Total Syntheses of Bistratamides J, E, and H from Two Types of ΔAla-Containing Oligopeptides

Hiroyuki Suzuki, Masanori Andoh, Yasuchika Yonezawa, Shoji Akai, Chung-gi Shin, and Ken-ichi Sato*

Laboratory of Organic Chemistry, Faculty of Engineering, Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama 221-8686

Received July 18, 2007; E-mail: satouk01@kanagawa-u.ac.jp

The total syntheses of naturally occurring bis- and tris(heterocyclic)cyclopeptide bistratamides J (**1**), H (**2**), and E (**3**) from two types of dehydropeptides are described. The strategy involves the preparation of the promising building blocks: *N*-{2-[(*S*)-1-(*N*-benzyloxycarbonyl)amino-2-methylpropyl]thiazol-4-ylcarbonyl}-L-Val-(*S*)NH_2 (**4**) as the left-half component, and methyl *N*-(3-bromo-2-oxopropanoyl)-L-Val-*O*-(*tert*-butyldiphenylsilyl)-L-threonate (**5**) as the right-half. The subsequent Hantzsch thiazole synthesis between **4** and **5** afforded a linear N,O-protected bis(heterocyclic)peptide as the precursor of **1**. Upon deprotection, the precursor was converted to **1** via macrocyclization under high-dilution condition, using BOP [benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate] as the condensing agent. Furthermore, **1** was converted to **2**, which was transformed into **3** via ring-opening and re-oxazolination.

Among the many tris(heterocyclic)cyclopeptides recently isolated from the southern Philippines ascidian *Lissoclinum bistratum*, bistratamides have exhibited activities in human colon tumor HCT-116 cell line assays.[1] As shown in Figure 1, bistratamide J (**1**), H (**2**), and E (**3**) have interesting macrocyclic structures that include various heterocyclic (oxazoline, oxazole, and thiazole) amino acid residues.

Various methodologies for the syntheses of heterocyclic amino acids have been reported,[2] among these, the total syntheses of bistratamide-like dendroamide A[3] and similar natural products, featuring stepwise elongation of the above-mentioned heterocyclic amino acids[4] followed by macrocyclization, have been achieved by Smith's and Pattenden's groups.[5,6] In addition, the latter successfully accomplished the assembly condensation of heterocyclic amino acids using a metal template to afford dendroamide A along with several similar combinatorial tris(heterocyclic)cyclopeptides.[6a] Bistratamides E–J and dendroamide A were synthesized by Kelly's group[7] employing stepwise elongation in 2004–2005. Bistratamide H was expeditiously synthesized by Nakamura's group employing both stepwise elongation and fluorous chemistry.[8] From the standpoint of the systematic synthesis of a series of bistratamides and their analogs, the above stepwise elongation method seems to be unfulfilled.

Recently, we reported the total syntheses of dendroamide A[9a] and bistratamides G[9b] and H (**2**) using a new synthetic method.[9c] As a continuing synthetic program, we present herein a novel total syntheses of **1**–**3** using dehydropeptides. As shown

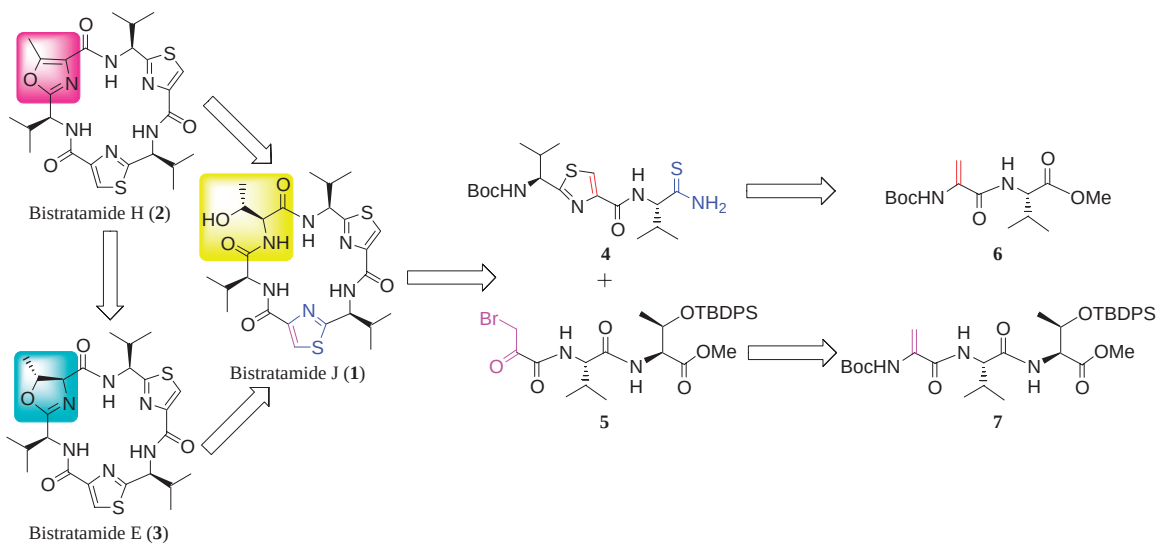


Figure 1. Retrosynthesis of **1**, **2**, and **3**.

Published on the web April 10, 2008; doi:10.1246/bcsj.81.495

in Figure 1, our scheme involves Hantzsch thiazole synthesis[2f,10] between **4**[9c] (Scheme 1) and **5** (Scheme 2), which were readily derived from Δ^1-dehydrodipeptide **6** and Δ^1-dehydrotripeptide **7**, respectively. Natural product **1** can be synthesized by macrocyclization of the linear N,O-deprotected peptide under high-dilution condition. Furthermore, natural product **2** can be derived from **1** using our novel method reported recently.[11] Natural product **3** can be derived by (1) oxazolination of **1**, (2) ring-opening of the oxazoline, and (3) re-oxazolination. Additionally, **2** can be derived by oxidation of **3** using MnO_2. In this paper, we report the synthesis of bistratamide J (**1**), H (**2**), and E (**3**) according to this outline.

