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# SYNTHESIS OF PERHYDROPYRROLO[1,2-*a*]PYRAZINE-1,4-DIONES AND THEIR SULFUR-ANALOGUES BY RING-ENLARGEMENT OF *N*-(2*H*-AZIRIN-3-YL)-L-PROLINATES

**Artur Budzowski,[1] Anthony Linden, and Heinz Heimgartner***

Institute of Organic Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland; E-mail: heimgart@oci.unizh.ch

(Dedicated to Dr. Pierre Potier on the occasion of his 70th birthday)

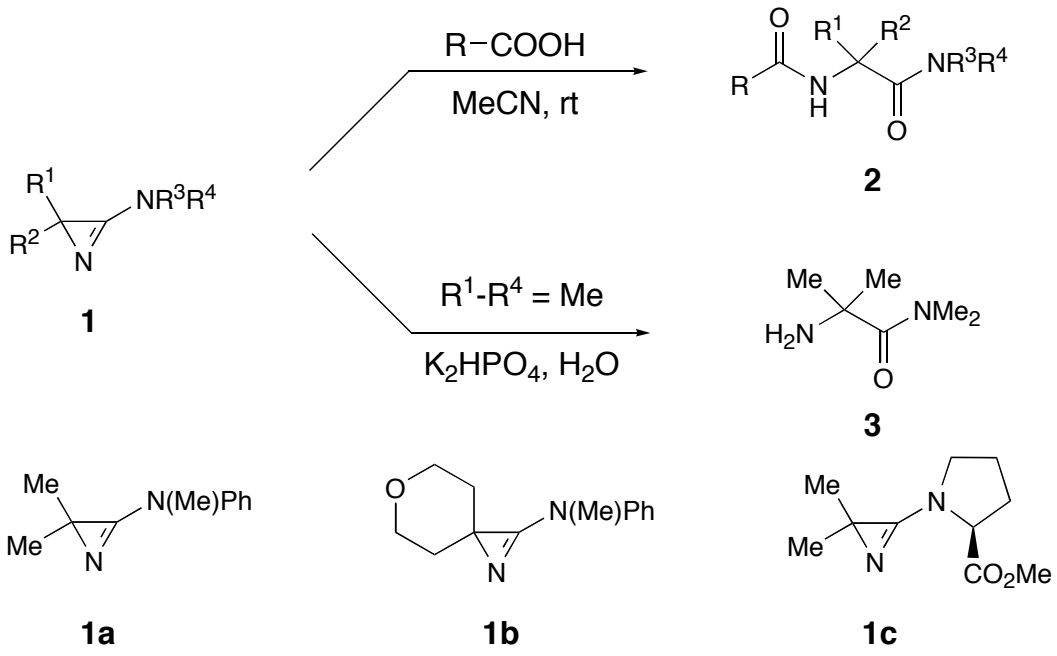
**Abstract** – The hydrolysis of methyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**1c**) at 50°C in the presence of silica gel afforded (*S*)-perhydro-3,3-dimethylpyrrolo[1,2-*a*]pyrazine-1,4-dione ((*S*)-**4a**), which was thionated chemoselectively to give the corresponding 1-thioxo derivative ((*RS*)-**5a**) as a racemic mixture. On the other hand, treatment of **1c** with hydrogen sulfide led to the 4-thioxo isomer ((*S*)-**6a**). Thionation with Lawesson reagent yielded the bisthioxo compound ((*RS*)-**7a**), again as a racemate. Analogous reactions were carried out with the heterospirocyclic *N*-(2*H*-azirin-3-yl)-L-prolinates (**1d**) and (**1e**). The structures of (*RS*)-**5a**, (*S*)-**6a**-**c**, and (*RS*)-**7a** have been established by X-Ray crystallography.

## INTRODUCTION

In the last few years, we have shown that 2,2-disubstituted 2*H*-azirine-3-amines (**1**) are versatile synthons of $\alpha,\alpha$-disubstituted $\alpha$-amino acids in the preparation of heterocycles and peptides.[2] For example, the reaction of **1** with carboxylic acids proceeds smoothly at room temperature to give diamides of type **2** (*Scheme 1*).[3] This reaction has been used extensively for the synthesis of peptides, which contain 2,2-disubstituted glycines.[4-6] In particular, the so-called 'azirine/oxazolone method' is very suitable for the preparation of peptaibols,[7-10] which are

natural oligopeptides containing α-aminoisobutyric acid (Aib, 2,2-dimethylglycine) and show antibiotic properties.

*Scheme 1*




To the best of our knowledge, there is only one report on the hydrolysis of **1** ($R^1$-$R^4$ = Me) known leading to the corresponding α-amino acid amide (**3**, *Scheme 1*).[11] As in the reactions with carboxylic acids, this hydrolysis occurs *via* cleavage of the N,C(3) bond of the azirine. On the other hand, under strong acidic conditions, e.g. with HCl, 4-toluenesulfonic acid, etc., **1** undergoes a dimerization reaction *via* cleavage of the azirine N,C(2) bond to give piperazine-2,5-bisiminium salts.[11-13]

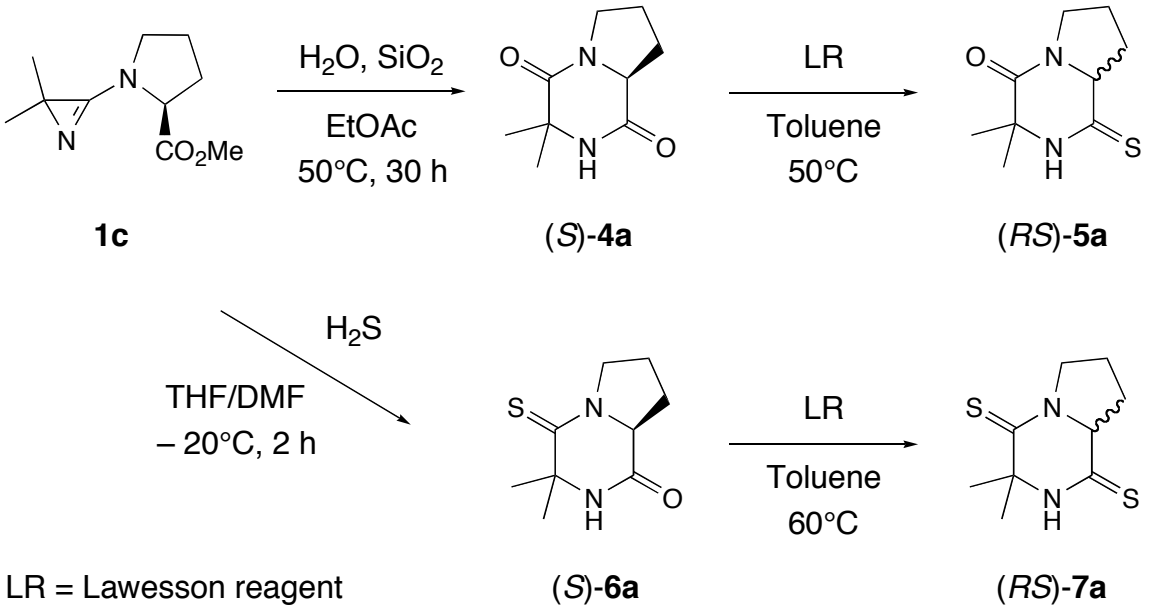
In addition to the Aib-synthon (**1a**),[14] a series of achiral and chiral 2*H*-azirin-3-amines with two alkyl groups at C(2),[15-17] carbo-[18-20] and heterospirocyclic examples of type (**1b**),[21-22] as well as dipeptide synthons of type (**1c**)[22-25] have been prepared and used in peptide synthesis.

In the present paper, we describe the results of the reactions of *N*-(2*H*-azirin-3-yl)-L-prolinates with water and hydrogen sulfide as well as the thionation of the products and their crystal structures.

