J. prakt. Chem. 339 (1997) 541–546

Journal für praktische Chemie
Chemiker-Zeitung

A New Enantioselective Synthetic Approach to β-Aminothio-Compounds *via* Enantioselective Reduction of *N,S*-Heterocyclic Imines

Iris Reiners, Harald Gröger and Jürgen Martens

Oldenburg, Fachbereich Chemie der Universität

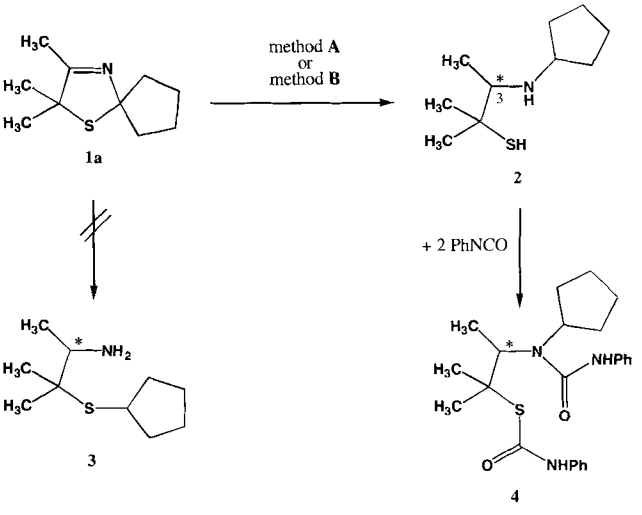
Received December 10th, 1996 respectively May 20th, 1997

Dedicated to Prof. Dr. Friedrich Asinger on the Occasion of his 90th Birthday

Abstract. The enantioselective reduction of *N,S*-heterocyclic imines, namely thiazolines **1a,b** and 2*H*-1,4-benzothiazine **1c**, *via* three different reduction methods is reported. The influence of reaction parameters, substituents, and the type of heterocycle was investigated. Reduction of the prochiral imines led to the corresponding amine derivatives **2**, **10**, **12** and **14**. The best result was obtained by stoichiometric enantioselective reduction of **1c** with 44% *ee*.

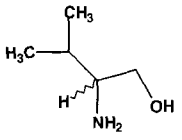
Reductions belong to traditional, but nevertheless most important and well investigated research topics in organic chemistry. In the course of the increasing attempts in stereochemical guidance of reactions in general, milestones in enantioselective synthesis have been reported especially in the field of reduction [1]. In the past most of research with enantioselective, catalytic reduction of C=X-double bonds has dealt with carbonyl compounds whereas the behaviour of the corresponding imine systems has been less investigated [2] and is often limited by low enantiomeric excesses [3]. Moreover, some efficient reduction methods are limited by the choice of starting components. For example enantioselective hydrogenation of prochiral imines in the presence of Pd catalysts [4] cannot be used for imines containing sulfur. Consequently, it was a challenge to search for a stereoselective, catalytic approach to the reduction of a variety of different *S*-containing, heterocyclic imines, well-known as precursor in pharmaceutical and biological applications [5]. To the best of our knowledge stereoselective reduction of *N,S*-heterocyclic imines have not yet been carried out until now [6]. In continuation of our research on stereoselective addition reactions to *S*-containing heterocyclic imines [7], we wish to report a new regio- and enantioselective synthetic approach to β-aminothio-systems *via* C=N-reduction of thiazolines **1a,b** and 2*H*-1,4-benzothiazine **1c**.

Concerning the aliphatic cyclic thiazolines in general, in 1959 Asinger first described the behaviour of these compounds towards several achiral reduction agents. Therefore, only the corresponding secondary β-aminothiol derivatives of type **2** were prepared by reduction and ring opening of thiazolines with lithium aluminium hydride [8]. The corresponding aminothioether derivatives of type **3** were not observed. Our search for a stereoselective preparation method of such secondary thio analogues of amino alcohols led us to the chiral amino alcohol catalyzed borane reduction method [9], which was very successful in enantioselective reduction of ketones [10, 11] (method **A**). Treatment of the prochiral thiazoline **1a** with borane in the pres-

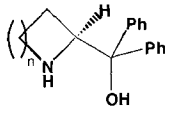


ence of racemic or enantiomeric pure amino alcohols in THF gave the new secondary aminothiol **2** in chemical yields up to 55%.

