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# Total synthesis of odoamide, a novel cyclic depsipeptide, from an Okinawan marine cyanobacterium $\dagger$ 

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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 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 26membered 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 $(3 \mathrm{c})^{8}$ 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,

[^0]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 $\mathrm{S}_{3}$ 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 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. ${ }^{3 e_{2} f, 14}$ 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 D -alloisoleucic acid residues of the linear precursor 6 for odoamide (5). ${ }^{11 d}$ Peptide 6 could be prepared by coupling of alcohol 7,

aurilide (1a)

lagunamide $A(3 a): R=$
lagunamide $\mathrm{B}(\mathbf{3 b})$ : $\mathrm{R}=$



aurilide $C$ (1c)



lagunamide C (3c)

kulokekahilide-2 (2)

palau'amide (4)

Fig. 1 Structures of aurilide-class depsipeptides.

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 $\mathbf{1 1}^{15}$ 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 $5 S, 7 R$-dihydroxy and $6 S, 8 S$-dimethyl groups. Additionally, aurilide-class depsipeptides $\mathbf{1 a} \mathbf{a} \mathbf{c}, \mathbf{2}$, and $\mathbf{3 a}, \mathbf{b}$ 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 (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 $\dagger$ ). ${ }^{11 a, 12}$ 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 ( $R$ )-Roche ester ent-13 in a similar manner (Scheme 2). ( $R$ )-Roche ester ent- $\mathbf{1 3}$ was converted to alcohol ent-15 via benzyl protection ${ }^{16}$ and $\mathrm{LiAlH}_{4}{ }^{-}$ mediated reduction. After Swern oxidation, an $n$ - $\mathrm{Bu}_{2}$ BOTfmediated Evans aldol reaction ${ }^{17}$ of the resulting aldehyde provided the $s y n$-aldol products $\mathbf{1 6 c}$ and $\mathbf{1 7 d}$. 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 $\mathbf{1 6 c}$ and $\mathbf{1 7 d}$ followed by removal of the chiral auxiliary with $\mathrm{LiBH}_{4}$ gave alcohols $20 \mathrm{c}^{18}$ and 21d. Swern oxidation of 20 c 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
(A)

(B)


12a: $5 S, 6 S, 7 R, 8 S$


12b: $5 S, 6 S, 7 R, 8 R$


12c: $5 S, 6 R, 7 R, 8 S$


Fig. 2 Structures of odoamide (5) (A) and the polyketide substructures in 5 (B).
$\mathrm{LiAlH}_{4}$-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 $\quad(25)^{20} \quad$ produced methyl ester 12c with a (5S)-hydroxy group (dr $>99: 1$ ). ${ }^{21}$ 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 $26 a^{22}$ and 12a provided 1,3-diols 27 a and 28a, which were treated with 2,2dimethoxypropane in the presence of PPTS to give acetonides 29a and 30a, respectively. It is known that ${ }^{13} \mathrm{C}$ 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 antiisomer exists in a twist-boat conformation to avoid the 1,3diaxial interaction that would be present in the chair conformation. Accordingly, it was demonstrated that 1,3-diol 28a,

odoamide (5a)

6


$\Downarrow$


Scheme 1 Retrosynthetic analysis of odoamide (5).
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. ${ }^{12}$ 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 $5 S, 6 S, 7 R, 8 S$ configuration (see the ESI $\dagger$ ). ${ }^{12}$

## 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


Scheme 2 Synthesis of esters 12c,d. Reagents and conditions: (a) benzyl 2,2,2-trichloroacetimidate, $\mathrm{TfOH}, \mathrm{CH}_{2} \mathrm{Cl}_{2}, \mathrm{cyclohexane}^{2} 0{ }^{\circ} \mathrm{C}$ to $\mathrm{rt}, 85 \%$; (b) $\mathrm{LiAlH}_{4}, \mathrm{THF}, 0^{\circ} \mathrm{C}$, $81 \%$; (c) $(\mathrm{COCl})_{2}$, DMSO, DIPEA, $\mathrm{CH}_{2} \mathrm{Cl}_{2},-78{ }^{\circ} \mathrm{C}$ to $0^{\circ} \mathrm{C}$; (d) ( $R$ )-4-benzyl-3-propionyl-2-oxazolidinone, $n$ - $\mathrm{Bu} \mathbf{l}_{2} \mathrm{BOTf}$, DIPEA, $\mathrm{CH}_{2} \mathrm{Cl}_{2},-78^{\circ} \mathrm{C}$ to $-10^{\circ} \mathrm{C}, 80 \%$ ( 2 steps); (e) (R)-4-benzyl-3-pentanoyl-2-oxazolidinone, $n$ - $\mathrm{Bu}_{2} \mathrm{BOTf}$, DIPEA, $\mathrm{CH}_{2} \mathrm{Cl}_{2},-78{ }^{\circ} \mathrm{C}$ to $-10{ }^{\circ} \mathrm{C}, 72 \%(2$ steps); (f) TBSOTf, 2,6-lutidine, $\mathrm{CH}_{2} \mathrm{Cl}_{2}, 0^{\circ} \mathrm{C}$ to $\mathrm{rt}, 89 \%(18 \mathrm{c})$ and $87 \%(19 \mathrm{~d}) ;(\mathrm{g}) \mathrm{LiBH}_{4}, \mathrm{MeOH}, \mathrm{THF}, 0^{\circ} \mathrm{C}$ to $\mathrm{rt}, 69 \%(20 \mathrm{c})$ and $80 \%(21 \mathrm{~d}) ;(\mathrm{h})(\mathrm{COCl}) 2, \mathrm{DMSO}$, DIPEA, $\mathrm{CH}_{2} \mathrm{Cl}_{2},-78^{\circ} \mathrm{C}$ to $0^{\circ} \mathrm{C}$; (i) ethyltriphenylphosphonium bromide, $n$ - $\mathrm{BuLi}, \mathrm{THF}, \mathrm{rt}, 69 \%\left(2\right.$ steps, $Z / E=7: 1$ ); (j) TsCl, $\mathrm{Et}_{3} \mathrm{~N}, \mathrm{Me} 3 \mathrm{~N} \cdot \mathrm{HCl}, \mathrm{CH} 2 \mathrm{Cl} 2, r t$; (k) $\mathrm{LiAlH}_{4}, \mathrm{THF}, 0^{\circ} \mathrm{C}$ to $\mathrm{rt}, 70 \%$ (2 steps) (l) $\mathrm{Pd} / \mathrm{C}, \mathrm{H}_{2}, \mathrm{EtOH}, \mathrm{rt}, 92 \%(23 \mathrm{c})$ and $85 \%(23 \mathrm{~d})$; (m) $(\mathrm{COCl})_{2}, \mathrm{DMSO}, \mathrm{DIPEA}, \mathrm{CH}_{2} \mathrm{Cl}_{2},-78{ }^{\circ} \mathrm{C}$ to $0{ }^{\circ} \mathrm{C}$; (n) 25 , $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{2}, \mathrm{Et}_{2} \mathrm{O},-78^{\circ} \mathrm{C}, 54 \%$ (12c) and $69 \%$ (12d) (2 steps).


$\square \quad 26 a(R=T B S)$
$\longrightarrow \quad 27 a(R=H)$

b $\downarrow$
$b \downarrow$


29a
|||

30a



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, $\mathrm{CH}_{2} \mathrm{Cl}_{2}, \mathrm{rt}, 86 \%$ (29a) and 90\% (30a).
using ( $5 S, 6 S, 7 R, 8 S$ )-ester 12a. Synthesis of odoamide (5) began with methylthiomethyl (MTM) protection of the secondary hydroxy group in 12a to give thioacetal 31
(Scheme 4). ${ }^{11 a, 24}$ Hydrolysis of 31 with LiOH followed by coupling with d-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 $\mathrm{Et}_{2} \mathrm{NH}$ 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 $\mathrm{Et}_{2} \mathrm{NH}$ ), the epimer mixture of the linear peptides was separated into the desired compound 6a (major, l-Ile) and undesired compound $\mathbf{6 b}$ (minor, d-allo-Ile) by HPLC purification. Cyclisation of $\mathbf{6 a}$ and $\mathbf{6 b}$ with HATU followed by deprotection of the MTM group with $\mathrm{AgNO}_{3}$ and 2,6-lutidine gave the desired odoamide $\mathbf{5 a}$ and its diastereomer $\mathbf{5 b}$. Both cyclisations of $\mathbf{6 a}$ and $\mathbf{6 b}$ proceeded smoothly within five hours without epimerisation. The configurations of L -Ile and d-allo-Ile in peptides $\mathbf{5 a}$ and $\mathbf{5 b}$, respectively, were determined by Marfey's analysis and ${ }^{1} \mathrm{H}$ NMR analysis after acid hydrolysis.

