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Total syntheses of lyngbyabellins A and B, potent cytotoxic lipopeptides from the marine cyanobacterium *Lyngbya majuscula*

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Abstract—The first total syntheses of lyngbyabellins A and B, *Lyngbya majuscula* derived lipopeptides, are described. The functionalized thiazole carboxylic acid units were prepared by the oxidative dehydrogenation of the corresponding thiazolidines with chemical manganese dioxide. The asymmetric synthesis of the dichlorinated β-hydroxy acid by a chiral oxazaborolidinone mediated aldol reaction. Finally, fragment condensation followed by macrolactamization provided lyngbyabellin A. The total synthesis of lyngbyabellin B was accomplished by formation of the sensitive thiazoline ring after the macrolactamization.

1. Introduction

Marine cyanobacteria have recently been recognized to be rich sources of numerous structurally diverse and biologically active secondary metabolites.[1] Moreover, as the rate of re-isolation of known natural products, or the isolation of metabolites closely related to known compounds from marine cyanobacteria increases, recognition continues to grow that a substantial number of metabolites isolated from and attributed to the metabolism of marine animals, such as sea hares and sponges, actually derive from marine cyanobacteria. However, often only small quantities of marine cyanobacteria derived natural products can be isolated from an exploration site, and many species have been resistant to laboratory culturing. Therefore, the evaluation of the biological potential of promising bioactive compounds frequently has to await the development of a suitable synthetic route.[2]

Lyngbyabellin A (**1**) was isolated from the marine cyanobacterium *Lyngbya majuscula* collected at Apra Harbor, Guam.[3] It exhibited attractive cytotoxic properties against the human cancer cell lines and was shown to be a potent disrupter of the cellular microfilament network. The subsequent isolation of lyngbyabellin B (**2**) was reported simultaneously from collections of *Lyngbya* from Guam[4a] and the Dry Tortugas National Park, Florida.[4b] The structure of lyngbyabellin B (**2**) is closely related to lyngbyabellin A (**1**). The isoleucine-derived unit in **1** is replaced by a valine-derived moiety in **2**, and one thiazole unit in **1** is replaced by a thiazoline ring in **2**. The in vitro cytotoxic activities of **2** are slightly weaker than **1**. Interestingly, these novel lipopeptides are structurally related to dolabellin (**3**),[5] a metabolite isolated from the sea hare *Dolabella auricularia*, and this striking structural relationship strongly supports a cyanobacterial origin for the latter metabolite (Fig. 1). The structural features of lyngbyabellins A and B that attracted

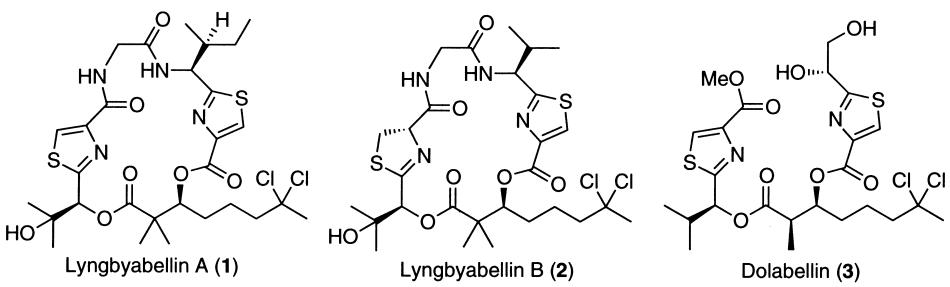

Figure 1. Structures of lyngbyabellins A and B, and dolabellin.

Keywords: lipopeptide; total synthesis; chemical manganese dioxide; macrolactamization.

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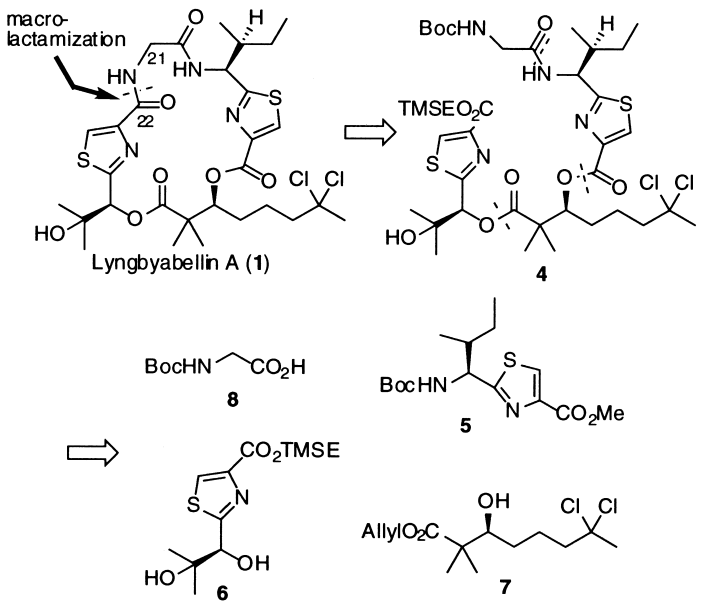


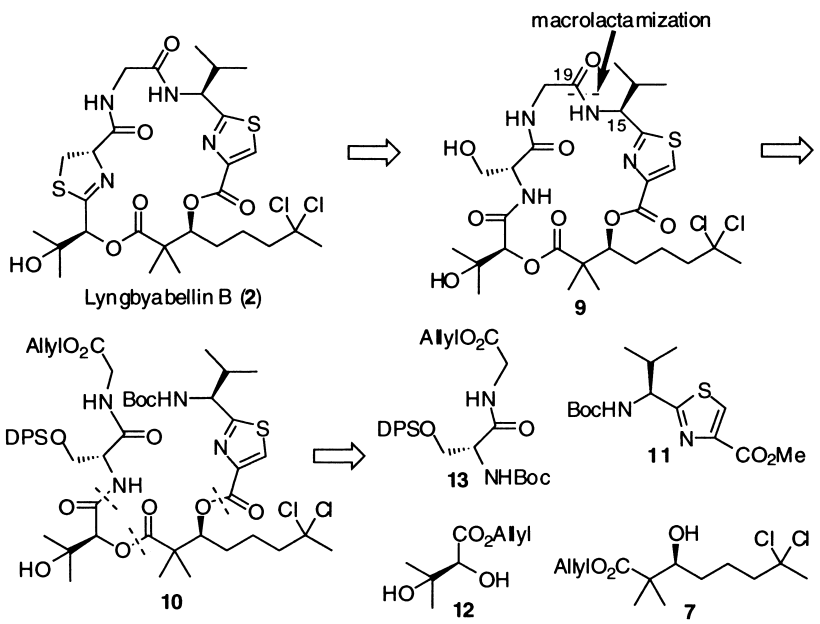
Scheme 1. Retrosynthetic analysis of lyngbyabellin A.

our interest are the functionalized thiazoles and thiazoline heterocycles, the dichlorinated β-hydroxy acid, and their cyclic natures. Therefore, their structural uniqueness as well as interesting biological activities have led us to focus on the total syntheses of lyngbyabellins A and B. In this paper, we wish to disclose our synthetic efforts toward lyngbyabellins A and B.[6]

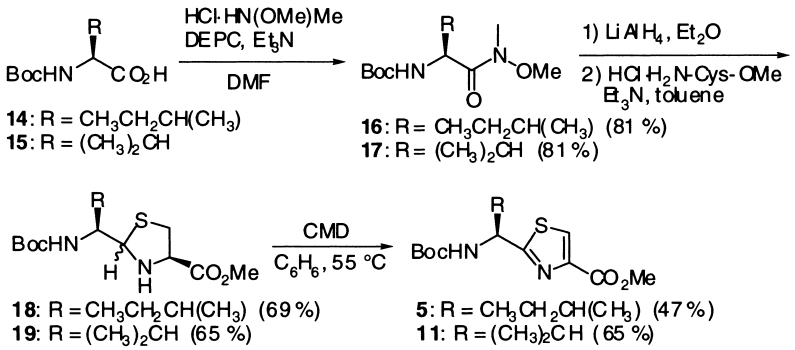
2. Synthetic strategy

Our retrosynthetic analysis of lyngbyabellin A (**1**) is shown in Scheme 1. For the macrocyclization of the linear precursor, macrolactamization will be much superior to macrolactonization due to the higher nucleophilicity of amino groups compared to hydroxy groups. Therefore, macrolactamization at the less hindered $C_{22}-C_{21}NH$ amide bond was chosen among the two amide bonds to provide the protected linear precursor **4**. The linear peptide **4** was further divided into the isoleucine-derived thiazole amino acid (Boc-L-(ile)Thz-OMe, **5**), the thiazole derivative **6**, the dichlorinated β-hydroxy acid **7**, and Boc-glycine (**8**).

For the synthesis of lyngbyabellin B (**2**), as the thiazoline ring is sensitive under acidic conditions and readily epimerized at the α-centers attached to the heterocycle under mild acidic or basic conditions, the final formation of the thiazoline ring by Wipf's oxazoline–thiazoline interconversion method[7] was employed to give the serine derived cyclic peptide **9**. Macrolactamization at the $C_{19}-C_{15}NH$ amide bond of **9** was chosen to avoid epimerization at the C terminus to provide the linear



Scheme 2. Retrosynthetic analysis of lyngbyabellin B.



Scheme 3. Syntheses of Boc-L-(ile)Thz-OMe (**5**) and Boc-L-(val)Thz-OMe (**11**).

peptide **10**. The linear precursor **10** was further separated into the valine-derived thiazole amino acid (Boc-L-(val)Thz-OMe, **11**), the dichlorinated β-hydroxy acid **7**, the dihydroxy ester (**12**), and Boc-D-Ser(DPS)-Gly-OAllyl (**13**) (Scheme 2).

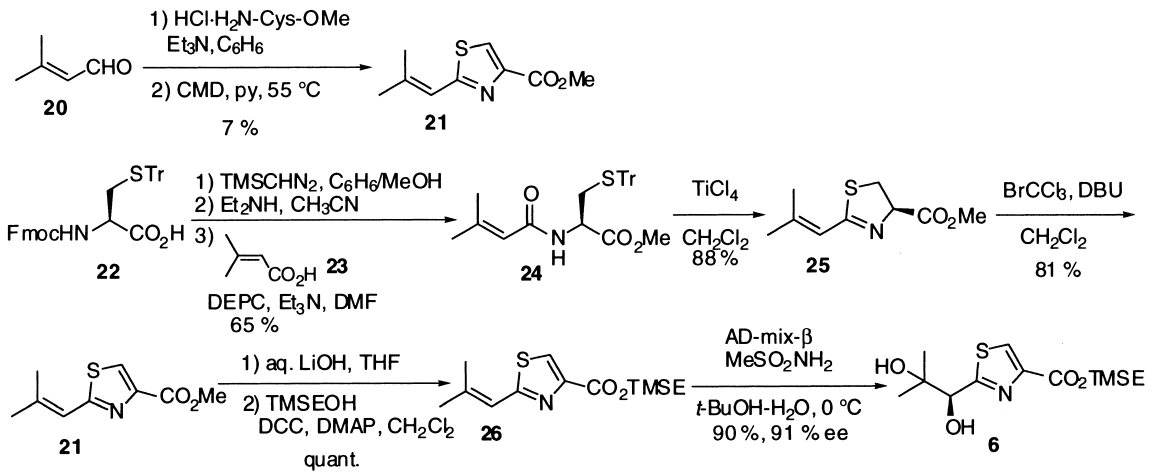
3. Synthesis of the thiazole fragments

Since we have developed the synthesis of thiazolidines from *N*-protected α-amino aldehydes and cysteine methyl ester which were subsequently dehydrogenated to thiazoles using chemical manganese dioxide (CMD) manufactured industrially for batteries,[8,9] we applied this methodology to the synthesis of the thiazole amino acid fragments **5**, **11**. The *N*-Boc protected α-amino aldehydes were prepared by coupling the corresponding *N*-Boc protected α-amino acids **14**, **15** with *N*,*O*-dimethylhydroxyl amine using diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$),[10] followed by reduction with lithium aluminum hydride.[11] Condensation of the amino aldehydes with cysteine methyl ester smoothly afforded the thiazolidines **18**, **19** as a mixture of *C*-2 epimers. Subsequent oxidation of the thiazolidines **18** and **19** to the thiazoles **5** and **11** was, respectively, performed with CMD, which was activated by azeotropic removal of water with benzene (Scheme 3).[12]

