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Total Synthesis of (−)-Apratoxin A, 34-Epimer, and Its Oxazoline Analogue

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Abstract: A concise and convergent total synthesis of the highly cytotoxic marine natural product apratoxin A is accomplished by an 18-step linear sequence. The high sensitivity of the thiazoline, bearing an adjacent β-hydroxyl group at the C35-position, results in the assembly process requiring the inclusion of appropriate protecting groups and the careful optimization of all individual transformations. In the synthesis of 3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid (Dtena), the three reagent-controlled asymmetric reactions enables us to introduce four chiral carbon centers in a dihydroxylated fatty acid moiety. Formation of the hindered ester and sterically-unfavorable *N*-methylamide bonds were successfully demonstrated. The thiazoline in apratoxin A was constructed by Tf_2O and Ph_3PO-mediated dehydrative cyclization, and final macrocyclization was achieved between *N*-methylisoleucine and proline residues. Moreover, an oxazoline analogue and a C34 epimer of apratoxin A have also been elaborated in a similar approach. This synthetic route would enable assembly of other analogues differing in stereocenters of Dtena and their amino acids.

Keywords: apratoxin A · cyclic depsipeptide · natural products · thiazoline · total synthesis

Introduction

Marine cyanobacteria are emerging as a valuable source of natural products possessing interesting molecular architectures and biological properties.[1] Among these metabolites are the fascinating family of cyclic peptides and depsipeptides, which offer unique scaffolds and nonribosomal amino acids.[2] Although novel structure and unusual amino acid units attract considerable interest for organic chemists, they often complicate structural determination and chemical synthesis.[3]

Apratoxin A (**1**), isolated from the marine cyanobacterium *Lyngbya majuscula*, exhibits potent cytotoxic activity.[4] The unique structural features of **1** are accompanied by high levels of cytotoxicity against KB and LoVo cancer cells, with in vitro IC_{50} values of 0.52 nM and 0.36 nM, respectively. Luesch et al. recently revealed the mode of action of **1** through a functional genomics approach.[5] According to the report, its biological activity is developed through the induction of G1 cell cycle arrest and an apoptotic cascade, which is at least partially initiated through antagonism of FGF signaling by STAT3. For further biological evaluation and identification of the molecular target or signal cascade, a chemical–biological approach using a labelled compound could also be effective. Having described the design and solid-phase synthesis[6] of effective fluorescent-labelled aeruginosin derivatives based on the information from structure–activity relationships, we became interested in the efficient synthesis of apratoxin A analogues. Apratoxin A is a 25-membered cyclic depsipeptide consisting of proline, three methylated amino acids (*N*-methylisoleucine, *N*-methylalanine, *O*-methyltyrosine), α,β-unsaturated modified cysteine residue (moCys), and dihydroxylated fatty acid moiety, 3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid (Dtena) (Figure 1). The total synthesis of **1** has been achieved by three groups, including ours.[7–9] The formation of the thiazoline ring is a crucial step in this synthesis. The stereogenic center at C34 has a risk of epimerization,[10] furthermore the hydroxyl group at C35 is sensitive toward acid-induced dehydration leading to (*E*)-34,35-dehydroapratoxin A (**3**).[11] Forsyth and Chen prepared a thiazoline moiety using a unique intramolecular Staudinger reduction-aza-Wittig process of an α-azido thioester.[7] We recently disclosed the total synthesis of apratoxin A through Ph_3PO/Tf_2O-mediat-

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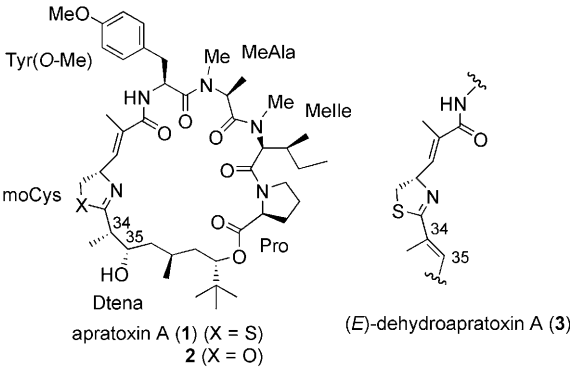


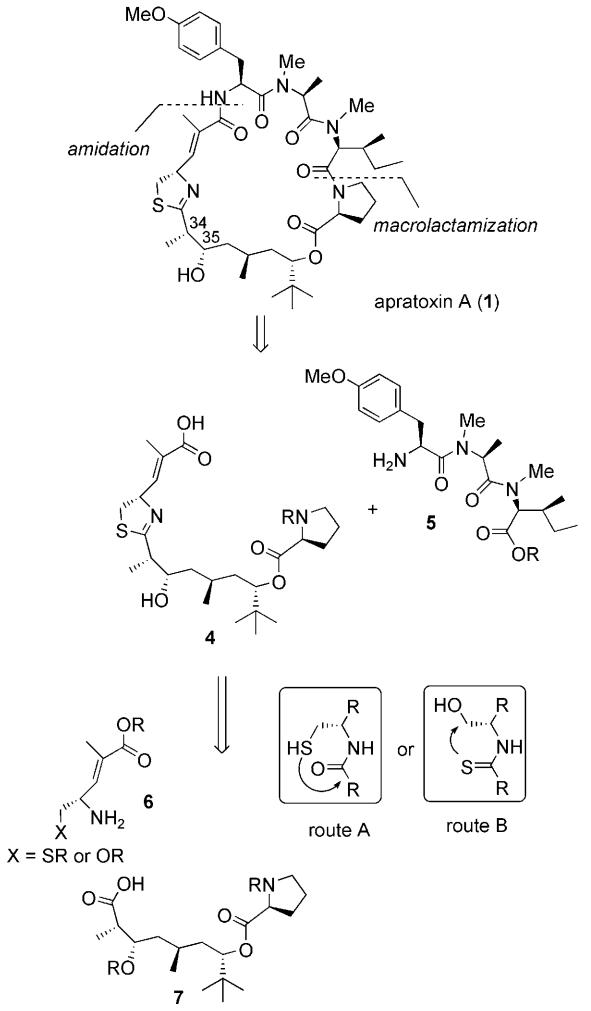
Figure 1. Structures of apratoxin A and its analogues.

ed thiazoline formation.[8] A similar approach of the thiazoline formation has been independently reported by Ma et al.[9] They also reported the synthesis of its oxazoline analogue **2**[12] and their biological evaluation in consideration of facile preparation of oxazolines compared with thiazolines.[9] In this paper, the details of an improved synthesis of the fatty acid moiety and a challenging approach to thiazoline formation towards the total synthesis of apratoxin A (**1**) and its oxazoline analogue **2** are described.

Results and Discussion

Retro Synthetic Analysis

Our synthetic strategy is illustrated in Scheme 1. Apratoxin A (**1**) can be synthesized by the coupling of **4** with tripeptide **5**, followed by macrolactamization between the proline amine and the *N*-methylisoleucine carboxylic acid. We selected this precursor to avoid the predictable side reactions, such as diketopiperadine formation, which are observed with other precursors for macrolactamization. The thiazoline formation of **4** is a crucial step as the thiazoline ring is labile for acid hydrolysis, and there is a risk of epimerization at the chiral center attached to the 2-position. We planned thiazoline formation by both routes A and B. In route A, nucleophilic attack of the cysteine thiol group on the amide carbonyl group of the residue, followed by dehydration, induces a thiazoline ring. In route B, in contrast, the side chain is transformed into an electrophile, which is attacked by the thioamide group of the residue. Both of the thiazoline precursors can be prepared from **6** (moCys or moSer residue) with the Dtena moiety **7**.



Scheme 1. Retrosynthetic analysis of apratoxin A

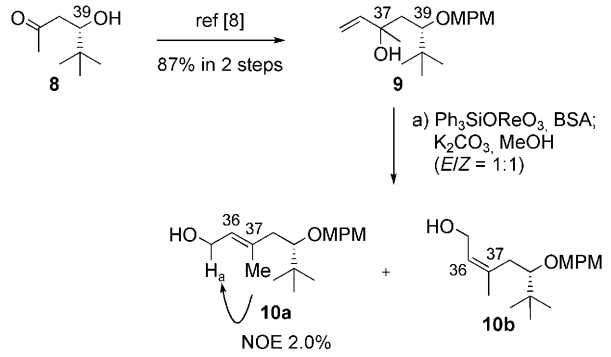
Abstract in Japanese:

アプラトキシンAはヒトの腫瘍細胞に対し強力な細胞毒性を有する25員環デプシペプチドである。我々は総工程数18段階で本化合物の全合成を達成した。3,7-ジヒドロキシ-2,5,8,8-テトラメチルノナン酸部位の合成においては、二つの反応剤制御による反応を組み合わせることにより高立体選択的に全ての立体化学の組み合わせを合成可能な合成ルートを確立した。システイン誘導体に対して、Ph_3PO/Tf_2Oを作用させることでチアゾリン構築を行い、トリペプチドを伸長後、プロリン残基とイソロイシン残基間のマクロラクタム化反応により全合成を達成した。

Stereoselective Syntheses of Dtena 20a and C34-epimer 20b

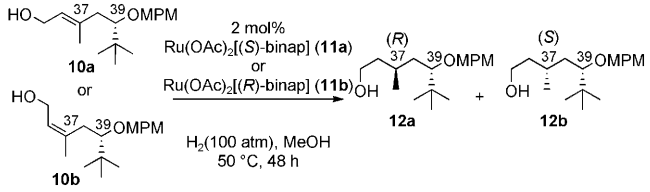
The synthesis of the Dtena **20a** was carried out by three asymmetric reactions for the construction of four chiral centers (Schemes 2 and 3 and Table 1). First, isomerization of allylic alcohol **9**[8] prepared by 2-step conversion from proline-catalyzed aldol product **8**[13] was conducted (Scheme 2). Rhenium-catalyzed isomerisation[14] of **9** and in situ silylation of the less-hindered primary alcohol with *N,O*-bis(trimethylsilyl)acetamide (BSA), followed by one-pot removal of the TMS group, afforded primary allylic alcohols **10a** and **10b** in 42% and 44% yields, respectively. The *E* geometry of the alkene (C36=C37) in **10a** was confirmed by the NOE observation between the proton of the vinylic methyl group and H_a (Scheme 2). Both isomers were independently used for the next asymmetric hydrogenation after separation by column chromatography.

Asymmetric hydrogenation[15] of allylic alcohol **10** was performed to introduce the chiral center at C37 (Table 1).



Scheme 2. Preparation of allylic alcohol (*E*)-**10a** and (*Z*)-**10b**. Reagents and conditions: a) $Ph_3SiOReO_3$, BSA, ether, 0°C; b) Et_3N, K_2CO_3, MeOH, 42% (for **10a**) and 44% (for **1b**). MPM = 4-methoxyphenylmethyl, BSA = *N*,*O*-bis(trimethylsilyl)acetamide.

Table 1. Asymmetric hydrogenation of allylic alcohols **10a** and **10b**. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

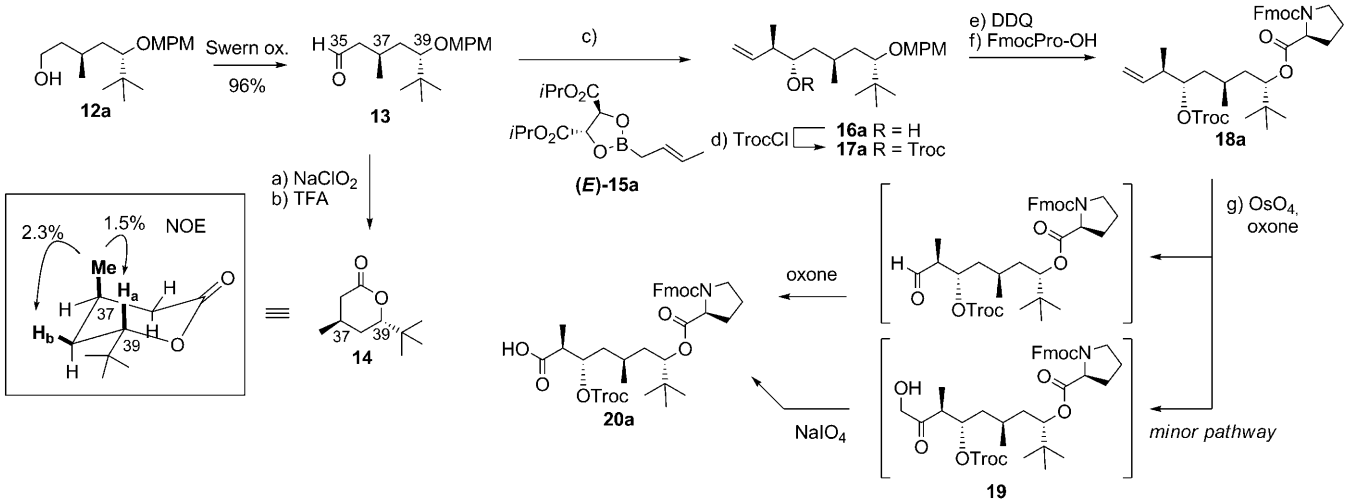


Entry	Substrate	Catalyst	Yield [%]	**12a**:**12b**
1	**10a**	**11a**	quant.	>95:5
2	**10b**	**11b**	quant.	90:10
3	**10a**	**11b**	quant.	5:>95
4	**10b**	**11a**	quant.	10:90

$Ru(OAc)_2$[(*S*)-binap] (**11a**) (2 mol%)-catalyzed asymmetric hydrogenation of (*E*)-**10a** was carried out at 50°C for 48 h under 100 atm of hydrogen to afford **12a** in quantitative yield (>95% ds) (Table 1, Entry 1). (*Z*)-**10b** was also converted into **12a** in quantitative yield (90% ds) under similar conditions. Here, $Ru(OAc)_2$[(*R*)-binap] (**11b**) was used as a catalyst (entry 2). The appropriate combination of geometries of the alkene and chirality of the catalysts enabled the control of the stereogenic center at the C37-position with (*R*)-configuration. Furthermore, the diastereomer **12b** that has (*S*)-configuration at the C37-position was provided from **10a** by using catalyst **11b**, and from **10b** with catalyst **11a** in a similar manner without any affect from the C39 stereogenic center (entries 3 and 4). Therefore, 37-epi apratoxin A can be also prepared from **12b**.

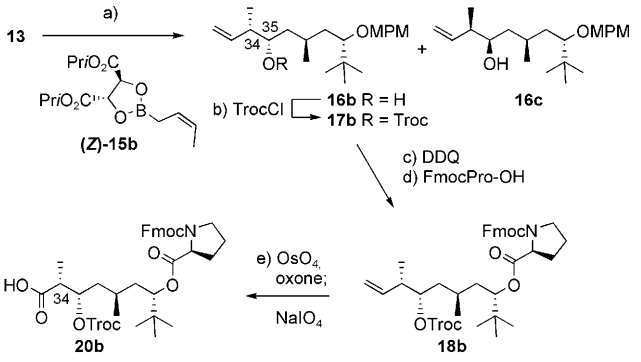
Swern oxidation of primary alcohol **12a** gave aldehyde **13** in 96% yield according to a reported procedure (Scheme 3).[8] To confirm the stereochemistry at the C37-position, **13** was converted into lactone **14**, which was in good accordance with that reported previously.[7,12] NOE observation in **14** also confirmed (*R*)-configuration at C37. In our advanced synthesis, Roush's crotylation[16] was utilized for the preparation of Dtena **20a**, and the produced olefin was used as a masked carboxylic acid. Crotylation of aldehyde **13** with (*E*)-crotylborate **15a** afforded **16a** in 95% yield (>95% ds).[17] Protection of the free hydroxy group with a Troc group, removal of the MPM group, and esterification with Fmoc-protected proline by the Yamaguchi method[18] provided prolyl ester **18a** in 92% overall yield. Ozonolysis of **18a** failed, thus we employed a modified oxidation of the double bond utilizing the OsO_4/oxone system[19] followed by a one-pot treatment with $NaIO_4$ to obtain **20a** in 79% yield. In this reaction, partially-produced β-hydroxy ketone **19** was also converted into the desired carboxylic acid **20a** by treatment with $NaIO_4$.

We confirmed the configuration at the C34-position after construction of the thiazoline ring because it has been reported that the α-position of thiazolines easily isomerizes



Scheme 3. Preparation of the carboxylic acid **20a**. Reagents and conditions: a) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4 aq., *t*BuOH, 0°C; b) TFA, CH_2Cl_2, 56% in 2 steps; c) (*E*)-**15a**, MS 4 Å, toluene, −78°C, 95% (>95% ds); d) TrocCl, DMAP, pyridine, CH_2Cl_2, 0°C, quant.; e) DDQ, H_2O, CH_2Cl_2; f) FmocPro-OH, $C_6H_2Cl_3COCl$, DIEA, DMAP, toluene, 92% in 2 steps; g) OsO_4, oxone, $NaHCO_3$, DMF then $NaIO_4$, H_2O, *t*BuOH, 79%. TFA = trifluoroacetic acid, Troc = 2,2,2-trichloroethoxycarbonyl, DMAP = 4-(dimethylamino)pyridine, DDQ = 2,3-dichloro-4,5-dicyanobenzoquinone, Fmoc = 9-fluorenylmethoxycarbonyl.

