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Synthetic studies of cyclic peptides stephanotic acid methyl ester, celogentin C, and moroidin

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ABSTRACT

An account of the total synthesis of stephanotic acid methyl ester and celogentin C is presented. The present synthesis features a tandem asymmetric Michael addition/bromination sequence for the synthesis of leucine-tryptophan moiety, and an oxidative coupling reaction to form the tryptophan-imidazole linkage. Moreover, the total synthesis of moroidin had also been studied, and three different synthetic strategies for the construction of the right-hand ring of moroidin were studied.

1. Introduction

Bicyclic peptides celogentins A–H and J, as well as moroidin (Fig. 1) were isolated by Kobayashi and co-workers from the seeds of *Celosia argentea*,[1] which is employed as a traditional herbal medicine for the treatment of liver and eye diseases in China and Japan.[2] Moroidin had been previously isolated by Williams and co-workers in 1986 from the leaves of the Australian rainforest bush *Laportea moroides*, and the structure of moroidin was further confirmed by a single crystal X-ray diffraction analysis.[3] Stephanotic acid (Fig. 1), corresponding to the left-hand part of this bicyclic peptide family, was isolated by Yoshikawa and co-workers in 2000 from *Stephanotis floribunda*.[4] The unique structure of these bicyclic peptides contains two unusual cross-links, one joining the tryptophan C-6 with the β-carbon of leucine, and the other connecting the tryptophan C-2 with the imidazole N-1 of histidine. Although N-linked His residues has been found in other macrocyclic peptides, the Leu-Trp linkage is extremely rare and poses a prominent synthetic challenge.

The bicyclic peptides of this family inhibit the tubulin polymerization, and the antimitotic activity was strongly dependent on the structure of the right-hand ring.[1] Celogentin C (IC_{50}=0.8 μM), the only member containing proline fragment, showed four times more potent than the known anti-cancer agent vinblastine (IC_{50}=3.6 μM) in a laboratory experiment. In comparison, moroidin and celogentins E–J (IC_{50}=2.0–4.0 μM) have similar antimitotic activity with vinblastine. Celogentins A, B, and D, the right-hand rings of which are tripeptides that lack proline residue, are significantly less active (IC_{50}=20–30 μM). However, stephanotic acid did not show any antimitotic activity.[4]

The impressive biological properties coupled with their unprecedented molecular architectures made the celogentins and related compounds enticing targets for chemical synthesis.[5–11] The groups of Hutton,[5] Wandless,[6] and Campagne[7] have reported synthetic studies in this area, respectively. Moody has reported the sole total synthesis of stephanotic acid methyl ester, in which, the key Leu-Trp moiety was constructed through a non-selective hydrogenation of dehydroamino acid precursors.[8a] Castle and co-workers accomplished the first total synthesis of celogentin C via an elegant NCS-mediated oxidative coupling for the Trp-His linkage and a novel Knoevenagel condensation/radical conjugate addition reaction for the synthesis of Leu-Trp moiety, albeit as a mixture of all four diastereomers.[9] Chen's group reported the asymmetric total synthesis of celogentin C by Pd-catalyzed stereoselective C–H activation.[10] Our group also accomplished the total synthesis of stephanotic acid methyl ester and celogentin C via a tandem asymmetric Michael addition/bromination reaction as the key step.[11] Herein, we present a full account of our explorations in the synthesis of stephanotic acid methyl ester, celogentin C and moroidin.

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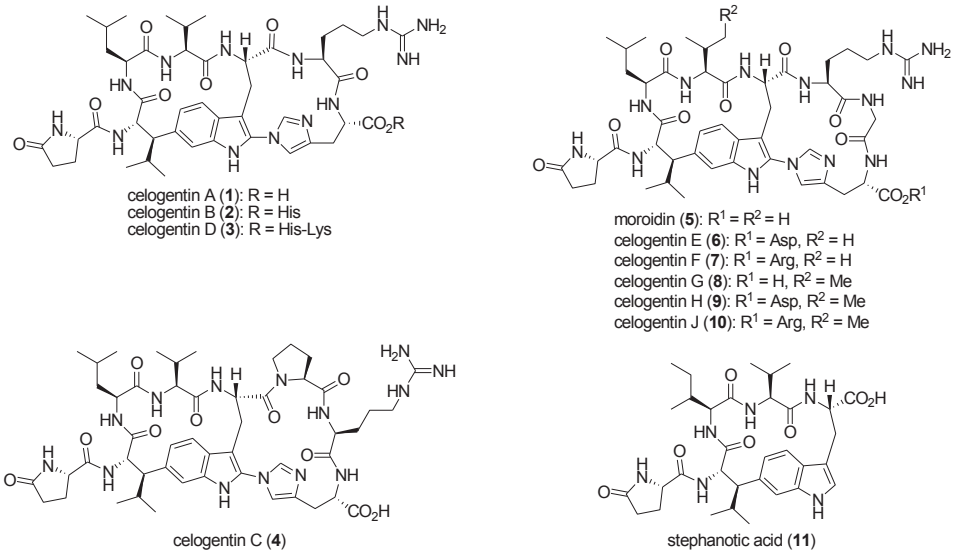


Fig. 1. Structures of moroidin, celogentins A–H, J, and stephanotic acid.

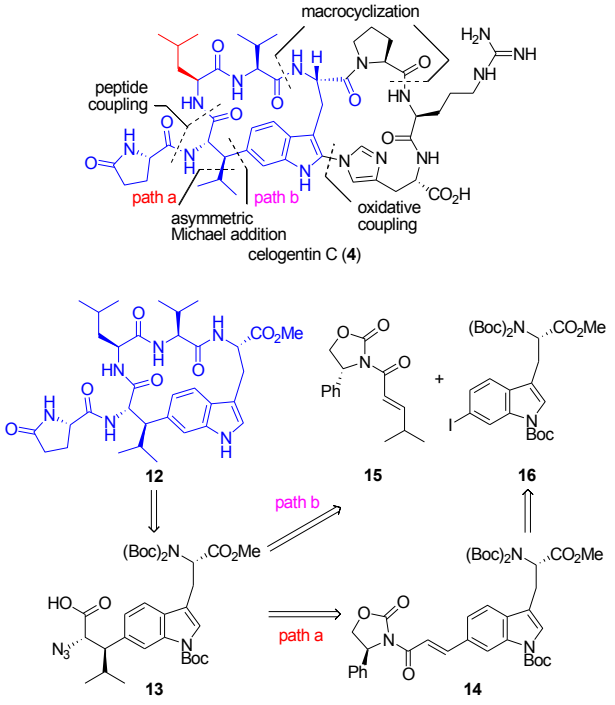
2. Results and discussions

2.1. Total synthesis of stephanotic acid methyl ester and celogentin C

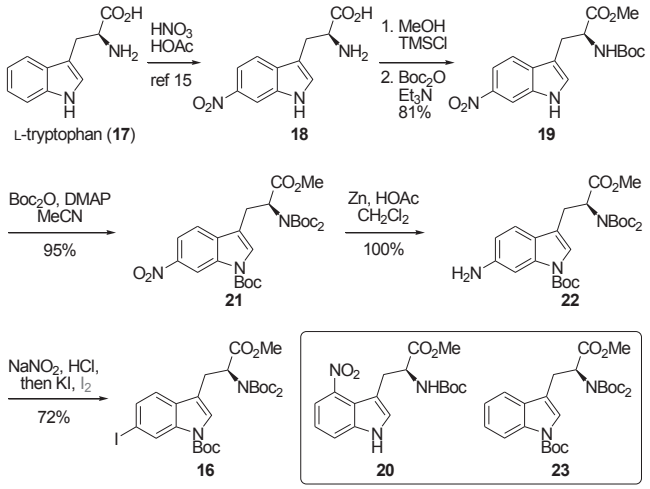
At the beginning of 2008, no total synthesis of the family of celogentins had been reported, and the efficient and stereoselective synthesis of the Leu-Trp moiety in the 'left hand' of the celogentin had also not been well resolved in previous reports. Our original plan was to achieve the stereo-controlled total synthesis of celogentin C.

Our synthetic plan of celogentin C is outlined in Scheme 1. A left-to-right sequence was adopted. The Trp-His C–N coupling and the final construction of the right-hand ring of **4** would follow the elegant sequence reported by Castle. The formation of the left-hand ring would be considered as the total synthesis of stephanotic acid methyl ester **12**, which could be achieved by macrolactamization at the Val-Trp site. For the stereoselective synthesis of the key Leu-Trp moiety **13**, we envisioned using a tandem asymmetric Michael addition/bromination followed by azidation strategy, which employs Evans' oxazolidinone auxiliary to control the configuration.[12] Accordingly, unsaturated carbonyl compounds **14** or **15**[13] could be used as Michael reaction acceptor, respectively, corresponding to the isopropyl Grignard reagent and L-tryptophan C6-Grignard reagent as the Michael reaction donor. In turn, the unsaturated carbonyl compounds **14** and L-tryptophan C6-Grignard reagent could be prepared from the known 6-iodo-L-tryptophan derivative **16**.[14]

Although the known 6-iodo-L-tryptophan derivative **16** has been prepared from the known Pd-catalyzed annulation method developed by Zhu and Jia,[14] considering the cost of the $Pd(OAc)_2$, it was not suitable for the large-scale preparation of compound **16**. Therefore, we began to pursue another synthetic approach towards compound **16** starting from the cheap and commercial available L-tryptophan **17** as outlined in Scheme 2. Nitration of L-tryptophan **17** with fuming nitric acid in acetic acid following the literature process gave the yellow crystal product **18**,[15] which was treated with



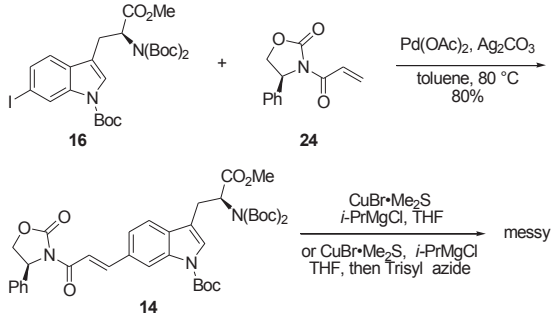
Scheme 1. Retrosynthetic analysis of celogentin C (**4**).



