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One-pot Enantiomeric Synthesis of Thiazole-containing Amino Acids: Total Synthesis of Venturamides A and B

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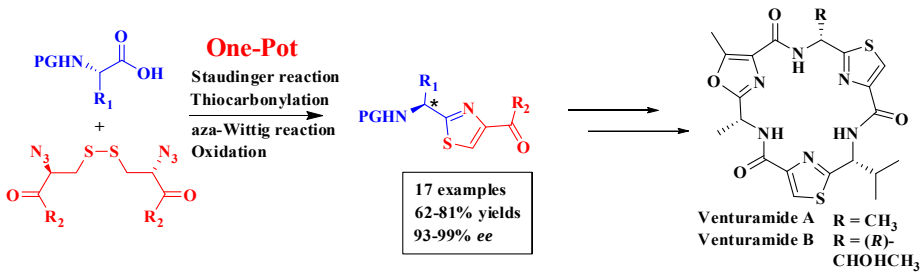
ABSTRACT

An effective one-pot procedure for enantiomerical synthesis of thiazole-containing amino acid (TCAA) has been established via a cascade disulfide cleavage / thiocarbonylation / intramolecular Staudinger Reduction / aza-Wittig / oxidation reaction. Starting from the commercially available amino acid building blocks, a number of TCAAs were prepared in good yields and in excellent optical purities. This method bears features of mild reaction conditions, wide substrate adaptability, and good functional group tolerance. The power of this method was also demonstrated through the concise total synthesis of cyclic hexapeptide Venturamides A and B.



INTRODUCTION

Cyclic peptides which contain 2, 4-disubstituted thiazole units have been continuously isolated from marine organisms and attracted significant interests in drug discovery

and development.[1-3] Researchers believe that these heterocycles play the key roles in favoring bioactive conformation with the decreased flexibility, inclining the lipophilicity of the whole molecule, serving as recognition targets, and even tuning the binding properties of biomolecules such as DNAs, RNAs, and proteins. Looking carefully about the chemical structures of those promising cyclic peptides (Figure 1), the specific α-stereogenic position of the thiazole units captured our attention due to the frequently reported racemization during the synthesis of thiazole-containing amino acids (TCAAs).[1,2]

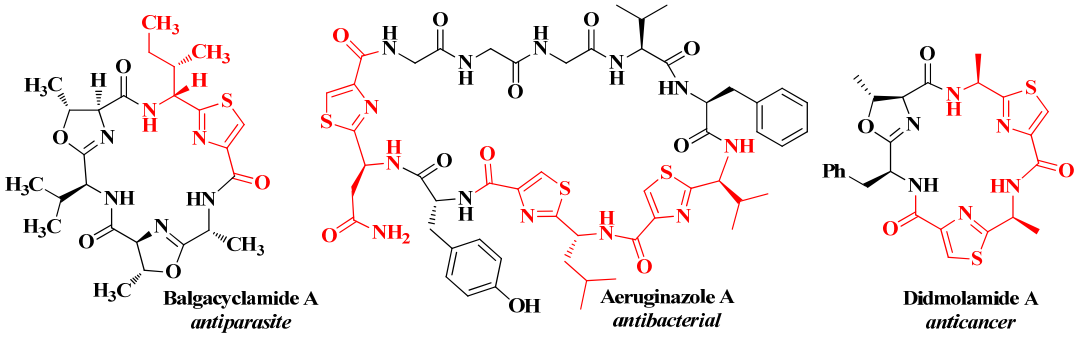


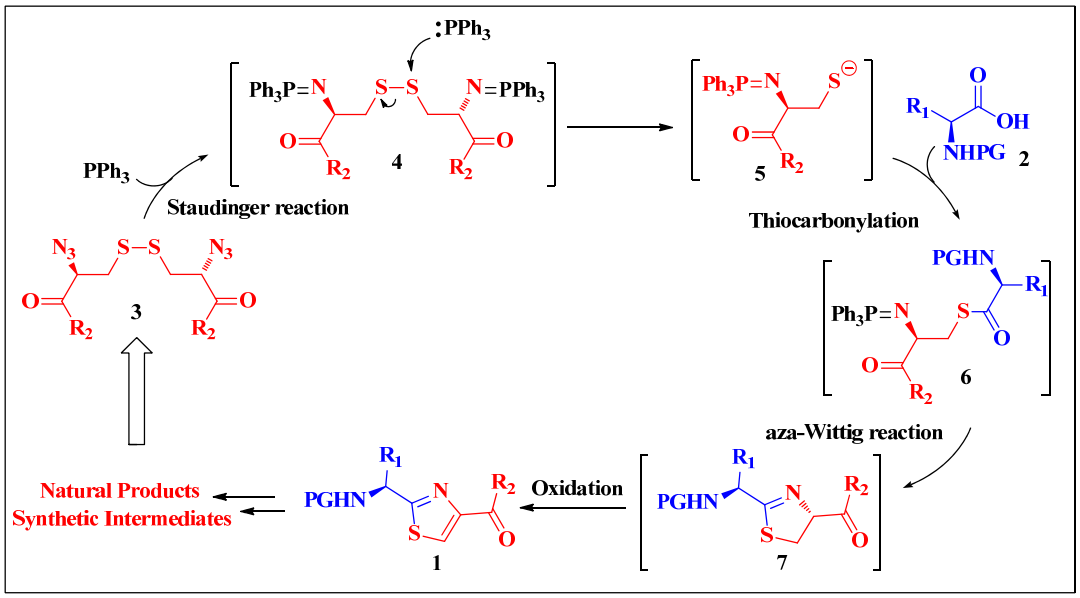
Figure 1. Representive natural products having TCAA building blocks

To date, there are very few practical approaches that adapt for the preparation of enantiomerically enriched TCAAs which are essential and unique substructures in various bioactive natural products and pharmaceutical lead compounds.[3] One currently well recognized procedure comes from the modified Hantzsch reaction using thioamides and α-halo carbonyl compounds as substrates, that requires relative harsh reaction conditions and suffers from partial epimerization at the α-stereogenic center in many case studies.[2] An alternative way for the preparation of optically pure TCAAs was through a dehydrogenation of pre-existing thiazoline or thiazolidine substrates via oxidation. However, only a few oxidants have been successfully applied to the total synthesis of natural products having TCAA building blocks.[1,4] In addition, the Lawesson reagent mediated thionation-cyclization of β-ketoamide derivatives,[5] as well as the asymmetric alkylation of pre-existing thiazole heterocycles[1,6] were also explored in the synthesis of chiral TCAA units. Unfortunately, the encountered generation of partial racemic products, requirement of stoichiometric amounts of organometallic reagents, and intolerance of sensitive functional groups under cyclization / dehydrogenation conditions have badly limited the practicability and generality of these methods.[1,2] Therefore, developing a straightforward and effective method to build TCAAs from easily available precursors is highly demanding.[4,7] Here

we would like to disclose our findings in one-pot cascade synthesis of thiazole-containing amino acid with elevated optical purity.

RESULTS AND DISCUSSION

Based on our previous studies,[7] we envisaged a tandem phosphine-promoted intramolecular Staudinger-aza-Wittig reaction[8] to form thiazoline intermediate **7** using N-protected amino acids **2** and *β*-azido disulfides **3** as substrates (Scheme 1), followed by a subsequent dehydrogenation of **7** to form the desired chiral TCAA **1** under suitable conditions. It was expected that the mild reaction conditions and the general applicability of Staudinger-aza-Wittig reaction could make this strategy a valuable tool in assembling high enantiomerically enriched TCAAs.

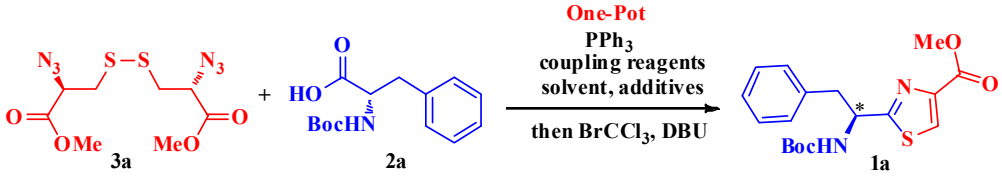


Scheme 1. Hypothetical mechanisms for TCAA synthesis

To test the feasibility, N-Boc-L-Phe-OH (**2a**) and *β*-azido disulfide ester (**3a**) were selected as the model substrates, EDCI/DIPEA as combined coupling reagents, PPh_3 as organophosphine source, and DBU/$BrCCl_3$ as dehydrogenation reagents.[9] The experiments turned out the desired thiazole **1a** in 73% yield, but showing only 55% of enantiomeric excess value (Table 1, entry 1) under the optimized reaction conditions. We initially ascribed this optical purity loss to the dehydrogenation under excessive 1,8-Diazabicycloundec-7-ene (DBU). Thus, the thiazoline residue Boc-L-Phe-thiazoline-OMe was firstly prepared[7a] and then subjected to neutral oxidant MnO_2,[10] instead of DBU/$BrCCl_3$ in CH_2Cl_2, to prepare the thiazole **1a**.

