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Synthesis and structural reconfirmation of bacillamide B†

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A concise total synthesis of the natural product bacillamide B was accomplished in 30% overall yield starting from L-cystine. The key step was a one-pot four-step process of thiazoline formation via a cascade disulfide cleavage/thiocarbonylation/Staudinger reduction/aza-Wittig reaction using β -azido disulfide and carboxylic acid as substrates. The absolute configuration of the natural bacillamide B was reconfirmed to be *S* and the specific optical rotation was revised to (–).

Introduction

Thiazoline and thiazole groups are structural features of many biologically active natural and synthetic products presenting pharmacological properties of antibiotic, anticancer, or anti-HIV agents, as well as showing anthelmintic or antifungal activities. Typically, thiazole is a characteristic structure of a class of natural alkaloids including tantazoles, mirabazoles, and thiagazole, while thiazoline is a structural segment of various cyclopeptide alkaloids, which were extracted from different marine organisms.^{1–5} The methodologies of making 2,4-disubstituted thiazolines have been well investigated, and the significant achievements in the construction of 2,4-disubstituted thiazoles, especially for the formation of poly-2,4-disubstituted thiazoles, have been extensively reviewed.^{6,7} We have recently reported a novel and efficient method for one-pot synthesis of 2,4-disubstituted thiazolines/thiazoles from carboxylic acids or anhydrides via a sequential disulfide cleavage/thiocarbonylation/intramolecular Staudinger reduction/aza-Wittig/oxidation reaction.^{8,9} Here we disclose our efforts in total synthesis and structural revision of natural bacillamide B, together with the synthesis of its ketone analogue bacillamide A, applying our new method of one-pot thiazoline/thiazole formation.

Bacillamide B was firstly isolated from a Bahamian hypersaline microbial mat in 2007 as an antimicrobial agent by Rowley and co-workers (Fig. 1, *R-B*).¹⁰ Another structural analog, bacillamide A, produced by a marine bacterium *Bacillus* sp. SY-1, was isolated by Okada and co-workers¹¹ in 2003 showing excellent algicidal activity against harmful dinoflagellates and raphidophytes. In 2011, both bacillamides A and B were also isolated from ascomycete fungus *Tricladium* sp. by Li's group, and their extensive bioassay indicated that bacillamide B also displayed an inhibitory effect on HIV-1 replication in C8166 cells.¹²

In the original natural product isolation work,¹⁰ bacillamide B was reported to give the specific optical rotation ($[\alpha]_D^{20}$) at +7.4 (c 0.095, MeOH), and the absolute configuration of bacillamide B was speculated as the *R*-enantiomer by comparison of its circular dichroism (CD) spectrum with the closely related bacterial metabolite *N*-3'- β -indolyethyl-2- α -aminoethylthiazole-4-carboxamide.¹³ In 2009, Bray's group completed the first total synthesis of *S*-bacillamide B with (*S*)-2-acetoxypionyl chloride as the chiral donor expecting to have the *S*-enantiomer of the natural bacillamide B. The specific optical rotation for their synthetic compound was measured as +10.1 (c 0.10, MeOH), instead of an expected (–) value, while the characteristics of the CD spectrum matched

Fig. 1 The structures of bacillamides A and B.

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with the literature report for the so-called natural (*R*)-bacillamide B. Accordingly, Bray revised the proposed stereochemistry of the natural bacillamide B from *R*- to *S*- configuration.¹⁴

As a continuation project to explore substrate suitability of our own thiazole formation method, as well as to verify the stereochemistry of the natural bacillamide B, we started the synthesis of bacillamides A and B taking advantages of existing chirality from natural *L*-lactic acid.

Results and discussion

Our strategy was to prepare (*S*)-bacillamide B, which had been prepared by Bray's group, to facilitate the physical data comparison between the natural and the artificial compounds. Apparently, the (*S*)-bacillamide B (**2**) could be derived from (*S*)-2-(*tert*-butyldiphenylsilyloxy)lactic acid (**3**), β -azidodisulfide di-carboxylic acid (**4**), and tryptamine (**5**) through our thiazoline/thiazole formation method. As a structural analog, bacillamide A (**1**) could be obtained through oxidation of the hydroxyl group on either *R* or *S* bacillamide B. The retrosynthetic analysis of bacillamide A and (*S*)-bacillamide B is summarized in Scheme 1.

