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Regioselective thionation of bicyclic piperazinediones

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Abstract—In order to modify and improve the reduction of bicyclic piperazinediones to yield enantiomerically pure piperazine derivatives the preparation and reduction of the corresponding thiolactams were investigated. With a reduced amount of *Lawesson* reagent the bicyclic piperazinediones reacted predominantly at the C-5 carbonyl moiety to provide C-5 monothiolactams. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

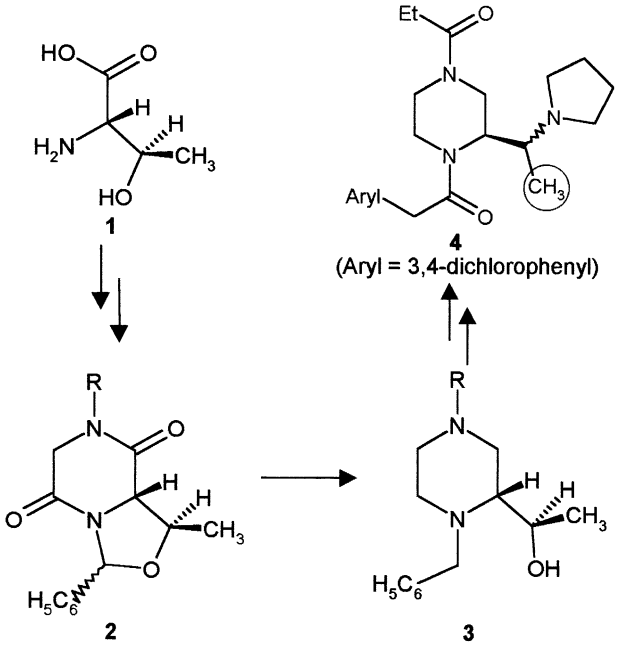
Recently we described the synthesis and the stereoselective κ-receptor binding of all four stereoisomeric piperazines **4**. The synthesis of the stereoisomeric piperazines **4** started from the proteinogenic amino acid threonine (**1**) or its enantiomer.[1] A crucial step in the synthesis of the piperazine derivatives **4** was the reaction of the bicyclic piperazinediones **2** with $LiAlH_4$, which led to reduction of both lactam carbonyl groups and reductive ring opening of the N/O-acetal establishing the N-benzyl protective group (→**3**). The reduction of the bicyclic piperazinediones **2** required, however, heating with a large excess of $LiAlH_4$ for a long period (48–72 h) and in some cases side reactions took place.[2] (Scheme 1)

In this communication we report on our attempts to improve this reaction step by transformation of the lactam carbonyl groups of **2** into *thio*lactam moieties. The reduction of thiolactam groups should be possible by more careful reaction conditions.[3]

2. Results and discussion

For this purpose the bicyclic piperazinedione **5a** was heated with 1.2 molar equivalents of *Lawesson* reagent (LR).[4–6] Surprisingly two products were formed which could be separated by flash chromatography. The mass spectrum of the less polar, minor compound (27%) indicated the incorporation of two sulfur atoms which is in accordance with the expected dithiolactam **6a**. In comparison with the molar mass of the piperazinedione **5a** the molar mass of the more polar, major product **7a** (54%) was increased by only 16 mass units. Obviously, only one carbonyl group has been transformed into a thiocarbonyl group. (Scheme 2)

A larger excess of *Lawesson* reagent or elongation of the reaction time did not improve the yield of the dithiolactam **6a**. However, reaction of the piperazinedione **5a** with only 0.5 molar equivalents of *Lawesson* reagent raised the yield of the monothiolactam **7a** to 86%. The dithiolactam **6a** was not detected. We assume, that steric effects are responsible for the preferred thionation in position 5. Whereas two branched substituents are adjacent to the C-8 carbonyl moiety the C-5 carbonyl moiety is shielded by only one large substituent (oxazolidine ring).



Scheme 1.

Keywords: medicinal chemistry; piperazines; regioselective thionation; thiolactams; reduction.