Scheme 2. Synthesis of 6-iodo-L-tryptophan derivative **16**.

Me_3SiCl in dry MeOH followed by the addition of Et_3N and Boc_2O to provide the desired mono-Boc product **19** in 81% yield (two steps) along with trace amounts of 4-nitro-L-tryptophan **20**. Compound **20** is an important intermediate in the total synthesis of natural product clavicipitic acid.[14h] Protection of **19** with Boc_2O followed by reduction of nitro group in **21** with Zn dust and HOAc in CH_2Cl_2 gave the 6-amino derivative **22**. Diazotization of aniline followed by iodination provided the desired product **16** in 72% yield along with 10% reduced compound **23**.[16] It was noteworthy that the addition of 1 equiv of I_2 was crucial for decreasing the yield of the reduced compound **23**.

With 6-iodo-L-tryptophan derivative **16** in hand, the stage was set for the construction of the key Leu-Trp moiety by using the tandem conjugate addition/bromination sequence. We first investigated the synthetic route of path a (Scheme 3). Heck reaction of **16** with α,β-unsaturated carbonyl compound **24** under the $Pd(OAc)_2/Ag_2CO_3$/toluene condition provided **14** in 80% yield.[14f,h] Unfortunately, attempts to Michael addition reaction or the tandem Michael addition/azidation reaction using **14** as Michael reaction acceptor under a variety of reported reaction conditions did not lead to the desired product.



Scheme 3. Failed Michael addition or tandem Michael addition/azidation reaction.

We then turned our attention to path b by using carbonyl compounds **15** as Michael reaction acceptor.[12] Accordingly, the L-tryptophan C6-Grignard reagent must be used as the Michael reaction donor. It was originally thought that the preparation of the L-tryptophan C6-Grignard reagent could be quite challenging due to its structural complex and bearing many base-sensitive functional groups. To our surprise, the L-tryptophan C6-Grignard reagent was readily prepared by iodo/magnesium exchange following the literature's procedure.[17] During optimizing the tandem Michael addition/bromination reaction conditions, we found that the amount of $CuBr\cdot Me_2S$ was crucial for the 1,4-conjugation addition, although the reason is still not clear (Table 1). When the tandem reaction was performed in the presence of 1.0 equiv of $CuBr\cdot Me_2S$, only a small amount of the expected product **25** was obtained (Table 1, entries 1 and 2). When 0.1 equiv of $CuBr\cdot Me_2S$ was used, the desired product **25** was obtained in 30% yield (Table 1, entry 3). Further optimized the amount of $CuBr\cdot Me_2S$ for the tandem reaction revealed that 0.2 equiv of Cu(I) catalyst gave the best yield of 65% (Table 1, entries 4 and 5). It is noteworthy that the selectivity in both stereoselective 1,4-addition and stereoselective bromination were excellent, compound **25** was obtained as a single detectable diastereomers, and none of other diastereomers were observed in the crude product.

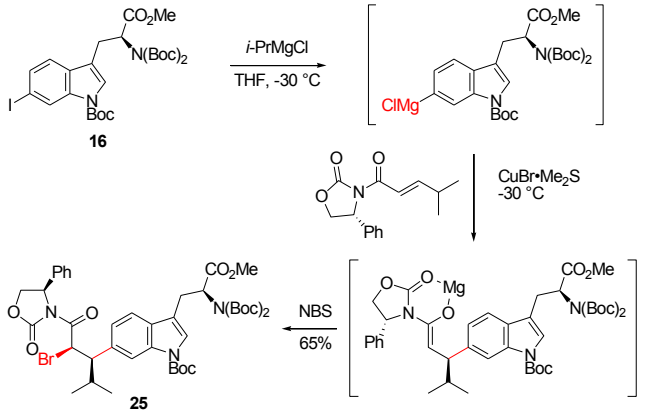
With the key intermediate **25** in hand, the synthesis of stephanotic acid methyl ester and celogentin C was illustrated in Scheme 4. S_N2 displacement of the bromo group with NaN_3 in DMF provided α-azido product **26** in 82% yield. We originally thought that selective removal of the chiral auxiliary under base condition might be problem since the amine di-Boc, indole-*N*-Boc, and methyl ester are base-sensitive. Surprisingly, chemoselective hydrolysis of **26** was effected exclusively by using LiOH in the presence of hydrogen peroxide to give the azido acid **13** in 95% yield. Coupling **13** with dipeptide Ile-Val-O^{t}Bu (**27**) provided cyclization precursor **28** in 82% yield.

Simultaneous deprotection of the *N*-Boc group and the *tert*-butyl ester of **28** with trifluoroacetic acid followed by macrolactamization under high-dilution conditions using HATU as coupling agent gave the macrocycle **29** in 48% overall yield as a single product. It should be mentioned that in Moody's total synthesis of stephanotic acid methyl ester, they conducted the macrocyclization via Leu-Val amide bond formation and found some epimerization had occurred during the formation of **29**. We were pleased to discover that macrolactamization at the Val-Trp site was devoid of epimerization.

Attempt to reduce the azide group of **29** under Staudinger condition failed to give the desired corresponding amine. Gratefully, reduction of **29** with HCO_2NH_4 in the presence of 10% Pd/C successfully provided the desired amine. Finally, coupling the amine with pyroglutamic acid using HATU gave stephanotic acid methyl ester **12** in 70% yield, whose physical properties (NMR, MS, and optical rotation) were essentially identical to those reported for the natural material.[4] Thus, the stereoselective total synthesis of (−)-stephanotic acid methyl ester was accomplished in longest linear 14 steps (4.6% overall yield). This result also confirmed the tandem Michael addition/bromination reaction yielded the right stereochemistry of compound **25**.

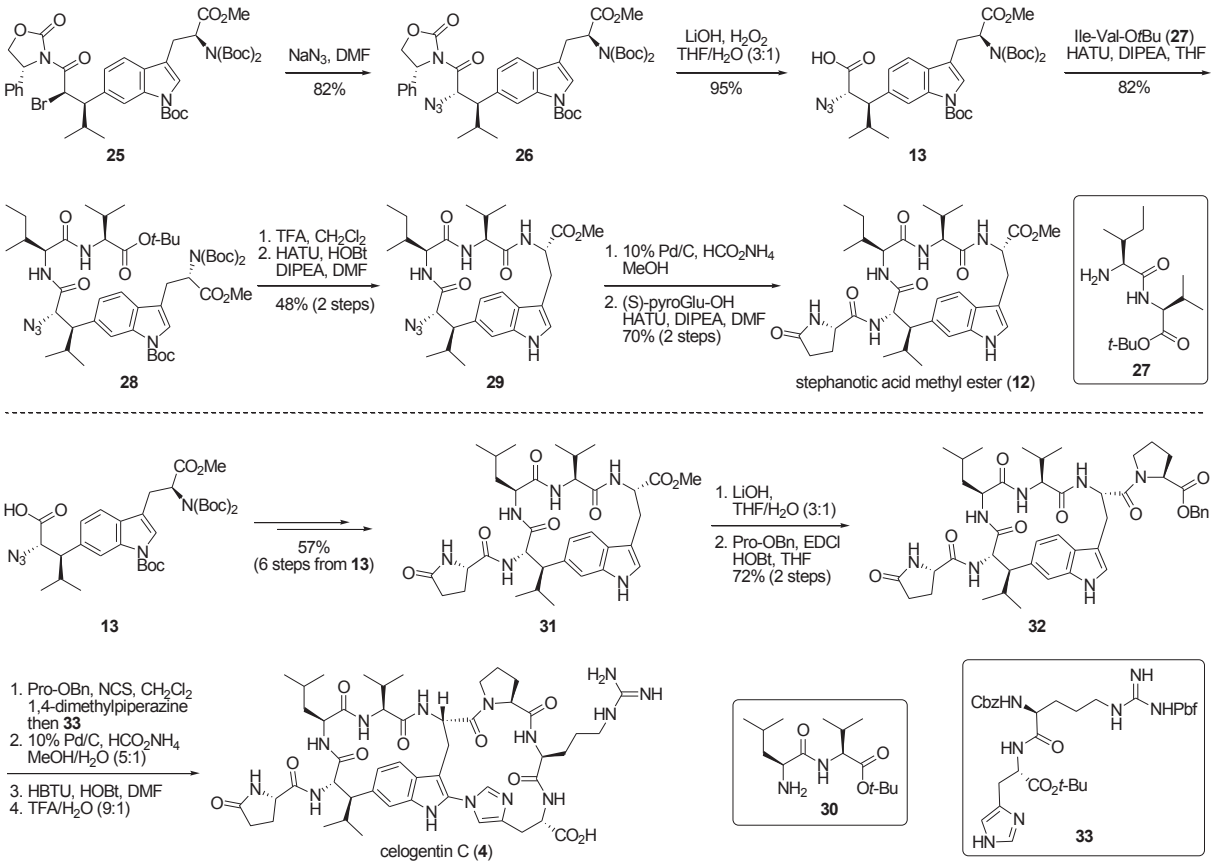
After completion of the synthesis of stephanotic acid methyl ester, we turned our attention to the total synthesis of celogentin C from the key intermediate **13**. Coupling of acid **13** with the dipeptide Leu-Val-O^{t}Bu (**30**),[18] following the same procedure as described for stephanotic acid methyl ester gave compound **31** in 57% yield. Treatment of **31** with LiOH in THF/H_2O (3:1) followed acidification using HCl gave the free acid. Coupling the free acid with Pro-OBn using EDCI and HOBt provided the key intermediate **32**, which was readily converted to (−)-celogentin C in a four-step sequence according to the protocol reported by Castle. Thus, our total synthesis of (−)-celogentin C was achieved in only 20 steps and 1.6% overall yield from the L-tryptophan.

