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Synthesis of Chiral Condensed S-Heterocycles via Stereoselective Michael-like Addition to Butenolides and α,ß-Unsaturated Lactams

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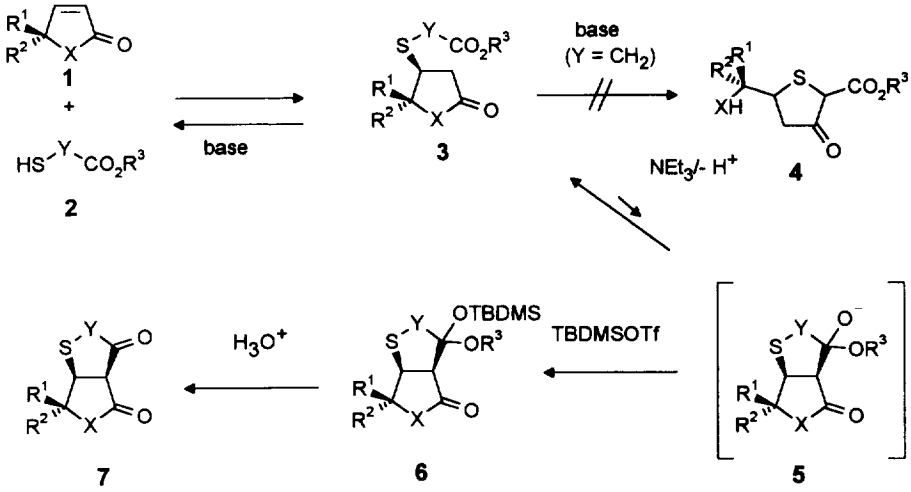
Abstract: The Michael-like addition of ω-thiohydroxyesters **2** to butenolides or α.ß-unsaturated lactams **1** exhibits *trans*-selectivity. Some of the adducts **3** undergo cyclization to novel condensed S-heterocycles **6** and the perhydrogenated thieno[2,3-c]furan **7** with ß-ketoester functionality. **7** can be C-alkylated to **8**, hydrolyzed to a muscarine analog **9** and ring transformed with hydrazine to the novel dihydrothieno[3,4-c]-pyrazole **10**. A novel bicyclic pyrrolo[3,2-b]-1,4-thiazine **16** is obtained by ring transformation of the pyrrolo[2,1-b]oxazolidine **1c** with 2-mercaptoaniline.

Recently we reported on the synthesis of novel ω-aminoalkylheterocycles[1,2] based on a special ring transformation of α,ß-unsaturated lactones or lactams, which were treated with binucleophiles, such as hydrazines or ß-aminothiols. Primary Michael-like *trans*-addition of the binucleophile to the C-C-double bond was followed by attack of the second nucleophilic center at the carbonyl carbon atom, thus forming a new heterocycle while the starting ring system was opened (ring chain transformation). The present work presents attempts to extend this concept to other binucleophiles and to the bicyclic lactam **1c**, which did not result in the desired ring transformation but in the stereoselective synthesis of novel condensed S-heterocycles.

Thioglycolates **2** (Y = CH_2) had successfully served as binucleophilic S-C-building blocks in the synthesis of thiophenes[3] and hence were considered as reactants for butenolides **1** (X = O) and α,ß-unsaturated lactams **1** (X = NR). A clean addition of ethyl thioglycolate **2** (Y = CH_2) to the C-C-double bond was observed. The same situation was found if butyl 3-thiohydroxypropionate **2** (Y = CH_2CH_2) and methyl 2-thiohydroxybenzoate **2** (X = o-C_6H_4) were treated with the butenolide **1a**. The resulting adducts **3** (mainly *trans*) were stereoselectively formed with diastereomeric ratios between 72 : 28 and 92 : 8. Usually it was possible to obtain the major *trans*-diastereomer **3** in pure form by column chromatography. Attempts to achieve the anticipated ring chain transformation of the adducts **3** (Y = CH_2) to thiophene-carboxylates **4**



