluoroacetate (TFDA)/NaF[8] failed, and a complex mixture including a desilylated product was obtained. Fortunately, the difluoromethylenation of the alkene **10**[7] using (bromodifluoromethyl)trimethylsilane/tetrabutylammonium bromide (TBAB)[9] proceeded smoothly to afford difluorocyclopropane **11** in 59% yield as a 1:1 diastereomer mixture.



Scheme 2. Synthesis of methyl ester **9a** and cyclopropyl derivatives **9d**–**9f**.

After hydrolysis of the methyl ester in **11**, amidation of the resulting acid with H-Pro-OBn was performed using PyBrop[10]/DIEA, gave the less polar **9e** (27% yield) and polar **9f** (29% yield), respectively, isolated by silica gel column chromatography. The absolute configurations of the newly formed stereocenters in **9e** and **9f** are not determined.

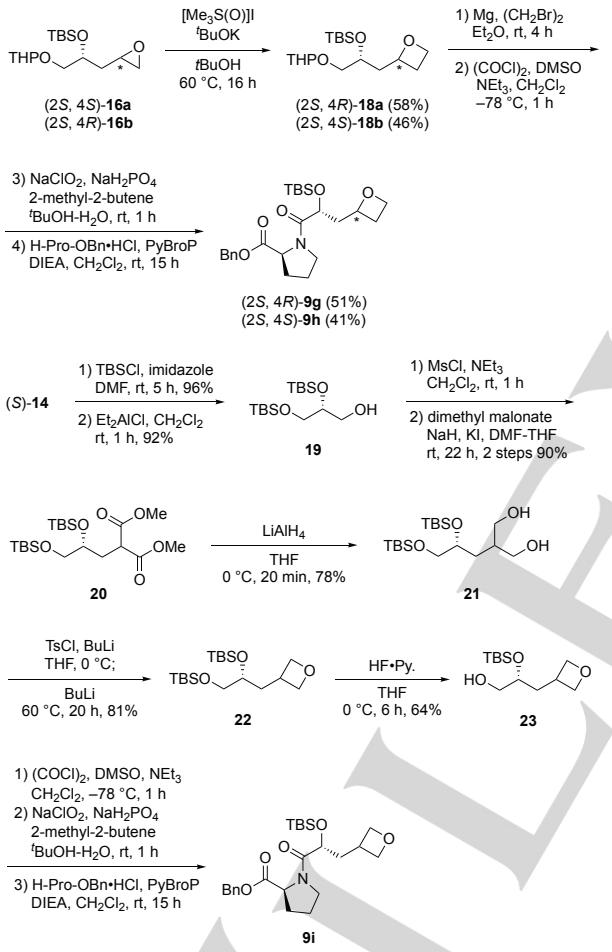
Oxetane derivatives of **9g**–**9i** were prepared from commercially available (±)-glycidol (**12**), and the details of the reaction are illustrated in Schemes 3 and 4. A hydrolytic kinetic resolution of the racemic epoxide **13** was carried out using the (*S*, *S*)-Salen-Co complex as a catalyst, and an enantio-enriched epoxide (*R*)-**13** was afforded in 47% yield concomitantly with diol (*S*)-**14**, obtained in 48% yield.[11,12] Alkenylation of (*R*)-**13** using vinylcuprate provided alkene **15** that was converted to a 1:1 diastereomeric mixture of epoxide **16** in 97% yield via epoxidation with *m*-CPBA and by protecting the resulting alcohol with a TBS group. A hydrolytic kinetic resolution of the epoxide moiety in **16** using the (*S*, *S*)-Salen-Co complex resulted in the formation of the diol (2*R*, 4*S*)-**17**[13] (48% yield) and the remaining epoxide (2*S*, 4*S*)-**16a** (41% yield) as a single diastereomer. The obtained diol (2*R*, 4*S*)-**17** was converted via two steps into the corresponding epoxide (2*S*, 4*R*)-**16b** in 72% yield.



Scheme 3. Preparation of epoxides (2*S*, 4*S*)-**16a** and (2*S*, 4*R*)-**16b.**

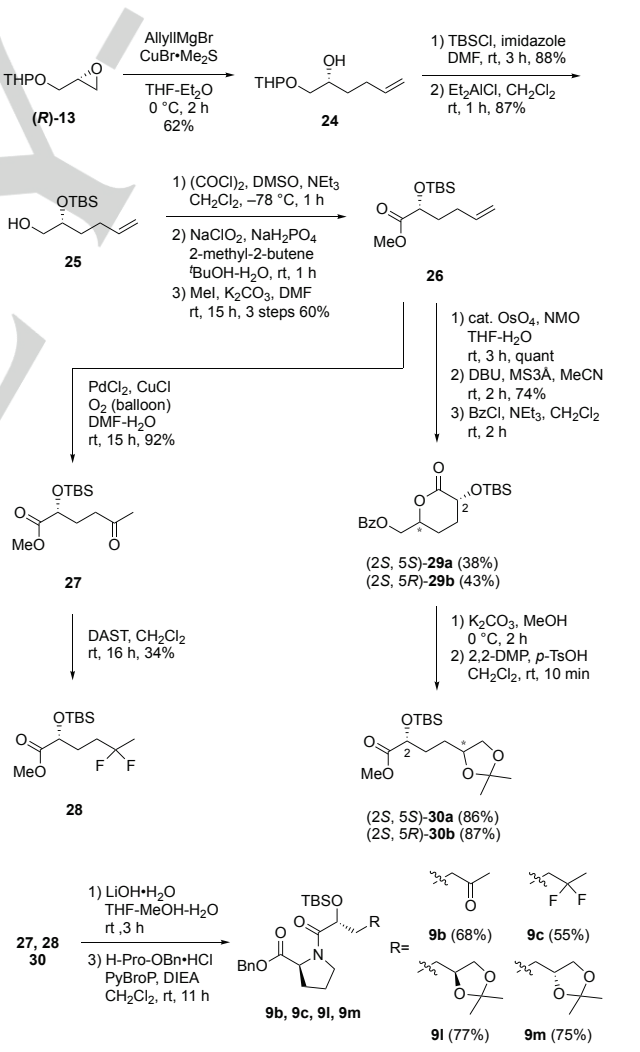
After synthesizing the desired epoxides, **16a** and **16b,** formation of oxetane was carried out by treatment with trimethylsulfonium iodide[14] under basic conditions to afford (2*S*, 4*R*)-**18a** and (2*S*, 4*S*)-**18b**, respectively (Scheme 4). THP group was removed, and the resulting alcohol was oxidized to acid, followed by amidation with H-Pro-OBn to produce the oxetane-containing