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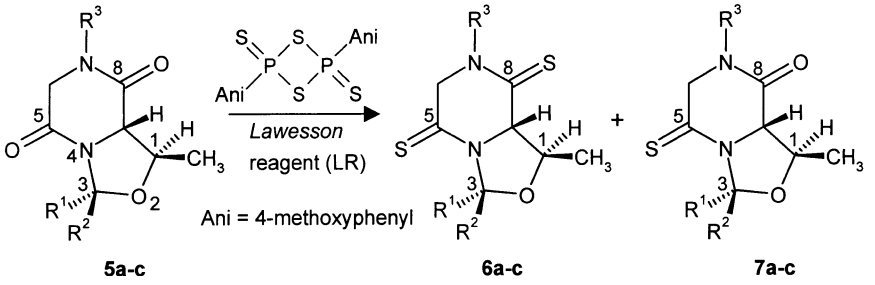


5 - 7	R^1	R^2	R^3
a	C_6H_5	H	$CH_2C_6H_5$
b	H	C_6H_5	$CH_2C_6H_5$
c	C_6H_5	H	C_6H_5

Scheme 2.

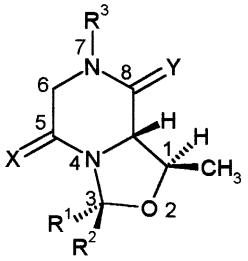
The same observations were made during thionation of the diastereomeric bicyclic piperazinedione **5b** with (*S*)-configuration in position 3. As described for **5a** 1.2 molar equivalents of *Lawesson* reagent led to the monothiolactam **7b** as main product (60%) and the dithiolactam **6b** as minor component (37%). Variation of the reaction conditions did not improve the yield of the dithiolactam **6b**. However, the yield of the monothiolactam **7b** could be increased by lowering the amount of *Lawesson* reagent to 0.5 molar equivalents. These results led to the conclusion, that the preferred thionation of the C-5 carbonyl moiety is not dependent on the stereochemistry in position 3 near at the reacting C-5 carbonyl moiety.

Next, we investigated the influence of the substituent in position 7 on the regioselective thionation with *Lawesson* reagent. Heating of the bicyclic piperazinedione **5c**, which differed from **5a** by a phenyl instead of a benzyl residue in position 7, with 1.2 molar equivalents of *Lawesson* reagent provided two products. In this case, however, the less polar dithiolactam **6c** predominated with an isolated yield of 58%, whereas the more polar monothiolactam **7c** was isolated in only 38% yield. Obviously, the difference in reactivity of the two carbonyl moieties in the phenyl substituted piperazinedione **5c** is smaller than in the benzyl substituted piperazinediones **5a** and **5b**. This may be due to the acetanilide substructure of **5c**, which enhances the C-8 carbonyl activity.

The number of sulfur atoms incorporated into the piperazine ring system is deduced from the mass spectra of the products **6** and **7**. In comparison with the piperazinediones **5** the molecular ion peak of the more polar monothio compounds **7** is increased by 16 mass units, whereas the molecular mass of the less polar dithiolactams **6** differ by 32 mass units. The IR spectra of the dithiolactams **6** reveal one absorption at 1490–1494 cm^{-1} for both thiolactam groups (amide II).[7] On the other hand two absorptions are seen in the IR spectra of the monothiolactams **7**, which are caused by the lactam carbonyl group (1669–1686 cm^{-1}, amide I) and the thiolactam moiety (1491–1494 cm^{-1}, amide II), respectively.[7]

