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 suc-

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cessfully 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.

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.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.200800365. 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 solidphase 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 25membered 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, 3,7dihydroxy-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 Ph₃PO/Tf₂O-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 thiazo-

Abstract in Japanese:

アブラ	トキシンA	はヒトの腫瘍	細胞に対し弟	〔力な細胞毒	性を有する	25 員環 ラ	ドブシベ	ブチドで
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メチル	ノナン酸部住	立の合成にお	いては、三つ	の反応剤制	御による反	応を組み	合わせる	ことによ
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ン誘導	本に対して、	Ph ₃ PO/Tf ₂ O	を作用させる	ことでチア	ゾリン構築	を行い、	トリペフ	チドを伸
長後、	ブロリン残暑	毒とインロイ	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。



Scheme 1. Retrosynthetic analysis of apratoxin A

line precursors can be prepared from 6 (moCys or moSer residue) with the Dtena moiety 7.

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) Ph₃SiOReO₃, BSA, ether, 0°C; b) Et₃N, K₂CO₃, MeOH, 42% (for **10a**) and 44% (for **1b**). MPM=4-methoxyphenyl-methyl, BSA = N, O-bis(trimethylsilyl)acetamide.

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



 $Ru(OAc)_2[(S)-binap]$ (11 a) (2 mol%)-catalyzed asymmetric hydrogenation of (*E*)-10 a was carried out at 50 °C for 48 h under 100 atm of hydrogen to afford 12 a in quantitative

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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 96% yield according to a reported procedure in (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 OsO4/oxone system^[19] followed by a one-pot treatment with NaIO₄ to obtain 20 a in 79% yield. In this reaction, partially-produced β -hydroxy ketone **19** was also converted into the desired carboxylic acid 20a by treatment with NaIO₄.

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) NaClO₂, 2-methyl-2-butene, NaH₂PO₄ aq., *t*BuOH, 0°C; b) TFA, CH₂Cl₂, 56% in 2 steps; c) (*E*)-**15a**, MS 4Å, toluene, -78 °C, 95% (>95% ds); d) TrocCl, DMAP, pyridine, CH₂Cl₂, 0°C, quant.; e) DDQ, H₂O, CH₂Cl₂; f) FmocPro-OH, C₆H₂Cl₃COCl, DIEA, DMAP, toluene, 92% in 2 steps; g) OsO₄, oxone, NaHCO₃, DMF then NaIO₄, H₂O, *t*BuOH, 79%. TFA=tri-fluoroacetic acid, Troc=2,2,2-trichloroethoxycarbonyl, DMAP=4-(dimethylamino)pyridine, DDQ=2,3-dichloro-4,5-dicyanobenzoquinone, Fmoc=9-fluorenylmethoxycarbonyl.

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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-epiapratoxin 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.

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



Scheme 4. Synthetic route of C34-epimer **20b**. Reagents and conditions: a) (*Z*)-**15b**, MS 4Å, toluene, 90% (**16b**:16c=10:1); b) TrocCl, DMAP, pyridine, CH₂Cl₂, quant.; c) DDQ, H₂O, CH₂Cl₂; d) FmocPro-OH, C₆H₂Cl₃COCl, DIEA, DMAP, toluene, 81% in 2 steps; e) OsO₄, oxone, NaHCO₃, DMF then NaIO₄, H₂O, *t*BuOH, 83%.

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, H₂O, THF, *t*BuOH, 85%; d) **25**, EDCI/HCl, HOBt, CH₂Cl₂, 82% (based on **24**); e) LiOH, THF, H₂O, 79%; f) HCl (4M)/EtOAc; g) **29**, HATU, DIEA, CH₂Cl₂, quant; h) HCl (4M)/EtOAc; i) **27**, HATU, DIEA, CH₂Cl₂, 21%; j) HCl (4M)/EtOAc; k) **33**, HATU, DIEA, CH₂Cl₂, 92%. Boc = *tert*-butoxycarbonyl, DIBAL-H = diisobutylaluminium hydride, EDCI = 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide, HOBt = 1-hydroxybenzotriazole, HATU = 7-azabenzotriazole-1-yl-1,1,3,3-tetramethyluronium hexafluorophosphate.

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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 Et₂NH,^[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, CH₂Cl₂; b) TBAF, THF; c) **35**, HATU, DIEA, CH₂Cl₂; d) TBAF, THF, 93% in 2 steps; e) DAST, CH₂Cl₂, -78 °C, 70%; f) TMSOTf, 2,6-lutidine, CH₂Cl₂; g) TBAF, THF, 93% in 2 steps; h) Pd-(PPh₃)₄, morpholine, THF i) HATU, DIEA, CH₂Cl₂ (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 Pd⁰ catalyst and morpholine. Final macrolactamization of the resulting amino acid was achieved using HATU/DIEA in 1 mM CH₂Cl₂ 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 H₂S/Et₃N 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 Ph₃PO/Tf₂O in CH₂Cl₂ 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/NH₄OAc 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** ($t_{\rm R}$ = 24.7 min) and **48b** ($t_{\rm R}$ = 24.1 min) confirmed that no epimerization was observed at C34 during the reactions. Removal of the allyl ester in 48a and

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Scheme 7. Attempts to construction of thiazoline using **38** and **42**. Reagents and conditions: a) H_2S , NEt₃, MeOH; b) allyl bromide, K_2CO_3 , DMF, 95%; c) TMSOTf, 2,6-lutidine, CH₂Cl₂, then MeOH; d) **35**, HATU, DIEA, CH₂Cl₂, 90%; e) Lawesson's reagent, toluene, 80°C, 1 h, 91%.

