Synthetic Studies of Peptide-Polyketide Hybrid Natural Products, Odoamide and Stereocalpin A

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Contents

Preface

Peptide secondary metabolites are a class of important bioactive compounds. Various peptide secondary metabolites from natural sources, including cyclic and N-methylated peptides, show attractive biological activities such as antitumor, antiviral, antimalarial and anti-inflammatory activities.[1] Because of their favorable drug-like properties, good membrane permeability and biostability,[2] a number of medicinal chemistry studies of these peptides have been carried out.[3] For example, cyclosporin A, a cyclic peptide isolated from fungi, is currently used as an immunosuppressive drug to prevent graft rejection after organ transplantation (Figure 1).[4] Interestingly, cyclosporin A is administered orally even though it violates the Lipinski rules.[5] Another example of such peptides is PF1022A, a cyclic depsipeptide isolated from mycelia that shows potent anthelmintic activity.[6] Emodepside, which is used as a broad spectrum anthelmintic, is a semisynthetic derivative of PF1022A.[7]

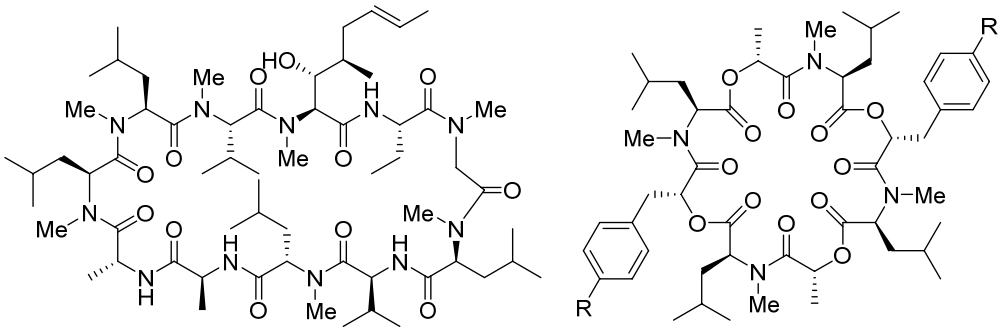

Figure 1. Cyclic peptides with potent biological activities.

Peptide secondary metabolites such as cyclosporin A are biosynthesized by nonribosomal peptide synthetases (NRPSs).[8] NRPSs organize assembly lines and construct linear nonribosomal peptides by sequential condensation of amino acids. The linear peptides are often cyclized and released from NRPSs. This biosynthetic strategy generates various peptide structures. Similarly, polyketides, one of the largest groups of natural products, are biosynthesized by multi-domain complexes of polyketide synthases (PKSs).[9] Polyketides arise from chain elongation by condensation of simple building blocks such as malonyl-CoA and methylmalonyl-CoA. Polyketides also possess diverse bioactivities including antitumor, antibiotic and antifungal activities.[9,10] For instance, erythromycin A is a well-known antibacterial agent (Figure 2).[11] Amphidinolide A, isolated from the marine dinoflagellate *Amphidinium* sp., shows antitumor activity.[12] Many related compounds of amphidinolide A with various structures have also been reported.[13]

It is interesting that NRPSs and PKSs share similar chain elongation systems, although the structures of peptide secondary metabolites and polyketides are apparently different. Many

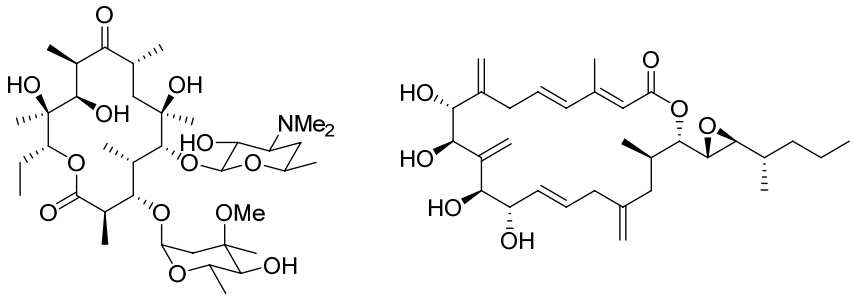

Figure 2. Bioactive polyketides.

previously reported peptide-polyketide hybrid natural products are synthesized by NRPS/PKS hybrid systems.[14] These hybrid compounds have unique and complex structures with a diverse range of biological activities, thus they are attractive targets of synthetic chemistry. An example of peptide-polyketide hybrid is emericellamide A, a 19-membered cyclic depsipeptide isolated from the marine-derived fungus *Emericella* sp. that shows antibacterial activity (Figure 3).[15] Aurilide is a 26-membered peptide-polyketide hybrid product isolated from the sea hare *Dolabella auricularia*.[16] Aurilide shows highly potent cytotoxic activity and some aurilide-class cyclic depsipeptides are reported. The related depsipeptides, aurilides B and C, from *Lyngbya majuscula* show potent cytotoxicity (Figure 4).[17] Other aurilide-class cyclic depsipeptides also possess highly potent antiproliferative activity against cancer cell lines. Kulokekahilide-2 is a structurally similar cytotoxic depsipeptide from the marine mollusk, *Philinopsis speciosa*, which exhibits two conformations of the 26-membered macrocycle in dichloromethane.[18] Lagunamides A and B from *Lyngbya majuscula* have antimalarial activity against *Plasmodium falciparum* at submicromolar concentrations.[19] Lagunamide C[20] and palau'amide[21] exhibit comparable cytotoxicity at nanomolar concentrations to other aurilide-class depsipeptides, although these peptides have unique 27-membered and 24-membered macrocycles, respectively.

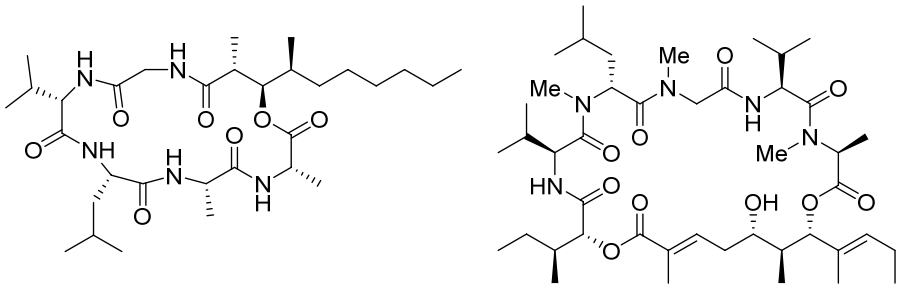

Figure 3. Peptide-polyketide hybrid natural products.

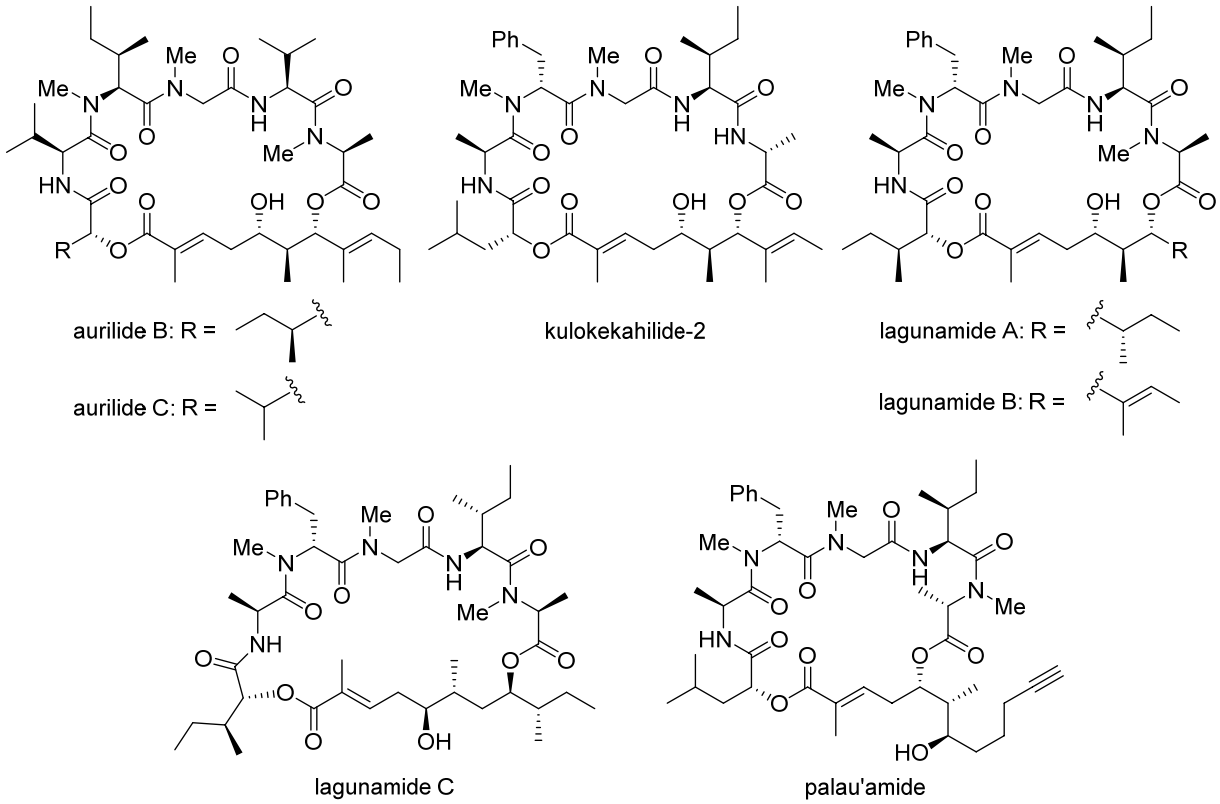

Figure 4. Structures of aurilide-class depsipeptides.

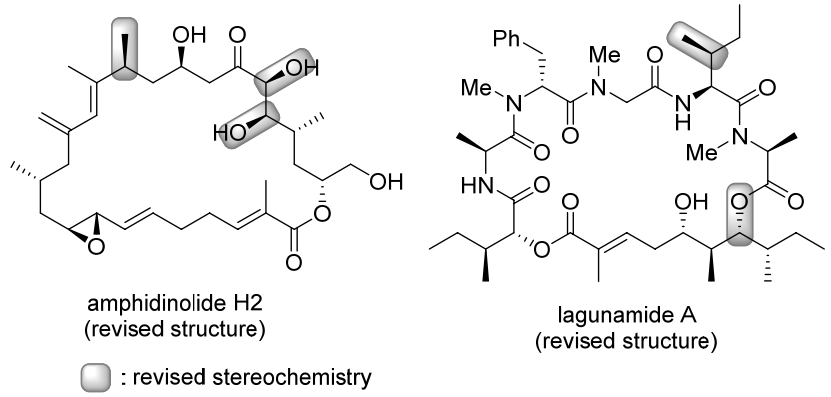

Figure 5. Revised structures of amphidinolide H2 and lagunamide A.

Various methods have been employed to determine the stereochemistry of these natural products. For example, the analysis of NOESY spectra and *j*-based configuration analysis (JBCA), which is a method for stereochemical assignment of acyclic substructures using proton-proton and carbon-proton spin-coupling constants,[22] are used for determination of absolute stereochemistry. Derivatizations including Mosher's method,[23] Marfey's method[24] and universal NMR database approach[25] are used for determination of relative stereochemistry. However, stereochemical misassignments of natural products have often occurred.[26] For example, amphidinolide H2 is a cytotoxic macrolide isolated from dinoflagellate *Amphidinium* sp. (Figure 5).[27] The stereochemistry of amphidinolide H2 was originally assigned by Mosher's method and analysis of the NOESY spectrum, but the revised stereochemistry was revealed by a later synthetic study.[28] The

stereochemistry of lagunamide A, an aurilide-class depsipeptide, was originally determined based on Marfey's method, analysis of NOESY spectrum and *j*-based configuration analysis.[19] Again, its stereochemistry was also revised in a subsequent synthetic study.[29] Whereas novel analytical techniques for stereochemical assignment have been developed, the synthetic approach is still one of the most reliable methods for validation of stereochemistry.

Some natural products exist as a mixture of isomers. FR900482, an antitumor antibiotic isolated from the fermentation broth of *Streptomyces sandaensis* No. 6897, exists as an equilibrium mixture of stereoisomers **A**, **B** and the 8-membered intermediate **C** (Figure 6).[30] For such natural products with interconvertible isomeric structures, it is even more difficult to determine the exact chemical structure(s) that contribute to their biological activity.

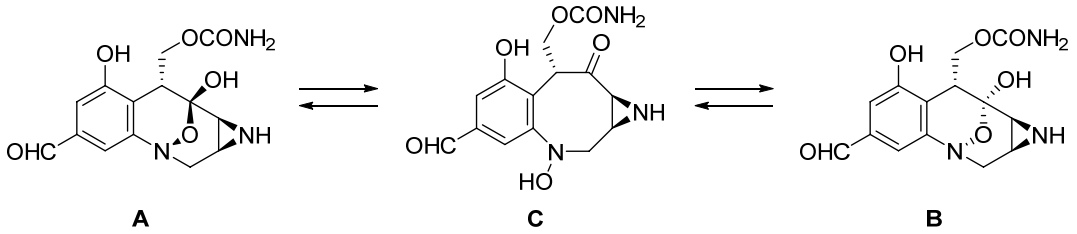

Figure 6. Structures of FR900482.

In this thesis, the author describes the synthetic studies of two peptide-polyketide hybrid natural products, namely the aurilide-class depsipeptides odoamide (a 26-membered cyclic depsipeptide) and stereocalpin A (a 12-membered cyclic depsipeptide) (Figure 7).

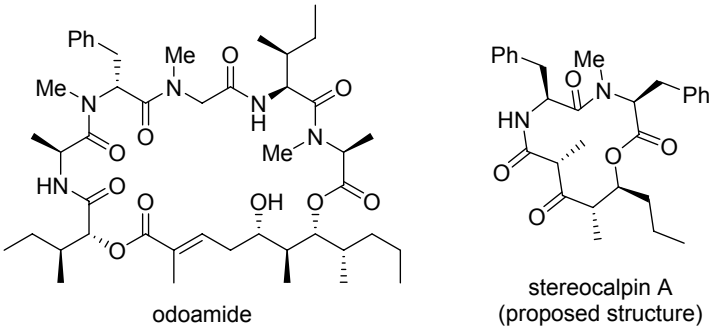

Figure 7. Synthetic targets in this thesis.

In Chapter 1, Section 1, the synthesis and stereochemical assignment of odoamide are described. Four possible diastereomers of the polyketide substructure were synthesized in a stereodivergent manner.

In Chapter 1, Section 2, the structure-activity relationship study of odoamide is described. Some derivatives showed comparable bioactivity to the parent odoamide.

In Chapter 2, the synthetic study of stereocalpin A is described. An efficient synthetic route to stereocalpin A was established and the stereochemical assignment was revised.

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Chapter 1. Synthetic and Structure-activity Relationship Studies of Odoamide

Section 1. Total Synthesis of Odoamide, a Novel Cyclic Depsipeptide from an Okinawan Marine Cyanobacterium

Summary

Odoamide is a cyclic depsipeptide with highly potent cytotoxic activity, which was isolated from the Okinawan marine cyanobacterium Okeania sp. It contains a 26-membered macrocycle composed of a polyketide moiety, a peptide segment and an isoleucic acid. To determine the stereochemical configurations in the polyketide substructure, the author synthesized four possible stereoisomers of the triol fragment, which can be obtained by lithium aluminum hydride-mediated reduction of odoamide. The first total synthesis of odoamide was also achieved. The structure of synthetic odoamide was verified by comparing its NMR spectra with those of the natural product.

Odoamide (**1**) is a cyclic depsipeptide from the Okinawan marine cyanobacterium *Okeania* sp. (Figure 1), which shows highly potent cytotoxic activity against HeLa S_3 cell lines.[1] The overall structure of the 26-membered macrocycle is similar to those of aurilide-class depsipeptides and comprises three substructures: a polyketide moiety, a peptide segment (Ala-D-MePhe-Sar-Ile-MeAla) and an isoleucic acid. At the initial stage of this study, the absolute configurations of the constituent amino acids and isoleucic acid in **1** were determined by chiral HPLC analysis and Marfey's analysis.[2] The absolute configuration of the 5,7-dihydroxy substructures of the polyketide

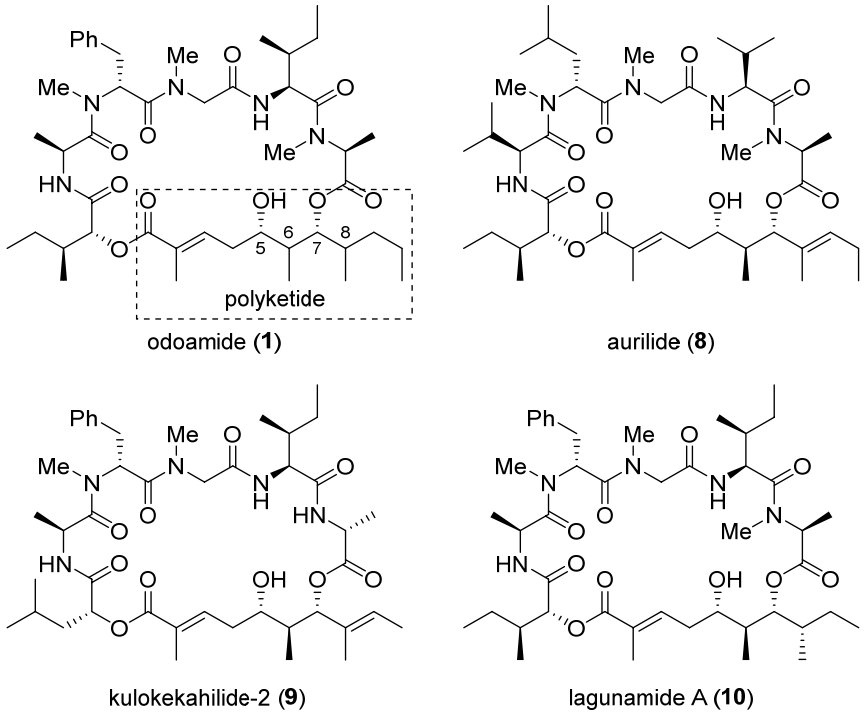
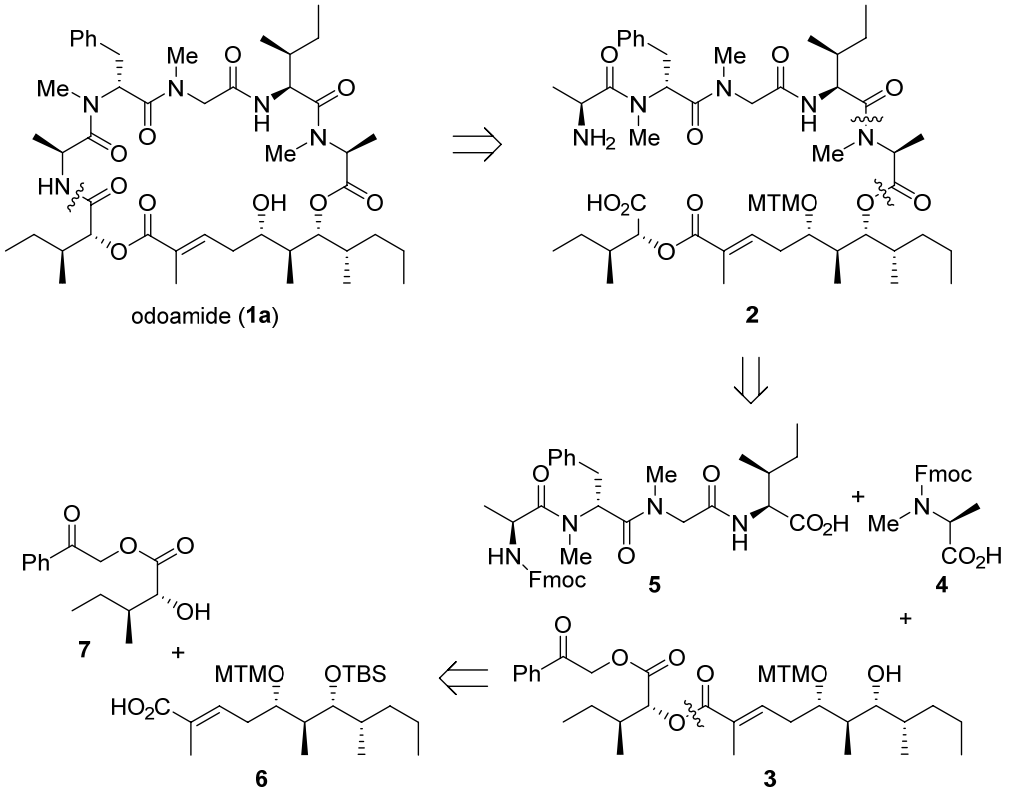


Figure 1. Structure of odoamide (**1**) and aurilide-class depsipeptides.

part were determined by Mosher's method[3] and derivatization to the acetonide,[4] while the remaining configurations of the polyketide were ambiguous. On the basis of these findings, the author carried out a synthetic study of odoamide to verify its structure and complete stereochemistry.

The synthetic strategy is illustrated in Scheme 1. During the cyclization of the linear peptide, epimerization and dimer formation are often problematic.[5] To avoid the less reactive process of N-methylated amide (CO-NMe) or ester bond formation compared with standard peptide bond (CO-NH) formation, the author chose macrocyclization of the Ala and D-*allo*-isoleucic acid residues of linear precursor **2** for odoamide (**1**).[6] Peptide **2** could be prepared by coupling of alcohol **3**, MeAla **4** and tetrapeptide **5**, which could be obtained by standard solid-phase peptide synthesis. The alcohol **3** could be synthesized by coupling of D-*allo*-isoleucic acid ester **7**[7] with a carboxylic acid **6**.



Scheme 1. Retrosynthetic analysis of odoamide (**1**).

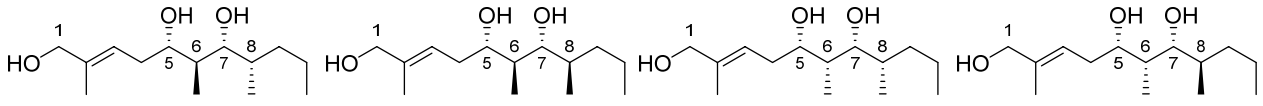
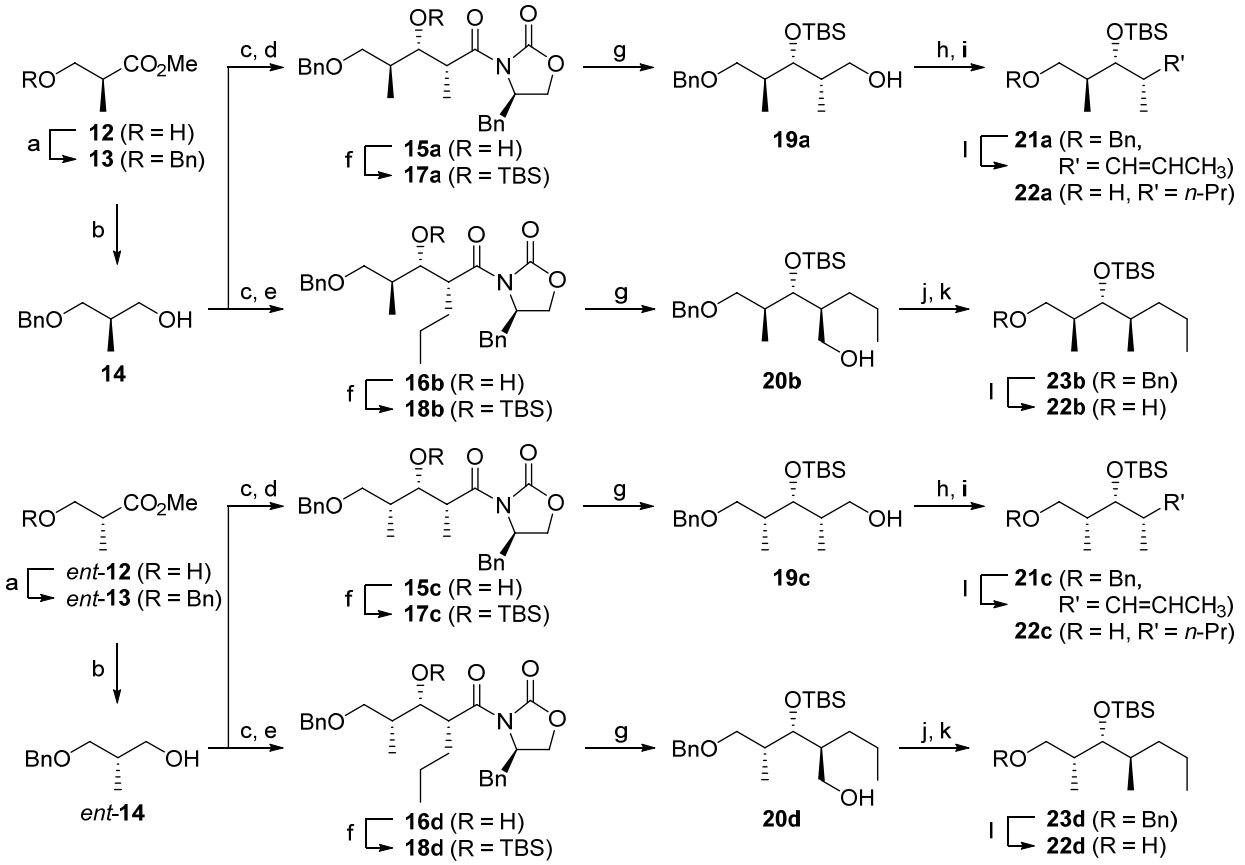


Figure 2. Possible triols obtained by $LiAlH_4$-mediated degradation of **1**.

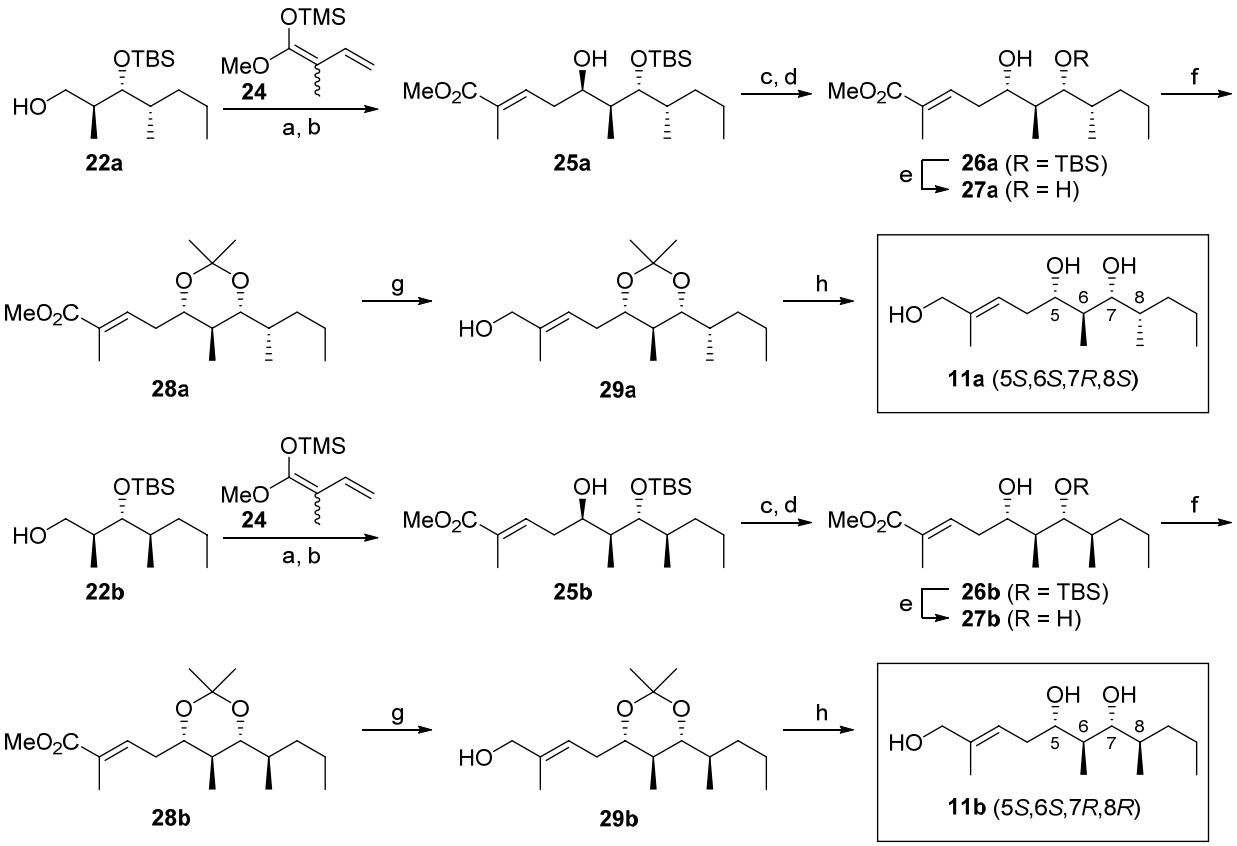
The stereochemistries of the polyketide part were unknown when the author started this study. Therefore, it was necessary to synthesize all the possible polyketide substructures in odoamide (**1**). The polyketide part in lagunamide A (**10**),[8] the closely related structural analogue of **1**, has 5*S*,7*R*-dihydroxy and 6*S*,8*S*-dimethyl substructures. Additionally, the aurilide-class depsipeptides **8**-**10**[9] possess the *syn*-1,3-diol moiety with a 5*S*-hydroxy configuration. On the basis of the structures of

these related molecules, the author expected that the plausible stereochemical configuration of the natural odoamide (**1**) was 5*S*,6*S*,7*R*,8*S*. Among these four stereocentres, the configuration at the C8-methyl group was ambiguous because attempts to determine it based on derivatization and NMR analysis of odoamide (**1**) were unsuccessful. It was also desirable to confirm the stereochemistry of the C6-methyl group. Therefore, the author designed four possible triol derivatives **11a-d**, which could be obtained by $LiAlH_4$-mediated reduction of natural odoamide **1** (Figure 2).



Scheme 2. Syntheses of alcohols **22a-d**. *Reagents and conditions*: (a) benzyl 2,2,2-trichloroacetimidate, TfOH, CH_2Cl_2, cyclohexane, 0 °C to rt, 88% (**13**) and 85% (*ent*-**13**); (b) $LiAlH_4$, THF, 0 °C, 75% (**14**) and 81% (*ent*-**14**); (c) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, –78 °C to 0 °C; (d) (*R*)-4-benzyl-3-propionyl-2-oxazolidinone, *n*-Bu_2BOTf, DIPEA, CH_2Cl_2, –78 °C to –10 °C, 83% (**15a**) and 85% (**15c**) (2 steps); (e) (*R*)-4-benzyl-3-pentanoyl-2-oxazolidinone, *n*-Bu_2BOTf, DIPEA, CH_2Cl_2, –78 °C to –10 °C, 69% (**16b**) and 72% (**16d**) (2 steps); (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 90% (**17a**), 90% (**18b**), 89% (**17c**) and 87% (**18d**); (g) $LiBH_4$, MeOH, THF, 0 °C to rt, 73% (**19a**), 72% (**20b**), 69% (**19c**) and 80% (**20d**); (h) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, –78 °C to 0 °C; (i) ethyltriphenylphosphonium bromide, *n*-BuLi, THF, rt, 72% (**21a**, *Z*/*E* = 7:1) and 69% (**21c**, *Z*/*E* = 7:1) (2 steps); (j) TsCl, Et_3N, $Me_3N{\cdot}HCl$, CH_2Cl_2, rt; (k) $LiAlH_4$, THF, 0 °C to rt, 57% (**23b**) and 70% (**23d**) (2 steps); (l) Pd/C, H_2, EtOH, rt, 85% (**22a**), 78% (**22b**), 92% (**22c**) and 85% (**22d**).

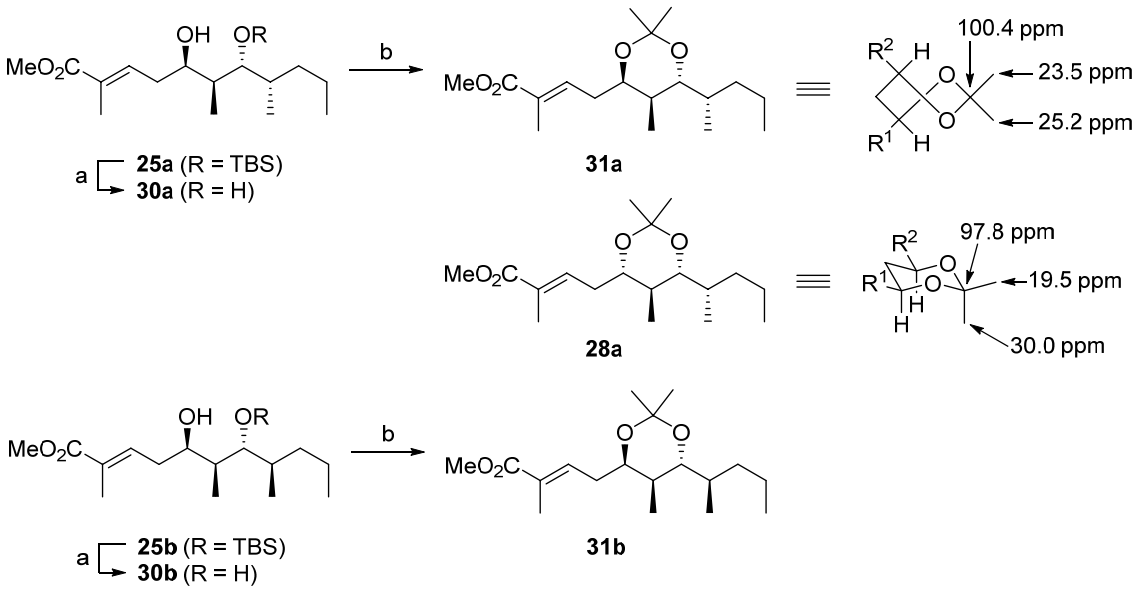
The triols **11a-d** were synthesized mostly based on the synthetic route for the triol substructure of kulokekahilide-2 (Schemes 2, 3 and 5).[9b] Preparation of (5*S*,6*S*,7*R*,8*S*)-triol **11a** and (5*S*,6*S*,7*R*,8*R*)-triol **11b** started from commercially available (*S*)-Roche ester **12**. (*S*)-Roche ester **12** was converted to alcohol **14** via benzyl protection[10] and $LiAlH_4$-mediated reduction (Scheme 2). After Swern oxidation, *n*-Bu_2BOTf-mediated Evans aldol reaction[11] of the resulting aldehyde provided *syn*-aldol products **15a** and **16b**. The requisite stereochemistries at the C8 chiral center in **11a** and **11b** were generated at this step by using propionyl- and pentanoyl-oxazolidinones, respectively. TBS protection of the secondary alcohol in **15a** and **16b** followed by removal of the chiral auxiliary with $LiBH_4$ gave alcohols **19a** and **20b**.[12] Swern oxidation of **19a** and the subsequent Wittig reaction of the resulting aldehyde with ethylidene-triphenylphosphorane provided olefin **21a** as an *E*/*Z* isomeric mixture. Hydrogenation of **21a** in the presence of Pd/C afforded the key alcohol **22a** with a *erythro*/*threo*-configuration. Separately, tosylation of **20b** followed by $LiAlH_4$-mediated reduction afforded benzyl ether **23b**, which was converted to the corresponding alcohol **22b** (with a *erythro*/*erythro*-configuration) by hydrogenation. Swern oxidation of **22a** followed by Mukaiyama



Scheme 3. Syntheses of triols **11a** and **11b**. *Reagents and conditions*: (a) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, –78 °C to 0 °C; (b) **24**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, Et_2O, –78 °C, 85% (**25a**) and 71% (**25b**) (2 steps); (c) Dess-Martin periodinane, CH_2Cl_2, rt; (d) $NaBH_4$, MeOH, –78 °C, 83% (**26a**, dr >97:3) and 71% (**26b**, dr >97:3) (2 steps); (e) TBAF, THF, rt, 81% (**27a**) and 93% (**27b**); (f) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, rt, 90% (**28a**) and 90% (**28b**); (g) DIBAL, toluene, THF, –78 °C, 90% (**29a**) and 96% (**29b**); (h) HCl, MeOH, H_2O, rt, 51% (**11a**) and 93% (**11b**).

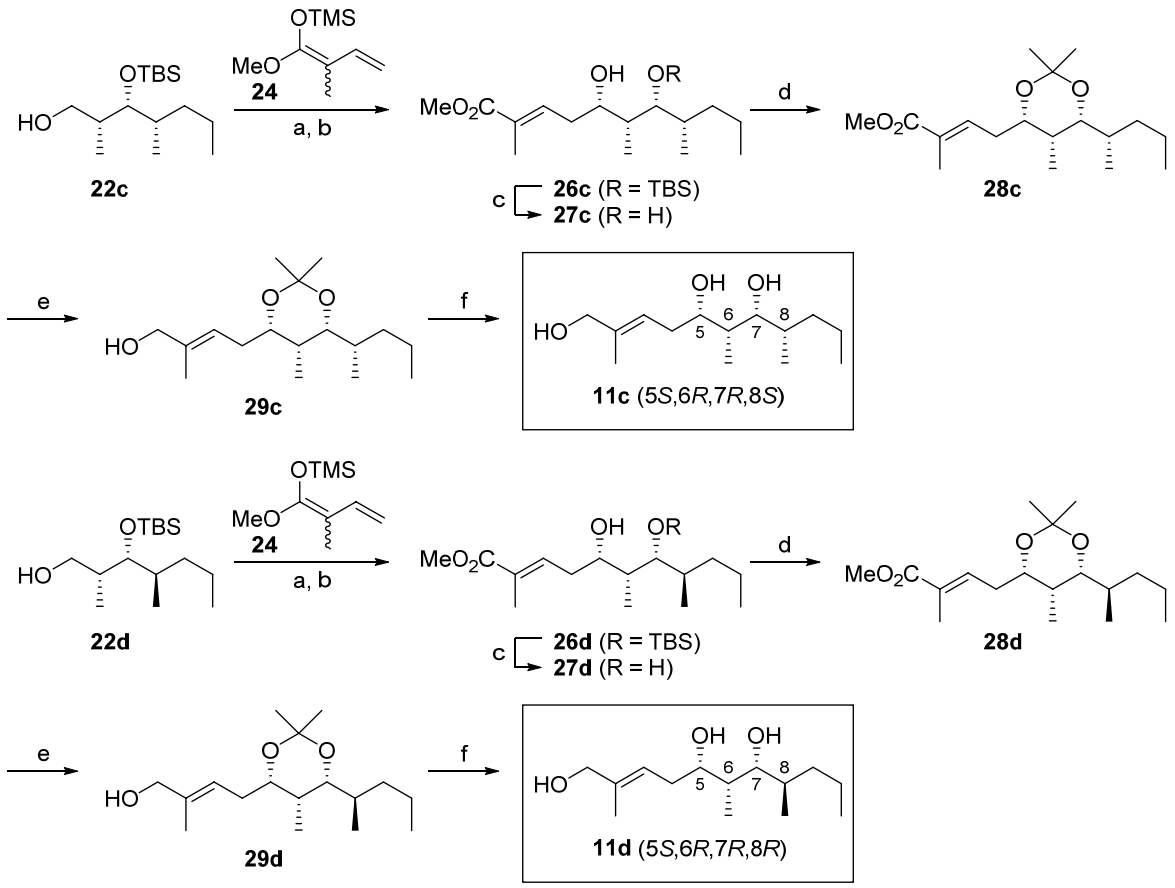
aldol reaction[13] with 1-methoxy-2-methyl-1-trimethylsiloxy-1,3-butadiene (**24**)[14] produced methyl ester **25a** with (5*R*)-hydroxy group (dr >99:1) (Scheme 3). The C5 configuration of **25a** was inversed by a Dess-Martin oxidation and stereoselective reduction with $NaBH_4$ to give **26a**. TBS deprotection of **26a** provided 1,3-diol **27a**, which was treated with 2,2-dimethoxypropane in the presence of PPTS to give acetonide **28a**. Reduction of **28a** with DIBAL and the subsequent removal of acetonide yielded the expected triol **11a**.

The stereochemistries of 5-hydroxy group in alcohols **25a** and **26a** were confirmed by the NMR analysis of the corresponding acetonides. The acetonide **31a** derived from **25a** was prepared in a similar manner (Scheme 4). It is known that ^{13}C NMR chemical shifts of the ketal methyl groups in *syn*- and *anti*-1,3-diol acetonides are different.[4] A *syn*-acetonide shows different chemical shifts between the two ketal methyl groups (e.g., 19.5 and 30.0 ppm for **28a**) because of its predominant chair conformation. In contrast, an *anti*-acetonide shows close chemical shifts (e.g., 23.5 and 25.2 ppm for **31a**), because the *anti*-isomer exists in a twist-boat conformation to avoid the 1,3-diaxial interaction that would be present in the chair conformation. Accordingly, it was demonstrated that 1,3-diol **27a**, the precursor of the acetonide **28a** has the desired 1,3-*syn* configuration.



Scheme 4. Stereochemical assignments of 1,3-diols. *Reagents and conditions*: (a) TBAF, THF, rt, 81% (**30a**) and 81% (**30b**); (b) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, rt, 86% (**31a**) and 78% (**31b**).

Triol **11b** was obtained from **22b** by the identical protocol to synthesis of triol **11a** (Scheme 3). The stereochemistries of 5-hydroxy group of the intermediates **25b** and **26b** were determined by the identical NMR analysis of the acetonides **31b** and **28b**. Similarly, triols **11c** and **11d** were prepared starting from (*R*)-Roche ester *ent*-**12** in a similar manner (Schemes 2 and 5). In these processes, the desired 5*S*-hydroxy configurations of **26c** and **26d** were constructed directly by Mukaiyama *syn*-aldol reaction without inversion of their C5 stereochemistries.[15]



Scheme 5. Syntheses of triols **11c** and **11d**. *Reagents and conditions*: (a) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, –78 °C to 0 °C; (b) **24**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, Et_2O, –78 °C, 54% (**26c**) and 69% (**26d**) (2 steps); (c) TBAF, THF, rt, 93% (**27c**) and 83% (**27d**); (d) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, rt, 77% (**28c**) and 93% (**28d**); (e) DIBAL, toluene, THF, –78 °C, 98% (**29c**) and 93% (**29d**); (f) HCl, MeOH, H_2O, rt, 75% (**11c**) and 96% (**11d**).

With the four possible diastereomers of the triols **11a-d** in hand, the author compared the ^{1}H NMR spectra with that of natural odoamide-derived triol (Figure 3). The spectrum of **11a** was identical with that of the triol derived from natural **1**. The relative stereochemistry of the polyketide substructure in **1** was assigned as 5*S**,6*S**,7*R**,8*S**. The absolute stereochemistry of the 5-hydroxy group of the natural odoamide-derived triol had been determined as *S* by the ^{1}H NMR analysis of the MTPA esters.[3] Taken together, the absolute configurations of the natural odoamide-derived triol were determined as 5*S*,6*S*,7*R*,8*S*, which is identical to that of lagunamide A (**10**).[1]

The author attempted the total synthesis of odoamide using (5*S*,6*S*,7*R*,8*S*)-ester **26a**, which is the synthetic intermediate of **11a**. Synthesis of odoamide (**1**) began with methylthiomethyl (MTM) protection of the secondary hydroxy group in **26a** to give thioacetal **32** (Scheme 6).[16,17] Hydrolysis of **32** with LiOH followed by coupling with D-*allo*-isoleucic acid phenacyl ester (**7**) with 2-methyl-6-nitrobenzoic anhydride (MNBA)[18] and DMAP afforded ester **33**. The TBS group in **33** was deprotected with HF·pyridine to produce the corresponding alcohol **3**. In the coupling of Fmoc-MeAla-OH **4** with **3** using DCC and DMAP, significant epimerization occurred. The coupling using

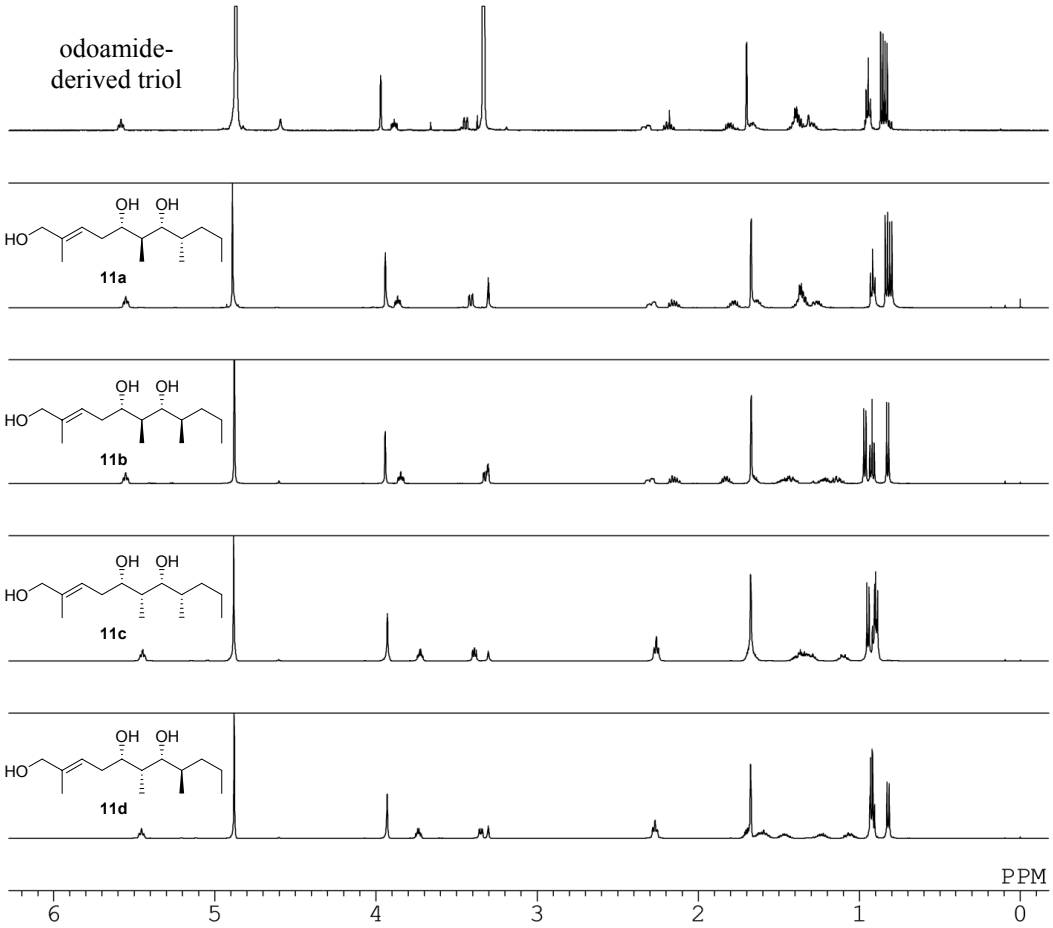


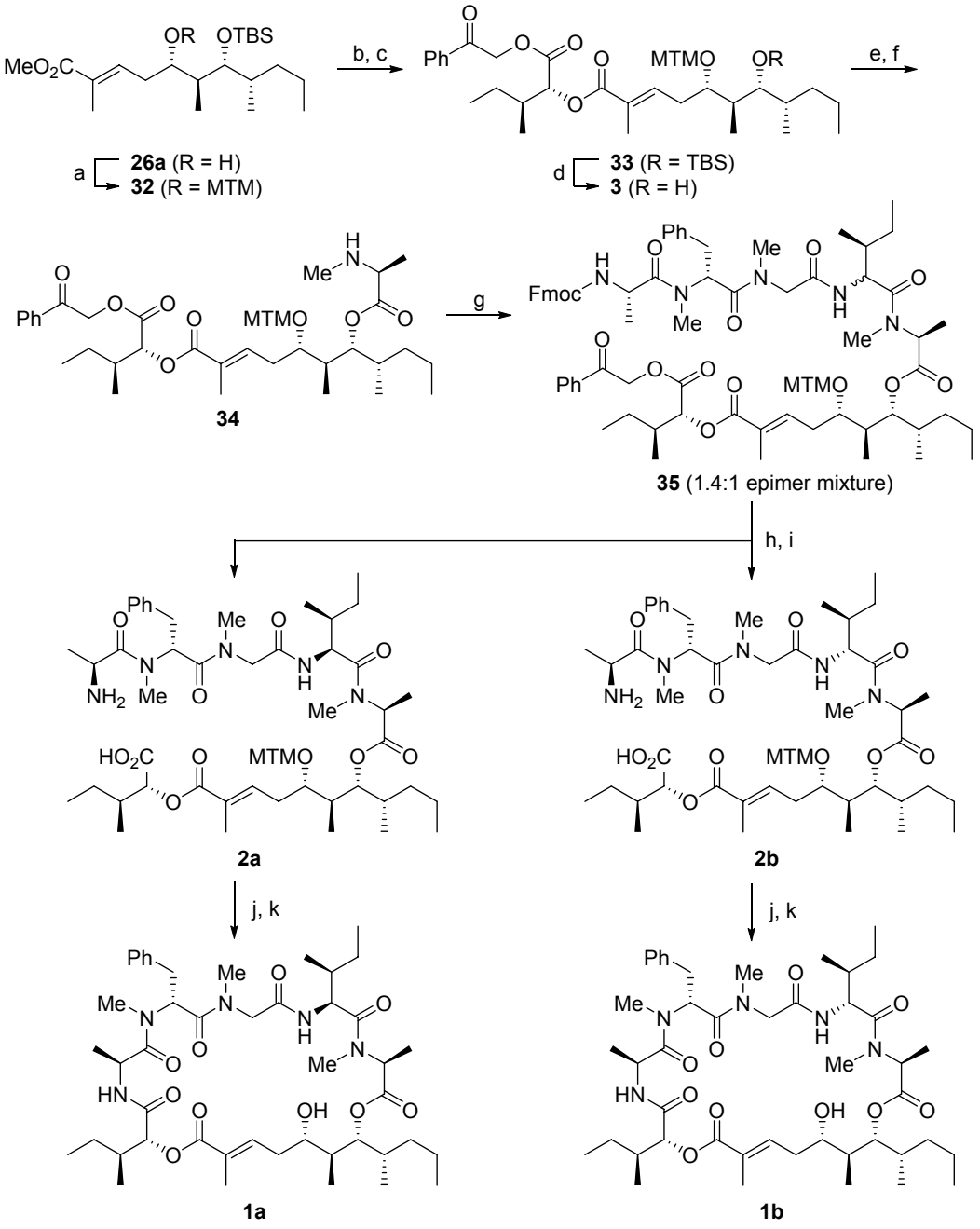
Figure 3. Comparison of ^{1}H NMR spectra between synthetic triols **11a-d** and natural product-derived triol (in CD_3OD).

Fmoc-MeAla-Cl[19] with **3** in the presence of DIPEA followed by Fmoc-deprotection with Et_2NH gave amine **34** in 54% yield (two steps) without epimerization.