However, the chiral analysis of **1a** achieved only 56% *ee* value (Table 1, entry 2). To have a better understanding of this racemic phenomenon, more conditions were investigated and some of the representative results are summarized in Table 1. To our surprise, all of the tested carbodiimide coupling reagents[11] (EDCI/DIPEA, EDCI/HOBt, EDC, DCC/DMAP and DCC/HOBt) afforded thiazole **1a** with unsatisfactory *ee* values (entries 1-6), while no target product was obtained when Mitsunobu reagent[12] was employed to the same reaction (entry 7). We postulated that carbodiimides may generate racemic TCAAs via oxazolone intermediate under our refluxing reaction conditions (see ESI, Scheme S1**)**.

Table 1. Screening of the optimal reaction conditions[a]

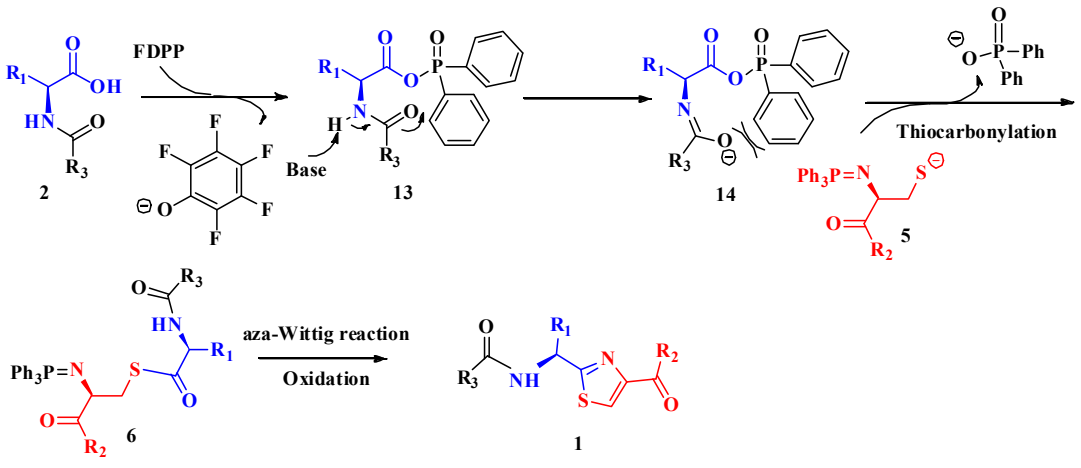


entry	coupling conditions[b]	solvent	yield (%)[c]	ee (%)[d]
1	EDCI, DIPEA	DCM	73	55
2	EDCI, DIPEA	DCM	71	56[e]
3	EDC	DCM	56	74
4	EDCI, HOBt (8.0 eq)	DCM	70	52
5	DCC, DMAP (0.2 eq)	DCM	71	25
6	DCC, HOBt (8.0 eq)	DCM	66	27
7	DEAD (4.0 eq), PPh_3 (4.0 eq)	THF	--	--
8	DPPA, TEA	DMF	trace	--
9	DPPA, TEA	DCM	15	96
10	DPP-Cl, TEA	DCM	72	65
11	DPP-Cl, DIPEA	DCM	75	47
12	DPP-Cl, TMEDA (2.0 eq)	DCM	69	55
13	SDPP, TEA	DCM	72	85
14	**FDPP, TEA**	**DCM**	**73**	**96**
15	NDPP, TEA	DCM	67	92

[a]Unless otherwise noted, the conditions were carried out with 0.125 mmol of **3a**, 0.5 mmol of

2a, 0.5 mmol of coupling combined reagents, 1.0 mmol organic base and 1.0 mmol PPh_3 in 10 ml DCM. After refluxed for 5 hrs, the solution was cooled down to 0 °C and 1.0 mmol $BrCCl_3$ and 1.5 mmol DBU was added. [b]DPPA: Diphenylphosphoryl Azide; TEA: Triethylamine; DPP-Cl: Diphenylphosphinyl Chloride; SDPP: N-Succinimidyl Diphenylphosphate; FDPP: Pentafluorophenyl Diphenylphosphinate; NDPP: Norborn-5-ene-2,3-dicarboximido Diphenylphosphate. [c]Isolated yields. [d]Determined by chiral HPLC (CHIRALPAK IA column). [e]Using activated MnO_2 (1.25 mmol) as oxidant.

Fortunately enough, when organophosphorous reagent DPPA[13] was used as coupling reagent (entries 8, 9) in CH_2Cl_2, a remarkable *ee* enhancement was observed (up to 96%) for the product despite of a very low yield. This result encouraged us to search more widely the better organophosphorous reagents.[11] Diphenylphosphinyl chloride (DPPCl)[14a] was firstly tried and got some positive results in this reaction (entries 10-12). The racemic by-product might be caused by the hydrogen chloride generated *in situ* (see also ESI, Scheme S1). When a number of halogen free organophosphorous reagents such as SDPP[14b], FDPP[14c], and NDPP[14d] were applied, the exciting results with dramatically increased *ee* values for the desired chiral products were obtained (entries 13-15). To our delight, FDPP so far gave the best result (73% yield, 96% *ee*, entry 14). The plausible mechanism for this stereo-selectivity is thus proposed based on our experimental results, as shown in Scheme 2. The bulky diphenylphosphinate blocked the oxazolone intermediate formation through an intramolecular SN_2 reaction.[15]

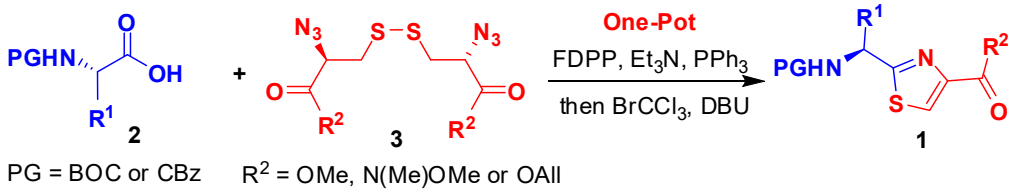


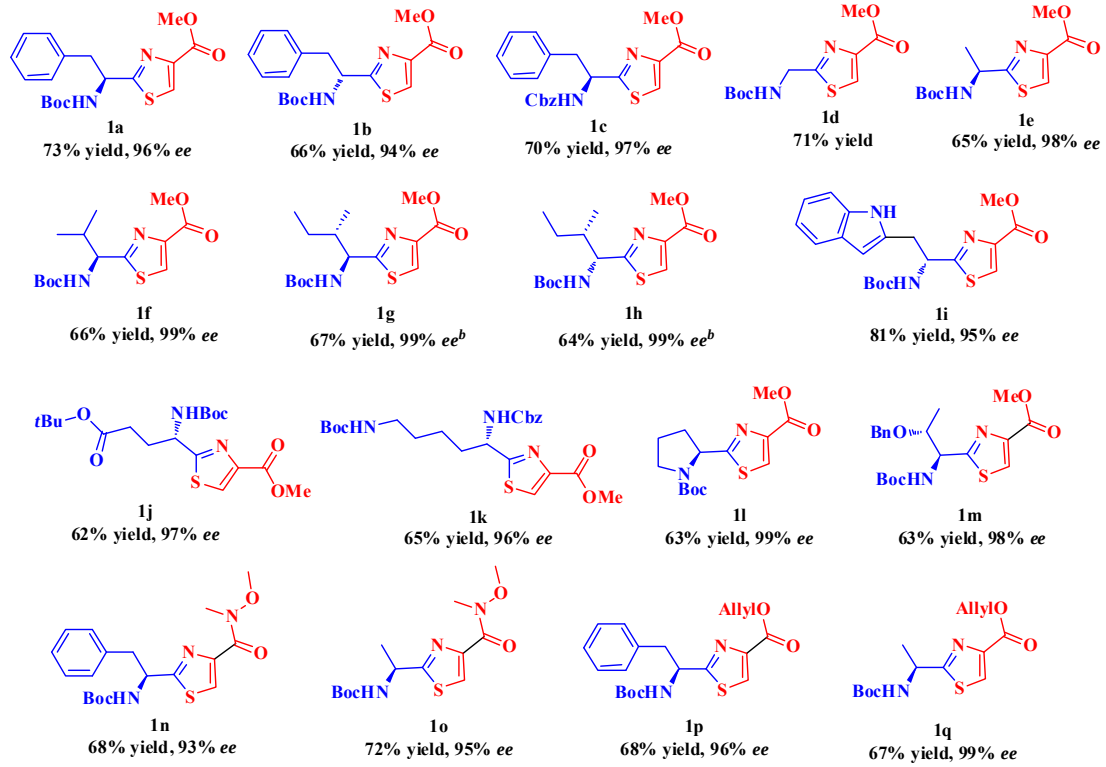
Scheme 2. Plausible mechanism for *ee* improvement