Results and Discussion

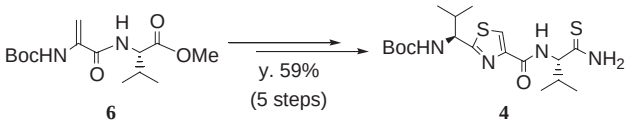
The syntheses of building blocks **4** (left-half) and **5** (right-half) were accomplished as described below. As shown in Scheme 1, **4** was prepared in five steps from *N*-Boc–*N*,*O*-Ip–L-Ser–L-Val–OMe (Boc = *tert*-butoxycarbonyl, Ip = isopropylidene group).[9c]

On the other hand, for the synthesis of **5** (Scheme 2), *N*-Boc–*N*,*O*-Ip–L-Ser–L-Thr–OMe **8** was protected to afford *N*-Boc–*N*,*O*-Ip–L-Ser–L-Val–(*O*-TBDPS)–L-Thr–OMe **9** (TBDPS = *tert*-butyldiphenylsilyl group), which was converted into *N*-Boc–L-Ser–L-Val–(*O*-TBDPS)–L-Thr–OMe **10** using trifluoroacetic acid (TFA) in $CHCl_3$ (4:96 v/v). Subsequent dehydration of the Ser residue of **10** using methanesulfonyl chloride (MsCl) in the presence of Et_3N followed by 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU)[12] afforded Δ^1-dehydrodipeptide, *N*-Boc–ΔAla–L-Val–(*O*-TBDPS)–L-Thr–OMe **7** (ΔAla = α-dehydroalanine) as syrupy liquid, which was used without further purification. Methoxy-bromination of **7** gave the corresponding β-bromo-α-methoxylated tripeptide **11**, which was in one-pot deprotected and hydrolyzed (to remove the Boc and methoxy groups) using TFA, and then H_2O to afford **5**, which was used without purification in the next step, a coupling with **4**.

The desired linear N,O-protected bis(heterocyclic)peptide **12** was synthesized by Hantzsch thiazole synthesis between **4** and **5**. Subsequent removal of the TBDPS group of **12** with 1 M (1 M = 1 mol dm^{-3}) tetrabutylammonium fluoride (TBAF) gave **13** in 95% yield. As shown in Scheme 3, the final transformation of **13** into **1** in 72% yield overall was carried out as follows: (1) saponification of the methyl ester using 1 M LiOH aq, (2) removal of the Boc group using TFA, and (3) macrocyclization of the resulting N,O-deprotected bis(heterocyclic)peptide using BOP and $(i\text{-Pr})_2$NEt in DMF–CH_2Cl_2 under high-dilution condition (1 mmol L^{-1}) at room temperature for 12 h.

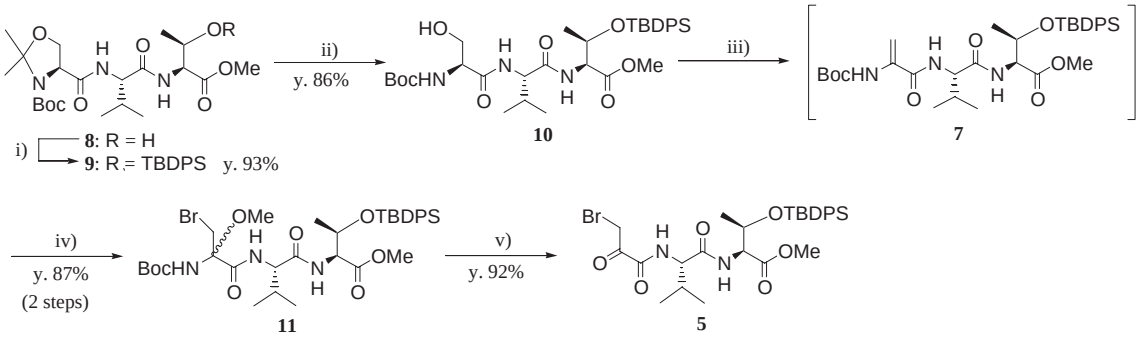
Furthermore, the dehydro analog of bistratamide J (**1**) was obtained by dehydration of the Thr residue of **1** using MsCl in the presence of Et_3N, followed by treatment with DBU. As shown in Scheme 4 (step i–iii), bromination of **14** using NBS in $CHCl_3$ yielded the β-Br–ΔAbu **15**, which was then oxazolated[13] using Cs_2CO_3 to give **2** in 70% yield in three steps without purification of the first and second intermediates.

Alternatively, the oxazoline ring also could be constructed by treatment of **1** with Burgess reagent. However, this method may invert the configuration at the β-carbon in the oxazoline ring,[14] and therefore our strategy was modified to incorporate

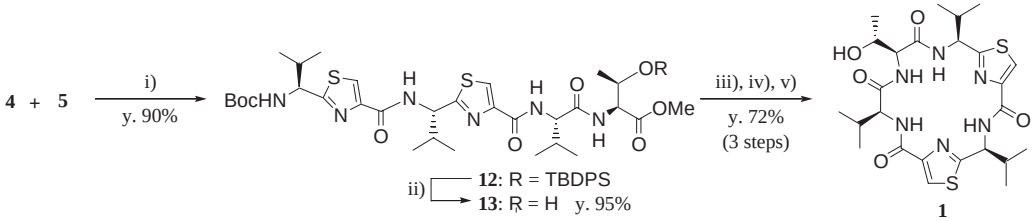


6 **4**

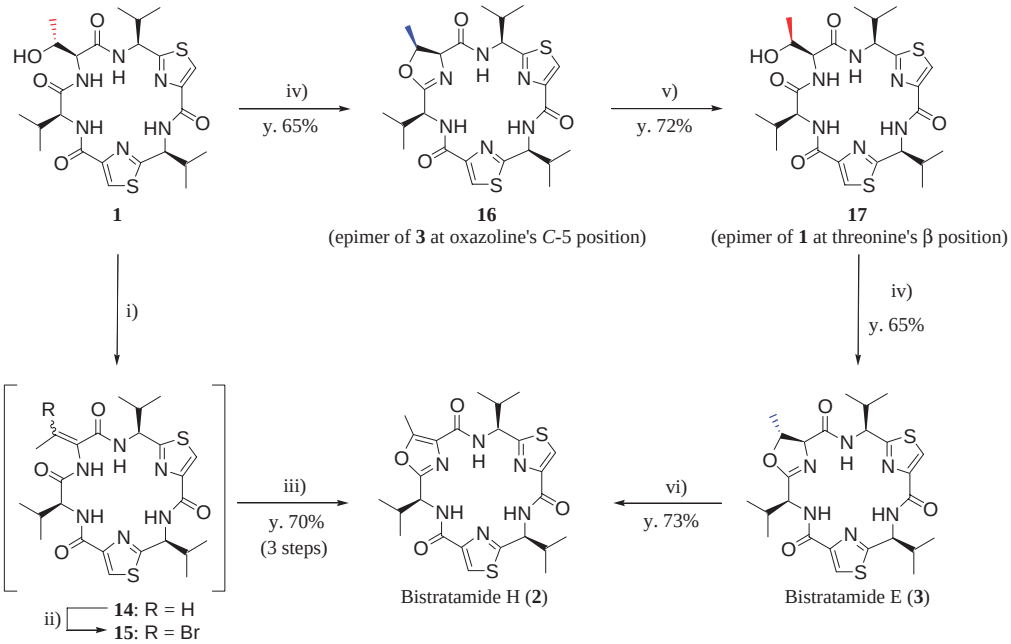
Scheme 1. Conversion of dehydrodipeptide **6** to **4**.