We analysed the ${ }^{1} \mathrm{H}$ NMR and ${ }^{13} \mathrm{C}$ NMR spectra of the natural and synthetic products (Fig. 3 and 4). The NMR spectra of the synthetic odoamide 5 a were identical to those of the
$\mathrm{MeO}_{2}$

b, c
$\rightarrow 31$ ( $\mathrm{R}=\mathrm{MTM}$ )


$$
\begin{aligned}
& \mathrm{d} \square \\
& \\
& \\
& \\
& \hline
\end{aligned}
$$



34 (1.4:1 epimer mixture)




6b


5b


Scheme 4 Synthesis of odoamide (5a) and its epimer 5b. Reagents and conditions: (a) $\mathrm{Ac}_{2} \mathrm{O}, \mathrm{DMSO}, \mathrm{AcOH}, \mathrm{rt}, 59 \%$; (b) $\mathrm{LiOH}, \mathrm{THF}, \mathrm{MeOH}, \mathrm{H}, \mathrm{O}, 0{ }^{\circ} \mathrm{C}$ to $30^{\circ} \mathrm{C}$; (c) 11, MNBA, DMAP, $\mathrm{CH}_{2} \mathrm{Cl}_{2}, ~ \mathrm{rt}, 87 \%$ (2 steps); (d) HF-pyridine, THF, pyridine, $0^{\circ} \mathrm{C}$ to rt , $74 \%$; (e) Fmoc-MeAla-Cl, DIPEA, 1,2-dichloroethane, $40^{\circ} \mathrm{C}$; (f) $\mathrm{Et}_{2} \mathrm{NH}, \mathrm{MeCN}, 0^{\circ} \mathrm{C}$ to rt, $54 \%$ (2 steps); (g) 9, EDCl. $\mathrm{HCl}, \mathrm{HOAt}, \mathrm{CH}_{2} \mathrm{Cl}_{2}, 0^{\circ} \mathrm{C}$ to rt; (h) $\mathrm{Zn}, \mathrm{CH}_{3} \mathrm{COOH}, \mathrm{H} 2 \mathrm{O}, \mathrm{EtOAc}, \mathrm{rt}$; (i) $\mathrm{Et} \mathrm{t}_{2} \mathrm{NH}, \mathrm{MeCN}, 0{ }^{\circ} \mathrm{C}$ to $\mathrm{rt}, 30 \%$ (6a) and $24 \%$ (6b) (3 steps); (j) HATU, HOAt, collidine, DMF, rt; (k) $\mathrm{AgNO}_{3}, 2,6$-lutidine, $\mathrm{THF}, \mathrm{H}_{2} \mathrm{O}, \mathrm{rt}$ to $70{ }^{\circ} \mathrm{C}, 85 \%$ ( 5 a ) and $62 \%$ ( 5 b ) (2 steps).
natural product 5, suggesting that the chemical structure of odoamide was the same as $\mathbf{5 a}$. The cytotoxicity of synthetic odoamides $\mathbf{5 a}$ and $\mathbf{5 b}$ against A549 cells was also evaluated by the MTS assay. Peptide 5a showed highly potent cytotoxicity $\left(\mathrm{IC}_{50}=2.1 \mathrm{nM}\right)$, corroborating our correct structural assignment of odoamide (5). However, the epimer peptide 5b showed significantly less potent antiproliferative activity $\left(\mathrm{IC}_{50}=\right.$ $0.54 \mu \mathrm{M}$ ), 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 $5 \mathbf{5}$ 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 ${ }^{1} \mathrm{H}$ NMR spectra between the natural compound 5 and the synthetic compound 5 a (in $\mathrm{CD}_{3} \mathrm{OD}$ ).


Fig. 4 Comparison of the ${ }^{13} \mathrm{C}$ NMR spectra between the natural compound 5 and the synthetic compound $5 a$ (in $\mathrm{CD}_{3} \mathrm{OD}$ ).