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

49 a and 34-epimer **49 b** were used for the further transformation (Scheme 9). After removal of the Fmoc group in **34** (Et₂NH/CH₃CN), coupling of the resulting amine with acids **49 a** and **49 b** provided **50 a** (t_R =24.8 min) and **50 b** (t_R =24.1 min). Cleavage of the *O*-allyl esters mediated by Pd-(PPh₃)₄/*N*-methylaniline, followed by removal of the Fmoc groups with Et₂NH/CH₃CN, afforded cyclization precursors **51 a** and **51 b**. Finally, the macrolactamization of **51 a** and **51 b** 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



Scheme 8. Thiazoline formation using moCys moiety **46a** and **46b**. Reagents and conditions: a) **45**, EDCI·HCl, HOAt, DIEA, CH₂Cl₂, 0 °C to RT., 81% (for **46a** from **20a**), and 84% (for **46b** from **20b**). b) Tf₂O, Ph₃PO, CH₂Cl₂, 0 °C; c) Zn, NH₄OAc, THF, 90% (for **48a**), and 95% (for **48b**) in 2 steps; d) Pd(PPh₃)₄, *N*-methylaniline, THF, 95% (for **49a**), and 95% (for **49b**). Trt=triphenylmethyl, HOAt=1-hydroxy-7-azaben-zotiazole.

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 Ph₃PO/Tf₂O. Furthermore, comparing the spectra of thiazoline 48 a with that of 34-epi 48 b, we conclude that no epimerization at C34, the a-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-

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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 ¹³C) 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 CDCl₃. ¹H NMR spectral data are reported as follows: chloroform (7.26 ppm) and dichloromethane (5.3 ppm). ¹³C 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 Ph₃SiOReO₃ (250 mg, 0.497 mmol) in diethyl ether (83 mL) was added *N*,*O*-bis(trime-thylsilyl)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 Et₃N (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 K₂CO₃ (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 NaHCO₃, brine, dried over MgSO₄, 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: $R_{\rm f}$ =0.45 (hexane/ethyl acetate=1:1); $[a]_{\rm D}^{22}$ =+1.40 (c=0.990, CHCl₃); IR (neat): $\tilde{\nu}$ =3391, 2870, 1614, 1515, 1248, 1078, 1037, 822 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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_i =0.50 (hexane/ethyl acetate =1:1); $[a]_D^{20}$ +44.9 (c=2.44, CHCl₃); IR (neat): \bar{v} =3341, 2959, 2870, 1614, 1514, 1249, 1077, 1036, 822 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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), 1.84 (s, 3H), 0.98 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃): 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_t =0.48 (hexane/ ethyl acetate=1:1); $[a]_{D}^{28}$ =-29.3 (*c*=0.990, CHCl₃); IR (neat): $\tilde{\nu}$ =3392, 2955, 1615, 1587, 1515, 1464, 1302, 1249, 1039, 821 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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: (3R,5S)-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**). $R_{\rm f}$ =0.45 (hexane/ethyl acetate =1:1); $[a]_{\rm D}^{18}$ =-24.8 (*c*=1.23, CHCl₃); IR (neat): $\tilde{\nu}$ =3394, 2955, 2871, 1514, 1249, 1077, 1038, 820 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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: (3R,5S)-5-tert-Butyl-3-methyl-8-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 NaH₂PO₄ (1.0 mL) was added 2-methyl-2-butene (0.3 mL) and NaClO₂ (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 CHCl₃. The combined organic layers were washed with brine, dried over Na2SO4, and concentrated in vacuo. The residue was used for the next reaction without further purification. To a solution of the crude carboxylic acid in CH₂Cl₂ (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. $R_{\rm f} = 0.53$ (hexane/ethyl acetate = 3:2); $[\alpha]_{\rm D}^{23} = +46.0$ (c = 1.49, CHCl₃); IR (neat): $\tilde{\nu} = 2960$, 2875, 1747, 1242, 1073, 1002 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): $\delta = 3.98$ (dd, J = 11.7, 3.9 Hz, 1 H), 2.51 (dd, J = 10.2, 10.2 Hz, 1 H), 2.16-2.24 (m, 2 H), 1.83 (ddd, J=14.2, 11.7, 7.3 Hz, 1 H), 1.51 (ddd, J=14.2, 5.0, 3.9 Hz, 1 H), 1.11 (d, J=6.8 Hz, 3 H), 0.97 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃): 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: (3R,4S,6S,8S)-8-(4-methoxybenzyloxy)-3,6,9,9-tetramethyldec-1-en-4-ol. To a suspension of crotyl borane (E)-15 a (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, 2M), 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 NaHCO₃, brine, dried over MgSO₄, 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. $R_{\rm f} = 0.68$ (hexane/ ethyl acetate=3:1); $[\alpha]_{D}^{24} = -50.9$ (c=1.09, CHCl₃); IR (neat): $\tilde{\nu} = 3478$, 2956, 2870, 1614, 1514, 1465, 1248, 1091, 1039, 915, 821 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): $\delta = 7.30$ (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, 1 H), 3.79 (s, 3 H), 3.50 (m, 1 H), 3.11 (dd, J=9.3, 2.9 Hz, 1 H), 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, 1 H), 1.35 (ddd, J=14.2, 9.3, 2.4 Hz, 1 H), 1.12 (ddd, J=13.7, 9.3, 2.4 Hz, 1 H), 1.03 (d, J=7.3 Hz, 3 H), 0.96 (d, J= 6.8 Hz, 3 H), 0.93 ppm (s, 9 H); $^{13}{\rm C}\,{\rm NMR}$ (100 MHz, CDCl₃): $\delta\!=\!159.0,$ 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 [C₂₂H₃₆O₃+H]⁺: 349.2743; found: 349.2747.

