New Optically Active Bis-Heterocycles Derived from (*S*)-Proline

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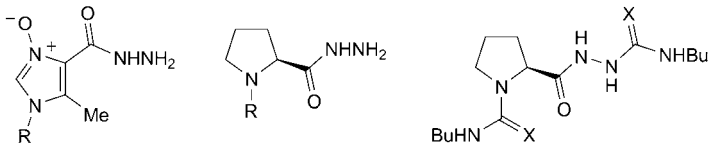
Enantiomerically pure bis-heterocycles containing a (*S*)-proline moiety have been prepared starting from (*S*)-*N*-benzylprolinehydrazide (**2b**). The reactions with isothiocyanates or butyl isocyanate in refluxing MeOH led to the corresponding thiosemicarbazide **5** and semicarbazide **9** with a *N*-benzylprolinoyl residue. The structure of the *tert*-butyl derivative **5d** was established by X-ray crystallography. Base-catalyzed cyclization of **5** and **9** led to (*S*)-3-(pyrrolidin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thiones **6** and the corresponding 5(4*H*)-one **8**, respectively, whereas, in concentrated H_2SO_4, compounds **5** undergo cyclization to give (*S*)-5-amino-2-(pyrrolidin-2-yl)-1,3,4-thiadiazoles **7**. Furthermore, **2b** reacted with hexane-2,5-dione in boiling ^{i}PrOH to yield the (*S*)-*N*-(2,5-dimethylpyrrol-1-yl)prolinamide **10**. In the case of the bis-heterocycle **8**, treatment with $HCOONH_4$ and Pd/C in MeOH gave the debenzylated product **12**.

1. Introduction. – The importance of (*S*)-proline and its derivatives for organocatalysis and asymmetric synthesis is well-documented [1–3]. Acccordingly, the preparation of diverse compounds *via* functionalization of proline is of current interest. To the best of our knowledge, prolinehydrazide was only scarcely studied for this purpose. On the other hand, carbohydrazides are known as versatile starting materials for the synthesis of five- and six-membered heterocycles containing N-, O-, and S-atoms [4]. In our recent publications, the preparation and reactivity of 3-oxidoimidazole-4-carbohydrazides **1** as well as prolinehydrazides **2** were described [5–8]. Semicarbazides and thiosemicarbazides obtained from hydrazides by treatment with isocyanates and isothiocyanates, respectively, are starting materials for cyclocondensations leading to pyrazolones, 1,3,4-oxadiazoles, 1,2,4-triazole-3-thiones, and 1,3,4-thiadiazoles. In a previous study, the non-protected prolinehydrazide **2a** (R = H) was shown to react with butyl isocyanate (BuNCO), as well as with butyl isothiocyanate (BuNCS), to yield bis-adducts of type **3** irrespective of the molar ratio of the reagents [7]. Therefore, for the present study aimed at the preparation of new bis-heterocycles derived from (*S*)-proline, the *N*-benzylprolinehydrazide (**2b**) was selected as the key substrate.

2. Results and Discussion. – The starting hydrazide **2b** was conveniently prepared by treatment of methyl (*S*)-*N*-benzylprolinate with $NH_2NH_2 \cdot H_2O$ [7]. Subsequent

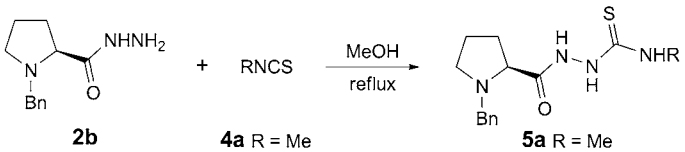
[1]) Part of the planned Ph.D. thesis of *A. M. P.*, University of Łódź.



1 **2a** R = H, **2b** R = Bn, **3** (X = O, S)

reaction of **2b** with isothiocyanates **4a**–**4d** in boiling MeOH afforded the corresponding thiosemicarbazides **5a**–**5d** in good yields (*Scheme 1*).

Scheme 1



2b + RNCS (**4a** R = Me, **4b** R = Bu, **4c** R = Ph, **4d** R = ^{t}Bu) → MeOH, reflux → **5a** R = Me, **5b** R = Bu, **5c** R = Ph, **5d** R = ^{t}Bu

The structures of the products were confirmed from their spectroscopic data. For example, the ^{13}C-NMR spectrum of **5a** exhibited the signals for C=O and C=S at 182.5 and 172.6 ppm, respectively. Finally, the structure of **5d** was established by X-ray crystallography (*Fig. 1*).

The compound in the crystal is enantiomerically pure, and the absolute configuration of the molecule has been determined independently by the diffraction experiment. The molecule has the expected (*S*)-configuration. There are two symmetry-independent molecules in the asymmetric unit. In one of them, the (*tert*-butylamino)thiocarbonyl group is disordered over two nearly equally occupied positions. Intermolecular H-bonds between the N–H groups on either side of the S-atom and the amide O-atom of the other molecule form a ring with a graph set motif [10] of $R_2^1(6)$ and link the two independent molecules into discrete pairs. These two opposing sets of interactions create another ring with a graph set motif of $R_2^2(10)$. The amide group forms an intramolecular H-bond with the heterocyclic ring N-atom to give a loop with a graph set motif of S(5).