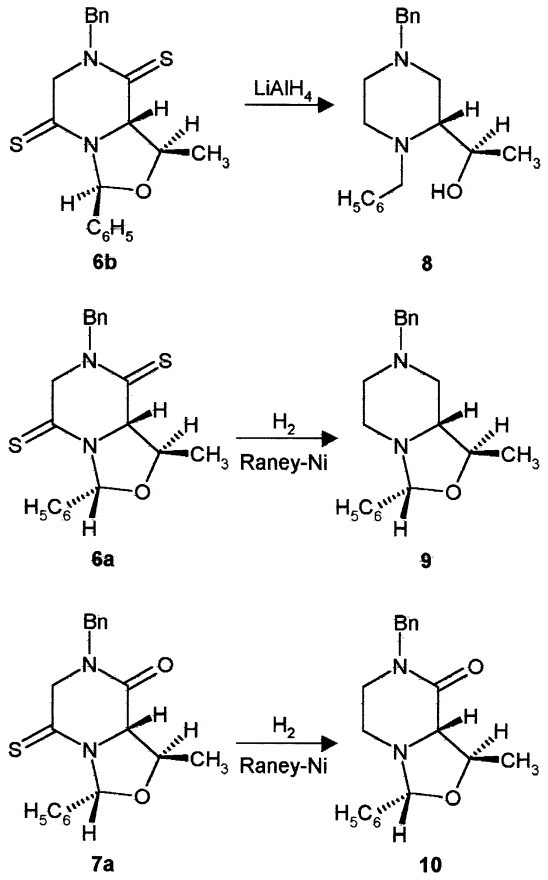
The position of the sulfur atom (thiocarbonyl moiety) in the monothiolactams **7** is derived from the ^1H NMR spectra. In Table 1 the signals caused by the aliphatic protons of the lactams **5**, the dithiolactams **6** and the monothiolactams **7** are summarized. Little differences in the chemical shifts of the protons in position 8a (8a-*H*) and the protons of the OC*H*CH_3 moiety are found. Introduction of a sulfur atom in position 5 (compounds **6** and **7**) leads to a downfield shift of about 0.4–0.6 ppm of the adjacent 6-CH_2-proton signals. A characteristic change is observed for the signals of the N–CH_2–Ph group. In the spectra of the monothiolactams **7** with the C-8-carbonyl moiety the signals for the N–CH_2–Ph protons appear at almost unchanged positions compared with the lactams **5**. In contrast, the corresponding spectra of the dithiolactams **6** (C-8-thiocarbonyl) reveal the

Table 1. Comparison of the ^1H NMR data ($CDCl_3$) of **5**–**7**: chemical shifts of the aliphatic protons



5: X = Y = O
6: X = Y = S
7: X = S, Y = O

Compound	1-H	CH–CH_3	3-H	6-H	6-H	N–CH_2Ph	N–CH_2Ph	8a-H
5a[2]	4.49	1.60	6.28	3.80	4.07	4.61	4.71	3.98
5b[2]	4.24	1.74	6.32	3.77	4.02	4.45	4.77	4.04
5c[2]	4.54	1.59	6.36	4.21	4.65	–	–	4.11
6a	4.64	1.61	6.50	4.29	4.58	5.17	5.33	3.96
6b	4.49	1.80	6.21	4.19–4.22	4.42	4.80	5.63	4.19–4.22
6c	4.66	1.61	6.59	4.66	4.66	–	–	4.14
7a	4.53	1.57	6.52	4.34	4.34	4.60	4.77	3.95
7b	4.21–4.32	1.64	6.35	4.21–4.32	4.21–4.32	4.21–4.32	4.84	4.04
7c	4.52	1.51	6.53	4.69	4.84	–	–	4.07



Scheme 3.

N–CH_2–Ph signals downfield shifted by about 0.5 ppm. Interestingly, the changes of the 3-H signals are depending on the configuration of the N/O-acetalic stereogenic center. In the (*R*)-series (**a** and **c** compounds) changing of the C-5-carbonyl into a C-5-thiocarbonyl moiety leads to a downfield shift of about 0.2 ppm, whereas the (3*S*)-configurated derivatives (**b** series) reveal almost unchanged chemical shifts for the 3-H proton signals.

Reduction of the dithiolactam **6b** with an excess of $LiAlH_4$ afforded the hydroxyethyl substituted 1,4-dibenzylpiperazine **8** in 76% yield. In comparison with the analogous reduction of the corresponding bicyclic piperazinedione **5b**[2] the yield of **8** was slightly increased whereas the reaction time was reduced from 48 h to 16 h. Hence, the $LiAlH_4$ reduction of bicyclic piperazine*dithiones* represents an attractive alternative for the preparation of **8** (Scheme 3).

Hydrogenation of the dithiolactam **6a** in the presence of the catalyst Raney–Nickel only led to reduction of the thiocarbonyl moieties.[8] In contrast to the reduction with $LiAlH_4$ the acetalic 1,3-oxazolidine substructure remains unaffected yielding the bicyclic piperazine derivative **9**. Treatment of the monothiolactam **7a** with hydrogen and Raney–Nickel provided the bicyclic piperazin-8-one **10** with intact C-8-lactam carbonyl and oxazolidine moieties. The reductive elimination of the C-5-thiocarbonyl moiety of **7a** additionally proves the position of the sulfur atom (thiocarbonyl group).