17a: (3 R,45,65,85)-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 CH₂Cl₂ (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 (1M) and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaHCO₃ and brine, dried over MgSO4, 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. $R_{\rm f} = 0.75$ (hexane/ethyl acetate = 3/1); $[a]_{\rm D}^{24} = -34.1$ (c = 1.53, CHCl₃); IR (neat): $\tilde{v} = 2958$, 2872, 1758, 1514, 1380, 1249, 1095, 1039, 945, 820, 734 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): $\delta = 7.28$ (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, 1 H), 4.78 (d, J = 12.2 Hz, 1 H), 4.58 (d, J = 10.8 Hz, 1 H), 4.50 (d, J 10.8 Hz, 1 H), 4.50 (d, J=12.2 Hz, 1 H), 3.79 (s, 3 H), 3.06 (dd, J=9.3, 2.4 Hz, 1 H), 2.48 (m, 1 H), 1.91 (ddd, J=14.2, 11.2, 2.4 Hz, 1 H), 1.78 (m, 1 H), 1.47 (ddd, J=14.2, 9.3, 3.9 Hz, 1 H), 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); ¹³C NMR (100 MHz, CDCl₃): $\delta =$ $159.0,\ 154.3,\ 138.9,\ 131.6,\ 129.0,\ 116.4,\ 113.8,\ 94.8,\ 85.2,\ 80.8,\ 76.6,\ 74.5,$ 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 [C₂₅H₃₇Cl₃O₅+Na]⁺: 545.1604; found: 545.1595.

Prolyl ester 18a: To a solution of 17a (2.26 g, 4.31 mmol) in CH₂Cl₂ (20 mL) and H₂O (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 NaHCO3, and the aqueous layer was extracted with CH2Cl2. The combined organic layers were washed with brine, dried over MgSO4, 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 H₂O and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous NH4Cl, saturated aqueous NaHCO3, brine, dried over Na2SO4, 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, CHCl₃); IR (neat): $\tilde{\nu}$ =2963, 1753, 1708, 1416, 1250, 739 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, mixture of rotamers): $\delta = 7.72 - 7.77$ (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, 0.5 H), 4.46 (dd, J=5.8, 2.9 Hz, 0.5 H), 4.15-4.45 (m, 3 H), 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, 0.5 H), 1.12 (ddd, J=14.7, 10.3, 2.0 Hz, 0.5 H), 1.04 (d, J= 6.8 Hz, 1.5 H), 1.02 (d, J=6.8 Hz, 1.5 H), 0.95 (d, J=6.8 Hz, 1.5 H), 0.88 (s, 4.5H), 0.86 (s, 4.5H), 0.74 ppm (d, J = 6.4 Hz, 1.5H); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers): $\delta = 172.5$, 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 20 a: To a solution of **18 a** (363 mg, 502 µmol) in DMF (5.0 mL) was added OsO₄ (63 µL, 2.5 wt% solution in 2-methyl-2-propanol, 5.0 µmol), oxone (1.24 g, 2.01 mmol), and NaHCO₃ (169 mg, 2.01 mmol) at room temperature. After being stirred at the same temperature for 12 h, the reaction mixture was diluted with H₂O (3.0 mL) and 2-methyl-2-propanol (6.0 mL). To the mixture was added NaIO₄ (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 CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with aqueous solution of Na₂S₂O₃ (10 wt%), brine, dried over Na₂SO₄, 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); $[a]_D^{22} = -45.3$ (*c*=0.99, CHCl₃); IR (neat):

 $\bar{\nu}$ =2962, 1756, 1742, 1708, 1451, 1419, 1248, 758, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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, 141.3, 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 [C₃₆H₄₃NO₉Cl₃+H]*: 740.2160; found: 740.2139.

Syn-selective crotylation of 13. To a suspension of crotyl borane (Z)-**15b** (3.53 mL, ca. 1.0M 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, 2M), 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 NaHCO₃, brine, dried over MgSO₄, 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 mLmin⁻¹, refractive index detection, $t_R=28.0$ min (**16b**), 33.5 min (**16c**)).

16b: $R_{\rm f}$ =0.66 (hexane/ethyl acetate =3:1); $[a]_{\rm D}^{21}$ = -65.3 (*c*=1.18, CHCl₃); IR (neat): $\bar{\nu}$ =3471, 2956, 2870, 1613, 1514, 1248, 1089, 1038, 820 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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 (brs, 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); ¹³C NMR (100 MHz, CDCl₃): 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 [C₂₂H₃₆O₃+H]+: 349.2743; found: 349.2727.

16 c: $R_{\rm f}$ =0.66 (hexane/ethyl acetate = 3:1); [*a*]_D²⁵ = -15 (*c* = 0.050, CHCl₃); ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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. $R_{\rm f}$ =0.75 (hexane/ethyl acetate = 3:1); $[a]_{\rm D}^{12} = -33.4$ (c=1.15, CHCl₃); IR (neat): \tilde{v} =2958, 1758, 1514, 1380, 1249, 1038, 820 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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=0.7 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 (dd, J=6.8 Hz, 3H), 0.99 (d, J=6.4 Hz, 3H), 0.92 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃): 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 [C₂₅H₃₇Cl₃O₅+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_t =0.62 (hexane/ethyl