## Experimental section

## Synthetic general method

NMR spectra were recorded using a JEOL ECA-500 spectrometer. Chemical shifts are reported in $\delta(\mathrm{ppm})$ relative to $\mathrm{Me}_{4} \mathrm{Si}$ (in $\mathrm{CDCl}_{3}$ ) as an internal standard. ${ }^{13} \mathrm{C}$ 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-IT-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 $\times$ 250 mm , Nacalai Tesque, Inc.) was employed with a linear gradient of $\mathrm{CH}_{3} \mathrm{CN}$ (with $0.1 \%(\mathrm{v} / \mathrm{v})$ TFA, except for the analysis of final products 5a,b using solvents without TFA) in $\mathrm{H}_{2} \mathrm{O}$ at a flow rate of $1 \mathrm{~cm}^{3} \mathrm{~min}^{-1}$, and eluting products were detected by UV at 220 nm . Preparative HPLC was performed using a Cosmosil 5C18-ARII preparative column $(20 \times 250 \mathrm{~mm}$, Nacalai Tesque, Inc.) at a flow rate of $8 \mathrm{~cm}^{3} \mathrm{~min}^{-1}$. The purity of peptides $\mathbf{5 a}, \mathbf{b}$ was determined by HPLC analysis ( $>95 \%$ ). The synthetic procedures for esters $\mathbf{1 2 a}, \mathbf{b}$ were described in our previous report. ${ }^{12}$
Methyl (R)-3-benzyloxy-2-methylpropanoate (ent-14). To a stirred solution of ent-13 ( $9.9 \mathrm{~g}, 83.8 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( $210 \mathrm{~cm}^{3}$ ) under argon were added benzyl 2,2,2-trichloroacetimidate ( $17.1 \mathrm{~cm}^{3}, 92.2 \mathrm{mmol}$ ) in cyclohexane $\left(420 \mathrm{~cm}^{3}\right)$ and triflic acid $\left(3.0 \mathrm{~cm}^{3}, 33.5 \mathrm{mmol}\right)$ at $0^{\circ} \mathrm{C}$. 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 saturated aqueous $\mathrm{NaHCO}_{3}$ and brine, and dried over $\mathrm{MgSO}_{4}$. 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 ( $14.8 \mathrm{~g}, 85 \%$ ) as a colorless oil. The spectral data were in good agreement with those previously reported. ${ }^{28}$
(S)-3-Benzyloxy-2-methylpropan-1-ol (ent-15). To a stirred suspension of $\mathrm{LiAlH}_{4}(4.0 \mathrm{~g}, 105.9 \mathrm{mmol})$ in THF $\left(175 \mathrm{~cm}^{3}\right)$ under argon was added dropwise a solution of ent-14 (14.7 g, $70.6 \mathrm{mmol})$ in THF $\left(175 \mathrm{~cm}^{3}\right)$ at $0^{\circ} \mathrm{C}$. After stirring for 1 h , the reaction mixture was poured into a saturated aqueous solution of sodium potassium tartrate at $0^{\circ} \mathrm{C}$ and stirred overnight at room temperature. The whole mixture was extracted with $\mathrm{Et}_{2} \mathrm{O}$ and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. 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 ( $10.3 \mathrm{~g}, 81 \%$ ) as a colorless oil. The spectral data were in good agreement with those previously reported. ${ }^{28}$
( $R$ )-4-Benzyl-3-[(2R,3S,4R)-5-benzyloxy-3-hydroxy-2,4-di-methylpentanoyl]oxazolidin-2-one (16c). To a stirred solution of oxalyl chloride ( $0.32 \mathrm{~cm}^{3}, 3.72 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(7.4 \mathrm{~cm}^{3}\right)$ under argon was added DMSO ( $0.53 \mathrm{~cm}^{3}, 7.44 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(1.2 \mathrm{~cm}^{3}\right)$ at $-78{ }^{\circ} \mathrm{C}$. After stirring for 30 min , a solution
of ent- 15 ( $334.7 \mathrm{mg}, 1.86 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(6.4 \mathrm{~cm}^{3}\right)$ was added dropwise and stirred at $-78{ }^{\circ} \mathrm{C}$ for $1 \mathrm{~h} . i-\mathrm{Pr}_{2} \mathrm{NEt}$ ( $1.62 \mathrm{~cm}^{3}, 9.3 \mathrm{mmol}$ ) was added and the reaction mixture was stirred at $0{ }^{\circ} \mathrm{C}$ for 30 min . The mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$. The whole mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. 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 ( $429.2 \mathrm{mg}, 1.84 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(9.2 \mathrm{~cm}^{3}\right)$ under argon were added $n$ - $\mathrm{Bu}_{2}$ BOTf ( $1.0 \mathrm{~mol} \mathrm{dm}{ }^{-3}$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2} ; 2.0 \mathrm{~cm}^{3}$, $2.00 \mathrm{mmol})$ and $i-\mathrm{Pr}_{2} \mathrm{NEt}\left(0.38 \mathrm{~cm}^{3}, 2.17 \mathrm{mmol}\right)$ at $-78^{\circ} \mathrm{C}$. After stirring for 1 h , the reaction mixture was warmed to $0^{\circ} \mathrm{C}$ and stirred for 30 min . To this solution was added the above aldehyde in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(3.9 \mathrm{~cm}^{3}\right)$ at $-78{ }^{\circ} \mathrm{C}$. After stirring for 1 h , the mixture was warmed to $-10{ }^{\circ} \mathrm{C}$ and stirred for 1 h . The mixture was quenched with pH 7.0 phosphate buffer solution $\left(1.8 \mathrm{~cm}^{3}\right)$ and $30 \% \mathrm{H}_{2} \mathrm{O}_{2}$ in $\mathrm{MeOH}\left(1: 2,4.2 \mathrm{~cm}^{3}\right)$ and stirred overnight at room temperature. The whole mixture was concentrated under reduced pressure and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The extract was washed with saturated aqueous $\mathrm{NaHCO}_{3}$, and dried over $\mathrm{MgSO}_{4}$. 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 $16 \mathrm{c}(610.7 \mathrm{mg}, 80 \%$, $\mathrm{dr}>15: 1)$ as a colorless oil. The minor isomer was removed by column chromatography: $[\alpha]_{\mathrm{D}}^{29}-43.2\left(c \quad 0.72, \mathrm{CHCl}_{3}\right)$; IR (neat) $\nu_{\max } / \mathrm{cm}^{-1}: 3504(\mathrm{OH})$, $1779(\mathrm{C}=\mathrm{O}) ;{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 1.05(3 \mathrm{H}, \mathrm{d}, J 6.9)$, $1.33(3 \mathrm{H}, \mathrm{d}, J 6.3), 1.87-1.93(1 \mathrm{H}, \mathrm{m}), 2.77\left(1 \mathrm{H}, \mathrm{dd}, J_{1} 13.2\right.$, $\left.J_{2} 9.7\right), 3.00(1 \mathrm{H}, \mathrm{d}, J 2.9), 3.25\left(1 \mathrm{H}, \mathrm{dd}, J_{1} 13.2, J_{2} 3.2\right)$, 3.46-3.52 (2H, m), 3.96-4.03 (2H, m), 4.16-4.21 (2H, m), 4.51 $(2 \mathrm{H}, \mathrm{s}), 4.65-4.69(1 \mathrm{H}, \mathrm{m}), 7.20-7.21(2 \mathrm{H}, \mathrm{m}), 7.26-7.36(8 \mathrm{H}$, $\mathrm{m}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 12.4,12.8,36.2,37.7,40.5$, 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 $\mathrm{C}_{24} \mathrm{H}_{29} \mathrm{NNaO}_{5}\left(\mathrm{MNa}^{+}\right): 434.1938$; found: 434.1938 .
(R)-4-Benzyl-3-[(2R,3S,4R)-5-benzyloxy-3-(tert-butyldimethyl-silyloxy)-2,4-dimethylpentanoyl]oxazolidin-2-one (18c). To a stirred solution of $\mathbf{1 6 c}(14.1 \mathrm{~g}, 34.3 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(137 \mathrm{~cm}^{3}\right)$ under argon were added TBSOTf $\left(9.5 \mathrm{~cm}^{3}, 41.2 \mathrm{mmol}\right)$ and $2,6-$ lutidine $\left(7.9 \mathrm{~cm}^{3}, 68.6 \mathrm{mmol}\right)$ at $0{ }^{\circ} \mathrm{C}$. 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. 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 $18 \mathrm{c}(16.0 \mathrm{~g}, 89 \%)$ as a colorless oil: $[\alpha]_{\mathrm{D}}^{27}-38.2$ (c 1.21, $\mathrm{CHCl}_{3}$ ); IR (neat) $\nu_{\max } / \mathrm{cm}^{-1}: 1780(\mathrm{C}=\mathrm{O}) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta: 0.04(3 \mathrm{H}, \mathrm{s}), 0.06(3 \mathrm{H}, \mathrm{s}), 0.90(9 \mathrm{H}, \mathrm{s}), 0.92$ (3H, d, $J 7.4), 1.25(3 \mathrm{H}, \mathrm{d}, J 6.9), 1.88-1.93(1 \mathrm{H}, \mathrm{m}), 2.75(1 \mathrm{H}$, dd, $\left.J_{1} 13.2, J_{2} 9.7\right), 3.24\left(1 \mathrm{H}, \mathrm{dd}, J_{1} 13.2, J_{2} 3.2\right), 3.28(1 \mathrm{H}, \mathrm{dd}$, $J_{1} 8.9, J_{2} 7.2$ ), $3.49\left(1 \mathrm{H}, \mathrm{dd}, J_{1} 8.9, J_{2} 6.6\right), 3.96-4.02(1 \mathrm{H}, \mathrm{m})$, 4.08-4.16 $(3 \mathrm{H}, \mathrm{m}), 4.46-4.52(2 \mathrm{H}, \mathrm{m}), 4.59-4.64(1 \mathrm{H}, \mathrm{m})$, 7.20-7.34 (10H, m); ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta:-4.1,-3.9$,
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 $\mathrm{C}_{30} \mathrm{H}_{43} \mathrm{NNaO}_{5} \mathrm{Si}\left(\mathrm{MNa}^{+}\right)$: 548.2803 ; found: 548.2808 .
(2S,3R,4R)-5-Benzyloxy-3-(tert-butyldimethylsilyloxy)-2,4-dimethylpentan-1-ol (20c). To a stirred solution of $18 \mathrm{c}(22.4 \mathrm{~g}$, 42.5 mmol ) in THF ( $213 \mathrm{~cm}^{3}$ ) and $\mathrm{MeOH}\left(5.2 \mathrm{~cm}^{3}\right.$, $127.6 \mathrm{mmol})$ under argon was added $\mathrm{LiBH}_{4}(2.78 \mathrm{~g}$, 127.6 mmol ) at $0{ }^{\circ} \mathrm{C}$. After stirring for 10 min , the reaction mixture was warmed to room temperature. After 4 h , the mixture was cooled to $0{ }^{\circ} \mathrm{C}$ and quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$. The whole mixture was extracted with EtOAc and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. 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 $20 \mathrm{c}(10.3 \mathrm{~g}, 69 \%)$ as a colorless oil: $[\alpha]_{\mathrm{D}}^{29}-0.41$ (c 1.23, $\mathrm{CHCl}_{3}$ ); IR (neat) $\nu_{\max } / \mathrm{cm}^{-1}: 3422(\mathrm{OH}) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta: 0.03(3 \mathrm{H}$, s), $0.08(3 \mathrm{H}, \mathrm{s}), 0.85(3 \mathrm{H}, \mathrm{d}, J 7.4), 0.89(9 \mathrm{H}, \mathrm{s}), 0.96(3 \mathrm{H}, \mathrm{d}$, $J$ 6.9), 1.93-1.98 (1H, m), 1.99-2.05 (1H, m), $2.32(1 \mathrm{H}, \mathrm{br} \mathrm{s})$, $3.26\left(1 \mathrm{H}, \mathrm{dd}, J_{1} 9.2, J_{2} 6.3\right), 3.39\left(1 \mathrm{H}, \mathrm{dd}, J_{1} 9.2, J_{2} 7.2\right)$, $3.47-3.51(1 \mathrm{H}, \mathrm{m}), 3.64-3.68(1 \mathrm{H}, \mathrm{m}), 3.88-3.89(1 \mathrm{H}, \mathrm{m})$, 4.46-4.51 ( $2 \mathrm{H}, \mathrm{m}$ ), 7.26-7.36 (5H, m); ${ }^{13} \mathrm{C}$ NMR ( 125 MHz , $\mathrm{CDCl}_{3}$ ) $\delta:-4.5,-4.2,12.8,12.9,18.2,26.0$ (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 $\mathrm{C}_{20} \mathrm{H}_{36} \mathrm{NaO}_{3} \mathrm{Si}\left(\mathrm{MNa}^{+}\right)$: 375.2326 ; found: 375.2324.
$\{[(2 R, 3 R, 4 S)$-1-(Benzyloxy)-2,4-dimethylhept-5-en-3-yl] oxy $\}$ (tertbutyl)dimethylsilane (22c). To a stirred solution of oxalyl chloride ( $0.11 \mathrm{~cm}^{3}$, 1.30 mmol ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(6.5 \mathrm{~cm}^{3}\right)$ under argon was added DMSO ( $0.18 \mathrm{~cm}^{3}, 2.60 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ $\left(0.43 \mathrm{~cm}^{3}\right)$ at $-78{ }^{\circ} \mathrm{C}$. After stirring for 30 min , a solution of 20c ( $228.9 \mathrm{mg}, 0.65 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(2.2 \mathrm{~cm}^{3}\right)$ was added dropwise and stirred at $-78{ }^{\circ} \mathrm{C}$ for $1.5 \mathrm{~h} . i-\mathrm{Pr}_{2} \mathrm{NEt}\left(0.57 \mathrm{~cm}^{3}\right.$, 3.25 mmol ) was added and the reaction mixture was stirred at $0^{\circ} \mathrm{C}$ for 30 min . The mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$. The whole mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. 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 ( $508.6 \mathrm{mg}, 1.37 \mathrm{mmol}$ ) in THF ( $5.5 \mathrm{~cm}^{3}$ ) under argon was added $n$-BuLi $\left(1.6 \mathrm{~mol} \mathrm{dm}{ }^{-3}\right.$ in hexane; $0.81 \mathrm{~cm}^{3}$, 1.30 mmol ) at room temperature. After stirring for 30 min , a solution of the above aldehyde in THF $\left(1.3 \mathrm{~cm}^{3}\right)$ was added and the reaction mixture was stirred for 1.5 h . The mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$. The whole mixture was extracted with EtOAc and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. 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$\mathrm{CHCl}_{3}$ (8:1) gave compound 22c as a diastereomixture ( $163.7 \mathrm{mg}, 69 \%, Z / E=7: 1$ ): colorless oil; $[\alpha]_{\mathrm{D}}^{27}+12.5$ (c 1.17, $\left.\mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 0.01(0.4 \mathrm{H}, \mathrm{s}), 0.02$ $(2.6 \mathrm{H}, \mathrm{s}), 0.04(0.4 \mathrm{H}, \mathrm{s}), 0.05(2.6 \mathrm{H}, \mathrm{s}), 0.84-0.86(3 \mathrm{H}, \mathrm{m}), 0.89$ $(1.2 \mathrm{H}, \mathrm{s}), 0.90(7.8 \mathrm{H}, \mathrm{s}), 0.94-0.97(3 \mathrm{H}, \mathrm{m}), 1.61(2.6 \mathrm{H}, \mathrm{dd}$,
$\left.J_{1} 6.9, J_{2} 1.7\right), 1.63$ ( $0.4 \mathrm{H}, \mathrm{d}, J 4.6$ ), 1.96-2.03 (1H, m), 2.23-2.30 $(0.1 \mathrm{H}, \mathrm{m}), 2.60-2.65(0.9 \mathrm{H}, \mathrm{m}), 3.22\left(1 \mathrm{H}, \mathrm{dd}, J_{1} 8.9, J_{2} 6.9\right), 3.40$ (1H, dd, $J_{1} 8.9, J_{2} 7.7$ ), 3.56 ( 1 H , dd, $J_{1} 8.0, J_{2} 1.7$ ), 4.43-4.52 $(2 \mathrm{H}, \mathrm{m}), 5.16-5.21(1 \mathrm{H}, \mathrm{m}), 5.35-5.42(1 \mathrm{H}, \mathrm{m}), 7.25-7.34(5 \mathrm{H}$, $\mathrm{m}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta:-4.1,-4.0,-3.6,-3.5,10.8$, 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 $\mathrm{C}_{22} \mathrm{H}_{38} \mathrm{NaO}_{2} \mathrm{Si}\left(\mathrm{MNa}^{+}\right): 385.2533$; found: 385.2534 .
(2R,3R,4S)-3-(tert-Butyldimethylsilyloxy)-2,4-dimethylheptan-1-ol (23c). To a stirred solution of $22 \mathrm{c}(1.3 \mathrm{~g}, 3.7 \mathrm{mmol})$ in EtOH ( $37.0 \mathrm{~cm}^{3}$ ) was added $10 \% \mathrm{Pd} / \mathrm{C}(787.5 \mathrm{mg}, 0.7 \mathrm{mmol})$ at room temperature and the mixture was treated with $\mathrm{H}_{2}$ 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 ( $938.1 \mathrm{mg}, 92 \%$ ) as a colorless oil: $[\alpha]_{\mathrm{D}}^{28}-12.7$ (c $1.13, \mathrm{CHCl}_{3}$ ); IR (neat) $\nu_{\text {max }} / \mathrm{cm}^{-1}: 3328(\mathrm{OH}) ;{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ : $0.06(3 \mathrm{H}, \mathrm{s}), 0.08(3 \mathrm{H}, \mathrm{s}), 0.85(3 \mathrm{H}, \mathrm{d}, J 6.9), 0.88-0.92(15 \mathrm{H}$, $\mathrm{m}), 1.09-1.16(1 \mathrm{H}, \mathrm{m}), 1.19-1.28(1 \mathrm{H}, \mathrm{m}), 1.31-1.41(2 \mathrm{H}, \mathrm{m})$, $1.60-1.66(1 \mathrm{H}, \mathrm{m}), 1.90-1.97(1 \mathrm{H}, \mathrm{m}), 2.07\left(1 \mathrm{H}, \mathrm{dd}, J_{1} 6.0\right.$, $\left.J_{2} 4.3\right), 3.45-3.50(1 \mathrm{H}, \mathrm{m}), 3.62-3.67(2 \mathrm{H}, \mathrm{m}) ;{ }^{13} \mathrm{C}$ NMR (125 MHz, $\mathrm{CDCl}_{3}$ ) $\delta:-4.2,-4.1,12.6,14.3,15.8,18.3,20.8$, 26.0 (3C), 35.9, 37.0, 39.5, 66.5, 77.4; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{34} \mathrm{NaO}_{2} \mathrm{Si}\left(\mathrm{MNa}^{+}\right): 297.2220$; found: 297.2221.