Table 1
Optimization of the conjugate addition/bromination cascade sequence



Entry	$CuBr\cdot Me_2S$ (equiv)	Solvent	25[a]
1	1.0	THF/Me_2S (1:1)	4%
2	1.0	THF	6%
3	0.1	THF	30%
4[b]	0.05	THF	—
5	0.2	THF	65%

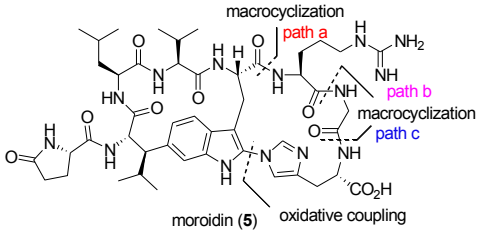
[a] Isolated yield.
[b] Reaction is messy, desired product was not detected.



Scheme 4. Total synthesis of stephanotic acid methyl ester (**12**) and celogentin C (**4**).

2.2. Synthetic studies of moroidin

Despite the total synthesis of celogentin C has been achieved by three groups, the total synthesis of other members of this family has not been described yet. Having accomplished the total synthesis of celogentin C and with a large amount of 'left-hand' compound **31** in hand, we turned our attention to the synthesis of moroidin (**5**). As outlined in Scheme 5, the left-to-right sequence was also adopted in our synthetic plan. We envisioned that the Trp-His linkage could be accomplished by NCS-mediated oxidative coupling, and the formation of the right-hand macrocycle could be achieved by macrolactamization at three different sites.



Scheme 5. Retrosynthetic analysis of moroidin (**5**).

We first investigated the macrocyclization at Trp-Arg site (path a) (Scheme 3). Saponification of the methyl ester of **31** (LiOH, THF/H_2O) followed by acidic treatment (HCl) afforded the free acid, which then coupled with BnOH using EDCI and DMAP provided **34** in 79% yield. Treatment of **34** with 1,4-dimethylpiperazine and NCS in CH_2Cl_2 followed addition of tripeptide **35** gave the key intermediate **36** in 78% yield. Simultaneous deprotection of the Cbz and the benzyl ester by hydrogenation provided the cyclization precursor. Disappointingly, macrolactamization using HATU as coupling agent failed to give the desired product (Scheme 6). Other coupling agents (HBTU, EDCI) were screened, but no desired product was formed.

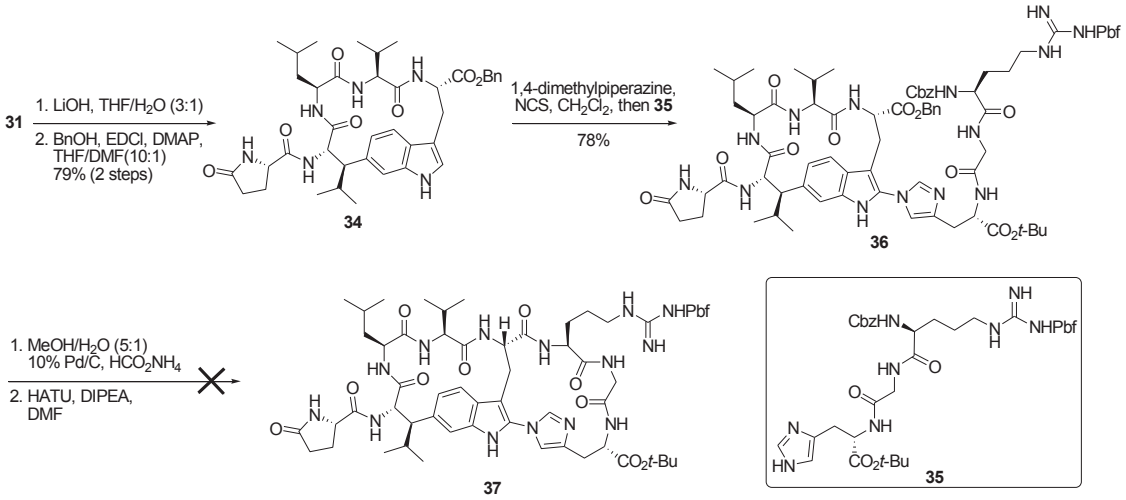
Since the final construction of the right-hand ring of celogentin C was successful by macrolactamization at the Pro-Arg site, we envisioned that the macrolactamization could be achieved at similar Arg-Gly site (path b) (Scheme 7). NCS-mediated oxidative coupling of **31** with dipeptide **38** gave the desired product **39** in 60% yield. Hydrolysis of the methyl ester of **39** followed by coupling with **40** using HBTU as coupling agent provided **41** in 45% yield. Saponification of the methyl ester and deprotection of the Cbz by hydrogenation the Cbz provided the cyclization precursor. Once again, macrolactamization failed to give the desired product. We were too distressed and confused to understand these results.

We then had to turn our attention to the macrolactamization at the Trp-His site (path c) (Scheme 8). The key intermediate **45** could be prepared from **31** following the similar procedure as described for **41**. The macrolactamization was performed after deprotection of the methyl ester and the Cbz of **45**. However, the desired macrocycle product was still not detected.

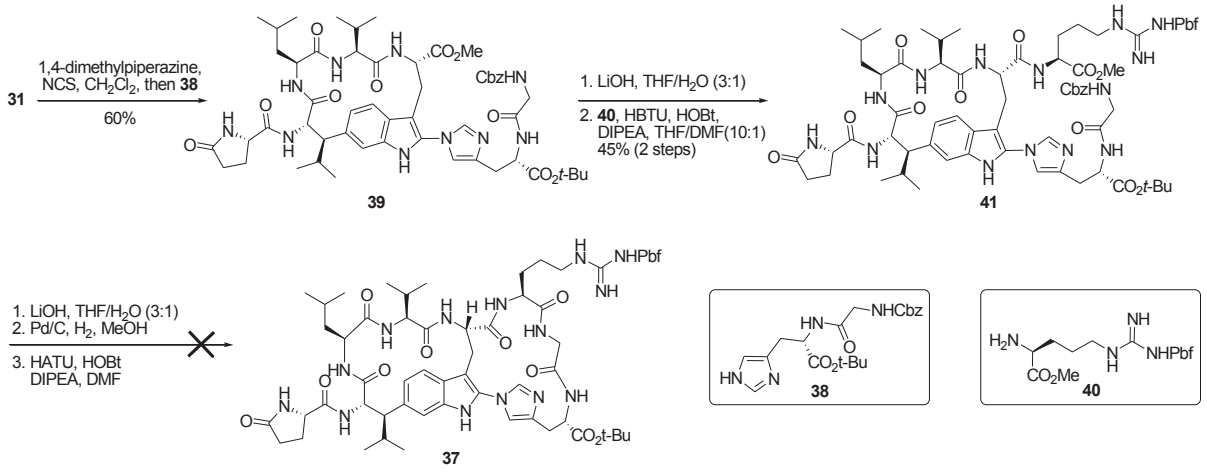
The reason why it is difficult for the macrolactamization of moroidin is still not clear, but these results could serve as a reference for further synthesis of moroidin.

3. Conclusion

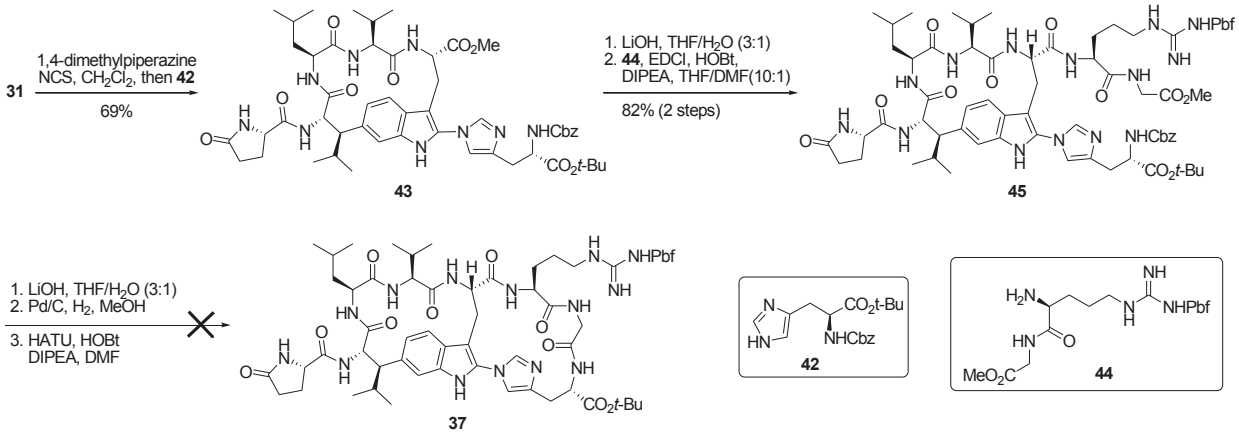
We have achieved the stereoselective total synthesis of stephanotic acid methyl ester and celogentin C in longest linear 14



Scheme 6. Synthetic studies of moroidin through path a.



Scheme 7. Synthetic studies of moroidin through path b.