Scheme 1 Retrosynthetic analysis of bacillamide A (**1**) and bacillamide B (**2**).

Treatment of commercially available *L*-cystine (**6**) with TfN_3 , using CuSO_4 as catalysts, afforded β -azidodisulfide di-carboxylic acid (**4**)¹⁵ in 83% yield (Scheme 2). Condensation of **4** with tryptamine (**5**) in the presence of DCC and HOBT at room temperature led to the key intermediate **7** in a yield of 85%. Coupling of β -azidodisulfide **7** with (*S*)-2-(*tert*-butyldiphenylsilyloxy)lactic acid (**3**)¹⁶ was carried out through our modified procedure: lactic acid derivative **3** (4.0 eq.), EDCI (4.0 eq.), and DIPEA (8.0 eq.) in DCM were stirred at room temperature for 15 min, then **7** and PPh_3 (8.0 eq.) were added into the mixture and stirred for a further 24 h reflux, generating thiazoline **8** in 75% isolated yield. The following oxidative dehydrogenation of thiazoline **8** to thiazole **9** was achieved with the help of BrCCl_3 in DBU in 67% yield. The planned one-pot five-step production^{8,9} of **9** from compounds **3** and **7** showed lower efficiency due to the excessive consumption of BrCCl_3 and DBU for this substrate,¹⁷ although the isolated yield was comparative for both procedures. The final removal of *tert*-butyldiphenylsilyl from thiazole **9** with TBAF in THF obtained (*S*)-bacillamide B (**2**) in a yield of 85%. Conveniently, bacillamide A (**1**) was obtained through one more step of oxidation of compound **2** with the Dess–Martin reagent in a yield of 90%. With our new method, we have successfully prepared *S*-bacillamide B in 30% overall yield, as well as bacillamide A in 27% total yield.

With (*S*)-bacillamide B in hand, we tested its CD spectrum and the specific optical rotation. The characteristics of the CD spectrum matched with those two reports from both synthetic and natural resources (see ESI-4†). However, the specific optical rotation of our compound gave $[\alpha]_{\text{D}}^{20} = -1.81$ (*c* 0.095, MeOH), which was *not* consistent with those reported data for the synthetic compound $[\alpha]_{\text{D}}^{20} = +10.1$ (*c* 0.10, MeOH) and natural product $[\alpha]_{\text{D}}^{20} = +7.4$ (*c* 0.095, MeOH). Curious about this unexpected result, we decided to put more effort on the structural determination/verification of the natural bacillamide B.

Firstly, the (*R*)-enantiomer of bacillamide B (**12**, Scheme 3) was synthesized from (*R*)-2-(*tert*-butyldiphenylsilyloxy)lactic

Scheme 2 Synthesis of (*S*)-bacillamide B. Reagents and conditions: (a) TfN_3 , CuSO_4 , K_2CO_3 , 83%; (b) tryptamine **5**, DCC, HOBT, rt, 5 h, 85%; (c) EDCI (4.0 eq.), DIPEA (8.0 eq.), (*S*)-2-(*tert*-butyldiphenylsilyloxy)lactic acid **3** (4.0 eq.) in DCM, 15 min, then PPh_3 (8.0 eq.), compound **7**, reflux, 24 h, 75%; (d) DBU (5.0 eq.), BrCCl_3 (5.0 eq.), DCM, rt, 4 h, 67%; (e) TBAF (1.5 eq.), THF, rt, 15 min, 85%; (f) Dess–Martin reagent (1.5 eq.), DCM, rt, 30 min, 90%.

Scheme 3 Synthesis of (*R*)-bacillamide B. Reagents and conditions: (a) (1) EDCI (4.0 eq.), DIPEA (8.0 eq.), (*R*)-2-(*tert*-butyldiphenylsilyloxy)lactic acid **10** (4.0 eq.) in DCM, 15 min; PPh₃ (8.0 eq.), compound **7**, reflux, 24 h; (2) DBU (5.0 eq.), BrCCl₃ (5.0 eq.), DCM, rt, 4 h, about 48% from **7**; (b) TBAF (1.5 eq.), THF, rt, 15 min, 85%.