Methyl (5S,6R,7R,8S,E)-7-(tert-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundec-2-enoate (12c). To a stirred solution of $i-\mathrm{Pr}_{2} \mathrm{NH}\left(0.16 \mathrm{~cm}^{3}, 1.16 \mathrm{mmol}\right)$ in THF $\left(2.4 \mathrm{~cm}^{3}\right)$ under argon was added $n$-BuLi $\left(2.6 \mathrm{~mol} \mathrm{dm}{ }^{-3}\right.$ in hexane; $0.45 \mathrm{~cm}^{3}$, $1.16 \mathrm{mmol})$ at $0^{\circ} \mathrm{C}$. After 20 min , methyl tiglate $\left(0.13 \mathrm{~cm}^{3}\right.$, $1.05 \mathrm{mmol})$ and TMSCl $\left(0.20 \mathrm{~cm}^{3}, 1.58 \mathrm{mmol}\right)$ in THF $\left(0.36 \mathrm{~cm}^{3}\right)$ were added successively at $-78^{\circ} \mathrm{C}$. The stirring was continued for 1 h at this temperature and for additional 1.5 h at room temperature. Then, pentane and cold saturated $\mathrm{NaHCO}_{3}$ were added to the reaction mixture. The whole mixture was extracted with pentane and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. The filtrate was concentrated under reduced pressure to give compound $\mathbf{2 5}$, which was used without further purification. ${ }^{20}$ To a stirred solution of oxalyl chloride $\left(0.060 \mathrm{~cm}^{3}, 0.70 \mathrm{mmol}\right)$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(3.5 \mathrm{~cm}^{3}\right)$ under argon was added DMSO ( $0.099 \mathrm{~cm}^{3}, 1.40 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(0.23 \mathrm{~cm}^{3}\right)$ at $-78{ }^{\circ} \mathrm{C}$. After stirring for 30 min , a solution of $23 \mathrm{c}(96.4 \mathrm{mg}, 0.35 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(1.2 \mathrm{~cm}^{3}\right)$ was added dropwise and stirred at $-78{ }^{\circ} \mathrm{C}$ for $1.5 \mathrm{~h} . i-\mathrm{Pr}_{2} \mathrm{NEt}$ $\left(0.49 \mathrm{~cm}^{3}, 2.8 \mathrm{mmol}\right)$ was added and the reaction mixture was stirred at $0{ }^{\circ} \mathrm{C}$ for 30 min . The mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$. The whole mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(2.7 \mathrm{~cm}^{3}\right)$ and $\mathrm{Et}_{2} \mathrm{O}\left(0.27 \mathrm{~cm}^{3}\right)$ under argon were added diene 25 and $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}\left(0.065 \mathrm{~cm}^{3}, 0.53 \mathrm{mmol}\right)$ at $-78{ }^{\circ} \mathrm{C}$. After stirring for 2 h , a mixture of $\mathrm{THF} / \mathrm{H}_{2} \mathrm{O} / 1 \mathrm{~N} \mathrm{HCl}$ ( $5: 1: 0.4 \mathrm{v} / \mathrm{v}, 1.8 \mathrm{~cm}^{3}$ ) was added to the reaction mixture. The
mixture was warmed to room temperature and stirred for 15 min. Then, saturated aqueous $\mathrm{NaHCO}_{3}$ was added to the mixture at $0{ }^{\circ} \mathrm{C}$. The whole mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. 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 ( $73.4 \mathrm{mg}, 54 \%$ ) as a colorless oil: $[\alpha]_{\mathrm{D}}^{26}-22.4\left(c 1.01, \mathrm{CHCl}_{3}\right.$ ); IR (neat) $\nu_{\max } / \mathrm{cm}^{-1}: 3523(\mathrm{OH}), 1716(\mathrm{C}=\mathrm{O}) ;{ }^{1} \mathrm{H}$ NMR $(500 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right) \delta: 0.08(3 \mathrm{H}, \mathrm{s}), 0.09(3 \mathrm{H}, \mathrm{s}), 0.85(3 \mathrm{H}, \mathrm{d}, J 6.9), 0.88-0.91$ $(12 \mathrm{H}, \mathrm{m}), 0.94(3 \mathrm{H}, \mathrm{d}, J 6.9), 1.04-1.11(1 \mathrm{H}, \mathrm{m}), 1.15-1.22(1 \mathrm{H}$, m), 1.35-1.42 ( $1 \mathrm{H}, \mathrm{m}$ ), 1.46-1.53 ( $1 \mathrm{H}, \mathrm{m}$ ), 1.63-1.69 ( $2 \mathrm{H}, \mathrm{m}$ ), $1.87(3 \mathrm{H}, \mathrm{s}), 1.96(1 \mathrm{H}, \mathrm{d}, J 4.0), 2.31-2.42(2 \mathrm{H}, \mathrm{m}), 3.65-3.66$ $(1 \mathrm{H}, \mathrm{m}), 3.74(3 \mathrm{H}, \mathrm{s}), 3.79-3.83(1 \mathrm{H}, \mathrm{m}), 6.79-6.82(1 \mathrm{H}, \mathrm{m})$; ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta:-4.2,-3.5,8.9,12.7,14.4,15.4$, 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 $\mathrm{C}_{21} \mathrm{H}_{42} \mathrm{NaO}_{4} \mathrm{Si}$ ( $\mathrm{MNa}^{+}$): 409.2745 ; found: 409.2748.
$\{[(2 R, 3 R, 4 R)$-1-(Benzyloxy)-2,4-dimethylheptan-3-yl $]$ oxy $\}$ (tertbutyl)dimethylsilane (24d). To a stirred solution of $21 \mathrm{~d}(7.3 \mathrm{~g}$, 19.1 mmol ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(191 \mathrm{~cm}^{3}\right)$ under argon were added $\mathrm{Et}_{3} \mathrm{~N}$ $\left(5.3 \mathrm{~cm}^{3}, 38.2 \mathrm{mmol}\right)$, $\mathrm{TsCl}(5.5 \mathrm{~g}, 28.7 \mathrm{mmol})$ and $\mathrm{Me}_{3} \mathrm{~N} \cdot \mathrm{HCl}$ $(1.8 \mathrm{~g}, 19.1 \mathrm{mmol})$ at room temperature. After stirring for 1 h , the reaction was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$. The whole mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. 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 $\mathrm{LiAlH}_{4}(2.2 \mathrm{~g}, 57.3 \mathrm{mmol})$ in THF $\left(100 \mathrm{~cm}^{3}\right)$ under argon was added dropwise a solution of the above tosylate in THF $\left(91 \mathrm{~cm}^{3}\right)$ at $0^{\circ} \mathrm{C}$. 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 $0{ }^{\circ} \mathrm{C}$ and stirred at room temperature for 1 h . The whole mixture was extracted with $\mathrm{Et}_{2} \mathrm{O}$ and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. 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 $24 \mathrm{~d}(4.9 \mathrm{~g}$, $70 \%$ ) as a colorless oil: $[\alpha]_{\mathrm{D}}^{27}+1.74$ (c 1.16, $\mathrm{CHCl}_{3}$ ); ${ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta: 0.00(3 \mathrm{H}, \mathrm{s}), 0.03(3 \mathrm{H}, \mathrm{s}), 0.86-0.89(18 \mathrm{H}$, m), 1.00-1.05 ( $1 \mathrm{H}, \mathrm{m}$ ), 1.18-1.26 ( $1 \mathrm{H}, \mathrm{m}$ ), 1.36-1.42 ( $2 \mathrm{H}, \mathrm{m}$ ), 1.56-1.60 ( $1 \mathrm{H}, \mathrm{m}$ ), 1.95-2.00 ( $1 \mathrm{H}, \mathrm{m}$ ), $3.22\left(1 \mathrm{H}, \mathrm{dd}, J_{1} 8.6\right.$, $J_{2} 6.6$ ), 3.37 ( $1 \mathrm{H}, \mathrm{dd}, J_{1} 8.6, J_{2} 7.4$ ), 3.62 ( $1 \mathrm{H}, \mathrm{dd}, J_{1} 5.7, J_{1} 2.3$ ), 4.45-4.52 ( $2 \mathrm{H}, \mathrm{m}$ ), 7.27-7.34 (5H, m); ${ }^{13} \mathrm{C}$ NMR ( 125 MHz , $\mathrm{CDCl}_{3}$ ) $\delta:-4.3,-3.9,11.9,14.4,15.9,18.4,20.7,26.1$ (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 $\mathrm{C}_{22} \mathrm{H}_{40} \mathrm{NaO}_{2} \mathrm{Si}\left(\mathrm{MNa}^{+}\right): 387.2690$; found: 387.2691 .