acylproline derivatives **9g** and **9h** in moderate yields. In addition, we also attempted to prepare the oxetane derivative **9i** from (*S*)-**14**. Protection of the diol in (*S*)-**14** with TBS groups, followed by removal of the THP group using Et_2AlCl afforded alcohol **19** in 92% yield.[12] After conversion of the resulting alcohol to mesylate, substitution with dimethyl malonate under basic conditions afforded dimethyl ester **20** in 90% yield. Treatment of dimethyl ester **20** with $LiAlH_4$ afforded diol **21**, and formation of an oxetane moiety was achieved smoothly using TsCl/BuLi[15] to provide **22** in 81% yield. Finally, the selective removal of the TBS group on the primary alcohol lead to **23**, this was then followed by coupling with H-Pro-OBn via three steps to produce **9i**, which possessed a symmetrical oxetane moiety.

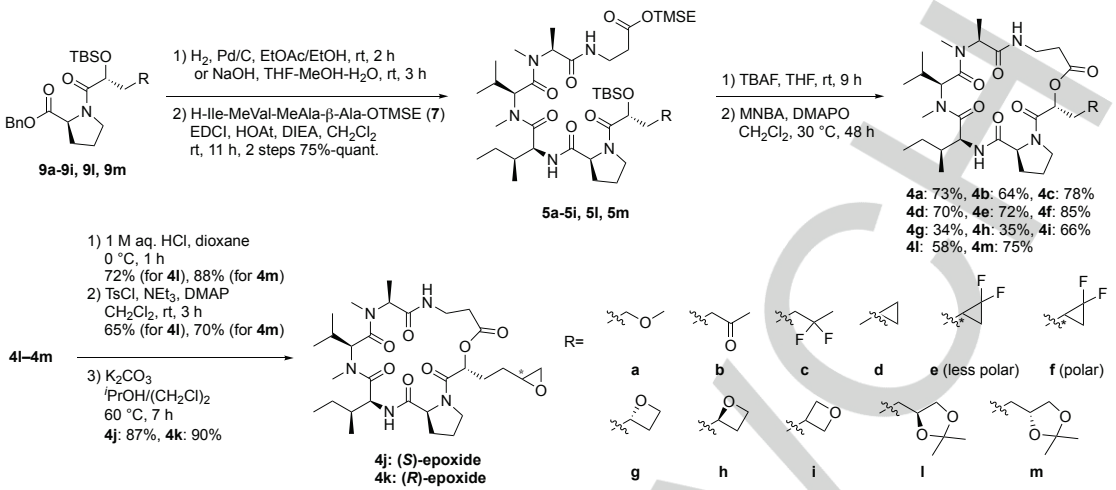


Scheme 4. Synthesis of oxetane derivatives **9g**–**9i**.

Next, we investigated the synthesis of acylproline derivatives **9b**, **9c**, **9l**, and **9m**, side-chains of which were elongated with one-carbon unit when compared with natural product **1** (Scheme 5). Nucleophilic addition of allyl copper reagent to epoxide (*R*)-**13** provided **24**, which was converted via two steps to afford primary alcohol **25**. Methyl ester **26** was prepared from **25** via three steps in 60% yield. Wacker oxidation of terminal alkene in **26** proceeded smoothly, leading to methyl ketone **27**, which was treated with diethylaminosulfur trifluoride (DAST) at room temperature to afford **28** in 34% yield. To achieve the synthesis of epoxide-containing analogs **4j** and **4k**, diol-containing acylprolines **9l** and **9m** were prepared from methyl hexenoate derivative **26**. Dihydroxylation of the terminal alkene **26** was performed by treatment with OsO_4/*N*-methylmorpholine *N*-oxide (NMO) to provide diols as a 1:1 mixture of diastereomers. The resulting mixture was subsequently subjected to basic conditions, and the primary alcohol in the resulting lactone was acylated with benzoyl chloride to afford benzoates (2*S*, 5*S*)-**29a** and (2*S*, 5*R*)-**29b**, respectively.[16] After separation of the above diastereomers by column chromatography, solvolysis was carried out under basic conditions, followed by protection of the resulting diol that provided methyl esters (2*S*, 5*S*)-**30a** and (2*S*, 5*R*)-**30b**. Finally, acylprolines **9** were synthesized as follows; hydrolysis of the methyl esters in **27**, **28**, and **30** using LiOH in the mixed solvents afforded the corresponding acids that were subsequently amidated with H-Pro-OBn using PyBroP/DIEA to provide the desired **9b**, **9c**, **9l**, and **9m** in moderate yields.



Scheme 5. Preparation of the acylprolines **9b**, **9c**, **9l**, and **9m**.



