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STUDIES ON SYNTHESIS OF AMINO ACID DERIVED THIAZOLES. PREPARATION OF BIS-THIAZOLES AS KEY FRAGMENTS OF AERUCYCLAMIDE ANALOGS

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Abstract:
In this work, the scope and limitations of Hantzsch, modified Hantzsch and Kelly methodologies for the synthesis of amino acid derived thiazoles are presented. In addition, the syntheses of bis-thiazoles as key fragments of natural products and analogs are described. The Kelly's methodology followed by oxidation provides the desired N-Cbz protected thiazole after purification. According with our results the Fmoc or Boc proctecting groups are not compatible with the conditions used in this methodology.
Modifications of the temperature and reagents used in the Hantzsch thiazole synthesis enabled the preparation of chiral thiazole building blocks without racemisation and in good yields.

Keywords: Thiazole, thiazoline, dipeptide, bis-thiazole

Introduction

The synthesis of 1,3-thiazoles has attracted the attention of many chemists due to their presence in a large number of natural products.[I] Most of these compounds display significant biological activities as antiparasitic, cytotoxic, antifungal, antiviral, and antibacterial. The structural diversity and the biological activity of complex natural products and analogs containing 1,3-thiazoles have ensured that new methods continue to be developed for their synthesis. Amino acid derived thiazoles are a common motif in biologically active cyclohexapeptides derived from cyanobacteria, Figure 1.[II] Aerucyclamides, cylohexapeptides isolated in 2008 by Gademann and co-workers from the toxic freshwater cyanobacterium *Microcystis aeruginosa* PCC 7806, display antitrypanosomal and antimalarial activities.[III] Our interest on the synthetic studies of natural products with antiparasitic activity,[IV] encouraged us to embark on a general program for the synthesis of aerucyclamides and analogs.[V] The successful synthesis of such natural products and analogs is dependent upon the ability to prepare amino acid derived thiazoles in high yield and enantiomeric purity.

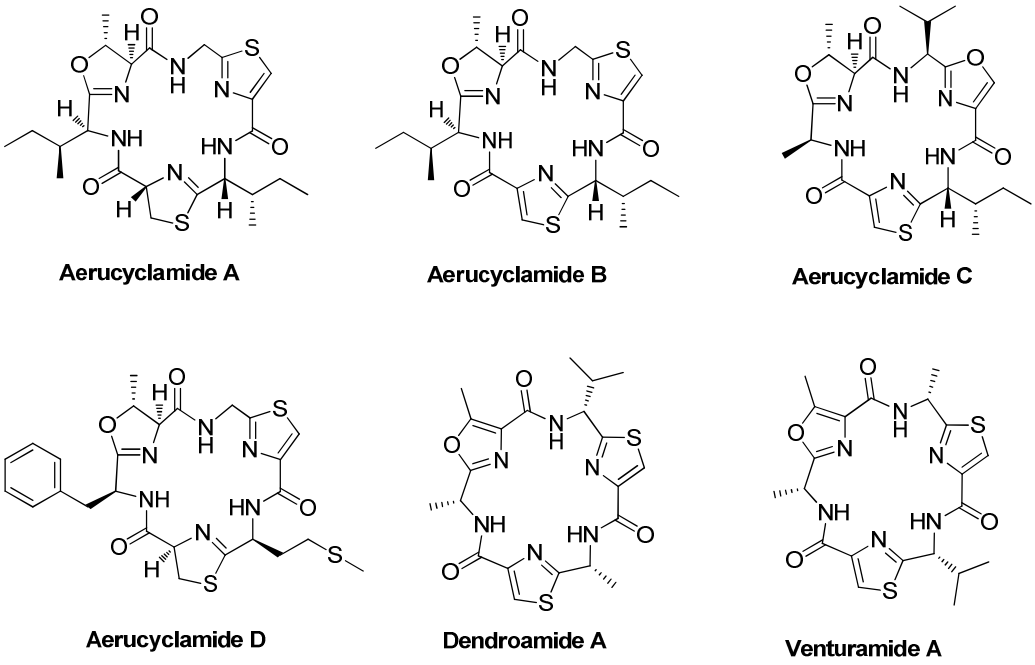
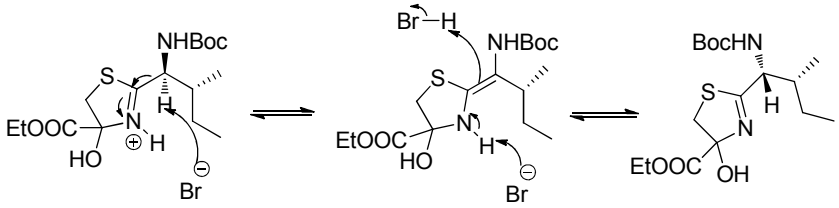


Figure 1

The most common method for the synthesis of thiazoles was developed by Hantzsch and entails the condensation of a suitably substituted α-haloketone with a thioamide in ethanol.[VI] It is known that using this reaction, epimerisation at the α-stereogenic centre occurred as a result of the formation of hydrogen bromide, Scheme 1.[VII]



