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Concise synthesis of 2,4-disubstituted thiazoles from β-azido disulfides and carboxylic acids or anhydrides: asymmetric synthesis of cystothiazole C†

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A novel and efficient method for the one-pot synthesis of 2,4-disubstituted thiazoles from carboxylic acids or anhydrides is presented. Based on this new method, the total synthesis of the bis-2,4-disubstituted bis(thiazoles) natural product cystothiazole C is also presented.

Introduction

2,4-Disubstituted thiazole is an important structural motif for many natural products, such as cystothiazoles A & C (**1–2**),[1] tristhiazole-containing cyclopeptide marthiapeptide A (**3**)[2] and thiopeptide thiocillin I.[3] 2,4-Disubstituted thiazole-containing derivatives also serve as useful building blocks in organic synthesis,[4] play significant pharmaceutical roles in medicinal chemistry, and show antitumor, antithrombotic, antimicrobial, antiviral and other biological activities.[5]

The syntheses of 2,4-disubstituted thiazoles have been extensively studied in the last few decades, and significant achievements in construction of 2,4-disubstituted thiazoles, especially for the formation of poly-2,4-substituted thiazoles, have been reported.[4d,f] Most of the current methodologies, however, suffer from one or more limitations such as low yield, multistep reactions, and the use of strong dehydrating reagents, which limit their applicability to complex substrates.[6] Developing a novel efficient one-pot procedure to prepare this heterocyclic system from easily available starting materials has remained to be of intense interest in organic chemistry and drug discovery.

Biosynthetically, 2,4-disubstituted thiazole was possibly formed from cysteine-containing peptides *via* sequential dehydration and oxidative dehydrogenation.[7] For the chemical synthesis of 2,4-disubstituted thiazoles, cysteine and cystine, or their easily available derivatives β-azido disulfides, should be ideal building blocks. Recently, our group developed a novel phosphine-promoted one-pot four-step synthesis of 2,4-disubstituted thiazoline from β-azido disulfides and carboxylic acids.[8]

As shown in Scheme 1, treatment of β-azido disulfides **6a** and carboxylic acids **7** with triphenylphosphine in the presence of EDCI and DIPEA obtained thiazolines **5** in good to excellent yields. The formation of thiazoline can be explained by the initial disulfide bond cleavage and subsequent formation of the β-azido thiolester **8**, which undergoes Staudinger reduction to form the phosphinimine (aza-ylide), followed by a ring closure through the intra-molecular aza-Wittig reaction. It is known that the thiazole is the aromatic form of thiazoline. The dehydrogenation of thiazoline can be conveniently employed for the preparation of the corresponding thiazole.[4f] These discoveries encouraged us to further explore an efficient method for making 2,4-disubstituted thiazole. The following sections describe our efforts toward the one-pot synthesis of these thiazoles from carboxylic acid or anhydrides, and the application of this protocol to the total synthesis of cystothiazole C. To the best of our knowledge, no method has been reported to prepare thiazoles directly from carboxylic acids or anhydrides in one pot.

Results and discussion

The direct oxidation of thiazoline with dehydrogenation reagents has been used extensively for the construction of thiazoles and several efficient oxidants have been suggested.[9] However, selection of oxidants and reaction conditions is crucial for the transformation due to the instability of thiazoline under some strong oxidants, such as $KMnO_4$, oxone, peracids and oxaziridines.[4f] We initially commenced our study by treating reactants β-azido disulfide ester **6a** and *n*-butyric acid

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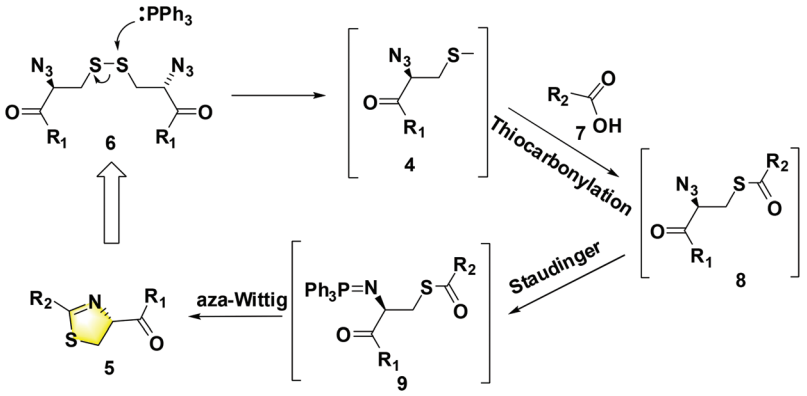
†Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra for compounds **10a–10g**, **10i–10m**, **10o**, **13**, **15a**, **15b**, **16–19** and **2**. See DOI: 10.1039/c4ob01460j



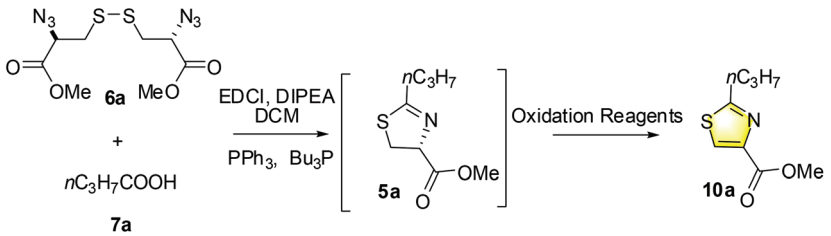
Scheme 1 Proposed mechanism for the thiazoline formation.

7a with activated manganese dioxide[9i] as the oxidation reagent in DCM.

To our surprise, activated manganese dioxide was an inappropriate reagent for this one-pot protocol and gave trace amounts of the target product (entry 1), which might be ascribed to the using of the low boiling point solvent DCM.[9h] Other dehydrogenation reagents were also investigated and are summarized in Table 1. Attempts to utilize Singh's copper salt oxidation methodology[10] in the one-pot protocol were also made, but no desired product was observed even at the elevated reaction temperature (entry 2). Gratifyingly, we found that the desired thiazole could be achieved in one pot using bromotrichloromethane ($BrCCl_3$) in combination with 1,5-diazabicyclo[5.4.0]undecane (DBU) as oxidative dehydrogenation reagent according to Williams's procedure[9c] (entries 3–8). The amount of DBU and $BrCCl_3$ was crucial to the transformation and the best result was obtained when the dosage of $BrCCl_3$/DBU was set at 8.0 eq./12.0 eq. furnishing the thiazole in good overall yield of 67% (entry 6). Several other brominating reagents, such as NBS or CBr_4, were also examined, but were found ineffective for this conversion (entries 9 and 10).