Scheme 2. Reagents and conditions: i) TBDPS–Cl, imidazole, $CHCl_3$; ii) TFA–$CHCl_3$ (4:96 v/v); iii) MsCl, Et_3N, DBU, THF; iv) NBS, MeOH; v) TFA–$CHCl_3$ (1:3 v/v) then H_2O.



Scheme 3. Reagents and conditions: i) [a] K_2CO_3, DME; [b] TFAA, Pyridine, THF; ii) 1 M TBAF, THF; iii) 1 M LiOH aq, H_2O–dioxane (1:1 v/v); iv) TFA–$CHCl_3$ (1:3 v/v); v) BOP, DIPEA, DMF–CH_2Cl_2 (1:2 v/v).



Scheme 4. Reagents and conditions: i) MsCl, Et_3N, DBU, $CHCl_3$; ii) NBS, Et_3N; iii) Cs_2CO_3; iv) Burgess reagent, THF; v) [a] 1 M HCl, THF; [b] K_2CO_3; [c] Al_2O_3; vi) MnO_2, THF.

a double inversion in this position of the Thr moiety. Accordingly, **16** (epimer of **3** at oxazoline's C-5 position) obtained in the above reaction was treated with aqueous HCl in THF (ring opening of the oxazoline ring),[15] and then treated with Burgess reagent (re-oxazolination) to give **3**. The structure of **16** was inferred by reaction mechanism, and comparing ^{1}H and ^{13}C NMR spectra and HR-ESI-MS with those of **3**. Additionally, oxidation of **3** using MnO_2 also gave **2** in 73% yield, as shown in Scheme 4 (step vi).

The spectral data (^{1}H and ^{13}C NMR), and specific rotations for synthetic bistratamides **1**–**3** are in good agreement with those reported by Kelly's group.[7,16] Also the structure was supported by IR, HR-ESI-MS, and elemental analyses. Thus, we have achieved the total syntheses of bistratamide **1**–**3**.

In conclusion, we have accomplished the total syntheses of bistratamide J (**1**), H (**2**), and E (**3**) in 7, 10, and 11 steps (36.6, 25.6, and 11.1% overall yields), respectively, from two types of ΔAla-containing oligopeptides **6** and **7** employing a modified Hantzsch thiazole synthesis developed in our laboratory as the crucial key transformation. Macrocyclization of the linear hexapeptide was achieved under high-dilution conditions (1 mmol L^{-1} DMF–CH_2Cl_2 solution) in 72% yield. Our modified Hantzsch thiazole synthetic method is surely applicable to the synthesis of not only bistratamide and its analogues, but also highly complex poly-azole compounds, such as telomestatin, mechercharmycin, etc.

Experimental

Melting points were measured using a Yanaco Model MP-J3 micro-melting point apparatus, and are uncorrected. IR spectra were recorded using a SHIMADZU IR Prestige-21 spectrometer in KBr. ^{1}H and ^{13}C NMR spectra were measured with JEOL JNM-ECA500 and 600 spectrometers in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane used as internal standard. Specific rotations were measured in 0.5 dm tubes using a JASCO P-1020 polarimeter in $CHCl_3$ or MeOH. Mass spectra were obtained on a SHIMADZU JMS-T100CS.

***N*-Boc–*N*,*O*-Ip–L-Ser–L-Val–L-(*O*-TBDPS)–L-Thr–OMe 9.** To a solution of *N*-Boc–*N*,*O*-Ip–L-Ser–L-Val–L-Thr–OMe[9c] **8** (2.56 g, 5.57 mmol) in $CHCl_3$ (50 mL) at 0 °C were added imidazole (758 mg, 11.1 mmol) and TBDPSCl (2.30 g, 8.36 mmol), and the mixture was stirred at 0 °C for 1 h, and then at room temperature for 6 h. The reaction mixture was washed with 10% citric acid (20 mL × 2) and brine (30 mL × 2). The combined organic phases were dried (Na_2SO_4), and the solvent was evaporated. The crude residue was purified on a silica gel column eluted with hexane–EtOAc (3:1 v/v) to give **9** as colorless syrup. Yield 93% (3.61 g): $[\alpha]_D^{25}$ −44.0° (*c* 0.95, $CHCl_3$); IR 3319, 2972, 1753, 1708, 1691, 1664, 1658, 1529, 1512, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3H, Val's CH_3, J = 6.0 Hz), 0.92 (d, 3H, Val's CH_3, J = 6.0 Hz), 0.99 (s, 9H, TBDPS's *t*-Bu), 1.27 (d, 3H, Thr's CH_3, J = 6.4 Hz), 1.37 (s, 9H, Boc's *t*-Bu), 1.45 (s, 3H, Ip's CH_3), 1.55 (s, 3H, Ip's CH_3), 2.05–2.08 (m, 1H, Val's β-H), 3.55 (s, 3H, COO*CH*$_3$), 3.87 (br m, 1H, Ser's β-H), 4.07 (br s, 1H, Ser's β-H), 4.35–4.45 (m, 5H, Ser's α-H, Thr's α-H, Thr's β-H, Val's α-H, BocN*H*), 7.40–7.70 (m, 11H, Ph*H* × 2 and N*H*); Anal. Calcd for $C_{37}H_{55}N_3O_8Si$: C, 63.67; H, 7.94; N, 6.02%. Found: C, 63.22; H, 7.52; N, 5.66%.