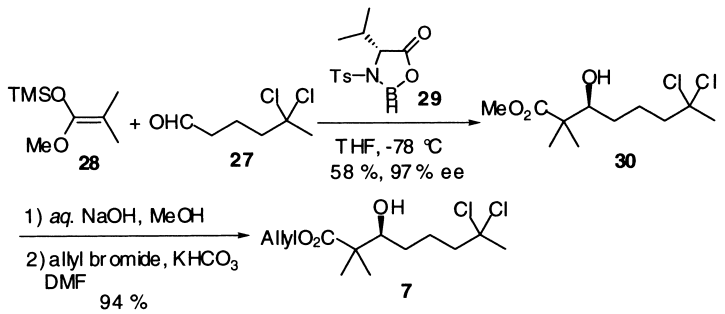
Next, we attempted the synthesis of the α,β-dihydroxy thiazole fragment **6** according to the same CMD methodology. Condensation of 3,3-dimethylacrolein (**20**) with the cysteine methyl ester gave the corresponding thiazolidine, which was directly used for the CMD oxidation to afford the desired thiazole **21** in 7% yield. Although we were unable to improve the yield of the oxidation due to the instability of the thiazolidine, the thiazole **21** was obtained in only two steps from the commercially available aldehyde **20**. Alternatively, we synthesized the thiazole **21** via the thiazoline **25** from the cysteine *N*-amide **24**. The fully protected cysteine *N*-amide **24** was prepared from (*R*)-Fmoc-*S*-trityl cysteine (**22**) through (1) methyl esterification using $TMSCHN_2$,[13] (2) deprotection of the Fmoc group, and (3) coupling with 3-methylcrotonic acid (**23**) using DEPC in 65% yield. The titanium(IV)-mediated tandem deprotection–dehydrocyclization of **24**[14] produced the thiazoline **25** in 88% yield, which was dehydrogenated with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU)/$BrCCl_3$[15] to give the thiazole **21** in 81% yield. Replacement of the methyl ester function with the trimethylsilylethyl (TMSE) one quantitatively afforded **26** in two steps. Asymmetric dihydroxylation[16] of the thiazole **26** with Sharpless' AD-mix-β in the presence of methanesulfonamide gave the required α,β-dihydroxy thiazole fragment **6** with 91% enantiomeric excess (ee)[17] in 90% yield (Scheme 4).

4. Synthesis of the dichlorinated β-hydroxy acid

The stereoselective synthesis of the dichlorinated



Scheme 4. Synthesis of the α,β-dihydroxy thiazole **6**.



Scheme 5. Synthesis of the dichlorinated β-hydroxy acid **7**.

β-hydroxy acid fragment was achieved by the enantioselective aldol reaction developed by Kiyooka.[18] The aldol reaction of the aldehyde **27**[5] with commercially available methyl trimethylsilyl ketene acetal (**28**) using a stoichiometric amount of the chiral oxazaborolidinone **29** derived from (*R*)-valine in THF proceeded to give the (*S*)-β-hydroxy ester **30** with 97% ee in 58% yield.[19] Although the 3*S* stereochemistry of the β-hydroxy acid residue, obtained by hydrolysis of one of methanolysis products of natural products, has been determined from the close compatibility of its $[\alpha]_D$ with that of (*S*)-3-hydroxy-2,2-dimethyl-octanoic acid, we confirmed the absolute stereochemistry of the synthetic **30** by transformation into the corresponding (*S*) and (*R*)-MTPA esters, and comparison of the ^{1}H NMR spectra as shown in Fig. 2.[20] Due to the diamagnetic effect of the benzene ring, $\Delta\delta$ values ($\delta_S-\delta_R$ ppm) on the right side of the MTPA plane must have positive values ($\Delta\delta>0$) and Δ values on the left side of the plane must have negative values ($\Delta\delta<0$). These results established that the absolute stereochemistry of **30** was *S*. Finally, replacement of the methyl ester with the allyl ester provided the desired β-hydroxy acid fragment **7** in 94% yield (Scheme 5).

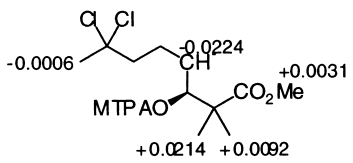
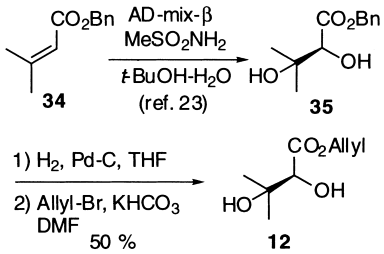


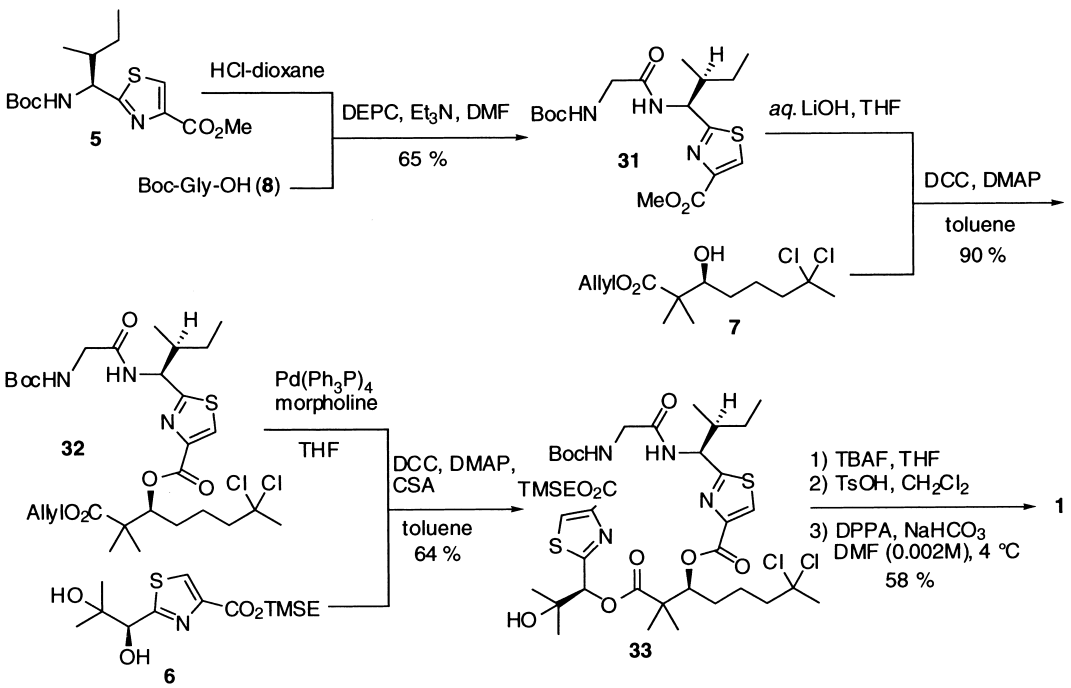
Figure 2. $\Delta\delta$ ($\delta_S-\delta_R$) values (ppm) obtained from ^{1}H NMR spectral data in $CDCl_3$.

5. Total synthesis of lyngbyabellin A

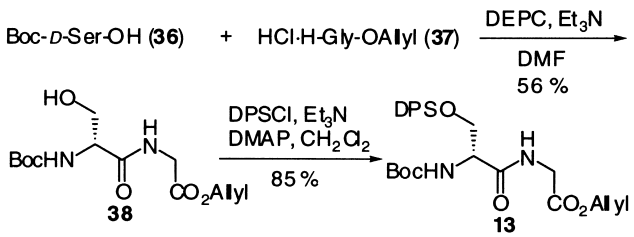
The total synthesis of lyngbyabellin A (**1**) was initiated by deprotection of the Boc group in **5** with hydrogen chloride



Scheme 7. Synthesis of the α,β-dihydroxy ester (**12**).



Scheme 6. Total synthesis of lyngbyabellin A (**1**).

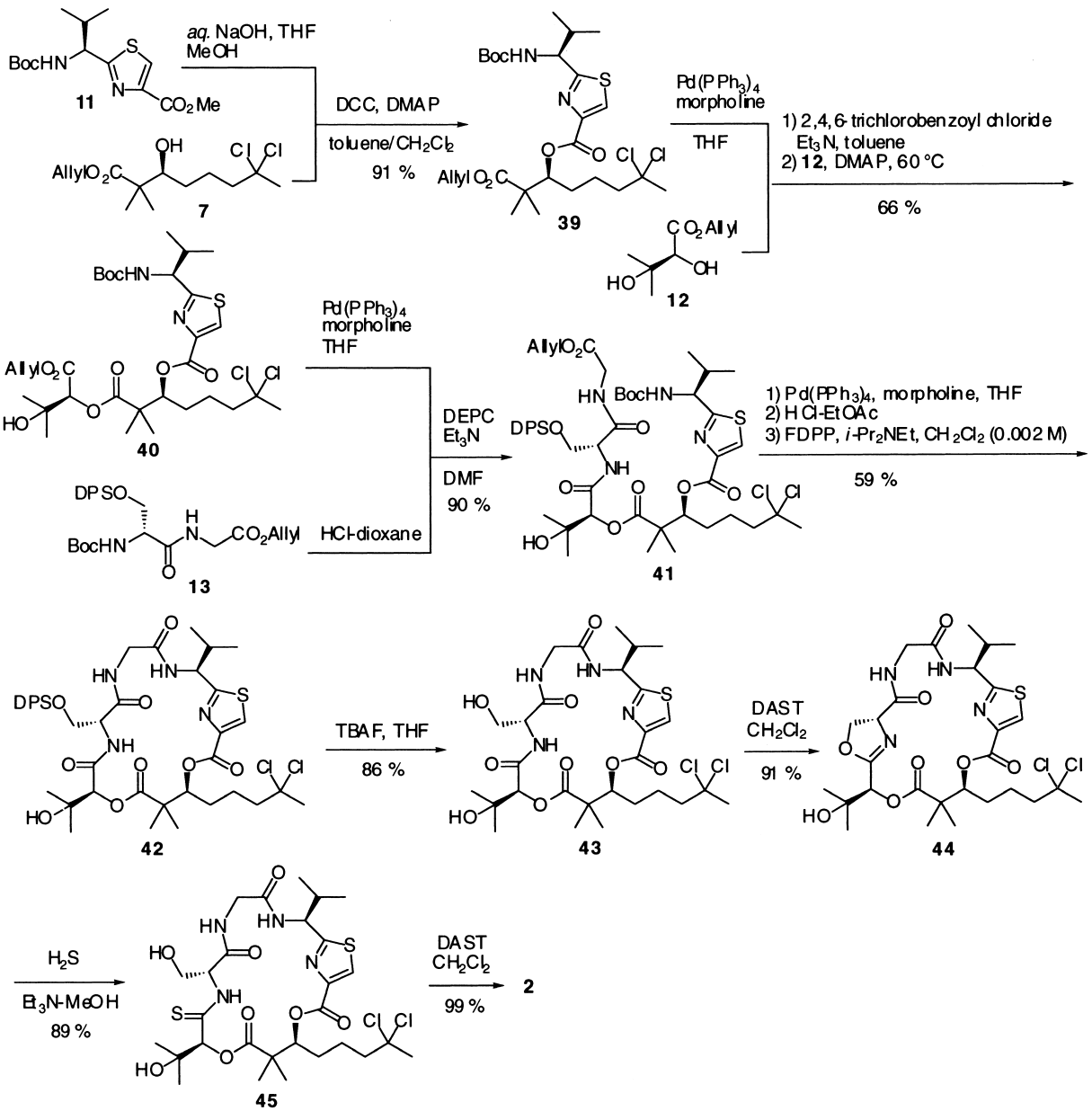


Scheme 8. Synthesis of Boc-D-Ser(DPS)-Gly-OAllyl (**13**).

