Total synthesis of odoamide, a novel cyclic depsipeptide, from an Okinawan marine cyanobacterium†

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Odoamide is a novel cyclic depsipeptide with highly potent cytotoxic activity isolated from the Okinawan marine cyanobacterium Okeania sp. It contains a 26-membered macrocycle composed of a fatty acid moiety, a peptide segment and isoleucic acid. Four possible stereoisomers of the odoamide polyketide substructure were synthesised using a chiral pool approach. The first total synthesis of odoamide was also successfully achieved. The structure of synthetic odoamide was verified by comparing its NMR spectra with those of the natural product.

Introduction

Many peptide secondary metabolites derived from natural resources show attractive biological activities.1 Because of their favourable drug-like properties including good membrane permeability and biostability,2 a number of synthetic and medicinal chemistry studies of macrocyclic peptides and highly N-methylated peptides have been carried out.3 Among them, aurilide-class cyclic depsipeptides exhibit highly potent antiproliferative activity against cancer cell lines (Fig. 1). The first 26-membered cyclic depsipeptide, aurilide (1a), was isolated from the sea hare Dolabella auricularia.4 The related depsipeptides, aurilide B (1b) and C (1c), from Lyngbya majuscula also show potent cytotoxicity.5 Kulokekahilide-2 (2) is a similar cytotoxic depsipeptide from a marine mollusk, Philinopsis speciosa, which has two conformers of the 26-membered macrocycle in dichloromethane.6 Lagunamide A (3a) and B (3b) from Lyngbya majuscula exhibit antimalarial activity against Plasmodium falciparum at submicromolar concentrations.7 Lagunamide C (3e)8 and palau’amide (4)9 exhibit cytotoxicity at nanomolar concentrations comparable to other aurilide-class depsipeptides, although these peptides have unique 27-membered and 24-membered macrocycles, respectively. The configurations of the component amino acids of the depsipeptides were investigated by chiral HPLC, chiral GC-MS, and Marfey’s analyses,10 while the stereoselective synthesis and the NMR analysis facilitated the determination of the absolute stereochemistries of the fatty acid substructure. In some cases, the structure was verified or revised through synthetic studies of natural products and their stereoisomers.11

Odoamide (5) is a novel cyclic depsipeptide from the Okinawan marine cyanobacterium Okeania sp. (Fig. 2A), which shows highly potent cytotoxic activity against HeLa S3 cell lines.12 The overall structure of the 26-membered macrocycle is similar to those of aurilide-class depsipeptides, and comprises three substructures: a fatty acid moiety, a peptide segment (Ala-D-MePhe-Sar-Ile-MeAla) and isoleucic acid. At the initial stage of this study, the absolute configurations of the constituent amino acids and isoleucic acid in 5 were determined by chiral HPLC analysis and Marfey’s analysis. The absolute configuration of the 5-hydroxy group of the polyketide part was determined by Mosher’s method,13 while the remaining configurations of the polyketide were ambiguous. In this study, we carried out a synthetic study of odoamide to verify its structure and complete stereochemistry.

The synthetic strategy is illustrated in Scheme 1. During the cyclisation of the linear peptide, epimerisation and dimer formation are often problematic.3e,f,14 To avoid the less reactive process of N-methylated amide (CO–NMe) or ester bond formation compared with standard peptide bond (CO–NH) formation, we chose macrocyclisation of the Ala and N-alloisoleucic acid residues of the linear precursor 6 for odoamide (5).11d Peptide 6 could be prepared by coupling of alcohol 7,
MeAla 8 and tetrapeptide 9, which could be obtained by standard solid-phase peptide synthesis. Alcohol 7 could be synthesised by coupling of d-allo-isoleucic acid ester 11 with carboxylic acid 10.

Results and discussion

Synthesis of the polyketide substructure of odoamide

The stereochemistries of the polyketide part were unknown when we started this study. Therefore, it was necessary to synthesise all the possible polyketide substructures of odoamide 5. The polyketide substructure in lagunamide A (3a), a closely related structural analogue of 5, has 5S,7R-dihydroxy and 6S,8S-dimethyl groups. Additionally, aurilide-class depsipeptides 1a–c, 2, and 3a,b possess the syn-1,3-diol moiety with a 5S-hydroxy configuration. On the basis of the structures of these related molecules, we expected that the plausible stereochimical configuration of the natural odoamide 5 was 5S,6S,7R,8S. Among these four stereocentres, the configuration at the C8-methyl group was ambiguous because attempts to determine it based on derivatisation and NMR analysis of odoamide (5) were unsuccessful. It was also desirable to confirm the stereochemistry of the C6-methyl group. Therefore, we designed four possible methyl group esters 12a–d as polyketide substructure substrates (Fig. 2B).

Methyl esters 12a,b were synthesised from (S)-Roche ester 13 according to a similar process described in previous reports by us and others (see the ESI†). Preparation of (5S,6R,7R,8S)-ester 12c and (5S,6R,7R,8S)-ester 12d started from the commercially available (R)-Roche ester ent-13 in a similar manner (Scheme 2). (R)-Roche ester ent-13 was converted to alcohol ent-15 via benzyl protection16 and LiAlH4-mediated reduction. After Swern oxidation, an n-Bu3BOTf-mediated Evans aldol reaction17 of the resulting aldehyde provided the syn-aldol products 16c and 17d. The requisite stereochemistries at the C8 chiral centre in 12c and 12d were generated at this step by using propionyl- and pentanoyl-oxazolidinones, respectively. TBS protection of the secondary alcohol in 16c and 17d followed by removal of the chiral auxiliary with LiBH4 gave alcohols 20c18 and 21d. Swern oxidation of 20c and the subsequent Wittig reaction of the resulting aldehyde with ethylidene–triphenylphosphorane provided olefin 22e as an E/Z isomeric mixture. Hydrogenation of 22e in the presence of Pd/C afforded the key alcohol 23c with a threo/threo-configuration. Separately, tosylation of 21d followed by
LiAlH₄-mediated reduction afforded benzyl ether 24d, which was converted to the corresponding alcohol 23d (with a threo/erythro-configuration) by hydrogenation. Swern oxidation of 23c followed by a Mukaiyama aldol reaction with 1-methoxy-2-methyl-1-trimethylsiloxy-1,3-butadiene (25) produced methyl ester 12c with a (5S)-hydroxy group (dr >99 : 1). Ester 12d was obtained from 23d by using the identical protocol.