***N*-Boc–L-Ser–L-Val–(*O*-TBDPS)–L-Thr–OMe 10.** A solution of **9** (2.35 g, 3.36 mmol) in a mixture of TFA and $CHCl_3$ (4:96 v/v) (100 mL) was stirred at room temperature for 3 h. The reaction mixture was neutralized with a saturated aqueous $NaHCO_3$ solution, and the organic layer was washed with brine (20 mL × 2), dried over anhydrous Na_2SO_4, and concentrated in vacuo giving a yellow syrup, which was purified on a silica gel column eluted with hexane–EtOAc (2:3 v/v) to give **10** as colorless syrup. Yield 86% (1.92 g): $[\alpha]_D^{25}$ −28.1° (*c* 1.09, $CHCl_3$); IR 3431, 3319, 2964, 1753, 1720, 1708, 1691, 1664, 1658, 1529, 1512 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3H, Val's CH_3, J = 7.2 Hz), 0.92 (d, 3H, Val's CH_3, J = 7.2 Hz), 1.01 (s, 9H, TBDPS's *t*-Bu), 1.28 (d, 3H, Thr's CH_3, J = 6.4 Hz), 1.41 (s, 9H, Boc's *t*-Bu),

2.18–2.21 (m, 1H, Val's β-H), 3.59 (s, 3H, COOCH_3), 4.15 (br s, 1H, OH), 4.57–4.75 (m, 6H, Ser's β-H × 2, Ser's α-H, Thr's α-H, Thr's β-H, BocNH), 7.12 (br s, 1H, NH), 7.26 (br s, 1H, NH), 7.32–7.62 (m, 10H, PhH × 2); Anal. Calcd for $C_{34}H_{51}N_3O_8Si$: C, 62.07; H, 7.81; N, 6.39%. Found: C, 62.01; H, 7.60; N, 6.51%.

***N*-Boc–ΔAla–L-Val–(*O*-TBDPS)–L-Thr–OMe 7.** A solution of **10** (2.13 g, 3.24 mmol) in $CHCl_3$ (50 mL) in the presences of Et_3N (721 mg, 7.13 mmol) and MsCl (631 mg, 5.51 mmol) was stirred at 0 °C for 1 h. Then, DBU (691 mg, 4.54 mmol) was added to the reaction mixture at 0 °C, and stirred at 0 °C for 30 min, and then at room temperature for 1 h. The reaction mixture was diluted with diethyl ether (30 mL), washed successively with 10% citric acid (30 mL × 2), a saturated aqueous $NaHCO_3$ solution (30 mL × 2), brine (30 mL × 2), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give **7** as colorless syrup, which was used in the next reaction, without further purification: ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 3H, Thr's CH_3, J = 6.0 Hz), 1.03 (s, 9H, TBDPS's *t*-Bu), 1.05 (d, 3H, Val's CH_3, J = 7.2 Hz), 1.06 (d, 3H, Val's CH_3, J = 7.2 Hz), 1.48 (s, 9H, Boc's *t*-Bu), 2.22–2.261 (m, 1H, Val's β-H), 3.60 (s, 3H, COOCH_3), 4.44–4.50 (m, 3H, Thr's α-H, Thr's β-H, Val's β-H), 5.16 (s, 1H, Olefin's H), 6.04 (s, 1H, Olefin's H), 6.52 (d, 1H, NH, J = 9.0 Hz), 6.90 (d, 1H, NH, J = 7.8 Hz), 7.30–7.64 (m, 10H, PhH × 2).

***N*-Boc–DL-(β-Br–α-MeO)Ala–L-Val–(*O*-TBDPS)–L-Thr–OMe 11.** To a solution of **7** (2.01 g, 3.14 mmol) in MeOH (50 mL) at 0 °C was added NBS (614 mg, 3.45 mmol), and the mixture was stirred at 0 °C for 30 min. The reaction mixture was poured into water (50 mL) and the resulting solution was extracted with EtOAc (30 mL × 2). The combined organic phases were dried over anhydrous Na_2SO_4 and then concentrated in vacuo to give brown syrup. Purification on a silica gel column eluted with hexane–EtOAc (2:3 v/v) gave **11** as colorless syrup. Diastereomer. Yield 87% (2.05 g): IR 3356, 2964, 1753, 1737, 1726, 1708, 1691, 1678, 1648, 1529 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02, 1.03 (each s, 9H, TBDPS's *t*-Bu), 1.08, 1.09 (each d, 3H, Val's CH_3, J = 6.6 Hz), 1.29 (d, 3H, Thr's CH_3, J = 6.4 Hz), 1.45, 1.46 (each s, 9H, Boc's *t*-Bu), 2.18–2.21 (m, 1H, Val's β-H), 3.23 (s, 3H, OCH_3), 3.59 (s, 3H, COOCH_3), 4.33–4.52 (m, 6H, Ser's β-H × 2, Ser's α-H, Thr's α-H, Thr's β-H, BocNH), 6.45 (br s, 1H, NH, J = 8.4 Hz), 7.15 (br s, 1H, NH, J = 8.4 Hz), 7.35–7.49 (m, 10H, PhH × 2); Anal. Calcd for $C_{35}H_{52}BrN_3O_8Si$: C, 55.99; H, 6.98; N, 5.60%. Found: C, 56.18; H, 6.85; N, 5.83%.

***N*-(3-Bromo-2-oxopropanoyl)–L-Val–(*O*-TBDPS)–L-Thr–OMe 5.** A solution of **11** (1.20 g, 1.60 mmol) and TFA (20 mL) in $CHCl_3$ (20 mL) was stirred at room temperature for 30 min. The resulting solution was further stirred with water (20 mL) for 10 min. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution (20 mL) and the organic layer was dried over anhydrous Na_2SO_4, and concentrated in vacuo gave **5** as colorless syrup, which was used intact in the next reaction, without purification. Yield 92% (0.91 g): ^{1}H NMR ($CDCl_3$) δ 1.02, 1.03 (each s, 9H, TBDPS's *t*-Bu), 1.08, 1.09 (each d, 3H, Val's CH_3, J = 6.6 Hz), 1.29 (d, 3H, Thr's CH_3, J = 6.4 Hz), 2.18–2.21 (m, 1H, Val's β-H), 3.61 (s, 3H, COOCH_3), 4.33–4.62 (m, 5H, Ser's β-H × 2, Ser's α-H, Thr's α-H, Thr's β-H), 6.45 (br s, 1H, NH, J = 8.4 Hz), 7.15 (br s, 1H, NH, J = 8.4 Hz), 7.35–7.49 (m, 10H, PhH × 2).