Scheme 6. Total synthesis of destruxin E analogs **4**

Successfully having the desired **9**, we synthesized destruxin E analogs **4**, details of which are illustrated in Scheme 6. Hydrogenolysis or hydrolysis of benzyl ester in **9a**–**9i**, **9l**, and **9m** were performed leading to the corresponding acids, which were subsequently amidated with the tetrapeptide **7**[7] using *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide (EDCI)/1-hydroxy-7-azabenzotriazole (HOAt) to afford hexapeptides **5a**–**5i**, **5l**, and **5m** in good to excellent yields. After removal of the protecting groups at the N- and C-terminus, macrolactonization of the resulting precursors was successfully achieved using 2-methyl-6-nitrobenzoic anhydride (MNBA)/4-(dimethylamino)pyridine *N*-oxide (DMAPO)[17] to provide the desired analogs **4a**–**4i**, **4l**, and **4m** in moderate yields (34–85%). In addition, the formation of epoxide from **4l** and **4m**, as well as the previously reported procedure,[4,7] furnished **4j** and **4k**, respectively.

The synthetic analogs were then evaluated for the morphological changes in OCLs,[18] and the results are summarized in Table 1. As we have previously reported, destruxin E (**1**), *epi*-**2**, and destruxin A (**3a**) and B (**3b**) induce morphological changes at minimum concentrations of 0.04, 5.0, 1.6, and 0.80 μM, respectively (entries 1–4). Biological activities of methyl ether **4a**, methyl ketone **4b**, difluoromethylene **4c**, and cyclopropyl analog **4d** were found to be similar to destruxin B (**3b**) (entries 5–8). In contrast, the biological activity of difluorocyclopropyl analogs **4e** and **4f** significantly decreased to 3.1 μM (entries 9 and 10), indicating that *gem*-difluorocyclopropane is not a bioisostere of the corresponding epoxide. Notably, the activity was not retained after the substitution of the epoxide by an oxetane moiety (entries 11–13). In addition, the (*S*)-epoxide homolog **4j** exhibited 10-fold less activity than destruxin E (**1**) and the (*R*)-epoxide homolog **4k** further diminished the activity (entries 14 and 15), although **4j** was found to be the most potent among the analogs **4a**–**4k**. Therefore, the epoxide moiety in the side chain of the α-hydroxy acid could play a crucial role in inducing the morphological changes at a lower concentration, and a target for destruxins in OCLs would recognize the orientation of the epoxide moiety to exhibit the desired biological activity.

Table 1. Biological Evaluation of Destruxin E Analogs for Morphological Changes in OCLs

Entry	Analog	R	Activity [μM][a]
1[b]	**1**		0.04
2[b]	**2**		5.0
3[c]	**3a**		1.6
4[c]	**3b**		0.80
5	**4a**		0.80
6	**4b**		1.6
7	**4c**		0.80
8	**4d**		0.80
9	**4e** (less polar)		3.1
10	**4f** (polar)		3.1

11	**4g**		6.3
12	**4h**		13
13	**4i**		25
14	**4j**		0.40
15	**4k**		3.1

[a]Minimum concentration for morphological changes. [b] See ref 5b. [c] See ref 6.

Conclusions

In conclusion, we investigated the synthesis and biological evaluation of destruxin E analogs that were replaced with various α-hydroxycarboxylic acid derivatives. Acylproline derivatives **9,** key components for the synthesis of the analog, were successfully prepared, and amidation of the resulting **9** with tetrapeptide, followed by macrolactonization in parallel furnished eleven analogs **4a**–**4k**, each possessed different functional groups in the side chain of α-hydroxycarboxylic acid moiety. Biological evaluation of the synthetic analogs against OCLs indicated that the modification of the side chain did not allow the biological activity of the parent destruxin E to be retained. Although, (*S*)-epoxide homolog **4j** was the most potent among the synthetic analogs, meaning that the (*S*)-epoxide moiety in the side chain of α-hydroxycarboxylic acid could be an essential factor for the induction of morphological changes of OCLs at a lower concentration. Destruxin E reversibly inhibits the bone-resorbing activity of OCLs, therefore elucidation of the mode of action could be interesting, in particular, to determine whether destruxin E binds to a target molecule in OCLs by a covalent linkage or not. Further investigation of the mode of action is underway by a chemical biology approach using a molecular probe of the destruxin E analogs.

Experimental Section

General

All commercially available reagents were used as received. Dry THF and CH_2Cl_2 (Kanto Chemical Co.) were obtained through commercially available pre-dried, oxygen-free formulations, and through activated alumina columns. MeOH was distilled from iodide and magnesium turnings. DMF was purchased from Wako (for peptide synthesis, grade: 99.5%). All reactions in the solution-phase were monitored by thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) with UV light, and visualized with anisaldehyde, or 10% ethanolic phosphomolybdic acid. Silica gel 60N (Kanto Chemical Co. 100–210 μm) was used for column chromatography. ^{1}H NMR spectra (400 or 600 MHz) and ^{13}C spectra (100 or 150 MHz) were recorded on JEOL JNM-AL400 or JEOL JNM-ECA600 spectrometers in the indicated solvent. Chemical shifts (δ) are reported in units parts per million (ppm), relative to the signal for the internal standard tetramethylsilane (0 ppm for ^{1}H) for solutions in $CDCl_3$. NMR spectral data are reported as follows: chloroform (7.26 ppm for ^{1}H) or chloroform-*d* (77.0 ppm for ^{13}C), DMSO (2.49 ppm for ^{1}H), DMSO-d_6 (39.5 ppm for ^{13}C) when the internal standard is not indicated. Multiplicities are reported by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet) dd (double doublet), dt (double triplet), ddd (double double doublet), br (broad singlet), and J (coupling constants in Herts). IR spectra were recorded on a JASCO FT/IR-4100. Only the strongest and/or structurally important absorption are recorded as the IR data afforded 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 and high-resolution mass spectra were measured on ThermoScienific™ Exactive™ Plus Orbitrap Mass Spectrometer (for ESI), JEOL JMS-DX303 (for EI) and JMS-700 (for FAB).

General procedure I: Macrolactonization Using MNBA/DMAPO

To a solution of hexapeptide **5** (1.00 equiv) in THF (5 mL/mmol) was slowly added a solution of TBAF (1 M in THF solution, 3 equiv) in THF at 0 ºC under an argon atmosphere. After the mixture was stirred at room temperature for 9 h, DOWEX 80WX8-400 (1 mg/μmol) was added at 0 ºC. The reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. The crude cyclization precursor was used for next reaction after short pass silica gel column chromatography.