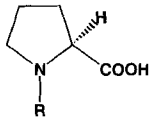
This was proved by treatment of the purified reduction product with phenylisocyanate which resulted in the disubstituted urea derivative **4**. For the determination of the enantiomeric excess of the chiral β-aminothiol **2**, the racemate of **2** was synthesized using the racemic amino alcohol *rac*-valinol *rac*-**5**. We successfully used optically pure (*S*)-*O*-acetylmandelic acid as chiral derivatizing agent [12]. For the enantioselective reduction of **1a** the enantiomeric pure amino alcohol (*S*)-**7** [13] was used as ligand (table 1).



rac-**5**



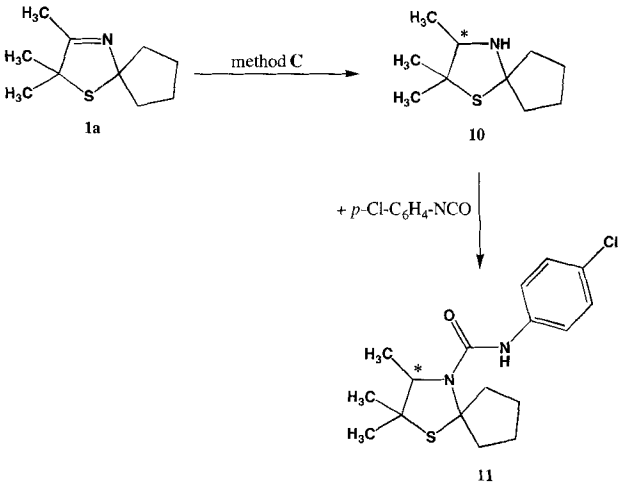
(*S*)-**6** (n=2)
(*S*)-**7** (n=1)



(*S*)-**8** (R = Boc)
(*S*)-**9** (R = Z)

The unsatisfactory result with low enantiomeric excess (*ee*) for **2** (6% *ee*) led us to investigate an earlier reduction method described by Iwakuma [14] (method **B**). Thus, stoichiometric amounts of chiral sodium acyloxyborohydrides of (*S*)-proline derivatives (*S*)-**8** and (*S*)-**9** were used as enantioselective reducing agent in the reaction with imine **1a**. As shown in table 1, the acyloxyborohydrides derived from (*S*)-acylproline (*S*)-**8** or (*S*)-**9** and sodium borohydride led to improved *ee*'s. In parallel, chemical yields increased up to 75%. Although stoichiometric amounts are necessary, (*S*)-**9** is inexpensive and furthermore *N*-(Boc)-proline (*S*)-**8** is recycable in nearly quantitative yield after the reduction [14]. The results obtained with catalytic *versus* stoichiometric enantioselective reduction method for the preparation of the secondary β-aminothiol **2** are summarized in table 1 (entries 1–4).

In addition we were interested to avoid ring-opening by preparing the corresponding ring closed thiazolidine **10** as reduction product. The prevention of ring opening of the thiazolidine system afforded a smooth enantioselective reduction agent.



We were pleased to find that a modification of the – in case of **2** – reported-borane reduction, in which the oxazaborolidines and catecholborane are used at room temperature in toluene [15] (method **C**), gave the thiazolidine **10** in chemical yields up to 58%. The structure of **10** was proved by treatment with *p*-chlorophenylisocyanate resulting in the formation of compound **11**. However, the reduction of **1a** by catecholborane in the presence of a chiral oxazaborolidine (containing (*S*)-**7**) as catalyst produced almost racemic thiazolidine **10** [16] (see table 1, entries 5, 6).

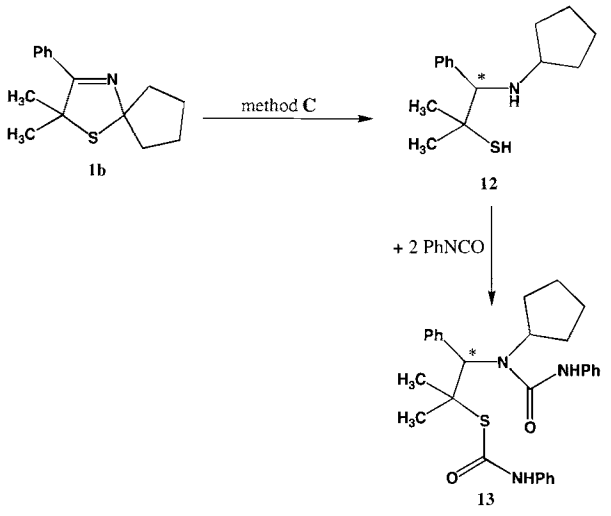
The ring-opening depends not only on the reaction method but also on the nature of the substituents in thiazolines **1a** and **1b**. This is underlined by the catecholborane reduction of the C=N-double bond in **1b** (method **C**). Here, the saturated heterocyclic thiazolidine ring is completely opened upon work up and gave the amino