3. Conclusion

The regioselective thionation of the bicyclic piperazinediones **5** combined with the reduction of the products under various conditions provides access to differently substituted mono- and bicyclic piperazines (e.g. **8**–**10**), which are valuable building blocks for the synthesis of pharmacologically active piperazine derivatives[1,9–11] as well as peptidomimetics.[12,13]

4. Experimental

4.1. General

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. Thin layer chromatography (tlc): Silica gel 60 F_{254} plates (Merck). Flash chromatography (fc)[14]: Silica gel 60, 0.040–0.063 mm (Merck); parentheses include: Diameter of the column [cm], eluent, fraction size [ml], R_f. Melting points: Melting point apparatus Dr Tottoli (Büchi), uncorrected. Optical rotation: Polarimeter 241 (Perkin–Elmer); λ=589 nm; 1.0 dm tube; concentration *c* [g/100 ml]. Elemental analyses: CHN elemental analyzer Rapid (Heraeus) and Elemental Analyzer 240 (Perkin Elmer). MS: Mass spectrometer 5989A (Hewlett–Packard), MAT 312, MAT 8200, MAT 4456, and TSQ 7000 (Finnigan); EI=electron impact, CI=chemical ionization. IR: IR spectrophotometer 1600 FT-IR, 2000 FT-IR, and 841-IR (Perkin–Elmer). ^{1}H NMR (400 MHz): GSX FT NMR spectrometer (Jeol); ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz): Unity 300 FT NMR spectrometer (Varian), tetramethylsilane as internal standard, δ in ppm; coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and of ^{1}H NMR signals were supported by two-dimensional NMR techniques (COSY, DEPT).

4.1.1. (1*R*,3*R*,8a*S*)-7-Benzyl-1-methyl-3-phenyl-1,6,7,8a-tetrahydro[1,3]oxazolo[3,4-*a*]-pyrazine-5,8-dithione (6a) and (1*R*,3*R*,8a*S*)-7-Benzyl-1-methyl-3-phenyl-5-thioxo-1,6,7,8a-tetrahydro[1,3]oxazolo-[3,4-*a*]pyrazin-8(5H)-one (7a). (a) Reaction of **5a** with 1.2 molar equivalents of *Lawesson* reagent. A mixture of **5a**[2] (1.62 g, 4.81 mmol), *Lawesson* reagent (2.66 g, 5.77 mmol) and THF abs. (50 mL) was heated to reflux for 24 h. The suspension was concentrated in vacuo and the residue purified by fc (4 cm, petroleum ether/ethyl acetate 3:1, 15 mL).

6a (R_f=0.60): Pale yellow solid, colorless needles (methanol), m.p. 208°C, yield 480 mg (27%). $[\alpha]^{25}$=+34.8 (c=1.52, CH_2Cl_2). $C_{20}H_{20}N_2OS_2$ (368.5) calcd. C 65.2 H 5.47 N 7.60 found C 65.0 H 5.62 N 7.55. MS (EI): *m/z* (%)=368 (M, 52), 335 (M-HS, 31), 91 (Bn, 100). IR (film): $\tilde{\nu}$=1490 (s, amide II$_{NC=S}$), 694 cm^{-1} (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.61 (d, *J*=5.9 Hz, 3 H, CHCH_3), 3.96 (d, *J*=8.8 Hz, 1 H, CSCH), 4.29 (d, *J*=17.1 Hz, 1 H, CSCH_2), 4.58 (d, *J*=17.1 Hz, 1 H, CSCH_2), 4.64 (dq, *J*=8.8/5.9 Hz, 1 H, C*H*CH$_3$), 5.17 (d, *J*=14.4 Hz, 1 H, CH_2Ph), 5.33 (d, *J*=14.6 Hz, 1 H, CH_2Ph), 6.50 (s, 1 H, NCHO), 7.07–7.11 (m, 2 H, arom.), 7.22–7.35 (m, 8 H, arom.).