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acetate = 3:1); $[\alpha]_{D}^{22} = -67.6$ (c = 1.41, CHCl₃); IR (neat): $\tilde{\nu} = 2963$, 1754, 1708, 1417, 1250, 1118, 758, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, mixture of rotamers): $\delta = 7.74-7.77$ (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, 0.5 H), 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, 1 H), 1.36–1.51 (m, 2 H), 1.31 (ddd, J=14.6, 10.2, 2.4 Hz, 0.5 H), 1.18 (ddd, J=14.6, 10.2, 2.0 Hz, 0.5 H), 1.04 (d, J=6.8 Hz, 1.5 H), 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, 1.5 H); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers): $\delta = 172.5$, 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, CHCl₃); IR (neat): $\tilde{\nu} = 2957$, 1752, 1741, 1707, 1420, 1249, 1183, 1121, 823 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, mixture of rotamers): $\delta = 7.75 - 7.77$ (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, 0.7 H), 4.88 (d, J = 12.2 Hz, 0.3 H), 4.79 (m, 0.3 H), 4.78 (s, 1.4 H), 4.70 (d, J =12.2 Hz, 0.3 H), 4.60 (dd, J=7.3, 3.4 Hz, 0.7 H), 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, 0.3 H), 1.11-1.49 (m, 2.3 H), 1.26 (d, J=6.8 Hz, 2.1 H), 1.24 (d, J=6.8 Hz, 0.9H), 1.00 (d, J=6.8 Hz, 2.1 H), 0.88 (s, 2.7 H), 0.87 (s, 6.3 H), 0.75 ppm (d, J = 6.8 Hz, 0.9 H); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers): $\delta\,{=}\,177.3,\,176.0,\,172.8,\,171.6,\,155.4,\,154.4,\,154.1,\,153.9,\,144.3,\,144.2,\,143.8,$ 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 CH₂Cl₂ (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 H2O and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NH₄Cl, saturated aqueous NaHCO₃, brine, dried over MgSO₄, 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. $R_{\rm f} = 0.60$ (hexane/ethyl acetate = 3:1); $[\alpha]_{\rm D}^{23} = -19.2$ (c = 1.34, CHCl₃); IR (neat): $\tilde{\nu}$ =3452, 2956, 2887, 1750, 1723, 1505, 1367, 1351, 1115, 836, 779 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): $\delta = 5.34$ (d, J =8.7 Hz, 1 H), 4.35 (m, 1 H), 4.04 (dd , J=9.7, 2.4 Hz, 1 H), 3.82 (dd, J= 9.7, 2.7 Hz, 1 H), 3.74 (s, 3 H), 1.46 (s, 9 H), 0.86 (s, 9 H), 0.03 (s, 3 H), 0.02 ppm (s, 3H); 13 C NMR (100 MHz, CDCl₃): $\delta = 171.3$, 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 [C₁₅H₃₁NO₅Si+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 Na₂SO₄, 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. $R_{\rm f} = 0.58$ (hexane/ethyl acetate = 2/1); $[\alpha]_{\rm D}^{27} =$ -6.71 (*c*=1.36, CHCl₃); IR (neat): $\tilde{\nu}$ =3373, 2957, 2932, 1717, 1515, 1367, 1254, 1173, 1112, 838, 778 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): $\delta = 6.64$ (dq, J=9.2, 1.0 Hz, 1 H), 4.93 (m, 1 H), 4.47 (m, 1 H), 4.13-4.25 (m, 2 H), 3.71 (dd, J=10.3, 3.4 Hz, 1 H), 3.61 (dd, J=10.3, 3.9 Hz, 1 H) 1.93 (d, J= 1.0 Hz, 3 H), 1.44 (s, 9 H), 1.28 (t, J=7.2 Hz, 3 H), 0.89 (s, 9 H), 0.05 ppm (s, 6H); 13 C NMR (100 MHz, CDCl₃): $\delta = 167.9$, 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 2methyl-2-propanol (23 mL), H₂O (6.0 mL), and THF (6.0 mL) was added LiOH·H₂O (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 NH₄Cl, and the aqueous layer was extracted with CHCl₃. The combined organic layers were washed with brine, dried over MgSO4, 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. $R_{\rm f} = 0.42$ (hexane/ethyl acetate = 1:1); $[\alpha]_{D}^{24} = +5.21$ (c=1.17, CHCl₃); IR (neat): $\tilde{\nu} = 3245$, 2931, 1692, 1500, 1473, 1393, 1254, 1168, 1116, 837, 778 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): $\delta = 6.76$ (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, 1 H), 3.62 (dd, J=10.1, 4.3 Hz, 1 H), 1.94 (d, J=1.0 Hz, 3H), 1.44 (s, 9H), 0.89 (s, 9H), 0.04 ppm (s, 6H); $^{13}\!\mathrm{C}\,\mathrm{NMR}$ (100 MHz, $CDCl_3$): $\delta = 172.9$, 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 [C₁₇H₃₃NO₅Si+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 CH2Cl2 twice, then dissolved in CH2Cl2 (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 CH2Cl2 (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 NaHCO3, brine, dried over MgSO4, 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. $R_{\rm f} = 0.45$ (hexane/ethyl acetate = 1:1); $[\alpha]_{\rm D}^{24} = +50.7$ (c = 1.40, CHCl₃); IR (neat): $\tilde{\nu} = 3340$, 2955, 2932, 1742, 1714, 1634, 1514, 1251, 1176, 838, 779 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): $\delta = 6.99$ (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, 1 H), 3.58 (dd, J=10.1, 4.3 Hz, 1 H), 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, CDCl₃): $\delta = 172.2$, 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), H₂O (1.0 mL), and THF (2.0 mL) was added LiOH·H₂O (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 NH₄Cl, and the aqueous layer was extracted with CHCl₃. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (5 % methanol in CHCl₃) to give carboxylic acid **27** (145 mg, 0.270 mmol, 79%) as a colorless oil. R_f =0.40 (CHCl₃/methanol=4:1); $[a]_D^{24}$ =+43.3 (*c*=1.53, CHCl₃); IR (neat): $\bar{\nu}$ =3324, 2930, 1715, 1669, 1614, 1463, 1366, 1247, 834 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 [C₂₇H₄₄N₂O₇Si+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 (4M) 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 CH2Cl2 twice, then dissolved in CH2Cl2 (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. $R_{\rm f} = 0.50$ (hexane/ethyl acetate = 2:1); $[a]_{\rm D}^{29} = -145$ (c=1.09, CHCl₃); IR (neat): $\tilde{\nu} = 3525$, 2937, 1739, 1694, 1661, 1456, 1392, 1183, 1077, 989, 772 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, major rotamer): $\delta =$ 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, 1 H), 4.52-4.69 (m, 2 H), 3.02 (s, 3 H), 2.76 (s, 3 H), 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); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers): $\delta = 172.6$, 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 [C₁₉H₃₄N₂O₅+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 (4M) 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 CH₂Cl₂ twice, then dissolved in CH₂Cl₂ (1.0 mL). To this solution was added a solution of **27** (94.6 mg, 0.176 mmol) and *N*,*N*-diisopropyl-ethylamine (0.153 mL, 0.880 mmol) in CH₂Cl₂ (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): $\bar{\nu}$ =2958, 1717, 1614, 1515, 1248, 1074, 823 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (67.8 MHz, CDCl₃): 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 [C₁₆H₂₄O₃+Na]⁺: 287.1618; found: 287.1617.