Under the optimal reaction conditions, the reaction scopes for reactions of two β-azido disulfide derivatives **6a–b** and carboxylic acids 7 bearing different substituents have been determined. As shown in Table 2, both aromatic acids and aliphatic acids could be efficiently incorporated into the thiazoles in

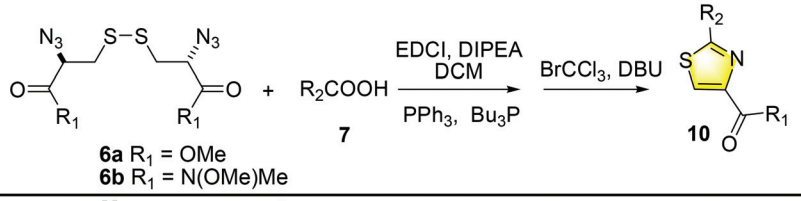
Table 1 Screening the oxidants under various conditions[a]

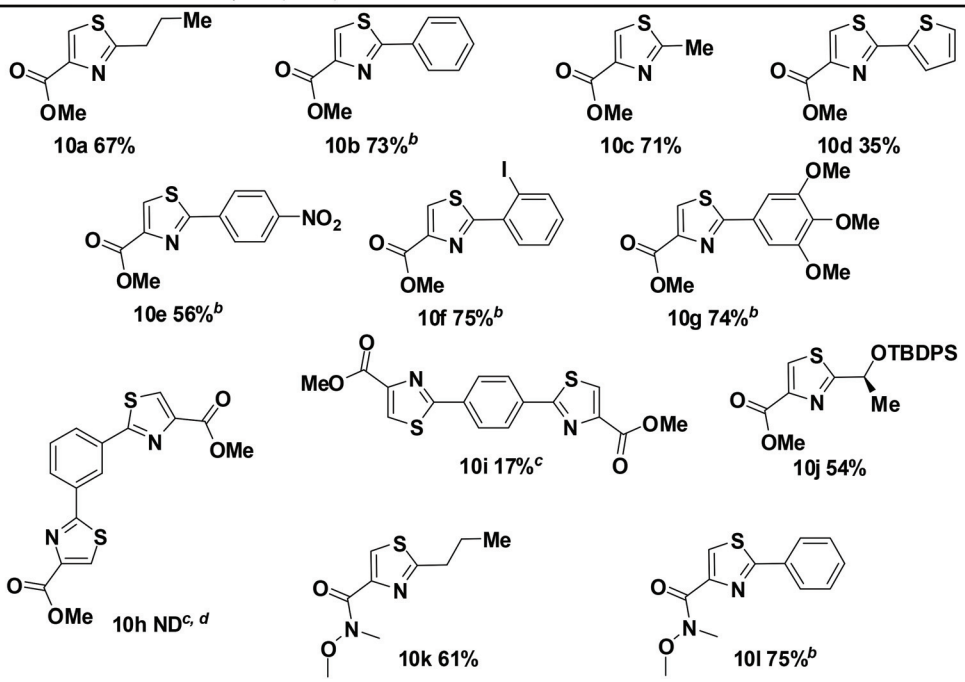


Entry	Oxidants[b]	Time	T (°C)	Yield[c] (%)
1	MnO_2	16 h	rt or reflux	<5
2	4.0 eq. $CuBr_2$/DBU/HMTA	16 h	rt or reflux	ND[d]
3	3.0 eq. $BrCCl_3$, 3.0 eq. DBU	3 h	rt	8
4	8.0 eq. $BrCCl_3$, 4.0 eq. DBU	1 h	rt	16
5	8.0 eq. $BrCCl_3$, 8.0 eq. DBU	0.5 h	rt	50
6	8.0 eq. $BrCCl_3$, 12.0 eq. DBU	0.5 h	rt	67
7	10.0 eq. $BrCCl_3$, 14.0 eq. DBU	0.5 h	rt	49
8	10.0 eq. $BrCCl_3$, 16.0 eq. DBU	0.5 h	rt	43
9	8.0 eq. NBS, 12.0 eq. DBU	24 h	rt	ND[d]
10	8.0 eq. CBr_4, 12.0 eq. DBU	24 h	rt	ND[d]
11	8.0 eq. $BrCCl_3$	24 h	rt	ND[d]
12	8.0 eq. DBU, 8.0 eq. $BrCCl_3$	5 h	reflux	15[e]
13	12.0 eq. DBU, 8.0 eq. $BrCCl_3$	5 h	reflux	40[e]
14	12.0 eq. DBU, 8.0 eq. $BrCCl_3$	48 h	rt	23[e]

[a] Unless otherwise noted, the acid (4.0 eq.), EDCI (4.0 eq.), DIPEA (8.0 eq.) in DCM were used at room temperature, 15 min later, dialkyl disulfide **6a** and nBu_3P (2.2 eq.) were added into the solution and stirred for 1 h at room temperature. PPh_3 (8.0 eq.) was then added into the mixture and refluxed for further 5 h and then oxidation reagents were added slowly into the reaction at room temperature. [b] HMTA: hexamethylenetetramine. [c] Isolated yield. [d] No desired product. [e] Using DBU instead of DIPEA as the base in the reaction.

Table 2 Thiazoles formation from carboxylic acids[a]





[a] Unless otherwise noted, the acid (4.0 eq.), EDCI (4.0 eq.), DIPEA (8.0 eq.) in DCM were used at room temperature. 15 min later, β-azido disulfide and nBu$_3$P (2.2 eq.) were added into the solution and stirred for 1 h at room temperature. PPh$_3$ (8.0 eq.) was then added into the mixture and refluxed for further 5 h and then DBU (12.0 eq.)/BrCCl$_3$ (8.0 eq.) were added slowly into the reaction mixture at room temperature. [b] 8.0 eq. DBU and 6.0 eq. BrCCl$_3$ was used. [c] 4.0 eq. EDCI, 8.0 eq. DIPEA, 1.2 eq. β-azido disulfide, 2.6 eq. nBu$_3$P and 9.6 eq. PPh$_3$ were used. [d] No desired product.