The stereochemistry of the 5-hydroxy group in alcohol 12a was confirmed by the NMR analysis of the corresponding acetonide (Scheme 3). TBS deprotection of 26a and 12a provided 1,3-diols 27a and 28a, which were treated with 2,2-dimethoxypropane in the presence of PPTS to give acetonides 29a and 30a, respectively. It is known that ¹³C NMR chemical shifts of the ketal methyl groups in syn- and anti-1,3-diol acetonides are different. A syn-acetonide shows different chemical shifts for the two ketal methyl groups (e.g., 19.5 and 30.0 ppm for 30a) because of its predominant chair conformation. In contrast, an anti-acetonide shows close chemical shifts (e.g., 23.5 and 25.2 ppm for 29a), 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 28a, the precursor of acetonide 30a has the desired 1,3-syn configuration. Of note, esters 12a–d were employed as the key substrates for the stereochemical assignment of the polyketide substructure in 5 in our previous research. Manipulations of esters 12a–d including DIBAL-mediated reductive transformation provided the corresponding triol derivatives. The comparative NMR analysis between the natural product-derived triol and synthetic triols demonstrated that the polyketide substructure had the 5S,6S,7R,8S configuration (see the ESI†). 

**Synthesis of odoamide and its biological evaluation**

After the determination of the stereochemistry of the polyketide part, we attempted the total synthesis of odoamide
using (5S,6S,7R,8S)-ester 12a. Synthesis of odoamide (5) began with methylthiomethyl (MTM) protection of the secondary hydroxy group in 12a to give thioacetal 31 (Scheme 4). 11a,24 Hydrolysis of 31 with LiOH followed by coupling with \( \nu \)-allo-isoleucic acid phenacyl ester (11) using 2-methyl-6-nitrobenzoic anhydride (MNBA) 25 and DMAP afforded ester 32. The TBS group in 32 was deprotected with HF·pyridine to produce the corresponding alcohol 7. In the coupling of Fmoc-MeAla-OH 8 with 7 using DCC and DMAP, significant epimerisation occurred. The coupling using Fmoc-MeAla-Cl 26 with 7 in the presence of DIPEA followed by Fmoc deprotection with Et2NH gave amine 33 in 54% yield (two steps) without epimerisation. Tetrapeptide 9 was conjugated with 33 using EDCI–HOAt to afford 34 as a 1.4 : 1 epimeric mixture at the \( \alpha \)-position of Ile. 27 After removal of the phenacyl (with Zn and AcOH) and Fmoc groups (with Et2NH), the epimer mixture of the linear peptides was separated into the desired compound 6a (major, L-Ile) and undesired compound 6b (minor, D-allo-Ile) by HPLC purification. Cyclisation of 6a and 6b with HATU followed by deprotection of the MTM group with AgNO3 and 2,6-lutidine gave the desired odoamide 5a and its diastereomer 5b. Both cyclisations of 6a and 6b proceeded smoothly within five hours without epimerisation. The configurations of L-Ile and \( \nu \)-allo-Ile in peptides 5a and 5b, respectively, were determined by Marfey’s analysis and \( ^{1} \)H NMR analysis after acid hydrolysis.

We analysed the \( ^{1} \)H NMR and \( ^{13} \)C NMR spectra of the natural and synthetic products (Fig. 3 and 4). The NMR spectra of the synthetic odoamide 5a were identical to those of the
natural product 5, suggesting that the chemical structure of odoamide was the same as 5a. The cytotoxicity of synthetic odoamides 5a and 5b against A549 cells was also evaluated by the MTS assay. Peptide 5a showed highly potent cytotoxicity (IC_{50} = 2.1 nM), corroborating our correct structural assignment of odoamide (5). However, the epimer peptide 5b 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.

Conclusions

In this study, the total synthesis of odoamide was completed via the synthesis of four possible polyketide substructures 12a–d. The NMR spectra of the synthetic peptide 5a were identical to those of the natural odoamide 5. Accordingly, the full structural assignment and first total synthesis of odoamide were achieved.
Fig. 3  Comparison of the $^1$H NMR spectra between the natural compound 5 and the synthetic compound $5a$ (in CD$_3$OD).

Fig. 4  Comparison of the $^{13}$C NMR spectra between the natural compound 5 and the synthetic compound $5a$ (in CD$_3$OD).
Experimental section