Tetrapeptide 31: R_f =0.52 (hexane/ethyl acetate =1:2); $[a]_D^{22} = -69.7$ (*c*= 1.06, CHCl₃); IR (neat): $\bar{\nu}$ =3335, 2932, 1737, 1712, 1635, 1513, 1406, 1249, 1177, 1107, 837, 782 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 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), 2.85 (dd, *J*=14.0, 3.4 Hz, 1H), 2.74 (s, 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); ¹³C NMR (100 MHz, CDCl₃, 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,

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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 [C₄₁H₆₈N₄O₉Si+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 (4M) 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 CH2Cl2 twice, then dissolved in CH2Cl2 (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. $R_{\rm f} = 0.40$ (hexane/ethyl acetate = 1:1); $[\alpha]_{\rm D}^{29} =$ -87.1 (*c* = 1.08, CHCl₃); IR (solid): $\tilde{\nu} = 3296$, 2965, 1718, 1636, 1512, 1243, 990, 741, 540 cm $^{-1}$; ¹H NMR (400 MHz, CDCl₃, mixture of rotamers): $\delta =$ 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, 3 H), 0.84–0.90 ppm (m, 3 H); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers): $\delta = 171.9$, 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 CH₃CN (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 CH₂Cl₂ twice, then dissolved in CH₂Cl₂ (0.5 mL). To this solution was added a solution of acid **24** (60.0 mg, 0.167 mmol) in CH₂Cl₂ (1.5 mL), *N*,*N*-diisopropylethylamine (87.0 μ L, 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 CH₂Cl₂ (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 NaHCO3 at 0°C. The aqueous layer was extracted with CHCl₃. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was used for the next reaction without further purification. To a solution of the silvlcarbamate 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 NaHCO₃, and the aqueous layer was extracted with CHCl₃. 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 CH2Cl2 twice, then dissolved in CH2Cl2 (0.5 mL). To this solution was added a solution of acid 35 (36.0 mg, 64.5 µmol) in CH₂Cl₂ (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 CHCl₃) 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 NaHCO₃, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na2SO4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (3 % methanol in $\mathrm{CHCl}_3)$ to give $\boldsymbol{37}$ (60.2 mg, 60.2 $\mu {\rm mol},$ 93 % in 2 steps) as a white amorphous solid. $R_{\rm f}{=}$ 0.45 (CHCl₃/methanol=9:1); $[a]_{D}^{17} = -62.9$ (c=1.34, CHCl₃); IR (solid): $\tilde{\nu} = 3321, 2967, 2937, 1738, 1695, 1644, 1514, 1404, 1249, 755 \text{ cm}^{-1};$ ¹H NMR (400 MHz, CDCl₃, major rotamer): $\delta = 7.08$ (d, J = 8.8 Hz, 2H), 6.78 (d, J=8.8 Hz, 2 H), 6.62 (d, J=7.8 Hz, 1 H) 6.43 (d, J=8.3 Hz, 1 H), 6.23 (dq, J=8.8, 1.0 Hz, 1 H), 5.88 (m, 1 H), 5.40 (q, J=6.8 Hz, 1 H), 5.31 (dd, J=17.1, 1.4 Hz, 1 H), 5.23 (dd, J=10.2, 1.4 Hz, 1 H), 5.20 (m, 1 H), 4.94 (d, J=10.2 Hz, 1 H), 4.86 (dd, J=11.7, 2.0 Hz, 1 H), 4.83 (m, 1 H), 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, 1 H), 3.61 (m, 1 H), 3.48-3.55 (m, 2 H), 3.38 (m, 1 H), 3.05 (dd, J=13.7, 7.8 Hz, 1 H), 2.96 (s, 3 H), 2.85 (dd, J=13.7, 5.4 Hz, 1 H), 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 (brd, J = 6.8 Hz, 3H×2), 0.92 (m, 1H), 0.88 (s, 9H), 0.88 ppm (t, J=8.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃, major rotamer): $\delta = 172.8$, 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 CH₂Cl₂ (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 NaHCO3 at -78°C, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na2SO4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1.5% methanol in CHCl₃) to give oxazoline 38 (17.2 mg, 17.5 µmol, 70%) as a colorless oil. $R_{\rm f} = 0.48$ (CHCl₃/methanol = 9:1); $[\alpha]_{\rm D}^{17} = -121$ (c = 0.860, CHCl₃); IR (neat): $\tilde{\nu} = 3331$, 2968, 1739, 1696, 1650, 1514, 1403, 1249, 1180, 754 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, major rotamer): $\delta = 7.09$ (d, J=8.8 Hz, 2 H), 6.78 (d, J=8.8 Hz, 2 H), 6.49 (m, 1 H), 6.16 (m, 1 H), 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, 1 H), 4.60 (m, 2 H), 4.31 (dd, J=8.3, 3.9 Hz, 1 H), 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 (brs, 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 CH₂Cl₂ (0.6 mL) was added dropwise trimethylsilyl trifluoromethanesulfonate (7.3 $\mu L,$ 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 NaHCO3 at 0°C. The aqueous layer was extracted with CHCl₃. The combined organic layer was washed with brine, dried over Na2SO4, 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 м 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 NaHCO3, and the aqueous layer was extracted with CHCl₃. The combined organic layers were washed with brine, dried over Na2SO4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (5.0% methanol in CHCl₃) to give amine 39 (6.6 mg, 7.5 $\mu mol,$ 93% in 2 steps) as a white amorphous solid. $R_{\rm f} = 0.50$ (CHCl₃/methanol=9:1); $[\alpha]_{\rm D}^{25} = -32.4$ (c= 0.150, MeOH): IR (neat): $\tilde{\nu} = 3315$, 2966, 2935, 2876, 1736, 1644, 1513, 1247, 1182 cm⁻¹; ¹H NMR (400 MHz, CD₂Cl₂): $\delta = 7.10$ (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, 1 H), 5.91 (m, 1 H), 5.37 (q, J=6.8 Hz, 1 H), 5.21-5.29 (m, 2 H),