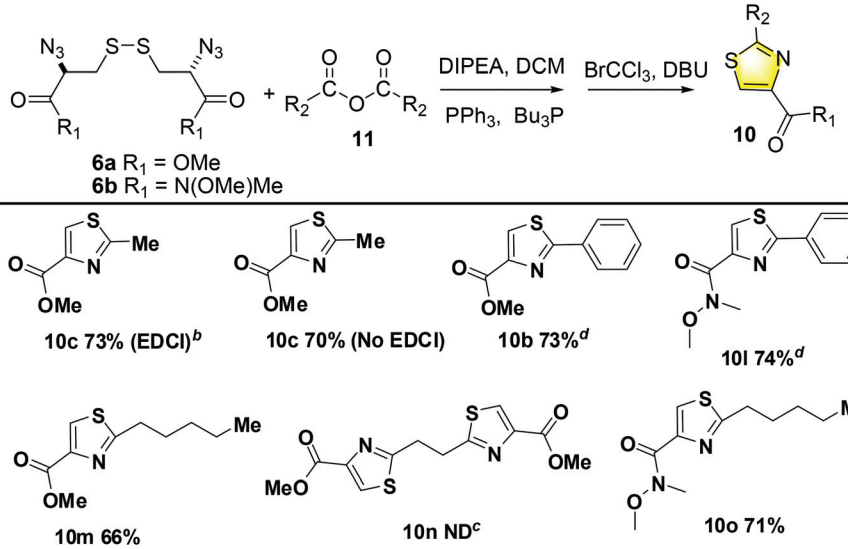
good yields. Each of the aromatic carboxylic acid substrates, containing either an electron-withdrawing or an electron-donating substituent on the aromatic ring, was converted to the corresponding thiazoles in good to excellent yields (56% to 75%). The position (*i.e.*, *p*-NO$_2$ and *o*-I) and the number (*i.e.*, 3,4,5-trimethoxy) of the substituent on the aromatic ring has little influence on the yields. Interestingly, we found that the desired bisthiazole could also be achieved in one pot using *p*-phthalic acid as the substrate albeit in 17% yield.

To test if the reaction conditions of the one-pot procedure are mild enough, the optically pure L-lactic acid derivative was used and no detectable epimerization was observed at the α-carbon of product **10j** (see ESI†). The same reaction performed with Weinreb amide **6b** also gave good yield and benzoic acid was obtained in the highest yield of 75%.

Anhydrides were also examined under these reaction conditions (Table 3). To our delight, we observed that acetic anhydride could participate in the one-pot reaction with β-azido disulfides in 73% yield. The coupling reagents EDCI was found unnecessary for the reaction when anhydrides were used as substrates. Various anhydrides and two β-azido disulfides underwent smooth conversion to produce thiazoles in excellent yields (from 66% to 74%). However, the bisthiazole could not be efficiently synthesized under current conditions.

The application of our one-pot formation of thiazole was immediately tested in a concise synthesis of bisthiazoles cystothiazole C. Cystothiazoles A and C, isolated from the myxobacterium culture broth of *Cystobacter fuscus* in 1998, possess a novel bis-2,4-disubstituted thiazole structure and a β-methoxyacrylate moiety.[1] Cystothiazole A (**1**) differs from cystothiazole C (**2**) at C5 whereby a methoxy group is present rather than the free hydroxyl group (Fig. 1). Both cystothiazoles have shown potent antifungal activity against a broad range of additional fungi such as the phytopathogenic fungus *Phytophthora capsics* (0.04 and 5 μg per disk, respectively) with no effect on bacterial growth. Their fungicidal activity appeared to be due to their ability to inhibit mitochondrial respiration by blocking electron transfer between cytochrome b and cytochrome c. Although structurally related to the known α-methoxyacrylic acid natural products myxothiazoles and melithiazoles,

Table 3 Thiazoles formation from anhydrides[a]



[a] Unless otherwise noted, β-azido disulfide, anhydride (4.0 eq.) and DIPEA (8.0 eq.) in DCM were used at room temperature. nBu$_3$P (2.2 eq.) was added into the solution and stirred for 1 h at room temperature. PPh$_3$ (8.0 eq.) was then added into the mixture and refluxed for further 5 h and then DBU (12.0 eq.)/BrCCl$_3$ (8.0 eq.) were added slowly into the reaction mixture at room temperature. [b] 4.0 eq. EDCI was used. [c] No desired product. [d] 8.0 eq. DBU and 6.0 eq. BrCCl$_3$ was used.

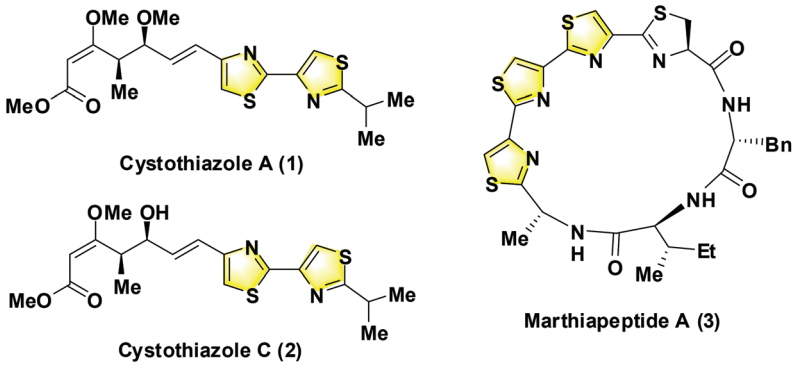
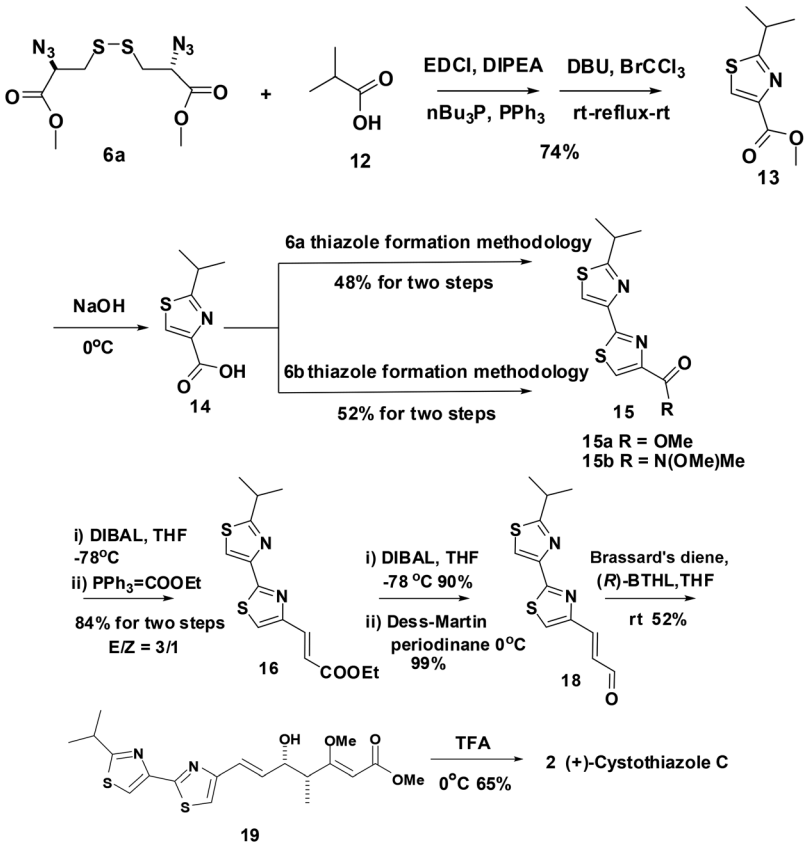