Scheme 1

In 1990, Holzapfel et al. reported a modification of the Hantzsch standard reaction conditions. These authors successfully prepared amino acid derived thiazoles in high enantiomeric purity by using a lower reaction temperature and basic reaction conditions.[VIII] The hydroxythiazoline intermediate formed during the reaction is activated by the addition of reagents to facilitate the elimination to furnish the thiazole.
Further studies by Meyers et al. conducted the reaction at –40 °C to –20 °C and differed from the Holzapfel method in the isolation of hydroxythiazoline intermediate and removal of the base prior to the elimination step.[IX]

Other methodology to obtain amino acid derived thiazoles is by oxidation of thiazolines using $BrCCl_3$/DBU.[X] A variety of methods have been reported for the synthesis of thiazolines, and the cyclodehydration protocol is perhaps the most popular. In 2003, You and Kelly reported a biomimetic synthesis of thiazolines from N-acylated cysteine using bis(triphenyl) oxodiphosphonium salts.[XI]

With a number of different literature procedures available for the preparation of amino acid derived thiazoles, an investigation into the most reliable method for its synthesis was undertaken. Isoleucine, methionine and glycine-derived thiazoles of type **1**, Figure 2, are key building blocks in our synthetic route towards the preparation of aerucyclamides and analogs. In this work the scope and limitations of Hantzsch, modified Hantzsch and Kelly methodologies to obtain compounds of type **1** are presented. In adittion, the syntheses of bis-thiazoles derived from **1** are described.

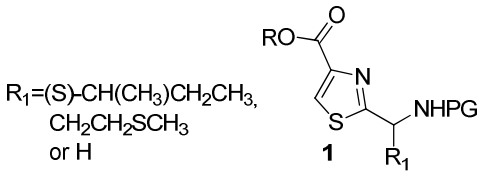
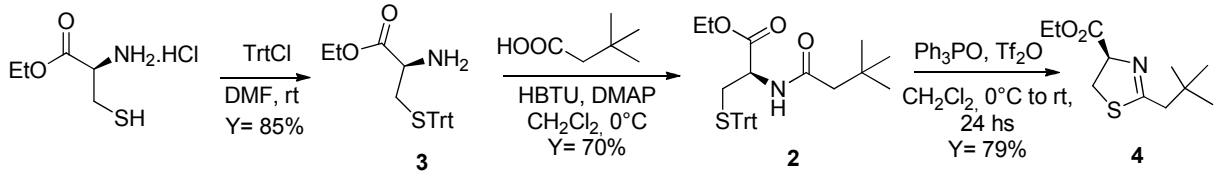


Figure 2

Results and discussion

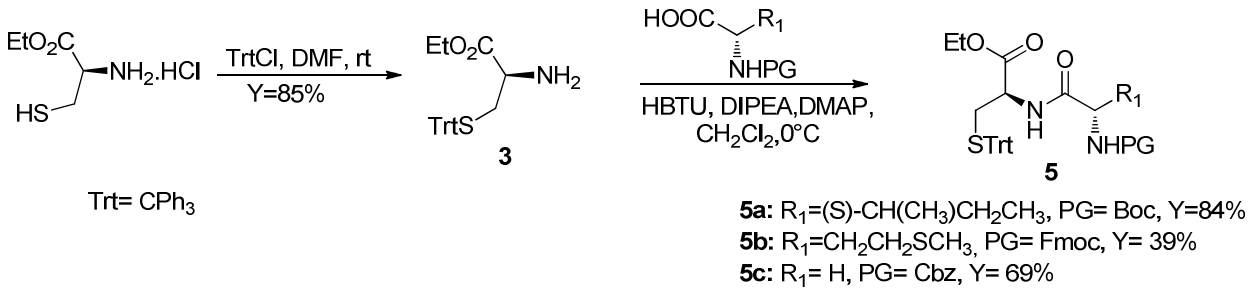
i) Cyclodehydration of cysteinamides using Kelly's methodology

In order to gain experience in Kelly's methodology and to evaluate the possible reaction time, the cysteinamide **2** was prepared from cysteine derivative (**3**) and 3,3-dimethylbutiric acid. The reagents Ph_3PO and Tf_2O in CH_2Cl_2 at 0 °C were stirred during 10 minutes and then amide **2** was added, Scheme 2. The stirring was continued at room temperature during 24 hrs, until the reaction was completed.



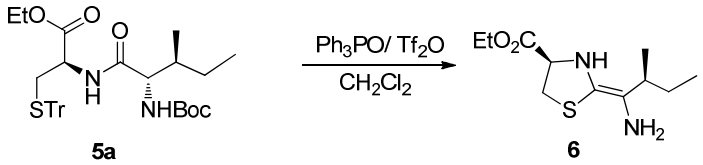
Scheme 2

Then, we decided to evaluate the stability and the influence of the protective groups of the amine presents in the precursors of compounds of type **1** in the cyclodehydration reaction. For this purpose three of the most used groups were selected: Boc, Fmoc and Cbz. The cysteinamides **5a**, **5b** and **5c** were obtained as is showed in Scheme 3. Coupling reaction of the trityl derivative of cysteine and the protected aminoacid using HBTU, allowed us to obtain the corresponding amides (**5**). The compound **5b** was prepared in moderated yield (39%) probably because the deprotection of the Fmoc group with the reactions conditions.