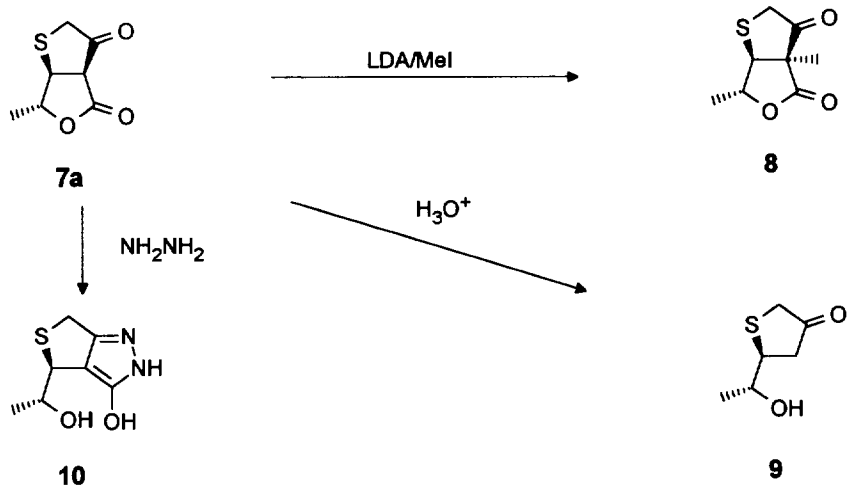
1	3	6	7	X	R^1	R^2	Y	R^3
a	a	a	a	O	H[1)]	Me[1)]	CH_2	Et
b	b	b		O	H	CH_2OH[2)]	CH_2	Et
c	c	c		N	O	Me	CH_2	Et
d	d			NBoc	H	$CH_2OTBDMS$	CH_2	Et
	e	e		O	H[1)]	Me[1)]	$(CH_2)_2$	n-Bu
	f	f		O	H[1)]	Me[1)]	o-C_6H_4	Me

[1)] racemic **1** was used affording racemic products **3**, **6**, or **7**

[2)] in case of **6b** CH_2OH had been transformed to $CH_2OTBDMS$

by deprotonation of the S-CH_2 group and further attack at the ring carbonyl carbon atom failed. Instead of deprotonating the exocyclic CH_2 group, the ring position α to carbonyl was attacked by the base (triethylamine, KOtBu or NaH) resulting in a retro-Michael-addition-like elimination of ethyl thioglycolate reproducing the starting α,ß-unsaturated carbonyl system **1**. Interestingly, the Mukaiyama-like [4] application of TBDMS-triflate/triethylamine to **3** leaves the ß-mercapto substituent in the molecule. Silylated tetrahydrothiophene hemiacetals **6** were obtained. Their formation can be explained again via deprotonation of the ring CH_2-position of **3**. The resulting anion is in equilibrium with the hemiacetal anion **5**, which is irreversibly removed by silylation. With the exception of the tricyclic product **6c** (appearing as mixtures of four diastereomers) only two stereoisomeric products **6** were observed. The relative configuration of the non-H substituent R^1 or R^2 in the furan or pyrrole ring with respect to the sulfur atom is *trans*, the fusion of both

heterocyclic rings in **6** can be assumed to be *cis*. The configuration at the acetal carbon atom was not determined. The cyclization can be extended to the higher homolog **3e** (Y = CH_2CH_2) and the benzo analog **3f** (Y = o-C_6H_4). The yields however were lower because of competing ß-elimination, affording **1** and corresponding S-silylation products of the thiohydroxyesters **2**. Compounds **6c** and **6e** or **6f** consist of hitherto unknown condensed heterocyclic ring systems; hydrogenated thieno[2,3-c]furans have also not been reported in the literature. [5] Acid hydrolysis of the racemic thienofuranone **6a** affords the corresponding



thienofurandione **7a**. Its structure was determined by X-ray crystal analysis (see Figure 1). The *trans*-orientation of the sulfur-atom and the methyl group also proves the stereochemistry of the reaction of the ω-thiohydroxyesters **2** with the α,ß-unsaturated carbonyl systems **1** as *trans*-addition. The racemic thienofurandione **7a** represents an interesting chiral bridged ß-ketoester system and gives some typical reactions, such as methylation with methyl iodide in the presence of LDA. The stereochemistry of the methylation product **8** is unambiguous because of the *cis* fusion of the two rings, directing the incoming methyl group *trans* with respect to the sulfur atom. Acid hydrolysis of the thienofuranone **7a** causes cleavage of the furanone ring and decarboxylation yielding the thiomuscarine analog **9** in modest yield. It is worth mentioning that the latter product corresponds to the thiophene **4** that could not be synthesized by ring transformation of **3**. Hydrazine hydrate attacks both electrophilic positions of **7a** resulting in the formation of a pyrazolinone system, adopting the enol structure **10** in solution. Interestingly, the reaction is not only a simple cyclization, but also, because of the bridged leaving group of the ß-ketoester moiety, represents a ring transformation since the furanone ring was cleaved while the pyrazole system was formed.