The scope of our one-pot TCAA formation was also explored as illustrated in Table 2. It was found that both D- and L-phenylalanine analogs were good substrates for

this reaction and the chirality of the corresponding thiazole was retained. Compounds with Boc- or Cbz-protected amine, as well as *t*-butyl or weinreb amide blocked carboxylic acids, were tolerant to the reaction conditions and afforded the products in excellent *ee* values and fairly good yields. Notably, the amino acid substrates with aliphatic substituent always afforded higher *ee* values, implying that electron donating aliphatic groups were more favorable to the retention of α-stereogenic center. Glycine, alanine, isoleucine, valine, tryptophan, glutamic acid, lysine, proline, and threonine are all good amino acid substrates for this one-pot cascade reaction (see Table 2).

Table 2. Synthesis of enantiomerically pure **TCAA**s[a]



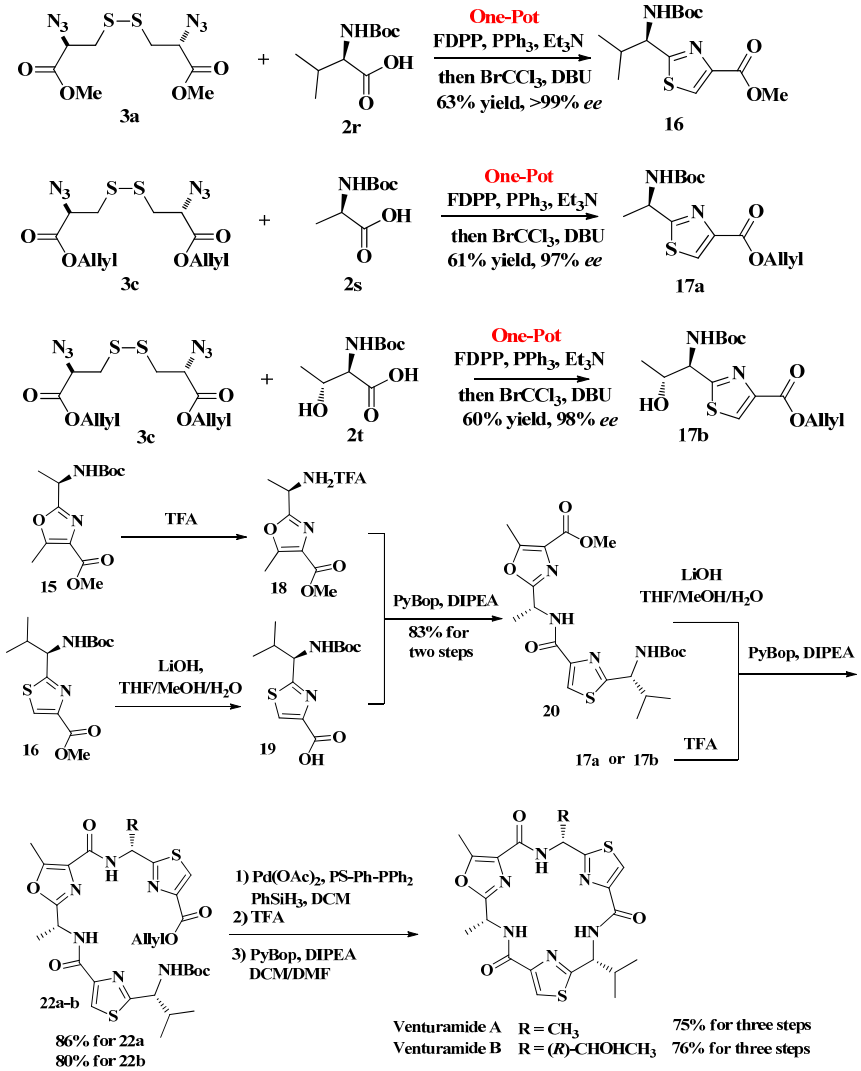


[a]Unless otherwise noted, the optimal conditions was used as described in experiment section; The *ee* (%) values were determined by HPLC (CHIRALPAK IA column). [b]Determined by ^{1}H NMR spectroscopy.

As the methodology has been established, we next turned our attention to the total synthesis of a bisthiazole-embodied cyclopeptide venturamides A and B[16] using our one-pot cascade process. These two cyclic hexapeptides, holding D-Val-Thz,

D-Ala-Thz or D-*allo*-Thr-Thz structural units (Thz stands for thiazole residue), were isolated from the marine cycanobacterium *Oscillatoria*sp and exhibited good antimalarial activity against *Plasmodium falciparum* with the IC_{50} values of 8.2 μM and 5.2 μM, respectively. Although the total synthesis of venturamide A has been reported[17] with a modified Hantzsch method, there is no report on the total synthesis of venturamide B so far.

Our synthetic strategy comes from the disconnection of three amide bonds generating three azole-based amino acid residues **15**[18], **16** and **17a,b** (Scheme 3). As expected, condensation of *β*-azido disulfides **3a** and **3c** with their amino acid counterparts N-Boc-D-Val-OH (**2r**), N-Boc-D-Ala-OH (**2s**) and N-Boc-D-*allo*-Thr-OH (**2t**) under our typical one-pot thiazole formation procedure afforded **TCAA** fragments N-Boc-D-Val-Thz-OMe (**16**), N-Boc-D-Ala-Thz-Oallyl (**17a**) and N-Boc-D-*allo*-Thr-Thz-Oallyl (**17b**) in 63% yield (> 99% *ee*), 61% yield (97% *ee*), and 60% yield (98% *ee*), respectively.



Scheme 3. Total synthesis of venturamides A and B

Assembling of three azole fragments to furnish the total syntheses of natural venturamides A and B (Scheme 3) was quite straightforward. Treatment of **16** with LiOH got **18** in free acid form, while removal of Boc on **15** with TFA afforded free amine salt **19**. PyBOP promoted coupling reaction between **18** and **19** rendered the bis-heterocycle **20** in a yield of 83%. After making free acid on **20** with LiOH and free amine on **17a,b** with TFA, compounds **22a** and **22b** were successfully prepared with these fragments in 86% and 80% yield applying PyBOP/DIPEA as coupling reagents. Cleavage of allyl groups from esters **22a** and **22b** with $Pd(OAc)_2$/$PhSiH_3$/polymer-supported triphenylphosphine[19] and removal of Boc with TFA, followed by PyBOP/DMAP/DIPEA catalyzed macrolactamization under diluted concentration (2 mM/L, DCM/DMF, v/v = 2/1) provided glassy venturamides A and B in yields of 75% and 76%, respectively. The physical data of the synthetic venturamides A and B were in consistent with those of the natural products {venturamide A: $[\alpha]^{25}_D$ +53.6 (*c* 1, MeOH), (lit.[16] $[\alpha]^{25}_D$ +53.4 (*c* 0.001, MeOH)); venturamide B: $[\alpha]^{25}_D$ +51.6 (*c* 0.5, MeOH), (lit.[16] $[\alpha]^{25}_D$ +53.6 (*c* 0.0004, MeOH))}.