Fig. 1 The structures of cystothiazoles A (**1**) and C (**2**), marthiapeptide A (**3**).

cystothiazole A showed greater IC$_{50}$ values when examined for *in vitro* cytotoxicity using human colon carcinoma HCT-116 and human leukemia K562 cells, the resulting IC$_{50}$ values were 130 ng ml^{-1} and 110 ng ml^{-1}, respectively.[10] Owing to their novel structural scaffolds and potential biological activities, cystothiazoles A and C are remarkable synthetic targets for chemists.[11]

The synthesis of (+)-cystothiazole C (Scheme 2) began with the reaction of β-azido disulfide **6a** and isobutyric acid **12** in the presence of EDCI, DIPEA, nBu$_3$P and PPh$_3$, followed by oxidation with BrCCl$_3$/DBU gave **13** in 74% overall yield. Removal of methyl ester from compound **13** with NaOH aqueous solution in THF afforded the corresponding acid **14** in quantitative yield. Without further purification, the crude acid was treated with β-azido disulfides **6a** or **6b** in a one-pot protocol as described above, afforded the bisthiazole **15** in 48% or 52% yield over two steps, respectively. The key bisthiazole unit **15b** was achieved from commercially available isobutyric acid in 38% yield and three synthetic steps. To the best of our knowledge, this is the shortest route towards bisthiazole fragment synthesis so far.

To avoid the reductive cleavage of the thiazole ring, THF was used as the solvent in the following reduction reaction.[12] Reduction of **15b** with DIBAL-H to the corresponding aldehyde and subsequent treatment with stable Wittig ylide (ethoxycarbonylmethylene)triphenyl phosphorane at room temperature delivered an easily separable mixture of *E*/*Z* isomers (3 : 1) in 84% yield for two steps. The resulting (*E*)-α, β-unsaturated esters **16** was then treated with DIBAL-H in dry THF at −78 °C again to afford the corresponding allyl alcohol. The alcohol was oxidized with Dess–Martin periodinane to afford aldehyde **18** quantitatively.



Scheme 2 Asymmetric synthesis of (+)-cystothiazole C.

According to Qu's method,[13] the (*R*)-BTHL (LiCl assisted BINOL-Ti species) catalyzed asymmetric vinylogous Mukaiyama aldol reaction between aldehyde and the Brassard's diene[14] was a good strategy for the formation of the vicinal stereogenic centers and the β-methoxy acrylate moiety with excellent enantioselectivities. As expected, catalyzed with 20% (*R*)-BINOL/Ti(OiPr)$_4$/LiCl/H_2O complex, the aldehyde **18** reacted smoothly with the known Brassard's diene and afforded the desired β-methoxy acrylate **19** in 52% yield. Finally, treatment of **19** with trifluoroacetic acid in $CHCl_3$ furnished the thermodynamically stable *E* isomer, (+)-cystothiazole C in 67% yield. The physical data of the synthetic (+)-cystothiazole C were consistent with those of the natural product {$[\alpha]_D^{20}$ +147 ((*c* 0.2, $CHCl_3$))}(lit.[1] $[\alpha]_D^{20}$ +145 (*c* 0.2, $CHCl_3$)). Based on our process, (+)-cystothiazole A could be easily achieved by methylation of the secondary alcohol group of (+)-cystothiazole C using Meerwein's reagent.[11h]

Conclusions

In conclusion, we have developed a novel and efficient approach for the synthesis of 2,4-disubstituted thiazoles directly from carboxylic acids or anhydrides with β-azido disulfides for the first time. A variety of commonly used carboxylic acids and anhydrides were transformed into thiazoles in good yields *via* a one-pot disulfide cleavage/thiocarbonylation/intramolecular Staudinger Reduction/aza-Wittig/oxidation reaction. The utility of the method was demonstrated by an efficient total synthesis of (+)-cystothiazole C (9 steps, 7.3% overall yield from isobutyric acid and β-azido disulfides) taking advantage of the most convenient synthesis of the key bisthiazole fragment (only 3 steps from isobutyric acid in 38% yield). Further applications of this strategy to the synthesis of related polythiazole-containing natural products are currently under investigation in our laboratory.

Experimental

General

All reactions were performed under an argon atmosphere and the solvents were dried according to the established procedures ahead of use. All reagents were purchased from commercial sources. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F_{254} plates. Flash chromatography (FC) was performed using silica gel (200–300 meshes) according to the protocol of Still, Kahn, and Mitra. Visualization was accomplished with UV light or $KMnO_4$ solution. Optical rotations were recorded on a polarimeter. 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. The ee value was determined using chiral HPLC with the Chiralcel 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 ^{1}H NMR or 77.23 for proton decoupled ^{13}C NMR), and coupling constants (J) in Hz. β-Azido disulfides **6** were prepared according to our previous method.[8]

General procedure for the formation of thiazoles from carboxylic acids

To a solution of acid **7** (1.0 mmol) in CH_2Cl_2 (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (191.7 mg, 1.0 mmol) and *N*,*N*′-diisopropylethylamine (DIPEA) (258.4 mg, 2.0 mmol) at room temperature. After stirring for 15 min, **6** (0.25 mmol) was added into the solution and then Bu_3P (111.3 mg, 0.55 mmol) was added slowly into the mixture away from light. The reaction mixture was stirred at room temperature for another 1 h. PPh_3 (524.6 mg, 2.0 mmol) was added into the solution and heated to reflux for further 5 h. The solution was cooled to room temperature, and 1,8-diazabicycloundec-7-ene (DBU) (456.6 mg, 3.0 mmol) was added. Bromotrichloromethane (396.5 mg, 2.0 mmol) was then introduced *via* a syringe over 3 min. The resulting mixture was stirred further for 30 min at room temperature. The solvent was quenched with saturated NH_4Cl solution, and then extracted with EtOAc (20 ml × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by FC to give compound **10**.