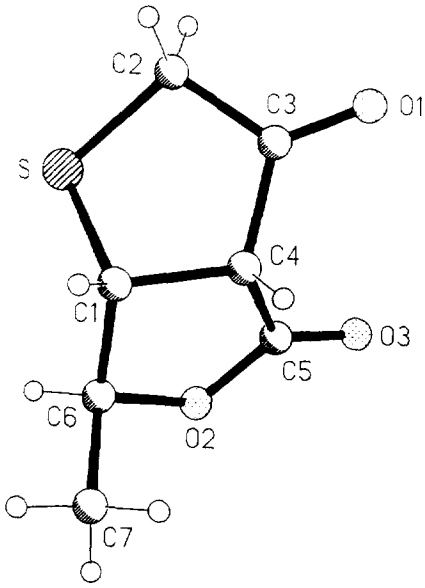
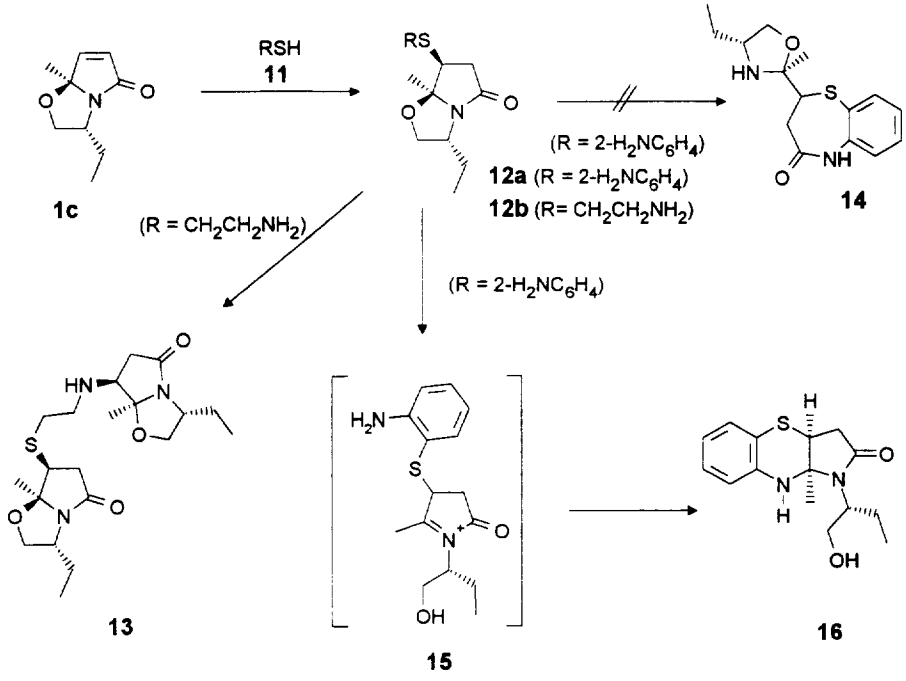


Fig. 1: X-Ray structural analysis of **7a**

We further investigated the ability of the bicyclic lactam **1c** to undergo ring transformations with 2-mercaptoaniline **11** (R = 2-$H_2NC_6H_4$) and 2-aminoethanothiol **11** (R = $CH_2CH_2NH_2$). These binucleophiles **11** gave clean ring transformations with monocyclic α,ß-unsaturated lactones or lactams **1** affording thiazepinones.[2] The bicyclic α,ß-unsaturated lactam **1c**, however, is a substrate with three electrophilic centers (CO, double bond and hemiaminal carbon atom). The interesting question arose as to which of the three electrophilic sites are involved in reactions with binucleophiles **11**. It was found that again primary Michael-like addition of the mercapto function occurs with diasteromeric ratios of products **12** between 80 : 20 and 91 : 9. The 2-aminoethylthio adduct **12b** was obtained as a mixture with the 1:2-adduct **13**, especially if the reaction temperature was raised. Products **12b** and **13** could be separated by column chromatography. The 3-mercaptopyrrolo[2,1-b]oxazolones **12** turned out to be reluctant to undergo ring transformation affording thiazepinones such as **14**. In trifluoroacetic acid / methanol, however, the diastereomeric mixture of 2-aminophenylthio derivatives **12a** gave a ring transformation where the hemiaminal of the oxazolidine ring was cleaved affording an interesting pyrrolo[3,2-b]-1,4-thiazine **16**.[6] The diastereomers **16** could be separated by chromatography. The X-ray crystal structure analysis of this major isomer (see Figure 2) proved its structure and revealed that the addition of 2-mercaptoaniline to the α,ß-unsaturated

lactam **1c** preferably occurred *trans* with respect to the methyl group. In the crystal lattice the