CONCLUSIONS

In summary, a flexible and efficient one-pot approach to prepare enantiomerical TCAA from commercially available N-protected amino acids was reported for the first time. This reaction showed a broad substrate scope and excellent functional group tolerance to afford versatile TCAAs in excellent *ee* values (93-99%) and good yields (63-81%). The distinctive advantages of this protocol were also demonstrated through the total synthesis of antimalarial natural cyclopeptide venturamides A and B (32.7% and 30.7% overall yield, respectively). Further application of this cascade one-pot reaction to the synthesis of other promising natural TCAAs, as well as their biological evaluations, is currently in progress in our Lab.

EXPERIMENTAL SECTION

General.

Unless other indicated, all reagents were purchased from commercial corporations. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F254 plates. Flash chromatography (FC) was performed using silica gel (200-300 meshes). Visualization was accomplished with UV light, iodine or $KMnO_4$

solution. Optical rotations were recorded on a Rudolph Polarimeter Autopol 111. High-resolution mass spectrometry data were acquired using a Q-TOF analyzer. Melting points were analyzed on a Melt-Temp II capillary melting point apparatus. High performance liquid chromatography (HPLC) analysis was performed using Waters® Alliance HT® liquid chromatograph with a CHIRALPAK IA column. ^{1}H NMR, ^{13}C NMR were measured on 400 MHz or 100 MHz spectrometers (NMR in $CDCl_3$ with TMS as an internal standard). Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform; δ 7.26 for 1H NMR or 77.23 for proton decoupled ^{13}C NMR), and coupling constants (J) in Hz. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ddt (doublet of doublets of triplets), dq (doublet of quartets), br s (broad singlet), m (multiplet). β-azido disulfides **3a** and **3b** were prepared according to our previous report[7]. Pentafluorophenyl Diphenylphosphinate (FDPP), N-Succinimidyl Diphenylphosphate (SDPP) and Norborn-5-ene-2,3-dicarboximido Diphenylphosphate (NDPP) were prepared according to the reported procedures.[14b-d]

Typical process of making chiral TCAAs: preparation of 1a from substrate 3a

To a solution of Boc-L-Phe-OH (133 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) was added Pentafluorophenyl Diphenylphosphinate (FDPP) (184 mg, 0.5 mmol) and triethylamine (TEA) (101 mg, 1.0 mmol) at room temperature. After stirring for 15 min, **3a** (40 mg, 0.125 mmol) and PPh_3 (262 mg, 1.0 mmol) was added into the solution and heated to reflux for further 5 h away from light. After cooling to 0 °C, 1,8-Diazabicycloundec-7-ene (DBU) (273 mg, 1.5 mmol) and Bromotrichloromethane (198 mg, 1.0 mmol) were introduced via spyringe over 5 min and stirred for further 30 min at room temperature. The solvent was quenched with saturated NH_4Cl solution and extracted with DCM (20 mL × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo (below 45 °C), and purified by FC (silica gel, Hexanes/EtOAc 3:1) to give compound **1a** (66 mg, 73% yield, 96% *ee*) as white solid; data are consistent with a previously characterized compound.[4a] m.p. 99-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38 (s, 9H), 3.19-3.36 (m, 2H), 3.96 (s, 3H), 5.29 (s, br, 2H), 7.08-7.10 (m, 2H), 7.20-7.27 (m, 3H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.4, 41.7, 52.7, 54.0, 80.5, 127.2, 127.7, 128.8, 129.6, 136.3, 147.1, 155.1, 162.0, 173.5; IR (film) 2979, 2931, 1718, 756 cm^{-1}; ESI-HRMS calcd for $C_{18}H_{22}N_2NaO_4S$ ($[M + Na]^+$) 385.1192, found 385.1214. The *ee* value was determined to be 96%. [Determined by HPLC with a Chiralpak IA-H column (90:10 hexane: isopropanol, 1

mL/ min, 254 nm, 20 °C); t (minor) = 11.7 min, t (major) = 13.9 min]. $[\alpha]_D^{20}$ -16.2 (*c* 1, $CHCl_3$). The absolute configuration was assigned as (S) by analogy.

(2R,2'R)-Diallyl-3,3'-disulfanediylbis(2-azidopropanoate) (3c)

A solution of tetrabutylammonium bromide (2.58 g, 8.0 mmol) and allyl bromide (1.93 g, 16.0 mmol) in DCM (50 mL) was added to a solution of pre-prepared crude acid (2*R*,2'*R*)-3,3'-disulfanediylbis(2-azidopropanic acid)[7a] and $NaHCO_3$ (1.3 g, 16.0 mmol) in H_2O (35 mL) at 0 °C. The suspension was stirred vigorously at room temperature overnight, then H_2O (60 mL) was added. The reaction mixture was extracted with DCM (40 mL × 3) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by FC (silica gel, Hexanes/EtOAc 3:1) yielded 1.01 g (72% from L-Cys) of compound **3c** as yellow oil; $[\alpha]_D^{20}$ -112.6 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 2.98 (dd, *J* = 8.0 Hz, *J* = 14.0 Hz, 2H), 3.19 (dd, *J* = 8.0 Hz, *J* = 14.0 Hz, 2H), 4.24 (dd, *J* = 5.6 Hz, *J* = 8.0 Hz, 2H), 4.69 (d, *J* = 6.0 Hz, 4H), 5.28 (dd, *J* = 1.2 Hz, *J* = 10.8 Hz, 2H), 5.36 (dd, *J* = 1.2 Hz, *J* = 15.2 Hz, 2H), 5.87-5.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 39.9, 61.0, 66.8, 119.6, 130.9, 168.4; IR (film) 2924, 2115, 1743 cm^{-1}; ESI-HRMS calcd for $C_{12}H_{16}N_6NaO_4S_2$ ($[M + Na]^+$) 395.0572, found 395.0561.

***Boc-D-Phe-Thz-OMe* (1b)**[4d]

Yield (66%). White solid, m.p. 99-100 °C; $[\alpha]_D^{20}$ +16.3 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.39 (s, 9H), 3.22-3.38 (m, 2H), 3.96 (s, 3H), 5.27 (s, br, 2H), 7.08-7.10 (m, 2H), 7.22-7.28 (m, 3H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 28.4, 41.7, 52.7, 54.0, 80.5, 127.2, 127.7, 128.8, 129.6, 136.3, 147.1, 155.1, 162.0, 173.5; IR (film) 2979, 2931, 1718, 756 cm^{-1}; ESI-HRMS calcd for $C_{18}H_{22}N_2NaO_4S$ ($[M + Na]^+$) 385.1192, found 385.1205. The *ee* value was determined to be 94%. [Determined by HPLC with a Chiralpak IA-H column (90:10 hexane: isopropanol, 1 mL/ min, 254 nm, 20 °C); t (major) = 11.6 min, t (minor) = 14.0 min]. The absolute configuration was assigned as (*R*) by analogy.

***Cbz-L-Phe-Thz-OMe* (1c)**[4e]

Yield (70%). Colorless gum; $[\alpha]_D^{20}$ -19.1 (*c* 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.34 (d, *J* = 6.4 Hz, 2H), 3.97 (s, 3H), 5.08 (s, 2H), 5.36 (dt, *J* = 6.4 Hz, *J* = 14.4 Hz, 1H), 5.53 (d, *J* = 7.6 Hz, 1H), 7.06-7.08 (m, 2H), 7.20-7.25 (m, 4H), 7.28-7.37 (m,

4H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 41.3, 52.3, 54.2, 66.9, 126.9, 127.4, 127.8, 128.0, 128.3, 128.5, 129.2, 135.6, 135.8, 146.7, 155.3, 161.6, 172.2; IR (film) 2968, 2925, 1716, 752 cm^{-1}; ESI-HRMS calcd for $C_{21}H_{20}N_2NaO_4S$ ([M + Na]$^+$) 419.1041, found 419.1073. The ee value was determined to be 97%. [Determined by HPLC with a Chiralpak IA-H column (90:10 hexane: isopropanol, 1 mL/ min, 254 nm, 20 ºC); t (major) = 27.0 min, t (minor) = 30.0 min]. The absolute configuration was assigned as (S) by analogy.

***Boc-Gly-Thz-OMe* (1d)**[4d]

Yield (71%). White solid, m.p. 111-113 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 3.94 (s, 3H), 4.64 (d, J = 6.0 Hz, 2H), 5.33 (s, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.2, 42.3, 52.4, 80.4, 128.0, 146.4, 155.5, 161.6, 170.0; IR (film) 2979, 2931, 1717, 756 cm^{-1}; ESI-HRMS calcd for $C_{11}H_{16}N_2NaO_4S$ ([M + Na]$^+$) 295.0723, found 295.0727.

