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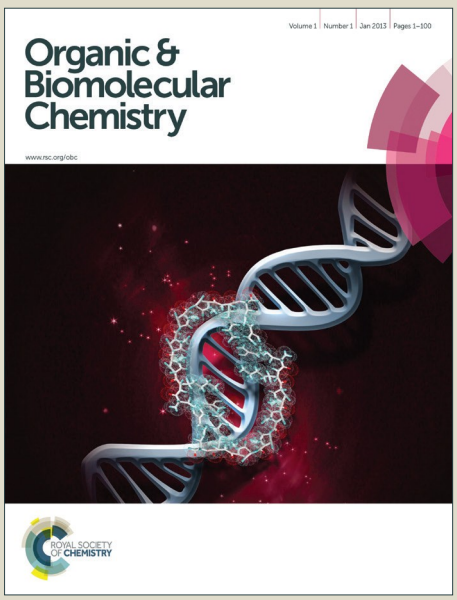

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Total synthesis of odoamide, a novel cyclic depsipeptide from an Okinawan marine cyanobacterium

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DOI: 10.1039/C6OB01583B

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Abstract

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 an 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.

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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 possess highly potent antiproliferative activity against cancer cell lines (Figure 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 exhibits two conformers of the 26-membered macrocycle in dichloromethane.[6] Lagunamide A (**3a**) and B (**3b**) from *Lyngbya majuscula* has antimalarial activity against *Plasmodium falciparum* at submicromolar concentrations.[7] Lagunamide C (**3c**)[8] and palau'amide (**4**)[9] exhibit comparable cytotoxicity at nanomolar concentrations 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. (Figure 2A), which shows highly potent cytotoxic activity against HeLa S_3 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 an 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

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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,3f,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 D-*allo*-isoleucic acid residues of 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. The alcohol **7** could be synthesised by coupling of D-*allo*-isoleucic acid ester **11**[15] with a 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 in odoamide **5**. The polyketide substructure in lagunamide A (**3a**), a closely related structural analogue of **5**, has 5*S*,7*R*-dihydroxy and 6*S*,8*S*-dimethyl groups. Additionally, the aurilide-class depsipeptides **1a-c**, **2**, and **3a,b** possess the *syn*-1,3-diol moiety with a 5*S*-hydroxy configuration. On the basis of the structures of these related molecules, we expected that the plausible stereochemical configuration of the natural odoamide **5** 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 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 esters **12a-d** as polyketide substructure substrates (Figure 2B).

The methyl esters **12a,b** were synthesised from the (*S*)-Roche ester **13** according to a similar process in previous reports by us and others (see supplementary information).[11a,12] Preparation of (5*S*,6*R*,7*R*,8*S*)-ester **12c** and (5*S*,6*R*,7*R*,8*R*)-ester **12d** started from the commercially available (*R*)-

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Roche ester *ent*-**13** in a similar manner (Scheme 2). (*R*)-Roche ester *ent*-**13** was converted to alcohol *ent*-**15** via benzyl protection[16] and $LiAlH_4$-mediated reduction. After Swern oxidation, a *n*-Bu_2BOTf-mediated Evans aldol reaction[17] 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 $LiBH_4$ gave alcohols **20c**[18] and **21d**. Swern oxidation of **20c** and the subsequent Wittig reaction of the resulting aldehyde with ethylidene-triphenylphosphorane provided olefin **22c** as an *E*/*Z* isomeric mixture. Hydrogenation of **22c** in the presence of Pd/C afforded the key alcohol **23c** with a *threo*/*threo*-configuration. Separately, tosylation of **21d** followed by $LiAlH_4$-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[19] with 1-methoxy-2-methyl-1-trimethylsiloxy-1,3-butadiene (**25**)[20] produced methyl ester **12c** with a (5*S*)-hydroxy group (dr >99:1).[21] The ester **12d** was obtained from **23d** by the identical protocol.

The stereochemistry of 5-hydroxy group in alcohol **12a** was confirmed by the NMR analysis of the corresponding acetonide (Scheme 3). TBS deprotection of **26a**[22] 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 ^{13}C NMR chemical shifts of the ketal methyl groups in *syn*- and *anti*-1,3-diol acetonides are different.[23] 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 the 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.[12] Manipulations of esters **12a-d** including DIBAL-mediated reductive

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transformation provided the corresponding triol derivatives. The comparative NMR analysis between natural product-derived triol and synthetic triols demonstrated that the polyketide substructure had the 5*S*,6*S*,7*R*,8*S* configuration (see supplementary information).[12]

Synthesis of odoamide and its biological evaluation

After the determination of the stereochemistry of the polyketide part,[12] we attempted the total synthesis of odoamide using the (5*S*,6*S*,7*R*,8*S*)-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 D-*allo*-isoleucic acid phenacyl ester (**11**) with 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 **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 Et_2NH gave amine **33** in 54% yield (two steps) without epimerisation. The tetrapeptide **9** was conjugated with **33** using EDCI-HOAt to afford **34** as a 1.4:1 epimeric mixture at the α-position of Ile.[27] After removal of the phenacyl (with Zn and AcOH) and Fmoc groups (with Et_2NH), the epimer mixture of the linear peptides was separated into the desired **6a** (major, L-Ile) and undesired **6b** (minor, D-*allo*-Ile) by HPLC purification. Cyclisation of **6a** and **6b** with HATU followed by deprotection of the MTM group with $AgNO_3$ 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 epimarisation. The configurations of L-Ile and D-*allo*-Ile in peptides **5a** and **5b**, respectively, were determined by Marfey 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 (Figures 3 and 4). The NMR spectra of the synthetic odoamide **5a** were identical with those of the natural product **5**, suggesting the chemical structure of odoamide was the same as **5a**. The cytotoxicity of synthetic **5a** and **5b** against A549 cells was also evaluated by the MTS assay. Peptide **5a** showed highly potent

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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 with those of the natural odoamide **5**. Accordingly, the full structural assignment and first total synthesis of odoamide were achieved.