After purification, the obtained thiosemicarbazides **5** were treated with 5% aqueous NaOH under reflux conditions, and the corresponding 1,2,4-triazole-3-thione derivatives **6a**–**6c** were obtained as crystalline products. However, in the case of **5d** with the bulky ^{t}Bu substituent, the attempted cyclization failed (*Scheme 2*).

The triazole-3-thiones **6** are optically active compounds and the enantiomeric purity of **6a** was tested by recording the ^{1}H-NMR spectrum in the presence of equimolar amounts of the chiral solvating agent (–)-(S_P)-(*tert*-butyl)(phenyl)phosphinothioic

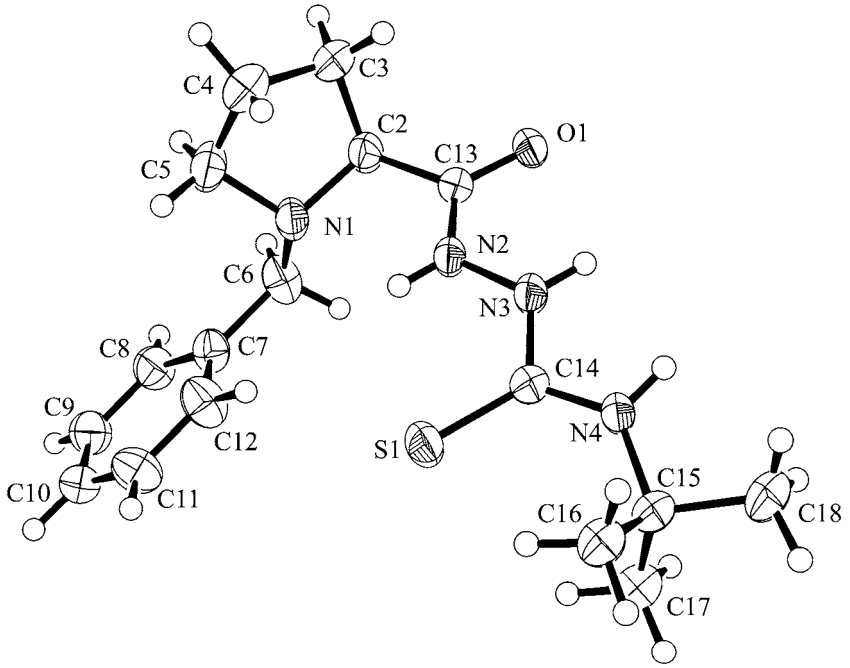
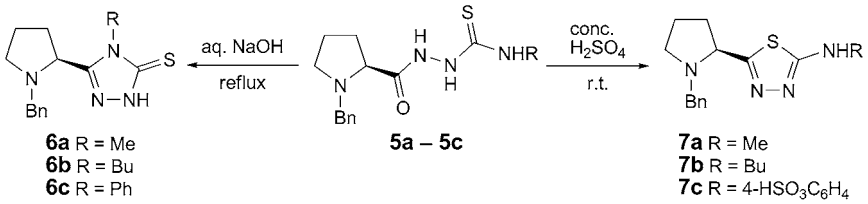


Fig. 1. *ORTEP Plot* [9] *of the molecular structure of one conformation of one of the two symmetry-independent molecules of* **5d** (50% probability ellipsoids; arbitrary numbering of the atoms)

Scheme 2



6a R = Me
6b R = Bu
6c R = Ph

5a – 5c

7a R = Me
7b R = Bu
7c R = 4-$HSO_3C_6H_4$

acid (MOD reagent) [11] (*Fig. 2*). For comparison, racemic triazole-3-thione *rac*-**6a** was synthesized starting with racemic *N*-benzylprolinehydrazide (*rac*-**2b**; *Schemes 1* and *2*). The ^{1}H-NMR spectrum of *rac*-**6a** obtained thereby was also recorded in the presence of MOD reagent. The registered spectra with diagnostic *AB* systems of the PhCH_2 groups are depicted in *Fig. 2*, and, in the case of *rac*-**6a**, two well-separated sets of *AB* signals were detected (8 lines). On the other hand, the spectrum of optically active **6a**, prepared from (*S*)-**2b**, showed only four lines typical for the *AB* system. Thus, the obtained results evidenced that the cyclization of (*S*)-**5a** under basic conditions gave the enantiomerically pure product, *i.e.*, occurred without racemization. Based on this result, enantiomeric purity was also attributed to the optically active triazole-3-thiones **6b** and **6c**, which were also tested with MOD reagent giving only one set of signals for the diagnostic *AB* system in each case.