followed by coupling with Boc-glycine (**8**) using DEPC to give the dipeptide **31** in 65% yield. Ester saponification of **31** followed by condensation with the β-hydroxy acid fragment **7** using dicyclohexyl carbodiimide (DCC) in the presence of *N*,*N*-(dimethylamino)pyridine (DMAP) produced the depsipeptide **32** in 90% yield. After cleavage of the allyl ester in **32** with $Pd(Ph_3P)_4$ in the presence of morpholine, coupling of the resulting carboxylic acid with the α,β-dihydroxy thiazole fragment **6** was accomplished under Keck conditions[21] to produce the linear precursor **33** in 64% yield. Finally, after removal of the TMSE group at the C terminus of **33** by tetra *n*-butylammonium fluoride (TBAF) and then deprotection of the Boc group at the N terminus with *p*-toluenesulfonic acid (TsOH), the macrolactamization was efficiently achieved using diphenyl phosphorazidate (DPPA, $(PhO)_2P(O)N_3$)[10,22] in the presence of sodium hydrogen carbonate to provide lyngbyabellin A (**1**) in 58% yield. The ^1H and ^{13}C NMR spectra as well as the specific rotation of our synthetic lyngbyabellin A (**1**) were completely identical with those published for the natural product (Scheme 6).

6. Total synthesis of lyngbyabellin B

For the total synthesis of lyngbyabellin B (**2**), it was



Scheme 9. Total synthesis of lyngbyabellin B (**2**).

necessary to prepare the remaining two fragments **12** and **13** before the segment condensation.

The Sharpless AD reaction of benzyl 3,3-dimethyl acrylate (**34**) provided the known diol **35**,[23] which was subjected to hydrogenolysis conditions followed by re-protection with the allyl group to give the required diol fragment **12** (Scheme 7).

The dipeptide **13** was prepared by coupling Boc-D-Ser-OH (**36**) with HCl·H-Gly-OAllyl (**37**) using DEPC and protection of the alcohol with a DPS (*tert*-butyldiphenylsilyl) group (Scheme 8).

The stage was now set for the total synthesis of lyngbyabellin B. Saponification of the methyl ester in **11** followed by esterification with β-hydroxy ester **7** using DCC-DMAP conditions afforded the ester **39** in 91% yield. After removal of the allyl ester in **39**, the initial attempt of the coupling with diol **12** using Keck conditions gave a complex mixture. After considerable experimentation, we found that Yamaguchi's esterification protocol[24] was suitable for this condensation to afford the coupled product **40** in 66% yield. Deprotection of the allyl group in **40** and the Boc group in **13** followed by coupling of the two deprotected fragments using DEPC afforded the protected linear peptide **41** in 90% yield. Deprotection of the allyl ester at the C terminus of **41**, acidic cleavage of the Boc group at the N terminus, and then the macrolactamization using pentafluorophenyl diphenylphosphinate (FDPP)[25] afforded the macrocycle **42** in 59% yield, which was subjected to desilylation of the serine residue with TBAF to provide **43** in 86% yield. After cyclodehydration of the serine residue in **43** with (diethylamino)sulfur trifluoride (DAST) to the oxazoline **44**,[26] we applied Wipf's oxazoline–thiazoline interconversion protocol for the conversion of **44** to the target heterocycle **2**.[7] Thiolysis of the oxazoline **44** with hydrogen sulfide in a solution of methanol/triethylamine (2:1) provided the thioamide intermediate **45** in 89% yield. Finally, a second cyclodehydration with DAST[27] proceeded to the desired lyngbyabellin B (**2**) in 99% yield. The synthetic lyngbyabellin B was identical in all respects with spectra provided for the natural product (Scheme 9).

7. Conclusion

In summary, we achieved the first total syntheses of the structurally and biologically attractive lyngbyabellins A and B. Our syntheses involve the oxidative dehydrogenation of thiazolidines to thiazoles using CMD, efficient fragment condensation, macrolactamization, and finally formation of the sensitive thiazoline ring. This strategy will be useful for the synthesis of other heterocycle containing cyclic peptides.[28]

8. Experimental

8.1. General information

Melting points were measured on a YANACO melting point apparatus and are uncorrected. Infrared spectra were recorded on a SHIMADZU FT IR-8100 spectrometer. Optical rotations were measured on a DIP-1000 digital polarimeters with a sodium lamp (λ=589 nm, D line) and are reported as follows: $[\alpha]_D^T$ (cg/100 mL, solvent).

^{1}H NMR spectra were recorded on a JEOL EX-270 (270 MHz) or ALPHA 500 (500 MHz) spectrometer. 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, br=broad, m=multiplet), coupling constants (Hz), and assignment. Lyngbyabellin numbering is used for assignments on all intermediates. ^{13}C NMR spectra were recorded on a JEOL EX-270 (67.8 MHz) or ALPHA 500 (125.7 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (chloroform: δ 77.0 ppm).

Analytical thin layer chromatography were 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 were performed on Merck Art. 5744, Kiselgel 60F_{254}/0.5 mm thickness plates. Elementary analysis (Anal) and high-resolution mass spectra (HRMS) were performed 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. Diethyl ether was distilled from lithium aluminum hydride. Dichloromethane (CH_2Cl_2) and hexamethylphosphoramide (HMPA) were distilled from calcium hydride. Toluene, acetonitrile (CH_3CN), and *N*,*N*-dimethylformamide (DMF) were dried over 4 Å molecular sieves. Triethylamine and *N*,*N*-diisopropylethylamine were dried over potassium hydroxide. All other commercially available reagents were used as received.

8.1.1. N^{α}-(*t*-Butoxycarbonyl)-L-isoleucine *N*-methoxy-*N*-methylamide (16). To a solution of Boc-L-Ile-OH (**14**) (10 g, 43.2 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (4.6 g, 47.2 mmol) in DMF (130 mL) at 0°C were successively added dropwise DEPC (7.2 mL, 47.5 mmol) and triethylamine (13.2 mL, 95.1 mmol). The resulting solution was stirred at 0°C for 2 h and at room temperature for 12 h. After dilution with EtOAc, the mixture was washed with 1 M aq. $KHSO_4$, water, sat. aq. $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=3:1) to afford the desired product **16** as a colorless oil (9.6 g, 81%): ^{1}H NMR spectrum was identical with the reported data (Ref. 11).

8.1.2. N^{α}-(*t*-Butoxycarbonyl)-L-valine *N*-methoxy-*N*-methylamide (17). According to the procedure for the synthesis of **16**, Boc-L-Val-OH (**15**) (10 g, 46.0 mmol) provided **17** as a colorless oil (10.2 g, 85%): ^{1}H NMR spectrum was identical with the reported data (Ref. 11).

8.1.3. 2-[(1*S*,2*S*)-1-*tert*-Butoxycarbonylamino-2-methyl-butyl]-thiazolidin-4-carboxylic acid methyl ester (18). To a solution of the amide **16** (9.21 g, 33.6 mmol) in ether (100 mL) at 0°C was added $LiAlH_4$ (1.59 g, 41.9 mmol). The resulting solution was stirred at 0°C for 15 min and quenched by dropwise addition of 1 M aq. $KHSO_4$. The mixture was extracted with ether (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated to afford the aldehyde (6.95 g, 32.3 mmol). The aldehyde and HCl·H-L-Cys-OMe (6.10 g, 35.5 mmol) were dissolved in toluene (100 mL), and to this suspension was added triethylamine (6.7 mL, 48.3 mmol) at 0°C. The resulting suspension was stirred at room temperature for 3 h, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=3:1) to afford the desired product **18** as a yellow oil (7.65 g, 69%), which was used for the next step. The NMR and thin-layer chromatography reveal **18** is a mixture of *C*-2 epimers.

8.1.4. 2-[(1*S*)-1-*tert*-Butoxycarbonylamino-2-methyl-propyl]-thiazolidin-4-carboxylic acid methyl ester (19). According to the procedure for the synthesis of **18**, the amide (**17**) (10.2 g, 39.1 mmol) provided **18** as a white solid (9.97 g, 65%), which was used for the next step. The NMR and thin-layer chromatography reveal **19** is a mixture of *C*-2 epimers.

8.1.5. Boc-L-(ile)Thz-OMe (5). A suspension of CMD (89.6 g, 103 mmol) in benzene (100 mL) was refluxed with stirring for 2 h using Dean–Stark apparatus (molecular sieves type 4 A). To the resulting suspension was added a solution of the thiazolidine **18** (3.43 mg, 10.3 mmol) in benzene (5 mL), and then the mixture was stirred at 55°C for 2 h. The resulting mixture was filtered through the pad of celite and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=3:1) to afford the thiazole **5** as a pale yellow oil (1.57 g, 47%): ^{1}H NMR spectrum was identical with the reported data (Ref. 8a).

8.1.6. Boc-L-(val)Thz-OMe (11). According to the procedure for the synthesis of **5**, the thiazolidine (**19**) (1 g, 2.53 mmol) provided **11** as white crystals (650 mg, 65%): ^{1}H NMR was identical with the reported data (Ref. 8a).

8.1.7. (2*R*)-2-(3-Methyl-but-2-enoylamino)-3-tritylsulfanyl-propionic acid methyl ester (24). A solution of N^{α}-Fmoc-Cys(*S*-trityl)-OH (**22**) (3.0 g, 5.12 mmol) in MeOH/benzene (26 mL; 1:4) was treated with $TMSCHN_2$ (3.1 mL of 2.0 M solution in hexanes, 6.2 mmol) at room temperature and the reaction progress was monitored by TLC (ca. 30 min). The reaction mixture was concentrated and the crude reaction mixture was used in the next step without purification.

Diethylamine (30.7 mL, 6 mL/mmol) was added to a solution of the crude methyl ester in CH_3CN (31 mL) and the resulting mixture was stirred at room temperature for 30 min to ensure complete removal of the Fmoc protecting group. After concentration, the mixture was azeotroped to dryness with CH_3CN (×2) and the residue was dissolved in DMF (17 mL). 3,3-Dimethylacrylic acid (560 mg, 5.59 mmol), DEPC (0.85 mL, 5.60 mmol) and triethylamine (1.56 mL, 11.2 mmol) were sequentially added at 0°C and the resulting mixture was stirred at room temperature overnight. After dilution with EtOAc, the mixture was washed with 1 M aq. $KHSO_4$, water, sat. aq. $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=8:1) to afford the desired product **24** as a white solid (1.54 g, 65%): $[\alpha]_D^{23}=+14.0$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{KBr} (cm^{-1}) 3330, 1728, 1667, 1634, 1518, 1504, 1489; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.86 (3H, s, C*H*$_3$), 2.13 (3H, s, C*H*$_3$), 2.66 (2H, d, *J*=5.1 Hz, Cys-C$_\beta$*H*$_2$), 3.71 (3H, s, CO_2CH_3), 4.62–4.69 (1H, m, Cys-C$_\alpha$*H*), 5.54 (1H, s, $(CH_3)_2C{=}CH-$), 5.80 (1H, d, *J*=7.6 Hz, N*H*), 7.21–7.39 (15H, m, Ph*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.0, 27.3, 34.0, 50.7, 52.6, 66.8, 117.8, 126.7, 127.8, 129.3, 144.1, 152.2, 165.9, 171.0; HRMS (EI) *m*/*z* calcd for $C_9H_{14}NO_3S$: 216.0694 (M^+-Tr). Found: 216.0711. Calcd for $C_{19}H_{15}$: 243.1174 (Tr^+). Found: 243.1167.