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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_4Si (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 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. 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 **5a,b** using solvents without TFA) in H_2O at a flow rate of 1 cm^3 min^{-1}, 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 cm^3 min^{-1}. The purity of the peptides **5a,b** were determined by HPLC analysis (>95%). The synthetic procedures for esters **12a,b** were described in our previous report.[12]

Methyl (*R*)-3-benzyloxy-2-methylpropanoate (*ent*-14). To a stirred solution of *ent*-**13** (9.9 g, 83.8 mmol) in CH_2Cl_2 (210 cm^3) under argon were added benzyl 2,2,2-trichloroacetimidate (17.1 cm^3, 92.2 mmol) in cyclohexane (420 cm^3) and triflic acid (3.0 cm^3, 33.5 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 *ent*-**14** (14.8 g, 85%) as a colorless oil. The spectral data were in good agreement with those previously reported.[28]

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(*S*)-3-Benzyloxy-2-methylpropan-1-ol (*ent*-15). To a stirred suspension of $LiAlH_4$ (4.0 g, 105.9 mmol) in THF (175 cm^3) under argon was added dropwise a solution of *ent*-**14** (14.7 g, 70.6 mmol) in THF (175 cm^3) at 0 °C. After stirring 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 *ent*-**15** (10.3 g, 81%) as a colorless oil. The spectral data were in good agreement with those previously reported.[28]

(*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*)-5-benzyloxy-3-hydroxy-2,4-dimethylpentanoyl]oxazolidin-2-one (16c). To a stirred solution of oxalyl chloride (0.32 cm^3, 3.72 mmol) in CH_2Cl_2 (7.4 cm^3) under argon was added DMSO (0.53 cm^3, 7.44 mmol) in CH_2Cl_2 (1.2 cm^3) at –78 °C. After stirring for 30 min, a solution of *ent*-**15** (334.7 mg, 1.86 mmol) in CH_2Cl_2 (6.4 cm^3) was added dropwise and stirred at –78 °C for 1 h. *i*-Pr_2NEt (1.62 cm^3, 9.3 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-propionyloxazolidin-2-one (429.2 mg, 1.84 mmol) in CH_2Cl_2 (9.2 cm^3) under argon were added *n*-Bu_2BOTf (1.0 M in CH_2Cl_2; 2.0 cm^3, 2.00 mmol) and *i*-Pr_2NEt (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_2Cl_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_2O_2 in MeOH (1:2, 4.2 cm^3) 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

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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: $[\alpha]^{29}_{D}$ –43.2 (*c* 0.72, $CHCl_3$); IR (neat) ν_{max}/cm^{-1}: 3504 (OH), 1779 (C=O); ^1H 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_1 13.2, J_2 9.7), 3.00 (1H, d, *J* 2.9), 3.25 (1H, dd, J_1 13.2, J_2 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 $C_{24}H_{29}NNaO_5$ (MNa^+): 434.1938; found: 434.1938.

(*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*)-5-benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentano-yl]oxazolidin-2-one (18c). To a stirred solution of **16c** (14.1 g, 34.3 mmol) in CH_2Cl_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 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 **18c** (16.0 g, 89%) as a colorless oil: $[\alpha]^{27}_{D}$ –38.2 (*c* 1.21, $CHCl_3$); IR (neat) ν_{max}/cm^{-1}: 1780 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.04 (3H, s), 0.06 (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_1 13.2, J_2 9.7), 3.24 (1H, dd, J_1 13.2, J_2 3.2), 3.28 (1H, dd, J_1 8.9, J_2 7.2), 3.49 (1H, dd, J_1 8.9, J_2 6.6), 3.96-4.02 (1H, m), 4.08-4.16 (3H, m), 4.46-4.52 (2H, m), 4.59-4.64 (1H, m), 7.20-7.34 (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), 129.4 (2C), 135.3, 138.6, 152.8, 175.9; HRMS (ESI) calcd for $C_{30}H_{43}NNaO_5Si$ (MNa^+): 548.2803; found: 548.2808.

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(2*S*,3*R*,4*R*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentan-1-ol (20c). To a stirred solution of **18c** (22.4 g, 42.5 mmol) in THF (213 cm^3) and MeOH (5.2 cm^3, 127.6 mmol) under argon was added $LiBH_4$ (2.78 g, 127.6 mmol) at 0 °C. After stirring 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 **20c** (10.3 g, 69%) as a colorless oil: $[\alpha]^{29}_D$ –0.41 (*c* 1.23, $CHCl_3$); IR (neat) ν_{max}/cm^{-1}: 3422 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.03 (3H, s), 0.08 (3H, s), 0.85 (3H, d, *J* 7.4), 0.89 (9H, s), 0.96 (3H, d, *J* 6.9), 1.93-1.98 (1H, m), 1.99-2.05 (1H, m), 2.32 (1H, br s), 3.26 (1H, dd, J_1 9.2, J_2 6.3), 3.39 (1H, dd, J_1 9.2, J_2 7.2), 3.47-3.51 (1H, m), 3.64-3.68 (1H, m), 3.88-3.89 (1H, m), 4.46-4.51 (2H, m), 7.26-7.36 (5H, m); ^{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) calcd for $C_{20}H_{36}NaO_3Si$ (MNa^+): 375.2326; found: 375.2324.

(4*S*,5*R*,6*R*)-7-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-4,6-dimethylhept-2-ene (22c). To a stirred solution of oxalyl chloride (0.11 cm^3, 1.30 mmol) in CH_2Cl_2 (6.5 cm^3) under argon was added DMSO (0.18 cm^3, 2.60 mmol) in CH_2Cl_2 (0.43 cm^3) at –78 °C. After stirring for 30 min, a solution of **20c** (228.9 mg, 0.65 mmol) in CH_2Cl_2 (2.2 cm^3) was added dropwise and stirred at –78 °C for 1.5 h. *i*-Pr_2NEt (0.57 cm^3, 3.25 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, 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 suspension of ethyltriphenylphosphonium bromide (508.6 mg, 1.37 mmol) in THF (5.5 cm^3) under argon was added *n*-BuLi (1.6 mol dm^{-3} in hexane; 0.81 cm^3, 1.30 mmol) at room temperature.

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After stirring for 30 min, a solution of the above aldehyde in THF (1.3 cm^3) 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, 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 (9:1). Further purification by flash chromatography over silica gel with hexane–$CHCl_3$ (8:1) gave compound **22c** 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 (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 (1.2H, s), 0.90 (7.8H, s), 0.94-0.97 (3H, m), 1.61 (2.6H, dd, J_1 6.9, J_2 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, J_1 8.9, J_2 6.9), 3.40 (1H, dd, J_1 8.9, J_2 7.7), 3.56 (1H, dd, J_1 8.0, J_2 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); ^{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) calcd for $C_{22}H_{38}NaO_2Si$ (MNa^+): 385.2533; found: 385.2534.

(2*R*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylheptan-1-ol (23c). To a stirred solution of **22c** (1.3 g, 3.7 mmol) in EtOH (37.0 cm^3) was added 10% Pd/C (787.5 mg, 0.7 mmol) at room temperature and the mixture was flushed with H_2 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: $[\alpha]^{28}_D$ –12.7 (*c* 1.13, $CHCl_3$); IR (neat) ν_{max}/cm^{-1}: 3328 (OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.06 (3H, s), 0.08 (3H, s), 0.85 (3H, d, *J* 6.9), 0.88-0.92 (15H, m), 1.09-1.16 (1H, m), 1.19-1.28 (1H, m), 1.31-1.41 (2H, m), 1.60-1.66 (1H, m), 1.90-1.97 (1H, m), 2.07 (1H, dd, J_1 6.0, J_2 4.3), 3.45-3.50 (1H, m), 3.62-3.67 (2H, m); ^{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) calcd for $C_{15}H_{34}NaO_2Si$ (MNa^+): 297.2220; found: 297.2221.

