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Synthesis of Optically Active Isothiazole Derivatives from *L*-(α)-Amino Acids

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Summary. Several enantiomerically pure 3,5-disubstituted isothiazol-5-ylideneamine hydrobromides were prepared by oxidation of chiral 3-amino-2,3-unsaturated thioamides. The starting thioamides derived from natural *L*-α-amino acids represent a novel group of synthetically useful chiral reactants.

Keywords. Unsaturated thioamides; Isothiazoles; Oxidations; Chirality; NMR spectroscopy.

Introduction

3,5-Disubstituted isothiazoles are known to show a wide range of biological activity [1]. They have also found applications in syntheses of highly selective 5-HT_{2B} receptor antagonists [2], human testosterone 5α-reductase inhibitors [3], dual cyclooxygenase/S-lipoxygenase inhibitors [4], interferon inducing agents [5], and antagonists of gonadotropin releasing hormon receptors [6]. A large group of 3,5-disubstituted isothiazole derivatives play an important role as highly selective herbicides [7]. Derivatives of 2,3-dimethylisothiazol-5-ylideneamine have been reported to be active indolamine *N*-methyltransferase inhibitors [8]. These various biological and pharmacological properties of 3,5-disubstituted and other high-substituted isothiazoles have brought about an increase of interest in isothiazole chemistry [9].

There are two synthesis routes to 3,5-disubstituted isothiazoles known: either construction of the isothiazole ring followed by substitution or preparation of substituted acyclic precursors followed by cyclisation [10]. Direct functionalization of the isothiazole ring is usually limited to reactions with electrophiles because of its weak stability towards nucleophiles [11]. Therefore, the more convenient method for synthesis of high-substituted isothiazoles is the preparation of appropriately substituted open-chain precursors.

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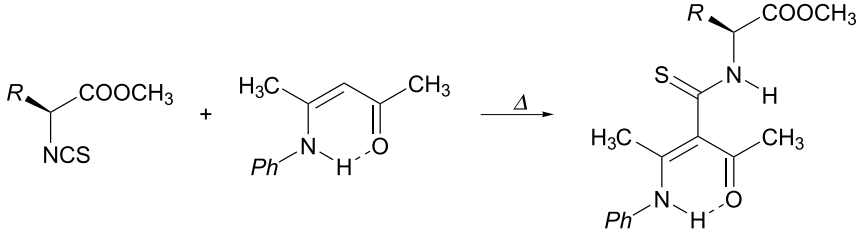
In our research we focused on syntheses of chiral unsaturated thioamides, which serve as substrates for the preparation of novel chiral 3,5-disubstituted isothiazoles. Our interest in these thioamides as precursors stemmed from their accessibility and stability. In fact, simple 3-amino-2,3-unsaturated thioamides have been known for many years as readily available and moderately reactive synthons [12] for syntheses of miscellaneous heterocyclic compounds including isothiazole derivatives [13].

Results and Discussions

Although a wide range of 2-amino-2,3-unsaturated thioamides has been reported we were unable to find examples of optically active derivatives. Thus we adjusted the well known procedure for the synthesis of 3-anilinothiocrotonate amides from isothiocyanates and enamines [14]. Accordingly, we applied optically active isothiocyanatocarboxylates **1** derived from natural *L*-α-amino acids and several enamines obtained from acetophenone. We expected to convert them into chiral 2-amino-2,3-unsaturated thioamides unsubstituted at the C-2 carbon atom. Unfortunately, all reactions failed due to the poor reactivity of isothiocyanatocarboxylates. Therefore we were forced to replace enamines with the more reactive enaminone 4-anilinopent-3-en-2-one (**2**).

Syntheses were carried solvent-free according to the above mentioned procedure and provided the optically active 3-anilinothiocrotonate amides **3** (Scheme 1).