## RESULTS AND DISCUSSION

Treatment of a solution of **1c** in ethyl acetate with 1.5 equiv. of water in the presence of silica gel at 50°C for 30 h led to the known (*S*)-perhydro-3,3-dimethylpyrrolo[1,2-*a*]pyrazine-1,4-dione ((*S*)-**4a**)[26] (*Scheme 2*). After chromatographic work-up ($SiO_2$, $CH_2Cl_2$/MeOH 20:1), the enantiomerically pure product was obtained in 56% yield. Thionation of (*S*)-**4a** was performed with 0.5 equiv. of Lawesson reagent in toluene at 50°C. After 70 min, all starting material was consumed (TLC), and the racemic monothione ((*RS*)-**5a**) was isolated in 82% yield after chromatography and recrystallization from ethyl acetate (*Scheme 2*). No dithionated product could be detected. Surprisingly, the 1-thioxo derivative (**5a**) could not be obtained in optically active form ($[\alpha]_D$ = 0°, c = 1.00 (MeOH)), although the starting material ((*S*)-**4a**) was enantiomerically pure.

*Scheme 2*




The reaction of **1c** with hydrogen sulfide in a mixture of THF and DMF occurred already at –20°C. After 2 h, no starting material was present and, after chromatographic purification ($SiO_2$, EtOAc) and crystallization, the monothione ((*S*)-**6a**) was isolated in 60% yield (*Scheme 2*). This product was optically active ($[\alpha]_D$ = –186.3°, c = 1.00 (MeOH)), and it was shown that (*S*)-**6a** is enantiomerically pure (HPLC, Chiracel OD-H). Thionation of (*S*)-**6a** with Lawesson reagent in

toluene at 60°C led to the racemic dithione ((*RS*)-**7a**) in almost quantitative yield ($[\alpha]_D$ = 0°, c = 1.00 (MeOH)).

The structures of (*RS*)-**5a**, (*S*)-**6a**, and (*RS*)-**7a** have been established by X-Ray crystallography (*Figure 1*). Since the space groups of (*RS*)-**5a** and (*RS*)-**7a** are centrosymmetric, the compounds in the crystals are racemic. On the other hand, the crystals of (*S*)-**6a** are enantiomerically pure and the absolute configuration of the molecule has been determined independently by the diffraction experiment; the molecule has the expected (*S*)-configuration.

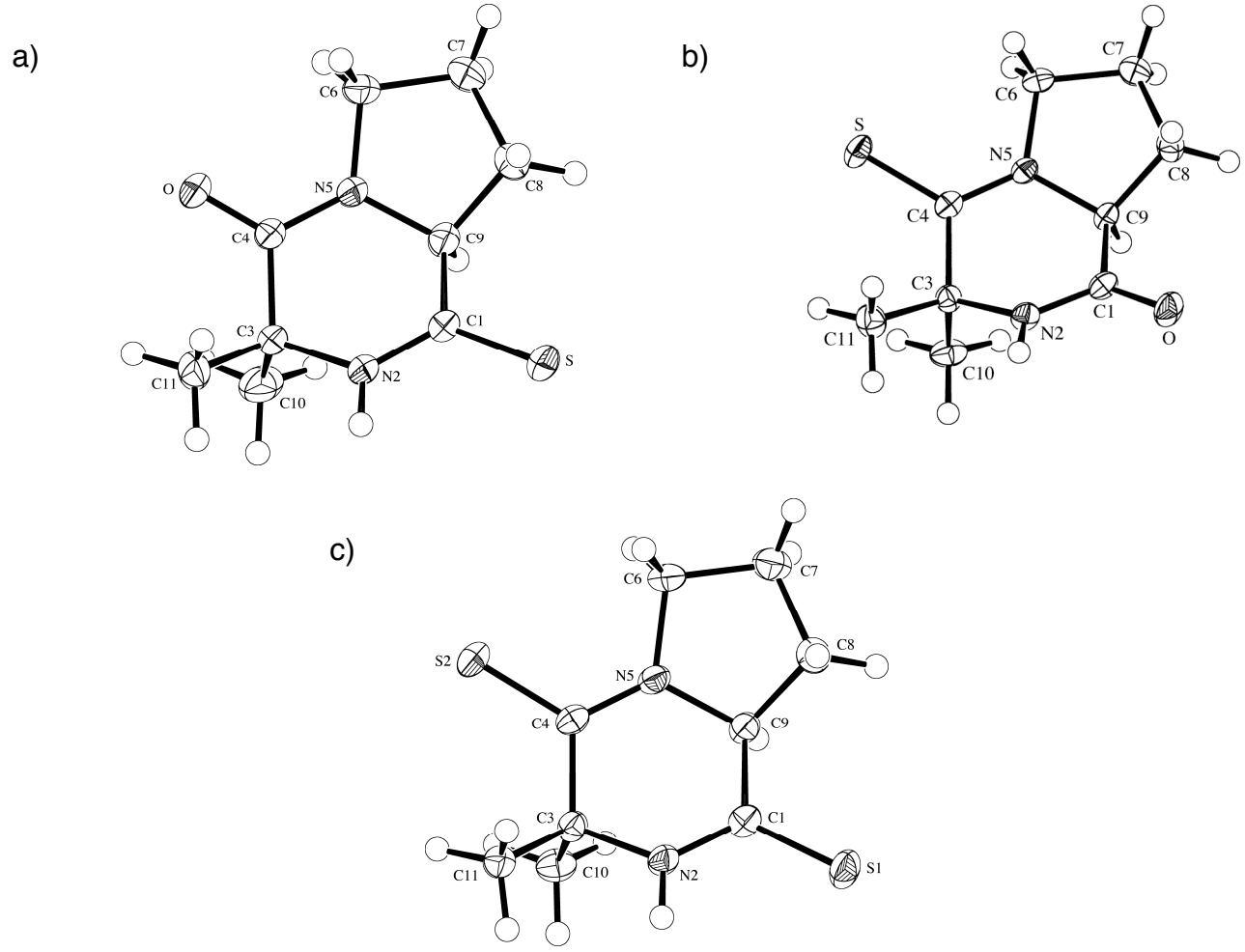


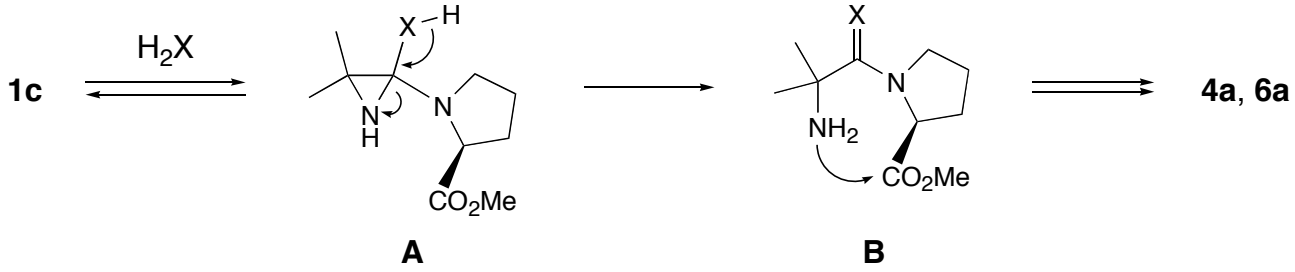

*Figure 1*. ORTEP plots[28] of the molecular structures of a) (*RS*)-**5a**, b) (*S*)-**6a**, and c) (*RS*)-**7a** (arbitrary numbering of atoms, 50% probability ellipsoids)

The crystal structures of (*RS*)-**5a**, (*S*)-**6a**, and (*RS*)-**7a** are very similar to that of (*S*)-**4a**.[29] In all examples, the six-membered piperazine ring assumes a boat conformation. The pyrrolidine ring

of (*RS*)-**5a** is a distorted half-chair twisted on C(7)-C(8), whereas it has an envelope conformation with C(8) as the flap in the cases of (*S*)-**6a**, and (*RS*)-**7a**. The NH groups of (*RS*)-**5a** and (*S*)-**6a** form intermolecular hydrogen bonds with the O-atom of a neighboring molecule and thereby link the molecules into extended chains which run parallel to the *y*-axis and have a graph set motif[30] of C(5) and C(4), respectively. In the case of the dithioxo derivative ((*RS*)-**7a**), the NH group forms an intermolecular hydrogen bond with the S(1)-atom of a neighboring molecule. In turn, the latter molecule has an identical interaction with the original molecule, so that pairs of molecules across centers of inversion are formed to give dimeric units with a graph set motif of $R_2^2(8)$.

