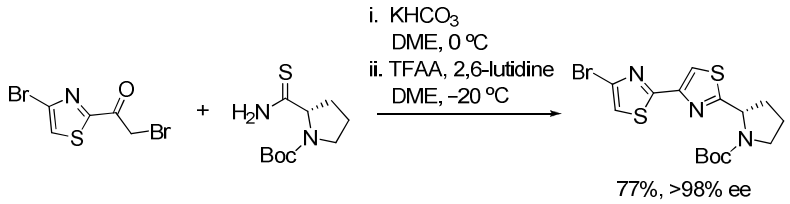
Graphical abstract



Highly Efficient, Multigram and Enantiopure Synthesis of 2-(2,4'-bithiazol-2-yl)pyrrolidine

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Abstract.

(*S*)-2-(4-Bromo-2,4'-bithiazole)-1-(*tert*-butoxycarbonyl)pyrrolidine (**(*S*)-1**) was obtained as a single enantiomer and in high yield by means of a two-step modified Hantzsch thiazole synthesis reaction when bromoketone **3** and thioamide **(*S*)-4** were used. Further conversion of **(*S*)-1** into trimethyltin derivative **(*S*)-2** broadens the scope for further cross-coupling reactions.

Keywords: Hantzsch cyclization; thiazole; thiopeptides; proline.

(insert Figure 1)

Polyheterocyclic scaffolds containing thiazole rings are common features of numerous biologically active natural products.[1] Chiral 2-(2,4'-bithiazole)amines

fragments can be found attached to the pyridine ring at the heterocyclic core of many thiopeptides (Figure 1).[2,3] The syntheses of a handful of these interesting natural antibiotics has been achieved using a range of different strategies.[2b] Those based on cross-coupling reactions have the need of pyridines and azoles properly functionalized as halides and/or organometallic derivatives. To date, only primary amines substituted with a suitable halogenated 2,4'-bithiazole have been described.[4] However, the methodology used so far cannot be applied when cyclic amines are pursued.[5] In this note we present the synthesis of enantiopure (*S*)-2-(4-bromo-2,4'-bithiazol-2'-yl)pyrrolidine **(*S*)-1**, which is easily converted into its trimethyltin derivative **(*S*)-2** for use in subsequent Stille cross-couplings (Scheme 1).

(insert Scheme 1)

In order to avoid any stereoselective steps, the use of starting materials directly derived from the chiral pool and therefore available in Kg scale should be mandatory.[6] Thus, racemisation can be avoided throughout the course of the synthesis.

During our investigations we found out that a 4-halo-2,4'-bithiazole fragment could not be accessed if the strategy relied on a key Hunsdiecker halodecarboxylation.[7,8] A more convergent approach involving the construction of the middle ring of **(*S*)-1**,[9] by means of a modified two-step Hantzsch thiazole synthesis[10] between **3**[11] and **(*S*)-4**,[12] afforded the optically pure product[13] in 77% yield (Scheme 1).[14] Bromoketone **3** was obtained after consecutive bromine/lithium exchange and acylation of **5**[15] and subsequent bromination under acidic conditions of the resulting 2-acylthiazole. Protection of prolylamide (**(*S*)-6**) with the Boc group[16] and further treatment with Lawesson's reagent gave thioamide **(*S*)-4** in excellent yield. The reaction was satisfactorily scaled-up without any loss of either optical purity or chemical yield and provided six grams of the desired biaryl **(*S*)-1**, which was subsequently converted into trimethyltin derivative **(*S*)-2** in high yield.[17]

In summary, an improved, convergent and high yield preparation of a 2-(2,4'-bithiazol-2'-yl)pyrrolidine fragment suitably functionalized in its thiazole-4-position either as bromide (**(*S*)-1**) or tin derivative (**(*S*)-2**) for use in cross-coupling reactions has been described. The products have been obtained in multigram scale without any loss of their optical integrity.

These building blocks will allow the preparation of those thiopeptide central cores bearing such moieties and that could not be accessed by previously reported methods. Further studies with these structures and their use in total synthesis of natural products are underway.

Acknowledgements

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References and Notes

(1) For a review about natural polyazoles see: Riego, E.; Hernández, D.; Albericio, F.; Álvarez, M. *Synthesis* **2005**, *12*, 1907−1922.

(2) (a) General review about thiopeptides: Bagley M. C.; Dale J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005,** *105*, 685. (b) Review about thiopeptide synthesis: (b) Hughes, R. A.; Moody, C. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 7930−7954. (c) Review about thiopeptide biosynthesis: Li, C.; Kelly, W. L. *Nat. Prod. Rep.* **2010**, *27*, 153−164.

