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Tetrahedron
Tetrahedron 60 (2004) 6859–6880

An expeditious total synthesis of kalkitoxins: determination of the absolute stereostructure of natural kalkitoxin☆

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Received 22 February 2004; revised 14 May 2004; accepted 3 June 2004

Abstract—Kalkitoxin, a potent neurotoxin isolated from the marine cyanobacteria *Lyngbya majuscula*, and its congeners (**1**–**7**) were efficiently synthesized utilizing Hruby's diastereoselective 1,4-addition and the Wipf's oxazoline-thiazoline conversion as key steps. These synthetic efforts in combination with spectral studies of natural kalkitoxin clearly determined the absolute stereostructure of kalkitoxin to be **7**.

1. Introduction

This paper describes an expeditious total synthesis of kalkitoxin, a novel potent neurotoxin, and its congeners via a highly convergent and versatile synthetic strategy, which clearly determined the absolute stereostructure of natural kalkitoxin. Kalkitoxin was isolated from the marine cyanobacterium *Lyngbya majuscula* aided by bioassay-guided fractionation using the brine shrimp and gold fish toxicity assays.[1,2] Kalkitoxin was revealed to be strongly ichthyotoxic to the common goldfish (*Carassius auratus*, LC_{50} 700 nM), potently brine shrimp toxic (*Artemia salina*, LC_{50} 170 nM), and potently inhibited cell division in a fertilized sea urchin embryo assay (IC_{50}~25 nM), while in a primary cell culture of rat neurons kalkitoxin displayed an exceptional level of neurotoxicity (LC_{50} 3.86 nM) and its effects were inhibitable with NMDA receptor antagonists.[3] In addition, kalkitoxin was highly active in an inflammatory disease model which measured IL-1β-induced $sPLA_2$ secretion from HepG2 cells (IC_{50} 27 nM). Furthermore, preliminary evidence suggests that kalkitoxin is a potent blocker of the voltage sensitive Na^+ channel in mouse neuro-2a cells (EC_{50} 1 nM).

Kalkitoxin is a lipoamide containing four methyl groups on the carbon chain and possessing five stereogenic centers, an *N*-methylamide, and a thiazoline ring. Free rotation around the chain precluded the NOE assignment of the structure, and the *N*-methylamide function causes restricted rotation resulting in a complex pattern in its NMR spectra. These structural characteristics precluded the determination of absolute stereostructure. In continuation of our interests on the total synthesis of biologically active aquatic natural products,[4,5] kalkitoxin's potent biological activity and limited natural availability prompted us to synthesize this unique molecule and its congeners and to determine its absolute configuration. Our synthetic efforts supplied kalkitoxin and its congeners (**1**–**7**), culminating in the determination of the absolute stereostructure of kalkitoxin to be **7** (Fig. 1).[1,6]

2. Synthetic strategy

When we initiated the synthetic studies of kalkitoxin, the stereochemical structure was still undetermined, which led us to adopt a highly flexible synthetic route to kalkitoxins having any possible stereostructure. As shown in Scheme 1, the whole molecule of kalkitoxin was divided into three building blocks **8**–**10**, of which the left fragment **8** is commercially available and the right fragment **10** would be

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.06.014

Keywords: Kalkitoxin; Marine cyanobacteria; Total synthesis; Absolute configuration; Stereoselective 1,4-addition.

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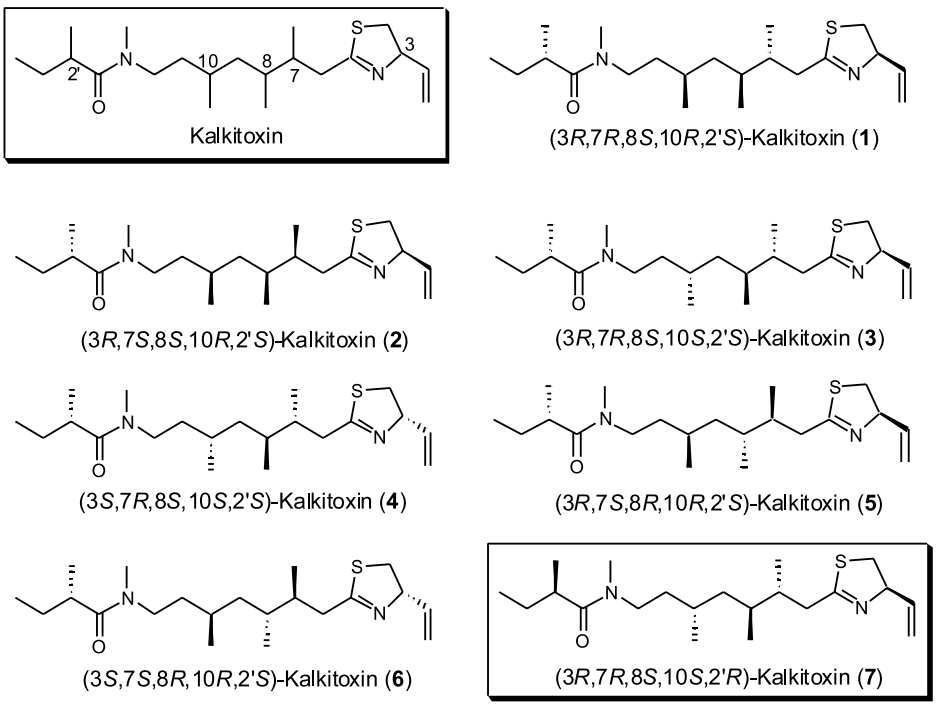
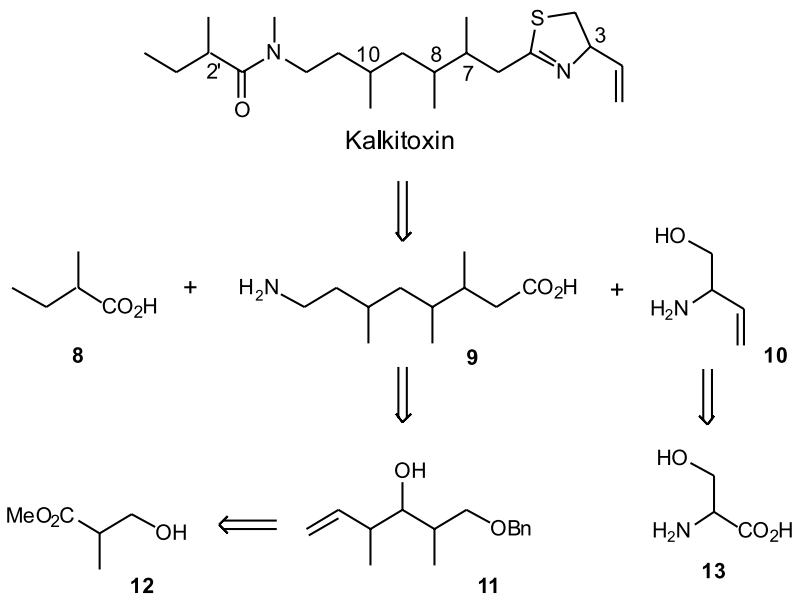


Figure 1.

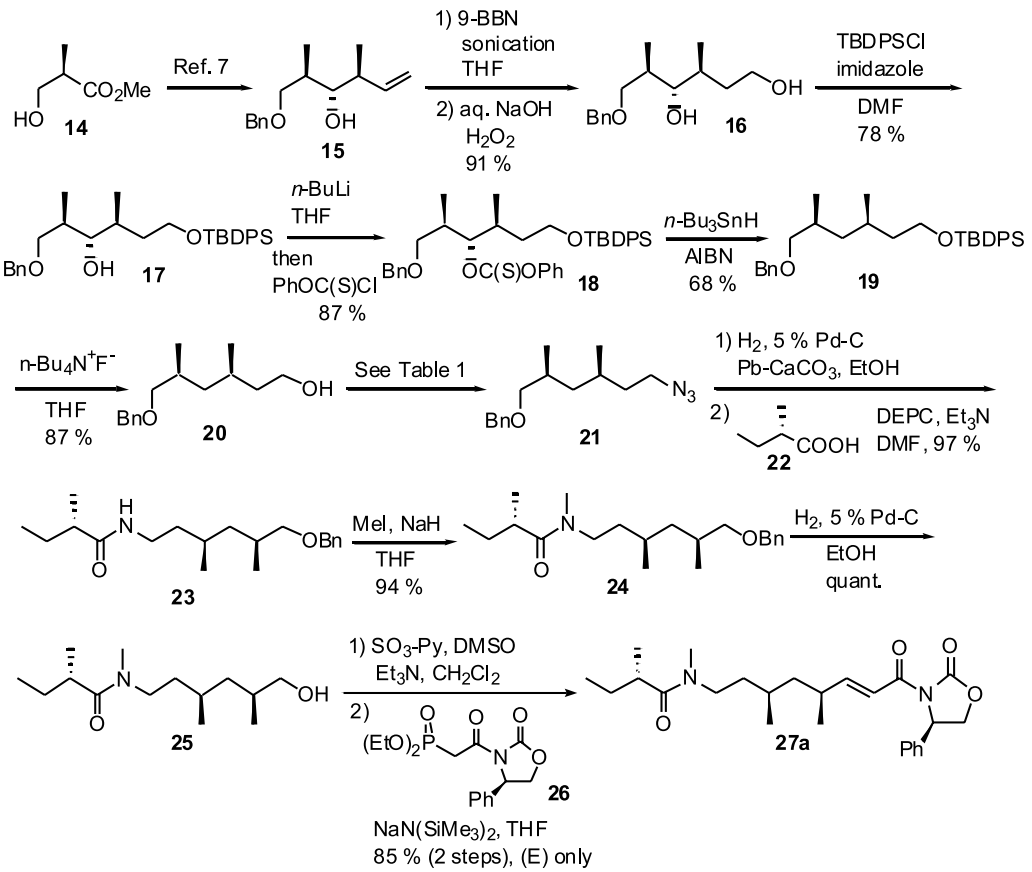


Scheme 1.

synthesized from serine (**13**). The central fragment **9** would be synthesized from methyl 3-hydroxy-2-methylpropionate (**12**) by asymmetric crotylation followed by deoxygenation of the resulting alcohol **11**. The stereogenic center at C7 would be introduced by 1,4-addition of the chiral oxazolidinone after coupling with the left fragment **8**. Since the thiazoline ring was thought to be fragile during synthesis, its construction should be carried out at the final stage of the synthesis. In addition, it was thought to be preferable that the starting materials adopted should be available in a stereochemically clear form and the reactions chosen should proceed in a highly stereoselective manner. According to this strategy, we launched the total synthesis of the kalkitoxins.

3. Results and discussion

We first started the synthesis of (3*R*,7*R*,8*S*,10*R*,2′*S*)-kalkitoxin (**1**) to establish the facile synthetic route toward kalkitoxins. The known[7] hexenol **15**, prepared from methyl (*R*)-3-hydroxy-2-methylpropionate (**14**) in 4 steps, was converted to the diol **16** by hydroboration with 9-BBN under sonication conditions[8] followed by oxidation, shown



Scheme 2.

in Scheme 2. After protection of the primary hydroxyl function with TBDPSCl (^{t}Bu(C_6H_5)$_2$SiCl), the secondary hydroxyl group of **17** was deoxygenated via the thiocarbonate **18** according to the Barton–McCombie procedure[9] by thiocarbonylation and then radical reduction. The deoxygenated product **19** was treated with TBAF ($Bu_4N^+F^-$) to give the alcohol **20**, which was converted to the azide **21** under various conditions, shown in Table 1. The ordinary two-step process of the mesylation and then azidation afforded the desired azide **21** in 88% yield. The one step procedure utilizing DPPA ((C_6H_5O)$_2$P(O)N_3) and DBU (1,8-diazabicyclo[5.4.0]unde-7-ene)[10] sluggishly proceeded at room temperature and required heating for a longer time. The use of *p*-NO_2-DPPA (*p*-NO_2–(C_6H_4O)$_2$P(O)N_3)[11] in place of DPPA accelerated the reaction and shortened the reaction time to give the azide **21** in good yield.

Table 1. One-pot azidation of using DPPA (C_6H_5O)$_2$P(O)N_3 or *p*-NO_2-DPPA (*p*-$NO_2C_6H_4O$)$_2$P(O)N_3

Entry	Reagent (equiv.)	Base (equiv.)	Reaction conditions	Yield (%)
1	DPPA (1.5)	DBU (1.5)	0 °C, 1.5 h; rt, 21 h	23[a]
2	DPPA (1.5)	DBU (1.5)	0 °C, 1.5 h; 65 °C, 21 h	97
3	*p*-NO_2-DPPA (1.5)	DBU (1.5)	0 °C, 1 h; rt, 7 h	79
4	*p*-NO_2-DPPA (1.5)	DBU (1.5)	0 °C, 1 h; 65 °C, 5 h	81

[a] Diphenyl phosphate was obtained in 63% yield.

The azide **21** thus obtained underwent catalytic hydrogenation over Lindlar catalyst[12] to give the corresponding amine, which was coupled with (*S*)-2-methylbutyric acid (**22**), the left fragment of kalkitoxins, by use of DEPC ((EtO)$_2$P(O)CN)[13] in the presence of triethylamine to produce the amide **23** in excellent yield. After the *N*-methylation, catalytic removal of the benzyl group from **24** afforded the alcohol **25**. The conversion of **25** to the (*E*)-enimide **27a** was smoothly accomplished by the Parikh–Doering oxidation[14] followed by the Horner–Wadsworth–Emmons reaction with the oxazolidinone **26** derived from (*R*)-phenylglycine.[15]

The next problem to overcome was the stereoselective introduction of the methyl group at the C7 position[16] by 1,4-addition. Hruby and co-workers[17] already revealed that the 1,4-addition of a methyl group into the optically active α,β-unsaturated acyl-4-phenyloxazolidinone by use of a combination of methyl magnesium bromide and cuprous bromide·dimethyl sulfide proceeded with high diastereoselectivity, and Romo and co-workers[15] utilized this method for the total synthesis of (−)-pateamine A. High stereoselectivity is explained by the fixed conformation due to the chelation of magnesium by the two carbonyl groups of the oxazolidinone and enimide, and by the attack of the methyl group from the opposite side of the phenyl group in the oxazolidinone, as shown in Figure 2.

Since both enantiomers of the 5-phenyloxazolidinone are

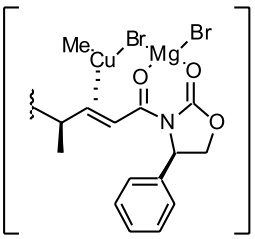
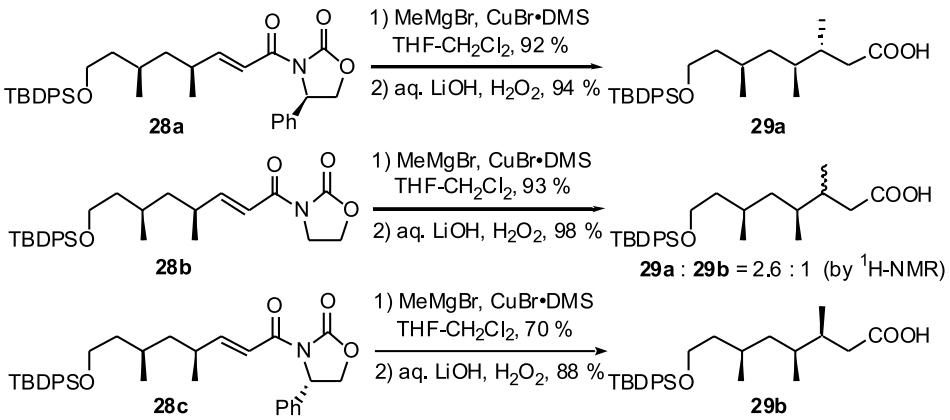


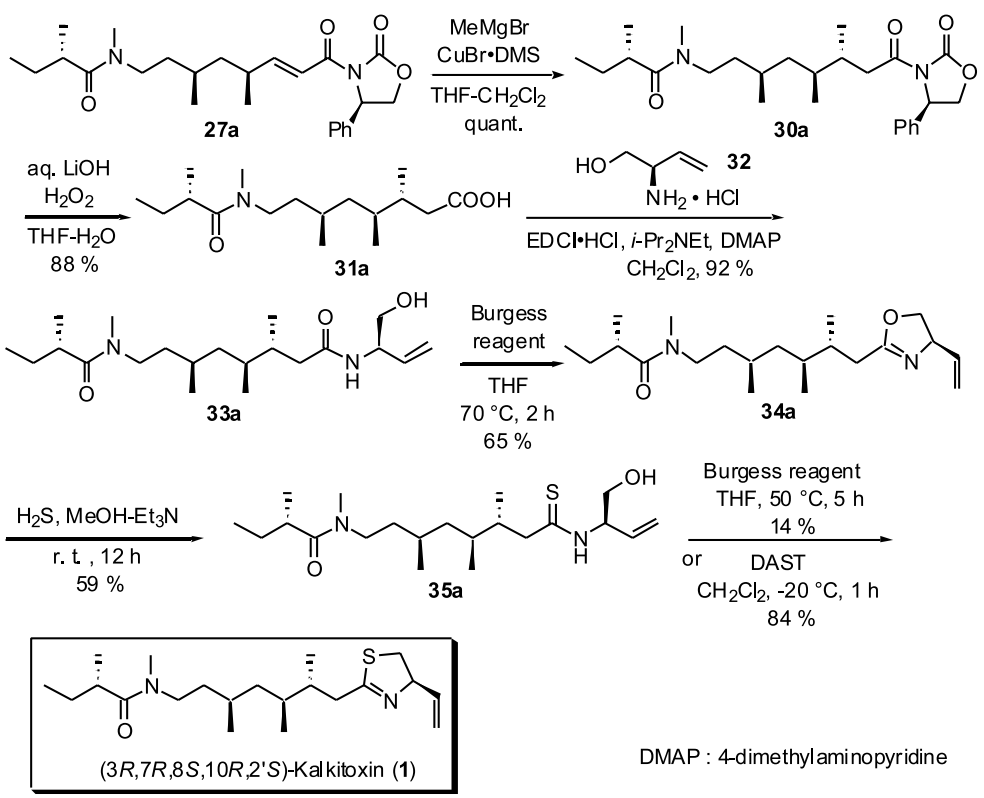
Figure 2.

easily available, their proper use will produce both enantiomers different at the C7 methyl function. This flexibility led us to adopt the Hruby's diastereoselective 1,4-addition method (Scheme 3).[18,19] Thus, the 1,4-addition reaction to the oxazolidinone **27a** was carried out under analogous conditions using methyl magnesium bromide and cuprous bromide·dimethyl sulfide, giving the (7*R*)-oxazolidinone **30a** quantitatively with complete stereoselectivity. Removal of the oxazolidinone moiety with alkaline hydrogen peroxide afforded the carboxylic acid **31a**.[20]

Coupling of the acid **31a** with (*R*)-2-amino-3-butenol hydrochloride (**32**)[21] smoothly proceeded by use of EDCI·HCl ($Me_2N(CH_2)_3-N{=}C{=}N-Et$) to give the amide **33a**, which was converted to the oxazoline **34a** with the Burgess reagent ($Et_3N^+SO_2N^-CO_2Me$),[22] as shown in Scheme 4. Transformation of the oxazoline ring in **34a** to the thiazoline ring in kalkitoxin (**1**) was accomplished according to the method of Wipf.[23] Thus, treatment of the oxazoline **34a** with hydrogen sulfide led to ring-opening to give the thioamide **35a**, which underwent the recyclization with the Burgess reagent to give kalkitoxin



Scheme 3.