Methyl (5S,6S,7R,8S,E)-7-(tert-butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undec-2-enoate (31). To a stirred solution of $\mathbf{1 2 a}(2.3 \mathrm{~g}, 6.0 \mathrm{mmol})$ in DMSO $\left(42.9 \mathrm{~cm}^{3}\right)$ under argon were added $\mathrm{Ac}_{2} \mathrm{O}\left(30.5 \mathrm{~cm}^{3}\right)$ and $\mathrm{AcOH}\left(5.5 \mathrm{~cm}^{3}\right)$ at room temperature. After stirring overnight, the reaction
mixture was cooled to $0{ }^{\circ} \mathrm{C}$ and quenched with saturated aqueous $\mathrm{NaHCO}_{3}$. The whole mixture was extracted with $\mathrm{Et}_{2} \mathrm{O}$ and the extract was washed with $\mathrm{H}_{2} \mathrm{O}$ and brine, and dried over $\mathrm{MgSO}_{4}$. 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 ( $1.6 \mathrm{~g}, 59 \%$ ) as a colorless oil: $[\alpha]_{\mathrm{D}}^{27}-75.4\left(c 0.72, \mathrm{CHCl}_{3}\right)$; IR (neat) $\nu_{\max } / \mathrm{cm}^{-1}: 1716(\mathrm{C}=\mathrm{O}) ;{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ : 0.05 ( $6 \mathrm{H}, \mathrm{s}$ ), 0.85-0.92 ( $18 \mathrm{H}, \mathrm{m}$ ), 1.15-1.28 ( $2 \mathrm{H}, \mathrm{m}$ ), 1.33-1.42 $(2 \mathrm{H}, \mathrm{m}), 1.62-1.66(1 \mathrm{H}, \mathrm{m}), 1.85(3 \mathrm{H}, \mathrm{d}, J 1.1), 1.98-2.05(1 \mathrm{H}$, $\mathrm{m}), 2.16(3 \mathrm{H}, \mathrm{s}), 2.26-2.39(2 \mathrm{H}, \mathrm{m}), 3.47\left(1 \mathrm{H}, \mathrm{dd}, J_{1} 6.9, J_{2} 2.9\right)$, $3.73(3 \mathrm{H}, \mathrm{s}), 4.00-4.03(1 \mathrm{H}, \mathrm{m}), 4.53(1 \mathrm{H}, \mathrm{d}, J 11.5), 4.63(1 \mathrm{H}, \mathrm{d}$, $J$ 11.5), 6.92-6.95 (1H, m); ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta:-3.7$, $-3.6,11.4,12.8,14.0,14.1,14.3,18.4,20.9,26.2$ (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 $\mathrm{C}_{23} \mathrm{H}_{46} \mathrm{NaO}_{4} \mathrm{SSi}\left(\mathrm{MNa}^{+}\right): 469.2778$; 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-butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undec-2-enoate (32). To a stirred solution of $31(1.14 \mathrm{~g}, 2.6 \mathrm{mmol})$ in $\mathrm{MeOH}\left(17 \mathrm{~cm}^{3}\right)$ and THF $\left(17 \mathrm{~cm}^{3}\right)$ was added $1 \mathrm{~N} \mathrm{LiOH}\left(17 \mathrm{~cm}^{3}\right)$ at $0{ }^{\circ} \mathrm{C}$. The reaction mixture was warmed to $30^{\circ} \mathrm{C}$ 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 $\mathrm{MgSO}_{4}$. 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 10 , which was used without further purification. To a stirred solution of acid 10 in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(12.8 \mathrm{~cm}^{3}\right)$ were added MNBA ( $1.32 \mathrm{~g}, 3.8 \mathrm{mmol}$ ), DMAP ( $935.0 \mathrm{mg}, 7.7 \mathrm{mmol}$ ) and $11(959.0 \mathrm{mg}, 3.8 \mathrm{mmol})$ at room temperature. After stirring overnight, the mixture was quenched with 1 N HCl . The whole mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. 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 $(1.48 \mathrm{~g}, 87 \%)$ as a colorless oil: $[\alpha]_{\mathrm{D}}^{26}-43.5\left(c 0.89, \mathrm{CHCl}_{3}\right)$; IR (neat) $\nu_{\text {max }} / \mathrm{cm}^{-1}: 1710(\mathrm{C}=\mathrm{O}) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ : $0.05(3 \mathrm{H}, \mathrm{s}), 0.07(3 \mathrm{H}, \mathrm{s}), 0.86-0.91(18 \mathrm{H}, \mathrm{m}), 0.98(3 \mathrm{H}, \mathrm{t}, J 7.4)$, 1.15 (3H, d, J 6.9), 1.18-1.28 ( $2 \mathrm{H}, \mathrm{m}$ ), 1.34-1.47 (3H, m), 1.52-1.58 (1H, m), 1.62-1.64 (1H, m), $1.89(3 \mathrm{H}, \mathrm{s}), 1.99-2.03$ $(1 \mathrm{H}, \mathrm{m}), 2.11(3 \mathrm{H}, \mathrm{s}), 2.19-2.25(1 \mathrm{H}, \mathrm{m}), 2.34-2.37(2 \mathrm{H}, \mathrm{m})$, $3.47\left(1 \mathrm{H}, \mathrm{dd}, J_{1} 7.4, J_{2} 2.9\right), 4.01-4.04(1 \mathrm{H}, \mathrm{m}), 4.52(1 \mathrm{H}, \mathrm{d}$, $J$ 11.5), 4.61 (1H, d, $J 11.5), 5.19$ ( $1 \mathrm{H}, \mathrm{d}, J 3.4$ ), 5.25 ( $1 \mathrm{H}, \mathrm{d}$, $J$ 16.6), 5.55 (1H, d, $J$ 16.6), $7.04-7.07(1 \mathrm{H}, \mathrm{m}), 7.49(2 \mathrm{H}, \mathrm{t}$, $J$ 7.7), 7.60-7.63 (1H, m), 7.89-7.91 (2H, m); ${ }^{13} \mathrm{C}$ NMR $\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta:-3.6,-3.5,11.3,11.8,12.7,14.1,14.2$ (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 $\mathrm{C}_{36} \mathrm{H}_{60} \mathrm{NaO}_{7} \mathrm{SSi}\left(\mathrm{MNa}^{+}\right)$: 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 $32(80.7 \mathrm{mg}$,
$0.12 \mathrm{mmol})$ in THF $\left(0.80 \mathrm{~cm}^{3}\right)$ and pyridine $\left(0.20 \mathrm{~cm}^{3}\right)$ was added HF-pyridine $\left(0.50 \mathrm{~cm}^{3}\right)$ at $0^{\circ} \mathrm{C}$. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into saturated aqueous $\mathrm{NaHCO}_{3}$ at $0^{\circ} \mathrm{C}$. The whole mixture was extracted with EtOAc, and the extract was washed with brine and 1 N HCl , and dried over $\mathrm{MgSO}_{4}$. 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 $(49.2 \mathrm{mg}, 74 \%)$ as a colorless oil: $[\alpha]_{\mathrm{D}}^{25}-5.29$ (c 1.08, $\mathrm{CHCl}_{3}$ ); IR (neat) $\nu_{\max } / \mathrm{cm}^{-1}: 3526(\mathrm{OH}), 1708(\mathrm{C}=\mathrm{O}) ;{ }^{1} \mathrm{H}$ NMR $(500 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right) \delta: 0.83-0.85(6 \mathrm{H}, \mathrm{m}), 0.89-0.91(3 \mathrm{H}, \mathrm{m}), 0.98(3 \mathrm{H}, \mathrm{t}$, $J 7.4), 1.15$ ( $3 \mathrm{H}, \mathrm{d}, J 6.9$ ), 1.24-1.37 ( $4 \mathrm{H}, \mathrm{m}$ ), 1.38-1.46 (1H, m), 1.50-1.59 (1H, m), 1.61-1.64 (1H, m), $1.90(3 \mathrm{H}, \mathrm{s}), 1.92-1.99$ $(1 \mathrm{H}, \mathrm{m}), 2.15-2.16(4 \mathrm{H}, \mathrm{m}), 2.19-2.26(1 \mathrm{H}, \mathrm{m}), 2.37-2.49(2 \mathrm{H}$, $\mathrm{m}), 3.38-3.41(1 \mathrm{H}, \mathrm{m}), 4.08-4.12(1 \mathrm{H}, \mathrm{m}), 4.64(2 \mathrm{H}, \mathrm{s}), 5.22$ (1H, d, J 2.9), 5.26 (1H, d, $J 16.6$ ), 5.55 (1H, d, $J 16.6$ ), $7.03-7.06$ $(1 \mathrm{H}, \mathrm{m}), 7.49(2 \mathrm{H}, \mathrm{t}, J 7.7), 7.60-7.63(1 \mathrm{H}, \mathrm{m}), 7.89-7.91(2 \mathrm{H}$, $\mathrm{m}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 11.4,11.7$ (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 $\mathrm{C}_{30} \mathrm{H}_{46} \mathrm{NaO}_{7} \mathrm{~S}$ ( $\mathrm{MNa}^{+}$): 573.2856; found: 573.2855 .
(2R,3S)-3-Methyl-1-oxo-1-(2-oxo-2-phenylethoxy)pentan-2-yl (5S,6S,7R,8S,E)-2,6,8-trimethyl-7-[( $N$-methyl-L-alanyl)oxy]-5-(methylthiomethoxy)undec-2-enoate (33). Fmoc-MeAla-Cl was synthesised by using the identical procedure reported previously. ${ }^{26}$ To a stirred solution of Fmoc-MeAla-OH ( 227.7 mg , $0.70 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(3.9 \mathrm{~cm}^{3}\right)$ were added DMF $\left(0.0054 \mathrm{~cm}^{3}\right.$, $0.070 \mathrm{mmol})$ and $\mathrm{SOCl}_{2}\left(0.508 \mathrm{~cm}^{3}, 7.0 \mathrm{mmol}\right)$ 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 ( $152.6 \mathrm{mg}, 0.28 \mathrm{mmol}$ ) and the above Fmoc-MeAla-Cl in 1,2dichloroethane $\left(2.8 \mathrm{~cm}^{3}\right)$ was added $i$ - $\operatorname{Pr}_{2} \mathrm{NEt}\left(0.244 \mathrm{~cm}^{3}\right.$, 1.40 mmol ) at room temperature. The reaction mixture was warmed to $40^{\circ} \mathrm{C}$ and stirred for 14 h . The mixture was cooled to room temperature and quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$. The whole mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and the extract was washed with brine, and dried over $\mathrm{MgSO}_{4}$. The filtrate was concentrated under reduced pressure and the residue was filtered through a short pad of silica gel with hexaneEtOAc ( $9: 1$ 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 $\operatorname{MeCN}\left(7.0 \mathrm{~cm}^{3}\right)$ was added $\mathrm{Et}_{2} \mathrm{NH}\left(2.3 \mathrm{~cm}^{3}\right)$ at $0{ }^{\circ} \mathrm{C}$. 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 $33(94.9 \mathrm{mg}, 54 \%$ ) as a yellow oil: $[\alpha]_{\mathrm{D}}^{27}-55.4$ (c 0.79, $\mathrm{CHCl}_{3}$ ); IR (neat) $\nu_{\text {max }} / \mathrm{cm}^{-1}: 1712$ $(\mathrm{C}=\mathrm{O}) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}\right) \delta: 0.78(3 \mathrm{H}, \mathrm{t}, J 7.2)$, $0.81-0.84(6 \mathrm{H}, \mathrm{m}), 0.86(3 \mathrm{H}, \mathrm{t}, J 7.4), 0.99(3 \mathrm{H}, \mathrm{d}, J 6.9)$, $1.02-1.08(1 \mathrm{H}, \mathrm{m}), 1.09-1.14(1 \mathrm{H}, \mathrm{m}), 1.16(3 \mathrm{H}, \mathrm{d}, J 7.1)$, 1.23-1.34 (3H, m), 1.39-1.47 (1H, m), 1.69-1.77 (4H, m), 1.95 $(3 \mathrm{H}, \mathrm{s}), 2.02-2.08(1 \mathrm{H}, \mathrm{m}), 2.13-2.17(1 \mathrm{H}, \mathrm{m}), 2.19-2.27(4 \mathrm{H}$,
$\mathrm{m}), 2.32-2.36(1 \mathrm{H}, \mathrm{m}), 3.13(1 \mathrm{H}, \mathrm{q}, J 7.1), 3.63\left(1 \mathrm{H}, \mathrm{dt}, J_{1} 10.3\right.$, $J_{2} 2.6$ ), $4.44(1 \mathrm{H}, \mathrm{d}, J 11.5), 4.55(1 \mathrm{H}, \mathrm{d}, J 11.5), 4.79(1 \mathrm{H}, \mathrm{dd}$, $\left.J_{1} 10.3, J_{2} 2.3\right), 5.05(1 \mathrm{H}, \mathrm{d}, J 3.4), 5.30(1 \mathrm{H}, \mathrm{d}, J 16.6), 5.42(1 \mathrm{H}$, d, $J 16.6), 6.78-6.81(1 \mathrm{H}, \mathrm{m}), 7.46(2 \mathrm{H}, \mathrm{t}, J 8.0), 7.57-7.61(1 \mathrm{H}$, m), 7.85-7.87 ( $2 \mathrm{H}, \mathrm{m}$ ); ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}$ ) $\delta 10.3$, 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 $\mathrm{C}_{34} \mathrm{H}_{54} \mathrm{NO}_{8} \mathrm{~S}\left(\mathrm{MH}^{+}\right): 636.3565$; found: 636.3569.