Table 1 Enantioselective reduction of cyclic imines **1a–c** by three different methods **A–C**

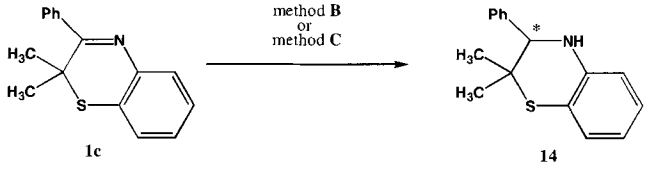
entry	imine	reducing agent	chiral compound	product	method	time (d)	temp. (°C)	yield (%)	*ee* (%)
1	**1a**	BH_3·THF	(*S*)-**7** [a] 0.2 equiv.	**2**	**A**	6	30	43	6
2	**1a**	$NaBH_4$	(*S*)-**8** [b] 1 equiv.	**2**	**B**	10	20	58	12
3	**1a**	$NaBH_4$	(*S*)-**9** [b] 2 equiv.	**2**	**B**	10	20	75	28
4	**1a**	$NaBH_4$	(*S*)-**9** [b] 2 equiv.	**2**	**B**	15	20	71	30
5	**1a**	Catecholboran 1.5 eq. [a]	(*S*)-**7** [a] 0.2 equiv.	**10**	**C**	2	20	58	4
6	**1a**	Catecholboran 1.5 eq. [a]	(*S*)-**6** [a] 0.2 equiv.	**10**	**C**	2	20	20	2
7	**1b**	Catecholboran 2 eq. [a]	(*S*)-**7** [a] 0.2 equiv.	**12**	**C**	2	20	58	12
8	**1b**	Catecholboran 3 eq. [a]	(*S*)-**7** [a] 0.2 equiv.	**12**	**C**	2	35	55	8
9	**1c**	$NaBH_4$	(*S*)-**8** [b] 3 equiv.	**14**	**B**	10	20	73	44
10	**1c**	Catecholboran	(*S*)-**7** [a] 0.2 equiv.	**14**	**C**	2	20	96	20 [c]

[a] number of equivalents related to the amount of the imine compound; [b] number of equivalents related to the amount of the reducing agent; [c] compared with entry 9, the enantiomer with the opposite absolute configuration was formed as major enantiomer.

thiol **12**. The structure of **12** has been proved by treatment of purified **12** with phenylisocyanate, which resulted in the formation of the substituted urea derivative **13**. However, if the boronates of the amino acids (*S*)-**8** or (*S*)-**9** were used as reducing agents (method **B**), the ring opening was incomplete.



Enantioselective reduction processes were carried out by the methods **B** and **C** starting from 2,2-dimethyl-3-phenyl-2*H*-1,4-benzothiazine **1c** to give product **14**.



Compared with the enantioselectivity observed in the reduction of the C=N-double bond of **1a,b**, the imine double bond of the benzothiazine **1c** was reduced with an increasing *ee* value up to 44% (determined by chiral HPLC analysis). The best result was obtained using the convenient stoichiometric enantioselective reduction method **B** [14] with a boronate of the *N*-acyl amino acid (*S*)-**8** (see table 1, entry 9). Consequently, regarding the low to modest enantioselectivities, obtained with the thiazolines **1a** and **1b**, respectively, the improved enantioselectivity in case of the aromatic heterocyclic benzothiazine **1c** might be explained by the more disk like shape of the heterocycle **1c**.

Acknowledgements: We thank the Degussa AG and the Hoechst AG for support. Iris Reiners thanks the Hermann Schlosser Stiftung for a Ph. D. fellowship and Harald Gröger thanks the Heinz Neumüller Stiftung for a Ph. D. fellowship.