Scheme 8. Synthetic studies of moroidin through path c.

steps (4.6% overall yield) and 20 steps (1.6% overall yield) from the commercially available L-tryptophan, respectively. The leucine-tryptophan moiety was constructed via a tandem asymmetric Michael addition/bromination followed by azidation strategy. The key Trp-His side-chain linkage was formed by an oxidative coupling reaction. The total synthesis of moroidin had also been studied. Three different synthetic strategies were performed for the construction of the right-hand ring of moroidin. Although the total

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synthesis of moroidin has not been accomplished, these results will be served as a reference for further synthesis of moroidin.

4. Experimental section

4.1. General information

All reagents were obtained from commercial suppliers unless otherwise stated. Tetrahydrofuran (THF) was distilled from potassium sodium alloys; dichloromethane and acetonitrile were distilled from calcium hydride. *N*,*N*-Dimethylformamide (DMF) was distilled from magnesium sulfate under vacuum. Methanol was distilled from magnesium methoxide. Flasks were flame-dried under vacuum and cooled under a stream of nitrogen or argon. Flash chromatography was performed using silica gel (200–300 mesh) with solvents distilled prior to use. Visualization was achieved under a UV lamp (254 nm and 365 nm), and by developing the plates with phosphomolybdic acid or triketohydrindene hydrate in ethanol. ^{1}H NMR were recorded at 300 MHz or 400 MHz NMR spectrometer, ^{13}C NMR at 75 MHz or 100 MHz NMR spectrometer unless otherwise stated. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, m: multiplet, br s: broad singlet for proton spectra. Coupling constants (*J*) are reported in Hertz (Hz). Infrared spectra were recorded with a thin layer of the product on a KBr disk.

4.2. Experimental procedure and physical data

*4.2.1. 6-Nitro-L-tryptophan derivative **21**.* To a stirred suspension of nitration of 6-nitro-L-tryptophan **18**[15] (6.39 g, 25.7 mmol) in dry MeOH (90 mL) was added slowly Me_3SiCl (25.0 mL, 196 mmol) in an ice-cold bath. After the addition was completed, the ice-cold bath was removed and the reaction was stirred at room temperature for 18.0 h. Then, Et_3N (50 mL, 361 mmol) and $(Boc)_2O$ (8.9 g, 40.8 mmol) were sequentially added. The reaction mixture was stirred until TLC showed complete protection. The solvent was removed under reduced pressure and the residue was extracted between water and EtOAc (3×60 mL). The combined organic layers were dried over Na_2SO_4, and then evaporated in vacuo.

To a solution of above crude product in dry CH_3CN (90 mL) was added DMAP (650 mg, 5.3 mmol) and $(Boc)_2O$ (12.4 g, 56.9 mmol) at room temperature. The mixture was stirred for 1 h, after which time TLC showed that some starting material still remained. More $(Boc)_2O$ (4.4 g, 20.2 mmol) was added and the mixture was additionally stirred overnight. The solvent was evaporated, and the crude purified by silica gel column chromatography to afford **21** (8.59 g, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.14 (dd, *J*=8.7, 2.1 Hz, 1H), 7.68 (s, 1H), 7.64 (d, *J*=8.7 Hz, 1H), 5.19 (dd, *J*=9.9, 5.3 Hz, 1H), 3.77 (s, 3H), 3.55 (dd, *J*=15.0, 5.3 Hz, 1H), 3.39 (dd, *J*=15.0, 9.9 Hz, 1H), 1.69 (s, 9H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 151.9 (2C), 148.6, 144.9, 135.3, 134.1, 129.3, 119.0, 117.7, 116.6, 111.5, 84.9, 83.1 (2C), 57.8, 52.3, 27.8 (3C), 27.5 (6C), 25.2.

*4.2.2. 6-Iodo-L-tryptophan derivative **16**.* To a solution of nitrotryptophan **20** (8.59 g, 15.3 mmol) and Zn dust (50.0 g) in CH_2Cl_2 (180 mL) was slowly added HOAc (14.0 mL) at 0 °C. The solution was stirred at room temperature for 20 min and then the solution was filtered. The filtrate was washed with saturated aqueous $NaHCO_3$, H_2O and brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was dissolved in THF (112 mL), H_2O (79 mL), and 5% HCl (43 mL). $NaNO_2$ was slowly added to the solution at 0 °C. After being stirred at 0 °C for 5 min, the mixture was added to the solution of KI (15.8 g 95.2 mmol) and I_2 (4.06 g 16.0 mmol) in H_2O (150 mL), then the resulting reaction mixture was continued to stir at room temperature for 1.0 h. The reaction mixture was basified to pH 7–8 with saturated aqueous $NaHCO_3$, extracted with EtOAc, and the combined organic phases were washed with saturated aqueous $NaHSO_3$, H_2O and brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 10–15% EtOAc in petroleum ether, then CH_2Cl_2 again) to provide the desired product **16** (7.08 g, 72%) and deiodo product (0.80 g 10%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.48 (d, *J*=7.8 Hz, 1H), 7.27 (s, 1H), 7.23 (d, *J*=7.8 Hz, 1H), 5.12 (dd, *J*=9.9, 5.1 Hz, 1H), 3.72 (s, 3H), 3.44 (dd, *J*=15.0, 5.1 Hz, 1H), 3.29 (dd, *J*=15.0, 9.9 Hz, 1H), 1.60 (s, 9H), 1.30 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 151.7 (2C), 149.0, 136.3, 131.3, 129.8, 124.4, 124.1, 120.4, 116.3, 88.7, 83.9, 83.0 (2C), 58.0, 52.3, 28.0 (3C), 27.6 (6C), 25.3.

*4.2.3. (S)-3-Acryloyl-4-phenyloxazolidin-2-one (**24**).* To the solution of acrylic acid (1.65 g, 22.9 mmol) and Et_3N (2.5 equiv) in THF (volume corresponded to 0.2 M of the oxazolidinone) was added trimethylacetyl chloride (2.54 g, 21.1 mmol) at −20 °C. A white solid was formed instantaneously. The mixture was stirred at −20 °C for 2.0 h. Lithium chloride (0.82 g, 19.4 mmol) was added, followed by the oxazolidinone (2.87 g, 17.6 mmol). The mixture was allowed to warm to room temperature slowly and stirred for 4.0 h. The reaction was quenched by addition of saturated NH_4Cl and the solution was extracted with EtOAc. The organic layer was washed subsequently with saturated $NaHCO_3$, brine and water, dried over anhydrous Na_2SO_4 and filtered. EtOAc was removed in vacuo, and the residue was purified by flash column chromatography (silica gel, 12% EtOAc in petroleum ether) provided the desired product **24** (2.73 g, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J*=11.2, 16.8 Hz, 1H), 7.32–7.41 (m, 5H), 6.48 (d, *J*=16.8 Hz, 1H); 5.88 (d, *J*=10.4 Hz, 1H), 5.50 (dd, *J*=3.6, 8.4 Hz, 1H), 4.72 (t, *J*=8.8 Hz, 1H), 4.31 (dd, *J*=3.6, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 153.5, 138.8, 132.0, 129.1, 128.7, 127.2, 125.9, 70.0, 57.7.

*4.2.4. Unsaturated carbonyl compounds **14**.* To a solution of compound **16** (323 mg, 0.50 mmol) and (*S*)-3-acryloyl-4-phenyloxazolidin-2-one **24** (132 mg, 0.60 mmol) in dry toluene (2.0 mL) was added $Pd(OAc)_2$ (5.7 mg, 0.025 mmol) and Ag_2CO_3 (83 mg, 0.3 mmol). The resulting reaction mixture was stirred at 80 °C for 1 day. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 20%–25% EtOAc in petroleum ether) to provide the desired product **14** (296 mg, 80%) as amorphous solid; $[\alpha]_D^{25}$ −52.0 (*c* 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.97 (d, *J*=15.6 Hz, 1H), 7.90 (d, *J*=15.6 Hz, 1H), 7.48–7.54 (m, 3H), 7.33–7.41 (m, 5H), 5.57 (dd, *J*=3.84, 8.68 Hz, 1H), 5.18 (q, *J*=4.96, 1H), 4.73 (t, *J*=8.76), 4.31 (dd, *J*=3.84, 8.84 Hz, 1H), 3.76 (s, 1H), 3.51 (dd, *J*=4.88, 14.96 Hz, 1H), 3.35 (dd, *J*=10.04, 14.92 Hz, 1H), 1.67 (s, 9H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 164.9, 153.8, 151.8, 149.3, 147.9, 139.2, 135.5, 132.9, 130.9, 129.1, 128.6, 126.6, 126.0, 123.0, 119.3, 116.7, 116.1, 115.5, 84.2, 83.0, 69.9, 58.1, 57.9, 52.3, 28.2, 27.7, 25.5; HRMS (ESI) *m*/*z* calcd for $C_{39}H_{47}N_3O_{11}Na$ $(M+Na)^+$ 756.3108; found 756.3112.

*4.2.5. (R,E)-3-(4-Methylpent-2-enoyl)-4-phenyloxazolidin-2-one (**15**).* To the solution of (2*E*)-isohexenoic acid (2.67 g, 23.4 mmol) and Et_3N (2.5 equiv) in THF (volume corresponded to 0.2 M of the oxazolidinone) was added trimethylacetyl chloride (2.62 g, 21.7 mmol) at −20 °C. A white solid was formed instantaneously. The mixture was stirred at −20 °C for 2.0 h. Lithium chloride (0.92 g, 21.6 mmol) was added, followed by the oxazolidinone (2.92 g, 17.9 mmol). The mixture was allowed to warm to room temperature slowly and stirred for 4.0 h. The reaction was quenched by addition of saturated NH_4Cl and the solution was extracted with EtOAc. The organic layer was washed subsequently with saturated $NaHCO_3$, brine and water, dried over anhydrous

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Na_2SO_4 and filtered. EtOAc was removed in vacuo, and the residue was purified by flash column chromatography (silica gel, 12% EtOAc in petroleum ether) provided the desired product **15** (4.33 g, 93%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 7.22 (dd, J=15.6, 1.2 Hz, 1H), 7.05 (dd, J=15.6, 6.6 Hz, 1H), 5.48 (dd, J=8.7, 3.9 Hz, 1H), 4.68 (t, J=9.0 Hz, 1H), 4.26 (dd, J=9.0, 3.9 Hz, 1H), 2.52 (m, 1H), 1.07 (d, J=6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 158.2, 153.8, 139.2, 129.1 (2C), 128.6, 126.0 (2C), 117.6, 69.8, 57.6, 31.3, 21.1, 21.0.