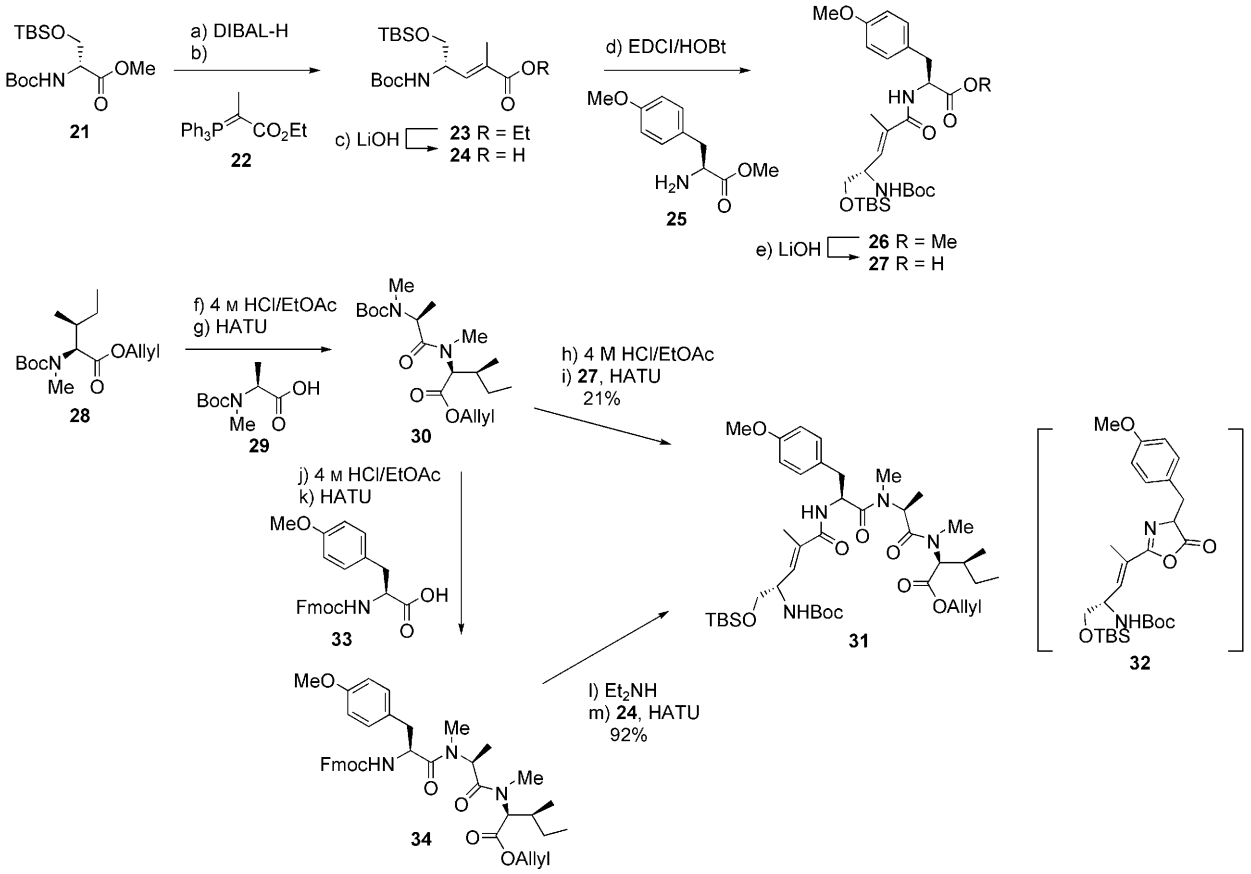
under relatively mild conditions.[10,11] Therefore, we decided to synthesize the 34-epimer to confirm that there is no epimerization at the C34-position during the synthesis. Additionally, we were also interested in the bioactivity of 34-epi-apratoxin A.[20] The 34-epi carboxylic acid **20b** was prepared using the same synthetic procedure as **20a**. Crotylation of aldehyde **13** utilizing (*Z*)-crotylborate **15b** afforded **16b** and **16c** in 90% yield as a 10:1 diastereomer mixture (Scheme 4). Isolation of **16b** was carefully achieved by silica gel column chromatography. Further transformations for the synthesis of carboxylic acid **20b** were conducted in good yields.



Scheme 4. Synthetic route of C34-epimer **20b**. Reagents and conditions: a) (*Z*)-**15b**, MS 4 Å, toluene, 90% (**16b**:**16c** = 10:1); b) TrocCl, DMAP, pyridine, CH_2Cl_2, quant.; c) DDQ, H_2O, CH_2Cl_2; d) FmocPro-OH, $C_6H_2Cl_3COCl$, DIEA, DMAP, toluene, 81% in 2 steps; e) OsO_4, oxone, $NaHCO_3$, DMF then $NaIO_4$, H_2O, *t*BuOH, 83%.

Synthesis of Oxazoline Analogue

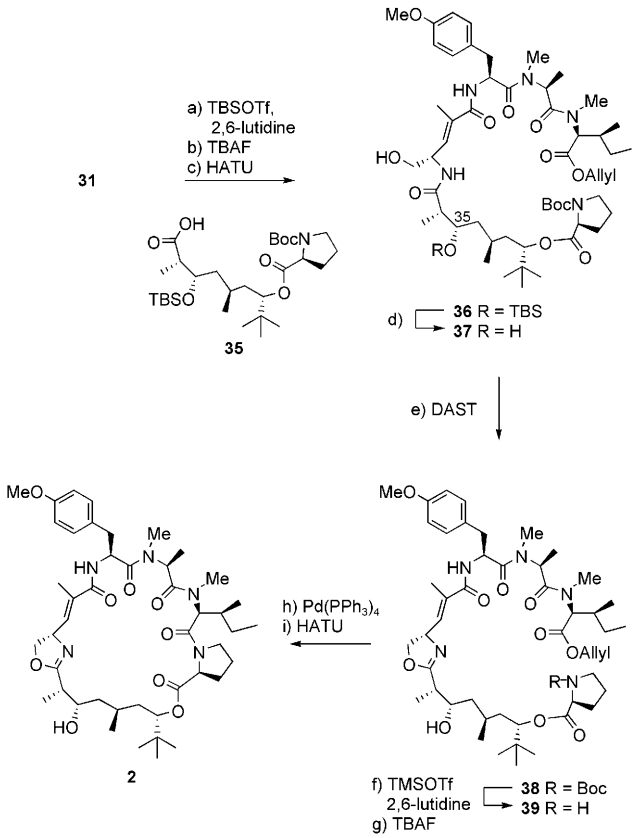
Achieving rapid access to carboxylic acid **20a** as a single diastereomer, we attempted the elongation of peptide segments in the course of the synthesis of oxazoline analogue **2** for estimation of a site for macrolactamization (Schemes 5 and 6). Furthermore, we initially planned the thiazoline formation by conversion of the corresponding oxazoline derivative as reported by Wipf et al. in the synthesis of lissoclinamides.[21] Boc-D-Ser(*O*-TBS)-OMe (**21**) was prepared from D-serine in 3 steps (Scheme 5). Reduction of methyl ester **21** by DIBAL-H and treatment of the resulting aldehyde with **22** provided α,β-unsaturated ethyl ester **23** as a single isomer. Saponification afforded carboxylic acid **24**. For the preparation of tetrapeptide **31**, a convergent strategy using



Scheme 5. Preparation of the tetrapeptide **31**. Reagents and conditions: a) DIBAL-H, toluene, −78 °C; b) **22**, toluene, 82% in 2 steps; c) LiOH, H_2O, THF, *t*BuOH, 85%; d) **25**, EDCI/HCl, HOBt, CH_2Cl_2, 82% (based on **24**); e) LiOH, THF, H_2O, 79%; f) HCl (4 M)/EtOAc; g) **29**, HATU, DIEA, CH_2Cl_2, quant; h) HCl (4 M)/EtOAc; i) **27**, HATU, DIEA, CH_2Cl_2, 21%; j) HCl (4 M)/EtOAc; k) **33**, HATU, DIEA, CH_2Cl_2, 79%; l) Et_2NH, CH_3CN; m) **24**, HATU, DIEA, CH_2Cl_2, 92%. Boc = *tert*-butoxycarbonyl, DIBAL-H = diisobutylaluminium hydride, EDCI = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, HOBt = 1-hydroxybenzotriazole, HATU = 7-azabenzotriazole-1-yl-1,1,3,3-tetramethyluronium hexafluorophosphate.

dipeptides **27** and **30** was initially conducted. Coupling of carboxylic acid **24** with amine **25** under EDCI/HOBt conditions afforded dipeptide segment **26** in 82% yield. Then, hydrolysis of **26** provided **27**. HATU mediated coupling[22] of Boc-MeAla-OH (**29**) with HCl·MeIle-OAllyl afforded dipeptide **30**. Despite several efforts for condensation of **27** and **30**, tetrapeptide **31** was obtained in low yield arising from an undesired reaction, which occurred on the activated ester producing azalactone **32**. Therefore, we employed stepwise elongation from the *C*-terminal. Removal of the Boc group in **30** and subsequent amidation of the resulting amine with Fmoc-Tyr(OMe)-OH (**33**) provided tripeptide **34** in 79% yield. Subsequently, removal of the Fmoc group of **34** with Et_2NH,[23] followed by the coupling with **24** using HATU/DIEA furnished the tetrapeptide fragment **31** in 92% yield based on **24**.

Treatment of tetrapeptide **31** with 4 M HCl/EtOAc for the removal of the Boc group did not give a satisfactory result. Therefore, we employed a two-step fashion to avoid strongly acidic conditions. This procedure involved conversion of the Boc group into the corresponding *tert*-butyldimethylsilyl carbamate with TBSOTf/2,6-lutidine,[24] desilylative carbamate



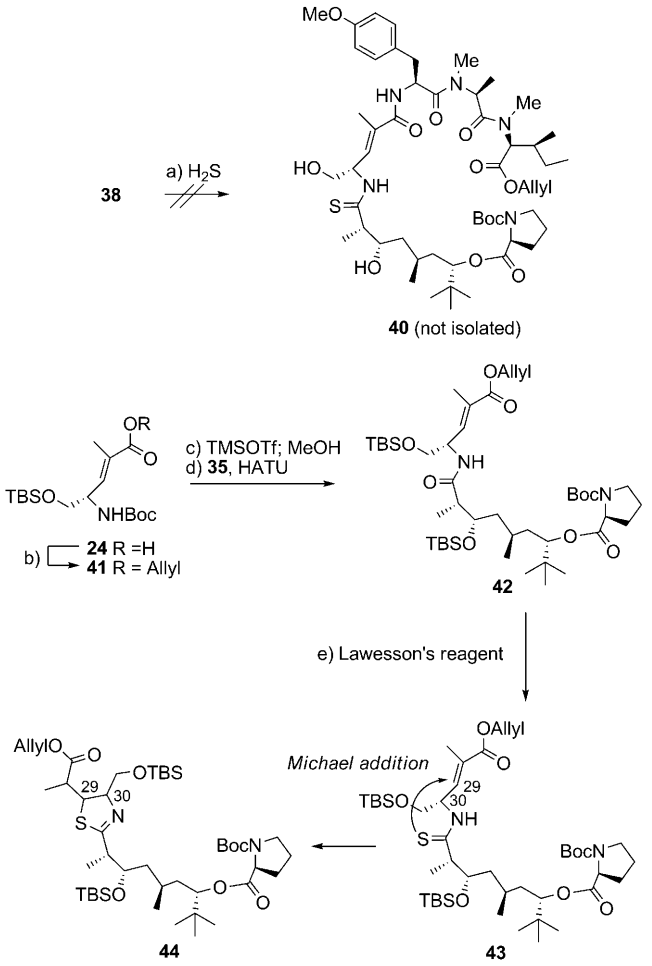
Scheme 6. Synthesis of oxazoline analogue **2**. Reagents and conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2; b) TBAF, THF; c) **35**, HATU, DIEA, CH_2Cl_2; d) TBAF, THF, 93% in 2 steps; e) DAST, CH_2Cl_2, −78 °C, 70%; f) TMSOTf, 2,6-lutidine, CH_2Cl_2; g) TBAF, THF, 93% in 2 steps; h) $Pd(PPh_3)_4$, morpholine, THF i) HATU, DIEA, CH_2Cl_2 (1.0 mM), 56% in 2 steps. TBAF = tetrabutylammonium fluoride, DAST = diethylaminosulfur trifluoride.

fragmentation, and cleavage of the TBS ether with TBAF to provide the free amino alcohol. Condensation of the resulting amine with carboxylic acid **35**[8] followed by desilylation of the C35 hydroxyl group in **36** afforded **37** in 93% yield (Scheme 6). The oxazoline formation of **37** was performed by using 3 equivalents of DAST[25] at −78 °C to provide **38**. Removal of the Boc group in **38** using TMSOTf/2,6-lutidine afforded ester **39**, which was converted to the carboxylic acid by treatment with Pd^0 catalyst and morpholine. Final macrolactamization of the resulting amino acid was achieved using HATU/DIEA in 1 mM CH_2Cl_2 solution to provide apratoxin A oxazoline analogue **2** in 56% yield over 2 steps.[12]

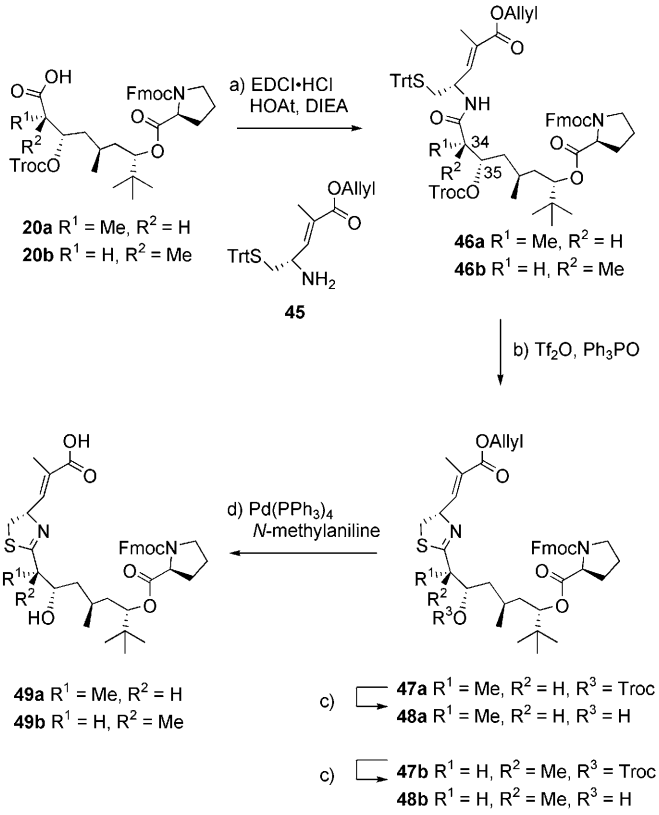
Thiazoline Formation

The key challenge towards the synthesis of **1** is the construction of the 2,4-substituted thiazoline ring, which is connected directly to the macrocycle in the presence of the β-hydroxyl group at the C35-position. For this purpose, we investigated two synthetic strategies. First, a modified serine-containing moiety was chosen as a thiazoline precursor because many kinds of thiazoline formations utilizing serine moieties have been reported, and the hydroxyl groups in serines can be transformed more easily compared with thiol groups in cysteines (Scheme 7).[26] Wipf's thiolysis[21] of oxazoline **38** with H_2S/Et_3N failed, resulting in complex mixtures (Scheme 7). To solve this problem, introduction of a sulfur atom by selective thiocarbonylation of amide **42** was carried out. Coupling of carboxylic acid **35** with moSer **41**, which is easily prepared from **24** afforded **42** in 90% yield. Although the attempt for thioamide formation from amide **42** using Lawesson's reagent[27] gave **43**, intramolecular Michael addition of the generated thioamide to α,β-unsaturated ester proceeded, leading to undesired thiazoline **44**.[28]

In the second strategy, we employed Kelly's method,[29] which was reported as dehydrative thiazoline formation involving deprotection of the *S*-Trt group from a protected cysteinamide moiety. The key intermediates **46a** and **46b** were prepared by coupling of amine **45**[8] with **20a** and **20b** (Scheme 8). In the thiazoline formation and further transformation, both intermediates of the natural isomer and its epimer were synthesized independently, and their NMR spectra and retention time measured in HPLC analysis were compared for the detection of epimerization at C34. Treatment of **46a** with Ph_3PO/Tf_2O in CH_2Cl_2 at 0 °C induced thiazoline formation. The reaction proceeded smoothly leading to desired thiazoline **47a**. Since β-elimination of the *O*-Troc group in **47a** was observed during silica gel column chromatography, crude **47a** was immediately treated with Zn/NH_4OAc to remove the Troc group and **48a** was obtained in 90% yield in 2 steps. In the same manner, thiazoline formation of **46b**, followed by removal of the Troc group, provided **48b**. HPLC analysis and comparison of spectra data of **48a** (t_R = 24.7 min) and **48b** (t_R = 24.1 min) confirmed that no epimerization was observed at C34 during the reactions. Removal of the allyl ester in **48a** and



Scheme 7. Attempts to construction of thiazoline using **38** and **42**. Reagents and conditions: a) H_2S, NEt_3, MeOH; b) allyl bromide, K_2CO_3, DMF, 95%; c) TMSOTf, 2,6-lutidine, CH_2Cl_2, then MeOH; d) **35**, HATU, DIEA, CH_2Cl_2, 90%; e) Lawesson's reagent, toluene, 80°C, 1 h, 91%.