Table 1 ¹H-NMR spectral data for MTPA esters of **12** (δ , CDCl₃)

Protons	<i>R</i> -Bacillamide B	(<i>S</i>)-MTPA	(<i>R</i>)-MTPA	$\Delta\delta = \delta S - \delta R$	Configuration
–CH ₃	1.609	1.752	1.687	+0.065 > 0	<i>R</i>

acid (**10**) following the same procedure as described in the preparation of (*S*)-bacillamide B (**2**). The specific optical rotation of our **12** was measured as $[\alpha]_D^{20} = +2.01$ (*c* 0.095, MeOH), having the same sign as those from literature data. However, the CD spectrum of **12** gave an opposite Cotton effect compared to the published synthetic data (see ESI-4†).

Secondly, the Mosher's ester derivatives of (*R*)-bacillamide B (**12**) were prepared, and the results confirmed the *R* absolute configuration of **12** as shown in Table 1.

Thirdly, the enantiomeric excess (ee) for both *S*- and *R*-synthetic compounds (**2** and **12**) were monitored by HPLC with a Chiralcel IA column (90/10 hexane–2-propanol, 1.0 mL min^{–1}) giving retention time for (*R*)-**12** at 19.5 min, and (*S*)-**2** at 22.7 min. The chiral HPLC data suggested that there was no detectable epimerization in our synthetic process (see ESI-2†). At this stage, we had prepared both enantiomeric pure *R*- and *S*-bacillamide B, but neither was in full agreement with the literature reports.

When checking Bray's work, we found that the key intermediate **15** could be made with our method in an easier way

(Scheme 4). Thus, 2,4-disubstituted thiazole **14** was synthesized directly from β -azido disulfide **13** and (*S*)-2-(*tert*-butyldiphenylsilyloxy)lactic acid **3** through a one-pot disulfide cleavage/thiocarbonylation/intramolecular Staudinger reduction/aza-Wittig/oxidation reaction according to our reported methodology.⁹ Desilylation of **14** with TBAF in THF and subsequent acetylation with Ac₂O in pyridine afforded the known compound **15**, which was consistent with the reports from both Bray's and the third part based on ¹H NMR, ¹³C NMR, HRMS, and the specific optical rotation.^{14,18} Following Bray's synthetic route, hydrolysis of di-ester **15** with 2 M LiOH in THF–MeOH gave thiazole carboxylic acid **16** in 83% yield. Condensation of thiazole carboxylic acid **16** with tryptamine in the presence of dipyrindyl disulfide and Ph₃P in CH₂Cl₂ furnished the target compound **2** in about 51% yield.

The specific optical rotation for compound **2** from Scheme 4 was measured as $[\alpha]_D^{20} = -2.6$ (*c* 1.0, MeOH) and $[\alpha]_D^{20} = -2.0$ (*c* 0.1, MeOH), instead of $[\alpha]_D^{20} = +10.1$ (*c* 0.10, MeOH) as reported in the literature.¹⁴ Meanwhile, the ¹H NMR, ¹³C NMR, HRMS, and CD spectra, as well as HPLC retention time

Scheme 4 Synthesis of (*S*)-bacillamide B with the reported method. Reagents and conditions: (a) EDCI (4.0 eq.), DIPEA (8.0 eq.), (*S*)-2-(*tert*-butyldiphenylsilyloxy)lactic acid **3** (4.0 eq.) in DCM, 15 min; PPh₃ (8.0 eq.), compound **13**, reflux, 5 h; DBU (12.0 eq.), BrCCl₃ (8.0 eq.), DCM, 0 °C, 15 min, 42%; (b) TBAF, THF, rt, 15 min; Ac₂O, Py, 81% for 2 steps; (c) 2 M LiOH, THF–MeOH, 20 °C, 24 h, 83%; (d) dipyrindyl disulfide, Ph₃P, tryptamine, CH₂Cl₂, 20 °C, 16 h, 51%.