The tetrapeptide **5** was conjugated with **34** using EDCI-HOAt to afford **35** as a 1.4:1 epimeric mixture at the α-position of Ile.[20] After removal of phenacyl (with Zn and AcOH) and Fmoc groups (with Et_2NH), the epimer mixture of the linear peptides was separated into the desired **2a** (major, L-Ile) and undesired **2b** (minor, D-*allo*-Ile) by HPLC purification. Cyclization of **2a** and **2b** with HATU followed by deprotection of the MTM group with $AgNO_3$ and 2,6-lutidine gave the desired odoamide **1a** and its diastereomer **1b**. Both cyclizations of **2a** and **2b** proceeded smoothly within five hours without epimarization. The configurations of L-Ile and D-*allo*-Ile in peptides **1a** and **1b**, respectively, were determined by Marfey analysis and ^{1}H NMR analysis after acid hydrolysis.

The author analyzed the ^{1}H NMR and ^{13}C NMR spectra of the natural and synthetic products (Figures 4 and 5). The NMR spectra of the synthetic odoamide **1a** were identical with those of the natural product **1**, suggesting the chemical structure of odoamide was the same as **1a**. The cytotoxicity of synthetic **1a** and **1b** against A549 cells was also evaluated by the MTS assay. Peptide **1a** showed highly potent cytotoxicity (IC_{50} = 2.1 nM), corroborating the correct structural

assignment of odoamide (**1**). However, the epimer peptide **1b** showed significantly less potent antiproliferative activity (IC_{50} = 0.54 μM), suggesting that the L-Ile configuration is crucial for the cytotoxic activity of odoamide.



Scheme 6. Syntheses of odoamide (**1a**) and its epimer **1b**. *Reagents and condition*s: (a) Ac_2O, DMSO, AcOH, rt, 59%; (b) LiOH, THF, MeOH, H_2O, 0 °C to 30 °C; (c) **7**, MNBA, DMAP, CH_2Cl_2, rt, 87% (2 steps); (d) HF·pyridine, THF, pyridine, 0 °C to rt, 74%; (e) Fmoc-MeAla-Cl, DIPEA, 1,2-dichloroethane, 40 °C; (f) Et_2NH, MeCN, 0 °C to rt, 54% (2 steps); (g) **5**, EDCI·HCl, HOAt, CH_2Cl_2, 0 °C to rt; (h) Zn, CH_3COOH, H_2O, EtOAc, rt; (i) Et_2NH, MeCN, 0 °C to rt, 30% (**2a**) and 24% (**2b**) (3 steps); (j) HATU, HOAt, collidine, DMF, rt; (k) $AgNO_3$, 2,6-lutidine, THF, H_2O, rt to 70 °C, 85% (**1a**) and 62% (**1b**) (2 steps).

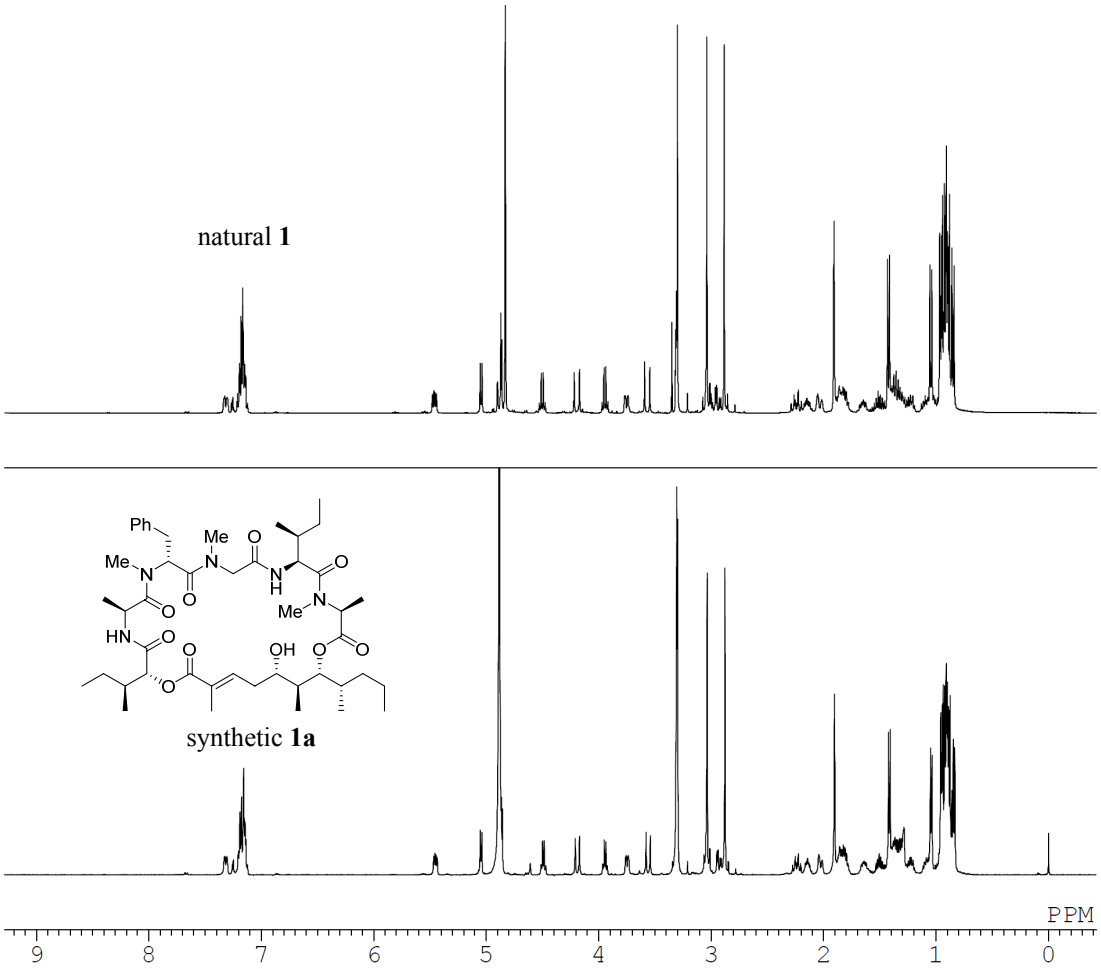


Figure 4. Comparison of the ^{1}H NMR spectra between the natural compound **1** and the synthetic **1a** (in CD_3OD).

In conclusion, the author assigned the stereochemistry of the polyketide substructure in cytotoxic cyclic depsipeptide odoamide (**1**) as 5*S*,6*S*,7*R*,8*S* configurations by the comparative ^{1}H NMR analysis of the synthetic triols and natural product-derived triol. On the basis of this findings, the author accomplished the synthesis of the putative structure of odoamide using the polyketide component. The NMR spectra of the synthetic peptide **1a** were identical with those of the natural odoamide **1**. Accordingly, the full structural assignment and first total synthesis of odoamide were achieved.

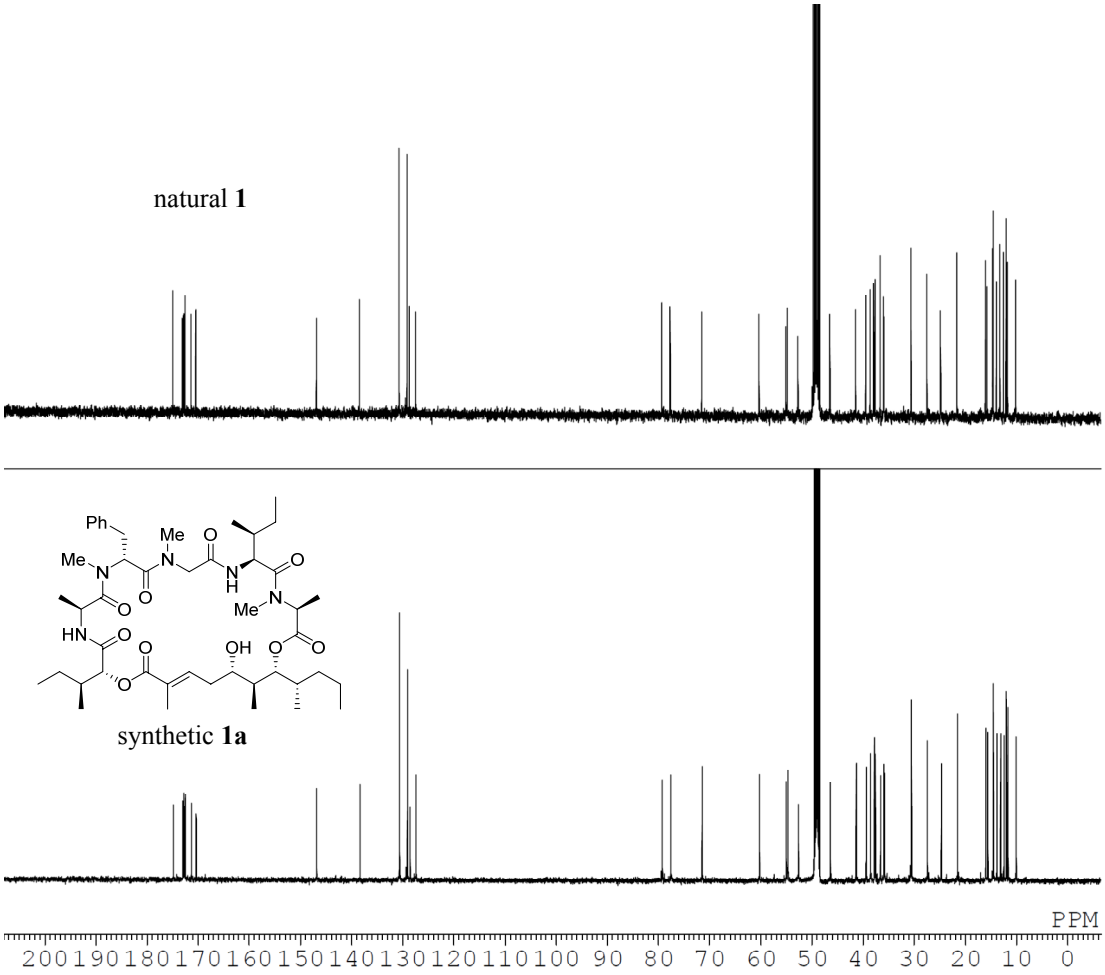


Figure 5. Comparison of the ^{13}C NMR spectra between the natural compound **1** and the synthetic **1a** (in CD_3OD).

Experimental Section

General Methods

^{1}H NMR spectra were recorded using a JEOL ECA-500 spectrometer. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in $CDCl_3$) as an internal standard. ^{13}C NMR spectra were recorded using a JEOL ECA-500 spectrometer and referenced to the residual solvent signal. ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (br: broad, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet), number of protons, and coupling constants. Melting points were measured by a hot stage melting points apparatus (uncorrected). Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer or a Shimadzu LC-ESI-IT-TOF-MS equipment. IR spectra were determined on a JASCO FT/IR-4100 spectrometer. Optical rotations were measured with a JASCO P-1020 polarimeter. For flash chromatography, Wakogel C-300E (Wako) was employed. For analytical HPLC, a Cosmosil 5C18-ARII column (4.6 × 250 mm, Nacalai Tesque, Inc.) was employed with a linear gradient of CH_3CN (with 0.1% (v/v) TFA, except for the analysis of final products **1a,b** using solvents without TFA) in H_2O at a flow rate of 1 mL/min, and eluting products were detected by UV at 220 nm. Preparative HPLC was performed using a Cosmosil 5C18-ARII preparative column (20 × 250 mm, Nacalai Tesque, Inc.) at a flow rate of 8 mL/min. The purity of the peptides **1a,b** were determined by HPLC analysis (>95%).

Methyl (*S*)-3-benzyloxy-2-methylpropanoate (13). To a stirred solution of **12** (11.8 g, 100.0 mmol) in CH_2Cl_2 (250 mL) under argon were added benzyl 2,2,2-trichloroacetimidate (20.4 mL, 110.0 mmol) in cyclohexane (500 mL) and triflic acid (3.5 mL, 40.0 mmol) at 0 °C. After 10 min, the reaction mixture was warmed to room temperature and stirred for 18 h. The precipitated trichloroacetamide was filtered off. The filtrate was washed with aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (50:1 to 10:1) to give compound **13** (18.4 g, 88%) as a colorless oil. The spectral data were in good agreement with those previously reported.[12]

(*R*)-3-Benzyloxy-2-methylpropan-1-ol (14). To a stirred suspension of $LiAlH_4$ (5.0 g, 132.6 mmol) in THF (295 mL) under argon was added dropwise a solution of **13** (18.4 g, 88.4 mmol) in THF (295 mL) at 0 °C. After being stirred for 1 h, the reaction mixture was poured into a saturated aqueous solution of sodium potassium tartrate at 0 °C and stirred overnight at room temperature. The whole was extracted with Et_2O and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (9:1 to 3:1) to give compound **14** (12.0 g, 75%) as a colorless oil. The spectral data were in good agreement with those previously reported.[17]

(*R*)-4-Benzyl-3-[(2*R*,3*S*,4*S*)-5-benzyloxy-3-hydroxy-2,4-dimethylpentanoyl]oxazolidin-2-one (15a). To a stirred solution of oxalyl chloride (0.93 mL, 10.8 mmol) in CH_2Cl_2 (21.6 mL) under

argon was added DMSO (1.53 mL, 21.6 mmol) in CH_2Cl_2 (3.6 mL) at –78 °C. After being stirred for 30 min, a solution of **14** (972.6 mg, 5.4 mmol) in CH_2Cl_2 (18.6 mL) was added dropwise and stirred at –78 °C for 1 h. (*i*-Pr)$_2$NEt (4.70 mL, 27.0 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. The mixture was quenched with aqueous saturated NH_4Cl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give the corresponding aldehyde, which was used without further purification. To a stirred solution of (*R*)-4-benzyl-3-propionyl-2-oxazolidinone (1.25 g, 5.4 mmol) in CH_2Cl_2 (26.8 mL) under argon were added *n*-Bu_2BOTf (1.0 M in CH_2Cl_2; 5.8 mL, 5.8 mmol) and (*i*-Pr)$_2$NEt (1.1 mL, 6.3 mmol) at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to 0 °C and stirred for 30 min. To this solution was added the above aldehyde in CH_2Cl_2 (11.4 mL) at –78 °C. After being stirred for 1 h, the mixture was warmed to –10 °C and stirred for 1 h. The mixture was quenched with pH 7.0 phosphate buffer solution (5.4 mL) and 30% H_2O_2 in MeOH (1:2, 12.2 mL) and stirred overnight at room temperature. The whole was concentrated under reduced pressure and extracted with CH_2Cl_2. The extract was washed with aqueous saturated $NaHCO_3$, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (5:1 to 3:1) to give compound **15a** (1.86 g, 83%, dr >15:1) as a colorless oil. The diastereomers were separated by column chromatography. The spectral data were in good agreement with those previously reported.[17]

(*R*)-4-Benzyl-3-[(2*R*,3*S*,4*S*)-5-benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentanoyl]-oxazolidin-2-one (17a). To a stirred solution of **15a** (10.7 g, 26.0 mmol) in CH_2Cl_2 (104 mL) under argon were added TBSOTf (7.2 mL, 31.1 mmol) and 2,6-lutidine (6.0 mL, 51.9 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2.5 h. The reaction was quenched with 1N HCl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (9:1) to give compound **17a** (12.2 g, 90%) as a colorless oil. The spectral data were in good agreement with those previously reported.[17]

(2*S*,3*R*,4*S*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentan-1-ol (19a). To a stirred solution of **17a** (699.8 mg, 1.33 mmol) in THF (6.7 mL) and MeOH (0.16 mL, 3,99 mmol) under argon was added $LiBH_4$ (86.9 mg, 3.99 mmol) at 0 °C. After being stirred for 10 min, the reaction mixture was warmed to room temperature. After 4 h, the mixture was cooled to 0 °C and quenched with aqueous saturated NH_4Cl. The whole was extracted with EtOAc and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (9:1) to give compound **19a** (341.8 mg, 73%) as a colorless oil. The spectral data were in good agreement with those previously reported.[17]

(4*S*,5*R*,6*S*)-7-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-4,6-dimethylhept-2-ene (21a). To a stirred solution of oxalyl chloride (7.3 mL, 85.6 mmol) in CH_2Cl_2 (428 mL) under argon was added DMSO

(12.2 mL, 171.2 mmol) in CH_2Cl_2 (29 mL) at –78 °C. After being stirred for 30 min, a solution of **19a** (15.1 g, 42.8 mmol) in CH_2Cl_2 (148 mL) was added dropwise and stirred at –78 °C for 1.5 h. (*i*-Pr)$_2$NEt (37.3 mL, 214.0 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. The mixture was quenched with aqueous saturated NH_4Cl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give the corresponding aldehyde, which was used without further purification. To a stirred suspension of ethyltriphenylphosphonium bromide (33.4 g, 89.9 mmol) in THF (360 mL) under argon was added *n*-BuLi (1.6 M in hexane; 55.2 mL, 85.6 mmol) at room temperature. After being stirred for 30 min, a solution of the above aldehyde in THF (86 mL) was added and the reaction mixture was stirred for 1.5 h. The mixture was quenched with aqueous saturated $NaHCO_3$. The whole was extracted with EtOAc and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was filtrated through a short pad of silica gel with hexane-EtOAc (9:1). Further purification by flash chromatography over silica gel with hexane-$CHCl_3$ (8:1) gave compound **21a** as a diastereomixture (11.2 g, 72%, *Z*/*E* = 7:1): colorless oil: $[\alpha]^{26}_D$ +4.17 (*c* 1.26, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.02 (s, 0.8H), 0.04 (s, 2.6H), 0.04 (s, 2.6H), 0.88 (s, 1.2H), 0.89 (s, 7.8H), 0.92 (d, *J* = 6.9 Hz, 2.6H), 0.94 (d, *J* = 6.9 Hz, 0.4H), 0.97-0.99 (m, 3.0H), 1.57 (dd, *J* = 6.9, 1.7 Hz, 2.6H), 1.62 (d, *J* = 4.0 Hz, 0.4H), 1.97-2.06 (m, 1.0H), 2.27-2.31 (m, 0.1H), 2.63-2.70 (m, 0.9H), 3.24-3.28 (m, 1.0H), 3.43-3.45 (m, 1.0H), 3.55-3.58 (m, 1.0H), 4.47 (s, 2.0H), 5.20-5.25 (m, 1.0H), 5.31-5.37 (m, 1.0H), 7.25-7.33 (m, 5.0H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.1, –3.9, –3.8, 13.0, 14.9, 15.2, 15.9, 17.2, 18.0, 18.4, 26.1(3C), 26.2 (3C), 35.0, 37.8, 38.4, 40.4, 72.7, 72.9, 78.4, 122.6, 123.9, 127.3, 127.5 (2C), 128.2 (2C), 134.9, 135.5, 138.8; HRMS (ESI-TOF) calcd for $C_{22}H_{38}NaO_2Si$ $[M+Na]^+$: 385.2533; found: 385.2533.

(2*S*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylheptan-1-ol (22a). To a stirred solution of **21a** (1.1 g, 3.1 mmol) in EtOH (30.9 mL) was added 10% Pd/C (657.7 mg, 0.6 mmol) at room temperature and the mixture was flushed with H_2 gas (1 atm). After being stirred for 1 h, the reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (10:1) to give compound **22a** (722.8 mg, 85%) as a colorless oil: $[\alpha]^{27}_D$ –20.0 (*c* 1.05, $CHCl_3$); IR (neat): 3374 (OH); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.08 (s, 3H), 0.11 (s, 3H), 0.89-0.93 (m, 15H), 0.96 (d, *J* = 6.9 Hz, 3H), 1.12-1.19 (m, 1H), 1.20-1.26 (m, 1H), 1.36-1.47 (m, 2H), 1.59-1.66 (m, 1H), 1.84-1.88 (m, 1H), 2.61 (dd, *J* = 6.3, 5.2 Hz, 1H), 3.50 (dd, *J* = 5.7, 4.0 Hz, 1H), 3.56-3.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.1, –4.0, 14.3, 15.1, 16.4, 18.3, 20.8, 26.1 (3C), 35.3, 37.5, 38.1, 66.3, 81.2; HRMS (ESI-TOF) calcd for $C_{15}H_{34}NaO_2Si$ $[M+Na]^+$: 297.2220; found: 297.2220.

Methyl (5*R*,6*S*,7*R*,8*S*,*E*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundec-2-enoate (25a). To a stirred solution of (*i*-Pr)$_2$NH (7.1 mL, 50.8 mmol) in THF (104 mL) under argon was added *n*-BuLi (2.6 M in hexane; 19.5 mL, 50.8 mmol) at 0 °C. After 20 min, methyl tiglate (5.6 mL, 46.2 mmol) and TMSCl (8.8 mL, 69.3 mmol) in THF (16 mL) were added successively at –78 °C. The reaction was continued for 1 h at this temperature and for additional 1.5 h at room

temperature. Then, pentane and cold saturated $NaHCO_3$ were added to the reaction mixture. The whole was extracted with pentane and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give compound **24**, which was used without further purification.[14] To a stirred solution of oxalyl chloride (2.6 mL, 30.8 mmol) in CH_2Cl_2 (154 mL) under argon was added DMSO (4.4 mL, 61.6 mmol) in CH_2Cl_2 (10 mL) at –78 °C. After being stirred for 30 min, a solution of **22a** (4.2 g, 15.4 mmol) in CH_2Cl_2 (53 mL) was added dropwise and stirred at –78 °C for 1.5 h. $(i\text{-Pr})_2NEt$ (21.5 mL, 123.2 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. The mixture was quenched with aqueous saturated NH_4Cl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give the corresponding aldehyde, which was used without further purification. To a stirred solution of the above aldehyde in CH_2Cl_2 (118 mL) and Et_2O (11.8 mL) under argon were added diene **24** and $BF_3{\cdot}OEt_2$ (2.9 mL, 23.1 mmol) at –78 °C. After being stirred for 2 h, a mixture of THF/H_2O/1N HCl (5:1:0.4 v/v, 77 mL) was added to the reaction mixture. The mixture was warmed to room temperature and stirred for 15 min. Then, aqueous saturated $NaHCO_3$ was added to the mixture at 0 °C. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (20:1 to 10:1) to give compound **25a** (5.1 g, 85%) as a colorless oil: $[\alpha]^{26}_D$ –0.35 (*c* 1.02, $CHCl_3$); IR (neat): 3503 (OH), 1716 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.10 (s, 3H), 0.12 (s, 3H), 0.88-0.92 (m, 15H), 1.02 (d, *J* = 7.4 Hz, 3H), 1.04-1.12 (m, 1H), 1.15-1.26 (m, 1H), 1.33-1.41 (m, 1H), 1.42-1.49 (m, 1H), 1.66-1.70 (m, 1H), 1.71-1.77 (m, 1H), 1.87 (s, 3H), 2.20-2.26 (m, 1H), 2.39-2.45 (m, 1H), 3.54-3.57 (m, 2H), 3.73 (s, 3H), 4.21-4.24 (m, 1H), 6.78-6.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –3.9, –3.8, 12.2, 12.6, 14.3, 16.4, 18.3, 20.7, 26.1 (3C), 34.2, 35.4, 37.6, 37.8, 51.7, 70.4, 83.0, 129.0, 138.8, 168.4; HRMS (ESI-TOF) calcd for $C_{21}H_{42}NaO_4Si$ $[M+Na]^+$: 409.2745; found: 409.2744.

Methyl (5*S*,6*S*,7*R*,8*S*,*E*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundec-2-enoate (26a). To a stirred solution of **25a** (10.7 g, 27.8 mmol) in CH_2Cl_2 (199 mL) under argon was added Dess-Martin periodinane (17.7 g, 41.7 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was quenched with aqueous saturated $NaHCO_3$ and $Na_2S_2O_3$. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (25:1 to 15:1) to give the corresponding ketone, which was used without further purification. To a stirred solution of the above ketone in MeOH (263 mL) under argon was added $NaBH_4$ (6.0 g, 157.8 mmol) at –78 °C. After being stirred for 20 h, the reaction mixture was quenched with aqueous saturated NH_4Cl and concentrated under reduced pressure. The residue was extracted with EtOAc and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (10:1) to give compound **26a** (8.9 g, 83%, dr

>97:3) as a colorless oil: $[\alpha]^{27}_D$ –9.16 (*c* 1.18, $CHCl_3$); IR (neat): 3522 (OH), 1716 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.10 (s, 3H), 0.12 (s, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.88-0.93 (m, 15H), 1.11-1.17 (m, 1H), 1.22-1.29 (m, 1H), 1.33-1.41 (m, 2H), 1.58-1.64 (m, 1H), 1.73-1.77 (m, 1H), 1.86 (s, 3H), 2.26-2.32 (m, 1H), 2.42-2.44 (m, 1H), 3.49 (dd, *J* = 5.4, 3.7 Hz, 1H), 3.52 (s, 1H), 3.68-3.71 (m, 1H), 3.73 (s, 3H), 6.94-6.97 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.2, –3.9, 12.7, 14.3, 14.8, 16.1, 18.2, 20.7, 26.0 (3C), 33.5, 35.5, 38.6, 41.9, 51.6, 73.0, 81.5, 128.7, 139.3, 168.5; HRMS (ESI-TOF) calcd for $C_{21}H_{42}NaO_4Si$ $[M+Na]^+$: 409.2745; found: 409.2743.

Methyl (5*S*,6*S*,7*R*,8*S*,*E*)-5,7-dihydroxy-2,6,8-trimethylundec-2-enoate (27a). To a stirred solution of **26a** (229.4 mg, 0.59 mmol) in THF (5.9 mL) under argon was added TBAF (1 M in THF; 1.8 mL, 1.8 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was quenched with aqueous saturated NH_4Cl. The whole was extracted with Et_2O and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (5:1 to 2:1) to give compound **27a** (130.6 mg, 81%) as a colorless oil: $[\alpha]^{26}_D$ –6.85 (*c* 0.95, $CHCl_3$); IR (neat): 3362 (OH), 1712 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.79 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H), 1.24-1.42 (m, 4H), 1.67-1.75 (m, 2H), 1.87 (s, 3H), 2.35-2.41 (m, 1H), 2.46-2.51 (m, 1H), 2.82 (br s, 1H), 3.54 (dd, *J* = 9.5, 2.0 Hz, 1H), 3.74 (s, 3H), 3.82 (td, *J* = 7.7, 3.4 Hz, 1H), 4.04 (br s, 1H), 6.91-6.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.8, 12.7, 12.9, 14.2, 20.4, 34.2, 34.6, 36.4, 40.7, 51.7, 75.9, 79.6, 129.4, 138.8, 168.5; HRMS (ESI-TOF) calcd for $C_{15}H_{28}NaO_4$ $[M+Na]^+$: 295.1880; found: 295.1870.

Methyl (*E*)-2-methyl-4-{(4*S*,5*S*,6*R*)-2,2,5-trimethyl-6-[(*S*)-pentan-2-yl]-1,3-dioxan-4-yl}but-2-enoate (28a). To a stirred solution of **27a** (100.0 mg, 0.37 mmol) in CH_2Cl_2 (3.7 mL) under argon were added 2,2-dimethoxypropane (453 μL, 3.7 mmol) and PPTS (93.0 mg, 0.37 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was quenched with aqueous saturated $NaHCO_3$. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (15:1) to give compound **28a** (103.6 mg, 90%) as a colorless oil: $[\alpha]^{26}_D$ –2.27 (*c* 0.78, $CHCl_3$); IR (neat): 1715 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.75 (d, *J* = 6.3 Hz, 3H), 0.83 (d, *J* = 6.3 Hz, 3H), 0.88-0.91 (m, 3H), 1.23-1.33 (m, 4H), 1.34 (s, 3H), 1.39 (s, 3H), 1.45-1.52 (m, 1H), 1.64-1.68 (m, 1H), 1.84 (d, *J* = 1.1 Hz, 3H), 2.26-2.32 (m, 1H), 2.46-2.51 (m, 1H), 3.42 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.57 (dt, *J* = 12.8, 4.4 Hz, 1H), 3.74 (s, 3H), 6.85-6.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.8, 12.5, 12.6, 14.3, 19.4, 20.4, 30.0, 32.7, 32.9, 35.3, 36.2, 51.7, 74.0, 75.7, 97.8, 128.5, 139.2, 168.6; HRMS (ESI-TOF) calcd for $C_{18}H_{32}NaO_4$ $[M+Na]^+$: 335.2193; found: 335.2186.

(*E*)-2-Methyl-4-{(4*S*,5*S*,6*R*)-2,2,5-trimethyl-6-[(*S*)-pentan-2-yl]-1,3-dioxan-4-yl}but-2-en-1-ol (29a). To a stirred solution of **28a** (87.0 mg, 0.28 mmol) in THF (2.8 mL) under argon was added DIBAL (1.0 M in toluene; 0.84 mL, 0.84 mmol) at –78 °C. After being stirred for 3 h, a saturated

aqueous solution of sodium potassium tartrate was added to the reaction mixture and the mixture was stirred at room temperature for 1 h. The whole was extracted with Et_2O and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (7:1 to 4:1) to give compound **29a** (71.7 mg, 90%) as a colorless oil: $[\alpha]^{27}_D$ –1.60 (*c* 1.03, $CHCl_3$); IR (neat): 3317 (OH); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.74 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.88-0.90 (m, 3H), 1.18-1.34 (m, 4H), 1.34 (s, 3H), 1.38 (s, 3H), 1.43-1.51 (m, 1H), 1.64-1.67 (m, 5H), 2.12-2.17 (m, 1H), 2.36-2.40 (m, 1H), 3.40 (dd, *J* = 10.3, 2.3 Hz, 1H), 3.47-3.52 (m, 1H), 4.01 (s, 2H), 5.52-5.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.8, 12.5, 13.9, 14.3, 19.5, 20.4, 30.0, 31.5, 32.7, 35.1, 36.2, 68.9, 74.6, 75.8, 97.7, 122.5, 135.9; HRMS (ESI-TOF) calcd for $C_{17}H_{32}NaO_3$ $[M+Na]^+$: 307.2244; found: 307.2247.

(5*S*,6*S*,7*R*,8*S*,*E*)-2,6,8-Trimethylundec-2-ene-1,5,7-triol (11a). To a stirred solution of **29a** (50.6 mg, 0.18 mmol) in MeOH (3.2 mL) was added 1N HCl (0.54 mL, 0.54 mmol) at room temperature. After being stirred overnight, the reaction mixture was quenched with aqueous saturated $NaHCO_3$. The whole was extracted with EtOAc and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (3:1 to 1:2) to give compound **11a** (22.5 mg, 51%) as a colorless oil: $[\alpha]^{29}_D$ –2.82 (*c* 1.00, $CHCl_3$); IR (neat): 3348 (OH); ^{1}H NMR (500 MHz CD_3OD) δ: 0.80 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.90-0.93 (m, 3H), 1.24-1.29 (m, 1H), 1.32-1.40 (m, 3H), 1.60-1.67 (m, 1H), 1.67 (s, 3H), 1.74-1.82 (m, 1H), 2.12-2.18 (m, 1H), 2.27-2.31 (m, 1H), 3.41 (dd, *J* = 9.7, 2.3 Hz, 1H), 3.85-3.88 (m, 1H), 3.94 (s, 2H), 5.54-5.57 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ: 12.0, 12.5, 14.1, 14.7, 21.5, 32.1, 35.7, 37.9, 42.3, 69.1, 75.4, 78.1, 123.9, 137.4; HRMS (FAB) calcd for $C_{14}H_{29}O_3$ $[M+H]^+$: 245.2111; found: 245.2115.

*Synthesis of triol **11b***

(*R*)-4-Benzyl-3-[(2*R*,3*S*,4*S*)-5-benzyloxy-3-hydroxy-4-methyl-2-propylpentanoyl]oxazolidin-2-one (16b). According to the procedure described for the preparation of **15a**, **14** (1.01 g, 5.6 mmol) was converted into **16b** (1.70 g, 69%) with (*R*)-4-benzyl-3-pentanoyl-2-oxazolidinone as a colorless oil: $[\alpha]^{29}_D$ –21.1 (*c* 0.96, $CHCl_3$); IR (neat): 3492 (OH), 1778 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.96 (t, *J* = 7.4 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.29-1.38 (m, 1H), 1.38-1.48 (m, 1H), 1.53-1.62 (m, 1H), 1.96-2.08 (m, 2H), 2.73 (dd, *J* = 13.2, 9.7 Hz, 1H), 3.35 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.53 (dd, *J* = 8.7, 6.9 Hz, 1H), 3.61-3.63 (m, 2H), 3.80-3.83 (m, 1H), 4.08 (td, *J* = 6.9, 3.4 Hz, 1H), 4.14 (d, *J* = 4.6 Hz, 2H), 4.47-4.53 (m, 2H), 4.66-4.73 (m, 1H), 7.21-7.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 14.4, 20.7, 27.5, 36.4, 37.9, 45.9, 55.7, 65.9, 73.5, 74.9, 76.0, 127.3, 127.7 (3C), 128.4 (2C), 128.9 (2C), 129.4 (2C), 135.4, 137.7, 153.2, 175.3; HRMS (ESI-TOF) calcd for $C_{26}H_{33}NNaO_5$ $[M+Na]^+$: 462.2251; found: 462.2247.

(*R*)-4-Benzyl-3-[(2*R*,3*S*,4*S*)-5-benzyloxy-3-(*tert*-butyldimethylsilyloxy)-4-methyl-2-propylpentanoyl]oxazolidin-2-one (18b). According to the procedure described for the preparation of **17a**, **16b**

(28.7 g, 65.2 mmol) was converted into **18b** (32.5 g, 90%) as a colorless oil: $[\alpha]^{28}_{D}$ –53.2 (*c* 0.89, $CHCl_3$); IR (neat): 1781 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 0.92 (t, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.29-1.39 (m, 2H), 1.71-1.75 (m, 2H), 1.91-1.95 (m, 1H), 2.64 (dd, *J* = 13.2, 10.3 Hz, 1H), 3.18 (dd, *J* = 9.2, 6.9 Hz, 1H), 3.31 (dd, *J* = 13.2, 3.4 Hz, 1H), 3.57 (dd, *J* = 9.2, 4.9 Hz, 1H), 3.79-3.80 (m, 1H), 3.98 (dd, *J* = 7.4, 3.4 Hz, 1H), 4.01 (dd, *J* = 8.9, 2.0 Hz, 1H), 4.12-4.16 (m, 1H), 4.39-4.48 (m, 2H), 4.48-4.52 (m, 1H), 7.20-7.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.0, –3.9, 14.4, 15.2, 18.3, 20.2, 26.1 (3C), 32.0, 37.9, 39.2, 46.4, 55.8, 65.6, 72.0, 72.9, 75.8, 127.2, 127.4, 127.5 (2C), 128.2 (2C), 128.9 (2C), 129.4 (2C), 135.5, 138.6, 152.9, 175.6; HRMS (ESI-TOF) calcd for $C_{32}H_{47}NNaO_5Si$ $[M+Na]^+$: 576.3116; found: 576.3117.

(2*S*,3*S*,4*S*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-4-methyl-2-propylpentan-1-ol (20b). According to the procedure described for the preparation of **19a**, **18b** (32.4 g, 58.5 mmol) was converted into **20b** (16.0 g, 72%) as a colorless oil: $[\alpha]^{28}_{D}$ –1.94 (*c* 1.05, $CHCl_3$); IR (neat): 3427 (OH); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.05 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.90 (t, *J* = 7.4 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.08-1.16 (m, 1H), 1.24-1.33 (m, 2H), 1.34-1.42 (m, 1H), 1.76-1.82 (m, 1H), 2.05-2.13 (m, 1H), 2.61 (t, *J* = 5.2 Hz, 1H), 3.31 (dd, *J* = 9.2, 7.4 Hz, 1H), 3.61-3.65 (m, 3H), 3.78 (dd, *J* = 5.2, 3.4 Hz, 1H), 4.49 (s, 2H), 7.27-7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -4.5, -4.3, 14.4, 16.2, 18.2, 21.4, 26.0 (3C), 29.9, 36.5, 45.1, 63.8, 72.9, 73.1, 76.4, 127.5, 127.6 (2C), 128.3 (2C), 138.4; HRMS (ESI-TOF) calcd for $C_{22}H_{40}NaO_3Si$ $[M+Na]^+$: 403.2639; found: 403.2640.

(2*S*,3*R*,4*R*)-1-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylheptane (23b). To a stirred solution of **20b** (1.0 g, 2.7 mmol) in CH_2Cl_2 (27.3 mL) under argon were added Et_3N (761 μL, 5.5 mmol), TsCl (781.7 mg, 4.1 mmol) and $Me_3N{\cdot}HCl$ (260.9 mg, 2.7 mmol) at room temperature. After being stirred for 1 h, the reaction was quenched with aqueous saturated NH_4Cl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the precipitated white solid was filtered off. The filtrate was concentrated under reduced pressure to give the corresponding tosylate, which was used without further purification. To a stirred suspension of $LiAlH_4$ (310.8 mg, 8.2 mmol) in THF (13.3 mL) under argon was added dropwise a solution of the above tosylate in THF (14 mL) at 0 °C. After being stirred for 10 min, the reaction mixture was warmed to room temperature. After 5 h, the reaction mixture was poured into a saturated solution of sodium potassium tartrate at 0 °C and stirred at room temperature for 1 h. The whole was extracted with Et_2O and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash chromatography over silica gel with hexane–EtOAc (100:0 to 70:1) to give compound **23b** (566.3 mg, 57%) as a colorless oil: $[\alpha]^{26}_{D}$ –8.33 (*c* 1.07, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.01 (s, 3H), 0.03 (s, 3H), 0.87-0.89 (m, 15H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.05-1.11 (m, 1H), 1.14-1.24 (m, 1H), 1.34-1.45 (m, 2H), 1.57-1.64 (m, 1H), 1.94-2.02 (m, 1H), 3.25-3.28 (m, 1H), 3.41-3.43 (m, 1H), 3.61 (dd, *J* = 8.9, 4.3 Hz, 1H), 4.48 (s, 2H), 7.25-7.29 (m, 1H), 7.33-7.34 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.2, –3.9, 14.4, 16.2, 16.5, 18.4, 20.8, 26.1 (3C), 34.3, 36.9,

37.3, 73.0, 73.1, 79.0, 127.3, 127.5 (2C), 128.3 (2C), 138.9; HRMS (ESI-TOF) calcd for $C_{22}H_{40}NaO_2Si$ $[M+Na]^+$: 387.2690; found: 387.2689.

(2*S*,3*R*,4*R*)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylheptan-1-ol (22b). According to the procedure described for the preparation of **22a**, **23b** (566.3 mg, 1.6 mmol) was converted into **22b** (340.7 mg, 78%) as a colorless oil: $[\alpha]^{25}_D$ –3.90 (*c* 1.07, $CHCl_3$); IR (neat): 3388 (OH); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.09 (s, 3H), 0.11 (s, 3H), 0.89-0.92 (m, 12H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 1.04-1.13 (m, 1H), 1.19-1.28 (m, 1H), 1.36-1.48 (m, 2H), 1.64-1.72 (m, 1H), 1.84-1.91 (m, 1H), 2.84 (t, *J* = 5.7 Hz, 1H), 3.52-3.54 (m, 1H), 3.55-3.60 (m, 1H), 3.65-3.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.3, –4.2, 14.3, 15.2, 16.9, 18.2, 20.8, 26.0 (3C), 35.1, 36.1, 38.8, 66.4, 81.9; HRMS (ESI-TOF) calcd for $C_{15}H_{34}NaO_2Si$ $[M+Na]^+$: 297.2220; found: 297.2220.

Methyl (5*R*,6*S*,7*R*,8*R*,*E*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundec-2-enoate (25b). According to the procedure described for the preparation of **25a**, **22b** (477.7 mg, 1.7 mmol) was converted into **25b** (479.4 mg, 71%) as a colorless oil: $[\alpha]^{27}_D$ +14.2 (*c* 1.06, $CHCl_3$); IR (neat): 3509 (OH), 1716 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.11 (s, 3H), 0.12 (s, 3H), 0.89-0.93 (m, 15H), 1.00-1.04 (m, 4H), 1.16-1.27 (m, 1H), 1.38-1.50 (m, 2H), 1.68-1.80 (m, 2H), 1.87 (s, 3H), 2.19-2.25 (m, 1H), 2.39-2.45 (m, 1H), 3.56 (dd, *J* = 6.9, 2.3 Hz, 1H), 3.69 (s, 1H), 3.73 (s, 3H), 4.23-4.25 (m, 1H), 6.79-6.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.1, –3.9, 12.5, 12.6, 14.2, 15.5, 18.2, 20.7, 26.1 (3C), 34.2, 35.8, 36.7, 38.2, 51.7, 70.5, 83.2, 129.0, 138.9, 168.4; HRMS (ESI-TOF) calcd for $C_{21}H_{42}NaO_4Si$ $[M+Na]^+$: 409.2745; found: 409.2747.

Methyl (5*S*,6*S*,7*R*,8*R*,*E*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundec-2-enoate (26b). According to the procedure described for the preparation of **26a**, **25b** (290.8 mg, 0.75 mmol) was converted into **26b** (206.4 mg, 71 %) as a colorless oil: $[\alpha]^{27}_D$ –3.10 (*c* 1.15, $CHCl_3$); IR (neat): 3523 (OH), 1715 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.10 (s, 3H), 0.12 (s, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.89-0.92 (m, 15H), 1.03-1.08 (m, 1H), 1.18-1.29 (m, 1H), 1.38-1.45 (m, 2H), 1.61-1.67 (m, 1H), 1.73-1.78 (m, 1H), 1.86 (s, 3H), 2.26-2.32 (m, 1H), 2.42-2.45 (m, 1H), 3.50-3.52 (m, 1H), 3.68-3.72 (m, 2H), 3.73 (s, 3H), 6.95-6.97 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.4, –4.2, 12.7, 14.3, 15.3, 16.9, 18.2, 20.8, 26.0 (3C), 33.5, 34.6, 39.5, 40.3, 51.6, 73.1, 82.4, 128.6, 139.5, 168.5; HRMS (ESI-TOF) calcd for $C_{21}H_{42}NaO_4Si$ $[M+Na]^+$: 409.2745; found: 409.2743.

Methyl (5*S*,6*S*,7*R*,8*R*,*E*)-5,7-dihydroxy-2,6,8-trimethylundec-2-enoate (27b). According to the procedure described for the preparation of **27a**, **26b** (122.0 mg, 0.32 mmol) was converted into **27b** (79.9 mg, 93%) as a colorless oil: $[\alpha]^{27}_D$ +1.17 (*c* 1.05, $CHCl_3$); IR (neat): 3368 (OH), 1714 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.81 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.10-1.26 (m, 2H), 1.35-1.41 (m, 1H), 1.43-1.50 (m, 1H), 1.71-1.82 (m, 2H), 1.88 (s, 3H), 2.35-2.42 (m, 2H), 2.47-2.51 (m, 1H), 3.46-3.48 (m, 1H), 3.64 (br s, 1H), 3.74 (s, 3H), 3.80-3.84 (m, 1H), 6.92-6.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.7, 13.2, 14.3, 17.0, 20.5, 30.5, 34.2, 34.7, 40.5, 51.7, 75.8, 82.0, 129.3, 138.9, 168.5; HRMS (ESI-TOF) calcd for $C_{15}H_{28}NaO_4$ $[M+Na]^+$: 295.1880; found: 295.1881.

Methyl (*E*)-2-methyl-4-{(4*S*,5*S*,6*R*)-2,2,5-trimethyl-6-[(*R*)-pentan-2-yl]-1,3-dioxan-4-yl}but-2-enoate (28b). According to the procedure described for the preparation of **28a**, **27b** (69.2 mg, 0.25 mmol) was converted into **28b** (70.1 mg, 90%) as a colorless oil: $[\alpha]^{28}_{D}$ +3.57 (*c* 1.29, $CHCl_3$); IR (neat): 1715 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.76 (d, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 1.13-1.22 (m, 2H), 1.31-1.37 (m, 4H), 1.38 (s, 3H), 1.40-1.46 (m, 1H), 1.48-1.54 (m, 1H), 1.67-1.71 (m, 1H), 1.84 (s, 3H), 2.26-2.32 (m, 1H), 2.46-2.50 (m, 1H), 3.36 (dd, *J* = 10.3, 1.7 Hz, 1H), 3.54-3.58 (m, 1H), 3.75 (s, 3H), 6.85-6.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.0, 12.7, 14.3, 17.1, 19.4, 20.8, 30.0, 31.0, 32.9, 33.0, 35.2, 51.7, 74.0, 78.6, 97.9, 128.6, 139.2, 168.6; HRMS (ESI-TOF) calcd for $C_{18}H_{32}NaO_4$ $[M+Na]^+$: 335.2193; found: 335.2188.

(*E*)-2-Methyl-4-{(4*S*,5*S*,6*R*)-2,2,5-trimethyl-6-[(*R*)-pentan-2-yl]-1,3-dioxan-4-yl}but-2-en-1-ol (29b). According to the procedure described for the preparation of **29a**, **28b** (57.9 mg, 0.19 mmol) was converted into **29b** (50.4 mg, 96%) as a colorless oil: $[\alpha]^{26}_{D}$ +8.97 (*c* 0.76, $CHCl_3$); IR (neat): 3359 (OH); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.75 (d, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 1.13-1.22 (m, 2H), 1.26 (t, *J* = 6.3 Hz, 1H), 1.33-1.36 (m, 4H), 1.38 (s, 3H), 1.41-1.47 (m, 1H), 1.49-1.53 (m, 1H), 1.67-1.69 (m, 4H), 2.12-2.18 (m, 1H), 2.36-2.40 (m, 1H), 3.34 (dd, *J* = 10.3, 1.7 Hz, 1H), 3.46-3.50 (m, 1H), 4.03 (d, *J* = 6.3 Hz, 2H), 5.53-5.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.0, 13.9, 14.3, 17.1, 19.5, 20.8, 30.1, 31.1, 31.5, 33.0, 35.0, 69.0, 74.6, 78.6, 97.8, 122.6, 135.9; HRMS (ESI-TOF) calcd for $C_{17}H_{32}NaO_3$ $[M+Na]^+$: 307.2244; found: 307.2241.

(5*S*,6*S*,7*R*,8*R*,*E*)-2,6,8-Trimethylundec-2-ene-1,5,7-triol (11b). According to the procedure described for the preparation of **11a**, **29b** (34.5 mg, 0.12 mmol) was converted into **11b** (27.7 mg, 93%) as a colorless oil: $[\alpha]^{27}_{D}$ +5.18 (*c* 0.98, $CHCl_3$); IR (neat): 3351 (OH); ^{1}H NMR (500 MHz CD_3OD) δ: 0.82 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 1.09-1.17 (m, 1H), 1.17-1.25 (m, 1H), 1.38-1.52 (m, 2H), 1.62-1.69 (m, 4H), 1.79-1.86 (m, 1H), 2.12-2.18 (m, 1H), 2.28-2.32 (m, 1H), 3.30-3.33 (m, 1H), 3.83-3.86 (m, 1H), 3.94 (s, 2H), 5.54-5.57 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ: 12.2, 14.1, 14.8, 17.7, 21.7, 32.1, 32.2, 36.1, 42.2, 69.1, 75.3, 80.7, 123.9, 137.4; HRMS (ESI-TOF) calcd for $C_{14}H_{28}NaO_3$ $[M+Na]^+$: 267.1931; found: 267.1933.

*Synthesis of triol **11c***

Methyl (*R*)-3-benzyloxy-2-methylpropanoate (*ent*-13). According to the procedure described for the preparation of **13**, *ent*-**12** (9.9 g, 83.8 mmol) was converted into *ent*-**13** (14.8 g, 85%) as a colorless oil. The spectral data were in good agreement with those previously reported.[21]

(*S*)-3-Benzyloxy-2-methylpropan-1-ol (*ent*-14). According to the procedure described for the preparation of **14**, *ent*-**13** (14.7 g, 70.6 mmol) was converted into *ent*-**14** (10.3 g, 81%) as a colorless oil. The spectral data were in good agreement with those previously reported.[21]

(*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*)-5-benzyloxy-3-hydroxy-2,4-dimethylpentanoyl]oxazolidin-2-one (15c). According to the procedure described for the preparation of **15a**, *ent*-**14** (334.7 mg, 1.86 mmol) was converted into **15c** (648.9 mg, 85%) as a colorless oil: $[\alpha]^{29}_{D}$ –43.2 (*c* 0.72, $CHCl_3$); IR (neat): 3504 (OH), 1779 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.05 (d, *J* = 6.9 Hz, 3H), 1.33 (d, *J* =

6.3 Hz, 3H), 1.87-1.93 (m, 1H), 2.77 (dd, *J* = 13.2, 9.7 Hz, 1H), 3.00 (d, *J* = 2.9 Hz, 1H), 3.25 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.46-3.52 (m, 2H), 3.96-4.03 (m, 2H), 4.16-4.21 (m, 2H), 4.51 (s, 2H), 4.65-4.69 (m, 1H), 7.20-7.21 (m, 2H), 7.26-7.36 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.4, 12.8, 36.2, 37.7, 40.5, 55.1, 66.0, 73.3, 73.9, 74.1, 127.4 (2C), 127.5 (2C), 128.3 (2C), 128.9 (2C), 129.4 (2C), 135.0, 138.1, 152.7, 177.0; HRMS (ESI-TOF) calcd for $C_{24}H_{29}NNaO_5$ $[M+Na]^+$: 434.1938; found: 434.1938.

(*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*)-5-benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentanoyl]-oxazolidin-2-one (17c). According to the procedure described for the preparation of **17a**, **15c** (14.1 g, 34.3 mmol) was converted into **17c** (16.0 g, 89%) as a colorless oil: $[\alpha]^{27}_D$ –38.2 (*c* 1.21, $CHCl_3$); IR (neat): 1780 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.04 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 0.92 (d, *J* = 7.4 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.88-1.93 (m, 1H), 2.75 (dd, *J* = 13.2, 9.7 Hz, 1H), 3.24 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.28 (dd, *J* = 8.9, 7.2 Hz, 1H), 3.49 (dd, *J* = 8.9, 6.6 Hz, 1H), 3.96-4.02 (m, 1H), 4.08-4.16 (m, 3H), 4.46-4.52 (m, 2H), 4.59-4.64 (m, 1H), 7.20-7.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.1, –3.9, 11.9, 15.0, 18.4, 26.1 (3C), 37.6, 38.8, 41.9, 55.4, 65.9, 72.8, 73.0, 73.4, 127.3, 127.4, 127.6 (2C), 128.3 (2C), 128.9 (2C), 129.4 (2C), 135.3, 138.6, 152.8, 175.9; HRMS (ESI-TOF) calcd for $C_{30}H_{43}NNaO_5Si$ $[M+Na]^+$: 548.2803; found: 548.2808.

(2*S*,3*R*,4*R*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentan-1-ol (19c). According to the procedure described for the preparation of **19a**, **17c** (22.4 g, 42.5 mmol) was converted into **19c** (10.3 g, 69%) as a colorless oil: $[\alpha]^{29}_D$ –0.41 (*c* 1.23, $CHCl_3$); IR (neat): 3422 (OH); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.03 (s, 3H), 0.08 (s, 3H), 0.85 (d, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 0.96 (d, *J* = 6.9 Hz, 3H), 1.93-1.98 (m, 1H), 1.99-2.05 (m, 1H), 2.32 (br s, 1H), 3.26 (dd, *J* = 9.2, 6.3 Hz, 1H), 3.39 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.47-3.51 (m, 1H), 3.64-3.68 (m, 1H), 3.88-3.89 (m, 1H), 4.46-4.51 (m, 2H), 7.26-7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.5, –4.2, 12.8, 12.9, 18.2, 26.0 (3C), 35.9, 40.1, 66.3, 72.9, 73.6, 74.4, 127.5 (3C), 128.3 (2C), 138.5; HRMS (ESI-TOF) calcd for $C_{20}H_{36}NaO_3Si$ $[M+Na]^+$: 375.2326; found: 375.2324.