Synthetic general method

NMR spectra were recorded using a JEOL ECA-500 spectrometer. Chemical shifts are reported in δ (ppm) relative to Me$_4$Si in (CDCl$_3$) as an internal standard. $^{13}$C NMR spectra were referenced to the residual solvent signal. Melting points were measured by a hot stage melting point apparatus (uncorrected). Exact mass (HRMS) spectra were recorded on a Shimadzu LC-ESI-TOF-MS instrument. IR spectra were recorded 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$_3$CN (with 0.1% (v/v) TFA, except for the analysis of pentol) and 30% H$_2$O$_2$ in MeOH (1:2, 4.2 cm$^3$) and stirred overnight at room temperature. The whole mixture 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-oxazolidin-2-one (429.2 mg, 1.84 mmol) in CH$_2$Cl$_2$ (9.2 cm$^3$) under argon were added n-Bu$_4$BOTf (1.0 mol dm$^{-3}$ in CH$_2$Cl$_2$, 2.0 cm$^3$, 2.00 mmol) and i-Pr$_2$NET (0.38 cm$^3$, 2.17 mmol) at −78 °C. The mixture was quenched with saturated aqueous NH$_4$Cl. The whole mixture was extracted with CH$_2$Cl$_2$ and the extract was washed with brine, and 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-oxazolidin-2-one (429.2 mg, 1.84 mmol) in CH$_2$Cl$_2$ (9.2 cm$^3$) under argon were added n-Bu$_4$BOTf (1.0 mol dm$^{-3}$ in CH$_2$Cl$_2$, 2.0 cm$^3$, 2.00 mmol) and i-Pr$_2$NET (0.38 cm$^3$, 2.17 mmol) at −78 °C. After stirring 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$_2$Cl$_2$ (3.9 cm$^3$) at −78 °C. After stirring 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 (1.8 cm$^3$) and 30% H$_2$O$_2$ in MeOH (1:2, 4.2 cm$^3$) and stirred overnight at room temperature. The whole mixture was concentrated under reduced pressure and extracted with CH$_2$Cl$_2$. The extract was washed with saturated aqueous NaHCO$_3$, 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 3:1) to give compound 16c (610.7 mg, 80%, dr >15:1) as a colorless oil. The minor isomer was removed by column chromatography: [α]$^2$$_D$ = −43.2 (c 0.72, CHCl$_3$); IR (neat) ν$_{max}$/cm$^{-1}$: 3504 (OH), 1779 (C=O); $^1$H NMR (500 MHz, CDCl$_3$) δ: 1.05 (3H, d, J 6.9), 1.33 (3H, d, J 6.3), 1.87–1.93 (1H, m), 2.77 (1H, dd, J 13.2, J 9.7), 3.00 (1H, d, J 2.9), 3.25 (1H, dd, J 13.2, J 3.2), 3.46–3.52 (2H, m), 3.96–4.03 (2H, m), 4.16–4.21 (2H, m), 4.51 (2H, s), 4.65–4.69 (1H, m), 7.20–7.21 (2H, m), 7.26–7.36 (8H, m); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 12.4, 12.8, 36.2, 37.7, 40.5, 55.1, 66.0, 73.3, 73.9, 74.1, 127.4 (2C), 127.5 (2C), 128.3 (2C), 128.9 (2C), 129.4 (2C), 135.0, 138.1, 152.7, 177.0; HRMS (ESI) calcd for C$_{32}$H$_{28}$O$_{10}$Na$_2$ (M$^+$): 434.1938; found: 434.1938. (R)-4-Benzyl-3-[2R,3S,4R]-5-benzyl-3-methoxy-3-(tert-butylmethylsilyloxy)-2,4-dimethylpentanoyl]oxazolidin-2-one (18c). To a stirred solution of 16c (14.1 g, 34.3 mmol) in CH$_2$Cl$_2$ (137 cm$^3$) under argon were added TBSOTf (9.5 cm$^3$, 41.2 mmol) and 2,6-lutidine (7.9 cm$^3$, 68.6 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2.5 h. The reaction was quenched with 1 N HCl. The whole mixture was extracted with CH$_2$Cl$_2$ and the extract was washed with brine, and dried over MgSO$_4$. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel with hexane–EtOAc (9:1) to give compound 18c (16.0 g, 89%) as a colorless oil: [α]$^2$$_D$ = −38.2 (c 1.21, CHCl$_3$); IR (neat) ν$_{max}$/cm$^{-1}$: 1780 (C=O); $^1$H NMR (500 MHz, CDCl$_3$) δ: 0.94 (3H, s), 0.96 (3H, s), 0.90 (9H, s), 0.92 (3H, d, J 7.4), 1.25 (3H, d, J 6.9), 1.88–1.93 (1H, m), 2.75 (1H, dd, J 13.2, J 9.7), 3.01 (1H, dd, J 13.2, J 3.2), 3.06 (1H, dd, J 13.2, J 3.2), 2.85 (2H, s), 4.52 (2H, m), 4.59–4.64 (2H, m), 4.68–4.75 (2H, m), 5.26–5.30 (3H, m), 5.70–5.74 (10H, m); $^{13}$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), 135.3, 138.6, 152.8, 175.9; HRMS (ESI) calcd for C83H85NaO3Si (MNa+): 910.4329; found: 910.4328.

(2S,3R,4R)-5-Benzoxyl-3-(tert-butylidimethylsilyloxy)-2,4-dimethylpentan-1-ol (20c). To a stirred solution of 18c (22.4 g, 42.5 mmol) in THF (213 cm³) and MeOH (5.2 cm³, 127.6 mmol) under argon was added LiBH₄ (2.78 g, 0.061 mmol) under argon was added DMSO (0.18 cm³, 2.60 mmol) in CH₂Cl₂ as a colorless oil: [α]D 938.1 mg, 92%) as a colorless oil: [α]D 9102 This journal is © The Royal Society of Chemistry 2016

C83H85NaO3Si (MNa+): 910.4329; found: 910.4328.

{(2R,3S,4R)-1-(Benzyloxy)-5-cm-3-ylloyl)[tert-butylidimethylsilane (22c). To a stirred solution of oxalyl chloride (0.11 cm³, 1.30 mmol) in CH₂Cl₂ (6.5 cm³) under argon was added DMSO (0.18 cm³, 2.60 mmol) in CH₂Cl₂ (0.43 cm³) at −78 °C. After stirring for 30 min, a solution of 20c (228.9 mg, 0.65 mmol) in CH₂Cl₂ (2.2 cm³) was added dropwise and stirred at −78 °C for 1.5 h. i-Pr₂NEt (0.57 cm³, 3.25 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. The mixture was quenched with saturated aqueous NH₄Cl. The whole mixture was extracted with CH₂Cl₂ (1.5 cm³) and the extract was washed with brine, and dried over MgSO₄. 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 22c (93.8 mg, 92%) as a colorless oil: [α]D 9104 This journal is © The Royal Society of Chemistry 2016

C15H34NaO2Si (MNa+): 297.2220; found: 297.2221.