Experimental

All reactions were carried out in oven dried glassware, under argon atmosphere and using anhydrous solvents. Melting points were taken on a melting point apparatus according to Dr. Linström and are uncorrected. IR spectra were recorded on a Philips PU 9706 spectrophotometer. The NMR spectra were registered on a Bruker AM 300 spectrometer. Mass spectra were recorded on a Finnigan-MAT 212 (data system 300; CI, *i*-butane). Elemental analyses (C, H, N) were performed on a Carlo Erba Stumentalione (MOD 1104) analyzer. All new compounds gave satisfactory analytical data for C, H and N. Chiral HPLC analysis was performed on a Merck/Hitachi Lichrograph, chiral column: Chiralpak AS, mobile phase: *n*-Hexane/Isopropanol = 98 : 2, flow rate 0.5 ml/min., detection: UV 254 nm. Commercially available chemicals were used. The compounds **1c** [17], *rac*-**5** [18], (*S*)-**6** [19], (*S*)-**7** [13], (*S*)-**8** [20], (*S*)-**9** [21] and *rac*-**14** [22] were prepared according to the literature.

Synthesis of the thiazolines 1a,b; General Procedure GP1

At a temperature between 0 and 10 °C the α-chloroketone (0.30 mol), dissolved in 30 ml of CH_2Cl_2, was added dropwise over 0.5 h to a mixture of aqueous ammonia (25%, 65 ml), cyclopentanone (29.4 g, 0.35 mol) and sodium hydrogen sulfide monohydrate (25.9 g, 0.35 mol). Subsequently, CH_2Cl_2 (100 ml) was added, and the mixture was stirred overnight. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 ml). Evaporation of the solvent of the dried ($MgSO_4$) recombined organic phases under reduced pressure led to the formation of a yellow oil, which was distilled in vacuo to give a colourless liquid.

Synthesis of the carbamoyl derivatives 4, 11, and 13; General Procedure GP2

1.25 mmol of the corresponding reduction product was dissolved in 10 ml of Et_2O. Subsequently, 1.30 mmol (in case of **11**) or 2.60 mmol (in case of **4**, **13**) of the isocyanate component was added dropwise. After addition of 5 ml cyclohexane the solution was stirred for 8 h. The solvent was removed and the solid was suspended in Et_2O and light petroleum (40/60). The product was filtered, washed with Et_2O and light petroleum (40/60) and dried *in vacuo*.

Enantioselective reduction of 1a with borane–THF complex to 2; General Procedure GP3 (Method A)

In a typical procedure a mixture of **1a** (0.92 g, 5 mmol) in 5 ml of dry THF was slowly added within 1 hour to a solution of the catalyst (20 mol%) and borane–THF complex (11 mmol, 2 equiv.) in 5 ml of dry THF at 30 °C. After stirring for six days at this temperature the mixture was hydrolyzed with 30 ml of H_2O and extracted three times with 20 ml of *tert*-butylmethyl ether. The combined organic layers were successively washed with 10 ml of 2N NaOH and two times with 10 ml of NaCl solution, dried ($MgSO_4$) and concentrated under reduced pressure. The oily product was purified by bulb to bulb distillation under reduced pressure.

Enantioselective Reduction of 1a and 1c with Sodium Acyloxyborohydrides to 2 and 14, respectively; General Procedure GP4 (Method B)

A solution of 20 mmol or 40 mmol of (*S*)-*N*-*tert*-butyloxycarbonyl- or (*S*)-*N*-benzyloxycarbonylproline (*S*)-**8** or (*S*)-**9** in 25 ml of dry THF was added to a stirred suspension of $NaBH_4$ (0.76 g, 20 mmol) in 5 ml of dry THF. The mixture was stirred at room temperature for 2 h after which time a solution of **1a** (0.92 g, 5 mmol) in 15 ml of THF was added at the respective temperature and stirred (reaction time see table 1; in case of entry 9 a solution of 5.09 g $Na(Boc\text{-}Pro)_3BH$ (7.5 mmol), prepared from (*S*)-**8** and $NaBH_4$ in 40 ml of dry CH_2Cl_2, was added to **1c** (0.76 g, 3 mmol) in 30 ml of dry CH_2Cl_2). The reaction mixture was quenched with 20 ml of 2N HCl and heated at 60–70 °C for 0.5 h. The solution was made basic with K_2CO_3 and extracted with AcOEt. The AcOEt extracts were washed with brine, dried with $MgSO_4$ and concentrated. The oily product **10** was purified by bulb to bulb distillation under reduced pressure. The product **14** was purified by chromatography (eluent: *n*-hexane/AcOEt = 9 : 1).