Linear peptides (6a,b). To a stirred solution of $33(59.5 \mathrm{mg}$, 0.094 mmol ), peptide $9(185.2 \mathrm{mg})$ and HOAt ( 38.4 mg , $0.28 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}\left(3.1 \mathrm{~cm}^{3}\right)$ was added EDCI•HCl ( $54.1 \mathrm{mg}, 0.28 \mathrm{mmol}$ ) at $0{ }^{\circ} \mathrm{C}$. The reaction mixture was warmed to room temperature and stirred for 24 h . The mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$. The whole mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and the extract was washed with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$, and dried over $\mathrm{MgSO}_{4}$. 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 $\mathrm{AcOH} / \mathrm{EtOAc} / \mathrm{H}_{2} \mathrm{O}(60: 35: 5$, $4.3 \mathrm{~cm}^{3}$ ) was added $\mathrm{Zn}(92.2 \mathrm{mg}, 1.4 \mathrm{mmol})$ 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 $\mathrm{MgSO}_{4}$. 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 $\left(2.4 \mathrm{~cm}^{3}\right)$ was added $\mathrm{Et}_{2} \mathrm{NH}\left(0.80 \mathrm{~cm}^{3}\right)$ at $0{ }^{\circ} \mathrm{C}$. 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 ( $59 \%$ $\mathrm{CH}_{3} \mathrm{CN}$ in $0.1 \%$ TFA solution) to give linear peptides $\mathbf{6 a}$ $(29.6 \mathrm{mg}, 30 \%$ from 33) and 6b ( $24.0 \mathrm{mg}, 24 \%$ from 33) as a colorless powder.