[(2R,3S,4R)-1-(Benzyloxy)-5-cm-3-ylloyl)[tert-butylidimethylsilane (22c). To a stirred solution of oxalyl chloride (0.11 cm³, 1.30 mmol) in CH₂Cl₂ (6.5 cm³) under argon was added DMSO (0.18 cm³, 2.60 mmol) in CH₂Cl₂ (0.43 cm³) at −78 °C. After stirring for 30 min, a solution of 20c (228.9 mg, 0.65 mmol) in CH₂Cl₂ (2.2 cm³) was added dropwise and stirred at −78 °C for 1.5 h. i-Pr₂NEt (0.57 cm³, 3.25 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. The mixture was quenched with saturated aqueous NH₄Cl. The whole mixture was extracted with CH₂Cl₂ and the extract was washed with brine, and dried over MgSO₄. 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 (508.6 mg, 1.37 mmol) in THF (5.5 cm³) under argon was added n-BuLi (1.6 mol dm⁻³ in hexane; 0.81 cm³, 1.30 mmol) at room temperature. After stirring for 30 min, a solution of the above aldehyde in THF (1.3 cm³) was added and the reaction mixture was stirred for 1.5 h. The mixture was quenched with saturated aqueous NaHCO₃. The whole mixture was extracted with EtOAc and the extract was washed with brine, and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was filtered through a short pad of silica gel with hexane–EtOAc (9 : 1). Further purification by flash chromatography over silica gel with hexane–CHCl₃ (8 : 1) gave compound 22c as a diastereomixture (163.7 mg, 69%, Z/E = 7 : 1) colorless oil: [α]D 12.5 ±12.5 (c 1.17, CHCl₃); 1H NMR (500 MHz, CDCl₃) δ: 0.01 (0.4H, s), 0.02 (2.6H, s), 0.04 (0.4H, s), 0.05 (2.6H, s), 0.84–0.86 (3H, m), 0.89 (12H, s), 0.90 (7.8H, s), 0.94–0.97 (3H, m), 1.61 (2.6H, dd, J₁ 6.9, J₂ 1.7), 1.63 (0.4H, d, J 4.6), 1.96–2.03 (1H, m), 2.23–2.30 (0.1H, m), 2.60–2.65 (0.9H, m), 3.22 (1H, dd, J₁ 8.9, J₂ 6.9), 3.40 (1H, dd, J₁ 8.9, J₂ 7.7), 3.56 (1H, dd, J₁ 8.0, J₂ 1.7), 4.43–4.52 (2H, m), 5.16–5.21 (1H, m), 5.35–5.42 (1H, m), 7.25–7.34 (5H, m); 13C NMR (125 MHz, CDCl₃) 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) calcd for C15H34NaO2Si (MNa+): 385.2352; found: 385.2354.

(2R,3S,4S)-3-(tert-Butylidimethylsilyloxy)-2,4-dimethylpentan-1-ol (23c). To a stirred solution of 22c (1.3 g, 3.7 mmol) in EtOH (37.0 cm³) was added 10% Pd/C (787.5 mg, 0.7 mmol) at room temperature and the mixture was treated with H₂ gas (1 atm). After stirring 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 23c (938.1 mg, 92%) as a colorless oil: [α]D 98100 This journal is © The Royal Society of Chemistry 2016

C15H34NaO2Si (MNa+): 297.2220; found: 297.2221.

Methyl [(5S,6R,7R,8S,8E)-7-(tert-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundec-2-enoate (12c). To a stirred solution of i-Pr₂NH (0.16 cm³, 1.16 mmol) in THF (2.4 cm³) under argon was added n-BuLi (2.6 mol dm⁻³ in hexane; 0.45 cm³, 1.16 mmol) at 0 °C. After 20 min, methyl tiglate (0.13 cm³, 1.05 mmol) and TMSCl (0.20 cm³, 1.58 mmol) in THF (0.36 cm³) were added successively at −78 °C. The stirring was continued for 1 h at this temperature and for additional 1.5 h at room temperature. Then, pentane and cold saturated NaHCO₃ were added to the reaction mixture. The whole mixture was extracted with pentane and the extract was washed with brine, and dried over MgSO₄. The filtrate was concentrated under reduced pressure to give compound 25, which was used without further purification. To a stirred solution of oxalyl chloride (0.060 cm³, 0.70 mmol) in CH₂Cl₂ (3.5 cm³) under argon was added DMSO (0.099 cm³, 1.40 mmol) in CH₂Cl₂ (0.23 cm³) at −78 °C. After stirring for 30 min, a solution of 23c (96.4 mg, 0.35 mmol) in CH₂Cl₂ (1.2 cm³) was added dropwise and stirred at −78 °C for 1.5 h. i-Pr₂NEt (0.49 cm³, 2.8 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. The mixture was quenched with saturated aqueous NH₄Cl. The whole mixture was extracted with CH₂Cl₂ and the extract was washed with brine, and dried over MgSO₄. 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 CH₂Cl₂ (2.7 cm³) and Et₂O (0.27 cm³) under argon were added diene 25 and BF₃·OEt₂ (0.065 cm³, 0.53 mmol) at −78 °C. After stirring for 2 h, a mixture of THF/H₂O/1 N HCl (5 : 1 : 0.4 v/v, 1.8 cm³) was added to the reaction mixture. The
mixture was warmed to room temperature and stirred for 15 min. Then, saturated aqueous NaHCO₃ was added to the mixture at 0 °C. The whole mixture was extracted with CH₂Cl₂ and the extract was washed with brine, and dried over MgSO₄. 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 12c (73.4 mg, 54%) as a colorless oil: [α]D²⁰ -22.4 (c 1.01, CHCl₃); IR (neat) νmax/cm⁻¹: 3523 (OH), 1716 (C=O); ¹H NMR (500 MHz, CDCl₃) δ: 0.08 (3H, s), 0.09 (3H, s), 0.85 (3H, d, J 6.9), 0.88-0.91 (12H, m), 0.94 (3H, d, J 6.9), 1.04-1.11 (1H, m), 1.15-1.22 (1H, m), 1.35-1.42 (1H, m), 1.46-1.53 (1H, m), 1.63-1.69 (2H, m), 1.87 (3H, s), 1.96 (1H, d, J 4.0), 2.31-2.42 (2H, m), 3.65-3.66 (1H, m), 3.74 (3H, s), 3.79-3.83 (1H, m), 6.79-6.82 (1H, m); ¹³C NMR (125 MHz, CDCl₃) δ: 42.3, 35.9, 22.0, 15.4, 13.8, 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) calcd for C₃₉H₄₁Na₂O₄Si (MNa⁺): 609.2745; found: 609.2748.