Table 2 Physical data summary for the synthetic and natural bacillamide B (*R/S*)

	Natural (Rowley's)	Synthetic (Bray's)	Synthetic (ours)	Synthetic (ours)	Natural (Li's)
Configuration	<i>R</i> (proposed)	<i>S</i>	<i>S</i>	<i>R</i>	<i>S</i>
$[\alpha]_{\text{D}}^{20}$	+	+	–	+	–
Cotton effect	Positive	Positive	Positive	Negative	Positive
Results	Revised to <i>S</i> ; $[\alpha]_{\text{D}}^{20}$ should be (–)	$[\alpha]_{\text{D}}^{20}$ should be (–)	Confirmed	Confirmed	Confirmed

($t_{\text{s}} = 22.6$ min) for **2** from Scheme 4 fully matched with the same compound obtained in Scheme 2. We were convinced that the published $[\alpha]_{\text{D}}^{20}$ for the synthetic (*S*)-bacillamide B is wrong, and the sign of the value should be in (–).

On comparing with the published physical data for the natural product, our synthetic compounds gave the identical ^1H NMR, ^{13}C NMR, and HRMS spectra, but the opposite Cotton effect for our (*R*)-enantiomer (**12**), and the opposite $[\alpha]_{\text{D}}^{20}$ symbol for the *S*-counterpart (**2**). The mystery was still there, considering the solid evidence from the CD spectrum of the natural bacillamide B provided in the ESI.^{†10} Fortunately, we recently obtained the natural product bacillamide B as a gift from Dr Er-wei Li and Dr Yongsheng Che of the CAS Institute of Microbiology, and the sample provided the same ^1H NMR, ^{13}C NMR, and HRMS spectra as our synthetic products. Chiral HPLC analysis for the mixing sample (**2** + gift natural product) showed the retention time at 22.8 min, indicating an *S*-configuration of this gift compound. Furthermore, the specific optical rotation of this natural bacillamide B was measured as negative ($[\alpha]_{\text{D}}^{20} = -1.25$ (c 0.16, MeOH)), the Cotton effect was observed on its CD spectrum as positive, both were in full agreement with our synthetic (*S*)-bacillamide B. The overall results are summarized in Table 2.

Conclusions

We have successfully accomplished the total synthesis of bacillamides A and B *via* a cascade disulfide cleavage/thiocarbonylation/intramolecular Staudinger reduction/aza-Wittig reaction. Our method provides a superior process for the preparation of bacillamides with respect to the simplicity and stereoselectivity.¹⁹ Our result indicates that the previous structural reports for both natural and artificial bacillamide B were imperfect. More importantly, we have reconfirmed that the absolute configuration for the natural bacillamide B should be *S*, and the specific optical rotation should be revised into (–). The structure is now strongly confirmed by ^1H NMR, ^{13}C NMR, HRMS, CD spectra, chiral HPLC analysis, and the specific optical rotation based on our synthetic *R*-, *S*-, and the authentic natural product.

Experimental

General

All reactions were performed under an argon atmosphere and solvents were dried according to the established procedures

ahead of use. All reagents were purchased from commercial corporations. Flash chromatography (FC) was performed on silica gel (200–300 meshes) columns. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F₂₅₄ plates. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using CDCl_3 or $\text{DMSO}-d_6$ as the solvent, and chemical shifts are reported as δ values in ppm based on internal $(\text{CH}_3)_4\text{Si}$ (0.00 ppm) or solvent peak. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet, whereby the prefix app is applied in cases where the true multiplicity is unresolved, and br when the signal is broadened. High-resolution mass spectrometry data were acquired using a Q-TOF analyzer. Optical rotations were recorded on an Autopol VI automatic polarimeter. Circular dichroism (CD) measurements were performed on a J-815 spectropolarimeter. The ee values were determined using chiral HPLC with a Chiralcel IA column.