8.1.8. (4*R*)-2-(2-Methyl-propenyl)-4,5-dihydro-thiazole-4-carboxylic acid methyl ester (25). A solution of the cysteine *N*-amide **24** (315 mg, 0.69 mmol) in CH_2Cl_2 (14 mL) was treated with $TiCl_4$ (2.1 mL of a 1.0 M solution in CH_2Cl_2, 2.1 mmol) at 0°C and stirred at room temperature for 12 h. The reaction mixture was quenched with cold sat. aq. $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=8:1) to afford the desired product **25** as an orange oil (96 mg, 88%), which was immediately used for the next step. **25**: $[\alpha]_D^{23}=+62.1$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3342, 1730, 1651, 1645, 1597, 1437; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.90 (3H, s, C*H*$_3$), 2.09 (3H, s, C*H*$_3$), 3.46–3.71 (2H, m, thiazoline–C$_5$*H*$_2$), 3.80 (3H, s, CO_2CH_3), 5.12 (1H, t, *J*=9.0 Hz, thiazoline–C$_4$*H*), 6.06 (1H, s, $(CH_3)_2C{=}CH-$).

8.1.9. 2-(2-Methyl-propenyl)-thiazole-4-carboxylic acid methyl ester (21). To a solution of the thiazoline **25** (233 mg, 1.17 mmol) in CH_2Cl_2 (3.9 mL) at 0°C were successively added $BrCCl_3$ (0.14 mL, 1.42 mmol) and DBU (0.21 mL, 1.40 mmol). The reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with EtOAc, washed with sat. aq. NH_4Cl, water, and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=6:1) to afford the desired product **21** as white crystals (188 mg, 81%): mp 81–82°C (EtOAc/hexane); IR ν_{max}^{KBr} (cm^{-1}) 1715, 1640, 1493, 1456, 1435, 1325, 1246, 1281; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.01 (3H, s, C*H*$_3$), 2.15 (3H, s, C*H*$_3$), 3.95 (3H, s, CO_2CH_3), 6.65 (1H, s, $(CH_3)_2C{=}CH-$), 8.10 (1H, s, Thz-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.8, 27.6, 52.4, 119.3, 126.1, 144.2, 146.1, 161.9, 166.0; HRMS (EI) *m*/*z* calcd for $C_9H_{11}NO_2S$: 197.0510. Found: 197.0510.

8.1.10. 2-(2-Methyl-propenyl)-thiazole-4-carboxylic acid trimethylsilylethyl ester (26). To a solution of the ester **21** (93 mg, 0.40 mmol) in THF (1.6 mL) at 0°C was added a 0.5 M aq. LiOH (1.6 mL, 0.8 mmol). The resulting mixture was stirred at 0°C for 15 min and at room temperature for

1 h. The reaction was quenched by the addition of 1 M aq. $KHSO_4$, and the resulting mixture was extracted with $CHCl_3$ (×3). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford the carboxylic acid (84 mg), which was used for the next step without purification.

To a solution of the carboxylic acid, 2-trimethylsilylethanol (0.060 mL, 0.42 mmol), and DMAP (1 mg, 0.008 mmol) in toluene (1.5 mL) at 0°C was added DCC (103 mg, 0.44 mmol). After being stirred at room temperature for 1 h, the mixture was diluted with ether and filtered through a pad of celite. The filtrate was concentrated, and purified by silica gel column chromatography (hexane/EtOAc=20:1) to afford the desired product **26** as a white powder (118 mg, quant.): mp 62–63°C; IR ν_{max}^{KBr} (cm^{-1}) 1719, 1644, 1458, 1204; ^1H NMR (270 MHz, $CDCl_3$) δ 0.08 (9H, s, $(CH_3)_3Si$), 1.16 (2H, t, J=8.6 Hz, $TMSCH_2CH_2$), 2.00 (3H, s, CH_3), 2.15 (3H, s, CH_3), 4.45 (2H, t, J=8.6 Hz, $TMSCH_2CH_2$), 6.64 (1H, s, $(CH_3)_2C{=}CH-$), 8.05 (1H, s, Thz-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −1.4, 17.6, 20.9, 27.7, 63.7, 119.3, 125.7, 144.0, 146.8, 161.6, 165.9; HRMS (EI) *m/z* calcd for $C_{13}H_{21}NO_2SSi$: 283.1062. Found: 283.1058.

8.1.11. 2-[(1*S*)-1,2-Dihydroxy-2-methyl-propyl]-thiazole-4-carboxylic acid 2-(trimethylsilyl)ethyl ester (6). To a solution of the thiazole **26** (29.7 mg, 0.105 mmol) in *tert*-butanol/water (1 mL, 1:1) at 0°C were added methanesulfonamide (10 mg, 0.105 mmol) and AD-mix-β (147 mg). The reaction mixture was stirred at 0°C for 35 h, and then sodium sulfite was added as solid and the mixture was stirred for 30 min. The mixture was extracted with EtOAc, and the extracts were washed with 1 M aq. $KHSO_4$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=2:1) to afford the desired product **6** as a colorless oil (29.9 mg, 90%, 91% ee). The ee of **6** was determined by chiral HPLC on a ChiralPak AS column (hexane/isopropanol=50:1; flow rate=1.0 mL/min, retention time 15.3 min, 18.2 min). **6**: $[\alpha]_D^{24}$=−18.1 (*c* 0.7, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3410, 1715, 1485, 1383, 1250; ^1H NMR (270 MHz, $CDCl_3$) δ 0.08 (9H, s, $(CH_3)_3Si$), 1.14 (2H, t, J=8.4 Hz, $TMSCH_2CH_2$), 1.20 (3H, s, CH_3), 1.33 (3H, s, CH_3), 3.12 (1H, brs, O*H*), 4.00 (1H, br, O*H*), 4.43 (2H, t, J=8.4 Hz, $TMSCH_2CH_2$), 4.85 (1H, d, J=4.9 Hz, C*H*), 8.12 (1H, s, Thz-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −1.3, 17.5, 25.2, 25.5, 63.8, 73.0, 77.6, 127.7, 146.4, 161.4, 172.4; Anal. calcd for $C_{13}H_{23}NO_4SSi$: C, 49.18; H, 7.30; N, 4.41. Found: C, 49.13; H, 7.41; N, 4.35.

8.1.12. (3*S*)-7,7-Dichloro-3-hydroxy-2,2-dimethyl-octanoic acid methyl ester (30). To a solution of *N*-tosyl-D-Val-OH (1.19 g, 4.38 mmol) in THF (40 mL) at room temperature under Ar was added BH_3–THF (4.4 mL of 1.0 M solution in THF, 4.4 mmol). The solution was stirred at room temperature for 30 min. To the resulting solution were successively added the aldehyde **27**[5] (676 mg, 4.00 mmol) and 1-(trimethylsiloxy)-1-methoxy-2-methyl-1-propene (**28**) (0.89 mL, 4.38 mmol) at −78°C. After being stirred at −78°C for 1 h, the reaction mixture was quenched by the addition of pH 7 buffer solution. The mixture was extracted with ether (×1), and the organic layer was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=15:1) to afford the desired product **30** as a white solid (629 mg, 58%, 97% ee). The ee of **30** (10.7 mg) was determined by ^1H NMR analysis in the presence of chiral shift reagent Eu(hfc)$_3$ (8.0 mg). **30**: mp 49–50°C; $[\alpha]_D^{23}$=−20.0 (*c* 0.13, MeOH) (Ref. 3: $[\alpha]_D^{27}$=−10.0 (*c* 0.13, MeOH)), $[\alpha]_D^{23}$=−17.1 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3517, 1723, 1470, 1464; ^1H NMR (270 MHz, $CDCl_3$) δ 1.18 (3H, s, C_2-CH_3), 1.21 (3H, s, C_2-CH_3), 1.37–1.60 (2H, m, C_5-CH_2), 1.74 (1H, m, C_6-CH_2), 1.95 (1H, m, C_6-CH_2), 2.15 (3H, s, C_8-CH_3), 2.25 (2H, dt, J=10.8, 5.3 Hz, C_4-CH_2), 2.56 (1H, d, J=6.7 Hz, O*H*), 3.61–3.67 (1H, m, C_3-CH), 3.71 (3H, s, CO_2CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.4, 22.5, 23.1, 30.9, 37.3, 47.2, 49.6, 52.1, 76.4, 90.6, 178.0; Anal. calcd for $C_{11}H_{20}Cl_2O_3$: C, 48.72; H, 7.43. Found: C, 48.71; H, 7.37.

8.1.13. (*S*)-MTPA ester of 30. To a solution of **30** (7.4 mg, 0.027 mmol) and (*S*)-MTPA (25.6 mg, 0.109 mmol) in toluene (0.2 mL) at 0°C were added DMAP (14.7 mg, 0.12 mmol) and DCC (24.8 mg, 0.12 mmol). After being stirred at room temperature for 4 days, the mixture was diluted with ether and filtered through a pad of celite. The filtrate was concentrated, and purified by silica gel column chromatography (hexane/EtOAc=10:1) to afford the (*S*)-MTPA ester as a colorless oil (13 mg, 98%): ^1H NMR (270 MHz, $CDCl_3$) δ 1.18 (3H, s, C_2-CH_3), 1.19 (3H, s, C_2-CH_3), 1.56–1.64 (5H, m, C_4, C_5, C_6-CH_2), 2.08 (3H, s, C_8-CH_3), 2.22–2.31 (1H, m, C_4-CH_2), 3.53 (3H, s, OCH_3), 3.65 (3H, s, CO_2CH_3), 5.48 (1H, d, J=7.9 Hz, C_3-CH), 7.26–7.56 (5H, m, Ph*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.9, 21.5, 22.4, 29.8, 37.3, 46.6, 49.3, 52.2, 55.4, 79.6, 90.0, 121.1, 127.5, 128.4, 129.6, 131.6, 165.9, 175.5.

8.1.14. (*R*)-MTPA ester of 30. According to the procedure for the synthesis of (*S*)-MTPA ester, **30** (9.3 mg, 0.034 mmol) provided (*R*)-MTPA ester as a colorless oil (15 mg, 91%): ^1H NMR (270 MHz, $CDCl_3$) δ 1.17 (6H, s, C_2-CH_3×2), 1.56–1.68 (5H, m, C_4, C_5, C_6-CH_2), 2.08 (3H, s, C_8-CH_3), 2.25–2.34 (1H, m, C_4-CH_2), 3.53 (3H, s, OCH_3), 3.65 (3H, s, CO_2CH_3), 5.49 (1H, d, J=9.1 Hz, C_3-CH), 7.26–7.57 (5H, m, Ph*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.4, 21.7, 22.5, 30.1, 37.2, 46.7, 49.2, 52.2, 55.3, 79.5, 90.0, 127.4, 128.4, 129.5, 131.7, 165.9, 175.4.