Scheme 4.

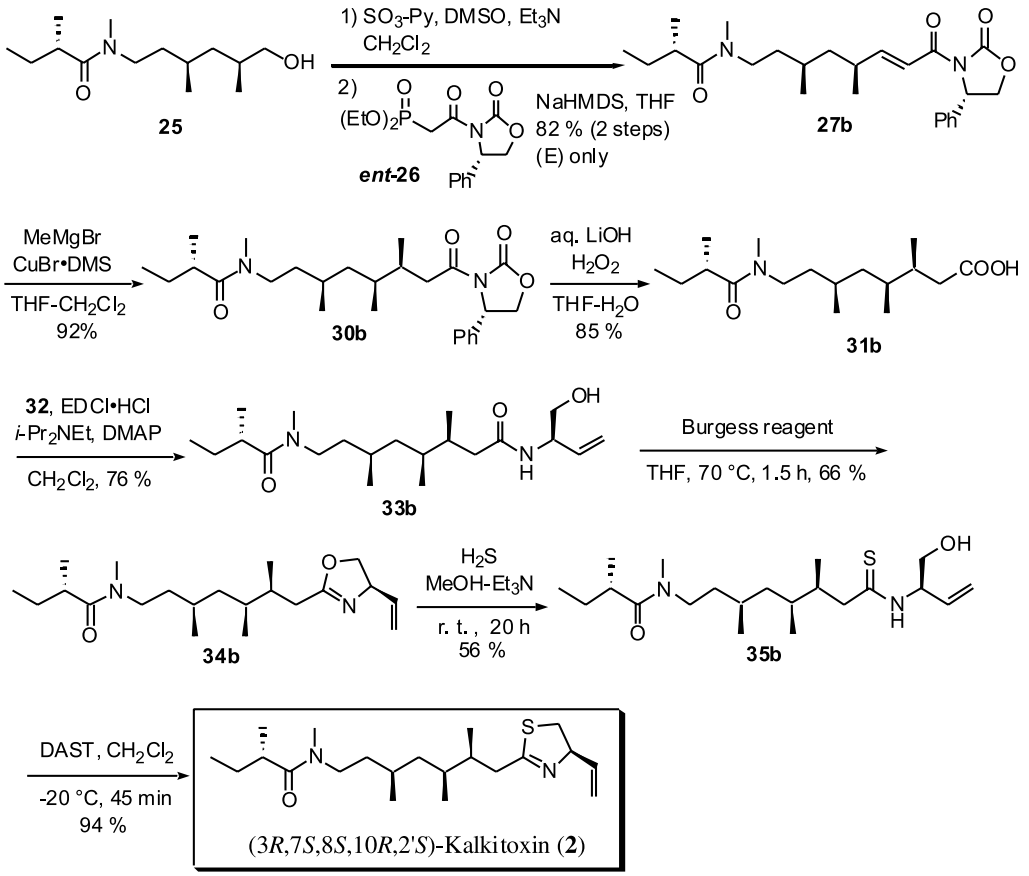
1 having (3*R*,7*R*,8*S*,10*R*,2′*S*)-configuration in 14% yield. Replacement of the Burgess reagent with DAST (Et_2NSF_3)[24] increased the yield to 84%.

Analogously, the enimide **27b** was synthesized by the oxidation of the alcohol **25** and then the Horner–Wadsworth–Emmons reaction with the (*S*)-phosphonate *ent*-**26**. The diastereoselective 1,4-addition of the methyl group to **27b**, followed by alkaline removal of the chiral auxiliary afforded the (7*S*)-carboxylic acid **31b**, which was coupled with **32** to give the amide **33b**. Analogous transformation of the amide **33b** as above produced kalkitoxin **2** with (3*R*,7*S*,8*S*,10R,2′S)-configuration, as shown in Scheme 5.

Although the kalkitoxin **1** exhibited a similar specific rotation, $[\alpha]_D$=+15.5, to that of natural kalkitoxin, $[\alpha]_D$=+16, the ^{13}C NMR spectra were slightly different from each other and, especially, the difference of 0.12–0.19 ppm was observed at the C10, C11, and *N*-methyl carbon signals. The ^1H NMR spectrum of **1** was also different at the chemical shift of the C10, C11, and C12 positions. The specific rotation of the kalkitoxin **2** was +49.6, and its ^{13}C NMR spectrum differed from that of the natural one at the signals of the C6 (δ 3.45 ppm) and C9 (δ 2.63 ppm) positions. In addition, the ^1H NMR spectrum was also not identical. These spectral features clearly showed that the synthesized kalkitoxins **1** and **2** have different stereochemistries from those of the natural product.

During the investigation of the above synthetic works, the Oregon group led by Gerwick determined the absolute configuration of the C3 position to be *R* [1,25] by obtaining cysteinic acid through ozonolysis and then acid hydrolysis of natural kalkitoxin and by identification of L-configuration through Marfey's analysis.[26] The relative stereochemistry of the three chiral centers within the aliphatic chain of kalkitoxin was also suggested to be 7*R**, 8*S**, and 10*S** by *J*-based configuration analysis[27] using the E.COSY NMR pulse sequence, HSQMBC,[28] and a cryoprobe NMR technology (see Supplementary data). Although the limited amount of natural kalkitoxin precluded determination of the C′2 stereochemistry, the above stereostructure studies reduced the total number of stereochemical possibilities to four: (3*R*,7*R*,8*S*,10*S*,2′*S*), (3*R*,7*R*,8*S*,10*S*,2′*R*), (3*R*,7*S*,8*R*,10*R*,2′*S*), or (3*R*,7*S*,8*R*,10*R*,2′*R*).

To determine the absolute configuration of natural kalkitoxin, the four kalkitoxins having possible configurations were synthesized. Since the 2-methylbutyric acid part is introduced at an early stage of our synthetic strategy (Scheme 2), efforts were required to synthesize kalkitoxins isomeric at the C2′ position. Thus the C2′ configuration of the intermediates was fixed to be *S*. Instead, both (3*R*)- and (3*S*)-isomers were synthesized because the thiazoline ring was introduced at the final stage of the synthesis. This strategy would furnish kalkitoxin having natural configuration or its antipode. Thus the (3*R*,7*R*,8*S*,10*S*,2′*S*), (3*S*,7*R*,8*S*,10*S*,2′*S*) (corresponding to the antipode of the

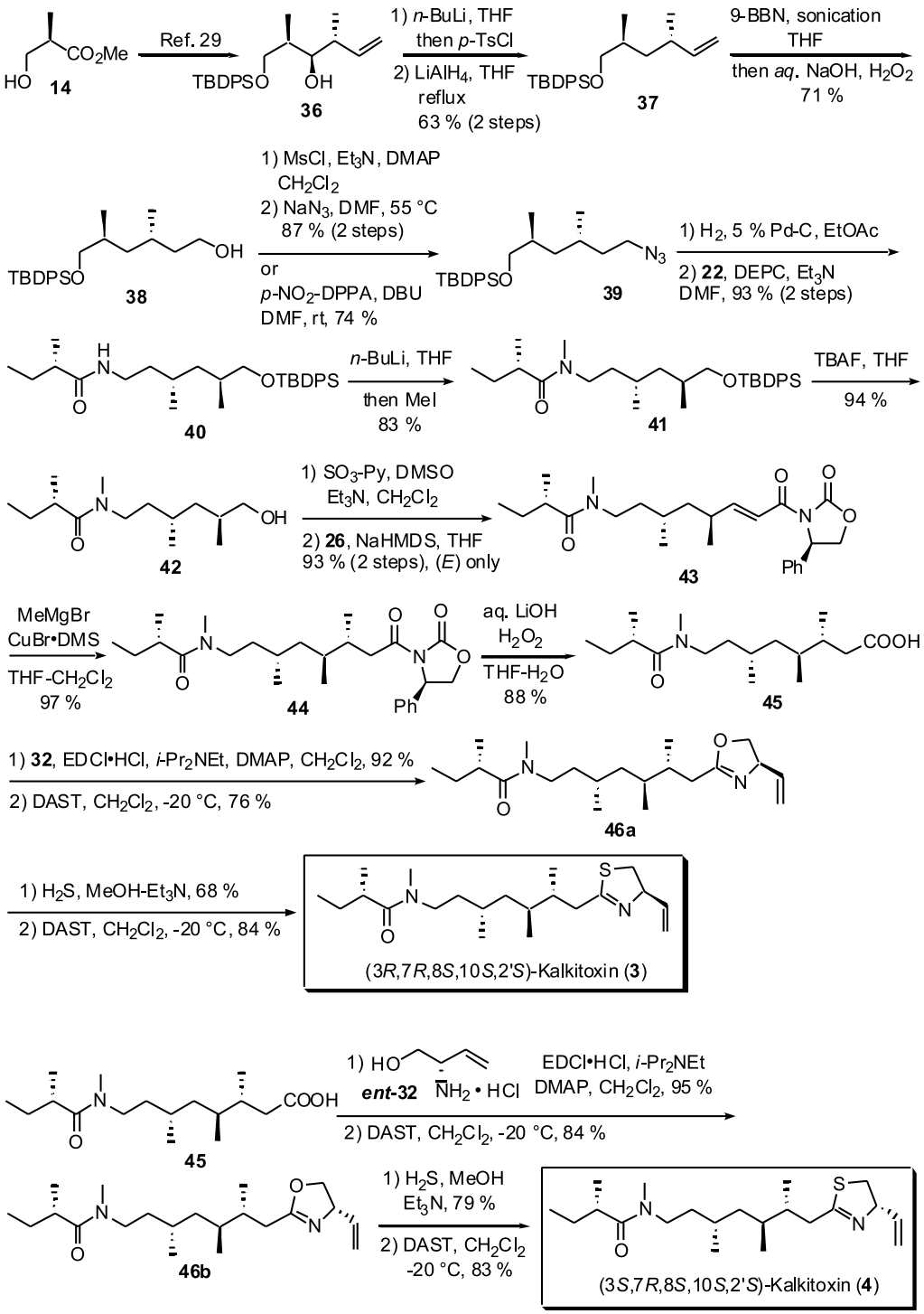


Scheme 5.

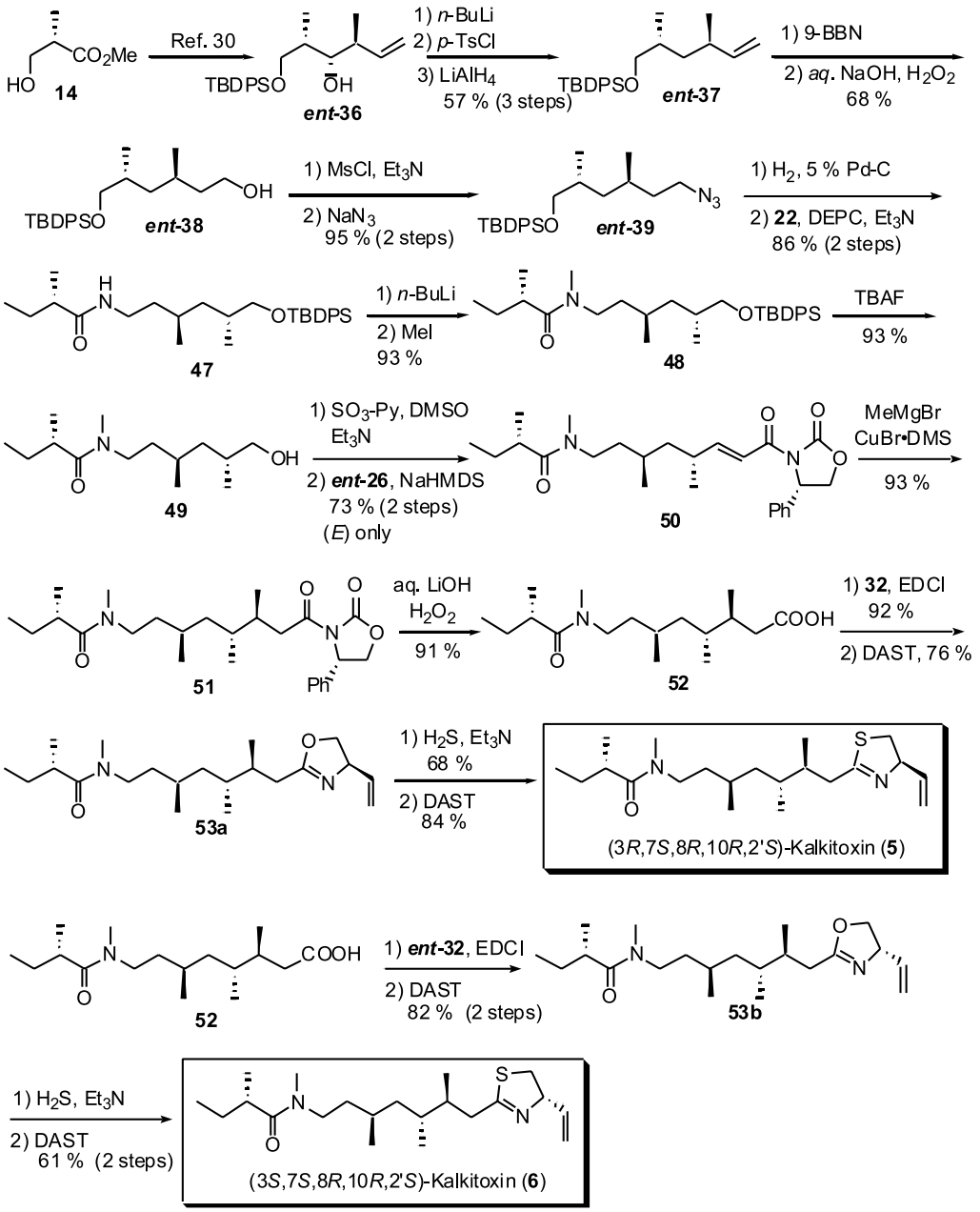
(3*R*,7*S*,8*R*,10*R*,2′*R*)-isomer), (3*R*,7*S*,8*R*,10*R*,2′*S*), and (3*S*,7*S*,8*R*,10*R*,2′*S*)-isomers (corresponding to the antipode of the (3*R*, 7*R*, 8*S*,10*S*,2′*R*)-isomer) were synthesized by use of analogous method, as shown in Schemes 6–8.

Starting from (*R*)-3-hydroxy-2-methylpropionic acid (**14**), the alcohol **36** with the TBDPS function was prepared according to the literature.[29] Removal of the hydroxyl group of **36** was carried out by tosylation followed by hydride reduction to give the deoxygenated compound **37**, as shown in Scheme 6. Sequence of the reactions analogous to the synthesis of **1** and **2** smoothly and stereoselectively afforded the carboxylic acid **45** utilizing (*S*)-2-methylbutyric acid (**22**) and the phosphonate **26**. Coupling of the acid **45** with (*R*)- and (*S*)-2-amino-3-buten-1-ol hydrochlorides (**32** and *ent*-**32**), followed by treatment with DAST, respectively, produced **46a** and **46b**, from which the thiazoline ring was constructed to give (3*R*,7*R*,8*S*,10*S*,2′*S*)-kalkitoxin (**3**) and its (3*S*)-isomer (**4**), respectively.

Analogously, the alcohol *ent*-**36** was prepared from the ester **14**.[30] Analogous reaction sequences as above afforded



Scheme 6.



Scheme 7.

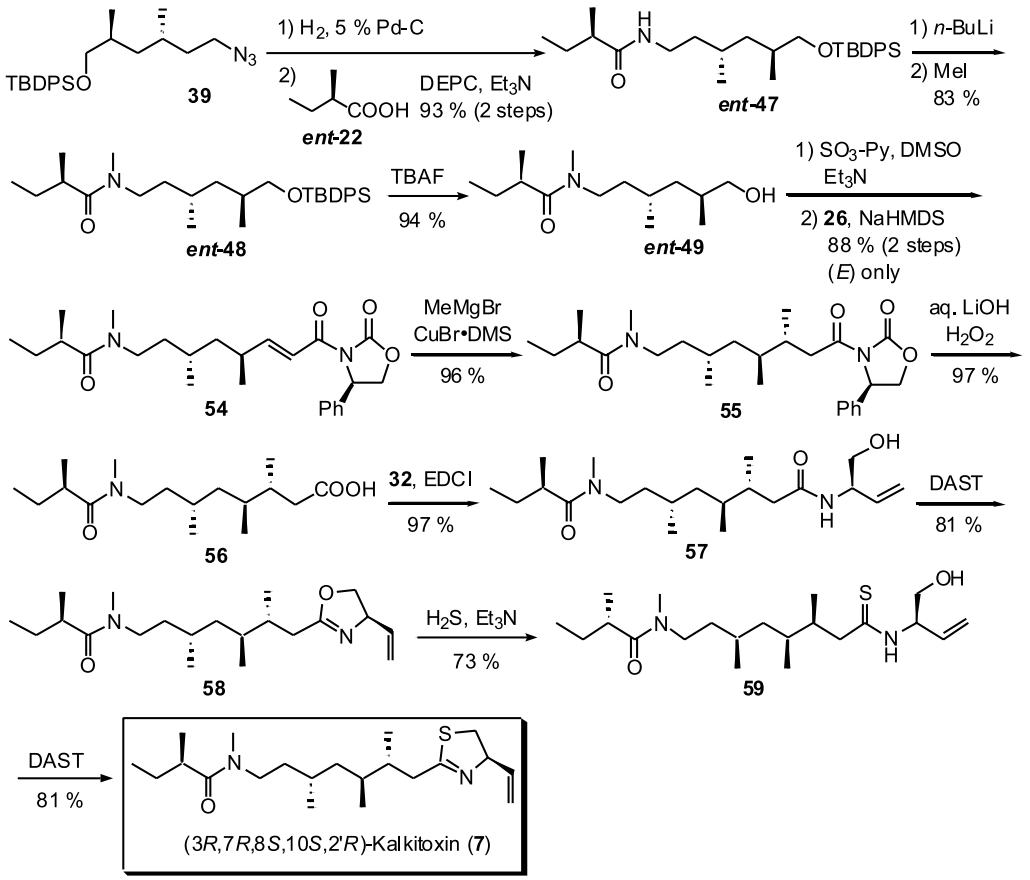
(3*R*,7*S*,8*R*,10*R*,2′*S*)-kalkitoxin (**5**) and its (3*S*)-isomer (**6**), as shown in Scheme 7.