Synthesis of β -azidodisulfide di-carboxylic acid (4**).** NaN_3 (3.0 g, 46.15 mmol) was suspended in DD H_2O (10 mL) and DCM (15 mL), then TiF_2O (1.56 mL, 9.30 mmol) was added dropwise at 0 °C. The organic layer was separated after stirring for 2 h under these conditions, and the aqueous phase was extracted with DCM (2×15 mL). The combined organic layer was washed with saturated Na_2CO_3 to obtain a solution of TiF_3 in DCM, which was used for the following reactions without further purification. To a solution of L-cystine (0.55 g, 2.30 mmol), K_2CO_3 (0.95 g, 6.9 mmol) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (5.8 mg, 0.023 mmol) in distilled H_2O (10 mL) and CH_3OH (20 mL) was added a solution of freshly made TiF_3 in DCM (45 mL). The mixture was stirred overnight at rt, and the organic solvents were removed under reduced pressure. The aqueous layer was acidified to pH 2 with concentrated HCl, then extracted with EtOAc (3×30 mL), and the combined organic phase was dried over Na_2SO_4 , and evaporated to dryness to obtain β -azidodisulfide di-carboxylic acid **4** as a white solid (0.56 mg, 83%) suitable for the next reaction without further purification.

(2*R*,2'*R*)-3,3'-Disulfanediybis(*N*-(2-(1*H*-indol-3-yl)ethyl)-2-azido-propanamide) (7**).** *N,N'*-Dicyclohexylcarbodiimide (DCC, 824 mg, 4.0 mmol), 1-hydroxybenzotriazole (HOBt, 540 mg, 4.0 mmol), and **4** (300 mg, 1.03 mmol) were mixed with tryptamine (660 mg, 4.0 mmol) in 20 mL of dry DCM–DMF (1 : 1) and stirred for 5 h at room temperature. After extraction with dichloromethane and water, the organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by FC (silica gel, hexanes–EtOAc 1 : 1) to give compound **7** as colorless oil (505 mg, yield of 85%). $[\alpha]_{\text{D}}^{20} = -14.2$ (c 3.8, CHCl_3); ^1H NMR

(400 MHz, CDCl₃): δ 2.81 (dd, J = 7.4 Hz, J = 14.0 Hz, 1H), 2.99 (t, J = 6.4 Hz, 2H), 3.23 (dd, J = 5.0 Hz, J = 14.0 Hz, 1H), 3.58–3.63 (m, 2H), 4.02 (dd, J = 5.0 Hz, J = 7.4 Hz, 1H), 6.76 (s, 1H), 7.01 (s, 1H), 7.13 (t, J = 7.4 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 8.28 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 25.0, 39.9, 41.3, 62.0, 111.4, 112.4, 118.6, 119.5, 122.26, 122.29, 127.2, 136.4, 167.9; ESI-HRMS calcd for C₂₆H₂₈N₁₀NaO₂S₂ ([M + Na]⁺) 599.1736, found 599.1745.

***R-N*-(2-(1*H*-Indol-3-yl)ethyl)-2-(*S*-1-(*tert*-butyldiphenylsilyloxy)-ethyl)-4,5-dihydrothiazole-4-carboxamide (8).** To a solution of (*S*)-2-(*tert*-butyldiphenylsilyloxy)lactic acid **3** (209 mg, 0.64 mmol) in DCM (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 123 mg, 0.64 mmol) and *N,N'*-diisopropylethylamine (DIPEA, 223 μ L, 1.28 mmol) at room temperature. After stirring for 15 min, 7 (92 mg, 0.16 mmol) and PPh₃ (335 mg, 1.28 mmol) were added into the solution and heated under reflux for 24 h. The reaction mixture was removed by reduced pressure. The crude yellowish residue was purified by FC (silica gel, hexanes–EtOAc 2 : 1) to give compound **8** as colorless oil (133 mg, 75%). [α]_D²⁰ = –36 (c 0.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 1.10 (s, 9H), 1.29 (d, J = 6.4 Hz, 3H), 2.95 (t, J = 6.8 Hz, 2H), 3.38 (dd, J = 10.0 Hz, J = 11.2 Hz, 1H), 3.48–3.58 (m, 2H), 3.60–3.67 (m, 1H), 4.62 (q, J = 6.4 Hz, 1H), 4.90 (t, J = 9.6 Hz, 1H), 6.59 (s, 1H), 6.90 (d, J = 1.6 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 7.26–7.47 (m, 7H), 7.59 (d, J = 7.6 Hz, 1H), 7.67–7.7 (m, 4H), 7.89 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 19.2, 23.3, 25.3, 26.8, 34.3, 39.7, 70.4, 79.1, 111.2, 112.9, 118.7, 119.4, 121.9, 122.1, 127.3, 127.65, 127.71, 129.91, 129.93, 133.2, 133.5, 135.8, 136.0, 136.3, 171.3, 181.0; ESI-HRMS calcd for C₃₂H₃₇N₃NaO₂SSi ([M + Na]⁺) 578.2273, found 578.2276.