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Methyl (5*S*,6*R*,7*R*,8*S*,*E*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundecen-2-oate (12c). To a stirred solution of *i*-Pr_2NH (0.16 cm^3, 1.16 mmol) in THF (2.4 cm^3) under argon was added *n*-BuLi (2.6 mol dm^{-3} in hexane; 0.45 cm^3, 1.16 mmol) at 0 °C. After 20 min, methyl tiglate (0.13 cm^3, 1.05 mmol) and TMSCl (0.20 cm^3, 1.58 mmol) in THF (0.36 cm^3) 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 $NaHCO_3$ were added to the reaction mixture. The whole was extracted with pentane and the extract was washed with brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give compound **25**, which was used without further purification.[20] To a stirred solution of oxalyl chloride (0.060 cm^3, 0.70 mmol) in CH_2Cl_2 (3.5 cm^3) under argon was added DMSO (0.099 cm^3, 1.40 mmol) in CH_2Cl_2 (0.23 cm^3) at –78 °C. After stirring for 30 min, a solution of **23c** (96.4 mg, 0.35 mmol) in CH_2Cl_2 (1.2 cm^3) was added dropwise and stirred at –78 °C for 1.5 h. *i*-Pr_2NEt (0.49 cm^3, 2.8 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, 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 the above aldehyde in CH_2Cl_2 (2.7 cm^3) and Et_2O (0.27 cm^3) under argon were added diene **25** and $BF_3{\cdot}OEt_2$ (0.065 cm^3, 0.53 mmol) at –78 °C. After stirring for 2 h, a mixture of THF/H_2O/1N HCl (5:1:0.4 v/v, 1.8 cm^3) 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 **12c** (73.4 mg, 54%) as a colorless oil: $[\alpha]^{26}_D$ –22.4 (*c* 1.01, $CHCl_3$); IR (neat) ν_{max}/cm^{-1}: 3523 (OH), 1716 (C=O); ^1H NMR (500 MHz, $CDCl_3$) 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,

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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); ^{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) calcd for $C_{21}H_{42}NaO_4Si$ (MNa^+): 409.2745; found: 409.2748.

(2*R*,3*R*,4*R*)-1-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylheptane (24d). To a stirred solution of **21d** (7.3 g, 19.1 mmol) in CH_2Cl_2 (191 cm^3) under argon were added Et_3N (5.3 cm^3, 38.2 mmol), TsCl (5.5 g, 28.7 mmol) and Me_3N·HCl (1.8 g, 19.1 mmol) at room temperature. After stirring 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, and 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 $LiAlH_4$ (2.2 g, 57.3 mmol) in THF (100 cm^3) under argon was added dropwise a solution of the above tosylate in THF (91 cm^3) at 0 °C. After stirring 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 **24d** (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 (3H, s), 0.03 (3H, s), 0.86-0.89 (18H, m), 1.00-1.05 (1H, m), 1.18-1.26 (1H, m), 1.36-1.42 (2H, m), 1.56-1.60 (1H, m), 1.95-2.00 (1H, m), 3.22 (1H, dd, J_1 8.6, J_2 6.6), 3.37 (1H, dd, J_1 8.6, J_2 7.4), 3.62 (1H, dd, J_1 5.7, J_1 2.3), 4.45-4.52 (2H, m), 7.27-7.34 (5H, m); ^{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) calcd for $C_{22}H_{40}NaO_2Si$ (MNa^+): 387.2690; found: 387.2691.

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Methyl (5*S*,6*S*,7*R*,8*S*,*E*)-7-(*tert*-butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)-undec-2-enoate (31). To a stirred solution of **12a** (2.3 g, 6.0 mmol) in DMSO (42.9 cm^3) under argon were added Ac_2O (30.5 cm^3) and AcOH (5.5 cm^3) at room temperature. After stirring 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, 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 (30:1) to give compound **31** (1.6 g, 59%) as a colorless oil: $[\alpha]^{27}_D$ –75.4 (*c* 0.72, $CHCl_3$); IR (neat) ν_{max}/cm^{-1}: 1716 (C=O); ^1H NMR (500 MHz, $CDCl_3$) 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_1 6.9, J_2 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); ^{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) calcd for $C_{23}H_{46}NaO_4SSi$ (MNa^+): 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 (32). To a stirred solution of **31** (1.14 g, 2.6 mmol) in MeOH (17 cm^3) and THF (17 cm^3) was added 1N LiOH (17 cm^3) 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 **10**, which was used without further purification. To a stirred solution of the acid **10** in CH_2Cl_2 (12.8 cm^3) were added MNBA (1.32 g, 3.8 mmol), 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 1N HCl. The whole was extracted with CH_2Cl_2 and the extract was washed with

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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 compound **32** (1.48 g, 87%) as a colorless oil: $[\alpha]^{26}_D$ –43.5 (*c* 0.89, $CHCl_3$); IR (neat) ν_{max}/cm^{-1}: 1710 (C=O); ^1H NMR (500 MHz, $CDCl_3$) 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), 1.89 (3H, s), 1.99-2.03 (1H, m), 2.11 (3H, s), 2.19-2.25 (1H, m), 2.34-2.37 (2H, m), 3.47 (1H, dd, J_1 7.4, J_2 2.9), 4.01-4.04 (1H, m), 4.52 (1H, d, *J* 11.5), 4.61 (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); ^{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) calcd for $C_{36}H_{60}NaO_7SSi$ (MNa^+): 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 (7). To a stirred solution of **32** (80.7 mg, 0.12 mmol) in THF (0.80 cm^3) and pyridine (0.20 cm^3) was added HF·pyridine (0.50 cm^3) 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 (6:1) to give compound **7** (49.2 mg, 74%) as a colorless oil: $[\alpha]^{25}_D$ –5.29 (*c* 1.08, $CHCl_3$); IR (neat) ν_{max}/cm^{-1}: 3526 (OH), 1708 (C=O); ^1H NMR (500 MHz, $CDCl_3$) 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*

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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); ^{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) calcd for $C_{30}H_{46}NaO_7S$ (MNa^+): 573.2856; found: 573.2855.