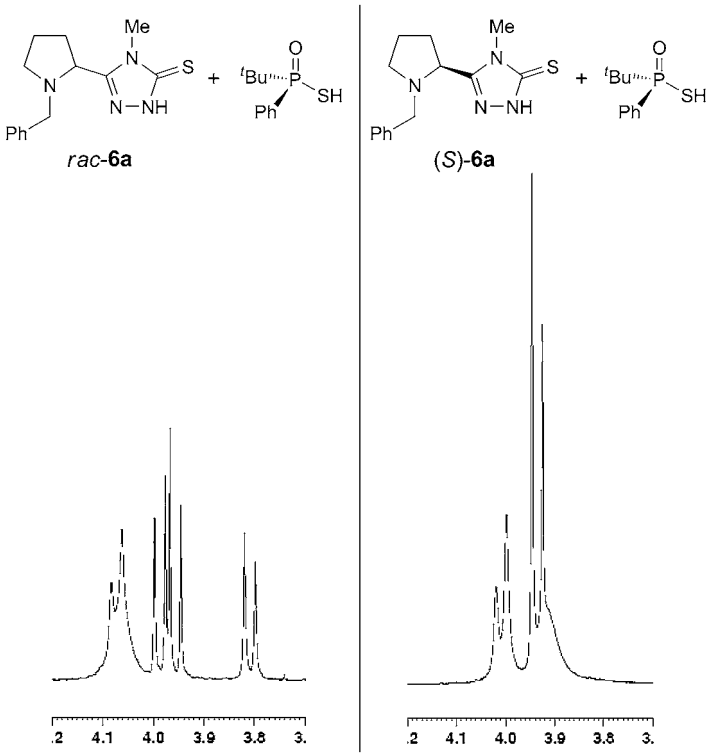


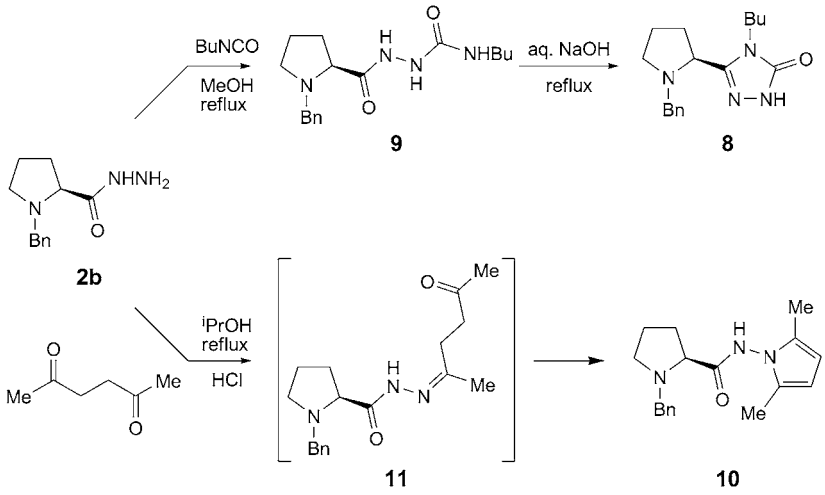
Fig. 2. *Selected* ^{1}*H-NMR signals of* rac-**6a** *and* (*S*)-**6a** *in* $CDCl_3$ *in the presence of 1 equiv. of (−)-*(S_P)*-(*tert*-butyl)(phenyl)phosphinothioic acid*

An alternative cyclization of thiosemicarbazides **5** was observed under acidic conditions. Thus, the reactions of **5a**–**5c** in concentrated H_2SO_4 at room temperature furnished 1,3,4-thiadiazol-2-amines **7a**–**7c** in fair yields (*Scheme 2*). Interestingly, under these conditions, **5c** was converted into **7c**, which contains a sulfonic acid group in the *para*-position of the phenyl ring. An analogous result was observed in the earlier described series of 1,3,4-thiadiazole-2-anilines derived from 3-oxidoimidazole carbohydrazides **1** [6]. Again, an important question was the enantiomeric purity of the obtained products **7**. In the case of **7a**, the ^{1}H-NMR spectrum recorded after addition of 1 mole-quiv. of (−)-(S_P)-(*tert*-butyl)(phenyl)phosphinothioic acid evidenced that no racemization occurred.

In an extension of the experiments described above, the synthesis of a 1,2,4-triazol-3-one **8**, the O-analogue of **6b**, was achieved. In the first step, the reaction of **2b** with BuNCO gave semicarbazide **9** [7], which subsequently was heated in aqeous NaOH, to yield the desired product **8** (*Scheme 3*). The isolated crystalline product was optically active ($[\alpha]_D^{25} = -39$, $c = 1.00$, $CHCl_3$).

In another case, a derivative of a pyrrol-1-yl-substituted (*S*)-proline fragment was prepared by reacting **2b** with hexane-2,5-dione. The reaction was performed in boiling

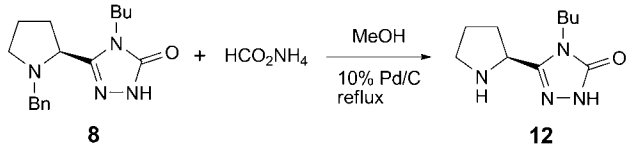
Scheme 3



^{i}PrOH in the presence of a small amount of concentrated HCl. The formation of the final product **10** (*Scheme 3*) results from the cyclocondensation of the *in situ* formed hydrazone **11**. The product displayed optical activity, thus confirming that its formation did not lead to racemization.