To a solution of the crude cyclization precursor and DMAPO (2.00 equiv) in dry CH_2Cl_2 (330 mL/mmol) was added MNBA (3.00 equiv) at 0 ºC under an argon atmosphere. After being stirred 30 ºC for 48 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ 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 silica gel column chromatography (eluted with $CHCl_3$/MeOH = 100/1) to afford macrolactone **4** as a yellow oil.

4a: Yield (2 steps): 73% (19.3 mg, 0.0324 mmol); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (1H, d, *J* = 8.5 Hz), 7.18 (1H, d, *J* = 9.2 Hz), 5.18 (1H, q, *J* = 6.7 Hz), 5.05 (1H, dd, *J* = 5.1, 8.5 Hz). 4.96 (1H, d, *J* = 10.9 Hz), 4.89 (1H, dd, *J* = 6.7, 9.2 Hz), 4.68 (1H, d, *J* = 7.5 Hz), 4.02–4.08 (1H, m), 3.90 (1H, brt, *J* = 9.2 Hz), 3.52–3.58 (2H, m), 3.42–3.46 (1H, m), 3.33 (3H, s), 3.23 (3H, s, j), 3.08 (1H, brt, *J* = 12.1 Hz), 2.73 (3H, s), 2.67 (1H, ddd, *J* = 1.9, 11.5, 18.4 Hz), 2.57 (1H, dd, *J* = 4.3, 18.4 Hz), 2.44–2.49 (1H, m), 2.28–2.35 (1H, m), 1.88–2.14 (6H, m), 1.39–1.45 (1H, m), 1.27–1.35 (4H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 6.5 Hz), 0.84–0.87 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 173.5, 171.1, 170.9, 169.7, 169.4, 70.6, 67.6, 60.7, 58.7, 58.0, 55.5, 53.6, 46.4, 37.5, 34.4, 33.2, 30.9, 30.8, 29.1, 28.1, 27.2, 24.4, 24.0, 20.0, 19.6, 15.4, 15.2, 11.4; IR (neat) 2965, 1731, 1668, 1631, 1517, 1444, 1180, 1120, 752 cm^{-1}; $[\alpha]^{24}_D$ –211 (*c* 0.634, $CHCl_3$); HRMS [ESI] calcd for $C_{29}H_{49}N_5O_8Na$ $[M+Na]^+$ 618.3473, found 618.3466.

4b: Yield (2 steps): 64% (23.1 mg, 0.0378 mmol); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (1H, d, *J* = 8.2 Hz), 7.16 (1H, d, *J* = 9.2 Hz), 5.20 (1H, q, *J* = 6.8 Hz), 4.93–4.95 (2H, m), 4.86 (1H, dd, *J* = 6.7, 9.2 Hz), 4.63 (1H, d, *J* = 7.2 Hz), 4.03–4.08 (1H, m), 3.85 (1H, dd, *J* = 1.8, 9.3 Hz), 3.65–3.70 (1H, m), 3.22 (3H, s), 3.04–3.09 (1H, m), 2.64–2.78 (6H, m), 2.56 (1H, m), 2.47–2.50 (1H, m), 2.28–2.36 (1H, m), 2.16 (3H, s), 1.89–2.11 (6H, m), 1.39–1.44 (1H, m), 1.26–1.32 (4H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 6.5 Hz), 0.83–0.86 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.7, 173.7, 173.5, 171.1, 171.0, 169.8, 169.0, 72.0, 60.7, 58.1, 55.5, 53.7,

46.6, 37.7, 37.5, 34.4, 33.2, 30.9, 30.1, 28.9, 28.1, 27.3, 24.5, 24.1, 23.5, 20.1, 19.6, 15.4, 15.3, 11.4; IR (neat) 3385, 3296, 2966, 1731, 1667, 1630, 1519, 1443 cm^{-1}; $[\alpha]^{28}_D$ –191 (*c* 0.426, $CHCl_3$); HRMS [ESI] calcd for $C_{30}H_{49}N_5O_8Na$ $[M+Na]^+$ 630.3473, found 630.3468.

4c: Yield (2 steps): 78% (13.6 mg, 0.0216 mmol); ^1H NMR (600 MHz, $CDCl_3$) δ 8.18 (1H, d, *J* = 8.2 Hz), 7.16 (1H, d, *J* = 9.2 Hz), 5.19 (1H, q, *J* = 6.8 Hz), 4.94–4.96 (2H, m), 4.87 (1H, dd, *J* = 6.7, 9.2 Hz), 4.67 (1H, d, *J* = 7.9 Hz), 4.03–4.08 (1H, m), 3.90 (1H, brt, *J* = 8.2 Hz), 3.44–3.49 (1H, m), 3.25 (3H, s), 3.08 (1H, brt, *J* = 13.0 Hz), 2.73 (3H, s), 2.67 (1H, ddd, *J* = 2.0, 11.5, 18.5 Hz), 2.58 (1H, dd, *J* = 3.8, 18.5 Hz), 2.49–2.52 (1H, m), 2.29–2.35 (1H, m), 1.90–2.14 (8H, m), 1.63 (3H, t, *J* = 18.5 Hz), 1.40–1.44 (1H, m), 1.27–1.31 (4H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 6.5 Hz), 0.84–0.88 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 173.5, 171.1, 170.8, 169.7, 168.8, 123.8 (t, *J* = 238.1 Hz), 72.3, 60.8, 58.1, 55.5, 53.7, 46.6, 37.5, 34.4, 33.2, 32.9 (t, *J* = 25.1 Hz), 30.9, 28.9, 28.1, 27.2, 24.5, 24.1, 23.8 (t, *J* = 28.0 Hz), 23.2, 20.0, 19.6, 15.4, 15.2, 11.4; IR (neat) 3385, 3297, 2964, 2931, 1732, 1668, 1630, 1441, 1181 cm^{-1}; $[\alpha]^{29}_D$ –184 (*c* 0.381, $CHCl_3$); HRMS [ESI] calcd for $C_{30}H_{49}F_2N_5O_7Na$ $[M+Na]^+$ 652.3492, found 652.3468.