For the formation of **4a** and **6a**, a reaction mechanism is proposed in *Scheme 3*. Addition of $H_2X$ onto the C=N bond of **1c** yields the aziridine (**A**), which undergoes a ring opening to give the dipeptide (**B**). Lactamization via nucleophilic attack of the $NH_2$ group at the ester group and subsequent elimination of methanol leads to the product. It is worth mentioning that no racemization takes place during these reactions, i.e. (*S*)-**4a** and (*S*)-**6a** are configurationally stable under the reaction conditions.

*Scheme 3*

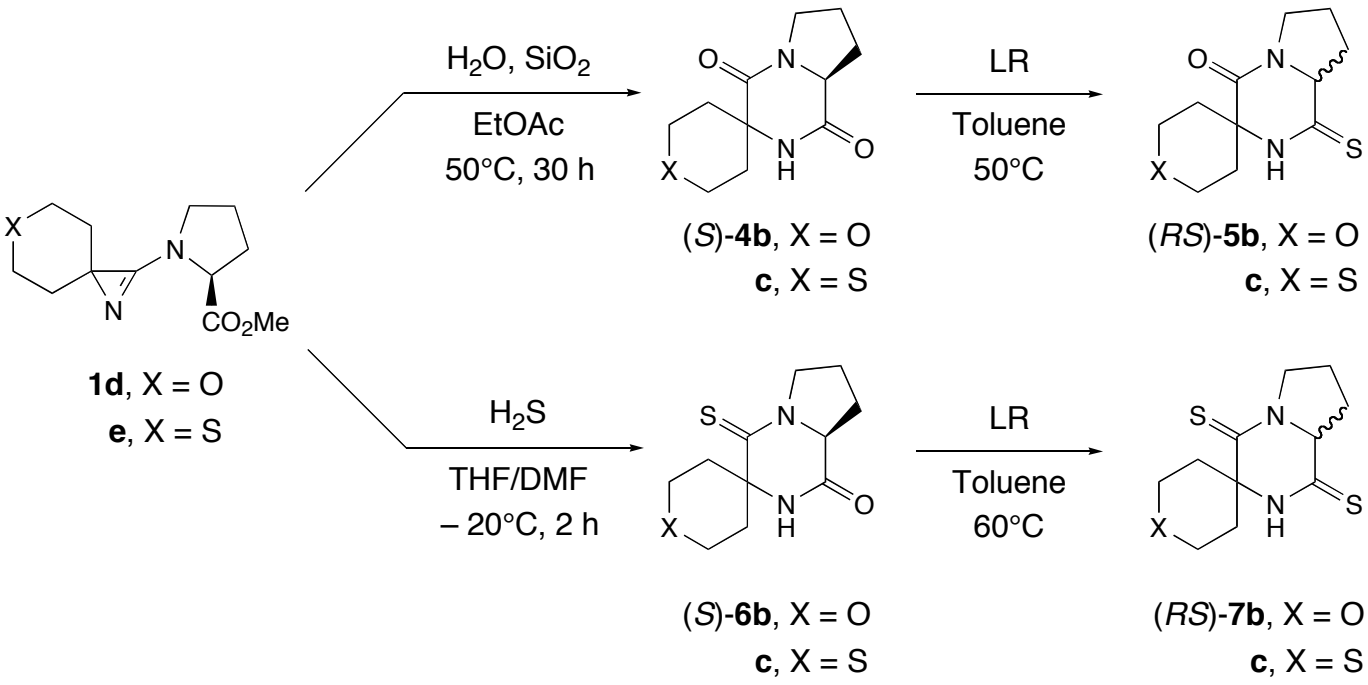



Similar reactions were performed with the heterospirocyclic *N*-(2*H*-azirin-3-yl)-L-prolinates (**1d**, X = O)[24] and (**1e**, X = S).[31] Again, the transformations with water and hydrogen sulfide, respectively, led to enantiomerically pure (*S*)-configured products of type (**4**) and (**6**), respectively (*Scheme 4*). Thionation of these products with Lawesson reagent resulted once more in racemic mixtures of the corresponding 1-thioxo derivatives ((*RS*)-**5** and (*RS*)-**7**), respectively.

In the cases of (*S*)-**6b** and (*S*)-**6c**, X-Ray crystal structure determinations were carried out,

which confirmed the proposed structures (*Figure 2*). The compounds in the crystals are enantiomerically pure and the absolute configuration of the molecules has been determined independently by the diffraction experiment.

*Scheme 4*




In both cases, the piperazine ring adopts a boat conformation as in the previously described examples. The five membered pyrrolidine ring of (*S*)-**6b** has an envelope conformation with C(6) as the flap, whereas a distorted half-chair twisted on C(6)-C(7) is adopted in the case of (*S*)-**6c**. Both, the tetrahydropyran ring of (*S*)-**6b** and the thiane ring of (*S*)-**6c** show a chair conformation. The NH group of (*S*)-**6b** forms a weak intermolecular hydrogen bond with the S-atom of a neighboring molecule and thereby links the molecules into extended chains which run parallel to the *y*-axis and have a graph set motif[30] of C(5). On the other hand, the NH group of (*S*)-**6c** forms an intermolecular hydrogen bond with the S-atom in the thiane ring of a neighboring molecule. This interaction links the molecules into extended chains which run parallel to the *x*-axis and have a graph set motif of C(6).

In conclusion, we have shown that the silica gel-catalyzed hydrolysis of methyl *N*-(2*H*-azirin-3-yl)-L-prolinates (**1c**-**e**) yields the fused diketopiperazines (**4a-c**) stereoselectively, and treatment

of **1c**-**e** with hydrogen sulfide at –20°C leads to the corresponding monothiones ((*S*)-**6a**-**c**) in a chemo- and stereoselective manner. On the other hand, thionation of diketopiperazines ((*S*)-**4a**-**c**) with Lawesson reagent yields racemic mixtures of the 1-thioxo derivatives ((*RS*)-**5a**-**c**). Similarly, the transformation of the 4-thioxo analogues ((*S*)-**6a**-**c**) into the 1,4-dithiones ((*RS*)-**7a**-**c**) also takes place by complete racemization. These findings are in agreement with the well-known fact that the enolization of thiocarbonyl compounds occurs easier in comparison with their carbonyl analogues, i.e. the configurational stability of C($\alpha$) of C=S derivatives is lower than that of C=O compounds.

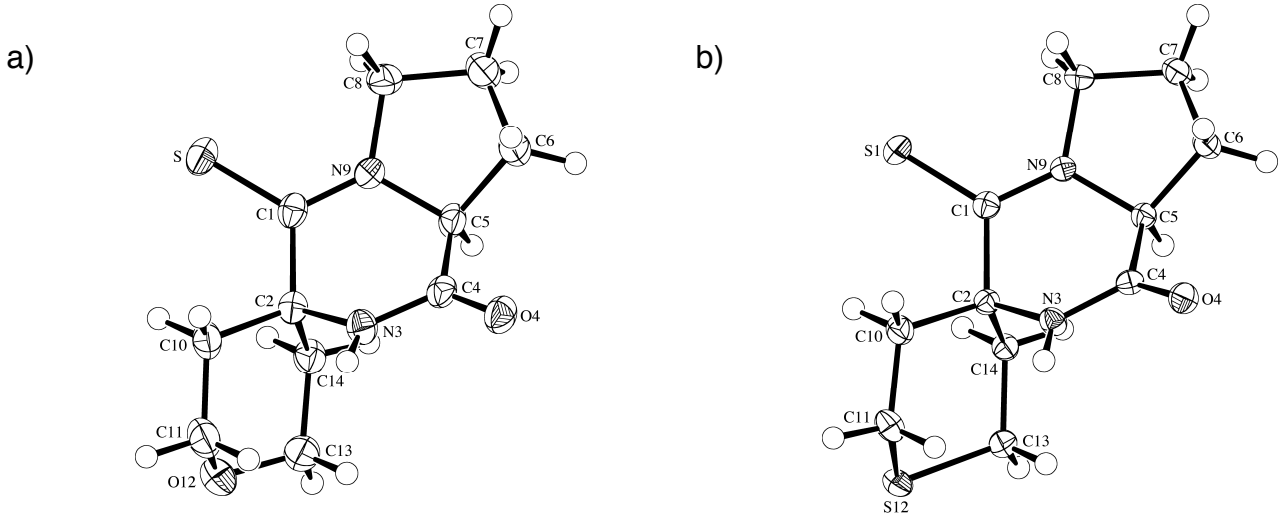



*Figure 2*. ORTEP plots[28] of the molecular structures of a) (*S*)-**6b** and b) (*S*)-**6c** (arbitrary numbering of atoms, 50% probability ellipsoids)