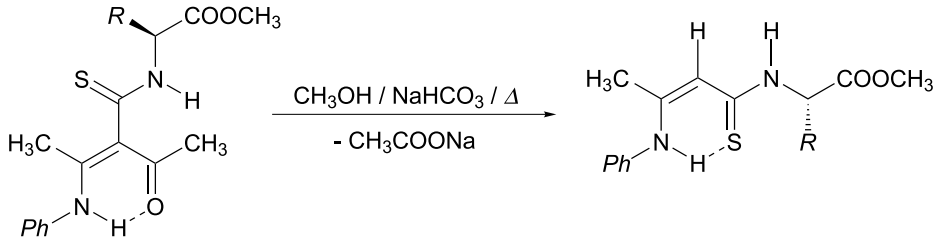
The structures of all the products were confirmed by their IR, NMR, and mass spectra. Based on the IR and NMR spectra we found that 3-anilinothiocrotonate amides **3** exist exclusively as (*E*) diastereomers. An NMR experiment indicated a N*O*ESY interaction between the acetyl group and both the amino groups. Although a low barrier of rotation has been reported for similar compounds [15], we did observe no traces of (*Z*) isomers. Rotation about the vinyl double bond was hindered by a strong intramolecular hydrogen bonding between the 3-amino and acetyl functionalities. In the IR spectra of **3** we observed two bands assigned to carbonyl groups. An absorption at $\bar{\nu} = 1740\,\mathrm{cm}^{-1}$ was attributed to the C=O stretch of the carbomethoxy group whereas a band at $\bar{\nu} = 1610\,\mathrm{cm}^{-1}$ must have been connected with the hydrogen-bonded, conjugated acetyl group. The ^{1}H NMR spectra showed crucial differences between two various NH protons supporting our



1a-1f **2** **3a-3f**

R = **a**: H; **b**: CH_3; **c**: $CH_2C_6H_5$; **d**: $CH_2CH(CH_3)_2$; **e**: $CH(CH_3)C_2H_5$; **f**: $CH_2CH_2SCH_3$

Scheme 1



Scheme 2

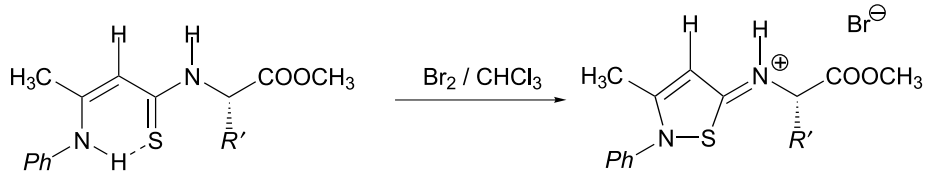
structural assignment. A signal of the NH–CS proton was observed at $\delta = 8.1$ ppm while the signal of the NH–Ph proton was shifted up to $\delta = 13.3$ ppm indicating an interaction with the neighboring acetyl group.

During our investigations we noted that **3** could loose the 2-acetyl substituent under relative mild conditions. This observation allowed us to convey the deacetylation of some thioamides **3** to prepare **4** which were applied as educts for the synthesis of 3,5-disubstituted isothiazoles. The deacetylations of **3** were carried out in boiling, anhydrous methanol with sodium hydrogencarbonate to yield **4** (Scheme 2). They proceed nearly quantitative and the loss of the acetyl group was confirmed by NMR and MS spectra. The absence of the 2-acetyl substituent resulted in significant differences in chemical shifts of NH protons. Thus, signals of the PhNH protons in **4** appeared at $\delta = 12.9$ ppm whereas signals of thioamide protons were shifted down to $\delta = 6.7$ ppm. Taking into consideration the mentioned spectra of **3** we assumed that **4** exist as (*Z*) diastereomers. In fact, the PhNH groups of **4** could form intramolecular hydrogen bonds with the sulfur atoms in this case only.

Generally, the preparation of isothiazoles from **4** consists in their oxidation using some oxidants, such as halogens, chloramines, hydrogen peroxide, trifluoromethylsulfenyl chloride, and others [16]. We applied bromine as described by *Goerdeler* and *Gnad* [17] yielding isothiazole hydrobromides **5** in very good yields (Scheme 3).

The constitutions of **5** were confirmed by IR spectra where we observed an absorption at $\bar{\nu} = 1740\,\mathrm{cm}^{-1}$ characteristic for a carbonyl group. Two absorptions bands at $\bar{\nu} = 1200$ and $1100\,\mathrm{cm}^{-1}$ were attributed to the antisymmetric and symmetric stretches of the ester C–O bond. A very strong and broad absorption was observed at $\bar{\nu} = 2400$–$3400\,\mathrm{cm}^{-1}$, which was assigned to the NH^+ stretch. In the ^{1}H NMR spectra of **5** a broad signal at $\delta = 10.3$ ppm was assigned to NH^+. The ^{13}C NMR spectra of **5** supported our structural assignments. As expected, we noticed an absence of signals characteristic for thiocarbonyl groups at $\delta = 190$–200 ppm while a new signal at 169.7 ppm appeared, which was assigned to C-5 of the isothiazole ring.