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(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 (33). Fmoc-MeAla-Cl was synthesised by the identical procedure reported previously.[26] To a stirred solution of Fmoc-MeAla-OH (227.7 mg, 0.70 mmol) in CH_2Cl_2 (3.9 cm^3) were added DMF (0.0054 cm^3, 0.070 mmol) and $SOCl_2$ (0.508 cm^3, 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 cm^3) was added (*i*-Pr)$_2$NEt (0.244 cm^3, 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, 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 (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 cm^3) was added Et_2NH (2.3 cm^3) 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: $[\alpha]^{27}_D$ –55.4 (*c* 0.79, $CHCl_3$); IR (neat) ν_{max}/cm^{-1}: 1712 (C=O); ^{1}H NMR (500 MHz, CD_3CN) δ: 0.78 (3H, t, *J* 7.2), 0.81-0.84 (6H, m), 0.86 (3H, t, *J* 7.4), 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_1 10.3, J_2 2.6), 4.44 (1H,

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d, *J* 11.5), 4.55 (1H, d, *J* 11.5), 4.79 (1H, dd, J_1 10.3, J_2 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); ^{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 $C_{34}H_{54}NO_8S$ (MH^+): 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 CH_2Cl_2 (3.1 cm^3) 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 **34** as a 1.4:1 diastereomixture, which was used without further purification. To a stirred solution of **34** in AcOH/EtOAc/H_2O (60:35:5, 4.3 cm^3) 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 1N HCl was added to the filtrate. The whole was extracted with EtOAc and the extract was washed with brine, dried over $MgSO_4$. 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 cm^3) was added Et_2NH (0.80 cm^3) 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 **6a** (29.6 mg, 30% from **33**) and **6b** (24.0 mg, 24% from **33**) both as a colorless powder.

6a: $[\alpha]^{27}_D$ –46.8 (*c* 0.89, $CHCl_3$); IR (neat) ν_{max}/cm^{-1}: 1645 (C=O); ^{1}H NMR (500 MHz, CD_3CN, 1:1 mixture of rotamers) δ: 0.77 (1.5H, d, *J* 7.0), 0.81-0.91 (18H, m), 0.96 (1.5H, d, *J* 3.1), 0.97 (1.5H, d, *J* 3.1), 1.06-1.22 (4.5H, m), 1.26-1.33 (3H, m), 1.37 (3H, d, *J* 7.3), 1.41-1.53 (2H, m), 1.74-1.84 (5H,

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m), 1.96-2.01 (1H, m), 2.07 (1.5H, s), 2.08 (1.5H, s), 2.20-2.38 (3H, m), 2.75-2.86 (4.5H, m), 3.00-3.12 (6.5H, m), 3.53 (0.5H, d, *J* 16.4), 3.70-3.71 (1H, m), 4.00 (0.5H, d, *J* 18.0), 4.05-4.09 (0.5H, m), 4.17 (0.5H, d, *J* 18.0), 4.24 (0.5H, d, *J* 16.4), 4.31-4.36 (0.5H, m), 4.48-4.50 (0.5H, m), 4.53 (0.5H, d, *J* 5.0), 4.55 (0.5H, d, *J* 5.0), 4.62 (0.5H, d, *J* 5.0), 4.64 (0.5H, d, *J* 5.0), 4.73-4.76 (0.5H, m), 4.87-4.89 (1H, m), 4.95 (0.5H, d, *J* 3.4), 4.96 (0.5H, d, *J* 3.4), 5.19 (0.5H, q, *J* 7.3), 5.24 (0.5H, q, *J* 7.3), 5.43-5.46 (0.5H, m), 5.63 (0.5H, dd, J_1 9.9, J_2 5.7), 6.82-6.89 (1H, m), 7.15-7.28 (6H, m), 7.64 (2H, br s); ^{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) calcd for $C_{48}H_{80}N_5O_{11}S$ (MH^+): 934.5570; found: 934.5567.

6b: $[\alpha]^{28}_D$ –23.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max}/cm^{-1}: 1648 (C=O); ^{1}H NMR (500 MHz, CD_3CN, 3:3:3:1 mixture of rotamers) δ: 0.74 (0.9H, d, *J* 6.9), 0.78-0.98 (21.9H, m), 1.05 (1.2H, d, *J* 6.9), 1.08-1.51 (11H, m), 1.75-1.90 (5H, m), 1.97-2.02 (1H, m), 2.05-2.06 (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_1 9.3, J_2 6.0), 5.33 (0.3H, dd, J_1 11.1, J_2 4.4), 5.46 (0.3H, dd, J_1 11.1, J_2 4.8), 5.52 (0.1H, dd, J_1 9.5, J_2 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); ^{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,

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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) calcd for $C_{48}H_{80}N_5O_{11}S$ (MH^+): 934.5570; found: 934.5580.

Odoamide (5a). To a stirred solution of **6a** (17.8 mg, 0.017 mmol), HOAt (11.6 mg, 0.085 mmol) and collidine (0.067 cm^3, 0.51 mmol) in DMF (17.0 cm^3) was added HATU (64.6 mg, 0.17 mmol) at room temperature. After stirring 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. To a stirred solution of the above cyclic peptide in THF/H_2O (4:1, 0.566 cm^3) were added 2,6-lutidine (0.0394 cm^3, 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 (**5a**) (12.4 mg, 85%) as a colorless powder: $[\alpha]^{28}_D$ –15.8 (*c* 1.14, CH_3OH); IR (neat) ν_{max}/cm^{-1}: 3305 (OH), 1645 (C=O); ^1H NMR (500 MHz, CD_3OD) δ: 0.83-0.96 (21H, m), 1.04-1.12 (4H, m), 1.19-1.26 (1H, m), 1.29-1.40 (4H, m), 1.42 (3H, d, *J* 6.9), 1.45-1.55 (1H, m), 1.57-1.67 (1H, m), 1.78-1.87 (3H, m), 1.90 (3H, s), 2.01-2.04 (1H, m), 2.12-2.16 (1H, m), 2.20-2.28 (1H, m), 2.85-2.95 (4H, m), 3.01-3.06 (4H, m), 3.30 (3H, s), 3.56 (1H, d, *J* 18.3), 3.74-3.76 (1H, m), 3.94 (1H, q, *J* 6.9), 4.19 (1H, d, *J* 18.3), 4.49 (1H, q, *J* 6.9), 4.86-4.89 (2H, m), 5.05

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(1H, d, *J* 6.3), 5.45 (1H, dd, J_1 10.3, J_2 5.2), 7.12-7.20 (5H, m), 7.31-7.32 (1H, m); ^{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) calcd for $C_{46}H_{73}N_5NaO_{10}$ (MNa^+): 878.5250; found: 878.5254.

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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^{-1} in 0.050 cm^3 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 cm^3 of the fresh culture medium to the cell cultures, 0.030 cm^3 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 cm^3 of the medium, the cell culture in each well was supplemented with 0.020 cm^3 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.