6a: $[\alpha]_{\mathrm{D}}^{27}-46.8$ (c $0.89, \mathrm{CHCl}_{3}$ ); IR (neat) $\nu_{\max } / \mathrm{cm}^{-1}: 1645$ $(\mathrm{C}=\mathrm{O}) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}, 1: 1\right.$ mixture of rotamers) $\delta: 0.77(1.5 \mathrm{H}, \mathrm{d}, J 7.0), 0.81-0.91(18 \mathrm{H}, \mathrm{m}), 0.96(1.5 \mathrm{H}, \mathrm{d}$, $J 3.1), 0.97(1.5 \mathrm{H}, \mathrm{d}, J 3.1), 1.06-1.22(4.5 \mathrm{H}, \mathrm{m}), 1.26-1.33(3 \mathrm{H}$, $\mathrm{m}), 1.37(3 \mathrm{H}, \mathrm{d}, J 7.3), 1.41-1.53(2 \mathrm{H}, \mathrm{m}), 1.74-1.84(5 \mathrm{H}, \mathrm{m})$, $1.96-2.01(1 \mathrm{H}, \mathrm{m}), 2.07(1.5 \mathrm{H}, \mathrm{s}), 2.08(1.5 \mathrm{H}, \mathrm{s}), 2.20-2.38(3 \mathrm{H}$, m), $2.75-2.86(4.5 \mathrm{H}, \mathrm{m}), 3.00-3.12(6.5 \mathrm{H}, \mathrm{m}), 3.53(0.5 \mathrm{H}, \mathrm{d}$, $J$ 16.4), $3.70-3.71(1 \mathrm{H}, \mathrm{m}), 4.00(0.5 \mathrm{H}, \mathrm{d}, J 18.0), 4.05-4.09$ $(0.5 \mathrm{H}, \mathrm{m}), 4.17(0.5 \mathrm{H}, \mathrm{d}, J 18.0), 4.24(0.5 \mathrm{H}, \mathrm{d}, J 16.4)$, $4.31-4.36(0.5 \mathrm{H}, \mathrm{m}), 4.48-4.50(0.5 \mathrm{H}, \mathrm{m}), 4.53(0.5 \mathrm{H}, \mathrm{d}, J 5.0)$, $4.55(0.5 \mathrm{H}, \mathrm{d}, J 5.0), 4.62(0.5 \mathrm{H}, \mathrm{d}, J 5.0), 4.64(0.5 \mathrm{H}, \mathrm{d}, J 5.0)$, $4.73-4.76(0.5 \mathrm{H}, \mathrm{m}), 4.87-4.89(1 \mathrm{H}, \mathrm{m}), 4.95(0.5 \mathrm{H}, \mathrm{d}, J 3.4)$, $4.96(0.5 \mathrm{H}, \mathrm{d}, J 3.4), 5.19(0.5 \mathrm{H}, \mathrm{q}, J 7.3), 5.24(0.5 \mathrm{H}, \mathrm{q}, J 7.3)$, $5.43-5.46(0.5 \mathrm{H}, \mathrm{m}), 5.63\left(0.5 \mathrm{H}, \mathrm{dd}, J_{1} 9.9, J_{2} 5.7\right), 6.82-6.89$ $(1 \mathrm{H}, \mathrm{m}), 7.15-7.28(6 \mathrm{H}, \mathrm{m}), 7.64\left(2 \mathrm{H}, \mathrm{br}\right.$ s); ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}$ ) $\delta: 10.2$ (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 $\mathrm{C}_{48} \mathrm{H}_{80} \mathrm{~N}_{5} \mathrm{O}_{11} \mathrm{~S}\left(\mathrm{MH}^{+}\right)$: 934.5570; found: 934.5567.