Although **3**, **4**, and **5** were non-racemic and displayed optical activities it was not certain that all reactions proceeded without partial racemisations. Determination of their enantiomeric purity by means of chiral lanthanide shift reagents failed – no interactions of europium complexes with these compounds were observed. Therefore we prepared a model amide **3e** from natural *L*-α-isoleucine containing two asymmetric centers. We assumed that any partial racemisation of **3e** during its deacetylation and cyclisation to isothiazole derivative **5e** was possible only on the C-α-carbon atom. However, the ^{1}H NMR spectra of **4e** and **5e** indicated no presence of a second diastereomer, thus excluding racemisation. Accordingly, all reactions starting from **1e** to the final **5e** proceed with



4b-4e **5b-5e**

Scheme 3

retention of configuration on both chiral centers. To examine the stability of the chiral center on C-2 in **3e** during deacetylation we repeated this reaction under more basic conditions using a 6 equivalent excess of sodium hydrogencarbonate in a small volume of methanol. After 2 hours reflux we obtained **4e** containing a small quantity of the second diastereomer with (*R*) configuration. Using NMR spectroscopy we estimated its amount to 16%. The reaction of **3** with bromine did not lead to the desired 3,4,5-trisubstituted isothiazole derivatives, but tars were formed.

In conclusion, the described work gives a simple, convenient procedure for the synthesis of chiral 3,5-disubstituted isothiazole derivatives of high enantiomeric purity using easily accessible β-dicarbonyl compounds and naturally occurring *L*-α-amino acids. The novel optically active 3-amino-2,3-unsaturated thioamides **4** proved to be very useful educts for the preparation of isothiazole derivatives **5** having a chiral ylidenamine group at C-5.

Experimental

NMR spectra were determined on a Bruker AMX 500 spectrometer (using *TMS* as an internal standard), IR spectra were measured with a Bruker IFS 48 FT spectrometer in KBr pellets, and MS were recorded on a Finnigan MAT 95S apparatus. Microanalyses were carried out using on Euro-EA 3018 analyser. Their results were in good agreement with the calculated values. Optical rotations were measured on Polamat A polarimeter with 0.5 dm tube.

Methyl isothiocyanatocarboxylates **1a–1f** were obtained from appropriate *L*-α-aminoacid methyl ester hydrochlorides by the "thiophosgene method" [18]; 4-anilinopent-3-en-2-one (**2**) was synthesized according to Ref. [19].

*General Procedure for the Synthesis of **3a–3f***

To a 25 cm^3 flask protected against air moisture were added 20 mmol **2** and 21 mmol **1a–1f**. The mixture was stirred and heated for 60–90 min at 85–95°C. After cooling, the residue was triturated with petroleum ether/*n*-hexane to remove an excess of the methyl isothiocyanatocarboxylate and the crude product was purified by crystallization from cyclohexane.

Methyl (2-acetyl-3-(phenylamino)but-2-enethioylamino)acetate (**3a**, $C_{15}H_{18}N_2O_3S$)

Reagents were heated for 90 min at 85°C. Recrystallization from cyclohexane afforded 5.41 g (88%) **3a**. Mp 163°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.09$ (s, CH_3), 2.24 (s, CH_3), 3.80 (s, OCH_3), 4.51 (d, $J = 5.05$ Hz, CH_2), 7.10 (m, 2H), 7.25 (m, 1H), 7.36 (m, 2H), 8.24 (t, NH), 13.34 (s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.3$ (CH_3), 27.6 (CH_3), 47.4 (CH_2), 52.5 (OCH_3), 115.9 (C), 125.6 (CH), 126.5 (CH), 129.2 (CH), 137.9 (C), 159.5 (C–NHPh), 168.9 (COO), 192.7 (C=S), 202.8 (C=O) ppm; IR (KBr): $\bar{\nu} = 3212$, 3023, 1747, 1594, 1354, 1281, 1213 cm^{-1}; MS (70 eV): m/z (%) = 306 (M^+, 16.0), 233 (7.8), 273 (20.8), 118 (19.1), 93 (100), 77 (38.4).

