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One-Pot Synthesis of 2,4-Disubstituted Thiazoline from β-Azido Disulfide and Carboxylic Acid

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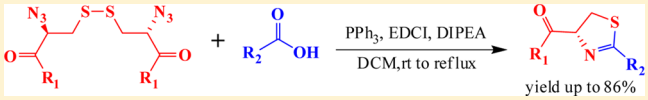
Supporting Information

ABSTRACT: A concise and efficient one-pot four-step synthesis of 2,4-disubstituted thiazoline via a cascade disulfide bond cleavage/thiocarbonylation/Staudinger reduction/aza-Wittig reaction is established. Treatment of various carboxylic acids with β-azido disulfides under this one-pot procedure obtained the desired thiazolines in good to excellent isolated yields.



Thiazoles and thiazolines are widely distributed in natural bioactive components and show a wide range of potential medicinal applications, such as antitumor, anti-HIV, antimicrobial, antiviral, and anti-inflammatory functions.[1] Thiazole is the aromatic form of thiazoline and can be obtained from direct oxidative dehydrogenation of the corresponding thiazoline. Due to their fascinating structures and promising biological activities, thiazoline/thiazole-containing natural products, such as largazole (**1**),[2] hoiamides (**2**),[3] and cystothiazoles (**3**),[4] have long been attractive targets in medicinal chemistry (Figure 1). Recently, the polyketide natural products thuggacins A (**4**) were isolated from the myxobacterium *Sorangium cellulosum* by Jansen et al.[5] The thuggacins show strong antibiotic activity against *Mycobacterium tuberculosis* strain H37RV by targeting the bacterial respiratory chain[6] and have attracted several synthetic efforts on total or partial structural synthesis.[7] Encouraged by the challenging molecular architecture and potential pharmacological activity of thuggacins, we started a project toward the total synthesis of these thiazole-containing natural compounds.

For the preparation of the C1−C12 fragment of thuggacin A (**4**), a facile synthesis of 2,4-disubstituted thiazoline moiety from readily available starting materials is needed. Various methods for the synthesis of 2,4-disubstituted thiazoline have been reported.[1,8−11] The general methods for construction of the thiazoline ring include condensation−dehydration of vicinal amino thiols with suitable carbonyl derivatives, such as carboxylic acids, esters, nitriles, iminoethers, and iminium triflates.[8] However, difficult access to vicinal amino thiols was a serious limitation of this method. In addition, due to the high reactivity and sensitivity, odoriferous amino thiols were not suitable for handling in the synthesis of complex compounds. The second method commences with more widely available amino alcohols and necessitates a multistep sequence of reactions (acylation/thionation/cyclization). In addition, conversion of oxazolines to thiazolines was also reported,[1,8] and the reaction could be carried out in one step by direct sulfurization of oxazoline with P_2S_5 in moderate yield[9] or multiple steps through oxazoline ring opening by Wipf's method.[10] Forsyth and others reported a novel thiazoline formation approach based on the intramolecular Staudinger reduction/aza-Wittig reaction of vicinal azido thiolesters in the presence of triphenylphosphine.[11] In this process, triphenylphosphine reduced azide to form the phosphinimine (aza-ylide) that reacted with the vicinal thioester carbonyl to give the desired thiazoline. The efficiency of this approach was also demonstrated in their total synthesis of apratoxins.[11b,c] It is worth noting that, in their work, vicinal azido thiolester also needed multiple steps to be prepared from carboxylic acid and β-azido thiol. Although various methodologies have been developed, the formation of the thiazoline is still limited with respect to yield and scope, especially with acid-sensitive or racemization-prone substrates.[12] The development of new synthetic methods for the efficient preparation of heterocycles containing thiazoline and/or thiazole ring is therefore an interesting challenge. Herein, we report a four-step one-pot process by using β-azido disulfides and carboxylic acid as substrate that leads to improved access to a wide range of thiazoline in good to excellent yields.

Our initial studies were focused on examining the feasibility of coupling between dialkyl β-azido disulfide and aliphatic acid since azido disulfides were much easier to prepare and handle than amino thiols and amino alcohols. Dialkyl β-azido disulfide derivatives were easily obtained from L-cystine in two steps or 2-methyl cysteine on a multigram scale through copper(II)-catalyzed diazo transfer method and the introduction of suitable functional groups.[13]

On the basis of phosphine-promoted transformation of diaryl disulfide to thiolester,[14−16] we envisaged that phosphine could