Scheme 3

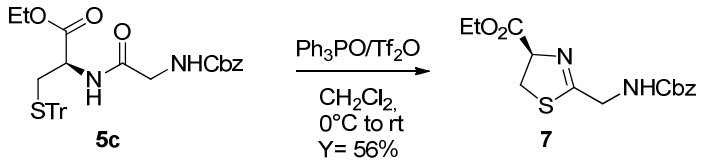
Under cyclodehydration conditions (Ph_3PO/ Tf_2O), product **5a** rendered a compound in 72% yield after purification. By the analysis of the ^{1}H-NMR spectrum, we concluded that deprotection of the NHBoc group occurred using these reaction conditions. In addition, the characteristic α proton of L-Ile residue was missed in the mentioned spectrum. The two proton signals of CH_2S at 3.95 and 3.74 ppm as dd (J_1= 11.4, J_2= 7.4 Hz and J_1= 11.4, J_2= 1.6 Hz respectively) prompted us to conclude that a heterocycle was formed. The HMBC experiment showed a correlation between the proton at δ =2.43 assignable to CH(Me)Et with two carbon signals at δ 113.2 and 119.0 ppm. These results allowed us to conclude that the isolated product is the enamine compound **6** (Scheme 4) that could be produced by deprotection of the amine group due to the acid conditions generated during the reaction.



Scheme 4

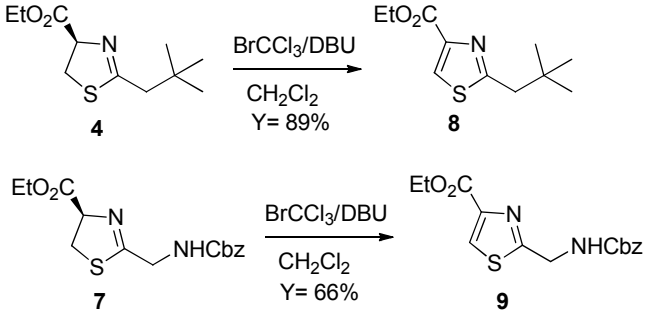
When compound **5b** was allowed to react using the same conditions, a mixture of compounds was obtained. By analysis of the spectra we concluded that none of the isolated products was the desired thiazoline. The reaction was repeated but a thiazoline could not be isolated from the reaction mixture. Probably, the Fmoc protective group was unstable under the reaction conditions.

From the amide **5c**, after several attempts to adjust the reaction time, the desired thiazoline containing the Cbz protecting group was obtained in 56% yield, Scheme 5. It is important to note that if the reagent were allowed to react for more than two hours, the thiazoline **7** decomposes.



Scheme 5

From the two obtained thiazolines, the corresponding thiazoles were obtained in very good yield using $BrCCl_3$/DBU, Scheme 6.

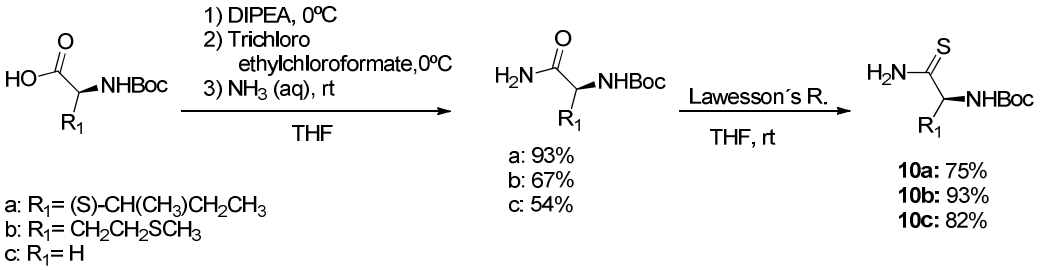


Scheme 6

It is noteworthy that the purification of the thiazolines obtained by Kelly's methodology by chromatographic column was very difficult because the polarity of these compounds is very similar to that of triphenylphosphine oxide formed during the reaction. This fact and the instability of the protecting groups in the reaction medium led us to evaluate another methodology to the synthesis of thiazoles.

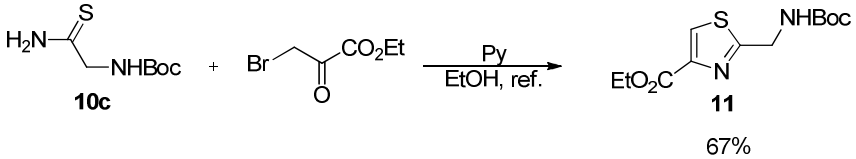
ii) Synthesis of thiazoles by Hantzsch and modified Hantzsch methodologies

In order to investigate Hantzsch methodology for the synthesis of thiazoles derived from aminoacids, the corresponding thioamides were obtained, Scheme 7. First the amides of L-Ile, L-Met and Gly were obtained using trichloroethyl chloroformate and NH_4OH at room temperature. Then, Lawesson's reagent in THF at room temperature rendered the thioamides (**10**) in very good yield.



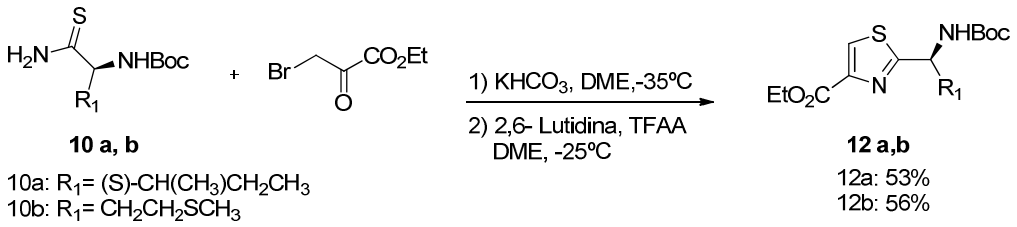
Scheme 7

Starting from **10c** and ethyl bromo piruvate, thiazole **11c** was prepared in good yield using Hantzsch classical conditions, pyridine in ethanol at reflux, Scheme 8.