A comparison of the ^{13}C NMR spectra of these synthesized four kalkitoxins **3**–**6** with that of natural kalkitoxin is shown in Figure 3. Close similarity was observed in the (3*S*,7*S*,8*R*,10*R*,2′*S*)-isomer **6**: the mean difference was 0.006 ppm and the maximal difference was 0.014 ppm. But its specific rotation showed −7.5 (*c* 0.8, $CHCl_3$) while that of natural kalkitoxin was +16 (*c* 0.07, $CHCl_3$). The CD spectra of both compounds exhibited the reverse Cotton effect (see Supplementary data). The ^1H NMR spectra of **6** and natural one were almost identical each other. These results indicated that **6** was the antipode of natural kalkitoxin.

Utilizing (*R*)-2-methylbutyric acid (*ent*-**22**), (3*R*,7*R*,8*S*,10*S*,2′*R*)-(+)-kalkitoxin (**7**) was synthesized through the same strategy, as shown in Scheme 8. This kalkitoxin was essentially identical to natural compound. Thus, the absolute stereochemistry of natural kalkitoxin was fully determined by this total synthesis in addition to spectral studies.

4. Biological activity

With seven kalkitoxins in hand, toxicity against brine shrimp (*Artemia salina*) was measured. Synthetic kalkitoxin **7** showed strong toxicity (LC_{50} 170 nM) which was the same as the natural material. Interestingly, the synthesized enantiomer **6** of kalkitoxin was 50 times less potent, LC_{50} 9300 nM. The isomer **3** with unnatural 2′*S* configuration, the isomer **1** with unnatural 2′*S* and 10*R* configurations, and the



Scheme 8.

isomer **4** with unnatural 2′*S* and 3*S* configurations were 3–10 times less potent: LC_{50} 550 nM for **3**, 1100 nM for **1**, and 1700 nM for 4. The configurations at the C7, C8, and C10 also affected the toxicity, which decreased as increasing the number of the reversed configurations. The isomers **2** and **5** were almost inactive.

In conclusion, we have succeeded in the total synthesis of

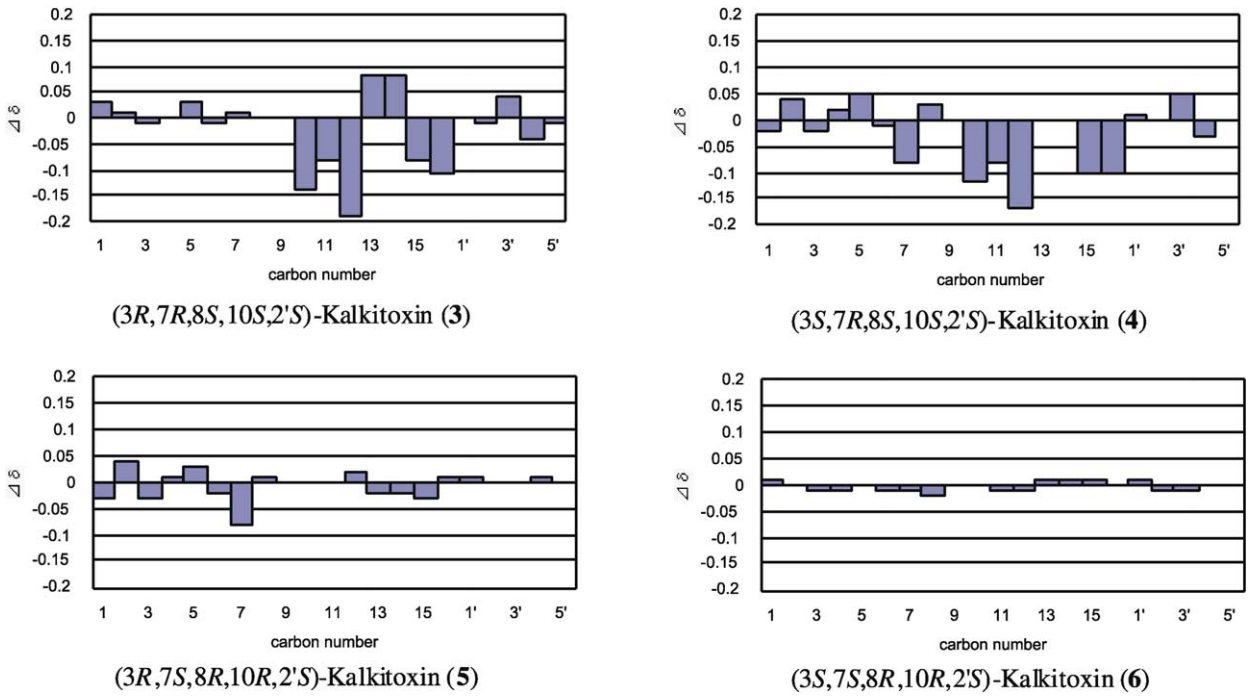


Figure 3. Comparison of ^{13}C NMR spectral difference (in DMSO-d_6 at 25 °C) of natural and synthetic kalkitoxins.

kalkitoxin and its congeners, which clearly elucidated the absolute configuration of this new marine neurotoxin. Our synthesis is straightforward, efficient, and suitable for large scale production, which will be useful for the detailed investigation of the biological properties of kalkitoxin.

5. Experimental

5.1. General

Melting points were measured on a YANACO melting point apparatus (hot plate) and are uncorrected. Infrared (IR) spectra were recorded on a SHIMADZU FT IR-8100 spectrometer. Optical rotations were measured on a DIP-1000 digital polarimeter with a sodium lamp (λ=589 nm, D line) and are reported as follows: $[\alpha]_D^T$ (c g/100 ml, solvent). ^{1}H NMR spectra were recorded on a JEOL EX-270 (270 MHz) spectrometer, unless otherwise stated. Chemical shifts are reported in ppm from tetramethylsilane as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, bd=broad, m=multiplet), coupling constants (Hz), and assignment. Kalkitoxin numbering is used for assignments on all intermediates. ^{13}C NMR spectra were recorded on a JEOL EX-270 (67.8 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane, deuterochloroform (δ_C 77.0 ppm) or d^6-dimethylsulfoxide (δ_C 39.5 ppm) with solvents as the internal standard. Analytical thin layer chromatography was performed on Merck Art. 5715, Kieselgel 60F_{254}/0.25 mm thickness plates. Visualization was accomplished with UV light, phosphomolybdic acid, or ninhydrin solution followed by heating. Preparative thin layer chromatography was performed on Merck Art. 5744, Kiselgel 60F_{254}/0.5 mm thickness plates. Elementary analysis (Anal) and high resolution mass spectra (HRMS) were done at the Analytical Facility at Nagoya City University.

Solvents for extraction and chromatography were reagent grade. Liquid chromatography was performed with forced flow (flash chromatography of the indicated solvent mixture on silica gel BW-820MH or BW-200 (Fuji Silysia Co.)). Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), methanol (MeOH), and acetonitrile (CH_3CN) were distilled from calcium hydride. *N*,*N*-Dimethylformamide (DMF) was dried over 4 Å molecular sieves. Triethylamine was dried over potassium hydroxide. All other commercially obtained reagents were used as received.

General procedures A–M were described for (3*R*,7*R*,8*S*,10*S*,2′*R*)-kalkitoxin (**7**)

5.1.1. General procedure A for the synthesis of (2*S*,4*R*)-2,4-dimethyl-1-(*tert*-butyldiphenylsilyloxy)-5-hexene (37) and its stereoisomers. To a solution of the alcohol **36**[29] (2.16 g, 5.65 mmol) in THF (15 mL) under argon at −78 °C was added *n*-BuLi (4.1 mL, 6.21 mmol, 1.5 M in hexane) dropwise via syringe. The solution was stirred at −78 °C for 30 min, then a solution of *p*-toluenesulfonyl chloride (1.3 g, 6.78 mmol) in THF (3 mL plus 1 mL–2 rinse) was added via cannula. After 10 min, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. Cold (0 °C) water was then added. After the mixture was stirred for 10 min, the layers were separated, and the aqueous layer was extracted with ether (×3). The organic extracts were combined and washed successively with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine. The solution was dried ($MgSO_4$), filtered, and concentrated to give the crude tosylate as a pale yellow oil (3.10 g). This intermediate was used in the next reaction without further purification.

To a solution of the above tosylate in THF (25 mL) under argon at room temperature was added $LiAlH_4$ (650 mg, 17.1 mmol). The resulting mixture was heated to reflux for 1.5 h. After the mixture was cooled to 0 °C, the reaction was quenched with cold brine (added dropwise). After the mixture was stirred for 10 min, the layers were separated, and the aqueous layer was extracted with ether (×2). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/ether=50:1–20:1) to afford the desired product **37** as a colorless oil (1.30 g, 63%): $[\alpha]_D^{26}$=+1.6 (c 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2959, 1472, 1428, 1113, 1086; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.92 (3H, d, J=1.5 Hz, C_8–CH_3), 0.94 (3H, d, J=1.5 Hz, C_{10}–CH_3), 1.07 (s, 9H, (CH_3)$_3$C), 1.28–1.41 (2H, m, C_9–CH_2), 1.67–1.78 (1H, m, C_8–CH), 2.09–2.19 (1H, m, C_{10}–CH), 3.39–3.56 (2H, m, CH_2O), 4.83–4.89 (2H, m, C_{12}–CH_2), 5.60–5.73 (1H, m, C_{11}–CH), 7.37–7.41 (6H, m, ArH), 7.65–7.67 (4H, m, ArH); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 17.5, 17.9, 20.3, 27.0, 27.6, 33.3, 35.3, 40.3, 68.7, 112.1, 127.5, 127.7, 129.3, 129.4, 133.9, 134.0, 135.5, 135.6, 145.1. HRMS (EI) *m*/*z* Calcd for $C_{20}H_{25}OSi$: 309.1675 (M$^+$−*t*-Bu). Found: 309.1688.

5.1.2. General procedure B for the synthesis of (3*S*,5*S*)-3,5-dimethyl-6-(*tert*-butyldiphenylsilyloxy)hexanol (38) and its stereoisomers. To a solution of the silyloxyhexene **37** (1.28 g, 3.49 mmol) in THF (17 mL) was added 9-borabicyclononane dimer (1.70 g, 6.97 mmol). The resulting solution was stirred for 10 min, and then placed in a water bath and sonicated for 40 min. Aqueous NaOH solution (4 M, 3.5 mL) and 30% aqueous H_2O_2 (3.5 mL) were added sequentially at −5 °C. The resulting mixture was diluted with water and extracted with $CHCl_3$ (×3). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=5:1) to afford the desired product **38** as a colorless oil (955 mg, 71%): $[\alpha]_D^{24}$=−10.6 (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3346, 2959, 1472, 1428, 1389, 1113, 1092, 1071; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.85 (3H, d, J=6.3 Hz, C_8–CH_3), 0.89 (3H, d, J=6.6 Hz, C_{10}–CH_3), 1.05 (s, 9H, (CH_3)$_3$C), 1.18–1.28 (1H, m, C_{11}–CH), 1.33–1.46 (1H, m, C_8–CH), 1.48–1.62 (3H, m, C_9–CH_2, C_{11}–CH), 1.68–1.79 (1H, m, C_{11}–CH), 3.39–3.51 (2H, m, CH_2O), 3.57–3.71 (2H, m, CH_2OH), 7.34–7.44 (6H, m, ArH), 7.65–7.67 (4H, m, ArH); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 16.7, 19.4, 19.5, 26.8, 27.0, 33.2, 40.8, 40.9, 61.1, 69.5, 127.5, 129.4, 133.9, 135.5. HRMS (EI) *m*/*z* Calcd for $C_{20}H_{27}O_2Si$: 327.1780 (M$^+$−*t*-Bu). Found: 327.1782.

5.1.3. General procedure C for the synthesis of (2*S*,4*S*)-6-azido-2,4-dimethyl-1-(*tert*-butyldiphenylsilyloxy)hexane (39) and its stereoisomers. *(a) MsCl–NaN$_3$ method*. To a solution of the alcohol **38** (873 mg, 2.27 mmol) in CH_2Cl_2 (7 mL) was added triethylamine (0.47 mL, 3.39 mmol), methanesulfonyl chloride (0.23 mL, 2.97 mmol), DMAP (10 mg, 0.082 mmol) at 0 °C. After 15 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with ether, and washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give the crude mesylate as a colorless oil (1.102 g). This intermediate was used in the next reaction without further purification.

To a solution of the above mesylate in DMF (7 mL) at room temperature was added sodium azide (738 mg, 11.4 mmol). The resulting mixture was diluted with ether, and washed with water (×2) and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820 MH, hexane/ether=30:1) to afford the desired product **39** as a colorless oil (807 mg, 87%).

(b) p-NO$_2$-DPPA method. To a solution of the alcohol **38** (42.7 mg, 0.111 mmol) in DMF (0.4 mL) was added bis(*p*-nitrophenyl)phosphorazidate (*p*-NO_2-DPPA) (61 mg, 0.166 mmol) and DBU (25 μL, 0.166 mmol) at 0 °C. After 1.5 h, the cooling bath was removed and the reaction mixture was stirred at room temperature for 20 h. The mixture was diluted with EtOAc, and washed with water (×2), 1 M aqueous $KHSO_4$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/ether=20:1) to afford the desired product **39** as a colorless oil (33.8 mg, 74%): $[\alpha]_D^{25}=-8.8$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2980, 2095, 1472, 1428, 1389, 1262, 1113, 1092; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.86 (3H, d, *J*=6.3 Hz, C_8-CH_3), 0.89 (3H, d, *J*=6.6 Hz, $C_{10}-CH_3$), 1.07 (9H, s, $(CH_3)_3C$), 1.19–1.31 (1H, m, $C_{10}-CH$), 1.33–1.49 (1H, m, C8–CH), 1.50–1.58 (3H, m, C9–CH_2, C11–CH), 1.67–1.78 (1H, m, C11–CH), 3.18–3.34 (2H, m, C12–CH2)88, $_3$.4$_1$–3.52 (2H, m, C7–CH2), 7.35–7.45 (6H, m, ArH), 7.65–7.68 (4H, m, ArH); ^{13}C NMR (67.8 MHz, CHCl3/CDCl3) δ 16.6, 19.2, 19.4, 26.9, 27.7, 33.2, 36.6, 40.5, 49.5, 69.4, 127.5, 129.4, 133.9, 135.5. HRMS (EI) *m*/*z* Calcd for $C_{20}H_{26}N_3OSi$: 352.1845 (M^+-t-Bu). Found: 352.1843.

5.1.4. General procedure D for the synthesis of (2*R*)-*N*-[(3*S*,5*S*)-3,5-dimethyl-6-(*tert*-butylsilyloxy)-hex-1-yl]-2-methylbutyramide (*ent*-47) and its stereoisomers. To a solution of the azide **39** (774 mg, 1.89 mmol) in EtOAc (7 mL) was added 5% Pd on carbon (100 mg) at room temperature. The black slurry was stirred under 1 atm H_2 for 1.5 h. The reaction mixture was filtered through a pad of celite (EtOAc rinse) and the filtrate was concentrated to give the crude amine as a pale brown oil (799 mg). This intermediate was used in the next reaction without further purification.

To a solution of the above amine and (*R*)-2-methylbutyric acid (*ent*-**22**) (0.24 mL, 2.10 mmol) in DMF (6 mL) at 0 °C was successively added diethyl phosphorocyanidate (0.32 mL, 2.11 mmol) and triethylamine (0.52 mL, 3.75 mmol). After 1 h, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 1.5 h. The mixture was diluted with EtOAc, and washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=4:1) to afford the desired product *ent*-**47** as a pale yellow oil (826 mg, 93%): $[\alpha]_D^{26}=-15.1$ (*c* 1.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3295 (bd), 2963, 1644, 1553, 1462, 1428, 1387, 1237, 1113, 1092; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.84–0.91 (9H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 1.05 (9H, s, $(CH_3)_3C$), 1.10 (3H, d, *J*=6.8 Hz, $C_{2'}-CH_3$), 1.19–1.80 (8H, m, $C_{3'}-CH_2$, C_9-CH_2, $C_{10}-CH$, $C_{11}-CH_2$), 1.96–2.09 (1H, m, $C_{2'}-CH$), 3.12–3.36 (2H, m, $C_{12}-CH_2$), 3.38–3.50 (2H, m, CH_2O), 5.30 (1H, bd-s, N*H*), 7.33–7.45 (6H, m, Ar*H*), 7.64–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 12.0, 16.7, 17.6, 19.3, 19.4, 26.9, 27.4, 27.9, 33.2, 37.4, 37.7, 40.7, 43.3, 69.4, 127.4, 129.4, 133.9, 134.0, 135.5, 176.1. HRMS (EI) *m*/*z* Calcd for $C_{25}H_{36}NO_2Si$ (M^+-t-Bu): 410.2516. Found: 410.2556.

5.1.5. General procedure E for the synthesis of (2*R*)-*N*-methyl-*N*-[(3*S*,5*S*)-dimethyl-6-(*tert*-butyldiphenylsilyl-oxy)-hex-1-yl]-2-methylbutyramide (*ent*-48) and its stereoisomers. To a solution of the amide *ent*-**47** (565 mg, 1.21 mmol) in THF (7 mL) under argon at −78 °C was added *n*-BuLi (0.94 mL, 1.41 mmol, 1.5 M in hexane) dropwise via syringe. The solution was stirred at −78 °C for 20 min, then MeI (0.3 mL, 4.82 mmol) was added. After 10 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. Saturated aqueous NH_4Cl was then added. After dilution with EtOAc and water, the organic layer was separated, and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=6:1) to afford the desired product *ent*-**48** as a pale brown oil (480 mg, 83%): $[\alpha]_D^{24}=-18.8$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2930, 1646, 1472, 1464, 1428, 1113, 1090; ^{1}H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.82–0.92 (9H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 1.05 (9H, s, 1 rotamer, $(CH_3)_3C$), 1.06 (9H, s, 1 rotamer, $(CH_3)_3C$), 1.05–1.11 (3H, m, $C_{2'}-CH_3$), 1.16–1.57 (4H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$), 1.58–1.80 (4H, m, C_9-CH_2, $C_{11}-CH_2$), 2.44–2.61 (1H, m, $C_{2'}-CH$), 2.90 (3H, s, 1 rotamer, $N-CH_3$), 2.98 (3H, s, 1 rotamer, $N-CH_3$), 3.19–3.50 (4H, m, $C_{12}-CH_2$, CH_2O), 7.32–7.44 (6H, m, Ar*H*), 7.63–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 12.1, 12.2, 16.6, 17.2, 17.9, 19.3, 19.4, 26.9, 27.1, 27.5, 28.1, 33.2, 33.7, 35.2, 37.0, 37.2, 37.4, 40.6, 40.7, 46.2, 48.0, 69.4, 69.5, 127.4, 129.3, 129.4, 133.9, 134.0, 135.5, 175.9, 176.2. HRMS (EI) *m*/*z* Calcd for $C_{26}H_{38}NO_2Si$ (M^+-t-Bu): 424.2672. Found: 424.2703.