## EXPERIMENTAL

**General remarks.** See ref.[22] Melting points (mp): *Mettler-FP-5* or *Büchi B-450* apparatus; uncorrected. IR spectra: *Perkin-Elmer-781* or *Perkin-Elmer-1600-FT-IR* spectrophotometer; in KBr ($cm^{-1}$). $^1H$- and $^{13}C$-NMR spectra: *Bruker-AC-300* or *Bruker-ARX-300* instrument (300 and 75.5 MHz, resp.) or *Bruker-DRX-600* instrument (600 and 150.9 MHz, resp.); in $CDCl_3$ (ppm, *J* in Hz). MS: *Finnigan MAT-90* or *Finnigan SSQ-700* instrument (EI, 70 eV, or CI ($NH_3$)). Optical rotations were recorded on *Perkin-Elmer-241* polarimeter at 22(1)°C (c = 1.0, in MeOH or

$CDCl_3$). Elemental analyses were performed by 'Mikroanalytisches Laboratorium des Organisch-chemischen Instituts der Universität Zürich'.

**General procedures.** *General procedure A* (*GP A*). To a solution of 1 equiv. of an azirine (**1c**-**e**) in ethyl acetate (EtOAc), $H_2O$ (1.5-2 equiv.) and $SiO_2$ (0.4 g per 1 mmol of **1c**-**e**) were added. The suspension was stirred vigorously for 30 h at 50ºC and filtered. The solvent was evaporated, and the residue was purified chromatographically ($SiO_2$).

*General procedure B* (*GP B*). Through a solution of 1 equiv. of an azirine (**1c**-**e**) in anhydrous THF/DMF 2:1 at –20ºC, $H_2S$ gas was bubbled for 2 h. Then, $N_2$ was bubbled through the mixture at –20ºC for 1 h in order to remove excess $H_2S$, and the mixture was left overnight at rt. The solvent was evaporated, and the residue was submitted to column chromatography ($SiO_2$).

*General procedure C* (*GP C*). To a solution of 1 equiv. of a piperazine-1,4-dione (**4a**-**c**) in dry toluene, 0.5 equiv. of Lawesson reagent (LR) were added. The suspension was stirred vigorously at 50ºC until the substrate was consumed (TLC). After cooling to rt, the mixture was filtered (*Celite*), the solvent was evaporated, and the crude product was purified by chromatography ($SiO_2$).

*General procedure D* (*GP D*). To a solution of 1 equiv. of a 4-thioxopiperazinone (**6a**-**c**) in dry toluene, 0.6 equiv. of LR were added. The suspension was stirred at 60ºC for 2 h. After cooling to rt, the mixture was filtered (*Celite*), the solvent was evaporated, and the crude product was purified chromatographically ($SiO_2$).

**Starting materials**. *Methyl* N-*(2,2-dimethyl-2*H*-azirin-3-yl)*-L-*prolinate* (**1c**),[23] *methyl* N-*(1-aza-6-oxaspiro[2.5]oct-1-en-2-yl)*-L-*prolinate* (**1d**),[24] and *methyl* N-*(1-aza-6-thiaspiro[2.5]oct-1-en-2-yl)*-L-*prolinate* (**1e**)[31] were synthesized according to procedures described in the literature.

**Synthesis of 3,3-dimethylpyrrolo[1,2-*a*]pyrazine derivatives.** – *(*S*)-Perhydro-3,3-dimethyl-pyrrolo[1,2-*a*]pyrazine-1,4-dione* ((*S*)-**4a**).[27] According to *GP A*, **1c** (92% purity; 216 mg, 1.00

mmol) and EtOAc (20 mL). Chromatography ($CH_2Cl_2$/MeOH 20:1) yielded 103 mg (56%) of (*S*)-**4a** as a colorless solid; mp 158-159ºC ($CH_2Cl_2$/MeOH). $[\alpha]_D$ = –138.2° (c = 1.00, MeOH). $^1$H-NMR ($CDCl_3$): 6.80 (br *s*, NH); 4.13 (*dd*, *J* = 9.2, 6.8 Hz, HC(8a)); 3.70-3.49 (*m*, $H_2$C(6)); 2.44-2.36 (*m*, HC(8)); 2.10-1.85 (*m*, HC(8), $H_2$C(7)); 1.49, 1.47 (2*s*, 2 Me). $^{13}$C-NMR ($CDCl_3$): 169.4, 168.6 (*2s*, 2 C=O); 58.8 (*d*, C(8a)); 57.3 (*s*, C(3)); 45.6 (*t*, C(6)); 28.9 (*t*, C(8)); 27.2, 25.4 (2*q*, 2 Me); 22.2 (*t*, C(7)).

*(*S*)-Perhydro-3,3-dimethyl-4-thioxopyrrolo[1,2-*a*]pyrazin-1-one* ((*S*)-**6a**). According to *GP B*, **1c** (92% purity; 326 mg, 1.52 mmol) and THF/DMF (18 mL). Chromatography (EtOAc) yielded 180 mg (60%) of (*S*)-**6a** as colorless crystals; mp 219-221ºC (EtOAc). $[\alpha]_D$ = –186.3° (c = 1.00, MeOH). IR (KBr): 3444*m*, 3304*s*, 2977*m*, 2856*w*, 1685*vs*, 1660*vs*, 1498*s*, 1462*m*, 1429*s*, 1403*m*, 1362*w*, 1333*w*, 1276*m*, 1253*w*, 1179*m*, 1151*s*, 1069*s*, 1014*w*, 976*m*, 960*m*. $^1$H-NMR ($CDCl_3$): 6.96 (br *s*, NH); 4.12 (*dd*, *J* = 10.7, 6.6 Hz, HC(8a)); 3.98 (*ddd*, *J* = 14.3, 10.3, 2.1 Hz, HC(6)); 3.93-3.79 (*m*, HC(6)); 2.57-2.48 (*m*, HC(8)); 2.19-1.97 (*m*, HC(8), $H_2$C(7)); 1.73, 1.53 (2*s*, 2 Me). $^{13}$C-NMR ($CDCl_3$): 197.5 (*s*, C=S); 168.2 (*s*, C=O); 62.5 (*s*, C(3)); 61.5 (*d*, C(8a)); 53.4 (*t*, C(6)); 30.0, 28.7 (2*q*, 2 Me); 28.9 (*t*, C(8)); 22.0 (*t*, C(7)). CI-MS: 200 (13), 199 (100, $[M+1]^+$). Anal. Calcd for $C_9H_{14}N_2OS$: C, 54.52; H, 7.12; N, 14.13; S, 16.17. Found: C, 54.41; H, 7.36; N, 14.11; S, 16.34.