[(2R,3R,4R)-1-(Benzylxoy)-2,4-dimethylyheptan-3-yl]oxy[(tert-butyl)dimethylsilane (24d). To a stirred solution of 21d (7.3 g, 19.1 mmol) in CH₂Cl₂ (191 cm³) under argon were added Et₃N (5.3 cm³, 38.2 mmol) and Me₂N·HCl (1.8 g, 19.1 mmol) at room temperature. After stirring for 1 h, the reaction was quenched with saturated aqueous NH₄Cl. The whole mixture was extracted with CH₂Cl₂ and the extract was washed with brine, and dried over MgSO₄. 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 LiAlH₄ (2.2 g, 57.3 mmol) in THF (100 cm³) under argon were added Ac₂O (30.5 cm³) and AcOH (5.5 cm³) and the whole mixture was warmed to room temperature. After 1 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 mixture was extracted with Et₂O and the extract was washed with brine, and dried over MgSO₄. 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 10, which was used without further purification. To a stirred solution of acid 10 in CH₂Cl₂ (12.8 cm³) were added DMAP (935.0 mg, 7.7 mmol) and 11 (959.0 mg, 3.8 mmol) at room temperature. After stirring overnight, the mixture was quenched with 1 N HCl. The whole mixture was extracted with EtOAc and the extract was washed with brine, and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was filtered through a short pad of silica gel with hexane–EtOAc (3:1) to give 31, which was used without further purification. To a stirred solution of 31 (1.14 g, 2.6 mmol) in MeOH (17 cm³) and THF (17 cm³) was added 1 N LiOH (17 cm³) at 0 °C. The reaction mixture was warmed to 30 °C and stirred overnight. The mixture was concentrated under reduced pressure and EtOAc and 1 N HCl were added to the residue. The whole mixture was extracted with EtOAc and the extract was washed with brine, and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was filtered through a short pad of silica gel with hexane–EtOAc (10:1) to give compound 32 (1.48 g, 87%) as a colorless oil: [α]D²⁰ -43.5 (c 0.89, CHCl₃); IR (neat) νmax/cm⁻¹: 1710 (C=O); ¹H NMR (500 MHz, CDCl₃) δ: 0.05 (3H, s), 0.07 (3H, s), 0.86-0.91 (18H, m), 0.98 (3H, t, J 7.4), 1.15 (3H, d, J 6.9), 1.18-1.28 (2H, m), 1.34-1.47 (3H, m), 1.52-1.58 (1H, m), 1.62-1.64 (1H, m), 1.69 (3H, s), 1.99-2.03 (1H, m), 2.11 (3H, s), 2.19-2.25 (1H, m), 2.34-2.37 (2H, m), 2.37 (1H, dd, J 6, 1.5), 4.51 (1H, d, J 11.5), 5.19 (1H, d, J 3.4), 5.25 (1H, d, J 16.6), 5.55 (1H, d, J 16.6), 7.04-7.07 (1H, m), 7.49 (2H, t, J 7.7), 7.60-7.63 (1H, m), 7.89-7.91 (2H, m); ¹³C NMR (125 MHz, CDCl₃) δ: 321, 135.9, 134.1, 133.9, 133.0, 132.6, 127.4, 127.3, 127.0, 126.9 (2C), 126.8, 130.2 (2C), 138.7; HRMS (ESI) calcd for C₃₇H₄₀N₂O₈Si (MNa⁺): 687.3721; found: 687.3720.