7a (R_f=0.49): Pale yellow solid, m.p. 161–164°C, yield

918 mg (54%). $[\alpha]^{25}=-36.4$ (c=1.38, CH_2Cl_2). $C_{20}H_{20}N_2O_2S$ (352.5) calcd. C 68.2 H 5.72 N 7.95 found C 67.9 H 5.80 N 7.96. MS (EI): *m/z* (%)=352 (M, 48), 319 (M-HS, 30), 105 (PhCO, 80), 91 (Bn, 100). IR (film): $\tilde{\nu}$=1676 (s, C=O), 1491 (s, amide $II_{NC=S}$), 700 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.57 (d, *J*=6.0 Hz, 3 H, $CHCH_3$), 3.95 (d, *J*=9.3 Hz, 1 H, COCH), 4.34 (s, 2 H, $CSCH_2$), 4.53 (dq, *J*=9.3/5.9 Hz, 1 H, $CHCH_3$), 4.60 (d, *J*=14.7 Hz, 1 H, CH_2Ph), 4.77 (d, *J*=14.7 Hz, 1 H, CH_2Ph), 6.52 (s, 1 H, NCHO), 7.14–7.21 (m, 2 H, arom.), 7.25–7.43 (m, 8 H, arom.).

(b) Reaction of **5a** with 0.5 molar equivalents of *Lawesson* reagent. A mixture of **5a** (475 mg, 1.41 mmol), *Lawesson* reagent (283 mg, 0.70 mmol) and THF abs. (20 mL) was heated to reflux for 16 h. Work-up and purification were performed as described under a) **7a** (R_f=0.49) pale yellow solid, m.p. 161–164°C, yield 426 mg (86%).

4.1.2. (1*R*,3*S*,8a*S*)-7-Benzyl-1-methyl-3-phenyl-1,6,7,8a-tetrahydro[1,3]oxazolo[3,4-*a*]pyrazine-5,8-dithione (6b) and (1*R*,3*S*,8a*S*)-7-Benzyl-1-methyl-3-phenyl-5-thioxo-1,6,7,8a-tetrahydro[1,3]oxazolo[3,4-*a*]-pyrazin-8(5H)-one (7b). As described for the synthesis of **6a/7a** under (a) a mixture of **5b**[2] (400 mg, 1.19 mmol), *Lawesson* reagent (577 mg, 1.43 mmol) and THF abs. (50 mL) was heated to reflux for 24 h. The residue was purified by fc (2 cm, petroleum ether/ethyl acetate 3: 1, 15 mL).

6b: (R_f=0.75): Colorless oil, yield 164 mg (37%). $[\alpha]^{20}=-1.11$ (c=0.21, CH_2Cl_2). $C_{20}H_{20}N_2OS_2$ (368.5) calcd. C 65.2 H 5.47 N 7.60 found C 65.3 H 5.49 N 7.52. MS (EI): *m/z* (%)=368 (M, 70), 335 (M-HS, 100). IR (film): $\tilde{\nu}$=1492 (s, amide $II_{NC=S}$), 696 cm^{-1} (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=1.80 (d, *J*=6.0 Hz, 3 H, $CHCH_3$), 4.19–4.22 (m, 2 H, CSCH and $CSCH_2$), 4.42 (d, *J*=16.7 Hz, 1 H, $CSCH_2$), 4.49 (dq, *J*=8.2, 5.9 Hz, 1 H, $CHCH_3$), 4.80 (d, *J*=14.1 Hz, 1 H, CH_2Ph), 5.63 (d, *J*=14.5 Hz, 1 H, CH_2Ph), 6.21 (s, 1 H, NCHO), 7.26–7.33 (m, 10 H, arom.).

7b (R_f=0.55): Colorless oil, yield 250 mg (60%). $[\alpha]^{20}=-37.1$ (c=0.81, CH_2Cl_2). $C_{20}H_{20}N_2O_2S$ (352.5). MS (EI): *m/z* (%)=352 (M, 60), 335 (M-HS, 100). IR (film): $\tilde{\nu}$=1669 (s, C=O), 1494 (s, amide $II_{NC=S}$), 736 (s), 699 cm^{-1} (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.64 (d, *J*=5.9 Hz, 3 H, $CHCH_3$), 4.04 (d, *J*=9.0 Hz, 1 H, COCH), 4.21–4.32 (m, 4 H, $CHCH_3$, $CSCH_2$ and CH_2Ph), 4.84 (d, *J*=14.5 Hz, 1 H, CH_2Ph), 6.35 (s, 1 H, NCHO), 7.14–7.21 (m, 2 H, arom.), 7.25–7.43 (m, 8 H, arom.).