Scheme 8. Thiazoline formation using moCys moiety **46a** and **46b**. Reagents and conditions: a) **45**, EDCI·HCl, HOAt, DIEA, CH_2Cl_2, 0°C to RT., 81% (for **46a** from **20a**), and 84% (for **46b** from **20b**). b) Tf_2O, Ph_3PO, CH_2Cl_2, 0°C; c) Zn, NH_4OAc, THF, 90% (for **48a**), and 95% (for **48b**) in 2 steps; d) $Pd(PPh_3)_4$, *N*-methylaniline, THF, 95% (for **49a**), and 95% (for **49b**). Trt = triphenylmethyl, HOAt = 1-hydroxy-7-azabenzotiazole.

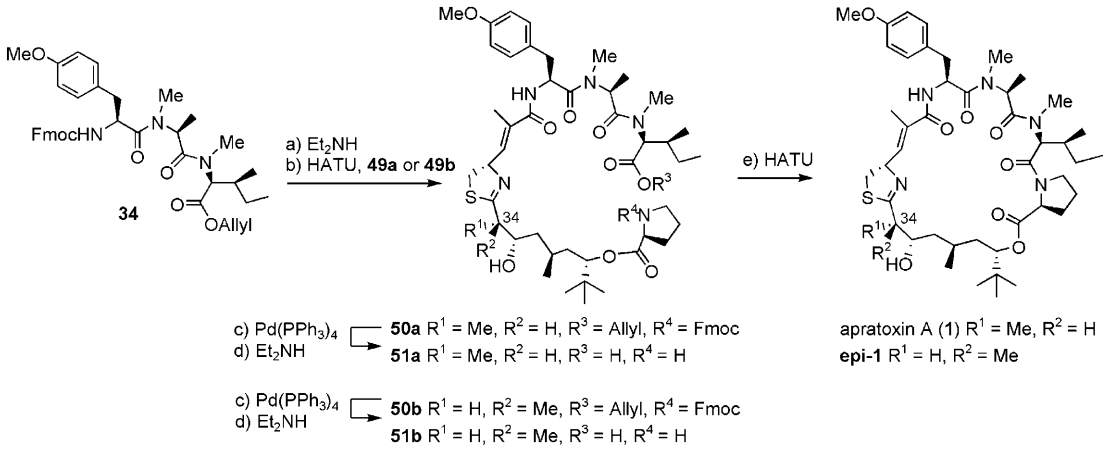
48b using $Pd(PPh_3)_4$/*N*-methylaniline[30] provided **49a** and **49b**, respectively.

Completion of the Syntheses of Apratoxin A and 34-epi Analogue

49a and 34-epimer **49b** were used for the further transformation (Scheme 9). After removal of the Fmoc group in **34** (Et_2NH/CH_3CN), coupling of the resulting amine with acids **49a** and **49b** provided **50a** (t_R = 24.8 min) and **50b** (t_R = 24.1 min). Cleavage of the *O*-allyl esters mediated by $Pd(PPh_3)_4$/*N*-methylaniline, followed by removal of the Fmoc groups with Et_2NH/CH_3CN, afforded cyclization precursors **51a** and **51b**. Finally, the macrolactamization of **51a** and **51b** was performed with HATU/DIEA at high dilution conditions (1 mM). After purification by silica gel column chromatography, apratoxin A (**1**) and 34-epi apratoxin A (**epi-1**) were isolated in 72% and 25% yields, respectively. The spectral data of synthetic **1** were identical to those of the natural product reported previously.[4] Interestingly, 34-epi apratoxin A was provided in lower yield, probably because it could be disadvantageous in the conformation for macrocyclization of **51b** rather than in **51a**.

Conclusions

In conclusion, the total synthesis of apratoxin A has been accomplished in 18 steps (longest linear sequence form hydroxyketone **8**) and 18% overall yield. The preparation of the Dtena fragment was performed through a stereoselective synthetic route based on three asymmetric reactions, which also enables the preparation of the other stereoisomers under similar conditions. Thiazoline formation in **1** was successfully accomplished from the moCys amide **46a** using Ph_3PO/Tf_2O. Furthermore, comparing the spectra of thiazoline **48a** with that of 34-epi **48b**, we conclude that no epimerization at C34, the α-position of the thiazoline ring, occurred. Finally, we have demonstrated a convergent total synthesis of apratoxin A by connection of tripeptide **34** and thiazoline–Dtena **49a**, followed by macrolactamization between *N*-methylisoleucine and proline residues using HATU. Moreover, the oxazoline analogue and 34-epi apra-



Scheme 9. Synthesis of apratoxin A (**1**) and C(34)-epimer **epi-1**. Reagents and conditions: a) Et_2NH, CH_3CN; b) **49a** or **49b**, HATU, DIEA, CH_2Cl_2, 75% (for **50a**), and 81% (for **50b**); c) $Pd(PPh_3)_4$, *N*-methylaniline, THF d) Et_2NH, CH_3CN; e) HATU, DIEA, CH_2Cl_2 (1.0 mM), 72% (for **1**), and 25% (for **epi-1**) in 3 steps.

toxin A were synthesized. The information from the synthetic analogues of apratoxin A should enable us to rationally design functional analogues well-adjusted for both biological activity and physical properties, which may be used as a new anticancer drug or probes for identification of the molecular target of apratoxin A.

Experimental Section

General Techniques

NMR spectra were recorded on a JEOL Model ECP-400 (400 MHz for ^1H, 100 MHz for ^{13}C) instrument in the indicated solvent. Chemical shifts are reported in units parts per million (ppm) relative to the signal for internal tetramethylsilane (0.00 ppm for ^1H) for solutions in $CDCl_3$. ^1H NMR spectral data are reported as follows: chloroform (7.26 ppm) and dichloromethane (5.3 ppm). ^{13}C NMR spectral data are reported as chloroform-*d* (77.1 ppm). Multiplicities are reported by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; *J*, coupling constants in Hertz. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrophotometer. Only the strongest and/or structurally important absorption is reported as the IR data given in cm^{-1}. Optical rotations were measured with a JASCO P-1020 polarimeter. All reactions were monitored by thin-layer chromatography carried out on 0.2 mm silica gel plates (60F-254, E. Merck) with UV light, visualized by *p*-anisaldehyde solution, ceric sulfate, or 10% ethanolic phosphomolybdic acid. Merck silica gel was used for column chromatography. ESI-TOF mass spectra were measured with Applied Biosystems TK-3500 Biospectrometry Workstation or Waters LCT Premier XE. HRMS (ESI-TOF) were calibrated with angiotensin I (SIGMA), bradykinin (SIGMA), and neurotensin (SIGMA) as an internal standard or with leucine enkephalin (SIGMA) as an external standard. High performance liquid chromatography (HPLC) for qualitative and quantitative analyses, were performed on a Nihon Seimitsu Kagaku apparatus with a Japan Analytical Industry Model R1–3H refractive detector or Waters 2695 Separation Module with Waters 2996 Photodiode Array detector.

*Rhenium-Catalyzed Isomerization of Allylic Alcohol **9** to **10a** and **10b***

To a solution of allylic alcohol **9** (4.84 g, 16.6 mmol) and $Ph_3SiOReO_3$ (250 mg, 0.497 mmol) in diethyl ether (83 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (4.94 mL, 19.9 mmol) at 0°C dropwise over 1 h by using a syringe pump. After being stirred at the same temperature for 1.5 h, the reaction mixture was quenched with Et_3N (1.0 mL), stirred at 0°C for 30 min, and concentrated in vacuo. The residue was diluted with MeOH (100 mL) and treated with K_2CO_3 (5.3 g, 38.4 mmol) at 0°C for 1 h. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo, and quenched with HCl (1 M). The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20% to 25% ethyl acetate/hexane) to give **10a** (2.06 g, 7.04 mmol, 42%) and **10b** (2.15 g, 7.35 mmol, 44%) as a colorless oil.

10a: R_f = 0.45 (hexane/ethyl acetate = 1:1); $[\alpha]_D^{28}$ = +1.40 (*c* = 0.990, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3391, 2870, 1614, 1515, 1248, 1078, 1037, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.54 (m, 1H), 4.45 (d, *J* = 11.1 Hz, 1H), 4.42 (d, *J* = 11.1 Hz, 1H), 4.15 (dd, *J* = 16.1, 7.3 Hz, 1H), 4.13 (dd, *J* = 16.1, 6.8 Hz, 1H), 3.79 (s, 3H), 3.16 (dd, *J* = 9.3, 3.0 Hz, 1H), 2.10–2.27 (m, 2H), 1.75 (s, 3H), 0.94 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 137.8, 131.4, 129.1, 126.0, 113.7, 85.9, 74.4, 59.5, 55.3, 41.6, 36.2, 26.5, 16.9 ppm; HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{18}H_{28}O_3+Na]^+$: 315.1931; found: 315.1930.

10b: R_f = 0.50 (hexane/ethyl acetate = 1:1); $[\alpha]_D^{20}$ = +44.9 (*c* = 2.44, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3341, 2959, 2870, 1614, 1514, 1249, 1077, 1036, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.71 (dd, *J* = 7.8, 6.8 Hz, 1H), 4.47 (d, *J* = 10.2 Hz, 1H), 4.42 (d, *J* = 10.2 Hz, 1H), 4.12 (dd, *J* = 12.2, 7.8 Hz, 1H), 3.87 (dd, *J* = 12.2, 6.8 Hz, 1H), 3.79 (s, 3H), 3.21 (dd, *J* = 11.2, 2.4 Hz, 1H), 2.63 (dd, *J* = 13.7, 11.2 Hz, 1H), 1.96 (dd, *J* = 13.7, 2.4 Hz, 1H), 1.84 (s, 3H), 0.98 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 138.2, 130.3, 129.4, 127.2, 113.7, 85.0, 75.2, 58.3, 55.2, 36.4, 33.4, 26.4, 23.8 ppm; HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{18}H_{28}O_3+Na]^+$: 315.1931; found: 315.1921.

12a: (3*S*,5*S*)-5-(4-methoxybenzyloxy)-3,6,6-trimethylheptan-1-ol. In a 50-mL autoclave, containing a glass tube, was placed $Ru(OAc)_2$[(*S*)-binap] (**11a**) (89.0 mg, 106 μmol), (*E*)-(*S*)-5-(4-methoxybenzyloxy)-3,6,6-trimethylhept-2-en-1-ol (**10a**) (1.55 g, 5.30 mmol), and degassed methanol (10 mL). The autoclave was filled with hydrogen (100 atm) after repeated (3 times) filling and purging of hydrogen. The reaction was carried out under an appropriate hydrogen pressure at 50°C for 24 h. The reaction mixture was diluted with hexane. This solution was stirred with Florisil at room temperature for 10 min, then filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexane) to give **12a** (1.54 g, 5.23 mmol, quant.) as a colorless oil. R_f = 0.48 (hexane/ethyl acetate = 1:1); $[\alpha]_D^{28}$ = −29.3 (*c* = 0.990, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3392, 2955, 1615, 1587, 1515, 1464, 1302, 1249, 1039, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.2 Hz, 2H),

4.54 (s, 2H), 3.80 (s, 3H), 3.72 (m, 1H), 3.62 (m, 1H), 3.10 (dd, J=6.8, 4.8 Hz, 1H), 1.72–1.83 (m, 2H), 1.39–1.42 (m, 2H), 1.29 (m, 1H), 0.95 (d, J=6.8 Hz, 3H), 0.93 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 159.0, 131.6, 129.1, 113.8, 85.5, 74.3, 61.2, 55.3, 39.4, 39.0, 36.2, 27.0, 26.6, 21.1 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{18}H_{30}O_3+Na]^+$: 317.2087; found: 317.2085.

12b: (3*R*,5*S*)-5-(4-methoxybenzyloxy)-3,6,6-trimethylheptan-1-ol. Following a similar procedure from **10a** to **12a**, **12b** was obtained from **10a** using Ru(OAc)$_2$[(*R*)-binap] (**11b**) instead of Ru(OAc)$_2$[(*S*)-binap] (**11a**). R_f=0.45 (hexane/ethyl acetate=1:1); $[\alpha]_D^{18}=-24.8$ (c=1.23, $CHCl_3$); IR (neat): $\tilde{\nu}$=3394, 2955, 2871, 1514, 1249, 1077, 1038, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.28 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 4.58 (d, J=10.8 Hz, 1H), 4.51 (d, J=10.8 Hz, 1H), 3.80 (s, 3H), 3.61–3.72 (m, 2H), 3.11 (dd, J=10.2, 1.5 Hz, 1H), 1.75 (m, 1H), 1.43–1.57 (m, 3H), 1.21 (ddd, J=14.2, 10.2, 1.5 Hz, 1H), 0.95 (d, J=7.3 Hz, 3H), 0.94 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.1, 131.5, 129.2, 113.8, 85.9, 75.0, 60.9, 55.3, 41.2, 38.7, 36.2, 26.6, 26.6, 19.9 ppm.

14: (3*R*,5*S*)-5-*tert*-Butyl-3-methyl-δ-valerolactone. To a solution of aldehyde **13** (58.8 mg, 0.200 mmol) in 2-methyl-2-propanol (2.0 mL) and 0.5 M NaH_2PO_4 (1.0 mL) was added 2-methyl-2-butene (0.3 mL) and $NaClO_2$ (27.1 mg, 0.300 mmol) at 0 °C. After being stirred at the same temperature for 40 min, the reaction mixture was diluted with brine and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was used for the next reaction without further purification. To a solution of the crude carboxylic acid in CH_2Cl_2 (4.0 mL) was added trifluoroacetic acid (2.0 mL) at 0 °C. After being stirred at 0 °C for 20 min, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexane) to give **14** (21.7 mg, 0.112 mmol, 56% in 2 steps) as a colorless oil. R_f=0.53 (hexane/ethyl acetate=3:2); $[\alpha]_D^{23}=+46.0$ (c=1.49, $CHCl_3$); IR (neat): $\tilde{\nu}$=2960, 2875, 1747, 1242, 1073, 1002 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.98 (dd, J=11.7, 3.9 Hz, 1H), 2.51 (dd, J=10.2, 10.2 Hz, 1H), 2.16–2.24 (m, 2H), 1.83 (ddd, J=14.2, 11.7, 7.3 Hz, 1H), 1.51 (ddd, J=14.2, 5.0, 3.9 Hz, 1H), 1.11 (d, J=6.8 Hz, 3H), 0.97 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.3, 83.8, 37.0, 34.0, 29.9, 25.5, 24.1, 21.3 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{10}H_{18}O_2+Na]^+$: 193.1199; found: 193.1196.