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Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research from JSPS, Japan (24659004 and 15J05499); Platform for Drug Discovery, Informatics, and Structural Life Science from MEXT, Japan; and Takeda Science Foundation. M.K. is grateful for JSPS Research Fellowships for Young

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

22. (5*R*)-Hydroxy ester **26a** is the substrate for the synthesis of (5*S*)-hydroxy ester **12a** (see supplementary information).[12]

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

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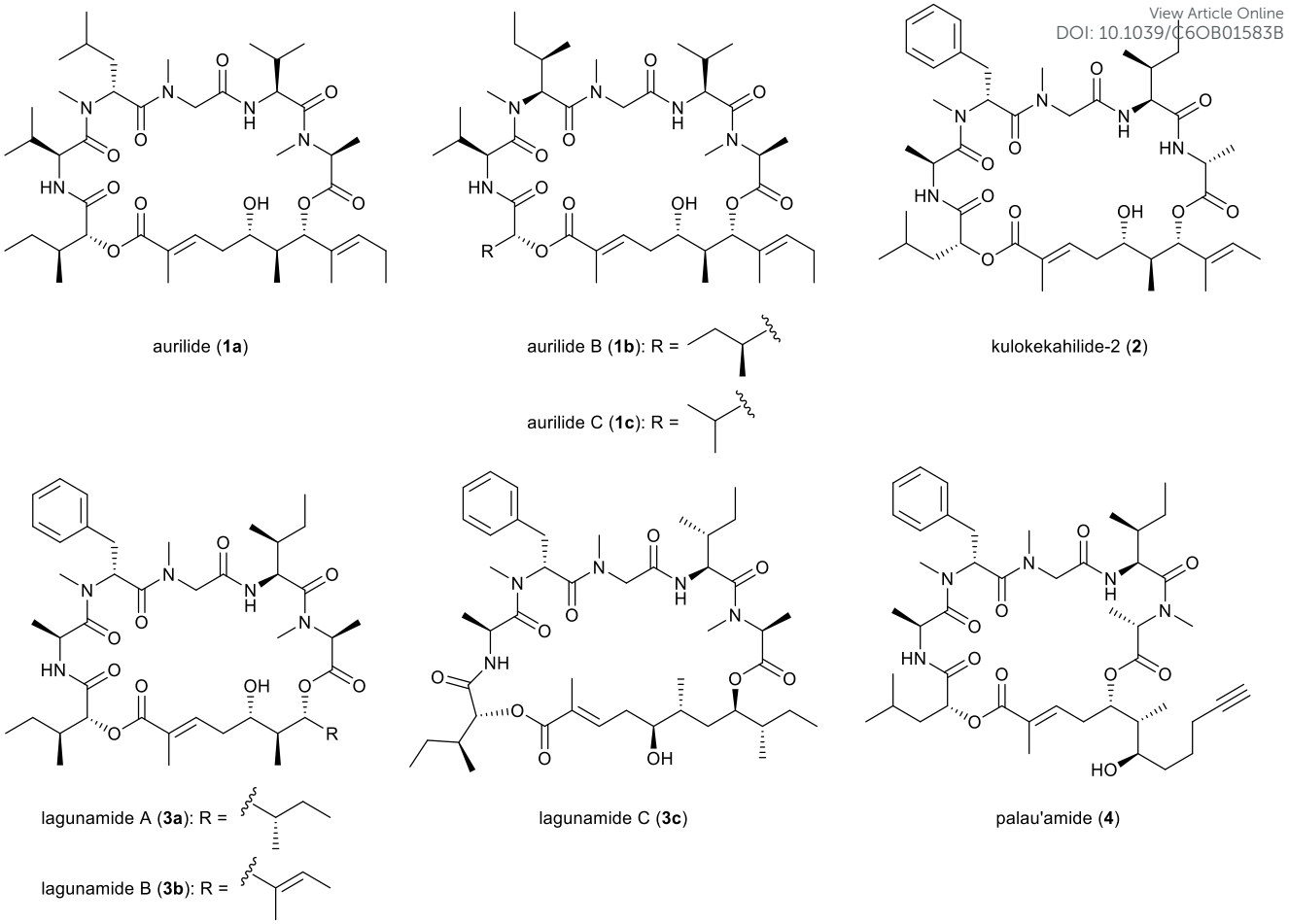

Figure 1. Structures of aurilide-class depsipeptides.

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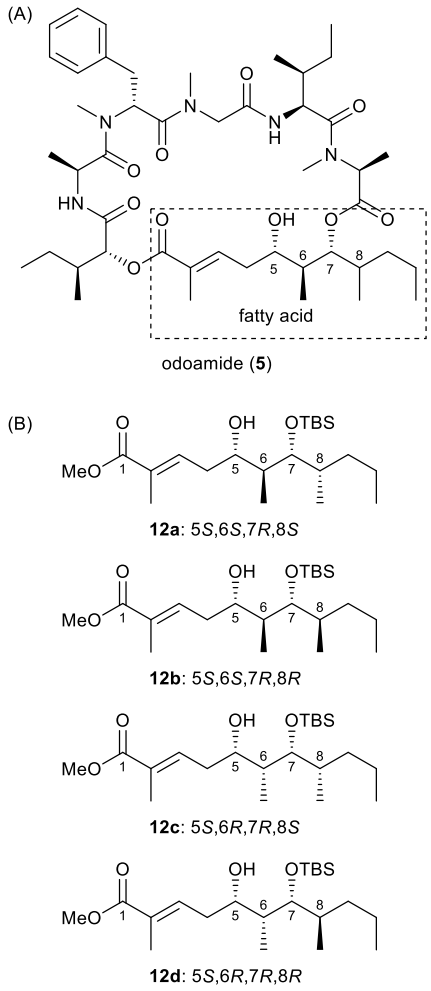

Figure 2. Structures of odoamide (**5**) (A) and the polyketide substructures in **5** (B).