(4*S*,5*R*,6*R*)-7-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-4,6-dimethylhept-2-ene (21c). According to the procedure described for the preparation of **21a**, **19c** (228.9 mg, 0.65 mmol) was converted into compound **21c** as a diastereomixture (163.7 mg, 69%, *Z*/*E* = 7:1): colorless oil; $[\alpha]^{27}_D$ +12.5 (*c* 1.17, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.01 (s, 0.4H), 0.02 (s, 2.6H), 0.04 (s, 0.4H), 0.05 (s, 2.6H), 0.84-0.86 (m, 3.0H), 0.89 (s, 1.2H), 0.90 (s, 7.8H), 0.94-0.97 (m, 3.0H), 1.61 (dd, *J* = 6.9, 1.7 Hz, 2.6H), 1.63 (d, *J* = 4.6 Hz, 0.4H), 1.96-2.03 (m, 1.0H), 2.23-2.30 (m, 0.1H), 2.60-2.65 (m, 0.9H), 3.22 (dd, *J* = 8.9, 6.9 Hz, 1.0H), 3.40 (dd, *J* = 8.9, 7.7 Hz, 1.0H), 3.56 (dd, *J* = 8.0, 1.7 Hz, 1.0H), 4.43-4.52 (m, 2.0H), 5.16-5.21 (m, 1.0H), 5.35-5.42 (m, 1.0H), 7.25-7.34 (m, 5.0H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.1, –4.0, –3.6, –3.5, 10.8, 11.1, 13.0, 17.6, 18.1, 18.3, 18.4, 18.5, 26.2 (6C), 35.9, 36.6, 37.1, 41.5, 72.7, 72.8, 73.6, 73.9, 76.0, 76.2, 122.7, 123.8, 127.4, 127.5 (2C), 128.3 (2C), 134.5, 134.9, 138.7 ; HRMS (ESI-TOF) calcd for $C_{22}H_{38}NaO_2Si$ $[M+Na]^+$: 385.2533; found: 385.2534.

(2*R*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylheptan-1-ol (22c). According to the procedure described for the preparation of **22a**, **21c** (1.3 g, 3.7 mmol) was converted into **22c** (938.1 mg, 92%) as a colorless oil: $[\alpha]^{28}_{D}$ –12.7 (*c* 1.13, $CHCl_3$); IR (neat): 3328 (OH); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.06 (s, 3H), 0.08 (s, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.88-0.92 (m, 15H), 1.09-1.16 (m, 1H), 1.19-1.28 (m, 1H), 1.31-1.41 (m, 2H), 1.60-1.66 (m, 1H), 1.90-1.97 (m, 1H), 2.07 (dd, *J* = 6.0, 4.3 Hz, 1H), 3.45-3.50 (m, 1H), 3.62-3.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.2, –4.1, 12.6, 14.3, 15.8, 18.3, 20.8, 26.0 (3C), 35.9, 37.0, 39.5, 66.5, 77.4; HRMS (ESI-TOF) calcd for $C_{15}H_{34}NaO_2Si$ $[M+Na]^+$: 297.2220; found: 297.2221.

Methyl (5*S*,6*R*,7*R*,8*S*,*E*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundec-2-enoate (26c). According to the procedure described for the preparation of **25a**, **22c** (96.4 mg, 0.35 mmol) was converted into **26c** (73.4 mg, 54%) as a colorless oil: $[\alpha]^{26}_{D}$ –22.4 (*c* 1.01, $CHCl_3$); IR (neat): 3523 (OH), 1716 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.08 (s, 3H), 0.09 (s, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.88-0.91 (m, 12H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.04-1.11 (m, 1H), 1.15-1.22 (m, 1H), 1.35-1.42 (m, 1H), 1.46-1.53 (m, 1H), 1.63-1.69 (m, 2H), 1.87 (s, 3H), 1.96 (d, *J* = 4.0 Hz, 1H), 2.31-2.42 (m, 2H), 3.65-3.66 (m, 1H), 3.74 (s, 3H), 3.79-3.83 (m, 1H), 6.79-6.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.2, –3.5, 8.9, 12.7, 14.4, 15.4, 18.3, 21.1, 26.0 (3C), 34.7, 35.3, 37.9, 40.1, 51.7, 73.7, 78.8, 129.3, 138.8, 168.4; HRMS (ESI-TOF) calcd for $C_{21}H_{42}NaO_4Si$ $[M+Na]^+$: 409.2745; found: 409.2748.

Methyl (5*S*,6*R*,7*R*,8*S*,*E*)-5,7-dihydroxy-2,6,8-trimethylundec-2-enoate (27c). According to the procedure described for the preparation of **27a**, **26c** (312.1 mg, 0.81 mmol) was converted into **27c** (206.1 mg, 93%) as a colorless oil: $[\alpha]^{26}_{D}$ –16.0 (*c* 1.06, $CHCl_3$); IR (neat): 3432 (OH), 1713 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.89 (t, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.98-1.03 (m, 1H), 1.22-1.31 (m, 2H), 1.34-1.42 (m, 1H), 1.57-1.64 (m, 1H), 1.71-1.75 (m, 1H), 1.87 (d, *J* = 1.1 Hz, 3H), 2.29-2.34 (m, 1H), 2.44-2.50 (m, 1H), 2.69 (br s, 1H), 3.45-3.48 (m, 2H), 3.74 (s, 3H), 3.94-3.97 (m, 1H), 6.78-6.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 4.7, 12.7, 14.2, 15.4, 19.6, 34.6, 34.8, 35.9, 37.6, 51.8, 75.8, 81.5, 129.4, 138.6, 168.5; HRMS (ESI-TOF) calcd for $C_{15}H_{28}NaO_4$ $[M+Na]^+$: 295.1880; found: 295.1885.

Methyl (*E*)-2-methyl-4-{(4*S*,5*R*,6*R*)-2,2,5-trimethyl-6-[(*S*)-pentan-2-yl]-1,3-dioxan-4-yl}but-2-enoate (28c). According to the procedure described for the preparation of **28a**, **27c** (154.8 mg, 0.57 mmol) was converted into **28c** (137.7 mg, 77%) as a colorless oil: $[\alpha]^{27}_{D}$ –7.61 (*c* 1.12, $CHCl_3$); IR (neat): 1716 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.84 (d, *J* = 6.9 Hz, 3H), 0.88-0.94 (m, 7H), 1.21-1.32 (m, 2H), 1.40 (s, 6H), 1.41-1.48 (m, 1H), 1.50-1.62 (m, 2H), 1.87 (s, 3H), 2.26-2.32 (m, 1H), 2.35-2.41 (m, 1H), 3.39 (dd, *J* = 9.7, 2.3 Hz, 1H), 3.75 (s, 3H), 3.94 (td, *J* = 7.2, 2.3 Hz, 1H), 6.72-6.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 4.7, 12.7, 14.2, 15.8, 19.5, 19.6, 29.9, 32.4, 32.5, 32.9, 33.6, 51.7, 72.6, 78.1, 98.9, 129.1, 138.1, 168.5; HRMS (ESI-TOF) calcd for $C_{18}H_{32}NaO_4$ $[M+Na]^+$: 335.2193; found: 335.2189.

(*E*)-2-Methyl-4-{(4*S*,5*R*,6*R*)-2,2,5-trimethyl-6-[(*S*)-pentan-2-yl]-1,3-dioxan-4-yl}but-2-en-1-ol (29c). According to the procedure described for the preparation of **29a**, **28c** (53.2 mg, 0.17 mmol) was converted into **29c** (47.6 mg, 98%) as a colorless oil: $[\alpha]^{27}_{D}$ –7.12 (*c* 1.02, $CHCl_3$); IR (neat): 3421 (OH); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.84 (d, *J* = 6.9 Hz, 3H), 0.87-0.92 (m, 7H), 1.20-1.34 (m, 3H), 1.40-1.46 (m, 7H), 1.50-1.60 (m, 2H), 1.69 (s, 3H), 2.15-2.29 (m, 2H), 3.37 (dd, *J* = 9.7, 1.7 Hz, 1H), 3.85 (td, *J* = 7.2, 1.9 Hz, 1H), 4.03 (s, 2H), 5.38-5.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 4.7, 14.0, 14.2, 15.8, 19.5, 19.6, 30.0, 31.2, 32.1, 32.9, 33.6, 68.7, 73.4, 78.2, 98.8, 121.2, 136.7; HRMS (ESI-TOF) calcd for $C_{17}H_{32}NaO_3$ $[M+Na]^+$: 307.2244; found: 307.2244.

(5*S*,6*R*,7*R*,8*S*,*E*)-2,6,8-Trimethylundec-2-ene-1,5,7-triol (11c). According to the procedure described for the preparation of **11a**, **29c** (23.6 mg, 0.083 mmol) was converted into **11c** (15.2 mg, 75%) as a colorless oil: $[\alpha]^{27}_{D}$ –9.66 (*c* 1.00, $CHCl_3$); IR (neat): 3334 (OH); ^{1}H NMR (500 MHz CD_3OD) δ: 0.89-0.92 (m, 6H), 0.95 (d, *J* = 6.9 Hz, 3H), 1.07-1.13 (m, 1H), 1.24-1.45 (m, 3H), 1.62-1.71 (m, 5H), 2.25-2.27 (m, 2H), 3.39 (dd, *J* = 6.3, 5.2 Hz, 1H), 3.73 (td, *J* = 6.6, 3.4 Hz, 1H), 3.93 (s, 2H), 5.44-5.46 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ: 7.8, 14.0, 14.7, 15.0, 20.9, 34.3, 36.3, 36.8, 39.8, 65.9, 75.1, 79.1, 123.0, 137.8; HRMS (ESI-TOF) calcd for $C_{14}H_{28}NaO_3$ $[M+Na]^+$: 267.1931; found: 267.1930.

*Synthesis of triol **11d***

(*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*)-5-benzyloxy-3-hydroxy-4-methyl-2-propylpentanoyl]oxazolidin-2-one (16d). According to the procedure described for the preparation of **15a**, *ent*-**14** (337.4 mg, 1.87 mmol) was converted into **16d** (591.5 mg, 72%) with (*R*)-4-benzyl-3-pentanoyl-2-oxazolidinone as a colorless oil: $[\alpha]^{28}_{D}$ –26.9 (*c* 1.08, $CHCl_3$); IR (neat): 3491 (OH), 1777 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.93 (t, *J* = 7.4 Hz, 3H), 1.02 (d, *J* = 7.4 Hz, 3H), 1.33-1.40 (m, 2H), 1.81-1.87 (m, 3H), 2.66 (dd, *J* = 13.2, 10.3 Hz, 1H), 2.81 (d, *J* = 3.4 Hz, 1H), 3.36 (dd, *J* = 13.2, 3.4 Hz, 1H), 3.48-3.54 (m, 2H), 4.00-4.03 (m, 1H), 4.13-4.15 (m, 2H), 4.20-4.24 (m, 1H), 4.48-4.54 (m, 2H), 4.65-4.69 (m, 1H), 7.22-7.36 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.7, 14.4, 20.0, 31.1, 36.5, 37.9, 45.6, 55.6, 65.8, 73.3, 74.4, 74.6, 127.3 (2C), 127.6 (2C), 128.3 (2C), 129.0 (2C), 129.3 (2C), 135.3, 138.1, 153.0, 176.1; HRMS (ESI-TOF) calcd for $C_{26}H_{33}NNaO_5$ $[M+Na]^+$: 462.2251; found: 462.2251.

(*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*)-5-benzyloxy-3-(*tert*-butyldimethylsilyloxy)-4-methyl-2-propylpentanoyl]oxazolidin-2-one (18d). According to the procedure described for the preparation of **18a**, **16d** (18.2 g, 41.4 mmol) was converted into **18d** (19.9 g, 87%) as a colorless oil: $[\alpha]^{28}_{D}$ –15.4 (*c* 1.02, $CHCl_3$); IR (neat): 1781 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.02 (s, 3H), 0.08 (s, 3H), 0.89-0.93 (m, 15H), 1.26-1.40 (m, 2H), 1.66-1.80 (m, 2H), 1.83-1.90 (m, 1H), 2.65 (dd, *J* = 13.2, 10.3 Hz, 1H), 3.26 (dd, *J* = 8.9, 7.2 Hz, 1H), 3.38 (dd, *J* = 13.2, 3.4 Hz, 1H), 3.45 (dd, *J* = 8.9, 6.6 Hz, 1H), 4.06-4.13 (m, 3H), 4.14-4.19 (m, 1H), 4.45-4.51 (m, 2H), 4.61-4.66 (m, 1H), 7.22-7.35 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.0, –3.8, 11.5, 14.4, 18.4, 20.3, 26.1 (3C), 32.9, 37.9, 38.6, 47.0, 55.9, 65.7, 72.8, 73.2, 74.0, 127.3, 127.4, 127.6 (2C), 128.3 (2C), 128.9 (2C), 129.4 (2C), 135.5, 138.6, 153.0, 175.7; HRMS (ESI-TOF) calcd for $C_{32}H_{47}NNaO_5Si$ $[M+Na]^+$: 576.3116; found: 576.3115.

(2*S*,3*S*,4*R*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-4-methyl-2-propylpentan-1-ol (20d). According to the procedure described for the preparation of **19a**, **18d** (13.7 g, 24.7 mmol) was converted into **20d** (7.5 g, 80%) as a colorless oil: $[\alpha]^{29}_{D}$ –3.78 (*c* 0.96, $CHCl_3$); IR (neat): 3431 (OH); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.03 (s, 3H), 0.10 (s, 3H), 0.87-0.89 (m, 12H), 0.97 (d, *J* = 6.9 Hz, 3H), 1.04-1.11 (m, 1H), 1.14-1.22 (m, 1H), 1.31-1.38 (m, 2H), 1.86-1.92 (m, 1H), 2.00-2.07 (m, 1H), 2.97-2.98 (m, 1H), 3.26 (dd, *J* = 8.6, 6.0 Hz, 1H), 3.31-3.35 (m, 1H), 3.57-3.62 (m, 1H), 3.72-3.76 (m, 1H), 4.04-4.06 (m, 1H), 4.48 (s, 2H), 7.26-7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.8, –4.2, 12.4, 14.3, 18.1, 21.0, 25.9 (3C), 30.5, 34.5, 45.6, 64.9, 72.8, 74.0, 74.4, 127.5 (3C), 128.3 (2C), 138.5; HRMS (ESI-TOF) calcd for $C_{22}H_{40}NaO_3Si$ $[M+Na]^+$: 403.2639; found: 403.2638.

(2*R*,3*R*,4*R*)-1-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylheptane (23d). According to the procedure described for the preparation of **23b**, **20d** (7.3 g, 19.1 mmol) was converted into **23d** (4.9 g, 70%) as a colorless oil: $[\alpha]^{27}_{D}$ +1.74 (*c* 1.16, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.00 (s, 3H), 0.03 (s, 3H), 0.86-0.89 (m, 18H), 1.00-1.05 (m, 1H), 1.18-1.26 (m, 1H), 1.36-1.42 (m, 2H), 1.56-1.60 (m, 1H), 1.95-2.00 (m, 1H), 3.22 (dd, *J* = 8.6, 6.6 Hz, 1H), 3.37 (dd, *J* = 8.6, 7.4 Hz, 1H), 3.62 (dd, *J* = 5.7, 2.3 Hz, 1H), 4.45-4.52 (m, 2H), 7.27-7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.3, –3.9, 11.9, 14.4, 15.9, 18.4, 20.7, 26.1 (3C), 35.5, 35.6, 38.3, 72.8, 74.4, 75.4, 127.4, 127.5 (2C), 128.3 (2C), 138.7; HRMS (ESI-TOF) calcd for $C_{22}H_{40}NaO_2Si$ $[M+Na]^+$: 387.2690; found: 387.2691.

(2*R*,3*R*,4*R*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethylheptan-1-ol (22d). According to the procedure described for the preparation of **22a**, **23d** (4.6 g, 12.7 mmol) was converted into **22d** (3.0 g, 85%) as a colorless oil: $[\alpha]^{27}_{D}$ –1.93 (*c* 1.05, $CHCl_3$); IR (neat): 3309 (OH); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.06 (s, 3H), 0.07 (s, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.89-0.91 (m, 15H), 1.04-1.08 (m, 1H), 1.18-1.28 (m, 1H), 1.37-1.48 (m, 2H), 1.62-1.64 (m, 1H), 1.72-1.74 (m, 1H), 1.86-1.91 (m, 1H), 3.47 (dt, *J* = 11.1, 5.2 Hz, 1H), 3.55-3.60 (m, 1H), 3.62 (dd, *J* = 5.2, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.3, –4.0, 11.9, 14.4, 16.4, 18.3, 20.7, 26.0 (3C), 35.4, 37.4, 38.4, 66.8, 76.7; HRMS (ESI-TOF) calcd for $C_{15}H_{34}NaO_2Si$ $[M+Na]^+$: 297.2220; found: 297.2216.

Methyl (5*S*,6*R*,7*R*,8*R*,*E*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundec-2-enoate (26d). According to the procedure described for the preparation of **25a**, **22d** (198.5 mg, 0.72 mmol) was converted into **26d** (175.5 mg, 69%) as a colorless oil: $[\alpha]^{27}_{D}$ –18.6 (*c* 0.80, $CHCl_3$); IR (neat): 3524 (OH), 1716 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.09 (s, 3H), 0.10 (s, 3H), 0.88-0.92 (m, 15H), 0.95 (d, *J* = 7.4 Hz, 3H), 1.04-1.12 (m, 1H), 1.17-1.33 (m, 2H), 1.36-1.45 (m, 1H), 1.65-1.73 (m, 2H), 1.87 (s, 3H), 2.25 (br s, 1H), 2.30-2.41 (m, 2H), 3.72-3.74 (m, 4H), 3.77-3.80 (m, 1H), 6.79-6.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.5, –3.4, 8.4, 12.7, 14.3, 15.4, 18.3, 20.8, 26.0 (3C), 34.3, 35.6, 38.6, 38.9, 51.7, 75.1, 79.2, 129.3, 138.8, 168.4; HRMS (ESI-TOF) calcd for $C_{21}H_{42}NaO_4Si$ $[M+Na]^+$: 409.2745; found: 409.2744.

Methyl (5*S*,6*R*,7*R*,8*R*,*E*)-5,7-dihydroxy-2,6,8-trimethylundec-2-enoate (27d). According to the procedure described for the preparation of **27a**, **26d** (314.0 mg, 0.81 mmol) was converted into **27d**

(181.9 mg, 83%) as a colorless oil: $[\alpha]^{27}_D$ +2.93 (*c* 1.04, $CHCl_3$); IR (neat): 3436 (OH), 1714 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.80 (d, *J* = 6.9 Hz, 3H), 0.91-0.93 (m, 6H), 1.04-1.12 (m, 1H), 1.19-1.29 (m, 1H), 1.42-1.49 (m, 1H), 1.53-1.66 (m, 2H), 1.68-1.72 (m, 1H), 1.87 (d, *J* = 1.1 Hz, 3H), 2.29-2.35 (m, 1H), 2.44-2.50 (m, 1H), 2.79 (br s, 1H), 3.45-3.47 (m, 1H), 3.51 (br s, 1H), 3.74 (s, 3H), 3.96-3.98 (m, 1H), 6.78-6.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 4.2, 12.6, 14.4, 15.3, 19.7, 34.6, 34.9, 36.3, 37.5, 51.8, 76.2, 81.5, 129.4, 138.5, 168.5; HRMS (ESI-TOF) calcd for $C_{15}H_{28}NaO_4$ $[M+Na]^+$: 295.1880; found: 295.1880.

Methyl (*E*)-2-methyl-4-{(4*S*,5*R*,6*R*)-2,2,5-trimethyl-6-[(*R*)-pentan-2-yl]-1,3-dioxan-4-yl}but-2-enoate (28d). According to the procedure described for the preparation of **28a**, **27d** (153.8 mg, 0.56 mmol) was converted into **28d** (162.2 mg, 93%) as a colorless oil: $[\alpha]^{26}_D$ +4.04 (*c* 1.08, $CHCl_3$); IR (neat): 1717 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.77 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.95-1.02 (m, 1H), 1.16-1.27 (m, 1H), 1.32-1.43 (m, 7H), 1.44-1.50 (m, 1H), 1.51-1.58 (m, 1H), 1.60-1.67 (m, 1H), 1.86 (s, 3H), 2.26-2.41 (m, 2H), 3.40 (dd, *J* = 9.7, 1.7 Hz, 1H), 3.74 (s, 3H), 3.95 (td, *J* = 7.2, 2.3 Hz, 1H), 6.71-6.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 4.5, 12.7, 14.0, 14.6, 19.5 (2C), 29.9, 32.5 (2C), 34.0, 35.2, 51.7, 72.8, 77.4, 98.9, 129.1, 138.0, 168.5; HRMS (ESI-TOF) calcd for $C_{18}H_{32}NaO_4$ $[M+Na]^+$: 335.2193; found: 335.2188.

(*E*)-2-Methyl-4-{(4*S*,5*R*,6*R*)-2,2,5-trimethyl-6-[(*R*)-pentan-2-yl]-1,3-dioxan-4-yl}but-2-en-1-ol (29d). According to the procedure described for the preparation of **29a**, **28d** (131.4 mg, 0.42 mmol) was converted into **29d** (111.5 mg, 93%) as a colorless oil: $[\alpha]^{27}_D$ +9.48 (*c* 0.74, $CHCl_3$); IR (neat): 3324 (OH); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.77 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.94-1.02 (m, 1H), 1.16-1.27 (m, 1H), 1.33-1.43 (m, 8H), 1.45-1.51 (m, 1H), 1.51-1.59 (m, 1H), 1.61-1.66 (m, 1H), 1.69 (s, 3H), 2.15-2.28 (m, 2H), 3.39 (dd, *J* = 9.7, 2.3 Hz, 1H), 3.86 (td, *J* = 7.3, 2.1 Hz, 1H), 4.02 (s, 2H), 5.37-5.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 4.5, 14.0 (2C), 14.6, 19.6 (2C), 30.0, 31.2, 32.2, 34.0, 35.2, 68.7, 73.5, 77.6, 98.8, 121.2, 136.7; HRMS (ESI-TOF) calcd for $C_{17}H_{32}NaO_3$ $[M+Na]^+$: 307.2244; found: 307.2242.

(5*S*,6*R*,7*R*,8*R*,*E*)-2,6,8-Trimethylundec-2-ene-1,5,7-triol (11d). According to the procedure described for the preparation of **11a**, **29d** (49.4 mg, 0.17 mmol) was converted into **11d** (39.0 mg, 96%) as a colorless oil: $[\alpha]^{28}_D$ +13.3 (*c* 0.93, $CHCl_3$); IR (neat): 3338 (OH); ^{1}H NMR (500 MHz CD_3OD) δ: 0.82 (d, *J* = 6.9 Hz, 3H), 0.90-0.93 (m, 6H), 1.02-1.09 (m, 1H), 1.18-1.28 (m, 1H), 1.41-1.51 (m, 1H), 1.55-1.66 (m, 2H), 1.67-1.72 (m, 4H), 2.26-2.28 (m, 2H), 3.35 (dd, *J* = 8.0, 3.4 Hz, 1H), 3.74 (td, *J* = 6.4, 3.8 Hz, 1H), 3.93 (s, 2H), 5.44-5.47 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ: 6.9, 14.1, 14.9, 16.2, 21.0, 34.2, 35.6, 37.0, 39.4, 68.9, 76.3, 80.2, 122.9, 137.8; HRMS (ESI-TOF) calcd for $C_{14}H_{28}NaO_3$ $[M+Na]^+$: 267.1931; found: 267.1931.

*Total synthesis of odoamide (**1a**)*

Methyl (5*S*,6*S*,7*R*,8*S*,*E*)-7-(*tert*-butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)-undec-2-enoate (32). To a stirred solution of **26a** (2.3 g, 6.0 mmol) in DMSO (42.9 mL) under argon were added Ac_2O (30.5 mL) and AcOH (5.5 mL) at room temperature. After being stirred overnight,

the reaction mixture was cooled to 0 °C and quenched with aqueous saturated $NaHCO_3$. The whole was extracted with Et_2O and the extract was washed with H_2O and brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (30:1) to give compound **32** (1.6 g, 59%) as a colorless oil: $[\alpha]^{27}_D$ –75.4 (*c* 0.72, $CHCl_3$); IR (neat): 1716 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.05 (s, 6H), 0.85-0.92 (m, 18H), 1.15-1.28 (m, 2H), 1.33-1.42 (m, 2H), 1.62-1.66 (m, 1H), 1.85 (d, *J* = 1.1 Hz, 3H), 1.98-2.05 (m, 1H), 2.16 (s, 3H), 2.26-2.39 (m, 2H), 3.47 (dd, *J* = 6.9, 2.9 Hz, 1H), 3.73 (s, 3H), 4.00-4.03 (m, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 6.92-6.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –3.7, –3.6, 11.4, 12.8, 14.0, 14.1, 14.3, 18.4, 20.9, 26.2 (3C), 29.1, 36.4, 36.6, 39.0, 51.6, 73.0, 75.9, 77.2, 128.4, 140.3, 168.5; HRMS (ESI-TOF) calcd for $C_{23}H_{46}NaO_4SSi$ $[M+Na]^+$: 469.2778; found: 469.2779.

(2*R*,3*S*)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl-(5*S*,6*S*,7*R*,8*S*,*E*)-7-(*tert*-butyl-dimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undec-2-enoate (33). To a stirred solution of **32** (1.14 g, 2.6 mmol) in MeOH (17 mL) and THF (17 mL) was added 1N LiOH (17 mL) at 0 °C. The reaction mixture was warmed to 30 °C and stirred overnight. The mixture was concentrated under reduced pressure and EtOAc and 1N HCl was added to the residue. The whole was extracted with EtOAc and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was filtrated through a short pad of silica gel with hexane-EtOAc (3:1) to give **6**, which was used without further purification. To a stirred solution of the acid **6** in CH_2Cl_2 (12.8 mL) were added MNBA (1.32 g, 3.8 mmol), DMAP (935.0 mg, 7.7 mmol) and **7** (959.0 mg, 3.8 mmol) at room temperature. After being stirred overnight, the mixture was quenched with 1N HCl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (10:1) to give compound **33** (1.48 g, 87%) as a colorless oil: $[\alpha]^{26}_D$ –43.5 (*c* 0.89, $CHCl_3$); IR (neat): 1710 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.05 (s, 3H), 0.07 (s, 3H), 0.86-0.91 (m, 18H), 0.98 (t, *J* = 7.4 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.18-1.28 (m, 2H), 1.34-1.47 (m, 3H), 1.52-1.58 (m, 1H), 1.62-1.64 (m, 1H), 1.89 (s, 3H), 1.99-2.03 (m, 1H), 2.11 (s, 3H), 2.19-2.25 (m, 1H), 2.34-2.37 (m, 2H), 3.47 (dd, *J* = 7.4, 2.9 Hz, 1H), 4.01-4.04 (m, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 5.19 (d, *J* = 3.4 Hz, 1H), 5.25 (d, *J* = 16.6 Hz, 1H), 5.55 (d, *J* = 16.6 Hz, 1H), 7.04-7.07 (m, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.60-7.63 (m, 1H), 7.89-7.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –3.6, –3.5, 11.3, 11.8, 12.7, 14.1, 14.2 (2C), 14.3, 18.4, 20.9, 26.2 (3C), 26.3, 29.4, 36.4, 36.6, 36.9, 39.2, 66.2, 73.0, 74.6, 76.1, 77.2, 127.7 (2C), 128.2, 128.9 (2C), 133.9, 134.1, 141.4, 167.4, 169.7, 191.6; HRMS (ESI-TOF) calcd for $C_{36}H_{60}NaO_7SSi$ $[M+Na]^+$: 687.3721; found: 687.3720.

(2*R*,3*S*)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (5*S*,6*R*,7*R*,8*S*,*E*)-7-hydroxy-2,6,8-trimethyl-5-(methylthiomethoxy)undec-2-enoate (3). To a stirred solution of **33** (80.7 mg, 0.12 mmol) in THF (0.80 mL) and pyridine (0.20 mL) was added HF·pyridine (0.50 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was

poured into aqueous saturated $NaHCO_3$ at 0 °C. The whole was extracted with EtOAc and the extract was washed with brine, 1N HCl and brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (6:1) to give compound **3** (49.2 mg, 74%) as a colorless oil: $[\alpha]^{25}_D$ –5.29 (*c* 1.08, $CHCl_3$); IR (neat): 3526 (OH), 1708 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.83-0.85 (m, 6H), 0.89-0.91 (m, 3H), 0.98 (t, *J* = 7.4 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.24-1.37 (m, 4H), 1.38-1.46 (m, 1H), 1.50-1.59 (m, 1H), 1.61-1.64 (m, 1H), 1.90 (s, 3H), 1.92-1.99 (m, 1H), 2.15-2.16 (m, 4H), 2.19-2.26 (m, 1H), 2.37-2.49 (m, 2H), 3.38-3.41 (m, 1H), 4.08-4.12 (m, 1H), 4.64 (s, 2H), 5.22 (d, *J* = 2.9 Hz, 1H), 5.26 (d, *J* = 16.6 Hz, 1H), 5.55 (d, *J* = 16.6 Hz, 1H), 7.03-7.06 (m, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.60-7.63 (m, 1H), 7.89-7.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.4, 11.7 (2C), 12.6, 14.2 (3C), 20.5, 26.3, 29.6, 34.4, 36.7, 36.9, 38.5, 66.2, 73.5, 74.6, 76.2, 78.3, 127.7 (2C), 128.4, 128.9 (2C), 133.9, 134.1, 140.7, 167.4, 169.7, 191.6; HRMS (ESI-TOF) calcd for $C_{30}H_{46}NaO_7S$ $[M+Na]^+$: 573.2856; found: 573.2855.

(2*R*,3*S*)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (5*S*,6*S*,7*R*,8*S*,*E*)-2,6,8-trimethyl-7-[(*N*-methyl-L-alanyl)oxy]-5-(methylthiomethoxy)undec-2-enoate (34). Fmoc-MeAla-Cl was synthesized by using the identical procedure reported previously.[19] To a stirred solution of Fmoc-MeAla-OH (227.7 mg, 0.70 mmol) in CH_2Cl_2 (3.9 mL) were added DMF (5.4 μL, 0.070 mmol) and $SOCl_2$ (508 μL, 7.0 mmol) at room temperature. After being stirred for 1 h, the mixture was concentrated under reduced pressure to give Fmoc-MeAla-Cl, which was used without further purification. To a stirred solution of **3** (152.6 mg, 0.28 mmol) and the above Fmoc-MeAla-Cl in 1,2-dichloroethane (2.8 mL) was added (*i*-Pr)$_2$NEt (244 μL, 1.40 mmol) at room temperature. The reaction mixture was warmed to 40 °C and stirred for 14 h. The mixture was cooled to room temperature and quenched with saturated aqueous NH_4Cl. The whole was extracted with CH_2Cl_2 and the extract was washed with washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was filtrated through a short pad of silica gel with hexane-EtOAc (9:1 to 3:1) to give crude Fmoc-protected amine, which was used without further purification. To a stirred solution of the above protected amine in MeCN (7.0 mL) was added Et_2NH (2.3 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1.5 h. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (3:1 to 1:2) to give compound **34** (94.9 mg, 54%) as a yellow oil: $[\alpha]^{27}_D$ –55.4 (*c* 0.79, $CHCl_3$); IR (neat): 1712 (C=O); ^{1}H NMR (500 MHz CD_3CN) δ: 0.78 (t, *J* = 7.2 Hz, 3H), 0.81-0.84 (m, 6H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.02-1.08 (m, 1H), 1.09-1.14 (m, 1H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.23-1.34 (m, 3H), 1.39-1.47 (m, 1H), 1.69-1.77 (m, 4H), 1.95 (s, 3H), 2.02-2.08 (m, 1H), 2.13-2.17 (m, 1H), 2.19-2.27 (m, 4H), 2.32-2.36 (m, 1H), 3.13 (q, *J* = 7.1 Hz, 1H), 3.63 (dt, *J* = 10.3, 2.6 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.79 (dd, *J* = 10.3, 2.3 Hz, 1H), 5.05 (d, *J* = 3.4 Hz, 1H), 5.30 (d, *J* = 16.6 Hz, 1H), 5.42 (d, *J* = 16.6 Hz, 1H), 6.78-6.81 (m, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.57-7.61 (m, 1H), 7.85-7.87 (m, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ 10.3, 12.0, 12.8, 13.1, 14.1, 14.4, 14.6, 18.7, 20.9, 26.8, 29.6, 34.4, 34.5,

36.7, 37.0, 37.7, 59.1, 67.7, 73.5, 75.3, 76.1, 78.3, 128.7 (2C), 129.0, 129.8 (2C), 134.9, 135.0, 142.4, 167.9, 170.5, 174.9, 193.2; HRMS(FAB) calcd for $C_{34}H_{54}NO_8S$ $[M+H]^+$: 636.3565; found: 636.3569.

Linear peptides (2a,b). To a stirred solution of **34** (59.5 mg, 0.094 mmol), peptide **5** (185.2 mg) and HOAt (38.4 mg, 0.28 mmol) in CH_2Cl_2 (3.1 mL) was added EDCI·HCl (54.1 mg, 0.28 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 24 h. The mixture was quenched with aqueous saturated $NaHCO_3$. The whole was extracted with CH_2Cl_2 and the extract was washed with aqueous saturated NH_4Cl, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (1:1 to 2:3) to give peptide **35** as a 1.4:1 diastereomixture, which was used without further purification. To a stirred solution of **35** in AcOH/EtOAc/H_2O (60:35:5, 4.3 mL) was added Zn (92.2 mg, 1.4 mmol) at room temperature. After being stirred for 8 h, the reaction mixture was filtered through Celite, and 1N HCl was added to the filtrate. The whole was extracted with EtOAc and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and AcOH was removed by azeotropic distillation with toluene to give the corresponding carboxylic acid, which was used without further purification. To a stirred solution of the above carboxylic acid in MeCN (2.4 mL) was added Et_2NH (0.80 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1.5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by reverse-phase preparative HPLC (59% CH_3CN in 0.1% TFA solution) to give linear peptides **2a** (29.6 mg, 30% from **34**) and **2b** (24.0 mg, 24% from **34**) as a colorless powder.

2a: $[\alpha]^{27}_D$ –46.8 (*c* 0.89, $CHCl_3$); IR (neat): 1645 (C=O); ^{1}H NMR (500 MHz CD_3CN, 1:1 mixture of rotamers) δ: 0.77 (d, *J* = 7.0 Hz, 1.5H), 0.81-0.91 (m, 18.0H), 0.96 (d, *J* = 3.1 Hz, 1.5H), 0.97 (d, *J* = 3.1 Hz, 1.5H), 1.06-1.22 (m, 4.5H), 1.26-1.33 (m, 3.0H), 1.37 (d, *J* = 7.3 Hz, 3.0H), 1.41-1.53 (m, 2.0H), 1.74-1.84 (m, 5.0H), 1.96-2.01 (m, 1.0H), 2.07 (s, 1.5H), 2.08 (s, 1.5H), 2.20-2.38 (m, 3.0H), 2.75-2.86 (m, 4.5H), 3.00-3.12 (m, 6.5H), 3.53 (d, *J* = 16.4 Hz, 0.5H), 3.70-3.71 (m, 1.0H), 4.00 (d, *J* = 18.0 Hz, 0.5H), 4.05-4.09 (m, 0.5H), 4.17 (d, *J* = 18.0 Hz, 0.5H), 4.24 (d, *J* = 16.4 Hz, 0.5H), 4.31-4.36 (m, 0.5H), 4.48-4.50 (m, 0.5H), 4.53 (d, *J* = 5.0 Hz, 0.5H), 4.55 (d, *J* = 5.0 Hz, 0.5H), 4.62 (d, *J* = 5.0 Hz, 0.5H), 4.64 (d, *J* = 5.0 Hz, 0.5H), 4.73-4.76 (m, 0.5H), 4.87-4.89 (m, 1.0H), 4.95 (d, *J* = 3.4 Hz, 0.5H), 4.96 (d, *J* = 3.4 Hz, 0.5H), 5.19 (q, *J* = 7.3 Hz, 0.5H), 5.24 (q, *J* = 7.3 Hz, 0.5H), 5.43-5.46 (m, 0.5H), 5.63 (dd, *J* = 9.9, 5.7 Hz, 0.5H), 6.82-6.89 (m, 1.0H), 7.15-7.28 (m, 6.0H), 7.64 (br s, 2.0H); ^{13}C NMR (125 MHz, CD_3CN) δ: 10.2 (2C), 11.1, 11.3, 11.9 (2C), 12.7 (2C), 13.0, 13.1, 14.2 (2C), 14.3 (2C), 14.8 (3C), 14.9, 15.5, 15.7, 16.0, 16.1, 20.8 (2C), 24.9, 25.1, 26.8 (2C), 29.3, 29.4, 30.5, 31.5, 32.5 (2C), 34.5, 34.6, 35.4, 35.6, 35.7, 36.8 (2C), 37.0 (3C), 37.2, 37.3 (2C), 37.7, 48.0, 48.6, 52.0, 52.3, 53.5 (2C), 53.7, 55.1, 55.3, 56.0, 73.6 (2C), 75.4, 75.6, 76.5 (2C), 78.9 (2C), 127.4, 127.7, 128.9, 129.0, 129.1 (2C), 129.2 (2C), 130.2 (2C), 130.3 (2C), 137.5, 137.8, 142.4 (2C), 168.3, 168.5, 168.9, 169.5, 170.0, 170.4, 171.2, 171.7, 172.2, 172.3, 172.5 (2C), 173.4, 174.0; HRMS (ESI-TOF) calcd for $C_{48}H_{80}N_5O_{11}S$ $[M+H]^+$: 934.5570; found: 934.5567.

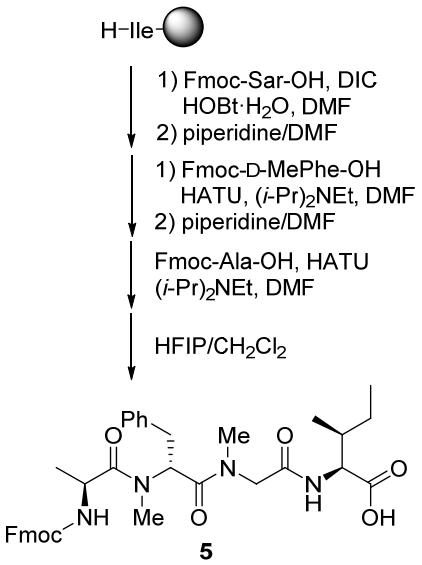
2b: $[\alpha]^{28}_{D}$ –23.5 (*c* 1.00, $CHCl_3$); IR (neat): 1648 (C=O); ^{1}H NMR (500 MHz CD_3CN, 3:3:3:1 mixture of rotamers) δ: 0.74 (d, *J* = 6.9 Hz, 0.9H), 0.78-0.98 (m, 21.9H), 1.05 (d, *J* = 6.9 Hz, 1.2H), 1.08-1.51 (m, 11.0H), 1.75-1.90 (m, 5.0H), 1.97-2.02 (m, 1.0H), 2.05-2.06 (m, 2.7H), 2.09 (s, 0.3H), 2.19-2.45 (m, 3.0H), 2.72 (s, 0.3H), 2.81-2.86 (m, 4.8H), 2.89-2.91 (m, 2.0H), 2.93 (s, 0.3H), 2.95 (s, 0.3H), 3.00-3.09 (m, 1.8H), 3.12-3.18 (m, 1.5H), 3.43 (d, *J* = 16.1 Hz, 0.1H), 3.55-3.56 (m, 0.1H), 3.61-3.76 (m, 1.6H), 4.09-4.16 (m, 0.6H), 4.25-4.36 (m, 1.3H), 4.45-4.48 (m, 0.4H), 4.52-4.64 (m, 1.9H), 4.70-4.73 (m, 0.3H), 4.79-5.00 (m, 3.0H), 5.08-5.12 (m, 0.7H), 5.26 (dd, *J* = 9.3, 6.0 Hz, 0.3H), 5.33 (dd, *J* = 11.1, 4.4 Hz, 0.3H), 5.46 (dd, *J* = 11.1, 4.8 Hz, 0.3H), 5.52 (dd, *J* = 9.5, 6.4 Hz, 0.1H), 6.84-6.91 (m, 1.0H), 6.97 (d, *J* = 9.2 Hz, 0.3H), 7.07-7.26 (m, 5.0H), 7.42 (d, *J* = 7.3 Hz, 0.3H), 7.69 (d, *J* = 6.7 Hz, 0.4H), 8.11 (br s, 2.0H); ^{13}C NMR (125 MHz, CD_3CN) δ: 10.3 (3C), 10.6, 12.0 (2C), 12.2 (2C), 12.8, 12.9, 13.2 (3C), 13.7, 14.2 (2C), 14.4 (2C), 14.6 (2C), 14.7, 14.8, 14.9 (2C), 15.1, 15.2, 15.9 (2C), 16.1 (2C), 16.2, 16.3, 20.8, 20.9, 26.8 (2C), 26.9 (2C), 27.0 (2C), 27.4, 29.4, 29.5(2C), 29.6, 30.4, 30.5, 30.6, 31.1, 31.9, 32.6, 32.7, 33.6, 34.5, 34.6, 34.7, 35.2, 35.3, 35.4, 35.5, 35.6, 35.9, 36.5, 36.8, 37.0 (4C), 37.1, 37.2, 37.4 (2C), 38.1, 38.4, 48.0 (2C), 48.6 (2C), 52.5, 52.6, 53.0, 53.2, 54.0, 54.3 (2C), 54.7, 54.8, 55.0, 56.4, 57.1, 58.1, 73.5, 75.3 (2C), 75.6 (2C), 75.9, 76.1 (2C), 78.6, 79.0, 79.6, 79.7, 127.5 (2C), 127.6, 129.1 (3C), 129.2 (3C), 129.3, 130.2 (2C), 130.3 (3C), 130.4 (2C), 137.5, 137.8, 138.1, 138.3, 141.4, 141.5, 141.9, 142.2, 167.9, 168.1, 168.2, 168.3, 168.7, 169.6, 170.1, 170.2, 170.3 (2C), 170.8, 171.2 (2C), 171.3, 171.4, 171.8, 172.0, 172.2 (2C), 172.5, 173.4, 174.4, 174.7; HRMS (ESI-TOF) calcd for $C_{48}H_{80}N_5O_{11}S$ $[M+H]^+$: 934.5570; found: 934.5580.

Odoamide (1a). To a stirred solution of **2a** (17.8 mg, 0.017 mmol), HOAt (11.6 mg, 0.085 mmol) and collidine (67 μL, 0.51 mmol) in DMF (17.0 mL) was added HATU (64.6 mg, 0.17 mmol) at room temperature. After being stirred for 5 h, the reaction mixture was concentrated under reduced pressure, and EtOAc and 1N HCl were added to the residue. The whole was extracted with EtOAc and the extract was washed with brine, aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (1:1 to 0:1) to give the corresponding cyclic peptide, which was used without further purification. To a stirred solution of the above cyclic peptide in THF/H_2O (4:1, 566 μL) were added 2,6-lutidine (39.4 μL, 0.34 mmol) and $AgNO_3$ (115.5 mg, 0.68 mmol) at room temperature. The reaction mixture was warmed to 70 °C and stirred for 4 h. The mixture was filtered through Celite, and 1N HCl was added to the filtrate. The whole was extracted with EtOAc and the extract was washed with H_2O, aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by reverse-phase preparative HPLC (72% CH_3CN in H_2O) to give odoamide (**1a**) (12.4 mg, 85%) as a colorless powder: $[\alpha]^{28}_{D}$ –15.8 (*c* 1.14, CH_3OH); IR (neat): 3305 (OH), 1645 (C=O); ^{1}H NMR (500 MHz, CD_3OD) δ: 0.83-0.96 (m, 21H), 1.04-1.12 (m, 4H), 1.19-1.26 (m, 1H), 1.29-1.40 (m, 4H), 1.42 (d, *J* = 6.9 Hz, 3H), 1.45-1.55 (m, 1H), 1.57-1.67 (m, 1H), 1.78-1.87 (m, 3H), 1.90 (s, 3H), 2.01-2.04 (m, 1H), 2.12-2.16 (m, 1H), 2.20-2.28 (m, 1H), 2.85-2.95 (m, 4H), 3.01-3.06 (m, 4H), 3.30 (s, 3H),

3.56 (d, J = 18.3 Hz, 1H), 3.74-3.76 (m, 1H), 3.94 (q, J = 6.9 Hz, 1H), 4.19 (d, J = 18.3 Hz, 1H), 4.49 (q, J = 6.9 Hz, 1H), 4.86-4.89 (m, 2H), 5.05 (d, J = 6.3 Hz, 1H), 5.45 (dd, J = 10.3, 5.2 Hz, 1H), 7.12-7.20 (m, 5H), 7.31-7.32 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ: 10.0, 11.7, 12.0, 12.1, 13.1, 13.8, 14.5, 14.6, 15.6, 16.0, 21.6, 24.7, 27.4, 30.5 (2C), 35.8, 35.9, 36.6, 37.6, 37.8, 38.5, 39.4, 41.3, 46.4, 52.6, 54.7, 55.0, 60.3, 71.5, 77.6, 79.2, 127.4, 128.6, 129.1 (2C), 130.6 (2C), 138.4, 146.8, 170.4, 171.3, 172.5, 172.7, 172.8, 173.0, 174.9; HRMS (ESI-TOF) calcd for $C_{46}H_{73}N_5NaO_{10}$ $[M+Na]^+$: 878.5250; found: 878.5254.

2-Oxo-2-phenylethyl (2*R*,3*S*)-2-hydroxy-3-methylpentanoate (7). To a stirred solution of D-*allo*-isoleucic acid (3.2 g, 24.5 mmol) in THF (143 mL) under argon were added Et_3N (3.6 mL, 25.7 mmol) and phenacyl bromide (5.4 g, 27.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was quenched with aqueous saturated NH_4Cl. The whole was extracted with Et_2O and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane-EtOAc (10:1 to 3:1) to give compound **7** (5.0 g, 82%) as a colorless solid: mp 52 °C; $[\alpha]^{27}_D$ –19.2 (*c* 1.07, $CHCl_3$); IR (neat): 3524 (OH), 1704 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97 (d, J = 6.9 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H), 1.37-1.45 (m, 1H), 1.56-1.64 (m, 1H), 1.96-2.04 (m, 1H), 2.66 (d, J = 6.3 Hz, 1H), 4.41 (dd, J = 6.3, 2.9 Hz, 1H), 5.39 (d, J = 16.0 Hz, 1H), 5.52 (d, J = 16.0 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.62-7.65 (m, 1H), 7.91-7.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.9, 13.0, 26.1, 38.5, 66.5, 73.0, 127.7 (2C), 128.9 (2C), 133.9, 134.1, 174.9, 191.3; Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.15; H, 7.24.

Tetrapeptide (5). Peptide **5** was synthesized by Fmoc-based solid-phase peptide synthesis using H-Ile-(2-Cl)Trt resin (0.85 mmol/g, 2.03 g, 1.72 mmol). For Fmoc deprotection during solid-phase peptide synthesis, the peptidyl resin was treated with piperidine/DMF (2:8) for 20 min.



Coupling reaction of Sar using DIC/HOBt: DIC (799 μL, 5.17 mmol) was added to a solution of Fmoc amino acid (5.17 mmol) and HOBt·H_2O (791.0 mg, 5.17 mmol) in DMF (11.5 mL). The whole was poured into the peptidyl resin (1.72 mmol), and the reaction was continued for 2 h.

Coupling reaction of D-MePhe and Ala using HATU/(i-Pr)$_2$NEt: To a solution of Fmoc amino acid (5.17 mmol) in DMF (11.5 mL) were added HATU (1.90 g, 4.99 mmol) and (i-Pr)$_2$NEt (1.80 mL, 10.33 mmol). The whole was poured into the peptidyl resin (1.72 mmol), and the reaction was continued for 2 h.

Cleavage from the resin. The peptidyl resin was treated with 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP)/CH_2Cl_2 (3:7) at room temperature for 2 h. After removal of the resin by filtration, the filtrate was concentrated under reduced pressure and the residue was filtrated through a short pad of silica

gel with $CHCl_3$-MeOH (10:0 to 7:1) to give peptide **5** as a colorless amorphous solid, which was used without further purification: purity 95%; HPLC retention time: 19.1 min (45 to 75% linear gradient of MeCN in 0.1% TFA solution over 30 min); $[\alpha]^{28}_D$ +55.1 (*c* 1.04, $CHCl_3$); IR (neat): 1634 (C=O); ^{1}H NMR (500 MHz, CD_3OD, 6:4 mixture of rotamers) δ: 0.76 (d, *J* = 6.9 Hz, 1.2H), 0.83-0.95 (m, 7.8H), 1.16-1.28 (m, 1.0H), 1.42-1.54 (m, 1.0H), 1.85-1.93 (m, 1.0H), 2.83-2.94 (m, 3.4H), 2.97-3.12 (m, 4.6H), 3.88 (d, *J* = 17.2 Hz, 0.4H), 4.04-4.18 (m, 2.2H), 4.22-4.33 (m, 2.0H), 4.35-4.46 (m, 2.0H), 4.55 (d, *J* = 17.2 Hz, 0.4H), 5.72 (dd, *J* = 10.0, 5.4 Hz, 0.4H), 5.83 (dd, *J* = 9.7, 5.7 Hz, 0.6H), 7.15-7.25 (m, 5.0H), 7.27-7.30 (m, 2.0H), 7.35-7.39 (m, 2.0H), 7.60-7.65 (m, 2.0H), 7.76-7.78 (m, 2.0H); ^{13}C NMR (125 MHz, CD_3OD) δ: 12.0, 12.1, 16.2, 16.3, 16.9, 17.1, 26.3 (2C), 30.8, 31.1, 35.8, 36.1 (2C), 37.3, 38.7 (2C), 48.4 (2C), 48.5 (2C), 52.4, 53.1, 55.2, 56.1, 58.3, 58.5, 68.0, 68.3, 121.1 (4C), 126.4 (2C), 126.5 (2C), 127.8 (2C), 128.3 (4C), 128.9 (2C), 129.0 (2C), 129.4 (4C), 130.6 (2C), 130.9 (2C), 138.4, 138.5, 142.7 (4C), 145.3 (2C), 145.4 (2C), 158.1, 158.3, 170.7, 170.9, 172.3, 172.7, 174.8, 174.9, 175.0, 175.3; HRMS (ESI-TOF) calcd for $C_{37}H_{44}N_4NaO_7$ $[M+Na]^+$: 679.3102; found: 679.3100.