General procedure for the formation of thiazoles from anhydrides

β-Azido disulfide **6** (0.25 mmol) was dissolved in CH_2Cl_2 (5 ml). Then acetic anhydride **11** (1.0 mmol) and *N*,*N*′-diisopropylethylamine (DIPEA) (258.5 mg, 2.0 mmol) were added into the solution at room temperature. After stirring for 5 min, nBu$_3$P (111.3 mg, 0.55 mmol) was added slowly into the mixture away from light. The reaction mixture was stirred at room temperature for another 0.5 h. PPh_3 (524.6 mg, 2.0 mmol) was added into the solution and heated to reflux for further 5 h. The solution was cooled to room temperature, and the DBU (456.6 mg, 3.0 mmol) was added. Bromotrichloromethane (396.5 mg, 2.0 mmol) was then introduced into the solution *via* a syringe over 3 min. The resulting mixture was stirred further for 30 min at room temperature. The reaction was quenched with saturated NH_4Cl solution, and then extracted with EtOAc (20 ml × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by FC to give compound **10**.

Methyl 2-propylthiazole-4-carboxylate (10a). The title compound was prepared according to the typical procedure, as described above in 67% yield as colorless oil; ^{1}H NMR (400 MHz) δ: 1.02 (t, J = 7.2 Hz, 3H), 1.80–1.87 (m, 2H), 3.04 (t, J = 7.2 Hz, 2H), 3.95 (s, 3H), 8.09 (s, 1H); ^{13}C NMR (100 MHz) δ: 13.6, 23.5, 35.5, 52.4, 127.1, 146.3, 162.0, 172.4; ESI-HRMS calcd for $C_8H_{11}NNaO_2S$ ($[M + Na]^+$) 208.0403, found 208.0381.

Methyl 2-phenylthiazole-4-carboxylate (10b). The title compound was prepared according to the typical procedure, as described above in 73% yield as a pale yellow solid; data are consistent with a previously characterized compound.[15] m.p. 71–72 °C; ^{1}H NMR (400 MHz) δ: 3.97 (s, 3H), 7.43–7.46 (m, 3H), 7.98–8.00 (m, 2H), 8.16 (s, 1H); ^{13}C NMR (100 MHz) δ: 52.5, 127.0, 127.3, 129.0, 130.8, 132.7, 147.7, 161.9, 169.0; ESI-HRMS calcd for $C_{11}H_9NNaO_2S$ ($[M + Na]^+$) 242.0246, found 242.0224.

Methyl 2-methylthiazole-4-carboxylate (10c). The title compound was prepared according to the typical procedure, as described above in 71% yield as a white solid; data are consistent with a previously characterized compound.[9d] m.p. 54–55 °C; ^{1}H NMR (400 MHz) δ: 2.77 (s, 3H), 3.94 (s, 3H), 8.05 (s, 1H); ^{13}C NMR (100 MHz) δ: 19.3, 52.4, 127.4, 146.5, 161.8, 166.9; ESI-HRMS calcd for $C_6H_7NNaO_2S$ ($[M + Na]^+$) 180.0090, found 180.0078.

Methyl 2-(thiophen-2-yl)thiazole-4-carboxylate (10d). The title compound was prepared according to the typical procedure, as described above in 35% yield as a yellow solid; m.p. 109–110 °C; ^{1}H NMR (400 MHz) δ: 3.96 (s, 3H), 7.08–7.11 (m, 1H), 7.45 (dd, J = 0.8 Hz, J = 5.2 Hz, 1H), 7.59 (dd, J = 0.8 Hz, J = 3.6 Hz, 1H), 8.10 (s, 1H); ^{13}C NMR (100 MHz) δ: 52.5, 126.6, 127.7, 127.9, 128.8, 136.2, 147.3, 161.7, 162.5; ESI-HRMS calcd for $C_9H_7NNaO_2S_2$ ($[M + Na]^+$) 247.9810, found 247.9843.

Methyl 2-(4-nitrophenyl)thiazole-4-carboxylate (10e). The title compound was prepared according to the typical procedure, as described above in 56% yield as a yellow solid; data are consistent with a previously characterized compound.[9g] m. p. 210–214 °C; ^{1}H NMR (400 MHz) δ: 4.00 (s, 3H), 8.18–8.21 (m, 2H), 8.30–8.32 (m, 3H); ^{13}C NMR (100 MHz) δ: 52.7, 124.4, 127.7, 128.8, 138.1, 148.6, 149.0, 161.5, 165.9; EI-HRMS calcd for $C_{11}H_8N_2O_4S$ ($[M]^+$) 264.0205, found 264.0209.

Methyl 2-(2-iodophenyl)thiazole-4-carboxylate (10f). The title compound was prepared according to the typical procedure, as described above in 75% yield as a white solid; m.p. 63–64 °C; ^{1}H NMR (400 MHz) δ: 3.96 (s, 3H), 7.11 (td, J = 1.6 Hz, J = 9.2 Hz, 1H), 7.41 (td, J = 1.2 Hz, J = 7.6 Hz, 1H), 7.71 (dd, J = 1.6 Hz, J = 7.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 8.30 (s, 1H); ^{13}C NMR (100 MHz) δ: 52.4, 96.6, 128.2, 128.8, 131.2, 131.4, 137.4, 140.3, 146.6, 161.9, 168.3; ESI-HRMS calcd for $C_{11}H_8INNaO_2S$ ($[M + Na]^+$) 367.9213, found 367.9201.

Methyl 2-(3,4,5-trimethoxyphenyl)thiazole-4-carboxylate (10g). The title compound was prepared according to the typical procedure, as described above in 74% yield as a white solid; m.p. 110–112 °C; ^{1}H NMR (400 MHz) δ: 3.86 (s, 3H), 3.91 (s, 6H), 3.93 (s, 3H), 7.17 (s, 2H), 8.12 (s, 1H); ^{13}C NMR (100 MHz) δ: 52.4, 56.4, 61.0, 104.3, 127.2, 128.2, 140.4, 147.5, 153.6, 161.8, 168.8; ESI-HRMS calcd for $C_{14}H_{15}KNO_5S$ ($[M + K]^+$) 348.0303, found 348.0309.