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), 1.20 (ddd, J=14.2, 10.8, 2.4 Hz, 1H), 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); 1RMS (ESI-TOF): m/z (%) calcd for $[C_{45}H_{69}N_5O_9+H]^+$: 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 CH2Cl2 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 CH₂Cl₂) to give apratoxin A oxazoline analogue 2 (3.5 mg, 4.2 µmol, 56% in 2 steps) as a white amorphous solid. $R_{\rm f} = 0.5$ (CHCl₃/methanol = 9:1); $[\alpha]_{\rm D}^{22} = -167$ (c=0.100, MeOH), lit.^[12] $[\alpha]_{\rm D}^{25} = -117.5$ (c=0.2, CHCl₃); IR (neat): $\tilde{\nu} =$ 3426, 2966, 2935, 1742, 1624, 1513, 1461, 1178, 754 cm $^{-1};\ ^1H$ NMR $(400 \text{ MHz}, \text{CD}_2\text{Cl}_2): \delta = 7.15 \text{ (d}, J = 8.8 \text{ Hz}, 2 \text{ H}), 6.81 \text{ (d}, J = 8.8 \text{ Hz}, 2 \text{ H}),$ 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, 1 H), 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, 1 H), 4.13-4.18 (m, 2 H), 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, 1 H), 2.87 (dd, J=8.3, 5.8 Hz, 1 H), 2.81 (s, 3 H), 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, 3 H), 0.96 (m, 1 H), 0.94 (d, J=6.8 Hz, 3 H), 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 NH₄Cl at 0°C. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with aqueous Na₂S₂O₃ (10%), saturated aqueous NaHCO₃, brine, dried over MgSO₄, 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. $R_{\rm f} = 0.58$ (hexane/ethyl acetate = 2:1); $[\alpha]_{\rm D}^{20} = +10.0$ (c = 1.14, CHCl₃); IR (neat): $\tilde{\nu} = 3375$, 2956, 2931, 1717, 1515, 1254, 1171, 1113, 838, 778 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): $\delta = 6.68$ (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, 1 H), 1.95 (d, J=1.4 Hz, 3 H), 1.44 (s, 9 H), 0.89 (s, 9 H), 0.05 ppm (s, 6H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 167.5$, 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 CH₂Cl₂ (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 NaHCO₃ at 0°C. The aqueous layer was ex-