16a: (3*R*,4*S*,6*S*,8*S*)-8-(4-methoxybenzyloxy)-3,6,9,9-tetramethyldec-1-en-4-ol. To a suspension of crotyl borane (*E*)-**15a** (5.27 mL, ca. 1.0 M solution in toluene, ca. 5.3 mmol) and molecular sieves 4 A (320 mg) in toluene (10.6 mL) was added a solution of aldehyde **13** (617 mg, 2.11 mmol) at −78 °C dropwise over 15 min. After being stirred at the same temperature for 7 h, the reaction mixture was quenched with NaOH (7.0 mL, 2 M), stirred at 0 °C for 30 min, and filtered through a pad of Celite. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with HCl (1 M), saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (5% ethyl acetate/hexane) to give **16a** (699 mg, 2.00 mmol, 95%) as colorless oil. R_f=0.68 (hexane/ethyl acetate=3:1); $[\alpha]_D^{24}=-50.9$ (c=1.09, $CHCl_3$); IR (neat): $\tilde{\nu}$=3478, 2956, 2870, 1614, 1514, 1465, 1248, 1091, 1039, 915, 821 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 5.75 (m, 1H), 5.10–5.14 (m, 2H), 4.63 (d, J=10.8 Hz, 1H), 4.51 (d, J=10.8 Hz, 1H), 3.79 (s, 3H), 3.50 (m, 1H), 3.11 (dd, J=9.3, 2.9 Hz, 1H), 2.17 (m, 1H), 1.96 (m, 1H), 1.57 (ddd, J=13.7, 10.7, 2.9 Hz, 1H), 1.47 (ddd, J=14.2, 8.8, 3.9 Hz, 1H), 1.35 (ddd, J=14.2, 9.3, 2.4 Hz, 1H), 1.12 (ddd, J=13.7, 9.3, 2.4 Hz, 1H), 1.03 (d, J=7.3 Hz, 3H), 0.96 (d, J=6.8 Hz, 3H), 0.93 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.0, 140.7, 131.7, 129.3, 116.4, 113.7, 85.3, 74.2, 72.4, 55.3, 45.3, 40.9, 39.9, 36.2, 26.7, 26.6, 21.0, 16.3 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{22}H_{36}O_3+H]^+$: 349.2743; found: 349.2747.

17a: (3*R*,4*S*,6*S*,8*S*)-8-(4-methoxybenzyloxy)-3,6,9,9-tetramethyldec-1-en-4-yl 2,2,2-trichloroethyl carbonate. To a solution of **16a** (1.52 g, 4.36 mmol) and pyridine (1.06 mL, 13.1 mmol) in CH_2Cl_2 (20 mL) was added 2,2,2-trichloroethoxycarbonyl chloride (0.70 mL, 5.23 mmol) and 4-dimethylaminopyridine (27 mg, 0.22 mmol) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was quenched with HCl (1 M) and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexane) to give carbonate **17a** (2.26 g, 4.31 mmol, quant.) as a colorless oil. R_f=0.75 (hexane/ethyl acetate=3/1); $[\alpha]_D^{24}=-34.1$ (c=1.53, $CHCl_3$); IR (neat): $\tilde{\nu}$=2958, 2872, 1758, 1514, 1380, 1249, 1095, 1039, 945, 820, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.28 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 5.57 (m, 1H), 5.06–5.13 (m, 2H), 4.89 (m, 1H), 4.78 (d, J=12.2 Hz, 1H), 4.58 (d, J=10.8 Hz, 1H), 4.50 (d, J=10.8 Hz, 1H), 4.50 (d, J=12.2 Hz, 1H), 3.79 (s, 3H), 3.06 (dd, J=9.3, 2.4 Hz, 1H), 2.48 (m, 1H), 1.91 (ddd, J=14.2, 11.2, 2.4 Hz, 1H), 1.78 (m, 1H), 1.47 (ddd, J=14.2, 9.3, 3.9 Hz, 1H), 1.34 (ddd, J=14.2, 9.8, 2.4 Hz, 1H), 1.16 (ddd, J=14.2, 9.3, 2.0 Hz, 1H), 1.07 (d, J=6.8 Hz, 3H), 0.99 (d, J=6.3 Hz, 3H), 0.92 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 159.0, 154.3, 138.9, 131.6, 129.0, 116.4, 113.8, 94.8, 85.2, 80.8, 76.6, 74.5, 55.4, 42.8, 39.8, 37.7, 36.2, 26.6, 26.4, 21.0, 15.7 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{25}H_{37}Cl_3O_5+Na]^+$: 545.1604; found: 545.1595.

Prolyl ester 18a: To a solution of **17a** (2.26 g, 4.31 mmol) in CH_2Cl_2 (20 mL) and H_2O (2.0 mL) was added 2,3-dichloro-5,6-dicyano-benzoquinone (1.19 g, 5.23 mmol) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was used for the next reaction without further purification. To a solution of *N*-Fmoc-L-proline (2.94 g, 8.72 mmol) in toluene (25 mL) was added *N*,*N*-diisopropylethylamine (2.25 mL, 13.1 mmol) and 2,4,6-trichlorobenzoyl chloride (2.05 mL, 13.1 mmol) at room temperature under argon. The solution was stirred at the same temperature for 10 min. To the resultant mixture was added a solution of the crude alcohol in toluene (25 mL) and 4-dimethylaminopyridine (1.87 g, 15.3 mmol) at 10 °C under argon. After being stirred at room temperature for 5 h, the reaction mixture was quenched with H_2O and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (10% to 15% ethyl acetate in hexane) to give **18a** (2.91 g, 4.02 mmol, 92% in 2 steps) as a colorless oil. R_f=0.60 (hexane/ethyl acetate=3:1); $[\alpha]_D^{23}=-65.7$ (c=1.66, $CHCl_3$); IR (neat): $\tilde{\nu}$=2963, 1753, 1708, 1416, 1250, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ=7.72–7.77 (m, 2H), 7.57–7.64 (m, 2H), 7.38–7.42 (m, 2H), 7.29–7.33(m, 2H), 5.65–5.77 (m, 1H), 5.00–5.12 (m, 2H), 4.68–4.85 (m, 4H), 4.51 (dd, J=8.8, 2.9 Hz, 0.5H), 4.46 (dd, J=5.8, 2.9 Hz, 0.5H), 4.15–4.45 (m, 3H), 3.48–3.67 (m, 2H), 2.47 (m, 0.5H), 2.41 (m, 0.5H), 2.05–2.34 (m, 2H), 1.91–2.01 (m, 2H), 1.78–1.85 (m, 1H), 1.35–1.60 (m, 3H), 1.26 (ddd, J=14.2, 9.8, 2.4 Hz, 0.5H), 1.12 (ddd, J=14.7, 10.3, 2.0 Hz, 0.5H), 1.04 (d, J=6.8 Hz, 1.5H), 1.02 (d, J=6.8 Hz, 1.5H), 0.95 (d, J=6.8 Hz, 1.5H), 0.88 (s, 4.5H), 0.86 (s, 4.5H), 0.74 ppm (d, J=6.4 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ=172.5, 172.4, 154.7, 154.4, 154.2, 154.1, 144.3, 144.0, 143.9, 141.4, 141.4, 141.3, 141.3, 138.9, 138.8, 127.8, 127.7, 127.2, 127.1, 127.1, 80.6, 80.4, 79.6, 79.4, 67.8, 67.5, 59.9, 59.5, 47.3, 47.3, 47.1, 46.5, 42.7, 42.4, 38.0, 37.8, 37.2, 37.0, 35.0, 34.8, 31.3, 30.1, 26.6, 26.5, 25.9, 24.5, 23.4, 20.4, 20.4, 15.6, 15.6 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{37}H_{46}NO_7Cl_3+H]^+$: 722.2418; found: 722.2418.

Carboxylic acid 20a: To a solution of **18a** (363 mg, 502 μmol) in DMF (5.0 mL) was added OsO_4 (63 μL, 2.5 wt% solution in 2-methyl-2-propanol, 5.0 μmol), oxone (1.24 g, 2.01 mmol), and $NaHCO_3$ (169 mg, 2.01 mmol) at room temperature. After being stirred at the same temperature for 12 h, the reaction mixture was diluted with H_2O (3.0 mL) and 2-methyl-2-propanol (6.0 mL). To the mixture was added $NaIO_4$ (214 mg, 1.0 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 5 h and poured into HCl (1 M) and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with aqueous solution of $Na_2S_2O_3$ (10 wt%), brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (40% ethyl acetate in hexane) to give **20a** (296 mg, 399 μmol, 79%) as a white amorphous solid. R_f=0.40 (hexane/ethyl acetate=1:1); $[\alpha]_D^{22}=-45.3$ (c=0.99, $CHCl_3$); IR (neat):

$\tilde{\nu}$ = 2962, 1756, 1742, 1708, 1451, 1419, 1248, 758, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 7.75–7.78 (m, 2H), 7.57–7.67 (m, 2H), 7.36–7.42 (m, 2H), 7.28–7.34 (m, 2H), 5.08–5.16 (m, 1H), 4.69–4.89 (m, 3H), 4.47–4.50 (m, 1H), 4.15–4.45 (m, 3H), 3.46–3.65 (m, 2H), 2.95 (dq, J = 7.3, 7.3 Hz, 0.7H), 2.87 (dq, J = 7.3, 7.3 Hz, 0.3H), 2.09–2.36 (m, 2H), 1.81–2.00 (m, 3H), 1.69 (m, 0.7H), 1.49–1.58 (m, 1.3H), 1.21–1.43 (m, 2H), 1.21 (d, J = 7.3 Hz, 0.9H), 1.19 (d, J = 7.3 Hz, 2.1H), 0.99 (d, J = 6.8 Hz, 2.1H), 0.88 (s, 2.7H), 0.87 (s, 6.3H), 0.76 ppm (d, J = 6.4 Hz, 0.9H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 172.7, 172.1, 155.1, 154.4, 153.8, 153.7, 144.3, 144.1, 143.9, 143.8, 141.4, 141.4, 141.3, 141.3, 127.8, 127.1, 125.4, 125.2, 120.1, 94.7, 79.1, 76.8, 67.9, 67.7, 59.8, 59.5, 47.3, 47.1, 46.5, 43.4, 37.3, 36.7, 36.4, 35.1, 34.8, 31.4, 30.1, 26.2, 26.0, 26.0, 25.9, 24.3, 23.5, 20.4, 20.0, 12.2, 12.1 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{36}H_{43}NO_9Cl_3+H]^+$: 740.2160; found: 740.2139.

***Syn*-selective crotylation of 13.** To a suspension of crotyl borane (*Z*)-**15b** (3.53 mL, ca. 1.0 M solution in toluene, ca. 3.5 mmol) and molecular sieves 4 A (230 mg) in toluene (8.0 mL) was added a solution of aldehyde **13** (343 mg, 1.17 mmol) at −78 °C dropwise over 15 min. After being stirred at the same temperature for 7 h, the reaction mixture was quenched with NaOH (4.0 mL, 2 M), stirred at 0 °C for 30 min, and filtered through a pad of Celite. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with HCl (1 M), saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (10% ethyl acetate/hexane) to give a mixture of **16b** and **16c** (367 mg, 1.50 mmol, 90%, dr = 10:1) as colorless oil. The diastereomers were analyzed by HPLC (Senshu Pack Silica-3301-N 8×300 mm, 10% ethyl acetate in hexane, 2.0 mL min^{-1}, refractive index detection, t_R = 28.0 min (**16b**), 33.5 min (**16c**)).

16b: R_f = 0.66 (hexane/ethyl acetate = 3:1); $[\alpha]_D^{21} = -65.3$ (c = 1.18, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3471, 2956, 2870, 1613, 1514, 1248, 1089, 1038, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.3 Hz, 2H), 5.79 (m, 1H), 5.11 (dd, J = 4.4, 1.0 Hz, 1H), 5.07 (br s, 1H), 4.61 (d, J = 10.2 Hz, 1H), 4.51 (d, J = 10.2 Hz, 1H), 3.76 (s, 3H), 3.60 (m, 1H), 3.10 (dd, J = 8.8, 2.4 Hz, 1H), 2.24 (m, 1H), 1.92 (m, 1H), 1.55 (ddd, J = 14.2, 7.8, 2.9 Hz, 1H), 1.47 (ddd, J = 14.6, 8.8, 4.4 Hz, 1H), 1.35 (ddd, J = 14.6, 9.3, 2.4 Hz, 1H), 1.11 (ddd, J = 14.2, 10.7, 2.0 Hz, 1H) 1.04 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.93 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 141.0, 131.7, 129.2, 115.4, 113.8, 85.3, 74.2, 72.5, 55.4, 44.6, 40.6, 39.8, 36.2, 26.8, 26.6, 21.0, 14.8 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{22}H_{36}O_3+H]^+$: 349.2743; found: 349.2727.

16c: R_f = 0.66 (hexane/ethyl acetate = 3:1); $[\alpha]_D^{25} = -15$ (c = 0.050, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.82 (m, 1H), 5.12 (m, 1H), 5.08 (m, 1H), 4.55 (d, J = 11.2 Hz, 1H), 4.49 (d, J = 11.2 Hz, 1H), 3.80 (s, 3H), 3.65 (m, 1H), 3.08 (dd, J = 7.8, 3.4 Hz, 1H), 2.26 (m, 1H), 1.75 (m, 1H), 1.52–1.61 (m, 2H), 1.32 (ddd, J = 14.6, 7.8, 5.9 Hz, 1H), 1.23 (m, 1H), 1.02 (d, J = 6.3 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.93 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 141.3, 131.6, 128.9, 115.5, 113.8, 86.2, 73.8, 73.0, 55.4, 43.2, 41.3, 39.1, 36.4, 28.4, 26.6, 22.2, 13.6 ppm.

Carbonate 17b. Following a similar procedure from **16a** to **17a**, **17b** was obtained from **16b** in quantitative yield. R_f = 0.75 (hexane/ethyl acetate = 3:1); $[\alpha]_D^{22} = -33.4$ (c = 1.15, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2958, 1758, 1514, 1380, 1249, 1038, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.77 (m, 1H), 5.08–5.13 (m, 2H), 4.86 (ddd, J = 11.2, 10.3, 2.0 Hz, 1H), 4.81 (d, J = 12.2 Hz, 1H), 4.58 (d, J = 10.7 Hz, 1H), 4.50 (d, J = 10.7 Hz, 1H), 4.47 (d, J = 12.2 Hz, 1H), 3.79 (s, 3H), 3.06 (dd, J = 9.3, 2.4 Hz, 1H), 2.50 (m, 1H), 1.88 (ddd, J = 14.6, 11.2, 2.4 Hz, 1H), 1.78 (m, 1H), 1.47 (ddd, J = 14.6, 9.3, 3.9 Hz, 1H), 1.34 (ddd, J = 14.6, 9.8, 2.4 Hz, 1H), 1.23 (ddd, J = 14.6, 10.3, 2.0 Hz, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H), 0.92 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 154.4, 139.1, 131.6, 128.9, 116.2, 113.8, 94.8, 85.2, 81.1, 76.6, 74.5, 55.4, 42.5, 39.8, 38.0, 36.2, 26.6, 26.4, 20.9, 15.6 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{25}H_{37}Cl_3O_5+Na]^+$: 545.1604; found: 545.1613.

Prolyl ester 18b. Following a similar procedure from **17a** to **18a**, **18b** was obtained from **17b** in 81% yield over 2 steps. R_f = 0.62 (hexane/ethyl acetate = 3:1); $[\alpha]_D^{22} = -67.6$ (c = 1.41, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2963, 1754, 1708, 1417, 1250, 1118, 758, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 7.74–7.77 (m, 2H), 7.58–7.66 (m, 2H), 7.38–7.43 (m, 2H), 7.28–7.34 (m, 2H), 5.66–5.81 (m, 1H), 5.04–5.10 (m, 2H), 4.68–4.89 (m, 4H), 4.51 (dd, J = 8.8, 2.9 Hz, 0.5H), 4.46 (dd, J = 8.8, 2.9 Hz, 0.5H), 4.15–4.44 (m, 3H), 3.48–3.67 (m, 2H), 2.49 (m, 0.5H), 2.42 (m, 0.5H), 2.09–2.36 (m, 2H), 1.91–2.03 (m, 2H), 1.77–1.85 (m, 1H), 1.53–1.64 (m, 1H), 1.36–1.51 (m, 2H), 1.31 (ddd, J = 14.6, 10.2, 2.4 Hz, 0.5H), 1.18 (ddd, J = 14.6, 10.2, 2.0 Hz, 0.5H), 1.04 (d, J = 6.8 Hz, 1.5H), 1.02 (d, J = 6.8 Hz, 1.5H), 0.95 (d, J = 6.8 Hz, 1.5H), 0.88 (s, 4.5H), 0.86 (s, 4.5H), 0.73 ppm (d, J = 6.8 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 172.5, 172.3, 154.7, 154.4, 154.3, 154.1, 144.3, 144.0, 143.9, 141.4, 141.4, 141.3, 141.3, 139.1, 127.8, 127.7, 127.2, 127.1, 127.1, 127.1, 125.5, 125.3, 125.3, 125.2, 120.0, 120.0, 116.2, 116.1, 94.9, 94.9, 80.8, 80.6, 79.6, 79.5, 67.8, 67.5, 59.9, 59.5, 47.3, 47.3, 47.1, 46.4, 42.5, 42.2, 38.0, 37.8, 37.7, 37.4, 35.0, 34.8, 31.3, 30.1, 26.7, 26.5, 25.9, 24.5, 23.4, 20.4, 20.3, 15.5, 15.3 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{37}H_{46}NO_7Cl_3+H]^+$: 722.2418; found: 722.2421.