Methyl (5S,6S,7R,8S,E)-7-(tert-butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undec-2-enolate (31). To a stirred solution of 12a (2.3 g, 6.0 mmol) in DMSO (42.9 cm³) under argon were added Ac₂O (30.5 cm³) and AcOH (5.5 cm³) at room temperature. After stirring overnight, the reaction mixture was cooled to 0 °C and quenched with saturated aqueous NaHCO₃. The whole mixture was extracted with EtOAc and the extract was washed with H₂O and brine, and dried over MgSO₄. 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 31 (1.6 g, 59%) as a colorless oil: [α]D²⁰ -75.4 (c 0.72, CHCl₃); IR (neat) νmax/cm⁻¹: 1716 (C=O); ¹H NMR (500 MHz, CDCl₃) δ: 0.05 (6H, s), 0.85-0.92 (18H, m), 1.15-1.28 (2H, m), 1.33-1.42 (2H, m), 1.62-1.66 (1H, m), 1.85 (3H, d, J 1.1), 1.98-2.05 (1H, m), 2.16 (3H, s), 2.26-2.39 (2H, m), 3.47 (1H, dd, J 6.9, J 2.9, 3.73 (3H, s), 4.00-4.03 (1H, m), 4.53 (1H, d, J 11.5), 4.63 (1H, d, J 11.5), 6.92-6.95 (1H, m); ¹³C NMR (125 MHz, CDCl₃) δ: -3.7, -3.6, 11.4, 12.8, 14.0, 14.1, 14.3, 18.4, 20.9, 26.2 (3C), 29.1, 34.6, 36.6, 39.0, 51.6, 73.0, 75.9, 77.2, 128.4, 140.3, 168.5; HRMS (ESI) calcd for C₂₅H₃₆N₂O₇SSi (MNa⁺): 469.2778; found: 469.2779.

(2R,3S)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (5S,6S,7R,8S,E)-7-hydroxy-2,6,8-trimethyl-5-(methylthiomethoxy)undec-2-enolate (7). To a stirred solution of 32 (80.7 mg,
0.12 mmol) in THF (0.80 cm³) and pyridine (0.20 cm³) was added HF-pyridine (0.50 cm³) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into saturated aqueous NaHCO₃ at 0 °C. The whole mixture was extracted with EtoAc, and the extract was washed with brine and 1 N HCl, and dried over MgSO₄. 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 7 (49.2 mg, 74%) as a colorless oil; [α]D²⁰ = −5.29 (c 1.08, CHCl₃); IR (neat) νmax/cm⁻¹: 3526 (OH), 1708 (C=O); ¹H NMR (500 MHz, CDCl₃) δ: 0.83–0.85 (6H, m), 0.89–0.91 (3H, m), 0.98 (3H, t, J 7.4), 1.15 (3H, d, J 6.9), 1.24–1.37 (4H, m), 1.38–1.46 (1H, m), 1.50–1.59 (1H, m), 1.61–1.64 (1H, m), 1.90 (3H, s), 1.92–1.99 (1H, m), 2.15–2.16 (4H, m), 2.19–2.26 (1H, m), 2.37–2.49 (2H, m), 3.38–3.41 (1H, m), 4.08–4.12 (1H, m), 4.64 (2H, s), 5.22 (1H, d, J 2.9), 5.26 (1H, d, J 16.6), 5.55 (1H, d, J 16.6), 7.03–7.06 (1H, m), 7.49 (2H, t, J 7.7), 7.60–7.63 (1H, m), 7.89–7.91 (2H, m); ¹³C NMR (125 MHz, CDCl₃) 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, 164.7, 169.1, 191.6; HRMS (ESI) calcd for C₉₀H₯₄NO₅S (MNa⁺): 573.2853; found: 573.2855.

(2R,3S)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (55,6S,7R,8S,E)-2,6,8-trimethyl-7-[N-(methyl-α-alanyloxy)-5-(methyldithiomethoxy)undec-2-enoate (33). Fmoc-MeAla-Cl was synthesised by using the identical procedure reported previously. To a stirred solution of Fmoc-MeAla-OH (227.7 mg, 0.70 mmol) in CH₂Cl₂ (3.9 cm³) were added DMF (0.0054 cm³, 0.070 mmol) and SOCl₂ (0.508 cm³, 7.0 mmol) at room temperature. After stirring 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 7 (152.6 mg, 0.28 mmol) and the above Fmoc-MeAla-Cl in 1,2-dichloroethane (2.8 cm³) was added i-Pr₂NET (0.244 cm³, 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 NH₄Cl. The whole mixture was extracted with CH₂Cl₂ and the extract was washed with brine, and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was filtered 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 cm³) was added Et₂NH (2.3 cm³) 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 33 (94.9 mg, 54%) as a yellow oil; [α]D²⁰ = −55.4 (c 0.79, CHCl₃); IR (neat) νmax/cm⁻¹: 1712 (C=O); ¹H NMR (500 MHz, CD₃CN) δ: 0.81–0.84 (6H, m), 0.86 (3H, t, J 7.2), 0.99 (3H, d, J 6.9), 1.02–1.08 (1H, m), 1.09–1.14 (1H, m), 1.16 (3H, d, J 7.1), 1.23–1.34 (3H, m), 1.39–1.47 (1H, m), 1.69–1.77 (4H, m), 1.95 (3H, s), 2.02–2.08 (1H, m), 2.13–2.17 (1H, m), 2.19–2.27 (4H, m), 2.32–2.36 (1H, m), 3.13 (1H, q, J 7.1), 3.63 (1H, dt, J 10.3, J 2.6), 4.44 (1H, d, J 11.5), 4.55 (1H, d, J 11.5), 4.79 (1H, dd, J 10.3, J 2.3), 5.05 (1H, d, J 3.4), 5.30 (1H, d, J 16.6), 5.42 (1H, d, J 16.6), 6.78–6.81 (1H, m), 7.46 (2H, t, J 8.0), 7.57–7.61 (1H, m), 7.85–7.87 (2H, m); ¹³C NMR (125 MHz, CD₃CN) 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, 78.1, 128.7 (2C), 129.0, 129.8 (2C), 134.9, 133.0, 142.4, 167.9, 170.5, 174.9, 193.2; HRMS (FAB) calcd for C₃₉H₄₆NaO₇S (M⁺): 636.3565; found: 636.3569.