(3) Examples of thiopeptides with a 2-(2,4'-bithiazol-2-yl)pyrrolidine fragment: (a) Ferrari, P.; Colombo, L.; Stella, S.; Selva, E.; Zerilli, L. F. *J. Antibiot.* **1995**, *48*, 1304−1311. (b) Morris, R. P.; Leeds, J. A.; Naegeli, H. U.; Oberer, L.; Memmert, K.; Weber, E.; LaMarche, M. J.; Parker, C. N.; Burrer, N.; Esterow, S.; Hein, A. E.; Schmitt, E. K.; Krastel, P. *J. Am. Chem. Soc.* **2009**, *131*, 5946−5955.

(4) (a) Spieβ, A.; Heckmann, G.; Bach, T. *Synlett* **2004**, 131−133. (b) Schultz-Fademrecht, C.; Kinzel, O.; Markó, I. E.; Pospisil, T.; Pesci, S.; Rowley, M.; Jones, P. *Tetrahedron* **2009**, *65*, 9487−9493.

(5) Previously described methodologies rely on the attack of an organometallic heteroarene to either a nitrile (see ref. **Error! Bookmark not defined.**a) or a sulfinylimine (see ref. **Error! Bookmark not defined.**b).

(6) Some of these can be found in the pool of Boc-protected amino acids, which are available in a great diversity at a very reasonable price.

(7) After extensive investigations on the Hunsdiecker halodecarboxylation process of thiazole-4-carboxylates of various metals, the desired 4-halothiazole was never obtained. The corresponding 5-halogenated thiazole-4-carboxylate was the only observed product when the starting material was not recovered.

(insert Scheme 2)

(8) Johnson, R. G.; Ingham, R. K. *Chem. Rev.* **1956**, *56*, 219−269.

(9) Classical Hantzsch conditions yielded the partially racemized product (42% ee). Prodecure: To a solution of thioamide **(*S*)-4** (58 mg, 0.25 mmol) and bromoketone **3** (60 mg, 0.21 mmol) in dry EtOH (3 mL) was added pyridine (25 μL, 0.32 mmol) and the resulting mixture was heated under reflux. After 4 h the solvent was removed under reduced pressure and the crude product was purified by silica flash chromatography (hex/EtOAc, 8:2) to yield the title compound as a tan solid (67 mg, 77%).

(10) (a) Bredenkamp, M. W.; Holzapfel, C. W.; van Zyl, W. J. *Synth. Commun.* **1990**, *20*, 2235−2249. (b) Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2473. (c) Boden, C. D. J.; Pattenden, G.; Ye, T. *Synlett* **1995**, 417−419. (d) Merritt, E. A.;

Bagley, M. C. *Synthesis* **2007**, *22*, 3535−3541. Nicolaou *et al.* revisited previous works on two-step Hantzsch cyclization and used those investigations for his landmark synthesis of thiostrepton: (e) Nicolaou, K. C.; Safina, B. S.; Zak, M.; Lee, S. H.; Nevalainen, M.; Bella, M.; Estrada, A. A.; Funke, C.; Zécri, F. J.; Bulat, S. *J. Am. Chem. Soc.* **2005**, *127*, 11159. (f) Nicolaou, K. C.; Zak, M.; Safina, B. S.; Estrada, A. A.; Lee, S. H.; Nevalainen, M. *J. Am. Chem. Soc.* **2005**, *127*, 11176.

(11) Preparation of 4-Bromo-2-(bromoacetyl)thiazole (**3**): A 33% HBr solution in AcOH (680 μL, 3.88 mmol), and bromine (200 μL, 3.88 mmol) were added to a solution of 2-acetyl-4-bromothiazole (800 mg, 3.88 mmol) in AcOH (43 mL) and the mixture was stirred at rt under N_2. After 5 h the mixture was poured over a suspension of ice in EtOAc (100 mL) and then solid Na_2CO_3 was added stepwise until basic pH was reached. The aqueous phase was extracted with EtOAc (2 × 100 mL) and the combined organic extracts dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by automated silica column chromatography (0 to 40% CH_2Cl_2 in hexanes), which yielded the product as a yellowish solid (887 mg, 80%). IR (KBr) 3113, 1704, 1454, 1379, 1191, 954, 640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.69 (s, 2 H), 7.67 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.6 (t), 126.4 (d), 127.8 (s), 163.8 (s), 183.9 (s) ppm. HRMS(ESI) m/z calcd for $C_5H_4Br_2NOS$ (M+H) 283.8375, found 283.8375.