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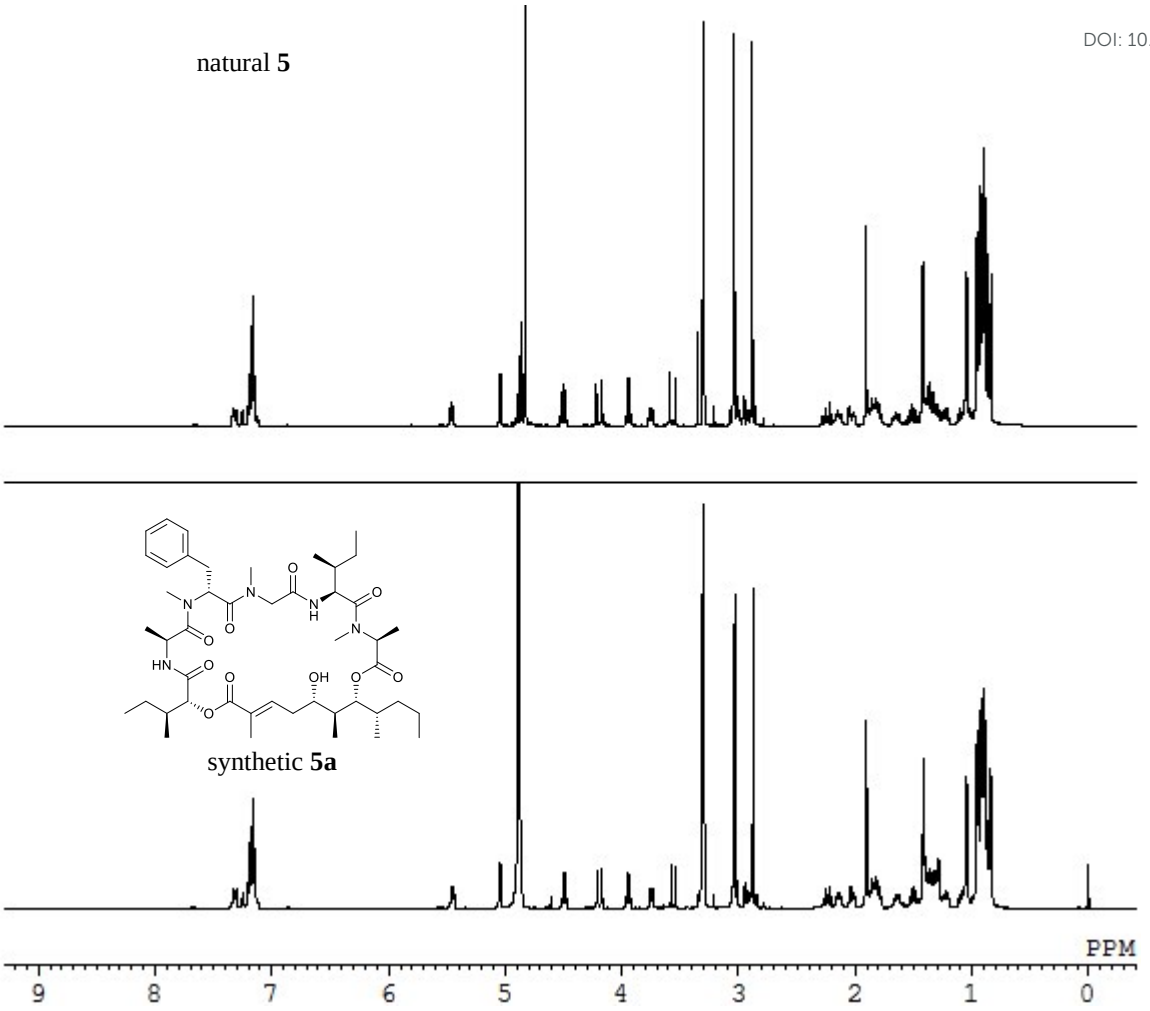

Figure 3. Comparison of the ^{1}H NMR spectra between the natural compound **5** and the synthetic **5a** (in CD_3OD).

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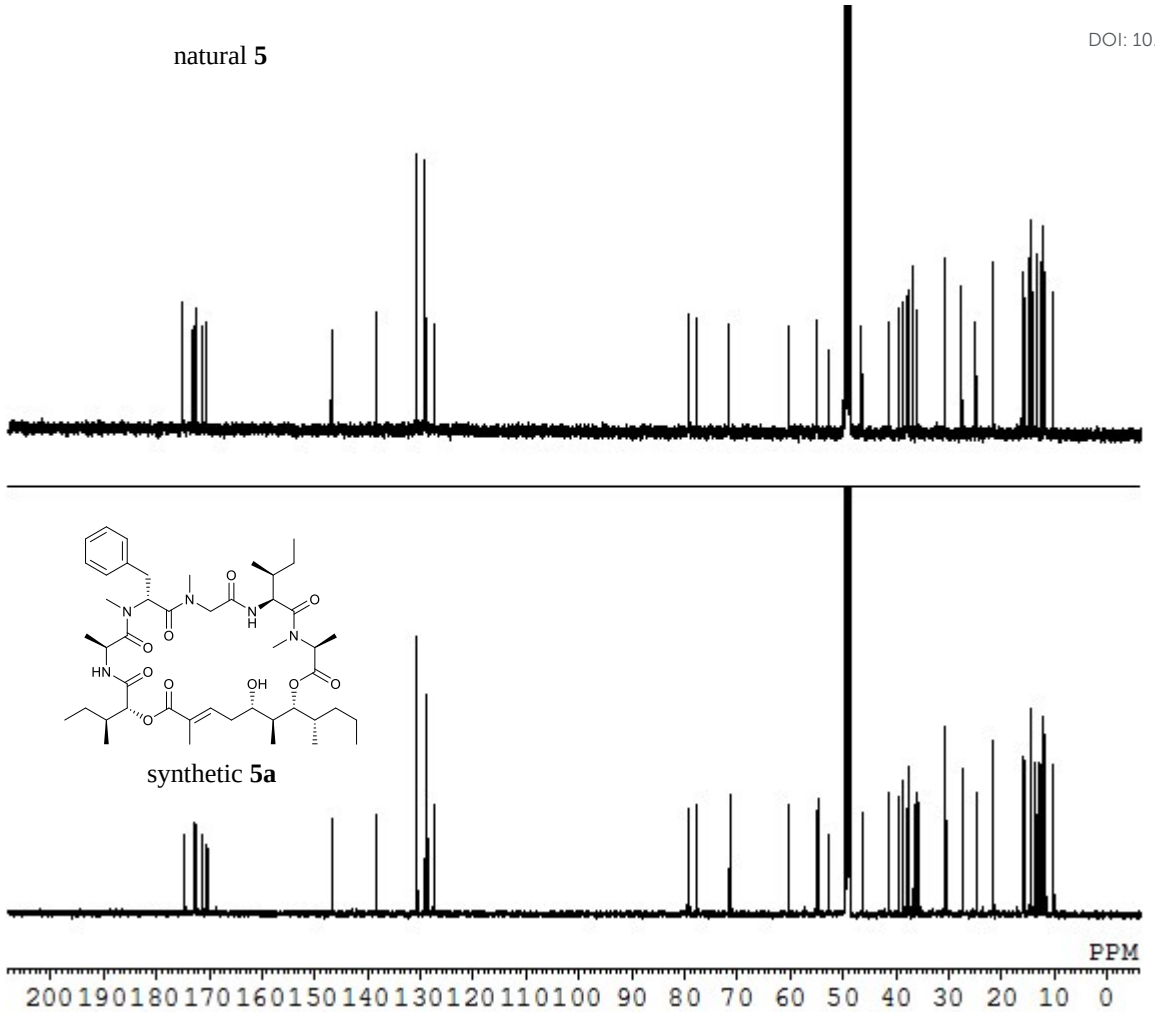

Figure 4. Comparison of the ^{13}C NMR spectra between the natural compound **5** and the synthetic **5a** (in CD_3OD).