Carboxylic acid 20b. Following a similar procedure from **18a** to **20a**, **20b** was obtained from **18b** in 83% yield. R_f = 0.40 (hexane/ethyl acetate = 1:1); $[\alpha]_D^{22} = -49.7$ (c = 1.01, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2957, 1752, 1741, 1707, 1420, 1249, 1183, 1121, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 7.75–7.77 (m, 2H), 7.60–7.66 (m, 2H), 7.38–7.42 (m, 2H), 7.29–7.33 (m, 2H), 5.03–5.10 (m, 1H), 4.88 (dd, J = 11.2, 2.0 Hz, 0.7H), 4.88 (d, J = 12.2 Hz, 0.3H), 4.79 (m, 0.3H), 4.78 (s, 1.4H), 4.70 (d, J = 12.2 Hz, 0.3H), 4.60 (dd, J = 7.3, 3.4 Hz, 0.7H), 4.49 (dd, J = 8.8, 3.4 Hz, 0.3H), 4.15–4.49 (m, 3H), 3.45–3.67 (m, 2H), 2.79 (dq, J = 8.3, 6.8 Hz, 0.7H), 2.71 (dq, J = 7.4, 6.8 Hz, 0.3H), 2.10–2.34 (m, 2H), 1.86–2.02 (m, 3H), 1.77 (m, 0.7H), 1.59 (ddd, J = 14.6, 11.2, 3.9 Hz, 0.7H), 1.52 (m, 0.3H), 1.11–1.49 (m, 2.3H), 1.26 (d, J = 6.8 Hz, 2.1H), 1.24 (d, J = 6.8 Hz, 0.9H), 1.00 (d, J = 6.8 Hz, 2.1H), 0.88 (s, 2.7H), 0.87 (s, 6.3H), 0.75 ppm (d, J = 6.8 Hz, 0.9H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 177.3, 176.0, 172.8, 171.6, 155.4, 154.4, 154.1, 153.9, 144.3, 144.2, 143.8, 141.4, 141.4, 141.3, 127.8, 127.2, 127.1, 125.5, 125.3, 125.3, 125.2, 120.1, 94.8, 79.8, 79.1, 79.0, 77.8, 68.0, 67.9, 59.7, 59.5, 47.3, 47.2, 47.1, 46.5, 44.1, 43.6, 38.9, 37.9, 37.7, 37.4, 35.3, 34.8, 31.3, 29.9, 29.8, 26.5, 26.1, 25.9, 25.8, 24.2 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{36}H_{43}NO_9Cl_3+H]^+$: 740.2160; found: 740.2156.

21: (*R*)-2-*N*-*tert*-Butoxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)propionic acid methyl ester. To a solution of Boc-Ser-OMe (6.94 g, 31.7 mmol) and imidazole (4.36 g, 63.4 mmol) in CH_2Cl_2 (120 mL) was added *tert*-butyldimethylsilyl chloride (6.21 g, 41.2 mmol) at 0 °C. After being stirred at room temperature for 1.5 h, the reaction mixture was quenched with methanol, then partitioned between H_2O and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (7% ethyl acetate in hexane) to give silyl ether **21** (10.0 g, 30.1 mmol, 95%) as a colorless oil. R_f = 0.60 (hexane/ethyl acetate = 3:1); $[\alpha]_D^{23} = -19.2$ (c = 1.34, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3452, 2956, 2887, 1750, 1723, 1505, 1367, 1351, 1115, 836, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.34 (d, J = 8.7 Hz, 1H), 4.35 (m, 1H), 4.04 (dd , J = 9.7, 2.4 Hz, 1H), 3.82 (dd, J = 9.7, 2.7 Hz, 1H), 3.74 (s, 3H), 1.46 (s, 9H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 155.5, 79.9, 63.9, 55.7, 52.3, 28.4, 25.8, 18.2, −5.5, −5.6 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{15}H_{31}NO_5Si+H]^+$:334.2050; found: 334.2050.

23: (*E*)-(*S*)-4-*N*-*tert*-Butoxycarbonylamino-5-(*tert*-butyldimethylsilyloxy)-2-methylpent-2-enoic acid ethyl ester. To a solution of **21** (3.86 g, 11.6 mmol) in toluene (60 mL) was added dropwise DIBAL-H (25.5 mL, 1.0 M in toluene, 25.5 mmol) at −78 °C over 15 min under argon. After being stirred at the same temperature for 15 min, the reaction mixture was poured into aqueous potassium sodium tartrate (10%) at 0 °C, stirred at room temperature for 1 h, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was used for the next reaction without further purification. To a solution of the crude aldehyde in toluene (60 mL) was added (carbethoxyethylidene) triphe-

nylphosphorane (**22**) (5.45 g, 14.7 mmol) at 0 °C under argon. After being at room temperature for 3 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexane) to give **23** (3.70 g, 9.55 mmol, 82% in 2 steps) as a colorless oil. R_f = 0.58 (hexane/ethyl acetate = 2/1); $[\alpha]_D^{27}$ = −6.71 (c = 1.36, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3373, 2957, 2932, 1717, 1515, 1367, 1254, 1173, 1112, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.64 (dq, J = 9.2, 1.0 Hz, 1H), 4.93 (m, 1H), 4.47 (m, 1H), 4.13–4.25 (m, 2H), 3.71 (dd, J = 10.3, 3.4 Hz, 1H), 3.61 (dd, J = 10.3, 3.9 Hz, 1H) 1.93 (d, J = 1.0 Hz, 3H), 1.44 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 155.3, 139.2, 129.9, 79.7, 65.0, 60.7, 50.6, 28.4, 25.9, 18.4, 14.3, 13.0, −5.4, −5.5 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{19}H_{37}NO_5Si+H]^+$: 388.2519; found: 388.2522.

24: (*E*)-(*S*)-4-*N*-*tert*-Butoxycarbonylamino-5-(*tert*-butyldimethylsilyloxy)-2-methylpent-2-enoic acid. To a solution of **23** (1.09 g, 2.81 mmol) in 2-methyl-2-propanol (23 mL), H_2O (6.0 mL), and THF (6.0 mL) was added $LiOH·H_2O$ (589 mg, 14.1 mmol) at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (40% ethyl acetate in hexane) to give **24** (859 mg, 2.39 mmol, 85%) as a colorless oil. R_f = 0.42 (hexane/ethyl acetate = 1:1); $[\alpha]_D^{24}$ = +5.21 (c = 1.17, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3245, 2931, 1692, 1500, 1473, 1393, 1254, 1168, 1116, 837, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.76 (dq, J = 8.7, 1.0 Hz, 1H), 4.98 (m, 1H), 4.49 (m, 1H), 3.71 (dd, J = 10.1, 4.3 Hz, 1H), 3.62 (dd, J = 10.1, 4.3 Hz, 1H), 1.94 (d, J = 1.0 Hz, 3H), 1.44 (s, 9H), 0.89 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 155.4, 141.5, 129.3, 79.8, 64.8, 50.6, 28.4, 25.9, 18.3, 12.6, −5.4, −5.5 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{17}H_{33}NO_5Si+H]^+$: 360.2206; found: 360.2206.

26: Boc-moSer(*O*-TBS)-Tyr(*O*-Me)-OMe. To Boc-Tyr(*O*-Me)-OMe (**25**) (118 mg, 0.381 mmol) was added HCl (4 M) in ethyl acetate (3.0 mL) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was azeotropically dried with toluene and CH_2Cl_2 twice, then dissolved in CH_2Cl_2 (2.0 mL) and DMF (0.8 mL). To this solution was added a solution of Boc-moSer(*O*-TBS)-OH **24** (93.7 mg, 0.293 mmol) in CH_2Cl_2 (2.0 mL), *N*,*N*-diisopropylethylamine (0.153 mL, 0.878 mmol), HOBt (59.5 mg, 0.439 mmol), and EDCI·HCl (84.3 mg, 0.439 mmol) at room temperature. After being stirred at the same temperature for 12 h, the reaction mixture was added with HCl (1 M) at 0 °C. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexane) to give **26** (132 mg, 0.239 mmol, 82%) as a colorless oil. R_f = 0.45 (hexane/ethyl acetate = 1:1); $[\alpha]_D^{24}$ = +50.7 (c = 1.40, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3340, 2955, 2932, 1742, 1714, 1634, 1514, 1251, 1176, 838, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.99 (d, J = 8.2 Hz, 2H), 6.81 (d, J = 8.2 Hz, 2H), 6.19 (m, 1H), 6.16 (d, J = 7.8 Hz, 1H), 4.88 (m, 1H), 4.84 (m, 1H), 4.43 (m, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.67 (dd, J = 10.1, 4.3 Hz, 1H), 3.58 (dd, J = 10.1, 4.3 Hz, 1H), 3.13 (dd, J = 14.0, 5.8 Hz, 1H), 3.07 (dd, J = 14.0, 5.3 Hz, 1H), 1.91 (d, J = 1.4 Hz, 3H), 1.44 (s, 9H), 0.88 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 168.2, 158.8, 155.3, 134.0, 132.8, 130.3, 127.8, 114.1, 79.7, 65.0, 55.2, 53.5, 52.4, 50.3, 37.0, 28.5, 25.9, 18.3, 13.3, −5.4 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{28}H_{46}N_2O_7Si+H]^+$: 551.3153; found: 551.3134.

27: Boc-moSer(*O*-TBS)-Tyr(*O*-Me)-OH. To a solution of methyl ester **26** (188 mg, 0.341 mmol) in 2-methyl-2-propanol (3.0 mL), H_2O (1.0 mL), and THF (2.0 mL) was added $LiOH·H_2O$ (51.0 mg, 1.02 mmol) at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (5% methanol in $CHCl_3$) to give carboxylic acid **27** (145 mg, 0.270 mmol, 79%) as a colorless oil. R_f = 0.40 ($CHCl_3$/methanol = 4:1); $[\alpha]_D^{24}$ = +43.3 (c = 1.53, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3324, 2930, 1715, 1669, 1614, 1463, 1366, 1247, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.07 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.18–6.28 (m, 2H), 4.94 (m, 1H), 4.83 (m, 1H), 4.40 (m, 1H), 3.76 (s, 3H), 3.55–3.64 (m, 2H), 3.19 (dd, J = 14.0, 5.8 Hz, 1H), 3.08 (dd, J = 14.0, 5.8 Hz, 1H), 1.87 (brs, 3H), 1.44 (s, 9H), 0.87 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7, 168.8, 158.8, 134.5, 132.7, 130.5, 127.9, 114.1, 80.6, 64.9, 55.2, 53.7, 50.6, 36.5, 28.5, 25.9, 18.3, 13.3, −5.4 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{27}H_{44}N_2O_7Si+H]^+$: 537.2996; found: 537.2997.

30: Boc-MeAla-MeIle-OAllyl. To Boc-MeIle-OAllyl (**28**) (2.30 g, 8.07 mmol) was added HCl (4 M) in ethyl acetate (10 mL) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was azeotropically dried with toluene and CH_2Cl_2 twice, then dissolved in CH_2Cl_2 (34 mL). To this solution was added Boc-MeAla-OH (**29**) (1.37 g, 6.72 mmol), *N*,*N*-diisopropylethylamine (2.93 mL, 16.8 mmol), and HATU (3.58 g, 9.41 mmol) at room temperature. After being stirred at the same temperature for 1.5 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (25% ethyl acetate in hexane) to give Boc-MeAla-MeIle-OAllyl (**30**) (2.47 g, 6.68 mmol, quant.) as a colorless oil. R_f = 0.50 (hexane/ethyl acetate = 2:1); $[\alpha]_D^{29}$ = −145 (c = 1.09, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3525, 2937, 1739, 1694, 1661, 1456, 1392, 1183, 1077, 989, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major rotamer): δ = 5.82–5.96 (m, 1H), 5.21–5.33 (m, 2H); 5.12 (q, J = 6.8 Hz, 1H), 4.97 (d, J = 10.6 Hz, 1H), 4.52–4.69 (m, 2H), 3.02 (s, 3H), 2.76 (s, 3H), 1.92–2.18 (m, 1H), 1.46 (s, 9H), 1.33–1.40 (m, 1H), 1.28 (d, J = 6.8 Hz, 3H), 1.01–1.10 (m, 1H), 0.85–0.99 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 172.6, 172.1, 171.9, 171.2, 171.1, 170.9, 170.2, 170.1, 155.5, 155.1, 154.8, 153.9, 131.8, 119.6, 119.4, 118.7, 118.6, 80.4, 80.1, 66.1, 65.9, 65.3, 63.9, 63.7, 60.6, 52.4, 52.2, 50.7, 50.6, 34.5, 34.3, 33.6, 33.3, 31.1, 30.8, 29.7, 29.5, 29.2, 29.0, 28.7, 28.5, 28.4, 25.5, 25.3, 25.0, 24.8, 16.0, 15.8, 14.8, 14.7, 14.6 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{19}H_{34}N_2O_5+Na]^+$: 393.2360; found: 393.2360.

Coupling of 30 and 27. To Boc-MeAla-MeIle-OAllyl (**30**) (102 mg, 0.282 mmol) was added HCl (4 M) in ethyl acetate (10 mL) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was azeotropically dried with toluene and CH_2Cl_2 twice, then dissolved in CH_2Cl_2 (1.0 mL). To this solution was added a solution of **27** (94.6 mg, 0.176 mmol) and *N*,*N*-diisopropylethylamine (0.153 mL, 0.880 mmol) in CH_2Cl_2 (3.0 mL), and HATU (200 mg, 0.528 mmol) at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (20% to 60% ethyl acetate in hexane) to give azalactone **32** (45.0 mg, 86.7 μmol, 49%) as a colorless oil and tetrapeptide **31** (23.0 mg, 37.6 μmol, 21%) as a white amorphous solid.

Azalactone 32: IR (neat): $\tilde{\nu}$ = 2958, 1717, 1614, 1515, 1248, 1074, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.26 (brd, J = 6.8 Hz, 1H), 4.93 (m, 1H), 4.45 (m, 1H), 4.12 (s, 2H), 3.79 (s, 3H), 3.69 (dd, J = 10.2, 4.4 Hz, 1H), 3.60 (dd, J = 10.2, 4.4 Hz, 1H), 1.96 (d, J = 1.0 Hz, 3H), 1.44 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 173.6, 166.7, 158.9, 155.3, 137.2, 132.9, 130.8, 130.7, 125.7, 114.2, 80.0, 64.7, 55.3, 50.6, 42.9, 28.5, 25.9, 18.4, 13.2, −5.3 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{16}H_{24}O_3+Na]^+$: 287.1618; found: 287.1617.

Tetrapeptide 31: R_f = 0.52 (hexane/ethyl acetate = 1:2); $[\alpha]_D^{22}$ = −69.7 (c = 1.06, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3335, 2932, 1737, 1712, 1635, 1513, 1406, 1249, 1177, 1107, 837, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major rotamer): δ = 7.09 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.38 (d, J = 8.7 Hz, 1H), 6.18 (brd, J = 7.7 Hz, 1H), 5.78–5.93 (m, 1H), 5.40 (q, J = 6.8 Hz, 1H), 5.30 (dd, J = 16.9, 1.4 Hz, 1H), 5.23 (dd, J = 9.2, 1.4 Hz, 1H), 5.21 (m, 1H), 4.94 (d, J = 10.6 Hz, 1H), 4.84 (m, 1H), 4.55–4.63 (m, 2H), 4.42 (m, 1H), 3.76 (s, 3H), 3.66 (dd, J = 10.1, 4.3 Hz, 1H), 3.57 (dd, J = 10.1, 4.3 Hz, 1H), 3.07 (dd, J = 14.0, 7.2 Hz, 1H), 2.97 (s, 3H), 2.85 (dd, J = 14.0, 3.4 Hz, 1H), 2.74 (s, 3H), 1.96 (m, 1H), 1.90 (d, J = 1.0 Hz, 3H), 1.43 (s, 9H), 1.24 (d, J = 6.7 Hz, 3H), 1.23 (m, 1H), 0.98 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.86 (t, J = 7.2 Hz, 3H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 171.8, 171.4, 170.7, 169.6, 168.1, 158.7, 155.3, 133.9, 132.8, 131.7, 130.5, 128.0, 118.7, 113.9,

79.6, 65.4, 65.0, 60.5, 55.2, 50.5, 49.7, 37.8, 33.3, 31.0, 30.6, 28.4, 25.9, 25.1, 18.3, 15.8, 14.9, 13.3, 10.6, −5.4 ppm; HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{41}H_{68}N_4O_9Si+H]^+$: 789.4834; found: 789.4837.