In view of the potential application of bis-heterocycles derived from (*S*)-proline in the field of amino catalysis, the availability of the non-protected proline moiety is of great importance. For this reason, the debenzylation of selected products obtained in this study was attempted. In a typical procedure, a methanolic solution of **8** and 5 equiv. of HCO_2NH_4 in the presence of catalytic amounts of Pd/C was heated to reflux for 1 h [12]. After usual workup, **12** was obtained in 95% yield (*Scheme 4*).

Scheme 4



Unfortunately, the attempted hydrogenolytic deprotections (HCO_2NH_4, Pd/C, heating or H_2, Pd/C) of 1,2,4-triazole-3-thione **6b** and 1,3,4-thiadiazole **7b** failed.

3. Conclusions. – This study revealed that the (*S*)-*N*-benzylprolinehydrazide (**2b**) smoothly undergoes reaction with butyl isocyanate and isothiocyanates to yield the desired semicarbazide **9** and thiosemicarbazides **5**, respectively, in good-to-excellent yields. These derivatives were used for cyclization reactions, which afforded bis-heterocycles such as (*S*)-pyrrolidin-2-yl-1,2,4-triazole-3-one **8** or (*S*)-pyrrolidin-2-yl-

1,2,4-triazole-3-thiones **6**, respectively, upon treatment with aqueous NaOH. On the other hand, cyclizations of thiosemicarbazides **5** performed in concentrated H_2SO_4 led to (*S*)-pyrrolidin-2-yl-1,3,4-thiadiazol-2-amines **7**. However, the analogous reaction of semicarbazide **9** with H_2SO_4, expected to yield a 1,3,4-oxadiazol-2-amine, was unsuccessful. Furthermore, the presence of the bulky *t*Bu group in thiosemicarbazides or in semicarbazides prevents the cyclization step, and in these cases no expected bis-heterocyclic products could be obtained. Another cyclization leading to (*S*)-pyrrolidin-2-yl-pyrrole derivative **10** was successfully carried out using hexane-2,5-dione as the substrate. All bis-heterocyclic products were isolated as optically active compounds, and the ^{1}H-NMR experiments performed with (−)-(S_P)-(*tert*-butyl)(phenyl)phosphinothioic acid (MOD reagent) established that they are enantiomerically pure substances. In addition, it was demonstrated that, in the case of *N*-benzylated pyrrolidin-2-yl-1,2,4-triazole-3-one **8**, debenzylation can be efficiently performed by treatment of the desired substrate with HCO_2NH_4/Pd,C. The enantiomerically pure semicarbazide, thiosemicarbazides, and bis-heterocycles described in these study constitute a new group of (*S*)-proline derivatives, which are of potential importance for new applications as ligands and organocatalysts for asymmetric synthesis.

The authors thank PD Dr. *L. Bigler*, University of Zurich, for recording of the HR-ESI-MS. *A. M. P.* thanks for financial support within the project co-funded by the *European Union* under the *European Social Fund ' HUMAN – BEST INVESTMENT!'*.

Experimental Part

1. *General.* M.p.: *Melt-Temp. II* (*Aldrich*) or *STUART SMP30* apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241 MC* polarimeter for λ 589 nm. IR Spectra: *NEXUS* FT-IR spectrophotometer; in KBr; absorptions in cm^{-1}. ^{1}H- and ^{13}C{^{1}H}-NMR spectra: *Bruker Avance III* (600 and 150 MHz, resp.), in $CDCl_3$, using solvent signal as reference; δ in ppm; coupling constants *J* in Hz; assignments of signals in ^{13}C-NMR spectra accomplished by HMQC experiments. HR-ESI-MS: *Bruker maXis* spectrometer.

2. *Starting Materials.* All solvents are commercially available and used as received. *(*S*)-N-Benzylprolinehydrazide* (**2b**) [7] was prepared according to known procedures.

3. *Synthesis of Thiosemicarbazides* **5a**–**5d** *and Semicarbazide* **9**. *General Procedure.* A mixture of **2b** (1 mmol) and the corresponding isothiocyanate (1.1 mmol) or isocyanate (1.1 mmol) in EtOH (5 ml) was heated to reflux for 2 h. Then, the formed product was filtered off, washed with Et_2O and crystallized from MeOH.

*1-({[(2*S*)-1-Benzylpyrrolidine-2-yl]carbonyl}amino)-3-methylthiourea* (**5a**). Yield: 0.263 g (90%). Pale yellow oil. $[\alpha]_D^{25} = -79$ ($c = 1.00$, $CHCl_3$). IR (film): 3262*s* (br., NH), 2969*s*, 1684v*s* (C=O), 1551*s*, 1495*m*, 1277*m*, 702*m*. ^{1}H-NMR ($CDCl_3$): 8.99 (br. *s*, NH); 7.44–7.30 (*m*, 5 arom. H); 6.66 (br. *s*, NH); 3.97, 3.66 (*AB*, $J_{AB} = 13.2$, PhCH_2); 3.40–3.37 (*m*, CH); 3.16–3.13 (*m*, 1 H, Pro); 3.06 (*d*, $J = 3.0$, Me); 2.50–2.46 (*m*, 1 H, Pro); 2.28–2.22 (*m*, 1 H, Pro); 2.05–1.86 (*m*, 3 H, Pro). ^{13}C-NMR ($CDCl_3$): 182.5, 172.6 (C=O, C=S); 138.2 (1 arom. C); 129.2, 128.6, 127.5 (5 arom. CH); 66.2 (CH); 60.4 (Ph*C*H$_2$); 54.5, 30.8, 24.3 (3 CH_2); 31.4 (Me). HR-ESI-MS: 293.1432 ([$M+1$]$^+$, $C_{14}H_{21}N_4OS^+$; calc. 293.1431).