Methyl (S)-(−)-2-(2-acetyl-3-(phenylamino)but-2-enethioylamino)-propionate (**3b**, $C_{16}H_{20}N_2O_3S$)

Reagents were heated for 70 min at 90°C. Recrystallization from toluene:petroleum ether (2:1) afforded 4.80 g (75%) **3b**. Mp 158°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.59$ (d, $J = 7.18$ Hz, CH_3), 2.07 (s, CH_3), 2.24 (s, CH_3), 3.78 (s, OCH_3), 5.19 (m, CH), 7.10 (m, 2H), 7.24 (m, 1H), 7.36 (m, 2H), 8.18 (d, $J = 6.51$ Hz, NH), 13.31 (s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 16.6$ (CH–$\underline{C}H_3$), 17.1 (CH_3), 27.5 (CH_3), 47.4 (CH_2), 52.6 (OCH_3), 53.7 (CH), 116.0 (C), 125.6 (CH), 126.4 (CH), 129.2 (CH), 137.8 (C), 159.3 (C–NHPh), 172.2 (COO), 192.5 (C=S), 201.6 (C=O) ppm; IR (KBr): $\bar{\nu} = 3199$, 3029, 1745, 1608, 1589, 1279, 1205, 1154 cm^{-1}; $[\alpha]_D^{20} = -14.3^\circ\ cm^2\ g^{-1}$ ($c = 5$, $CHCl_3$).

Methyl (S)-(+)-2-(2-acetyl-3-(phenylamino)but-2-enethioylamino)-3-phenylpropionate (**3c**, $C_{22}H_{24}N_2O_3S$)

Reagents were heated for 60 min at 90°C. Recrystallization from cyclohexane afforded 7.13 g (90%) **3c**. Mp 145°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.91$ (s, CH_3), 2.08 (s, CH_3), 3.20 (dd, $C\underline{H}_aH_b$), 3.42 (dd, $CH_a\underline{H}_b$), 3.78 (s, OCH_3), 5.51 (m, CH), 7.03 (m, 2H), 7.19–7.35 (m, 8H), 7.84 (d, $J = 7.1$ Hz, NH), 13.28 (s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 16.9$ (CH_3), 27.4 (CH_3), 36.9 (CH_2), 52.5 (OCH_3), 58.8 (CH), 115.9 (C), 125.5 (CH), 126.4 (CH), 127.4 (CH), 128.8 (CH), 128.9 (CH), 129.2 (CH), 135.4 (C), 137.7 (C), 159.3 (C–NHPh), 171.0 (COO), 192.7 (C=S), 202.4 (C=O) ppm; IR (KBr): $\bar{\nu} = 3205$, 3023, 1743, 1606, 1594, 1279, 1210 cm^{-1}; $[\alpha]_D^{20} = +21.1^\circ\ cm^2\ g^{-1}$ ($c = 4.5$, $CHCl_3$).

Methyl (S)-(−)-2-(2-acetyl-3-(phenylamino)but-2-enethioylamino)-4-methylpentanoate (**3d**, $C_{19}H_{26}N_2O_3S$)

Reagents were heated for 90 min at 85°C. Recrystallization from cyclohexane afforded 4.93 g (68%) **3d**. Mp 134°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.97$ (d, $J = 6.4$ Hz, $2CH_3$), 1.73 (m, CH), 1.82 (m, CH_2), 2.07 (s, CH_3), 2.24 (s, CH_3), 3.74 (s, OCH_3), 5.21 (2d, $J = 7.6$ Hz, CH), 7.09 (d, 2H), 7.23 (t, 1H), 7.34 (m, 2H), 8.03 (d, $J = 7.2$ Hz, NH), 13.29 (s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.1$ (CH_3), 21.9 (CH_3), 22.7 (CH_3), 26.9 (CH), 27.5 (CH_3), 40.4 (CH_2), 52.3 (OCH_3), 56.9 (CH), 116.1 (C), 125.6 (CH), 126.4 (CH), 129.2 (CH), 137.9 (C), 159.3 (C–NHPh), 171.9 (COO), 192.6 (C=S), 202.5 (C=O) ppm; IR (KBr): $\bar{\nu} = 3205$, 3029, 1740, 1601, 1597, 1278, 1203 cm^{-1}; $[\alpha]_D^{20} = -9.3^\circ\ cm^2\ g^{-1}$ ($c = 3$, $CHCl_3$).