Scheme 8

To avoid epimerization, for the synthesis of thiazoles derived from quiral aminoacids (**12a** and **12b**, Scheme 9), modified Hantzsch reaction was performed in two steps. For the first step we used $KHCO_3$ at – 35 °C in dimethoxyethane optimizing the reaction time (18-20 hs) for the cyclization. Then the dehydration process took place using 2,6-lutidine and trifluroacetic anhydride (TFAA) in dimethoxyethane at -25 °C. The NMR spectroscopic data of compounds **12a** allowed us to conclude that under these conditions no epimerization occurred.



10 a, b

10a: R_1= (S)-$CH(CH_3)CH_2CH_3$
10b: R_1= $CH_2CH_2SCH_3$

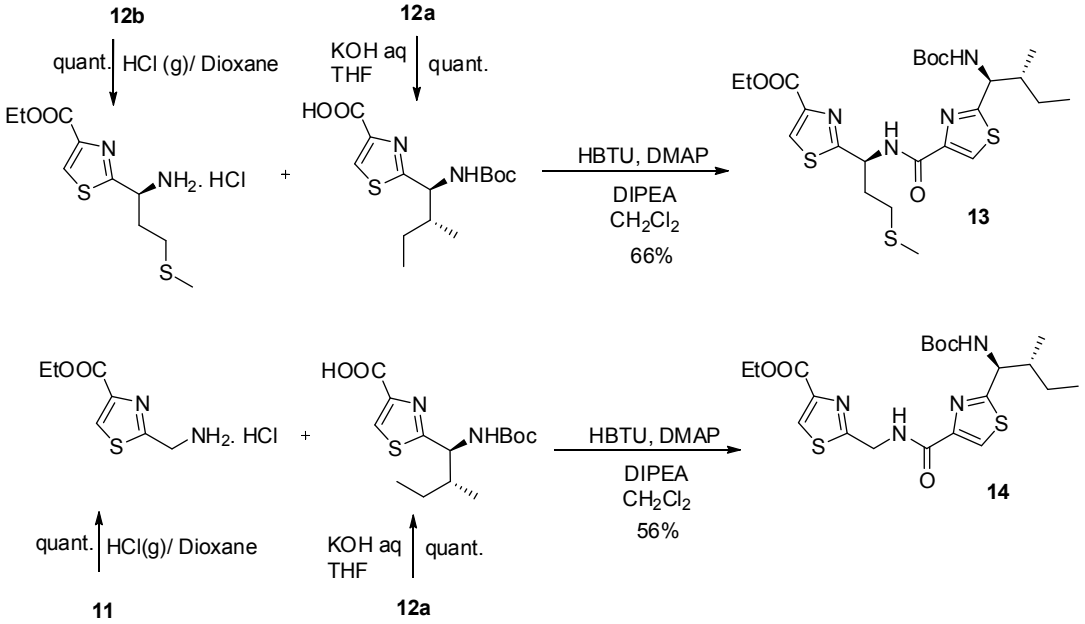
12 a,b

12a: 53%
12b: 56%

Scheme 9

iii) Preparation of Bis-thiazoles

Bis-thiazoles are structural motifs present in several natural products as Aerucyclamide B, Dendroamide A and Venturamide A, Figure 1. Bis-thiazole **13** was prepared by ethyl ester hydrolysis of **12a** followed by coupling with the N-deprotected derivative of thiazole **12b** using HBTU, Scheme 10. Following a similar procedure, bis-thiazole **14** was obtained from thiazoles **11** and **12a**.



Scheme 10

In conclusion, several conditions have been investigated for the synthesis of thiazolines and thiazoles from amino acid without racemisation. The Kelly's methodology followed by oxidation provides the desired N-Cbz protected thiazole after purification. According with our results the Fmoc or Boc proctecting groups are not compatible with the conditions used in this methodology.
Modifications of the temperature and reagents used in the Hantzsch thiazole synthesis enabled the preparation of chiral thiazole building blocks without racemisation and in good yields.
Bis-thiazoles as key fragments in the synthesis of natural products analogs were obtained in good yield.

Experimental

General methods

Optical rotation was measured using a Kruss Optronic GmbH P8000 polarimeter with a 0.5 mL cell. IR spectra were recorded on a Shimadzu FTIR 8101A spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance DPX- 400. Chemical shifts are related to TMS as an internal standard. High resolution mass spectra (HRMS) were obtained on a micro Q-TOF (ESI) (Bruker Daltonics). Flash column chromatography was carried out with Silica gel 60 (J.T. Baker, 40 μm average particle diameter). All reactions and chromatographic separations were monitored by TLC, conducted on 0.25 mm Silica gel plastic sheets (Macherey/Nagel, Polygram_ SIL G/UV 254). TLC plates were analyzed under 254 nm UV light, iodine vapor, p-hydroxybenzaldehyde spray or ninhydrine spray. Yields are reported for chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure compounds.
All solvents were purified according to literature procedures.[XII] All reactions were carried out in dry, freshly distilled solvents under anhydrous conditions unless otherwise stated.