34: FmocTyr(O-Me)-MeAla-MeIle-OAllyl. To a dipeptide **30** (2.43 g, 5.83 mmol) was added HCl (4 M) in ethyl acetate (10 mL) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was azeotropically dried with toluene and CH_2Cl_2 twice, then dissolved in CH_2Cl_2 (25 mL). To this solution was added Fmoc-(*O*-Me)Tyr-OH (**33**) (2.21 g, 5.30 mmol), *N*,*N*-diisopropylethylamine (2.77 mL, 15.9 mmol), and HATU (3.02 g, 7.95 mmol) at room temperature. After being stirred at the same temperature for 12 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (40% ethyl acetate in hexane) to give the *N*-Fmoc-protected tripeptide **34** (2.80 g, 4.18 mmol, 79%) as a white amorphous solid. R_f = 0.40 (hexane/ethyl acetate = 1:1); $[\alpha]_D^{29}$ = −87.1 (*c* = 1.08, $CHCl_3$); IR (solid): $\tilde{\nu}$ = 3296, 2965, 1718, 1636, 1512, 1243, 990, 741, 540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 7.75 (m, 2H), 7.55 (m, 2H), 7.39 (m, 2H), 7.27–7.32 (m, 2H), 7.11 (d, *J* = 7.4 Hz, 2H), 6.80 (d, *J* = 7.4 Hz, 2H), 6.70–6.74 (m, 1H), 5.72–5.92 (m, 1H), 5.58 (d, *J* = 9.3 Hz, 1H), 5.42 (q, *J* = 7.4 Hz, 1H), 5.20–5.33 (m, 2H), 4.85–4.96 (m, 1H), 4.53–4.66 (m, 2H), 4.11–4.50 (m, 3H), 3.74 (s, 3H), 2.99–3.05 (m, 1H), 2.98 (s, 3H), 2.81–2.87 (m, 1H), 2.76 (s, 3H), 1.96 (m, 1H), 1.28 (d, *J* = 7.4 Hz, 3H), 1.23–1.27 (m, 1H), 1.00 (m, 1H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.84–0.90 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 171.9, 171.7, 170.7, 158.7, 155.8, 143.8, 141.3, 131.8, 130.5, 130.4, 128.0, 127.8, 127.1, 125.2, 125.1, 120.0, 118.7, 114.0, 67.1, 65.4, 60.5, 55.2, 52.3, 49.8, 47.2, 38.1, 33.3, 31.0, 30.6, 25.1, 15.8, 14.4, 10.6 ppm; HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{39}H_{47}N_3O_7+Na]^+$: 692.3306; found: 692.3314; elemental analysis: calcd (%) for $C_{39}H_{47}N_3O_7$: C 69.93, H 7.07, N 6.27; found: C 69.57, H 7.39, N 6.19.

Coupling of 24 and 34. To a solution of the *N*-Fmoc-protected tripeptide **34** (134 mg, 0.200 mmol) in CH_3CN (2.0 mL) was added diethylamine (1.0 mL) at room temperature. After being stirred at the same temperature for 20 min, the reaction mixture was concentrated in vacuo. The residue was azeotropically dried with toluene and CH_2Cl_2 twice, then dissolved in CH_2Cl_2 (0.5 mL). To this solution was added a solution of acid **24** (60.0 mg, 0.167 mmol) in CH_2Cl_2 (1.5 mL), *N*,*N*-diisopropylethylamine (87.0 μL, 0.502 mmol), and HATU (95.0 mg, 0.251 mmol) at room temperature. After being stirred at the same temperature for 7 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (60% ethyl acetate in hexane) to give **31** (121 mg, 0.153 mmol, 92%) as a white amorphous solid.

Coupling product 37. To a solution of the *N*-Boc protected tetrapeptide **31** (76.4 mg, 96.8 μmol) and 2,6-lutidine (68.0 μL, 0.580 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise *tert*-butyldimethylsilyl trifluoromethanesulfonate (51.0 μL, 0.290 mmol) at room temperature under argon. After being stirred at the same temperature for 2 h, the reaction mixture was quenched with methanol and saturated aqueous $NaHCO_3$ at 0 °C. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was used for the next reaction without further purification. To a solution of the silylcarbamate in tetrahydrofuran (3.0 mL) was added TBAF (0.323 mL, 1.0 M solution in tetrahydrofuran, 0.323 mmol) at 0 °C under argon. After being stirred at the same temperature for 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was azeotropically dried with toluene and CH_2Cl_2 twice, then dissolved in CH_2Cl_2 (0.5 mL). To this solution was added a solution of acid **35** (36.0 mg, 64.5 μmol) in CH_2Cl_2 (1.5 mL), *N*,*N*-diisopropylethylamine (34.0 μL, 0.194 mmol), and HATU (31.0 mg, 96.8 μmol) at room temperature. After being stirred at the same temperature for 10 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (2.5% methanol in $CHCl_3$) to give amide **36** as a colorless oil. To a solution of amide **36** in tetrahydrofuran (1.5 mL) was added TBAF (96.8 μL, 1.0 M solution in tetrahydrofuran, 96.8 μmol) at 0 °C under argon. After being stirred at room temperature for 1.5 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (3% methanol in $CHCl_3$) to give **37** (60.2 mg, 60.2 μmol, 93% in 2 steps) as a white amorphous solid. R_f = 0.45 ($CHCl_3$/methanol = 9:1); $[\alpha]_D^{17}$ = −62.9 (*c* = 1.34, $CHCl_3$); IR (solid): $\tilde{\nu}$ = 3321, 2967, 2937, 1738, 1695, 1644, 1514, 1404, 1249, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major rotamer): δ = 7.08 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 7.8 Hz, 1H) 6.43 (d, *J* = 8.3 Hz, 1H), 6.23 (dq, *J* = 8.8, 1.0 Hz, 1H), 5.88 (m, 1H), 5.40 (q, *J* = 6.8 Hz, 1H), 5.31 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.23 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.20 (m, 1H), 4.94 (d, *J* = 10.2 Hz, 1H), 4.86 (dd, *J* = 11.7, 2.0 Hz, 1H), 4.83 (m, 1H), 4.59 (m, 2H), 4.30 (dd, *J* = 8.8, 3.4 Hz, 1H), 3.76 (s, 3H), 3.71 (dd, *J* = 11.2, 3.4 Hz, 1H), 3.61 (m, 1H), 3.48–3.55 (m, 2H), 3.38 (m, 1H), 3.05 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.96 (s, 3H), 2.85 (dd, *J* = 13.7, 5.4 Hz, 1H), 2.74 (s, 3H), 2.21 (dq, *J* = 6.8, 6.4 Hz, 1H), 2.19 (m, 1H), 1.92–2.05 (m, 3H), 1.19 (d, *J* = 1.0 Hz, 3H), 1.85–1.89 (m, 2H), 1.64 (m, 1H), 1.54 (m, 1H), 1.43 (s, 9H), 1.35 (m, 1H), 1.27 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.12 (m, 1H), 0.94 (br d, *J* = 6.8 Hz, 3H × 2), 0.92 (m, 1H), 0.88 (s, 9H), 0.88 ppm (t, *J* = 8.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 172.8, 171.9, 171.5, 170.7, 158.8, 154.9, 132.5, 131.8, 130.5, 130.4, 128.0, 118.8, 114.0, 80.3, 78.6, 71.8, 65.5, 64.7, 60.6, 59.1, 55.3, 50.6, 49.7, 46.8, 40.2, 37.8, 37.7, 37.3, 34.8, 33.4, 31.0, 30.6, 30.1, 29.8, 28.6, 28.4, 26.1, 26.0, 26.0, 25.9, 25.3, 24.2, 20.3, 15.9, 14.5, 13.4, 10.7 ppm; HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{53}H_{85}N_5O_{13}+H]^+$: 1000.6222; found: 1000.6221.

Oxazoline 38. To a solution of **37** (25.1 mg, 25.1 μmol) in CH_2Cl_2 (1.5 mL) was added DAST (3.3 μL, 25 μmol) at −78 °C. The solution was stirred at the same temperature for 1 h, and DAST (3.3 μL, 25 μmol) was added. After being stirred for another 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ at −78 °C, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1.5% methanol in $CHCl_3$) to give oxazoline **38** (17.2 mg, 17.5 μmol, 70%) as a colorless oil. R_f = 0.48 ($CHCl_3$/methanol = 9:1); $[\alpha]_D^{17}$ = −121 (*c* = 0.860, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3331, 2968, 1739, 1696, 1650, 1514, 1403, 1249, 1180, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major rotamer): δ = 7.09 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.49 (m, 1H), 6.16 (m, 1H), 5.84–5.94 (m, 1H), 5.41 (q, *J* = 6.8 Hz, 1H), 5.30 (dd, *J* = 17.6, 1.5 Hz, 1H), 5.17–5.25 (m, 2H), 4.95 (m, 1H), 4.94 (d, *J* = 10.2 Hz, 1H), 4.87 (dd, *J* = 11.7, 2.0 Hz, 1H), 4.60 (m, 2H), 4.31 (dd, *J* = 8.3, 3.9 Hz, 1H), 3.77 (s, 3H), 3.76 (m, 1H), 3.35–3.52 (m, 3H), 3.00–3.10 (m, 2H), 2.97 (s, 3H), 2.86 (m, 1H), 2.76 (s, 3H), 1.90–2.21 (m, 6H), 1.89 (br s, 3H), 1.87 (m, 1H), 1.57–1.69 (m, 3H), 1.45 (s, 9H), 1.21–1.40 (m, 8H), 0.81–1.01 ppm (m, 19H); HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{53}H_{83}N_5O_{12}+H]^+$: 982.6116; found: 982.6115.

Amine 39. To a solution of the *N*-Boc-protected precursor **38** (8.0 mg, 8.1 μmol) and 2,6-lutidine (14.0 μL, 122 μmol) in CH_2Cl_2 (0.6 mL) was added dropwise trimethylsilyl trifluoromethanesulfonate (7.3 μL, 41 μmol) at room temperature under argon. After being stirred at the same temperature for 2 h, the reaction mixture was quenched with methanol and saturated aqueous $NaHCO_3$ at 0 °C. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was used for the next reaction without further purification. To a solution of the resulting silyl ether in tetrahydrofuran (1.0 mL) was added TBAF (24 μL, 1.0 M solution in tetrahydrofuran, 24 μmol) at 0 °C under argon. After being stirred at the same temperature for 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (5.0% methanol in $CHCl_3$) to give amine **39** (6.6 mg, 7.5 μmol, 93% in 2 steps) as a white amorphous solid. R_f = 0.50 ($CHCl_3$/methanol = 9:1); $[\alpha]_D^{25}$ = −32.4 (*c* = 0.150, MeOH); IR (neat): $\tilde{\nu}$ = 3315, 2966, 2935, 2876, 1736, 1644, 1513, 1247, 1182 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): δ = 7.10 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 8.3 Hz, 1H), 6.15 (dq, *J* = 8.8, 1.4 Hz, 1H), 5.91 (m, 1H), 5.37 (q, *J* = 6.8 Hz, 1H), 5.21–5.29 (m, 2H),

5.16 (m, 1H), 4.95 (ddd, J=9.8, 8.8, 8.8 Hz, 1H), 4.88 (dd, J=11.2, 2.4 Hz, 1H), 4.87 (d, J=10.2 Hz, 1H), 4.58 (m, 2H), 4.43 (dd, J=9.8, 8.3 Hz, 1H), 3.90 (dd, J=8.8, 8.3 Hz, 1H), 3.85 (dd, J=8.3, 5.9 Hz, 1H), 3.76 (s, 3H), 3.66 (ddd, J=10.8, 5.8, 2.0 Hz, 1H), 3.01–3.08 (m, 2H), 2.96 (s, 3H), 2.94 (m, 1H), 2.84 (dd, J=13.6, 6.3 Hz, 1H), 2.71 (s, 3H), 2.42 (dq, J=6.8, 5.8 Hz, 1H), 2.14 (m, 1H), 1.97 (m, 1H), 1.90 (m, 1H), 1.87 (d, J=1.4 Hz, 3H), 1.75–1.82 (m, 3H), 1.53–1.63 (m, 2H), 1.37 (ddd, J=14.6, 10.8, 2.4 Hz, 1H), 1.23–1.29 (m, 2H), 1.22 (d, J=6.8 Hz, 3H), 1.19 (d, J=6.8 Hz, 3H), 1.02 (ddd, J=14.2, 10.8, 2.4 Hz, 1H), 0.93 (d, J=6.8 Hz, 3H), 0.92 (d, J=6.8 Hz, 3H), 0.89 (s, 9H), 0.85 ppm (t, J=7.3 Hz, 3H); HRMS (ESI-TOF): m/z (%) calcd for $[C_{45}H_{69}N_5O_9+H]^+$: 882.5592; found: 882.5571.

Apratoxin A oxazoline analogue 2. To a solution of amine **39** (6.6 mg, 7.5 μmol) and morpholine (7.1 μL, 81 μmol) in tetrahydrofuran (0.7 mL) was added tetrakis(triphenylphosphine)palladium (1.0 mg, 1.0 μmol) at room temperature under argon. After being stirred at the same temperature for 3 h, the reaction mixture was concentrated in vacuo. The residue was azeotropically dried with toluene and CH_2Cl_2 twice, then dissolved in CH_2Cl_2 (7.5 mL). To this solution was added *N,N*-diisopropylethylamine (8.3 μL, 48 μmol) and HATU (5.1 mg, 16 μmol) at room temperature under argon. After being stirred at the same temperature for 48 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (1% to 3% methanol in CH_2Cl_2) to give apratoxin A oxazoline analogue **2** (3.5 mg, 4.2 μmol, 56% in 2 steps) as a white amorphous solid. R_f=0.5 ($CHCl_3$/methanol=9:1); $[\alpha]_D^{22}=-167$ (c=0.100, MeOH), lit.[12] $[\alpha]_D^{25}=-117.5$ (c=0.2, $CHCl_3$); IR (neat): $\tilde{\nu}$= 3426, 2966, 2935, 1742, 1624, 1513, 1461, 1178, 754 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): δ=7.15 (d, J=8.8 Hz, 2H), 6.81 (d, J=8.8 Hz, 2H), 6.07 (dq, J=9.3, 1.0 Hz, 1H), 5.97 (d, J=9.3 Hz, 1H), 5.17 (d, J= 11.7 Hz), 5.03 (ddd, J=10.8, 9.3, 4.9 Hz, 1H), 4.95 (dd, J=12.7, 2.4 Hz, 1H), 4.75 (ddd, J=9.3, 9.3, 5.8 Hz, 1H), 4.52 (d, J=11.2 Hz, 1H), 4.31 (dd, J=9.3, 8.3 Hz, 1H), 4.13–4.18 (m, 2H), 4.07 (dd, J=8.3, 5.8 Hz, 1H), 3.76 (s, 3H), 3.63 (m, 1H), 3.55 (m, 1H), 3.29 (m, 1H), 3.06 (dd, J= 12.7, 4.9 Hz, 1H), 2.87 (dd, J=8.3, 5.8 Hz, 1H), 2.81 (s, 3H), 2.67 (s, 3H), 2.35 (dq, J=10.2, 6.8 Hz, 1H), 2.22–2.33 (m, 2H), 2.04–2.12 (m, 2H), 1.85–1.93 (m, 2H), 1.88 (d, J=1.0 Hz, 3H), 1.77 (m, 1H), 1.50 (m, 1H), 1.24–1.36 (m, 2H), 1.14 (d, J=6.8 Hz, 3H), 1.11 (m, 1H), 1.03 (d, J=6.8 Hz, 3H), 0.96 (m, 1H), 0.94 (d, J=6.8 Hz, 3H), 0.90 (d, J=6.8 Hz, 3H), 0.89 (t, J=6.8 Hz, 3H), 0.87 ppm (s, 9H); HRMS (ESI-TOF): m/z (%) calcd for $[C_{45}H_{69}N_5O_9+H]^+$: 824.5174; found: 824.5199.

41: (*E*)-(*S*)-4-*N*-*tert*-Butoxycarbonylamino-5-(*tert*-butyldimethylsilyloxy)-2-methylpent-2-enoic acid allyl ester. To a solution of carboxylic acid **24** (543 mg, 1.51 mmol) in DMF (7.5 mL) was added potassium carbonate (270 mg, 1.97 mmol) and allyl bromide (0.160 mL, 1.81 mmol) at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was diluted with diethyl ether, filtered through a pad of Celite, and the filtrate was acidified with saturated aqueous NH_4Cl at 0°C. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with aqueous $Na_2S_2O_3$ (10%), saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (7% ethyl acetate in hexane) to give **41** (571 mg, 1.43 mmol, 95%) as a colorless oil. R_f=0.58 (hexane/ethyl acetate=2:1); $[\alpha]_D^{20}=+10.0$ (c=1.14, $CHCl_3$); IR (neat): $\tilde{\nu}$=3375, 2956, 2931, 1717, 1515, 1254, 1171, 1113, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.68 (dq, J=9.2, 1.4 Hz, 1H), 5.89–5.99 (m, 1H), 5.32 (m, 1H), 5.23 (m, 1H), 4.93 (m, 1H), 4.59–4.69 (m, 2H), 4.48 (m, 1H), 3.71 (dd, J=9.7, 3.9 Hz, 1H), 3.61 (dd, J= 9.7, 3.9 Hz, 1H), 1.95 (d, J=1.4 Hz, 3H), 1.44 (s, 9H), 0.89 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.5, 155.3, 139.7, 132.4, 129.6, 118.0, 79.7, 65.4, 65.0, 50.6, 28.4, 25.9, 18.4, 13.0, −5.4, −5.5 ppm; HRMS (ESI-TOF): m/z (%) calcd for $[C_{20}H_{37}NO_5Si+H]^+$: 400.2519; found: 400.2520.