***N*-(2-(1*H*-Indol-3-yl)ethyl)-2-(*S*-1-(*tert*-butyldiphenylsilyloxy)-ethyl)thiazole-4-carboxamide (9).** To a solution of **8** (30 mg, 0.054 mmol) in dry DCM (3 mL) were added 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 40 μ L, 0.27 mmol) and bromotrichloromethane (26.6 μ L, 0.27 mmol) dropwise at 0 °C. The reaction was complete after stirring for 4 h at room temperature and then quenched by NH₄Cl (aq.). After extraction with dichloromethane and water, the organic phase was dried over Na₂SO₄ and evaporated. The crude yellowish mixture was purified by FC (silica gel, hexanes–EtOAc 2 : 1) to give compound **9** as colorless oil (20 mg, 67%). [α]_D²⁰ = –30 (c 0.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 1.13 (s, 9H), 1.38 (d, J = 6.4 Hz, 3H), 3.06 (t, J = 7.0 Hz, 2H), 3.75 (dt, J = 6.4 Hz, J = 7.0 Hz, 2H), 5.06 (q, J = 6.4 Hz, 1H), 7.03 (d, J = 2 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 7.31–7.49 (m, 8H), 7.61–7.65 (m, 3H), 7.70–7.72 (m, 2H), 8.02 (s, 1H), 8.16 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 19.3, 25.1, 25.6, 26.9, 39.6, 70.3, 111.2, 113.1, 118.8, 119.4, 122.0, 122.1, 122.6, 127.4, 127.7, 127.8, 129.99, 130.0, 132.7, 133.5, 135.8, 135.9, 136.4, 149.8, 161.4, 177.2; ESI-HRMS calcd for C₃₂H₃₅N₃NaO₂SSi ([M + Na]⁺) 576.2111, found 576.2102.

***N*-(2-(1*H*-Indol-3-yl)ethyl)-2-(*R*-1-(*tert*-butyldiphenylsilyloxy)-ethyl)thiazole-4-carboxamide (11).** The same procedure as

that of making **9** was performed using (*R*)-2-(*tert*-butyldiphenylsilyloxy)lactic acid **10** to give the corresponding thiazole **11** as colorless oil (48% yield). For the corresponding thiazoline intermediate: [α]_D²⁰ = +44 (c 0.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 1.11 (s, 9H), 1.18 (d, J = 6.6 Hz, 3H), 2.95 (t, J = 6.8 Hz, 2H), 3.37 (dd, J = 10.0 Hz, J = 11.2 Hz, 1H), 3.51 (dd, J = 10.0 Hz, J = 11.2 Hz, 1H), 3.58 (dt, J = 6.4 Hz, J = 6.8 Hz, 2H), 4.62 (q, J = 6.6 Hz, 1H), 4.86 (t, J = 10.0 Hz, 1H), 6.67–6.70 (m, 1H), 6.96 (d, J = 2.0 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 7.31–7.48 (m, 7H), 7.58 (d, J = 8.0 Hz, 1H), 7.68–7.70 (m, 4H), 8.14 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 19.3, 23.1, 25.3, 26.9, 34.4, 39.6, 70.2, 79.1, 111.2, 112.8, 118.7, 119.4, 122.0, 122.2, 127.3, 127.7, 129.9, 130.0, 132.9, 133.5, 135.8, 136.0, 136.3, 171.4, 181.1; ESI-HRMS calcd for C₃₂H₃₇N₃NaO₂SSi ([M + Na]⁺) 578.2268, found 578.2245; For thiazole **11**: [α]_D²⁰ = +40.8 (c 0.1, CHCl₃). The ¹H and ¹³C NMR spectra were identical to those of **9**.