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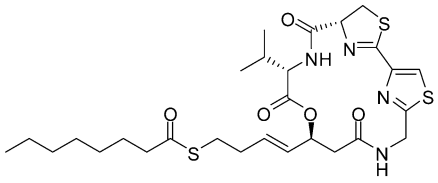
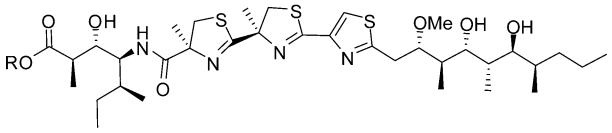
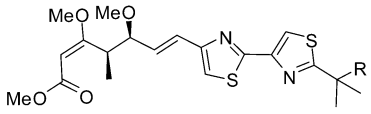


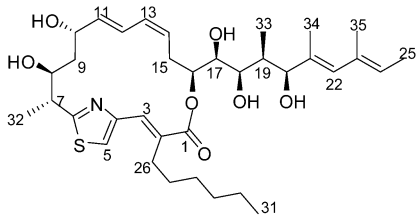
Largazole (**1**)



Hoiamide C (**2a**, R = C_2H_5); Hoiamide D (**2b**, R= H);



Cystothiazole A (**3a**, R = H); Cystothiazole B (**3b**, R= OH);



Thuggacin A (**4**)

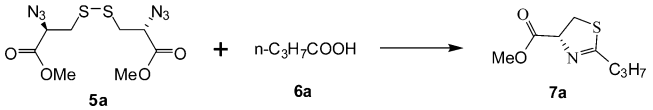
Figure 1. Structures of largazole (**1**), hoiamides (**2**), cystothiazoles (**3**), and thuggacins A (**4**).

trigger sequential disulfide cleavage/thiocarbonylation/intramolecular Staudinger reduction/aza-Wittig reactions to form thiazoline from azido disulfides and carboxylic acid in one pot. We began our investigation by treating β-azido disulfide ester with *n*-butyric acid under Forsyth's thiocarbonylation condition and obtained only recovered starting materials (Table 1, entry 2).[11a] Several conditions, such as activated carboxylic acid with *p*-toluenesulfonyl chloride[17] or Mitsunobu conditions,[18] were also investigated, and no desired product was observed (entries 3 and 4). However, we found that desired thiazoline could be achieved in the presence of DCC and DMAP albeit in 20% yield (entry 5).[19] After an extensive screening, we were pleased to find that both EDCI and DCC could generate good yields of thiazoline formation in one pot. So we set EDCI/DIPEA as the coupling reagents for the further study.

The role of each component in the reaction was examined. Control experiments indicated that the reaction did not occur without Ph_3P and EDCI. In the absence of DIPEA, the reaction also proceeds with modest yield (58%), implying that this protocol could be potentially applicable to the synthesis of thiazolines with base-sensitive functional groups.[12]

We also found that the temperature was important for this transformation (entries 6−10). Lower yields and longer reaction times were found using lower temperatures (entry 8). However, increasing the temperature presumably accelerates the rate-limiting step by formation of phosphinimine intermediate (aza-ylide), dramatically reducing the reaction time with an acceptable reaction yield (53%).

Table 1. Screening the Coupling Reagents under Various Conditions[a]



5a **6a** **7a**

entry	reagent sources and solvent[b]	PPh_3 (equiv)	*T* (°C)	time (h)	yield (%)[c]
1	DCM	8.0	rt or reflux[e]	6	ND[d]
2	DPPA (3.0 equiv), Et_3N (4.0 equiv), DMF	8.0	0 °C or rt	12	ND[d]
3	TsCl (3.0 equiv), *N*-methimidizole (8.0 equiv), DMF	8.0	rt	24	ND[d]
4	DEAD (4.0 equiv), THF	8.0	rt−reflux[e]	12	trace
5	DCC (4.0 equiv), DMAP (0.1 equiv), DCM	8.0	rt	48	20
6	DCC (4.0 equiv), HOBt (4.0 equiv), DMF	8.0	rt	6	<5
7	DCC (3.0 equiv), DMAP (0.1 equiv), DCM	8.0	rt−reflux[e]	6	47[f]
8	EDCI (2.4 equiv), DIPEA (4.0 equiv), DCM	8.0	rt	72	46[f]
9	EDCI (2.4 equiv), DIPEA (4.0 equiv), DCM	8.0	rt−reflux[e]	6	50[f]
10	EDCI (2.4 equiv), DIPEA (4.0 equiv), DCM	8.0	rt−reflux[e]	6	53[f]

[a]Unless otherwise noted, butyric acid was 3.0 equiv to the dialkyl disulfide. The coupling reagents and butyric acid were introduced into the solvent and stirred for 0.5 h at rt, and then PPh_3 was added into the mixture. [b]DEAD, azodicarboxylic acid diethyl ester; DPPA, phosphoric acid diphenyl ester azide; HOBt, 1-hydroxybenzotriazole; DIPEA, *N*,*N*-diisopropylethylamine; EDCI, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; [c]Isolated yield. [d]No desired product. [e]The reaction was heated to reflux after PPh_3 was added. [f]No racemization was observed.