Boc-L-Ala-Thz-OMe (1e)[4e]

Yield (65%). White solid, m.p. 86-89 ºC; $[\alpha]_D^{20}$ -36.4 (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.61 (d, J = 6.4 Hz, 3H), 3.93 (s, 3H), 5.03-5.14 (m, 1H), 5.20 (s, br, 1H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.7, 28.3, 48.9, 52.4, 80.3, 127.4, 146.8, 154.8, 161.8, 175.1; IR (film) 2979, 1715, 758 cm^{-1}; ESI-HRMS calcd for $C_{12}H_{18}N_2NaO_4S$ ([M + Na]$^+$) 309.0885, found 309.0883. The ee value was determined to be 98%. [Determined by HPLC with a Chiralpak IA-H column (95:5 hexane: isopropanol, 1 mL/ min, 254 nm, 20 ºC); t (major) = 27.2 min, t (minor) = 30.4 min]. The absolute configuration was assigned as (*S*) by analogy.

***Boc-L-Val-Thz-OMe* (1f)**[4d]

Yield (66%). White solid, m.p. 116-118 ºC; $[\alpha]_D^{20}$ -16.3 (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 1.43 (s, 9H), 2.40-2.45 (m, 1H), 3.93 (s, 3H), 4.88 (dd, J = 6.0 Hz, J = 8.0 Hz, 1H), 5.28 (d, J = 8.0 Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.2, 19.4, 28.3, 33.3, 52.5, 58.0, 80.2, 127.1, 146.9, 155.5, 161.8, 173.5; IR (film) 2967, 1716, 757 cm^{-1}; ESI-HRMS calcd for $C_{14}H_{22}N_2NaO_4S$ ([M + Na]$^+$) 337.1192, found 337.1214. The *ee* value was determined to be 99%. [Determined by HPLC with a Chiralpak IA-H column (96:4 hexane: isopropanol, 0.5 mL/ min, 254 nm, 20 ºC); t (minor) = 26.7 min, t (major) = 28.6 min]. The absolute configuration was assigned as (*S*) by analogy.

***Boc-L-Ile-Thz-OMe* (1g)**[4d]

Yield (67%). Colorless oil; $[\alpha]_D^{20}$ -18.2 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.87-0.93 (m, 6H), 1.10-1.17 (m, 1H), 1.43 (s, 9H), 2.08-2.26 (m, 1H), 3.93 (s, 3H), 4.92 (s, 1H), 5.31 (d, *J* = 7.2 Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.4, 15.7, 24.4, 28.2, 39.6, 52.4, 57.4, 80.1, 127.0, 146.8, 155.3, 161.8, 173.2; IR (film) 2967, 2932, 1717, 759 cm^{-1}; ESI-HRMS calcd for $C_{15}H_{24}N_2NaO_4S$ ($[M + Na]^+$) 351.1349, found 351.1365. The *ee* value was determined by ^1H NMR chiral shift.

Boc-D-*allo*-Ile-Thz-OMe (1h)[20a]

Yield (64%). White solid, m.p. 101-103 °C; $[\alpha]_D^{20}$ +14.1 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.81 (d, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H), 1.21-1.26 (m, 1H), 1.42 (s, 9H), 2.20-2.23 (m, 1H), 3.91 (s, 3H), 5.03 (s, 1H), 5.24 (d, *J* = 7.2 Hz, 1H), 8.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.4, 13.7, 26.4, 28.2, 39.5, 52.3, 57.5, 80.2, 127.0, 146.9, 155.4, 161.7, 174.5; IR (film) 2968, 2934, 1717, 758 cm^{-1}; ESI-HRMS calcd for $C_{15}H_{24}N_2NaO_4S$ ($[M + Na]^+$) 351.1349, found 351.1375. The *ee* value was determined by ^1H NMR chiral shift.

***Boc-D-Trp-Thz-OMe* (1i)**

Yield (81%). Yellow solid, m.p. 109-111 °C; $[\alpha]_D^{20}$ +33.5 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.27 (s, 9H), 3.44 (dd, *J* = 4.0 Hz, *J* = 13.2 Hz, 1H), 3.54 (d, *J* = 13.2 Hz, 1H), 3.97 (s, 3H), 5.38 (s, br, 2H), 6.88 (d, *J* = 0.8 Hz, 1H), 7.07 (dd, *J* = 7.6 Hz, *J* = 7.6 Hz, 1H), 7.17 (dd, *J* = 7.6 Hz, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 8.02 (s, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.9, 30.9, 52.1, 53.1, 79.9, 109.7, 110.8, 118.3, 119.4, 121.9, 122.9, 127.2, 135.7, 146.4, 154.7, 161.6, 173.9; IR (film) 2924, 2855, 1715, 741 cm^{-1}; ESI-HRMS calcd for $C_{20}H_{23}N_3NaO_4S$ ($[M + Na]^+$) 424.1307, found 424.1321. The *ee* value was determined to be 95%. [Determined by HPLC with a Chiralpak IA-H column (96:6.7:3.3 hexane: alcohol: dichloromethane, 1.0 mL/ min, 254 nm, 20 °C); t (major) = 17.7 min, t (minor) = 19.9 min]. The absolute configuration was assigned as (*R*) by analogy.

***Boc-L-Glu(OtBu)-Thz-OMe* (1j)**

Yield (62%). White solid, m.p. 135-136 °C; $[\alpha]_D^{20}$ -22.8 (*c* 0.3 $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.43 (s, 18H), 2.11-2.20 (m, 1H), 2.32-2.42 (m, 3H), 3.92 (s, 3H),

4.95-5.02 (m, 1H), 5.56 (d, J = 7.2 Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.7, 27.9, 29.9, 31.6, 52.1, 52.7, 79.9, 80.6, 127.1, 146.7, 154.9, 161.4, 172.2, 173.8; IR (film) 2979, 1721, 1697, 750 cm^{-1}; ESI-HRMS calcd for $C_{18}H_{28}N_2NaO_6S$ ([M + Na]$^+$) 423.1566, found 423.1527. The *ee* value was determined to be 97%. [Determined by HPLC with a Chiralpak IA-H column (95:5 hexane: isopropanol, 1.0 mL/ min, 254 nm, 20 ºC); t (minor) = 22.3 min, t (major) = 26.0 min]. The absolute configuration was assigned as (*S*) by analogy.

N-Cbz-N'-Boc-L-Lys-Thz-OMe **(1k)**

Yield (65%). Colorless gum; $[\alpha]_D^{20}$ -25.8 (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38 (s, 9H), 1.39-1.48 (m, 4H), 1.86-1.91 (m, 1H), 2.00-2.02 (m, 1H), 3.06 (t, J = 5.6 Hz, 2H), 3.91 (s, 3H), 4.65 (s, br, 1H), 5.01-5.05 (m, 1H), 5.09 (s, 2H), 5.90 (d, J = 2.4 Hz, 2H), 7.32 (s, 5H), 8.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.6, 28.5, 29.8, 35.0, 39.7, 52.6, 53.6, 67.3, 79.3, 127.5, 128.3, 128.6, 136.2, 147.0, 156.1, 156.4, 161.9, 173.9; IR (film) 2949, 1716, 751 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{31}N_3NaO_6S$ ([M + Na]$^+$) 500.1831, found 500.1789. The *ee* value was determined to be 96%. [Determined by HPLC with a Chiralpak IA-H column (92:8 hexane: isopropanol, 1.0 mL/ min, 254 nm, 20 ºC); t (major) = 45.5 min, t (minor) = 51.7 min]. The absolute configuration was assigned as (*S*) by analogy.