***S*-Bacillamide B (2).** To a solution of **9** (25 mg, 0.045 mmol) in THF (3 mL) was added tetrabutylammonium fluoride (TBAF, 17.7 mg, 0.068 mmol). The reaction was complete after stirring for 15 min at room temperature and quenched by saturated aqueous NH₄Cl (1 mL). The aqueous phase was extracted twice with EtOAc (2 $\times$ 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude yellow mixture was purified by FC (silica gel, EtOAc–hexanes 1 : 1) to give compound **2** as colorless oil (12.0 mg, 85%). [α]_D²⁰ = –1.81 (c 0.095, MeOH); ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.45 (d, J = 6.4 Hz, 3H), 2.92 (t, J = 7.4 Hz, 2H), 3.53 (dt, J = 6.8 Hz, J = 7.4 Hz, 2H), 4.93 (dq, J = 5.6, J = 6.4 Hz, 1H), 6.21 (d, J = 5.2 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 7.15 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 8.31 (t, J = 6.0 Hz, 1H), 10.78 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 24.1, 25.3, 66.6, 111.3, 111.7, 118.2, 118.4, 120.9, 122.5, 122.9, 127.2, 136.2, 149.9, 160.5, 178.5; ESI-HRMS calcd for C₁₆H₁₇N₃NaO₂S ([M + Na]⁺) 338.0934, found 338.0938.

***R*-Bacillamide B (12).** The same procedure as described in the preparation of **2** was performed to give the corresponding thiazole **12** (85% yield) as a colorless oil; [α]_D²⁰ = +2.01 (c 0.095, MeOH); ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.45 (d, J = 6.4 Hz, 3H), 2.91 (t, J = 7.4 Hz, 2H), 3.52 (dt, J = 6.8 Hz, J = 7.4 Hz, 2H), 4.92 (dq, J = 5.6, J = 6.4 Hz, 1H), 6.24 (d, J = 5.2 Hz, 1H), 6.95 (dd, J = 7.2 Hz, J = 8.0 Hz, 1H), 7.04 (dd, J = 7.2 Hz, J = 8.0 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 8.35 (t, J = 5.8 Hz, 1H), 10.80 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 24.1, 25.3, 66.6, 111.3, 111.7, 118.2, 118.4, 120.9, 122.5, 122.9, 127.2, 136.2, 149.8, 160.5, 178.6.

Bacillamide A (1). To a solution of **2** (30 mg, 0.095 mmol) in DCM (5 mL) was added the Dess–Martin reagent (60.6 mg, 0.14 mmol). The reaction was complete after stirring for 30 min at room temperature. The aqueous phase was extracted twice with DCM (2 $\times$ 10 mL) and saturated aqueous NaHCO₃. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude yellow mixture was purified by FC (silica gel, hexanes–EtOAc 2 : 1) to give compound **1**

as a yellow solid (27 mg, 90%). ^1H NMR (400 MHz, DMSO-d_6): δ 2.70 (s, 3H), 2.98 (t, J = 7.8 Hz, 2H), 3.59 (dt, J = 6.8, 7.8 Hz, 2H), 6.98 (t, J = 7.4 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 8.66 (s, 2H), 10.84 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.2, 25.7, 39.5, 111.3, 111.6, 118.2, 118.3, 120.9, 122.6, 127.2, 130.5, 136.2, 151.5, 159.8, 166.2, 191.4; ESI-HRMS calcd for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{NaO}_2\text{S}$ ($[\text{M} + \text{Na}]^+$) 336.0777, found 336.0756.