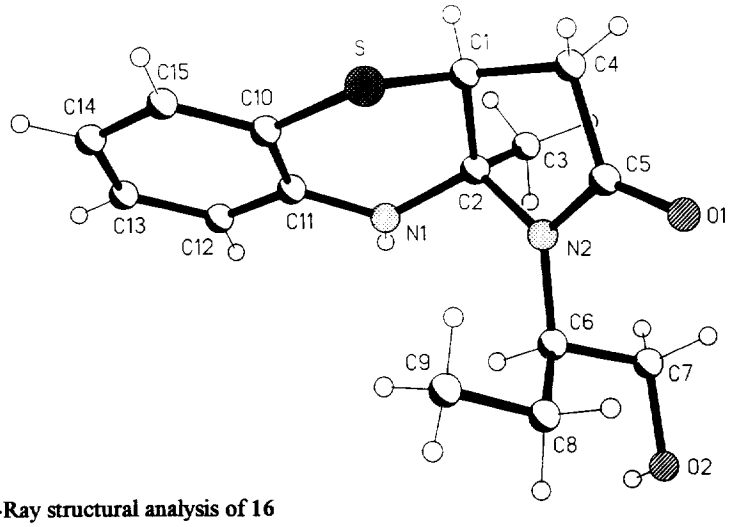


Fig. 2: X-Ray structural analysis of **16**

molecules of **16** are connected into bands by hydrogen bonds of the form O2-H···O1 and N1-H···O2. The acid catalyzed ring transformation of the adduct **12a** to the pyrrolobenzothiazine **16** can be assumed to take place via a cyclic N-acyliminium salt **15**, by analogy to known reactions of other 3-alkoxylactams with nucleophiles. [7]

Experimental

NMR spectra were recorded in DMSO-d_6 with a Bruker AC 300 and refer to the major diastereomers. The splitting patterns were designated as follows: s (singlet), d (doublet), dd (double of doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Mass spectra (70 eV) were recorded with HP 5995 A (Hewlett-Packard). Melting points were performed on a Boetius hot stage apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a 1 ml cell. Silica gel 60 from Merck was used for column chromatography.

The α,ß-unsaturated lactones **1a, b** and lactams **1c,d** were prepared according to known procedures. [8]

S-Substituted 3-Mercaptolactones and Lactams (3)

2.54 g (25 mmol) triethylamine were added to a solution of 25 mmol ω-thiohydroxyester **2** in 10 ml of dry DMSO or DMF under an argon atmosphere. After 15 min stirring at room temperature 25 mmol of the α,ß-unsaturated lactone or lactam **1** were added. The solution was stirred for further 3 - 7h. DMF was removed by vacuum distillation. The products are colorless oils, which were separated and purified by column chromatography at silica gel (eluent: hexane/ ethyl acetate = 1:1).

trans-4-(Ethoxycarbonylmethylthio)-5-methyl-tetrahydrofuran-2-one (3a) (racemic mixture). Yield: 4.5 g, 85 % (DMSO, 22°C, dr: 88:12); ^{1}H NMR: 1.25 (t, 3H, J=7) CH_3-CH_2; 1.45 (d, 3H, J=6) CH_3-C-O; 2.54 (dd, 1H, J_1=17, J_2=8) CH_2-CO; 2.98 (dd, 1H, J_1=17, J_2=8) CH_2-CO; 3.25-3.49 (m, 3H) CH-S, CH_2-S; 4.16 (q, 2H, J=7) O-CH_2-CH_3; 4.38 (m, 1H) CH-O; ^{13}C NMR: 14.1 ($\underline{C}H_3$-CH_2); 19.7 ($\underline{C}H_3$-C-O); 33.3 ($\underline{C}H_2$-CO); 36.7 (CH_2-S); 45.9 (CH-S); 61.8 (O-$\underline{C}H_2$-CH_3); 81.3 (CH-O); 169.7 (CO-O); 174.1 (CO_2Et); Anal. calc. for $C_9H_{14}O_4S$ (218.29): C, 49.51; H, 6.45; S, 14.68; found: C, 49.56; H, 6.64; S, 14.11.