*1-({[(2*S*)-1-Benzylpyrrolidine-2-yl]carbonyl}amino)-3-butylthiourea* (**5b**). See [7].

*1-({[(2*S*)-1-Benzylpyrrolidine-2-yl]carbonyl}amino)-3-phenylthiourea* (**5c**). Yield: 0.336 g (95%). Pale yellow oil. $[\alpha]_D^{25} = -59$ ($c = 1.00$, $CHCl_3$). IR (film): 3243*s* (br., NH), 2971*s*, 1662v*s* (C=O), 1600*s*, 1497*s*, 1450*m*, 1320*m*, 698*m*. ^{1}H-NMR ($CDCl_3$): 9.93, 8.83 (2 br. *s*, 2 NH); 7.52–7.22 (*m*, 10 arom. H); 4.04, 3.58 (*AB*, $J_{AB} = 13.2$, PhCH_2); 3.41–3.38 (*m*, CH); 3.12–3.08 (*m*, 1 H, Pro); 2.43–2.38 (*m*, 1 H, Pro); 2.25–2.20 (*m*, 1 H, Pro); 2.04–1.79 (*m*, 3 H, Pro). ^{13}C-NMR ($CDCl_3$): 177.2, 170.6 (C=O, C=S);

137.7, 129.6 (2 arom. C); 129.2, 128.5, 128.4, 127.5, 126.0, 123.9 (10 arom. CH); 66.2 (CH); 60.2 (Ph*C*H_2); 54.0, 30.7, 24.2 (3 CH_2). HR-ESI-MS: 355.1592 ($[M+1]^+$, $C_{19}H_{23}N_4OS^+$; calc. 355.1587).

*1-({[(2*S*)-1-Benzylpyrrolidine-2-yl]carbonyl}amino)-3-(*tert*-butyl)thiourea* (**5d**). Yield: 0.321 g (96%). Colorless crystals. M.p. 154–156° (^{i}PrOH). $[\alpha]_D^{25} = -63$ ($c = 1.00$, $CHCl_3$). IR (KBr): 3306*s* (NH), 3228*s* (NH), 2962*s*, 1652v*s* (C=O), 1558*s*, 1482*m*, 1362*m*, 1277*m*. ^{1}H-NMR ($CDCl_3$): 9.25 (br. *s*, NH); 7.46–7.25 (*m*, 5 arom. H); 6.97 (br. *s*, NH); 4.01, 3.55 (*AB*, $J_{AB} = 13.2$, PhCH_2); 3.34–3.31 (*m*, CH); 3.08–3.05 (*m*, 1 H, Pro); 2.39–2.35 (*m*, 1 H, Pro); 2.25–2.18 (*m*, 1 H, Pro); 2.00–1.81 (*m*, 3 H, Pro); 1.51 (*s*, 3 Me). ^{13}C-NMR ($CDCl_3$): 178.1, 169.6 (C=O, C=S); 137.9 (1 arom. C); 129.1, 128.5, 127.5 (5 arom. CH); 66.2 (CH); 60.2 (Ph*C*H_2); 53.9, 30.8, 24.2 (3 CH_2); 53.7 (Me_3C); 29.0 (Me_3C). HR-ESI-MS: 335.1906 ($[M+1]^+$, $C_{17}H_{27}N_4OS^+$; calc. 335.1900).

Suitable crystals of **5d** for the X-ray crystal-structure determination were grown from ^{i}PrOH.

*1-({[(2*S*)-1-Benzylpyrrolidine-2-yl]carbonyl}amino)-3-butylurea* (**9**). See [7].

4. *Synthesis of Optically Active 1,2,4-Triazole-3-thiones* **6** *and 1,2,4-Triazole-3-one* **8**. *General Procedure.* A mixture of **5** (1 mmol) or **9** [7] (1 mmol), and a 2% aq. soln. of NaOH (5 ml) was heated to reflux for 2 h. Then, the soln. was neutralized with AcOH, and the formed precipitate was filtered off and crystallized from H_2O.

Racemic **6a** was obtained from *rac*-**5a** by the same procedure.