The amount of PPh_3 was crucial to the yield, and the acceptable PPh_3 loading was thus determined to be 6.0−12.0 equiv (67−71%). The same reaction in the presence of more activated *n*-Bu_3P (0.5−8.0 equiv) led only to unidentified decomposition products. Interestingly, we observed a dramatic improvement (up to 15%) when Bu_3P was used as an additive. The loading of *n*-Bu_3P with less than 1.0 equiv did not increase the yield significantly, whereas the yield was obviously enhanced by adding more than 2.0 equiv of *n*-Bu_3P. However, further increase of *n*-Bu_3P sharply decreased the yield. Under the optimized conditions, treatment of β-azido disulfides and carboxylic acid in DCM with 8 equiv of Ph_3P and 2.2 equiv of Bu_3P furnished the desired product in excellent yield (86%). In order to avoid the tedious work in product purification, commercially available polymer-supported triphenylphosphine (8.0 equiv, loading 3 mmol/g) was applied to the same reaction. It was found that the desired thiazoline **7a** could be generated in 54% yield without adding *n*-Bu_3P or in 67% yield in the presence of *n*-Bu_3P (2.2 equiv) under the optimized reaction conditions.

The solvent had a great effect on the reaction in view of the yield. All of the chlorinated solvents gave excellent results, and dichloromethane (DCM) was recommended. The same reaction performed in DMSO or Et_2O did not give satisfactory results. All solvents were used directly without pretreatment because there was no increase observed in the yield when anhydrous solvent was employed. As noted in Table 1,

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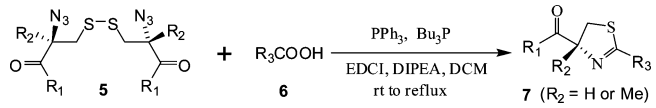
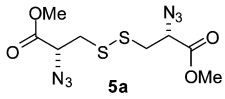
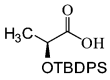
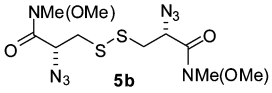
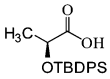
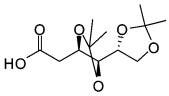
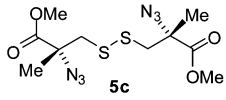
Table 2. Thiazoline Formation from Dialkyl Disulfides and Carboxylic Acids[a]



entry	Dialkyl Disulfides (**5a-c**)	Acid	product	yield (%)[b]
1	 **5a**	*n*-C_3H_7COOH	**7a**	86
2	**5a**	PhCOOH	**7b** [21]	71
3	**5a**	CF_3COOH	**7c**	< 5
4	**5a**	CH_3COOH	**7d** [22]	73
5	**5a**	1-Pyrenebutyric acid	**7e**	69
6	**5a**	HCOOH	**7f** [23]	42
7	**5a**		**7g**	51 [c]
8	 **5b**	*n*-C_3H_7COOH	**7h**	83 [c]
9	**5b**	PhCOOH	**7i** [24]	78
10	**5b**		**7j**	53 [c]
11	**5b**		**7k**	57 [c]
12	 **5c**	PhCOOH	**7l** [25]	49 [c]

[a]Unless otherwise noted, the acid (4.0 equiv), EDCI (4.0 equiv), and DIPEA (8.0 equiv) in DCM were used at room temperature; 15 min later, dialkyl disulfide and *n*-Bu3P (2.2 equiv) was added into the solution and stirred for 1 h at room temperature, then PPh_3 (8.0 equiv) was added into the mixture and refluxed for a further 5 h. [b]Isolated yield. [c]No epimerization was observed.

increasing the temperature dramatically shortens the reaction time. The optimal temperature was found where Bu_3P reacted with dialkyl disulfide in DCM at room temperature and then PPh_3 was added into the solution and refluxed for a further 5 h.

With the optimized reaction conditions in hand, we investigated the scope and limitations of the reaction by treating various carboxylic acids with *β*-azido disulfide derivatives. Under the optimized reaction conditions, both aliphatic and aromatic carboxylic acid afforded good to high yield of thiazolines ranging from 42 to 86% (Table 2), and butyric acid had the highest yield at 86% (entries 1, 2, 8, and 9). The reaction with bulky steric hinder acid and formic acid also achieved moderate yield (entries 6, 7, and 10). The special 1-pyrenebutyric acid also furnished a 69% yield (entry 5). However, a strong acid, such as trifluoroacetic acid, gave only trace amounts of the target product (entry 3).