(4S,5R)-4-(Ethoxycarbonylmethylthio)-5-hydroxymethyl-tetrahydrofuran-2-one (3b). Yield: 4.85 g, 83 % (DMSO, 0°C, dr: 92:8, eluent: hexane/ethyl acetate = 1:9); ^{1}H NMR: 1.22 (t, 3H, J= 7.1) CH_3-CH_2; 2.45 (dd, 1H, J_1=18.2 J_2=7.5) CH_2-CO-O; 3.04 (dd, 1H, J_1=18.2, J_2=8.8) CH_2-CO-O; 3.26 (d, 2H, J=2.3) CH_2-S; 3.77 (d, 2H J=2.0) CH_2-OH; 3.88 (d, 1H, J=12.8) CH-S; 4.13 (q, 2H, J=7.1) CH_2-CH_3; 4.35 (m, 1H) CH-O; ^{13}C NMR: 14.0 ($\underline{C}H_3$-CH_2); 33.4 ($\underline{C}H_2$-CO-O); 36.8 ($\underline{C}H_2$-S); 40.0 (CH-S); 61.9 (O-CH_2); 85.5 (CH-O); 170.0 (CO-O); 175.3 (CO_2Et); $[\alpha]_D^{22}$ = +42.1° (c=1, $CHCl_3$); Anal. calc. for $C_9H_{14}O_5S$ (234.29): C, 46.14; H, 6.04; S, 13.68; found: C, 45.44; H, 6.13; S, 13.20.

(3R,7S,7aS)-7-(Ethoxycarbonylmethylthio)-3-ethyl-7a-methyl-2,3,6,7-tetrahydro-pyrrolo[2,1-b]oxazole (3c). Yield: 5.45 g, 76% (DMSO, 22°C, dr: 88:12), ^{1}H NMR: 0.89 (t, 3H, J=7.4) CH_3-CH_2; 1.21 (t, 3H, J=7.1) O-CH_2-CH_3; 1.42 (s, 3H) CH_3-C; 1.58 (m, 2H) CH_2-CH_3; 2.53 (dd, 1H, J_2=15.8, J_2=2.6) CH_2-CO-O; 2.67 (dd, 1H, J_1=15.8 J_2=8.1) CH_2-CO-O; 3.25 (d, 2H, J=17) CH_2-S; 3.68 (dd, 1H, J_1=8.9, J_2=1.6) CH-S; 3.80 (dd, 2H, J_1=8.0, J_2=2.5) O-CH_2-CH; 4.09 (m, 1H) CH-N; 4.12 (q, 2H, J=7.1) O-CH_2-CH_3; ^{13}C NMR: 10.7 ($\underline{C}H_3$-CH_2); 13.4 ($\underline{C}H_3$-CH_2-O); 26.5 ($\underline{C}H_3$-C_{qu}); 27.3 ($\underline{C}H_2$-CH_3); 33.5 ($\underline{C}H_2$-CO-O); 40.1 (CH_2-S);

50.3 (CH-S); 56.3 (CH-N); 61.3 (O-$\underline{C}H_2$-CH_3); 73.2 (O-$\underline{C}H_2$-CH); 100.4 (O-C_{qu}-N); 169.9 (CO-O); 174.8 (CO_2Et); $[\alpha]_D^{22}$ = -85.3° (c=1, $CHCl_3$); Anal. calc. for $C_{13}H_{21}NO_4S$ (287.41): C, 54.33; H, 7.37; N, 4.87; S, 11.16; found: C, 54.20; H, 8.19; N, 4.82; S, 11.03.