Methyl (S,S)-(−)-2-(2-acetyl-3-(phenylamino)but-2-enethioylamino)-3-methylpentanoate (**3e**, $C_{19}H_{26}N_2O_3S$)

Reagents were heated for 80 min at 95°C. Recrystallization from cyclohexane afforded 4.42 g (61%) **3e**. Mp 141°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 6.71$ Hz, CH_3), 0.99 (t, $J = 7.43$ Hz, CH_3), 1.34 (ddq, CH_3–$CH_a\underline{H}_b$), 1.58 (ddq, CH_3–$C\underline{H}_aH_b$), 2.06 (s, CH_3), 2.17 (m, CH), 2.24 (s, CH_3), 3.78 (s, OCH_3), 5.23 (dd, CH), 7.10 (d, 2H), 7.23 (t, 1H), 7.36 (t, 2H), 7.99 (d, $J = 7.61$ Hz, NH), 13.32 (s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.5$ (CH_3), 15.6 (CH_3–$\underline{C}H_2$), 17.1 (CH_3), 26.0 (CH_3), 27.5 (CH_3), 37.2 (CH), 52.2 (OCH_3), 62.4 (CH), 116.3 (C), 125.6 (CH), 126.4 (CH), 129.2 (CH), 137.9(C), 159.1 (C–NHPh), 171.0 (COO), 192.6 (C=S), 202.5 (C=O) ppm; IR (KBr): $\bar{\nu} = 3180$, 3012, 1740, 1612, 1585, 1280, 1208 cm^{-1}; $[\alpha]_D^{20} = -0.7^\circ\ cm^2\ g^{-1}$ ($c = 3$, $CHCl_3$).

Methyl (S)-(+)-2-(2-acetyl-3-(phenylamino)but-2-enethioylamino)-4-(methylsulfanyl)butanoate (**3f**, $C_{18}H_{24}N_2O_3S_2$)

Reagents were heated for 120 min at 90°C. Recrystallization from toluene:petroleum ether = 3:1 afforded 6.16 g (81%) **3f**. Mp 128°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.08$ (s, CH_3), 2.11 (s, SCH_3), 2.25 (s, CH_3), 2.26 (m, CH–$C\underline{H}_aH_b$), 2.37 (m, CH–$CH_a\underline{H}_b$), 2.60 (t, $J = 7.32$ Hz, SCH_2), 3.77 (s, OCH_3), 5.33 (m, CH), 7.10 (m, 2H), 7.24 (m, 1H), 7.36 (m, 2H), 8.36 (d, $J = 7.17$ Hz, NH), 13.32 (s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 15.5$ (CH–$\underline{C}H_2$), 17.2 (CH_3), 27.6 (CH_3), 30.2 (SCH_3), 30.2 (SCH_2), 52.6 (OCH_3), 57.4 (CH), 116.0 (C), 125.6 (CH), 126.4 (CH),

129.2 (CH), 137.8 (C), 159.4 (C–NHPh), 171.1 (COO), 192.5 (C=S), 202.4 (C=O) ppm; IR (KBr): $\bar{\nu} = 3186$, 3011, 1745, 1608, 1584, 1286, 1208 cm^{-1}; $[\alpha]_D^{20} = +8.5^\circ\ cm^2\ g^{-1}$ ($c = 4$, $CHCl_3$).

*Deacetylation of **3**; General Procedure for the Synthesis of **4b–4e***

A mixture of 8 mmol **3b–3e** and 32 mmol $NaHCO_3$ (2.688 g) in 100 cm^3 of absolute methanol was refluxed until TLC showed that all the starting material had been converted (90 min). After cooling an inorganic precipitate was filtered off and the filtrate was evaporated. The crude product was dried in vacuum at 50°C and dissolved in anhydrous CH_2Cl_2. After filtration the solvent was evaporated and oily products **4b–4e** were purified by column chromatography on silica gel ($CHCl_3$:methanol = 50:1).