*(*RS*)-Perhydro-3,3-dimethyl-1-thioxopyrrolo[1,2-*a*]pyrazin-4-one* ((*RS*)-**5a**). According to *GP C*, (*S*)-**4a** (84 mg, 0.46 mmol), LR (93 mg, 0.23 mmol), and toluene (20 mL); reaction time: 70 min. Purification by chromatography ($CH_2Cl_2$/EtOAc 20:1) and recrystallization from EtOAc yielded 75 mg (82%) of (*RS*)-**5a** as pale yellow crystals; mp 184-186ºC. $[\alpha]_D$ = 0° (c = 1.00, MeOH). IR (KBr): 3443*m*, 3157*s*, 3038*w*, 2976*m*, 2885*w*, 1655*vs*, 1551*s*, 1498*w*, 1470*s*, 1455*s*, 1362*w*, 1316*w*, 1303*w*, 1276*w*, 1256*m*, 1193*m*, 1149*w*, 1119*s*, 981*m*. $^1$H-NMR ($CDCl_3$): 8.42 (broad *s*, NH); 4.12 (*dd*, *J* = 9.9, 6.0 Hz, HC(8a)); 3.64-3.59 (*m*, $H_2$C(6)); 2.68-2.59 (*m*, HC(8)); 2.23-1.86 (*m*, HC(8), $H_2$C(7)); 1.56, 1.50 (2*s*, 2 Me). $^{13}$C-NMR ($CDCl_3$): 198.3 (*s*, C=S); 167.1 (*s*, C=O); 64.5 (*d*, C(8a)); 60.4 (*s*, C(3)); 46.0 (*t*, C(6)); 33.3 (*t*, C(8)); 25.9, 24.8 (2*q*, 2 Me); 22.1 (*t*, C(7)). CI-MS: 200 (11), 199 (100, $[M+1]^+$). Anal. Calcd for $C_9H_{14}N_2OS$: C, 54.52; H, 7.12; N, 14.13; S, 16.17. Found: C, 52.51; H, 7.01; N, 14.00; S, 15.90.

*(*RS*)-Perhydro-3,3-dimethylpyrrolo[1,2-*a*]pyrazine-1,4-dithione* ((*RS*)-**7a**). According to *GP D*, (*S*)-**6a** (150 mg, 0.758 mmol), LR (184 mg, 0.45 mmol), and toluene (20 mL). Chromatography ($CH_2Cl_2$/EtOAc 50:1) yielded 157 mg (97%) of (*RS*)-**7a** as pale yellow crystals; mp 211-212ºC (EtOAc). $[\alpha]_D$ = 0° (c = 1.00, MeOH). IR (KBr): 3444*m*, 3145*s*, 2972*m*, 2929*w*, 2845*w*, 1540*s*, 1488*s*, 1466*m*, 1499*m*, 1415*m*, 1366*m*, 1328*m*, 1279*w*, 1233*w*, 1165*w*, 1125*s*, 1061*w*, 992*m*. $^1$H-NMR ($CDCl_3$): 8.64 (br *s*, NH); 4.32 (*dd*, *J* = 10.8, 5.7 Hz, HC(8a)); 4.04 (*dd*, *J* = 13.9, 9.0 Hz, HC(6)); 3.87-3.76 (*m*, HC(6)); 2.80-2.71, 2.37-2.23 (2*m*, $H_2C$(8)); 2.19-1.98 (*m*, $H_2C$(7)); 1.80, 1.56 (2*s*, 2 Me). $^{13}$C-NMR ($CDCl_3$): 196.3, 195.5 (2*s*, 2 C=S); 66.5 (*d*, C(8a)); 65.2 (*s*, C(3)); 53.9 (*t*, C(6)); 33.2 (*t*, C(8)); 29.4, 27.5 (2*q*, 2 Me); 21.9 (*t*, C(7)). CI-MS: 216 (13), 215 (100, $[M+1]^+$). Anal. Calcd for $C_9H_{14}N_2S_2$: C, 50.43; H, 6.58; N, 13.07; S, 29.91. Found: C, 50.37; H, 6.61; N, 13.07; S, 29.93.

**Synthesis of spiro[*4H*-pyran-4,3'-(4'*H*)pyrrolo[1,2-*a*]pyrazine] derivatives.** – *(*S*)-Perhydro-spiro[4*H*-pyran-4,3'-(4'*H*)pyrrolo[1,2-*a*]pyrazine]-1',4'-dione* ((*S*)-**4b**). According to *GP A,* **1d** (90% purity; 328 mg, 1.24 mmol) and EtOAc (40 mL). Chromatography ($CH_2Cl_2$/MeOH 20:1), and recrystallization from EtOAc yielded 169 mg (61%) of (*S*)-**4b** as colorless crystals; mp 190-192ºC, $[\alpha]_D$ = –122.2° (c = 1.00, MeOH). IR (KBr): 3443*m*, 3308*w*, 3220*s*, 3134*w*, 3074*m*, 2970*m*, 2926*w*, 2866*m*, 1663*vs*, 1491*w*, 1440*vs*, 1389*m*, 1323*w*, 1294*m*, 1247*w*, 1213*w*, 1181*w*, 1149*m*, 1105*s*, 1024*m*, 978*m*, 923*m*. $^1$H-NMR ($CDCl_3$): 7.31 (br *s*, NH); 4.16-4.09 (*m*, 2H); 3.86-3.48 (*m*, 5H); 2.52 (*ddd*, *J* = 14.0, 9.8, 4.7 Hz, HC(3)); 2.44-2.36 (*m*, HC(8')); 2.11-1.80 (*m*, 4H); 1.75 (*dddd*, *J* = 13.6, 5.1, 2.9, 1.8 Hz, HC(5)); 1.55 (*dddd*, *J* = 14.0, 4.8, 3.4, 1.7 Hz, HC(3)). $^{13}$C-NMR ($CDCl_3$): 169.9, 167.5 (2*s*, 2 C=O); 63.3, 62.7 (2*t*, 2 $CH_2O$); 58.4 (*d*, C(8a')); 56.5 (*s*, C(4)); 45.8 (*t*, C(6')); 34.8, 32.3, 28.9, 22.3 (4*t*, 4 $CH_2$). CI-MS: 226 (11), 225 (100, $[M+1]^+$). Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.67; H, 7.28; N, 12.44.

*(*S*)-Perhydro-4'-thioxospiro[4*H*-pyran-4,3'-(4'*H*)pyrrolo[1,2-*a*]pyrazin]-1'-one* ((*S*)-**6b**). According to *GP B*, **1d** (90% purity; 239 mg, 1.0 mmol) and THF/DMF (12 mL). Chromatography (EtOAc) and recrystallization from EtOAc yielded 128 mg (59%) of (*S*)-**6b** as colorless crystals; mp 194-196ºC. $[\alpha]_D$ = –89.0° (c = 1.00, MeOH). IR (KBr): 3383*m*, 2973*m*, 2925*w*, 2852*s*, 1680*vs*,

1498*s*, 1435*s*, 1386*w*, 1343*w*, 1312*w*, 1245*m*, 1236*w*, 1152*m*, 1141*s*, 1106*s*, 1092*m*, 1063*w*, 1020*w*, 1010*w*. $^1$H-NMR ($CDCl_3$, 600 MHz): 6.86 (broad *s*, NH); 4.13-4.07 (*m*, HC(8a'), HC(2)); 3.99 (*ddd*, *J* = 13.5, 10.0, 1.0 Hz, HC(6')); 3.92 (*ddd*, *J* = 12.1, 4.6, 2.2 Hz, HC(6)); 3.87-3.81 (*m*, HC(6')); 3.67-3.61 (*m*, HC(2), HC(6)); 3.27 (*ddd*, *J* = 14.5, 13.0, 5.4 Hz, HC(3)); 2.55-2.50 (*m*, HC(8')); 2.21-2.13 (*m*, HC(8'), HC(7')); 2.10 (*ddd*, *J* = 13.6, 12.4, 4.6 Hz, HC(5)); 2.04-1.96 (*m*, HC(7')); 1.73 (*dddd*, *J* = 13.6, 2.4, 2.3, 2.2 Hz, HC(5)); 1.55 (*dddd*, *J* = 14.5, 2.4, 2.3, 2.2 Hz, HC(3)). $^{13}$C-NMR ($CDCl_3$): 196.1 (*s*, C=S); 168.5 (*s*, C=O); 62.9, 62.7 (2*t*, 2 $CH_2O$); 61.9 (*s*, C(4)); 61.1 (*d*, C(8a')); 53.8 (*t*, C(6')); 35.5, 34.9, 28.8, 21.9 (4*t*, 4 $CH_2$). ESI-MS: 263 (100, $[M+Na]^+$). Anal. Calcd for $C_{11}H_{16}N_2O_2S$: C, 54.98; H, 6.71 N, 11.66; S, 13.34. Found: C, 54.85; H, 6.70; N, 11.55; S, 13.31.