Methyl (*S*,*S*,*S*)-2-[2-(1-{2-[1-(*N*-Boc)Amino-2-methylpropyl]-thiazole-4-carbonylamino}-2-methylpropyl)thiazole-4-carbonyl]-(*O*-TBDPS)-L-threonate (12). To a solution of **4**[9c] (300 mg, 0.72 mmol) in DME (10 mL) at 0 °C were added K_2CO_3 (796 mg, 5.76 mmol) and a solution of **5** (672 mg, 1.09 mmol) in DME (10 mL), and the mixture was stirred at 0 °C for 30 min, then at room temperature for 10 h. The reaction mixture was concentrated in vacuo to give brown syrup, which was diluted with $CHCl_3$ (10 mL) and washed with water (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give brown syrup, which was dissolved with DME (10 mL). To the solution were added TFAA (trifluoroacetic anhydride) (203 µL, 1.44 mmol) and pyridine (254 µL, 3.17 mmol) at 0 °C for 30 min. Concentration in vacuo gave brown syrup, which was further dissolved with EtOAc (15 mL). The reaction mixture was washed with brine (10 mL × 2) and stirred with 28% aqueous NH_3 at 0 °C. After stirring for 15 min, the reaction mixture was washed with brine (10 mL) and dried over anhydrous Na_2SO_4, and concentrated in vacuo giving a brown syrup, which was purified on a silica gel column eluted with hexane–EtOAc (2:1 v/v) to give **12** as yellow syrup. Yield 90% (606 mg): $[\alpha]_D^{24}$ −35.2° (*c* 1.00, MeOH); IR 3399, 2965, 1610, 1530, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3H, Val's CH_3, J = 6.4 Hz), 0.98 (d, 3H, Val's CH_3, J = 6.4 Hz), 1.01 (s, 9H, TBDPS's *t*-Bu), 1.02 (d, 3H, Val's CH_3, J = 6.4 Hz), 1.04 (d, 3H, Val's CH_3, J = 7.2 Hz), 1.06 (d, 3H, Val's CH_3, J = 7.2 Hz), 1.07 (d, 3H, Val's CH_3, J = 6.6 Hz), 1.28 (d, 3H, Thr's CH_3, J = 7.2 Hz), 1.38 (s, 9H, Boc's *t*-Bu), 2.25–2.61 (m, 3H, Val's β-H × 3), 3.61 (s, 3H, COOCH_3), 4.45 (m, 1H, Thr's β-H), 4.62 (m, 1H, Val's α-H), 4.78 (m, 1H, Thr's α-H), 4.87 (dd, 1H, Val's α-H, J = 5.4, 8.6 Hz), 5.16 (d, 1H, NH, J = 8.9 Hz), 5.56 (m, 1H, Val's α-H), 6.61 (d, 1H, NH, J = 5.5 Hz), 7.26–7.63 (m, 10H, PhH × 2), 8.01 (d, 1H, NH, J = 5.0 Hz), 8.03 (s, 1H, thiazole's ring-H), 8.05 (s, 1H, thiazole's ring-H), 8.10 (d, 1H, NH, J = 6.0 Hz); Anal. Calcd for $C_{47}H_{66}N_6O_8S_2Si$: C, 60.36; H, 7.11; N, 8.99%. Found: C, 60.54; H, 7.58; N, 9.09%.

Methyl (*S*,*S*,*S*)-2-[2-(1-{2-[1-(*N*-Boc)Amino-2-methylpropyl]-thiazole-4-carbonylamino}-2-methylpropyl)thiazole-4-carbonyl]-L-threonate (13). To a solution of **12** (200 mg, 0.21 mmol) in THF (2 mL) at 0 °C was added 1 M TBAF (tetrabutylammonium fluoride 1 mol L^{-1} THF solution) (321 µL), and the mixture was stirred at 0 °C for 1 h, then at room temperature for 1 h. The reaction mixture was concentrated in vacuo to give brown syrup, which was purified on a silica gel column eluted with hexane–acetone (3:2 v/v) to give **13** as colorless syrup. Yield 95% (139 mg): $[\alpha]_D^{24}$ −52.2° (*c* 1.00, MeOH); IR 3400, 2965, 1610, 1530, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3H, Val's CH_3, J = 6.4 Hz), 0.98 (d, 3H, Val's CH_3, J = 6.4 Hz), 1.02 (d, 3H, Val's CH_3, J = 6.4 Hz), 1.04 (d, 3H, Val's CH_3, J = 7.2 Hz), 1.06 (d, 3H, Val's CH_3, J = 7.2 Hz), 1.07 (d, 3H, Val's CH_3, J = 6.6 Hz), 1.28 (d, 3H, Thr's CH_3, J = 7.2 Hz), 1.38 (s, 9H, Boc's *t*-Bu), 2.25–2.61 (m, 3H, Val's β-H × 3), 3.61 (s, 3H, COOCH_3), 4.45 (m, 1H, Thr's β-H), 4.62 (m, 1H, Val's α-H), 4.78 (m, 1H, Thr's α-H), 4.87 (dd, 1H, Val's α-H, J = 5.4, 8.6 Hz), 5.16 (d, 1H, NH, J = 8.9 Hz), 5.56 (m, 1H, Val's α-H), 6.61 (d, 1H, NH, J = 5.5 Hz), 8.01 (d, 1H, NH, J = 5.0 Hz), 8.03 (s, 1H, thiazole's ring-H), 8.05 (s, 1H, thiazole's ring-H), 8.10 (d, 1H, NH, J = 6.0 Hz); Anal. Calcd for $C_{31}H_{48}N_6O_8S_2$: C, 53.43; H, 6.94; N, 12.06%. Found: C, 53.65; H, 7.08; N, 12.36%.

Bistratamide J (1). To a solution of **13** (139 mg, 0.20 mmol) in a mixture of THF and water (1:1 v/v) (20 mL) at 0 °C was added 1 M LiOH (5 mL), and the mixture was stirred for 1 h and then at room temperature for 2 h. The reaction mixture was acidified with citric acid. The resulting solution was extracted with EtOAc (20 mL × 3) and the organic phases were washed with brine (10 mL × 2) and then dried over anhydrous Na_2SO_4, and concentrated in vacuo giving (*S*,*S*,*S*)-2-[2-(1-{2-[1-(*N*-Boc)amino-2-methylpropyl]thiazole-4-carbonylamino}-2-methylpropyl)thiazole-4-car-

bonyl]-L-Thr–OH as colorless syrup. To remove the Boc group, we stirred a solution of the above product in a mixture of TFA and $CHCl_3$ (1:3 v/v) (20 mL) at room temperature for 2 h. The reaction mixture was concentrated in vacuo to give (*S*,*S*,*S*)-2-(2-{1-[2-(1-amino-2-methylpropyl)thiazole-4-carbonylamino]-2-methylpropyl}thiazole-4-carbonyl)-L-Thr–OH as colorless crystals. To the solution of this product in a mixture of dry DMF and CH_2Cl_2 (1:2 v/v) (20 mL) at 0 °C were added a solution of BOP (132 mg, 0.30 mmol) and $(i\text{-Pr})_2$NEt (30.0 mg, 0.24 mmol) in dry DMF (5 mL), and the mixture was stirred at 0 °C for 1 h, then at room temperature for 2 days. The reaction mixture was diluted with water (25 mL) and extracted with EtOAc (50 mL × 4). The combined extracts were washed with brine (20 mL × 2) and then dried over anhydrous Na_2SO_4, and concentrated in vacuo giving brown syrup, which was purified on a silica gel column eluted with hexane–EtOAc (1:3 v/v) to give **1** as white solid. Yield 72% (81 mg).