*5-[(2*S*)-1-Benzylpyrrolidin-2-yl]-2,4-dihydro-4-methyl-3*H*-1,2,4-triazole-3-thione* (**6a**). Yield: 0.219 g (80%). Colorless crystals. M.p. 130–132° (H_2O). $[\alpha]_D^{25} = -42$ ($c = 1.00$, $CHCl_3$). IR (KBr): 3142*m*, 2941*s*, 2552*m* (br.), 1571*s*, 1453*m*, 1333*m*, 1071*m*. ^{1}H-NMR ($CDCl_3$): 11.36 (br. *s*, HN); 7.29–7.18 (*m*, 5 arom. H); 3.76, 3.41 (*AB*, $J_{AB} = 13.2$, PhCH_2); 3.71 (*s*, Me); 3.75–3.72 (*m*, CH); 3.14–3.11 (*m*, 1 H); 2.36–2.22 (*m*, 2 H); 1.99–1.89 (*m*, 3 H). ^{13}C-NMR ($CDCl_3$): 168.9 (C=S); 152.6, 137.7 (1 arom. C, C(3)); 128.7, 128.3, 127.6 (5 arom. CH); 60.8 (CH); 58.5 (Ph*C*H_2); 53.6, 29.1, 22.9 (3 CH_2); 31.3 (Me). HR-ESI-MS: 275.1327 ($[M+1]^+$, $C_{17}H_{27}N_4OS^+$; calc. 275.1325).

rac-*5-(1-Benzylpyrrolidin-2-yl)-4-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione* (*rac*-**6a**). Yield: 0.222 g (81%). Colorless crystals. M.p. 166–167° (H_2O).

*5-[(2*S*)-1-Benzylpyrrolidin-2-yl]-4-butyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione* (**6b**). See [7].

*5-[(2*S*)-1-Benzylpyrrolidin-2-yl]-2,4-dihydro-4-phenyl-3*H*-1,2,4-triazole-3-thione* (**6c**). Yield: 0.286 g (85%). Colorless crystals. M.p. 129–131° (H_2O). $[\alpha]_D^{25} = -55$ ($c = 1.00$, $CHCl_3$). IR (KBr): 3223*m* (NH), 3029*m*, 2934*m* (br.), 1560*m*, 1497*s*, 1312*m*, 695*m*. ^{1}H-NMR ($CDCl_3$): 11.03 (br. *s*, NH); 7.52–7.20 (*m*, 10 arom. H); 3.86, 3.47 (*AB*, $J_{AB} = 13.2$, PhCH_2); 3.55–3.53 (*m*, CH); 3.01–2.97 (*m*, 1 H); 2.36–2.31 (*m*, 1 H); 1.98–1.61 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 169.5 (C=S); 154.4, 137.9, 133.6 (2 arom. C, C(3)); 130.0, 129.6, 128.9, 128.5, 128.3, 127.2 (10 arom. CH); 59.0 (CH); 58.0 (Ph*C*H_2); 52.9, 30.7, 22.9 (3 CH_2). HR-ESI-MS: 337.1487 ($[M+1]^+$, $C_{19}H_{21}N_4S^+$; calc. 337.1481).

*5-[(2*S*)-1-Benzylpyrrolidin-2-yl]-4-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one* (**8**). Yield: 0.165 g (55%). Colorless oil. $[\alpha]_D^{25} = -39$ ($c = 1.00$, $CHCl_3$). IR (film): 3197*m* (br., NH), 2959*s*, 1701v*s* (C=O), 1468*m*, 1102*m*. ^{1}H-NMR ($CDCl_3$): 9.63 (br. *s*, NH); 7.30–7.22 (*m*, 5 arom. H); 3.95–3.91 (*m*, 1 H, CH_2 of Bu); 3.86, 3.37 (*AB*, $J_{AB} = 13.2$, PhCH_2); 3.66–3.62 (*m*, 1 H, CH_2 of Bu); 3.57–3.54 (*m*, CH); 3.09–3.07 (*m*, 1 H); 2.30–2.20 (*m*, 2 H); 1.97–1.87 (*m*, 3 H); 1.72–1.36 (*m*, 2 CH_2, Bu); 0.94 (*t*, $J = 7.8$, Me). ^{13}C-NMR ($CDCl_3$): 156.4 (C=O); 148.4, 138.0 (1 arom. C, C(3)); 128.8, 128.2, 127.1 (5 arom. CH); 61.3 (CH); 58.2 (Ph*C*H_2); 53.2, 29.5, 22.8 (3 CH_2); 41.7, 31.0, 20.1 (3 CH_2, Bu); 13.7 (Me). HR-ESI-MS: 301.2026 ($[M+1]^+$, $C_{17}H_{25}N_4O^+$; calc. 301.2023).

5. *Synthesis of 1,3,4-Thiadiazoles* **7**. *General Procedure.* A soln. of **5** (1 mmol) in conc. H_2SO_4 (5 ml) was kept at r.t. for 1 d. After neutralization of the soln. with dil. NH_4OH, the solid product was filtered off, dried *i.v.*, and crystallized from H_2O.

Racemic **7a** was obtained from *rac*-**5a** by the same procedure.