*(*RS*)-Perhydro-1'-thioxospiro[4*H*-pyran-4,3'-(4*'H*)pyrrolo[1,2-*a*]pyrazin]-4'-one* ((*RS*)-**5b**). According to *GP C*, (*S*)-**4b** (102 mg, 0.46 mmol), LR (93 mg, 0.23 mmol), and toluene (30 mL); reaction time: 80 min. Purification by chromatography ($CH_2Cl_2$/EtOAc 5:1 → 2:1), and recrystallization from EtOAc yielded 91 mg (83%) of (*RS*)-**5b** as pale yellow crystals; mp 178-180°C. $[\alpha]_D$ = 0° (c = 1.00, $CDCl_3$). IR (KBr): 3444*m*, 3207*s*, 2968*s*, 2852*s*, 2758*w*, 1651*vs*, 1521*vs*, 1466*s*, 1449*s*, 1408*m*, 1384*m*, 1311*w*, 1298*w*, 1275*w*, 1247*w*, 1221*m*, 1192*w*, 1178*w*, 1150*m*, 1122*m*, 1107*s*, 1077*s*, 1027*s*, 927*w*, 906*m*. $^1$H-NMR ($CDCl_3$): 8.28 (broad *s*, NH); 4.32 (*dd*, *J* = 9.9, 6.5 Hz, HC(8a')); 4.22 (*ddd*, *J* = 12.2, 6.2, 4.3 Hz, HC(2)); 4.16-3.54 (*m*, 5 H); 2.62 (*dddd*, *J* = 12.8, 6.5, 6.4, 1.9 Hz, HC(8')); 2.51 (*dddd*, *J* = 14.0, 8.3, 4.3, 0.8 Hz, HC(3)); 2.21 (*dddd*, *J* = 12.8, 12.3, 9.9, 6.9 Hz, HC(8')); 2.10-1.78 (*m*, 4 H); 1.66 (*dddd*, *J* = 14.0, 6.2, 3.8, 1.2 Hz, HC(3)). $^{13}$C-NMR ($CDCl_3$): 199.4 (*s*, C=S); 166.2 (*s*, C=O); 64.1 (*d*, C(8a')); 63.7, 62.9 (2*t*, 2 $CH_2O$); 59.4 (*s*, C(4)); 46.3 (*t*, C(6')); 33.7, 33.3, 32.1, 22.1 (4*t*, 4 $CH_2$). EI-MS: 241 (13), 240 (87, $M^{+\cdot}$), 197 (13), 196 (100), 183 (12), 182 (11), 163 (19), 70 (51), 53 (10). Anal. Calcd for $C_{11}H_{16}N_2O_2S$: C, 54.98; H, 6.71; N, 11.66; S, 13.34. Found: C, 54.80; H, 6.53; N, 11.59; S, 13.18.

*(*RS*)-Perhydrospiro[4*H*-pyran-4,3'-(4*'H*)pyrrolo[1,2-*a*]pyrazine]-1',4'-dithione* ((*RS*)-**7b**). According to *GP D*, (*S*)-**6b** (132 mg, 0.55 mmol), LR (133 mg, 0.33 mmol), and toluene (30 mL). Chromatography ($CH_2Cl_2$/EtOAc 20:1 → 10:1) and recrystallization from EtOAc yielded 137 mg

(97%) of (*RS*)-**7b** as yellow crystals; mp 184-186ºC. $[\alpha]_D$ = 0° (c = 1.00, $CDCl_3$). IR (KBr): 3443*m*, 3240*m*, 2966*w*, 2862*m*, 1522*s*, 1484*vs*, 1408*w*, 1386*w*, 1329*w*, 1280*w*, 1246*m*, 1224*w*, 1174*w*, 1116*s*, 1093*m*, 1031*w*, 1019*m*. $^1$H-NMR ($CDCl_3$, 600 MHz): 8.29 (br *s*, NH); 4.30 (*dd*, *J* = 10.7, 6.4 Hz, HC(8a')); 4.17 (*ddd*, *J* = 12.7, 5.3, 2.3 Hz, HC(2)); 4.04 (*ddd*, *J* = 13.8, 8.9, 0.8 Hz, HC(6')); 3.94 (*ddd*, *J* = 12.2, 4.6, 2.6 Hz, HC(6)); 3.80 (*dddd*, *J* = 13.8, 10.9, 7.5, 1.6 Hz, HC(6')); 3.72 (*ddd*, *J* = 12.7, 12.6, 2.4 Hz, HC(2)); 3.62 (*ddd*, *J* = 12.2, 12.0, 2.3 Hz, HC(6)); 3.28 (*ddd*, *J* = 14.7, 12.6, 5.3 Hz, HC(3)); 2.74 (*ddd*, *J* = 13.0, 6.4, 6.3 Hz, HC(8')); 2.35 (*dddd*, *J* = 13.1, 13.0, 10.7, 6.9 Hz, HC(8')); 2.17-2.12 (*m*, HC(7')); 2.09 (*ddd*, *J* = 13.8, 12.0, 4.6 Hz, HC(5)); 2.05-1.95 (*m*, HC(7')); 1.83 (*dddd*, *J* = 13.8, 2.6, 2.5, 2.3 Hz, HC(5)); 1.64 (*dddd*, *J* = 14.7, 2.5, 2.4, 2.3 Hz, HC(3)). $^{13}$C-NMR ($CDCl_3$): 197.4, 194.0 (2*s*, 2 C=S); 66.2 (*d*, C(8a')); 64.3 (*s*, C(4)); 63.0, 62.9 (2*t*, 2 $CH_2O$); 54.2 (*t*, C(6')); 34.8, 34.1, 33.3, 21.8 (4*t*, 4 $CH_2$). CI-MS: 259 (10), 258 (16), 257 (100, $[M+1]^+$). Anal. Calcd for $C_{11}H_{16}N_2OS_2$: C, 51.53; H, 6.29; N, 10.93; S, 25.01. Found: C, 51.41; H, 6.28; N, 10.83; S, 25.10.

**Synthesis of spiro[*4H*-pyrrolo[1,2-*a*]pyrazine-3,4'-(4'*H*)thiopyran] derivatives.** – *(S)-Perhydrospiro[4*H*-pyrrolo[1,2-*a*]pyrazine-3,4'-(4'*H*)thiopyran]-1,4-dione* ((*S*)-**4c**). According to *GP A*, **1e** (75% purity; 188 mg, 0.56 mmol) and EtOAc (20 mL). Chromatography ($CH_2Cl_2$/EtOAc 1:1) and recrystallization from EtOAc yielded 57 mg (43%) of (*S*)-**4c** as colorless crystals; mp 220-222ºC. $[\alpha]_D$ = –144.8° (c = 1.00, $CDCl_3$). IR (KBr): 3443*m*, 3309*s*, 3202*s*, 3121*w*, 3069*m*, 2973*m*, 2901*w*, 1674*vs*, 1641*vs*, 1441*vs*, 1339*w*, 1316*m*, 1289*m*, 1277*w*, 1255*w*, 1207*m*, 1155*w*, 1124*w*, 1077*w*, 1002*w*, 934*m*, 915*m*. $^1$H-NMR ($CDCl_3$): 6.79 (br *s*, NH); 4.10 (*dd*, *J* = 9.3, 6.9 Hz, HC(8a)); 3.69-3.49 (*m*, $H_2C$(6)); 3.02-2.94 (*m*, 1 H); 2.86-2.74 (*m*, 2 H); 2.64-2.54 (*m*, 2 H); 2.45-2.36 (*m*, HC(8)); 2.18 (*ddd*, *J* = 13.6, 10.3, 3.3 Hz, 1 H); 2.10-1.70 (*m*, 5 H). $^{13}$C-NMR ($CDCl_3$): 169.4, 167.6 (2*s*, 2 C=O); 58.4 (*d*, C(8a)); 57.9 (*s*, C(3)); 45.8, 35.5, 33.5, 29.0, 23.2, 22.9, 22.1 (7*t*, 7 $CH_2$). ESI-MS: 503 (38, $[2M+Na]^+$), 263 (84, $[M+Na]^+$), 241 (100, $[M+1]^+$). Anal. Calcd for $C_{11}H_{16}N_2O_2S$: C, 54.98; H, 6.71; N, 11.66; S, 13.34. Found: C, 54.74; H, 6.82; N, 11.53; S, 13.14.