5.1.6. General procedure F for the synthesis of (2*R*)-*N*-methyl-*N*-((3*S*,5*S*)-3,5-dimethyl-6-hydroxy-hex-1-yl)-2-methylbutyramide (*ent*-49) and its stereoisomers. To a solution of the *N*-methylamide *ent*-**48** (446 mg,

0.926 mmol) in THF (5 mL) was added TBAF (610 mg, 2.33 mmol) at 0 °C. After 30 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc, and washed with water (×2) and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=6:1) to afford the desired product *ent*-**49** as a pale yellow oil (211 mg, 94%): $[\alpha]_D^{24}=-38.4$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3432(bd), 2963, 1626, 1464, 1415, 1379, 1048; ^1H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.85–0.94 (9H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 1.08 (3H, d, J=6.3 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.11 (3H, d, J=6.3 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.15–1.28 (2H, m, C_9-CH_2), 1.29–1.50 (4H, m, $C_{3'}-CH_2$, $C_{11}-CH_2$), 1.51–1.94 (3H, m, C_8-CH, $C_{10}-CH$, O*H*), 2.49–2.66 (1H, m, $C_{2'}-CH$), 2.92 (3H, s, 1 rotamer, $N-CH_3$), 3.24–3.52 (4H, m, $C_{12}-CH_2$, CH_2O); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 12.0, 12.2, 16.3, 16.4, 17.1, 17.8, 19.2, 19.4, 27.0, 27.4, 27.9, 28.0, 33.1, 33.7, 35.0, 35.3, 37.0, 37.1, 37.4, 40.4, 40.6, 46.1, 48.0, 68.6, 68.7, 176.0, 176.3. HRMS (EI) *m/z* Calcd for $C_{14}H_{29}NO_2$: 243.2199. Found: 243.2207.

5.1.7. (4*R*)-3-[(Diethylphosphoro)-acetyl]-4-phenyl-2-oxazolidinone (26). This compound was prepared according to the published procedure (see Ref. 15).

To a flask equipped with a reflux condenser and charged with (*R*)-3-(bromoacetyl)-4-phenyl-2-oxazolidinone (2.02 g, 7.11 mmol) was added triethyl phosphite (2.6 mL, 14.2 mmol), and the mixture was heated to 100 °C. After 3 h, the reaction mixture was cooled to room temperature and then purified by silica gel column chromatography (BW-820MH, $CHCl_3$/MeOH=50:1) to afford the desired (*R*)-phosphonate **26** as a pale orange oil (1.72g, 71%): $[\alpha]_D^{25}=-61.6$ (*c* 2.5, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2986, 1779, 1705, 1392, 1330, 1260, 1208, 1163; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 1.28 (6H, app q, J=7.0 Hz, CH_3CH_2), 3.68–3.89 (2H, m, CH_2), 4.06–4.17 (4H, m, CH_3CH_2), 4.28 (1H, dd, J=3.9, 8.8 Hz, CH_2O), 4.71 (1H, t, J=8.8 Hz, Ar–C*H*), 5.46 (1H, dd, J=3.9, 8.8 Hz, CH_2O), 7.29–7.41 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 16.3 (Jp=2.5 Hz), 34.5 (Jp=13.2 Hz), 57.9, 62.7 (Jp=3.4 Hz), 69.8, 125.9, 128.6, 129.0, 153.4, 164.2 (Jp=6.7 Hz). HRMS (EI) *m/z* Calcd for $C_{15}H_{20}NO_6P$: 341.1028. Found: 341.1020.

5.1.8. General procedure G for the synthesis of (4*R*)-phenyl-3-[(4*R*,6*S*)-4,6-dimethyl-8-((2*R*)-*N*-methyl-2-methylbutyramido)-(*E*)-2-octenoyl]-2-oxazolidinone (54) and its stereoisomers. To a solution of the alcohol *ent*-**49** (126 mg, 0.517 mmol) in CH_2Cl_2 (3 mL) was added DMSO (1 mL), triethylamine (0.36 mL), sulfur trioxide-pyridine complex (420 mg, 2.59 mmol) at 0 °C. After 10 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 50 min. After addition of ice water, the mixture was diluted with EtOAc, and washed with 1 M aqueous $KHSO_4$, water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give the crude aldehyde as a colorless oil (191 mg). This intermediate was used in the next reaction without further purification.

To a solution of the (*R*)-phosphonate **26** (265 mg, 0.776 mmol) in THF (2 mL) under argon was added sodium bis(trimethysilyl)amide solution (0.62 mL, 0.621 mmol, 1.0 M in THF) at 0 °C. After 5 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature. After 45 min, a solution of crude aldehyde in THF (0.8 mL plus 0.3 mL ×2 rinse) was added via cannula at 0 °C. After 2 h, pH 7 buffer was added and the mixture was diluted with EtOAc, washed successively with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=2:1–1:1) to afford the desired product **54** as a colorless oil (195 mg, 88%): $[\alpha]_D^{25}=-51.9$ (*c* 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2964, 1779, 1688, 1634, 1456, 1383, 1362, 1329, 1200, 1103, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.73–0.89 (9H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.97 (3H, d, J=6.2 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.99 (3H, d, J=6.2 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.12–1.38 (5H, m, C_9-CH_2, $C_{10}-CH$, $C_{11}-CH_2$), 1.39–1.61 (2H, m, $C_{3'}-CH_2$), 2.40–2.66 (2H, m, $C_{2'}-CH$, C_8-H), 2.78 (3H, s, 1 rotamer, $N-CH_3$), 2.92 (3H, s, 1 rotamer, $N-CH_3$), 3.19–3.42 (2H, m, $C_{12}-CH_2$), 4.18 (1H, dd, J=3.6, 8.6 Hz, CH_2O), 4.75 (1H, t, J=8.6 Hz, Ar–C*H*), 5.50 (1H, dd, J=3.6, 8.6 Hz, CH_2O), 6.82 (1H, dd, J=7.7, 15.4 Hz, C_6-CH), 7.16 (1H, d, J=15.4 Hz, C_7-CH), 7.27–7.40 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 17.2, 19.1, 19.6, 26.6, 27.5, 33.4, 33.8, 34.5, 36.2, 39.4, 42.7, 57.0, 70.1, 118.5, 125.7, 127.8, 128.6, 139.7, 153.5, 155.5, 163.6, 174.6. HRMS (EI) *m/z* Calcd for $C_{25}H_{36}N_2O_4$: 428.2675. Found: 428.2676.

5.1.9. General procedure H for the synthesis of (4*R*)-4-phenyl-3-[(3*R*,4*S*,6*S*)-3,4,6-trimethyl-8-((2*R*)-*N*-methyl-2-methylbutyramido)-octanoyl]-2-oxazolidinone (55) and its stereoisomers. To a slurry of copper (I) bromide-dimethylsulfide complex (290 mg, 1.39 mmol) in THF (2.4 mL) was added dimethylsulfide (1.6 mL) under argon, and cooled to −78 °C. Methyl magnesium bromide (2.0 mL, 1.87 mmol, 0.93 M in THF) was slowly added. After 20 min, the mixture was warmed to 0 °C for 20 min and then recooled to −78 °C before being transferred via cannula to a cooled (−78 °C) solution of the enimide **54** (239 mg, 0.559 mmol) in THF (1.4 mL) and CH_2Cl_2 (0.7 mL). After 30 min, the mixture was warmed to −30 °C over 1 h and stirred at this temperature for 1 h. Phosphate buffer (pH 7) was added to the mixture, which was diluted with EtOAc, and washed with 1 M aqueous $KHSO_4$ (×2), water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/Acetone=3:1) to afford the desired product **55** as a colorless oil (238 mg, 96%): $[\alpha]_D^{26}=-58.6$ (*c* 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2965, 1781, 1705, 1634, 1456, 1385, 1325, 1198, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.74–0.81 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, J=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, J=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$),1.00–1.11 (2H, m, C_9-CH_2), 1.13–1.59 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.82–1.96 (1H, m, C_7-CH), 2.54–2.83 (3H, m, $C_{2'}-CH$, C_6-CH_2), 2.78 (3H, s, 1 rotamer, $N-CH_3$), 2.95 (3H, s, 1 rotamer, $N-CH_3$),

3.21–3.38 (2H, m, $C_{12}-CH_2$), 4.14 (1H, dd, J=3.6, 8.7 Hz, CH_2O), 4.72 (1H, t, J=8.7 Hz, Ar–C*H*), 5.46 (1H, dd, J=3.6, 8.7 Hz, CH_2O), 7.26–7.40 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 16.1, 17.1, 18.9, 26.6, 27.4, 33.5, 34.1, 34.7, 36.2, 36.7, 38.2, 39.4, 44.9, 69.9, 125.7, 127.9, 128.7, 140.0, 153.7, 171.9, 174.8. HRMS (EI) *m/z* Calcd for $C_{26}H_{40}N_2O_4$: 444.2988. Found: 444.2997.

5.1.10. General procedure I for the synthesis of (3*R*,4*S*,6*S*)-3,4,6-trimethyl-8-((2*R*)-*N*-methyl-2-methylbutyramido)-octanoic acid (56) and its stereoisomers. To a solution of the imide **55** (203 mg, 0.457 mmol) in THF–water (4:1, 1.9 mL) was added 30% aqueous H_2O_2 (0.26 mL), followed by the addition of 0.5 M aqueous LiOH (2.7 mL) at 0 °C. After 30 min, the mixture was stirred at room temperature for 10 h. After dilution with water, the aqueous layer was acidified by the addition of 1 N aqueous HCl and extracted with EtOAc (×3). The combined organic extracts were washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=1:1) to afford the desired product **56** as a colorless oil (132 mg, 97%): $[\alpha]_D^{26}=-40.9$ (c 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3154 (bd), 2964, 1713, 1615, 1462, 1406, 1383, 1250, 1194; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.74–0.84 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.01–1.15 (2H, m, C_9-CH_2), 1.16–1.61 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.74–2.00 (2H, m, C_6-CH, C_7-CH), 2.16–2.27 (1H, m, C_6-CH), 2.54–2.68 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.21–3.35 (2H, m, $C_{12}-CH_2$), 12.0 (1H, bd-s, COO*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 16.0, 16.4, 17.1, 19.1, 26.7, 27.5, 33.6, 34.6, 34.7, 36.2, 36.7, 37.8, 39.4, 44.9, 174.4, 174.8. HRMS (EI) *m/z* Calcd for $C_{17}H_{33}NO_3$: 299.2460. Found: 299.2440.

5.1.11. General procedure J for the synthesis of *N*-((2*R*)-3-butenol-2-yl)-[(3*R*,4*S*,6*S*)-trimethyl-8-((2*R*)-*N*-methyl-2-methylbutyramido)]octanamide (57) and its stereoisomers. (2*R*)-*N*-Boc-amino-3-butenol **32**[21] (68.0 mg, 0.361 mmol) was dissolved in 4 N HCl–EtOAc at 0 °C. After 15 min, the mixture was warmed to room temperature. The solution was concentrated after 1 h, and the residue was azeotropically concentrated with toluene (×4). The resulting residue and the carboxylic acid (2′*R*)-**56** (72.1 mg, 0.241 mmol) were dissolved in CH_2Cl_2 (1.2 mL), and *i*-Pr_2NEt (0.10 mL, 0.60 mmol) and then DMAP (15 mg, 0.120 mmol) were added. EDCI·HCl (138 mg, 0.722 mmol) was added after 10 min and the reaction mixture was stirred for 13 h. After dilution with water, the aqueous layer was acidified by the addition of 1 N aqueous HCl and extracted with EtOAc (×4). The combined organic extracts were washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, $CHCl_3$/MeOH=20:1) to afford the desired product **57** as a colorless oil (85.8 mg, 97%): $[\alpha]_D^{26}=-10.8$ (c 0.84, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3304, 2964, 1717, 1651, 1539, 1464, 1381, 1252, 1082; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.74–0.86 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.95 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.00–1.14 (2H, m, C_9-CH_2), 1.15–1.61 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.68–2.01 (2H, m, C_6-CH,C_7-CH), 2.02–2.15 (1H, m, C_6-CH), 2.54–2.71 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.97 (3H, s, 1 rotamer, $N-CH_3$), 3.27–3.45 (4H, m, C_4-CH_2, $C_{12}-CH_2$), 4.26–4.39 (1H, m, C_4-OH), 4.66–4.75 (1H, m, C_3-CH), 5.05 (1H, d, J=11.7 Hz, C_1-CH), 5.10 (1H, d, J=17.0 Hz, C_1-CH), 5.83 (1H, ddd, J=6.4, 11.7, 17.0 Hz, C_2-CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 16.0, 16.1, 17.1, 19.1, 26.7, 27.5, 33.1, 33.7, 34.7, 35.0, 36.2, 36.8, 39.4, 44.9, 52.7, 63.4, 114.7, 137.2, 171.5, 174.8. HRMS (EI) *m/z* Calcd for $C_{21}H_{40}N_2O_3$: 368.3039. Found: 368.3035.

5.1.12. General procedure K for the synthesis of (4*R*)-4-ethenyl-2-[(2*R*,3*S*,5*S*)-2,3,5-trimethyl-7-((2*R*)-*N*-methyl-2-methylbutyramido)-heptyl]oxazoline (58) and its stereoisomers. To a solution of the amide **57** (75.3 mg, 0.204 mmol) in CH_2Cl_2 (2 mL) was added DAST (30 μL, 0.224 mmol) at −20 °C under argon. After 30 min, 4 M aqueous NH_3 was added and then the mixture was diluted with water. The aqueous layer was extracted with EtOAc (×3) and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=1:3) to afford the desired product **58** as a colorless oil (57.8 mg, 81%): $[\alpha]_D^{26}=+18.6$ (c 0.76, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 1666, 1646, 1456, 1381, 1196; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.86 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.00–1.14 (2H, m, C_9-CH_2), 1.15–1.61 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.74–1.89 (1H, bd-m, C_7-CH), 1.90–2.03 (1H, m, C_6-CH), 2.17–2.28 (1H, m, C_6-CH), 2.54–2.68 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.25–3.35 (2H, m, $C_{12}-CH_2$), 3.84 (1H, app t, J=8.0 Hz, C_4-CH), 4.31 (1H, app t, J=9.1 Hz, C_4-CH), 4.48–4.59 (1H, m, C_3-CH), 5.07 (1H, d, J=10.5 Hz, C_1-CH), 5.18(1H, d, J=17.2 Hz, C_1-CH), 5.80 (1H, ddd, J=6.8, 10.5, 17.2 Hz, C_2-CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 15.9, 16.2, 17.1, 19.1, 26.6, 27.4, 31.1, 33.5, 34.7, 35.3, 36.7, 39.4, 44.9, 67.4, 71.1, 115.3, 139.1, 166.6, 174.8. HRMS (EI) *m/z* Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2922.

5.1.13. General procedure L for the synthesis of *N*-((2*R*)-3-butenol-2-yl)-[(3*R*,4*S*,6*S*)-trimethyl-8-((2*R*)-*N*-methyl-2-methylbutyramido)]octanethioamide (59) and its stereoisomers. The oxazoline (2′*R*)-**58** (44.2 mg, 0.126 mmol) was dissolved in MeOH–triethylamine (1:1, 2 mL, saturated with H_2S), and stirred at room temperature for 12 h. The mixture was concentrated and the residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=6:1) to afford the desired product **59** as a pale yellow oil (35.6 mg, 73%): $[\alpha]_D^{25}=+9.6$ (c 0.44, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3340 (bd), 2964, 1622, 1464, 1415, 1381, 1217, 1080; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ

0.73–0.87 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.95 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.04–1.16 (2H, m, C_9–CH_2), 1.17–1.62 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 2.05–2.28 (1H, bd-m, C_7–CH), 2.38–2.51 (2H, m, C_6–CH_2), 2.54–2.73 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.98 (3H, s, 1 rotamer, N–CH_3), 3.23–3.35 (2H, m, C_{12}–CH_2), 3.44–3.58 (2H, m, C_4–CH_2), 4.88 (1H, t, J=5.6 Hz, C_3–CH), 5.05–5.21 (3H, m, C_1–CH_2, C_4–OH), 5.85 (1H, ddd, J=6.4, 11.4, 16.5 Hz, C_2–CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 15.1, 16.2, 17.1, 19.1, 26.7, 27.4, 33.1, 33.7, 34.7, 36.2, 36.6, 38.0, 39.4, 44.9, 59.0, 67.4, 115.9, 135.1, 174.8, 203.8. HRMS (EI) m/z Calcd for $C_{21}H_{40}N_2O_2S$: 384.2810. Found: 384.2825.

5.1.14. General procedure M for the synthesis of (3*R*,7*R*,8*S*,10*S*,2′*R*)-kalkitoxin (7) and its stereoisomers. To a solution of thioamide 59 (27.9 mg, 0.0725 mmol) in CH_2Cl_2 (0.7 mL) was added DAST (11 μL, 0.0797 mmol) at −20 °C under argon. After 30 min, 4 M aqueous NH_3 was added and then the mixture was diluted with water. The aqueous layer was extracted with EtOAc (×3) and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=1:1) to afford the synthetic (3*R*,7*R*,8*S*,10*S*,2′*R*)-kalkitoxin (7) as a pale yellow oil (21.6 mg, 81%): $[\alpha]_D^{26}$=+7.0 (*c* 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2930, 2874, 1646, 1464, 1412, 1381, 1082; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.88 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.95 (3H, d, J=7.1 Hz, $C_{2'}$–CH_3), 0.97 (3H, d, J=7.1 Hz, $C_{2'}$–CH_3), 1.01–1.16 (2H, m, C_9–CH_2), 1.17–1.62 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.73–1.89 (1H, bd–m, C_7–CH), 2.17–2.30 (1H, m, C_6–CH_2), 2.40–2.47 (1H, m, C_6–CH_2), 2.54–2.69 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.97 (3H, s, 1 rotamer, N–CH_3), 3.02 (1H, dd, J=8.4, 11.0 Hz, C_4–CH), 3.25–3.39 (2H, m, C_{12}–CH_2), 3.48 (1H, dd, J=8.4, 11.0 Hz, C_4–CH), 4.84–4.97 (1H, m, C_3–CH), 5.10 (1H, d, J=10.4 Hz, C_1–CH), 5.23 (1H, d, J=17.1 Hz, C_1–CH), 5.90 (1H, ddd, J=6.4, 10.4, 17.1 Hz, C_2–CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.70, 16.02(CH_3×2), 17.14, 19.08, 26.64, 27.47, 33.39, 34.70, 34.92, 36.20, 36.68, 37.49, 37.85, 39.40, 44.88, 77.90, 115.27, 137.97, 169.20, 174.80. HRMS (EI) m/z Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2722.