Methyl (S)-(−)-2-(3-(phenylamino)but-2-enethioylamino)propionate (**4b**, $C_{14}H_{18}N_2O_2S$)

Chromatography afforded 1.27 g (57%) **4b**. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.49$ (d, $J = 7$ Hz, CH_3), 2.00 (s, CH_3), 3.77 (s, OCH_3), 5.09 (m, CH), 5.20 (s, CH), 6.67 (d, $J = 8$ Hz, NH), 7.09–7.18 (m, 3H), 7.38 (t, $J = 7.5$ Hz, 2H), 12.95 (s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 16.8$ (CH_3), 21.7 (CH_3), 51.1 (OCH_3), 52.4 (CH), 97.5 (CH), 125.0 (CH), 129.0 (CH), 129.2 (CH), 138.9 (C), 157.5 (C–NHPh), 172.1 (COO), 188.7 (C=S) ppm; IR (film): $\bar{\nu} = 3312$, 2982, 2948, 1728, 1610, 1582, 1403, 1198, 1165 cm^{-1}; $[\alpha]_D^{20} = -20.0^\circ\ cm^2\ g^{-1}$ ($c = 2$, $CHCl_3$).

Methyl (S)-(+)-3-phenyl-2-(3-(phenylamino)but-2-enethioylamino)-propionate (**4c**, $C_{20}H_{22}N_2O_2S$)

Chromatography afforded 2.41 g (85%) **4c**. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.00$ (s, CH_3), 3.23 (dd, $J_{HaH} = 5.5$ Hz, $J_{HaHb} = 14$ Hz, $C\underline{H}_aH_b$), 3.35 (dd, $J_{HbH} = 6.5$ Hz, $CH_a\underline{H}_b$), 3.73 (s, OCH_3), 5.17 (s, CH), 5.54 (m, CH), 6.61 (d, $J = 6.5$ Hz, NH), 7.15–7.36 (m, 10H), 12.97 (s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.7$ (CH_3), 37.5 (CH_2), 52.2 (OCH_3), 56.2 (CH), 97.6 (CH), 125.0 (CH), 125.4 (CH), 127.0 (CH), 128.5 (CH), 129.0 (CH), 129.3 (CH), 136.1 (C), 138.9 (C), 157.7 (C–NHPh), 172.2 (COO), 188.6 (C=S) ppm; IR (film): $\bar{\nu} = 3327$, 1728, 1579, 1489, 1341, 1198, 1175 cm^{-1}; MS (70 eV): m/z (%) = 354 (M^+, 97.4), 321 (35.2), 279 (49.2), 176 (92.7), 162 (70.3), 159 (78.0), 131 (100), 118 (84.7), 103 (28.0); $[\alpha]_D^{20} = +42.7^\circ\ cm^2\ g^{-1}$ ($c = 2$, $CHCl_3$).

Methyl (S)-(−)-4-methyl-2-(3-(phenylamino)but-2-enethioylamino)-pentanoate (**4d**, $C_{17}H_{24}N_2O_2S$)

Chromatography afforded 1.90 g (74%) **4d**. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.97$ (d, $J = 5.97$ Hz, CH_3), 0.98 (d, $J = 6.15$ Hz, CH_3), 1.66–1.81 (m, CH and CH_2), 2.00 (s, CH_3), 3.76 (s, OCH_3), 5.21 (s, CH), 5.26 (m, CH), 6.58 (d, $J = 6.41$ Hz, NH), 7.12–7.18 (m, 3H), 7.32 (t, 2H), 12.96 (s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.7$ (CH_3), 22.3 (CH_3), 22.7 (CH_3), 25.0 (CH), 41.5 (CH_2), 52.2 (OCH_3), 54.0 (CH), 97.6 (CH), 125.0 (CH), 125.3 (CH), 129.0 (CH), 138.9 (C), 157.5 (C–NHPh), 173.7 (COO), 189.4 (C=S) ppm; IR (film): $\bar{\nu} = 3312$, 3030, 2956, 1728, 1613, 1594, 1495, 1197, 1030 cm^{-1}; $[\alpha]_D^{20} = -18.4^\circ\ cm^2\ g^{-1}$ ($c = 2$, $CHCl_3$).