[D-*allo*-Ile]-Odoamide (1b). According to the procedure described for the preparation of **1a**, **2b** (5.8 mg, 0.0055 mmol) was converted into **1b** (2.9 mg, 62%) as a colorless powder: $[\alpha]^{27}_D$ +4.36 (*c* 0.99, CH_3OH); IR (neat): 3297 (OH), 1640 (C=O); ^{1}H NMR (500 MHz, CD_3OD, 6:4 mixture of rotamers) δ: 0.67 (d, *J* = 6.9 Hz, 1.2H), 0.84-1.03 (m, 22.8H), 1.12-1.49 (m, 11.0H), 1.77-1.88 (m, 5.0H), 1.91-1.97 (m, 0.6H), 1.99-2.14 (m, 1.4H), 2.22-2.24 (m, 1.0H), 2.39-2.43 (m, 1.0H), 2.76 (s, 1.2H), 2.81-2.86 (m, 0.4H), 2.89 (s, 1.8H), 2.95 (s, 1.8H), 2.97-3.06 (m, 2.2H), 3.07-3.16 (m, 3.6H), 3.72 (d, *J* = 16.0 Hz, 0.4H), 3.77 (d, *J* = 16.9 Hz, 0.6H), 3.79-3.83 (m, 1.0H), 4.41 (d, *J* = 16.9 Hz, 0.4H), 4.60-4.67 (m, 1.6H), 4.77-4.80 (m, 1.0H), 4.88-4.91 (m, 1.0H), 4.97 (dd, *J* = 10.3, 1.7 Hz, 0.6H), 5.05-5.10 (m, 1.0H), 5.18 (d, *J* = 3.4 Hz, 0.4H), 5.65 (dd, *J* = 9.7, 5.2 Hz, 0.4H), 5.85 (dd, *J* = 10.6, 5.4 Hz, 0.6H), 6.89-6.92 (m, 0.4H), 6.96-6.99 (m, 0.6H), 7.12-7.24 (m, 5.0H), 7.61 (d, *J* = 6.9 Hz, 0.6H), 7.91-7.94 (m, 1.0H), 8.19 (d, *J* = 7.4 Hz, 0.4H); ^{13}C NMR (125 MHz, CD_3OD) δ: 10.2, 10.4, 11.9, 12.0 (2C), 12.2, 12.8, 13.0, 13.1, 13.4, 14.5, 14.6, 14.7, 14.8 (2C), 14.9, 15.1, 15.4, 16.6, 17.3, 21.3 (2C), 27.1 (2C), 27.6, 27.8, 30.4, 31.0, 31.4, 32.0, 33.0, 33.4, 34.9, 35.0, 35.2, 35.8, 36.0, 36.5, 37.7, 37.8 (2C), 38.5, 38.7, 38.9, 42.4, 42.6, 46.0, 46.8, 51.3, 52.8, 54.1, 54.5, 54.7, 55.1, 55.5, 56.8, 70.1 (2C), 76.8, 77.5, 79.1, 79.2, 127.5, 127.7, 129.2 (2C), 129.3 (2C), 129.5 (2C), 130.7 (2C), 130.8 (2C), 137.9, 138.5, 142.1, 143.3, 168.3, 168.4, 170.2, 171.0, 171.6, 172.2, 172.3 (2C), 172.5, 172.9, 173.0, 173.1, 173.6, 174.2; HRMS (ESI-TOF) calcd for $C_{46}H_{73}N_5NaO_{10}$ $[M+Na]^+$: 878.5250; found: 878.5252.

Determination of relative configuration of the two hydroxy groups

Methyl (5*R*,6*S*,7*R*,8*S*,*E*)-5,7-dihydroxy-2,6,8-trimethylundec-2-enoate (30a). According to the procedure described for the preparation of **27a**, **25a** (121.0 mg, 0.31 mmol) was converted into **30a** (69.1 mg, 81%) as a colorless oil: $[\alpha]^{26}_D$ +21.1 (*c* 1.04, $CHCl_3$); IR (neat): 3410 (OH), 1713 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.89-0.93 (m, 9H), 1.16-1.22 (m, 1H), 1.28-1.42 (m, 3H), 1.65-1.68 (m, 1H), 1.85-1.87 (m, 1H), 1.88 (s, 3H), 2.13 (d, *J* = 4.6 Hz, 1H), 2.28-2.34 (m, 1H), 2.44-2.51 (m,

1H), 2.84 (d, *J* = 5.2 Hz, 1H), 3.51-3.54 (m, 1H), 3.74 (s, 3H), 4.01-4.05 (m, 1H), 6.84-6.87 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.7, 12.7, 13.1, 14.3, 20.2, 32.9, 35.0, 36.0, 38.7, 51.8, 72.6, 78.1, 129.2, 139.3, 168.5; HRMS (ESI-TOF) calcd for $C_{15}H_{28}NaO_4$ $[M+Na]^+$: 295.1880; found: 295.1882.

Methyl (*E*)-2-methyl-4-{(4*R*,5*S*,6*R*)-2,2,5-trimethyl-6-[(*S*)-pentan-2-yl]-1,3-dioxan-4-yl}but-2-enoate (31a). According to the procedure described for the preparation of **28a**, **30a** (30.6 mg, 0.11 mmol) was converted into **31a** (29.4 mg, 86%) as a colorless oil: $[\alpha]^{26}_D$ –6.65 (*c* 1.07, $CHCl_3$); IR (neat): 1716 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.84 (d, *J* = 6.9 Hz, 3H), 0.88-0.91 (m, 6H), 1.17-1.23 (m, 1H), 1.24-1.35 (m, 7H), 1.35-1.42 (m, 2H), 1.48-1.55 (m, 1H), 1.77-1.84 (m, 1H), 1.85 (s, 3H), 2.20-2.34 (m, 2H), 3.17 (dd, *J* = 8.0, 3.4 Hz, 1H), 3.74 (s, 3H), 3.86-3.90 (m, 1H), 6.73-6.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.4, 12.7, 14.1, 14.2, 20.5, 23.5, 25.2, 30.4, 35.7, 35.8, 36.4, 51.7, 68.6, 77.4, 100.3, 128.8, 138.8, 168.5; HRMS (ESI-TOF) calcd for $C_{18}H_{32}NaO_4$ $[M+Na]^+$: 335.2193; found: 335.2194.

Methyl (5*R*,6*S*,7*R*,8*R*,*E*)-5,7-dihydroxy-2,6,8-trimethylundec-2-enoate (30b). According to the procedure described for the preparation of **27a**, **25b** (26.1 mg, 0.068 mmol) was converted into **30b** (14.9 mg, 81%) as a colorless oil: $[\alpha]^{27}_D$ +36.6 (*c* 0.75, $CHCl_3$); IR (neat): 3394 (OH), 1714 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.87 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 7.4 Hz, 3H), 1.07-1.15 (m, 1H), 1.19-1.30 (m, 1H), 1.41-1.51 (m, 1H), 1.53-1.59 (m, 1H), 1.65-1.73 (m, 1H), 1.81-1.86 (m, 1H), 1.88 (s, 3H), 2.26-2.31 (m, 1H), 2.44-2.50 (m, 2H), 3.08 (br s, 1H), 3.38-3.40 (m, 1H), 3.74 (s, 3H), 4.08-4.11 (m, 1H), 6.81-6.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.6, 12.7, 14.4, 16.2, 20.1, 33.4, 33.6, 35.6, 37.7, 51.8, 71.6, 80.6, 129.4, 138.8, 168.4; HRMS (ESI-TOF) calcd for $C_{15}H_{28}NaO_4$ $[M+Na]^+$: 295.1880; found: 295.1880.

Methyl (*E*)-2-methyl-4-{(4*R*,5*S*,6*R*)-2,2,5-trimethyl-6-[(*R*)-pentan-2-yl]-1,3-dioxan-4-yl}but-2-enoate (31b). According to the procedure described for the preparation of **28a**, **30b** (11.5 mg, 0.042 mmol) was converted into **31b** (10.2 mg, 78%) as a colorless oil: $[\alpha]^{27}_D$ –1.27 (*c* 0.96, $CHCl_3$); IR (neat): 1716 (C=O); ^{1}H NMR (500 MHz $CDCl_3$) δ: 0.87 (d, *J* = 6.9 Hz, 3H), 0.89-0.93 (m, 6H), 1.10-1.17 (m, 1H), 1.18-1.25 (m, 1H), 1.32 (s, 6H), 1.39-1.48 (m, 2H), 1.54-1.58 (m, 1H), 1.76-1.82 (m, 1H), 1.86 (d, *J* = 1.1 Hz, 3H), 2.19-2.25 (m, 1H), 2.27-2.34 (m, 1H), 3.14 (dd, *J* = 7.2, 4.9 Hz, 1H), 3.74 (s, 3H), 3.87-3.90 (m, 1H), 6.72-6.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.7 (2C), 14.4, 15.7, 20.4, 23.4, 25.5, 30.4, 33.9, 36.1, 36.7, 51.7, 68.6, 78.7, 100.3, 128.9, 138.8, 168.5; HRMS (ESI-TOF) calcd for $C_{18}H_{32}NaO_4$ $[M+Na]^+$: 335.2193; found: 335.2187.

Growth Inhibition Assay

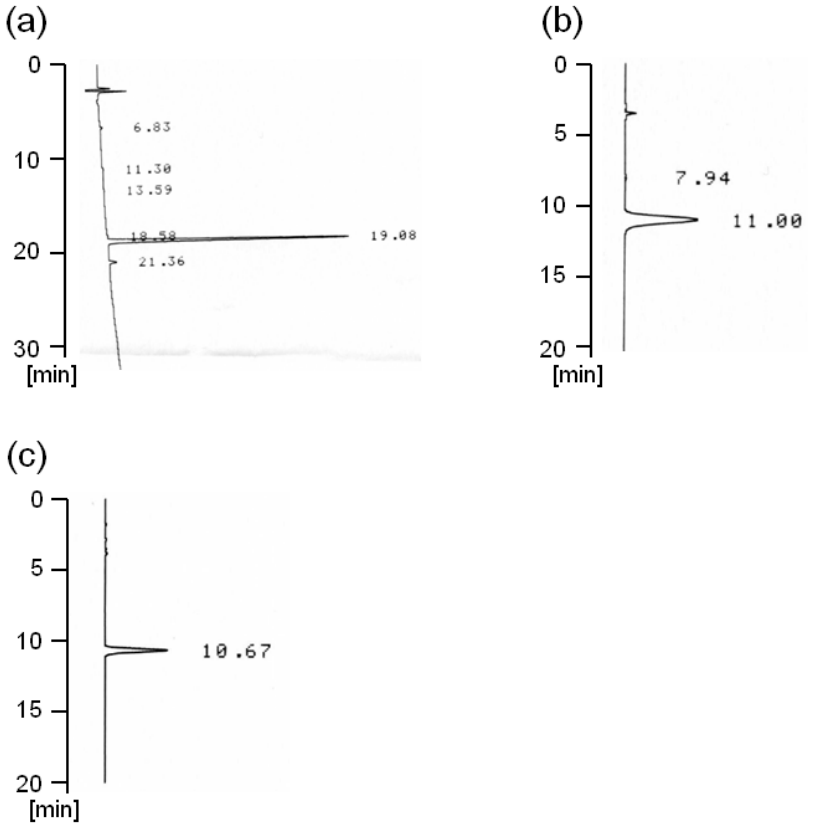
A549 cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Sigma) supplemented with 10% (v/v) fetal bovine serum at 37 °C in a 5% CO_2-incubator. Growth inhibition assays using A549 cells were performed in 96-well plates (BD Falcon). A549 cells were seeded at 500 cells/well in 50 μL of culture media, respectively, and were cultured for 6 h. Chemical compounds in DMSO were diluted 250-fold with the culture medium in advance. Following the addition of 40 μL of the fresh culture medium to the cell cultures, 30 μL of the chemical diluents were also added. The final

volume of DMSO in the medium was equal to 0.1% (v/v). The cells under chemical treatment were incubated for further 72 h. The wells in the plates were washed twice with the cultured medium without phenol-red. After 1 h incubation with 100 μL of the medium, the cell culture in each well was supplemented with 20 μL of the MTS reagent (Promega), followed by incubation for additional 40 min. Absorbance at 490 nm of each well was measured using a Wallac 1420 ARVO SX multilabel counter (Perkin Elmer). Three experiments were performed per condition and the averages of inhibition rates in each condition were evaluated to determine IC_{50} values using the GraphPad Prism software.

Absolute configurations of Ile in 1a and 1b

The synthetic odoamide **1a** was treated with 5N HCl (0.5 mL) at 105 °C for 12 h. The hydrolysate was concentrated to dryness and partitioned between H_2O-EtOAc (1:1). The aqueous layer was subjected to HPLC [Cosmosil HILIC (4.6×250 mm), MeCN/10 mM $AcONH_4$ 85:15 at 1.0 mL/min, UV detection at 215 nm] to yield an Ile residue. Ile was added with 0.1% solution of Nα-(5-fluoro-2,4-dinitrophenyl)-L-alaninamide (L-FDAA, Marfey's reagent, 200 μL) in acetone and 0.5 M $NaHCO_3$ (100 μL) followed by heating at 40 °C for 90 min. After cooling to room temperature, the reaction mixture was neutralized with 2N HCl (25 μL) and diluted with MeOH (300 μL). The L-FDAA derivatives of Ile were prepared by the same procedure. The solution of Ile from the hydrolysate and the authentic standards were subjected to chiral HPLC [DAICEL CHIRALPAK QN-AX (4.6×150 mm), MeOH/MeCN/H_2O 49:49:2 (50 mM HCOOH, 25 mM Et_2NH) at 1.0 mL/min, UV detection at 340 nm], respectively. The retention times of the authentic standards were as follows: L-*allo*-Ile (9.4), L-Ile (10.2), D-Ile (14.8) and D-*allo*-Ile (15.2). The retention time of the L-FDAA derivative of Ile from the hydrolyzate was 10.2 min, proving the configuration of Ile was L. The absolute configuration of Ile in **1b** was also investigated by the same protocol. The retention time of the L-FDAA derivative of Ile from **1b** was 15.2 min, proving the configuration of Ile was D-*allo*.

HPLC Chromatograms. (a) peptide **5**. *HPLC conditions*: 45 to 75% linear gradient of MeCN in 0.1% TFA solution over 30 min; (b) odoamide **1a**. *HPLC conditions*: 76% MeCN in H_2O; (c) [D-*allo*-Ile]-odoamide **1b**. *HPLC conditions*: 76% MeCN in H_2O.



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Chapter 1. Synthetic and Structure-activity Relationship Studies of Odoamide

Section 2. Structure-activity Relationship Study of a Cyclic Depsipeptide, Odoamide

Summary

For an efficient structure-activity relationship study of the peptide part of odoamide, a facile synthetic protocol was established using a solid-phase peptide synthesis. Among a series of peptides, the D-MeAla6 isomer exhibited a more potent cytotoxicity than natural odoamide. It was also demonstrated that the 26-membered natural odoamide and the 24-membered isomer with comparable cytotoxicities were slowly interconvertible and both isomers contributed to the potent cytotoxicity of odoamide. Examination of the physicochemical properties revealed that the in vitro cytotoxicity was affected by the serum-protein binding of odoamide derivatives, while the differences in the macrocyclic structures had no significant effect on the membrane permeability.

Aurilide-class depsipeptides share similar peptide and polyketide substructures, while individual peptides have unique sets of structural motifs. The configurations of the chiral centers in odoamide (**1a**) are identical those of aurilide (**2**),[1] with three of the amino acids having different side-chains (Figure 1). Kulokekahilide-2 (**3**),[2] which comprises similar amino acid components to **1a**, contains a D-Ala at the L-MeAla6 position of **1a**. Lagunamide C (**4**)[3] and palau'amide (**5**)[4] have 27-membered and 24-membered macrocycles, respectively. Twenty-four-membered cyclic peptides such as palau'amide **5** have shown highly potent cytotoxicities despite the apparently alternative global conformations.[4,5]

There have been several structure-activity relationship studies of aurilide-class depsipeptides for the design of molecular probes for target identification, as well as to determine the absolute stereochemistry of the natural products.[2b,6] In these studies, the natural isomers were more cytotoxic compared with a number of depsipeptide epimers. A possible intramolecular ester exchange between the polyketide 5- and 7-hydroxy groups was also investigated in kulokekahilide-2 (**3**). Twenty-six-membered macrocycle (**3**) and the palau'amide-type 24-membered isomer were interconverted by acyl transfer reactions in a low polarity solvent such as CD_2Cl_2; no transformation was observed in polar solvents.[7] The 1,3-acyl shift of **3** and the derivatives was dependent on the presence of D-Ala6 and appropriate conformations.[5b] However, the stability of a series of peptides in aqueous media was not assessed because of their low solubility.[5b] The author expected that an improved detection system would facilitate the evaluation of the postulated acyl transfers between two possible odoamide isomers (**1a** and **6**) under bioassay conditions (Figure 2). Based on the previous findings of aurilide-class depsipeptides, the author investigated the structure-activity relationship of the cytotoxicities and physicochemical properties, including serum protein binding and membrane permeability, of odoamide derivatives.

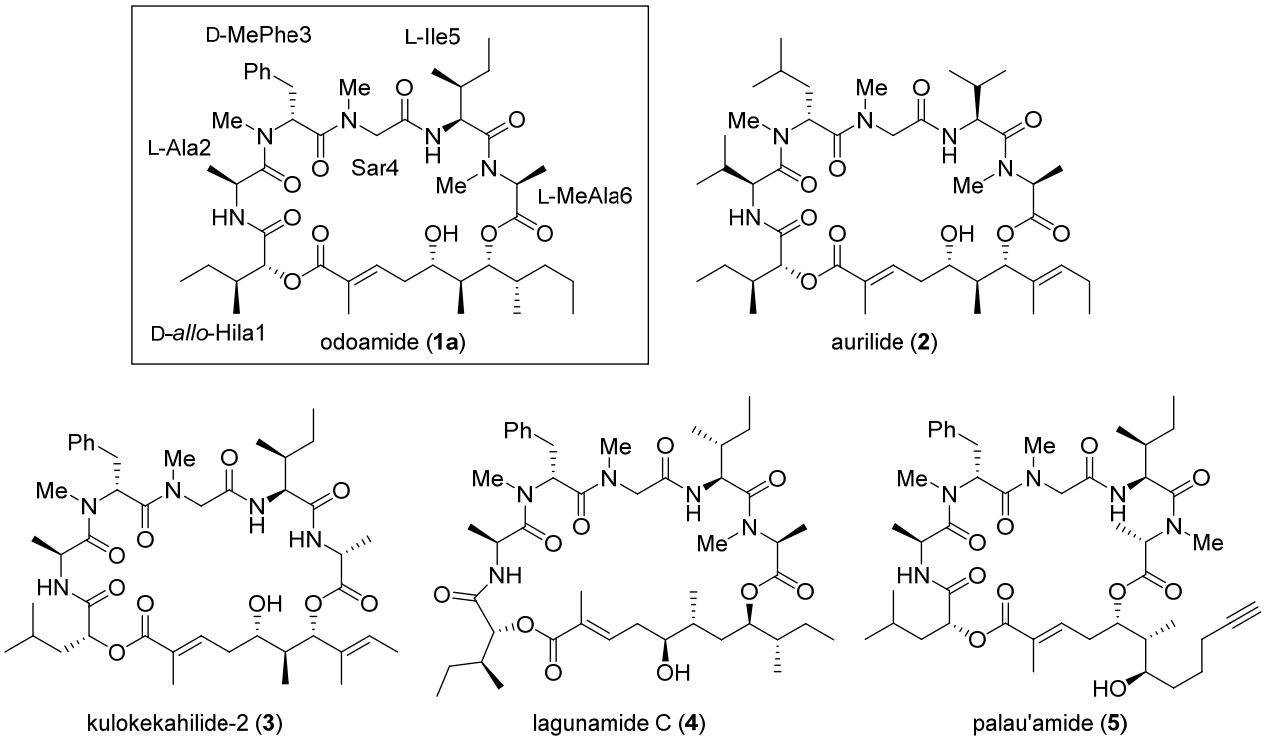


Figure 1. Structures of odoamide (**1a**) and aurilide-class depsipeptides. *Abbreviation*: Hila: isoleucic acid; Sar: sarcosine.

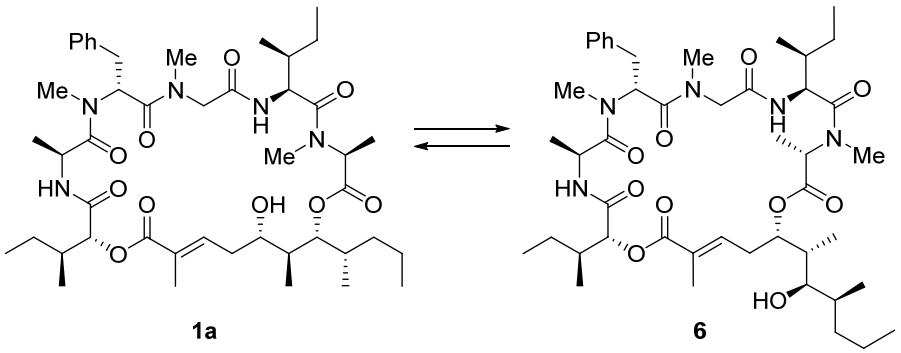
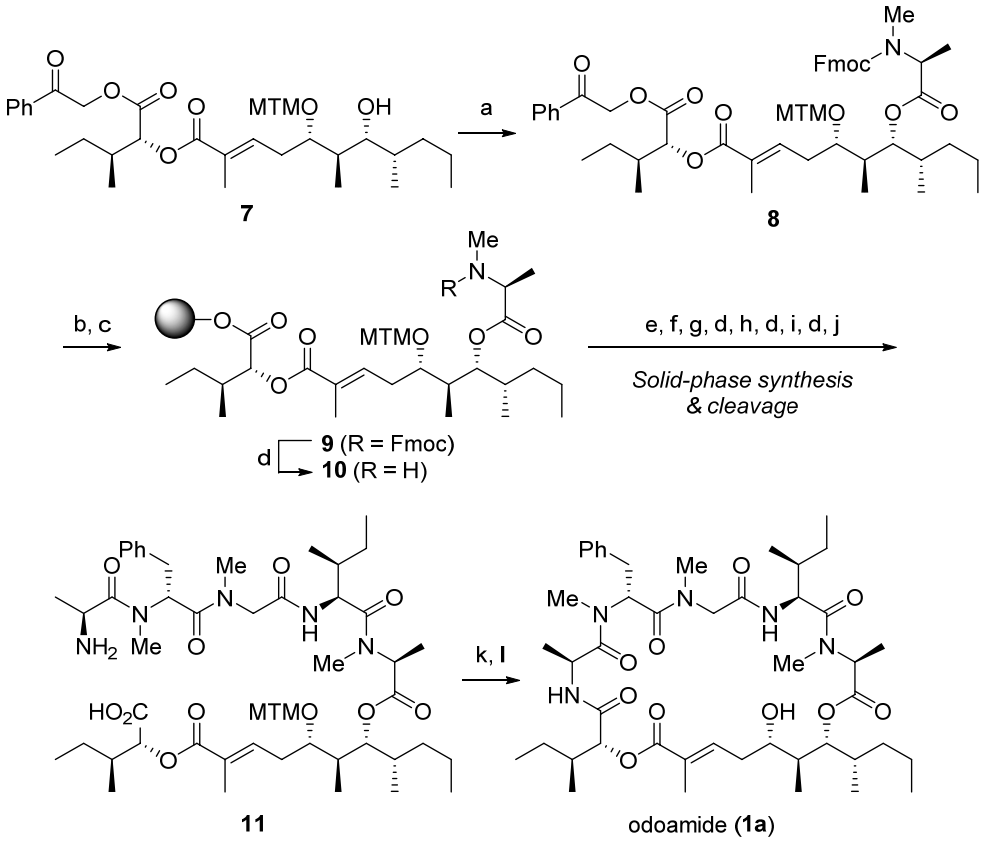


Figure 2. Possible acyl transfers between 1,3-diol in odoamide (**1a**) and 24-membered macrocyclic derivative (**6**).

As mentioned in Chapter 1, Section 1, the author achieved the total synthesis of odoamide using a convergent approach via conjugation of a tetrapeptide fragment with a polyketide portion. However, significant epimerization at the α-position of the Ile was observed during the coupling of tetrapeptide. Additionally, preparations of a variety of tetrapeptide fragments in advance was required for the diversification of the peptide substructure in odoamide. To overcome these disadvantages for the structure-activity relationship study of odoamide, the author initially set out to establish an efficient synthetic route for the late-stage derivatizations of odoamide analogues.

The synthesis began with key alcohol intermediate **7** in Chapter 1, Section 1 (Scheme 1). Acylation of the polyketide 7-hydroxy group in **7** with Fmoc-MeAla-Cl gave a fully-protected amine **8**. Deprotection of the phenacyl ester in **8**, followed by loading the resulting carboxylic acid onto Cl-



Scheme 1. Synthesis of odoamide (**1a**) via solid-phase peptide synthesis. *Reagents and conditions*: (a) Fmoc-L-MeAla-Cl, (*i*-Pr)$_2$NEt, 1,2-dichloroethane, 40 °C; (b) Zn, AcOH, rt; (c) Cl-(2-Cl)Trt resin, (*i*-Pr)$_2$NEt, CH_2Cl_2, rt; (d) 20% piperidine/DMF, rt; (e) Alloc-L-Ile-OH, DIC, HOAt, DMF, rt; (f) $Pd(PPh_3)_4$, $PhSiH_3$, CH_2Cl_2, rt; (g) Fmoc-Sar-OH, HOBt·H_2O, DIC, DMF, rt; (h) Fmoc-D-MePhe-OH, HATU, (*i*-Pr)$_2$NEt, DMF, rt; (i) Fmoc-L-Ala-OH, HATU, (*i*-Pr)$_2$NEt, DMF, rt; (j) 30% HFIP/CH_2Cl_2, rt; (k) HATU, HOAt, collidine, DMF, rt; (l) $AgNO_3$, 2,6-lutidine, THF, H_2O, rt to 70 °C.

(2-Cl)Trt resin provided resin **9**, which was amenable to solid-phase peptide synthesis. After deprotection of the Fmoc group in **9**, Fmoc-Ile-OH was used in the coupling reaction on resin **10**. However, significant elimination of a diketopiperazine consisting of Ile and MeAla dipeptide was observed during the subsequent piperidine treatment for removal of the Fmoc group.[8] To avoid the simultaneous formation of the diketopiperazine under the basic conditions, Alloc protection was chosen for the Ile, as it can be removed under neutral conditions.[9] After coupling of Alloc-Ile-OH with amine **10**, the Alloc group was removed by treatment with $Pd(PPh_3)_4$ and $PhSiH_3$. The sequential coupling of Fmoc amino acids followed by cleavage from the resin provided the linear precursor **11** without epimerization. Odoamide (**1a**) was obtained by same protocol as Section 1 from **11**. A series of odoamide analogues (**1b**, **1c**, **1e**, **6** and **12**-**17**) were also synthesized using this protocol (Figures 3, 5 and 6). The analog **1d** was synthesized in Section 1.

The cytotoxicities of the resulting odoamide analogues against A549 cells were evaluated using an MTS assay. The cultured cells were exposed to each peptide for 72 h. Initially, the author

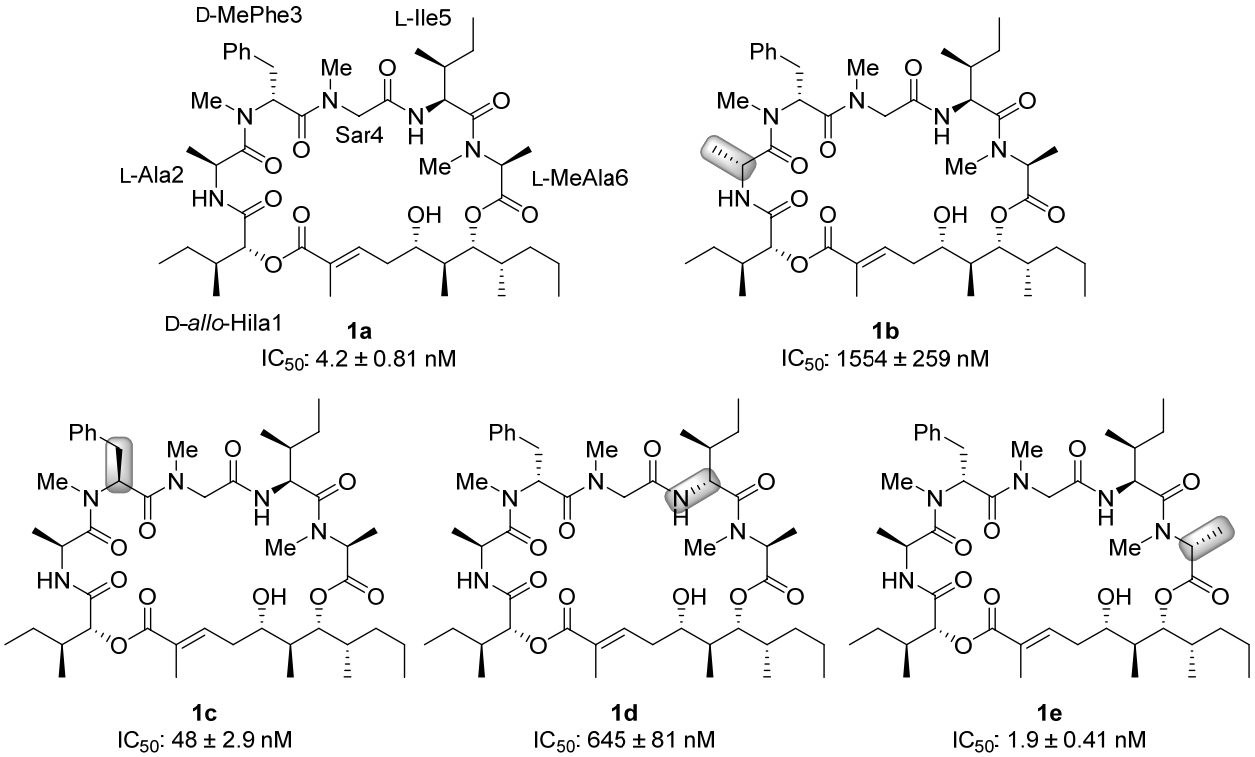


Figure 3. Structures and cytotoxicities of odoamide derivatives with an amino acid epimer. IC_{50} values are the concentrations for 50% growth inhibition of A549 cells (n = 3). *Abbreviation*: Hila: isoleucic acid; Sar: sarcosine.

investigated odoamide epimers **1b**-**e**, which could exhibit different global conformations of the macrocycles compared with that of natural **1a** (Figure 3). D-Ala2 epimer **1b** and D-*allo*-Ile5 epimer **1d** showed significantly less potent cytotoxicities (IC_{50} **1b** = 1.55 μM; IC_{50} **1d** = 645 nM). Substitution of D-MePhe3 with L-MePhe also led to a 10-fold decrease in the bioactivity (IC_{50} **1c** = 48 nM). Significant decrease or loss of the cytotoxicity by the stereoinversion at these positions in kulokelahilide-2 and aurilide have been previously reported,[5,6a] indicating that L-amino acids at positions 2 and 5, and a D-amino acid at position 3 are needed for potent bioactivity of the aurilide family peptides. In contrast, D-MeAla6 epimer **1e** has exhibited slightly more potent bioactivity (IC_{50} = 1.9 nM) compared with odoamide **1a**. Interestingly, the arrangement of the stereochemical configurations in **1e** are identical to that of kulokekahilide-2 (**3**), which has an unmethylated D-Ala at the L-MeAla6 position of **1a**. In the previous SAR study of kulokelahilide-2 derivatives, natural kulokekahilide-2 (**3**) had better cytotoxic profiles against a number of cell lines than the L-Ala6 epimer.[5b] This implies that the D-configuration at the MeAla6 position, regardless of the presence or absence of the *N*-methyl group, would give the appropriate global conformation for the potent cytotoxicities of aurilide family peptides.

Next, the author investigated the intramolecular ester exchange at the polyketide 1,3-diol unit in odoamide (**1a**) under aqueous conditions. In previous research,[7] organic solvents such as CH_2Cl_2 and DMSO were used to dissolve the peptides at high concentrations, which was necessary for

detection by UV absorbance but are not physiological conditions. The author chose liquid chromatography-mass spectrometry (LC-MS) for quantitative analysis to analyze the interconversion between 26- and 24-membered isomers in the range of concentrations of biological evaluations without any pretreatment. Twenty-four-membered isomer **6** was synthesized by the similar protocol to Scheme 1. When natural **1a** (300 nM) was incubated in Dulbecco's modified Eagle medium (DMEM) at 37 °C for 72 h, 31% of **1a** was converted into 24-membered isomer **6** (Figure 4). Vice versa, 26% of **6** (300 nM) was subjected to ring-expansion to provide 26-membered **1a** under the same condition. These results suggest that odoamide is in a slow equilibrium between 26-membered form **1a** and 24-membered form **6**. The 24-membered macrocycle **6** exhibited highly potent cytotoxicity (IC_{50} = 4.5 nM) by 72-h exposure to A549 cells (Figure 5), which correlated with the results for palau'amide (**5**) and the 24-membered analog of kulokekahilide-2.[4,5a] It is unlikely that the bioactivity of the 24-membered peptide **6** was solely derived from natural **1a** generated by acyl transfer of **6**, because the potency difference between peptides **1a** and **6** was minimal. Indeed, calculated from their potencies and conversion yields after 72-h incubation, 24-membered **6** itself (without acyl transfer) displays cytotoxic effect with an IC_{50} values of <4.7 nM. Therefore, the author concluded that natural 26-membered form **1a** and 24-membered isomer **6** both contribute to the potent cytotoxicity of odoamide.

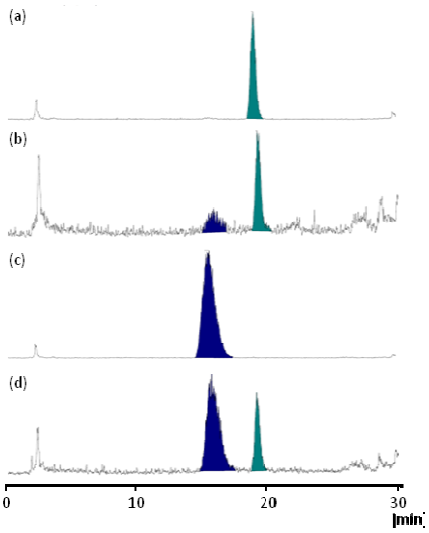
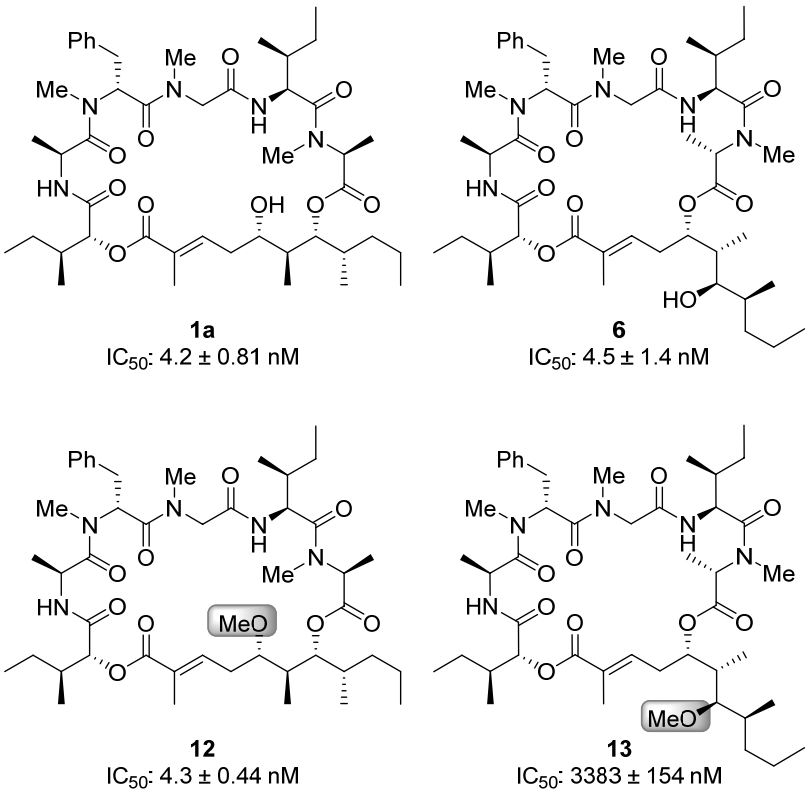


Figure 4. LC-MS chromatograms of odoamide **1a** and the 24-membered ring isomer **6**. (a) odoamide **1a**; (b) odoamide **1a** after 72-h incubation in cell culture media; (c) 24-membered ring isomer **6**; (d) 24-membered ring isomer **6** after 72-h incubation in cell culture media. *HPLC conditions*: 60 to 90% linear gradient of MeCN in 0.1% TFA solution over 30 min.

Two methoxy derivatives **12** and **13** were synthesized, which would prevent the polyketide component in **1a** and **6** from undergoing acyl transfer reactions. The 26-membered macrocycle **12** retained the cytotoxic activity of odoamide **1a** (IC_{50} = 4.3 nM), while the 24-membered isomer **13** showed significantly less potent activity (IC_{50} = 3.38 μM). These results suggest that the 5-hydroxy

group of the polyketide component in odoamide **1a** is not essential for its bioactivity, and that the 7-hydroxy group in **6** was essential. Given the acyl transfer toward the 7-hydroxy group is not needed for the cytotoxicity of 24-membered macrocycle **6** as discussed above, this hydroxy group may have an important role for increasing membrane permeability and/or interaction with the target molecule(s). The polyketide 7-methoxy group of **13** would be unfavorable for the bioactivity due to the loss of the essential hydrogen bond and/or the increased steric hindrance.



1a
IC_{50}: 4.2 ± 0.81 nM

6
IC_{50}: 4.5 ± 1.4 nM

12
IC_{50}: 4.3 ± 0.44 nM

13
IC_{50}: 3383 ± 154 nM

Figure 5. Structures and cytotoxicities of 24-membered macrocyclic odoamide derivatives. IC_{50} values are the concentrations for 50% growth inhibition of A549 cells (n = 3).

Several other odoamide derivatives with alternative macrocyclic scaffolds were designed and synthesized (Figure 6). Peptide **14** without the polyketide 5-hydroxy group was prepared using a conjugated diene byproduct, which was obtained during the synthesis of the common polyketide intermediate. The slightly lower potency of **14** (IC_{50} = 28 nM) suggested that planarity at the polyketide 4,5-position was less favorable compared with the parent structure in **1a**. However, the 26-membered form **1a** was bioactive even without acyl transfer toward the 24-membered isomer **6**. Substitution of sarcosine (Sar) with *N*-methyl-β-alanine (**15**) and glycine (Gly, **16**) also led to slight decrease in the cytotoxicity (IC_{50} **15** = 74 nM; IC_{50} **16** = 31 nM). Subtle conformational changes by ring expansion to 27-membered macrocycle (**15**) and loss of *N*-methyl group (**16**) did not improve the bioactivity of **1a**. Peptide **17**, with a D-Phe3 substituent, also gave a high cytotoxicity (IC_{50} = 5.4 nM). Even though the opposite chirality at this position in **1c** resulted in a decrease of the bioactivity, the loss of the *N*-methyl group at the same position in **17** was tolerable, suggesting that this *N*-methyl group in **1a** would have no effect on the global conformations, and thereby the bioactivity.

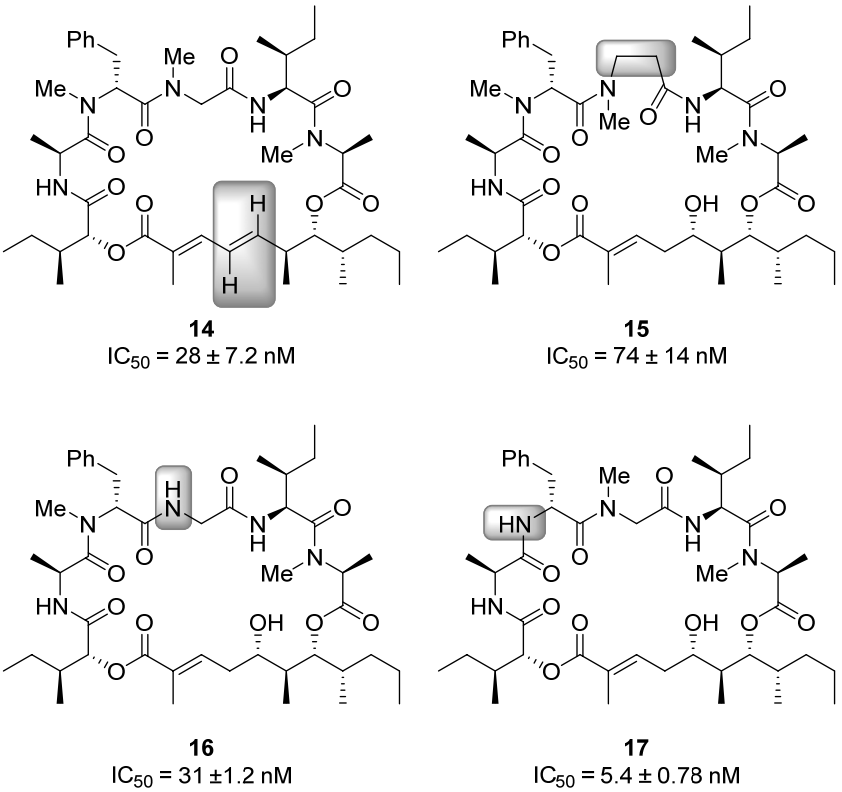


Figure 6. Structures and cytotoxicities of odoamide derivatives with modified macrocyclic scaffold. IC_{50} values are the concentrations for 50% growth inhibition of A549 cells (n = 3).

In growth inhibition assay, serum protein binding and membrane permeability of compounds often affect their activity values. To rationalize the structure-activity relationships of the odoamide derivatives, the physicochemical properties under in vitro bioassay conditions were evaluated (Figure 7 and Table 1).[10] The author evaluated serum protein-binding of the representative peptides in cell culture medium supplemented with 10% (v/v) fetal bovine serum. No direct correlations were observed between serum protein binding and the cytotoxic potency of the peptides (Figure 7A). For example, peptides **1a** and **1e** with relatively low serum protein binding (75.9 and 85.5%, respectively) had highly potent cytotoxicity, while peptide **12** also exhibited bioactivity in spite of the high protein binding (97.2%). When the normalized IC_{50} values were calculated based on the ratio of unbound peptide (normalized IC_{50} = IC_{50} × unbound peptide ratio), the cytotoxic potencies under hypothetical serum-free conditions of peptides **1a**, **1e**, **12**, **15** and **16** were similar (in the range of 0.12–1.5 nM), suggesting that these modifications had significant effect on the serum protein binding rather than altering the interaction with the potential target protein(s) of intact peptide **1a**. Additionally, the author assessed the membrane permeability of these representative peptides using a parallel artificial membrane permeability assay (PAMPA). Interestingly, all peptides exhibited good passive diffusion [$>1.0 \times 10^{-6}$ cm/sec,[11] except for a slightly moderate value for peptide **13** (0.82×10^{-6} cm/sec)] across the phospholipid layers, leading to similar concentrations of peptides across the extracellular and intracellular compartments. This indicated that the membrane permeability into the intracellular compartment had no significant effect on their cytotoxicities (Figure 7B). Accordingly,

the significantly lower cytotoxicity of **1b** and **13** may be attributed to lower affinity to the target protein and high serum protein-binding.

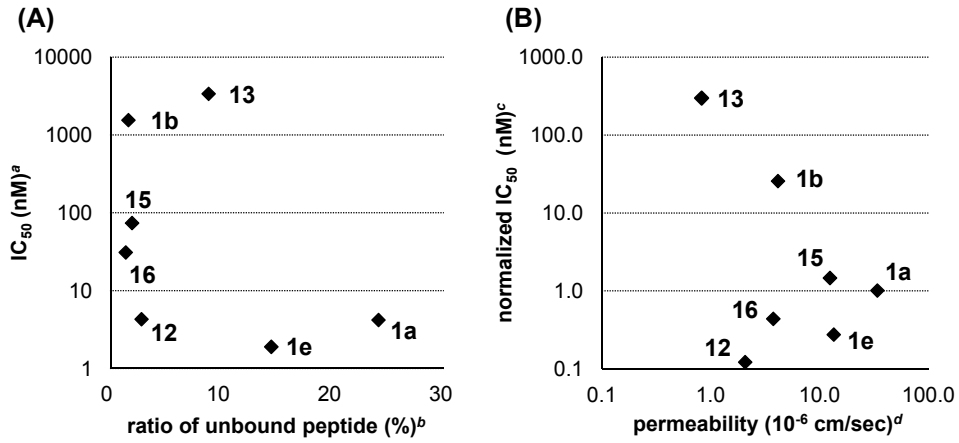


Figure 7. The relationships between physicochemical properties and cytotoxicity. (A) Scatter plot between ratio of unbound peptide and cytotoxicity IC_{50}. (B) Scatter plot between normalized IC_{50} and membrane permeability. [a] IC_{50} values are the concentrations for 50% growth inhibition of A549 cells. [b] Ratio of unbound peptide was evaluated in medium supplemented with 10% (v/v) fetal bovine serum. [c] Normalized IC_{50} = IC_{50} × unbound peptide ratio; [d] Membrane permeability was evaluated by PAMPA (pH = 7.4).

Table 1. Physicochemical properties of odoamide derivatives.

compound	IC_{50} (nM)[a]	ratio of unbound peptide (%)[b]	normalized IC_{50} (nM)[c]	membrane permeability (10^{-6} cm/sec)[d]
1a	4.2	24.1	1.0	33.9
1b	1554	1.7	25.8	4.1
1e	1.9	14.5	0.28	13.5
12	4.3	2.8	0.12	2.1
13	3383	8.9	300	0.82
15	74	2.0	1.5	12.4
16	31	1.4	0.44	3.8

[a] IC_{50} values are the concentrations for 50% growth inhibition of A549 cells (n = 3). [b] Ratio of unbound peptide was evaluated in medium supplemented with 10% (v/v) fetal bovine serum. [c] Normalized IC_{50} = IC_{50} × unbound peptide ratio; [d] Membrane permeability was evaluated by PAMPA (pH = 7.4).

In conclusion, the author have established an efficient synthetic procedure for odoamide derivatives using solid-phase techniques. Taking advantage of this protocol, structure-activity relationships of the peptide part of odoamide were investigated. The amino acid configurations of L-Ala2, D-MePhe3 and L-Ile5 in odoamide (**1a**) were essential for potent cytotoxicity, while the D-MeAla6 isomer **1e** exhibited more potent bioactivity. This suggests that the kulokekahikide-2-type arrangement of chiral components is more favorable for a high potency of the odoamide derivatives. Additionally, it was demonstrated that 26-membered odoamide (**1a**) and the 24-membered isomer **6**, which were slowly interconverted via an intramolecular ester exchange at the polyketide 1,3-diol moiety, both contributed to the highly potent cytotoxicity of odoamide. The assessment of physicochemical properties revealed that odoamide derivatives exhibited good membrane permeability but had different serum protein binding behaviors to affect their cytotoxicities. This information will be useful for further optimization of aurilide-class depsipeptides, including odoamide derivatives, in which the interaction with the molecular target(s) as well as lower serum protein binding should be considered.

Experimental Section

General Methods

^{1}H NMR spectra were recorded using a JEOL ECA-500 spectrometer. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in $CDCl_3$) as an internal standard. ^{13}C NMR spectra were recorded using a JEOL ECA-500 spectrometer and referenced to the residual solvent signal. ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (br: broad, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet), number of protons, and coupling constants. Exact mass (HRMS) spectra were recorded on a Shimadzu LC-ESI-IT-TOF-MS equipment. IR spectra were determined on a JASCO FT/IR-4100 spectrometer. Optical rotations were measured with a JASCO P-1020 polarimeter. For flash chromatography, Wakogel C-300E (Wako) was employed. For analytical HPLC, a Cosmosil 5C18-ARII column (4.6 × 250 mm, Nacalai Tesque, Inc.) was employed with a linear gradient of CH_3CN (with 0.1% (v/v) TFA) in H_2O at a flow rate of 1 mL/min, and eluting products were detected by UV at 220 nm. Preparative HPLC was performed using a Cosmosil 5C18-ARII preparative column (20 × 250 mm, Nacalai Tesque, Inc.) at a flow rate of 8 mL/min.

*Solid-phase synthesis of odoamide (**1a**)*

(2*R*,3*S*)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (5*S*,6*S*,7*R*,8*S*,*E*)-7-[(*N*-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}-*N*-methyl-L-alanyl)oxy]-2,6,8-trimethyl-5-[(methylthio)-methoxy]undec-2-enoate (8). To a stirred solution of Fmoc-MeAla-OH (61.8 mg, 0.19 mmol) in CH_2Cl_2 (1.1 mL) were added DMF (1.5 μL, 0.019 mmol) and $SOCl_2$ (138 μL, 1.9 mmol) at room temperature. After being stirred for 1 h, the mixture was concentrated under reduced pressure to give Fmoc-MeAla-Cl, which was used for the next step without further purification. To a stirred solution of **7** (41.7 mg, 0.076 mmol) and the above Fmoc-MeAla-Cl in 1,2-dichloroethane (510 μL) was added (i-Pr)$_2$NEt (66 μL, 0.38 mmol) at room temperature. The reaction mixture was warmed to 40 °C and stirred overnight. The mixture was cooled to room temperature and quenched with saturated aqueous NH_4Cl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (9:1 to 3:1) to give crude Fmoc-protected amine. The protected amine was purified by preparative TLC over silica gel with toluene–EtOAc (6:1) to give compound **8** (36.5 mg, 56%) as a colorless oil: $[\alpha]^{27}_D$ –37.3 (*c* 1.05, $CHCl_3$); IR (neat): 1707 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ: 0.77 (t, J = 7.4 Hz, 1H), 0.83-0.88 (m, 5H), 0.91-0.98 (m, 6H), 1.05-1.13 (m, 4H), 1.20-1.35 (m, 3H), 1.36-1.56 (m, 5H), 1.72-1.76 (m, 1H), 1.89 (s, 3H), 2.06 (s, 1H), 2.11 (s, 2H), 2.17-2.24 (m, 2H), 2.28-2.35 (m, 1H), 2.40-2.45 (m, 1H), 2.94 (s, 3H), 3.73-3.76 (m, 1H), 4.22-4.29 (m, 1.3H), 4.38-4.41 (m, 1.4H), 4.46-4.53 (m, 1.3H), 4.58-4.63 (m, 1H), 4.87-4.95 (m, 2H), 5.18-5.22 (m, 2H), 5.49 (d, J = 16.6 Hz, 1H), 6.91-6.97 (m, 1H), 7.29-7.32 (m, 2H), 7.38-7.41 (m, 2H), 7.45-7.48 (m, 2H), 7.53-7.62 (m, 3H), 7.74-7.77 (m, 2H), 7.86-7.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.2, 10.3, 11.7, 12.6, 12.8, 12.9, 13.9, 14.0 (2C), 14.1, 14.2 (2C), 15.1, 15.7, 20.2 (2C), 26.2, 28.7 (2C), 30.3 (2C), 33.8, 33.9,

35.9, 36.0 (2C), 36.2, 36.9, 47.2, 54.1, 54.3, 66.1, 67.7, 67.9, 72.9, 73.1, 74.6, 75.2, 78.0, 78.1, 119.9 (2C), 125.1 (2C), 127.0 (2C), 127.6 (2C), 127.7 (2C), 128.4, 128.8 (2C), 133.8, 134.0, 140.9, 141.0, 141.2, 143.9, 144.1, 155.8, 156.4, 167.4 (2C), 169.6, 171.7, 172.0, 191.6; HRMS (ESI-TOF) calcd for $C_{49}H_{63}NNaO_{10}S$ $[M+Na]^+$: 880.4065; found: 880.4064.