*(S)-Perhydro-4-thioxospiro[4*H*-pyrrolo[1,2-*a*]pyrazine-3,4'-(4'*H*)thiopyran]-1-one* ((*S*)-**6c**). According to *GP B*, **1e** (75% purity; 260 mg, 0.77 mmol) and THF/DMF (12 mL). Chromatography

(EtOAc) and recrystallization from EtOAc yielded 120 mg (62%) of (*S*)-**6c** as colorless crystals; mp 215-218ºC. $[\alpha]_D$ = –256.1° (c = 1.00, MeOH). IR (KBr): 3456*m*, 3358*w*, 3289*s*, 2986*m*, 2951*w*, 2925*w*, 2907*w*, 2875*w*, 1689*vs*, 1485*s*, 1425*s*, 1399*w*, 1312*m*, 1244*m*, 1193*m*, 1156*w*, 1064*m*, 1054*m*, 1000*w*, 976*w*, 926*w*, 917*w*. $^1$H-NMR ($CDCl_3$): 6.75 (br *s*, NH); 4.10 (*dd*, *J* = 10.0, 6.9 Hz, HC(8a)); 3.98 (*ddd*, *J* = 14.7, 9.8, 1.9 Hz, HC(6)); 3.84 (*m*, HC(6)); 3.20 (*ddd*, *J* = 14.3, 13.4, 4.4 Hz, 1 H); 2.96-2.85 (*m*, 2 H); 2.70 (*dddd*, *J* = 14.5, 4.1, 3.8, 1.7 Hz, 1 H); 2.57-2.48 (*m*, 2 H); 2.23-1.88 (*m*, 6 H). $^{13}$C-NMR ($CDCl_3$): 196.4 (*s*, C=S); 167.9 (*s*, C=O); 63.1 (*s*, C(3)); 61.0 (*d*, C(8a)); 53.8, 36.5, 35.6, 28.9, 23.0, 22.8, 21.8 (7*t*, 7 $CH_2$). CI-MS: 259 (11), 258 (21), 257 (100, $[M+1]^+$). Anal. Calcd for $C_{11}H_{16}N_2OS_2$: C, 51.53; H, 6.29; N, 10.93; S, 25.01. Found: C, 51.63; H, 5.89; N, 10.77; S, 24.76.

*(*RS*)-Perhydro-1-thioxospiro[4*H*-pyrrolo[1,2-*a*]pyrazine-3,4'-(4*'H*)thiopyran]-4-one* ((*RS*)-**5c**). According to *GP C*, (*S*)-**4c** (57 mg, 0.24 mmol), LR (48 mg, 0.12 mmol), and toluene (50 mL); reaction time: 90 min. Purification by chromatography ($CH_2Cl_2$/EtOAc 5:1) and recrystallization from EtOAc yielded 55 mg (90%) of (*RS*)-**5c** as colorless crystals; mp 213-216ºC. $[\alpha]_D$ = 0° (c = 1.00, $CDCl_3$). IR (KBr): 3446*m*, 3184*s*, 2949*m*, 2910*m*, 1646*vs*, 1524*s*, 1463*s*, 1447*s*, 1408*m*, 1358*w*, 1309*w*, 1287*m*, 1276*m*, 1232*m*, 1206*w*, 1142*m*, 1110*m*, 1085*w*, 1064*m*, 1028*w*, 1014*w*. $^1$H-NMR ($CDCl_3$): 8.10 (br *s*, NH); 4.31 (*dd*, *J* = 10.0, 6.6 Hz, HC(8a)); 3.69-3.53 (*m*, $H_2C$(6)); 3.17 (*ddd*, *J* = 14.1, 6.8, 3.8 Hz, 1 H); 2.84-2.57 (*m*, 5 H); 2.26-1.81 (*m*, 6 H). $^{13}$C-NMR ($CDCl_3$): 199.1 (*s*, C=S); 166.3 (*s*, C=O); 64.1 (*d*, C(8a)); 60.8 (*s*, C(3)); 46.2, 34.6, 33.5, 33.2, 23.6, 23.1, 22.0 (7*t*, 7 $CH_2$). ESI-MS: 258 (13), 257 (100, $[M+1]^+$). Anal. Calcd for $C_{11}H_{16}N_2OS_2$: C, 51.53; H, 6.29; N, 10.93; S, 25.01. Found: C, 51.55; H, 6.42; N, 10.83; S, 24.75.

*(*RS*)-Perhydrospiro[4*H*-pyrrolo[1,2-*a*]pyrazine-3,4'-(4*'H*)thiopyran]-1,4-dithione* ((*RS*)-**7c**). According to *GP D*, (*S*)-**6c** (56 mg, 0.22 mmol), LR (54 mg, 0.13 mmol), and toluene (40 mL). Chromatography ($CH_2Cl_2$) and recrystallization from EtOAc yielded 58 mg (97%) of (*RS*)-**7c** as pale yellow crystals; mp 205-206ºC. $[\alpha]_D$ = 0° (c = 1.00, $CDCl_3$). IR (KBr): 3444*m*, 3257*s*, 2980*w*, 2935*w*, 2901*w*, 2849*w*, 1516*m*, 1489*s*, 1443*s*, 1357*w*, 1317*w*, 1271*m*, 1248*m*, 1230*m*, 1196*m*, 1184*w*, 1155*s*, 1108*m*, 1048*m*, 1026*w*, 961*w*, 931*w*. $^1$H-NMR ($CDCl_3$): 8.06 (br *s*, NH); 4.28 (*dd*, *J* = 10.5, 6.5 Hz, HC(8a)); 4.03 (*dd*, *J* = 14.0, 8.8 Hz, HC(6)); 3.80 (*dddd*, *J* = 14.0,

10.7, 7.5, 1.5 Hz, HC(6)); 3.22 (*ddd*, *J* = 14.6, 12.8, 4.9 Hz, 1 H); 2.97-2.71 (*m*, 4 H); 2.55 (*dddd*, *J* = 14.2, 3.8, 3.7, 1.5 Hz, 1 H); 2.38-1.90 (*m*, 6 H). $^{13}$C-NMR ($CDCl_3$): 197.1, 194.4 (2*s*, 2 C=S); 66.2 (*d*, C(8a)); 65.4 (*s*, C(3)); 54.2, 35.8, 34.9, 33.4, 23.2, 23.0, 21.7 (7*t*, 7 $CH_2$). ESI-MS: 274 (15), 273 (100, $[M+1]^+$). Anal. Calcd for $C_{11}H_{16}N_2S_3$: C, 48.50; H, 5.92; N, 10.28; S, 35.30. Found: C, 48.39; H, 5.92; N, 10.19; S, 35.42.