8.1.15. (3*S*)-7,7-Dichloro-3-hydroxy-2,2-dimethyl-octanoic acid allyl ester (7). To a solution of the ester **30** (41 mg, 0.151 mmol) in methanol (0.2 mL) at 0°C was added 4N aq. NaOH (0.2 mL, 0.8 mmol). The reaction mixture was stirred at 0°C for 30 min, and then at room temperature for 11.5 h. The reaction was quenched by the addition of 1N HCl and the mixture was extracted with ether. The organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford the carboxylic acid (45 mg).

The hydroxy acid was dissolved in DMF (0.5 mL), and $KHCO_3$ (31 mg, 0.31 mmol) was added, followed by the addition of allyl bromide (0.018 mL, 0.212 mmol). The mixture was stirred at room temperature for 10 h. After dilution with ether, the mixture was washed with with 1 M aq. $KHSO_4$, water, sat. aq. $NaHCO_3$, water, and brine. The

organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=10:1) to afford the desired product **7** as a colorless oil (42 mg, 94%): $[\alpha]_D^{24}=-16.8$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3517, 1717, 1649, 1470, 1271, 1169, 1138, 1105; ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (3H, s, C_2-CH_3), 1.22 (3H, s, C_2-CH_3), 1.37–1.56 (2H, m, C_5-CH_2), 1.75 (1H, m, C_6-CH_2), 1.91–2.04 (1H, m, C_6-CH_2), 2.15 (3H, s, C_8-CH_3), 2.22 (2H, dt, *J*=10.6, 5.2 Hz, C_4-CH_2), 2.55 (1H, d, *J*=6.4 Hz, O*H*), 3.66 (1H, br, C_3-CH), 4.60 (2H, d, *J*=5.4 Hz, $CH_2CH=CH_2$), 5.23–5.36 (2H, m, $CH_2CH=CH_2$), 5.84–5.99 (1H, m, $CH_2CH=CH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.4, 22.4, 23.1, 30.9, 37.3, 47.2, 49.6, 65.3, 76.4, 90.6, 118.3, 131.8, 177.1; Anal. calcd for $C_{13}H_{22}Cl_2O_3$: C, 52.53; H, 7.46. Found: C, 52.41; H, 7.47.

8.1.16. 2-[(1*S*,2*S*)-1-(2-*tert*-Butoxycarbonylamino-acetylamino)-2-methyl-butyl]-thiazole-4-carboxylic acid methyl ester (31). Boc-L-(ile)Thz-OMe (**5**) (132 mg, 0.402 mmol) was treated with 4N HCl/dioxane (1 mL) at 0°C. The mixture was stirred at room temperature for 20 min. The mixture was concentrated and dried to afford the crude hydrochloride salt. To a solution of Boc-Gly-OH (**8**) (77 mg, 0.439 mmol) and the above crude hydrochloride salt in DMF (1.4 mL) at 0°C were successively added dropwise DEPC (0.075 mL, 0.494 mmol) and triethylamine (0.14 mL, 1.01 mmol). The resulting solution was stirred at 0°C for 2 h and at room temperature for 10 h. After dilution with EtOAc, the mixture was washed with 1 M aq. $KHSO_4$, water, sat. aq. $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=2:1–1:1) to afford the desired product **31** as white crystals (101 mg, 65%): mp 183–184°C (EtOAc); $[\alpha]_D^{24}=-49.8$ (*c* 1.0, MeOH); IR ν_{max}^{KBr} (cm^{-1}) 3410, 1736, 1701, 1655; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88–0.93 (6H, m, Ile-$C_\delta H_3$ and $C_\gamma H_3$), 1.46 (11H, s and m, $(CH_3)_3C$, Ile-$C_\gamma H_2$), 2.20 (1H, br, Ile-$C_\beta H$), 3.83 (2H, t, *J*=5.7 Hz, Gly-CH_2), 3.94 (3H, s, CO_2CH_3), 5.16 (1H, br, BocN*H*), 5.20–5.25 (1H, dd, *J*=8.9, 8.7 Hz, Ile-$C_\alpha H$), 7.02 (1H, br, N*H*), 8.09 (1H, s, Thz-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.3, 15.9, 24.7, 28.3, 39.5, 44.7, 52.5, 55.6, 80.5, 127.1, 146.8, 156.0, 161.6, 169.1, 171.3; Anal. calcd for $C_{17}H_{27}N_3O_5S$: C, 52.97; H, 7.06; N, 10.90. Found: C, 52.76; H, 7.00; N, 10.61.

8.1.17. [2(1*S*,2*S*),1*S*]-2-[1-(2-*tert*-Butoxycarbonylamino-acetylamino)-2-methyl-butyl]-thiazole-4-carboxylic acid 1-(1-allyloxycarbonyl-1-methyl-ethyl)-5,5-dichloro-hexyl ester (32). To a solution of the ester **31** (99 mg, 0.257 mmol) in THF/methanol (2:1, 1.5 mL) at 0°C was added 0.5N aq. LiOH (1.5 mL, 0.75 mmol). The reaction mixture was stirred at 0°C for 15 min, and then at room temperature for 70 min. The reaction was quenched by the addition of 1 M aq. $KHSO_4$ and the mixture was extracted with $CHCl_3$. The organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford the carboxylic acid (105 mg) as a white amorphous solid, which was used for the next step without purification.

To a solution of the carboxylic acid (40 mg, 0.108 mmol) and the alcohol **7** (29 mg, 0.097 mmol) in toluene/CH_2Cl_2 (4:1, 0.5 mL) at room temperature were added DMAP (15 mg, 0.123 mmol) and DCC (25 mg, 0.121 mmol). The reaction mixture was stirred at room temperature for 9 h, and then concentrated. The residue was purified by preparative thin layer chromatography (0.5 mm thickness, hexane/EtOAc=1:1) to afford the desired product **32** as a colorless oil (57 mg, 90%): $[\alpha]_D^{25}=-17.2$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3320, 1732, 1682, 1526; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (3H, t, *J*=7.4 Hz, Ile-$C_\delta H_3$), 0.91 (3H, d, *J*=6.6 Hz, Ile-$C_\gamma H_3$), 1.16–1.27 (2H, m, C_4-CH_2), 1.28 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.46 (9H, s, $(CH_3)_3C$), 1.62–1.81 (2H, m, C_5-CH_2), 2.10 (3H, s, C_8-CH_3), 2.17 (2H, m, C_6-CH_2), 3.27–3.28 (1H, m, Ile-$C_\beta H$), 3.81 (1H, d, *J*=6.1 Hz, Gly-CH_2), 3.88 (1H, dd, *J*=16.7, 5.8 Hz, Gly-CH_2), 4.55 (2H, d, *J*=5.3 Hz, $CH_2CH=CH_2$), 5.18–5.33 (4H, m, $CH_2CH=CH_2$, BocN*H*, C_3-CH), 5.44 (1H, d, *J*=9.4 Hz, Ile-$C_\alpha H$), 5.79–5.94 (1H, m, $CH_2CH=CH_2$), 7.03 (1H, br, N*H*), 8.04 (1H, s, Thz-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.5, 15.9, 20.8, 22.2, 22.4, 24.8, 28.3, 30.0, 37.3, 39.6, 47.0, 47.0, 49.3, 55.5, 65.6, 77.2, 77.8, 90.2, 118.6, 127.1, 131.7, 146.6, 160.4, 169.1, 174.8; Anal. calcd for $C_{29}H_{45}Cl_2N_3O_7S$: C, 53.53; H, 6.97; N, 6.46. Found: C, 53.82; H, 7.09; N, 6.27.

8.1.18. Protected linear precursor (33). To a solution of the allyl ester **32** (33 mg, 0.051 mmol) in THF (0.6 mL) were added morpholine (0.045 mL, 0.516 mmol) and $Pd(Ph_3P)_4$ (6 mg, 0.005 mmol). After being stirred at room temperature for 15 min, the mixture was diluted with ether, and washed with 1 M aq. $KHSO_4$, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to afford the corresponding carboxylic acid, which was used for the next step without further purification.

To a solution of the above carboxylic acid and the diol **6** (12 mg, 0.037 mmol) in toluene (0.5 mL) at room temperature were added DMAP (2 mg, 0.016 mmol), CSA (2 mg, 0.009 mmol), and DCC (20 mg, 0.086 mmol). After being stirred at room temperature for 19 h, the mixture was diluted with ether and filtered through a pad of celite. The filtrate was concentrated, and purified by silica gel column chromatography (hexane/acetone=5:1) to afford the desired product **33** as a colorless oil (22 mg, 64%): $[\alpha]_D^{25}=-49.1$ (*c* 0.6, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3346, 1738, 1717, 1682, 1505; ^1H NMR (270 MHz, $CDCl_3$) δ 0.08 (9H, s, $(CH_3)_3Si$), 0.81 (3H, d, *J*=6.8 Hz, Ile-$C_\gamma H_3$), 0.92 (3H, t, *J*=7.3 Hz, Ile-$C_\delta H_3$), 1.15 (2H, t, *J*=8.9 Hz, $TMSCH_2CH_2$), 1.20 (3H, s, CH_3), 1.24–1.26 (4H, m, Ile-$C_\gamma H_2$, C_4-CH_2), 1.28 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.40 (9H, s, $(CH_3)_3C$), 1.44 (3H, s, CH_3), 1.68–1.85 (2H, m, Ile-$C_\beta H$, C_5-CH_2), 2.09 (3H, s, C_8-CH_3), 2.10–2.12 (1H, m, C_6-CH_2), 2.23–2.34 (1H, m, C_6-CH_2), 3.58 (1H, dd, *J*=16.8, 4.9 Hz, Gly-CH_2), 3.83 (1H, br, Gly-CH_2), 4.45 (1H, dd, *J*=9.6, 6.9 Hz, $TMSCH_2CH_2$), 4.87 (1H, br, O*H*), 5.05 (1H, br, BocN*H*), 5.14 (1H, t, *J*=8.9 Hz, C_3-CH), 5.32 (1H, br, Ile-$C_\alpha H$), 6.20 (1H, s, $C_{26}-CH$), 7.98 (1H, d, *J*=9.2 Hz, N*H*), 8.18 (1H, s, Thz-*H*), 8.27 (1H, s, Thz-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −1.36, 0.12, 11.2, 16.1, 17.7, 22.1, 22.8, 22.9, 25.4, 25.6, 27.8, 28.3, 37.5, 39.6, 46.5, 46.7, 49.0, 54.7, 63.8, 72.2, 76.3, 76.4, 77.2, 90.0, 128.6, 128.8, 146.6, 150.4, 161.1, 161.2, 161.2, 166.5, 168.7, 172.6, 177.7; Anal. calcd for $C_{39}H_{62}Cl_2N_4O_{10}S_2Si$·acetone: C, 52.11; H, 7.08; N, 5.79. Found: C, 52.43; H, 7.08; N, 5.90.