*4.2.6. Compound **25**.* To a solution of iodo-tryptophan **16** (1.29 g, 2.0 mmol) in dry THF (4.0 mL) was added *i*-PrMgCl (2.0 M, 1.0 mL, 2.0 mmol) dropwise at −30 °C and the reaction mixture was stirred at the same temperature for 30 min. CuBr·Me_2S (83 mg, 0.4 mmol) was added to the reaction at −30 °C and the mixture was warmed to −20 °C over 20 min. The unsaturated amide **15** (519 mg, 2.0 mmol) in dry THF (2.0 mL) was added slowly at −15 to −10 °C. After being stirred at the same temperature for 4.0 h, the reaction mixture was cooled to −78 °C, and NBS (357 mg, 2.0 mmol) in dry THF (5.0 mL) was added. After an additional 2.0 h, the mixture was slowly warmed to 0 °C and then was stirred at 0 °C for 2.0 h the reaction mixture was quenched with saturated $NaHSO_3$ and extracted with EtOAc (3×30 mL). The combined organic phase was washed with water (30 mL), brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 12%–17% EtOAc in petroleum ether) to afford the desired product **25** (1.11 g, 65%); $[\alpha]_D^{30}$ −64.5 (*c* 1.00, MeOH); IR (neat): 2979, 1784, 1735, 1481, 1442, 1370, 1326, 1257, 1139, 1087, 851, 765, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.46 (d, J=8.2 Hz, 1H), 7.40 (s, 1H), 7.37–7.32 (m, 5H), 7.05 (d, J=8.2 Hz, 1H), 6.36 (d, J=10.4 Hz, 1H), 5.46 (dd, J=8.8, 4.4 Hz, 1H), 5.21 (dd, J=10.0, 4.6 Hz, 1H), 4.82 (t, J=8.8 Hz, 1H), 4.30 (dd, J=8.8, 4.4 Hz, 1H), 3.76 (s, 3H), 3.50 (dd, J=15.2, 4.6 Hz, 1H), 3.45 (dd, J=10.4, 5.2 Hz, 1H), 3.34 (dd, J=15.2, 10.0 Hz, 1H), 2.09 (m, 1H), 1.65 (s, 9H), 1.32 (s, 18H), 0.90 (d, J=6.8 Hz, 3H), 0.80 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 167.9, 152.9, 151.6, 149.6, 137.7, 135.1, 134.1, 129.7, 129.1, 128.8, 125.8, 124.5, 118.1, 116.3, 83.5, 82.9, 70.0, 58.1, 53.8, 52.2, 30.8, 28.1, 27.7, 25.6, 21.9, 17.9; HRMS (ESI) *m*/*z* calcd for $C_{42}H_{58}BrN_4O_{11}$ $(M+NH_4)^+$ 873.3280; found 873.3279.

*4.2.7. Compound **26**.* To a solution of compound **25** (5.74 g, 6.7 mmol) in DMF (21 mL) was added NaN_3 (1.14 g, 17.5 mmol) in one portion at room temperature. After being stirred for one day, DMF was removed under vacuum. The residue was diluted with EtOAc (50 mL) and water (50 mL), and the aqueous phase was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with water (2×50 mL), brine (2×50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10%–12% EtOAc in petroleum ether) to afford the desired product **26** (4.52 g, 82%); $[\alpha]_D^{34}$ −29.9 (*c* 1.00, MeOH); IR (neat): 2978, 2104, 1785, 1736, 1698, 1482, 1443, 1370, 1329, 1267, 1255, 1158, 1141, 1089, 851, 762, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.47 (s, 1H), 7.31 (d, J=8.0 Hz, 1H), 6.97 (t, J=7.6 Hz, 1H), 6.93 (d, J=8.0 Hz, 1H), 6.69 (t, J=7.6 Hz, 2H), 6.35 (d, J=7.6 Hz, 2H), 5.78 (d, J=11.6 Hz, 1H), 5.26 (dd, J=8.8, 4.4 Hz, 1H), 5.23 (dd, J=10.0, 5.0 Hz, 1H), 4.57 (t, J=8.8 Hz, 1H), 4.02 (dd, J=8.8, 4.4 Hz, 1H), 3.78 (s, 3H), 3.55 (dd, J=14.8, 5.0 Hz, 1H), 3.38 (dd, J=14.8, 10.0 Hz, 1H), 3.22 (dd, J=11.6, 4.0 Hz, 1H), 2.34 (m, 1H), 1.66 (s, 9H), 1.35 (s, 18H), 0.94 (d, J=6.8 Hz, 3H), 0.80 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.4, 152.8, 151.7, 149.3, 137.0, 134.9, 132.1, 129.7, 128.2, 127.7, 125.0, 124.6, 124.5, 118.3, 116.1, 115.9, 83.8, 82.9, 69.5, 58.9, 57.7, 57.3, 52.4, 52.2, 28.5, 28.0, 27.7, 25.4, 21.0, 17.1; HRMS (ESI) *m*/*z* calcd for $C_{42}H_{54}N_6NaO_{11}$ $(M+Na)^+$ 841.3743; found 841.3738.

*4.2.8. Compound **28**.* To a solution of azido compound **26** (409 mg, 0.50 mmol) in THF (6.0 mL) was added water (2.0 mL). The solution was stirred at 0 °C for 15 min, and then 30% H_2O_2 (0.45 mL, 8 equiv) was added dropwise followed by dropwise addition of lithium hydroxide monohydrate (81 mg, 1.93 mmol) in water (1.0 mL). The resulting mixture was stirred at 0 °C for 6 h. The reaction was quenched with saturated Na_2SO_3 and stirred at room temperature for 30 min. The mixture was acidified with 6 N HCl to pH=2 and extracted with EtOAc (3×20 mL). The combined organic phase was washed with water (30 mL), brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo to give crude product, which was used directly in the next step.

A solution of above acid and Ile-Val-O^{t}Bu (**27**) in dry THF (3.0 mL) at 0 °C was treated with HATU (263 mg, 0.69 mmol) and DIPEA (0.30 mL, 223 mg, 1.73 mmol). The resulting mixture was stirred at room temperature for 1 d. The reaction mixture was diluted with EtOAc. The organic phase was washed with 1% HCl (20 mL), saturated $NaHCO_3$ (20 mL), water (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 12%–17% EtOAc in petroleum ether) to afford the desired product **28** (367 mg) in a total yield of 78% for two steps; $[\alpha]_D^{22}$ −35.0 (*c* 1.00, MeOH); IR (neat): 3401, 2975, 2108, 1736, 1699, 1655, 1516, 1443, 1370, 1257, 1155, 1088, 851, 768 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.36 (s, 1H), 7.06 (d, J=8.0 Hz, 1H), 6.71 (d, J=8.1 Hz, 1H), 6.14 (d, J=8.4 Hz, 1H), 5.18 (dd, J=10.2, 5.0 Hz, 1H), 4.34 (d, J=5.4 Hz, 1H), 4.28 (dd, J=8.7, 4.8 Hz, 1H), 4.08 (t, J=7.8 Hz, 1H), 3.75 (s, 3H), 3.48 (dd, J=15.0, 5.0 Hz, 1H), 3.29 (dd, J=15.0, 10.2 Hz, 1H), 3.02 (dd, J=8.4, 5.4 Hz, 1H), 2.52 (m, 1H), 2.08–2.01 (m, 2H), 1.64 (s, 9H), 1.43 (s, 9H), 1.31 (s, 18H), 1.31–1.15 (m, 1H), 1.04 (d, J=6.3 Hz, 3H), 0.85–0.66 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.5, 170.2, 168.2, 151.6, 149.4, 135.5, 129.6, 124.4, 123.9, 118.6, 116.2, 115.5, 83.4, 82.9, 82.0, 67.0, 58.0, 57.7, 57.6, 55.0, 52.3, 36.9, 31.2, 28.8, 28.1, 27.9, 27.7, 25.5, 24.9, 21.4, 20.4, 18.7, 17.6, 14.9, 11.1; HRMS (ESI) *m*/*z* calcd for $C_{48}H_{75}N_7NaO_{12}$ $(M+Na)^+$ 964.5366; found 964.6365.