5.1.15. Natural kalkitoxin. Pure natural kalkitoxin showed the following physicochemical data: $[\alpha]_D^{25}$=+16 (*c* 0.07, $CHCl_3$); CD *c* 0.022, EtOH λ_{ext} 226 nm (Δε+4.75), 207.8 (0.0) and see Figure 6 in Supplementary data; IR ($CHCl_3$) 2961, 2928, 2880, 1643, 1464, 1086, 1410, 1380 cm^{-1}; UV (MeOH) λ_{max} 250 nm (ε=2600); ^{1}H NMR (benzene-d_6, 500 MHz) δ 0.76 (3H, d, J=6.8 Hz), 0.85 (3H, d, J=6.1 Hz), 0.88 (3H, d, J=7.5 Hz), 0.95 (d, 3H, J=6.8 Hz), 1.02 (1H, m), 1.10 (1H, m), 1.10 (3H, d, J=6.7 Hz), 1.24 (1H, m), 1.34 (1H, m), 1.38 (1H, m), 1.39 (1H, m), 1.54 (1H, m), 1.87 (1H, m), 2.05 (1H, m), 2.28 (1H, m), 2.31 (1H, m), 2.43 (3H, s), 2.55 (1H, m), 2.72 (1H, dd, J=10.7, 8.4 Hz), 2.94 (1H, dd, J=10.5, 8.8 Hz), 3.35 (2H, m), 4.75 (1H, dd, J=7.8, 7.5 Hz), 5.01 (1H, d, J=10.3 Hz), 5.24 (1H, ddd, J=17.2, 1.6, 1.6 Hz), 5.85 (1H, ddd, J=17.2, 10.3, 6.1 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 11.69 (C-4′), 16.0 (C-13), 16.0 (C-14), 17.13 (C-5′), 19.07 (C-15), 26.64 (C-3′), 27.47 (C-10), 33.40 (C-8), 34.70 (C-16), 34.92 (C-11), 36.20 (C-2′), 36.68 (C-7), 37.49 (C-6), 37.85 (C-4), 39.4 (C-9), 44.88 (C-12), 77.91 (C-3), 115.24 (C-1), 137.96 (C-2), 169.18 (C-5), 174.79 (C-1′); ^{13}C NMR (benzene-d_6, 125 MHz, from HSQC and HSQMBC data sets) δ 12.4 (C-4′), 16.4 (C-13), 16.4 (C-14), 17.8 (C-5′), 19.5 (C-15), 27.8 (C-3′), 28.3 (C-10), 34.4 (C-8), 34.5 (C-16), 36.0 (C-11), 37.5 (C-7), 37.6 (C-2′), 38.6 (C-6), 38.9 (C-4), 40.3 (C-9), 46.0 (C-12), 79.2 (C-3), 115.3 (C-1), 138.3 (C-2), 170.2 (C-5), 175.5 (C-1′).

Description of tertiary amide isomers in the NMR spectra of kalkitoxin. Complication in the NMR-based strategy for structure elucidation of kalkitoxin resulted from a 3:2 ratio of tertiary amide isomers in its room temperature ^{1}H NMR (DMSO-d_6, 298 K). This required that structure elucidation of kalkitoxin **7** be based on a combination of data sets for experiments run at both 298 and 340 K. The origin of the 'twinning'of signals was confirmed by observing alterations in the signal ratios as a function of different NMR solvents (ratio between *E* and *Z* olefin isomers ranged from a low of 0.5:1.0 in benzene-d_6 to a high of 1.58:1.0 in acetone-d_6) and temperature. At relatively high temperature (340 K) these 'twinned' signals coalesced to singlets; however, the value of this elevated temperature experiment was compromised because, for reasons that we do not understand, several ^{13}C NMR signals and ^{1}H–^{13}C NMR correlations that should have been present were lost.

HRMS (EI) m/z obs. $[M]^+$ 366.2696 (15.9, 0.9 mmu dev. for $C_{21}H_{38}N_2OS$); HR-EIMS cleavages between C6–C7 in kalkitoxin obs. *m/s* 240.2329 for $[C_{15}H_{30}NO]^+$ (25%, 0.2 mmu dev.) and m/z 127.0459 for $[C_6H_9NS]^+$ (26%, 0.3 mmu dev.); cleavage C7–C8 obs. m/z 154.0683 for $[C_8H_{12}NS]^+$ (100%, 0.8 mmu dev.).

5.1.16. (2*S*)-*N*-[(3*S*,5*S*)-3,5-Dimethyl-6-(*tert*-butylsilyloxy)-hex-1-yl]-2-methylbutyramide (40). According to general procedure D (using (*S*)-2-methylbutyric acid **22**), the azide **39** (774 mg, 1.89 mmol) provided the amide **40** as a pale yellow oil (826 mg, 93%): $[\alpha]_D^{25}$=−3.7 (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3295, 2930, 1644, 1553, 1462, 1428, 1387, 1237, 1113, 1094; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.82–0.91 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 1.05 (9H, s, (CH_3)$_3$C), 1.11 (3H, d, J=6.9 Hz, $C_{2'}$–CH_3), 1.18–1.79 (8H, m, $C_{3'}$–CH_2, C_9–CH_2, C_{10}–CH, C_{11}–CH_2), 1.95–2.09 (1H, m, $C_{2'}$–CH), 3.16–3.31 (2H, m, C_{12}–CH_2), 3.37–3.51 (2H, m, CH_2O), 5.27 (1H, bd-s, NH), 7.35–7.42 (6H, m, ArH), 7.63–7.67 (4H, m, ArH); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 12.0, 16.7, 17.7, 19.3, 19.4, 26.9, 27.4, 27.9, 33.2, 37.4, 37.7, 40.7, 43.3, 69.4, 127.4, 129.4, 133.9, 134.0, 135.5, 176.0. HRMS (EI) m/z Calcd for $C_{25}H_{36}NO_2Si$: 410.2515 (M^+−*t*-Bu). Found: 410.2491.

5.1.17. (2*S*)-*N*-Methyl-*N*-[(3*S*,5*S*)-dimethyl-6-(*tert*-butyldiphenylsilyloxy)-hex-1-yl]-2-methylbutyramide (41). According to general procedure E, the amide **40** (565 mg, 1.21 mmol) provided the *N*-methylamide **41** as a pale brown oil (480 mg, 83%): $[\alpha]_D^{24}$=+3.0 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat}

cm^{-1} 2961, 1646, 1472, 1464, 1428, 1113, 1090; ^1H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.82–0.93 (9H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 1.05 (9H, s, 1 rotamer, $(CH_3)_3C$), 1.06 (9H, s, 1 rotamer, $(CH_3)_3C$), 1.07–1.12 (3H, m, $C_{2'}-CH_3$), 1.19–1.56 (4H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$), 1.57–1.80 (4H, m, C_9-CH_2, $C_{11}-CH_2$), 2.45–2.61 (1H, m, $C_{2'}-CH$), 2.90 (3H, s, 1 rotamer, N–CH3), 2.97 (3H, s, 1 rotamer, N–CH_3), 3.20–3.34 (2H, m, $C_{12}-CH_2$), 3.35–3.52 (2H, m, CH_2O), 7.36–7.45 (6H, m, Ar*H*), 7.62–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 12.1, 12.2, 16.6, 17.2, 17.9, 19.3, 19.4, 26.9, 27.1, 27.5, 28.0, 28.1, 33.2, 33.3, 33.7, 35.2, 37.0, 37.2, 37.4, 40.6, 40.7, 46.0, 48.0, 69.4, 69.5, 127.4, 129.3, 129.4, 133.8, 133.9, 134.0, 135.5, 175.9, 176.2. HRMS (EI) *m*/*z* Calcd for $C_{26}H_{38}NO_2Si$: 424.2672 (M^+-t-Bu). Found: 424.2654.

5.1.18. (2*S*)-*N*-Methyl-*N*-((3*S*,5*S*)-3,5-dimethyl-6-hydroxy-hex-1-yl)-2-methylbutyramide (42). According to general procedure F, the *N*-methylamide **41** (446 mg, 0.926 mmol) provided the alcohol **42** as a pale yellow oil (211 mg, 94%): $[\alpha]_D^{24}=+6.0$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3432, 2928, 1626, 1464, 1414, 1379, 1048; ^1H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.85–0.93 (9H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 1.07–1.14 (3H, m, $C_{2'}-CH_3$), 1.15–1.27 (2H, m, C_9-CH_2), 1.28–1.62 (4H, m, $C_{3'}-CH_2$, $C_{11}-CH_2$), 1.63–1.80 (2H, m, C_8-CH, $C_{10}-CH$), 2.46–2.64 (1H, m, $C_{2'}-CH$), 2.92 (3H, s, 1 rotamer, N–CH_3), 3.01 (3H, s, 1 rotamer, N–CH_3), 3.20–3.56 (4H, m, $C_{12}-CH_2$, CH_2O); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 12.0, 12.2, 16.2, 16.3, 17.1, 17.8, 19.2, 19.4, 27.1, 27.4, 27.8, 28.0, 33.1, 33.7, 35.0, 35.2, 37.0, 37.1, 37.3, 40.4, 40.6, 46.0, 48.1, 68.6, 68.7, 176.0, 176.3. HRMS (EI) *m*/*z* Calcd for $C_{14}H_{29}NO_2$: 243.2199. Found: 243.2203.

5.1.19. (4*R*)-Phenyl-3-[(4*R*,6*S*)-4,6-dimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-(*E*)-2-octenoyl]-2-oxazolidinone (43). According to general procedure G, the alcohol **42** (204 mg, 0.838 mmol) provided the enimide **43** as a colorless oil (333 mg, 93%): $[\alpha]_D^{24}=-27.5$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2980, 1779, 1688, 1634, 1456, 1383, 1362, 1329, 1200, 1103, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.67–0.88 (9H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.92–1.00 (3H, m, $C_{2'}-CH_3$), 1.09–1.37 (5H, m, C_9-CH_2, $C_{10}-CH$, $C_{11}-CH_2$), 1.39–1.68 (2H, m, $C_{3'}-CH_2$), 2.42–2.63 (2H, m, $C_{2'}-CH$, C_8-CH), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.90 (3H, s, 1 rotamer, N–CH_3), 3.06–3.51 (2H, m, $C_{12}-CH_2$), 4.18 (1H, dd, *J*=8.5, 3.3 Hz, CH_2O), 4.75 (1H, t, *J*=8.5 Hz, Ar–C*H*), 5.50 (1H, dd, *J*=8.5, 3.3 Hz, CH_2O), 6.82 (1H, dd, *J*=15.4, 7.8 Hz, C_6-CH), 7.16 (1H, d, *J*=15.4 Hz, C_7-CH), 7.28–7.38 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 17.1, 19.1, 19.5, 26.7, 27.3, 33.2, 33.8, 34.4, 36.2, 39.4, 42.8, 57.1, 70.1, 118.9, 125.9, 128.0, 128.8, 139.7, 153.8, 155.7, 163.8, 174.8. HRMS (EI) *m*/*z* Calcd for $C_{25}H_{36}N_2O_4$: 428.2675. Found: 428.2673.

5.1.20. (4R)-4-Phenyl-3-[(3R,4S,6S)-3,4,6-trimethyl-8-((2S)-*N*-methyl-2-methylbutyramido)-octanoyl]-2-oxazolidinone (44). According to general procedure H, the enimide 43 (86 mg, 0.201 mmol) provided the imide **44** as a colorless oil (87 mg, 97%): [α]D^{25} −32.8 (*c* 1.5, CHCl3); IR ν maxneat cm−1 2930, 1782, 1705, 1636, 1458, 1385, 1325, 1198, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.74–0.81 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, *J*=6.6 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=6.6 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.00–1.08 (2H, m, C_9-CH_2), 1.15–1.58 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.82–1.96 (1H, m, C_7-CH), 2.50–2.76 (3H, m, $C_{2'}-CH$, C_6-CH_2), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.95 (3H, s, 1 rotamer, N–CH_3), 3.15–3.42 (2H, m, $C_{12}-CH_2$), 4.14 (1H, dd, *J*=8.7, 3.5 Hz, CH_2O), 4.72 (1H, t, *J*=8.7 Hz, Ar–C*H*), 5.46 (1H, dd, *J*=8.7, 3.5 Hz, CH_2O), 7.26–7.40 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 16.1, 17.1, 18.8, 26.7, 27.3, 33.5, 34.1, 34.6, 36.2, 36.8, 38.2, 39.4, 44.7, 57.0, 69.9, 125.7, 127.9, 128.7, 140.0, 153.7, 171.8, 174.8. HRMS (EI) *m*/*z* Calcd for $C_{26}H_{40}N_2O_4$: 444.2988. Found: 444.2990.

5.1.21. (3*R*,4*S*,6*S*)-3,4,6-Trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)octanoic acid (45). According to general procedure I, the imide **44** (212 mg, 0.476 mmol) provided the carboxylic acid **45** as a colorless oil (126 mg, 88%): $[\alpha]_D^{25}=-2.9$ (*c* 1.1, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3346 (bd), 2964, 1732, 1634, 1404, 1383, 1252, 1190; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.74–0.84 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, *J*=6.9 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=6.9 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.01–1.14 (2H, m, C_9-CH_2), 1.16–1.60 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.74–1.99 (2H, m, C_6-CH, C_7-CH), 2.15–2.27 (1H, m, C_6-CH), 2.52–2.70 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.12–3.25 (2H, m, $C_{12}-CH_2$), 10.20 (1H, bd-s, COO*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 16.0, 16.5, 17.2, 19.0, 26.7, 27.4, 33.7, 34.6, 34.9, 36.2, 36.8, 37.8, 39.4, 44.7, 174.1, 174.5. HRMS (EI) *m*/*z* Calcd for $C_{17}H_{33}NO_3$: 299.2460. Found: 299.2458.

5.1.22. (4*R*)-4-Ethenyl-2-[(2*R*,3*S*,5*S*)-2,3,5-trimethyl-7-((2*S*)-*N*-methyl-2-methylbutyramido)-heptyl]oxazoline (46a). According to general procedures J and K, the carboxylic acid **45** (79.3 mg, 0.265 mmol) provided the oxazoline **46a** as a colorless oil (45.1 mg, 70%, 2 steps): $[\alpha]_D^{25}=+53.0$ (*c* 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 1660, 1646, 1464, 1381, 1196; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.86 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.00–1.14 (2H, m, C_9-CH_2), 1.15–1.62 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.71–1.89 (1H, m, C_7-CH), 1.90–2.08 (1H, m, C_6-CH), 2.15–2.30 (1H, m, C_6-CH), 2.55–2.69 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.12–3.37 (2H, m, $C_{12}-CH_2$), 3.84 (1H, app t, *J*=7.9 Hz, C_4-CH), 4.31 (1H, app t, *J*=8.9 Hz, C_4-CH), 4.45–4.61 (1H, m, C_3-CH), 5.07 (1H, d, *J*=10.2 Hz, C_1-CH), 5.17 (1H, d, *J*=16.8 Hz, C_1-CH), 5.80 (1H, ddd, *J*=17.1, 10.4, 6.6 Hz, C_2-CH); 13C NMR (67.8 MHz, DMSO/DMSO-d6), the major rotamer, δ 11.7, 16.3, 17.2, 19.0, 26.7, 27.3, 31.1, 33.5, 34.8, 35.3, 36.2, 36.7, 39.4, 44.7, 67.4, 71.1, 115.1, 138.9, 166.4, 174.5. HRMS (EI) *m*/*z* Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2944.

5.1.23. (3*R*,7*R*,8*S*,10*S*,2′*S*)-Kalkitoxin (3). According to general procedures L and M, the oxazoline **46a** (42.9 mg, 0.122 mmol) provided the synthetic (3R,7R,8S,10S,2′S)-kalkitoxin (**3**) as a pale yellow oil (24.2 mg, 57%, 2 steps): $[\alpha]_D^{25}$=+39.7 (*c* 0.88, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2930, 2874, 1646, 1412, 1381, 1082; ^1H NMR (270MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.88 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.95 (3H, d, *J*=7.0 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=7.0 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.01–1.17 (2H, m, C_9-CH_2), 1.19–1.64 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.71–1.90 (1H, bd-m, C_7-CH), 2.16–2.30 (1H, m, C_6-CH_2), 2.39–2.46 (1H, m, C_6-CH_2), 2.54–2.71 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.02 (1H, dd, *J*=8.4, 10.9 Hz, C_4-CH), 3.12–3.30 (2H, m, $C_{12}-CH_2$), 3.48 (1H, dd, *J*=8.4, 10.9 Hz, C_4-CH), 4.83–4.97 (1H, m, C_3-CH), 5.10 (1H, d, *J*=10.2 Hz, C_1-CH), 5.23 (1H, d, *J*=17.1 Hz, C_1-CH), 5.90 (1H, ddd, *J*=6.3, 10.2, 17.1 Hz, C_2-CH); ^{13}C NMR (67.8MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.65, 16.08 (CH_3×2), 17.12, 18.99, 26.68, 27.33, 33.40, 34.59, 34.84, 36.19, 36.69, 37.48, 37.85, 39.40, 44.69, 77.90, 115.27, 137.97, 169.21, 174.79. HRMS (EI) *m*/*z* Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2722.

5.1.24. (4*S*)-4-Ethenyl-2-[(2*R*,3*S*,5*S*)-2,3,5-trimethyl-7-((2*S*)-*N*-methyl-2-methylbutyramido-heptyl)]oxazoline (46b). According to general procedure J (using (2*S*)-*N*-Boc-amino-3-butenol *ent*-**32**) and procedure K, the carboxylic acid **45** (69.9 mg, 0.233 mmol) provided the oxazoline **46b** as a colorless oil (64.4 mg, 80%, 2 steps): $[\alpha]_D^{26}$=−62.7 (*c* 0.19, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2968, 1666, 1646, 1464, 1381, 1196; ^1H NMR (270 MHz, DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.85 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.00–1.15 (2H, m, C_9-CH_2), 1.16–1.62 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.70–1.88 (1H, bd-m, C_7-CH), 1.90–2.03 (1H, m, C_6-CH), 2.16–2.29 (1H, m, C_6-CH), 2.54–2.71 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.95 (3H, s, 1 rotamer, $N-CH_3$), 3.10–3.24 (2H, m, $C_{12}-CH_2$), 3.84 (1H, app t, *J*=7.8 Hz, C_4-CH), 4.31 (1H, app t, *J*=8.6 Hz, C_4-CH), 4.46–4.61 (1H, m, C_3-CH), 5.07 (1H, d, *J*=10.2 Hz, C_1-CH), 5.17 (1H, d, *J*=17.2 Hz, C_1-CH), 5.79 (1H, ddd, *J*=6.4, 10.2, 17.2 Hz, C_2-CH); ^{13}C NMR (67.8 MHz, DMSO-d_6), the major rotamer, δ 11.6, 15.9, 16.2, 17.1, 18.9, 26.7, 27.3, 31.0, 33.5, 34.6, 35.2, 36.2, 36.7, 39.4, 44.7, 67.4, 71.1, 115.2, 139.1, 166.6, 174.8. HRMS (EI) *m*/*z* Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2943.