Synthesized: Mp 165.0–166.0 °C; $[\alpha]_D^{25}$ −139.9° (*c* 0.50, MeOH); IR 3380, 2955, 2903, 1661, 1535, 1502, 1490 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6, 1.00 mg/0.75 mL) δ 0.81 (d, 3H, Val's CH_3, $J = 6.5$ Hz), 0.91 (d, 3H, Val's CH_3, $J = 6.5$ Hz), 0.99 (d, 3H, Val's CH_3, $J = 6.7$ Hz), 1.03 (d, 3H, Val's CH_3, $J = 6.5$ Hz), 1.04 (d, 3H, Val's CH_3, $J = 6.5$ Hz), 1.05 (d, 3H, Val's CH_3, $J = 6.4$ Hz), 1.10 (d, 3H, Thr's CH_3, $J = 6.4$ Hz), 2.11–2.19 (m, 2H, Val's β-H × 2), 2.20–2.25 (m, 1H, Val's β-H), 4.10–4.15 (m, 1H, Thr's β-H), 4.30 (dd, 1H, Thr's α-H, $J = 2.2$, 10.0 Hz), 4.34 (t, 1H, Val's α-H, $J = 10.8$ Hz), 5.19 (t, 1H, Val's α-H, $J = 9.1$ Hz), 5.28 (br d, 1H, OH, $J = 4.8$ Hz), 5.32 (dd, 1H, Val's α-H, $J = 7.4$, 10.1 Hz), 8.08 (d, 1H, N*H*, $J = 10.0$ Hz), 8.15 (d, 1H, N*H*, $J = 9.3$ Hz), 8.24 (s, 1H, thiazole's ring-H), 8.30 (s, 1H, thiazole's ring-H), 8.44 (d, 1H, N*H*, $J = 9.8$ Hz), 8.50 (d, 1H, N*H*, $J = 10.7$ Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 18.6, 18.8, 18.9, 19.4, 19.5, 19.8, 21.2, 30.8, 34.2, 34.6, 55.0, 55.4, 59.0, 61.4, 67.7, 124.1, 125.3, 148.3, 149.0, 159.7, 160.0, 169.4, 169.9, 170.0, 170.1; HR-ESI-MS Calcd for $C_{25}H_{36}N_6NaO_5S_2$: 587.2086. Found: m/z 587.2090 ($M + Na^+$).

Lit:[7] White solid, mp 165.0–167.0 °C; $[\alpha]_D$ −134.9° (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.81 (d, 3H, $J = 6.6$ Hz), 0.91 (d, 3H, $J = 6.6$ Hz), 0.99 (d, 3H, $J = 6.6$ Hz), 1.03 (d, 3H, $J = 6.6$ Hz), 1.04 (d, 3H, $J = 5.8$ Hz), 1.05 (d, 3H, $J = 6.1$ Hz), 1.11 (d, 3H, $J = 6.6$ Hz), 2.11–2.16 (m, 2H), 2.22 (m, 1H), 4.14 (m, 1H), 4.32 (dd, 1H, $J = 2.0$, 10.1 Hz), 4.35 (t, 1H, $J = 11.0$ Hz), 5.20 (dd, 1H, $J = 9.2$, 9.7 Hz), 5.22 (t, 1H, $J = 4.8$ Hz), 5.33 (dd, 1H, $J = 7.4$, 10.1 Hz), 8.08 (d, 1H, $J = 10.1$ Hz), 8.13 (d, 1H, $J = 9.3$ Hz), 8.24 (s, 1H), 8.30 (s, 1H), 8.43 (d, 1H, $J = 9.7$ Hz), 8.49 (d, 1H, $J = 10.5$ Hz), ^{13}C NMR (150 MHz, DMSO-d_6) δ 18.6, 18.8, 18.9, 19.4, 19.5, 19.8, 21.3, 30.8, 34.3, 34.7, 55.0, 55.4, 58.8, 61.3, 67.7, 124.2, 125.4, 148.3, 149.0, 159.7, 159.9, 169.4 (2C), 170.1 (2C).

Compound 16. A solution of **1** (66.7 mg, 0.12 mmol) and Burgess reagent (methyl *N*-[(triethylammonio)sulfonyl]carbamate) (113 mg, 0.47 mmol) in THF (5 mL) was stirred at 80 °C for 2 h. The reaction mixture was concentrated in vacuo to give brown syrup, which was purified on a silica gel column with acetone to give **16** as clear crystals. Yield 65% (42.0 mg): mp 92–94 °C; $[\alpha]_D^{25}$ −34.6° (*c* 0.5, MeOH); IR 3380, 2960, 2903, 1660, 1538, 1502, 1494 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.87 (d, 3H, Val's CH_3, $J = 6.9$ Hz), 0.89 (d, 3H, Val's CH_3, $J = 7.0$ Hz), 0.91 (d, 3H, Val's CH_3, $J = 6.7$ Hz), 0.92 (d, 3H, Val's CH_3, $J = 6.9$ Hz), 0.95 (d, 3H, Val's CH_3, $J = 6.9$ Hz), 0.99 (d, 3H, Val's CH_3, $J = 6.9$ Hz), 1.25 (d, 3H, oxazoline's ring CH_3, $J = 6.5$ Hz), 2.01–2.07 (m, 1H, Val's β-H), 2.19–2.24 (m, 1H, Val's β-H), 2.32–2.35 (m, 1H, Val's β-H), 4.76–4.79 (m, 2H, oxazoline's 4-H and Val's α-H), 5.27 (dq, 1H, oxazoline's 5-H, $J = 6.5$, 10.7 Hz), 5.37 (dd, 1H, Val's α-H, $J = 5.2$, 9.5 Hz), 5.51 (dd, 1H, Val's α-H, $J = 4.8$, 8.9 Hz), 7.96 (d, 1H, N*H*, $J = 9.6$ Hz), 8.16 (d, 1H, N*H*, $J = 9.8$ Hz), 8.36 (s, 1H, thiazole's ring-H), 8.38 (s, 1H, thiazole's ring-H), 8.56 (d, 1H, N*H*, $J = 9.8$ Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 16.0, 16.9, 17.5, 18.1, 18.7, 18.8, 22.0, 30.5, 34.4, 34.5, 51.0, 53.8, 54.7, 69.9, 79.6, 125.0, 125.1, 147.6, 148.2, 158.8, 159.3, 167.6, 168.0, 168.1, 168.9; HR-ESI-MS Calcd for $C_{25}H_{35}N_6KO_4S_2$: 585.1720. Found: m/z 595.1666 ($M + K^+$).