42: Boc-Pro-Dtena-moSer-OAllyl. To a solution of **41** (75.0 mg, 188 μmol) and 2,6-lutidine (171 μL, 1.69 mmol) in CH_2Cl_2 (2.0 mL) was added slowly trimethylsilyl trifluoromethanesulfonate (102 μL, 0.563 mmol) at room temperature under argon. After being stirred at the same temperature for 2 h, the reaction mixture was quenched with methanol and saturated aqueous $NaHCO_3$ at 0°C. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was azeotropically dried with toluene and CH_2Cl_2 twice, then dissolved in CH_2Cl_2 (0.5 mL). To this solution was added a solution of acid **35** (68.0 mg, 122 μmol) in CH_2Cl_2 (2.0 mL), *N,N*-diisopropylethylamine (98.0 μL, 0.564 mmol), and HATU (107 mg, 282 μmol) at room temperature. After being stirred at the same temperature for 10 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexane) to give **42** (92.3 mg, 110 μmol, 90%) as a colorless oil. R_f=0.44 (hexane/ethyl acetate=2:1); $[\alpha]_D^{19}=-26.8$ (c=0.960, $CHCl_3$); IR (neat): $\tilde{\nu}$=3357, 2957, 2931, 1718, 1702, 1674, 1399, 1257, 1119, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ=6.84 (d, J=7.8 Hz, 0.5H), 6.77 (d, J=7.8 Hz, 0.5H), 6.71 (dq, J=8.8, 1.4 Hz, 1H), 5.88–5.98 (m, 1H), 5.21–5.34 (m, 2H), 4.78 (m, 1H), 4.71–4.73 (m, 1H), 4.58–4.68 (m, 2H), 4.35 (dd, J=5.4, 2.9 Hz, 0.5H), 4.32 (dd, J=5.4, 2.9 Hz, 0.5H), 3.77–3.82 (m, 1H), 3.61–3.70 (m, 2H), 3.35–3.53 (m, 2H), 2.42 (m, 1H), 2.17 (m, 1H), 1.96–2.04 (m, 1H), 1.95 (d, J=1.4 Hz, 3H), 1.86–1.92 (m, 2H), 1.48–1.60 (m, 1H), 1.44 (s, 4.5H), 1.42 (s, 4.5H), 1.20–1.38 (m, 4H), 1.19 (d, J=7.3 Hz, 3H), 0.86–0.92 (m, 30H), 0.03–0.13 ppm (m, 12H); HRMS (ESI-TOF): m/z (%) calcd for $[C_{44}H_{82}N_2O_9Si_2+H]^+$: 839.5637; found: 839.5652.

Thioamide 43. To a solution of **42** (9.8 mg, 11.7 μmol) in toluene (1.0 mL) was added Lawesson's reagent (7.1 mg, 17.5 μmol) at room temperature. After being stirred at 80°C for 1 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ at 0°C, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexane) to give thioamide **43** (9.1 mg, 10.6 μmol, 91%) as a colorless oil. R_f=0.56 (hexane/ethyl acetate=2:1); IR (neat): $\tilde{\nu}$=3291, 2956, 2931, 1720, 1702, 1399, 1257, 1160, 1116, 837, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ=9.02 (d, J=7.8 Hz, 0.5H), 8.93 (d, J=7.8 Hz, 0.5H), 6.83 (m, 1H), 5.88–5.98 (m, 1H), 5.42 (m, 1H), 5.21–5.34 (m, 2H), 4.56–4.72 (m, 3H), 4.34 (m, 1H) 3.67–3.91 (m, 3H), 3.35–3.53 (m, 2H), 3.11 (m, 1H), 2.00–2.25 (m, 2H), 1.96 (d, J=1.4 Hz, 3H), 1.86–1.92 (m, 2H), 1.59 (m, 1H), 1.44 (s, 4.5H), 1.43 (s, 4.5H), 1.16–1.42 (m, 7H), 0.85–0.98 (m, 30H), 0.03–0.14 ppm (m, 12H); HRMS (ESI-TOF): m/z (%) calcd for $[C_{44}H_{82}N_2O_8SSi_2+H]^+$: 855.5409; found: 855.5410.

Coupling of 20a and 45. To a solution of **45** (147 μmol) in CH_2Cl_2 (0.5 mL) was added a solution of **20a** (83.8 mg, 113 μmol) in CH_2Cl_2 (1.0 mL), *N,N*-diisopropylethylamine (79.0 μL, 452 μmol), HOAt (18.0 mg, 136 μmol), and EDCI·HCl (26.0 mg, 136 μmol) at 0°C under argon. After being stirred at the same temperature for 12 h, the reaction mixture was diluted with ethyl acetate and poured into ice-cooled HCl (1 M). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (25% ethyl acetate in hexane) to give **46a** (107 mg, 91.7 μmol, 81%) as white amorphous solid. R_f=0.56 (hexane/ethyl acetate=1:1); $[\alpha]_D^{26}=-34.6$ (c=1.35, $CHCl_3$); IR (solid): $\tilde{\nu}$=3329, 2962, 1755, 1709, 1523, 1449, 1420, 1248, 1119, 946, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ=7.74–7.78 (m, 2H), 7.57–7.62 (m, 2H), 7.18–7.42 (m, 19H), 6.35–6.41 (m, 1.6H), 5.80–5.99 (m, 1H), 5.44 (d, J=7.8 Hz, 0.4H), 5.32 (dd, J=17.6, 1.4 Hz, 0.4H), 5.25 (dd, J=17.6, 1.5 Hz, 0.6H), 5.23 (dd, J= 10.2, 1.4 Hz, 0.4H), 5.17 (dd, J=10.7, 1.5 Hz, 0.6H), 4.97 (m, 1H), 4.84 (dd, J=8.2, 3.9 Hz, 0.6H), 4.81 (d, J=12.2 Hz, 0.6H), 4.80 (dd, J=10.2, 5.8 Hz, 0.4H), 4.71 (d, J=12.2 Hz, 0.4H), 4.48–4.67 (m, 5H), 4.36–4.42 (m, 1H), 4.19–4.30 (m, 2H), 3.46–3.66 (m, 2H), 2.09–2.54 (m, 5H), 1.89–2.02 (m, 3H), 1.73 (br s, 3H), 1.58–1.62 (m, 1H), 1.22–1.49 (m, 3H), 1.09 (d, J=6.8 Hz, 1.8H), 1.06 (d, J=7.3 Hz, 1.2H), 0.92 (d, J=6.8 Hz, 1.8H), 0.87 (s, 3.6H), 0.85 (s, 5.4H), 0.73 ppm (d, J=6.4 Hz, 1.2H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ=172.6, 172.2, 171.9, 167.2, 154.9, 154.5, 153.9, 153.8, 144.6, 144.5, 144.1, 143.9, 143.8, 141.4, 141.2, 139.6, 139.4, 132.3, 130.4, 130.2, 129.7, 128.1, 128.0, 127.8, 127.2, 127.0, 126.9, 125.6, 125.3, 125.2, 120.0, 118.3, 118.1, 94.9, 79.3, 79.1, 78.8, 78.5, 67.9, 67.5, 67.2, 67.1, 65.6, 65.5, 59.8, 59.5, 47.3, 47.2, 47.1, 46.4, 45.3, 44.7, 38.1, 37.5, 36.8, 36.4, 35.8, 35.1, 34.8, 31.3, 30.1, 26.1, 25.9, 25.8, 24.3, 23.5,

20.4, 19.9, 13.5, 13.0, 12.9 ppm; HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{64}H_{71}Cl_3N_2O_{10}S+Na]^+$: 1187.3787; found: 1187.3796; elemental analysis: calcd (%) for $C_{64}H_{71}Cl_3N_2O_{10}S$: C 65.81, H 6.48. N 2.25; found: C 65.8, H 6.13. N 2.40.

Amide 46b. Following a similar procedure from **20a** to **46a**, **46b** was obtained from **20b** in 84% yield. R_f=0.55 (hexane/ethyl acetate=1:1); $[\alpha]_D^{19}=-45.8$ (c=1.21, $CHCl_3$); IR (solid): $\tilde{\nu}$=3338, 2961, 1758, 1712, 1675, 1420, 1249, 757, 742, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ=7.73–7.77 (m, 2H), 7.56–7.59 (m, 2H), 7.15–7.41 (m, 19H), 6.48 (dq, J=9.3, 1.5 Hz, 0.5H), 6.40 (dq, J=8.8, 1.5 Hz, 0.5H), 6.20 (d, J=7.8 Hz, 0.5H), 5.85–5.95 (m, 1H), 5.59 (d, J=7.8 Hz, 0.5H), 5.18–5.31 (m, 2H), 5.00 (ddd, J=8.3, 8.3, 3.4 Hz, 0.5H), 4.93 (m, 0.5H), 4.68–4.82 (m, 3H), 4.53–4.63 (m, 3H), 4.49 (dd, J=8.8, 2.9 Hz, 0.5H), 4.38–4.43 (m, 1.5H), 4.15–4.31 (m, 2H), 3.48–3.64 (m, 2H), 2.07–2.58 (m, 5H), 1.93–2.01 (m, 2H), 1.67–1.80 (m, 4H), 1.22–1.60 (m, 3H), 1.14 (d, J=6.8 Hz, 1.5H), 1.11 (d, J=7.3 Hz, 1.5H), 1.00–1.07 (m, 1H), 0.90 (d, J=6.3 Hz, 1.5H), 0.85 (s, 4.5H), 0.83 (s, 4.5H), 0.66 ppm (d, J=6.8 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ=172.8, 172.5, 172.4, 172.1, 167.2, 167.1, 154.9, 154.4, 154.0, 153.9, 144.6, 144.4, 144.3, 144.1, 144.0, 143.8, 141.4, 141.3, 139.4, 139.1, 132.4, 132.3, 130.5, 130.3, 129.6, 129.6, 128.1, 128.0, 127.7, 127.2, 127.1, 127.0, 126.9, 125.5, 125.3, 125.2, 120.0, 118.2, 118.1, 94.9, 94.8, 79.8, 79.6, 79.4, 78.7, 67.9, 67.6, 67.2, 67.2, 65.5, 65.4, 59.9, 59.4, 47.6, 47.3, 47.3, 47.1, 47.1, 46.5, 45.9, 44.9, 38.5, 38.2, 38.0, 35.9, 35.7, 35.0, 34.7, 31.4, 30.1, 26.2, 25.9, 25.8, 24.5, 23.4, 20.9, 20.6, 14.2, 13.9, 13.0 ppm; HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{64}H_{71}Cl_3N_2O_{10}S+H]^+$: 1165.3973; found: 1165.3995.

Thiazoline 48a. To a solution of triphenylphosphineoxide (72.0 mg, 257 μmol) in CH_2Cl_2 (1.0 mL) was added dropwise Tf_2O (22.0 μL, 129 μmol) at 0°C under argon. The solution was stirred at the same temperature for 10 min. To the resultant mixture was added **46a** (50.9 mg, 42.9 μmol) at 0°C. After being stirred at the same temperature for 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0°C, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was used for the next reaction without further purification. To a solution of the crude thiazoline **47a** in tetrahydrofuran (2.0 mL) and aqueous NH_4OAc (0.50 mL, 1.0 M) was added Zn dust (28.0 mg, 429 μmol) at room temperature. After being stirred at the same temperature for 30 min, the reaction mixture was partitioned between ethyl acetate and brine. The solution was extracted five times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexane) to give **48a** (28.2 mg, 38.6 μmol, 90% in 2 steps) as a white amorphous solid. R_f= 0.37 (hexane/ethyl acetate=2:1); $[\alpha]_D^{26}=-62.4$ (c=0.900, $CHCl_3$); IR (solid): $\tilde{\nu}$=3475, 2960, 2874, 1712, 1610, 1451, 1419, 1362, 1245, 1089, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ=7.75 (d, J=7.3 Hz, 2H), 7.63 (dd, J=6.8, 7.3 Hz, 2H), 7.39 (dd, J=7.3, 7.3 Hz, 2H), 7.28–7.32 (m, 2H), 6.78–6.82 (m, 1H), 5.84–6.00 (m, 1H), 5.16–5.35 (m, 3H), 4.90 (dd, J=11.6, 1.9 Hz, 0.8H), 4.82 (dd, J=10.6, 1.4 Hz, 0.2H), 4.59–4.66 (m, 2H), 4.33–4.53 (m, 3H), 4.19–4.31 (m, 1H), 3.80 (m, 0.8H), 3.69 (m, 0.2H), 3.62 (m, 1H), 3.52 (m, 1H), 3.43 (dd, J=11.1, 8.7 Hz, 0.2H), 3.31 (dd, J=11.2, 8.8 Hz, 0.8H), 2.92–3.02 (m, 1H), 2.65–2.72 (m, 1H), 2.25 (m, 1H), 1.98–2.10 (m, 3H), 1.97 (d, J=1.5 Hz, 0.6H), 1.95 (d, J=1.0 Hz, 2.4H), 1.38–1.74 (m, 4H), 1.25 (d, J=7.3 Hz, 0.6H), 1.21 (d, J=6.8 Hz, 2.4H), 0.99 (m, 1H), 0.95 (d, J=6.8 Hz, 2.4H), 0.88 (s, 9H), 0.79 ppm (d, J=6.4 Hz, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ=172.5, 167.3, 154.9, 154.4, 144.3, 144.1, 143.9, 141.4, 141.3, 140.3, 132.3, 127.7, 127.0, 125.5, 125.4, 125.3, 119.9, 118.3, 118.1, 79.4, 78.4, 74.1, 71.4, 67.9, 67.8, 65.6, 65.5, 59.6, 47.3, 47.2, 47.0, 46.5, 45.9, 45.3, 40.2, 39.1, 37.9, 37.6, 37.5, 34.8, 34.6, 31.6, 31.2, 30.0, 29.8, 26.1, 25.6, 25.0, 24.6, 23.3, 22.7, 20.6, 20.4, 16.2, 15.6, 14.2, 13.1 ppm; HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{42}H_{54}N_2O_7S+Na]^+$: 753.3544; found: 753.3542.

Thiazoline 48b. Following a similar procedure from **46a** to **48a**, **48b** was obtained from **46b** in 95% yield. R_f=0.37 (hexane/ethyl acetate=2:1); $[\alpha]_D^{16}=-79.3$ (c=0.660, $CHCl_3$); IR (solid): $\tilde{\nu}$=3477, 2961, 1740, 1713, 1452, 1423, 1264, 1124, 758, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major rotamer): δ=7.76 (d, J=7.8 Hz, 2H), 7.61–7.67 (m, 2H), 7.39 (m, 2H), 7.30 (m, 2H), 6.78 (m, 1H), 5.92 (m, 1H), 5.32 (dd, J=17.6, 1.5 Hz, 1H), 5.22 (dd, J=10.8, 1.5 Hz, 1H), 5.18 (m, 1H, e), 5.91 (dd, J=11.7, 1.9 Hz, 1H), 4.64 (m, 2H), 4.43 (m, 1H), 4.37 (dd, J=8.3, 3.4 Hz, 1H), 4.18–4.35 (m, 2H), 3.82 (m, 1H), 3.66 (m, 1H), 3.54 (m, 1H), 3.37 (dd, J=10.8, 8.8 Hz, 1H), 2.94 (dd, J=11.2, 8.8 Hz, 1H), 2.17–2.31 (m, 2H), 2.00–2.08 (m, 3H), 1.97 (d, J=1.4 Hz, 3H), 1.72–1.84 (m, 2H), 1.63 (m, 1H), 1.30 (m, 1H), 1.19–1.26 (m, 3H), 0.96 (d, J=6.8 Hz, 3H), 0.92 (m, 1H), 0.88 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ= 172.5, 167.4, 155.1, 144.3, 144.0, 141.4, 141.4, 141.3, 140.6, 132.4, 127.7, 127.1, 125.4, 125.3, 120.0, 118.3, 118.2, 79.8, 78.6, 70.9, 70.6, 67.9, 67.8, 65.5, 59.7, 47.3, 47.0, 46.6, 46.1, 39.9, 39.7, 37.9, 37.8, 37.7, 37.6, 34.8, 34.6, 31.3, 30.0, 26.1, 26.0, 25.2, 23.4, 20.7, 20.6, 14.6, 14.2, 13.2 ppm; HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{42}H_{54}N_2O_7S+H]^+$: 731.3730; found: 731.3744.