5.1.25. (3*S*,7*R*,8*S*,10*S*,2′*S*)-Kalkitoxin (4). According to general procedures L and M, the oxazoline **46b** (60.7 mg, 0.173 mmol) provided the synthetic (3*S*,7*R*,8*S*,10*S*,2′*S*)-kalkitoxin (**4**) as a pale yellow oil (40.4 mg, 66%, 2 steps): $[\alpha]_D^{25}$=−46.1 (*c* 0.81, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2930, 2874, 1646, 1464, 1412, 1381, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.88 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, *J*=6.7 Hz, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=6.7 Hz, $C_{2'}-CH_3$), 1.01–1.17 (2H, m, C_9-CH_2), 1.18–1.65 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.71–1.90 (1H, bd–m, C_7-CH), 2.18–2.32 (1H, m, C_6-CH), 2.39–2.46 (1H, m, C_6-CH), 2.55–2.72 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.03 (1H, dd, *J*=7.9, 10.4 Hz, C_4-CH), 3.12–3.29 (2H, m, $C_{12}-CH_2$), 3.48 (1H, dd, *J*=7.9, 10.4 Hz, C_4-CH), 4.86–5.00 (1H, m, C_3-CH), 5.10 (1H, d, *J*=10.2 Hz, C_1-CH), 5.22 (1H, d, *J*=17.2 Hz, C_1-CH), 5.90 (1H, ddd, *J*=6.6, 10.2, 17.2 Hz, C_2-CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.66, 16.00 (CH_3×2), 17.13, 18.97, 26.69, 27.35, 33.43, 34.60, 34.84, 36.20, 36.60, 37.48, 37.87, 39.4, 44.71, 77.89, 115.22, 138.00, 169.23, 174.80. HRMS (EI) *m*/*z* Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2694.

5.1.26. (2*R*,4*S*)-2,4-Dimethyl-1-(*tert*-butyldiphenylsilyloxy)-5-hexene (*ent*-37). According to general procedure A, the alcohol *ent*-**36**[30] (5.37 g, 14.04 mmol) provided the silyloxyhexene *ent*-**37** as a pale yellow oil (2.95 g, 57%): $[\alpha]_D^{25}$=−1.1 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2957, 1428, 1113, 804; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 0.92 (3H, d, *J*=1.6 Hz, C_8-CH_3), 0.94 (3H, d, *J*=1.6 Hz, $C_{10}-CH_3$), 1.07 (9H, s, $(CH_3)_3C$), 1.27–1.43 (2H, m, C_9-CH_2), 1.66–1.78 (1H, m, C_8-CH), 2.09–2.19 (1H, m, $C_{10}-CH$), 3.39–3.56 (2H, m, CH_2O), 4.83–4.89 (2H, m, $C_{12}-CH_2$), 5.60–5.73 (1H, m, $C_{11}-CH$), 7.35–7.41 (6H, m, Ar*H*), 7.65–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 17.5, 17.9, 20.3, 27.0, 27.6, 33.3, 35.3, 40.3, 68.7, 112.1, 127.5, 127.7, 129.3, 129.4, 133.9, 134.0, 135.5, 135.6, 145.1. HRMS (EI) *m*/*z* Calcd for $C_{20}H_{25}OSi$: 309.1675 (M^+-t-Bu). Found: 309.1688.

5.1.27. (3*R*,5*R*)-3,5-Dimethyl-6-(*tert*-butyldiphenylsilyloxy)hexanol (*ent*-38). According to general procedure B, the silyloxyhexene *ent*-**37** (2.95 g, 8.05 mmol) provided the alcohol *ent*-**38** as a colorless oil (2.10 g, 68%): $[\alpha]_D^{24}$=+11.2 (*c* 1.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3346, 2859, 1472, 1428, 1389, 1113, 1091, 1071; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 0.85 (3H, d, *J*=6.4 Hz, C_8-CH_3), 0.89 (3H, d, *J*=6.6 Hz, $C_{10}-CH_3$), 1.05 (9H, s, $(CH_3)_3C$), 1.18–1.28 (1H, m, $C_{11}-CH$), 1.33–1.46 (1H, m, C_8-CH), 1.49–1.62 (3H, m, C_9-CH_2, $C_{11}-CH$), 1.68–1.78 (1H, m, $C_{11}-CH$), 3.39–3.51 (2H, m, CH_2O), 3.58–3.70 (2H, m, CH_2OH), 7.35–7.44 (6H, m, Ar*H*), 7.64–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 16.7, 19.4, 19.5, 26.8, 26.9, 33.2, 40.7, 40.8, 60.9, 69.4, 127.4, 129.4, 133.9, 135.5. HRMS (EI) *m*/*z* Calcd for $C_{20}H_{27}O_2Si$: 327.1781 (M^+-t-Bu). Found: 327.1782.

5.1.28. (2*R*,4*R*)-6-Azido-2,4-dimethyl-1-(*tert*-butyldiphenylsilyloxy)hexane (*ent*-39). According to general procedure C, the alcohol *ent*-**38** (1.90 g, 4.95 mmol) provided the azide *ent*-**39** as a colorless oil (1.93 g, 95%): $[\alpha]_D^{24}$=+8.5 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2959, 2095, 1472, 1428, 1389, 1262, 1113, 1092; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 0.85 (3H, d, *J*=6.4 Hz, C_8-CH_3), 0.89 (3H, d, *J*=6.8 Hz, $C_{10}-CH_3$), 1.05 (9H, s, $(CH_3)_3C$), 1.19–1.30 (1H, m, $C_{10}-CH$), 1.33–1.49 (1H, m, C_8-CH), 1.50–1.58 (3H, m, C_9-CH_2, $C_{11}-CH$), 1.67–1.77 (1H, m, $C_{11}-CH$), 3.17–3.33 (2H, m, $C_{12}-CH_2$), 3.40–3.50 (2H, m, C_7-CH_2), 7.35–7.45 (6H, m, Ar*H*), 7.64–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 16.6, 19.2, 19.4, 26.9, 27.7, 33.2, 36.5, 40.5, 49.5, 69.4, 127.5, 129.4, 133.9, 135.5. HRMS (EI) *m*/*z* Calcd for $C_{20}H_{26}N_3OSi$: 352.1845 (M^+-t-Bu). Found: 352.1835.

5.1.29. (2*S*)-*N*-[(3*R*,5*R*)-3,5-Dimethyl-6-(*tert*-butylsilyloxy)-hex-1-yl]-2-methylbutyramide (47). According to general procedure D (using (*S*)-2-methylbutyric acid **22**), the azide *ent*-**39** (1.87 g, 4.57 mmol) provided the amide **47** as a pale yellow oil (1.84 g, 86%): $[\alpha]_D^{24}$=+13.8 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3325, 2963, 1644, 1553, 1462, 1427, 1389, 1237, 1113, 1094; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 0.84–0.91 (9H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 1.05 (9H, s, $(CH_3)_3C$), 1.10 (3H, d, *J*=6.9 Hz, $C_{2'}-CH_3$), 1.18–1.76 (8H, m, $C_{3'}-CH_2$, C_9-CH_2, $C_{10}-CH$, $C_{11}-CH_2$), 1.98–2.09 (1H, m, $C_{2'}-CH$), 3.16–3.33 (2H, m, $C_{12}-CH_2$), 3.38–3.52 (2H, m, CH_2O), 5.27 (1H, bd-s, N*H*), 7.35–7.45 (6H, m, Ar*H*), 7.63–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 12.0, 16.7, 17.6, 19.3, 19.4, 26.9, 27.4, 27.9, 33.2, 37.4, 37.7, 40.7, 43.3, 69.4, 127.4, 129.4, 133.9, 135.5, 176.0. HRMS (EI) *m*/*z* Calcd for $C_{25}H_{36}NO_2Si$: 410.2515 (M^+-t-Bu). Found: 410.2537.

5.1.30. (2*S*)-*N*-Methyl-*N*-[(3*R*,5*R*)-dimethyl-6-(*tert*-butyldiphenylsilyloxy)-hex-1-yl]-2-methylbutyramide (48). According to general procedure E, the amide **47** (1.83 g, 3.91 mmol) provided the *N*-methylamide **48** as a pale brown oil (1.76 g, 93%): $[\alpha]_D^{25}$=+17.8 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2930, 1646, 1472, 1464, 1428, 1113, 1090; ^1H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.83–0.90 (9H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 1.05 (9H, s, 1 rotamer, $(CH_3)_3C$), 1.06 (9H, s, 1 rotamer, $(CH_3)_3C$), 1.07 (3H, d, *J*=6.7 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.10 (3H, d, *J*=6.7 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.19–1.55 (4H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$), 1.58–1.75 (4H, m, C_9-CH_2, $C_{11}-CH_2$), 2.49–2.61 (1H, m, $C_{2'}-CH$), 2.90 (3H, s, 1 rotamer, N–CH_3), 2.98 (3H, s, 1 rotamer, N–CH_3), 3.22–3.51 (4H, m, $C_{12}-CH_2$, CH_2O), 7.35–7.44 (6H, m, Ar*H*), 7.64–7.66 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 12.1, 12.2, 16.6, 17.2, 17.9, 19.3, 19.4, 26.9, 27.1, 27.5, 28.1, 33.1, 33.2, 33.7, 35.2, 36.9, 37.2, 37.4, 40.6, 40.7, 46.1, 48.0, 69.3, 69.5, 127.4, 129.3, 129.4, 133.8, 133.9, 135.4, 175.9, 176.2. HRMS (EI) *m*/*z* Calcd for $C_{26}H_{38}NO_2Si$: 424.2672 (M^+-t-Bu). Found: 424.2675.

5.1.31. (2*S*)-*N*-Methyl-*N*-((3*R*,5*R*)-3,5-dimethyl-6-hydroxy-hex-1-yl)-2-methylbutyramide (49). According to general procedure F, the *N*-methylamide **48** (1.72 g, 3.57 mmol) provided the alcohol **49** as a pale yellow oil (804 mg, 93%): $[\alpha]_D^{24}$=+35.2 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3432, 2928, 1626, 1464, 1414, 1379, 1048; ^1H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.85–0.93 (9H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 1.08 (3H, d, *J*=6.3 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.11 (3H, d, *J*=6.3 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.14–1.29 (2H, m, C_9-CH_2), 1.30–1.60 (4H, m, $C_{3'}-CH_2$, $C_{11}-CH_2$), 1.61–1.80 (2H, m, C_8-CH, $C_{10}-CH$), 2.51–2.63 (1H, m, $C_{2'}-CH$), 2.93 (3H, s, 1 rotamer, N–CH_3), 3.01 (3H, s, 1 rotamer, N–CH_3), 3.18–3.45 (4H, m, $C_{12}-CH_2$, CH_2O); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 12.0, 12.2, 16.3, 16.4, 17.1, 17.8, 19.2, 19.4, 27.1, 27.4, 27.9, 28.0, 33.1, 33.7, 35.0, 35.3, 37.0, 37.2, 37.4, 40.4, 40.6, 46.1, 48.0, 68.6, 68.7, 176.0, 176.3. HRMS (EI) *m*/*z* Calcd for $C_{14}H_{29}NO_2$: 243.2199. Found: 243.2204.

5.1.32. (4*S*)-Phenyl-3-[(4*S*,6*R*)-4,6-dimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-(*E*)-2-octenoyl]-2-oxazolidinone (50). According to general procedure G (using (*S*)-phosphonate *ent*-**26**), the alcohol **49** (115 mg, 0.472 mmol) provided the enimide **50** as a colorless oil (147 mg, 73%): $[\alpha]_D^{25}$=+52.8 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2966, 1779, 1688, 1634, 1458, 1383, 1329, 1200, 1103, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.76–0.88 (9H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.95–0.98 (3H, m, $C_{2'}-CH_3$), 1.15–1.39 (5H, m, C_9-CH_2, $C_{10}-CH$, $C_{11}-CH_2$), 1.40–1.53 (2H, m, $C_{3'}-CH_2$), 2.39–2.61 (2H, m, $C_{2'}-CH$, C_8-CH), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.92 (3H, s, 1 rotamer, N–CH_3), 3.20–3.42 (2H, m, $C_{12}-CH_2$), 4.17 (1H, dd, *J*=3.4, 8.6 Hz, CH_2O), 4.75 (1H, t, *J*=8.6 Hz, Ar–C*H*), 5.50 (1H, dd, *J*=3.4, 8.6 Hz, CH_2O), 6.83 (1H, dd, *J*=15.4, 7.5 Hz, C_6-CH), 7.16 (1H, d, *J*=15.4 Hz, C_7-CH), 7.31–7.38 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.8, 17.2, 19.2, 19.6, 26.6, 27.5, 33.4, 33.8, 34.5, 36.2, 39.4, 42.7, 57.1, 70.1, 118.5, 125.7, 127.8, 128.6, 139.7, 153.6, 155.5, 163.6, 174.7. HRMS (EI) *m*/*z* Calcd for $C_{25}H_{36}N_2O_4$: 428.2675. Found: 428.2673.

5.1.33. (4*S*)-4-Phenyl-3-[(3*S*,4*R*,6*R*)-3,4,6-trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-octanoyl]-2-oxazolidinone (51). According to general procedure H, the enimide **50** (172 mg, 0.402 mmol) provided the imide **51** as a colorless oil (167 mg, 93%): $[\alpha]_D^{24}$=+55.9 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2930, 1782, 1705, 1634, 1458, 1385, 1327, 1198, 1136; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.74–0.81 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.96 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.03–1.11 (2H, m, C_9-CH_2), 1.15–1.53 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.84–1.95 (1H, m, C_7-CH), 2.50–2.74 (3H, m, $C_{2'}-CH$, C_6-CH_2), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.95 (3H, s, 1 rotamer, N–CH_3), 3.22–3.38 (2H, m, $C_{12}-CH_2$), 4.14 (1H, dd, *J*=8.7, 3.4 Hz, CH_2O), 4.72 (1H, t, *J*=8.7 Hz, Ar–C*H*), 5.46 (1H, dd, *J*=8.7, 3.4 Hz, CH_2O), 7.26–7.40 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 16.1, 17.1, 18.8, 18.9, 26.6, 27.5, 33.5, 34.1, 34.9, 36.2, 36.7, 38.2, 39.4, 44.9, 56.9, 69.8, 125.5, 127.7, 128.5, 139.7, 153.5, 171.6, 174.5. HRMS (EI) *m*/*z* Calcd for $C_{26}H_{40}N_2O_4$: 444.2988. Found: 444.2983.

5.1.34. (3*S*,4*R*,6*R*)-3,4,6-Trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)octanoic acid (52). According to general procedure I, the imide **51** (167 mg, 0.375 mmol) provided the carboxylic acid **52** as a colorless oil (102 mg, 91%): $[\alpha]_D^{25}$=+38.4 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3218, 2964, 1728, 1634, 1456, 1404, 1381, 1246, 1192, 1084; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.77–0.82 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.04–1.09 (2H, m, C_9-CH_2), 1.15–1.60 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.76–1.95 (2H, m, C_6-CH, C_7-CH), 2.17–2.26 (1H, m, C_6-CH), 2.54–2.69 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.23–3.33 (2H, m, $C_{12}-CH_2$), 12.0 (1H, bd-s, COO*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 16.0, 16.4, 17.2, 19.1, 26.7, 27.5, 33.7, 34.6, 34.7, 36.2, 36.7, 37.8, 39.4, 44.9, 174.1, 174.5. HRMS (EI) *m*/*z* Calcd for $C_{17}H_{33}NO_3$: 299.2460. Found: 299.2450.

5.1.35. (4*S*)-4-Ethenyl-2-[(2*S*,3*R*,5*R*)-2,3,5-trimethyl-7-((2*S*)-*N*-methyl-2-methylbutyramido-heptyl)]oxazoline (53b). According to general procedure J (using (2*S*)-*N*-Boc-amino-3-butenol *ent*-**32**) and procedure K, the carboxylic acid **52** (61.2 mg, 0.204 mmol) provided the oxazoline **53b** as a colorless oil (56.0 mg, 82%, 2 steps): $[\alpha]_D^{26}=-13.7$ (*c* 0.11, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2961, 1667, 1647, 1464, 1379, 1196; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.86 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, *J*=7.3 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=7.3 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.00–1.14 (2H, m, C_9-CH_2), 1.15–1.61 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.73–1.89 (1H, bd-m, C_7-CH), 1.90–2.05 (1H, m, C_6-CH), 2.16–2.29 (1H, m, C_6-CH), 2.54–2.69 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.24–3.32 (2H, m, $C_{12}-CH_2$), 3.84 (1H, app t, *J*=8.1 Hz, C_4-CH), 4.31 (1H, app t, *J*=8.4 Hz, C_4-CH), 4.47–4.60 (1H, m, C_3-CH), 5.07 (1H, d, *J*=10.2 Hz, C_1-CH), 5.18 (1H, d, *J*=17.1 Hz, C_1-CH), 5.80 (1H, ddd, *J*=6.6, 10.2, 17.1 Hz, C_2-CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 15.9, 16.2, 17.1, 19.1, 26.6, 27.4, 31.1, 33.5, 34.7, 35.3, 36.2, 36.7, 39.4, 44.9, 67.4, 71.1, 115.3, 139.1, 166.6, 174.8. HRMS (EI) *m*/*z* Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2940.

5.1.36. (3*S*,7*S*,8*R*,10*R*,2′*S*)-Kalkitoxin (6). According to general procedures L and M, the oxazoline **53b** (54.1 mg, 0.154 mmol) provided the synthetic (3*S*,7*S*,8*R*,10*R*,2′*S*)-kalkitoxin (**6**) as a pale yellow oil (33.7 mg, 61%, 2 steps): $[\alpha]_D^{26}=-7.5$ (*c* 0.80, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2928, 2874, 1646, 1464, 1412, 1381, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.88 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.95 (3H, d, *J*=7.1 Hz, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=7.1 Hz, $C_{2'}-CH_3$), 1.01–1.16 (2H, m, C_9-CH_2), 1.17–1.62 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.73–1.89 (1H, bd-m, C_7-CH), 2.17–2.30 (1H, m, C_6-CH), 2.40–2.47 (1H, m, C_6-CH), 2.55–2.68 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.97 (3H, s, 1 rotamer, $N-CH_3$), 3.02 (1H, dd, *J*=8.0, 10.9 Hz, C_4-CH), 3.25–3.39 (2H, m, $C_{12}-CH_2$), 3.48 (1H, dd, *J*=8.0, 10.9 Hz, C_4-CH), 4.85–4.97 (1H, m, C_3-CH), 5.10 (1H, d, *J*=10.4 Hz, C_1-CH), 5.23 (1H, d, *J*=17.1 Hz, C_1-CH), 5.90 (1H, ddd, *J*=6.4, 10.4, 17.1 Hz, C_2-CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.69, 16.01(CH_3×2), 17.13, 19.08, 26.63, 27.47, 33.38, 34.70, 34.91, 36.19, 36.67, 37.48, 37.84, 39.40, 44.87, 77.90, 115.25, 137.96, 169.18, 174.80. HRMS (EI) *m*/*z* Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2693.