6b: $[\alpha]_{\mathrm{D}}^{28}-23.5\left(c 1.00, \mathrm{CHCl}_{3}\right)$; IR (neat) $\nu_{\max } / \mathrm{cm}^{-1}: 1648$ $(\mathrm{C}=\mathrm{O}) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}, 3: 3: 3: 1\right.$ mixture of rotamers) $\delta: 0.74(0.9 \mathrm{H}, \mathrm{d}, J 6.9), 0.78-0.98(21.9 \mathrm{H}, \mathrm{m}), 1.05(1.2 \mathrm{H}$, d, $J 6.9), 1.08-1.51(11 \mathrm{H}, \mathrm{m}), 1.75-1.90(5 \mathrm{H}, \mathrm{m}), 1.97-2.02(1 \mathrm{H}$, m), 2.05-2.06 (2.7H, m), $2.09(0.3 \mathrm{H}, \mathrm{s}), 2.19-2.45(3 \mathrm{H}, \mathrm{m}), 2.72$ $(0.3 \mathrm{H}, \mathrm{s}), 2.81-2.86(4.8 \mathrm{H}, \mathrm{m}), 2.89-2.91(2 \mathrm{H}, \mathrm{m}), 2.93(0.3 \mathrm{H}$, s), $2.95(0.3 \mathrm{H}, \mathrm{s}), 3.00-3.09(1.8 \mathrm{H}, \mathrm{m}), 3.12-3.18(1.5 \mathrm{H}, \mathrm{m}), 3.43$ $(0.1 \mathrm{H}, \mathrm{d}, \mathrm{J} 16.1), 3.55-3.56(0.1 \mathrm{H}, \mathrm{m}), 3.61-3.76(1.6 \mathrm{H}, \mathrm{m})$, $4.09-4.16(0.6 \mathrm{H}, \mathrm{m}), 4.25-4.36(1.3 \mathrm{H}, \mathrm{m}), 4.45-4.48(0.4 \mathrm{H}, \mathrm{m})$, $4.52-4.64(1.9 \mathrm{H}, \mathrm{m}), 4.70-4.73(0.3 \mathrm{H}, \mathrm{m}), 4.79-5.00(3 \mathrm{H}, \mathrm{m})$, $5.08-5.12(0.7 \mathrm{H}, \mathrm{m}), 5.26\left(0.3 \mathrm{H}, \mathrm{dd}, J_{1} 9.3, J_{2} 6.0\right), 5.33(0.3 \mathrm{H}$, dd, $\left.J_{1} 11.1, J_{2} 4.4\right), 5.46\left(0.3 \mathrm{H}, \mathrm{dd}, J_{1} 11.1, J_{2} 4.8\right), 5.52(0.1 \mathrm{H}$, dd, $\left.J_{1} 9.5, J_{2} 6.4\right), 6.84-6.91(1 \mathrm{H}, \mathrm{m}), 6.97(0.3 \mathrm{H}, \mathrm{d}, J 9.2)$, $7.07-7.26(5 \mathrm{H}, \mathrm{m}), 7.42(0.3 \mathrm{H}, \mathrm{d}, J 7.3), 7.69(0.4 \mathrm{H}, \mathrm{d}, J 6.7)$, $8.11\left(2 \mathrm{H}\right.$, br s); ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}$ ) $\delta: 10.3$ (3C), 10.6, 12.0 (2C), 12.2 (2C), 12.8, 12.9, 13.2 (3C), 13.7, 14.2 (2C), 14.4 (2C), 14.6 (2C), 14.7, 14.8, 14.9 (2C), 15.1, 15.2, 15.9 (2C), 16.1 (2C), 16.2, 16.3, 20.8, 20.9, 26.8 (2C), 26.9 (2C), 27.0 (2C), 27.4, 29.4, 29.5 (2C), 29.6, 30.4, 30.5, 30.6, 31.1, 31.9, 32.6, $32.7,33.6,34.5,34.6,34.7,35.2$, $35.3,35.4,35.5,35.6$, 35.9, 36.5, 36.8 , 37.0 (4C), 37.1 , 37.2 , 37.4 (2C), 38.1, 38.4 , 48.0 (2C), 48.6 (2C), 52.5, 52.6, 53.0, 53.2, 54.0, 54.3 (2C), 54.7, $54.8,55.0,56.4,57.1,58.1,73.5,75.3$ (2C), 75.6 (2C), 75.9, 76.1 (2C), 78.6, 79.0, 79.6, 79.7, 127.5 (2C), 127.6, 129.1 (3C), 129.2 (3C), 129.3, 130.2 (2C), 130.3 (3C), 130.4 (2C), 137.5, 137.8, 138.1, 138.3, 141.4, 141.5, 141.9, 142.2, 167.9, 168.1, 168.2, $168.3,168.7,169.6,170.1,170.2,170.3$ (2C), 170.8, 171.2 (2C), 171.3, 171.4, 171.8, 172.0, 172.2 (2C), 172.5, 173.4, 174.4, 174.7; HRMS (ESI) calcd for $\mathrm{C}_{48} \mathrm{H}_{80} \mathrm{~N}_{5} \mathrm{O}_{11} \mathrm{~S}\left(\mathrm{MH}^{+}\right)$: 934.5570; found: 934.5580.

Odoamide (5a). To a stirred solution of $\mathbf{6 a}(17.8 \mathrm{mg}$, 0.017 mmol ), HOAt ( $11.6 \mathrm{mg}, 0.085 \mathrm{mmol}$ ) and collidine $\left(0.067 \mathrm{~cm}^{3}, 0.51 \mathrm{mmol}\right)$ in DMF $\left(17.0 \mathrm{~cm}^{3}\right)$ was added HATU $(64.6 \mathrm{mg}, 0.17 \mathrm{mmol})$ at room temperature. After stirring for 5 h , the reaction 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 saturated aqueous $\mathrm{NaHCO}_{3}$, and dried over $\mathrm{MgSO}_{4}$. 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 $\mathrm{THF} / \mathrm{H}_{2} \mathrm{O}\left(4: 1,0.566 \mathrm{~cm}^{3}\right)$ were added 2,6lutidine $\left(0.0394 \mathrm{~cm}^{3}, 0.34 \mathrm{mmol}\right)$ and $\mathrm{AgNO}_{3}(115.5 \mathrm{mg}$, 0.68 mmol ) at room temperature. The reaction mixture was warmed to $70{ }^{\circ} \mathrm{C}$ and stirred for 4 h . The 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 $\mathrm{H}_{2} \mathrm{O}$, saturated aqueous $\mathrm{NaHCO}_{3}$ and brine, and dried over $\mathrm{MgSO}_{4}$. The filtrate was concentrated under reduced pressure and the residue was purified by reverse-phase preparative $\mathrm{HPLC}\left(72 \% \mathrm{CH}_{3} \mathrm{CN}\right.$ in $\left.\mathrm{H}_{2} \mathrm{O}\right)$ to give odoamide (5a) $(12.4 \mathrm{mg}, 85 \%)$ as a colorless powder: $[\alpha]_{\mathrm{D}}^{28}-15.8$ (c 1.14, $\left.\mathrm{CH}_{3} \mathrm{OH}\right)$; IR (neat) $\nu_{\max } / \mathrm{cm}^{-1}$ : $3305(\mathrm{OH}), 1645(\mathrm{C}=\mathrm{O}) ;{ }^{1} \mathrm{H}$ NMR (500 MHz, CD $\left.{ }_{3} \mathrm{OD}\right) \delta: 0.83-0.96(21 \mathrm{H}, \mathrm{m}), 1.04-1.12(4 \mathrm{H}$, $\mathrm{m}), 1.19-1.26(1 \mathrm{H}, \mathrm{m}), 1.29-1.40(4 \mathrm{H}, \mathrm{m}), 1.42(3 \mathrm{H}, \mathrm{d}, J 6.9)$, 1.45-1.55 ( $1 \mathrm{H}, \mathrm{m}$ ), 1.57-1.67 (1H, m), 1.78-1.87 (3H, m), 1.90 $(3 \mathrm{H}, \mathrm{s}), 2.01-2.04(1 \mathrm{H}, \mathrm{m}), 2.12-2.16(1 \mathrm{H}, \mathrm{m}), 2.20-2.28(1 \mathrm{H}$, $\mathrm{m}), 2.85-2.95(4 \mathrm{H}, \mathrm{m}), 3.01-3.06(4 \mathrm{H}, \mathrm{m}), 3.30(3 \mathrm{H}, \mathrm{s}), 3.56$ $(1 \mathrm{H}, \mathrm{d}, J 18.3), 3.74-3.76(1 \mathrm{H}, \mathrm{m}), 3.94(1 \mathrm{H}, \mathrm{q}, J 6.9), 4.19(1 \mathrm{H}$, d, $J 18.3$ ), $4.49(1 \mathrm{H}, \mathrm{q}, J 6.9), 4.86-4.89(2 \mathrm{H}, \mathrm{m}), 5.05(1 \mathrm{H}, \mathrm{d}$, $J 6.3), 5.45\left(1 \mathrm{H}, \mathrm{dd}, J_{1} 10.3, J_{2} 5.2\right), 7.12-7.20(5 \mathrm{H}, \mathrm{m}), 7.31-7.32$ $(1 \mathrm{H}, \mathrm{m}) ;{ }^{13} \mathrm{C}$ NMR ( $\left.125 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta: 10.0,11.7,12.0,12.1$, $13.1,13.8,14.5,14.6,15.6,16.0,21.6,24.7,27.4,30.5$ (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 $\mathrm{C}_{46} \mathrm{H}_{73} \mathrm{~N}_{5} \mathrm{NaO}_{10}\left(\mathrm{MNa}^{+}\right)$: 878.5250; found: 878.5254.

## Growth inhibition assay

A549 cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Sigma) supplemented with $10 \%(\mathrm{v} / \mathrm{v})$ fetal bovine serum at $37{ }^{\circ} \mathrm{C}$ in a $5 \% \mathrm{CO}_{2}$-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 $0.050 \mathrm{~cm}^{3}$ 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 $0.040 \mathrm{~cm}^{3}$ of the fresh culture medium to the cell cultures, $0.030 \mathrm{~cm}^{3}$ of the chemical diluents were also added. The final volume of DMSO in the medium was equal to $0.1 \%(\mathrm{v} / \mathrm{v})$. 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 $0.100 \mathrm{~cm}^{3}$ of the medium, the cell culture in each well was supplemented with $0.020 \mathrm{~cm}^{3}$ 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 average of inhibition rates in each condition was evaluated to determine $\mathrm{IC}_{50}$ values using the GraphPad Prism software.

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