*5-[(2*S*)-1-Benzylpyrrolidin-2-yl]-*N*-methyl-1,3,4-thiadiazol-2-amine* (**7a**). Yield: 0.241 g (88%). Yellowish crystals. M.p. 128–130° (H_2O). $[\alpha]_D^{25} = -78$ ($c = 1.00$, $CHCl_3$). IR (KBr): 3250*s* (HN), 3024*m*, 1546*s*, 1520*m*, 1153*m*, 1113*m*. ^{1}H-NMR ($CDCl_3$): 7.33–7.25 (*m*, 5 arom. H); 5.43 (br. *s*, NH); 4.02, 3.38 (*AB*, $J_{AB} = 13.2$, PhCH_2); 3.99–3.96 (*m*, CH); 3.07–3.04 (*m*, 1 H, Me); 2.36–2.30 (*m*, 2 H); 1.96–1.80 (*m*, 3 H). ^{13}C-NMR ($CDC1_3$): 171.7, 142.7 (thiadiazol C(2), C(5)); 138.4 (1 arom. C); 128.8, 128.3, 127.2 (5 arom. CH); 63.7 (CH); 58.0 (Ph*C*H_2); 53.0, 33.3, 22.9 (3 CH_2); 33.2 (Me). HR-ESI-MS: 275.1326 ($[M+1]^+$, $C_{14}H_{19}N_4S^+$; calc. 275.1325).

rac-*5-(1-Benzylpyrrolidin-2-yl)*-N-*methyl-1,3,4-thiadiazol-2-amine* (*rac*-**7a**). Yield: 0.247 g (90%). Yellowish crystals. M.p. 158–159° (H_2O).

*5-[(2*S*)-1-Benzylpyrrolidin-2-yl]*-N-*butyl-1,3,4-thiadiazol-2-amine* (**7b**). See [7].

*4-({5-[(2*S*)-1-Benzylpyrrolidin-2-yl]-1,3,4-thiadiazol-2-yl}amino)benzenesulfonic Acid* (**7c**). Yield: 0.225 g (54%). Yellowish crystals. M.p. 262–264° (H_2O). $[\alpha]_D^{25} = -89$ ($c = 1.00$, $CHCl_3$). IR (KBr): 3550–3100*m* (br.), 3266*s* (NH), 2979*m*, 1603*m*, 1508*s*, 1220*m* (br.), 1132*m*. ^{1}H-NMR ($CDCl_3$): 10.32 (br. *s*, NH); 7.53–7.24 (*m*, 9 arom. H); 3.96–3.94 (*m*, CH); 3.91, 3.39 (*AB*, $J_{AB} = 13.2$, PhCH_2); 2.92–2.89 (*m*, 1 H, Me); 2.38–2.28 (*m*, 2 H); 1.83–1.79 (*m*, 3 H). ^{13}C-NMR ($CDCl_3$): 171.1, 142.5 (thiadiazol C(2), C(5)); 139.1, 128.9, 127.0 (3 arom. C); 128.7, 127.4, 127.1, 116.6, 112.7 (9 arom. CH); 63.4 (CH); 58.0 (PhCH_2); 53.1, 33.6, 23.2 (3 CH_2). HR-ESI-MS: 415.0909 ($[M-1]^+$, $C_{19}H_{19}N_4O_3S_2^+$; calc. 415.0904).

6. *Synthesis of (2*S*)-1-Benzyl*-N-*(2,5-dimethylpyrrol-1-yl)pyrrolidine-2-carboxamide* (=*1-Benzyl*-N-*(2,5-dimethyl-1*H*-pyrrol-1-yl)*-L-*prolinamide*; **10**). A mixture of **2b** (1 mmol), hexane-2,5-dione (3 mmol), ^{i}PrOH (15 ml), and conc. HCl (0.5 ml) was heated to reflux for 4 h, then cooled, and H_2O (15 ml) was added. The mixture was extracted with $CHCl_3$, the org. layer was dried (Na_2SO_4), and the solvent was evaporated. The crude product **10** was purified by flash chromatography and crystallization. Yield: 0.199 g (67%). Colorless crystals. M.p. 131–132° (MeOH). $[\alpha]_D^{25} = -69$ ($c = 1.00$, $CHCl_3$). IR (KBr): 3250*s* (br.), (NH), 2973*m*, 1678v*s* (C=O), 1473*m*, 1416*m*, 699*m*. ^{1}H-NMR ($CDCl_3$): 9.45 (br. *s*, NH); 7.36–7.28 (*m*, 5 arom. H); 5.80 (*s*, 2 pyrrol CH=); 4.05, 3.60 (*AB*, $J_{AB} = 13.2$, PhCH_2); 3.52–3.50 (*m*, CH); 3.12–3.10 (*m*, 1 H); 2.48–2.32 (*m*, 2 H); 2.10–1.84 (*m*, 3 H, 2 Me). ^{13}C-NMR ($CDC1_3$): 173.2 (C=O); 138.1 (1 arom. C); 128.8, 128.7, 127.7, 127.6 (5 arom. CH and 2 pyrrole C); 104.1 (2 CH=); 66.9 (CH); 60.3 (PhCH_2); 54.1, 31.1, 24.4 (3 CH_2); 11.1 (2 Me). HR-ESI-MS: 298.1914 ($[M+1]^+$, $C_{18}H_{24}N_3O^+$; calc. 298.1914).