4d: Yield (2 steps): 70% (17.6 mg, 0.0297 mmol); ^1H NMR (600 MHz, $CDCl_3$) δ 8.21 (1H, d, *J* = 8.5 Hz), 7.19 (1H, d, *J* = 9.2 Hz), 5.17 (1H, q, *J* = 6.8 Hz), 4.96 (1H, d, *J* = 10.9 Hz), 4.92 (1H, t, *J* = 7.2 Hz), 4.89 (1H, dd, *J* = 6.7, 9.2 Hz), 4.67 (1H, d, *J* = 6.8 Hz), 4.02–4.06 (1H, m), 3.96 (1H, t, *J* =8.4 Hz), 3.55–3.39 (1H, m), 3.22 (3H, s), 3.09 (1H, m), 2.73 (3H, s), 2.67 (1H, ddd, *J* = 1.7, 11.8, 18.2 Hz), 2.56 (1H, dd, *J* = 4.8, 18.2 Hz), 2.48 (1H, d, *J* = 6.5 Hz), 2.29–2.34 (1H, m), 1.89–2.07 (5H, m), 1.53–1.58 (1H, m), 1.40–1.46 (1H, m), 1.28–1.34 (4H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 6.5 Hz), 0.85–0.87 (6H, m), 0.75–0.81 (1H, m), 0.51–0.56 (1H, m), 0.44–0.48 (1H, m), 0.16–0.20 (1H, m), 0.08–0.12 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.64, 173.56, 171.1, 171.0, 169.7, 169.6, 73.6, 60.9, 58.1, 55.5, 53.7, 46.6, 37.5, 35.8, 34.5, 33.3, 30.9, 29.1, 28.1, 27.3, 24.4, 24.1, 20.0, 19.7, 15.4, 15.2, 11.4, 6.7, 4.8, 4.3; IR (neat) 2965, 1730, 1668, 1631, 1516, 1447, 1181, 753 cm^{-1}; $[\alpha]^{26}_D$ –216 (*c* 0.712, $CHCl_3$); HRMS [ESI] calcd for $C_{30}H_{49}N_5O_7Na$ $[M+Na]^+$ 614.3524, found 614.3518.

4e: Yield (2 steps): 72% (7.8 mg, 0.0124 mmol); ^1H NMR (600 MHz, $CDCl_3$) δ 8.18 (1H, d, *J* = 8.2 Hz), 7.15 (1H, d, *J* = 8.9 Hz), 5.17 (1H, q, *J* = 6.8 Hz), 4.96 (1H, d, *J* = 10.9 Hz), 4.88–4.93 (2H, m), 4.68 (1H, d, *J* = 7.2 Hz), 4.03–4.08 (1H, m), 3.95 (1H, t, *J* = 8.2 Hz), 3.47–3.51 (1H, m), 3.23 (3H, s), 3.06–3.11 (1H, m), 2.66–2.72 (4H, m), 2.57 (1H, dd, *J* = 3.8, 18.5 Hz), 2.50 (1H, d, *J* = 6.5 Hz), 2.29–2.35 (1H, m), 1.88–2.01 (5H, m), 1.60–1.68 (1H, m), 1.43–1.46 (1H, m), 1.48–1.42 (1H, m), 1.27–1.33 (4H, m), 0.99–1.14 (1H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 0.84–0.87 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.5, 173.4, 171.0, 170.7, 169.7, 168.4, 113.4 (t, *J* = 284 Hz), 71.8, 60.9, 58.1, 55.5, 53.6, 46.6, 37.5, 34.4, 33.2, 30.8, 29.0, 28.10, 28.07, 27.2, 24.3, 24.0, 20.0, 19.6, 18.0 (t, *J* = 11.5 Hz), 16.0 (t, *J* = 10.8 Hz), 15.4, 15.2, 11.3; IR (neat) 2965, 1732, 1668, 1632, 1475, 1446, 1179, 754 cm^{-1}; $[\alpha]^{32}_D$ –183 (*c* 0.451, $CHCl_3$); HRMS [ESI] calcd for $C_{30}H_{47}F_2N_5O_7Na$ $[M+Na]^+$ 650.3336, found 650.3317.

4f: Yield (2 steps): 85% (5.6 mg, 8.92 μmol); ^1H NMR (600 MHz, $CDCl_3$) δ 8.19 (1H, d, *J* = 8.2 Hz), 7.15 (1H, d, *J* = 9.2 Hz), 5.18 (1H, q, *J* = 6.8 Hz), 4.95 (1H, d, *J* = 10.9 Hz), 4.91 (1H, dd, *J* = 3.8, 9.2 Hz), 4.88 (1H, dd, *J* = 6.7, 9.2 Hz), 4.66 (1H, d, *J* = 7.5 Hz), 4.04–4.09 (1H, m), 3.92 (1H, t, *J* = 8.9 Hz), 3.44–3.48 (1H, m), 3.23 (3H, s), 3.09 (1H, m), 2.67–2.73 (4H, m), 2.60 (1H, dd, *J* = 4.4, 17.8 Hz), 2.49–2.52 (1H, m), 2.26–2.35 (2H, m), 2.04–2.08 (1H, m), 1.90–2.00 (3H, m), 1.75–1.83 (1H, m), 1.64–1.69 (1H, m), 1.51–1.57 (1H, m), 1.38–1.46 (1H, m), 1.26–1.32 (4H, m), 1.03–1.08 (1H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 0.85–0.87 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 173.5, 171.1, 170.8, 169.7, 168.5, 113.7 (t, *J* = 284 Hz), 72.9, 60.8, 58.1, 55.5, 53.7, 46.6, 37.5, 34.4, 33.2, 30.8, 28.9, 28.6, 28.1, 27.2, 24.4, 24.0, 20.0, 19.6, 18.5 (t, *J* = 10.0 Hz), 16.5 (t, *J* = 10.8 Hz), 15.4, 15.2, 11.4; IR (neat) 2966, 1732, 1668, 1632, 1474, 1447, 1180, 754 cm^{-1}; $[\alpha]^{31}_D$ –177 (*c* 0.287, $CHCl_3$); HRMS [ESI] calcd for $C_{30}H_{47}F_2N_5O_7Na$ $[M+Na]^+$ 650.3336, found 650.3320.