Linear peptides (6a,b). To a stirred solution of 33 (59.5 mg, 0.094 mmol), peptide 9 (185.2 mg) and HOAt (38.4 mg, 0.28 mmol) in CH₃Cl₂ (3.1 cm³) 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 saturated aqueous NaHCO₃. The whole mixture was extracted with CH₂Cl₂ and the extract was washed with saturated aqueous NH₄Cl and dried over MgSO₄. 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 34 as a 1:1 diastereomixure, which was used without further purification. To a stirred solution of 34 in AcOH/EtOAc/H₂O (60:35:5, 4.3 cm³) was added Zn (92.2 mg, 1.4 mmol) at room temperature. After stirring for 8 h, the reaction mixture was filtered through Celite, and 1 N HCl was added to the filtrate. The whole mixture was extracted with EtoAc and the extract was washed with brine, and dried over MgSO₄. After the filtrate was concentrated under reduced pressure, 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 acid in MeCN (2.4 cm³) was added Et₃NH (0.80 cm³) 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% CH₃CN in 0.1% TFA solution) to give linear peptides 6a (29.6 mg, 30% from 33) and 6b (24.0 mg, 24% from 33) as a colorless powder.
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, 37.6, 37.8 (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, 168.8, 169.0, 170.0, 170.4, 171.2, 171.7, 172.2, 172.3, 172.5 (2C), 173.4, 174.0; HRMS (ESI) calec for C_{48}H_{80}N_{10}O_{13}S (MH^+): 934.5570; found: 934.5567.

6b: [α]_{D}^{23} = –23.5 (c 1.00, CHCl₃); IR (neat) ν_{max}/cm⁻¹: 1648 (C=O); 1H NMR (500 MHz, CD₃CN, 3:3:3:3:3:1 mixture of rotamers): δ: 0.74 (0.9H, d, J = 6.9), 0.78–0.89 (21.9H, m), 1.05 (1.2H, d, J = 6.9), 1.08–1.51 (11H, m), 1.75–1.90 (5H, m), 1.97–2.07 (1H, m), 2.05–0.26 (2.7H, m), 2.09 (0.3H, s), 2.19–2.45 (3H, m), 2.72 (0.3H, s), 2.81–2.86 (4.8H, m), 2.89–2.91 (2H, m), 2.93 (0.3H, s), 2.95 (0.3H, s), 3.00–3.09 (1.8H, m), 3.12–3.18 (1.5H, m), 3.43 (0.1H, d, J = 16.1), 3.55–3.56 (0.1H, m), 3.61–3.76 (1.6H, m), 4.09–4.16 (0.6H, m), 4.25–4.36 (1.3H, m), 4.45–4.48 (0.4H, m), 4.52–4.64 (1.9H, m), 4.70–4.73 (0.3H, m), 4.79–5.00 (3H, m), 5.08–5.12 (0.7H, m), 5.26 (0.3H, dd, J = 9.3, J = 6.0), 5.33 (0.3H, dd, J = 11.1, J = 4.4), 5.46 (0.3H, dd, J = 11.1, J = 4.8), 5.52 (0.1H, dd, J = 9.5, J = 6.4), 6.84–6.91 (1H, m), 6.97 (0.3H, d, J = 9.2), 7.07–7.26 (5H, m), 7.42 (0.3H, d, J = 7.3), 7.69 (0.4H, d, J = 6.7), 8.11 (2H, br s); 13C NMR (125 MHz, CD₃CN): 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 (3C), 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), 132.9 (2C), 129.3, 130.2 (2C), 130.3 (2C), 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, 173.3, 174.4, 174.7; HRMS (ESI) calec for C_{48}H_{80}N_{10}O_{13}S (MH^+): 934.5570; found: 934.5580.

**Odoamide (5a).** To a stirred solution of 6a (17.8 mg, 0.017 mmol), HOAc (11.6 mg, 0.085 mmol) and collidine (0.067 cm³, 0.51 mmol) in DMF (17.0 cm³) was added HATU (0.067 mmol), HOAt (11.6 mg, 0.085 mmol) and collidine (0.017 mmol), 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 average of inhibition rates in each condition was evaluated to determine IC₅₀ values using the GraphPad Prism software.

**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% CO₂ incubator. Growth inhibition assays using A549 cells were performed in 96-well plates (BD Falcon). A549 cells were seeded at 500 cells per well in 0.050 cm³ 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 0.040 cm³ of the culture medium to the cell cultures, 0.030 cm³ 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 0.100 cm³ of the medium, the cell culture in each well was supplemented with 0.020 cm³ 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 average of inhibition rates in each condition was evaluated to determine IC₅₀ values using the GraphPad Prism software.

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References

1 For reviews, see: (a) Y. Hamada and T. Shioiri, Chem. Rev., 2005, 105, 4441–4482; (b) S. Sivanathan and J. Scherkenbeck, Molecules, 2014, 19, 12368–12420.

2 For reviews, see: (a) J. Chatterjee, C. Gilon, A. Hoffman and H. Kessler, Angew. Chem., Int. Ed., 2013, 52, 254–269.

3 (a) W. Huang, R. G. Ren, H. Q. Dong, B. G. Wei and G. Q. Lin, J. Org. Chem., 2013, 78, 10747–10762; (b) J. Tulla-Puche, S. Auriemma, C. Falciani and F. Albericio, J. Med. Chem., 2013, 56, 5587–5600; (c) M. Pelay-Gimeno, A. Meli, J. Tulla-Puche and F. Albericio, J. Med. Chem., 2013, 56, 9780–9788; (d) R. Nabika, S. Oishi, R. Misu, H. Ohno and N. Fujii, Bioorg. Med. Chem., 2014, 22, 6156–6162; (e) W. He, H.-B. Qui, Y.-J. Chen, J. Xi and Z.-J. Yao, Tetrahedron Lett., 2014, 55, 6109–6112; (f) R. Nabika, T. L. Suyama, A. M. Hau, R. Misu, H. Ohno, J. E. Ishmael, K. L. McPhail, S. Oishi and N. Fujii, Bioorg. Med. Chem. Lett., 2015, 25, 302–306; (g) G. Yao, Z. Fan, C. Wu, W. Wang, L. Fang and W. Su, J. Am. Chem. Soc., 2015, 137, 13488–13491.