4.1.3. (1*R*,3*R*,8a*S*)-1-Methyl-3,7-diphenyl-1,6,7,8a-tetrahydro[1,3]oxazolo[3,4-*a*]pyrazine-5,8-dithione (6c) and (1*R*,3*R*,8a*S*)-1-Methyl-3,7-diphenyl-5-thioxo-1,6,7,8a-tetrahydro[1,3]oxazolo[3,4-*a*]-pyrazin-8(5H)-one (7c). As described for the synthesis of **6a/7a** under a) a mixture of **5c**[2] (394 mg, 1.22 mmol), *Lawesson* reagent (560 mg, 1.39 mmol) and THF abs. (20 mL) was heated to reflux for 24 h. The residue was purified by fc (4 cm, petroleum ether/ethyl acetate 4: 1, 10 mL).

6c (R_f=0.75): Pale yellow solid, m.p. 180°C, yield 250 mg (58%). $[\alpha]^{20}=-128.6$ (c=0.86, H_2Cl_2). $C_{19}H_{18}N_2OS_2$ (354.5). MS (EI): *m/z* (%)=354 (M, 81), 321 (M-HS, 100). IR (film): $\tilde{\nu}$=1494 (s, amide $II_{NC=S}$), 696 cm^{-1} (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.61 (d, *J*=5.8 Hz, 3 H, $CHCH_3$), 4.14 (d, *J*=8.7 Hz, 1 H, CSCH), 4.66 (dq, *J*=8.5/5.9 Hz, 1 H, $CHCH_3$), 4.66 (s, 2 H, $CSCH_2$), 6.59 (s, 1 H, NCHO), 7.16–7.26 (m, 4 H, arom.), 7.30–7.39 (m, 4 H, arom.), 7.41–7.49 (m, 2 H, arom.).

7c (R_f=0.55): Pale yellow oil, yield 158 mg (38%). $[\alpha]^{20}=-8.0$ (c=0.18, CH_2Cl_2). $C_{19}H_{18}N_2O_2S$ (338.4). MS (EI): *m/z* (%)=338 (M, 72), 105 (PhCO, 100). IR (film): $\tilde{\nu}$=1686 (s, C=O), 1494 (s, amide $II_{NC=S}$), 734 (m), 695 cm^{-1} (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.51 (d, *J*=6.0 Hz, 3 H, $CHCH_3$), 4.07 (d, *J*=9.2 Hz, 1 H, COCH), 4.52 (dq, *J*=9.2/5.9 Hz, 1 H, $CHCH_3$), 4.69 (d, *J*=17.1 Hz, 1 H, $CSCH_2$), 4.84 (d, *J*=17.1 Hz, 1 H, $CSCH_2$), 6.53 (s, 1 H, NCHO), 7.15–7.43 (m, 10 H, arom.).

4.1.4. (1*R*)-1-[(2*R*)-1,4-Dibenzylpiperazin-2-yl]ethan-1-ol (8).[2] A solution of $LiAlH_4$ (1 M in Et_2O, 1.7 mL, 1.7 mmol) was added to a solution of **6b** (63 mg, 0.17 mmol) in THF (25 mL) and the reaction mixture was heated to reflux for 16 h. H_2O (0.5 mL) and 3 N NaOH (0.3 mL) were cautiously added and the mixture was heated to reflux for 30 min. The precipitate was separated by filtration, the filtrate was concentrated in vacuo, the residue was dissolved in ethyl acetate and the organic layer was washed with 2N NaOH (2 x) and a saturated solution of NaCl. The organic layer was dried ($MgSO_4$), evaporated in vacuo and the residue was purified by fc (3 cm, petroleum ether/ethyl acetate 1: 2, 20 mL, R_f=0.26). Pale yellow oil, yield 40 mg (76%). Analytical and spectroscopic data see ref. 2.