8.1.19. Lyngbyabellin A (1). To a solution of the linear peptide **33** (24 mg, 0.026 mmol) in THF (0.3 mL) at 0°C was added TBAF (21 mg, 0.080 mmol). The reaction mixture was stirred at 0°C for 10 min, and then at room temperature for 1.5 h. After dilution with EtOAc, the mixture was washed with 1 M aq. $KHSO_4$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in CH_2Cl_2 (0.5 mL), and treated with *p*-TsOH·H_2O (25 mg, 0.129 mmol) at room temperature for 1 h. After the reaction was quenched by the addition of triethylamine, the mixture was azeotroped to dryness with toluene (×3) and the residue was dissolved in DMF (13 mL). Solid $NaHCO_3$ (44 mg, 0.524 mmol) and DPPA (0.012 mL, 0.056 mmol) were sequentially added at 0°C and the resulting mixture was stirred at 0°C for 48 h. After concentration, the residue was purified by preparative thin layer chromatography (hexane/acetone=3:2) to afford the desired product **1** as a white amorphous solid (10 mg, 58%): $[\alpha]_D^{25}=-67.0$ (*c* 0.4, $CHCl_3$) (Ref. 3: $[\alpha]_D^{27}=-74.0$ (*c* 0.5, $CHCl_3$)); IR ν_{max}^{KBr} (cm^{-1}) 3453, 1726, 1655, 1543, 1237; ^1H NMR (500 MHz, $CDCl_3$) δ 0.76 (3H, d, *J*=6.7 Hz, $C_{19}-CH_3$), 0.91 (3H, t, *J*=7.3 Hz, $C_{18}-CH_3$), 1.11–1.17 (1H, m, $C_{17}-CH_2$), 1.25 (3H, s, $C_{28}-CH_3$), 1.32 (3H, s, C_9-CH_3), 1.31–1.34 (1H, m, C_4-CH_2), 1.35 (3H, s, $C_{10}-CH_3$), 1.38 (3H, s, $C_{29}-CH_3$), 1.47–1.52 (1H, m, $C_{17}-CH_2$), 1.57–1.64 (2H, m, C_5-CH_2), 1.69–1.76 (1H, m, C_4-CH_2), 1.95–1.97 (1H, m, $C_{16}-CH$), 1.98–2.02 (1H, m, C_6-CH_2), 2.05 (3H, s, C_8-CH_3), 2.22 (1H, ddd, *J*=14.4, 11.0, 5.2 Hz, C_6-CH_2), 3.69 (1H, dd, *J*=17.1, 4.3 Hz, $C_{21}-CH_2$), 4.72 (1H, dd, *J*=17.1, 9.2 Hz, $C_{21}-CH_2$), 5.25 (1H, dd, *J*=8.9, 6.7 Hz, $C_{15}-CH$), 5.30 (1H, dd, *J*=10.7, 2.1 Hz, C_3-CH), 6.14 (1H, d, *J*=0.6 Hz, $C_{26}-CH$), 7.13 (1H, d, *J*=8.9 Hz, $C_{15}-NH$), 7.90 (1H, dd, *J*=9.2, 4.3 Hz, $C_{21}-NH$), 8.09 (1H, s, $C_{13}-CH$), 8.23 (1H, d, *J*=0.9 Hz, $C_{24}-CH$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 11.3, 14.9, 20.5, 22.3, 24.1, 25.4, 25.8, 27.0, 29.4, 37.1, 40.1, 42.9, 46.6, 49.3, 55.1, 71.8, 77.0, 78.1, 90.0, 126.4, 127.8, 146.8, 148.1, 161.0, 161.5, 164.6, 168.1, 168.5, 173.0; HRMS (EI) *m/z* calcd for $C_{29}H_{40}^{35}Cl_2N_4O_7S_2$: 690.1715. Found: 690.1716.

8.1.20. (2*S*)-2,3-Dihydroxy-3-methyl-butyric acid allyl ester (12). To a solution of the benzyl ester **35**[23] (302 mg, 1.48 mmol) in THF (3 mL) was added 5% Pd on carbon (40 mg) at room temperature. The black slurry was stirred under 1 atm H_2 for 30 min. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated. The residue was dissolved in DMF (3 mL), and $KHCO_3$ (300 mg, 3 mmol) was added, followed by the addition of allyl bromide (0.18 mL, 2.13 mmol). The mixture was stirred at room temperature for 7 h. After dilution with EtOAc, the mixture was washed with with 1 M aq. $KHSO_4$, water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=2:1) to afford the desired product **12** as a colorless oil (129 mg, 50%): $[\alpha]_D^{25}=+10.3$ (*c* 0.7, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3453, 1732, 1649, 1375, 1275, 1200, 1092; ^1H NMR (270 MHz, $CDCl_3$) δ 1.23 (3H, s, CH_3), 1.31 (3H, s, CH_3), 2.69 (1H, brs, O*H*), 3.27 (1H, br, O*H*), 4.00 (1H, t, *J*=6.8 Hz, C*H*), 4.72 (2H, d, *J*=5.6 Hz, $CH_2CH=CH_2$), 5.29–5.42 (2H, m, $CH_2CH=CH_2$), 5.89–6.02 (1H, m, $CH_2CH=CH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.0, 25.8, 66.5, 72.1, 77.2, 119.7, 130.9, 172.7; Anal. calcd for $C_8H_{14}O_4\cdot 1/5H_2O$: C, 54.04; H, 8.16. Found: C, 54.42; H, 8.05.

8.1.21. Boc-D-Ser-Gly-OAllyl (38). A mixture of Boc-Gly-OAllyl (197 mg, 0.195 mmol) in 4N HCl/dioxane (3 mL) was stirred at room temperature for 25 min and concentrated. The residue was azeotropically concentrated with toluene. The resulting HCl·(*S*)-Thr-OAllyl (**37**) and Boc-D-Ser-OH (**36**) (185 mg, 0.902 mmol) were dissolved in DMF (3 mL) and cooled to 0°C. DEPC (0.15 mL, 0.989 mmol) and Et_3N (0.30 mL, 2.16 mmol) were successively added, and the mixture was stirred at 0°C for 2 h and at room temperature for 10 h. After dilution with EtOAc, the mixture was washed with 1 M aq. $KHSO_4$, 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 (hexane/EtOAc=1:1–1:2) to afford the desired product **38** as a colorless oil (154 mg, 56%): $[\alpha]_D^{24}=+21.5$ (*c* 1.2, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3346, 1748, 1715, 1671, 1534, 1167; ^1H NMR (270 MHz, $CDCl_3$) δ 1.46 (9H, s, $(CH_3)_3C$), 3.06 (1H, dd, *J*=8.1, 5.1 Hz, disappeared with D_2O, O*H*), 3.63–3.73 (1H, br, changed to dd with D_2O, *J*=11.4, 5.1 Hz, Ser-$C_\beta H_2$), 4.06–4.22 (3H, m, Ser-$C_\beta H_2$, Gly-CH_2), 4.65 (2H, d, *J*=5.8 Hz, $CH_2CH=CH_2$), 4.66 (1H, br, Ser-$C_\alpha H$), 5.26–5.37 (2H, m, $CH_2CH=CH_2$), 5.55 (1H, br, BocN*H*), 5.84–5.98 (1H, m, $CH_2CH=CH_2$), 7.09 (1H, br, N*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.2, 41.3, 55.5, 62.9, 66.1, 80.3, 118.9, 131.2, 155.8, 169.5, 171.5; Anal. calcd for $C_{13}H_{22}N_2O_6\cdot 1/12CHCl_3$: C, 50.32; H, 7.13; N, 8.97. Found: C, 50.63; H, 7.36; N, 8.91.

8.1.22. Boc-D-Ser(DPS)-Gly-OAllyl (13). To a solution of the alcohol **38** (81 mg, 0.268 mmol) in CH_2Cl_2 (0.9 mL) at 0°C were successively added triethylamine (0.074 mL, 0.533 mmol), DMAP (1 mg, 0.008 mmol), and *tert*-butyldiphenylchlorosilane (DPSCl, 0.084 mL, 0.323 mmol). The reaction mixture was stirred at 0°C for 3 min, and then at room temperature for 7 h. After concentration, the residue was purified by silica gel column chromatography (hexane/EtOAc=5:1) to afford the desired product **13** as white crystals (123 mg, 85%): mp 83–84°C (ether/pentane); $[\alpha]_D^{25}=-5.4$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{KBr} (cm^{-1}) 3424, 3387, 1746, 1713, 1651, 1553, 1204, 1113; ^1H NMR (270 MHz, $CDCl_3$) δ 1.05 (9H, s, $(CH_3)_3C$), 1.44 (9H, s, $(CH_3)_3C$), 3.79 (1H, dd, *J*=10.1, 5.8 Hz, Ser-$C_\beta H_2$), 4.06–4.11 (3H, m, Ser-$C_\beta H_2$, Gly-CH_2), 4.30 (1H, br, Ser-$C_\alpha H$), 4.64 (2H, d, *J*=5.8 Hz, $CH_2CH=CH_2$), 5.24–5.36 (3H, m, $CH_2CH=CH_2$, BocN*H*), 5.83–5.95 (1H, m, $CH_2CH=CH_2$), 6.92 (1H, br, N*H*), 7.36–7.43 (6H, m, Ph*H*), 7.62–7.64 (4H, m, Ph*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.3, 26.8, 28.3, 41.4, 55.8, 64.0, 66.0, 80.3, 118.9, 127.7, 129.8, 131.3, 132.3, 132.7, 135.3, 135.4, 155.3, 168.9, 170.3; Anal. calcd for $C_{29}H_{40}N_2O_6Si$: C, 64.42; H, 7.46; N, 5.18. Found: C, 64.22; H, 7.43; N, 5.48.

8.1.23. [1(1*S*),2(1*S*)]-2-(1-*tert*-Butoxycarbonylamino-2-methyl-propyl)-thiazole-4-carboxylic acid 1-(1-allyloxycarbonyl-1-methyl-ethyl)-5,5-dichloro-hexyl ester (39). To a solution of the ester **11** (229 mg, 0.728 mmol) in THF (1 mL)–MeOH (1.4 mL) at 0°C was added 1 M aq. NaOH (1.4 mL, 1.4 mmol). The resulting mixture was stirred at 0°C for 10 min and then at room temperature for 1 h. After

dilution with water, the mixture was washed with ether. The aqueous layer was acidified to pH 3 by the addition of 1 M aq. $KHSO_4$ and salted out. The mixture was extracted with ether (×3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford the corresponding carboxylic acid (224 mg), which was used for the next step without further purification.

To a solution of the carboxylic acid (86 mg, 0.286 mmol) and the alcohol **7** (85 mg, 0.286 mmol) in toluene/CH_2Cl_2 (4:1, 1 mL) at 0°C were added DMAP (42 mg, 0.344 mmol) and DCC (71 mg, 0.344 mmol). The reaction mixture was stirred at 0°C for 10 min, and then at room temperature for 4 h, and then concentrated. The mixture was diluted with ether and filtered through a pad of celite. The filtrate was concentrated, and purified by silica gel column chromatography (hexane/ether=2:1) to afford the desired product **39** as white crystals (151 mg, 91%): mp 108–109°C (EtOAc/pentane); $[\alpha]_D^{27}=-23.2$ (*c* 1.2, $CHCl_3$); IR ν_{max}^{KBr} (cm^{-1}) 3397, 1723, 1489, 1211; ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (3H, d, *J*=6.8 Hz, Val-$C_\gamma H_3$), 0.99 (3H, d, *J*=6.8 Hz, Val-$C_\gamma H_3$), 1.28 (6H, s, CH_3×2), 1.45 (9H, s, $(CH_3)_3C$), 1.63–1.75 (4H, m, C_4 and C_5–CH_2), 2.10 (3H, s, C_8–CH_3), 2.17–2.19 (1H, m, C_6–CH_2), 2.28–2.37 (1H, m, C_6–CH_2), 2.41–2.49 (1H, m, Val-$C_\beta H$), 4.57 (2H, d, *J*=5.6 Hz, CH_2CH=CH_2), 4.90 (1H, br, Val-$C_\alpha H$), 5.19–5.34 (3H, m, CH_2CH=CH_2, BocN*H*), 5.46 (1H, d, *J*=9.4 Hz, C_3–C*H*), 5.81–5.94 (1H, m, CH_2CH=CH_2), 8.03 (1H, s, Thz-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.3, 19.4, 20.6, 22.3, 22.4, 28.3, 29.9, 33.3, 37.2, 46.9, 49.3, 58.0, 65.5, 77.2, 80.0, 90.2, 118.5, 126.9, 131.7, 146.6, 155.2, 160.4, 173.1, 174.8; HRMS (EI) *m/z* calcd for $C_{20}H_{40}^{35}Cl_2N_2O_6S$: 578.1984. Found: 578.1989.