Boc-L-Pro-Thz-OMe (1l)[20b]

Yield (63%). Pale yellow solid, m.p. 69-71 ºC; $[\alpha]_D^{20}$ -34.7 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) (multiple rotamers) δ: 1.29&1.46 (s, 9H), 1.85-1.93 (m, 2H), 2.20-2.36 (m, 2H), 3.40-3.60 (m, 2H), 3.93 (s, 3H), 5.15-5.24 (m, 1H), 8.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (multiple rotamers) δ: 23.0&23.8, 28.1&28.3, 32.9&34.2, 46.6&47.0, 52.3, 59.1&59.5, 80.4, 126.9&127.2, 146.7, 154.1&154.6, 161.8, 176.1&177.1; IR (film) 2976, 1739, 1698, 765 cm^{-1}; ESI-HRMS calcd for $C_{14}H_{20}N_2NaO_4S$ ([M + Na]$^+$) 335.1036, found 335.1052. The *ee* value was determined to be 99%. [Determined by HPLC with a Chiralpak IA-H column (92:6.4:1.6 hexane: isopropanol: dichloromethane, 0.4 mL/ min, 254 nm, 20 ºC); t (major) = 29.3 min, t (minor) = 31.6 min]. The absolute configuration was assigned as (*S*) by analogy.

Boc-L-Thr(Bzl)-Thz-OMe **(1m)**

Yield (63%). Colorless gum; $[\alpha]_D^{20}$ -34.6 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$)

δ: 1.30 (d, J = 6.4 Hz, 3H), 1.47 (s, 9H), 3.94 (s, 3H), 4.23 (d, J = 11.2 Hz, 1H), 4.33-4.37 (m, 1H), 4.47 (d, J = 11.2 Hz, 1H), 5.04 (d, J = 8.4 Hz, 1H), 5.71 (d, J = 8.4 Hz, 1H), 7.04-7.06 (m, 2H), 7.23-7.26 (m, 3H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.5, 28.4, 52.5, 57.7, 71.6, 76.3, 80.5, 127.5, 127.7, 127.8, 128.4, 137.8, 147.0, 155.8, 161.9, 174.5; IR (film) 3445, 1725, 750 cm^{-1}; ESI-HRMS calcd for $C_{20}H_{26}N_2NaO_5S$ ([M + Na]$^+$) 429.1460, found 429.1431. The *ee* value was determined to be 98%. [Determined by HPLC with a Chiralpak IA-H column (97:3 hexane: alcohol, 1.0 mL/ min, 254 nm, 20 ºC); t (major) = 18.5 min, t (minor) = 23.7 min].

***Boc-L-Phe-Thz-N(OMe)Me* (1n)**

Yield (68%). Colorless oil; $[\alpha]_D^{20}$ -12.5 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.39 (s, 9H), 3.30-3.35 (m, 2H), 3.40 (s, 3H), 3.76 (s, 3H), 5.27 (s, br, 2H), 7.07-7.09 (m, 2H), 7.20-7.26 (m, 3H), 7.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.2, 34.2, 41.4, 53.7, 61.4, 80.1, 124.8, 126.8, 129.3, 136.2, 148.4, 154.9, 162.8, 171.2; IR (film) 2978, 2932, 1712, 1640, 754 cm^{-1}; ESI-HRMS calcd for $C_{19}H_{25}N_3NaO_4S$ ([M + Na]$^+$) 414.1457, found 414.1451. The *ee* value was determined to be 93%. [Determined by HPLC with a Chiralpak IA-H column (90:10 hexane: isopropanol, 1.0 mL/ min, 254 nm, 20 ºC); t (minor) = 17.7 min, t (major) = 22.0 min]. The absolute configuration was assigned as (*S*) by analogy.

***Boc-L-Ala-Thz-N(OMe)Me* (1o)**

Yield (72%). Colorless oil; $[\alpha]_D^{20}$ -28 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.62 (d, J = 6.4 Hz, 1H), 3.42 (s, 3H), 3.79 (s, 3H), 5.11-5.16 (m, 2H), 7.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5, 28.2, 34.3, 48.6, 61.5, 80.1, 124.8, 148.3, 154.8, 162.9, 172.8; IR (film) 2978, 2933, 1712, 1642, 758 cm^{-1}; ESI-HRMS calcd for $C_{13}H_{21}N_3NaO_4S$ ([M + Na]$^+$) 338.1145, found 338.1153. The *ee* value was determined to be 95%. [Determined by HPLC with a Chiralpak IA-H column (97:3 hexane: methanol, 0.3 mL/ min, 254 nm, 20 ºC); t (major) = 84.3 min, t (minor) = 91.7 min]. The absolute configuration was assigned as (*S*) by analogy.

***Boc-L-Phe-Thz-OAllyl* (1p)**

Yield (68%). Colorless oil; $[\alpha]_D^{20}$ -16.5 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.39 (s, 9H), 3.32-3.37 (m, 2H), 4.87 (d, J = 7.0 Hz, 2H), 5.25-5.30 (m, 2H), 5.31 (dd, J = 1.6 Hz, J = 10.4 Hz, 1H), 5.42 (dd, J = 1.6 Hz, J = 17.2 Hz, 1H), 6.00-6.10 (m,

1H), 7.09-7.11 (m, 2H), 7.22-7.28 (m, 3H), 8.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.2, 41.4, 53.8, 65.9, 80.2, 118.9, 126.9, 127.4, 128.5, 129.3, 131.8, 136.1, 146.8, 154.8, 160.9, 173.0; IR (film) 2978, 2930, 1716, 756 cm^{-1}; ESI-HRMS calcd for $C_{20}H_{24}N_2NaO_4S$ ([M + Na]$^+$) 411.1349, found 411.1338. The *ee* value was determined to be 96%. [Determined by HPLC with a Chiralpak IA-H column (90:10 hexane: isopropanol, 1.0 mL/ min, 254 nm, 20 ºC); t (major) = 12.4 min, t (minor) = 14.9 min]. The absolute configuration was assigned as (*S*) by analogy.

***Boc-L-Ala-Thz-OAllyl* (1q)**

Yield (67%). Colorless oil; $[\alpha]_D^{20}$ -28.6 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.61 (d, *J* = 6.8 Hz, 3H), 4.85 (d, *J* = 5.6 Hz, 2H), 5.07-5.14 (m, 2H), 5.22 (s, br, 1H), 5.29 (dd, *J* = 1.2 Hz, *J* = 10.4 Hz, 1H), 5.40 (dd, *J* = 1.2 Hz, *J* = 10.4 Hz, 1H), 6.02 (ddt, *J* = 1.2 Hz, *J* = 10.4 Hz, *J* = 16.0 Hz, 1H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.7, 28.2, 48.8, 65.9, 80.2, 118.8, 127.4, 131.8, 146.7, 154.8, 160.9, 174.9; IR (film) 2979, 2932, 1716, 757 cm^{-1}; ESI-HRMS calcd for $C_{14}H_{20}N_2NaO_4S$ ([M + Na]$^+$) 335.1036, found 335.1037. The *ee* value was determined to be 99%. [Determined by HPLC with a Chiralpak IA-H column (90:10 hexane: isopropanol, 1.0 mL/ min, 254 nm, 20 ºC); t (minor) = 8.2 min, t (major) = 10.2 min]. The absolute configuration was assigned as (*S*) by analogy.

***Boc-D-Ala-Oxz-OMe* (15)**[10]

The compound **15** was obtained in 188 mg (66% yield, 99% *ee*) as white solid from Boc-D-Ala-L-Thr-OMe (304 mg, 1.0 mmol) following the reported procedure[10]. m.p. 69-72 ºC; $[\alpha]_D^{20}$ +46.6 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (s, 9H), 1.51 (d, *J* = 7.2 Hz, 3H), 2.60 (s, 3H), 3.89 (s, 3H), 4.86-4.95 (m, 1H), 5.19 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.9, 20.2, 28.2, 44.5, 51.9, 80.0, 127.2, 154.8, 156.4, 162.5, 162.9; IR (film) 2979, 1717, 1518 cm^{-1}; ESI-HRMS calcd for $C_{13}H_{20}N_2NaO_5$ ([M + Na]$^+$) 307.1264, found 307.1254. The *ee* value was determined to be 99%. [Determined by HPLC with a Chiralpak IA-H column (95:5 hexane: isopropanol, 1.0 mL / min, 240 nm, 20 ºC); t (major) = 9.6 min, t (minor) = 14.0 min]. The absolute configuration was assigned as (*R*) by analogy.