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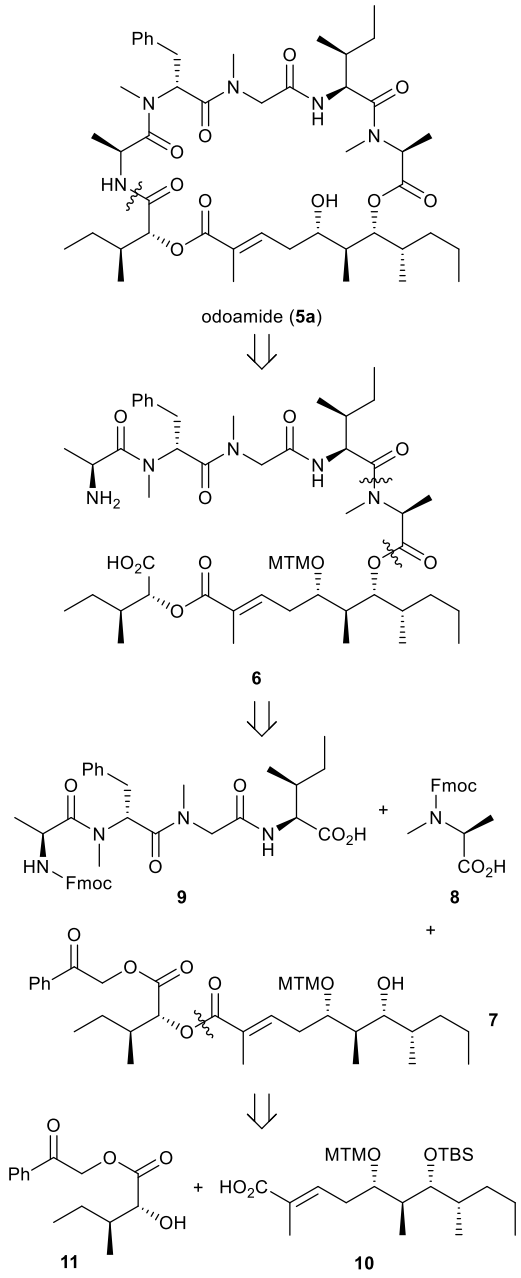

Scheme 1. Retrosynthetic analysis of odoamide (**5**).

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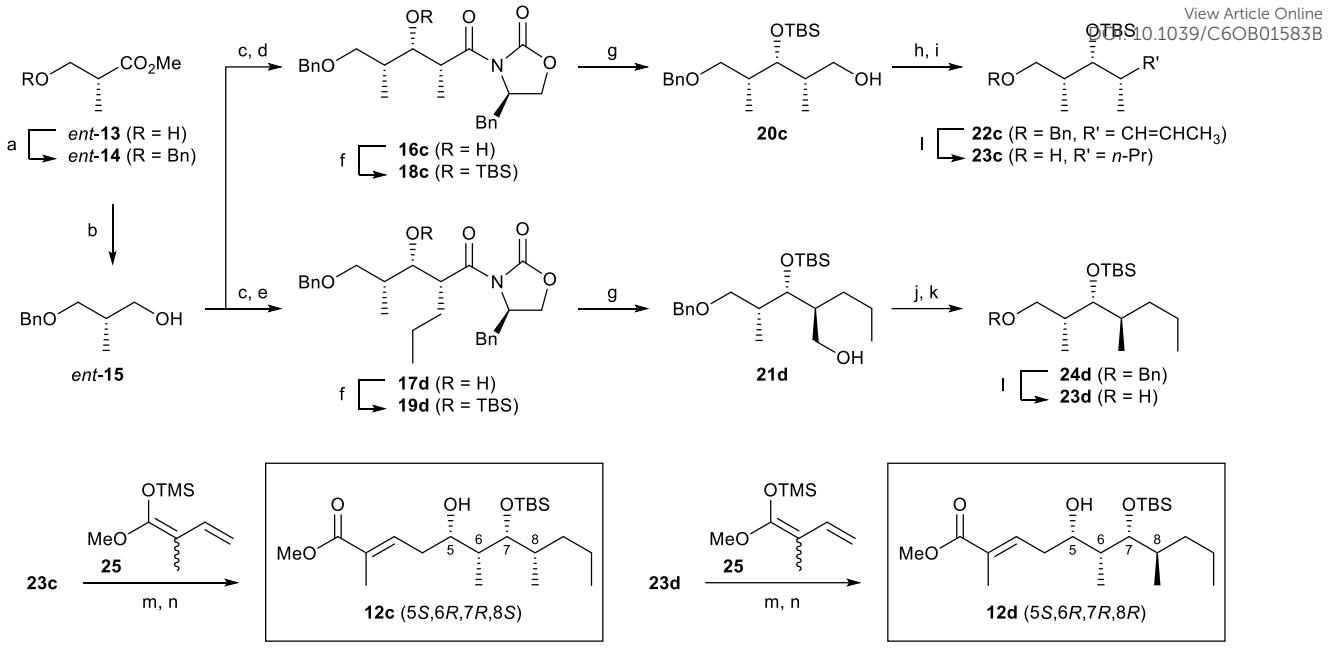

Scheme 2. Synthesis of esters **12c**,**d**. *Reagents and conditions*: (a) benzyl 2,2,2-trichloroacetimidate, TfOH, CH_2Cl_2, cyclohexane, 0 °C to rt, 85%; (b) $LiAlH_4$, THF, 0 °C, 81%; (c) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, –78 °C to 0 °C; (d) (*R*)-4-benzyl-3-propionyl-2-oxazolidinone, *n*-Bu_2BOTf, DIPEA, CH_2Cl_2, –78 °C to –10 °C, 80% (2 steps); (e) (*R*)-4-benzyl-3-pentanoyl-2-oxazolidinone, *n*-Bu_2BOTf, DIPEA, CH_2Cl_2, –78 °C to –10 °C, 72% (2 steps); (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 89% (**18c**) and 87% (**19d**); (g) $LiBH_4$, MeOH, THF, 0 °C to rt, 69% (**20c**) and 80% (**21d**); (h) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, –78 °C to 0 °C; (i) ethyltriphenylphosphonium bromide, *n*-BuLi, THF, rt, 69% (2 steps, *Z*/*E* = 7:1); (j) TsCl, Et_3N, $Me_3N{\cdot}HCl$, CH_2Cl_2, rt; (k) $LiAlH_4$, THF, 0 °C to rt, 70% (2 steps) (l) Pd/C, H_2, EtOH, rt, 92% (**23c**) and 85% (**23d**); (m) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, –78 °C to 0 °C; (n) **25**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, Et_2O, –78 °C, 54% (**12c**) and 69% (**12d**) (2 steps).