7. *Synthesis of 4-Butyl-2,4-dihydro-5-[(2*S*)-pyrrolidin-2-yl]-3*H*-1,2,4-triazol-3-one*; **12**). To a magnetically stirred soln. of **8** (1 mmol) in MeOH (2 ml) were added 10% Pd/C (165 mg) and HCO_2NH_4 (5 mmol). The mixture was heated at reflux for 1 h. After cooling to r.t., Pd/C was filtered, and the resulting soln. was concentrated under reduced pressure. The crude product **12** was purified by short flash chromatography. Yield: 0.199 g (95%). Colorless oil. $[\alpha]_D^{25} = -87$ ($c = 1.00$, $CHCl_3$). IR (film): 3169*m* (br., NH), 2963*s*, 1702v*s* (C=O), 1652*m*, 1393*m*, 743*m*. ^{1}H-NMR ((D$_6$)DMSO): 8.34 (br. *s*, NH); 4.07–4.05 (*m*, CH); 3.60–3.56 (*m*, 1 CH_2, Bu); 2.85–2.70 (*m*, 2 H); 2.08–2.04 (*m*, 1 H); 1.91–1.74 (*m*, 2 H); 1.67–1.56 (*m*, 1 H, 1 CH_2 of Bu); 1.30–1.25 (*m*, 1 CH_2, Bu); 0.89 (*t*, $J = 7.8$, Me). ^{13}C-NMR ((D$_6$)DMSO): 165.2 (C=O); 149.3 (C(3)); 53.8 (CH); 46.9, 28.7, 23.7 (3 CH_2); 41.7, 31.1, 19.9 (3 CH_2, Bu); 14.0 (Me). HR-ESI-MS: 211.1554 ($[M+1]^+$, $C_{10}H_{19}N_4O^+$; calc. 211.1553).

8. *X-Ray Crystal-Structure Determination of* **5d** (*Table* and *Fig. 1*)[2]). All measurements were made on an *Agilent Technologies SuperNova* area-detector diffractometer [13] using CuK_α radiation ($\lambda =$ 1.54184 Å) from a micro-focus X-ray source and an *Oxford Instruments Cryojet XL* cooler. Data reduction was performed with *CrysAlisPro* [13]. The intensities were corrected for *Lorentz* and polarization effects, and an empirical absorption correction using spherical harmonics [13] was applied. The space group was determined from packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure. Equivalent reflections, other than *Friedel* pairs, were merged. The data collection and refinement parameters are compiled in the *Table*. A view of the molecule is shown in *Fig. 1*. The structure was solved by direct methods using *SHELXS97* [14], which revealed the positions of all non-H-atoms. There are two symmetry-independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program PLATON [15], but none could be found. In one of them, the (*tert*-butylamino)thiocarbonyl group is disordered over two nearly equally occupied positions. Two sets of positions were defined for the atoms of the ^{t}Bu group and the neighboring N-atom, and the site occupation factor of the major conformation of these groups was refined to 0.564(7). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered atoms, while neighboring atoms within and between each conformation of the disordered

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[2]) CCDC-897913 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

Table 1. *Crystallographic Data for Compound* **5d**

Crystallized from		^{i}PrOH
Empirical formula		$C_{17}H_{26}N_4OS$
Formula weight [g mol^{-1}]		334.48
Crystal color, habit		Colorless, prism
Crystal dimensions [mm]		$0.18 \times 0.20 \times 0.25$
Temp. [K]		160(1)
Crystal system		monoclinic
Space group		$P2_1$
Z		4
Reflections for cell determination		13773
2θ Range for cell determination [°]		6–15
Unit cell parameters	a [Å]	11.72165(12)
	b [Å]	11.54445(12)
	c [Å]	14.70502(17)
	β [°]	105.5398(11)
V [Å^3]		1917.14(4)
D_x [g cm^{-3}]		1.159
μ(CuK_α) [mm^{-1}]		1.567
Scan type		ω
$2\theta_{(max)}$ [°]		153.3
Transmission factors (min; max)		0.722; 1.000
Total reflections measured		20475
Symmetry independent reflections		7676
Reflections with $I > 2\sigma(I)$		7427
Reflections used in refinement		7676
Parameters refined; restraints		492; 120
Final	$R(F)$ [$I > 2\sigma(I)$ reflections]	0.0241
	$wR(F^2)$ (all data)	0.0654
Weights:	$w = [\sigma^2(F_o^2) + (0.0370P)^2 + 0.1103P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$	
Goodness-of-fit		1.019
Secondary extinction coefficient		0.0009(2)
Final Δ_{max}/σ		0.001
$\Delta\rho$ (max; min) [e Å^{-3}]		0.15; −0.13

region were restrained to have similar atomic displacement parameters. The non-H-atoms were refined anisotropically. Except for the disordered group, the amide H-atoms were placed in the positions indicated by a difference electron-density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom (1.5 U_{eq} for Me groups). The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Refinement of the absolute structure parameter [16] yielded a value of 0.001(8), which confidently confirms that the refined coordinates represent the true enantiomorph. Neutral atom scattering factors for non-H-atoms were taken from [17a], and the scattering factors for H-atoms were taken from [18]. Anomalous dispersion effects were included in F_c [19]; the values for f' and f'' were those of [17b]. The values of the mass attenuation coefficients are those of [17c]. The SHELXL97 program [14] was used for all calculations.

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