Loading of polyketide component on the solid support. To a stirred solution of **8** (38.5 mg, 0.045 mmol) in AcOH (900 μL) was added Zn (44.1 mg, 0.68 mmol) at room temperature. After being stirred overnight, the reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (3:1) to $CHCl_3$–MeOH (9:1) to give the crude carboxylic acid (14.7 mg, ca. 0.020 mmol), which was employed for the next step without further purification. To a solution of the above carboxylic acid (14.7 mg) in CH_2Cl_2 (300 μL), (*i*-Pr)$_2$NEt (14 μL, 0.080 mmol) was added. The whole was poured into Cl-(2-Cl)Trt resin (1.6 mmol/g, 41.9 mg, 0.067 mmol), and the reaction was continued for 2 h to give peptidyl resin **9**.

General procedure for solid-phase peptide synthesis: synthesis of peptide 11.

Deprotection of Fmoc group. The Fmoc-protected peptidyl resin was treated with piperidine/DMF (2:8) for 20 min.

Coupling reaction of Ile. N,N'-Diisopropylcarbodiimide (DIC, 16 μL, 0.10 mmol) was added to a solution of Alloc-Ile-OH (21.5 mg, 0.10 mmol) and HOAt (13.6 mg, 0.10 mmol) in DMF (250 μL). The whole was poured into the peptidyl resin, and the reaction was continued for 2 h.

Deprotection of Alloc group. To the peptidyl resin were added $PhSiH_3$ (49 μL, 0.40 mmol) and $Pd(PPh_3)_4$ (4.6 mg, 0.0040 mmol) in CH_2Cl_2 (400 μL). After 10 min, the resin was washed with CH_2Cl_2. This deprotection process was repeated twice.

Coupling reaction of Sar. DIC (9.3 μL, 0.060 mmol) was added to a solution of Fmoc-Sar-OH (18.7 mg, 0.060 mmol) and HOBt·H_2O (9.2 mg, 0.060 mmol) in DMF (250 μL). The whole was poured into the peptidyl resin, and the reaction was continued for 2 h.

Coupling reaction of D-MePhe and Ala. To a solution of Fmoc amino acid (0.060 mmol) in DMF (400 μL) were added HATU (22.1 mg, 0.058 mmol) and (*i*-Pr)$_2$NEt (20.9 μL, 0.12 mmol). The whole was poured into the peptidyl resin, and the reaction was continued for 2 h.

Cleavage from the resin. The peptidyl resin was treated with 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP)/CH_2Cl_2 (3:7) at room temperature for 2 h. After removal of the resin by filtration, the filtrate was concentrated under reduced pressure to give crude peptide **11**, which was used for the next step without further purification.

General procedure for macrocyclization of the linear peptide: synthesis of odoamide (1a). Odoamide (**1a**) was synthesized by the identical procedure in Section 1. To a stirred solution of peptide **11**, HOAt (13.6 mg, 0.10 mmol) and collidine (79 μL, 0.60 mmol) in DMF (20 mL) was added HATU (76.0 mg, 0.20 mmol) at room temperature. After being stirred for 5 h, the reaction mixture was concentrated under reduced pressure, and EtOAc and 1N HCl were added to the residue.

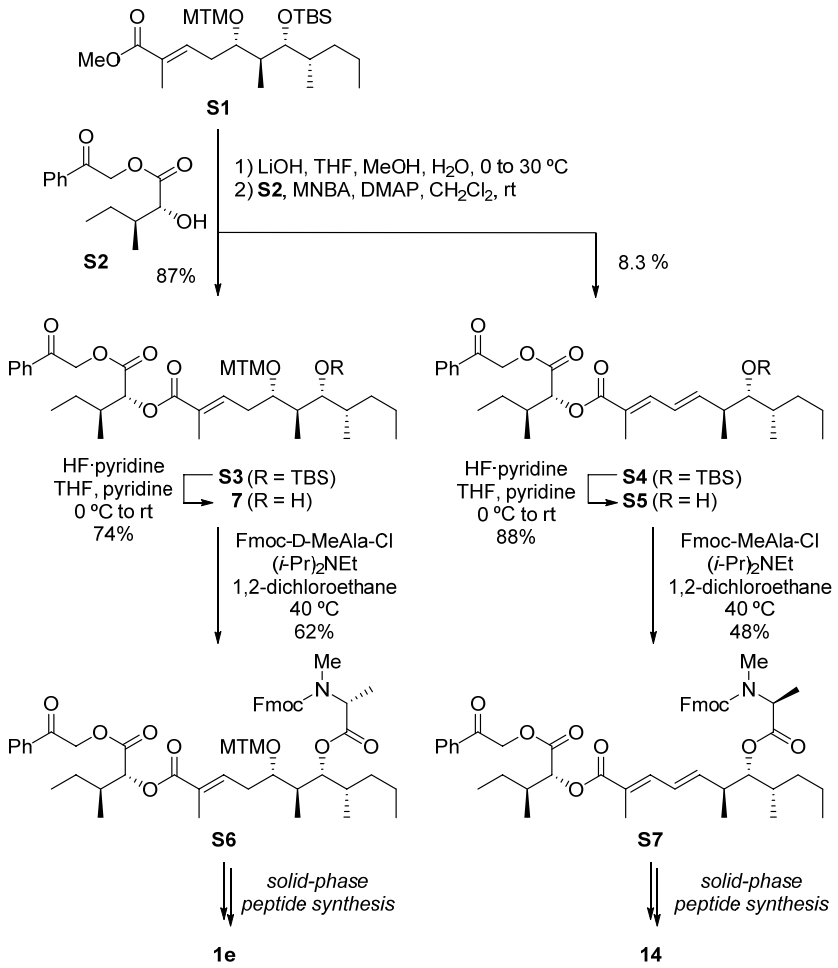
The whole was extracted with EtOAc and the extract was washed with brine, aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give the MTM-protected cyclic peptide, which was used without further purification. To a stirred solution of the above cyclic peptide in THF/H_2O (4:1, 1 mL) were added 2,6-lutidine (46 μL, 0.40 mmol) and $AgNO_3$ (135.9 mg, 0.80 mmol) at room temperature. The reaction mixture was warmed to 70 °C and stirred for 4 h. The mixture was filtered through Celite, and 1N HCl was added to the filtrate. The whole was extracted with EtOAc and the extract was washed with H_2O, aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by reverse-phase preparative HPLC (72% CH_3CN in H_2O) to give odoamide (**1a**) (4.7 mg, 12% from **8**) as a colorless powder. The spectral data were shown in Section 1.

Synthesis of odoamide derivatives

[D-Ala2]-Odoamide (1b). According to the procedure described for the preparation of **1a**, peptidyl resin **9** (0.46 mmol/g, 59.7 mg, 0.028 mmol) was converted into **1b** (11.4 mg, 48% from resin) as a colorless powder: $[\alpha]^{28}_D$ –15.5 (*c* 0.52, $CHCl_3$); IR (neat): 3460 (OH), 1634 (C=O); ^{1}H NMR (500 MHz, CD_3OD, 4:1 mixture of rotamers) δ: 0.76-1.06 (m, 22H), 1.08-1.25 (m, 3H), 1.27-1.58 (m, 10H), 1.75-1.94 (m, 5H), 2.01-2.05 (m, 1H), 2.10-2.18 (m, 2H), 2.34-2.39 (m, 1H), 2.54 (s, 2.4H), 2.87 (s, 0.6H), 2.89 (s, 0.6H), 3.02-3.14 (m, 5H), 3.26-3.30 (m, 3.2H), 3.50 (d, *J* = 18.3 Hz, 0.2H), 3.67-3.69 (m, 0.8H), 3.99-4.04 (m, 0.4H), 4.62-4.92 (m, 3.8H), 4.99-5.03 (m, 1H), 5.18 (q, *J* = 7.6 Hz, 0.8H), 5.22-5.26 (m, 0.4H), 5.43 (d, *J* = 2.3 Hz, 0.8H), 7.05-7.34 (m, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ: 9.5, 9.8, 10.2, 10.8, 11.3, 11.7, 11.8, 12.1, 12.3, 13.0, 14.5, 15.2 (2C), 15.6, 16.2, 16.4, 17.8, 18.1, 21.3, 21.4, 26.0, 26.1, 27.0, 27.1, 30.5, 30.6, 31.3, 31.7, 32.1, 32.8, 34.8, 35.3, 35.7, 36.0 (2C), 36.7, 37.4, 37.7, 38.5, 38.7, 39.4, 39.9, 41.9, 42.0, 48.3, 52.2, 52.7, 53.2, 54.4, 55.0, 58.1, 70.5, 71.3, 76.1, 76.6, 78.9, 79.0, 128.1, 128.4, 128.7, 129.6, 129.8 (2C), 130.2 (2C), 130.5 (2C), 137.1, 137.9, 143.4, 143.8, 167.1, 168.1, 169.8, 170.0, 171.5, 172.0, 172.6 (2C), 172.9, 173.4, 173.6, 173.9, 175.6 (2C); HRMS (ESI-TOF) calcd for $C_{46}H_{73}N_5NaO_{10}$ $[M+Na]^+$: 878.5250; found: 878.5249.

[L-MePhe3]-Odoamide (1c). According to the procedure described for the preparation of **1a**, **8** (38.5 mg, 0.045 mmol) was converted into **1c** (4.9 mg, 13% from **8**) as a colorless powder: $[\alpha]^{27}_D$ –38.3 (*c* 0.19, $CHCl_3$); IR (neat): 3412 (OH), 1632 (C=O); ^{1}H NMR (500 MHz, CD_3OD, 3:2 mixture of rotamers) δ: 0.82-0.96 (m, 21H), 1.09-1.61 (m, 14H), 1.79-1.93 (m, 5H), 1.98-2.05 (m, 1H), 2.07-2.14 (m, 1.4H), 2.17-2.25 (m, 0.6H), 2.37-2.46 (m, 1H), 2.74-2.97 (m, 3.8H), 3.02-3.04 (m, 3H), 3.13-3.20 (m, 4.2H), 3.42 (d, *J* = 17.2 Hz, 0.6H), 3.53 (d, *J* = 17.2 Hz, 0.4H), 3.66-3.69 (m, 0.6H), 3.85-3.88 (m, 0.4H), 4.02 (d, *J* = 17.2 Hz, 0.4H), 4.50 (d, *J* = 17.2 Hz, 0.6H), 4.59-4.62 (m, 0.6H), 4.69-4.82 (m, 2H), 4.87-4.93 (m, 2.4H), 5.10 (d, *J* = 3.4 Hz, 0.4H), 5.15 (d, *J* = 3.4 Hz, 0.6H), 7.07-7.15 (m, 1H), 7.18-7.33 (m, 5H); ^{13}C NMR (125 MHz, CD_3OD) δ: 10.1, 10.8, 11.1, 11.3, 12.0, 12.1, 12.9, 13.0, 13.1, 13.3, 14.5 (2C), 14.7, 14.8, 14.9 (2C), 15.7, 15.9, 17.8, 17.9, 21.4 (2C), 25.3, 25.9, 27.1 (2C), 31.1, 31.7, 33.9, 34.1 (3C), 34.8, 35.3, 35.4, 36.1 (2C), 37.2, 37.4, 37.6, 37.8 (2C), 38.6, 38.9, 41.9 (2C), 46.8, 47.0, 53.2, 53.5, 54.7, 55.6, 56.1, 56.6, 60.0 (2C), 70.6, 71.0, 77.3, 77.4, 78.9, 79.0, 128.0, 128.2, 128.9, 129.1, 129.5 (2C), 129.7 (2C), 130.4 (4C), 138.1 (2C), 143.1 (2C), 168.6,

168.8, 170.4, 170.7, 171.4, 171.9, 172.8, 172.9, 173.2, 173.9 (2C), 174.0 (3C); HRMS (ESI-TOF) calcd for $C_{46}H_{73}N_5NaO_{10}$ $[M+Na]^+$: 878.5250; found: 878.5246.



(2*R*,3*S*)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl-(5*S*,6*S*,7*R*,8*S*,*E*)-7-(*tert*-butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undec-2-enoate (S3) and (2*R*,3*S*)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (2*E*,4*E*,6*S*,7*R*,8*S*)-7-(*tert*-butyldimethylsilyloxy)-2,6,8-trimethylundeca-2,4-dienoate (S4). To a stirred solution of **S1** (1.14 g, 2.6 mmol) in MeOH (17 mL) and THF (17 mL) was added 1N LiOH (17 mL) at 0 °C. The reaction mixture was warmed to 30 °C and stirred overnight. The mixture was concentrated under reduced pressure and EtOAc and 1N HCl were added to the residue. The whole was extracted with EtOAc and the extract was washed with brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was filtrated through a short pad of silica gel with hexane-EtOAc (3:1) to give crude carboxylic acid, which was used without further purification.[12] To a stirred solution of the above acid in CH_2Cl_2 (12.8 mL) were added MNBA (1.32 g, 3.8 mmol), DMAP (935.0 mg, 7.7 mmol) and **S2** (959.0 mg, 3.8 mmol) at room temperature. After being stirred overnight, the mixture was quenched with 1N HCl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (10:1) to give compounds **S3** (1.48 g,

87%; major product) and **S4** (124.4 mg, 8.3%; minor product) both as a colorless oil. The spectral data of **S3** were shown in Section 1.

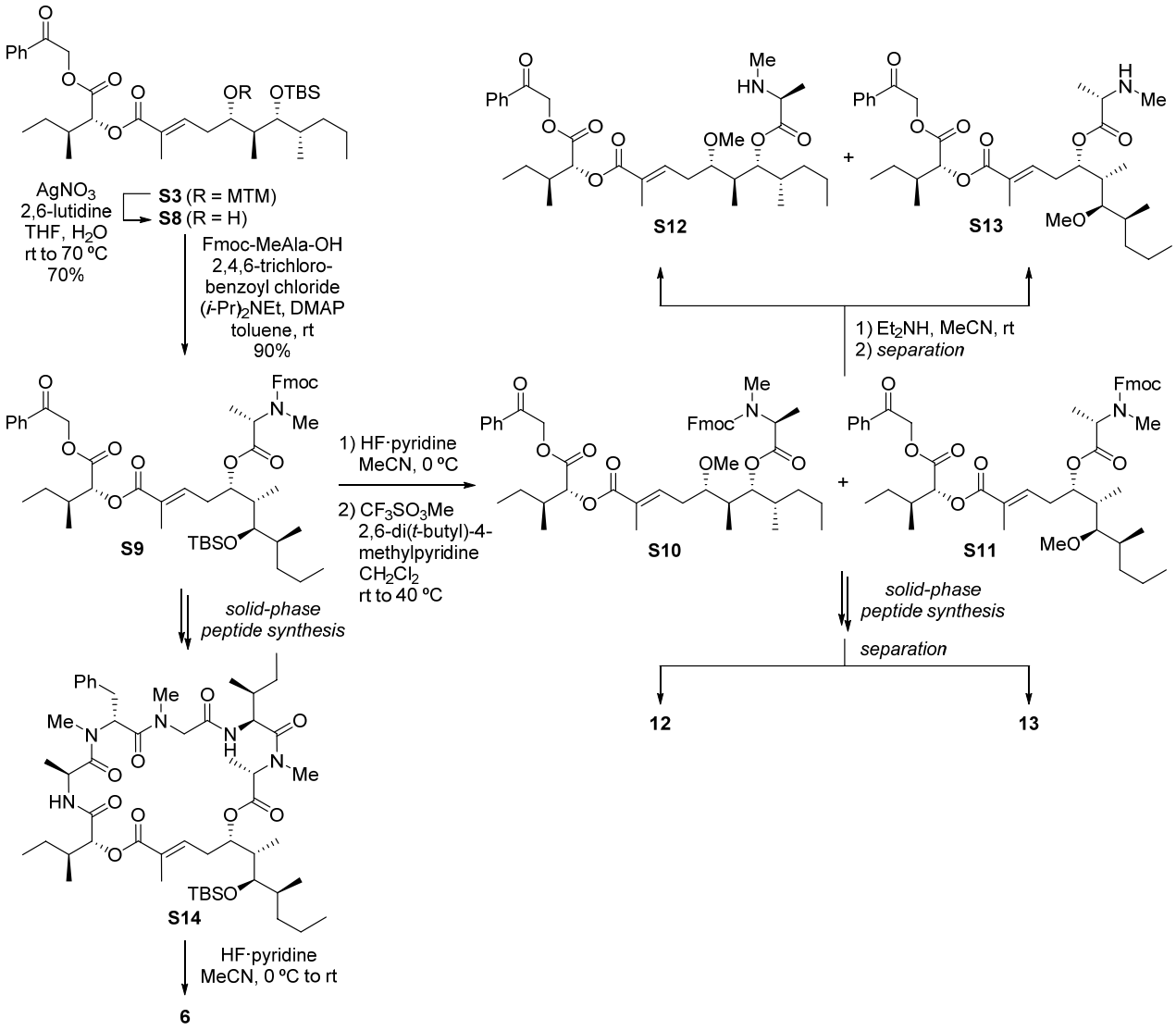
S4: $[\alpha]^{26}_{D}$ –15.5 (*c* 1.30, $CHCl_3$); IR (neat): 1709 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.01 (s, 3H), 0.03 (s, 3H), 0.84-0.89 (m, 15H), 0.98 (t, *J* = 7.4 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.07-1.12 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.18-1.25 (m, 1H), 1.30-1.36 (m, 2H), 1.40-1.46 (m, 1H), 1.53-1.60 (m, 2H), 1.96 (s, 3H), 2.19-2.27 (m, 1H), 2.48-2.52 (m, 1H), 3.42-3.44 (m, 1H), 5.23 (d, *J* = 2.9 Hz, 1H), 5.27 (d, *J* = 16.0 Hz, 1H), 5.55 (d, *J* = 16.0 Hz, 1H), 6.14 (dd, *J* = 14.9, 8.6 Hz, 1H), 6.30 (dd, *J* = 14.9, 11.2 Hz, 1H), 7.25 (d, *J* = 11.2 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.59-7.62 (m, 1H), 7.89-7.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –3.7 (2C), 11.7, 12.5, 14.2, 14.8, 18.3 (2C), 18.4, 20.7, 26.1 (3C), 26.3, 36.2, 36.9 (2C), 42.0, 66.2, 74.6, 79.4, 124.1, 125.0, 127.8 (2C), 128.9 (2C), 133.9, 134.1, 140.3, 147.6, 168.2, 169.8, 191.7; HRMS (ESI-TOF) calcd for $C_{34}H_{54}NaO_6Si$ $[M+Na]^+$: 609.3582; found: 609.3582.

(2*R*,3*S*)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (2*E*,4*E*,6*S*,7*R*,8*S*)-7-hydroxy-2,6,8-trimethylundeca-2,4-dienoate (S5). To a stirred solution of **S4** (187.9 mg, 0.32 mmol) in THF (2.1 mL) and pyridine (530 μL) was added HF·pyridine (1.3 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into aqueous saturated $NaHCO_3$ at 0 °C. The whole was extracted with EtOAc, and the extract was washed with brine, 1N HCl and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (5:1) to give compound **S5** (134.2 mg, 88%) as a colorless oil: $[\alpha]^{26}_{D}$ –34.1 (*c* 1.12, $CHCl_3$); IR (neat): 3546 (OH), 1704 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$,) δ: 0.88-0.92 (m, 6H), 0.99 (t, *J* = 7.4 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.22-1.48 (m, 6H), 1.51-1.60 (m, 1H), 1.61-1.66 (m, 1H), 1.98 (s, 3H), 2.19-2.27 (m, 1H), 2.44-2.52 (m, 1H), 3.29 (dd, *J* = 7.4, 4.0 Hz, 1H), 5.24 (d, *J* = 3.4 Hz, 1H), 5.27 (d, *J* = 16.6 Hz, 1H), 5.54 (d, *J* = 16.6 Hz, 1H), 6.07 (dd, *J* = 15.2, 8.9 Hz, 1H), 6.44 (dd, *J* = 15.2, 11.2 Hz, 1H), 7.25-7.27 (m, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.59-7.62 (m, 1H), 7.89-7.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.7, 12.6, 12.9, 14.3 (2C), 17.0, 20.2, 26.3, 34.5, 36.2, 36.9, 41.4, 66.2, 74.7, 77.7, 125.3, 126.8, 127.7 (2C), 128.9 (2C), 133.9, 134.1, 139.3, 145.7, 168.0, 169.8, 191.7; HRMS (ESI-TOF) calcd for $C_{28}H_{40}NaO_6$ $[M+Na]^+$: 495.2717; found: 495.2712.

(2*R*,3*S*)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (5*S*,6*S*,7*R*,8*S*,*E*)-7-[(*N*-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}-*N*-methyl-D-alanyl)oxy]-2,6,8-trimethyl-5-[(methylthio)methoxy]undec-2-enoate (S6). According to the procedure described for the preparation of **8**, **7** (43.0 mg, 0.078 mmol) was converted into **S6** (41.2 mg, 62%) with Fmoc-D-MeAla-Cl as a colorless oil: $[\alpha]^{26}_{D}$ –27.9 (*c* 1.02, $CHCl_3$); IR (neat): 1705 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ: 0.80 (t, *J* = 7.4 Hz, 1H), 0.84-0.89 (m, 5H), 0.91-0.93 (m, 3H), 0.97 (t, *J* = 7.4 Hz, 3H), 1.02-1.15 (m, 4H), 1.21-1.35 (m, 3H), 1.37-1.58 (m, 5H), 1.71-1.77 (m, 1H), 1.90-1.91 (m, 3H), 2.09-2.11 (m, 3H), 2.19-2.24 (m, 2H), 2.27-2.34 (m, 1H), 2.36-2.43 (m, 1H), 2.90 (s, 1H), 2.94 (s, 2H), 3.71-3.74 (m, 1H), 4.22-4.25 (m, 1H), 4.30-4.33 (m, 0.7H), 4.39 (dd, *J* =

10.6, 7.2 Hz, 1H), 4.45-4.52 (m, 1.3H), 4.61-4.64 (m, 1H), 4.79 (q, *J* = 7.3 Hz, 0.3H), 4.87-4.89 (m, 1H), 4.97 (q, *J* = 7.3 Hz, 0.7H), 5.20-5.26 (m, 2H), 5.49-5.54 (m, 1H), 6.91-6.96 (m, 1H), 7.29-7.32 (m, 2H), 7.37-7.49 (m, 4H), 7.53-7.61 (m, 3H), 7.75-7.76 (m, 2H), 7.84-7.85 (m, 1.4H), 7.88-7.90 (m, 0.6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.1, 10.2, 11.7, 12.6, 12.8, 12.9, 13.9, 14.0, 14.1, 14.2, 15.0, 15.6, 20.2, 26.2, 28.7, 30.2, 33.8, 36.0 (2C), 36.1, 36.9, 47.1, 47.3, 53.7, 54.0, 66.2, 67.7, 72.9, 73.1, 74.6, 74.7, 75.0, 77.7, 77.9, 119.9 (2C), 124.9, 125.1 (2C), 127.0 (4C), 127.7 (6C), 128.4, 128.8 (2C), 133.8, 134.0, 140.8, 141.1, 141.2, 143.9, 144.1, 155.7, 156.5, 167.4, 169.5, 171.5, 171.7, 191.6; HRMS (ESI-TOF) calcd for $C_{49}H_{63}NNaO_{10}S$ $[M+Na]^+$: 880.4065; found: 880.4066.

(2*R*,3*S*)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (2*E*,4*E*,6*S*,7*R*,8*S*)-7-[(*N*-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}-*N*-methyl-L-alanyl)oxy]-2,6,8-trimethylundeca-2,4-dienoate (S7). According to the procedure described for the preparation of **8**, **S5** (108.6 mg, 0.23 mmol) was converted into **S7** (86.1 mg, 48%) as a yellow oil: $[\alpha]^{27}_D$ –9.2 (*c* 1.16, $CHCl_3$); IR (neat): 1706 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ: 0.79-0.88 (m, 6H), 0.95-0.99 (m, 3H), 1.01-1.04 (m, 3H), 1.07-1.15 (m, 4H), 1.19-1.45 (m, 7H), 1.49-1.58 (m, 1H), 1.70-1.77 (m, 1H), 1.93 (s, 1H), 1.97 (s, 2H), 2.17-2.25 (m, 1H), 2.61-2.67 (m, 1H), 2.85-2.86 (m, 3H), 4.20-4.32 (m, 1.3H), 4.37-4.43 (m, 1.4H), 4.47-4.50 (m, 0.3H), 4.77 (q, *J* = 7.3 Hz, 0.3H), 4.84-4.86 (m, 1H), 4.90 (q, *J* = 7.3 Hz, 0.7H), 5.21-5.26 (m, 2H), 5.49-5.53 (m, 1H), 5.91-6.00 (m, 1H), 6.32-6.37 (m, 1H), 7.18-7.23 (m, 1H), 7.28-7.32 (m, 2H), 7.38-7.41 (m, 2H), 7.45-7.48 (m, 2H), 7.52-7.61 (m, 3H), 7.74-7.77 (m, 2H), 7.87-7.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.7, 12.6, 13.8, 13.9, 14.1 (2C), 14.2, 15.0, 15.5, 17.4, 19.9, 26.2, 30.1, 33.8, 33.9, 35.5, 35.6, 36.9, 39.9, 40.0, 47.2, 54.0, 54.1, 66.2, 67.6, 67.8, 74.8, 80.0, 80.1, 119.9 (2C), 125.0 (2C), 125.4, 125.6, 126.4, 126.5, 127.0 (2C), 127.6 (2C), 127.7 (4C), 128.8 (2C), 133.9, 134.0, 138.9, 139.1, 141.3 (2C), 143.8, 143.9, 144.0, 144.2, 155.9, 156.4, 167.8, 167.9, 169.7, 171.6, 171.8, 191.6; HRMS (ESI-TOF) calcd for $C_{47}H_{57}NNaO_9$ $[M+Na]^+$: 802.3926; found: 802.3925.



(2*R*,3*S*)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (5*S*,6*S*,7*R*,8*S*,*E*)-7-[(*tert*-butyldimethylsilyl)oxy]-5-hydroxy-2,6,8-trimethylundec-2-enoate (S8). To a stirred solution of **S3** (397.6 mg, 0.60 mmol) in THF/H_2O (4:1, 12 mL) were added 2,6-lutidine (1.4 mL, 12.0 mmol) and $AgNO_3$ (4.08 g, 24 mmol) at room temperature. The reaction mixture was warmed to 70 °C and stirred for 3 h. The mixture was filtered through Celite, and 1N HCl was added to the filtrate. The whole was extracted with EtOAc and the extract was washed with H_2O, aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (9:1 to 5:1) to give compound **S8** (255.0 mg, 70%) as a colorless oil: $[\alpha]^{26}_D$ –3.9 (*c* 1.37, $CHCl_3$); IR (neat): 3504 (OH), 1709 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.09 (s, 3H), 0.12 (s, 3H), 0.85 (d, *J* = 7.4 Hz, 3H), 0.88-0.92 (m, 15H), 0.97 (t, *J* = 7.4 Hz, 3H), 1.10-1.19 (m, 4H), 1.20-1.28 (m, 1H), 1.34-1.46 (m, 3H), 1.51-1.62 (m, 2H), 1.71-1.78 (m, 1H), 1.89 (s, 3H), 2.17-2.24 (m, 1H), 2.29-2.35 (m, 1H), 2.42-2.45 (m, 1H), 3.51 (dd, *J* = 5.7, 3.4 Hz, 1H), 3.54 (br s, 1H), 3.70-3.74 (m, 1H), 5.19 (d, *J* = 3.4 Hz, 1H), 5.26 (d, *J* = 16.6 Hz, 1H), 5.54 (d, *J* = 16.6 Hz, 1H), 7.05-7.09 (m, 1H), 7.47-7.50 (m, 2H),

7.59-7.62 (m, 1H), 7.89-7.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.2, –4.1, 11.7, 12.6, 14.2, 14.3, 14.8, 16.1, 18.2, 20.7, 26.0 (3C), 26.3, 33.5, 35.4, 36.9, 38.6, 41.8, 66.2, 72.9, 74.7, 81.4, 127.7 (2C), 128.2, 128.9 (2C), 133.9, 134.1, 141.0, 167.4, 169.8, 191.7; HRMS (ESI-TOF) calcd for $C_{34}H_{56}NaO_7Si$ $[M+Na]^+$: 627.3688; found: 627.3691.

(2*R*,3*S*)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (5*S*,6*S*,7*R*,8*S*,*E*)-5-[(*N*-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}-*N*-methyl-L-alanyl)oxy]-7-[(*tert*-butyldimethylsilyl)oxy]-2,6,8-trimethylundec-2-enoate (S9). To a stirred solution of Fmoc-MeAla-OH (94.3 mg, 0.29 mmol) in toluene (800 μL) were added 2,4,6-trichlorobenzoyl chloride (56.3 μL, 0.36 mmol), (*i*-Pr)$_2$NEt (83.6 μL, 0.48 mmol) and a solution of **S8** (147.3 mg, 0.24 mmol) and DMAP (58.6 mg, 0.48 mmol) at room temperature. After being stirred for 2 h, the reaction was quenched with 1N HCl. The whole was extracted with EtOAc and the extract was washed with brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (10:1 to 5:1) to give compound **S9** (201.6 mg, 90%) as a colorless oil: $[\alpha]^{27}_D$ –4.6 (*c* 1.09, $CHCl_3$); IR (neat): 1709 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ: 0.04 (s, 6H), 0.85-0.91 (m, 18H), 0.96 (t, *J* = 7.4 Hz, 3H), 1.12-1.25 (m, 5H), 1.34-1.43 (m, 6H), 1.48-1.56 (m, 1H), 1.60-1.64 (m, 1H), 1.86-1.88 (m, 3H), 1.99-2.08 (m, 1H), 2.18-2.22 (m, 1H), 2.45-2.52 (m, 1H), 2.56-2.62 (m, 1H), 2.83-2.85 (m, 3H), 3.49-3.51 (m, 0.3H), 3.54-3.56 (m, 0.7H), 4.20-4.27 (m, 1H), 4.32-4.46 (m, 2H), 4.77 (q, *J* = 7.3 Hz, 0.3H), 4.90 (q, *J* = 7.3 Hz, 0.7H), 5.18-5.28 (m, 3H), 5.47-5.51 (m, 1H), 6.82-6.87 (m, 1H), 7.29-7.32 (m, 2H), 7.38-7.41 (m, 2H), 7.44-7.48 (m, 2H), 7.52-7.61 (m, 3H), 7.74-7.77 (m, 2H), 7.85-7.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.0 (2C), –3.9, 11.7 (2C), 12.6, 14.2, 14.3, 14.7, 14.8, 15.0, 18.3, 20.8, 26.1 (3C), 26.3, 30.0, 30.2, 36.0, 36.2, 36.9, 37.0, 40.7, 40.9, 47.2, 47.3, 54.2, 54.3, 66.2, 67.7, 67.8, 74.7, 75.0, 75.1, 76.6, 119.9 (2C), 125.1 (4C), 127.0 (4C), 127.6 (2C), 127.7 (2C), 128.8 (2C), 129.2, 133.9, 134.0, 138.7, 141.3 (2C), 143.9, 144.1, 156.3, 167.0, 167.1, 169.6, 171.0, 171.1, 191.6; HRMS (ESI-TOF) calcd for $C_{53}H_{73}NNaO_{10}Si$ $[M+Na]^+$: 934.4896; found: 934.4892.

(2*R*,3*S*)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (5*S*,6*S*,7*R*,8*S*,*E*)-5-methoxy-2,6,8-trimethyl-7-[(*N*-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}-*N*-methyl-L-alanyl)oxy]undec-2-enoate (S12) and (2*R*,3*S*)-3-methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (5*S*,6*S*,7*R*,8*S*,*E*)-7-methoxy-2,6,8-trimethyl-5-[(*N*-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}-*N*-methyl-L-alanyl)oxy]undec-2-enoate (S13). To a stirred solution of **S9** (201.6 mg, 0.22 mmol) in MeCN (2.2 mL) was added HF·pyridine (550 μL) at 0 °C. After being stirred overnight, the reaction mixture was poured into aqueous saturated $NaHCO_3$ at 0 °C. The whole was extracted with EtOAc, and the extract was washed with brine, 1N HCl and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (3:1) to give the crude alcohol, which was used without further purification.[13] To a stirred solution of the above alcohol in CH_2Cl_2 (1.3 mL) were added 2,6-di(*t*-butyl)-4-methylpyridine (164.3 mg, 0.80 mmol) and CF_3SO_3Me (65.6 μL, 0.60 mmol) at room temperature. The reaction mixture was warmed to 40 °C and stirred overnight. The reaction was

quenched with aqueous saturated $NaHCO_3$. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (9:1 to 4:1) to give the inseparable mixture of compounds **S10** and **S11** (121.9 mg, 68%).

Compounds **S10** and **S11** were characterized after deprotection of the Fmoc group followed by separation. Briefly, to a stirred solution of the above mixture (84.0 mg, 0.10 mmol) in MeCN (3.3 mL) was added Et_2NH (1.1 mL) at room temperature. After being stirred for 1.5 h, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (3:1 to 1:1) to give the mixture of **S12** and **S13**. The regioisomeric mixture of **S12** and **S13** was separated by preparative TLC over silica gel with $CHCl_3$–EtOAc (1:4) to give compounds **S12** (31.3 mg, 53%) and **S13** (16.5 mg, 28%) both as a colorless oil. The chemical structures of **S12** and **S13** were identified by 2D NMR analysis.

S12: $[\alpha]^{27}_D$ –17.7 (*c* 1.47, $CHCl_3$); IR (neat): 1712 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.86-0.92 (m, 9H), 0.97 (t, *J* = 7.4 Hz, 3H), 1.07-1.16 (m, 4H), 1.21-1.28 (m, 1H), 1.30-1.45 (m, 6H), 1.49-1.56 (m, 1H), 1.75-1.80 (m, 1H), 1.89 (s, 3H), 2.19-2.28 (m, 3H), 2.36-2.43 (m, 4H), 3.14-3.17 (m, 1H), 3.24 (q, *J* = 6.9 Hz, 1H), 3.31 (s, 3H), 4.90 (dd, *J* = 9.7, 2.9 Hz, 1H), 5.18 (d, *J* = 3.4 Hz, 1H), 5.26 (d, *J* = 16.6 Hz, 1H), 5.54 (d, *J* = 16.6 Hz, 1H), 6.90-6.93 (m, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.59-7.62 (m, 1H), 7.89-7.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.2, 11.7, 12.6, 12.9, 14.1, 14.2, 19.5, 20.3, 26.3, 29.1, 34.0, 34.7, 35.9, 36.2, 36.9, 57.4, 58.6, 66.2, 74.6, 77.3, 80.6, 127.7 (2C), 128.1, 128.8 (2C), 133.9, 134.1, 141.1, 167.5, 169.7, 175.4, 191.6; HRMS (ESI-TOF) calcd for $C_{33}H_{52}NO_8$ $[M+H]^+$: 590.3687; found: 590.3688.

S13: $[\alpha]^{27}_D$ –2.9 (*c* 0.83, $CHCl_3$); IR (neat): 1712 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88-0.98 (m, 12H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.23-1.32 (m, 5H), 1.38-1.44 (m, 3H), 1.48-1.56 (m, 1H), 1.64-1.67 (m, 1H), 1.90 (s, 3H), 2.06-2.10 (m, 1H), 2.19-2.23 (m, 1H), 2.32 (s, 3H), 2.53-2.56 (m, 2H), 2.91 (dd, *J* = 7.4, 4.0 Hz, 1H), 3.19 (q, *J* = 6.9 Hz, 1H), 3.43 (s, 3H), 5.19 (d, *J* = 3.4 Hz, 1H), 5.24-5.31 (m, 2H), 5.53 (d, *J* = 16.6 Hz, 1H), 6.85-6.88 (m, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.60-7.63 (m, 1H), 7.89-7.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.7, 12.2, 12.6, 13.8, 14.2, 14.3, 18.9, 20.6, 26.3, 29.7, 34.4, 35.3, 36.9 (2C), 39.0, 58.4, 60.7, 66.2, 74.3, 74.7, 86.9, 127.7 (2C), 128.9 (2C), 129.0, 133.9, 134.1, 139.4, 167.2, 169.6, 174.7, 191.6; HRMS (ESI-TOF) calcd for $C_{33}H_{52}NO_8$ $[M+H]^+$: 590.3687; found: 590.3684.

[D-MeAla6]-Odoamide (1e). According to the procedure described for the preparation of **1a**, **S6** (55.4 mg, 0.065 mmol) was converted into **1e** (6.3 mg, 11% from **S6**) as a colorless powder: $[\alpha]^{27}_D$ –16.5 (*c* 0.27, $CHCl_3$); IR (neat): 3321 (OH), 1644 (C=O); ^{1}H NMR (500 MHz, CD_3OD) δ: 0.83 (d, *J* = 6.9 Hz, 3H), 0.87-0.98 (m, 21H), 1.06-1.16 (m, 1H), 1.19-1.27 (m, 2H), 1.31-1.41 (m, 3H), 1.47-1.53 (m, 4H), 1.70-1.75 (m, 1H), 1.81-1.90 (m, 6H), 2.00-2.03 (m, 1H), 2.14-2.18 (m, 1H), 2.24-2.31 (m, 1H), 2.88 (s, 3H), 2.93-2.97 (m, 1H), 3.02-3.05 (m, 4H), 3.24 (s, 3H), 3.52 (d, *J* = 18.3 Hz, 1H), 3.82-3.84 (m, 1H), 4.23 (d, *J* = 18.3 Hz, 1H), 4.47-4.54 (m, 2H), 4.86-4.89 (m, 2H), 4.96 (d, *J* = 7.4 Hz, 1H), 5.50 (dd, *J* = 10.3, 5.2 Hz, 1H), 7.02-7.05 (m, 1H), 7.13-7.27 (m, 5H); ^{13}C NMR (125 MHz,

CD_3OD) δ: 10.3, 11.6, 11.9, 12.6, 13.4, 14.5 (2C), 15.0, 15.7, 15.8, 21.5, 25.0, 27.5, 30.6, 31.0, 33.7, 35.7, 35.8, 36.4, 37.7, 38.6, 39.2, 41.6, 46.3, 52.7, 55.0, 55.4, 57.5, 71.7, 77.6, 79.4, 127.5, 129.1 (3C), 130.6 (2C), 138.3, 146.0, 170.2, 171.5, 172.3, 172.5, 172.6, 173.9, 174.9; HRMS (ESI-TOF) calcd for $C_{46}H_{73}N_5NaO_{10}$ $[M+Na]^+$: 878.5250; found: 878.5253.

24-Membered ring odoamide isomer (6). According to the procedure described for the preparation of **1a**, **S9** (48.9 mg, 0.053 mmol) was converted into **S14**. To a stirred solution of **S14** in MeCN (1.7 mL) was added HF·pyridine (420 μL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was poured into aqueous saturated $NaHCO_3$ at 0 °C. The whole was extracted with EtOAc, and the extract was washed with brine, 1N HCl and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by reverse-phase preparative HPLC (67% CH_3CN in H_2O) to give compound **6** (13.8 mg, 30% from **S9**) as a colorless powder: $[\alpha]^{27}_D$ –109.9 (*c* 0.51, $CHCl_3$); IR (neat): 3357 (OH), 1637 (C=O); ^{1}H NMR (500 MHz, CD_3OD) δ: 0.80-0.84 (m, 9H), 0.89-0.98 (m, 15H), 1.23-1.46 (m, 9H), 1.48-1.53 (m, 1H), 1.57-1.60 (m, 1H), 1.82-1.93 (m, 3H), 1.96 (s, 3H), 2.01-2.08 (m, 1H), 2.40-2.47 (m, 1H), 2.75-2.80 (m, 1H), 2.87 (s, 3H), 2.94-3.06 (m, 5H), 3.18 (d, *J* = 18.9 Hz, 1H), 3.32-3.35 (m, 4H), 3.85 (q, *J* = 6.7 Hz, 1H), 4.20 (d, *J* = 18.9 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 1H), 4.88-4.91 (m, 2H), 5.18-5.21 (m, 1H), 5.44 (dd, *J* = 10.3, 5.7 Hz, 1H), 6.85-6.88 (m, 1H), 7.12-7.21 (m, 5H); ^{13}C NMR (125 MHz, CD_3OD) δ: 11.0, 11.8, 12.0, 12.7, 12.8, 13.7, 14.4, 14.7, 15.3, 15.5, 21.5, 25.5, 27.6, 28.1, 30.5, 35.7, 35.8, 36.5, 37.8, 38.7 (2C), 39.1, 40.6, 46.5, 52.6, 53.8, 55.1, 61.1, 76.2 (2C), 77.7, 127.4, 129.0, 129.1 (2C), 130.6 (2C), 138.3, 142.5, 170.1, 170.5, 171.8, 172.4, 172.5, 172.7, 175.0; HRMS (ESI-TOF) calcd for $C_{46}H_{73}N_5NaO_{10}$ $[M+Na]^+$: 878.5250; found: 878.5250.

Peptides 12 and 13. According to the procedure described for the preparation of **1a**, the mixture of **S10** and **S11** (131.7 mg, 0.16 mmol) was converted into **12** (15.8 mg, 11% from the mixture of **S10** and **S11**) and **13** (10.6 mg, 7.6% from the mixture of **S10** and **S11**) both as a colorless powder.

12: $[\alpha]^{28}_D$ –2.3 (*c* 0.79, $CHCl_3$); IR (neat): 1644 (C=O); ^{1}H NMR (500 MHz, CD_3OD) δ: 0.85-0.89 (m, 12H), 0.92-0.96 (m, 9H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.09-1.41 (m, 6H), 1.43-1.53 (m, 5H), 1.79-1.84 (m, 1H), 1.86-1.91 (m, 5H), 2.01-2.04 (m, 1H), 2.26-2.38 (m, 2H), 2.83 (s, 3H), 3.00-3.05 (m, 5H), 3.17 (s, 3H), 3.23 (s, 3H), 3.45 (d, *J* = 18.3 Hz, 1H), 3.66-3.68 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 1H), 4.34 (d, *J* = 18.3 Hz, 1H), 4.57-4.61 (m, 1H), 4.81 (d, *J* = 4.0 Hz, 1H), 4.86-4.90 (m, 1H), 5.00 (d, *J* = 4.6 Hz, 1H), 5.52 (dd, *J* = 9.7, 5.7 Hz, 1H), 7.13-7.26 (m, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ: 9.8, 11.9, 12.1, 12.5, 13.0, 14.4, 14.5 (2C), 16.0, 16.5, 21.5, 24.1, 27.5, 30.0, 30.6, 35.2, 35.7 (2C), 36.0, 36.1, 37.8, 38.7 (2C), 46.0, 53.0, 55.2, 56.2, 57.3, 58.7, 77.6, 78.4, 81.1, 127.5, 128.6, 129.1 (2C), 130.6 (2C), 138.3, 146.5, 170.2, 171.5, 172.3, 172.4, 173.0, 173.5, 174.8; HRMS (ESI-TOF) calcd for $C_{47}H_{75}N_5NaO_{10}$ $[M+Na]^+$: 892.5406; found: 892.5396.

13: $[\alpha]^{29}_D$ –102.3 (*c* 0.53, $CHCl_3$); IR (neat): 1639 (C=O); ^{1}H NMR (500 MHz, CD_3OD) δ: 0.83 (d, *J* = 6.9 Hz, 3H), 0.88-0.98 (m, 21H), 1.22-1.54 (m, 10H), 1.64-1.68 (m, 1H), 1.83-1.91 (m, 3H), 1.96 (s, 3H), 2.05-2.08 (m, 1H), 2.35-2.41 (m, 1H), 2.79-2.84 (m, 1H), 2.88 (s, 3H), 2.94-3.06 (m, 6H), 3.17 (d, *J* = 18.9 Hz, 1H), 3.35 (s, 3H), 3.41 (s, 3H), 3.83 (q, *J* = 6.9 Hz, 1H), 4.21 (d, *J* = 18.9 Hz,

1H), 4.47 (q, *J* = 6.9 Hz, 1H), 4.87-4.91 (m, 2H), 4.99-5.02 (m, 1H), 5.44 (dd, *J* = 10.3, 5.7 Hz, 1H), 6.81-6.84 (m, 1H), 7.12-7.21 (m, 5H); ^{13}C NMR (125 MHz, CD_3OD) δ: 11.0, 12.0, 12.1, 12.8, 13.7, 14.4, 14.5, 14.6, 15.3, 15.5, 21.6, 25.5, 27.6, 29.2, 30.5, 35.8, 36.6 (2C), 38.0, 38.6, 38.7, 39.3, 40.5, 46.5, 52.7, 53.8, 55.1, 61.0, 61.4, 76.0, 77.7, 88.5, 127.4, 129.1 (2C), 129.3, 130.6 (2C), 138.3, 142.2, 170.0, 170.4, 171.7, 172.3, 172.5, 172.7, 175.0; HRMS (ESI-TOF) calcd for $C_{47}H_{75}N_5NaO_{10}$ $[M+Na]^+$: 892.5406; found: 892.5407.

Peptide 14. According to the procedure described for the preparation of **1a**, **S7** (86.0 mg, 0.11 mmol) was converted into **14** (18.5 mg, 20% from **S7**) as a colorless powder: $[\alpha]^{28}_D$ +34.0 (*c* 0.85, $CHCl_3$); IR (neat): 1636 (C=O); ^{1}H NMR (500 MHz, CD_3OD, 4:1 mixture of rotamers) δ: 0.84-1.08 (m, 24H), 1.11-1.24 (m, 3.2H), 1.28-1.59 (m, 7.8H), 1.84-2.10 (m, 6H), 2.63-2.68 (m, 1H), 2.81-2.82 (m, 3H), 2.94-3.05 (m, 4.8H), 3.11-3.16 (m, 2.6H), 3.21-3.26 (m, 0.8H), 3.59 (d, *J* = 17.2 Hz, 0.8H), 4.20 (q, *J* = 6.9 Hz, 0.2H), 4.31 (d, *J* = 17.2 Hz, 0.8H), 4.55-4.62 (m, 1.8H), 4.73-4.82 (m, 1.4H), 4.86-4.94 (m, 1.6H), 5.20 (d, *J* = 4.6 Hz, 0.2H), 5.49-5.57 (m, 1H), 5.81-5.86 (m, 0.2H), 6.36-6.47 (m, 1.8H), 7.14-7.25 (m, 5.2H), 7.39 (d, *J* = 10.3 Hz, 0.8H); ^{13}C NMR (125 MHz, CD_3OD) δ: 11.2, 11.9, 12.0 (2C), 12.7, 12.9, 13.1, 14.2, 14.5 (3C), 14.9, 15.0, 15.3, 15.6, 16.2 (2C), 16.3, 17.2, 18.1, 20.9, 21.3, 24.2, 25.6, 26.9, 27.5, 30.7, 31.9, 32.5, 34.8, 35.6, 35.7, 36.0, 36.5, 37.0, 37.6, 37.7, 38.3, 38.4, 39.0, 39.2, 40.7, 46.3, 46.5, 52.5, 52.8, 54.1, 55.4, 56.1, 56.3, 77.0, 77.2, 80.9, 82.0, 125.1, 125.5, 126.7, 127.5, 127.6, 128.0, 129.2 (2C), 129.3 (2C), 130.6 (4C), 138.3, 140.4, 143.2, 145.5, 148.5, 168.8, 169.7, 170.3, 171.2, 171.5, 171.8, 172.2, 172.3, 172.5, 173.3, 173.4, 173.5, 174.3, 174.5; HRMS (ESI-TOF) calcd for $C_{46}H_{71}N_5NaO_9$ $[M+Na]^+$: 860.5144; found: 860.5143.

Peptide 15. According to the procedure described for the preparation of **1a**, peptidyl resin **9** (0.46 mmol/g, 63.3 mg, 0.029 mmol) was converted into **15** (9.9 mg, 39% from resin) as a colorless powder: $[\alpha]^{27}_D$ –9.1 (*c* 0.49, $CHCl_3$); IR (neat): 3317 (OH), 1636 (C=O); ^{1}H NMR (500 MHz, CD_3OD, 3:2 mixture of rotamers) δ: 0.76-0.80 (m, 3H), 0.85-0.99 (m, 19.8H), 1.06-1.14 (m, 2H), 1.15-1.49 (m, 10.2H), 1.80-1.98 (m, 6H), 2.07-2.33 (m, 3H), 2.39-2.48 (m, 0.6H), 2.49-2.59 (m, 1.4H), 2.79 (s, 1.8H), 2.86-3.17 (m, 9.6H), 3.48-3.53 (m, 0.6H), 3.86-3.91 (m, 0.6H), 4.09-4.13 (m, 1.4H), 4.60-4.67 (m, 1.4H), 4.69 (d, *J* = 4.0 Hz, 0.6H), 4.76 (q, *J* = 6.7 Hz, 0.4H), 4.83-4.95 (m, 2.6H), 5.70-5.73 (m, 0.4H), 5.81 (dd, *J* = 9.2, 6.3 Hz, 0.6H), 7.16-7.31 (m, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ: 9.8, 10.1, 11.7, 11.9 (3C), 12.6, 12.8, 12.9, 13.0, 14.5 (3C), 14.6, 14.8, 14.9, 16.2, 16.3, 17.6, 17.7, 21.4 (2C), 24.5, 24.6, 27.4 (2C), 30.8, 31.0 (2C), 31.1, 32.4, 32.6, 33.9, 34.1, 35.2 (2C), 35.6, 36.1, 36.3, 37.1, 37.7 (2C), 37.9, 38.0, 38.3, 38.4, 41.8 (2C), 45.4, 45.9, 46.0, 46.5, 55.2, 55.7, 55.8 (2C), 55.9, 56.1, 70.8, 71.1, 76.9, 77.7 (2C), 79.0, 127.6, 127.7, 128.3, 128.8, 129.3 (2C), 129.4 (2C), 130.5 (4C), 138.4, 138.5, 146.1, 147.5, 169.6, 170.1, 171.0 (2C), 171.1 (2C), 172.7, 173.1, 173.4, 173.5, 173.6, 173.8, 173.9, 174.0; HRMS (ESI-TOF) calcd for $C_{47}H_{75}N_5NaO_{10}$ $[M+Na]^+$: 892.5406; found: 892.5410.