Enantioselective Reduction of 1a–c with Catecholborane to 10, 12 and 14, respectively; General Procedure GP5 (Method C)

To the amino alcohol (20 mol%) in 5 ml of dry THF at –70 °C was added borane–THF complex (3 eq.). The reaction mixture was stirred for 1/2 h at 20 °C and 2 h at 60 °C. Subsequently, the solvent was removed at room temperature under reduced pressure and a white solid remained. This oxazaborolidine was dissolved in 10 ml of dry toluene and **1a** (0.55 g, 3 mmol), **1b** (0.61 g, 2.5 mmol) or **1c** (0.4 g, 1.6 mmol) in 2 ml of dry toluene was added at the respective temperature. To this mixture a solution of freshly distilled catecholborane (for equivalents, see table 1) was added slowly (20 min) in 5 ml of dry toluene at room temperature and stirred (reaction time see table 1). The solution was quenched with 15 ml of water. The organic layer was washed three times with 20 ml of 2N NaOH to remove catechol and washed with 15 ml of NaCl solution. Drying with $MgSO_4$ and concentration *in vacuo* afforded the crude product. The oily products **10** and **12**, respectively, were purified by bulb to bulb distillation under reduced pressure. The product **14** was purified by chromatography (eluent: *n*-hexane/AcOEt = 9 : 1).

2,2,3-Trimethyl-1-thia-4-aza-spiro[4.4]non-3-ene (**1a**):

Prepared according to **GP1** from 36.2 g (0.3 mol) 3-chloro-3-methylbutan-2-one [23], Yield 31.9 g (58%); *b.p.* 51–53 °C ($1 \cdot 10^{-2}$ mbar). – IR (NaCl): ν = 1645 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ/ppm = 1.04–2.13 (m, 8H, $-(CH_2)_4-$), 1.48 (s, 6H, $C2(CH_3)_2$), 1.93 (s, 3H, C3-CH_3). – ^{13}C NMR ($CDCl_3$): δ/ppm = 14.71 ($C2(\underline{C}H_3)_2$), 24.32, 29.95 ($4CH_2$), 43.73 (C3-$\underline{C}H_3$), 65.15 (C2), 91.32 (C5), 172.07 (C3). – MS (CI-Isobutane): *m/z* (%) = 184 (100) (MH^+); $C_{10}H_{17}NS$ (183.3).

2,2-Dimethyl-3-phenyl-1-thia-4-aza-spiro[4.4]non-3-ene (**1b**)

Prepared according to **GP1** from 54.6 g (0.3 mol) 2-chloro-2-methylpropiophenone [24], Yield 37.8 g (51%); *b.p.* 110 °C ($4 \cdot 10^{-3}$ mbar). – IR (NaCl): ν = 1660 cm^{-1} (C=N). – ^1H NMR (CDCl3): δ/ppm = 1.70 (s, 6H, $C2(CH_3)_2$), 1.77–2.32 (m, 8H, $-(CH_2)_4-$), 7.38–7.58 (m, 5H, aromat. H). – ^{13}C NMR (CDCl3): δ/ppm = 24.7 ($C2(\underline{C}H_3)_2$), 30.87, 44.01 ($4CH_2$), 65.7 (C2), 90.74 (C5), 128.17–134.18 (aromat. C), 172.67 (C3). – MS (CI-Isobutane): *m/z* (%) = 246 (100) (MH^+); $C_{15}H_{19}NS$ (245.4).

*rac-3-Cyclopentylamino-2-methyl-butane-2-thiol (rac-***2**)

Prepared according to method **A/GP3**. Catalyst: *rac*-Valinol; Yield 0.50 g (55%); *b.p.* 135–140 °C (15 mbar, short-path distillation). – IR (NaCl): ν = 3300 cm^{-1} (NH), 2550 (SH). – ^1H NMR ($CDCl_3$): δ/ppm = 1.09 (d, *J* = 6.5 Hz, 3H, C3-CH_3), 1.27, 1.28 (s, 6H, $C2(CH_3)_2$), 1.25–1.88 (m, 8H, $-(CH_2)_4-$), 2.47 (q, *J* = 6.3 Hz, 1H, C3-H), 3.17 (quint, *J* = 6.0 Hz, 1H, cyclopentyl-CH). – ^{13}C NMR ($CDCl_3$): δ/ppm = 15.41 (C3-$\underline{C}H_3$), 23.59, 23.77, 32.52, 34.19 ($4CH_2$), 28.04, 30.57 ($C2(\underline{C}H_3)_2$), 49.58 (C2), 57.70, 61.06 (2CHN). – MS (CI-Isobutane): *m/z* (%) = 188 (100) (MH^+); $C_{10}H_{21}NS$ (187.3).