4.1.5. (1*R*,3*R*,8a*R*)-7-Benzyl-1-methyl-3-phenyl-1,5,6,7,8,8a-hexahydro[1,3]oxazolo[3,4-*a*]-pyrazine (9). Ethanol (10 mL) was added to a suspension of Raney Nickel (1.5 g in water). The solvent was decanted and ethanol (10 mL) was added. Then, a solution of **6a** (175 mg, 0.48 mmol) in ethanol (15 mL) was added and the suspension was stirred at room temperature under an atmosphere of hydrogen (1.3 bar) for 16 h. The suspension was filtered, the filtrate was concentrated in vacuo and the residue was purified by fc (2 cm, petroleum ether/ethyl acetate 2: 1, 10 mL, R_f=0.38). Pale yellow oil, yield 40 mg (27%). $[\alpha]^{20}=+35.2$ (c=0.78, CH_2Cl_2). $C_{20}H_{24}N_2O$ (308.4). MS (EI): *m/z* (%)=308 (M, 10), 91 ($PhCH_2$, 100). IR (film): $\tilde{\nu}$=3030 (w, CH_{arom}), 2931 (m, CH_{alkyl}), 2811 (m, CH_{alkyl}), 741 (m), 699 cm^{-1} (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.20 (d, *J*=5.9 Hz, 3 H, $CHCH_3$), 2.10 ("t", *J*=9.5 Hz, 1 H, 8-H), 2.18 (dd, *J*=10.3/2.6 Hz, 1 H, 6-H), 2.26 (td, *J*=10.3/2.7 Hz, 1 H, 5-H), 2.39 (td, *J*=9.0/2.6 Hz, 1 H, 8a-H), 2.53 (dt, *J*=9.8/2.7 Hz, 1 H, 5-H), 2.67 (d broad, *J*=10.7 Hz, 1 H, 6-H), 2.88 (d broad, *J*=10.1 Hz, 1 H, 8-H), 3.55 (s, 2 H, CH_2Ph), 3.94 (dq, *J*=8.8/6.0 Hz, 1 H, $CHCH_3$), 4.76 (s, 1 H, NCHO), 7.18–7.32 (m, 8 H, arom.), 7.36–7.43 (m, 2 H, arom.). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm)=18.2 (1 C, $CHCH_3$), 46.1 (1 C, C-5), 51.9 (1 C, C-6), 53.7 (1 C, C-8), 62.8 (1 C, CH_2Ph), 68.1 (1 C, C-8a), 75.8 (1 C, $CHCH_3$), 95.4 (1 C, NCHO), 127.2 (1 C, arom. CH), 127.9 (2 C, arom. CH), 128.3 (4 C, arom. C), 128.9 (1 C, arom. CH), 129.1 (2 C, arom. CH), 13.9 (1 C, arom. C), (1 C, arom. C).

4.1.6. (1*R*,3*R*,8a*S*)-7-Benzyl-1-methyl-3-phenyl-1,6,7,8a-tetrahydro[1,3]oxazolo[3,4-*a*]pyrazin-8(5H)-one (10). As described for **9** a solution of the monothiolactam **7a** (200 mg, 0.57 mmol) in ethanol (40 mL) was hydrogenated (1.3 bar) with the catalyst Raney Nickel (1.5 g). The product was isolated by fc (2 cm, petroleum ether/ethyl acetate 1: 1, 10 mL, R_f=0.49). Pale yellow oil, yield 48 mg (26%). $[\alpha]^{20}$=−52.7 (c=0.84, CH_2Cl_2). $C_{20}H_{22}N_2O_2$ (322.4). MS (CI): *m/z* (%)=.323 (M+H, 100). IR (film): $\tilde{\nu}$=1646 (s, C=O), 1449 (m), 736 (m), 702 cm^{-1} (m). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.51 (d, *J*=6.1 Hz, 3 H, CHCH_3), 2.22 (dt, *J*=11.5/3.5 Hz, 1 H, 5-H), 2.46 (td, *J*=11.2/3.7 Hz, 1 H, 5-H), 2.95 (dt, *J*=12.2/3.3 Hz, 1 H, 6-H), 3.27 (td, *J*=12.0/3.6 Hz, 1 H, 6-H), 3.59 (d, *J*=8.1 Hz, 1 H, 8a-H), 4.31 (dq, *J*=8.3/6.1 Hz, 1 H, C*H*CH_3), 4.47 (d, *J*=14.7 Hz, 1 H, CH_2Ph), 4.58 (d, *J*=14.7 Hz, 1 H, CH_2Ph), 5.47 (s, 1 H, NCHO), 7.12–7.32 (m, 8 H, arom.), 7.39 (dd, *J*=7.6/1.5 Hz, 2 H, arom.).

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