Attempts to extend this methodology to other useful substrates were also explored successfully. The same reactions performed with Weinreb amide (**5b**) and *β*-azido disulfide ester with a *tert*-butyl group[26] (**5c**) gave satisfactory results that broadened the versatility of the protocol (entries 8−12). Both the butyric acid and benzoic acid achieved excellent yields. Especially, 2-deoxy-D-glucose derivative as the substrate was also obtained with good yield (entry 11). The reaction between benzoic acid and (*S*)-2-methylcystine methyl ester derivative (**5c**) led to the 4-methylthiazoline in 49% yield (entry 12), indicating that this protocol could be applicable to the synthesis of 4-methylthiazole-containing natural products, such as hoiamide C and D. In all cases studied, the thiazoline was

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formed without any detectable epimerization at the α-carbon when optically pure carboxylic acids were used. We believe that these results clearly demonstrate the potential usage of this methodology to allow access to highly functionalized targets.

In conclusion, we have, for the first time, successfully demonstrated a facile transformation of dialkyl disulfides into thiazolines via a cascade disulfide cleavage/thiocarbonylation/intramolecular Staudinger reduction/aza-Wittig reaction. This one-pot procedure permits convenient access to the desired thiazoline products starting from suitable β-azido dialkyl disulfides and carboxylic acids in a cost-effective way. Application of this methodology to the total synthesis of thuggacin A and its analogues is currently underway and will be reported in due course.

EXPERIMENTAL SECTION

General Experimental. All solvents were dried according to the established procedures before use. All reagents were purchased from commercial corporations. Flash chromatography (FC) was performed using silica gel (200−300 meshes) according to the protocol of Still, Kahn, and Mitra.[20] All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F254 plates. Optical rotations were measured using a polarimeter with a thermally jacketed 5 cm cell at approximately 20 °C. Infrared spectra were recorded as KBr discs using a FT-IR spectrophotometer with wave numbers expressed in cm^{-1}. High-resolution mass spectrometry data (HRMS) were acquired using a Q-TOF analyzer. ^1H NMR and ^{13}C NMR were measured on 400 or 100 MHz spectrometers (NMR in $CDCl_3$ with TMS as an internal standard). Chemical shifts (δ) are given in parts per million and coupling constants (*J*) in hertz.

Synthesis of Dialkyl β-Azido Disulfides. *(2R,2′R)-Dimethyl-3,3′-disulfanediylbis(2-azidopropanoate) (**5a**):* To a mixture of NaN_3 (6.0 g, 89.95 mmol) dissolved in distilled H_2O (20 mL) with DCM (30 mL) was carefully added triflyl anhydride (3.12 mL, 18.62 mmol) with vigorous stirring at 0 °C for a further 2 h. The organic layer was separated, and the aqueous layer was extracted with DCM (2 × 15 mL). The combined organic layer was washed with saturated Na_2CO_3 and used without further purification. To a solution of (L-Cys)$_2$ (1.1 g, 4.60 mmol) and K_2CO_3 (1.9 g, 13.80 mmol) in distilled H_2O (20 mL) and CH_3OH (40 mL) was added $CuSO_4$ pentahydrate (11.5 mg, 0.046 mmol) into the solution and stirred for 5 min. The triflyl azide in DCM (60 mL, as prepared above) was added, and the mixture was stirred at ambient temperature overnight. The organic solvents were removed under reduced pressure, and the aqueous slurry was acidified to pH 2 with concentrated HCl. The aqueous layer was extracted with EtOAc (3 × 30 mL). These EtOAc extracts were combined, dried (Na_2SO_4), and evaporated to dryness to obtain a white solid as α-azido carboxylic acid with no need for further purification.[13] Crude α-azido carboxylic acid was dissolved in MeOH (20 mL), and $SOCl_2$ (1.3 mL, 18.4 mmol) was added dropwise into the solution under an ice bath. The mixture was stirred for 6 h at room temperature. The solution was removed by reduced pressure. The crude was purified by FC (silica gel, hexanes/EtOAc 4:1) to give compound **5a** as colorless oil (1.22 g, 83% for two steps): $[\alpha]_D^{20}$ −188.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz) δ 2.99 (dd, *J* = 8.0 Hz, *J* = 14.0 Hz, 1H), 3.19 (dd, *J* = 5.2 Hz, *J* = 14.0 Hz, 1H), 3.83 (s, 3H), 4.26 (dt, *J* = 5.2 Hz, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 40.0, 53.1, 61.0, 169.3; IR (film) 3005, 2955, 2117, 1744, 1436, 1250, 1209, 1009 cm^{-1}; ESI-HRMS calcd for $C_8H_{12}N_6O_4S_2$ ([M + Na]$^+$) 343.0254, found 343.0213.