Methyl (S,S)-(+)-3-methyl-2-(3-(phenylamino)but-2-enethioylamino)-pentanoate (**4e**, $C_{17}H_{24}N_2O_2S$)

Chromatography afforded 1.74 g (68%) of **4e**. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.94$ (d, $J = 6.90$ Hz, CH_3), 0.97 (t, $J = 7.34$ Hz, CH_3), 1.28 (ddq, $CH_3–CH_a\underline{H}_b$), 1.58 (ddq, $CH_3–C\underline{H}_aH_b$), 1.99 (s, CH_3), 2.03 (m, CH), 3.75 (s, OCH_3), 5.22 (s, CH), 5.26 (dd, CH), 6.71 (d, $J = 7.07$ Hz, NH), 7.12 (d, 2H), 7.17 (t, 1H), 7.33 (t, 2H), 12.97 (s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.6$ (CH_3), 15.3 ($CH_3–\underline{C}H_2$), 21.7 (CH_3), 25.9 (CH_3), 38.0 (CH), 51.9 (OCH_3), 59.4 (CH), 97.7 (CH), 115.1 (CH), 125.0 (CH), 129.0 (CH), 138.9 (C), 157.4 (C–NHPh), 172.5 (COO), 189.3 (C=S) ppm; IR (film): $\bar{\nu} = 3315$, 3020, 2955, 1731, 1610, 1595, 1495, 1188, 1026 cm^{-1}; $[\alpha]_D^{20} = +2.7^\circ\ cm^2\ g^{-1}$ ($c = 2.5$, $CHCl_3$).

*Oxidation of **4** with Bromine; General Procedure for the Synthesis of **5***

A three-necked, 150 cm^3 flask equipped with a stirrer, an Ar inlet, a condenser, and an addition funnel was charged under Ar with 60 cm^3 of anhydrous $CHCl_3$ and 5 mmol **4b**–**4e**. The mixture was cooled to 0°C on an ice bath and then a solution of 6 mmol (0.96 g, 0.31 cm^3) Br_2 in 10 cm^3 $CHCl_3$ was added dropwise over 20 min. The reaction mixture was stirred for 30 min at 0°C and allowed to warm to room temperature over 1 h, then filtered and evaporated on a rotatory evaporator. The crude products were dried and purified by chromatography using silica gel ($R_f = 0.25$–0.31, $CHCl_3$:$CH_3OH = 8{:}1$).

Methyl (S)-(−)-2-(3-methyl-2-phenyl-2H-isothiazol-5-ylideneamino)-propionate hydrobromide (**5b**, $C_{14}H_{17}N_2O_2SBr$)

Column chromatography afforded 1.34 g (75%) **5b**. Mp 108°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.67$ (d, $J_{HH} = 6.94$ Hz, CH_3), 2.23 (s, CH_3), 3.77 (s, OCH_3), 4.22 (m, CH), 6.05 (s, CH), 7.29–7.31 (m, 2H), 7.49–7.50 (m, 3H), 10.08 (br. s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 15.8$ (CH_3), 17.2 (CH_3), 52.7 (OCH_3), 54.7 (CH), 99.9 (CH), 127.3 (CH), 130.1 (CH), 130.7 (CH), 134.8 (C), 161.4 (C–NPh), 170.8 (S–C=NH^+), 171.4 (COO) ppm; IR (KBr): $\bar{\nu} = 3095$, 2958, 2927, 1743, 1559, 1214, 1142 cm^{-1}; $[\alpha]_D^{20} = -7.7°\ cm^2\ g^{-1}$ ($c = 1.5$, $CHCl_3$).