(12) Preparation of (*S*)-1-(*tert*-Butoxycarbonyl)prolinthioamide (**(S)-4**)**:** A solution of (*S*)-1-(*tert*-butoxycarbonyl)prolinamide (9.0 g, 42.0 mmol) and Lawesson's reagent (8.5 g, 21.0 mmol) in dry THF (55 mL) was stirred at rt under N_2 for 3.5 h. The solvent was removed under reduced pressure, saturated aq. $NaHCO_3$ (100 mL) was added and the mixture stirred for 1 h. The aqueous suspension was extracted with EtOAc/CH_2Cl_2 (1:1) (400 mL), the organic fraction was washed with saturated aq. $NaHCO_3$ (2 × 100 mL) and the combined aqueous fractions were extracted with EtOAc/CH_2Cl_2 (200 mL). The combined organics extracts were dried over Na_2SO_4 and then concentrated *in vacuo* to obtain the title compound as a white solid (8.74 g, 90%), mp (EtOAc) 190−192 °C. $[\alpha]_D$ −103.4 (c = 1.00, $CHCl_3$). IR (KBr) 3380, 3202, 2981, 2881, 1671, 1411, 1166 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$) δ = 1.41−1.50 (m, 9 H), 1.65−2.75 (m, 4 H), 3.22−3.74 (m, 2 H), 4.67 (dd, *J* = 8.0 and 3.6 Hz, 1 H) ppm. HRMS(ESI) m/z calcd for $C_{10}H_{19}N_2O_2S$ (M+H) 231.1162, found 231.1161.

(13) The ee was determined by HPLC on a chiral stationary phase CHIRALPAK IA 250 × 4.6 mm 5 μm Analytical Column, flow rate 1 mL min^{-1}; H_2O (0.045% TFA):MeOH, 20:80; detected at 254 nm.

(14) Preparation of (*S*)-*tert*-Butyl 2-(4-bromo-2,4'-bithiazol-2'-yl)pyrrolidine-1-carboxylate (**(*S*)-1**): A mixture of thioamide **(*S*)-4** (6.51 g mg, 28.27 mmol) and $KHCO_3$ (15.09 g, 150.72 mmol) in dry DME (23 mL) under N_2 was stirred at rt. After 15 min the mixture was placed in an ice bath. A solution of bromoketone **3** (5.37 g, 18.84 mmol) in dry DME (22 mL) was added dropwise and the resulting mixture was stirred at 0 °C. After 23 h the mixture was allowed to reach rt, filtered through celite and washed with Et_2O. After removing the volatiles the crude hydroxythiazoline was redissolved in dry DME (47 mL) and cooled to −20 °C. A mixture of trifluoroacetic

anhydride (15.5 mL, 75.36 mmol) and 2,6-lutidine (18.7 mL, 160.14 mmol) was added dropwise and the resulting solution was stirred at −20 °C. After 4 h the mixture was diluted with CH_2Cl_2 (200 mL), washed with 1 N HCl (200 mL) and saturated aq. $NaHCO_3$ (200 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by silica flash column chromatography (hex/EtOAc, 8:2). The title product was obtained as a yellowish solid (6.04 g, 77%), mp (EtOAc) 134−137 °C. $[\alpha]_D$ −72.3 (c 1.00, CH_2Cl_2). IR (KBr) 3120, 2972, 2868, 1688, 1395 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.29−1.57 (m, 9 H), 1.85−2.10 (m, 2 H), 2.15−2.50 (m, 2 H), 3.30−3.70 (m, 2 H), 5.10−5.30 (m, 1 H), 7.23 (s, 1 H), 7.91 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.4 and 24.2 (t), 28.5 and 28.6 (q), 32.9 and 34.3 (t), 46.8 and 47.1 (t), 59.1 and 59.5 (d), 80.6 (s), 116.5 and 116.8 (d), 117.5 (d), 126.2 (s), 148.2 (s), 154.3 and 155.0 (s), 163.8 (s), 176.8 (s) ppm. HRMS(ESI) m/z calcd for $C_{15}H_{19}BrN_3O_2S_2$ (M+H) 416.0097, found 416.0096.

(15) Acylation of **5** was performed as descrived in Gebauer, J.; Arseniyadis, S.; Cossy, J. *Org. Lett*. **2007**, *9*, 3425.

(16) (*S*)-1-(*tert*-Butoxycarbonyl)prolinamide was either purchased or prepared as described in Scheme 1. The spectroscopic data of the protected product prepared in our labs was identical to the commercially available compound.