*4.2.9. Macrocycle compound **29**.* Trifluoroacetic acid (5.0 mL) was added slowly to a solution of compound **28** (283 mg, 0.30 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C. After 2.0 h the reaction mixture was concentrated ensuring all excess trifluoroacetic had been removed. The residue was dissolved in anhydrous DMF (150 mL), cooled to 0 °C, DIPEA (0.75 mL, 4.31 mmol) and HATU (1.14 g, 3.0 mmol) were added sequentially. The reaction mixture was allowed to warm to room temperature, was stirred for 9 days, and then was concentrated. The residue was dissolved in EtOAc (50 mL) and was washed with 1% HCl (20 mL), saturated $NaHCO_3$ (2×30 mL), and brine (30 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60%–90% EtOAc in petroleum ether) to give the product **29** (82 mg, 48%); $[\alpha]_D^{27}$ −18.5 (*c* 1.00, MeOH); IR (neat): 3328, 2965, 2101, 1745, 1661, 1513, 1460, 1384, 1211 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (d, J=8.4 Hz, 1H), 7.01 (s, 1H), 6.98 (s, 1H), 6.87 (d, J=8.4 Hz, 1H), 5.48 (m, 1H), 4.03 (d, J=8.4 Hz, 1H), 3.92 (d, J=11.6 Hz, 1H), 3.83 (d, J=6.0 Hz, 1H), 3.78 (s, 3H), 3.48 (dd, J=14.8, 5.6 Hz, 1H), 3.20–3.11 (m, 2H), 2.32 (m, 1H), 2.02 (m, 1H), 1.64 (m, 1H), 1.45 (m, 1H), 1.11 (m, 1H), 1.03 (d, J=6.4 Hz, 3H), 0.96 (d, J=6.4 Hz, 3H), 0.92–0.89 (m, 12H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.7, 172.2, 171.7, 171.1, 138.4, 131.2, 127.1, 125.6, 120.2, 118.7, 115.8, 110.0, 66.6, 60.0, 59.4, 53.4, 52.8, 51.9, 38.9, 32.4, 30.1, 28.7, 26.0, 22.0, 19.0, 18.9, 15.9, 11.0; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{42}N_7O_5$ $(M+H)^+$ 568.3242; found 568.3247.

*4.2.10. Stephanotic acid methyl ester (**12**).* A solution of compound **29** (80 mg, 0.14 mmol) in MeOH (3.0 mL) was degassed for 20 min, then HCO_2NH_4 (115 mg) and 10% Pd/C (190 mg) was added sequentially. The reaction mixture was stirred under argon at room temperature for 10 h and filtered through filter paper. The filter pad

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was washed with MeOH, and the filtrate was concentrated. The residue was dissolved in EtOAc (30 mL) and was washed with saturated $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give crude product, which was used directly in the next step.

A solution of above crude product in dry DMF (2.0 mL) at 0 °C was treated with (*S*)-pyroglutamic acid (32 mg, 0.25 mmol), DIPEA (0.1 mL, 0.58 mmol), and HATU (107 mg, 0.28 mmol). The reaction mixture was allowed to warm to room temperature overnight and the solvent was removed under vacuum. The residue was dissolved in EtOAc (30 mL) and was washed with HCl (1 M; 10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 3%–4% MeOH in CH_2Cl_2) to give stephanotic acid methyl ester **12** (64 mg, 70%); $[\alpha]_D^{22}$ −112.4 (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.52 (d, *J*=9.2 Hz, 1H), 8.30 (d, *J*=10.0 Hz, 1H), 7.87 (s, 1H), 7.43 (d, *J*=8.4 Hz, 1H), 7.36 (d, *J*=8.4 Hz, 1H), 6.99–6.97 (m, 3H), 6.88 (s, 1H), 5.23 (m, 1H), 4.86 (t, *J*=10.4 Hz, 1H), 4.11 (dd, *J*=8.8, 3.6 Hz, 1H), 3.88 (dd, *J*=7.6, 6.0 Hz, 1H), 3.76 (dd, *J*=10.4, 8.4 Hz, 1H), 3.65 (s, 3H), 3.27 (m, 1H), 3.13 (dd, *J*=15.2, 8.8 Hz, 1H), 2.99 (dd, *J*=11.6, 3.6 Hz, 1H), 2.24 (m, 1H), 2.13 (m, 1H), 2.08 (m, 2H), 2.01 (m, 1H), 1.71 (m, 1H), 1.62 (m, 1H), 1.22 (m, 2H), 0.92 (d, *J*=6.8 Hz, 3H), 0.89 (d, *J*=6.8 Hz, 3H), 0.85 (d, *J*=6.8 Hz, 3H), 0.77 (d, *J*=8.6 Hz, 3H), 0.68–0.63 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.5, 172.2, 171.8, 170.7, 170.0, 169.7, 136.1, 129.8, 125.5, 123.5, 119.0, 117.8, 114.4, 108.4, 58.0, 57.7, 55.2, 55.1, 52.0, 51.9, 51.1, 37.2, 30.5, 29.0, 27.1, 26.8, 25.6, 24.1, 21.8, 18.7, 17.9, 17.3, 15.4, 10.4; HRMS (ESI) *m*/*z* calcd for $C_{34}H_{49}N_6O_7$ $(M+H)^+$ 653.3657; found 653.3664.

*4.2.11. Compound **31**.* Compound **31** was prepared from azido acid **13** according to the same procedure as that described for stephanotic acid methyl ester **12**; $[\alpha]_D^{34}$ −200.5 (*c* 1.00, MeOH); IR (neat): 3310, 2960, 1741, 1649, 1521, 1456, 1368, 1264, 1214 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.53 (d, *J*=8.8 Hz, 1H), 8.39 (d, *J*=10.0 Hz, 1H), 7.86 (s, 1H), 7.37 (d, *J*=8.4 Hz, 1H), 7.31 (d, *J*=8.4 Hz, 1H), 6.98 (s, 1H), 6.97 (d, *J*=8.0 Hz, 1H), 6.90 (s, 1H), 6.80 (d, *J*=8.0 Hz, 1H), 5.22 (m, 1H), 4.86 (t, *J*=10.4 Hz, 1H), 4.11 (dd, *J*=8.4, 2.8 Hz, 1H), 4.03 (t, *J*=9.2 Hz, 1H), 3.88 (t, *J*=7.0 Hz, 1H), 3.65 (s, 3H), 3.28 (m, 1H), 3.15 (dd, *J*=15.2, 8.4 Hz, 1H), 2.99 (dd, *J*=11.8, 3.0 Hz, 1H), 2.24 (m, 1H), 2.12–2.04 (m, 4H), 1.70 (m, 1H), 1.40–1.35 (m, 2H), 1.23 (m, 1H), 0.91 (d, *J*=6.8 Hz, 3H), 0.87 (d, *J*=6.4 Hz, 3H), 0.85 (d, *J*=6.0 Hz, 3H), 0.79–0.75 (m, 6H), 0.69 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 172.3, 172.1, 171.7, 169.9, 169.8, 136.0, 129.9, 125.6, 123.4, 119.0, 117.7, 114.5, 108.4, 58.2, 55.14, 55.05, 52.0, 51.9, 51.7, 51.3, 42.9, 30.5, 29.0, 27.0, 26.8, 25.5, 23.7, 23.1, 21.8, 20.9, 18.6, 17.6, 17.3; HRMS (ESI) *m*/*z* calcd for $C_{34}H_{49}N_6O_7$ $(M+H)^+$ 653.3657; found 653.3651.

*4.2.12. Compound **32**.* To a solution of compound **31** (33 mg, 0.05 mmol) in THF/H_2O (3:1, 2.0 mL) was added lithium hydroxide monohydrate (21 mg, 0.50 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 3 h. The reaction mixture was acidified with 6 N HCl to pH=2 and was diluted with EtOAc (30 mL). The mixture was dried over Na_2SO_4, and concentrated in vacuo to give crude product, which was used directly in the next step.

A solution of above crude product and L-proline benzyl ester (20 mg, 0.10 mmol) in anhydrous THF (3.0 mL) was treated with HOBt (13 mg, 0.10 mmol), EDCI (21 mg, 0.11 mmol), and DIPEA (25 μL, 0.14 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 2 days. The reaction was treated with saturated $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (6×5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Preparative TLC (silica gel, 1:10 MeOH/CH_2Cl_2 elution) afforded **32** (30 mg, 72%). $[\alpha]_D^{34}$ −128.0 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H), 8.51 (d, *J*=9.2 Hz, 1H), 8.33 (d, *J*=9.2 Hz, 1H), 7.86 (s, 1H), 7.39–7.38 (m, 5H), 7.35–7.34 (m, 2H), 6.98 (s, 1H), 6.93 (d, *J*=8.4 Hz, 1H), 6.87 (s, 1H), 6.73 (d, *J*=8.0 Hz, 1H), 5.31 (m, 1H), 5.18 (d, *J*=12.4 Hz, 1H), 5.12 (d, *J*=12.4 Hz, 1H), 4.85 (t, *J*=10.2 Hz, 1H), 4.41 (dd, *J*=8.4, 5.6 Hz, 1H), 4.11 (dd, *J*=8.4, 2.8 Hz, 1H), 4.02 (m, 1H), 3.90–3.82 (m, 2H), 3.76 (m, 1H), 3.23 (dd, *J*=15.2, 4.6 Hz, 1H), 3.04 (dd, *J*=15.2, 7.6 Hz, 1H), 2.98 (dd, *J*=11.6, 3.2 Hz, 1H), 2.28–2.20 (m, 2H), 2.13–2.06 (m, 4H), 2.03–1.95 (m, 2H), 1.85 (m, 1H), 1.69 (m, 1H), 1.39–1.34 (m, 2H), 1.24 (m, 1H), 0.85 (d, *J*=6.8 Hz, 6H), 0.80–0.75 (m, 9H), 0.69 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.5, 172.2, 171.9, 171.8, 170.0, 169.5, 169.2, 135.9, 129.5, 128.5, 128.1, 128.0, 126.0, 124.2, 118.7, 117.9, 114.3, 108.0, 66.0, 58.7, 57.6, 55.2, 55.0, 52.0, 51.7, 50.0, 46.7, 42.8, 30.3, 29.0, 28.6, 26.8, 26.2, 25.6, 24.9, 23.8, 23.2, 21.8, 20.9, 18.8, 17.7, 17.3; HRMS (ESI) *m*/*z* calcd for $C_{45}H_{60}N_7O_8$ $(M+H)^+$ 826.4498; found 826.4496.