Methyl (S)-(−)-2-(3-methyl-2-phenyl-2H-isothiazol-5-ylideneamino)-3-phenylpropionate hydrobromide (**5c**, $C_{20}H_{21}N_2O_2SBr$)

Column chromatography afforded 1.75 g (75%) **5c**. Mp 98°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.15$ (s, CH_3), 3.29 (dd, $J_{HaH} = 8.76$ Hz, $J_{HaHb} = 13.85$ Hz, C$\underline{H}_a$H$_b$), 3.37 (dd, $J_{HbH} = 5.61$ Hz, CH$_a\underline{H}_b$), 3.75 (s, OCH_3), 4.27 (m, CH), 5.88 (s, CH), 7.23–7.49 (m, 10H), 10.30 (br. s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 15.6$ (CH_3), 38.1 (CH_2), 52.8 (OCH_3), 61.7 (CH), 99.8 (CH), 127.3 (CH), 127.3 (CH), 128.7 (CH), 129.5 (CH), 130.1 (CH), 130.6 (CH), 134.9 (C), 161.1 (C–NPh), 169.7 (S–C=NH^+), 171.6 (COO) ppm; IR (KBr): $\bar{\nu} = 3088$, 2948, 2923, 1743, 1549, 1487, 1208, 1029 cm^{-1}; MS (70 eV): m/z (%) = 352 (3.4), 321 (12.2), 293 (21.0), 261 (100), 215 (38.0), 176 (31.8), 169 (16.8), 163 (8.8), 131 (16.6), 118 (81.0); $[\alpha]_D^{20} = -24.1°\ cm^2\ g^{-1}$ ($c = 1$, $CHCl_3$).

Methyl (S)-(−)-4-methyl-2-(3-methyl-2-phenyl-2H-isothiazol-5-ylideneamino)pentanoate hydrobromide (**5d**, $C_{17}H_{23}N_2O_2SBr$)

Column chromatography afforded 1.43 g (72%) **5d**. Mp 83°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.95$ (d, $J = 6.42$ Hz, CH_3), 1.01 (d, $J = 6.45$ Hz, CH_3), 1.87 (m, C$\underline{H}_a$H$_b$), 1.97 (m, CH), 2.02 (m, CH$_a\underline{H}_b$), 2.26 (s, CH_3), 3.78 (s, OCH_3), 4.14 (ddd, $J = 6.74$ Hz, CH), 6.05 (s, CH), 7.32–7.34 (m, 2H), 7.51–7.53 (m, 3H), 10.08 (br. s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 15.7$ (CH_3), 21.6 (CH_3), 22.5 (CH_3), 24.7 (CH_3), 40.1 (CH_2), 52.6 (OCH_3), 58.0 (CH), 99.5 (CH), 127.3 (CH), 130.1 (CH), 130.6 (CH), 134.9 (C), 161.3 (C–NPh), 170.8 (S–C=NH^+), 171.4 (COO) ppm; IR (KBr): $\bar{\nu} = 3098$, 2954, 2922, 1744, 1555, 1487, 1210, 1139 cm^{-1}; $[\alpha]_D^{20} = -26.4°\ cm^2\ g^{-1}$ ($c = 1.4$, $CHCl_3$).

Methyl (S,S)-(−)-3-methyl-2-(3-methyl-2-phenyl-2H-isothiazol-5-ylideneamino)pentanoate hydrobromide (**5e**, $C_{17}H_{23}N_2O_2SBr$)

Column chromatography afforded 1.29 g (65%) **5e**. Mp 87°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.97$ (t, $J = 7.39$ Hz, CH_3), 1.11 (d, $J = 6.86$ Hz, CH_3), 1.55 (ddq, CH_3–CH$_a\underline{H}_b$), 1.67 (ddq, CH_3–C$\underline{H}_a$H$_b$), 2.22 (m, CH), 2.24 (s, CH_3), 3.79 (s, OCH_3), 3.89 (dd, CH), 5.99 (s, CH), 7.30 (m, 3H), 7.52 (t, 2H), 10.11 (br s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.3$ (CH_3), 15.7 (CH_3–$\underline{C}H_2$), 15.8 (CH_3), 25.3 (CH_3), 37.3 (CH), 52.5 (OCH_3), 64.6 (CH), 99.4 (CH), 127.3 (CH), 130.1 (CH), 130.6 (CH), 135.0 (C), 161.1 (C–NPh), 170.1 (S–C=NH^+), 171.8 (COO) ppm; IR (KBr): $\bar{\nu} = 3092$, 2955, 2927, 1740, 1555, 1219, 1150 cm^{-1}; $[\alpha]_D^{20} = -8.1°\ cm^2\ g^{-1}$ ($c = 1.5$, $CHCl_3$).

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