Compound 17. To a solution of **16** (38.2 mg, 0.07 mmol) in THF (5 mL) at 0 °C was added 1 M HCl (5 mL), and the mixture was stirred at 0 °C for 30 min, then at room temperature for 1 h. The solution was then made alkaline (pH 9.5) by addition of solid K_2CO_3. The reaction mixture was extracted with EtOAc (10 mL × 2), and the organic phases were concentrated in vacuo giving colorless syrup. The resulting residue was dissolved in MeOH (5 mL) at room temperature then to it was added basic alumina (57.1 mg, 0.56 mmol), and the mixture was heated to reflux for 4 h. The reaction mixture was cooled to room temperature, sonicated for 5 min, and then vacuum filtered to remove the alumina. The filtrate was concentrated in vacuo and purified on a silica gel column eluted with hexane–acetone (1:3 v/v) to give **17** as clear crystals. Yield 72% (24.5 mg): $[\alpha]_D^{24}$ −42.0° (*c* 0.92, $CHCl_3$); IR 3375, 3306, 2955, 1660, 1595, 1535, 1530 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.85 (d, 3H, Val's CH_3, $J = 6.7$ Hz), 0.91 (d, 3H, Val's CH_3, $J = 6.7$ Hz), 0.99 (d, 6H, Val's CH_3 × 2, $J = 6.7$ Hz), 1.04 (d, 3H, Val's CH_3, $J = 6.5$ Hz), 1.05 (d, 3H, Val's CH_3, $J = 6.3$ Hz), 1.14 (d, 3H, Thr's CH_3, $J = 6.5$ Hz), 2.10–2.18 (m, 3H, Val's β-H × 3), 4.26 (t, 1H, Val's α-H, $J = 10.8$ Hz), 4.42 (dd, 1H, Thr's α-H, $J = 3.4$, 10.3 Hz), 5.12 (t, 1H, Val's α-H, $J = 8.4$ Hz), 5.32 (dd, 1H, Val's α-H, $J = 7.6$, 10.0 Hz), 5.46 (br s, 1H, OH), 8.07 (d, 1H, N*H*, $J = 8.9$ Hz), 8.24 (s, 1H, thiazole's ring-H), 8.29 (s, 1H, thiazole's ring-H), 8.42 (d, 1H, N*H*, $J = 10.0$ Hz), 8.48 (d, 1H, N*H*, $J = 10.7$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.1, 18.6, 18.9, 19.1, 19.6, 20.2, 29.8, 34.4, 34.7, 56.1, 57.8, 62.2, 67.0, 123.3, 123.4, 147.8, 149.8, 160.0, 161.0, 168.9, 169.1, 170.3, 172.1; HR-ESI-MS Calcd for $C_{25}H_{36}N_6NaO_5S_2$: 587.2086. Found: m/z 587.2069 ($M + Na^+$).

Bistratamide H (2). Method A: Similarly to the case of **7**, the dehydration of **1** (52.3 mg, 0.09 mmol) with Et_3N (20.0 mg, 0.20 mmol), MsCl (17.5 mg, 0.15 mmol), and DBU (19.2 mg, 0.13 mmol) in $CHCl_3$ (10 mL) was worked up to give a brown residue **14**. To a solution of the residue in $CHCl_3$ (10 mL) at 0 °C was added NBS (17.6 mg, 0.10 mmol), and the mixture was stirred at room temperature for 3 h. Then, Et_3N (10.1 mg, 0.10 mmol) was added to the reaction mixture at 0 °C, and stirred at 0 °C for 30 min, then at room temperature for 5 h. The reaction mixture was diluted with diethyl ether (10 mL) and washed successively with 10% citric acid (15 mL × 2), a saturated $NaHCO_3$ solution (15 mL × 2), brine (15 mL × 2), then dried over anhydrous Na_2SO_4, and concentrated in vacuo gave brown syrup **15**, which was dissolved with dioxane (10 mL). Cs_2CO_3 (75.0 mg, 0.23 mmol) was added to the solution at room temperature, the reaction mixture was stirred overnight at 60 °C. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL × 3). The organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give brown syrup, which was purified on a silica gel column eluted with hexane–acetone (1:3 v/v) to give **2** as colorless crys-

tals. Yield 70% (34.3 mg).

Method B: Into a solution of **3** (11.5 mg, 0.02 mmol) in THF (5 mL) at room temperature was added MnO_2 (6.96 mg, 0.08 mmol), and the mixture was stirred at 70 °C for 5 h. The mixture was cooled to room temperature, and then vacuum filtered to remove the MnO_2. The filtrate was concentrated in vacuo to give brown syrup, which was purified on a silica gel column with acetone to give **2** as white solid. Yield 73% (7.95 mg).

Synthesized: Mp 199.0–200.0 °C; $[\alpha]_D^{25}$ −92.5° (*c* 1.00, MeOH); IR 3380, 3305, 2955, 1660, 1595, 1535, 1530 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6, 1.00 mg/0.75 mL) δ 0.91 (d, 3H, Val's CH_3, $J = 6.9$ Hz), 0.940 (d, 3H, Val's CH_3, $J = 6.9$ Hz), 0.943 (d, 3H, Val's CH_3, $J = 6.9$ Hz), 0.95 (d, 3H, Val's CH_3, $J = 7.2$ Hz), 0.97 (d, 3H, Val's CH_3, $J = 7.0$ Hz), 0.99 (d, 3H, Val's CH_3, $J = 6.7$ Hz), 2.16–2.28 (m, 3H, Val's β-H × 3), 2.59 (s, 3H, oxazole's ring CH_3), 5.07 (dd, 1H, Val's α-H, $J = 5.2$, 8.4 Hz), 5.35 (dd, 1H, Val's α-H, $J = 5.5$, 8.6 Hz), 5.45 (dd, 1H, Val's α-H, $J = 6.7$, 9.8 Hz), 8.33 (s, 1H, thiazole's ring-H), 8.34 (s, 1H, thiazole's ring-H), 8.36 (d, 1H, N*H*, $J = 8.6$ Hz), 8.50 (d, 1H, N*H*, $J = 8.6$ Hz), 8.52 (d, 1H, N*H*, $J = 9.8$ Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 11.2, 17.9, 18.0, 18.1, 18.3, 18.5, 18.9, 32.8, 34.4, 34.5, 52.2, 54.5, 54.8, 124.8, 125.3, 127.8, 147.8, 148.3, 153.2, 159.0, 159.4, 159.7, 160.5, 168.4, 168.9; HR-ESI-MS Calcd for $C_{25}H_{33}N_6NaO_4S_2$: 567.1824. Found: m/z 567.1757 ($M + Na^+$).