***Boc-D-Val-Thz-OMe* (16)**[4d]

The compound **16** was obtained in 1.18 g (63% yield, >99% *ee*) as white solid from **3a** (0.96 g, 3.0 mmol) and Boc-D-Val-OH (1.95 g, 9.0 mmol) following the typical

procedure as described above. m.p. 116-118 ºC; $[\alpha]_D^{20}$ +16.6 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.89 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 9H), 2.40-2.45 (m, 1H), 3.94 (s, 3H), 4.88 (dd, *J* = 6.0 Hz, *J* = 8.0 Hz, 1H), 5.27 (d, *J* = 8.0 Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.1, 19.3, 28.2, 33.2, 52.4, 58.0, 80.1, 127.0, 146.9, 155.3, 161.8, 173.5; IR (film) 2967, 1717, 1503, 756 cm^{-1}; ESI-HRMS calcd for $C_{14}H_{22}N_2NaO_4S$ ($[M + Na]^+$) 337.1192, found 337.1202. The *ee* was determined to be >99%. [Determined by HPLC with a Chiralpak IA-H column (96:4 hexane: isopropanol, 0.5 mL/ min, 254 nm, 20 ºC); t (major) = 26.5 min, t (minor) = 29.2 min]. The absolute configuration was assigned as (*R*) by analogy.

***Boc-D-Ala-Thz-OAllyl* (17a)**

The compound **17a** was obtained in 1.15 g (61% yield, 97% *ee*) as colorless oil from **3c** (1.12 g, 3.0 mmol), Boc-D-Ala-OH (1.70 g, 9.0 mmol) following the typical procedure as described above. $[\alpha]_D^{20}$ +28.7 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.61 (d, *J* = 6.8 Hz, 3H), 4.83 (d, *J* = 6.0 Hz, 2H), 5.07-5.14 (m, 1H), 5.23 (s, br, 1H), 5.28 (dd, *J* = 1.2 Hz, *J* = 10.4 Hz, 1H), 5.40 (dd, *J* = 1.2 Hz, *J* = 10.4 Hz, 1H), 6.02 (ddt, *J* = 1.2 Hz, *J* = 10.4 Hz, *J* = 16.0 Hz, 1H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 28.1, 48.7, 65.7, 80.0, 118.7, 127.3, 131.6, 146.5, 154.8, 160.7, 175.0; IR (film) 2980, 2935, 1717, 755 cm^{-1}; ESI-HRMS calcd for $C_{14}H_{20}N_2NaO_4S$ ($[M + Na]^+$) 335.1036, found 335.1060. The *ee* was determined to be 97%. [Determined by HPLC with a Chiralpak IA-H column (90:10 hexane: isopropanol, 1.0 mL/ min, 254 nm, 20 ºC); t (major) = 8.3 min, t (minor) = 10.3 min]. The absolute configuration was assigned as (*R*) by analogy.

***Boc-D-allo-Thr-Thz-OAllyl* (17b)**

The compound **17b** was obtained in 204 mg (60% yield, 99% *ee*) as colorless oil as colorless oil from **3c** (186 mg, 0.5 mmol), Boc-D-*allo*-Thr-OH (438 mg, 2.0 mmol) following the typical procedure as described above. $[\alpha]_D^{20}$ +22.8 (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.20 (d, *J* = 6.4 Hz, 3H), 1.39 (s, 9H), 3.73 (br, 1H), 4.19 (dq, *J* = 1.2 Hz, *J* =6.4 Hz, 1H), 4.79 (d, *J* = 6.4 Hz, 2H), 4.91 (s, 1H), 5.26 (dd, *J* = 1.2 Hz, *J* = 10.4 Hz, 1H), 5.36 (dd, *J* = 1.2 Hz, *J* = 16.4 Hz, 1H), 5.81 (d, *J* = 8.4 Hz, 1H), 5.98 (ddt, *J* = 1.2 Hz, *J* = 6.4 Hz, *J* = 10.4 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.6, 28.2, 57.1, 65.8, 69.9, 80.3, 118.8, 127.9, 131.7, 146.3, 155.3, 160.7, 170.3; IR (film) 2926, 1709, 753 cm^{-1}; ESI-HRMS calcd for $C_{15}H_{22}N_2NaO_5S$ ($[M + Na]^+$) 365.1147, found 365.1165. The 98% *ee* was determined by ^1H NMR

chiral shift.

***Boc-L-Thr-Thz-OAllyl* (17c)**

The compound **17c** was obtained in 232 mg (68% yield, 99% *ee*) as colorless oil from **3c** (186 mg, 0.5 mmol), Boc-L-Thr-OH (438 mg, 2.0 mmol) following the typical procedure as described above. This compound was used to make a clear structural determination for **17b**. $[\alpha]_D^{20}$ -59.2 (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.28 (d, J = 6.0 Hz, 3H), 1.44 (s, 9H), 3.28 (br, 1H), 4.61 (d, J = 6.0 Hz, 1H), 4.79 (d, J = 6.0 Hz, 2H), 4.89 (d, J = 8.4 Hz, 1H), 5.26 (dd, J = 1.6 Hz, J = 10.4 Hz, 1H), 5.38 (dd, J = 1.6 Hz, J = 17.2 Hz, 1H), 5.76 (d, J = 8.4 Hz, 1H), 5.99 (ddt, J = 1.6 Hz, J = 6.0 Hz, J = 10.4 Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.2, 28.2, 57.1, 65.9, 68.3, 80.2, 118.9, 127.9, 131.7, 146.3, 155.8, 160.8, 173.0; IR (film) 2979, 1712, 764 cm^{-1}; ESI-HRMS calcd for $C_{15}H_{22}N_2NaO_5S$ ($[M + Na]^+$) 365.1147, found 365.1183. The 99% *ee* was determined by ^1H NMR chiral shift.

***Boc-D-Val-Thz-D-Ala-Oxz-Me* (20)**[20c]

Thiazole fragment **16** (314 mg, 1.0 mmol) was dissolved in THF/MeOH/H_2O (2/2/1) (15 ml), and 0.5 N LiOH (5.0 ml) was slowly added to the solution at 0ºC. The reaction was stirred at 0 ºC and monitored by TLC until thiazole **16** was depleted. The solution was then diluted with water and carefully acidified with saturated aqueous $KHSO_4$ to pH 3~4. The aqueous layer was extracted with EA (30 ml × 3). The combined organic extracts were washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo to give crude carboxylic acid. The crude acid was used in the next step without further purification.

In another flask, trifluoracetic acid (3 mL) was added to a solution of **15** (284 mg, 1.0 mmol) in DCM (7 mL) at 0 ºC, and the resulting mixture was stirred at room temperature for 1 h to ensure complete removal of the Boc protecting group. After concentration in vacuo, the reaction mixture was azeotroped to dryness with toluene (2 × 20 mL), and the resulting free amine was dissolved in DCM (20 mL). A solution of above free carboxylic acid, PyBOP (780 mg, 1.5 mmol), DIPEA (258 mg, 2.0 mmol) in 20 ml DCM was added. The resulting mixture was stirred for overnight. Regular workup and purified by FC (silica gel, Hexanes/EtOAc 2:1) to yield 387 mg of compound **20** (83% yield) as colorless oil. data are consistent with a previously characterized compound[20c]. $[\alpha]_D^{25}$ +9.6 (*c* 0.5, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 1.44 (s, 9H), 1.67 (d, J = 6.8 Hz,

3H), 2.29-2.41 (m, 1H), 2.60 (s, 3H), 3.88 (s, 3H), 4.82 (dd, J = 6.0 Hz, J = 8.4 Hz, 1H), 5.24 (d, J = 8.4 Hz, 1H), 5.43 (dq, J = 6.8 Hz, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 8.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.0, 17.5, 19.4, 19.7, 28.3, 33.1, 42.8, 52.0, 57.9, 80.2, 123.4, 127.4, 149.3, 155.4, 156.6, 160.3, 162.5, 162.6, 172.7; IR (film) 3585, 2927, 1710, 750 cm^{-1}; ESI-HRMS calcd for $C_{21}H_{30}N_4NaO_6S$ ($[M + Na]^+$) 489.1784, found 489.1789.

***Boc-D-Val-Thz-D-Ala-Oxz-D-Ala-Thz-OAllyl* (22a)**

Compound **20** (107 mg, 0.23 mmol) was dissolved in THF/MeOH/H_2O (2/2/1) (10 ml), and 0.5 N LiOH (4.0 ml) was slowly added into the solution at 0ºC. The reaction was stirred at 0 ºC and monitored by TLC until compound **20** was depleted. The solution was then diluted with water and carefully acidified with saturated aqueous $KHSO_4$ to pH 3~4. The aqueous layer was extracted with EA (30 ml × 3). The combined organic extracts were washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo to give crude carboxylic acid. The crude acid was used in the next step without further purification.