General procedure for amide bond formation

HBTU (1.2 eq), DIPEA (2.2 eq) and 4-DMAP (0.2 eq) were added to a stirred solution of the respective amine (1.0 eq) and acid (1.0 eq.) under N_2 atmosphere in dry CH_2Cl_2 at 0 ºC. The resulting mixture was stirred at room temperature overnight. Then was filtered through celite, washed with $CHCl_3$ and evaporated *in vacuo.* The crude was redissolved in EtOAc, washed with 5% HCl and then with saturated solution of $NaHCO_3$, dried with $MgSO_4$, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography using the corresponding eluent to give the amide.

General procedure for oxidation of thiazolines

Bromotrichloromethane (4 eq.) was added dropwise to the reaction mixture, followed by DBU (4 eq.). The reaction was stirred at room temperature overnight and then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc, and the combined organic layer were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography gave the desired oxazole/thiazole.

General procedure for hydrolisis of methyl/ethyl esters.

KOH aq. (10%) was added to a solution of the ester in THF and the reaction mixture was stirred at room temperature for 1h. The pH was brought to 4 by addition of 5M HCl and then extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the acid.

General procedure for deprotection of NH-Boc compounds:
A solution of HCl (4 M) in dioxane was added to the protected amino acid and the mixture was stirred at room temperature under N_2 atmosphere for 2-4 h. The solvent was removed under reduced pressure.

(*R*)-Ethyl 2-(3,3-dimethylbutanamido)-3- (tritylthio)propanoate (2): The title compound was obtained from Cys (Trt)-OEt (360 mg, 0.9 mmol) and 3,3-dimethylbutiric acid (109 mg, 0.9 mmol following the general procedure for amide bond formation and further purification by flash chromatography. White solid (65 %).
2: Rf=0.70 (AcOEt: *n*-hexane 1:2). ^{1}H NMR (400 MHz, $CDCl_3$**)** δ (ppm)**:** 1.05 (s, 9 H); 1.28 (t, *J*=7.2 Hz, 3 H); 2.05 (d, *J*= 4.0 Hz, 2 H); 2.61 (m, 2 H); 4.17 (q, *J*=7.2 Hz, 2 H); 4.65 (m, 1 H); 5.96 (m, 1 H); 7.23 (m, 3 H); 7.30 (m, 6H); 7.42 (m, 6 H).

(*R*)-Ethyl 2-neopentyl-4,5-dihydrothiazole-4-carboxylate (4): To a solution of Ph_3PO (259 mg, 0.9 mmol) in 5 mL of CH_2Cl_2 under N_2, Tf_2O (78 µL, 0.5 mmol) was added, and the reaction mixture was stirred during 10 min. at 0ºC. Then, a solution of **2** (150 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added and the reaction was stirred at room temperature during 24 hs. After regular workup, the resulting crude product was purified by flash chromatography. Yellow oil (79%).
4: Rf=0.50 (AcOEt: *n*-hexane, 1:2). ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm)**:** 1.05 (s, 9 H); 1.32 (t, *J*=7.1 Hz, 3 H); 2.50 (s, 2 H); 3.57 (m, 2 H); 4.27 (c, *J*= 7.1 Hz, 2 H); 5.11 (t, *J*=8.7 Hz, 1H).

(*R*)-Ethyl 2-((2*S*,3*R*)-2-((tert-butoxycarbonyl)amino)-3-methylpentanamido)-3- (tritylthio) (5a): The title compound was obtained from Cys (Trt)-OEt (300 mg, 0.8 mmol) and Boc-Ile (178 mg, 0.78 mmol) following the general procedure for amide bond formation and further purification by flash chromatography. White solid (84%).
5a: Rf=0.55 (AcOEt: *n*-hexane1:2.5). ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm)**:** 0.93 (t, *J*=7.1 Hz, 3 H); 1.14 (m, 1 H); 1.28 (t, *J*=7.1 Hz, 3 H); 1.48 (m, 1 H); 1.46 (s, 9 H); 1.88 (m, 1 H); 2.65 (m, 2 H); 4.00 (m, 1 H); 4.18 (q, *J*=7.1 Hz, 2 H); 4.56 (m, 1 H); 5.07 (s, 1 H); 6.31 (s, 1 H); 7.24 (m, 3 H); 7.31 (m, 6 H); 7.61 (m, 6 H).

(*R*)-Ethyl 2-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(methylthio)butanamido)-3-(tritylthio)propanoate (5b): The title compound was obtained from Cys (Trt)-OEt (200 mg, 0.5 mmol) and Fmoc-Met (190 mg, 0.5 mmol) following the general procedure for amide bond formation and further purification by flash chromatography. White solid (39%).
5b: Rf= 0.65 ($CHCl_3$: MeOH 3: 0.2). ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm)**:** 1.26 (t, *J*=7.2 Hz, 3 H); 2.02 (m, 2 H); 2.11 (d, *J*=11.6 Hz, 1 H); 2.61 (m, 2 H); 4.20 (m, 2 H); 4.40 (m, 1 H); 4.52 (m, 1 H); 5.57 (m, 1 H); 6.49 (m, 1 H); 7.22 (m, 3 H); 7.31 (m, 6 H); 7.41 (m, 6 H); 7.60 (m, 4 H); 7.79 (m, 4 H).