(4S,5R)-4-(Ethoxycarbonylmethylthio)-5-tert-butyldimethylsilyloxymethyl-pyrrolidin-2-one (3d).
Yield: 4.62 g, 79 % (DMF, rt, dr: 76:24), ^{1}H NMR:- 0.02 (s, 3H) CH_3-Si; 0.00 (s, 3H) CH_3-Si; 0.82 (s, 9H) $(CH_3)_3$C-Si; 1.25 (t, 3H, J=7) $C\underline{H}_3$-CH_2; 1.49 (s, 9H) $(CH_3)_3$-C-O; 2.33 (dd, 1H, J_1=18, J_2=1.4) CH_2-CO; 3.10 (dd, 1H, J_1=18.3, J_2=8.5) CH_2-CO; 3.23 (m, 2H) CH_2-S; 3.56 (m, 1H) CH-S; 3.72 (dd, 1H, J_1=11, J_2=2) CH_2-O; 3.91 (dd, 1H, J_1=11, J_2=4) CH_2-O; 4.09 (m, 1H) CH-N; 4.16 (q, 2H, J=7) CH_2-CH_3; ^{13}C NMR: -5.6 [$(CH_3)_2$-Si)]; 14.1 ($\underline{C}H_3$-CH_2); 18.1 (C_{qu}-Si); 25.8 [$(CH_3)_3$C-Si)]; 28.0 [$(CH_3)_3$C-O)]; 33.0 (CH_2-S); 38.6 (CH-S); 39.5 (CH_2-$\underline{C}O$); 61.9 (CH_2-O); 63.6 (O-$\underline{C}H_2$-CH_3); 65.2 (CH-N); 83.2 (C_{qu}-O); 149.8 (O-C=O); 172.0 (CO); $[\alpha]_D$ = +2.6° (c=0.9, CH_3OH); Anal. calc. for $C_{20}H_{37}O_6NSSi$ (234.29): C, 53.66; H, 8.33; N, 3.18; found: C, 53.59; H, 7.89; S, 3.52.

trans Butyl 3-(2-Methyl-5-oxo-tetrahydro-furan-3-ylsulfanyl)-propionate (3e) (racemic mixture).
Yield: 4.94 g, 76% (DMSO, 22°C, 3h, dr: 79:21), ^{1}H NMR: 0.86 (t, 3H, J=7.3) CH_3-CH_2; 1.31 (m, 2H) CH_3-CH_2; 1.41 (d, 3H, J=6.3) CH_3-CH; 1.54 (m, 2H) O-CH_2-CH_2 2.47 (dd, 1H, J_1=17.2, J_2=1.9) CH_2-CO; 2.55 (t, 2H, J=5.3) CH_2-CH_2-CO; 2.80 (t, 2H, J=5.4) CH_2-S; 2.9 (dd, 1H, J_1=18.0, J_2=3.4) CH_2-CO; 3.1 (q, 1H, J=7.4) CH-S; 4.06 (t, 2H, J=6.7) O-CH_2-CH_3; 4.31 (m, 1H) CH-O; ^{13}C NMR: 13.6 ($\underline{C}H_3$-CH_2); 19.05 ($\underline{C}H_2$-CH_3); 19.6 ($\underline{C}H_3$-CH); 26.6 (O-CH_2-$\underline{C}H_2$); 30.5 (S-CH_2-$\underline{C}H_2$); 34.7 ($\underline{C}H_2$-CO); 37.1 (CH_2-S); 46.0 (CH-S); 64.8 (O-CH_2); 81.7 (CH-O); 171.4 (CO-O); 174.2 ($\underline{C}O_2$-CH_2); Anal. calc. for $C_{12}H_{20}O_4S$ (260.38): C, 55.35; H, 7.76; S, 12.31; found: C, 55.24; H, 8.20; S, 12.07.

trans Methyl 2-(2-Methyl-5-oxo-tetrahydro-furan-3-ylsulfanyl)-benzoate (3f) (racemic mixture).
Yield: 5.05 g, 76%, (DMSO, 22°C, dr: 88:12), ^{1}H NMR: 1.43 (d, 3H, J=6.3) CH_3-CH; 2.54 (dd, 1H, J_1=18.0 J_2=7.3) CH_2-CO-O; 3.10 (dd, 1H, J_1=18.1 J_2=7.2) CH_2-CO-O; 3.71 (m, 1H) CH-S; 3.85 (s, 3H) CH_3-O; 4.49 (m, 1H) CH-O; 7.23 (m, 2H) CH_{arom}; 7.41 (m, 1H) CH_{arom}; 7.89 (m, 1H) CH_{arom}; ^{13}C NMR: 20.1 ($\underline{C}H_3$-CH); 36.5 ($\underline{C}H_2$-CO-O); 46.0 (CH-S); 52.3 (CH_3-O); 80.7 (CH-O); 125.8, 128.1, 131.4, 132.5 (4 CH_{arom}); 137.4 (S-C_{qu}); 166.8 ($\underline{C}_{qu}$-CO2); 174.2 (CO_2-Me); Anal. calc. for $C_{13}H_{14}O_4S$ (266.33): C, 58.62; H, 5.31; S, 12.04; found: C, 58.75; H, 5.36; S, 11.64.