4g: Yield (2 steps): 34% (6.5 mg, 0.0107 mmol); ^1H NMR (600 MHz, $CDCl_3$) δ 8.21 (1H, d, *J* = 7.9 Hz), 7.13 Hz, d, *J* = 9.2 Hz), 5.15 (1H, q, *J* = 6.8 Hz), 5.03 (1H, dd, *J* = 5.6, 8.4 Hz), 4.97 (1H, d, *J* = 10.9 Hz), 4.90 (1H, dd, *J* = 6.2, 9.2 Hz), 4.80–4.85 (1H, m), 4.66–4.71 (2H, m), 4.55 (1H, dt, *J* = 4.5, 11.2 Hz), 4.01–4.07 (1H, m), 3.88 (1H, brt, *J* = 8.4 Hz), 3.57–3.62 (1H, m), 3.22 (3H, s), 3.08 (1H, brt, *J* =13.3 Hz), 2.74–2.79 (1H, m), 2.72 (3H, s), 2.67 (1H, ddd, *J* = 1.7, 11.3, 18.4 Hz), 2.56 (1H, dd, *J* = 3.9, 18.4 Hz), 2.38–2.47 (3H, m), 2.29–2.35 (1H, m), 2.21 (1H, ddd, *J* = 4.1, 8.4, 14.0 Hz), 1.87–2.07 (4H, m), 1.39–1.43 (1H, m), 1.28–1.31 (4H, m), 0.93 (3H, d, *J* = 6.8 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 0.84–0.87 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.57, 173.55, 171.1, 170.9, 169.7, 169.0, 78.1, 69.0, 68.6, 60.9, 58.0, 55.5, 53.6, 46.5, 38.7, 37.4, 34.5, 33.2, 30.8, 29.3, 28.1, 27.4, 27.2, 24.3, 24.0, 20.0, 19.6, 15.4, 15.2, 11.4; IR (neat) 2963, 2926, 1732, 1667, 1632, 1519, 1446, 1180 cm^{-1}; $[\alpha]^{31}_D$ –171 (*c* 0.344, $CHCl_3$); HRMS [ESI] calcd for $C_{30}H_{49}N_5O_8Na$ $[M+Na]^+$ 630.3473, found 630.3458.

4h: Yield (2 steps) : 35% (3.2 mg, 5.27 μmol); ^1H NMR (600 MHz, $CDCl_3$) δ 8.18 (1H, d, *J* = 8.5 Hz), 7.17 (1H, d, *J* = 9.2 Hz), 5.18 (1H, q, *J* = 6.8 Hz), 5.00–5.05 (1H, m), 4.94–4.97 (2H, m), 4.87 (1H, dd, *J* = 6.7, 9.2 Hz), 4.67–4.72 (2H, m), 4.55 (1H, dt, *J* = 4.6, 11.1 Hz), 4.01–4.06 (1H, m), 3.89 (1H, brt, *J* = 8.2 Hz), 3.52–3.56 (1H, m), 3.22 (3H, s), 3.06 (1H, brt, *J* = 13.0 Hz), 2.77–2.83 (1H, m), 2.72 (3H, s), 2.65 (1H, ddd, *J* = 2.0, 11.5, 18.4 Hz), 2.55 (1H, dd, *J* = 3.9, 18.4 Hz), 2.47–2.50 (1H, m), 2.28–2.40 (2H, m), 2.22 (1H, ddd, *J* = 3.1, 10.7, 14.4 Hz), 2.14 (1H, ddd, *J* = 2.4, 9.7, 14.4 Hz), 2.05–2.09 (1H, m), 1.89–2.02 (3H, m), 1.38–1.45 (1H, m), 1.27–1.31 (4H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 6.5 Hz), 0.83–0.86 (6H, m; ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 173.4, 171.1, 170.9, 169.8, 169.1, 78.2, 69.5, 68.4, 60.8, 58.1, 55.5, 53.7, 46.6, 38.8, 37.5, 34.4, 33.2, 30.9, 29.0, 28.1, 27.5, 27.3, 24.5, 24.0, 20.1, 19.7, 15.4, 15.3, 11.4; IR (neat) 2964, 2932, 1732, 1669, 1632, 1519, 1443, 1178 cm^{-1}; $[\alpha]^{27}_D$ –174 (*c* 0.163, $CHCl_3$); HRMS [ESI] calcd for $C_{30}H_{49}N_5O_8Na$ $[M+Na]^+$ 630.3473, found 630.3456.