Dimethyl 2,2′-(1,4-phenylene)dithiazole-4-carboxylate (10i). The title compound was prepared according to the typical procedure, as described above in 17% yield as a white solid; m.p. 160–161 °C; ^{1}H NMR (400 MHz) δ: 4.00 (s, 3H), 8.11 (s, 2H),

8.23 (s, 1H); ^{13}C NMR (100 MHz) δ: 52.5, 127.5, 127.7, 134.6, 148.0, 161.8, 167.7; ESI-HRMS calcd for $C_{16}H_{12}N_2NaO_4S_2$ ($[M + Na]^+$) 383.0131, found 383.0111.

(*S*)-Methyl 2-(1-(*tert*-butyldiphenylsilyloxy)ethyl)thiazole-4-carboxylate (10j). The title compound was prepared according to the typical procedure, as described above in 54% yield as colorless oil with 99.9% ee; $[\alpha]_D^{20}$ −121.5 (*c* 2.3, $CHCl_3$); ^{1}H NMR (400 MHz) δ: 1.13 (s, 9H), 1.41 (d, J = 6.4 Hz, 3H), 3.91 (s, 3H), 5.23 (q, J = 6.4 Hz, 1H), 7.31–7.46 (m, 6H), 7.61 (d, J = 6.8 Hz, 2H), 7.71 (d, J = 6.8 Hz, 2H), 8.12 (s, 1H); ^{13}C NMR (100 MHz) δ: 19.3, 25.4, 26.9, 52.3, 70.6, 127.3, 127.7, 127.8, 129.9, 130.0, 132.5, 133.4, 135.7, 135.8, 146.5, 162.0, 178.6; Enantiomeric excess was determined by HPLC with a Chiralcel IA column (99.5/0.5 hexane–2-propanol), 0.2 ml min^{-1}; for our **10j**, t_R = 49.5 min, for its enantiomer, t_R = 46.9 min. ESI-HRMS calcd for $C_{23}H_{27}KNO_3SSi$ ($[M + K]^+$) 464.1112, found 464.1115.

***N*-Methoxy-*N*-methyl-2-propylthiazole-4-carboxamide (10k).** The title compound was prepared according to the typical procedure, as described above in 61% yield as colorless oil; ^{1}H NMR (400 MHz) δ: 1.01 (t, J = 7.6 Hz, 3H), 1.79–1.88 (m, 2H), 3.00 (t, J = 7.6 Hz, 2H), 3.43 (s, 3H), 3.77 (s, 3H), 7.88 (s, 1H); ^{13}C NMR (100 MHz) δ: 13.6, 23.2, 34.5, 35.4, 61.5, 124.2, 148.1, 163.2, 170.5; ESI-HRMS calcd for $C_9H_{14}N_2NaO_2S$ ($[M + Na]^+$) 237.0668, found 237.0596.

***N*-Methoxy-*N*-methyl-2-phenylthiazole-4-carboxamide (10l).** The title compound was prepared according to the typical procedure, as described above in 75% yield as colorless oil; data are consistent with a previously characterized compound.[16] ^{1}H NMR (400 MHz) δ: 3.49 (s, 3H), 3.88 (s, 3H), 7.44–7.45 (m, 3H), 7.96–7.98 (m, 2H), 8.01 (s, 1H); ^{13}C NMR (100 MHz) δ: 34.4, 61.7, 124.9, 126.7, 129.0, 130.4, 133.2, 149.7, 167.4; ESI-HRMS calcd for $C_{12}H_{12}N_2NaO_2S$ ($[M + Na]^+$) 271.0512, found 271.0538.

Methyl 2-pentylthiazole-4-carboxylate (10m). The title compound was prepared according to the typical procedure, as described above in 66% as colorless oil; ^{1}H NMR (400 MHz) δ: 0.87 (t, J = 7.2 Hz, 3H), 1.29–1.37 (m, 4H), 1.73–1.79 (m, 2H), 3.02 (t, J = 8.0 Hz, 2H), 3.91 (s, 3H), 8.04 (s, 1H); ^{13}C NMR (100 MHz) δ: 13.8, 22.2, 29.7, 31.1, 33.5, 52.3, 127.0, 146.2, 161.9, 172.5; ESI-HRMS calcd for $C_{10}H_{15}NNaO_2S$ ($[M + Na]^+$) 236.0715, found 236.0671.

***N*-Methoxy-*N*-methyl-2-pentylthiazole-4-carboxamide (10o).** The title compound was prepared according to the typical procedure, as described above in 71% yield as colorless oil; ^{1}H NMR (400 MHz) δ: 0.88 (t, J = 7.2 Hz, 3H), 1.33–1.38 (m, 4H), 1.75–1.83 (m, 2H), 3.00 (t, J = 7.2 Hz, 2H), 3.41 (s, 3H), 3.75 (s, 3H), 7.86 (s, 1H); ^{13}C NMR (100 MHz) δ: 13.9, 22.3, 29.5, 31.2, 33.4, 34.5, 61.4, 124.2, 148.1, 163.1, 170.7; ESI-HRMS calcd for $C_{11}H_{18}N_2NaO_2S$ ($[M + Na]^+$) 265.0981, found 265.0979.

Methyl 2-isopropylthiazole-4-carboxylate (13). To a solution of isobutyric acid **12** (2.2 g, 25.0 mmol) in CH_2Cl_2 (100 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (4.8 g, 25.0 mmol) and *N*,*N*′-diisopropylethylamine (DIPEA) (6.5 g, 50.0 mmol) at room temperature. After stirring for 15 min, **6a** (2.0 g, 6.25 mmol) was added into the solution and then Bu_3P (2.8 g, 13.7 mmol) was added slowly into the mixture away from light. The reaction mixture was stirred at room temperature for another 0.5 h. PPh_3 (13.1 g, 50.0 mmol) was added into the solution and heated to reflux for further 5 h. The solution was cooled to room temperature, and then DBU (11.4 g, 75.0 mmol) was added. Bromotrichloromethane (9.9 g, 50.0 mmol) was then introduced *via* a syringe over 10 min. After stirring at room temperature for 40 min the reaction mixture was quenched with saturated NH_4Cl solution, and then extracted with EtOAc (50 ml × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by FC (silica gel, hexanes–EtOAc 3 : 1) to give compound **13** as a white solid (1.69 g, 73%). m.p. 112–114 °C; ^{1}H NMR (400 MHz) δ: 1.41 (d, J = 6.8 Hz, 6H), 3.41 (sept, J = 6.8 Hz, 1H), 3.93 (s, 3H), 8.06 (s, 1H); ^{13}C NMR (100 MHz) δ: 23.2, 33.6, 52.4, 126.6, 146.2, 162.1, 179.1; ESI-HRMS calcd for $C_8H_{11}NNaO_2S$ ($[M + Na]^+$) 208.0403, found 208.0423.