4 (a) K. Suenaga, T. Mutou, T. Shibata, T. Itoh, H. Kigoshi and K. Yamada, Tetrahedron Lett., 1996, 37, 6771–6774; (b) K. Suenaga, T. Mutou, T. Shibata, T. Itoh, T. Fujita, N. Takada, K. Hayamizu, M. Takagi, T. Irihune, H. Kigoshi and K. Yamada, Tetrahedron, 2004, 60, 8509–8527.

5 B. Han, H. Gross, D. E. Goeger, S. L. Mooberri and W. H. Gerwick, J. Nat. Prod., 2006, 69, 572–575.

6 Y. Nakao, W. Y. Yoshida, Y. Takada, J. Kimura, L. Yang, S. L. Mooberri and P. J. Scheuer, J. Nat. Prod., 2004, 67, 1332–1340.

7 A. Tripathi, J. Puddick, M. R. Prinsep, M. Rottmann and L. T. Tan, J. Nat. Prod., 2010, 73, 1810–1814.

8 A. Tripathi, J. Puddick, M. R. Prinsep, M. Rottmann, K. P. Chan, D. Y. Chen and L. T. Tan, Phytochemistry, 2011, 72, 2369–2375.

9 P. G. Williams, W. Y. Yoshida, M. K. Quon, R. E. Moore and V. J. Paul, J. Nat. Prod., 2003, 66, 1545–1549.

10 P. Marfey, Carlsberg Res. Commun., 1984, 49, 591–596.

11 (a) T. Mutou, K. Suenaga, T. Fujita, T. Itoh, N. Takada, K. Hayamizu, H. Kigoshi and K. Yamada, Synlett, 1997, 199–201; (b) Y. Takada, E. Mori, M. Umehara, Y. Nakao and J. Kimura, Tetrahedron Lett., 2007, 48, 7653–7656; (c) Y. Takada, M. Umehara, Y. Nakao and J. Kimura, Tetrahedron Lett., 2008, 49, 1163–1165; (d) L. Dai, B. Chen, H. Lei, Z. Wang, Y. Liu, Z. Xu and T. Ye, Chem. Commun., 2012, 48, 8697–8699.

12 The isolation and structural assignment of odoamide were reported in our previous article, see: K. Sueyoshi, M. Kaneda, S. Sumimoto, S. Oishi, N. Fujii, K. Suenaga and T. Teruya, Tetrahedron, 2016, 72, 5472–5478.

13 I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, J. Am. Chem. Soc., 1991, 113, 4092–4096.

14 E. Marcucci, J. Tulla-Puche and F. Albericio, Org. Lett., 2012, 14, 612–615.

15 (a) G. C. Stelakatos, A. Paganou and L. Zervas, J. Chem. Soc. C, 1966, 1191–1199; (b) T. Takahashi, H. Nagamiya, T. Doi, P. G. Griffiths and A. M. Bray, J. Comb. Chem., 2003, 5, 414–428.

16 T. Kawabata, Y. Kimura, Y. Ito, S. Terashima, A. Sasaki and M. Sunagawa, Tetrahedron, 1988, 44, 2149–2165.

17 (a) D. A. Evans, J. Bartroli and T. L. Shih, J. Am. Chem. Soc., 1981, 103, 2127–2129; (b) D. A. Evans, J. V. Nelson, E. Vogel and T. R. Taber, J. Am. Chem. Soc., 1981, 103, 3099–3111.

18 Alcohol 20e was synthesised from ent-13 according to a similar process in a previous report, see: A. Zampella, M. Sorgente and M. V. D’Auria, Tetrahedron: Asymmetry, 2002, 13, 681–685.

19 (a) T. Mukaiyama, K. Banno and K. Narasaka, J. Am. Chem. Soc., 1974, 96, 7503–7509; (b) D. A. Evans, M. J. Dart, J. L. Duffy and M. G. Yang, J. Am. Chem. Soc., 1996, 118, 4322–4343.

20 (a) D. W. Cameron, M. G. Looney and J. A. Pattermann, Tetrahedron Lett., 1995, 36, 7555–7558; (b) G. T. Kim, M. Wenz, J. I. Park, J. Hasserodt and K. D. Janda, Bioorg. Med. Chem., 2002, 10, 1249–1262.

21 Two hydroxyl group configurations in 12c and 12d were determined by the NMR analysis of the corresponding acetonides.

22 (5S)-Hydroxy ester 26a is the substrate for the synthesis of (5S)-hydroxy ester 12a (see the ESIF).12

23 S. D. Rychkovsky, B. Rogers and G. Yang, J. Org. Chem., 1993, 58, 3511–3515.

24 P. M. Pojer and S. J. Angyal, Aust. J. Chem., 1978, 31, 1031–1040.

25 (a) I. Shiina, R. Ibuka and M. Kubota, Chem. Lett., 2002, 31, 286–287; (b) I. Shiina, M. Kubota, H. Oshiumi and M. Hashizume, J. Org. Chem., 2004, 69, 1822–1830.

26 L. A. Carpino, B. J. Cohen, K. E. Stephens, Jr., S. Y. Sadat-Aalaei, J. H. Tien and D. C. Langridge, J. Org. Chem., 1986, 51, 3732–3734.

27 Among several conditions investigated for coupling of peptide 9, EDCI–HOAt provided the desired compound 6a in higher chemical yield; however, significant epimerization at the C-terminal L-Ile occurred.

28 J. D. White and M. Kawasaki, J. Org. Chem., 1992, 57, 5292–5300.