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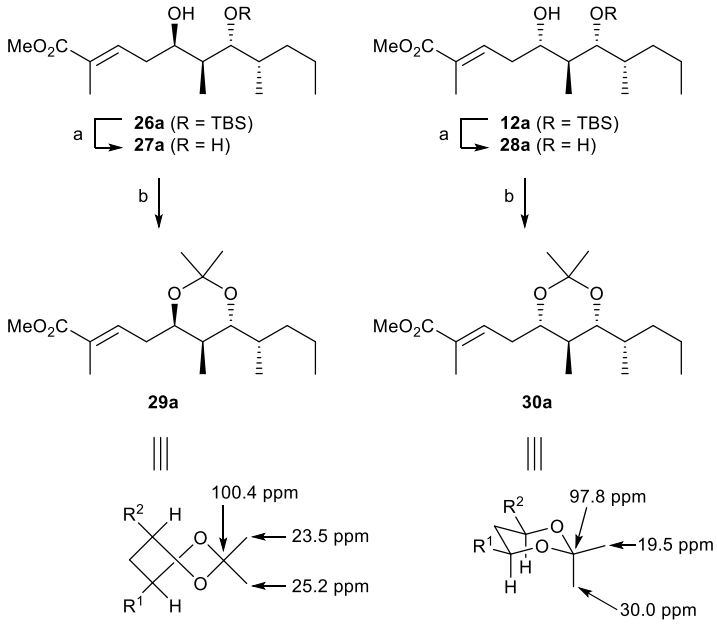

Scheme 3. Stereochemical assignment of 1,3-diols. *Reagents and conditions*: (a) TBAF, THF, rt, 81% (**27a**) and 81% (**28a**); (b) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, rt, 86% (**29a**) and 90% (**30a**).

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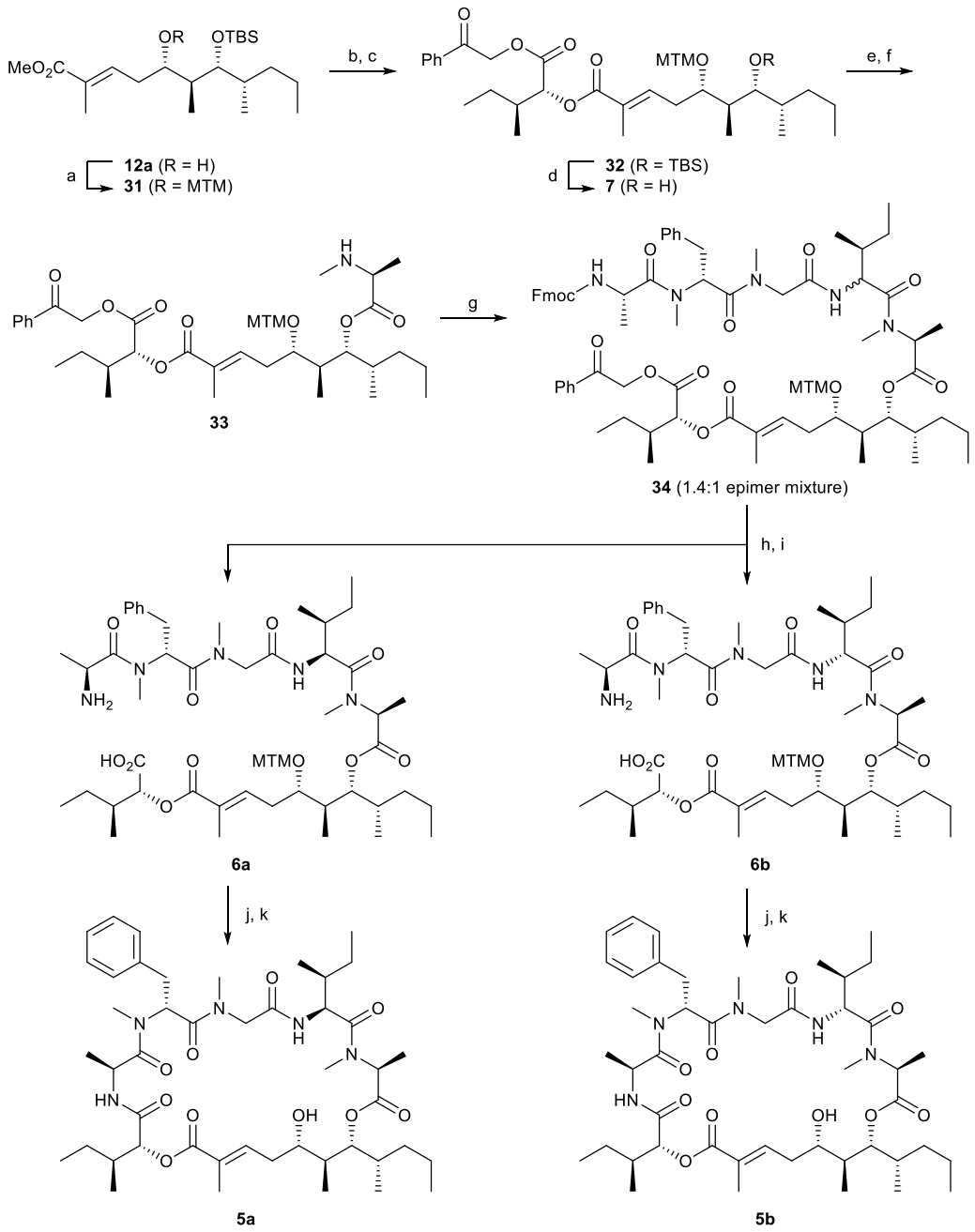

Scheme 4. Synthesis of odoamide (**5a**) and its epimer **5b**. *Reagents and conditions*: (a) Ac_2O, DMSO, AcOH, rt, 59%; (b) LiOH, THF, MeOH, H_2O, 0 °C to 30 °C; (c) **11**, MNBA, DMAP, CH_2Cl_2, rt, 87% (2 steps); (d) HF·pyridine, THF, pyridine, 0 °C to rt, 74%; (e) Fmoc-MeAla-Cl, DIPEA, 1,2-dichloroethane, 40 °C; (f) Et_2NH, MeCN, 0 °C to rt, 54% (2 steps); (g) **9**, 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% (**6a**) and 24% (**6b**) (3 steps); (j) HATU, HOAt, collidine, DMF, rt; (k) $AgNO_3$, 2,6-lutidine, THF, H_2O, rt to 70 °C, 85% (**5a**) and 62% (**5b**) (2 steps).

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