2′-Isopropyl-*N*-methoxy-*N*-methyl-2,4′-bithiazole-4-carboxamide (15b). To a solution of **13** (500 mg, 2.7 mmol) in MeOH (15 ml) was added 1 N NaOH solution 5 ml under an ice-bath. After stirring at 0 °C for 2 h, the mixture was diluted with 15 ml H_2O and the pH adjusted to 2.0 using 1 N HCl. The resulting solution was extracted with EtOAc 5 times. The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue **14** was used for the next reaction without further purification. The acid **14** was dissolved in 35 ml CH_2Cl_2, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (517.6 mg, 2.7 mmol) and *N*,*N*′-diisopropylethylamine (DIPEA) (697.9 mg, 5.4 mmol) at room temperature. After stirring for 15 min, **6b** (529.2 mg, 1.4 mmol) was added into the solution and then Bu_3P (622.2 mg, 3.1 mmol) was added slowly into the mixture away from light. The reaction mixture was stirred at room temperature for another 1 h. PPh_3 (2.94 g, 11.3 mmol) was added into the solution and heated to reflux for further 5 h. The solution was cooled to room temperature, and then DBU (2.56 g, 16.8 mmol) was added. Bromotrichloromethane (2.24 g, 11.3 mmol) was then introduced *via* a syringe over 10 min. After stirring at room temperature for further 40 min the reaction mixture was quenched with saturated NH_4Cl solution, and then extracted with EtOAc (20 ml × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by FC (silica gel, hexanes–EtOAc 1 : 1) to give compound **15b** as colorless oil (417.4 mg, 52% for two steps). ^{1}H NMR (400 MHz) δ: 1.44 (d, J = 7.2 Hz, 6H), 3.37 (sept, J = 7.2 Hz, 1H), 3.46 (s, 3H), 3.82 (s, 3H), 7.89 (s, 1H), 8.00 (s, 1H); ^{13}C NMR (100 MHz) δ: 23.1, 33.3, 34.3, 61.5, 115.4, 125.1, 148.2, 149.2, 162.3, 163.1, 178.8; ESI-HRMS calcd for $C_{12}H_{15}N_3NaO_2S_2$ ($[M + Na]^+$) 320.0498, found 320.0534.

Methyl 2′-isopropyl-2,4′-bithiazole-4-carboxylate (15a). Following the procedure described above, starting from methyl 2-isopropylthiazole-4-carboxylate **13** (100.0 mg, 0.54 mmol) and β-azido disulfide ester **6a** (89.6 mg, 0.28 mmol), we obtained the title product **15a** as a white solid (70.2 mg, 48% for two steps). m.p. 98–99 °C; ^{1}H NMR (400 MHz) δ: 1.44

(d, J = 6.8 Hz, 6H), 3.36 (sept, J = 6.8 Hz, 1H), 3.98 (s, 3H), 8.02 (s, 1H), 8.18 (s, 1H); ^{13}C NMR (100 MHz) δ: 23.1, 33.3, 52.5, 116.2, 127.9, 147.5, 147.7, 162.0, 163.9, 178.7; ESI-HRMS calcd for $C_{11}H_{12}KN_2O_2S_2$ ($[M + K]^+$) 306.9972, found 306.9967.

(*E*)-Ethyl 3-(2′-isopropyl-2,4′-bithiazol-4-yl)acrylate (16). To a solution of **15b** (100 mg, 0.34 mmol) in dry THF (15 ml) at −78 °C was added diisobutylaluminum hydride (1.0 M in hexanes, 1.68 ml, 1.68 mmol)) dropwise. The mixture was stirred at −78 °C for 1 h. The reaction was quenched with 20% aqueous sodium-potassium tartrate (15 ml) and diluted with EtOAc (15 ml). After being warmed to room temperature, the solution was stirred vigorously for 1 h. The organic phase was separated, and the aqueous phase was re-extracted with EtOAc 3 times. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was used for the next step without further purification. The crude product was dissolved in dry CH_2Cl_2 (15 ml) and stirred at room temperature and then ethyl (triphenylphosphoranylidene)acetate (586.3 mg, 1.68 mmol) in dry CH_2Cl_2 (10 ml) was slowly added into the mixture. The resulting mixture was stirred for 1 h. Then the solvent was removed by reduced pressure. The crude product was estimated to be comprised of a 3 : 1 ratio of *E*/*Z* olefin isomers by ^{1}H NMR signal interpretation and was purified by flash silica gel chromatography (hexanes–EtOAc 10 : 1) to give *E* isomer **16** as colorless oil (65.7 mg, 63% for two steps). ^{1}H NMR (400 MHz) δ: 1.34 (t, J = 7.2 Hz, 3H), 1.44 (d, J = 7.2 Hz, 6H), 3.37 (sept, J = 7.2 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 6.82 (d, J = 15.6 Hz, 1H), 7.42 (s, 1H), 7.62 (d, J = 15.6 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (100 MHz) δ: 14.3, 23.1, 33.4, 60.5, 115.6, 120.8, 121.8, 136.3, 148.3, 152.5, 163.6, 167.2, 178.9; ESI-HRMS calcd for $C_{14}H_{16}N_2NaO_2S_2$ ($[M + Na]^+$) 331.0545, found 331.0561.