Natural: Clear solid; $[\alpha]_D$ −92.9° (*c* 1.0, MeOH); IR 3390, 2955, 1670, 1530, 1505, 1490 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.90 (d, 3H, $J = 7.0$ Hz), 0.93 (d, 3H, $J = 7.0$ Hz), 0.94 (d, 3H, $J = 7.0$ Hz), 0.95 (d, 3H, $J = 7.0$ Hz), 0.96 (d, 3H, $J = 7.0$ Hz), 0.97 (d, 3H, $J = 7.0$ Hz), 2.21 (m, 3H, $J = 6.0$ Hz), 2.58 (s, 3H), 5.06 (dd, 1H, $J = 5.0$, 8.5 Hz), 5.34 (dd, 1H, $J = 5.0$, 8.5 Hz), 5.44 (dd, 1H, $J = 6.5$, 9.5 Hz), 8.32 (s, 1H), 8.34 (s, 1H), 8.35 (d, 1H, $J = 9.5$ Hz), 8.48 (d, 1H, $J = 9.0$ Hz), 8.52 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.3, 18.0, 18.1, 18.2, 18.3, 18.5, 18.9, 32.8, 34.4, 34.5, 52.2, 54.5, 54.7, 124.5, 125.0, 127.6, 147.5, 148.0, 152.9, 158.7, 159.1, 159.4, 160.2, 168.1, 168.6.

Bistratamide E (3). Similarly to the case of **16**, the cyclization of **17** (44.0 mg, 0.08 mmol) with Burgess reagent (76.3 mg, 0.32 mmol) in THF (3 mL) was worked up to give **3** as white solid. Yield 65% (28.4 mg).

Synthesized: Mp 91.0–96.0 °C; $[\alpha]_D^{25}$ −32.3° (*c* 1.0, MeOH); IR 3380, 3305, 2955, 1660, 1595, 1535, 1530 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6, 1.00 mg/0.75 mL) δ 0.85 (d, 6H, Val's CH_3 × 2, $J = 6.6$ Hz), 0.86 (d, 3H, Val's CH_3, $J = 6.1$ Hz), 0.89 (d, 3H, Val's CH_3, $J = 6.6$ Hz), 0.90 (d, 3H, Val's CH_3, $J = 7.0$ Hz), 0.95 (d, 3H, Val's CH_3, $J = 7.0$ Hz), 1.47 (d, 3H, oxazoline's CH_3, $J = 6.1$ Hz), 2.03–2.06 (m, 1H, Val's β-H), 2.20–2.27 (m, 1H, Val's β-H), 2.32–2.36 (m, 1H, Val's β-H), 4.24 (dd, 1H, oxazoline's 4-H, $J = 1.8$, 8.8 Hz), 4.78 (dq, 1H, oxazoline's 5-H, $J = 6.1$, 8.3 Hz), 4.83 (m, 1H, Val's α-H), 5.30 (dd, 1H, Val's α-H, $J = 5.3$, 8.8 Hz), 5.52 (dd, 1H, Val's α-H, $J = 4.4$, 8.3 Hz), 7.79 (d, 1H, N*H*, $J = 8.8$ Hz), 8.05 (d, 1H, N*H*, $J = 9.7$ Hz), 8.36 (s, 1H, thiazole's ring-H), 8.39 (s, 1H, thiazole's ring-H), 8.57 (d, 1H, N*H*, $J = 8.3$ Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 16.0, 17.4, 17.5, 17.9, 18.1, 18.9, 21.4, 30.5, 34.2, 34.3, 51.2, 53.9, 54.8, 72.8, 81.9, 124.7, 125.0, 147.6, 147.9, 158.8, 159.1, 167.9, 168.0, 168.2, 169.4; HR-ESI-MS Calcd for $C_{25}H_{35}N_6NaO_4S_2$: 569.1981. Found: m/z 569.1977 ($M + Na^+$).

Natural: Clear glass; $[\alpha]_D$ −31.0° (*c* 1.0, MeOH); IR 3390, 2955, 1670, 1535, 1510, 1495 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.84 (d, 6H, $J = 7.0$ Hz), 0.86 (d, 3H, $J = 7.0$ Hz), 0.88 (d, 3H, $J = 7.0$ Hz), 0.90 (d, 3H, $J = 7.0$ Hz), 0.95 (d, 3H, $J = 7.0$ Hz), 1.46 (d, 3H, $J = 6.0$ Hz), 2.04 (m, 1H), 2.21 (m, 1H), 2.32 (m, 1H), 4.22 (dd, 1H, $J = 5.0$, 9.0 Hz), 4.79 (m, 2H), 5.29 (dd, 1H, $J = 5.0$, 9.0 Hz), 5.51 (dd, 1H, $J = 4.5$, 8.5 Hz), 7.78 (d, 1H, $J = 9.0$ Hz), 8.04 (d, 1H, $J = 9.5$ Hz), 8.36 (s, 1H), 8.38 (s, 1H), 8.56 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.0, 17.4, 17.5, 17.9, 18.2, 18.9, 21.4, 30.4, 34.2, 34.3, 51.1, 53.9, 54.7, 72.7, 81.9, 124.7, 124.9, 147.3, 147.8, 158.5, 159.0, 167.5, 167.6, 167.9, 169.0.

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16 In general, it is known that the chemical shifts of amide protons change dependent on concentration. In this work, ^{1}H NMR data of synthetic bistratamides **1**–**3** measured at the concentration (1.00 mg/0.75 mL DMSO-d_6) were in good agreement with that reported by Kelly's group. However, the data measured at (0.50 mg/0.75 mL DMSO-d_6) were not in agreement.