4i: Yield (2 steps): 66% (5.3 mg, 8.72 μmol); ^1H NMR (600 MHz, $CDCl_3$) δ 8.14 (1H, d, *J* = 7.9 Hz), 7.13 (1H, d, *J* = 9.2 Hz), 5.19 (1H, q, *J* = 6.8 Hz), 4.95 (1H, d, *J* = 10.9 Hz), 4.87 (1H, dd, *J* = 6.7, 9.2 Hz), 4.80–4.83 (3H, m), 4.65 (1H, d, *J* = 7.5 Hz), 4.39–4.42 (2H, m), 4.02–4.07 (1H, m), 3.89 (1H, brt, *J* = 8.0 Hz), 3.42 (1H, m), 3.24–3.30 (1H, m), 3.22 (3H, s), 3.60 (1H, brt, *J* = 12.5 Hz), 2.72 (3H, s), 2.64 (1H, ddd, *J* = 1.9, 11.5, 18.6 Hz), 2.52–2.56 (2H, m), 2.27–2.34 (2H, m), 2.17 (1H, ddd, *J* = 4.0, 7.8, 14.4 Hz), 1.89–2.09 (4H, m), 1.38–1.42 (1H, m), 1.27–1.31 (4H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0,89 (3H, d, *J* = 6.5 Hz), 0.83–0.85 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 173.5, 171.1, 170.7, 169.8, 168.6, 77.5, 76.8, 71.8, 60.9, 58.1, 55.5, 53.8, 46.6, .37.5, 34.4, 33.9, 33.2, 31.7, 30.9, 28.9, 28.1, 27.3, 24.5, 24.1, 20.1, 19.6, 15.4, 15.2, 11.4; IR (neat) 2964, 2931, 1731, 1667, 1631, 1445, 1180 cm^{-1}; $[\alpha]^{28}_D$ –210 (*c* 0.137, $CHCl_3$); HRMS [ESI] calcd for $C_{30}H_{49}N_5O_8Na$ $[M+Na]^+$ 630.3473, found 630.3455.

4l: Yield (2 steps): 58% (29.0 mg, 0.0436 mmol); ^1H NMR (600 MHz, $CDCl_3$) δ 8.19 (1H, d, *J* = 8.2 Hz), 7.17 (1H, d, *J* = 9.2 Hz), 5.19 (1H, q, *J* = 6.7 Hz), 4.95 (1H, d, *J* = 10.9 Hz), 4.92 (1H, dd, *J* = 4.3, 8.7 Hz), 4.87 (1H, dd, *J* = 6.8, 9.2 Hz), 4.65 (1H, d, *J* = 7.5 Hz), 4.03–4.12 (3H, m), 3.91 (1H, brt, *J* = 8.9 Hz), 3.54 (1H, t, *J* = 7.2 Hz), 3.45–3.50 (1H, m), 3.22 (3H, s), 3.08 (1H, brt, *J* = 12.1 Hz), 2.73 (3H, s), 2.67 (1H, ddd, *J* = 1.9, 11.5, 18.4 Hz), 2.56 (1H, dd, *J* = 4.4, 18.4 Hz), 2.49–2.51 (1H, m), 2.29–2.36 (1H, m), 2.04–2.08 (1H, m), 1.87–2.00 (6H, m), 1.79–1.84 (1H,

m), 1.60–1.68 (1H, m), 1.27–1.45 (11H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 6.5 Hz), 0.84–0.87 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 173.5, 171.0, 170.9, 169.7, 169.2, 109.0, 75.8, 73.1, 69.2, 60.8, 58.1, 55.4, 53.6, 46.6, 37.5, 34.4, 33.2, 30.8, 29.1, 28.9, 28.1, 27.2, 27.0, 26.9, 25.6, 24.4, 24.1, 20.0, 19.6, 15.4, 15.2, 11.3; IR (neat) 3384, 3298, 2966, 1730, 1670, 1630, 1442, 1181 cm^{-1}; $[\alpha]^{19}_D$ –184 (*c* 1.00, $CHCl_3$); HRMS [ESI] calcd for $C_{33}H_{55}N_5O_9Na$ $[M+Na]^+$ 688.3892, found 688.3882.

4m: Yield (2 steps): 75% (47.0 mg, 0.0706 mmol); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (1H, d, *J* = 9.9 Hz), 7.17 (1H, d, *J* = 6.8 Hz), 5.18 (1H, q, *J* = 6.8 Hz), 4,95 (1H, d, *J* = 11.3 Hz), 4.90 (1H, dd, *J* = 5.0, 8.4 Hz), 4.88 (1H, dd, *J* = 6.8, 9.2 Hz), 4.67 (1H, d, *J* = 7.2 Hz), 4.11–4.15 (1H, m), 4.03–4.07 (2H, m), 3.90 (1H, brt, *J* = 8.4 Hz), 3.49–3.55 (2H, m), 3.22 (3H, s), 3.08 (1H, brt, *J* = 12.6 Hz), 2.72 (3H, s), 2.67 (1H, ddd, *J* = 1.7, 11.5, 18.0 Hz), 2.56 (1H, dd. *J* = 4.6, 18.0 Hz), 2.49–2.51 (1H, m), 2.29–2.36 (1H, m), 1.84–2.06 (6H, m), 1.66–1.79 (2H, m), 1.27–1.44 (11H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 6.5 Hz), 0.84–0.87 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.61, 173.60, 171.1, 170.9, 169.7, 169.1, 109.0, 74.9, 72.7, 69.1, 60.8, 58.1, 55.5, 53.7, 46.6, 37.5, 34.5, 33.2, 30.9, 29.0, 28.5, 28.1, 27.3, 27.0, 26.3, 25.6, 24.5, 24.1, 20.1, 19.7, 15.4, 15.3, 11.4; IR (neat) 3384, 3299, 2966, 1730, 1670, 1629, 1442, 1180 cm^{-1}; $[\alpha]^{25}_D$ –176 (*c* 0.969, $CHCl_3$); HRMS [ESI] calcd for $C_{33}H_{55}N_5O_9Na$ $[M+Na]^+$ 688.3892, found 688.3883.

General procedure II: Formation of the Epoxide

To a solution of the macrolactones **4l** and **4m** (1.00 equiv) in dioxane (1.0 mL) was added 1 M aqueous HCl (2.00 mL) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, and dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by silica gel flash column chromatography (eluted with $CHCl_3$/MeOH = 30:1) to afford the diols **S6** as a colorless oil. (Data for **S6** are shown in the Supporting Information.)