8.1.24. [1*S*,2(1*S*)]-2-(1-*tert*-Butoxycarbonylamino-2-methyl-propyl)-thiazole-4-carboxylic acid 1-[(1*S*)-1-(1-allyloxycarbonyl-2-hydroxy-2-methyl-propoxycarbonyl)-1-methyl-ethyl]-5,5-dichloro-hexyl ester (40). To a solution of the allyl ester **39** (100 mg, 0.173 mmol) in THF (1.7 mL) were added morpholine (0.13 mL, 1.49 mmol) and $Pd(Ph_3P)_4$ (20 mg, 0.017 mmol). After being stirred at room temperature for 25 min, the mixture was diluted with ether, and washed with 1 M aq. $KHSO_4$, water, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=4:1–2:1) to afford the corresponding carboxylic acid (90 mg).

The above carboxylic acid and triethylamine (0.031 mL, 0.223 mmol) were dissolved in toluene (0.6 mL) and treated with 2,4,6-trichlorobenzoyl chloride (0.031 mL, 0.198 mmol) dropwise at room temperature. After 30 min at room temperature, a solution of the alcohol **12** (41 mg, 0.235 mmol) and DMAP (42 mg, 0.344 mmol) in toluene (0.4 mL, +0.4 mL rinse) was added via cannula and warmed up to 60°C and stirring was continued for 13 h. After dilution with ether, the mixture was washed with 1 M aq. $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=5:1–4:1) to afford the desired product **40** as a colorless oil (80 mg, 66%): $[\alpha]_D^{25}=-75.8$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3475, 3368, 1740, 1717, 1503, 1478, 1233, 1204, 1169; ^1H NMR (270 MHz, $CDCl_3$) δ 0.85 (3H, d, *J*=6.6 Hz, Val-$C_\gamma H_3$), 0.96 (3H, d, *J*=6.8 Hz, Val-$C_\gamma H_3$), 1.30 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.45 (9H, s, $(CH_3)_3C$), 1.67–1.70 (4H, m, C_4 and C_5–CH_2), 2.07 (3H, s, C_8–CH_3), 2.14–2.19 (1H, m, C_6–CH_2), 2.24–2.31 (2H, m, Val-$C_\beta H$, C_6–CH_2), 3.79 (1H, s, C_{26}–O*H*), 4.65 (2H, d, *J*=5.8 Hz, CH_2CH=CH_2), 4.77–4.81 (1H, m, Val-$C_\alpha H$), 4.81 (1H, s, C_{25}–C*H*), 5.24–5.38 (3H, m, CH_2CH=CH_2, BocN*H*), 5.82–5.94 (1H, m, CH_2CH=CH_2), 6.26 (1H, d, *J*=9.6 Hz, C_3–C*H*), 8.16 (1H, s, Thz-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.3, 19.5, 22.2, 22.3, 22.5, 24.8, 26.0, 28.5, 29.8, 33.9, 37.3, 46.7, 49.1, 57.7, 66.0, 71.1, 77.2, 78.0, 79.7, 90.1, 119.2, 127.7, 131.1, 146.6, 155.3, 161.1, 167.7, 172.3, 174.0; HRMS (EI) *m/z* calcd for $C_{31}H_{48}^{35}Cl_2N_2O_9S$: 694.2458. Found: 694.2457.

8.1.25. [1(1*S*),2(1*S*)]-2-(1-*tert*-Butoxycarbonylamino-2-methyl-propyl)-thiazole-4-carboxylic acid 1-(1-{(1*S*)-1-[(2*R*)-1-(allyloxycarbonylmethyl-carbamoyl)-2-(*tert*-butyl-diphenyl-silanyloxy)-ethylcarbamoyl]-2-hydroxy-2-methyl-propoxycarbonyl}-1-methyl-ethyl)-5,5-dichloro-hexyl ester (41). To a solution of the allyl ester **40** (30 mg, 0.043 mmol) in THF (0.5 mL) were added morpholine (0.038 mL, 0.436 mmol) and $Pd(Ph_3P)_4$ (5 mg, 0.004 mmol). After being stirred at room temperature for 30 min, the mixture was diluted with ether, and washed with 1 M aq. $KHSO_4$, water, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to afford the corresponding carboxylic acid, which was used for the next step without further purification.

A mixture of Boc-D-Ser(DPS)-Gly-OAllyl (**13**) (44 mg, 0.081 mmol) in 4N HCl/dioxane (0.8 mL) was stirred at room temperature for 30 min and concentrated. The residue was azeotropically concentrated with toluene. The resulting HCl salt and the above carboxylic acid were dissolved in DMF (0.3 mL) and cooled to 0°C. DEPC (0.013 mL, 0.086 mmol) and triethylamine (0.021 mL, 0.151 mmol) were successively added, and the mixture was stirred at 0°C for 2 h and at room temperature for 17 h. After dilution with EtOAc, the mixture was washed with 1 M aq. $KHSO_4$, 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 (hexane/EtOAc=2:1) to afford the desired product **41** as a white amorphous solid (42 mg, 90%): $[\alpha]_D^{24}=-35.3$ (*c* 0.7, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3346, 1736, 1719, 1684, 1509, 1233, 1200, 1169; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90–1.05 (6H, m, Val-$C_\gamma H_3$×2), 1.01 (9H, s, $(CH_3)_3C$), 1.26 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.33 (3H, s, CH_3×2), 1.44 (9H, s, $(CH_3)_3C$), 1.60–1.85 (4H, m, C_4 and C_5–CH_2), 2.07 (3H, s, C_8–CH_3), 2.10–2.20 (1H, m, C_6–CH_2), 2.25–2.27 (1H, m, C_6–CH_2), 2.32–2.40 (1H, m, Val-$C_\beta H$), 3.75 (1H, dd, *J*=10.1, 5.1 Hz, Ser-$C_\beta H_2$), 3.88 (1H, s, C_{26}–O*H*), 3.96–4.16 (2H, m, Gly-CH_2), 4.20 (1H, dd, *J*=10.2, 3.3 Hz, Ser-$C_\beta H_2$), 4.55 (1H, m, Ser-$C_\alpha H$), 4.63 (2H, d, *J*=5.8 Hz, CH_2CH=CH_2), 4.80–4.85 (1H, br, Val-$C_\alpha H$), 4.87 (1H, s, C_{25}–C*H*), 5.23–5.36 (3H, m, CH_2CH=CH_2, BocN*H*), 5.80 (1H, d, *J*=11.0 Hz, C_3–C*H*), 5.84–5.95 (1H, m, CH_2CH=CH_2), 6.94 (1H, d, *J*=7.4 Hz, N*H*), 7.18 (1H, br, N*H*), 7.39–7.42 (6H, m, Ph*H*), 7.59–7.61 (4H, m, Ph*H*),

8.17 (1H, s, Thz-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 15.4, 19.2, 19.5, 22.0, 22.3, 22.4, 25.8, 25.8, 26.8, 28.4, 29.8, 33.6, 37.3, 41.6, 46.8, 49.1, 54.4, 57.8, 63.5, 66.0, 71.4, 77.2, 77.8, 80.1, 90.1, 118.8, 127.7, 129.9, 129.9, 131.3, 131.9, 132.6, 135.3, 135.5, 146.4, 155.3, 160.9, 168.0, 168.8, 169.5, 172.8, 173.9; Anal. calcd for $C_{52}H_{74}Cl_2N_4O_{12}SSi$: C, 57.92; H, 6.92; N, 5.20. Found: C, 57.64; H, 7.10; N, 5.14.

8.1.26. [2*S*,8*R*,11(1*S*),15*S*]8-(*tert*-Butyl-diphenyl-silanyl-oxymethyl)-15-(4,4-dichloro-pentyl)-11-(1-hydroxy-1-methyl-ethyl)-2-isopropyl-14,14-dimethyl-12,16-dioxa-20-thia-3,6,9,21-tetraaza-bicyclo[16.2.1]heneicosa-1(21),18-diene-4,7,10,13,17-pentaone (42). To a solution of the allyl ester **41** (30 mg, 0.028 mmol) in THF (0.3 mL) were added morpholine (0.025 mL, 0.287 mmol) and $Pd(Ph_3P)_4$ (3 mg, 0.003 mmol). After being stirred at room temperature for 30 min, the mixture was diluted with EtOAc, and washed with 1 M aq. $KHSO_4$, and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated to afford the corresponding carboxylic acid, which was used for the next step without further purification.

The carboxylic acid was dissolved in EtOAc (0.2 mL), and treated with 4N HCl/EtOAc (0.5 mL). After being stirred at room temperature for 30 min, the mixture was concentrated and then azeotropically concentrated with toluene to afford the free peptide.

The above free peptide was dissolved in CH_2Cl_2 (14 mL) and cooled to 0°C. FDPP (22 mg, 0.057 mmol) and *i*-Pr_2NEt (0.028 mL, 0.161 mmol) were successively added, and the mixture was stirred at 0°C for 4 h, and then at room temperature for 38 h. After the bulk of solvent was removed in vacuo, the residue was diluted with EtOAc. The mixture was washed with 1 M aq. $KHSO_4$, water, sat. aq. $NaHCO_3$, water, and brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=1:1–1:2–1:3) to afford the desired product **42** as a white amorphous solid (15 mg, 59%): $[\alpha]_D^{24}=-53.2$ (*c* 0.8, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3389, 1740, 1719, 1686, 1524, 1231, 1113; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.67 (9H, s, $(CH_3)_3C$), 0.92 (3H, d, *J*=6.8 Hz, Val-$C_\gamma H_3$), 1.05 (3H, d, *J*=6.8 Hz, Val-$C_\gamma H_3$), 1.19 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.68–1.74 (3H, m, C_4 and C_5-CH_2), 1.90–2.00 (1H, m, C_4-CH_2), 2.03–2.15 (1H, m, C_6-CH_2), 2.10 (3H, s, C_8-CH_3), 2.21–2.33 (2H, m, Val-C_βH, C_6-CH_2), 3.72 (1H, d, *J*=9.6 Hz, Gly-CH_2), 3.78 (1H, dd, *J*=7.7, 2.8 Hz, Ser-$C_\beta H_2$), 4.31 (1H, dd, *J*=10.2, 2.8 Hz, Ser-$C_\beta H_2$), 4.47 (1H, dd, *J*=16.3, 8.7 Hz, Val-C_αH), 4.69 (1H, d, *J*=9.4 Hz, Gly-CH_2), 5.24–5.32 (2H, m, C_3-CH, Ser-C_αH), 5.36 (1H, s, $C_{26}-OH$), 5.85 (1H, s, $C_{25}-CH$), 6.91 (1H, d, *J*=9.6 Hz, NH), 7.30–7.41 (7H, m, PhH, NH), 7.46–7.51 (4H, m, PhH), 8.22 (1H, d, *J*=9.7 Hz, NH), 8.33 (1H, s, Thz-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.7, 19.0, 19.7, 22.0, 22.9, 23.6, 25.5, 26.6, 28.0, 29.7, 34.4, 37.6, 44.3, 46.5, 48.9, 54.5, 55.6, 63.5, 73.4, 78.9, 79.0, 89.9, 127.6, 127.7, 129.7, 129.8, 130.0, 131.0, 133.1, 135.0, 135.8, 146.4, 160.8, 167.0, 167.0, 168.7, 171.8, 171.9.