**X-Ray Crystal-Structure Determination of** (*RS*)-**5a**, (*S*)-**6a**, (*RS*)-**7a**, (*S*)-**6b**, and (*S*)-**6c** (see *Table 1* and *Figures 1* and *2*).[32] All measurements were performed on a *Nonius KappaCCD* area-detector diffractometer[33] using graphite-monochromated Mo$K_\alpha$ radiation ($\lambda$ 0.71073 Å) and with an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in *Table 1*, and views of the molecules are shown in *Figures 1* and *2*. Data reduction for was performed with *HKL Denzo* and *Scalepack*.[34] The intensities were corrected for *Lorentz* and polarization effects, and absorption corrections based on the multi-scan method[35] were applied. Each structure was solved by direct methods using SIR92,[36] which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The amide and sulfamide 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 in each structure were placed in geometrically calculated positions and each 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 the methyl groups). The refinement of each structure was carried out on $F^2$ using full-matrix least-squares procedures, which minimised the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied in the cases of (*S*)-**6a** and (*S*)-**6b**. The absolute configuration for (*S*)-**6a**, (*S*)-**6b**, and (*S*)-**6c** was confirmed confidently by refinement of the absolute structure parameter,[37] which yielded values of -0.02(6), 0.01(7) and -0.07(6), respectively. Neutral atom scattering factors for non-H-atoms were taken from ref.[38a], and the scattering factors for H-atoms were taken from ref.[39] Anomalous dispersion effects were included in $F_c$;[40] the values for $f'$ and $f''$ were those of ref.[38b] The values of the mass attenuation coefficients are those of ref.[38c] All calculations were performed using the SHELXL97 program.[41]

Table 1. *Crystallographic Data of* (*RS*)-**5a**, (*S*)-**6a**, (*RS*)-**7a**, (*S*)-**6b**, and (*S*)-**6c**

| | | (*RS*)-**5a** | (*S*)-**6a** | (*RS*)-**7a** |
|---|---|---|---|---|
| Crystallized from | | EtOAc | $CDCl_3$ | EtOAc |
| Empirical formula | | $C_9H_{14}N_2OS$ | $C_9H_{14}N_2OS$ | $C_9H_{14}N_2S_2$ |
| Formula weight [g mol$^{-1}$] | | 198.28 | 198.28 | 214.34 |
| Crystal color, habit | | colorless, prism | colorless, prism | colorless, prism |
| Crystal dimensions [mm] | | 0.15 × 0.25 × 0.25 | 0.20 × 0.30 × 0.30 | 0.15 × 0.20 × 0.27 |
| Temperature [K] | | 160(1) | 160(1) | 160(1) |
| Crystal system | | monoclinic | monoclinic | monoclinic |
| Space group | | $P2_1/n$ | $P2_1$ | $P2_1/n$ |
| $Z$ | | 4 | 2 | 4 |
| Reflections for cell determination | | 14993 | 18179 | 41000 |
| $2\theta$ range for cell determination [°] | | 4 – 60 | 4 – 60 | 4 – 50 |
| Unit cell parameters | $a$ [Å] | 8.6975(2) | 7.5523(2) | 10.6468(2) |
| | $b$ [Å] | 10.9848(4) | 6.9594(2) | 7.0753(2) |
| | $c$ [Å] | 10.6894(3) | 9.0815(3) | 14.6604(4) |
| | $\beta$ [°] | 104.657(2) | 90.479(1) | 111.099(1) |
| | $V$ [Å$^3$] | 988.03(5) | 477.30(2) | 1030.32(5) |
| $D_X$ [g cm$^{-3}$] | | 1.333 | 1.380 | 1.382 |
| $\mu$(Mo$K\alpha$) [mm$^{-1}$] | | 0.290 | 0.300 | 0.472 |
| Scan type | | $\phi$ and $\omega$ | $\phi$ and $\omega$ | $\phi$ and $\omega$ |
| $2\theta_{(max)}$ [°] | | 60 | 60 | 50 |
| Transmission factors (min; max) | | 0.870; 0.960 | 0.852; 0.944 | 0.812; 0.936 |
| Total reflections measured | | 20250 | 13500 | 23544 |
| Symmetry independent reflections | | 2881 | 2791 | 1821 |
| Reflections with $I > 2\sigma(I)$ | | 2320 | 2600 | 1574 |
| Reflections used in refinement | | 2880 | 2787 | 1819 |
| Parameters refined | | 124; 0 | 125; 1 | 124; 0 |
| Final $R(F)$ [$I>2\sigma(I)$ reflections] | | 0.0426 | 0.0311 | 0.0344 |
| $wR(F^2)$ (all data) | | 0.1150 | 0.0732 | 0.0863 |
| Weighting parameters* [$a$; $b$] | | 0.0532; 0.5242 | 0.0321; 0.1082 | 0.0386; 0.7213 |
| Goodness of fit | | 1.028 | 1.030 | 1.096 |
| Secondary extinction coefficient | | - | 0.05(1) | - |
| Final $\Delta_{max}/\sigma$ | | 0.001 | 0.001 | 0.001 |
| $\Delta\rho$ (max; min) [e Å$^{-3}$] | | 0.67; -0.39 | 0.24; -0.23 | 0.23; -0.25 |

* $w = [\sigma^2(F_o^2) + (aP)^2 + bP]^{-1}$, where $P = (F_o^2+2F_c^2)/3$

Table 1. *Crystallographic Data of* (*RS*)-**5a**, (*S*)-**6a**, (*RS*)-**7a**, (*S*)-**6b**, and (*S*)-**6c** (continued)

| | | (*S*)-**6b** | (*S*)-**6c** |
|---|---|---|---|
| Crystallized from | | EtOAc | EtOAc |
| Empirical formula | | $C_{11}H_{16}N_2O_2S$ | $C_{11}H_{16}N_2OS_2$ |
| Formula weight [g mol$^{-1}$] | | 240.32 | 256.38 |
| Crystal color, habit | | colorless, prism | colorless, prism |
| Crystal dimensions [mm] | | 0.12 × 0.22 × 0.25 | 0.12 × 0.25 × 0.32 |
| Temperature [K] | | 160(1) | 160(1) |
| Crystal system | | monoclinic | orthorhombic |
| Space group | | $P2_1$ | $P2_12_12_1$ |
| $Z$ | | 2 | 4 |
| Reflections for cell determination | | 20533 | 21172 |
| $2\theta$ range for cell determination [°] | | 4−55 | 4−60 |
| Unit cell parameters | $a$ [Å] | 9.9137(4) | 6.9538(1) |
| | $b$ [Å] | 5.7123(2) | 8.2768(1) |
| | $c$ [Å] | 10.2515(4) | 20.1089(4) |
| | $\beta$ [°] | 97.026(2) | 90 |
| | $V$ [Å$^3$] | 576.18(4) | 1157.37(3) |
| $D_X$ [g cm$^{-3}$] | | 1.385 | 1.471 |
| $\mu$(Mo$K\alpha$) [mm$^{-1}$] | | 0.268 | 0.440 |
| Scan type | | $\phi$ and $\omega$ | $\phi$ and $\omega$ |
| $2\theta_{(max)}$ [°] | | 55 | 60 |
| Transmission factors (min; max) | | 0.882; 0.971 | 0.892; 0.950 |
| Total reflections measured | | 14218 | 21865 |
| Symmetry independent reflections | | 2615 | 3383 |
| Reflections with $I > 2\sigma(I)$ | | 2382 | 3053 |
| Reflections used in refinement | | 2614 | 3382 |
| Parameters refined | | 151; 1 | 149; 0 |
| Final $R(F)$ [$I>2\sigma(I)$ reflections] | | 0.0347 | 0.0325 |
| $wR(F^2)$ (all data) | | 0.0812 | 0.0731 |
| Weighting parameters* [$a$; $b$] | | 0.0375; 0.1504 | 0.0300; 0.3506 |
| Goodness of fit | | 1.060 | 1.080 |
| Secondary extinction coefficient | | 0.030(7) | - |
| Final $\Delta_{max}/\sigma$ | | 0.001 | 0.001 |
| $\Delta\rho$ (max; min) [e Å$^{-3}$] | | 0.20; -0.18 | 0.23; -0.27 |

*$w = [\sigma^2(F_o^2) + (aP)^2 + bP]^{-1}$, where $P = (F_o^2+2F_c^2)/3$

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