To a solution of the diol **S6** (1.00 equiv), triethylamine (1.50 equiv) and DMAP (0.100 equiv) in dry CH_2Cl_2 (15 mL/mmol) was added *p*-toluenesulfonyl chloride (1.20 equiv) at 0 °C under argon. After being stirred at room temperature for 3 h, the reaction mixture was poured into saturated aqueous NH_4Cl and the aqueous layer was extracted with $CHCl_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by silica gel flash column chromatography (eluted with $CHCl_3$/MeOH = 50:1) to afford tosylate **S7** as a colorless oil. (Data for **S7** are shown in the Supporting Information.)

To a solution of tosylate **S7** (1.00 equiv) in *i*-PrOH (100 mL/mmol) and 1,2-DCE (10 mL/mmol) was added K_2CO_3 (4.00 equiv) at 0 °C under argon. After being stirred at 60 °C for 7 h, the reaction mixture was poured into saturated aqueous NH_4Cl and the aqueous layer was extracted with $CHCl_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by silica gel flash column chromatography (eluted with $CHCl_3$/MeOH = 70:1) to afford destruxin E derivative **4j-k** as a colorless oil.

4j: Yield 87% (8.1 mg, 0.0133 mmol); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (1H, d, *J* = 8.2 Hz), 7.17 (1H, d, *J* = 9.0 Hz), 5.19 (1H, q, *J* = 6.8 Hz), 4.92–4.96 (2H, m), 4.88 (1H, dd, *J* = 6.5, 9.0 Hz), 4.68 (1H, d, *J* = 7.5 Hz), 4.02–4.07 (1H, m), 3.92 (1H, brt, *J* = 9.1 Hz), 3.46–3.51 (1H, m), 3.22 (3H, s), 3.07 (1H, brt, *J* = 12.7 Hz), 2.93–2.96 (1H, m), 2.78 (1H, t, *J* = 4.4 Hz), 2.72 (3H, s), 2.66 (1H, ddd, *J* = 2.1, 11.6, 18.5 Hz), 2.56 (1H, d, *J* = 4.1, 18.5 Hz), 2.46–2.51 (2H, m), 2.29–2.35 (1H, m), 1.90–2.10 (7H, m), 1.39–1.51 (2H, m), 1.27–1.36 (4H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 6.5 Hz), 0.84–0.86 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.60, 173.58, 171.1, 170.9, 169.7, 169.1, 72.9, 60.8, 58.1, 55.5, 53.7, 51.9, 46.7, 46.6, 37.5, 34.4, 33.2, 30.8, 29.0, 28.2, 28.1, 27.24, 27.22, 24.4, 24.1, 20.0, 19.6, 15.3, 15.2, 11.4; IR (neat) 2965, 2935, 1732, 1668, 1634, 1520, 1441, 1180, 752 cm^{-1}; $[\alpha]^{25}_D$ –193 (*c* 0.456, $CHCl_3$); HRMS [ESI] calcd for $C_{30}H_{49}N_5O_8Na$ $[M+Na]^+$ 630.3473, found 630.3468.

4k: Yield 90% (18.1 mg, 0.0298 mmol); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (1H, d, *J* = 8.2 Hz), 7.16 (1H, d, *J* = 9.0 Hz), 5.19 (1H, q, *J* = 6.8 Hz), 4.96 (1H, d, *J* = 10.9 Hz), 4.93 (1H, dd, *J* = 4.1, 8.5 Hz), 4.87 (1H, dd, *J* = 6.7, 9.0 Hz), 4.66 (1H, d, *J* = 7.5 Hz), 4.03–4.08 (1H, m), 3.91 (1H, brt, *J* = 9.1 Hz), 3.48–3.52 (1H, m), 3.22 (3H, s), 3.08 (1H, brt, *J* = 13.1 Hz), 2.98–3.00 (1H, m), 2.79 (1H, dd, *J* = 4.1, 4.8 Hz), 2.72 (3H, s), 3.08 (1H, ddd, *J* = 1.9, 11.5, 18.0 Hz), 2.58 (1H, dd, *J* = 4.8, 18.0 Hz), 2.47–2.52 (2H, m), 2.29–2.35 (1H, m), 1.87–2.07 (7H, m), 1.61–1.66 (1H, m), 1.39–1.46 (1H, m), 1.27–1.36 (4H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 0.84–0.86 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 171.0, 170.9, 169.7, 168.9, 72.6, 60.8, 58.1, 55.5, 53.7, 51.2, 46.8, 46.6, 37.5, 34.4, 33.2, 30.8, 28.9, 28.1, 27.3 27.2, 26.2, 24.4, 24.1, 20.0, 19.6, 15.4, 15.2, 11.3; IR (neat) 2966, 1732, 1668, 1631, 1441, 1179, 752 cm^{-1}; $[\alpha]^{26}_D$ –193 (*c* 0.905, $CHCl_3$); HRMS [ESI] calcd for $C_{30}H_{49}N_5O_8Na$ $[M+Na]^+$ 630.3473, found 630.3464.

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Layout 2:

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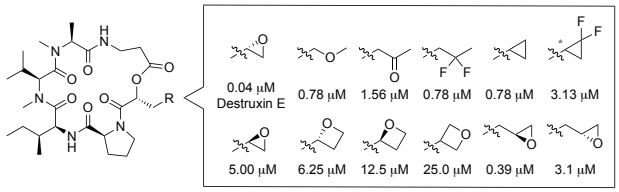

Synthesis and biological evaluation of destruxin E analogs possessing various functional groups in the α-hydroxycarboxylic acid moiety have been achieved. The (*S*)-epoxide moiety in the side chain of α-hydroxycarboxylic acid could be an essential factor for the induction of morphological changes in OCLs at a lower concentration.

Structure-Activity Relationships

*M. Yoshida, K. Adachi, H. Murase, H. Nakagawa, and T. Doi**

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Parallel Synthesis and Biological Evaluation of Destruxin E Analogs Modified with a Side Chain in the α-Hydroxycarboxylic Acid Moiety