N,S-Diphenylcarbamoyl-3-cyclopentylamino-2-methyl-butane-2-thiol (**4**)

Prepared from 0.21 g *rac*-**2** (1.25 mmol) according to **GP2**. Yield 0.39 g (85 %); *m.p.* 166–167 °C. – IR (KBr): ν = 1645 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ/ppm = 1.40, 1.79 (s, 6H, $C2(CH_3)_2$), 1.48 (d, *J* = 6.7 Hz, 3H, C3-CH_3), 1.75–2.37 (m, 8H, $-(CH_2)_4-$), 3.55 (quint, *J* = 8.5 Hz, 1H, cyclopentyl-CH), 4.81 (q, *J* = 6.5 Hz, 1H, C3-H), 6.95–7.64 (m, 11H, NH, aromat. CH), 8.50 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ/ppm = 14.67 (C3-$\underline{C}H_3$), 24.34, 25.73, 28.99, 31.22 ($4CH_2$), 25.87, 26.14 ($C2(\underline{C}H_3)_2$), 55.42 (C2), 55.86, 56.95 (2CHN), 119.72–140.32 (aromat. C), 155.07, 167.00 (2C=O). – MS (CI-Isobutane): *m/z* (%) = 426 (15) (MH^+), 307 (22) ($MH^+ - H_5C_6NCO$), 188 (100) ($MH^+ - 2H_5C_6NCO$). – $C_{24}H_{31}N_3O_2S$ (425.5).

*rac-2,2,3-Trimethyl-1-thia-4-aza-spiro[4.4]nonane (rac-***10**)

Prepared according to method **C/GP5**. Catalyst: 2-Amino-2-methyl-1-propanol; Yield 0.32 g (34%); *b.p.* 130 °C (22 mbar, short-path distillation). – IR (NaCl): ν = 3295 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ/ppm = 1.08 (d, *J* = 6.5 Hz, 3H, C3-CH_3), 1.17, 1.39 (s, 6H, $C2(CH_3)_2$), 1.33–2.20 (m, 8H, $-(CH_2)_4-$), 3.09 (q, *J* = 6.6 Hz, 1H, C3-H). – ^{13}C NMR ($CDCl_3$): δ/ppm = 13.44 (C3-$\underline{C}H_3$), 23.73, 24.20, 42.22, 44.30 ($4CH_2$), 25.88, 27.65 ($C2(\underline{C}H_3)_2$), 59.64 (C2), 66.91 (C3), 81.29 (C5). – MS (CI-Isobutane): *m/z* (%) = 186 (100) (MH^+). – $C_{10}H_{19}NS$ (185.3).

N-(4-Chlorophenyl)carbamoyl-2,2,3-trimethyl-1-thia-4-aza-spiro-[4.4]nonane (**11**)

Prepared from 0.23 g *rac*-**10** (1.25 mmol) according to **GP2**. Yield 0.35 g (81%); *m.p.* 190–192 °C. – IR (KBr): ν = 1620 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ/ppm = 1.31, 1.62 (s, 6H, $C2(CH_3)_2$), 1.43 (d, *J* = 6.4 Hz, 3H, C3-CH_3), 1.67–2.14 (m, 6H, $-(CH_2)_4-$), 2.79–3.00 (m, 2H, $-(CH_2)_4-$), 3.87 (q, *J* = 6.4 Hz, 1H, C3-H), 6.26 (s, 1H, NH), 7.23–7.38 (m, 4H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ/ppm = 17.35 (C3-$\underline{C}H_3$), 23.51, 31.87 ($C2(\underline{C}H_3)_2$), 24.85, 40.90, 41.48 ($4CH_2$), 51.66 (C2), 67.79 (C3), 80.65 (C5), 121.47–137.42 (aromat. C),

151.97 (C=O). – MS (CI-Isobutane): *m/z* (%) = 339 (100) (MH^+), 186 (34) ($MH^+ - H_4C_6ClNCO$). – $C_{17}H_{23}ClN_2OS$ (338.9).

*rac-1-Cyclopentylamino-2-methyl-1-phenyl-propane-2-thiol (rac-***12***)*

Prepared according to method **C/GP5**. Catalyst: 2-Amino-2-methyl-1-propanol; Yield 0.35 g (56%); *b.p.* 185–195 °C (21 mbar, short-path distillation). – IR (NaCl): $\nu = 3300\ cm^{-1}$ (NH), 2540 (SH). – ^1H NMR ($CDCl_3$): δ/ppm = 1.24, 1.39 (s, 6H, C2-$(CH_3)_2$), 1.25–1.95 (m, 10 H, $-(CH_2)_4-$, NH, SH), 2.30 (quint, J = 6.2 Hz, 1H, cyclopentyl-CH), 3.57 (s, 1H, C1-H), 7.28–7.37 (m, 5H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ/ppm = 23.72, 32.02, 34.07 ($-(CH_2)_4-$), 28.34, 31.70 (C2-($\underline{C}H_3)_2$), 49.06 (C2), 57.01 (cyclopentyl-$\underline{C}$H), 71.21 (C1), 127.16–128.99 (aromat. C), 140.50 (q. aromat. C). – MS (CI-Isobutane): *m/z* (%) = 250 (100) (MH^+). – $C_{15}H_{23}NS$ (249.4).