Silylated Hemiacetals 6

A solution of 4.6 mmol of the S-substituted 3-mercaptolactone or lactam **3** in 10 ml of dry THF under argon is cooled to -78°C. 0.77 ml (5.5 mmol) triethylamine is added dropwise to the cooled solution. After 10 min stirring 1.35 ml (5.95 mmol) TBDMSOTf are added dropwise. The mixture is stirred at -78°C for 2 h and at room temperature for 5 h. The solvent was evaporated with a rotatory evaporator without heating. The remaining oily diastereomeric products [9] were purified by chromatography (silica gel; hexane/ethyl acetate 9:1) affording the major diastereomer in pure form.

***trans*-3-(*tert*-Butyldimethylsilyloxy)-3-ethoxy-6-methyl-hexahydro-thieno[2,3-c]furan-4-one (6a) (racemic mixture).** Yield: 12.67 g, 83% (dr: 63:37), ^{1}H NMR: 0.21 (s, 6H) $(CH_3)_2Si$; 0.90 (s, 9H) $(CH_3)_3C$-Si; 1.23 (t, 3H, J=7) CH_3-CH_2; 1.34 (d, 3H, J=6.5) CH_3-C-O; 2.99 (d, 1H, J=12) CH_2-S; 3.35 (m, 2H) 3.31 (m, 2H) CH_2-S, CH-CO; 3.66-3.73 (m, 3H) CH-S, CH_2-O; 4.62 (m, 1H) CH-O; ^{13}C NMR: -3.5 $(CH_3)Si$; -3.4 CH_3Si; 15.1 ($\underline{C}H_3$-CH_2); 18.3 (C_{qu}-Si); 20.4 ($\underline{C}H_3$-C-O); 25.6 (($\underline{C}H_3)_3$C-Si; 40.3 (CH_2-S); 50.7 (CH-S); 54.9 ($\underline{C}$H-CO); 59.1 (CH_2-O); 82.7 (CH-O); 108.9 (O-C_{qu}-O); 171.6 (CO); Anal. calc. for $C_{15}H_{28}O_4SSi$ (332.58): C, 54.17; H, 8.50; S, 9.64; found: C, 54.28; H, 9.29; S, 9.44.

(3a*S*,6*R*,6a*S*)-3-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldimethylsilyloxymethyl)-3-ethoxy-hexahydro-thieno[2,3-c]furan-4-ones (6b). Yield: 14.66 g, 69%, (dr: 65:35), ^{1}H NMR: -0.19 (s, 12H) 2 $(CH_3)_2Si$; 0.85 (s, 18H) 2 $((CH_3)_3$-C); 1.23 (t, 3H, J=7.0) CH_3-CH_2; 3.11 (d, 2H, J=3.1) O-CH_2-CH; 3.46 (d, 1H J=6.7) CH-CO-O; 3.71-3.84 (d, 2H, J=2.0) O-CH_2-CH; (q, 2H, J=6.8) CH_2-CH_3; 3.97 (m, 1H) CH-S; 4.49 (m, 1H) CH-O; ^{13}C NMR: -3.3 (2 $(CH_3)_2Si$); 15.0 ($\underline{C}H_3$-CH_2); 18.0 ($\underline{C}$-$(CH_3)_3$); 25.6 (($\underline{C}H_3)_3$-C); 39.9 (CH_2-S); 46.6 (CH-S); 54.6 ($\underline{C}$H-CO-O); 59.7 (O-$\underline{C}H_2$-CH_3); 64.0 (Si-O-CH_2); 85.4 (CH-O); 109.3 (C_{qu}-O-Si); 171.7 (CO-O); $[\alpha]_D^{22}$ = +44.2° (c=1, $CHCl_3$); Anal. calc. for $C_{21}H_{42}O_5SSi$ (462.86): C, 54.49; H, 9.16; S, 6.93; found: C, 54.43; H, 9.29; S, 6.80.