[Gly4]-Odoamide (16). According to the procedure described for the preparation of **1a**, peptidyl resin **9** (0.46 mmol/g, 60.1 mg, 0.028 mmol) was converted into **16** (9.4 mg, 40% from resin) as a

colorless powder: $[\alpha]^{28}_{D}$ +9.7 (*c* 0.47, $CHCl_3$); IR (neat): 3327 (OH), 1637 (C=O); ^{1}H NMR (500 MHz, CD_3OD, 9:1 mixture of rotamers) δ: 0.81-1.01 (m, 18H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.09-1.17 (m, 4H), 1.19-1.50 (m, 9.7H), 1.59 (d, *J* = 7.4 Hz, 0.3H), 1.80-1.94 (m, 5H), 2.03-2.08 (m, 1H), 2.11-2.19 (m, 1.9H), 2.22-2.27 (m, 0.1H), 2.31-2.35 (m, 1H), 2.75 (s, 2.7H), 2.88 (s, 0.3H), 2.98-3.05 (m, 0.5H), 3.17 (s, 2.7H), 3.22-3.35 (m, 1.8H), 3.64-3.91 (m, 3H), 4.57-4.68 (m, 2H), 4.74-4.84 (m, 1.9H), 4.91-4.93 (m, 1H), 5.11 (d, *J* = 3.4 Hz, 1H), 5.30 (q, *J* = 7.4 Hz, 0.1H), 6.75-6.78 (m, 0.1H), 7.12-7.15 (m, 0.9H), 7.17-7.28 (m, 5H); ^{13}C NMR (125 MHz, CD_3OD) δ: 10.2, 10.3, 11.1, 11.2, 11.9, 12.0, 12.8, 13.1 (2C), 13.3, 14.5, 14.6, 14.7, 15.1, 15.9, 16.1, 16.3, 17.1, 17.6, 21.2, 21.4, 25.3, 25.6, 27.1, 30.3, 31.1, 31.4, 33.0, 34.1, 34.6, 34.9, 35.3, 36.5, 37.7, 38.0, 38.5, 38.6, 39.0, 42.0, 42.7, 44.3, 44.6, 47.1, 54.1, 54.6, 55.4, 56.7, 64.7, 70.5, 71.0, 77.6, 78.7, 79.8, 127.7, 127.9, 128.8, 129.5 (2C), 129.7 (2C), 129.8 (2C), 130.2 (2C), 138.7, 138.9, 143.3, 143.9, 169.0, 169.2, 171.5, 171.7, 172.1, 172.4, 172.5, 172.7, 173.2, 173.4, 173.7, 174.6, 176.1; HRMS (ESI-TOF) calcd for $C_{45}H_{71}N_5NaO_{10}$ $[M+Na]^+$: 864.5093; found: 864.5089.

[D-Phe3]-Odoamide (17). According to the procedure described for the preparation of **1a**, peptidyl resin **9** (0.46 mmol/g, 61.1 mg, 0.028 mmol) was converted into **17** (11.3 mg, 48% from resin) as a colorless powder: $[\alpha]^{29}_{D}$ –103.9 (*c* 0.56, $CHCl_3$); IR (neat): 3327 (OH), 1644 (C=O); ^{1}H NMR (500 MHz, CD_3OD, 3:2 mixture of rotamers) δ: 0.79 (t, *J* = 7.2 Hz, 1.2H), 0.86-1.01 (m, 19.8H), 1.06-1.59 (m, 14H), 1.76-2.07 (m, 6H), 2.11-2.25 (m, 3H), 2.84 (s, 1.8H), 2.88-2.94 (m, 1H), 3.00-3.04 (m, 0.6H), 3.07 (s, 1.2H), 3.13-3.17 (m, 1.6H), 3.24 (s, 1.8H), 3.67-3.70 (m, 0.4H), 3.73 (d, *J* = 17.8 Hz, 0.6H), 3.77-3.80 (m, 0.6H), 3.91-3.96 (m, 1H), 4.06 (d, *J* = 16.0 Hz, 0.4H), 4.18 (q, *J* = 7.1 Hz, 0.6H), 4.23 (q, *J* = 7.1 Hz, 0.6H), 4.43 (q, *J* = 7.1 Hz, 0.4H), 4.72 (d, *J* = 6.3 Hz, 0.4H), 4.76 (dd, *J* = 8.9, 6.0 Hz, 0.6H), 4.85-4.91 (m, 2.4H), 4.97 (d, *J* = 6.9 Hz, 0.6H), 4.99 (dd, *J* = 9.2, 5.7 Hz, 0.4H), 6.90-6.94 (m, 0.4H), 7.16-7.27 (m, 5.6H); ^{13}C NMR (125 MHz, CD_3OD) δ: 9.9, 10.0, 11.4, 11.6, 11.9, 12.0, 12.7, 12.9, 13.0 (2C), 14.3, 14.5 (2C), 14.6, 14.9, 15.2, 16.0, 16.2, 17.3, 17.5, 21.4, 21.5, 24.9 (2C), 26.8, 27.4, 30.6, 30.8, 32.7, 35.1, 35.7, 35.9, 36.1, 37.4, 37.7 (2C), 37.8, 38.3, 38.5 (2C), 38.7, 38.9, 41.6, 41.9, 49.2, 50.3, 51.6, 52.9, 53.1, 53.7, 54.8, 55.0, 55.4, 58.4, 70.8, 71.0, 77.8, 78.7, 78.9, 79.1, 127.6, 127.9, 128.7, 129.2 (2C), 129.4, 129.6 (2C), 130.4 (2C), 130.7 (2C), 138.2, 138.5, 144.1, 145.8, 169.2, 169.9, 170.4, 171.0, 172.3, 172.4, 173.0, 173.1, 173.3 (2C), 173.5, 173.6, 174.0, 174.3; HRMS (ESI-TOF) calcd for $C_{45}H_{71}N_5NaO_{10}$ $[M+Na]^+$: 864.5093; found: 864.5090.

Growth Inhibition Assay

A549 cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Sigma) supplemented with 10% (v/v) fetal bovine serum at 37 °C in a 5% CO_2-incubator. Growth inhibition assays using A549 cells were performed in 96-well plates (BD Falcon). A549 cells were seeded at 500 cells/well in 50 μL of culture media, respectively, and were cultured for 6 h. Chemical compounds in DMSO were diluted 250-fold with the culture medium in advance. Following the addition of 40 μL of the fresh culture medium to the cell cultures, 30 μL of the chemical diluents were also added. The final volume of DMSO in the medium was equal to 0.1% (v/v). The cells under chemical treatment were incubated for further 72 h. The wells in the plates were washed twice with the cultured medium

without phenol-red. After 1-hour incubation with 100 μL of the medium, the cell culture in each well was supplemented with 20 μL of the MTS reagent (Promega), followed by incubation for additional 40 min. Absorbance at 490 nm of each well was measured using a Wallac 1420 ARVO SX multilabel counter (Perkin Elmer). Three experiments were performed per condition and the averages of inhibition rates in each condition were evaluated to determine IC_{50} values using the GraphPad Prism software.

Parallel artificial membrane permeability assay (PAMPA)

The membrane permeability of odoamide derivatives was evaluated using a PAMPA assay (Corning® Gentest™ Pre-coated PAMPA Plate System) according to the previous protocol with a slight modification.[14] Phosphate buffer solution (0.1 M, pH 7.4) was used as donor and acceptor buffer, and initial donor solutions were prepared by diluting DMSO solutions in phosphate buffer solution to be 10 μM. Permeability of the compounds was calculated using the equation described in the previous study.[14]

Evaluation of serum protein binding of odoamide derivatives

Serum protein binding of odoamide derivatives in cell culture medium was evaluated using a rapid equilibrium dialysis device (Single-Use RED Plate with Inserts, 8K MWCO, Thermo Scientific), according to the previous protocol with a slight modification.[15] Phosphate buffer solution (0.1 M, pH 7.4) was used as dialysis buffer, and initial compound solutions were prepared by diluting DMSO solutions in cell culture medium (DMEM containing 10% fetal bovine serum) to 1 μM. The free fraction ratio of the compounds was calculated as the ratio of concentration in the buffer chamber to that in the serum chamber.

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(12) The diene byproduct was obtained at this step.

(13) 1,3-Acyl transfer reaction occurred at this step.

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Chapter 2. Total Synthesis and Stereochemical Revision of Stereocalpin A

Summary

Stereocalpin A is a cyclic depsipeptide with cytotoxic activity isolated from the Antarctic lichen Stereocaulon alpinum. Although a number of synthetic investigations of the unprecedented 12-membered macrocycle of stereocalpin A with a dipeptide segment and a polyketide substructure have been conducted, the configurational assignment has not been completed. In this chapter, the author describes the first total synthesis and stereochemical revision of stereocalpin A. To facilitate the comprehensive assessment of eight possible stereocalpin A isomers, four stereoisomers of polyketide precursors were conjugated with L-Phe-L-MePhe and D-Phe-D-MePhe dipeptides to provide four possible isomers and four mirror-image structures of the remaining isomers, respectively. The comparative NMR analysis of a series of stereoisomers revealed that stereocalpin A possesses 2R,4S,5R-configurations, which is unique among the related 12-membered hybrid peptide-polypeptide natural products reported recently. The NOE correlations in the polyketide substructure of stereocalpin A were also retrospectively analyzed among the eight possible stereoisomers.

Stereocalpin A (**1a**) is a cyclic depsipeptide isolated from the Antarctic lichen *Stereocaulon alpinum* that shows cytotoxic activity against several human cell lines (Figure 1).[1] Stereocalpin A shows inhibitory activities against protein tyrosine phosphatase 1B (PTP1B)[1] and the TNF-α-mediated expression of adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) in vascular smooth muscle cells.[2] Thus, stereocalpin A is a promising lead natural product for anti-tumor and anti-inflammatory agents. The unique macrocyclic structure of stereocalpin A consists of a unprecedented polyketide part (5-hydroxy-2,4-dimethyl-3-oxooctanoic acid, HDMOO) and a Phe-MePhe dipeptide segment. This 12-membered hybrid peptide-polyketide scaffold is shared with several natural products such as taumycins A and B,[3] tausalarin C,[4] and dahurelmusin A[5]. The polyketide substructure of these macrocycles contains the α-unsubstituted or α,α-disubstituted β-keto carboxamide moiety, whereas stereocalpin A solely possesses a potentially labile α-methyl β-keto carboxamide, in which the 2-methyl group in **1a** could be subjected to configuration change and be converted into the 2-*epi* form **1b** via the enol (enolate) forms **E1** and/or **E2** during synthetic and/or purification processes (Figure 2). In the original report on the identification of stereocalpin A, the absolute configurations of Phe and MePhe were assigned as both L-isomers by Marfey's analysis.[6] The proposed stereochemistries of the polyketide part were based on detailed analysis of NOE correlations in the NOESY spectrum.

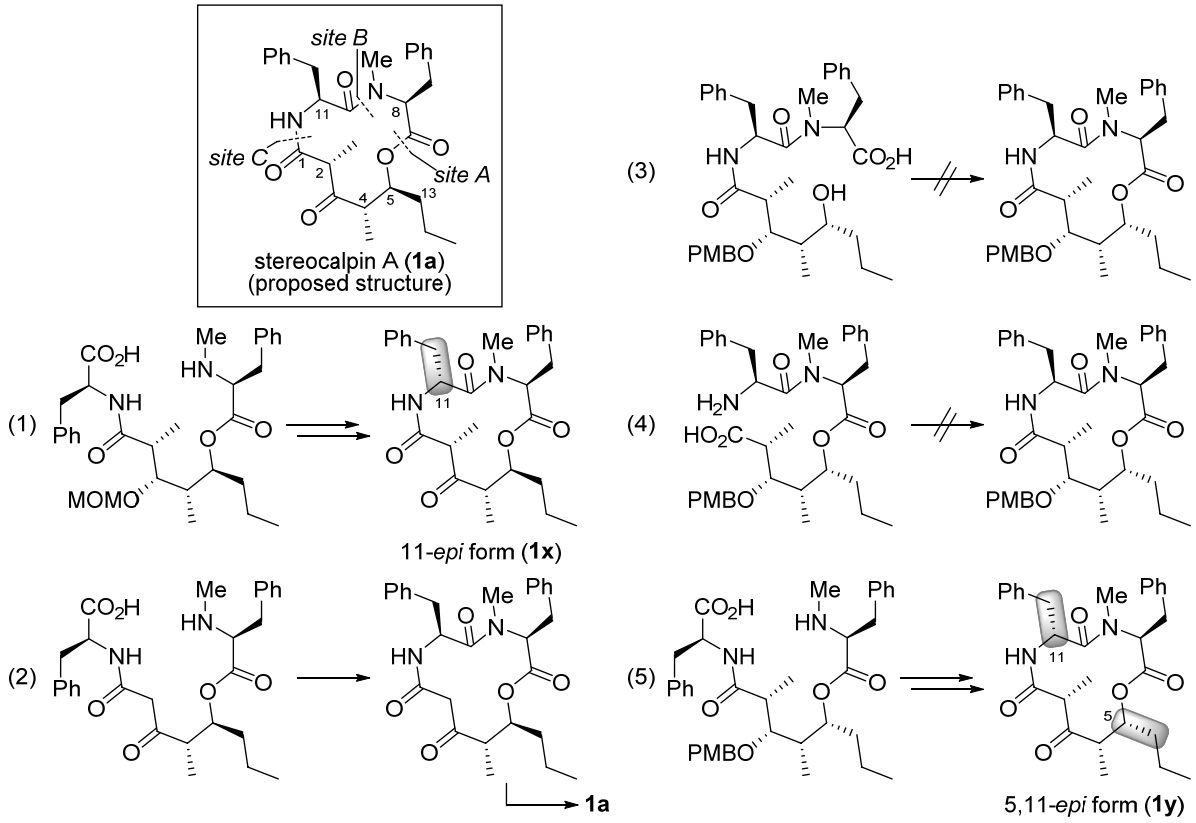


Figure 1. Structures of the proposed stereocalpin A and previously synthesized stereocalpin A stereoisomers.

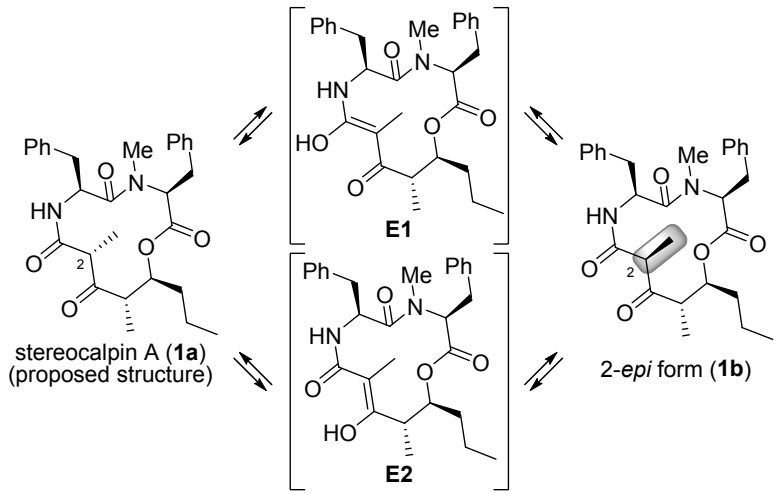


Figure 2. Possible stereoconversion of the 2-methyl group of the proposed stereocalpin A.

There have been several synthetic studies on stereocalpin A and the stereoisomers.[7] The first total synthesis of the proposed structure **1a** of stereocalpin A was achieved by Ghosh *et al.*[7a] In their initial investigation, macrocyclization was attempted at site B, which resulted in complete epimerization at the precursor C-terminal Phe to give 11-*epi*-stereocalpin A **1x** with D-Phe (Figure 1, eq 1).[7a] The proposed structure **1a** was obtained by cyclization of the C2-unmethylated substrate

followed by methylation under basic conditions (eq 2); however, the NMR spectra of synthetic stereocalpin A **1a** were inconsistent with those of the natural product. In other reports,[7b-d] some alternative approaches via macrocyclization at sites A and C were designed, but failed to obtain the expected product **1a** (eq 3 and 4). The synthetic efforts for 5-*epi* stereocalpin A via cyclization at site B also led to formation of 5,11-*epi* form **1y** because of the epimerization of Phe (eq 5).[7b]

On the basis of these findings, a comprehensive assessment of a series of possible stereoisomers is needed to confirm the stereochemical assignment of stereocalpin A, thereby avoiding plausible isomerization at the 2-methyl group and misleading from possible error(s) during the synthetic process. In this chapter, the author reports the total synthesis and stereochemical assignment of stereocalpin A via an effective mirror-image strategy (vide infra) by concomitant uses of key substrates. The retrospective study on the assignment process of the natural product was also carried out using NMR data of a series of synthetic stereocalpin A stereoisomers.

Stereocalpin A contains five stereogenic centers, which gives rise to possible 32 stereoisomers. In the original report,[1] the stereocalpin A was identified to contain L-Phe and L-MePhe by comparative HPLC analysis of Marfey's derivatives of the hydrolysate, in which L- and D-isomers of Phe and MePhe eluted at substantially different retention times. Co-injection of the derivatized hydrolysate and an authentic sample also supported the presence of both L-isomers. Therefore, the stereochemistries of L-Phe and L-MePhe were assumed to be correct. The eight possible stereoisomers **1a–h** with the L-Phe-L-MePhe dipeptide unit are shown in Figure 3A. The four 4*S*-isomers **1a–d** contain the corresponding HDMOO substructures **3a–d**, respectively (Figure 4A), which could be obtained via sequential manipulations from alcohol precursors **4a–d** followed by oxidation of the β-hydroxy group (Figure 4B).

Next, the author postulated that the same HDMOO isomers **3a–d** could be conjugated with the D-Phe-D-MePhe dipeptide. The 4*S*,5*R*,8*R*-isomers **2a–d** would be obtained through the identical synthetic process for **1a–d** but using D-amino acids (Figure 3B). The resulting macrocycles **2a–d** correspond to the mirror-image structures of the 4*R*-isomers **1e–h** with the L-Phe-L-MePhe dipeptide, respectively, which could be used as appropriate surrogates to determine the relative stereochemistries of natural stereocalpin A. In this process, a pair of macrocycles such as **1a** and **2a** can share a common HDMOO unit **3a**. Thus, the stereoselective preparations of four alcohols **4a–d** with a common 4*R*-configuration were needed for the synthesis of eight stereoisomers **1a–d** and **2a–d** of stereocalpin A. Of note, the alcohols **4a–d** possess a combination of required stereochemistries at the C2 and C5 positions, whereas the configurations of the C3-hydroxy group position of choice were based on a facile synthetic process.

For the synthesis of stereocalpin A, three sites for macrocyclization by acylation (sites A, B and C) are possible (Figure 3): site A is for ester bond formation between a carboxylic acid of L-MePhe and the 5-hydroxy group of the HDMOO unit; site B is for the formation of the *N*-methylamide bond between L-Phe and L-MePhe; and site C is for the formation of a standard peptide bond between the carboxylic acid of HDMOO (or precursor) and the L-Phe amino group. Among

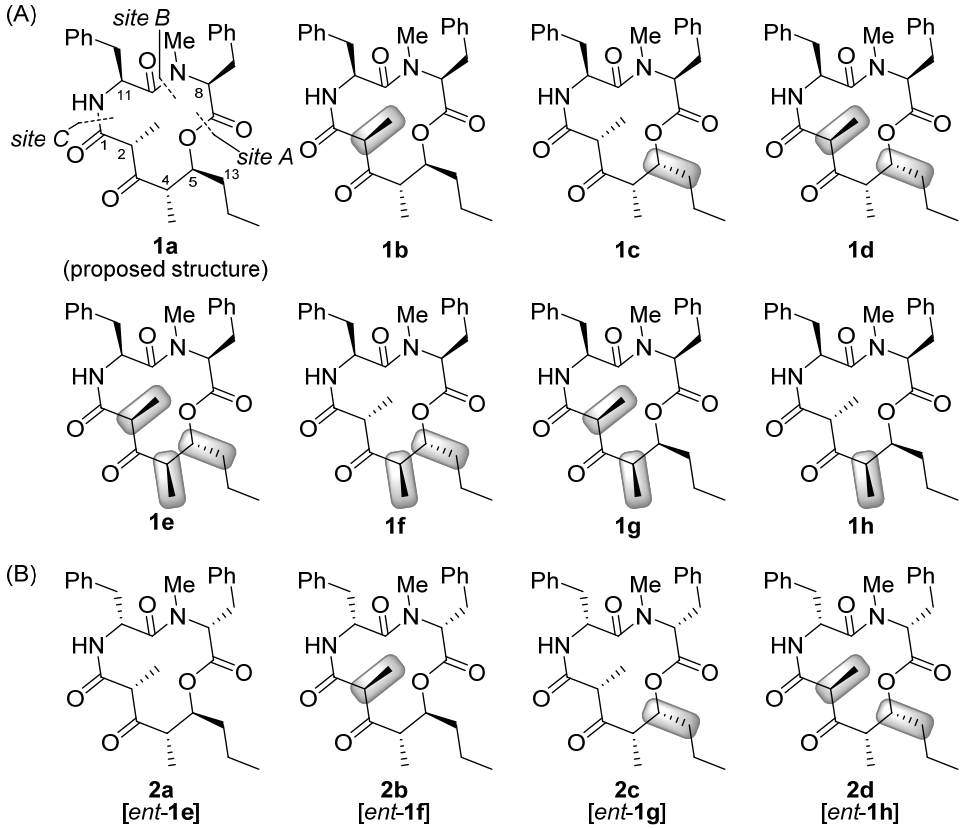


Figure 3. Possible structures of stereocalpin A stereoisomers. (A) Eight stereoisomers containing the L-Phe-L-MePhe dipeptide substructures (**1a–h**). (B) Enantiomers of compounds **1e–h** (**2a–d**).

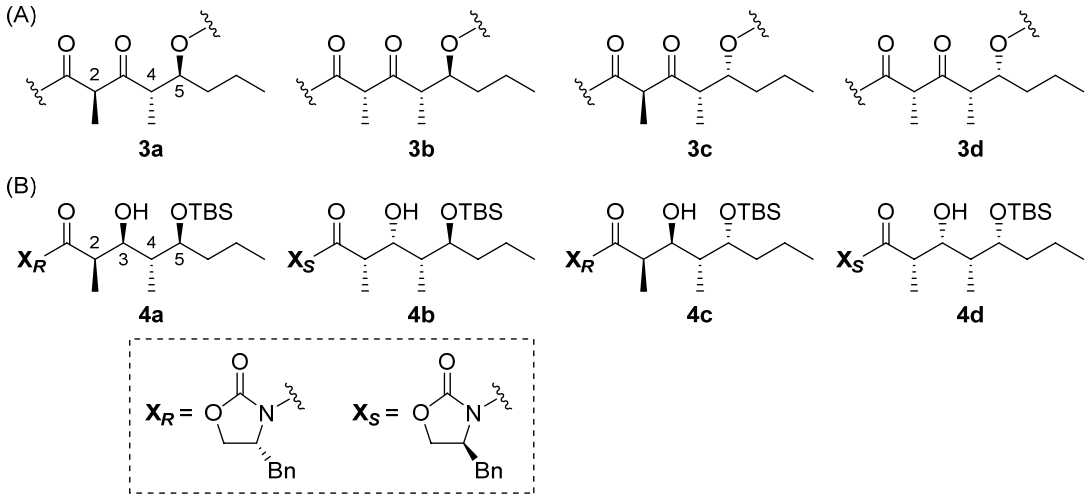


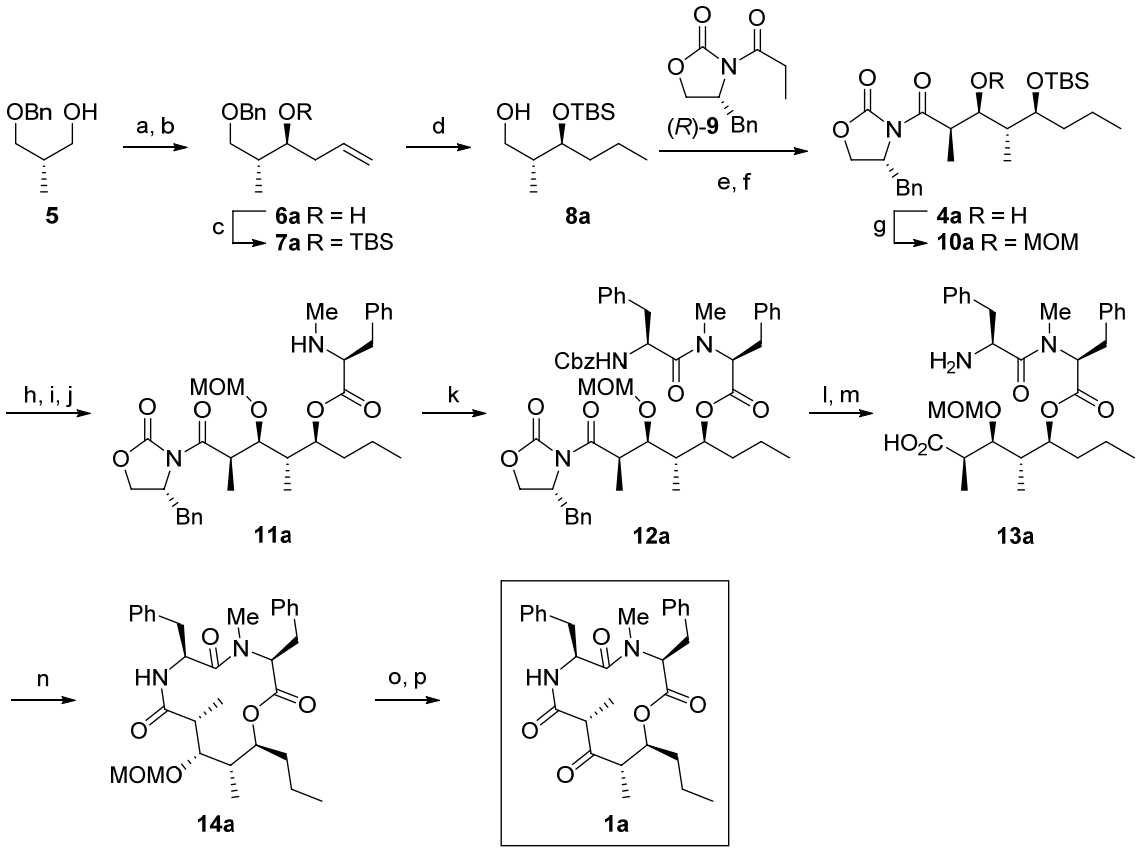
Figure 4. Structures of polyketide parts. (A) Common polyketide substructures **3a–d** in peptides **1a–d** and **2a–d**. (B) Possible synthetic precursors **4a–d** for polyketide substrucutures **3a–d**.

these, a typical epimerization problem at L-MePhe should be considered in macrolactonization, which is associated with longer reaction times because of the poor reactivity of the hydroxy group.[8] Additionally, significant epimerization of L-Phe was observed during cyclization at site B in previous synthetic studies (Figure 1, eq 1 and 5).[7a,b] Because the formation of the L-Phe-D-MePhe or

D-Phe-L-MePhe dipeptide via epimerizations at site A or site B should be avoided for this strategy of stereochemical assignment, the author chose site C for macrocyclization. Even though possible epimerization at the C2 chiral center (2-methyl group) would occur during the macrocyclization step at site C, the onset of epimerization could be characterized easily by comparative analysis with the authentic sample prepared through an alternative route (for example, epimerization of peptide **1a** to **1b**, and vice versa).

Initially, the author established the synthetic process for the proposed structure of stereocalpin A (**1a**) via the HDMOO precursor **4a**. The synthesis began with a known alcohol **5**,[9] which can be obtained by manipulations of an (*R*)-Roche ester (Scheme 1). The Roche ester-derived stereochemistry reflects on the 4*R*-configuration common in alcohols **4a–d**. Swern oxidation of **5** followed by $SnCl_4$-mediated addition of allyltributylstannane gave an *anti*-homoallyl alcohol **6a** with 15:1 diastereoselectivity.[10] Adjustment of the protecting groups via TBS protection of alcohol **6a**[11] and hydrogenation in the presence of Pd/C provided the primary alcohol **8a**.[12] Swern oxidation of **8a** and the subsequent Evans aldol reaction with chiral oxazolidinone (*R*)-**9** predominantly afforded the *syn*-aldol product **4a**.[13] The protected alcohol **10a** was generated by methoxymethyl (MOM) protection of the 3-hydroxy group in **4a**. After the TBS group in **10a** was removed with HF·pyridine, the resulting alcohol was acylated by coupling with Fmoc-protected L-MePhe. Deprotection of the Fmoc group with Et_2NH gave an amine **11a** in 82% yield (3 steps). Cbz-protected Phe was conjugated with **11a** using *O*-(7-aza-1*H*-benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (HATU) and $(i\text{-Pr})_2NEt$ to produce a protected peptide **12a**.

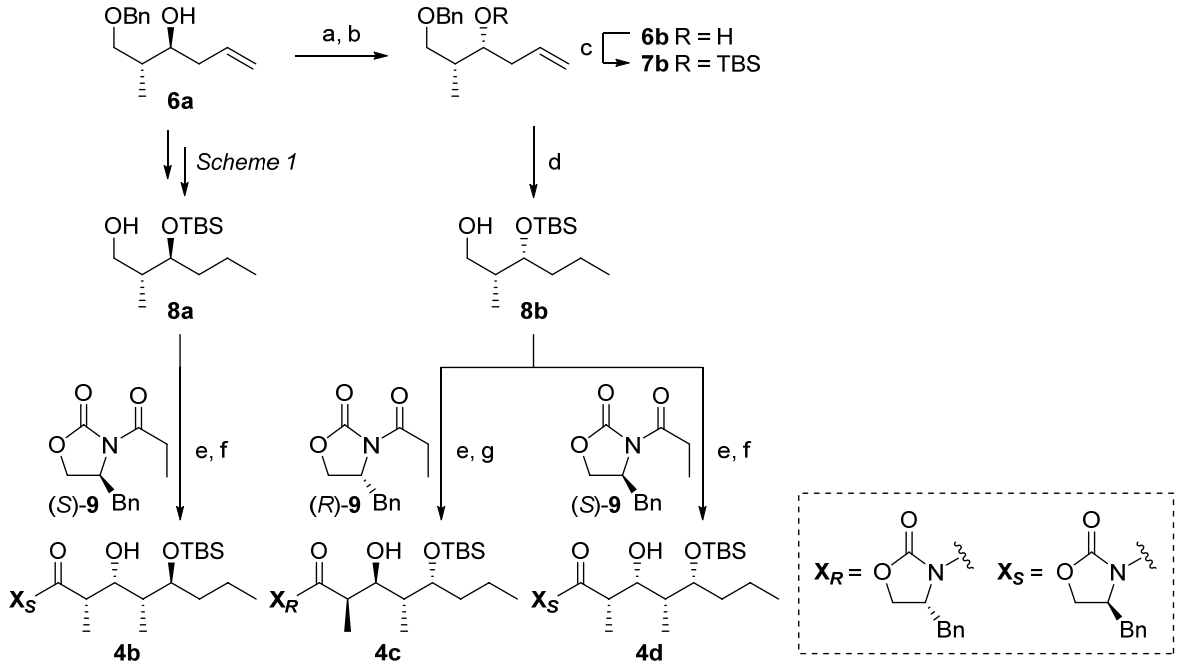
Macrocyclization at site C was attempted in a recent report describing the attempted synthesis of stereocalpin A.[7d] Removal of the Cbz group on L-Phe of a similar linear substrate led to concurrent formation of diketopiperazine consisting of L-MePhe and L-Phe to provide no macrocyclic product.[7d] The author hypothesized that the rapid process between removal of Cbz protection and the cyclization steps could avoid formation of this adverse intramolecular lactam bond. After the removal of the chiral auxiliary in **12a** with $LiOH\text{-}H_2O_2$, the Cbz group was deprotected by hydrogenation to provide a MeOH solution of linear peptide **13a**, which was used for the next step after direct high dilution with DMF without removal of Pd/C. HATU/HOAt-mediated cyclization of **13a** proceeded smoothly to give macrocycle **14a** in satisfying yield. This one-pot deprotection–cyclization process was critical in minimizing the possible side reaction of diketopiperazine formation. Deprotection of MOM group in **14a** with HCl aq. followed by Dess-Martin oxidation of the resulting secondary hydroxy group afforded the proposed structure of stereocalpin A (**1a**). The spectral data of **1a** were identical with those of the synthetic sample of the previously proposed structure.[7a]



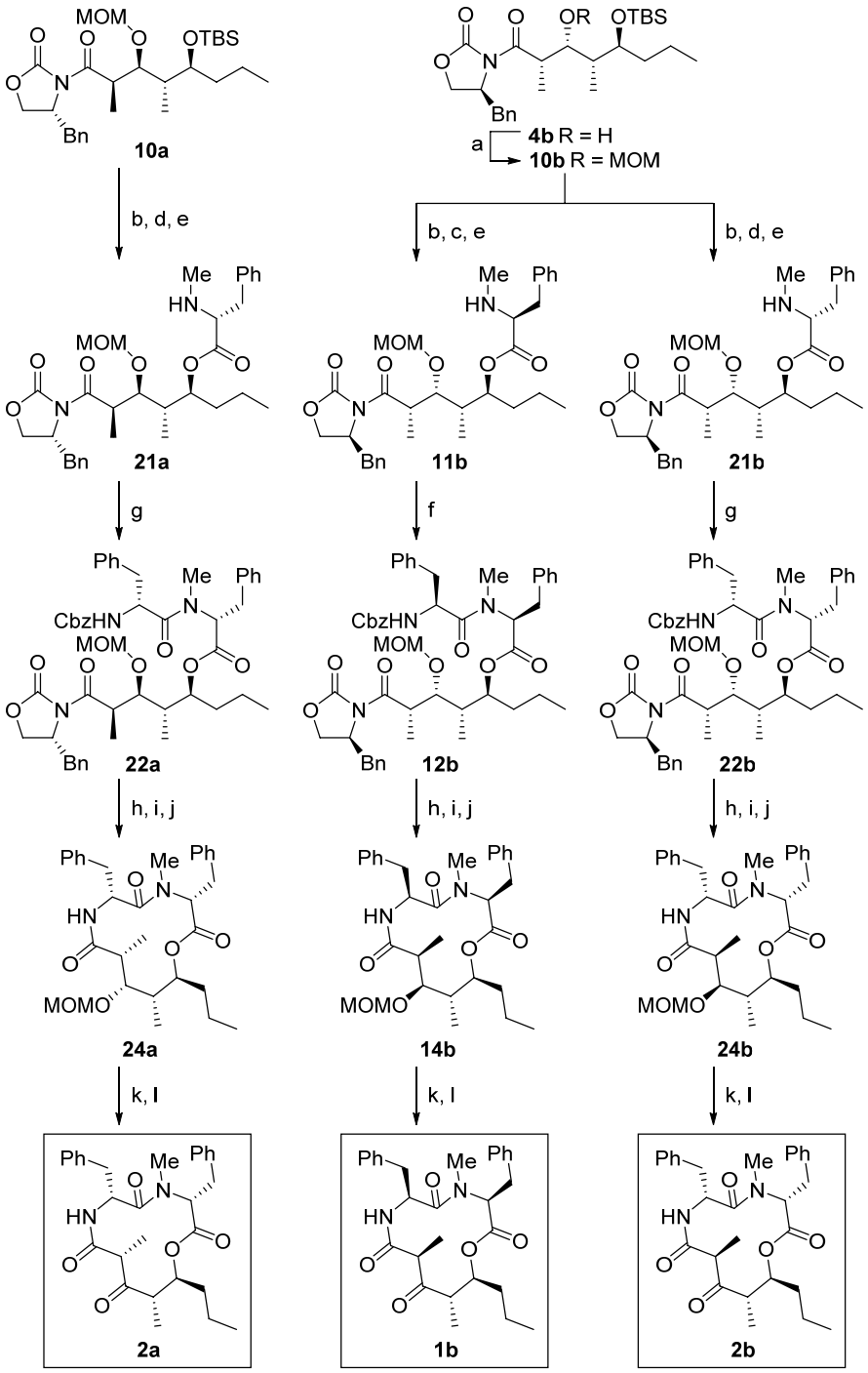
Scheme 1. Synthesis of the proposed structure of stereocalpin A (**1a**). *Reagents and conditions*: (a) $(COCl)_2$, DMSO, $(i\text{-Pr})_2NEt$, CH_2Cl_2, –78 °C to 0 °C; (b) allyltributylstannane, $SnCl_4$, CH_2Cl_2, –78 °C, 80% (2 steps, dr 15:1); (c) TBSCl, imidazole, DMF, 0 °C to rt, 91%; (d) Pd/C, H_2, EtOH, rt, 87%; (e) $(COCl)_2$, DMSO, $(i\text{-Pr})_2NEt$, CH_2Cl_2, –78 °C to 0 °C; (f) (*R*)-**9**, *n*-Bu_2BOTf, $(i\text{-Pr})_2NEt$, CH_2Cl_2, –78 °C to –10 °C, 86% (2 steps); (g) MOMCl, $(i\text{-Pr})_2NEt$, 1,2-dichloroethane, rt to 40 °C, 93%; (h) HF·pyridine, THF, pyridine, 0 °C to rt; (i) Fmoc-L-MePhe-OH, EDCI·HCl, DMAP, CH_2Cl_2, 0 °C; (j) Et_2NH, MeCN, rt, 82% (3 steps); (k) Cbz-L-Phe-OH, HATU, $(i\text{-Pr})_2NEt$, CH_2Cl_2, 0 °C to rt, 91%; (l) LiOH, H_2O_2, THF, H_2O, 0 °C to rt; (m) Pd/C, H_2, MeOH, rt; (n) HATU, HOAt, $(i\text{-Pr})_2NEt$, DMF, rt, 54% (3 steps); (o) HCl, MeOH, H_2O, 0 °C to 40 °C; (p) Dess-Martin periodinane, CH_2Cl_2, rt to 40 °C, 78% (2 steps).

Having established an efficient synthetic route of the stereocalpin A structure, the author proceeded to synthesize the other stereoisomers **1b–d** and **2a–d** by a similar process via four precursors **4a–d** (Schemes 2-4). For the preparation of the (2*S*,5*S*)-alcohol **4b**, the (*S*)-isomer of Evans chiral auxiliary (*S*)-**9** was employed for the aldol reaction (Scheme 2). The syntheses of 5*R*-isomers **4c** and **4d** began with the *syn* homoallyl alcohol **6b**, which was obtained by Mitsunobu inversion of alcohol **6a**.[10b] After protecting group manipulations and hydrogenation of **6b**, the resulting alcohol **8b** was converted into the β-hydroxy esters **4c** and **4d** by Swern oxidation followed by the Evans aldol reaction with chiral oxazolidinones (*R*)-**9** and (*S*)-**9**, respectively. Using the four HDMOO precursors **4a–d**, the cyclic depsipeptides **1b–d** and **2a–d** were synthesized successfully by the same process used to synthesize **1a** (Schemes 3 and 4). The yields of the deprotection and macrocyclization process varied (54–89%), depending on the precursor stereochemistries. Cbz-

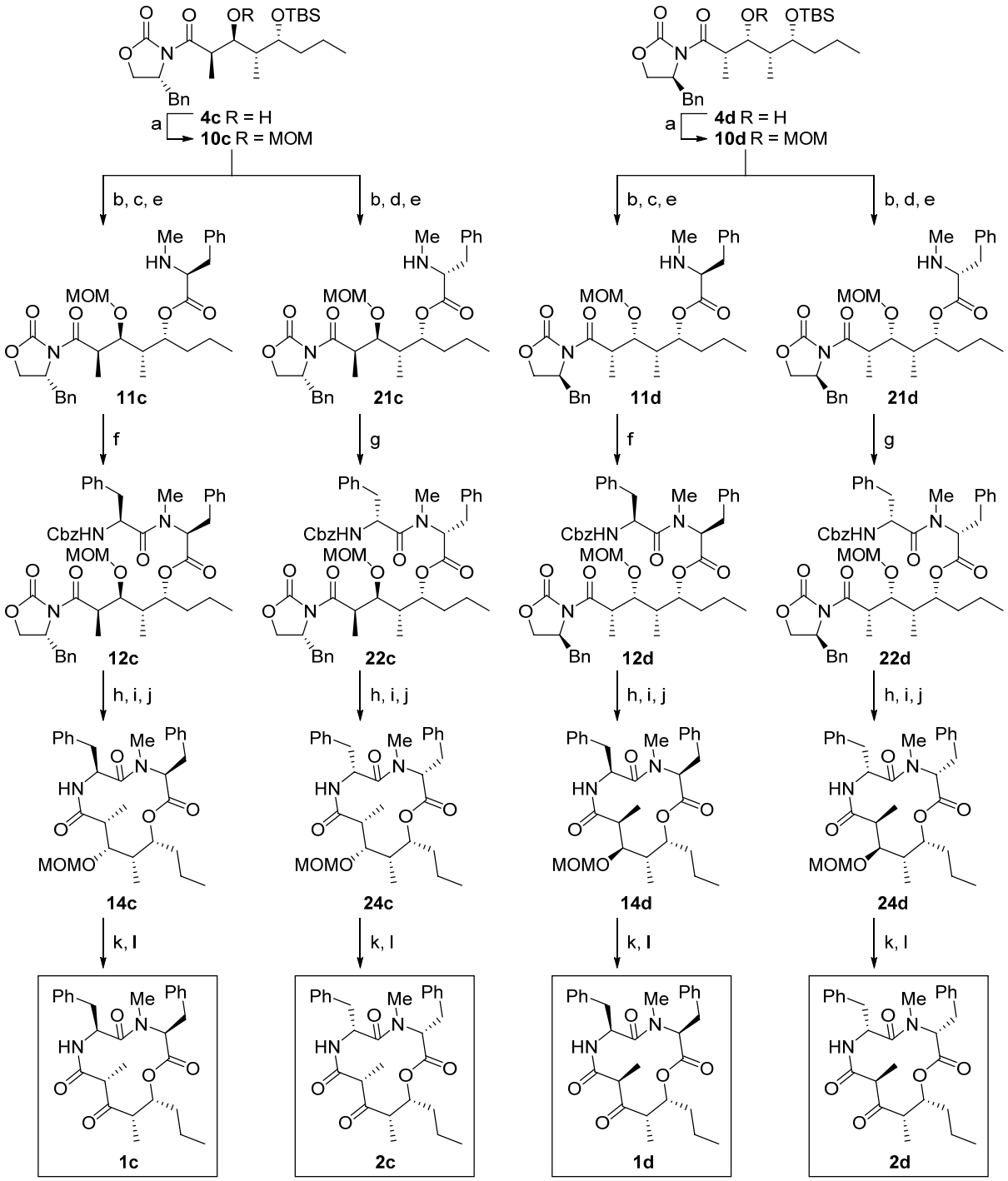
deprotection by rapid hydrogenation within 1.5 h and immediate HATU-mediated peptide bond formation were effective in suppressing the inevitable L-Phe-L-MePhe diketopiperazine formation. Fortunately, no epimerization at the C2 methyl group in the enolizable β-keto ester moiety of HDMOO was observed during the synthetic and purification process of any stereocalpin A stereoisomers.



Scheme 2. Syntheses of alcohols **4b–d**. *Reagents and conditions*: (a) *p*-nitrobenzoic acid, Ph_3P, DEAD, THF, 0 °C to rt; (b) NaOH, MeOH, 0 °C to rt, 70% (2 steps); (c) TBSCl, imidazole, DMF, 0 °C to rt, 87%; (d) Pd/C, H_2, EtOH, rt, 88%; (e) $(COCl)_2$, DMSO, $(i\text{-Pr})_2NEt$, CH_2Cl_2, –78 °C to 0 °C; (f) (*S*)-**9**, $n\text{-Bu}_2BOTf$, $(i\text{-Pr})_2NEt$, CH_2Cl_2, –78 °C to –10 °C, 87% (**4b**) and 94% (**4d**) (2 steps); (g) (*R*)-**9**, $n\text{-Bu}_2BOTf$, $(i\text{-Pr})_2NEt$, CH_2Cl_2, –78 °C to –10 °C, 82% (2 steps).



Scheme 3. Syntheses of 4*S*,5*S*-isomers **1b** and **2a,b**. *Reagents and conditions*: (a) MOMCl, (*i*-Pr)$_2$NEt, 1,2-dichloroethane, rt to 40 °C, 88% (**10b**); (b) HF·pyridine, THF, pyridine, 0 °C to rt; (c) Fmoc-L-MePhe-OH, EDCI·HCl, DMAP, CH_2Cl_2, 0 °C; (d) Fmoc-D-MePhe-OH, EDCI·HCl, DMAP, CH_2Cl_2, 0 °C; (e) Et_2NH, MeCN, rt, 85% (**21a**), 80% (**11b**) and 66% (**21b**) (3 steps); (f) Cbz-L-Phe-OH, HATU, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0 °C to rt, 81% (**12b**); (g) Cbz-D-Phe-OH, HATU, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0 °C to rt, 94% (**22a**) and 88% (**22b**); (h) LiOH, H_2O_2, THF, H_2O, 0 °C to rt; (i) Pd/C, H_2, MeOH, rt; (j) HATU, HOAt, (*i*-Pr)$_2$NEt, DMF, rt, 80% (**24a**), 89% (**14b**) and 63% (**24b**) (3 steps); (k) HCl, MeOH, H_2O, 0 °C to 40 °C; (l) Dess-Martin periodinane, CH_2Cl_2, rt to 40 °C, 97% (**2a**), 89% (**1b**) and 89% (**2b**) (2 steps).



Scheme 4. Syntheses of 4*S*,5*R*-isomers **1c,d** and **2c,d**. *Reagents and conditions*: (a) MOMCl, (*i*-Pr)$_2$NEt, 1,2-dichloroethane, rt to 40 °C, 97% (**10c**) and 90% (**10d**); (b) HF·pyridine, THF, pyridine, 0 °C to rt; (c) Fmoc-L-MePhe-OH, EDCI·HCl, DMAP, CH_2Cl_2, 0 °C; (d) Fmoc-D-MePhe-OH, EDCI·HCl, DMAP, CH_2Cl_2, 0 °C; (e) Et_2NH, MeCN, rt, 60% (**11c**), 64% (**21c**), 71% (**11d**) and 76% (**21d**) (3 steps); (f) Cbz-L-Phe-OH, HATU, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0 °C to rt, 88% (**12c**) and 94% (**12d**); (g) Cbz-D-Phe-OH, HATU, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0 °C to rt, 92% (**22c**) and 80% (**22d**); (h) LiOH, H_2O_2, THF, H_2O, 0 °C to rt; (i) Pd/C, H_2, MeOH, rt; (j) HATU, HOAt, (*i*-Pr)$_2$NEt, DMF, rt, 69% (**14c**), 89% (**24c**), 59% (**14d**) and 74% (**24d**) (3 steps); (k) HCl, MeOH, H_2O, 0 °C to 40 °C; (l) Dess-Martin periodinane, CH_2Cl_2, rt to 40 °C, 84% (**1c**), 89% (**2c**), 79% (**1d**) and 39% (**2d**) (2 steps).

Table 1. Comparison of the ^{1}H NMR spectra between natural stereocalpin A and the synthetic **1c** (in $CDCl_3$).

Natural stereocalpin A	Synthetic **1c**[a]
0.89 (t, *J* = 7.3 Hz, 3H)	0.90 (t, *J* = 7.4 Hz, 3H)
0.99 (d, *J* = 7.0 Hz, 3H)	1.00 (d, *J* = 6.9 Hz, 3H)
1.18 (m, 2H)	1.18 (m, 2H)
1.27 (m, 1H)	1.27 (m, 1H)
1.30 (d, *J* = 7.3 Hz, 3H)	1.31 (d, *J* = 7.4 Hz, 3H)
1.48 (m, 1H)	1.48 (m, 1H)
2.57 (m, 1H)	2.57 (m, 1H)
2.80 (dd, *J* = 14.3, 8.8 Hz, 1H)	2.81 (dd, *J* = 14.0, 8.3 Hz, 1H)
2.99 (dd, *J* = 14.2, 4.0 Hz, 1H)	3.02 (m, 1H)
3.05 (s, 3H)	3.06 (s, 3H)
3.11 (m, 1H)	3.11 (m, 1H)
3.14 (m, 1H)	3.14 (m, 1H)
3.87 (q, *J* = 7.0 Hz, 1H)	3.87 (q, *J* = 6.9 Hz, 1H)
4.66 (dd, *J* = 9.9, 5.9 Hz, 1H)	4.67 (dd, *J* = 10.0, 6.0 Hz, 1H)
4.97 (m, 1H)	4.99 (m, 1H)
5.30 (m, 1H)	5.30 (m, 1H)
5.80 (d, *J* = 9.9 Hz, 1H)	5.76 (d, *J* = 10.3 Hz, 1H)
7.06-7.32 (m, 10H)	7.04-7.37 (m, 10H)

[a] Data of the major conformer are shown.

The author performed a comparative analysis of NMR spectra of the natural product and eight synthetic stereoisomers **1a–d** and **2a–d**. The ^{1}H and ^{13}C NMR spectra of natural stereocalpin A were identical with those of the (2*R*,4*S*,5*R*)-isomer **1c** with the L-Phe-L-MePhe dipeptide (Tables 1 and 2).[14] Therefore, the stereochemistry of stereocalpin A should be revised from **1a** to **1c**. The 4*S*,5*R*-configurations in the polyketide substructure of natural stereocalpin A **1c** are different from those of the related 12-membered cyclic depsipeptides: taumycin A/B [4*R*,5*S*-configurations], tausalarin C and dahurelmusin A [4*S*,5*S*-configurations]. Of note, hydrogen/deuterium (H/D) exchange of the C2-proton in the β-keto carboxamide part of natural **1c** and the C2-epimer **1d** by 72-

Table 2. Comparison of the ^{13}C NMR spectra between natural stereocalpin A and the synthetic **1c** (in $CDCl_3$).

Natural stereocalpin A	Synthetic **1c**[a]	Natural stereocalpin A	Synthetic **1c**[a]
10.4	10.3	126.6	126.5
13.9	13.7	127.3	127.2
15.0	14.9	128.2	128.2
18.9	18.8	128.7	128.7
30.0	30.0	128.9	128.8
32.8	32.8	129.6	129.6
36.0	36.0	135.8	135.7
38.4	38.2	137.0	137.0
48.8	48.7	167.0	166.9
50.9	50.8	169.9	169.9
52.4	52.4	170.6	170.4
58.9	58.8	210.7	210.6
76.3	76.2		

[a] Data of the major conformer are shown.

h incubation in CD_3OD was not observed, and so natural stereocalpin A **1c** is stable without epimerization at the C2 methyl group during the isolation process.[1]

In the original report describing the structure determination of natural stereocalpin A, the assignment of the 5*S*-configuration was based on two key NOE correlations of C4-H/C5-CH_2 (methylene of *n*-Pr) and C4-CH_3/C5-H in the NOESY spectra.[1] When the author carefully analyzed the NOESY spectrum of synthetic **1c**, an NOE correlation between C4-H and C5-H was observed, suggesting that these two protons would exist in the *cis* configurations (Figure 5). Additionally, the presence of an NOE correlation between C4-H and C5-CH_2 was ambiguous, because the C5-CH_2 signals overlapped with that of C4-CH_3. Similarly, it was difficult to distinguish between the proposed C4-CH_3/C5-H cross peak and a plausible C5-CH_2/C5-H cross peak.

The observed NOEs of C2-H/C4-CH_3 and C2-CH_3/C4-H in **1a** corresponded with the directions of the 2- and 4-methyl groups toward opposite sides from the macrocycle ring (Figure 5). The NOEs of C4-H/C5-CH_2 (*n*-Pr) and C4-CH_3/C5-H were also observed, supporting the *trans* configurations at the HDMOO C4 and C5 positions. Interestingly, NOE correlations of vicinal C4-

H/C5-H protons of **1c** were shared with **1a**, indicating that the presence or absence of this NOE correlation cannot be corroborative of 4,5-*cis* or *trans* configurations.