(*R*)-Ethyl 2-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-(tritylthio)propanoate (5c): The title compound was obtained from Cys (Trt)-OEt (563 mg, 1.4mmol) and CBz-Gly (300 mg, 1.4

mmol) following the general procedure for amide bond formation and further purification by flash chromatography. White solid (69%).
5c: Rf= 0.55 (AcOEt: *n*-hexane 1.5:1). ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm)**:** 1.28 (t, *J*=7.1 Hz, 3 H); 2.68 (m, 2 H); 3.87 (d, *J*=5.3 Hz, 2 H); 4.19 (q, *J*=7.1 Hz, 2 H); 4.57 (m, 1 H); 5.14 (s, 2 H); 5.33 (m, 1 H); 6.26 (m, 1 H); 7.24 (m, 3 H); 7.30 (m, 8 H); 7.38 (m, 9 H).

(*E*)-Ethyl 2-(1-amino-2-methylbutylidene)thiazolidine-4-carboxylate (6): To a solution of Ph_3PO (539 mg, 2 mmol) in 5 mL of CH_2Cl_2 under N_2, Tf_2O (151 µL, 1 mmol) was added, and the reaction mixture was stirred during 10 min. at 0ºC. Then, a solution of **5a** (390 mg, 0.7 mmol) in CH_2Cl_2 (5 mL) was added and the reaction was stirred at room temperature during 24 hs. After regular workup, the resulting crude product was purified by flash chromatography. Yellow Oil (72%).
6: Rf= 0.52 (AcOEt:MeOH 3:0.3). ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm)**:** 0.89 (t, *J*=7.4 Hz, 3H); 1.17 (d, *J*=7.0 Hz, 3H); 1.30 (t, *J*=7.1 Hz, 3H); 1.53 (m, 2H); 2.43 (m, 1H); 3.95 (dd, *J* = 11.4, 7.4 Hz, 1H); 3.74 (dd, *J* = 11.4, 1.6 Hz, 1H); 4.27 (q, *J*= 7.1 Hz, 2H); 4.89 (dd, *J* = 7.4, 1.6 Hz, 1H). EIMS (20 eV)**,** *m/z* (%): 243.0 (M^+, 1.7); 157.1 ((M- $CH_3CH_2COOCH)^+$ 100.0); 86.1 ($(CH_3CH_2COOCH)^+$ 26.4); 57.0 ($C(Me)CH_2CH_3^+$, 68.6).

(*R*)-Ethyl 2-((((benzyloxy)carbonyl)amino)methyl)-4,5-dihydrothiazole-4-carboxylate (7): To a solution of Ph_3PO (467 mg, 1.7 mmol) in 5 mL of CH_2Cl_2 under N_2, Tf_2O (141 µL, 0.8 mmol) was added, and the reaction mixture was stirred during 10 min. at 0ºC. Then, a solution of **5c** (323 mg, 0.6 mmol) in CH_2Cl_2 (5 mL) was added and the reaction was stirred at room temperature during 2 hs. After regular workup, the resulting crude product was purified by flash chromatography. Yellow Oil (56%).
7: Rf= 0.47 (AcOEt: $CHCl_3$ 2:1). ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm)**:** 1.33 (t, *J*=7.2 Hz, 3H); 3.52 (dd, J = 11.5, 1.5 Hz, 1H); 3.80 (dd, *J* = 11.5, 7.7 Hz, 1H); 3.92 (d, *J*=8.9 Hz, 1H); 4.05 (d, *J*=8.9 Hz, 1H); 4.29 (m, 2H); 4.87 (dd, *J* = 7.7, 1.5 Hz, 1H) 5.54 (s, H); 6.84 (s, 1H); 7.20-7.72 (m, 5H).

Ethyl 2-(((*tert*-butoxycarbonyl)amino)methyl)thiazole-4-carboxylate (11). Ethyl bromopyruvate 0.14 mL, 1.06 mmol) and pyridine (0.13 mL, 1.59 mmol) were added to a solution of thioamide **10c** (100 mg, 0.53 mmol) in dry EtOH (2 mL) under N_2 atmosphere. The reaction mixture was refluxed 6 hs. The volatile components were removed *in vacuo*. The resulting residue was dissolved in EtOAc (40 mL), washed with water (30 mL) and brine (30 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography afforded **11**. Brown solid (67%).
11: Rf= 0.52, (EtOAc/*n*-Hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.42 (t, *J*= 7.1Hz, 3H), 1.48 (s, 9H)), 4.44 (c, *J*= 7.1, 2H), 4.67 (d, *J*= 6.2 Hz, 2H), 5.32 (m, 1H), 8.14 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.4, 28.3, 42.4, 61.5¿, 80.5, 127.9, 146.9, 155.6, 161.3, 170.0.