N,S-Diphenylcarbamoyl-1-(cyclopentylamino)-2-methyl-1-phenyl-propane-2-thiol (**13**)

Prepared from 0.12 g *rac*-**12** (0.5 mmol) according to **GP2**. Yield 0.20 g (83%); *m.p.* 144–146 °C. – IR (KBr): $\nu = 1650\ cm^{-1}$ (C=O). – ^1H NMR ($CDCl_3$): δ/ppm = 1.77, 1.88 (s, 6H, $(CH_3)_2$), 0.92–2.25 (m, 8H, $-(CH_2)_4-$), 3.72–3.85 (m, 1H, cyclopentyl-CH), 6.08 (s, 1H, C$\underline{H}$-Ph), 6.97–7.60 (m, 16H, NH, aromat. H), 9.46 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ/ppm = 25.44, 25.75, 29.80, 29.94 ($-(CH_2)_4-$), 26.89, 27.11 ($(CH_3)_2$), 56.53 ($\underline{C}(CH_3)_2$), 58.76, 65.33 (2CHN), 119.65–139.62 (aromat. C), 155.39, 166.18 (2C=O). – MS (CI-Isobutane): *m/z* (%) = 488.5 (52) (MH^+), 269.5 (19) ($MH^+ - H_5C_6NCO$), 250.3 (87) ($MH^+ - 2H_5C_6NCO$). – $C_{29}H_{33}N_3O_2S$ (487.7).

References

[1] For a review see: Methods of Organic Chemistry-Stereoselective Synthesis-(Houben–Weyl), Workbench Edition E21, Vol. 7, (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Georg–Thieme-Verlag, Stuttgart, New York 1996

[2] For reviews see: a) H.–U. Blaser, F. Spindler, Chem. Today **1995**, 11; b) J. Martens in: Methods of Organic Chemistry-Stereoselective Synthesis-(Houben–Weyl), Workbench Edition E21, Vol. 7,(Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Georg–Thieme-Verlag, Stuttgart, New York 1996, p. 4199

[3] a) D. Scarpi, G. Menchi, E. G. Occhiato, A. Guarna, J. Mol. Cat. **110** (1996) 129; b) R. Sablong, J. A. Osborn, Tetrahedron Lett. **37** (1996) 4937

[4] a) A. Tungler, M. Kajtar, T. Máthé, G. Toth, E. Fogassy, J. Petró, Catal. Today **5** (1989) 159; b) A. Tungler, T. Máthé, J. Petró, T. Tarnai, J. Mol. Catal. **61** (1990) 259

[5] a) J. Martens, H. Offermanns, P. Scherberich, Angew. Chem. **93** (1981) 680; Angew. Chem., Int. Ed. Engl. **20** (1981) 668; b) K. J. M. Andrews, Eur. Pat. 33919; Chem. Abstr. **96** (1982) 52498; c) K. Drauz, H. G. Koban, J. Martens, W. Schwarze, Liebigs Ann. Chem. **1985**, 448

[6] In parallel and indepently from our research the enantioselective C=N-reduction of a further thiocontaining heterocycle (a pyrrolo-benzothiadiazine derivative) was reported recently, see: P. D. P. Serkiz, P. Morain, J. Lepagnol, A. Cordy, Bioorg. Med. Chem. Lett. **6** (1996) 3003

[7] a) J. Martens, J. Kintscher, K. Lindner, S. Pohl, W. Saak, D. Haase, Liebigs Ann. Chem. **1991**, 305; b) H. Gröger, J. Martens, Synth. Commun. **26** (1996) 1903; c) H. Gröger, Y. Saida, S. Arai, J. Martens, H. Sasai, M. Shibasaki, Tetrahedron Lett. **37** (1996) 9291