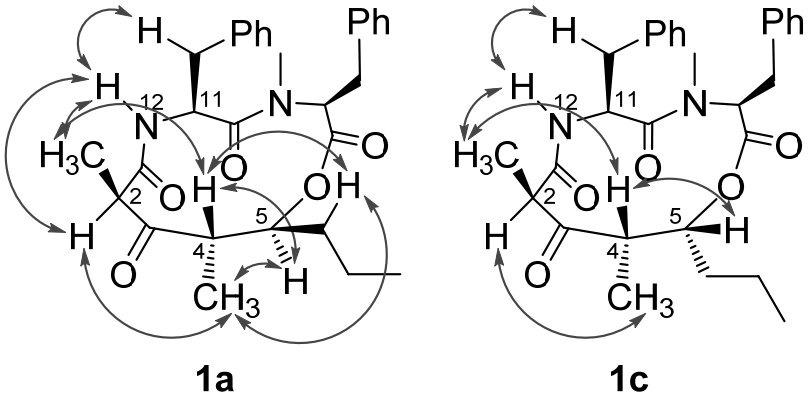


Figure 5. Key NOESY correlations of peptides **1a** and **1c**.

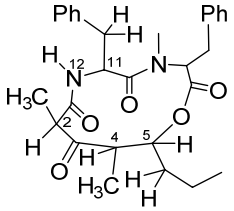
The author also investigated the relationships between the relative stereochemistries and the characteristics of the NMR spectroscopic data among a series of cyclic depsipeptides **1a–d** and **2a–d** (Table 3). The NOE correlations between the Phe amide proton (N12-H) and the Phe benzyl CH_2 (C11-CH_2) were shared among all eight peptides, suggesting that the N–H bonds of **1a–d** are directed upward (β-face) on the macrocycle, whereas those of **2a–d** are directed downward (α-face) and are positioned below the macrocycle. This amide proton had a significant NOE correlation with either C2-H or C2-CH_3, except that peptide **1a** has two correlations with both C2-H and C2-CH_3. These observations indicate that C2-H or C2-CH_3 is normally on the same side of the macrocycle as the L-Phe side-chain.

The NOE correlations between C2-H and C4-H were observed for only four (2*S*,4*S*)-isomers **1b**, **1d**, **2b** and **2d**, implying that the presence or absence of this characteristic signal can be useful for the identification of the relative stereochemistry at HDMOO C2- and C4-positions. The significant NOE correlations between C2-H and C4-CH_3 were observed in (2*R*,4*S*)-isomers **1a** and **1c** with the L-Phe-L-MePhe dipeptide. Similarly, (2*R*,4*S*)-isomers **2a** and **2c** with the D-Phe-D-MePhe dipeptide shared NOE correlations between C2-CH_3 and C4-H. As such, the NOE correlations over the N12–C2–C4 conjunction can serve as useful references for stereochemical assignment, although some exceptional cross peaks may be observed depending on the peptide conformations.

In contrast, a number of vicinal NOE correlations at the C4 and C5 positions were observed among all eight peptides. Only a characteristic cross peak between C4 and C5 may be the C4-H/C5-CH_2, which was observed in (4*S*,5*S*)-isomers **1a**, **1b** and **2b**; however, the same C4-H/C5-CH_2 correlation of the (4*S*,5*S*)-isomer **2a** was ambiguous because of overlapping signals. In the case of the natural stereoisomer **1c**, the overlapping signals of C4-CH_3 and C5-CH_2 prevented unambiguous assignment of cross peaks. On the basis of these results, the author concluded that the C5-stereochemistry of stereocalpin A cannot be determined solely from NOESY spectra of **1c** because

there were several signals in overlap in the ^{1}H NMR spectrum of **1c** and a number of NOE correlations for possible key determinants for stereochemical assignment were commonly observed among the stereoisomers. A number of incorrect assignments of constitutions and configurations of macrocyclic natural products have been reported, although remarkable advances have been made in spectroscopic techniques and simulation technologies.[6] Complementary approaches including

Table 3. Observed NOE correlations of stereocalpin A and the stereoisomers.[a]



	natural (**1c**)[1]	**1a**	**1b**	**1c**	**1d**	**2a**	**2b**	**2c**	**2d**
N12-H – C11-CH_2	+	++	++	++	++	++	++	++	++
N12-H – C2-CH_3	+	++	+	++	–	–	++	–	++
N12-H – C2-H	–	++	++	–	++	++	–	++	–
C2-H – C4-H	–	–	++	–	++	–	++	–	++
C2-H – C4-CH_3	+	++	+	++	++	–	+	+	–
C2-CH_3 – C4-H	–	++	–	+	–	++	+	++	–
C2-CH_3 – C4-CH_3	–	–	–	–	–	++	–	–	–
C4-H – C5-H	–	++	++	++	++	++	±[d]	++	++
C4-H – C5-CH_2 (*n*-Pr)	+	++	++	±[b]	–	±[c]	++	–	–
C4-CH_3 – C5-H	+	++	++	±[b]	++	++	++	++	++
C4-CH_3 – C5-CH_2 (*n*-Pr)	–	+	++	±[b]	++	++	++	++	++

[a] The NOE crosspeaks of synthetic **1a–d** and **2a–d** were classified into three groups. ++: strong NOE; +: weak NOE; ±: ambiguous; –: no crosspeak. [b] The signals derived from C4-CH_3 and C5-CH_2 overlapped. [c] The signal of C5-CH_2 overlapped with the signal of C2-CH_3 (minor conformation). This crosspeak may possibly be derived from correlations between C4-H and C2-CH_3. [d] The signal of C5-H (major conformation) was in overlap with that of C11-H (minor conformation). The signal of C4-H was in overlap with those of C8-H (minor conformation) and C11-CH_2 (minor conformation). This crosspeak may possibly be derived from the correlations of these signals.

synthetic studies and derivatization of degraded product(s) should enable researchers to consolidate ambiguities arising from NMR data.[15]

In conclusion, the author established the facile synthetic route of stereocalpin A to provide its eight stereoisomers via a stereoselective syntheses of four diastereomers of the polyketide substructure from a common (*R*)-Roche ester. Using the resulting key polyketide precursors, four possible stereoisomers **1a-d** of stereocalpin A and four mirror-image structures **2a-d** of the remaining four possible stereoisomers were prepared through stepwise conjugation with L-Phe-L-MePhe and D-Phe-D-MePhe, respectively, followed by macrocyclization. The structures of the resulting eight stereoisomers were stably maintained without possible epimerization of the C2-methyl group in the HDMOO β-keto carboxamide substructure during the synthetic and isolation process. The NMR spectra of natural stereocalpin A were coincident with those of peptide **1c**, suggesting that the HDMOO substructure possesses the 2*R*,4*S*,5*R*-configuration. The comprehensive analysis of NOESY spectra of peptides **1a–d** and **2a–d** indicated that the stereochemistry of HDMOO the C5-position cannot be determined solely by NOE correlations. The structural assignment of stereocalpin A (**1c**) in this study should facilitate chemical biology research for target identification and medicinal chemistry efforts aimed at finding new highly potent anti-inflammatory agents.

Experimental Section

General Methods

^{1}H NMR spectra were recorded using a JEOL ECA-500 spectrometer. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in $CDCl_3$) as an internal standard. ^{13}C NMR spectra were recorded using a JEOL ECA-500 spectrometer and referenced to the residual solvent signal. ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (br: broad, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet), number of protons, and coupling constants. Melting points were measured by a hot stage melting points apparatus (uncorrected). Exact mass (HRMS) spectra were recorded on a Shimadzu LC-ESI-IT-TOF-MS equipment. IR spectra were determined on a JASCO FT/IR-4100 spectrometer. Optical rotations were measured with a JASCO P-1020 polarimeter. For flash chromatography, Wakogel C-300E (Wako) was employed.

*Synthesis of proposed stereocalpin A (**1a**)*

(2*R*,3*S*)-1-(Benzyloxy)-2-methylhex-5-en-3-ol (6a). To a stirred solution of oxalyl chloride (9.5 mL, 111 mmol) in CH_2Cl_2 (222 mL) under argon was added DMSO (15.8 mL, 222 mmol) in CH_2Cl_2 (37.0 mL) at –78 °C. After being stirred for 30 min, a solution of alcohol **5** (10.0 g, 55.5 mmol) in CH_2Cl_2 (191 mL) was added dropwise and stirred at –78 °C for 1 h. (*i*-Pr)$_2$NEt (48.3 mL, 278 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. The mixture was quenched with aqueous saturated NH_4Cl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give the corresponding aldehyde, which was used for the next step without further purification. To a stirred solution of allyltributylstannane (23.8 mL, 77.7 mmol) in CH_2Cl_2 (130 mL) under argon were added $SnCl_4$ (1.0 M in CH_2Cl_2; 77.7 mL, 77.7 mmol) and the above aldehyde in CH_2Cl_2 (66.0 mL) at –78 °C. After being stirred for 1 h, the mixture was quenched with aqueous KF and allowed to warm to room temperature. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over 10% w/w anhydrous K_2CO_3-silica gel[16] with hexane–EtOAc (9:1 to 5:1) to give compound **6a** (9.8 g, 80%, dr 15:1) as a colorless oil. The spectral data were in good agreement with those previously reported.[10b]

{[(2*R*,3*S*)-1-(Benzyloxy)-2-methylhex-5-en-3-yl]oxy}(*tert*-butyl)dimethylsilane (7a). To a stirred solution of alcohol **6a** (9.7 g, 44.2 mmol) in DMF (147 mL) under argon were added imidazole (10.5 g, 154.7 mmol) and TBSCl (13.3 g, 88.4 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure, and Et_2O and H_2O were added to the residue. The whole was extracted with Et_2O and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–$CHCl_3$ (9:1 to 1.5:1) to

give compound **7a** (13.4 g, 91%) as a colorless oil. The spectral data were in good agreement with those previously reported.[11]

(2*R*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylhexan-1-ol (8a). To a stirred solution of alkene **7a** (425.1 mg, 1.3 mmol) in EtOH (12.7 mL) was added 10% Pd/C (135.2 mg, 0.13 mmol) at room temperature and the mixture was flushed with H_2 gas (1 atm). After being stirred for 3 h, the reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (7:1) to give compound **8a** (273.8 mg, 87%) as a colorless oil: $[\alpha]^{26}_{D}$ +15.1 (*c* 1.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.08 (s, 3H), 0.09 (s, 3H), 0.90-0.93 (m, 12H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.27-1.35 (m, 2H), 1.52-1.56 (m, 2H), 1.72-1.79 (m, 1H), 2.79-2.81 (m, 1H), 3.51-3.55 (m, 1H), 3.69-3.72 (m, 1H), 3.78-3.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.8, –4.3, 14.3, 14.7, 18.0, 18.1, 25.8 (3C), 37.1, 37.7, 65.4, 77.3; HRMS (ESI-TOF) calcd for $C_{13}H_{30}NaO_2Si$ $[M+Na]^+$: 269.1907; found: 269.1906.

(*R*)-4-Benzyl-3-{(2*R*,3*S*,4*R*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-2,4-dimethyl-octanoyl}-1,3-oxazolidin-2-one (4a). To a stirred solution of oxalyl chloride (189 μL, 2.2 mmol) in CH_2Cl_2 (11.0 mL) under argon was added DMSO (313 μL, 4.4 mmol) in CH_2Cl_2 (733 μL) at –78 °C. The mixture was stirred for 30 min, a solution of alcohol **8a** (273.3 mg, 1.1 mmol) in CH_2Cl_2 (3.8 mL) was added dropwise and the mixture was stirred at –78 °C for 1 h. (*i*-Pr)$_2$NEt (958 μL, 5.5 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. The mixture was quenched with aqueous saturated NH_4Cl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give the corresponding aldehyde, which was used for the next step without further purification. To a stirred solution of oxazolidinone (*R*)-**9** (282.3 mg, 1.2 mmol) in CH_2Cl_2 (6.1 mL) under argon were added (*n*-Bu)$_2$BOTf (1.0 M in CH_2Cl_2; 1.3 mL, 1.3 mmol) and (*i*-Pr)$_2$NEt (249 μL, 1.4 mmol) at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 30 min. To this solution was added the above aldehyde in CH_2Cl_2 (2.5 mL) at –78 °C. After being stirred for 20 min, the mixture was warmed to –10 °C and stirred for 1 h. The mixture was quenched with phosphate buffer solution (pH 7.0, 1.2 mL) and 30% H_2O_2 in MeOH (1:2, 2.8 mL), and stirred for 1 h at room temperature. The whole was extracted with CH_2Cl_2 and the extract was washed with aqueous saturated $NaHCO_3$, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (9:1 to 6:1) to give compound **4a** (452.1 mg, 86%) as a colorless oil: $[\alpha]^{26}_{D}$ –36.8 (*c* 1.69, $CHCl_3$); IR (neat): 3546 (OH), 1785 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.07 (s, 6H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 12H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.25-1.33 (m, 1H), 1.36-1.40 (m, 2H), 1.43-1.50 (m, 1H), 1.77-1.84 (m, 1H), 2.78 (dd, *J* = 13.2, 9.5 Hz, 1H), 3.30 (dd, *J* = 13.2, 3.4 Hz, 1H), 3.40 (d, *J* = 2.3 Hz, 1H), 3.75-3.78 (m, 1H), 3.85-3.89 (m, 1H), 3.94-3.97 (m, 1H), 4.18-4.20 (m, 2H), 4.66-4.71 (m, 1H), 7.20-7.22 (m, 2H), 7.28-7.29 (m, 1H), 7.32-7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.5 (2C), 8.9, 11.0, 14.3, 18.1, 18.8, 25.9 (3C), 34.6, 37.7, 39.8, 40.8, 55.4, 66.2, 73.2, 73.9, 127.4, 128.9 (2C), 129.4 (2C),

135.2, 153.0, 177.4; HRMS (ESI-TOF) calcd for $C_{26}H_{43}NNaO_5Si$ $[M+Na]^+$: 500.2803; found: 500.2804.

(*R*)-4-Benzyl-3-{(2*R*,3*S*,4*R*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-3-(methoxymethoxy)-2,4-dimethyloctanoyl}-1,3-oxazolidin-2-one (10a). To a stirred solution of alcohol **4a** (14.8 g, 31.0 mmol) in 1,2-dichloroethane (207 mL) under argon were added (*i*-Pr)$_2$NEt (54.0 mL, 310.0 mmol) and MOMCl (18.8 mL, 248.0 mmol) at room temperature. The reaction mixture was warmed to 40 °C and stirred overnight. The mixture was quenched with 1N HCl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (10:1 to 7:1) to give compound **10a** (15.0 g, 93%) as a colorless oil: $[\alpha]^{25}_D$ –54.9 (*c* 1.36, $CHCl_3$); IR (neat): 1782 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.04 (s, 3H), 0.05 (s, 3H), 0.89-0.92 (m, 15H), 1.15-1.23 (m, 4H), 1.25-1.39 (m, 2H), 1.47-1.52 (m, 1H), 1.86-1.93 (m, 1H), 2.76 (dd, *J* = 13.2, 10.3 Hz, 1H), 3.31 (s, 3H), 3.36 (dd, *J* = 13.2, 2.9 Hz, 1H), 3.73 (dd, *J* = 9.7, 2.3 Hz, 1H), 3.80-3.84 (m, 1H), 3.84-3.89 (m, 1H), 4.15-4.21 (m, 2H), 4.50 (s, 2H), 4.54-4.58 (m, 1H), 7.22-7.23 (m, 2H), 7.27-7.29 (m, 1H), 7.32-7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.6, –4.4, 9.2, 9.9, 14.3, 18.1, 19.8, 25.9 (3C), 33.5, 37.6, 41.2, 42.9, 56.3, 56.8, 66.2, 72.2, 82.0, 98.5, 127.2, 128.9 (2C), 129.4 (2C), 135.6, 153.3, 175.1; HRMS (ESI-TOF) calcd for $C_{28}H_{47}NNaO_6Si$ $[M+Na]^+$: 544.3065; found: 544.3067.

(4*S*,5*S*,6*S*,7*R*)-8-[(*R*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-Methyl-L-phenylalaninate (11a). To a stirred solution of silyl ether **10a** (268.1 mg, 0.51 mmol) in THF (3.4 mL) and pyridine (0.85 mL) was added HF·pyridine (2.1 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was poured into aqueous saturated $NaHCO_3$ at 0 °C. The whole was extracted with EtOAc, and the extract was washed with 1N HCl, brine, aqueous saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was filtrated through a short pad of silica gel with hexane–EtOAc (2:1) to give the crude alcohol, which was used for the next step without further purification. To a stirred solution of the above alcohol in CH_2Cl_2 (3.4 mL) were added Fmoc-L-MePhe-OH (309.1 mg, 0.77 mmol), EDCI·HCl (195.5 mg, 1.0 mmol) and DMAP (31.8 mg, 0.26 mmol) at 0 °C. After being stirred for 2 h, the mixture was quenched with 1N HCl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was filtrated through a short pad of silica gel with hexane–EtOAc (3:1) to give the crude Fmoc-protected amine, which was used for the next step without further purification. To a stirred solution of the above protected amine in MeCN (5.1 mL) was added Et_2NH (1.7 mL) at room temperature. After being stirred for 1 h, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (2:1 to 1:1) to give compound **11a** (241.5 mg, 82%) as a colorless oil: $[\alpha]^{27}_D$ –44.6 (*c* 1.33, $CHCl_3$); IR (neat): 1779 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.71 (d, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 1.15-1.22 (m, 1H), 1.25-1.32 (m, 4H),

1.41-1.53 (m, 2H), 1.66-1.72 (m, 1H), 2.34 (s, 3H), 2.78 (dd, *J* = 13.2, 9.7 Hz, 1H), 2.85 (dd, *J* = 13.5, 7.7 Hz, 1H), 2.94 (dd, *J* = 13.5, 6.3 Hz, 1H), 3.27 (dd, *J* = 13.2, 3.4 Hz, 1H), 3.37-3.39 (m, 4H), 3.68-3.70 (m, 1H), 3.95-4.00 (m, 1H), 4.14 (dd, *J* = 8.9, 2.0 Hz, 1H), 4.23-4.27 (m, 1H), 4.55-4.61 (m, 3H), 5.03 (dt, *J* = 10.5, 2.9 Hz, 1H), 7.15-7.36 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.7, 12.8, 13.8, 19.2, 30.6, 34.7, 37.8, 39.6, 39.8, 40.8, 55.8, 56.6, 64.8, 66.4, 74.9, 82.8, 98.9, 126.7, 127.2, 128.4 (2C), 128.9 (2C), 129.2 (2C), 129.4 (2C), 135.5, 137.1, 153.4, 174.4, 175.2; HRMS (ESI-TOF) calcd for $C_{32}H_{45}N_2O_7$ $[M+H]^+$: 569.3221; found: 569.3221.

(4*S*,5*S*,6*S*,7*R*)-8-[(*R*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-{[(Benzyloxy)carbonyl]-L-phenylalanyl}-*N*-methyl-L-phenylalaninate (12a). To a stirred solution of amine **11a** (200.9 mg, 0.35 mmol) in CH_2Cl_2 (3.5 mL) were added Cbz-L-Phe-OH (116.7 mg, 0.39 mmol), HATU (201.5 mg, 0.53 mmol) and (*i*-Pr)$_2$NEt (183 μL, 1.1 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The mixture was quenched with aqueous saturated NH_4Cl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (5:1 to 2.5:1) to give compound **12a** (271.3 mg, 91%) as a colorless oil: $[\alpha]^{27}_D$ –58.1 (*c* 1.76, $CHCl_3$); IR (neat): 1778 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 4:1 mixture of rotamers) δ: 0.80 (t, *J* = 7.4 Hz, 0.6H), 0.84-0.92 (m, 5.4H), 1.07-1.31 (m, 5.0H), 1.32-1.39 (m, 0.2H), 1.41-1.49 (m, 1.0H), 1.52-1.58 (m, 0.8H), 1.86-1.91 (m, 0.2H), 1.93-1.98 (m, 0.8H), 2.44 (dd, *J* = 13.2, 6.3 Hz, 0.2H), 2.56 (dd, *J* = 13.7, 8.6 Hz, 0.2H), 2.67 (dd, *J* = 13.2, 7.4 Hz, 0.2H), 2.75-2.82 (m, 1.8H), 2.86 (s, 2.4H), 2.90 (s, 0.6H), 2.94-3.02 (m, 1.6H), 3.18-3.25 (m, 1.2H), 3.30 (dd, *J* = 14.6, 6.0 Hz, 0.8H), 3.36 (s, 0.6H), 3.39 (s, 2.4H), 3.75 (dd, *J* = 6.6, 4.9 Hz, 0.2H), 3.79-3.82 (m, 0.8H), 3.95-4.03 (m, 1.0H), 4.04-4.14 (m, 1.2H), 4.21-4.25 (m, 0.8H), 4.55-4.64 (m, 3.0H), 4.74-4.87 (m, 1.4H), 4.97-5.05 (m, 2.8H), 5.20-5.23 (m, 0.8H), 5.26 (d, *J* = 8.6 Hz, 0.8H), 5.35 (d, *J* = 9.2 Hz, 0.2H), 6.96-6.97 (m, 0.4H), 7.11-7.37 (m, 19.6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.8, 12.4, 13.0, 13.7, 13.9 (2C), 29.4, 31.3, 32.2, 32.9, 34.7, 34.9, 37.8, 37.9, 38.9, 39.2, 39.7, 39.8, 40.3, 41.3, 51.0, 51.9, 55.5, 55.7, 56.4, 56.5, 58.8, 61.1, 66.2, 66.3, 66.4, 66.6, 75.8, 76.4, 81.7, 82.4, 98.6, 98.7, 126.6, 126.7, 126.8, 127.1, 127.2, 127.3, 127.5, 127.9 (2C), 128.0 (2C), 128.2 (2C), 128.4 (8C), 128.8 (2C), 128.9 (4C), 129.4 (4C), 129.6 (2C), 135.4, 135.5, 136.0 (2C), 136.3, 136.4, 136.5, 136.7, 153.4, 153.6, 155.0, 155.3, 169.0, 170.1, 171.5, 172.1, 175.3, 175.6; HRMS (ESI-TOF) calcd for $C_{49}H_{59}N_3NaO_{10}$ $[M+Na]^+$: 872.4093; found: 872.4097.

Cyclic peptide (14a). To a stirred solution of oxazolidinone **12a** (101.5 mg, 0.12 mmol) in THF (1.2 mL) were added a solution of $LiOH·H_2O$ (10.1 mg, 0.24 mmol) in H_2O (120 μL) and 30% H_2O_2 (62 μL, 0.60 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was quenched with 1N HCl. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (2:1 to 1:1) to give the crude carboxylic acid **13a**, which was used for the next step without further purification. To a

stirred solution of the above carboxylic acid **13a** in MeOH (1.2 mL) was added 10% Pd/C (63.9 mg, 0.060 mmol) at room temperature and the mixture was flushed with H_2 gas (1 atm). After being stirred for 1.5 h, the reaction mixture was diluted with DMF (120 mL). To this mixture were added HATU (136.9 mg, 0.36 mmol), HOAt (49.0 mg, 0.36 mmol) and $(i\text{-Pr})_2$NEt (125 μL, 0.72 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and EtOAc and 1N HCl were added to the residue. The whole was extracted with EtOAc and the extract was washed with brine, aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash chromatography over silica gel with $CHCl_3$–EtOAc (15:1) to hexane–EtOAc (1:1) to give compound **14a** (35.0 mg, 54%) as a white solid: mp 230 °C; $[\alpha]^{26}_D$ –148.4 (*c* 1.34, $CHCl_3$); IR (neat): 1742 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ: 0.92 (t, *J* = 7.4 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 7.4 Hz, 3H), 1.26-1.35 (m, 2H), 1.54-1.58 (m, 2H), 2.14-2.19 (m, 1H), 2.48-2.54 (m, 1H), 2.82 (s, 3H), 2.84-2.96 (m, 3H), 3.29 (dd, *J* = 14.6, 3.7 Hz, 1H), 3.34 (s, 3H), 3.60-3.62 (m, 1H), 4.17 (br s, 1H), 4.56-4.61 (m, 2H), 4.87-4.90 (m, 1H), 5.08-5.10 (m, 1H), 5.49-5.50 (m, 1H), 6.89-6.90 (m, 2H), 7.12-7.29 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ: 13.8, 15.8 (2C), 18.6, 29.7, 34.1, 35.1, 37.5, 39.3, 44.2, 50.9, 55.9, 61.8, 76.7, 80.2, 96.5, 126.4, 126.9, 128.3 (2C), 128.8 (4C), 129.2 (2C), 137.5, 137.9, 169.7, 170.9, 172.0; HRMS (ESI-TOF) calcd for $C_{31}H_{43}N_2O_6$ $[M+H]^+$: 539.3116; found: 539.3118.

Proposed structure of stereocalpin A (1a: 5*S*-stereoisomer of natural product). To a stirred solution of ether **14a** (21.6 mg, 0.040 mmol) in MeOH (4.0 mL) was added 6N HCl (1.0 mL) at 0 °C. The reaction mixture was warmed to 40 °C and stirred overnight. The reaction mixture was concentrated under reduced pressure, and CH_2Cl_2 and 1N HCl were added to the residue. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give the crude alcohol, which was used for the next step without further purification. To a stirred solution of the above alcohol in CH_2Cl_2 (4.0 mL) was added Dess-Martin periodinane (169.7 mg, 0.40 mmol) at room temperature. The reaction mixture was warmed to 40 °C and stirred overnight. The reaction was quenched with aqueous saturated $NaHCO_3$ and $Na_2S_2O_3$. The whole was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (1.2:1) to give compound **1a** (15.1 mg, 78%) as a white solid. The spectral data were in good agreement with those previously reported[7a]: $[\alpha]^{27}_D$ –207.6 (*c* 0.73, CH_2Cl_2).

*Synthesis of 2S,5S-stereoisomer of stereocalpin A (**1b**)*

(*S*)-4-Benzyl-3-{(2*S*,3*R*,4*R*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-2,4-dimethyloctanoyl}-1,3-oxazolidin-2-one (4b). According to the procedure described for the preparation of **4a**, alcohol **8a** (97.0 mg, 0.39 mmol) was converted into compound **4b** (163.5 mg, 87%) as a colorless oil: $[\alpha]^{28}_D$ +54.0 (*c* 1.37, $CHCl_3$); IR (neat): 3503 (OH), 1782 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.09 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.99 (d, *J* =

7.4 Hz, 3H), 1.21-1.28 (m, 1H), 1.35-1.43 (m, 4H), 1.52-1.59 (m, 1H), 1.66-1.71 (m, 1H), 1.75-1.83 (m, 1H), 2.77 (dd, *J* = 13.5, 9.5 Hz, 1H), 3.23 (dd, *J* = 13.5, 3.2 Hz, 1H), 3.72-3.75 (m, 1H), 3.87 (s, 1H), 3.92-3.98 (m, 1H), 4.16-4.22 (m, 2H), 4.31 (dd, *J* = 9.2, 1.7 Hz, 1H), 4.65-4.70 (m, 1H), 7.21-7.22 (m, 2H), 7.27-7.29 (m, 1H), 7.32-7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.8, –4.4, 12.0, 14.3, 15.2, 17.9, 18.7, 25.8 (3C), 36.3, 37.2, 37.6, 41.2, 54.9, 65.8, 71.2, 78.6, 127.4, 128.9 (2C), 129.4 (2C), 135.0, 152.7, 175.9; HRMS (ESI-TOF) calcd for $C_{26}H_{43}NNaO_5Si$ $[M+Na]^+$: 500.2803; found: 500.2808.

(*S*)-4-Benzyl-3-{(2*S*,3*R*,4*R*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-3-(methoxymethoxy)-2,4-dimethyloctanoyl}-1,3-oxazolidin-2-one (10b). According to the procedure described for the preparation of **10a**, alcohol **4b** (1.37 g, 2.9 mmol) was converted into compound **10b** (1.31 g, 88%) as a colorless oil: $[\alpha]^{27}_D$ +29.7 (*c* 1.48, $CHCl_3$); IR (neat): 1783 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.06 (s, 3H), 0.08 (s, 3H), 0.89-0.93 (m, 15H), 1.27-1.33 (m, 4H), 1.35-1.45 (m, 3H), 1.75-1.81 (m, 1H), 2.74 (dd, *J* = 13.2, 10.3 Hz, 1H), 3.31-3.36 (m, 4H), 3.63-3.66 (m, 1H), 3.80-3.82 (m, 1H), 3.97-4.03 (m, 1H), 4.14-4.19 (m, 2H), 4.54-4.60 (m, 1H), 4.61 (s, 2H), 7.22-7.23 (m, 2H), 7.27-7.29 (m, 1H), 7.32-7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.4 (2C), 10.2, 12.1, 14.2, 18.1, 18.4, 25.9 (3C), 34.4, 37.7, 41.4, 42.3, 56.2, 56.4, 66.1, 73.1, 81.3, 98.4, 127.3, 128.9 (2C), 129.4 (2C), 135.5, 153.2, 174.8; HRMS (ESI-TOF) calcd for $C_{28}H_{47}NNaO_6Si$ $[M+Na]^+$: 544.3065; found: 544.3068.

(4*S*,5*S*,6*R*,7*S*)-8-[(*S*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-methyl-L-phenylalaninate (11b). According to the procedure described for the preparation of **11a**, silyl ether **10b** (295.2 mg, 0.57 mmol) was converted into compound **11b** (258.1 mg, 80%) as a colorless oil: $[\alpha]^{27}_D$ +20.4 (*c* 1.54, $CHCl_3$); IR (neat): 1780 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.74 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 1.23-1.31 (m, 5H), 1.41-1.49 (m, 1H), 1.55-1.62 (m, 1H), 1.69-1.75 (m, 1H), 2.38 (s, 3H), 2.76 (dd, *J* = 13.2, 9.7 Hz, 1H), 2.92-2.96 (m, 1H), 3.02 (dd, *J* = 13.7, 6.9 Hz, 1H), 3.30 (dd, *J* = 13.2, 2.9 Hz, 1H), 3.34 (s, 3H), 3.43-3.46 (m, 1H), 3.70-3.72 (m, 1H), 3.97-4.02 (m, 1H), 4.15-4.21 (m, 2H), 4.55 (s, 2H), 4.60-4.64 (m, 1H), 4.91-4.94 (m, 1H), 7.20-7.35 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.3, 12.1, 13.8, 18.7, 31.5, 34.8, 37.6, 39.6, 40.2, 41.5, 55.9, 56.5, 65.0, 66.1, 75.4, 80.4, 98.7, 126.6, 127.3, 128.4 (2C), 128.9 (2C), 129.2 (2C), 129.4 (2C), 135.4, 137.5, 153.1, 174.4, 174.7; HRMS (ESI-TOF) calcd for $C_{32}H_{45}N_2O_7$ $[M+H]^+$: 569.3221; found: 569.3224.

(4*S*,5*S*,6*R*,7*S*)-8-[(*S*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-{[(benzyloxy)carbonyl]-L-phenylalanyl}-*N*-methyl-L-phenylalaninate (12b). According to the procedure described for the preparation of **12a**, amine **11b** (57.1 mg, 0.10 mmol) was converted into compound **12b** (68.7 mg, 81%) as a colorless oil: $[\alpha]^{27}_D$ –10.4 (*c* 1.29, $CHCl_3$); IR (neat): 1779 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 3:1 mixture of rotamers) δ: 0.80-0.83 (m, 1.5H), 0.87-0.90 (m, 4.5H), 1.10-1.16 (m, 0.5H), 1.20-1.31 (m, 4.7H), 1.41-1.53 (m, 1.0H), 1.60-1.69 (m, 1.0H), 1.76-1.82 (m, 0.8H), 2.43 (dd, *J* = 13.7, 5.7 Hz, 0.2H), 2.63 (dd, *J* = 13.7, 7.4 Hz, 0.2H), 2.73

(dd, *J* = 13.2, 9.7 Hz, 0.8H), 2.77-2.85 (m, 1.2H), 2.90 (s, 2.3H), 2.95 (s, 0.7H), 3.01-3.09 (m, 1.6H), 3.20-3.27 (m, 1.0H), 3.33 (s, 0.7H), 3.34 (s, 2.3H), 3.37-3.41 (m, 0.2H), 3.45-3.49 (m, 0.8H), 3.69 (dd, *J* = 7.7, 2.6 Hz, 0.2H), 3.88 (dd, *J* = 6.6, 3.7 Hz, 0.8H), 4.00-4.07 (m, 1.5H), 4.12-4.15 (m, 1.5H), 4.46-4.53 (m, 0.5H), 4.58-4.64 (m, 2.3H), 4.70-4.83 (m, 1.2H), 4.85-4.93 (m, 1.4H), 4.96-5.04 (m, 1.8H), 5.20-5.23 (m, 0.8H), 5.34 (d, *J* = 9.2 Hz, 0.8H), 5.55 (d, *J* = 8.6 Hz, 0.2H), 6.90 (dd, *J* = 6.6, 3.2 Hz, 0.5H), 7.10-7.36 (m, 19.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.1, 10.2, 13.4, 13.9, 14.0 (2C), 17.9, 18.1, 29.5, 32.5, 32.9, 33.2, 34.5, 34.7, 37.6, 37.7, 38.8, 39.1, 40.1, 41.2, 41.4, 41.7, 51.3, 52.0, 55.3, 55.6, 56.2, 56.4, 59.4, 61.3, 66.1 (2C), 66.3, 66.5, 76.3 (2C), 79.7, 79.9, 98.5, 98.8, 126.5, 126.6, 126.7, 127.1, 127.2, 127.6, 127.7 (2C), 127.9 (2C), 128.0 (2C), 128.1 (2C), 128.3 (2C), 128.4 (4C), 128.8 (2C), 128.9 (2C), 129.3 (4C), 129.4 (2C), 135.3, 135.4, 136.2 (2C), 136.4, 136.8, 137.1, 153.1, 153.3, 155.1, 155.4, 169.1, 169.9, 171.6, 172.1, 174.9, 175.1; HRMS (ESI-TOF) calcd for $C_{49}H_{59}N_3NaO_{10}$ $[M+Na]^+$: 872.4093; found: 872.4090.

Cyclic peptide (14b). According to the procedure described for the preparation of **14a**, oxazolidinone **12b** (55.2 mg, 0.065 mmol) was converted into compound **14b** (31.0 mg, 89%) as a white solid: mp 53 °C; $[\alpha]^{26}_D$ –105.9 (*c* 1.71, $CHCl_3$); IR (neat): 1737 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.89-0.93 (m, 6H), 0.96 (d, *J* = 6.9 Hz, 3H), 1.23-1.32 (m, 2H), 1.46-1.54 (m, 1H), 1.60-1.66 (m, 1H), 1.78-1.84 (m, 1H), 2.13-2.18 (m, 1H), 2.79-2.81 (m, 5H), 2.91 (dd, *J* = 14.9, 11.5 Hz, 1H), 3.36-3.41 (m, 5H), 4.58-4.62 (m, 2H), 4.71-4.76 (m, 1H), 4.81-4.85 (m, 1H), 5.36 (dd, *J* = 11.5, 3.4 Hz, 1H), 5.78 (d, *J* = 10.3 Hz, 1H), 6.87-6.89 (m, 2H), 7.12-7.28 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.4, 14.0, 15.1, 17.7, 29.8, 33.9, 34.2, 37.6, 44.9, 49.0, 50.0, 56.3, 61.7, 79.9, 81.6, 98.4, 126.3, 126.9, 128.2 (2C), 128.7 (4C), 128.9 (2C), 136.7, 137.0, 169.6, 171.6, 174.0; HRMS (ESI-TOF) calcd for $C_{31}H_{42}N_2NaO_6$ $[M+Na]^+$: 561.2935; found: 561.2939.

2*S*,5*S*-Stereoisomer of stereocalpin A (1b). According to the procedure described for the preparation of **1a**, ether **14b** (31.0 mg, 0.058 mmol) was converted into compound **1b** (25.1 mg, 89%) as a white solid: mp 246 °C; $[\alpha]^{27}_D$ –252.7 (*c* 1.03, $CHCl_3$); IR (neat): 1738 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.92 (t, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.3 Hz, 3H), 1.28-1.34 (m, 2H), 1.45-1.53 (m, 1H), 1.66-1.73 (m, 1H), 2.80-2.87 (m, 6H), 3.07-3.13 (m, 1H), 3.35 (dd, *J* = 14.6, 3.2 Hz, 1H), 3.50 (q, *J* = 6.3 Hz, 1H), 4.46-4.48 (m, 1H), 4.99 (dd, *J* = 11.5, 3.2 Hz, 1H), 5.04-5.08 (m, 1H), 6.22 (d, *J* = 9.7 Hz, 1H), 6.81-6.82 (m, 2H), 7.14-7.27 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.6, 13.7, 14.0, 17.4, 29.9, 33.4, 33.8, 37.4, 49.9, 50.0, 56.4, 61.7, 77.7, 126.4, 127.0, 128.3 (2C), 128.7 (2C), 128.8 (4C), 136.6, 136.7, 166.0, 168.6, 171.0, 207.7; HRMS (ESI-TOF) calcd for $C_{29}H_{37}N_2O_5$ $[M+Na]^+$: 493.2697; found: 493.2697.

*Synthesis of stereocalpin A (**1c**, natural isomer)*

(2*R*,3*R*)-1-(Benzyloxy)-2-methylhex-5-en-3-ol (6b). Alcohol **6b** was synthesized by the similar procedure reported previously.[10b] To a stirred solution of alcohol **6a** (5.17 g, 23.5 mmol) in THF (118 mL) under argon were added *p*-nitrobenzoic acid (7.85 g, 47.0 mmol), Ph_3P (12.3 g, 47.0 mmol) and DEAD (2.2 M in toluene; 21.4 mL, 47.0 mmol) at 0 °C. The reaction mixture was

warmed to room temperature and stirred overnight. The mixture was quenched with aqueous saturated $NaHCO_3$. The whole was extracted with Et_2O and the extract was washed with brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was filtrated through a short pad of silica gel with hexane–EtOAc (12:1) to give the crude ester, which was used for the next step without further purification. To a stirred solution of the above ester in MeOH (235 mL) was added NaOH (4.7 g, 117.5 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated under reduced pressure, and EtOAc and aqueous saturated $NaHCO_3$ were added to the residue. The whole was extracted with EtOAc and the extract was washed with brine, dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (10:1 to 5:1) to give compound **6b** (3.63 g, 70%) as a colorless oil. The spectral data were in good agreement with those previously reported.[10b]

{[(2*R*,3*R*)-1-(Benzyloxy)-2-methylhex-5-en-3-yl]oxy}(*tert*-butyl)dimethylsilane (7b). According to the procedure described for the preparation of **7a**, alcohol **6b** (3.53 g, 16.0 mmol) was converted into compound **7b** (4.63 g, 87%) as a colorless oil: $[\alpha]^{27}_D$ +4.0 (*c* 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.02 (s, 3H), 0.04 (s, 3H), 0.87-0.89 (m, 12H), 1.87-1.94 (m, 1H), 2.18-2.28 (m, 2H), 3.27 (dd, *J* = 8.9, 6.6 Hz, 1H), 3.44 (dd, *J* = 8.6, 6.6 Hz, 1H), 3.84-3.87 (m, 1H), 4.43-4.52 (m, 2H), 4.99-5.05 (m, 2H), 5.71-5.79 (m, 1H), 7.25-7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.8, –4.1, 10.7, 18.1, 25.9 (3C), 37.5, 39.6, 71.7, 72.9, 73.0, 116.6, 127.4, 127.6 (2C), 128.3 (2C), 135.4, 138.7; HRMS (ESI-TOF) calcd for $C_{20}H_{34}NaO_2Si$ $[M+Na]^+$: 357.2220; found: 357.2215.

(2*R*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylhexan-1-ol (8b). According to the procedure described for the preparation of **8a**, ether **7b** (1.50 g, 4.49 mmol) was converted into compound **8b** (977.9 mg, 88%) as a colorless oil: $[\alpha]^{27}_D$ +4.5 (*c* 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.07 (s, 3H), 0.10 (s, 3H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.90-0.93 (m, 12H), 1.19-1.28 (m, 1H), 1.38-1.49 (m, 3H), 1.93-2.00 (m, 1H), 2.74 (br s, 1H), 3.51-3.53 (m, 1H), 3.68-3.72 (m, 1H), 3.75-3.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.5 (2C), 12.0, 14.3, 18.0, 19.5, 25.8 (3C), 34.5, 39.5, 66.0, 75.8; HRMS (ESI-TOF) calcd for $C_{13}H_{31}O_2Si$ $[M+H]^+$: 247.2088; found: 247.2093.

(*R*)-4-Benzyl-3-{(2*R*,3*S*,4*R*,5*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-2,4-dimethyl-octanoyl}-1,3-oxazolidin-2-one (4c). According to the procedure described for the preparation of **4a**, alcohol **8b** (648.9 mg, 2.63 mmol) was converted into compound **4c** (1.03 g, 82%) as a colorless oil: $[\alpha]^{27}_D$ –7.3 (*c* 1.56, $CHCl_3$); IR (neat): 1783 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.08 (s, 3H), 0.12 (s, 3H), 0.85 (d, *J* = 7.4 Hz, 3H), 0.89-0.93 (m, 12H), 1.18-1.23 (m, 4H), 1.42-1.56 (m, 3H), 1.80-1.87 (m, 1H), 2.75 (dd, *J* = 13.2, 9.7 Hz, 1H), 3.36 (dd, *J* = 13.2, 2.9 Hz, 1H), 3.84-3.88 (m, 2H), 4.02-4.04 (m, 1H), 4.17 (dd, *J* = 8.9, 2.0 Hz, 1H), 4.21-4.24 (m, 1H), 4.32 (br s, 1H), 4.68-4.71 (m, 1H), 7.21-7.22 (m, 2H), 7.26-7.28 (m, 1H), 7.31-7.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.7, –4.4, 8.4, 12.3, 14.2, 17.9, 19.8, 25.8 (3C), 34.1, 37.7, 39.6, 40.7, 55.8, 66.1, 73.1, 76.6, 127.2, 128.9 (2C), 129.4 (2C), 135.5, 153.2, 175.9; HRMS (ESI-TOF) calcd for $C_{26}H_{43}NNaO_5Si$ $[M+Na]^+$:

500.2803; found: 500.2804.

(*R*)-4-Benzyl-3-{(2*R*,3*S*,4*R*,5*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-3-(methoxymethoxy)-2,4-dimethyloctanoyl}-1,3-oxazolidin-2-one (10c). According to the procedure described for the preparation of **10a**, alcohol **4c** (990.2 mg, 2.07 mmol) was converted into compound **10c** (1.05 g, 97%) as a colorless oil: $[\alpha]^{28}_{D}$ –47.8 (*c* 1.77, $CHCl_3$); IR (neat): 1781 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.03 (s, 3H), 0.06 (s, 3H), 0.86-0.88 (m, 12H), 0.91 (t, *J* = 7.4 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.21-1.29 (m, 2H), 1.45-1.56 (m, 2H), 1.60-1.66 (m, 1H), 2.78 (dd, *J* = 13.2, 9.7 Hz, 1H), 3.30 (s, 3H), 3.37 (dd, *J* = 13.2, 2.9 Hz, 1H), 3.87-3.89 (m, 2H), 3.93-3.97 (m, 1H), 4.08-4.15 (m, 2H), 4.50-4.54 (m, 2H), 4.66 (d, *J* = 6.9 Hz, 1H), 7.22-7.24 (m, 2H), 7.25-7.28 (m, 1H), 7.32-7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.7, –3.0, 8.4, 8.5, 14.3, 18.3, 19.1, 25.9 (3C), 37.6, 37.9, 40.2, 41.0, 56.5, 56.6, 66.2, 70.9, 82.8, 98.7, 127.2, 128.9 (2C), 129.4 (2C), 135.8, 153.2, 175.4; HRMS (ESI-TOF) calcd for $C_{28}H_{47}NNaO_6Si$ $[M+Na]^+$: 544.3065; found: 544.3071.

(4*R*,5*S*,6*S*,7*R*)-8-[(*R*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-methyl-L-phenylalaninate (11c). According to the procedure described for the preparation of **11a**, silyl ether **10c** (303.3 mg, 0.58 mmol) was converted into compound **11c** (198.5 mg, 60%) as a colorless oil: $[\alpha]^{28}_{D}$ –14.1 (*c* 1.31, $CHCl_3$); IR (neat): 1776 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.85 (t, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 7.4 Hz, 3H), 1.07-1.21 (m, 5H), 1.25-1.33 (m, 1H), 1.40-1.47 (m, 1H), 1.73-1.79 (m, 1H), 2.33 (s, 3H), 2.76 (dd, *J* = 13.2, 10.3 Hz, 1H), 2.90-2.92 (m, 2H), 3.28 (s, 3H), 3.35 (dd, *J* = 13.2, 2.9 Hz, 1H), 3.44-3.47 (m, 1H), 3.65 (dd, *J* = 8.9, 2.6 Hz, 1H), 3.82-3.86 (m, 1H), 4.06-4.12 (m, 2H), 4.50-4.59 (m, 3H), 5.03-5.06 (m, 1H), 7.20-7.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 8.9, 9.3, 13.9, 18.9, 34.6, 34.7, 37.6, 39.5, 39.8, 41.0, 56.6, 56.8, 64.5, 66.4, 73.3, 82.1, 99.3, 126.6, 127.2, 128.3 (2C), 128.9 (2C), 129.2 (2C), 129.4 (2C), 135.7, 137.3, 153.4, 174.5, 174.6; HRMS (ESI-TOF) calcd for $C_{32}H_{45}N_2O_7$ $[M+H]^+$: 569.3221; found: 569.3219.

(4*R*,5*S*,6*S*,7*R*)-8-[(*R*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-{[(benzyloxy)carbonyl]-L-phenylalanyl}-*N*-methyl-L-phenylalaninate (12c). According to the procedure described for the preparation of **12a**, amine **11c** (45.1 mg, 0.079 mmol) was converted into compound **12c** (58.8 mg, 88%) as a colorless oil: $[\alpha]^{27}_{D}$ –64.2 (*c* 1.16, $CHCl_3$); IR (neat): 1770 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 4:1 mixture of rotamers) δ: 0.88-0.97 (m, 6.0H), 1.19-1.28 (m, 5.0H), 1.36-1.46 (m, 1.0H), 1.59-1.62 (m, 1.0H), 1.65-1.78 (m, 1.0H), 2.11 (dd, *J* = 13.7, 4.3 Hz, 0.2H), 2.57 (dd, *J* = 13.7, 9.2 Hz, 0.2H), 2.68-2.88 (m, 4.2H), 2.95-3.00 (m, 1.6H), 3.17 (dd, *J* = 13.5, 7.2 Hz, 0.8H), 3.25-3.33 (m, 4.0H), 3.39 (dd, *J* = 13.2, 2.9 Hz, 1.0H), 3.67-3.73 (m, 1.0H), 3.79-3.89 (m, 1.4H), 4.14-4.16 (m, 0.8H), 4.25-4.28 (m, 0.8H), 4.31-4.34 (m, 0.2H), 4.46-4.66 (m, 4.0H), 4.75-4.79 (m, 1.0H), 5.00 (s, 1.8H), 5.09-5.12 (m, 0.2H), 5.28-5.30 (m, 0.8H), 5.40 (d, *J* = 9.2 Hz, 0.2H), 6.05 (d, *J* = 9.2 Hz, 0.8H), 6.87-6.92 (m, 2.0H), 7.02-7.36 (m, 18.0H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 8.7, 8.8, 9.1 (2C), 13.9 (2C), 18.9, 19.1, 30.1, 34.4 (2C), 35.1, 35.3, 37.5, 38.0, 38.5, 39.9, 40.9, 41.3, 50.6, 52.1, 56.4, 56.6, 56.7, 56.8, 61.8, 62.0, 66.0, 66.2, 66.4, 66.7, 73.6,

75.2, 81.6, 82.4, 99.1, 99.9, 126.3, 126.5, 126.7, 126.8, 127.1, 127.2, 127.5 (2C), 127.6 (2C), 127.8 (2C), 128.0 (2C), 128.2 (2C), 128.3 (4C), 128.4 (2C), 128.8 (2C), 128.9 (2C), 129.4 (4C), 129.5 (2C), 129.7 (2C), 135.8, 135.9, 136.6 (2C), 136.7, 136.8, 136.9, 137.4, 153.8, 154.0, 155.6, 169.2, 170.3, 171.0, 172.1, 174.6 (2C); HRMS (ESI-TOF) calcd for $C_{49}H_{59}N_3NaO_{10}$ $[M+Na]^+$: 872.4093; found: 872.4097.

Cyclic peptide (14c). According to the procedure described for the preparation of **14a**, oxazolidinone **12c** (38.5 mg, 0.045 mmol) was converted into compound **14c** (16.5 mg, 69%) as a white solid: mp 234 °C; $[\alpha]^{26}_D$ –95.4 (*c* 0.53, $CHCl_3$); IR (neat): 1684 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ: 0.83-0.94 (m, 3H), 1.04-1.13 (m, 8H), 1.41-1.50 (m, 2H), 2.13-2.16 (m, 1H), 2.58-2.61 (m, 1H), 2.94-3.06 (m, 5H), 3.12 (dd, *J* = 14.3, 6.3 Hz, 1H), 3.19 (dd, *J* = 14.0, 5.4 Hz, 1H), 3.33-3.45 (m, 4H), 4.26 (br s, 1H), 4.55-4.66 (m, 3H), 4.91-4.93 (m, 1H), 5.52-5.54 (m, 1H), 7.08-7.27 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ: 13.7, 17.2 (2C), 19.3, 29.4, 32.8, 36.0, 37.8, 40.7, 45.0, 52.7, 56.1, 59.8, 78.2, 83.9, 98.3, 126.5, 127.1, 128.4 (2C), 128.8 (4C), 129.5 (2C), 136.3, 138.3, 169.9, 170.2, 173.6; HRMS (ESI-TOF) calcd for $C_{31}H_{43}N_2O_6$ $[M+Na]^+$: 539.3116; found: 539.3116.

Stereocalpin A (1c). According to the procedure described for the preparation of **1a**, ether **14c** (10.5 mg, 0.020 mmol) was converted into compound **1c** (8.3 mg, 84%) as a white solid: mp 174 °C; $[\alpha]^{27}_D$ –6.1 (*c* 0.44, CH_2Cl_2); IR (neat): 1744 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 3:1 mixture of rotamers) δ: 0.88-0.95 (m, 3.0H), 1.00 (d, *J* = 6.9 Hz, 2.3H), 1.15-1.22 (m, 1.8H), 1.24-1.32 (m, 3.3H), 1.35 (d, *J* = 7.4 Hz, 0.7H), 1.38 (d, *J* = 6.9 Hz, 0.7H), 1.46-1.51 (m, 1.0H), 1.87-1.94 (m, 0.2H), 2.53 (s, 0.7H), 2.56-2.58 (m, 1.0H), 2.81 (dd, *J* = 14.0, 8.3 Hz, 0.8H), 2.91-3.08 (m, 3.5H), 3.10-3.19 (m, 2.0H), 3.28 (dd, *J* = 10.9, 3.4 Hz, 0.2H), 3.86-3.91 (m, 0.8H), 3.97 (q, *J* = 6.9 Hz, 0.2H), 4.67 (dd, *J* = 10.0, 6.0 Hz, 0.8H), 4.98-5.00 (m, 0.8H), 5.09-5.14 (m, 0.2H), 5.26-5.33 (m, 1.0H), 5.76 (d, *J* = 10.3 Hz, 0.8H), 6.08 (d, *J* = 9.7 Hz, 0.2H), 6.61-6.62 (m, 0.5H), 7.04-7.37 (m, 9.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.3, 10.9, 13.7, 13.8, 14.6, 14.9, 18.8, 19.0, 30.0, 32.1, 32.8, 34.7, 36.0, 37.2, 38.2, 39.3, 46.9, 48.7, 49.8, 50.8, 52.4, 54.6, 58.8, 67.6, 76.2 (2C), 126.3, 126.5, 127.1, 127.2, 128.2 (2C), 128.4 (2C), 128.7 (2C), 128.8 (2C), 128.9 (2C), 129.1 (2C), 129.4 (2C), 129.6 (2C), 135.7, 136.2, 137.0, 138.3, 166.9, 168.4, 168.6, 169.9, 170.4, 171.5, 209.5, 210.6; HRMS (ESI-TOF) calcd for $C_{29}H_{37}N_2O_5$ $[M+H]^+$: 493.2697; found: 493.2699.