tracted with CHCl₃. The combined organic layers were washed with brine, dried over Na2SO4, and concentrated in vacuo. The residue was azeotropically dried with toluene and CH2Cl2 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 CH2Cl2 (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 μ mol, 90%) as a colorless oil. $R_f = 0.44$ (hexane/ethyl acetate=2:1); $[\alpha]_{D}^{19} = -26.8$ (c=0.960, CHCl₃); IR (neat): $\tilde{\nu} = 3357$, 2957, 2931, 1718, 1702, 1674, 1399, 1257, 1119, 837, 776 cm $^{-1};\ ^1H$ NMR (400 MHz, CDCl₃, mixture of rotamers): $\delta = 6.84$ (d, J = 7.8 Hz, 0.5 H), 6.77 (d, J=7.8 Hz, 0.5 H), 6.71 (dq, J=8.8, 1.4 Hz, 1 H), 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, 0.5 H), 4.32 (dd, J = 5.4, 2.9 Hz, 0.5 H), 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 NaHCO3 at 0°C, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na₂SO₄, 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 μ mol, 91 %) as a colorless oil. $R_f = 0.56$ (hexane/ethyl acetate=2:1); IR (neat): \tilde{v} =3291, 2956, 2931, 1720, 1702, 1399, 1257, 1160, 1116, 837, 778 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, mixture of rotamers): $\delta = 9.02$ (d, J = 7.8 Hz, 0.5 H), 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 CH₂Cl₂ (0.5 mL) was added a solution of 20 a (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 NaHCO3, brine, dried over MgSO4, 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. $R_{\rm f} = 0.56$ (hexane/ethyl acetate = 1:1); $[\alpha]_{\rm D}^{26} =$ $-34.6 (c = 1.35, CHCl_3); IR (solid): \tilde{\nu} = 3329, 2962, 1755, 1709, 1523, 1449,$ 1420, 1248, 1119, 946, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, mixture of rotamers): $\delta = 7.74 - 7.78$ (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, 0.4 H), 5.25 (dd, J=17.6, 1.5 Hz, 0.6 H), 5.23 (dd, J= 10.2, 1.4 Hz, 0.4 H), 5.17 (dd, J=10.7, 1.5 Hz, 0.6 H), 4.97 (m, 1 H), 4.84 (dd, J=8.2, 3.9 Hz, 0.6 H), 4.81 (d, J=12.2 Hz, 0.6 H), 4.80 (dd, J=10.2, 5.8 Hz, 0.4 H), 4.71 (d, J=12.2 Hz, 0.4 H), 4.48-4.67 (m, 5 H), 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 (brs, 3H), 1.58-1.62 (m, 1H), 1.22-1.49 (m, 3H), 1.09 (d, J=6.8 Hz, 1.8 H), 1.06 (d, J=7.3 Hz, 1.2 H), 0.92 (d, J=6.8 Hz, 1.8 H), 0.87 (s, 3.6H), 0.85 (s, 5.4H), 0.73 ppm (d, J = 6.4 Hz, 1.2H); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers): $\delta = 172.6$, 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, CHCl₃); IR (solid): $\tilde{\nu} = 3338$, 2961, 1758, 1712, 1675, 1420, 1249, 757, 742, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 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, 0.5 H), 6.40 (dq, J=8.8, 1.5 Hz, 0.5 H), 6.20 (d, J = 7.8 Hz, 0.5 H), 5.85–5.95 (m, 1 H), 5.59 (d, J = 7.8 Hz, 0.5 H), 5.18-5.31 (m, 2H), 5.00 (ddd, J=8.3, 8.3, 3.4 Hz, 0.5 H), 4.93 (m, 0.5 H), 4.68–4.82 (m, 3H), 4.53–4.63 (m, 3H), 4.49 (dd, J=8.8, 2.9 Hz, 0.5 H), 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, 1.5 H), 1.11 (d, J=7.3 Hz, 1.5 H), 1.00-1.07 (m, 1 H), 0.90 (d, J = 6.3 Hz, 1.5 H), 0.85 (s, 4.5 H), 0.83 (s, 4.5 H), 0.66 ppm (d, J = 6.8 Hz, 1.5H); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers): $\delta = 172.8$, 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 48 a. To a solution of triphenylphosphineoxide (72.0 mg, 257 µmol) in CH₂Cl₂ (1.0 mL) was added dropwise Tf₂O (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 NaHCO3 at 0°C, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, 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 NH₄OAc (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 Na₂SO₄ 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 μ mol, 90% in 2 steps) as a white amorphous solid. $R_{\rm f}$ = 0.37 (hexane/ethyl acetate=2:1); $[\alpha]_D^{26} = -62.4$ (c=0.900, CHCl₃); IR (solid): $\tilde{\nu} = 3475$, 2960, 2874, 1712, 1610, 1451, 1419, 1362, 1245, 1089, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, mixture of rotamers): $\delta = 7.75$ (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, 0.8 H), 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, 0.2 H), 3.31 (dd, J=11.2, 8.8 Hz, 0.8 H), 2.92-3.02 (m, 1 H), 2.65-2.72 (m, 1H), 2.25 (m, 1H), 1.98-2.10 (m, 3H), 1.97 (d, J=1.5 Hz, 0.6 H), 1.95 (d, J=1.0 Hz, 2.4 H), 1.38-1.74 (m, 4 H), 1.25 (d, J=7.3 Hz, 0.6 H), 1.21 (d, J=6.8 Hz, 2.4 H), 0.99 (m, 1 H), 0.95 (d, J=6.8 Hz, 2.4 H), 0.88 (s, 9H), 0.79 ppm (d, J=6.4 Hz, 0.6H); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers): $\delta = 172.5$, 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_i =0.37 (hexane/ethyl acetate=2:1); $[\alpha]_D^{16}$ =-79.3 (c=0.660, CHCl₃); IR (solid): $\tilde{\nu}$ =3477, 2961, 1740, 1713, 1452, 1423, 1264, 1124, 758, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers): δ = 172.5, 167.4, 155.1, 144.3, 144.0, 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 48 a and 48 b. The **48 a** and **48 b** were analyzed by reversed-phase HPLC (Inertsil C₁₈ ODS-3, 3 μ m, 4.6×250 mm, 1.0 mLmin⁻¹, UV detection at 254 nm) using a CH₃CN-H₂O linear gradient (75% for 4 min, 75–95% over 21 min, 95–100% over 5 min and then 100% CH₃CN 5 min). **48 a** and **48 b** 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 Nmethylaniline (10.3 $\mu L,~96.5~\mu mol)$ 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 49 a (25.4 mg, 36.7 $\mu mol,$ 95 %) as a white amorphous solid. $R_{\rm f} = 0.40$ (CHCl₃/methanol = 9:1); $[\alpha]_{\rm D}^{26} = -76.3$ (c = 1.11, CHCl₃); IR (solid): $\tilde{\nu} = 3464$, 2957, 1962, 1607, 1419, 1359, 1178, 1124, 988, 758 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, mixture of rotamers): $\delta = 7.63$ (d, J=7.3 Hz, 2H), 7.63 (m, 2H), 7.38 (m, 2H), 7.30 (m, 2H), 6.84-6.89 (m, 1 H), 5.14–5.28 (m, 1 H), 4.90 (dd, J=11.7, 1.5 Hz, 0.7 H), 4.82 (br d, J=10.3 Hz, 0.3 H), 4.18-4.53 (m, 4 H), 3.39-3.81 (m, 3 H), 3.36 (dd, J=10.8, 7.8 Hz, 0.3 H), 3.30 (dd, J=10.8, 8.8 Hz, 0.7 H), 2.97 (m, 1 H), 2.72 (m, 1H), 2.23 (m, 1H), 1.94-2.07 (m, 3H), 1.94 (brs, 0.9H), 1.92 (d, J= 1.0 Hz, 2.1 H), 1.84 (m, 1 H), 1.29–1.78 (m, 4 H), 1.24 (d, J=7.3 Hz, 0.9 H), 1.21 (d, J = 7.3 Hz, 2.1 H), 0.96 (d, J = 6.4 Hz, 2.1 H), 0.89 (s, 2.7 H), 0.87 (s, 6.3 H), 0.78 ppm (d, J = 6.8 Hz, 0.9 H); ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers): $\delta = 173.0$, 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 50 a. To a solution of tripeptide 34 (36.9 mg, 55.1 µmol) in CH₃CN (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 CH₂Cl₂ twice, then dissolved in CH₂Cl₂ (0.5 mL). To this solution was added a solution of acid 49a (25.4 mg, 36.7 µmol) in CH₂Cl₂ (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. $R_{\rm f} = 0.60$ (CHCl₃/methanol = 9:1); $[\alpha]_{\rm D}^{26} = -89.0$ $(c = 1.28, \text{CHCl}_3)$; IR (solid): $\tilde{\nu} = 3465, 3328, 2960, 2876, 1735, 1707, 1625,$ 1513, 1478, 1416, 1299, 1179, 1087, 988, 741, 545 cm $^{-1};\ ^1\mathrm{H}\,\mathrm{NMR}$ (400 MHz, CDCl₃, mixture of rotamers): $\delta = 7.75$ (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 (brd, 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 (brd, 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 (brs, 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