*(2R,2′R)-3,3′-Disulfanediylbis(2-azido-N-methoxy-N-methylpropanamide) (**5b**):* The α-azido carboxylic acid was prepared according to the typical procedure, as described above from (L-Cys)$_2$ (1.1 g, 4.60 mmol). The α-azido carboxylic acid and *N*,*O*-dimethylhydroxylamine hydrochloride (1.76 g, 18.40 mmol) were dissolved in dry DCM (40 mL). Dicyclohexylcarbodiimide (DCC) (3.79 g, 18.40 mmol) and 4-dimethylaminopyridine (DMAP) (56 mg, 0.46 mmol) were added into the mixture at room temperature and stirred for a further 30 h. The reaction was quenched by H_2O (40 mL) and extracted with EtOAc (3 × 30 mL). Combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified by FC (silica gel, hexanes/EtOAc 3:1) to give compound **5b** as a pale yellow oil (0.97 g, 56% for two steps): $[\alpha]_D^{20}$ 40.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz) δ 2.99 (dd, *J* = 7.2 Hz, *J* =14.0 Hz, 1H), 3.19 (dd, *J* =7.2 Hz, *J* =14.0 Hz, 1H), 3.24 (s, 3H), 3.76 (s, 3H), 4.47 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz) δ 32.3, 38.3, 57.0, 62.0, 168.7; IR (film) 2974, 2941, 2113, 1668, 1424, 1258, 1177, 990 cm^{-1}; ESI-HRMS calcd for $C_{10}H_{18}N_8O_4S_2$ ([M + Na]$^+$) 401.0761, found 401.0776.

*(2R,2′R)-Dimethyl-3,3′-disulfanediylbis(2-azido-2-methylpropanoate) (**5c**):* To a stirred solution of (*R*)-2-methylcysteine hydrochloride[26a] (514 mg, 3 mmol) in 5 mL of H_2O were added NaI (4.5 mg, 0.03 mmol) and 30% H_2O_2 (0.39 mL, 3.5 mmol), and the mixture was stirred at room temperature for a further 0.5 h. After the mixture was cooled to 0 °C, Na_2SO_3 was carefully added into the solution to quench the reaction. The solution was removed by reduced pressure, and the crude β-amino disulfide ester was used for next step without further purification. The α-azido ester **5c** was prepared from the crude product according to the typical procedure, as described above for **5a**: $[\alpha]_D^{20}$ −128 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz) δ 1.59 (s, 3H), 3.12 (d, *J* = 14.0 Hz, 1H), 3.24 (d, *J* = 14.0 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz) δ 22.1, 48.9, 53.1, 66.5, 171.5; IR (film) 2955, 2115, 1742, 1245, 1175, 1103 cm^{-1}; ESI-HRMS calcd for $C_{10}H_{16}N_6O_4S_2$ ([M + Na]$^+$) 371.0546, found 371.0567.

General Procedure for the Formation of Thiazolines. *Typical Procedure for the Formation of Thiazoline **7a**.* To a solution of butyric acid (55.1 mg, 0.63 mmol) in DCM (6 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (119.8 mg, 0.63 mmol) and *N*,*N*′-diisopropylethylamine (DIPEA) (161.6 mg, 1.26 mmol) at room temperature. After stirring for 15 min, **5a** (50 mg, 0.156 mmol) was added into the solution and then Bu_3P (69.4 mg, 0.343 mmol) was added slowly into the mixture away from light. The reaction was stirred at room temperature for another 1 h. PPh_3 (327.8 mg, 1.25 mmol) was added into the solution and heated to reflux for a further 5 h. The reaction solution was removed by reduced pressure. The crude yellow mixture was purified by FC (silica gel, hexanes/EtOAc 3:1) to give compound **7a** as colorless oil (50.2 mg, 86%).

Characterization of Compounds. *(R)-Methyl-2-propyl-4,5-dihydrothiazole-4-carboxylate (**7a**):* The title compound was prepared according to the typical procedure, as described above in 86% yield as colorless oil: $[\alpha]_D^{20}$ 36.4 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz) δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.67 (q, *J* = 7.2 Hz, 2H), 2.53 (t, *J* = 8.0 Hz, 2H), 3.49 (dd, *J* = 9.6 Hz, *J* = 11.2 Hz, 1H), 3.57 (dd, *J* = 9.6 Hz, *J* = 11.2 Hz, 1H), 3.79 (s, 3H), 5.06 (t, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz) δ 13.6, 21.1, 35.4, 36.3, 52.8, 77.8, 171.4, 175.2; IR (film) 2958, 2931, 2872, 1743, 1621, 1436, 1200, 1036 cm^{-1}; ESI-HRMS calcd for $C_8H_{13}NO_2S$ ([M + Na]$^+$) 210.0559, found 210.0552.