Ethyl 2-((1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-2-methylbutyl)thiazole-4-carboxylate (12a): $KHCO_3$ (146 mg; 4.0 mmol) was added to a solution of thioamide **10a** (326 mg; 1.3 mmol) in 5 mL of dimethoxiethane (DME) under N_2 atmosphere at room temperature, and the resulting mixture was stirred during 10 min. Then the mixture was cooled to -35ºC, ethyl bromopiruvate (780 mg, 4.0 mmol) was added and the stirring was continued during 18 h. the

reaction mixture was filtered through a pad of Celite® and the pad was washed with $CHCl_3$ (3 x 10 mL). The filtrate was concentrated *in* vacuo, DME(4 mL) was added under N_2 and the mixture was cooled at -25ºC. Then a solution of trifluoroactetic anhydride (TFAA) (0.74 mL, 5.32 mmol) and 2,6-lutidine (1.4 mL, 12 mmol) in 0.5 mL of DME was added and the mixture was stirred at -25ºC until monitoring of the reaction by TLC indicated that all the starting material had been consumed (*ca.* 5 h). Then the mixture was washed with saturated aqueous $NaHCO_3$, HCl and brine. The organic layer was dried ($MgSO_4$) filtered and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography. Yellow oil (53%).
12a: Rf=0.6 (AcOEt : *n*-hexane, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.92 (t, *J*= 7.3 Hz, 3H), 0.95 (d, *J*= 6.9 Hz, 3H), 1.16 (m, 1H), 1.46 (s, 9H), 2.19 (m, 1H), 4.43 (c, *J*=7.1 Hz, 1H), 4.95 (m, 1H), 5.35 (m, 1H), 8.09 (s, 1H). ^{13}C NMR (100 MHz, CDCl3): 11.6, 14.4, 15.8, 24.5, 28.3, 39.8, 57.5, 61.4, 80.1, 126.8, 147.4, 155.4, 161.4, 172.9. EIMS (20 eV)**,** *m/z* (%): 342.3 (M^+, 0.6); 285.2 (($M-C(CH_3)_3)^+$, 18.2); 229.1 (($M– CH_3CH_2COOCH(N)CH+ 1)^+$, 50.8); 57.0 ($C(CH_3)_3^+$, 100.0).

(*S*)-Ethyl 2-(1-((*tert*-butoxycarbonyl)amino)-3-(methylthio)propyl)thiazole-4-carboxylate 12b: $KHCO_3$ (146 mg; 4.0 mmol) was added to a solution of thioamide **10b** (326 mg; 1.3 mmol) in 5 mL of 2,2-dimethoxiethane (DME) under N_2 atmosphere at room temperature, and the resulting mixture was stirred during 10 min. Then the mixture was cooled to -35ºC, ethyl bromopiruvate (780 mg, 4.0 mmol) was added and the stirring was continued during 18 h. the reaction mixture was filtered through a pad of Celite® and the pad was washed with $CHCl_3$ (3 x 10 mL). The filtrate was concentrated *in* vacuo, DME(4 mL) was added under N_2 and the mixture was cooled at -25ºC. Then a solution of trifluoroactetic anhydride (TFAA) (0.74 mL, 5.32 mmol) and 2,6-lutidine (1.4 mL, 12 mmol) in 0.5 mL of DME was added and the mixture was stirred at -25ºC until until monitoring of the reaction by TLC indicated that all the starting material had been consumed (*ca* 1 h). Then the mixture was washed with saturated aqueous $NaHCO_3$, HCl and brine. The organic layer was dried ($MgSO_4$) filtered and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography. Yellow oil (56%)
12b: Rf= 0.62 (EtOAc/*n*-Hexano, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.42 (t, *J*=7.2 Hz, 3H),1.46 (s, 9H), 2.13 (s, 3H), 2.31 (m, 1H), 2.42 (m, 1H), 2.59 (m, 2H), 4.43 (c, *J*=7.2 Hz, 2H), 5.19 (m, 1H), 5.45 (s, 1H), 8.11 (s, 1H). ^{13}C NMR (100 MHz, CDCl3) δ (ppm):14.1, 15.5, 28.3, 30.2, 34.8, 35.0, 52.2, 61.5, 80.4, 127.4, 147.4, 155.1, 161.3, 172.9. . IR ν(cm^{-1}) 1242, 1323, 1369, 1447, 1512, 1640, 1713, 2874, 2932, 2978, 3383, 3399 HRMS *m/z* calc. for $C_{15}H_{24}N_2O_4S_2$ ($[M+Na]^+$) 383.1070, found 383.1067.

Ethyl 2-((*S*)-1-(2-((1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-2-methylbutyl)thiazole-4-carboxamido)-3-(methylthio)propyl)thiazole-4-carboxylate (13): Compound **12a** (117 mg, 0.267 mmol) was treated according to general procedure for ester hydrolysis and compound **12b** was treated according to general procedure for NH-Boc deprotection. The bis-thiazole **13** was obtained from the acid derivative of **12a** (65.2 mg, 0.22mmol) and amino derivative of **12b** (70 mg, 0.22 mmol) following the general procedure for amide bond formation and further purification by flash chromatography. Yellow oil (66%)
13: Rf= 0.81, (EtOAc/*n*-Hexano, 1:1); $[\alpha]_D^{25}$= -6.3 (*c* 1.40, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 0.95 (t, *J*=7.3 Hz, 3H), 0.96 (d, *J*=6.6 Hz, 3H), 1.17 (m, 1H), 1.42 (t, *J*=7.1 Hz, 3H), 1.47 (s, 9H), 1.47 (m, 1H), 2.11 (m, 1H), 2.15 (s, 3H), 2.43 (m, 1H), 2.57 (m, 1H), 2.65 (m, 2H), 4.44 (dd, *J*=7.1, 7.1 Hz, 2H), 4.94 (m, 1H), 5.24 (m, 1H), 5.70 (m, 1H), 8.06 (s, 1H), 8.08 (s,

1H), 8.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 11.7, 14.4, 15.5, 15.7, 24.7, 28.3 (3), 30.4, 33.8, 39.8, 50.2, 57.2, 61.5, 80.3, 123.7, 127.6, 146.6, 149.1, 155.3, 160.7, 161.3, 171.3, 171.4. IR ν(cm^{-1}) 1238, 1366, 1489, 1535, 1667, 1709, 2878, 2932, 2970, 3121, 3325. HRMS *m/z* calc. for $C_{24}H_{36}N_4O_5S_3$ ($[M+Na]^+$) 579.1740, found 579.1665.