In another flask, trifluoracetic acid (2 mL) was added to a solution of **17a** (94 mg, 0.30 mmol) in DCM (6 mL) at 0 ºC, and the resulting mixture was stirred at room temperature for 1 h to ensure complete removal of the Boc protecting group. After concentration in vacuo, the reaction mixture was azeotroped to dryness with toluene (2 × 10 mL), and the resulting free amine was dissolved in DCM (15 mL). A solution of above free carboxylic acid, PyBOP (260 mg, 0.5 mmol), DIPEA (129 mg, 1.0 mmol) in 5 ml DCM was added into the mixture. The resulting mixture was stirred for overnight. Regular workup and the residues purified by FC (silica gel, Hexanes/EtOAc 1:1) to yield 127 mg of compound **22a** (86% yield) as white solid. m.p. 90-91 ºC; $[\alpha]_D^{25}$ +67.3 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.43 (s, 9H), 1.65 (d, J = 6.8 Hz, 3H), 1.74 (d, J = 6.8 Hz, 3H), 2.29-2.34 (m, 1H), 2.60 (s, 3H), 4.82-4.84 (m, 2H), 4.84-4.86 (m, 1H), 5.18 (d, J = 8.4 Hz, 1H), 5.27 (dd, J = 1.2 Hz, J = 10.4 Hz, 1H), 5.36-5.43 (m, 2H), 5.53 (dq, J = 6.8 Hz, J = 13.6 Hz, 1H), 6.03 (ddt, J = 1.2 Hz, J = 5.6 Hz, J = 10.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.9, 17.7, 19.5, 19.6, 21.2, 28.5, 33.3, 43.1, 47.0, 58.2, 66.1, 80.5, 119.0, 123.7, 127.8, 128.7, 132.0, 147.0, 149.5, 154.3, 155.5, 160.5, 161.1, 161.4, 161.5, 173.3, 173.8; IR (film) 3339, 2925, 2852, 1715,

1661, 757 cm^{-1}; ESI-HRMS calcd for $C_{29}H_{38}N_6NaO_7S_2$ ($[M + Na]^+$) 669.2136, found 669.2185.

***Boc-D-Val-Thz-D-Ala-Oxz-D-allo-Thr-Thz-OAllyl* (22b)**

The compound was prepared following the typical procedure from fragment **17b** (103 mg, 0.3 mmol) and **20** (93 mg, 0.2 mmol) as described above. Compound **22b** was obtained in 108 mg (80% yield) as colorless oil; $[\alpha]_D^{25}$ +8 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.93 (d, J = 6.4 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 1.27 (d, J = 6.4 Hz, 3H), 1.42 (s, 9H), 1.62 (d, J = 6.4 Hz, 3H), 2.25-2.34 (m, 1H), 2.58 (s, 3H), 4.32-4.43 (m, 1H), 4.81 (d, J = 6.4 Hz, 2H), 4.81-4.86 (m, 1H), 5.27 (dd, J = 0.8 Hz, J = 10.4 Hz, 2H), 5.34-5.40 (m, 3H), 5.99 (ddt, J = 1.6 Hz, J = 10.8 Hz, J = 16.4 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 8.04 (s, 1H), 8.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.4, 17.2, 19.0, 19.7, 27.9, 32.7, 42.6, 54.8, 57.6, 65.6, 69.4, 79.9, 118.6, 123.2, 127.8, 128.0, 131.4, 146.0, 148.9, 153.9, 155.1, 160.0, 160.3, 160.8, 161.1, 169.0, 172.7; IR (film) 3396, 2971, 1660, 831 cm^{-1}; ESI-HRMS calcd for $C_{30}H_{40}N_6NaO_8S_2$ ($[M + Na]^+$) 699.2247, found 669.2275.

Venturamide A

$Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and PS-triphenylphosphine (151 mg, 1.59 $mmolg^{-}1$, 0.24 mmol) were added to a flask containing DCM (15 mL). After stirring for 10 min, compound **22a** (100 mg, 0.155 mmol) and $PhSiH_3$ (54 mg, 0.5 mmol) were added separately. TLC showed that the starting material disappeared in 1 h. After removing the solvent, the residue was passed through a short silica gel column and eluted with $CHCl_3$/MeOH to give the crude carboxylic acid. The crude acid dissolved in 5 ml DCM and then trifluoracetic acid (5 mL) was added into the solution at 0 ºC. The mixture was stirred at room temperature for 1 h. After concentration in vacuo, the reaction mixture was azeotroped to dryness with toluene (2 × 20 mL), and the resulting amino acid was dissolved in 50 mL DCM/DMF (2/1). The mixture of PyBOP (161 mg, 0.31 mmol), DIPEA (60 mg, 3.0 mmol) and DMAP (3.6 mg, 0.03 mmol) in 25 ml DCM/DMF (2/1) was added into the solution slowly. After the addition was complete, the resulting mixture was stirred for overnight. Regular workup and the residues purified by FC (silica gel, Hexanes/EtOAc 1:1) to yield 57 mg of Venturamide A (75% yield) as colorless glass; $[\alpha]_D^{25}$ +53.2 (*c* 1, MeOH) (lit.[16] $[\alpha]^{25}_D$ +53.4 (c 0.001, MeOH)); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.01 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 1.68 (d, J = 6.8 Hz, 3H), 1.72 (d, J = 6.8 Hz, 3H), 2.28

(dq, J = 6.8 Hz, J = 13.2 Hz, 1H), 2.68 (s, 3H), 5.27 (dq, J = 6.8 Hz, J = 13.2 Hz, 1H), 5.42 (dq, J = 6.8 Hz, J = 13.2 Hz, 1H), 5.47 (dd, J = 6.0 Hz, J = 13.2 Hz, 1H), 8.10 (s, 1H), 8.14 (s, 1H), 8.44 (d, J = 8.8 Hz, 1H), 8.60 (d, J = 6.8 Hz, 1H), 8.63 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.6, 18.5, 18.8, 20.8, 24.9, 35.5, 44.0, 47.5, 55.7, 123.2, 124.2, 128.4, 148.7, 149.2, 153.9, 159.6, 159.9, 160.5, 161.7, 168.4, 171.3; IR (film) 3396, 2930, 1672, 759 cm^{-1}; ESI-HRMS calcd for $C_{21}H_{24}N_6NaO_4S_2$ ($[M + Na]^+$) 511.1192, found 511.1196.

Venturamide B

The compound was prepared following the typical procedure from linear macrocycles precursors **22b** (80 mg, 0.118 mmol) as described above. Venturamide B was obtained in 47 mg (76 % yield) as colorless glass; $[\alpha]_D^{25}$ +51.6 (*c* 0.5, MeOH) (lit.[16] $[\alpha]^{25}{}_D$ +53.6 (c 0.0004, MeOH)); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.01 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 1.24 (d, J = 6.8 Hz, 3H), 1.69 (d, J = 6.8 Hz, 3H), 2.27 (dq, J = 6.8 Hz, J = 13.2 Hz, 1H), 2.69 (s, 3H), 4.25 (dq, J = 6.0 Hz, J = 10.0 Hz, 1H), 5.28 (dq, J = 6.8 Hz, J = 13.2 Hz, 1H), 5.47 (dd, J = 6.0 Hz, J = 11.2 Hz, 1H), 5.49 (t, J = 6.0 Hz, 1H), 8.10 (s, 1H), 8.21 (s, 1H), 8.38 (d, J = 9.2 Hz, 1H), 8.60 (d, J = 6.8 Hz, 1H), 8.65 (d, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.8, 18.1, 18.5, 18.9, 20.8, 35.5, 44.0, 55.7, 58.1, 73.0, 123.3, 125.1, 127.8, 148.9, 149.1, 154.8, 159.5, 159.9, 161.9, 162.5, 166.4, 168.4; IR (film) 3390, 2973, 1670, 769 cm^{-1}; ESI-HRMS calcd for $C_{22}H_{26}N_6NaO_5S_2$ ($[M + Na]^+$) 541.1304, found 541.1300.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Additional information for optimization of the reaction conditions. Chiral-phase HPLC analysis and ^{1}H, ^{13}C NMR spectra of **1a-1q**, **15**, **16**, **17a**, **17b**, **17c**, **22a**, **22b**, Venturamide A, Venturamide B in JEPG format (JEPG).

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