5.1.37. (4*R*)-4-Ethenyl-2-[(2*S*,3*R*,5*R*)-2,3,5-trimethyl-7-((2*S*)-*N*-methyl-2-methylbutyramido-heptyl)]oxazoline (53a). According to general procedures J and K, the carboxylic acid **52** (57.8 mg, 0.193 mmol) provided the oxazoline **53a** as a colorless oil (52.0 mg, 82%): $[\alpha]_D^{25}=+95.4$ (*c* 0.89, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2964, 1660, 1645, 1464, 1381, 1196; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.86 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, *J*=7.0 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=7.0 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.00–1.15 (2H, m, C_9-CH_2), 1.16–1.61 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.71–1.89 (1H, m, C_7-CH), 1.90–2.05 (1H, m, C_6-CH), 2.16–2.28 (1H, m, C_6-CH), 2.54–2.69 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.24–3.34 (2H, m, $C_{12}-CH_2$), 3.84 (1H, app t, *J*=8.1 Hz, C_4-CH), 4.31 (1H, app t, *J*=8.4 Hz, C_4-CH), 4.46–4.60 (1H, m, C_3-CH), 5.07 (1H, d, *J*=10.4 Hz, C_1-CH), 5.17 (1H, d, *J*=17.1 Hz, C_1-CH), 5.80 (1H, ddd, *J*=17.1, 10.6, 6.6 Hz, C1–CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 15.9, 16.2, 17.2, 19.1, 26.7, 27.5, 31.1, 33.5, 34.9, 35.2, 36.2, 36.7, 44.9, 67.4, 71.1, 115.1, 138.9, 166.3, 174.5. HRMS (EI) *m*/*z* Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2934.

5.1.38. (3*R*,7*S*,8*R*,10*R*,2′*S*)-Kalkitoxin (5). According to general procedures L and M, the oxazoline **53a** (48.4 mg, 0.138 mmol) provided the synthetic (3*R*,7*S*,8*R*,10*R*,2′*S*)-kalkitoxin (**5**) as a pale yellow oil (33.6 mg, 70%, 2 steps): $[\alpha]_D^{26}=+77.2$ (*c* 0.83, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2930, 2876, 1640, 1464, 1412, 1381, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.88 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.95 (3H, d, *J*=7.1 Hz, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=7.1 Hz, $C_{2'}-CH_3$), 1.01–1.17 (2H, m, C_9-CH_2), 1.18–1.63 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.72–1.90 (1H, bd-m, C_7-CH), 2.18–2.31 (1H, m, C_6-CH), 2.38–2.46 (1H, m, C_6-CH), 2.54–2.70 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.97 (3H, s, 1 rotamer, $N-CH_3$), 3.03 (1H, dd, *J*=8.3, 10.9 Hz, C_4-CH), 3.25–3.36 (2H, m, $C_{12}-CH_2$), 3.48 (1H, dd, *J*=8.3, 10.9 Hz, C_4-CH), 4.85–4.98 (1H, m, C_3-CH), 5.10 (1H, d, *J*=10.4 Hz, C_1-CH), 5.23 (1H, d, *J*=17.1 Hz, C_1-CH), 5.90 (1H, ddd, *J*=6.6, 10.4, 17.1 Hz, C_2-CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.70, 15.98 (CH_3×2), 17.13, 19.04, 26.64, 27.47, 33.41, 34.71, 34.92, 36.20, 36.66, 37.47, 37.86, 39.40, 44.90, 77.88, 115.21, 138.00, 169.21, 174.80. HRMS (EI) *m*/*z* Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2710.

5.1.39. (2*R*,3*R*,4*S*)-1-Benzyloxy-2,4-dimethyl-3,6-hexanediol (16). To a solution of the benzyloxyhexene **15**[7] (101 mg, 0.431 mmol) in THF (2 mL) was added 9-borabicyclononane dimer (322 mg, 1.29 mmol). The resulting solution was stirred for 10 min, and then placed in a water bath and sonicated for 40 min. Aqueous NaOH solution (4 N, 1 mL) and 30% aqueous H_2O_2 (1 mL) were added sequentially at −5 °C. The resulting mixture was diluted with water and extracted with EtOAc (×2). The combined organic extracts were washed with 1 M aqueous $KHSO_4$ and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=1:1) to afford the desired product **16** as a colorless oil (99 mg, 91%): $[\alpha]_D^{24}=+7.9$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3367 (bd), 2875, 1454, 1363, 1089; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 0.86 (3H, d, *J*=6.7 Hz, C_8-CH_3), 0.98 (3H, d, *J*=6.7 Hz, $C_{10}-CH_3$), 1.54–1.96 (4H, m, C_7-CH_2, C_8-CH, $C_{10}-CH$), 3.49–3.64 (4H, m, CH_2O, CH_2OH), 3.71–3.79 (1H, m, C_9-CH), 4.49 (1H, d, *J*=11.9 Hz, Ar–CH_2), 4.54 (1H, d, *J*=11.9 Hz, Ar–CH_2), 7.28–7.38 (5H, m, ArH); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 9.5, 17.5, 34.7, 34.9, 37.9, 61.2, 73.5, 76.5, 78.5, 127.5, 127.7, 128.4, 137.8. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.14; H, 9.66.

5.1.40. (2*R*,3*R*,4*S*)-1-Benzyloxy-2,4-dimethyl-6-(*tert*-butyldiphenylsilyloxy)-3-hexanol (17). To a solution of the diol **16** (1.08 g, 4.29 mmol) in DMF (20 mL) was added *tert*-butyldiphenylsilyl chloride (1.3 mL, 4.72 mmol), imidazole (585 mg, 8.58 mmol) at 0 °C. After 5 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with ether, and washed with water (×5), 1 M aqueous $KHSO_4$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=9:1–4:1–2:1) to afford the desired product **17** as a colorless oil (1.65 g, 78%): $[\alpha]_D^{25}=+3.9$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3453 (bd), 2858, 1496, 1427, 1111, 1089; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 0.81 (3H, d, *J*=6.9 Hz, C_8-CH_3), 0.95 (3H, d, *J*=6.9 Hz, $C_{10}-CH_3$), 1.05 (s, 9H, $(CH_3)_3C$), 1.45–2.04 (4H, m, C_7-CH_2, C_8-CH, $C_{10}-CH$), 3.46–3.82 (5H, m, CH_2O ×2, C_9-CH), 4.51 (2H, s, Ar–CH_2), 7.27–7.73 (15H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3/CDCl_3$) δ 9.8, 16.5, 19.1, 26.8, 33.7, 35.3, 35.8, 62.3, 73.3, 75.0, 76.8, 127.5, 127.6, 127.7, 128.3, 128.4, 129.6, 133.6, 134.8, 135.6, 138.4. Anal. Calcd for $C_{31}H_{42}O_3Si$: C, 75.87; H, 8.63. Found: C, 75.70; H, 8.66.

5.1.41. (2*R*,3*R*,4*S*)-*O*-Phenyl-3-[1-benzyloxy-2,4-dimethyl-6-(*tert*-butyldiphenylsilyloxy)-hexyl]thiocarbonate (18). To a solution of the alcohol **17** (297 mg, 0.606 mmol) in THF (19 mL) under argon at −78 °C was added *n*-BuLi (0.46 mL, 0.727 mmol, 1.6 M in hexane) dropwise via syringe. The solution was stirred at −78 °C for 5 min, then phenyl chlorothionoformate (0.10 mL, 0.727 mmol) was added dropwise. After 15 min, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature over 1 h. Cold (0 °C) water was then added. The mixture was diluted with ether and washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine. The solution was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=12:1) to afford the desired product **18** as a yellow oil (330 mg, 87%): $[\alpha]_D^{25}=-9.6$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2858, 1740, 1489, 1282, 1197, 1111; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 0.90 (3H, d, *J*=6.7 Hz, C_8-CH_3), 1.01 (3H, d, *J*=6.7 Hz, $C_{10}-CH_3$), 1.06 (s, 9H, $(CH_3)_3C$), 1.25–1.45 (1H, m, C_8-CH), 1.82–1.98 (1H, m, $C_{10}-CH$), 2.12–2.30 (2H, m, C_7-CH_2), 3.34–3.47 (2H, m, CH_2O), 3.63–3.77 (2H, m, CH_2O), 4.43 (1H, d, *J*=11.6 Hz, Ar–CH_2), 4.51 (1H, d, *J*=11.6 Hz, Ar–CH_2), 5.52 (1H, dd, *J*=4.3, 6.9 Hz, C_9-CH), 7.00–7.68 (20H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3/CDCl_3$) δ 11.7, 15.9, 19.2, 26.9, 31.8, 34.5, 35.6, 61.7, 72.6, 73.3, 90.1, 121.9, 126.3, 127.5, 127.6, 127.7, 128.3, 129.4, 129.6, 133.8, 133.9, 135.5, 138.3, 153.4, 195.6. Anal. Calcd for $C_{38}H_{46}O_4SSi$: C, 72.80; H, 7.40. Found: C, 72.62; H, 7.32.

5.1.42. (2*S*,4*R*)-1-Benzyloxy-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexane (19). Under argon, the thiocarbonate **18** (247 mg, 0.394 mmol) was dissolved in *n*-Bu_3SnH (1 mL) and AIBN (3 mg) was added. The mixture was heated to 100 °C. After 20 min, the reaction mixture was cooled to room temperature and then purified by silica gel column chromatography (BW-200, hexane–hexane/Et_2O=20:1) to afford the desired product **19** as a colorless oil (128 mg, 68%): $[\alpha]_D^{26}=-3.3$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2857, 1495, 1427, 1361, 1207, 1111; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 0.80 (3H, d, *J*=6.6 Hz, C_8-CH_3), 0.89 (3H, d, *J*=6.6 Hz, $C_{10}-CH_3$), 1.04 (s, 9H, $(CH_3)_3C$), 1.10–1.62 (4H, m, C_7-CH_2,C_9-CH_2), 1.65–1.95 (2H, m, C_8-CH, $C_{10}-CH$), 3.17–3.32 (2H, m, CH_2O), 3.62–3.74 (2H, m, CH_2O), 4.46 (1H, d, *J*=12.2 Hz, Ar–CH_2), 4.51 (1H, d, *J*=12.2 Hz, Ar–CH_2), 7.27–7.69 (15H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3/CDCl_3$) δ 17.2, 19.6, 19.7, 26.8, 27.2, 31.2, 40.9, 41.4, 62.4, 73.3, 76.9, 127.7, 127.8, 127.9, 128.6, 129.8, 134.5, 135.9, 139.2. Anal. Calcd for $C_{31}H_{42}O_2Si$: C, 78.43; H, 8.92. Found: C, 78.37; H, 8.90.

5.1.43. (3*R*,5*S*)-6-Benzyloxy-3,5-dimethylhexanol (20). To a solution of the deoxyganated product **19** (90 mg, 0.189 mmol) in THF (1 mL) was added TBAF (100 mg, 0.380 mmol) at 0 °C. After 15 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 35 min. The reaction mixture was diluted with EtOAc, and washed with water (×2) and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=4:1) to afford the desired product **20** as a colorless oil (39 mg, 87%): $[\alpha]_D^{26}=-11.0$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3368 (bd), 2928, 1454, 1377, 1096, 1074; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 0.88 (3H, d, *J*=6.7 Hz, C_8-CH_3), 0.91 (3H, d, *J*=6.6 Hz, $C_{10}-CH_3$), 1.05–1.36 (2H, m, C_9-CH_2), 1.36–1.65 (3H, m, C_7-CH_2, O*H*), 1.82–1.95 (1H, m, $C_{10}-CH$), 3.24 (1H, dd, *J*=6.6, 8.9 Hz, CH_2O), 3.30 (1H, dd, *J*=6.6, 8.9 Hz, CH_2O), 3.62–3.69 (2H, m, CH_2OH), 4.50 (2H, s, Ar–CH_2), 7.27–7.35 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3/CDCl_3$) δ 16.9, 19.3, 26.6, 30.8, 40.6, 41.2, 60.9, 72.9, 76.5, 127.4, 127.5, 128.3, 138.7. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.94; H, 10.43.

5.1.44. (2*S*,4*R*)-5-Azido-1-benzyloxy-2,4-dimethylhexane (21). To a solution of the alcohol **20** (1.04 g, 4.40 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (1.2 mL, 8.8 mmol), methanesulfonyl chloride (0.51 mL, 6.6 mmol), DMAP (16 mg, 0.132 mmol) at 0 °C. After 15 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 11 h. The mixture was diluted with EtOAc, and washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give the crude mesylate as a pale yellow oil (1.38 g). This intermediate was used in the next reaction without further purification.

To a solution of the above mesylate in DMF (15 mL) at room temperature was added sodium azide (855 mg, 13.2 mmol), and then the mixture was heated to 50 °C. After 2 h, the resulting mixture was diluted with ether, and washed with water (×5) and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=12:1) to afford the desired product **21** as a colorless oil (1.01 mg, 88%): $[\alpha]_D^{26}=-8.2$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2925, 2096, 1728, 1454, 1265, 1099; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 0.88 (3H, d, *J*=7.3 Hz, C_8-CH_3), 0.91 (3H, d, *J*=6.9 Hz, $C_{10}-CH_3$), 1.03–1.31 (2H, m, C_9-CH_2), 1.35–1.72 (3H, m, C_7-CH_2, C_8-CH),

1.79–1.95 (1H, m, C_{10}–C*H*), 3.20–3.34 (4H, m, CH_2O, CH_2N$_3$), 4.50 (2H, s, Ar–CH_2), 7.33 (5H, s, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 16.8, 18.9, 27.5, 30.8, 36.5, 40.8, 49.4, 72.9, 76.5, 127.4, 127.5, 128.3, 138.7. Anal. Calcd for $C_{15}H_{23}N_3O$: C, 68.93; H, 8.87; N, 16.08. Found: C, 69.01; H, 8.83; N, 15.77.

5.1.45. (2*S*)-*N*-((3*R*,5*S*)-3,5-Dimethyl-6-benzyloxyhexyl)-2-methylbutyramide (23). To a solution of the azide **21** (248 mg, 0.950 mmol) in EtOH (10 mL) was added Lindlar catalyst (5% Pd on carbon/Pb–$CaCO_3$) (100 mg) at room temperature. The black slurry was stirred under 1 atm H_2 for 1 h. The reaction mixture was filtered through a pad of celite (EtOAc rinse) and the filtrate was concentrated to give the crude amine as a yellow oil (228 mg). This intermediate was used in the next reaction without further purification.

To a solution of the above amine and (*S*)-2-methylbutyric acid (**22**) (0.11 mL, 0.97 mmol) in DMF (2 mL) at 0 °C was successively added diethyl phosphorocyanidate (0.18 mL, 1.07 mmol) and triethylamine (0.27 mL, 1.94 mmol). After 15 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with EtOAc, and washed with water (×5) and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=2:1) to afford the desired product **23** as a pale yellow oil (298 mg, 97%): $[\alpha]_D^{25}=-1.1$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3296, 2874, 1645, 1556, 1454, 1377, 1236, 1101; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.86–0.91 (9H, m, C_8–CH_3, C_{10}–CH_3, $C_{3'}$–CH_3), 1.11(3H, d, *J*=6.6 Hz, $C_{2'}$–CH_3), 1.19–1.70 (7H, m, C_9–CH_2, C_{10}–C*H*, C_{11}–CH_2), 1.82–1.91(1H, m, C_8–C*H*), 1.99–2.07 (1H, m, $C_{2'}$–C*H*), 3.23–3.32 (4H, m, CH_2O, C_{12}–CH_2), 4.50 (2H, s, Ar–CH_2), 5.50 (1H, bd-s, N*H*), 7.27–7.35 (5H, s, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 12.2, 17.2, 17.9, 19.5, 27.6, 28.1, 31.1, 37.6, 37.9, 41.3, 43.6, 73.3, 76.9, 127.7, 127.8, 128.6, 139.0, 176.6. Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.19; H, 10.41; N, 4.38. Found: C, 75.11; H, 10.28; N, 4.37.

5.1.46. (2*S*)-*N*-Methyl-*N*-((3*R*,5*S*)-3,5-dimethyl-6-benzyloxy-hexyl)-2-methylbutyramide (24). To a solution of the amide **23** (108 mg, 0.333 mmol) in THF (1.5 mL) under argon at 0 °C was added NaH (133 mg, 3.33 mmol). The solution was stirred at −78 °C for 20 min, then CH_3I (0.3 mL, 4.82 mmol) was added. After 10 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature. After 20 h, water was added to the mixture, which was diluted with EtOAc, and washed with water, 1 M aqueous $KHSO_4$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=2:1) to afford the desired product **24** as a pale yellow oil (106 mg, 94%): $[\alpha]_D^{28}=+9.9$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2874, 1643, 1454, 1410, 1375, 1099; ^{1}H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.75–0.87 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.93–0.98 (3H, m, $C_{2'}$–CH_3), 1.06–1.57 (7H, m, $C_{3'}$–CH_2, C_9–CH_2, C_8–C*H*, C_{11}–CH_2), 1.71–1.85 (1H, m, C_{10}–C*H*), 2.51–2.67 (1H, m, $C_{2'}$–C*H*), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.93 (3H, s, 1 rotamer, N–CH_3), 3.12–3.47 (4H, m, C_{12}–CH_2, CH_2O), 4.44 (2H, s, Ar–C*H*2), 7.22–7.37 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 11.6, 11.8, 16.7, 17.1, 17.8, 19.1, 26.7, 27.0, 27.1, 27.3, 30.3, 33.1, 34.4, 34.5, 36.1, 36.2, 36.4, 40.6, 41.1, 44.7, 47.1, 71.9, 75.6, 75.7, 127.3, 128.2, 128.6, 138.7, 174.8, 175.0. Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20. Found: C, 75.45; H, 10.65; N, 4.23.

5.1.47. (2*S*)-*N*-Methyl-*N*-((3*R*,5*S*)-3,5-dimethyl)-6-hexanol (25). To a solution of the amide **24** (91 mg, 0.269 mmol) in EtOH (1.5 mL) was added 5% Pd on carbon (40 mg) at room temperature. The black slurry was stirred under 1 atm H_2 for 1 h. The reaction mixture was filtered through a pad of celite (EtOAc rinse) and the filtrate was concentrated. The residue was purified by silica gel column chromatography (BW-8280 MH, hexane/EtOAc=1:1–EtOAc) to afford the desired product **25** as a colorless oil (67 mg, quant.): $[\alpha]_D^{29}=+8.2$ (*c* 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3410 (bd), 2874, 1628, 1464, 1416, 1379, 1045; ^{1}H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.76–0.87 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.93–0.99 (3H, m, $C_{2'}$–CH_3), 1.07–1.62 (8H, m, C_9–CH_2, $C_{3'}$–CH_2, C_{11}–CH_2, C_8–C*H*, C_{10}–C*H*), 2.51–2.67 (1H, m, $C_{2'}$–C*H*), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.12–3.49 (4H, m, C_{12}–CH_2, CH_2O), 4.33–4.41 (1H, bd-m, O*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 11.6, 11.8, 16.4, 16.5, 17.1, 17.8, 19.2, 26.7, 27.0, 27.2, 27.4, 32.8, 33.1, 34.6, 34.7, 36.1, 36.2, 36.6, 40.4, 40.8, 44.8, 47.2, 66.8, 66.9, 174.8, 175.0. Anal. Calcd for $C_{14}H_{29}NO_2$: C, 69.09; H, 12.01; N, 5.75. Found: C, 68.81; H, 12.07; N, 5.66.