*Synthesis of 2S-stereoisomer of stereocalpin A (**1d**)*

(*S*)-4-Benzyl-3-{(2*S*,3*R*,4*R*,5*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-2,4-dimethyloctanoyl}-1,3-oxazolidin-2-one (4d). According to the procedure described for the preparation of **4a**, alcohol **8b** (545.7 mg, 2.21 mmol) was converted into compound **4d** (995.1 mg, 94%) as a colorless oil: $[\alpha]^{27}_D$ +17.7 (*c* 1.76, $CHCl_3$); IR (neat): 3545 (OH), 1784 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.07 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 0.90-0.94 (m, 6H), 1.18-1.27 (m, 2H), 1.32 (d, *J* = 6.9 Hz, 3H), 1.40-1.46 (m, 1H), 1.50-1.57 (m, 1H), 1.62-1.67 (m, 1H), 2.77 (dd, *J* = 13.5, 9.7 Hz, 1H), 3.24 (dd, *J* = 13.5, 3.2 Hz, 1H), 3.28 (d, *J* = 1.7 Hz, 1H), 3.81-3.84 (m, 1H), 3.91-3.96

(m, 1H), 3.99-4.02 (m, 1H), 4.18-4.19 (m, 2H), 4.66-4.69 (m, 1H), 7.20-7.22 (m, 2H), 7.28-7.29 (m, 1H), 7.32-7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.8, –3.6, 7.2, 12.9, 14.3, 18.0, 18.8, 25.8 (3C), 37.0, 37.7, 37.9, 40.5, 55.0, 66.0, 74.3, 75.3, 127.4, 128.9 (2C), 129.4 (2C), 135.0, 152.7, 177.3; HRMS (ESI-TOF) calcd for $C_{26}H_{43}NNaO_5Si$ $[M+Na]^+$: 500.2803; found: 500.2806.

(*S*)-4-Benzyl-3-{(2*S*,3*R*,4*R*,5*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-3-(methoxymethoxy)-2,4-dimethyloctanoyl}-1,3-oxazolidin-2-one (10d). According to the procedure described for the preparation of **10a**, alcohol **4d** (889.9 mg, 1.86 mmol) was converted into compound **10d** (873.4 mg, 90%) as a colorless oil: $[\alpha]^{28}_D$ +54.3 (*c* 1.74, $CHCl_3$); IR (neat): 1784 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.04 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 0.91-0.95 (m, 6H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.31-1.37 (m, 2H), 1.49-1.56 (m, 1H), 1.58-1.68 (m, 2H), 2.78 (dd, *J* = 13.5, 9.7 Hz, 1H), 3.27 (dd, *J* = 13.5, 3.2 Hz, 1H), 3.38 (s, 3H), 3.67-3.70 (m, 1H), 3.87 (dd, *J* = 6.6, 3.7 Hz, 1H), 4.06-4.12 (m, 1H), 4.15-4.20 (m, 2H), 4.60-4.64 (m, 1H), 4.68 (s, 2H), 7.21-7.22 (m, 2H), 7.28-7.29 (m, 1H), 7.32-7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.5, –4.1, 10.4, 13.7, 14.5, 17.3, 18.2, 26.0 (3C), 36.6, 37.6, 40.7, 41.6, 55.6, 56.2, 66.0, 73.3, 80.3, 98.2, 127.3, 128.9 (2C), 129.4 (2C), 135.3, 152.9, 175.5; HRMS (ESI-TOF) calcd for $C_{28}H_{47}NNaO_6Si$ $[M+Na]^+$: 544.3065; found: 544.3066.

(4*R*,5*S*,6*R*,7*S*)-8-[(*S*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-methyl-L-phenylalaninate (11d). According to the procedure described for the preparation of **10a**, silyl ether **10d** (254.5 mg, 0.49 mmol) was converted into compound **11d** (198.5 mg, 71%) as a colorless oil: $[\alpha]^{27}_D$ +64.8 (*c* 1.59, $CHCl_3$); IR (neat): 1782 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (t, *J* = 7.4 Hz, 3H), 0.91 (d, *J* = 7.4 Hz, 3H), 1.09-1.24 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.48-1.60 (m, 2H), 1.72-1.78 (m, 1H), 2.38 (s, 3H), 2.75 (dd, *J* = 13.5, 9.7 Hz, 1H), 2.89 (dd, *J* = 13.7, 8.0 Hz, 1H), 2.99 (dd, *J* = 13.7, 6.3 Hz, 1H), 3.25 (dd, *J* = 13.5, 3.2 Hz, 1H), 3.42 (s, 3H), 3.48 (dd, *J* = 8.0, 6.3 Hz, 1H), 3.87 (dd, *J* = 6.9, 4.0 Hz, 1H), 4.06-4.11 (m, 1H), 4.15-4.23 (m, 2H), 4.60-4.65 (m, 2H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.97-5.01 (m, 1H), 7.20-7.35 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.4, 13.8, 14.0, 18.3, 33.9, 34.8, 37.7, 39.5, 39.8, 41.4, 55.5, 56.5, 64.4, 66.1, 75.4, 80.2, 98.4, 126.6, 127.3, 128.4 (2C), 128.9 (2C), 129.2 (2C), 129.4 (2C), 135.2, 137.6, 152.9, 174.3, 175.2; HRMS (ESI-TOF) calcd for $C_{32}H_{45}N_2O_7$ $[M+H]^+$: 569.3221; found: 569.3216.

(4*R*,5*S*,6*R*,7*S*)-8-[(*S*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-{[(benzyloxy)carbonyl]-L-phenylalanyl}-*N*-methyl-L-phenylalaninate (12d). According to the procedure described for the preparation of **12a**, amine **11d** (57.1 mg, 0.10 mmol) was converted into compound **12d** (80.2 mg, 94%) as a colorless oil: $[\alpha]^{28}_D$ +8.9 (*c* 1.11, $CHCl_3$); IR (neat): 1780 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 4:1 mixture of rotamers) δ: 0.88-0.94 (m, 6.0H), 1.14-1.31 (m, 5.0H), 1.54-1.69 (m, 2.0H), 1.72-1.79 (m, 1.0H), 2.41-2.44 (m, 0.2H), 2.51 (dd, *J* = 14.3, 7.4 Hz, 0.2H), 2.71-2.81 (m, 1.8H), 2.88 (s, 2.4H), 2.92-3.05 (m, 2.4H), 3.25-3.28 (m, 1.0H), 3.33-3.43 (m, 4.0H), 3.84-3.86 (m, 1.0H), 3.95-4.01 (m, 0.2H), 4.03-4.08 (m, 0.8H), 4.11-4.17 (m, 2.0H), 4.57-4.66 (m, 2.0H), 4.69-4.87 (m, 2.2H), 4.95-5.07 (m, 2.8H), 5.14-5.16 (m, 0.2H), 5.25-5.28 (m, 0.8H), 5.37 (d, *J* = 9.2 Hz, 0.2H), 5.43 (d, *J* = 9.2 Hz, 0.8H), 6.81-6.83 (m, 0.4H), 7.10-7.36

(m, 19.6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.1, 10.2, 12.7, 13.3, 13.9 (2C), 18.6, 33.1, 33.9, 34.1, 34.6, 35.2, 37.5, 37.6, 38.5, 38.7, 39.7, 40.0, 41.3, 41.5, 51.2, 52.0, 55.6, 55.7, 56.5 (2C), 59.2, 66.1 (2C), 66.3, 66.6, 75.9, 76.3, 80.6 (2C), 98.7 (2C), 126.5, 126.6, 126.7, 127.2, 127.3, 127.5, 127.8 (2C), 128.0 (2C), 128.3 (4C), 128.4 (2C), 128.8 (2C), 128.9 (4C), 129.2 (2C), 129.4 (4C), 129.5 (2C), 135.3, 135.4, 136.1, 136.2, 136.4, 136.8 (2C), 153.0, 153.1, 155.1, 155.4, 169.4, 170.2, 171.4, 172.1, 174.8, 175.2; HRMS (ESI-TOF) calcd for $C_{49}H_{59}N_3NaO_{10}$ $[M+Na]^+$: 872.4093; found: 872.4097.

Cyclic peptide (14d). According to the procedure described for the preparation of **14a**, oxazolidinone **12d** (57.8 mg, 0.068 mmol) was converted into compound **14d** (21.8 mg, 59%) as a white solid: mp 165 °C; $[\alpha]^{27}_D$ –74.3 (*c* 1.06, $CHCl_3$); IR (neat): 1739 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 5:4 mixture of rotamers) δ: 0.81 (d, *J* = 6.9 Hz, 1.3H), 0.88-0.94 (m, 4.3H), 1.02 (d, *J* = 7.4 Hz, 1.7H), 1.16-1.23 (m, 2.1H), 1.28-1.33 (m, 1.6H), 1.41-1.47 (m, 0.4H), 1.57-1.61 (m, 1.2H), 1.64-1.75 (m, 1.0H), 1.91-1.96 (m, 0.4H), 2.04-2.10 (m, 0.4H), 2.24-2.30 (m, 0.6H), 2.59 (s, 1.7H), 2.86 (dd, *J* = 14.0, 8.3 Hz, 0.4H), 2.96-3.05 (m, 2.9H), 3.09-3.17 (m, 1.0H), 3.22-3.27 (m, 1.0H), 3.34 (dd, *J* = 11.2, 3.2 Hz, 0.6H), 3.37 (s, 1.3H), 3.38 (s, 1.7H), 3.77-3.80 (m, 1.0H), 4.61-4.65 (m, 0.9H), 4.71-4.76 (m, 1.5H), 4.92-4.99 (m, 1.0H), 5.07-5.12 (m, 0.4H), 5.13-5.18 (m, 0.6H), 5.99 (d, *J* = 9.2 Hz, 0.6H), 6.09 (d, *J* = 10.3 Hz, 0.4H), 6.53-6.54 (m, 1.1H), 7.02-7.42 (m, 8.9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.6, 12.1, 13.8, 14.1, 14.3, 15.9, 19.5, 19.8, 29.9, 30.0, 31.1, 35.0, 35.4, 37.0, 38.2, 39.5, 43.4, 44.3, 49.0, 49.6, 50.2, 50.3, 56.3 (2C), 59.6, 67.1, 77.8, 78.0, 78.4, 79.3, 98.0, 98.6, 126.2, 126.5, 127.1, 127.2, 128.3 (2C), 128.5 (4C), 128.9 (2C), 129.0 (2C), 129.1 (2C), 129.5 (4C), 136.1, 136.2, 136.9, 138.4, 169.4, 170.7, 171.2, 171.7, 173.6, 175.7; HRMS (ESI-TOF) calcd for $C_{31}H_{42}N_2NaO_6$ $[M+Na]^+$: 561.2935; found: 561.2932.

2*S*-Stereoisomer of stereocalpin A (1d). According to the procedure described for the preparation of **1a**, ether **14d** (21.0 mg, 0.039 mmol) was converted into compound **1d** (15.3 mg, 79%) as a white solid: mp 203 °C; $[\alpha]^{28}_D$ –181.3 (*c* 0.73, $CHCl_3$); IR (neat): 1727 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ: 0.85-0.91 (m, 3.0H), 1.01-1.11 (m, 4.7H), 1.15 (d, *J* = 7.4 Hz, 1.0H), 1.17-1.26 (m, 1.3H), 1.29 (d, *J* = 6.5 Hz, 1.0H), 1.62-1.68 (m, 0.7H), 1.76 (tt, *J* = 17.8, 6.0 Hz, 1.3H), 2.56 (s, 1.0H), 2.94-3.10 (m, 4.3H), 3.15-3.28 (m, 2.0H), 3.31-3.36 (m, 1.0H), 3.45 (q, *J* = 6.5 Hz, 0.7H), 3.51 (q, *J* = 6.5 Hz, 0.3H), 4.71-4.74 (m, 0.7H), 4.96 (dd, *J* = 11.2, 4.3 Hz, 0.7H), 5.04-5.07 (m, 0.3H), 5.14-5.19 (m, 0.7H), 5.20-5.26 (m, 0.3H), 6.58-6.60 (m, 0.7H), 6.74 (d, *J* = 9.2 Hz, 0.3H), 7.04-7.39 (m, 9.3H), 7.53 (d, *J* = 10.3 Hz, 0.7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.5, 13.6, 13.7, 13.9, 14.6, 16.1, 19.5, 20.0, 29.2, 29.6, 31.9, 34.9, 35.4, 37.0, 38.2, 39.7, 47.1, 48.5, 49.9, 50.3, 55.9, 56.8, 59.6, 67.3, 77.0, 77.4, 126.4, 126.6, 127.2, 127.3, 128.3 (2C), 128.4 (2C), 128.5 (2C), 128.9 (2C), 129.0 (4C), 129.1 (2C), 129.3 (2C), 135.6, 135.7, 136.6, 138.0, 167.0, 168.3, 169.1, 171.0, 171.2, 171.8, 205.6, 205.9; HRMS (ESI-TOF) calcd for $C_{29}H_{37}N_2O_5$ $[M+H]^+$: 493.2697; found: 493.2699.

*Synthesis of 5S,8R,11R-stereoisomer of stereocalpin A (**2a**)*

(4*S*,5*S*,6*S*,7*R*)-8-[(*R*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-

oxooctan-4-yl *N*-methyl-D-phenylalaninate (21a). According to the procedure described for the preparation of **11a**, silyl ether **10a** (240.0 mg, 0.46 mmol) was converted into compound **21a** (222.3 mg, 85%) as a colorless oil: $[\alpha]^{26}_{D}$ –65.0 (*c* 1.41, $CHCl_3$); IR (neat): 1780 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.81 (t, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.99-1.13 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.39-1.56 (m, 2H), 1.95-2.01 (m, 1H), 2.36 (s, 3H), 2.78 (dd, *J* = 13.2, 9.7 Hz, 1H), 2.89-2.91 (m, 2H), 3.23 (dd, *J* = 13.2, 2.9 Hz, 1H), 3.39-3.42 (m, 4H), 3.74-3.77 (m, 1H), 4.02-4.08 (m, 1H), 4.13 (dd, *J* = 8.9, 2.0 Hz, 1H), 4.21-4.24 (m, 1H), 4.53-4.58 (m, 1H), 4.59-4.63 (m, 2H), 4.94-4.97 (m, 1H), 7.15-7.35 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.3, 13.4, 13.9, 18.9, 31.2, 34.7, 37.9, 39.5, 39.6, 40.8, 55.7, 56.5, 64.9, 66.4, 75.2, 83.0, 99.0, 126.6, 127.2, 128.4 (2C), 128.9 (2C), 129.1 (2C), 129.4 (2C), 135.5, 137.2, 153.4, 174.2, 175.3; HRMS (ESI-TOF) calcd for $C_{32}H_{45}N_2O_7$ $[M+H]^+$: 569.3221; found: 569.3219.

(4*S*,5*S*,6*S*,7*R*)-8-[(*R*)-4-Benzyl-1,3-oxazolidin-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-{[(benzyloxy)carbonyl]-D-phenylalanyl}-*N*-methyl-D-phenylalaninate (22a). According to the procedure described for the preparation of **11a**, amine **21a** (185.3 mg, 0.33 mmol) was converted into compound **22a** (264.7 mg, 94%) as a colorless oil: $[\alpha]^{27}_{D}$ +2.4 (*c* 1.64, $CHCl_3$); IR (neat): 1779 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 4:1 mixture of rotamers) δ: 0.82-0.93 (m, 6.0H), 1.09-1.28 (m, 5.0H), 1.41-1.50 (m, 1.0H), 1.53-1.59 (m, 1.0H), 1.96-2.02 (m, 1.0H), 2.37 (dd, *J* = 13.7, 5.2 Hz, 0.2H), 2.56 (dd, *J* = 13.7, 8.0 Hz, 0.2H), 2.76-2.82 (m, 4.2H), 2.92-2.96 (m, 1.6H), 3.02 (dd, *J* = 13.7, 6.9 Hz, 0.8H), 3.22-3.32 (m, 2.0H), 3.37 (s, 3.0H), 3.75-3.77 (m, 0.2H), 3.80-3.83 (m, 0.8H), 4.01-4.08 (m, 1.0H), 4.11-4.16 (m, 1.0H), 4.24-4.28 (m, 1.0H), 4.58-4.61 (m, 1.4H), 4.65-4.71 (m, 1.8H), 4.75-4.80 (m, 0.8H), 4.83 (d, *J* = 12.6 Hz, 0.2H), 4.88 (dd, *J* = 9.5, 5.4 Hz, 0.2H), 4.93 (dd, *J* = 10.3, 5.2 Hz, 0.8H), 4.98-5.07 (m, 2.8H), 5.29 (d, *J* = 9.2 Hz, 0.2H), 5.46 (d, *J* = 9.2 Hz, 0.8H), 6.84-6.86 (m, 0.4H), 7.03-7.04 (m, 1.6H), 7.10-7.37 (m, 18.0H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.9 (2C), 12.9, 13.4, 13.9, 14.0, 19.0, 29.9, 31.2, 31.6, 33.9, 34.7, 35.2, 37.8, 37.9, 38.5, 38.8, 39.7, 40.0, 40.1, 40.5, 51.1, 51.9, 55.7, 56.4, 56.5, 60.1, 61.6, 66.3, 66.4, 66.6, 66.7, 75.9, 81.9, 82.2, 98.7 (2C), 126.6, 126.7, 126.8, 127.2, 127.7, 127.9 (3C), 128.0 (2C), 128.2, 128.4 (4C), 128.8 (2C), 128.9 (4C), 129.1 (2C), 129.4 (4C), 129.5 (2C), 135.5, 136.2, 136.4, 136.9, 153.5 (2C), 155.3, 155.4, 169.5, 170.1, 171.3, 172.1, 175.3, 175.6; HRMS (ESI-TOF) calcd for $C_{49}H_{59}N_3NaO_{10}$ $[M+Na]^+$: 872.4093; found: 872.4094.

Cyclic peptide (24a). According to the procedure described for the preparation of **14a**, oxazolidinone **22a** (214.9 mg, 0.25 mmol) was converted into compound **24a** (98.3 mg, 80%) as a white solid: mp 110 °C; $[\alpha]^{27}_{D}$ +53.5 (*c* 1.77, $CHCl_3$); IR (neat): 1739 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.83 (t, *J* = 7.4 Hz, 3H), 0.93-0.95 (m, 6H), 1.08-1.16 (m, 2H), 1.41-1.53 (m, 2H), 2.13-2.19 (m, 1H), 2.36-2.42 (m, 1H), 2.80 (dd, *J* = 14.0, 7.7 Hz, 1H), 2.98 (dd, *J* = 14.3, 10.3 Hz, 1H), 3.03 (s, 3H), 3.05-3.13 (m, 2H), 3.34 (s, 3H), 3.58-3.59 (m, 1H), 4.62 (d, *J* = 6.9 Hz, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.81-4.85 (m, 2H), 5.08-5.13 (m, 1H), 6.13 (d, *J* = 10.3 Hz, 1H), 7.09-7.11 (m, 2H), 7.15-7.27 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1 (2C), 17.3, 18.0, 29.4, 34.8, 35.9, 37.2, 38.5, 43.8, 50.1, 56.2, 59.3, 74.9, 83.8, 98.1, 126.3, 127.1, 128.2 (2C), 128.6 (2C), 128.8 (2C), 129.4 (2C),

135.9, 137.4, 170.0, 171.2, 171.7; HRMS (ESI-TOF) calcd for $C_{31}H_{42}N_2NaO_6$ $[M+Na]^+$: 561.2935; found: 561.2933.

5*S*,8*R*,11*R*-Stereoisomer of stereocalpin A (2a). According to the procedure described for the preparation of **1a**, ether **24a** (43.0 mg, 0.080 mmol) was converted into compound **2a** (38.2 mg, 97%) as a white solid: mp 126 °C; $[\alpha]^{26}_D$ –15.7 (*c* 1.07, $CHCl_3$); IR (neat): 1749 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 4:1 mixture of rotamers) δ: 0.85-0.90 (m, 3.0H), 1.01 (d, *J* = 6.9 Hz, 3.0H), 1.08-1.16 (m, 1.0H), 1.18-1.31 (m, 3.4H), 1.38-1.48 (m, 1.6H), 1.54-1.61 (m, 0.8H), 1.82-1.89 (m, 0.2H), 2.58 (s, 0.6H), 2.78 (dd, *J* = 13.7, 7.4 Hz, 0.8H), 2.94-3.01 (m, 3.4H), 3.09-3.14 (m, 1.8H), 3.17-3.26 (m, 2.4H), 3.38 (q, *J* = 6.9 Hz, 0.2H), 4.67 (dd, *J* = 10.9, 4.6 Hz, 0.8H), 4.92-4.96 (m, 0.8H), 5.08-5.14 (m, 1.2H), 6.45 (d, *J* = 10.3 Hz, 0.8H), 6.68-6.72 (m, 0.6H), 7.07-7.37 (m, 9.6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.5, 11.6, 14.0, 14.3, 14.5, 14.7, 16.3, 17.7, 29.7, 31.8, 33.4, 34.6, 35.9, 37.0, 38.1, 39.5, 41.6, 44.0, 50.2, 51.2, 57.2, 57.5, 59.0, 68.1, 75.9, 76.2, 126.2, 126.3, 127.0, 127.2, 128.2 (2C), 128.4 (4C), 128.8 (2C), 128.9 (2C), 129.1 (2C), 129.3 (2C), 129.4 (2C), 135.6, 136.3, 137.3, 138.5, 165.5, 167.7, 168.5, 169.7, 170.0, 171.7, 208.3, 210.8; HRMS (ESI-TOF) calcd for $C_{29}H_{37}N_2O_5$ $[M+H]^+$: 493.2697; found: 493.2697.

*Synthesis of 2S,5S,8R,11R-stereoisomer of stereocalpin A (**2b**)*

(4*S*,5*S*,6*R*,7*S*)-8-[(*S*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-methyl-D-phenylalaninate (21b). According to the procedure described for the preparation of **11a**, silyl ether **10b** (335.3 mg, 0.64 mmol) was converted into compound **21b** (239.1 mg, 66%) as a colorless oil: $[\alpha]^{27}_D$ +8.9 (*c* 1.52, $CHCl_3$); IR (neat): 1780 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.82 (t, *J* = 7.4 Hz, 3H), 0.90 (d, *J* = 7.4 Hz, 3H), 1.03-1.10 (m, 2H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.37-1.44 (m, 1H), 1.51-1.57 (m, 1H), 1.85-1.91 (m, 1H), 2.40 (s, 3H), 2.76 (dd, *J* = 13.2, 9.7 Hz, 1H), 2.93-3.01 (m, 2H), 3.30 (dd, *J* = 13.2, 2.9 Hz, 1H), 3.34 (s, 3H), 3.48-3.50 (m, 1H), 3.76-3.78 (m, 1H), 3.99-4.04 (m, 1H), 4.15-4.20 (m, 2H), 4.58 (s, 2H), 4.59-4.64 (m, 1H), 4.85-4.89 (m, 1H), 7.23-7.32 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.4, 12.5, 13.9, 18.2, 31.7, 34.6, 37.6, 39.5, 40.0, 41.6, 55.9, 56.5, 64.8, 66.1, 75.6, 80.3, 98.7, 126.6, 127.3, 128.4 (2C), 128.9 (2C), 129.2 (2C), 129.4 (2C), 135.4, 137.4, 153.1, 174.4, 174.7; HRMS (ESI-TOF) calcd for $C_{32}H_{45}N_2O_7$ $[M+H]^+$: 569.3221; found: 569.3226.

(4*S*,5*S*,6*R*,7*S*)-8-[(*S*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-{[(benzyloxy)carbonyl]-D-phenylalanyl}-*N*-methyl-D-phenylalaninate (22b). According to the procedure described for the preparation of **12a**, amine **21b** (56.7 mg, 0.10 mmol) was converted into compound **22b** (75.2 mg, 88%) as a colorless oil: $[\alpha]^{27}_D$ +48.1 (*c* 1.17, $CHCl_3$); IR (neat): 1781 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 3:1 mixture of rotamers) δ: 0.84-0.91 (m, 6.0H), 1.14-1.30 (m, 2.7H), 1.35 (d, *J* = 6.9 Hz, 2.3H), 1.39-1.51 (m, 1.0H), 1.59-1.66 (m, 1.0H), 1.70-1.75 (m, 0.2H), 1.84-1.90 (m, 0.8H), 2.51 (dd, *J* = 13.7, 5.7 Hz, 0.2H), 2.67-2.75 (m, 1.2H), 2.83-2.93 (m, 3.3H), 2.99-3.04 (m, 1.5H), 3.10 (dd, *J* = 13.7, 6.9 Hz, 0.8H), 3.18-3.25 (m, 1.0H), 3.30 (dd, *J* = 14.6, 4.9 Hz, 0.2H), 3.34-3.35 (m, 3.0H), 3.38-3.42 (m, 0.8H), 3.66-3.69 (m, 0.2H), 3.75 (dd, *J* = 6.9, 3.4

Hz, 0.2H), 3.82-3.84 (m, 0.8H), 3.92 (dd, *J* = 9.2, 2.3 Hz, 0.2H), 4.01-4.15 (m, 2.6H), 4.43-4.52 (m, 1.2H), 4.57-4.63 (m, 2.0H), 4.73 (d, *J* = 12.6 Hz, 0.2H), 4.77-4.87 (m, 1.0H), 4.89-4.96 (m, 1.0H), 4.99-5.07 (m, 1.8H), 5.13 (dd, *J* = 10.0, 5.4 Hz, 0.8H), 5.53 (d, *J* = 9.2 Hz, 0.8H), 5.95 (d, *J* = 9.7 Hz, 0.2H), 6.90-6.91 (m, 0.5H), 7.04-7.35 (m, 19.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.1, 10.2, 13.0, 13.5, 14.0 (2C), 17.9, 18.3, 29.6, 32.1, 32.7, 33.4, 34.6, 35.0, 37.5 (2C), 38.6, 38.7, 39.9, 40.2, 41.4, 41.5, 51.3, 52.0, 55.4, 55.6, 56.2, 56.5, 59.7, 61.3, 65.8, 66.0, 66.5, 66.6, 76.3, 76.6, 79.7, 80.1, 98.5, 98.7, 126.3, 126.6, 126.7, 127.1, 127.3, 127.5, 127.8 (2C), 127.9 (2C), 128.0 (4C), 128.3 (2C), 128.4 (2C), 128.8 (2C), 128.9 (2C), 129.3 (4C), 129.4 (2C), 129.5 (2C), 129.6 (2C), 135.1, 135.2, 136.3 (2C), 136.4, 136.6, 136.7, 136.9, 153.0 (2C), 155.4 (2C), 169.3, 170.1, 171.3, 174.9, 175.2; HRMS (ESI-TOF) calcd for $C_{49}H_{59}N_3NaO_{10}$ $[M+Na]^+$: 872.4093; found: 872.4095.

Cyclic peptide (24b). According to the procedure described for the preparation of **14a**, oxazolidinone **22b** (74.8 mg, 0.088 mmol) was converted into compound **24b** (29.6 mg, 63%) as a white solid: mp 182 °C; $[\alpha]^{27}_D$ +68.2 (*c* 1.44, $CHCl_3$); IR (neat): 1742 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ: 0.85-0.88 (m, 6.0H), 1.09 (d, *J* = 7.4 Hz, 1.0H), 1.19-1.27 (m, 4.0H), 1.33-1.40 (m, 0.7H), 1.43-1.54 (m, 0.6H), 1.61-1.68 (m, 0.7H), 1.98-2.04 (m, 0.7H), 2.09-2.15 (m, 0.3H), 2.38-2.47 (m, 1.0H), 2.60 (s, 2.0H), 2.85-2.90 (m, 0.3H), 2.97-3.04 (m, 2.7H), 3.12-3.20 (m, 0.6H), 3.24-3.33 (m, 1.7H), 3.38-3.42 (m, 2.1H), 3.45-3.47 (m, 2.3H), 4.57-4.62 (m, 0.7H), 4.68-4.73 (m, 1.6H), 4.88-4.92 (m, 0.7H), 4.97-5.01 (m, 0.6H), 5.10-5.15 (m, 0.7H), 6.11 (d, *J* = 10.3 Hz, 0.7H), 6.35 (br s, 0.3H), 6.90-6.91 (m, 1.3H), 7.05-7.30 (m, 8.7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.7, 13.5, 13.8, 14.2, 17.2, 18.3, 29.7, 33.8, 34.8, 35.5, 37.7, 38.0, 39.5, 39.6, 43.3, 47.5, 50.4, 56.2, 56.3, 59.8, 68.4, 77.3, 78.7, 80.6, 81.6, 98.2, 99.4, 126.3, 126.4, 127.0, 127.1, 128.2 (4C), 128.5 (2C), 128.8 (4C), 128.9 (2C), 129.2 (2C), 135.7, 136.1, 137.6, 138.8, 169.1, 170.5, 173.7 (2C), 176.7; HRMS (ESI-TOF) calcd for $C_{31}H_{42}N_2NaO_6$ $[M+Na]^+$: 561.2935; found: 561.2932.

2*S*,5*S*,8*R*,11*R*-Stereoisomer of stereocalpin A (2b). According to the procedure described for the preparation of **1a**, ether **24b** (28.0 mg, 0.052 mmol) was converted into compound **2b** (22.8 mg, 89%) as a white solid: mp 76 °C; $[\alpha]^{27}_D$ –26.3 (*c* 0.61, $CHCl_3$); IR (neat): 1748 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 3:1 mixture of rotamers); δ: 0.84-0.90 (m, 3.0H), 0.97-0.99 (m, 3.0H), 1.07-1.14 (m, 3.1H), 1.15-1.29 (m, 1.2H), 1.36 (d, *J* = 6.9 Hz, 0.7H), 1.39-1.47 (m, 1.0H), 1.53-1.59 (m, 0.8H), 1.81-1.88 (m, 0.2H), 2.57 (s, 0.7H), 2.80 (dd, *J* = 13.7, 7.4 Hz, 0.8H), 2.96-3.02 (m, 3.1H), 3.08-3.27 (m, 3.6H), 3.65 (q, *J* = 6.9 Hz, 0.8H), 3.75 (q, *J* = 6.9 Hz, 0.2H), 4.64 (dd, *J* = 10.3, 5.2 Hz, 0.8H), 4.97-5.01 (m, 0.8H), 5.06-5.12 (m, 1.0H), 5.18-5.22 (m, 0.2H), 6.07-6.14 (m, 1.0H), 6.68-6.69 (m, 0.5H), 7.13-7.27 (m, 9.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.1, 13.6, 14.0 (2C), 14.3, 14.9, 16.3, 17.7, 29.9, 31.9, 33.6, 34.6, 36.0, 37.3, 38.1, 39.5, 47.2, 49.9, 50.4, 50.6, 57.2, 57.6, 59.0, 68.0, 75.3, 76.2, 126.3, 126.4, 127.1, 127.2, 128.2 (2C), 128.4 (2C), 128.5 (2C), 128.8 (2C), 128.9 (2C), 129.0 (2C), 129.3 (2C), 129.5 (2C), 135.6, 136.2, 137.0, 138.6, 166.7, 168.4, 168.9, 169.8, 169.9, 171.6, 207.5, 211.2; HRMS (ESI-TOF) calcd for $C_{29}H_{37}N_2O_5$ $[M+H]^+$: 493.2697; found: 493.2693.

*Synthesis of 8R,11R-stereoisomer of stereocalpin A (**2c**)*

(4*R*,5*S*,6*S*,7*R*)-8-[(*R*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-methyl-D-phenylalaninate (21c). According to the procedure described for the preparation of **11a**, silyl ether **10c** (77.7 mg, 0.15 mmol) was converted into compound **21c** (54.7 mg, 64%) as a colorless oil: $[\alpha]^{26}_{D}$ –32.8 (*c* 1.49, $CHCl_3$); IR (neat): 1775 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.90 (t, *J* = 7.4 Hz, 3H), 1.02 (d, *J* = 7.4 Hz, 3H), 1.21-1.29 (m, 5H), 1.43-1.50 (m, 1H), 1.61-1.68 (m, 1H), 1.78-1.84 (m, 1H), 2.33 (s, 3H), 2.74 (dd, *J* = 13.2, 10.3 Hz, 1H), 2.83 (dd, *J* = 13.7, 8.3 Hz, 1H), 3.04 (dd, *J* = 13.7, 5.7 Hz, 1H), 3.29 (s, 3H), 3.34 (dd, *J* = 13.2, 2.9 Hz, 1H), 3.42 (dd, *J* = 8.3, 5.7 Hz, 1H), 3.70 (dd, *J* = 8.9, 2.6 Hz, 1H), 3.84-3.89 (m, 1H), 4.04-4.09 (m, 2H), 4.51-4.58 (m, 3H), 5.09-5.12 (m, 1H), 7.18-7.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.0, 9.4, 13.9, 19.0, 34.8, 34.9, 37.6, 39.0, 40.0, 41.0, 56.5, 56.8, 64.7, 66.4, 73.3, 81.8, 99.2, 126.5, 127.2, 128.3 (2C), 128.9 (2C), 129.2 (2C), 129.4 (2C), 135.7, 137.6, 153.4, 173.4, 174.6; HRMS (ESI-TOF) calcd for $C_{32}H_{45}N_2O_7$ $[M+H]^+$: 569.3221; found: 569.3220.

(4*R*,5*S*,6*S*,7*R*)-8-[(*R*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-{[(benzyloxy)carbonyl]-D-phenylalanyl}-*N*-methyl-D-phenylalaninate (22c). According to the procedure described for the preparation of **12a**, amine **21c** (81.6 mg, 0.14 mmol) was converted into compound **22c** (112.3 mg, 92%) as a colorless oil: $[\alpha]^{28}_{D}$ +6.2 (*c* 1.11, $CHCl_3$); IR (neat): 1774 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 9:1 mixture of rotamers) δ: 0.87-0.94 (m, 3.0H), 0.95-1.00 (m, 3.0H), 1.15-1.21 (m, 3.0H), 1.23-1.31 (m, 2.0H), 1.39-1.46 (m, 1.0H), 1.61-1.68 (m, 1.0H), 1.74-1.80 (m, 1.0H), 2.41 (dd, *J* = 13.7, 5.2 Hz, 0.1H), 2.51 (dd, *J* = 13.7, 8.0 Hz, 0.1H), 2.67-2.79 (m, 3.9H), 2.83-2.87 (m, 0.9H), 2.91-2.95 (m, 0.9H), 3.13-3.19 (m, 1.0H), 3.22 (s, 2.7H), 3.26-3.31 (m, 0.5H), 3.34-3.42 (m, 1.9H), 3.67-3.74 (m, 0.2H), 3.80-3.86 (m, 1.8H), 3.99-4.02 (m, 0.1H), 4.06-4.12 (m, 1.0H), 4.17-4.22 (m, 0.9H), 4.43-4.44 (m, 0.1H), 4.50-4.62 (m, 2.9H), 4.69-4.85 (m, 2.0H), 4.95-5.07 (m, 1.9H), 5.11-5.14 (m, 0.9H), 5.23-5.33 (m, 0.2H), 5.42 (d, *J* = 9.2 Hz, 0.1H), 5.52 (d, *J* = 8.6 Hz, 0.9H), 6.85 (t, *J* = 3.7 Hz, 0.2H), 7.09-7.36 (m, 19.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 8.7, 9.4, 9.6, 13.8, 14.2, 19.0, 19.1, 34.2, 34.6, 34.7, 34.9, 37.6, 38.4, 39.1, 40.2, 40.3, 41.0, 51.4, 52.2, 56.4, 56.6, 56.8 (2C), 61.4, 66.3, 66.6, 74.1, 81.8, 99.1, 126.5, 126.7, 127.2, 127.7, 127.9 (2C), 128.0, 128.1, 128.4 (4C), 128.8 (4C), 128.9 (2C), 129.4 (6C), 135.6, 135.8, 136.3 (2C), 136.4, 136.5, 136.8, 137.5, 153.4, 155.3, 155.5, 170.2, 171.5, 174.6; HRMS (ESI-TOF) calcd for $C_{49}H_{59}N_3NaO_{10}$ $[M+Na]^+$: 872.4093; found: 872.4097.

Cyclic peptide (24c). According to the procedure described for the preparation of **14a**, oxazolidinone **22c** (77.4 mg, 0.091 mmol) was converted into compound **24c** (43.7 mg, 89%) as a white solid: mp 139 °C; $[\alpha]^{27}_{D}$ +119.4 (*c* 1.69, $CHCl_3$); IR (neat): 1735 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.94 (t, *J* = 7.4 Hz, 3H), 0.97 (d, *J* = 7.4 Hz, 3H), 1.02 (d, *J* = 6.3 Hz, 3H), 1.23-1.37 (m, 2H), 1.43-1.50 (m, 1H), 1.62-1.69 (m, 1H), 2.18-2.22 (m, 1H), 2.24-2.30 (m, 1H), 2.75-2.89 (m, 6H), 3.36 (s, 3H), 3.51-3.57 (m, 2H), 4.61-4.66 (m, 2H), 4.85-4.91 (m, 2H), 5.55 (dd, *J* = 11.5, 3.4 Hz, 1H), 5.87 (d, *J* = 10.3 Hz, 1H), 6.94-6.96 (m, 2H), 7.08-7.10 (m, 2H), 7.14-7.22 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 8.6, 13.8, 16.4, 19.2, 29.8, 34.0, 34.1, 37.4, 39.5, 43.7, 48.1, 56.0, 62.1, 78.5,

84.7, 97.5, 126.5, 126.8, 128.4 (4C), 128.7 (2C), 128.9 (2C), 136.6, 137.1, 169.9, 171.9, 173.0; HRMS (ESI-TOF) calcd for $C_{31}H_{43}N_2O_6$ $[M+H]^+$: 539.3116; found: 539.3121.

8*R*,11*R*-Stereoisomer of stereocalpin A (2c). According to the procedure described for the preparation of **1a**, ether **24c** (33.8 mg, 0.063 mmol) was converted into compound **2c** (27.7 mg, 89%) as a white solid: mp 136 °C; $[\alpha]^{27}_D$ +85.2 (*c* 1.31, $CHCl_3$); IR (neat): 1738 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$); δ: 0.90 (t, *J* = 7.4 Hz, 3H), 1.08 (d, *J* = 7.4 Hz, 3H), 1.11-1.20 (m, 1H), 1.23-1.33 (m, 4H), 1.58-1.70 (m, 2H), 2.67 (dd, *J* = 14.3, 6.3 Hz, 1H), 2.76-2.80 (m, 4H), 2.88 (dd, *J* = 14.6, 11.2 Hz, 1H), 3.12 (q, *J* = 6.9 Hz, 1H), 3.34-3.39 (m, 1H), 3.48 (dd, *J* = 14.6, 3.2 Hz, 1H), 4.73-4.78 (m, 1H), 4.95-4.99 (m, 1H), 5.44 (dd, *J* = 11.2, 3.2 Hz, 1H), 6.35 (d, *J* = 10.3 Hz, 1H), 6.89-6.90 (m, 2H), 7.13-7.28 (m, 8H)^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.6, 13.7, 15.5, 19.7, 30.2 (2C), 34.1, 37.6, 42.1, 48.9, 57.9, 62.3, 77.4, 126.4, 127.0, 128.3 (2C), 128.6 (2C), 128.8 (2C), 128.9 (2C), 136.6, 136.9, 166.3, 169.7, 171.0, 209.2; HRMS (ESI-TOF) calcd for $C_{29}H_{37}N_2O_5$ $[M+H]^+$: 493.2697; found: 493.2699.

*Synthesis of 2S,8R,11R-stereoisomer of stereocalpin A (**2d**)*

(4*R*,5*S*,6*R*,7*S*)-8-[(*S*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-methyl-D-phenylalaninate (21d). According to the procedure described for the preparation of **11a**, silyl ether **10d** (234.0 mg, 0.45 mmol) was converted into compound **21d** (195.7 mg, 76%) as a colorless oil: $[\alpha]^{28}_D$ +55.9 (*c* 1.57, $CHCl_3$); IR (neat): 1782 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.83 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H), 1.21-1.38 (m, 5H), 1.56-1.64 (m, 1H), 1.68-1.75 (m, 2H), 2.36 (s, 3H), 2.76 (dd, *J* = 13.2, 9.7 Hz, 1H), 2.85 (dd, *J* = 13.7, 8.6 Hz, 1H), 3.06 (dd, *J* = 13.7, 5.7 Hz, 1H), 3.25 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.43-3.46 (m, 4H), 3.89 (dd, *J* = 7.4, 3.4 Hz, 1H), 4.07-4.12 (m, 1H), 4.15-4.23 (m, 2H), 4.61-4.65 (m, 2H), 4.73 (d, *J* = 7.4 Hz, 1H), 5.01-5.05 (m, 1H), 7.20-7.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.3, 14.0, 14.2, 18.4, 34.1, 34.7, 37.7, 39.0, 40.2, 41.4, 55.4, 56.4, 64.7, 66.0, 75.7, 80.1, 98.4, 126.6, 127.3, 128.4 (2C), 128.9 (2C), 129.2 (2C), 129.4 (2C), 135.1, 137.7, 152.9, 174.1, 175.3; HRMS (ESI-TOF) calcd for $C_{32}H_{45}N_2O_7$ $[M+H]^+$: 569.3221; found: 569.3217.

(4*R*,5*S*,6*R*,7*S*)-8-[(*S*)-4-Benzyl-1,3-oxazolidin-2-on-3-yl]-6-(methoxymethoxy)-5,7-dimethyl-8-oxooctan-4-yl *N*-{[(benzyloxy)carbonyl]-D-phenylalanyl}-*N*-methyl-D-phenylalaninate (22d). According to the procedure described for the preparation of **12a**, amine **21d** (57.1 mg, 0.10 mmol) was converted into compound **22d** (68.3 mg, 80%) as a colorless oil: $[\alpha]^{28}_D$ +44.9 (*c* 1.13, $CHCl_3$); IR (neat): 1776 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 3:2 mixture of rotamers) δ: 0.82 (d, *J* = 6.9 Hz, 1.2H), 0.89-0.94 (m, 4.8H), 1.19-1.35 (m, 5.0H), 1.48-1.62 (m, 2.0H), 1.77-1.83 (m, 1.0H), 2.00 (dd, *J* = 13.7, 4.6 Hz, 0.4H), 2.10 (dd, *J* = 13.7, 8.0 Hz, 0.4H), 2.69-2.74 (m, 1.0H), 2.81 (dd, *J* = 13.7, 6.9 Hz, 0.6H), 2.87 (s, 1.8H), 2.94 (s, 1.2H), 2.99-3.09 (m, 1.6H), 3.26-3.28 (m, 1.8H), 3.35-3.40 (m, 2.8H), 3.49-3.52 (m, 0.4H), 3.77 (dd, *J* = 7.7, 3.2 Hz, 0.4H), 3.81-3.84 (m, 0.6H), 3.90-3.94 (m, 0.4H), 3.98-4.06 (m, 1.4H), 4.12-4.17 (m, 1.2H), 4.43-4.49 (m, 0.8H), 4.54-4.65 (m, 2.2H), 4.75-4.79 (m, 1.0H), 4.87-4.92 (m, 0.8H), 4.97-5.04 (m, 2.2H), 5.17-5.20 (m, 1.0H), 5.26 (d, *J* = 8.6 Hz,

0.6H), 5.41 (d, *J* = 9.2 Hz, 0.4H), 6.71-6.73 (m, 0.8H), 7.05-7.36 (m, 19.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.7, 9.8, 10.0, 12.2, 13.9, 18.7 (2C), 29.7, 33.5, 33.9, 34.1, 34.3 (2C), 37.5, 37.6, 38.4, 38.5, 38.8, 39.6, 41.0, 41.4, 51.0, 51.8, 55.8, 56.3, 56.6, 56.8, 59.7, 62.3, 65.9, 66.2, 66.3, 66.6, 75.0, 75.1, 81.1, 82.5, 98.8 (2C), 126.2, 126.5, 126.7, 127.1 (3C), 127.2, 127.3, 127.6 (2C), 127.8 (2C), 128.0 (2C), 128.2 (2C), 128.3 (2C), 128.4 (2C), 128.8 (2C), 128.9 (2C), 129.3 (2C), 129.4 (2C), 129.5 (2C), 129.7 (2C), 135.4, 135.9, 136.0, 136.1, 136.4, 136.9, 137.2, 137.4, 153.1, 154.1, 154.7, 155.3, 170.1 (2C), 171.4, 172.9, 174.6, 174.7; HRMS (ESI-TOF) calcd for $C_{49}H_{59}N_3NaO_{10}$ $[M+Na]^+$: 872.4093; found: 872.4089.

Cyclic peptide (24d). According to the procedure described for the preparation of **14a**, oxazolidinone **22d** (50.9 mg, 0.074 mmol) was converted into compound **24d** (29.6 mg, 74%) as a white solid: mp 141 °C; $[\alpha]^{29}_D$ +97.5 (*c* 1.49, $CHCl_3$); IR (neat): 1735 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.91-0.94 (m, 6H), 0.96 (d, *J* = 6.9 Hz, 3H), 1.21-1.37 (m, 2H), 1.48-1.54 (m, 1H), 1.64-1.72 (m, 1H), 2.11-2.16 (m, 1H), 2.20-2.26 (m, 1H), 2.50 (dd, *J* = 14.0, 4.9 Hz, 1H), 2.81-2.93 (m, 5H), 3.39 (s, 3H), 3.49 (dd, *J* = 14.3, 2.9 Hz, 1H), 3.72-3.74 (m, 1H), 4.59 (d, *J* = 6.9 Hz, 1H), 4.70-4.74 (m, 2H), 4.97-5.01 (m, 1H), 5.21-5.23 (m, 1H), 6.44 (d, *J* = 9.7 Hz, 1H), 6.90-6.92 (m, 2H), 7.14-7.31 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.6, 13.7, 15.1, 19.5, 29.5, 30.5, 34.3, 37.8, 41.9, 48.1, 50.4, 56.1, 62.6, 77.5, 79.2, 97.6, 126.5, 127.0, 128.2 (2C), 128.7 (2C), 128.8 (2C), 129.1 (2C), 136.6, 137.1, 169.8, 171.7, 172.6; HRMS (ESI-TOF) calcd for $C_{31}H_{43}N_2O_6$ $[M+H]^+$: 539.3116; found: 539.3117.

2*S*,8*R*,11*R*-Stereoisomer of stereocalpin A (2d). According to the procedure described for the preparation of **1a**, ether **24d** (29.6 mg, 0.055 mmol) was converted into compound **2d** (10.5 mg, 39%) as a white solid: mp 214 °C; $[\alpha]^{28}_D$ +39.7 (*c* 0.46, $CHCl_3$); IR (neat): 1735 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.91 (t, *J* = 7.4 Hz, 3H), 1.01-1.05 (m, 6H), 1.11-1.21 (m, 1H), 1.23-1.33 (m, 1H), 1.64-1.79 (m, 2H), 2.60 (dd, *J* = 14.3, 5.7 Hz, 1H), 2.76-2.81 (m, 4H), 2.89 (dd, *J* = 14.3, 11.5 Hz, 1H), 3.30-3.35 (m, 1H), 3.41 (q, *J* = 7.1 Hz, 1H), 3.48 (dd, *J* = 14.3, 3.4 Hz, 1H), 4.67-4.72 (m, 1H), 4.96-5.00 (m, 1H), 5.32 (dd, *J* = 11.5, 3.4 Hz, 1H), 5.61 (d, *J* = 10.3 Hz, 1H), 6.90-6.92 (m, 2H), 7.15-7.33 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.8, 13.7, 14.2, 19.7, 29.9, 30.3, 34.0, 37.5, 46.6, 48.8, 58.2, 62.1, 77.3, 126.5, 127.0, 128.3 (2C), 128.7 (2C), 128.8 (2C), 129.1 (2C), 136.5, 136.9, 166.4, 169.6, 170.7, 208.1; HRMS (ESI-TOF) calcd for $C_{29}H_{37}N_2O_5$ $[M+H]^+$: 493.2697; found: 493.2695.

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Chapter 3. Conclusions

1. The author assigned the stereochemistry of the polyketide substructure of odoamide by the comparing ^{1}H NMR spectra between the synthetic triols and natural-derived triol. The synthesis of the putative structure of odoamide was also achieved. The NMR spectra of the synthetic odoamide were in good agreement with those of the natural odoamide. Accordingly, the full structural assignment and first total synthesis of odoamide were achieved.

2. The author established the efficient synthetic route of odoamide derivatives by using solid-phase synthesis for the structure-activity relationship study of odoamide. Several derivatives showed comparable bioactivity to natural odoamide. Additionally, it was demonstrated that 26-membered natural odoamide and the 24-membered isomer were slowly interconverted via the intramolecular ester exchange at the polyketide 1,3-diol moiety. The assessment of physicochemical properties revealed that odoamide derivatives exhibited good membrane permeability but had different serum protein binding behaviors to affect their cytotoxicities.

3. The author established the facile synthetic route of stereocalpin A to give its eight stereoisomers via a stereoselective syntheses of four diastereomers of the polyketide substructure. The NMR spectra of one of the synthetic isomers were identical with those of natural stereocalpin A. Thus, the structural revision and the first total synthesis of stereocalpin A were achieved.

In summary, the author achieved the total syntheses of two peptide-polyketide hybrid natural products, odoamide and stereocalpin A, in which stereochemistries were unclear at the initial stage of this study. The derivatives of two peptides were easily synthesized by the developed synthetic routes via stereodivergent approach. These synthetic procedures would facilitate the further structure-activity relationship strudies and the biochemical research for the target identification.

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List of Publications

This study was and will be published in the following papers.

Chapter 1.

Section 1. Total Synthesis of Odoamide, a Novel Cyclic Depsipeptide from an Okinawan Marine Cyanobacterium
Masato Kaneda, Kosuke Sueyoshi, Toshiaki Teruya, Hiroaki Ohno, Nobutaka Fujii, and Shinya Oishi
Org. Biomol. Chem. **2016**, *14*, 9093–9104.

Section 2. SAR Study of Cyclic Depsipeptide, Odoamide: Insights into the Bioactivities of Aurilide-family Hybrid Peptide-polyketides
Masato Kaneda, Shinsaku Kawaguchi, Nobutaka Fujii, Hiroaki Ohno, and Shinya Oishi
Manuscript submitted.

Chapter 2. Total Synthesis and Stereochemical Revision of Stereocalpin A: Mirror-image Approach for Stereochemical Assignments of the Peptide-polyketide Macrocycle
Masato Kaneda, Shinsuke Inuki, Hiroaki Ohno, and Shinya Oishi
Manuscript submitted.