4.2.13. Celogentin C. Celogentin C was prepared from compound **32** according to the literature procedure;[9] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 9.33 (s, 1H), 8.81 (d, *J*=8.8 Hz, 1H), 8.54 (d, *J*=8.8 Hz, 1H), 8.34 (d, *J*=9.6 Hz, 1H), 8.14 (d, *J*=8.8 Hz, 1H), 7.88 (s, 1H), 7.76 (s, 1H), 7.62 (br s, 1H), 7.56 (d, *J*=8.4 Hz, 1H), 7.01 (d, *J*=8.4 Hz, 1H), 6.95 (d, *J*=10.4 Hz, 1H), 6.94 (s, 1H), 6.81 (d, *J*=6.4 Hz, 1H), 5.62 (dd, *J*=15.8, 9.0 Hz, 1H), 4.90 (t, *J*=10.6 Hz, 1H), 4.83 (t, *J*=10.4 Hz, 1H), 4.20 (dd, *J*=15.8, 9.0 Hz, 1H), 4.15–4.09 (m, 2H), 3.99–3.94 (m, 2H), 3.82–3.74 (m, 1H), 3.56 (t, *J*=7.6 Hz, 1H), 3.42 (d, *J*=16.0 Hz, 1H), 3.32 (dd, *J*=15.4, 5.8 Hz, 1H), 3.12–3.06 (m, 3H), 2.93 (dd, *J*=15.2, 12.8 Hz, 1H), 2.59 (dd, *J*=15.2, 11.6 Hz, 1H), 2.27–2.20 (m, 2H), 2.16–2.12 (m, 1H), 2.12–2.06 (m, 2H), 2.03–1.96 (m, 2H), 1.87–1.74 (m, 3H), 1.72–1.65 (m, 1H), 1.63–1.58 (m, 1H), 1.48–1.37 (m, 4H), 1.23–1.15 (m, 1H), 0.83 (d, *J*=6.4 Hz, 3H), 0.77 (d, *J*=6.0 Hz, 1H), 0.73–0.70 (m, 9H), 0.67 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 172.1, 171.3, 171.2, 170.9, 169.3, 169.1, 156.8, 136.5, 132.8, 131.5, 131.1, 128.6, 124.9, 119.5, 114.0, 100.9, 61.6, 57.2, 55.1, 54.7, 52.1, 51.3, 49.9, 47.2, 46.9, 41.5, 40.5, 31.1, 29.7, 29.0, 26.6, 25.5, 25.0, 23.9, 23.0, 21.7, 20.9, 18.6, 18.2, 17.0; HRMS (ESI) *m*/*z* calcd for $C_{45}H_{60}N_7O_8$ $(M+H)^+$ 1027.5472; found 1027.5455.

*4.2.14. Compound **34**.* To a solution of compound **31** (40 mg, 0.06 mmol) in THF/H_2O (3:1, 2.0 mL) was added lithium hydroxide monohydrate (9 mg, 0.20 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was acidified with 6 N HCl to pH=2 and was diluted with EtOAc (30 mL). The mixture was dried over Na_2SO_4, and concentrated in vacuo to give crude product, which was used directly in the next step.

A solution of above crude product and benzyl alcohol (108 mg, 1. mmol) in anhydrous THF/DMF (3:1, 3.0 mL) was treated with DMAP (12 mg, 0.10 mmol) and EDCI (17 mg, 0.09 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 1 day. The reaction was treated with saturated $NaHCO_3$ (5 mL) and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Preparative TLC (silica gel, 1:10 MeOH/CH_2Cl_2 elution) afforded **34** (35 mg, 79%). $[\alpha]_D^{25}$ −121.4 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 8.54 (d, *J*=9.2 Hz, 1H), 8.39 (d, *J*=9.6 Hz, 1H), 7.87 (s, 1H), 7.39 (m, 7H), 6.98 (d, *J*=8.0 Hz, 1H), 6.91 (s, 1H), 6.82 (m, 2H), 5.29 (m, 1H), 5.21 (d, *J*=12.4 Hz, 1H), 5.12 (d, *J*=12.4 Hz, 1H), 4.87 (t, *J*=10.4 Hz, 1H), 4.12 (dd, *J*=8.8, 2.0 Hz, 1H), 4.04 (m, 1H), 3.89 (t, *J*=6.8 Hz, 1H), 3.30 (m, 1H), 3.16 (dd, *J*=14.4, 8.8 Hz, 1H), 3.01 (dd, *J*=11.6, 2.4 Hz, 1H), 2.24 (m, 1H), 2.14–2.01 (m, 4H), 1.71 (m, 1H), 1.41–1.36 (m, 2H), 1.23 (m, 1H), 0.90–0.84 (m, 9H), 0.79 (d, *J*=7.6 Hz, 3H), 0.78 (d, *J*=6.4 Hz, 3H), 0.70 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 172.2, 172.0, 171.0, 169.9, 169.8, 136.0, 135.8, 129.8, 128.4, 128.1, 128.0, 125.5, 123.4, 118.9, 117.7, 114.4, 108.2, 79.1, 66.0, 58.1, 55.1, 55.0, 52.0, 51.9, 51.7, 51.2, 42.8, 30.4, 28.9, 27.0, 26.8, 25.5, 23.7, 23.1, 21.8, 20.9, 18.6, 17.6, 17.3; HRMS (ESI) *m*/*z* calcd for $C_{40}H_{53}N_6O_7$ $(M+H)^+$ 729.3976; found 729.3961.

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*4.2.15. Compound **36**.* A solution of **34** (23 mg, 0.031 mmol) in anhydrous CH_2Cl_2 (4.0 mL) was treated with *N*,*N*′-dimethylpiperazine (30 μL), followed by NCS (4.1 mg, 0.031 mmol). The resulting solution was stirred at room temperature for 6 h, then treated with Cbz-Arg(Pbf)-Gly-His-O^{t}Bu (**35**, 105 mg, 0.13 mmol), stirred at room temperature for 24 h, and concentrated in vacuo. Preparative TLC (silica gel, 1:10 MeOH/CH_2Cl_2 elution) afforded **36** (36 mg, 78%). $[\alpha]_D^{25}$ −60.7 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (br s, 1H), 8.54 (d, *J*=8.8 Hz, 1H), 8.34 (d, *J*=9.2 Hz, 1H), 8.27–8.26 (m, 2H), 8.14 (d, *J*=7.8 Hz, 1H), 7.92 (s, 1H), 7.88 (s, 1H), 7.49–7.47 (m, 2H), 7.36–7.26 (m, 12H), 7.12 (d, *J*=7.2 Hz, 1H), 6.96 (d, *J*=8.0 Hz, 1H), 6.86 (s, 1H), 6.66 (br s, 1H), 6.38 (br s, 1H), 5.56 (m, 1H), 5.14 (d, *J*=12.4 Hz, 1H), 5.05–4.94 (m, 3H), 4.83 (t, *J*=10.0 Hz, 1H), 4.47 (m, 1H), 4.10 (dd, *J*=8.4, 2.8 Hz, 1H), 4.03–4.00 (m, 2H), 3.74–3.70 (m, 3H), 3.35 (m, 1H), 3.11–2.90 (m, 10H), 2.47 (s, 3H), 2.41 (s, 3H), 2.25 (m, 1H), 2.12–2.08 (m, 3H), 1.98 (s, 3H), 1.83 (m, 1H), 1.69–1.63 (m, 2H), 1.44–1.35 (m, 2H), 1.38 (s, 6H), 1.35 (s, 9H), 1.25–1.15 (m, 4H), 0.82 (d, *J*=6.4 Hz, 3H), 0.78–0.72 (m, 12H), 0.68 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 172.2, 171.5, 171.4, 170.5, 169.9, 169.4, 168.6, 157.4, 156.0, 137.4, 137.2, 136.8, 135.6, 134.2, 132.8, 131.4, 130.9, 128.9, 128.3, 128.27, 128.0, 127.9, 127.7, 127.6, 124.8, 124.3, 119.0, 117.9, 116.2, 114.0, 100.7, 86.2, 80.6, 66.3, 65.5, 62.8, 58.2, 57.5, 55.1, 54.8, 54.4, 52.8, 52.0, 51.4, 45.8, 42.4, 42.0, 41.7, 31.2, 30.1, 28.9, 28.2, 27.6, 26.6, 25.5, 23.9, 23.0, 21.7, 20.9, 18.9, 18.4, 18.2, 17.5, 17.1, 12.2; HRMS (ESI) *m*/*z* calcd for $C_{79}H_{104}N_{15}O_{16}S$ $(M+H)^+$ 1537.7548; found 1537.7517.