5.1.48. (4*R*)-Phenyl-3-[(4*R*,6*R*)-4,6-dimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-(*E*)-2-octenoyl]-2-oxazolidinone (27a). According to general procedure G, the alcohol **25** (67 mg, 0.275 mmol) provided the enimide **27a** as a colorless oil (104 mg, 85%): $[\alpha]_D^{25}=-30.7$ (*c* 1.1, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2964, 1770, 1687, 1633, 1456, 1383, 1197; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.65–0.87 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.91–0.99 (3H, m, $C_{2'}$–CH_3), 1.13–1.38 (5H, m, C_9–CH_2, C_{10}–C*H*, C_{11}–CH_2), 1.39–1.58 (2H, m, $C_{3'}$–CH_2), 2.39–2.60 (2H, m, $C_{2'}$–C*H*, C_8–*H*), 2.77 (3H, s, 1 rotamer, N–CH_3), 2.89 (3H, s, 1 rotamer, N–CH_3), 3.05–3.16 (2H, m, 1 rotamer, C_{12}–CH_2), 3.18–3.35 (2H, m, 1 rotamer, C_{12}–CH_2), 4.16 (1H, dd, *J*=3.6, 8.7 Hz, CH_2O), 4.75 (1H, t, *J*=8.7 Hz, Ar–C*H*), 5.49 (1H, dd, *J*=3.6, 8.7 Hz, CH_2O), 6.81 (1H, ddd, *J*=2.3, 7.9, 15.3 Hz, C_6–C*H*), 7.15 (1H, d, *J*=15.3 Hz, C_7–C*H*), 7.27–7.40 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.5, 17.1, 19.1, 19.5, 26.7, 27.4, 33.2, 33.8, 34.4, 36.2, 39.4, 42.8, 57.1, 70.1, 118.7, 125.9, 128.0, 128.8, 139.9, 153.7, 155.6, 163.8, 174.8. Anal. Calcd For $C_{25}H_{36}N_2O_4$: C, 70.06; H, 8.47; N, 6.54. Found: C, 69.92; H, 8.74; N, 6.34.

5.1.49. (4*R*)-4-Phenyl-3-[(3*R*,4*S*,6*R*)-3,4,6-trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-octanoyl]-2-oxazolidinone (30a). According to general procedure H, the enimide **27a** (37 mg, 0.0864 mmol) provided the imide **30a** as a colorless oil (41 mg, quant.): $[\alpha]_D^{25}=-35.2$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2963, 1782, 1705, 1639, 1456, 1385, 1323, 1197; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both

rotamers unless stated otherwise, δ 0.71–0.82 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, J=6.6 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.96 (3H, d, J=6.6 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.02–1.12 (2H, m, C_9-CH_2), 1.16–1.59 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.82–1.98 (1H, m, C_7-CH), 2.50–2.76 (3H, m, $C_{2'}-CH$, C_6-CH_2), 2.78 (3H, s, 1 rotamer, $N-CH_3$), 2.95 (3H, s, 1 rotamer, $N-CH_3$), 3.11–3.42 (2H, m, $C_{12}-CH_2$), 4.13 (1H, dd, J=8.6, 3.6 Hz, CH_2O), 4.72 (1H, t, J=8.6 Hz, Ar–CH), 5.46 (1H, dd, J=8.6, 3.6 Hz, CH_2O), 7.26–7.41 (5H, m, ArH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.9, 16.4, 17.4, 18.0, 19.1, 27.0, 27.6, 33.8, 34.4, 34.9, 36.4, 36.5, 37.1, 39.4, 45.0, 57.3, 70.2, 126.0, 128.2, 129.0, 140.3, 154.0, 172.1, 175.1. Anal. Calcd For $C_{26}H_{40}N_2O_4\cdot$ or 1/5H_2O: C, 69.67; H, 9.09; N, 6.25. Found: C, 69.81; H, 9.14; N, 6.24.

5.1.50. (3*R*,4*S*,6*R*)-3,4,6-Trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)octanoic acid (31a). According to general procedure I, the imide **30a** (84 mg, 0.189 mmol) provided the carboxylic acid **31a** as a colorless oil (50 mg, 88%): $[\alpha]_D^{25}=-3.9$ (c 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3278 (bd), 2964, 1728, 1634, 1456, 1379, 1247, 1184, 1102; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.73–0.86 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.02–1.12 (2H, m, C_9-CH_2), 1.17–1.59 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.72–1.98 (2H, m, C_6-CH, C_7-CH), 2.16–2.27 (1H, m, C_6-CH), 2.52–2.71 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.24–3.42 (2H, m, $C_{12}-CH_2$), 12.0 (1H, bd-s, COOH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 15.9, 16.4, 17.1, 19.0, 26.7, 27.4, 33.7, 34.6, 34.8, 36.2, 36.8, 37.8, 39.4, 44.7, 174.4, 174.8. Anal. Calcd For $C_{17}H_{33}NO_3\cdot$ or 1/4H_2O: C, 67.18; H, 11.11; N, 4.61. Found: C, 67.16; H, 11.20; N, 4.63.

5.1.51. (4*R*)-4-Ethenyl-2-[(2*R*,3*S*,5*R*)-2,3,5-trimethyl-7-((2*S*)-*N*-methyl-2-methylbutyramido)-heptyl]oxazoline (34a). According to general procedure J, the carboxylic acid **31a** (60.1 mg, 0.201 mmol) provided the amide **33a** as a colorless oil (68.4 mg, 92%), which was directly used for the next step. To a solution of amide (61.0 mg, 0.166 mmol) in THF (1 mL) was added Burgess reagent (83 mg, 0.662 mmol) under argon. The mixture was heated to 70 °C. After 2 h, the reaction mixture was cooled to room temperature and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=1:3) to afford the desired oxazoline **34a** as a colorless oil (37.8 mg, 65%): $[\alpha]_D^{28}=+41.6$ (c 0.68, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2968, 1667, 1644, 1464, 1379, 1196; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.86 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, J=6.9 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, J=6.9 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.00–1.15 (2H, m, C_9-CH_2), 1.16–1.62 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.71–1.88 (1H, m, C_7-CH), 1.89–2.03 (1H, m, C_6-CH), 2.15–2.27 (1H, m, C_6-CH), 2.56–2.72 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.15–3.25 (2H, m, $C_{12}-CH_2$), 3.84 (1H, app t, J=7.9 Hz, C_4-CH), 4.31 (1H, app t, J=8.3 Hz, C_4-CH), 4.47–4.60 (1H, m, C_3-CH), 5.07 (1H, d, J=10.2 Hz, C_1-CH), 5.17 (1H, d, J=16.8 Hz, C_1-CH), 5.80 (1H, ddd, J=17.2, 10.6, 6.9 Hz, C_2-CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 16.0, 16.3, 17.1, 19.0, 26.7, 27.3, 31.1, 33.5, 34.8, 35.3, 36.2, 36.8, 39.4, 44.7, 67.4, 115.3, 139.1, 166.6, 174.8. HRMS (EI) m/z Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2935.

5.1.52. (3*R*,7*R*,8*S*,10*R*,2′*S*)-Kalkitoxin (1). According to general procedures L and M, the oxazoline **34a** (37.0 mg, 0.105 mmol) provided the synthetic (3*R*,7*R*,8*S*,10*R*,2′*S*)-kalkitoxin (**1**) as a pale yellow oil (18.9 mg, 50%, 2 steps): $[\alpha]_D^{27}=+15.5$ (c 0.75, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2928, 2874, 1646, 1464, 1412, 1379, 1084; ^{1}H NMR (270MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.76–0.86 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, J=6.9 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, J=6.9 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.01–1.15 (2H, m, C_9-CH_2), 1.17–1.63 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.71–1.90 (1H, bd–m, C_7-CH), 2.17–2.29 (1H, m, C_6-CH_2), 2.39–2.46 (1H, m, C_6-CH_2), 2.53–2.71 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.02 (1H, dd, J=8.3, 11.2 Hz, C_4-CH), 3.11–3.31 (2H, m, $C_{12}-CH_2$), 3.45 (1H, dd, J=8.3, 11.2 Hz, C_4-CH), 4.84–4.96 (1H, m, C_3-CH), 5.10 (1H, d, J=10.9 Hz, C_1-CH), 5.23 (1H, d, J=16.8 Hz, C_1-CH), 5.90 (1H, ddd, J=6.6, 10.9, 16.8 Hz, C_2-CH); ^{13}C NMR (67.8MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.65, 16.07 ($CH_3\times2$), 17.11, 19.00, 26.69, 27.35, 33.43, 34.59, 34.85, 36.19, 36.70, 37.49, 37.87, 39.39, 44.69, 77.90, 115.26, 137.95, 169.24, 174.81. HRMS (EI) m/z Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2715.

5.1.53. (4*S*)-Phenyl-3-[(4*R*,6*R*)-4,6-dimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-(*E*)-2-octenoyl]-2-oxazolidinone (27b). According to general procedure G (using (*S*)-phosphonate *ent*-**26**), the alcohol **25** (131 mg, 0.538 mmol) provided the enimide **27b** as a colorless oil (188 mg, 82%): $[\alpha]_D^{24}=+93.9$ (c 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2960, 1779, 1688, 1634, 1458, 1383, 1200; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.72–0.91 (9H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.92–1.01 (3H, m, $C_{2'}-CH_3$), 1.15–1.38 (5H, m, C_9-CH_2, $C_{10}-CH$, $C_{11}-CH_2$), 1.39–1.61 (2H, m, $C_{3'}-CH_2$), 2.40–2.66 (2H, m, $C_{2'}-CH$, C_8-CH), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.95 (3H, s, 1 rotamer, $N-CH_3$), 3.15–3.42 (2H, m, $C_{12}-CH_2$), 4.18 (1H, dd, J=3.4, 8.7 Hz, CH_2O), 4.76 (1H, t, J=8.7 Hz, Ar–CH), 5.51 (1H, dd, J=3.4, 8.7 Hz, CH_2O), 6.83 (1H, dd, J=15.5, 7.9 Hz, C_6-CH), 7.15 (1H, d, J=15.5 Hz, C_7-CH), 7.27–7.41 (5H, m, ArH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 17.1, 18.9, 19.5, 26.7, 27.5, 33.1, 33.8, 34.5, 36.2, 42.7, 57.1, 70.1, 118.5, 125.9, 128.0, 128.8, 139.8, 153.8, 155.8, 163.9, 175.0. HRMS (EI) m/z Calcd for $C_{25}H_{36}N_2O_4$: 428.2675. Found: 428.2670.

5.1.54. (4*S*)-4-Phenyl-3-[(3*S*,4*S*,6*R*)-3,4,6-trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-octanoyl]-2-oxazolidinone (30b). According to general procedure H, the enimide **27b** (259 mg, 0.604 mmol) provided the imide **30b** as a colorless oil (246 mg, 92%): $[\alpha]_D^{27}=+39.2$ (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2964, 1782, 1705, 1639, 1385, 1242, 1198; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both

rotamers unless stated otherwise, δ 0.68–0.86 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, J=6.1 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.96 (3H, d, J=6.1 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.02–1.13 (2H, m, C_9-CH_2), 1.14–1.61 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.84–2.00 (1H, m, C_7-CH), 2.50–2.70 (1H, m, $C_{2'}-CH$), 2.72–2.90 (2H, m, C_6-CH_2), 2.77 (3H, s, 1 rotamer, $N-CH_3$), 2.93 (3H, s, 1 rotamer, $N-CH_3$), 3.10–3.49 (2H, m, $C_{12}-CH_2$), 4.13 (1H, dd, J=8.7, 3.6 Hz, CH_2O), 4.72 (1H, t, J=8.7 Hz, Ar–C*H*), 5.46 (1H, dd, J=8.7, 3.6 Hz, CH_2O), 7.26–7.39 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 14.1, 17.1, 17.8, 19.2, 26.7, 27.3, 32.8, 33.1, 33.3, 34.5, 36.1, 36.2, 39.4, 44.6, 57.0, 70.0, 125.7, 127.9, 128.8, 140.0, 153.7, 171.7, 174.8. HRMS (EI) *m*/*z* Calcd for $C_{26}H_{40}N_2O_4$: 444.2988. Found: 444.2996.

5.1.55. (3*S*,4*S*,6*R*)-3,4,6-Trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)octanoic acid (31b). According to general procedure I, the imide **30b** (217 mg, 0.489 mmol) provided the carboxylic acid **31b** as a colorless oil (124 mg, 85%): $[\alpha]_D^{25}$=+8.6 (*c* 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3250 (bd), 2964, 1724, 1614, 1464, 1383; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.70–0.89 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.95 (3H, d, J=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, J=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.03–1.15 (2H, m, C_9-CH_2), 1.16–1.61 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.77–1.91 (1H, m, C_7-CH), 1.93–2.09 (1H, m, C_6-CH), 2.13–2.27 (1H, m, C_6-CH), 2.54–2.60 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.10–3.52 (2H, m, $C_{12}-CH_2$), 12.0 (1H, bd-s, COO*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 14.3, 14.5, 17.1, 19.2, 26.7, 27.2, 33.0, 33.7, 33.8, 34.3, 34.5, 36.2, 39.4, 44.6, 174.2, 174.8. HRMS (EI) *m*/*z* Calcd for $C_{17}H_{33}NO_3$: 299.2460. Found: 299.2462.

5.1.56. (4*R*)-4-Ethenyl-2-[(2*S*,3*S*,5*R*)-2,3,5-trimethyl-7-((2*S*)-*N*-methyl-2-methylbutyramido)-heptyl]oxazoline (34b). According to general procedure J, the carboxylic acid **31b** (78.0 mg, 0.260 mmol) provided the amide **33b** as a colorless oil (72.5 mg, 76%), which was directly used for the next step. To a solution of the amide **33b** (70.4 mg, 0.191 mmol) in THF (1.5 mL) was added Burgess reagent (97 mg, 0.764 mmol) under argon. The mixture was heated to 70 °C. After 1.5 h, the reaction mixture was cooled to room temperature and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=1:3) to afford the desired oxazoline **34b** as a colorless oil (44.1 mg, 66%): $[\alpha]_D^{25}$=+63.5 (*c* 0.98, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 1663, 1646, 1458, 1379, 1196; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.73–0.89 (12H, m, C_3-CH_3, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, J=7.3 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, J=7.3 Hz, 1 rotamer, C_2-CH_3), 1.01–1.16 (2H, m, C_9-CH_2), 1.17–1.63 (6H, m, C_3-CH_2,C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.73–1.90 (1H, m, C_7-CH), 1.95–2.12 (1H, m, C_6-CH), 2.15–2.27 (1H, m, C_6-CH), 2.55–2.72 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.11–3.36 (2H, m, $C_{12}-CH_2$), 3.85 (1H, app t, J=7.9 Hz, C_4-CH), 4.26–4.36 (1H, m, C_4-CH), 4.47–4.62 (1H, m, C_3-CH), 5.07 (1H, d, J=10.6 Hz, C_1-CH), 5.17 (1H, d, J=16.8 Hz, C_1-CH), 5.80 (1H, ddd, J=16.8, 10.6, 6.6 Hz, C_2-CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 14.2, 17.1, 19.2 (CH_3×2), 26.7, 26.7, 27.2, 32.6, 33.1, 34.2, 34.5, 36.1, 36.2, 39.4, 44.5, 67.5, 71.1, 115.3, 139.1, 166.5, 174.8. HRMS (EI) *m*/*z* Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2930.

5.1.57. (3*R*,7*S*,8*S*,10*R*,2′*S*)-Kalkitoxin (2). According to general procedures L and M, the oxazoline **34b** (43.5 mg, 0.124 mmol) provided the synthetic (3*R*,7*S*,8*S*,10*R*,2′*S*)-kalkitoxin (**2**) as a pale yellow oil (22.9 mg, 53%, 2 steps): $[\alpha]_D^{26}$=+49.6 (*c* 0.64, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2929, 2874, 1646, 1464, 1412, 1381, 1082; ^{1}H NMR (270MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.71–0.87 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, J=6.9 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, J=6.9 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.01–1.18 (2H, m, C_9-CH_2), 1.19–1.67 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.72–1.90 (1H, bd–m, C_7-CH), 2.22–2.37 (1H, m, C_6-CH_2), 2.38–2.49 (1H, m, C_6-CH_2), 2.55–2.71 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.03 (1H, dd, J=8.3, 10.2 Hz, C_4-CH), 3.09–3.25 (2H, m, $C_{12}-CH_2$), 3.48 (1H, dd, J=8.3, 10.2 Hz, C_4-CH), 4.86–4.99 (1H, m, C_3-CH), 5.10 (1H, d, J=10.3 Hz, C_1-CH), 5.23 (1H, d, J=17.0 Hz, C_1-CH), 5.90 (1H, ddd, J=6.3, 10.3, 17.0 Hz, C_2-CH); ^{13}C NMR (67.8MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.99, 14.40 (CH_3×2), 17.47, 19.63, 27.01, 27.53, 32.89, 34.52, 34.89, 36.52 (CH ×2), 38.90, 40.94, 42.03, 44.89, 78.22, 115.60, 138.28, 169.42, 175.11. HRMS (EI) *m*/*z* Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2706.

Acknowledgements

Work in Nagoya was partially supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan (to F. Y. and T. S.) and Nagoya City University (to F. Y.). Work in Oregon was supported by NIH GM 86354 and the MFBS Center at OSU (ES03850), and a JSPS fellowship to T. O.

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18. There are two possible influential factors in the methylation of the oxazolidinone **27**: the stereogenic methyl group at the γ-position to the imidocarbonyl group[19] and the phenyl group in the oxazolidinone nucleus. Since the presence of the rotational isomers caused by the *N*-methylamide function gives rise to a complex pattern in ^{1}H NMR spectra, the model compounds **28a–c** without the *N*-methylamide group were chosen as reaction substrates to investigate the stereoselectivity of the 1,4-addition, and the stereoselectivity was determined as the carboxylic acid **29** by ^{1}H NMR spectra after removal of the oxazolidinone group. As shown in, the 1,4-addition of methyl magnesium bromide to the achiral oxazolidinone **28b** in the presence of cuprous bromide(dimethyl sulfide followed by alkaline hydroxide afforded a diastereoisomeric mixture of the carboxylic acid **29** in a ratio of 2.6:1 in preference of the (*R*)-isomer **29a**. This will be due to the influence of the stereogenic γ-methyl function.[19] The α,β-unsaturated carbonyl compound **28a** having the Hruby's (*R*)-4-phenyloxazolidinone auxiliary, in which the γ-methyl group would not be influential, diastereoselectively and solely afforded the (3*R*)-carboxylic acid **29a**. On the other hand, the 1,4-addition of the compound **28c** having the (*S*)-4-phenyloxazolidinone moiety also diastereoselectively proceeded through the influence of the (*S*)-phenyl substituent to give the (3*S*)-carboxylic acid **29b** as a sole product. These experiments proved that the influence of the γ-stereogenic center to the 1,4-addition reaction would be little if any (Scheme 3).
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