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(s, 9 H), 0.76–0.84 ppm (m, 3 H); ¹³C NMR (100 MHz, CDCl₃, 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 [C₆₃H₈₅N₅O₁₁S+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. $R_f = 0.60$ (CHCl₃/methanol=9:1); $[\alpha]_{\rm D}^{22} = -84.8$ (c = 0.780, CHCl₃); IR (solid): $\tilde{\nu} = 3474$, 3329, 2965, 2934, 1738, 1693, 1636, 1452, 1180 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 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, 1 H), 6.27 (dq, J=8.8, 1.5 Hz, 1 H), 5.84–5.93 (m, 1 H), 5.41 (q, J=6.8 Hz, 1 H), 5.30 (dd, J=17.1, 1.5 Hz, 1 H), 5.23 (dd, J=10.3, 1.5 Hz, 1 H), 5.20 (m, 1 H), 5.11 (m, 1 H), 4.94 (d, J=10.2 Hz, 1 H), 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 C₁₈ ODS-3, 3 μ m, 4.6×250 mm, 1.0 mLmin⁻¹, UV detection at 254 nm) using a CH₃CN-H₂O linear gradient (75% for 4 min, 75–95% over 21 min, 95–100% over 5 min and then 100% CH₃CN 5 min). **50a** and **50b** were eluted at $t_{\rm R}$ =24.8 min and $t_{\rm R}$ = 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 CHCl₃) to give the N-Fmoc-protected acid as a white amorphous solid. To a solution of the N-Fmoc-protected acid in CH3CN (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 CH2Cl2 twice, then dissolved in CH₂Cl₂ (40 mL). To this solution was added N,N-diisopropylethylamine (62.7 $\mu L,\,360\,\mu mol)$ and HATU (38.4 mg, 120 $\mu mol)$ at $0\,{}^{o}\mathrm{C}$ 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 CH₂Cl₂) 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 μ mol, 72 % in 3 steps) as a white amorphous solid. $R_{\rm f}$ = 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; ¹H NMR (400 MHz, CDCl₃): $\delta =$ 7.15 (d, J=8.8 Hz, 2 H), 6.80 (d, J=8.8 Hz, 2 H), 6.35 (d, J=9.8 Hz, 1 H), 6.05 (d, J=9.3 Hz, 1 H), 5.25 (ddd, J=9.8, 8.7, 4.3 Hz, 1 H), 5.20 (d, J= 11.6 Hz, 1 H), 5.05 (ddd, J=10.7, 9.3, 4.9 Hz, 1 H), 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 (brq, J=6.8 Hz, 1H), 3.14 (dd, J=11.1, 4.3 Hz, 1H), 3.11 (dd, J=12.2, 10.7 Hz, 1 H), 2.86 (dd, J=12.2, 4.9 Hz, 1 H), 2.81 (s, 3 H), 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, 3 H), 0.95 (d, J=6.8 Hz, 3 H), 0.91 (m, 1 H), 0.90 (t, J= 6.8 Hz, 3 H), 0.87 ppm (s, 9 H); 13 C NMR (100 MHz, CDCl₃): $\delta = 177.5$, 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. $R_{\rm f}$ =0.35 (ethyl acetate); $[\alpha]_{\rm D}^{24}$ =-197 (c=0.115, methanol); IR (neat): $\tilde{\nu} = 3438$, 2964, 2934, 1744, 1628, 1512, 1453, 1248, 1177, 754 cm⁻¹; ¹H NMR (400 MHz, CD₂Cl₂, mixture of rotamers): $\delta = 7.13$ (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, 0.7 H), 6.24 (dq, J=10.2, 1.0 Hz, 0.7 H), 6.17 (dq, J=9.8, 1.0 Hz, 0.3 H), 5.97 (d, J=9.3 Hz, 0.3 H), 5.29–5.34 (m, 1.7 H), 5.12 (d, J=11.7 Hz, 0.3 H), 5.01 (m, 0.3 H), 4.95 (dd, J=12.7, 2.0 Hz, 0.3 H), 4.88 (dd, J=12.7, 3.4 Hz, 0.7 H), 4.82 (d, J=11.2 Hz, 0.7 H), 4.75 (q, J=6.8 Hz, 0.7 H), 4.35 (dd, J = 8.3, 5.9 Hz, 0.7 H), 3.99–4.14 (m, 2.3 H), 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, 0.7 H), 3.27 (brs, 0.3 H), 3.04-3.17 (m, 2 H), 2.89 (dd, J=13.2, 5.4 Hz, 0.7 H), 2.87 (s, 0.9 H), 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, 1 H), 1.68-2.08 (m, 7 H), 1.94 (d, J=1.0 Hz, 2.1 H), 1.91 (d, J=1.0 Hz, 0.9 H), 1.21-1.30 (m, 2 H), 1.12 (d, J=6.8 Hz, 0.9 H), 1.10 (d, J = 6.8 Hz, 2.1 H), 1.07 (d, J = 6.8 Hz, 0.9 H), 1.04 (d, J = 6.8 Hz, 2.1 H), 0.97 (d, J=6.8 Hz, 2.1 H), 0.96 (d, J=6.8 Hz, 0.9 H), 0.90 (d, J=6.8 Hz, 0.9 H), 0.84--0.89 (m, 2 H), 0.86 (s, 6.3 H), 0.85 (s, 2.7 H), 0.81 (t, J =7.3 Hz, 2.1 H), 0.77 (t, J = 7.3 Hz, 0.9 H), 0.61 ppm (d, J = 6.8 Hz, 2.1 H); 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 mLmin⁻¹, UV detection at 220 nm) using an isocratic system of aqueous CH₃CN (80%). 1 and **epi-1** were eluted at $t_R = 11.1$ min and $t_R = 13.6$ min, respectively.

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