(17) Preparation of (*S*)-*tert*-Butyl 2-[4-(trimethyltin)-2,4'-bithiazol-2'-yl]pirolidine-1-carboxylate (**(*S*)-2**): To a stirred solution of bithiazole **(*S*)-1** (1.97 g, 4.73 mmol) and hexamethyldistannane (8.3 mL, 40.22 mmol) in degassed dry toluene (160 mL) was added $[Pd(PPh_3)_4]$ (543 mg, 0.47 mmol) and the mixture was stirred at 100 °C under argon. After 2 h the mixture was allowed to reach rt and the solvent was removed under reduced pressure. The crude product was purified by neutral alumina column chromatography column (hex/EtOAc, 95:5 to 90:10) to yield the title compound as a white solid (2.11 g, 89%), mp (hexanes) 111−113 °C. $[\alpha]_D$ −63.8 (c = 0.99, CH_2Cl_2). IR (KBr) 3131, 3094, 2977, 1699, 1386 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 0.39 (s, 9 H), 1.28−1.54 (m, 9 H), 1.88−2.04 (m, 2 H), 2.16−2.45 (m, 2 H), 3.36−3.70 (m, 2 H), 5.10−5.30 (m, 1 H), 7.38 (s, 1 H), 7.88 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = −8.6 (q), 23.4 and 24.1 (t), 28.5 (q), 33.0 and 34.4 (t), 46.8 and 47.1 (t), 59.2−59.6 (d), 80.5 (s), 115.3 and 115.7 (d), 126.3 (d), 149.9 (s), 154.4 (s) 161.3 (s), 163.7 (s), 176.3 (s) ppm. HRMS(ESI) m/z calcd for $C_{18}H_{28}N_3O_2S_2Sn$ (M+H) 502.0639, found 502.0639.

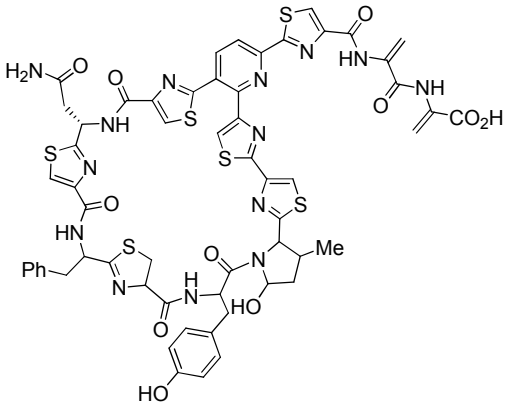
Legends

Figure 1. Thiopeptides containing chiral bithiazole amine moieties.

Scheme 1. Synthesis of 2-(4-bromo-2,4'-bithiazol-2-yl)pyrrolidine **(S)-1** and trimethyltin derivative **(S)-2**.

Figures

Figure 1:



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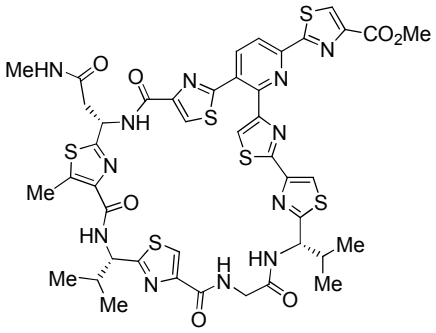

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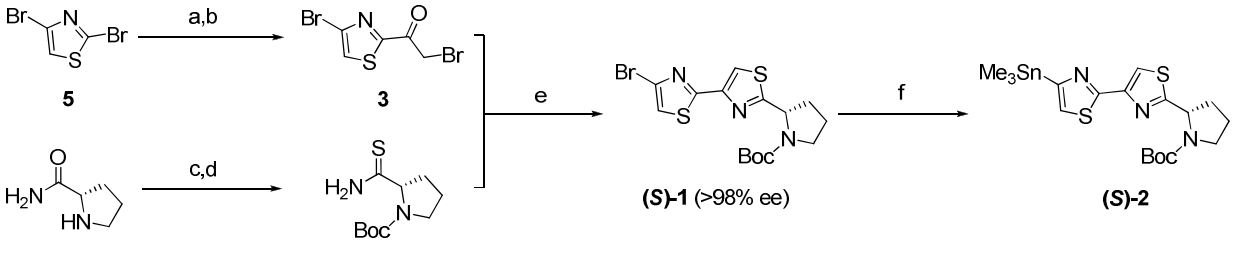
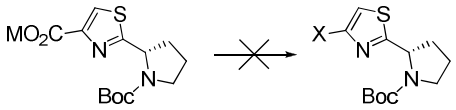
Schemes

Scheme 1:



(a) i. *n*BuLi, THF, –78 °C. ii. *N*-acetylmorpholine, –78 °C (67%). (b) Br_2, HBr, AcOH, rt (80%).(c) $(Boc)_2O$, H_2O, 1,4-dioxane, rt (quant.). (d) Lawesson's reagent, THF, rt (quant.). (e) i. $KHCO_3$, DME, 0 °C. ii. TFAA, 2,6-lutidine, DME, –20 °C (77%). (f) $Me_3SnSnMe_3$, $[Pd(PPh_3)_4]$, toluene, 100 °C (89%).

Scheme 2:



M = Ag, Li X = Br, I