(*E*)-3-(2-(2-Isopropylthiazol-4-yl)thiazol-4-yl)acrylaldehyde (18). To a solution of **16** (50 mg, 0.162 mmol) in dry THF (10 ml) at −78 °C was added diisobutylaluminum hydride (1.0 M in hexanes, 0.81 ml, 0.81 mmol) dropwise. The mixture was stirred at −78 °C for 1 h. The reaction mixture was quenched with aqueous 20% sodium-potassium tartrate (10 ml) and diluted with EtOAc (10 ml). After warming to room temperature, the solution was stirred vigorously for 1 h. The phases were separated, and the aqueous phase was re-extracted with EtOAc 3 times. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The reaction solvent was removed by reduced pressure. The crude yellow mixture was purified by flash silica gel chromatography (hexanes–EtOAc 3 : 1) to give the title alcohol **17** as colorless oil (38.9 mg, 90%). Data are consistent with a previously characterized compound.[3] ^{1}H NMR (400 MHz) δ: 1.44 (d, J = 7.2 Hz, 6H), 3.37 (sept, J = 7.2 Hz, 1H), 4.37 (dd, J = 1.2 Hz, J = 5.2 Hz, 2H), 6.67 (d, J = 15.6 Hz, 1H), 6.79 (dt, J = 5.2 Hz, J = 15.6 Hz, 1H), 7.09 (s, 1H), 7.87 (s, 1H); ^{13}C NMR (100 MHz) δ: 23.1, 33.3, 63.2, 115.0, 115.5, 123.5, 131.8, 148.6, 154.2, 162.9, 178.7; ESI-HRMS calcd for $C_{12}H_{14}N_2NaOS_2$ ($[M + Na]^+$) 289.0440, found 289.0438; To a solution of the alcohol (40 mg, 0.15 mmol) in dry CH_2Cl_2 (7 ml) was added $NaHCO_3$ (20 mg) and the mixture was stirred at room temperature. Dess–Martin periodinane (319 mg, 0.75 mmol) was added into the solution at 0 °C. After stirring at room temperature for 0.5 h, saturated aqueous $NaHCO_3$ was added. The aqueous phase was extracted with EtOAc 3 times. Combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The reaction solution was removed by reduced pressure. The crude yellow mixture was purified by flash silica gel chromatography (hexanes–EtOAc 5 : 1) to give the title aldehyde **18** as a white solid (39.3 mg, 99%). Data are consistent with a previously characterized compound.[11a] ^{1}H NMR (400 MHz) δ: 1.45 (d, J = 6.8 Hz, 6H), 3.37 (sept, J = 6.8 Hz, 1H), 7.02 (dd, J = 7.6 Hz, J = 15.6 Hz, 1H), 7.45 (d, J = 15.6 Hz, 1H), 7.58 (s, 1H), 7.92 (s, 1H), 9.74 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz) δ: 23.1, 33.4, 116.0, 123.4, 130.5, 143.6, 148.0, 152.2, 164.0, 179.0, 193.6; EI-HRMS calcd for $C_{12}H_{12}N_2OS_2$ ($[M]^+$) 264.0391, found 264.0396.

(2*Z*,4*S*,5*R*,6*E*)-Methyl 5-hydroxy-7-(2′-isopropyl-2,4′-bithiazol-4-yl)-3-methoxy-4-methylhepta-2,6-dienoate (19). Under a N_2 atmosphere in a dry bottle, a mixture of $Ti(OiPr)_4$ (56.8 mg, 0.2 mmol) and (*R*)-BINOL (57.3 mg, 0.2 mmol) was stirred in THF (16 ml) at room temperature for 20 min. Then to the mixture was added H_2O (3.6 mg, 0.2 mmol). After another 20 min, anhydrous LiCl (8.6 mg, 0.2 mmol) kept in a Schlenk tube was quickly added bottle to bottle under a N_2 atmosphere. After the mixture was stirred for 30 min, 4.8 ml of the catalyst solution was transferred to another bottle and the aldehyde **18** (80 mg, 0.3 mmol) and Brassard's diene (324.5 mg 1.5 mmol) were added successively into the solution. After stirring for 36 h at room temperature, the reaction solution was cooled to 0 °C and quenched with 5 drops of 1 N HCl. After an additional 3 min, the mixture was neutralized with saturated $NaHCO_3$. The aqueous phase was extracted with EtOAc 3 times. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The reaction solution was removed by reduced pressure. The crude mixture was purified by flash silica gel chromatography (hexanes–EtOAc 2 : 1) to give the product **19** as colorless oil (64.2 mg, 52%). $[\alpha]_D^{20}$ +120 (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz) δ: 1.18 (d, J = 7.2 Hz, 3H), 1.44 (d, J = 6.8 Hz, 6H), 2.54–2.60 (m, 1H), 3.37 (sept, J = 6.8 Hz, 1H), 3.67 (s, 3H), 3.97 (s, 3H), 4.50 (dd, J = 4.4 Hz, J = 4.4 Hz, 1H), 5.14 (s, 1H), 6.61–6.71 (m, 2H), 7.09 (s, 1H), 7.89 (s, 1H); ^{13}C NMR (100 MHz) δ: 12.5, 23.2, 33.4, 40.5, 51.1, 55.7, 74.8, 91.5, 115.0, 115.1, 123.4, 132.8, 148.7, 154.5, 162.6, 168.7, 176.9, 178.6; ESI-HRMS calcd for $C_{19}H_{24}N_2NaO_4S_2$ ($[M + Na]^+$) 431.1075, found 431.1085.

(+)-Cystothiazole C (2). To a solution of aldol product **19** (30 mg, 0.07 mmol) in 2 ml chloroform was added one drop of CF_3COOH in ice bath. The reaction mixture was stirred in ice bath for 0.5 h and then the solvent was neutralized with saturated $NaHCO_3$. The mixture was extracted with EtOAc 3 times. Combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The reaction solution was removed by reduced pressure. The crude mixture was purified by flash silica gel chromatography (hexanes–EtOAc 2 : 1) to give the (+)-cystothiazole C as colorless oil (19.5 mg, 65%); data are consistent with a previously characterized compound.[1] $[\alpha]_D^{20}$ +147 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz) δ: 1.18 (d, J =

7.2 Hz, 3H), 1.44 (d, J = 6.8 Hz, 6H), 2.92 (br, 1H), 3.37 (sept, J = 6.8 Hz, 1H), 3.66 (s, 3H), 3.70 (s, 3H), 4.17 (dq, J = 4.4 Hz, J = 6.8 Hz, 1H), 4.52 (dd, J = 4.4 Hz, J = 4.4 Hz, 1H), 5.09 (s, 1H), 6.61 (dd, J = 4.8 Hz, J = 16.0 Hz, 1H), 6.71 (d, J = 16.0 Hz, 1H), 7.06 (s, 1H), 7.86 (s, 1H); ^{13}C NMR (100 MHz) δ: 12.4, 23.1, 33.3, 40.4, 51.1, 55.7, 74.8, 91.5, 114.9, 115.1, 123.4, 132.7, 148.7, 154.5, 162.6, 168.7, 176.9, 178.6; ESI-HRMS calcd for $C_{19}H_{24}N_2NaO_4S_2$ ($[M + Na]^+$) 431.1075, found 431.1080.

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