*(R)-Methyl-2-phenyl-4,5-dihydrothiazole-4-carboxylate (**7b**):* The title compound was prepared according to the typical procedure, as described above to give compound **7b** as a white solid (49.0 mg, 71%). Data are consistent with a previously characterized compound.[21]

*(R)-Methyl-2-methyl-4,5-dihydrothiazole-4-carboxylate (**7d**):* The title compound was prepared according to the typical procedure, as described above to give compound **7d** as colorless oil (36.3 mg, 73%). Data are consistent with a previously characterized compound.[22]

*(R)-Methyl-2-(3-(pyren-1-yl)propyl)-4,5-dihydrothiazole-4-carboxylate (**7e**):* The title compound was prepared according to the typical procedure, as described above to give compound **7e** as a pale yellow oil (88.3 mg, 73%): $[\alpha]_D^{20}$ 34.0 (*c* 2.4, $CHCl_3$); ^1H NMR (400 MHz) δ 2.21−2.27 (m, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 3.40 (t, *J* = 7.2 Hz, 2H), 3.51 (dd, *J* = 8.8 Hz, *J* = 11.2 Hz, 1H), 3.63 (dd, *J* = 8.8 Hz, *J* = 11.2 Hz, 1H), 3.83 (s, 3H), 5.11 (t, *J* = 9.2 Hz, 1H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.97−8.02 (m, 3H), 8.10 (d, *J* = 8.4 Hz, 2H), 8.14−8.17 (m, 2H), 8.28 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz) δ 29.3, 32.5, 34.0, 35.4, 52.6, 77.8, 123.2, 124.5, 124.6, 124.7, 124.8, 124.9, 125.6, 126.5, 127.2, 127.3, 128.5, 129.7, 130.7, 131.2, 135.5, 171.2, 174.3; IR (film) 3039, 2949, 2867, 1742, 1620, 1435, 1339, 1201, 1179, 1108,

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1023, 845, 758, 721, 682, 620 cm^{-1}; EI-HRMS calcd for $C_{23}H_{19}NO_2S$ ($[M]^+$) 387.1293, found 387.1298.

*(R)-Methyl-4,5-dihydrothiazole-4-carboxylate (**7f**):* The title compound was prepared according to the typical procedure, as described above to give compound **7f** as colorless oil (19.1 mg, 42%). Data are consistent with a previously characterized compound.[23]

*(R)-Methyl-2-((S)-1-(tert-butyldiphenylsilyloxy)ethyl)-4,5-dihydrothiazole-4-carboxylate (**7g**):* The title compound was prepared according to the typical procedure, as described above to give compound **7g** as colorless oil (72.7 mg, 51%): $[\alpha]_D^{20}$ 10.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz) δ 1.12 (s, 9H), 1.29 (d, *J* = 6.4 Hz, 3H), 3.39−3.51 (m, 2H), 3.79 (s, 3H), 4.78 (q, *J* = 6.4 Hz, 1H), 5.08 (t, *J* = 9.2 Hz, 1H), 7.34−7.43 (m, 6H), 7.67−7.69 (m, 4H); ^{13}C NMR (100 MHz) δ 19.3, 23.4, 26.9, 33.6, 52.7, 70.4, 78.2, 127.6, 127.7, 129.8, 129.9, 132.8, 133.6, 135.8, 135.9, 171.2, 181.5; IR (film) 3070, 2953, 2932, 2892, 2857, 1745, 1622, 1428, 1173, 1110, 1026, 922, 822, 703, 612, 504 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{29}NO_3SSi$ ($[M+Na]^+$) 450.1559, found 450.1551.

*(R)-N-Methoxy-N-methyl-2-propyl-4,5-dihydrothiazole-4-carboxamide (**7h**):* The title compound was prepared according to the typical procedure, as described above to give compound **7h** as a pale yellow oil (47.4 mg, 83%): $[\alpha]_D^{20}$ 134.8 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz) δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.66 (dq, *J* = 7.2 Hz, *J* = 14.8 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 3.23 (s, 3H), 3.37 (t, *J* = 9.6 Hz, 1H), 3.61 (t, *J* = 9.6 Hz, 1H), 3.79 (s, 3H), 5.41 (t, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz) δ 13.6, 21.0, 32.4, 34.8, 36.2, 61.7, 75.4, 170.9, 173.9; IR (film) 2962, 2934, 2873, 2892, 1666, 1621, 1460, 1424, 1385, 1176, 1119, 993 cm^{-1}; ESI-HRMS calcd for $C_9H_{16}N_2O_2S$ ($[M+H]^+$) 217.1011, found 217.1010.