8.1.27. [2*S*,8*R*,11(1*S*),15*S*]-15-(4,4-Dichloro-pentyl)-8-hydroxymethyl-11-(1-hydroxy-1-methyl-ethyl)-2-isopropyl-14,14-dimethyl-12,16-dioxa-20-thia-3,6,9,21-tetraaza-bicyclo[16.2.1]heneicosa-1(21),18-diene-4,7,10,13,17-pentaone (43). To a solution of the silyl ether **42** (19.7 mg, 0.0214 mmol) in THF (0.1 mL) at 0°C was added a solution of TBAF (12.0 mg, 0.0459 mmol) in THF (0.1 mL). The reaction mixture was stirred at 0°C for 10 min, and then at room temperature for 80 min. After dilution with EtOAc, the mixture was washed with water and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=1:0–30:1) to afford the desired product **43** as a white amorphous solid (12.5 mg, 86%): $[\alpha]_D^{24}=-55.0$ (*c* 0.5, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3368, 1723, 1674, 1532, 1233, 1154; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.81 (3H, d, *J*=6.8 Hz, Val-$C_\gamma H_3$), 1.01 (3H, d, *J*=6.8 Hz, Val-$C_\gamma H_3$), 1.36 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.74–1.77 (3H, m, C_4 and C_5-CH_2), 1.90–2.00 (1H, m, C_4-CH_2), 2.04–2.15 (1H, m, C_6-CH_2), 2.09 (3H, s, C_8-CH_3), 2.24–2.45 (3H, m, C_6-CH_2, Val-$C_\beta H$, O*H*), 3.30–3.45 (1H, br, Ser-$C_\beta H_2$), 3.60 (1H, dd, *J*=16.5, 4.8 Hz, Gly-CH_2), 4.17–4.25 (2H, m, Gly-CH_2, Val-$C_\alpha H$), 4.53 (1H, d, *J*=8.9 Hz, Ser-$C_\beta H_2$), 5.09 (1H, t, *J*=9.7 Hz, C_3-CH), 5.30 (1H, s, $C_{26}-OH$), 5.32–5.35 (1H, m, Ser-$C_\alpha H$), 5.36 (1H, s, $C_{25}-CH$), 7.15–7.19 (2H, br, N*H*×2), 7.90 (1H, d, *J*=9.9 Hz, N*H*), 8.28 (1H, s, Thz-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.2, 20.0, 21.9, 22.9, 23.9, 25.6, 28.4, 29.8, 33.5, 37.5, 44.1, 46.9, 48.9, 52.1, 55.8, 61.2, 72.8, 78.3, 79.2, 89.9, 129.1, 146.5, 160.8, 167.6, 168.3, 171.0, 171.6, 172.3; HRMS (EI) *m*/*z* calcd for $C_{28}H_{42}{}^{35}Cl_2N_4O_9S$: 680.2050. Found: 680.2053.

8.1.28. Oxazoline (44). To a solution of the alcohol **43** (10.1 mg, 0.0148 mmol) in CH_2Cl_2 (0.2 mL) at −78°C was added DAST (0.0025 mL, 0.0189 mmol). The reaction mixture was slowly warmed up to −20°C during 15 min, and then stirred at same temperature for 15 min. The reaction was quenched by the addition of sat. aq. $NaHCO_3$, and the resulting mixture was 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 ($CHCl_3$/MeOH=30:1) to afford the desired product **44** as a white amorphous solid (8.9 mg, 91%): $[\alpha]_D^{25}=-159.2$ (*c* 0.26, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3346, 1736, 1663, 1530, 1235; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.81 (3H, d, *J*=6.6 Hz, Val-$C_\gamma H_3$), 1.02 (3H, d, *J*=6.6 Hz, Val-$C_\gamma H_3$), 1.26 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.69–1.77 (3H, m, C_4 and C_5-CH_2), 1.80 (3H, s, CH_3), 1.89–2.00 (1H, m, C_4-CH_2), 2.05–2.16 (1H, m, C_6-CH_2), 2.10 (3H, s, C_8-CH_3), 2.24–2.33 (1H, m, C_6-CH_2), 2.39–2.47 (1H, m, Val-$C_\beta H$), 3.67 (1H, dd, *J*=18.0, 2.8 Hz, Gly-CH_2), 4.22 (1H, t, *J*=9.9 Hz, oxz-CH_2), 4.52–4.57 (1H, m, oxz-CH_2), 4.62 (1H, dd, *J*=18.0, 10.4 Hz, Gly-CH_2), 4.71 (1H, dd, *J*=10.1, 3.8 Hz, Val-$C_\alpha H$), 5.13 (1H, t, *J*=9.7 Hz, C_3-CH), 5.22 (1H, s, $C_{26}-OH$), 5.29 (1H, d, *J*=10.1 Hz, oxz-C*H*), 5.52 (1H, s, $C_{25}-CH$), 6.94 (1H, d, *J*=8.1 Hz, N*H*), 7.89 (1H, d, *J*=9.6 Hz, N*H*), 8.27 (1H, s, Thz-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.3, 20.1, 22.0, 22.9, 24.3, 26.1, 28.9, 29.7, 33.7, 37.5, 42.5, 47.2, 48.9, 55.7, 68.7, 70.1, 73.0, 74.5, 78.3, 90.0, 129.1, 146.8, 161.1, 166.7, 167.6, 170.7, 171.9, 173.5; HRMS (EI) *m*/*z* calcd for $C_{28}H_{40}{}^{35}Cl_2N_4O_8S$: 662.1944. Found: 662.1945.

8.1.29. Thioamide (45). A solution of the oxazoline **44** (8.9 mg, 0.0134 mmol) in MeOH/triethylamine (2:1, 1 mL) was saturated with H_2S gas at −10°C. The reaction mixture was stirred at room temperature for 18 h, and concentrated. The residue was diluted with EtOAc, washed with 1 M aq. $KHSO_4$, water, and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=30:1) to afford the desired product **45** as a white amorphous solid (8.3 mg, 89%): $[\alpha]_D^{25}$=+37.2 (*c* 0.22, $CHCl_3$); IR ν_{max}^{neat} (cm^{-1}) 3325, 1731, 1669, 1543, 1235; ^1H NMR (270 MHz, $CDCl_3$) δ 0.81 (3H, d, *J*=6.6 Hz, Val-$C_\gamma H_3$), 1.01 (3H, d, *J*=6.6 Hz, Val-$C_\gamma H_3$), 1.36 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.51 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.60–1.65 (1H, br, O*H*), 1.73–1.80 (3H, m, C_4 and C_5–CH_2), 1.95–2.02 (1H, m, C_4–CH_2), 2.05–2.15 (1H, m, C_6–CH_2), 2.09 (3H, s, C_8–CH_3), 2.23–2.33 (2H, m, Val-C_βH, C_6–CH_2), 3.41 (1H, br, Ser-$C_\beta H_2$), 3.61 (1H, dd, *J*=16.7, 5.1 Hz, Gly-CH_2), 4.19–4.25 (2H, m, Ser-$C_\beta H_2$, Gly-CH_2), 5.09 (1H, t, *J*=9.7 Hz, C_3–CH), 5.31 (1H, s, C_{26}–OH), 5.31–5.35 (2H, m, Ser-C_αH, Val-C_αH), 5.76 (1H, s, C_{25}–CH), 7.16 (1H, br, NH), 7.89 (1H, d, *J*=9.9 Hz, NH), 8.27 (1H, s, Thz-H), 8.59 (1H, d, *J*=9.1 Hz, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.3, 19.9, 21.9, 23.0, 24.0, 27.4, 28.9, 29.9, 33.5, 37.5, 44.1, 47.0, 48.8, 55.7, 57.2, 60.7, 72.5, 78.3, 85.2, 89.9, 128.8, 146.7, 160.8, 167.5, 169.3, 171.5, 172.0, 195.8; HRMS (EI) *m/z* calcd for $C_{28}H_{42}{}^{35}Cl_2N_4O_8S_2$: 696.1821. Found: 696.1821.

8.1.30. Lyngbyabellin B (2). To a solution of the thioamide **45** (8.3 mg, 0.0119 mmol) in CH_2Cl_2 (0.4 mL) at −78°C was added DAST (0.0025 mL, 0.0189 mmol). The reaction mixture was slowly warmed up to −20°C during 10 min, and then stirred at same temperature for 10 min. The reaction was quenched by the addition of sat. aq. $NaHCO_3$, and the resulting mixture was 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 ($CHCl_3$/MeOH=1:0–60:1) to afford the desired product **2** as a white amorphous solid (8.0 mg, 99%): $[\alpha]_D^{27}$=−207.5 (*c* 0.15, $CHCl_3$) (Ref. 4a: $[\alpha]_D^{25}$=−152 (*c* 0.06, $CHCl_3$));[29] IR ν_{max}^{neat} (cm^{-1}) 3339, 1734, 1717, 1682, 1539, 1505, 1472; ^1H NMR (270 MHz, $CDCl_3$) δ 0.78 (3H, d, *J*=6.8 Hz, C_{18}–CH_3), 1.02 (3H, d, *J*=6.8 Hz, C_{17}–CH_3), 1.36 (3H, s, C_{10}–CH_3), 1.45 (3H, s, C_9–CH_3), 1.48 (3H, s, C_{27}–CH_3), 1.64–1.75 (3H, m, C_4 and C_5–CH_2), 1.85 (3H, s, C_{28}–CH_3), 1.96–2.00 (1H, m, C_4–CH_2), 2.05–2.15 (1H, m, C_6–CH_2), 2.09 (3H, s, C_8–CH_3), 2.22–2.27 (1H, m, C_6–CH_2), 2.33–2.41 (1H, m, C_{16}–C*H*), 3.30 (1H, dd, *J*=11.0, 10.1 Hz, C_{23}–CH_2), 3.65 (1H, d, *J*=17.8 Hz, C_{20}–CH_2), 3.77 (1H, d, *J*=11.5 Hz, C_{23}–CH_2), 4.67 (1H, dd, *J*=18.0, 10.1 Hz, C_{20}–CH_2), 5.13 (1H, dd, *J*=9.7, 9.6 Hz, C_{15}–C*H*), 5.29–5.37 (2H, m, C_3–C*H*, C_{22}–C*H*), 5.56 (1H, s, C_{26}–O*H*), 5.75 (1H, s, C_{25}–C*H*), 6.71 (1H, d, *J*=8.4 Hz, C_{20}–N*H*), 8.11 (1H, d, *J*=9.6 Hz, C_{15}–N*H*), 8.30 (1H, s, C_{13}–C*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.5, 19.8, 21.8, 23.0, 24.6, 26.2, 29.3, 29.5, 34.0, 34.5, 37.5, 43.2, 47.3, 48.8, 55.6, 74.2, 78.5, 78.7, 78.7, 90.0, 129.4, 146.7, 160.9, 167.5, 170.7, 170.8, 172.4, 177.2; HRMS (EI) *m/z* calcd for $C_{28}H_{40}{}^{35}Cl_2N_4O_7S_2$: 678.1715. Found: 678.1725.

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28. After our work has been completed, isolation and synthesis of hectochlorin, a structurally analogous lipopeptide, were reported: (a) Isolation Marquez, B. L.; Watts, K. S.; Yokochi, A.; Roberts, M. A.; Verdier-Pinard, P.; Jimenez, J. I.; Hamel, E.; Scheuer, P. J.; Gerwick, W. H. *J. Nat. Prod.* **2002**, *65*, 866–871. Synthesis (b) Cetusic, J. R. P.; Green, III., F. R.; Graupner, P. R.; Oliver, M. P. *Org. Lett.* **2002**, *4*, 1307–1310.
29. In the Ref. 4b, this paper reports the optical rotation of natural lyngbyabellin B as $[\alpha]_D^{25}=+33$ (*c* 0.2, CH_2Cl_2). Since the optical rotation of our synthetic material is $[\alpha]_D^{25}=-270.2$ (*c* 0.14, CH_2Cl_2), the reported value of the natural product should be revised.