[8] For the reduction of 3-thiazolines with achiral reducing agents in general, see: M. Thiel, F. Asinger, K. Häussler, T. Körner, Liebigs Ann. Chem. **622** (1959) 107 (however, the thiazolines **1a,b** are new and have not been reduced before)

[9] Until now only several acyclic imines were reduced via this method using stoichiometric amounts of chiral agents, see: B. T. Cho, Y. S. Chun, Tetrahedron: Asymmetry **3** (1992) 1583

[10] For reviews, see: a) S. Wallbaum, J. Martens, Tetrahedron: Asymmetry **3** (1992) 1475; b) M. M. Midland, L. A. Morrell in: Methods of Organic Chemistry-Stereoselective Synthesis-(Houben–Weyl), Workbench Edition E21, Vol. 7, (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Georg–Thieme-Verlag, Stuttgart, New York 1996, p. 4049

[11] a) I. Reiners, J. Martens, S. Schwarz, H. Henkel, Tetrahedron: Asymmetry **7** (1996) 1763; b) J. Wilken, J. Martens, Synth. Commun. **26** (1996) 4477

[12] The ^1H NMR spectra of the crude product showed for the resulting diastereomers nonequivalence of the C$\underline{H}$–OAc singlet with $\Delta\delta = 0.22$ ppm in case of **2** (signals at $\delta = 6.10$ ppm and 6.32 ppm) and nonequivalence of the C$\underline{H}$(Ph)N singlet with $\Delta\delta = 0.03$ ppm in case of **12** (signals at $\delta = 4.24$ ppm and 4.27 ppm). For the procedure of this CDA-derivatization method, see: a) D. Parker, J. Chem. Soc., Perkin Trans. II **1983**, 83; b) D. Parker, Chem. Rev. **91** (1991) 1441

[13] W. Behnen, Ch. Dauelsberg, S. Wallbaum, J. Martens, Synth. Commun. **22** (1992) 2143

[14] K. Yamada, M. Takeda, T. Iwakuma, J. Chem. Soc., Perkin Trans. I **1983**, 265

[15] a) E. J. Corey, J. O. Link, Tetrahedron Lett. **30** (1989) 6275; b) E. J. Corey, R. K. Bakshi, Tetrahedron Lett. **31** (1990) 611; c) E. J. Corey, J. O. Link, Tetrahedron Lett. **33** (1992) 3431

[16] For the determination of the enantiomeric ratio the derivatizing method with (*S*)-*O*-acetylmandelic acid was not successful. In contrast, the formation of the corresponding urea derivatives with (*R*)-phenylethylisocyanate functioned well with $\Delta\delta = 0.57$ ppm in the resulting ^1H NMR spectra (resonances for C$\underline{H}$Ph were centered at δ = 4.48 ppm and 5.05 ppm). For this CDA-derivatization method, see: K. C. Rice, A. Brossi, J. Org. Chem. **45** (1980) 592

[17] a) G. Liso, G. Trapani, A. Reho, A. Latrofa, F. Morlacchi, Synthesis **1983**, 755; b) For characterization, see: V. Carelli, F. M. Moracci, F. Liberatore, M. Cardelline,

M. G. Lucarelli, P. Marchini, G. Paolo, A. Reho, Int. J. Sulfur Chem. **3** (1973) 267; Chem. Abstr. **79** (1973) 126422

[18] Preparation according to the synthesis of (*L*)-valinol: L. F. Tietze, T. Eicher, Reaktionen und Synthesen, 2 nd. Ed., Thieme-Verlag, Stuttgart 1991, p. 456

[19] E. J. Corey, R. K. Bakshi, S. Shibata, J. Am. Chem. Soc. **109** (1987) 5551

[20] N. J. Miles, P. G. Sammes, P. D. Kennewell, R. Westwood, J. Chem. Soc., Perkin Trans. I **1985**, 2299

[21] E. Abderhalden, K. Heyns, Ber. Dtsch. Chem. Ges. **67** (1934) 530

[22] The synthesis of *rac*-**14** was carried out by catecholborane reduction (method **C**). However, an alternative route to *rac*-**14** was reported earlier in: P. Marchini, G. Liso, A. Reho, J. Org. Chem. **40** (1975) 3453 (for characterization, see ref. [17])

[23] P. Delbaere, Bull. Soc. Chim. Belg. **51** (1942) 1

[24] L. Stevens, B. Ettling, J. Am. Chem. Soc. **77** (1955) 5412

Address for correspondence:
Prof. Dr. Jürgen Martens
Fachbereich Chemie
Universität Oldenburg
Postfach 2503
D-26111 Oldenburg