*(R)-N-Methoxy-N-methyl-2-phenyl-4,5-dihydrothiazole-4-carboxamide (**7i**):* The title compound was prepared according to the typical procedure, as described above to give compound **7i** as colorless oil (51.6 mg, 78%). Data are consistent with a previously characterized compound.[24]

*(R)-2-((S)-1-(tert-Butyldiphenylsilyloxy)ethyl)-N-methoxy-N-methyl-4,5-dihydrothiazole-4-carboxamide (**7j**):* The title compound was prepared according to the typical procedure, as described above to give compound **7j** as colorless oil (59.9 mg, 53%): $[\alpha]_D^{20}$ 42.5 (*c* 2.0, $CHCl_3$); ^1H NMR (400 MHz) δ 1.11 (s, 9H), 1.28 (d, *J* = 6.4 Hz, 3H), 3.25 (s, 3H), 3.33 (t, *J* = 10.0 Hz, 1H), 3.62 (t, *J* = 10.0 Hz, 1H), 3.74 (s, 3H), 4.71−4.75 (m, 1H), 5.44 (t, *J* = 6.4 Hz, 1H), 7.36−7.43 (m, 6H), 7.69−7.72 (m, 4H); ^{13}C NMR (100 MHz) δ 19.3, 23.3, 26.9, 32.4, 33.3, 61.7, 70.4, 76.1, 127.6, 127.7, 129.7, 129.8, 132.8, 133.9, 135.9, 136.0, 170.7, 180.2; IR (film) 3070, 2949, 2932, 2857, 1669, 1620, 1469, 1427, 1387, 1366, 1182, 1110, 999, 926, 822, 741, 704, 611, 504 cm^{-1}; ESI-HRMS calcd for $C_{24}H_{32}N_2O_3SSi$ ($[M+Na]^+$) 479.1801, found 479.1802.

*(R)-N-Methoxy-N-methyl-2-(((4S,4′R,5R)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)methyl)-4,5-dihydrothiazole-4-carboxamide (**7k**):* The title compound was prepared according to the typical procedure, as described above to give compound **7k** as colorless oil (58.5 mg, 57%): $[\alpha]_D^{20}$ 31.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz) δ 1.32 (s, 3H), 1.36 (s, 3H), 1.38 (s, 3H), 1.39 (s, 3H), 2.87 (dd, *J* = 8.4 Hz, *J* = 15.2 Hz, 1H), 3.02−3.06 (m, 1H), 3.25 (s, 3H), 3.41 (t, *J* = 10.0 Hz, 1H), 3.61 (t, *J* = 8.0 Hz, 1H), 3.66 (t, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.93 (dd, *J* = 4.8 Hz, *J* = 8.0 Hz, 1H), 4.02−4.07 (m, 1H), 4.11 (dd, *J* = 6.0 Hz, *J* = 8.4 Hz, 1H), 4.23 (dt, *J* = 4.8 Hz, *J* = 8.0 Hz, 1H), 5.45 (t, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz) δ 25.2, 26.7, 26.9, 27.2, 32.4, 34.9, 38.4, 61.8, 67.6, 75.1, 76.9, 77.8, 80.6, 109.7, 109.8, 170.5, 170.8; IR (film) 2984, 2932, 1667, 1620, 1458, 1437, 1374, 1213, 1156, 1068, 994, 841 cm^{-1}; ESI-HRMS calcd for $C_{17}H_{28}N_2O_6S$ ($[M+Na]^+$) 411.1566, found 411.1577.

*(R)-Methyl-4-methyl-2-phenyl-4,5-dihydrothiazole-4-carboxylate (**7l**):* The title compound was prepared according to the typical procedure, as described above to give compound **7l** as a white solid (34.0 mg, 49%). Data are consistent with a previously characterized compound.[25]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249−263. (b) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115−2134. (c) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143−1191. (d) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2011**, *28*, 196−268. (e) Houssen, W. E.; Jaspars, M. *ChemBioChem* **2010**, *11*, 1803−1815.

(2) For recent reviews, see: (a) Newkirk, T. L.; Bowers, A. A.; Williams, R. M. *Nat. Prod. Rep.* **2009**, *26*, 1293−1320. (b) Morris, J. C.; Phillips, A. J. *Nat. Prod. Rep.* **2010**, *27*, 1186−1203. (c) Hong, J.; Luesch, H. J. *Nat. Prod. Rep.* **2012**, *29*, 449−456.

(3) For recent total syntheses of hoiamides, see: (a) Wang, L.; Xu, Z. S.; Ye, T. *Org. Lett.* **2011**, *13*, 2506−2509. (b) Malloy, K. L.; Choi, H.; Fiorilla, C.; Valeriote, F. A.; Matainaho, T.; Gerwick, W. H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 683−688.