Ethyl 2-((2-((1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-2-methylbutyl)thiazole-4-carboxamido)methyl)thiazole-4-carboxylate (14): Compound **12a** was treated according to general procedure for ester hydrolysis and compound **12c** was treated according to general procedure for NH-Boc deprotection. The bis-thiazole **13** was obtained from the acid derivative of **12a** (68 mg, 0.3mmol) and amino derivative of **11** (83 mg, 0.3 mmol) following the general procedure for amide bond formation and further purification by flash chromatography. Yellow oil (56%).

14: Rf= 0.65, (EtOAc/*n*-Hexano, 1:1); $[\alpha]_D^{25}$= -22.7 (*c* 4.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (d, *J*=6.8 Hz, 3H), 0.93 (t, *J*=7.3 Hz, 3H), 1.17 (m, 1H), 1.42 (t, *J*=7.1 Hz, 3H),1.46 (s, 9H), 1.46 (m, 1H), 2.04 (m, 1H), 4.44 (c, *J*=7.2 Hz, 2H), 4.91 (m, 1H), 4.99 (d, *J*=6.4 Hz, 2H), 5.28 (m, 1H), 8.08 (s, 1H), 8.08 (s, 1H), 8.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):11.6, 14.4, 15.7, 24.8, 28.3, 39.6, 40.8, 57.2, 61.6, 80.3, 123.6, 128.4, 146.9, 148.9, 155.3, 161.3, 161.3, 168.3, 172.7. IR ν(cm^{-1}) 1169,1238, 1369, 1493, 1647, 1709, 2877, 2932, 2970, 3116, 3263. HRMS *m/z* calc. for $C_{21}H_{30}N_4O_5S_2$ ($[M+Na]^+$) 505,1550, found 505,1564.

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References and Notes

I. For excellent review see: Jin, Z. *Nat. Prod. Rep*. **2013**, *30*, 869 and references therein.

II. (a) Wipf, P. *Chem. Rev*., **1995**, *95*, 2115; (b) Jin, Z. *Nat. Prod. Rep*, **2011**, *28*, 1143. ; (c) D. Davyt and G. Serra, Mar. Drugs, **2010**, *8*, 2755.

III. 1 Portmann, C.; Blom, J. F.; Gademann, K.; Jüttner, F. *J. Nat. Prod*. **2008**, 71, 1193. b) Portmann, C.; Blom, J. F.; Kaiser, M.; Brun, R.; Jüttner, F.; Gademann, K. *J. Nat. Prod*. **2008**, *71*,1891.

IV. (a) Mahler, G.; Serra, G.; Dematteis, S.; Saldaña, J.; Domínguez, L.; Manta, E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1309. (b) Sellanes, D.; Scarone, L.; Mahler, G.; Manta, E.; Baz, A.; Dematteis, S.; Saldaña, J.; Domìnguez, L.; Serra, G. *Lett. Drug. Design Disc.* **2006**, *3*, 625. (c) Scarone, L.; Fajardo, J.; Saldaña, J.; Domínguez, L.; Espósito, P.; Demastteis, S.; Wipf, P.; Manta, E.; Serra, G. *Lett. Drug Design Disc*., **2009, *6,*** 413. (d) Sellanes, D.; Manta, E.; Serra, G. *Tetrahedron Lett.* **2007**, *48*, 1827. (e) . Sellanes, D.; Campot, F.; Nuñez, I.; Lin, G.; Espósito, P.; Saldaña, J.; Domínguez, L.; Manta, E.; Serra, G. *Tetrahedron* **2010**, *66,* 5384.

V. (a) Peña, S; Scarone, L.; Manta, E.; Serra, G. *Tetrahedron Lett.* **2013**, *54*, 2806. (b) Peña, S.; Scarone L.; Medeiros, A.; Manta, E.; Comini, M.; Serra G. *Med. Chem. Comm.* **2012**, *3*, 1443. (c) Peña, S.; Scarone, L.; Manta, E.; Stewart, L.; Yardley, V.; Croft, S.; Serra, G. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4994.

VI. Hantzsch, A. *Ann. Chem.* **1888**, *249,* 1.

VII. Bagley, M.; Merritt, E. *Synthesis* **2007**, *22*, 3535.

VIII. Bredenkamp, M. W.; Holzapfel, C. W.; van Zyl, W. J. *Synth. Commun.* **1990**, *20*, 2235.

IX. Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2473.

X. Williams, D. R.; Lowder, P. D.; Gu, Y. G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331.

XI. (a) You, S. L.; Razavi, H.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 83. (b) You, S. L.; Kelly, J. W. *J. Org. Chem.* **2003**, *68*, 9506.

XII. Perrin, D. D.; Armarego, W. L. F. "Purification of Laboratory Chemicals", 3th Ed. Pergamon Press, Oxford, 1988.

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