*4.2.16. Compound **39**.* Compound **39** was prepared from compound **31** and Cbz-Gly-His-O^{t}Bu (**38**) according to the same procedure as that described for compound **36**; $[\alpha]_D^{25}$ −78.2 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.49 (br s, 1H), 8.56 (d, *J*=9.2 Hz, 1H), 8.36 (d, *J*=9.6 Hz, 1H), 8.25 (d, *J*=7.6 Hz, 1H), 8.13 (d, *J*=8.8 Hz, 1H), 7.91 (s, 1H), 7.89 (s, 1H), 7.51 (t, *J*=4.5 Hz, 1H), 7.46 (d, *J*=8.4 Hz, 1H), 7.34–7.29 (m, 6H), 7.11 (d, *J*=8.0 Hz, 1H), 6.98 (d, *J*=8.4 Hz, 1H), 6.87 (s, 1H), 5.45 (m, 1H), 5.00 (s, 2H), 4.84 (t, *J*=10.0 Hz, 1H), 4.46 (m, 1H), 4.11 (dd, *J*=8.8, 3.6 Hz, 1H), 3.99 (m, 1H), 3.77 (t, *J*=8.0 Hz, 1H), 3.65 (d, *J*=4.5 Hz, 2H), 3.58 (s, 3H), 3.31 (m, 1H), 3.05–2.90 (m, 4H), 2.25 (m, 1H), 2.15–2.07 (m, 3H), 1.89 (m, 1H), 1.70 (m, 1H), 1.41 (m, 1H), 1.38 (s, 9H), 1.20 (m, 1H), 0.86–0.77 (m, 12H), 0.74 (d, *J*=6.4 Hz, 3H), 0.69 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 172.2, 172.0, 171.6, 170.5, 169.4, 169.1, 156.5, 137.5, 137.0, 132.8, 130.9, 128.9, 128.3, 127.7, 127.6, 124.9, 119.7, 118.9, 118.0, 114.0, 100.6, 80.6, 65.4, 57.6, 55.1, 54.8, 52.7, 52.0, 51.9, 51.4, 49.0, 48.6, 45.7, 43.3, 42.1, 31.2, 30.0, 29.0, 27.6, 26.6, 25.5, 25.3, 23.9, 23.1, 21.7, 20.9, 18.3, 17.1; HRMS (ESI) *m*/*z* calcd for $C_{54}H_{73}N_{10}O_{12}$ $(M+H)^+$ 1053.5409; found 1053.5464.

*4.2.17. Compound **41**.* To a solution of compound **39** (31 mg, 0.03 mmol) in THF/H_2O (3:1, 2.0 mL) was added lithium hydroxide monohydrate (13 mg, 0.30 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 3 h. The reaction mixture was acidified with 6 N HCl to pH=2 and was diluted with EtOAc (30 mL). The mixture was dried over Na_2SO_4, and concentrated in vacuo to give crude product, which was used directly in the next step.

A solution of above crude product and L-Arg(Pbf)-OMe (20 mg, 0.045 mmol) in anhydrous THF/DMF (10:1, 2.0 mL) was treated with HOBt (27 mg, 0.20 mmol), HBTU (76 mg, 0.2 mmol), and DIPEA (40 μL, 0.22 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 2 days. The reaction was treated with saturated $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (6×5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Preparative TLC (silica gel, 1:10 MeOH/CH_2Cl_2 elution) afforded **41** (19 mg, 45%). $[\alpha]_D^{25}$ −42.5 (*c* 0.20, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 (br s, 1H), 8.55 (d, *J*=8.8 Hz, 1H), 8.35–8.23 (m, 4H), 7.92 (s, 1H), 7.88 (s, 1H), 7.58 (d, *J*=8.4 Hz, 1H), 7.50 (t, *J*=4.5 Hz, 1H), 7.36–7.26 (m, 7H), 7.10 (d, *J*=8.0 Hz, 1H), 6.94 (d, *J*=8.0 Hz, 1H), 6.85 (s, 1H), 6.73 (br s, 1H), 6.44 (br s, 1H), 5.54 (m, 1H), 4.99 (s, 2H), 4.82 (t, *J*=10.0 Hz, 1H), 4.44 (m, 1H), 4.23 (m, 1H), 4.10 (dd, *J*=8.4, 2.8 Hz, 1H), 3.95 (m, 1H), 3.70–3.62 (m, 3H), 3.59 (s, 3H), 3.14 (m, 1H), 3.05–2.98 (m, 3H), 2.95 (s, 2H), 2.93–2.82 (m, 3H), 2.48 (s, 3H), 2.42 (s, 3H), 2.24 (m, 1H), 2.15–2.07 (m, 3H), 2.00 (s, 3H), 1.78 (m, 1H), 1.72–1.68 (m, 2H), 1.59 (m, 1H), 1.46–1.33 (m, 4H), 1.40 (s, 6H), 1.37 (s, 9H), 0.84–0.68 (m, 18H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 172.2, 172.0, 171.9, 170.5, 169.5, 169.3, 169.1, 157.4, 156.4, 156.0, 137.6, 137.4, 137.2, 137.0, 134.2, 132.8, 131.4, 130.7, 128.8, 127.7, 127.6, 124.8, 124.3, 119.5, 119.4, 118.0, 116.2, 113.9, 101.3, 86.3, 80.6, 65.4, 59.7, 57.3, 55.1, 54.8, 52.8, 52.1, 51.8, 51.79, 51.3, 43.3, 42.4, 41.8, 31.3, 29.9, 29.0, 28.3, 27.6, 27.5, 26.5, 26.4, 25.5, 23.9, 23.1, 21.8, 20.9, 18.9, 18.6, 18.3, 17.6, 17.1, 12.2; HRMS (ESI) *m*/*z* calcd for $C_{73}H_{101}N_{14}O_{16}S$ $(M+H)^+$ 1641.7241; found 1641.7235.

*4.2.18. Compound **43**.* Compound **43** was prepared from compound **31** and Cbz-His-O^{t}Bu (**42**) according to the same procedure as that described for Compound **36**; $[\alpha]_D^{25}$ −89.2 (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (br s, 1H), 8.56 (d, *J*=9.2 Hz, 1H), 8.36 (d, *J*=10.0 Hz, 1H), 8.12 (d, *J*=8.4 Hz, 1H), 7.93 (s, 1H), 7.88 (s, 1H), 7.62 (d, *J*=8.0 Hz, 1H), 7.46 (d, *J*=8.4 Hz, 1H), 7.34–7.28 (m, 6H), 7.09 (d, *J*=7.6 Hz, 1H), 6.99 (d, *J*=8.4 Hz, 1H), 6.86 (s, 1H), 5.43 (m, 1H), 5.07–4.98 (m, 2H), 4.84 (t, *J*=10.0 Hz, 1H), 4.27 (m, 1H), 4.10 (dd, *J*=8.4, 2.8 Hz, 1H), 3.99 (m, 1H), 3.77 (t, *J*=8.0 Hz, 1H), 3.56 (s, 3H), 3.32 (m, 1H), 3.05–2.86 (m, 4H), 2.23 (m, 1H), 2.11–2.09 (m, 3H), 1.91 (m, 1H), 1.69 (m, 1H), 1.41 (m, 1H), 1.38 (s, 9H), 1.20 (m, 1H), 0.85–0.74 (m, 15H), 0.69 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 172.2, 172.0, 171.6, 171.0, 170.0, 169.4, 155.9, 137.6, 137.5, 136.9, 132.7, 130.8, 128.8, 128.3, 127.8, 127.2, 124.9, 119.7, 118.8, 117.9, 114.0, 100.4, 80.6, 65.4, 57.6, 55.1, 54.8, 54.6, 52.0, 51.9, 51.4, 49.1, 42.1, 31.1, 29.7, 29.0, 27.6, 27.4, 26.6, 25.5, 25.3, 23.9, 23.1, 21.7, 20.9, 18.3, 17.1; HRMS (ESI) *m*/*z* calcd for $C_{52}H_{70}N_9O_{11}$ $(M+H)^+$ 996.5195; found 996.5236.

*4.2.19. Compound **45**.* Compound **45** was prepared from compound **43** and Arg(Pbf)-Gly-OMe (**44**) according to the same procedure as that described for compound **41**. $[\alpha]_D^{25}$ −66.4 (*c* 0.25, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (br s, 1H), 8.52 (d, *J*=8.8 Hz, 1H), 8.45 (t, *J*=6.0 Hz, 1H), 8.35–8.31 (m, 3H), 7.94 (s, 1H), 7.91 (d, *J*=7.9 Hz, 1H), 7.86 (s, 1H), 7.61–7.57 (m, 2H), 7.33–7.25 (m, 6H), 7.11 (d, *J*=8.0 Hz, 1H), 6.93 (d, *J*=8.0 Hz, 1H), 6.84 (s, 1H), 6.64 (br s, 1H), 6.42 (br s, 1H), 5.56 (m, 1H), 5.06–4.98 (m, 2H),4.82 (t, *J*=10.4 Hz, 1H), 4.34 (m, 1H), 4.26 (m, 1H), 4.10 (dd, *J*=8.4, 3.2 Hz, 1H), 3.96 (m, 1H), 3.92–3.80 (m, 2H), 3.68 (t, *J*=8.0 Hz, 1H), 3.62 (s, 3H), 3.14–2.84 (m, 9H), 2.48 (s, 3H), 2.43 (s, 3H), 2.23 (m, 1H), 2.15–2.07 (m, 3H), 2.00 (s, 3H), 1.76 (m, 1H), 1.72–1.62 (m, 2H), 1.52 (m, 1H), 1.46–1.31 (m, 3H), 1.40 (s, 6H), 1.36 (s, 9H), 1.17 (m, 1H), 0.83 (d, *J*=6.8 Hz, 3H), 0.79 (d, *J*=6.4 Hz, 3H), 0.75–0.69 (m, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.3, 172.1, 171.5, 171.3, 171.1, 170.9, 170.0, 169.7, 169.2, 157.4, 156.0, 155.8, 137.5, 137.2, 136.9, 134.2, 132.8, 131.4, 130.6, 128.7, 128.2, 127.7, 124.8, 124.2, 119.5, 119.4, 118.0, 116.2, 113.8, 101.2, 86.2, 80.5, 79.1, 65.4, 57.2, 55.1,54.8,54.5, 52.0, 51.8, 51.6, 51.3, 49.3, 42.4, 41.8, 40.4, 31.3, 30.0, 29.6, 28.9, 28.2, 27.6, 26.5, 26.0, 25.5, 25.0, 23.9, 23.0, 21.7, 20.9, 18.8, 18.5, 18.2, 17.5, 17.1, 12.2; HRMS (ESI) *m*/*z* calcd for $C_{73}H_{101}N_{14}O_{16}S$ $(M+H)^+$ 1641.7241; found 1641.7257.

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