(4) For recent total syntheses of cystothiazoles, see: (a) Shao, J.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3083−3085. (b) Akita, H.; Sutou, N.; Sasaki, T.; Kato, K. *Tetrahedron* **2006**, *62*, 11592−11598. (c) Chu, Y.; Gao, B.; Yue, Q.; Wang, Y.; Wang, S. *Sci. China, Ser. B: Chem.* **2008**, *51*, 661−668.

(5) Steinmetz, H.; Irschik, H.; Kunze, B.; Reichenbach, H.; Hofle, G.; Jansen, R. *Chem.—Eur. J.* **2007**, *13*, 5822−5832.

(6) (a) Bock, M.; Muller, R.; Buntin, K.; Kirschning, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2308−2311. (b) Irschik, H.; Reichenbach, H.; Hofle, G.; Jansen, R. *J. Antibiot.* **2007**, *60*, 733−738.

(7) (a) Bock, M.; Dehn, R.; Kirschning, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9134−9137. (b) Tang, S.; Xu, Z.; Ye, T. *Tetrahedron: Asymmetry* **2009**, *20*, 2027−2032. (c) Zarate-Ruiz, G. A.; Figueiredo, R. M.; Niel, G.; Campagne, J. M. *Synlett* **2012**, *23*, 219−222.

(8) For selected reviews, see: (a) Nora De Souza, M. V. *J. Sulfur Chem.* **2005**, *26*, 429−449. (b) Gaumont, A. C.; Gulea, M.; Levillain, J. *Chem. Rev.* **2009**, *109*, 1371−1401. (c) Xu, Z. S.; Ye, T. *Heterocycles in Natural Product Synthesis: Thiazoline and Thiazole and their Derivatives*; Wiley-VCH Verlag GmbH&Co. KGaA: Weinheim, Germany, 2011, Chapter 13.

(9) Aitken, R. A.; Armstrong, D. P.; Galt, R. H. B.; Mesher, S. T. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 935−944.

(10) Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358−12367.

(11) (a) Chen, J.; Forsyth, C. J. *Org. Lett.* **2003**, *5*, 1281−1283. (b) Chen, J.; Forsyth, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 8734−8735. (c) Chen, J.; Forsyth, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12067−12072. (d) Riedrich, M.; Harkal, S.; Arndt, H. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2701−2703.

(12) (a) You, S. L.; Razavi, H.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 83−85. (b) Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908−909. (c) Fernandez, X.; Fellous, R.; Dunach, E. *Tetrahedron Lett.* **2000**, *41*, 3381−3384. (d) Muir, J. C.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2243−2250.

(13) Lundquist, J. T.; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781−783.

(14) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614–5616.
(15) (a) Overman, L. E.; O'Connor, E. M. *J. Am. Chem. Soc.* **1976**, *98*, 771–775. (b) Amos, R. A.; Fawcett, S. M. *J. Org. Chem.* **1984**, *49*, 2637–2639.
(16) (a) Brindaban, C. R.; Tanmay, M. *J. Org. Chem.* **2004**, *69*, 5793–5795. (b) Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. *Chem.—Eur. J.* **2005**, *11*, 719–727.
(17) Wakasugi, K.; Iida, A.; Misaki, T.; Nishii, Y.; Tanabe, Y. *Adv. Synth. Catal.* **2003**, *345*, 1209–1213.
(18) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935–939.
(19) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395.
(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(21) Raman, P.; Razavi, H.; Kelly, J. W. *Org. Lett.* **2000**, *2*, 3289–3292.
(22) Emtenäs, H.; Alderin, L.; Almqvist, F. *J. Org. Chem.* **2001**, *66*, 6756–5761.
(23) Emtenäs, H.; Carlsson, M; Pinkner, J. S.; Hultgren, S. J.; Almqvist, F. *Org. Biomol. Chem.* **2003**, *1*, 1308–1314.
(24) Lu, Y.; Li, C. M.; Wang, Z.; Ross, C. R.; Chen, J.; Dalton, J. T.; Li, W.; Miller, D. D. *J. Med. Chem.* **2009**, *52*, 1701–1711.
(25) Han, F. S.; Osajima, H.; Cheung, M.; Tokuyama, H.; Fukuyama, T. *Chem.—Eur. J.* **2007**, *13*, 3026–3038.
(26) (a) Pattenden, G.; Thom, S. M.; Jones, M. F. *Tetrahedron* **1993**, *49*, 2131–2138. (b) Kirihara, M.; Asai, Y.; Ogawa, S.; Noguchi, T.; Hatano, A.; Hirai, Y. *Synthesis* **2007**, *21*, 3286–3289.

dx.doi.org/10.1021/jo301030k | *J. Org. Chem.* 2012, 77, 7108–7113