(2*R*,2'*R*)-Diethyl-3,3'-disulfanediyldis(2-azidopropanoate) (13). Compound **4** (300 mg, 1.03 mmol) was dissolved in EtOH (20 mL), and SOCl_2 (0.3 mL, 4.12 mmol) was added dropwise into the solution in an ice bath. The mixture was stirred for 2 h at room temperature. The solution was removed by reduced pressure. The crude was purified by FC (silica gel, hexanes–EtOAc 5 : 1) to give compound **13** as colorless oil (328 mg, 92%). $[\alpha]_{\text{D}}^{20}$ = –23 (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 1.33 (t, J = 7.2 Hz, 3H), 2.99 (dd, J = 8.0 Hz, J = 14.0 Hz, 1H), 3.20 (dd, J = 5.2 Hz, J = 14.0 Hz, 1H), 4.22 (dd, J = 5.2 Hz, J = 8.0 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.6, 39.5, 60.5, 62.0, 168.3; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{16}\text{N}_6\text{NaO}_4\text{S}_2$ ($[\text{M} + \text{Na}]^+$) 371.0567, found 371.0566.

2-[*S*-1-(*tert*-Butyldiphenylsilyloxy)-ethyl]-thiazole-4-carboxylic acid ethyl ester (14). To a solution of *S*-2-(*tert*-butyldiphenylsilyloxy)lactic acid **3** (834 mg, 2.54 mmol) in DCM (10 mL) were added EDCI (486 mg, 2.53 mmol) and DIPEA (881 μL , 5.06 mmol) at room temperature. After stirring for 15 min, **13** (220 mg, 0.63 mmol) and PPh_3 (1.3 g, 5.06 mmol) were added into the solution and stirred under reflux for 5 h. The reaction mixture was cooled to 0 $^\circ\text{C}$, and DBU (1.1 mL, 7.56 mmol) and BrCCl_3 (495 μL , 5.04 mmol) were added dropwise. The reaction was complete after stirring for 15 min at room temperature, and then quenched by saturated aqueous NH_4Cl (1 mL). The aqueous phase was extracted twice with DCM (2×10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude yellowish mixture was purified by FC (silica gel, hexanes–EtOAc 5 : 1) to give compound **14** as colorless oil (233 mg, 42%). $[\alpha]_{\text{D}}^{20}$ = –25 (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 1.12 (s, 9H), 1.36–1.42 (m, 6H), 4.40 (q, J = 7.2 Hz, 2H), 5.23 (q, J = 6.4 Hz, 1H), 7.31–7.45 (m, 6H), 7.60–7.62 (m, 2H), 7.69–7.71 (m, 2H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.9, 18.8, 24.9, 26.4, 60.8, 70.1, 126.5, 127.2, 127.3, 129.47, 129.53, 132.0, 132.9, 135.25, 135.29, 146.4, 161.1, 178.0; ESI-HRMS calcd for $\text{C}_{24}\text{H}_{29}\text{NNaO}_3\text{SSi}$ ($[\text{M} + \text{Na}]^+$) 462.1530, found 462.1543.

2-(*S*-1-Acetoxyethyl)-thiazole-4-carboxylic acid ethyl ester (15). To a solution of **14** (100 mg, 0.23 mmol) in THF (3 mL) was added TBAF (89 mg, 0.34 mmol). The reaction was complete after stirring for 15 min at room temperature and quenched by saturated aqueous NH_4Cl (1 mL). The aqueous phase was extracted twice with EtOAc (2×10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. After purification by FC (silica gel, hexanes/EtOAc 2 : 1), the product obtained was dissolved in Pyr/ Ac_2O .

Concentration of the mixture *in vacuo* 30 min later and purification by FC (silica gel, hexanes–EtOAc 4 : 1) gave compound **15** as a colorless oil (45 mg, 81% for 2 steps). $[\alpha]_{\text{D}}^{20}$ = –40 (c 1.0, CHCl_3); The ^1H NMR, ^{13}C NMR are consistent with that reported before;^{14,18} ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{NNaO}_4\text{S}$ ($[\text{M} + \text{Na}]^+$) 266.0463, found 266.0476.

2-(*S*-1-Hydroxy-ethyl)-thiazole-4-carboxylic acid (16). $[\alpha]_{\text{D}}^{20}$ = –2.5 (c 2.0, MeOH); The ^1H NMR, ^{13}C NMR are consistent with that reported before;¹⁴ ESI-HRMS calcd for $\text{C}_6\text{H}_6\text{NO}_3\text{S}$ ($[\text{M} - \text{H}]^-$) 172.0068, found 172.0080.

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