HPLC analysis of 48a and 48b. The **48a** and **48b** were analyzed by reversed-phase HPLC (Inertsil C_{18} ODS-3, 3 μm, 4.6×250 mm, 1.0 mL min^{-1}, UV detection at 254 nm) using a CH_3CN–H_2O linear gradient (75% for 4 min, 75–95% over 21 min, 95–100% over 5 min and then 100% CH_3CN 5 min). **48a** and **48b** were eluted at t_R=24.7 min and t_R= 24.1 min, respectively.

Carboxylic acid 49a. To a solution of **48a** (28.2 mg, 38.6 μmol) and *N*-methylaniline (10.3 μL, 96.5 μmol) in tetrahydrofuran (2.5 mL) was added tetrakis(triphenylphosphine)palladium (4.5 mg, 3.9 μmol) at room temperature under argon. After being stirred at the same temperature for 40 min, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (3.0% methanol in $CHCl_3$) to give acid **49a** (25.4 mg, 36.7 μmol, 95%) as a white amorphous solid. R_f=0.40 ($CHCl_3$/methanol=9:1); $[\alpha]_D^{26}=-76.3$ (c=1.11, $CHCl_3$); IR (solid): $\tilde{\nu}$=3464, 2957, 1962, 1607, 1419, 1359, 1178, 1124, 988, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ=7.63 (d, J=7.3 Hz, 2H), 7.63 (m, 2H), 7.38 (m, 2H), 7.30 (m, 2H), 6.84–6.89 (m, 1H), 5.14–5.28 (m, 1H), 4.90 (dd, J=11.7, 1.5 Hz, 0.7H), 4.82 (br d, J= 10.3 Hz, 0.3H), 4.18–4.53 (m, 4H), 3.39–3.81 (m, 3H), 3.36 (dd, J=10.8, 7.8 Hz, 0.3H), 3.30 (dd, J=10.8, 8.8 Hz, 0.7H), 2.97 (m, 1H), 2.72 (m, 1H), 2.23 (m, 1H), 1.94–2.07 (m, 3H), 1.94 (br s, 0.9H), 1.92 (d, J= 1.0 Hz, 2.1H), 1.84 (m, 1H), 1.29–1.78 (m, 4H), 1.24 (d, J=7.3 Hz, 0.9H), 1.21 (d, J=7.3 Hz, 2.1H), 0.96 (d, J=6.4 Hz, 2.1H), 0.89 (s, 2.7H), 0.87 (s, 6.3H), 0.78 ppm (d, J=6.8 Hz, 0.9H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ=173.0, 172.5, 172.0, 155.1, 155.0, 154.4, 144.3, 144.2, 144.1, 144.0, 143.8, 142.3, 141.4, 141.3, 141.2, 127.7, 127.6, 127.1, 125.5, 125.3, 119.9, 79.5, 78.6, 78.4, 71.5, 70.9, 67.9, 67.8, 59.6, 47.3, 47.2, 47.1, 47.0, 46.5, 46.0, 45.3, 40.1, 39.4, 39.0, 37.9, 37.6, 37.4, 34.8, 34.6, 31.2, 30.0, 26.0, 25.5, 25.1, 24.9, 24.6, 23.4, 20.5, 20.3, 16.2, 14.5, 12.9, 12.8 ppm; HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{39}H_{50}N_2O_7S+Na]^+$: 713.3231; found: 713.3234.

Cyclic precursor 50a. To a solution of tripeptide **34** (36.9 mg, 55.1 μmol) in CH_3CN (2.0 mL) was added diethylamine (1.0 mL) at room temperature. After being stirred at the same temperature for 20 min, the reaction mixture was concentrated in vacuo. The residue was azeotropically dried with toluene and CH_2Cl_2 twice, then dissolved in CH_2Cl_2 (0.5 mL). To this solution was added a solution of acid **49a** (25.4 mg, 36.7 μmol) in CH_2Cl_2 (1.5 mL), *N*,*N*-diisopropylethylamine (19.2 μL, 110 μmol), and HATU (17.6 mg, 55.1 μmol) at room temperature. After being stirred at the same temperature for 8.0 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (17% acetone in toluene) to give **50a** (30.7 mg, 27.4 μmol, 75%) as a white amorphous solid. R_f=0.60 ($CHCl_3$/methanol=9:1); $[\alpha]_D^{26}=-89.0$ (c=1.28, $CHCl_3$); IR (solid): $\tilde{\nu}$=3465, 3328, 2960, 2876, 1735, 1707, 1625, 1513, 1478, 1416, 1299, 1179, 1087, 988, 741, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ=7.75 (d, J=7.3 Hz, 2H), 7.63 (d, J=7.3 Hz, 2H), 7.39 (dd, J=7.7, 7.3 Hz, 2H), 7.31 (dd, J=7.7, 7.3 Hz, 2H), 7.09 (d, J=6.8 Hz, 2H), 6.76–6.79 (m, 3H), 6.30 (d, J=8.3 Hz, 1H), 5.87 (m, 1H), 5.37 (br d, J=6.8 Hz, 1H), 5.19–5.32 (m, 2H), 5.18 (m, 1H), 5.11 (m, 1H), 4.80–4.94 (m, 2H), 4.59 (br d, J=5.8 Hz, 2H), 4.15–4.20 (m, 3H), 3.77 (m, 1H), 3.75 (s, 3H), 3.64 (m, 1H), 3.53 (m, 1H), 3.24 (m, 1H), 2.98–3.06 (m, 2H), 2.95 (s, 3H), 2.78–2.93 (m, 2H), 2.73 (s, 3H), 2.66 (m, 1H), 2.23 (m, 1H), 1.91–2.20 (m, 4H), 1.92 (br s, 3H), 1.81 (m, 1H), 1.60–1.74 (m, 2H), 1.20–1.50 (m, 9H), 0.89–1.07 (m, 7H), 0.88

(s, 9H), 0.76–0.84 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 172.6, 171.9, 171.5, 170.7, 168.1, 158.7, 155.0, 144.1, 144.0, 142.9, 141.4, 141.3, 131.8, 127.7, 130.5, 127.7, 127.1, 125.4, 120.0, 118.7, 114.0, 78.4, 71.5, 67.9, 65.4, 60.5, 59.7, 59.6, 55.2, 49.7, 47.2, 46.6, 45.9, 39.1, 37.7, 37.6, 34.8, 39.1, 37.7, 37.6, 34.8, 33.3, 32.0, 31.0, 30.7, 30.6, 30.1, 30.0, 29.8, 29.7, 26.1, 25.1, 25.0, 23.4, 22.8, 20.4, 15.8, 14.5, 13.6, 10.7 ppm; HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{63}H_{85}N_5O_{11}S+Na]^+$: 1142.5859; found: 1142.5858.

50b. Following a similar procedure from **48a** to **50a**, **50b** was obtained from **48b** in 77% yield over 2 steps. R_f = 0.60 ($CHCl_3$/methanol = 9:1); $[\alpha]_D^{22} = -84.8$ (c = 0.780, $CHCl_3$); IR (solid): $\tilde{\nu}$ = 3474, 3329, 2965, 2934, 1738, 1693, 1636, 1452, 1180 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, major rotamer): δ = 7.74–7.77 (m, 2H), 7.60–7.66 (m, 2H), 7.37–7.42 (m, 2H), 7.28–7.32 (m, 2H), 7.08 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.42 (d, J = 8.8 Hz, 1H), 6.27 (dq, J = 8.8, 1.5 Hz, 1H), 5.84–5.93 (m, 1H), 5.41 (q, J = 6.8 Hz, 1H), 5.30 (dd, J = 17.1, 1.5 Hz, 1H), 5.23 (dd, J = 10.3, 1.5 Hz, 1H), 5.20 (m, 1H), 5.11 (m, 1H), 4.94 (d, J = 10.2 Hz, 1H), 4.91 (m, 1H), 4.60 (m, 2H), 4.16–4.47 (m, 4H), 3.78 (m, 1H), 3.76 (s, 3H), 3.48–3.69 (m, 2H), 3.34 (dd, J = 11.2, 8.8 Hz, 1H), 3.30 (m, 1H), 2.97 (s, 3H), 2.90 (dd, J = 11.2, 9.3 Hz, 1H), 2.84 (m, 1H), 2.75 (s, 3H), 2.67 (m, 1H), 1.93–2.30 (m, 6H), 1.92 (d, J = 1.5 Hz, 3H), 1.75 (m, 1H), 1.62 (m, 1H), 1.27–1.34 (m, 2H), 1.26 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H), 1.00 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H), 0.90 (m, 1H), 0.88 (s, 9H), 0.96 ppm (t, J = 7.3 Hz, 3H); HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{63}H_{85}N_5O_{11}S+H]^+$: 1120.6045; found: 1120.6042.

HPLC analysis of 50a and 50b. The **50a** and **50b** were analyzed by reversed-phase HPLC (Inertsil C_{18} ODS-3, 3 μm, 4.6×250 mm, 1.0 mL min^{-1}, UV detection at 254 nm) using a CH_3CN–H_2O linear gradient (75% for 4 min, 75–95% over 21 min, 95–100% over 5 min and then 100% CH_3CN 5 min). **50a** and **50b** were eluted at t_R = 24.8 min and t_R = 24.1 min, respectively.

1: Apratoxin A. To a solution of **50a** (44.9 mg, 40.0 μmol) and *N*-methylaniline (13.0 μL, 120 μmol) in tetrahydrofuran (1.5 mL) was added tetrakis(triphenylphosphine)palladium (2.3 mg, 2.0 μmol) at room temperature under argon. After being stirred at the same temperature for 45 min, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (5.0% methanol in $CHCl_3$) to give the *N*-Fmoc-protected acid as a white amorphous solid. To a solution of the *N*-Fmoc-protected acid in CH_3CN (4.0 mL) was added diethylamine (2.0 mL) at room temperature. After being stirred at the same temperature for 20 min, the reaction mixture was concentrated in vacuo. The residue was azeotropically dried with toluene and CH_2Cl_2 twice, then dissolved in CH_2Cl_2 (40 mL). To this solution was added *N*,*N*-diisopropylethylamine (62.7 μL, 360 μmol) and HATU (38.4 mg, 120 μmol) at 0 °C under argon. After being stirred at 0 °C to room temperature for 20 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (3.0% to 6.0% 2-propanol in CH_2Cl_2) and solid phase extraction (VARIAN Bond ELUT C18, eluting with 85% MeOH in H_2O to 100% MeOH) to give apratoxin A (**1**) (24.0 mg, 28.6 μmol, 72% in 3 steps) as a white amorphous solid. R_f = 0.33 (ethyl acetate); $[\alpha]_D^{23} = -161$ (c = 0.625, methanol), lit.[4] $[\alpha]_D^{25} = -161$ (c = 1.33, methanol); IR (solid): $\tilde{\nu}$ = 3420, 2933, 2958, 2874, 1740, 1622, 1511, 1455, 1371, 1246, 1177, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 6.35 (d, J = 9.8 Hz, 1H), 6.05 (d, J = 9.3 Hz, 1H), 5.25 (ddd, J = 9.8, 8.7, 4.3 Hz, 1H), 5.20 (d, J = 11.6 Hz, 1H), 5.05 (ddd, J = 10.7, 9.3, 4.9 Hz, 1H), 4.97 (dd, J = 12.6, 1.9 Hz, 1H), 4.70 (d, J = 10.6 Hz, 1H), 4.24 (m, 1H), 4.19 (t, J = 7.7 Hz, 1H), 3.78 (s, 3H), 3.66 (m, 1H), 3.54 (m, 1H), 3.46 (dd, J = 11.1, 8.7 Hz, 1H), 3.28 (br q, J = 6.8 Hz, 1H), 3.14 (dd, J = 11.1, 4.3 Hz, 1H), 3.11 (dd, J = 12.2, 10.7 Hz, 1H), 2.86 (dd, J = 12.2, 4.9 Hz, 1H), 2.81 (s, 3H), 2.71 (s, 3H), 2.64 (m, 1H), 2.15–2.30 (m, 3H), 2.05 (m, 1H), 1.97 (s, 3H), 1.85–1.90 (m, 2H), 1.79 (m, 1H), 1.57 (m, 1H), 1.31 (m, 1H), 1.25 (m, 1H), 1.21 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 1.06 (m, 1H), 0.99 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.91 (m, 1H), 0.90 (t, J = 6.8 Hz, 3H), 0.87 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 172.7, 170.7, 170.5, 170.1, 169.6, 158.7, 136.4, 130.7, 130.5, 128.3, 114.2, 114.0, 77.4, 72. 5, 71.7, 60.8, 59.8, 56.7, 55.4, 50.6, 49.2, 47.7, 38.2, 37.7, 37.6, 37.2, 36.8, 35.0, 31.8, 30.6, 29.3, 26.1, 25.7, 24.3, 19.9, 16.7, 14.1, 14.0, 13.4, 9.1 ppm; HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{45}H_{69}N_5O_8S+Na]^+$: 862.4759; found: 862.4749.

epi-1: 34-epi apratoxin A. Using the same procedure with **50b**, 34-epi apratoxin A **epi-1** was obtained as a white amorphous solid in 25% over 3 steps. R_f = 0.35 (ethyl acetate); $[\alpha]_D^{24} = -197$ (c = 0.115, methanol); IR (neat): $\tilde{\nu}$ = 3438, 2964, 2934, 1744, 1628, 1512, 1453, 1248, 1177, 754 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2, mixture of rotamers): δ = 7.13 (d, J = 8.8 Hz, 1.4H), 7.12 (d, J = 8.8 Hz, 0.6H), 6.79 (d, J = 8.8 Hz, 2H), 6.29 (d, J = 9.8 Hz, 0.7H), 6.24 (dq, J = 10.2, 1.0 Hz, 0.7H), 6.17 (dq, J = 9.8, 1.0 Hz, 0.3H), 5.97 (d, J = 9.3 Hz, 0.3H), 5.29–5.34 (m, 1.7H), 5.12 (d, J = 11.7 Hz, 0.3H), 5.01 (m, 0.3H), 4.95 (dd, J = 12.7, 2.0 Hz, 0.3H), 4.88 (dd, J = 12.7, 3.4 Hz, 0.7H), 4.82 (d, J = 11.2 Hz, 0.7H), 4.75 (q, J = 6.8 Hz, 0.7H), 4.35 (dd, J = 8.3, 5.9 Hz, 0.7H), 3.99–4.14 (m, 2.3H), 3.74 (s, 0.9H), 3.74 (s, 2.1H), 3.54–3.60 (m, 1H), 3.48 (dd, J = 11.2, 8.8 Hz, 0.3H), 3.43 (dd, J = 11.2, 8.3 Hz, 0.7H), 3.27 (br s, 0.3H), 3.04–3.17 (m, 2H), 2.89 (dd, J = 13.2, 5.4 Hz, 0.7H), 2.87 (s, 0.9H), 2.83 (dd, J = 13.2, 5.4 Hz, 0.3H), 2.67 (s, 2.1H), 2.66 (s, 0.9H), 2.55 (s, 2.1H), 2.48–2.54 (m, 1H), 2.21–2.29 (m, 1H), 1.68–2.08 (m, 7H), 1.94 (d, J = 1.0 Hz, 2.1H), 1.91 (d, J = 1.0 Hz, 0.9H), 1.21–1.30 (m, 2H), 1.12 (d, J = 6.8 Hz, 0.9H), 1.10 (d, J = 6.8 Hz, 2.1H), 1.07 (d, J = 6.8 Hz, 0.9H), 1.04 (d, J = 6.8 Hz, 2.1H), 0.97 (d, J = 6.8 Hz, 2.1H), 0.96 (d, J = 6.8 Hz, 0.9H), 0.90 (d, J = 6.8 Hz, 0.9H), 0.84–0.89 (m, 2H), 0.86 (s, 6.3H), 0.85 (s, 2.7H), 0.81 (t, J = 7.3 Hz, 2.1H), 0.77 (t, J = 7.3 Hz, 0.9H), 0.61 ppm (d, J = 6.8 Hz, 2.1H); HRMS (ESI-TOF): *m/z* (%) calcd for $[C_{45}H_{69}N_5O_8S+H]^+$: 840.4945; found: 840.4968.

HPLC analysis of 1 and epi-1. Apratoxin A (**1**) and **epi-1** were analyzed by reversed-phase HPLC (Inertsil C_{18} ODS, 5 μm, 7.6×250 mm, 2.5 mL min^{-1}, UV detection at 220 nm) using an isocratic system of aqueous CH_3CN (80%). **1** and **epi-1** were eluted at t_R = 11.1 min and t_R = 13.6 min, respectively.

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