(3a*S*, 3b*S*, 6*R*, 7a*S*)-1-(*tert*-Butyldimethylsilyloxy)-1-ethoxy-6-ethyl-3b-methyl-hexahydro-4-oxa-3-thia-6a-aza-cyclopenta[a]pentalen-7-one (6c). Yield: 13.86 g, 75% (dr: 35:32:18:15), ^{1}H NMR: 0.06 (s, 3H) CH_3-Si; 0.10 (s, 3H) CH_3-Si; 0.80 (s, 9H) $(CH_3)_3C$; 0.86 (t, 3H, J=7.3) CH_3-CH_2; 1.12 (t, 3H, J=7.0); 1.42 (s, 3H) CH_3-C_{qu}; 1.45 (m, 2H) CH_2-CH_3; 2.67 (d, 1H, J=11.0) CH_2-S; 2.97 (d, 1H, J=11.0) CH_2-S; 3.35 (d, 1H, J=5.1) CH-CO-O; 3.63 (q, 2H, J=7.0) O-CH_2-CH_3; 3.78 (m, 2H) O-CH_2-CH; 3.93 (m, 1H) CH-S; 4.26 (m, 1H) CH-N; ^{13}C NMR: -3.5 (CH_3-Si); -3.2 (CH_3-Si); 10.7 ($\underline{C}H_3$-CH_2); 15.0 ($\underline{C}H_3$-CH_2-O); 18.0 ($\underline{C}(CH_3)_3$); 25.6 (($\underline{C}H_3)_3$C); 27.0 ($\underline{C}H_3$-C_{qu}); 27.1 ($\underline{C}H_2$-CH_3); 39.2 (CH_2-S); 56.5 (CH-S); 58.0 (CH-N); 58.7 ($\underline{C}$H-CO-O); 60.3 (O-$\underline{C}H_2$-CH_3); 73.6 (O-$\underline{C}H_2$-CH); 97.3 (O-C_{qu}-N); 109.1 (C_{qu}-O-Si); 171.9 (CO-O); $[\alpha]_D^{22}$ = +8.4° (c=1, $CHCl_3$); Anal. calc. for $C_{19}H_{35}NO_4SSi$ (402.71): C, 56.66; H, 9.03; N, 3.48; S, 7.96; found: C, 56.04; H, 9.30; N, 3.21; S, 7.53.

***trans*-4-Butoxy-4-(*tert*-butyldimethylsilyloxy)-7-methyl-hexahydro-thiopyrano[2,3-c]furan-5-one (6e) (racemic mixture).** Yield: 8.97 g, 52%; (dr: 55:45), m.p. 136-138°C, ^{1}H NMR: 0.04 (s, 3H) CH_3-Si; 0.05 (s, 3H) CH_3-Si; 0.80 (s, 9H) $(CH_3)_3C$; 0.85 (t, 3H, J=7.3) CH_3-CH_2; 1.32 (d, 3H, J=6.3) CH_3-CH; 1.51 (m, 2H) CH_2-CH_3; 1.90 (m, 2H) CH_2-CH_3; 2.54 (dd, 1H, J_1=13.4, J_2=4.3) CH-S; 2.87 (d, 1H, J=7.9) CH-S; 3.02 (d; 2H) CH_2-S; 3.48 (m, 2H) O-CH_2; 4.51 (m, 1H) CH-O; ^{13}C NMR: -2.8 (CH_3-Si); -2,8 (CH_3-Si); 13.8 ($\underline{C}H_3$-CH_2); 17.9 ($\underline{C}(CH_3)_3$); 18.3 ($\underline{C}H_3$-CH); 19.1 ($\underline{C}H_2$-CH_3); 19.6 (O-CH_2-$\underline{C}H_2$); 25.9 (($\underline{C}H_3)_3$C); 31.9 (CH_2-S); 35.6 ($\underline{C}H_2$-C_{qu}-O-Si); 45.4 ($\underline{C}$H-CO-O); 46.4 (CH-S); 78.5 (CH-O); 98.1 (C-O-Si); 172.3 (CO-O); Anal. calc. for $C_{18}H_{34}O_4SSi$ (375.68): C, 57.54; H, 9.41; S, 8.53; found: C, 57.80; H, 9.50; S, 8.81.

***trans*-9-Butoxy-9-(*tert*-butyldimethylsilyloxy)-3-methyl-3,3a,9,9a-tetrahydro-2-oxa-4-thiacyclopenta[b]-naphthalen-1-one (6f) (racemic mixture).** Yield: 3.32 g, 19%, (dr: 62:38), ^{1}H NMR: 0.06 (s, 3H) CH_3-Si;

0.07 (s, 3H) CH_3-Si; 0.88 (s, 9H) $(CH_3)_3C$; 1.42 (d, 3H, J=6.5) CH_3-CH-O; 3.5 (s, 3H) CH_3-O; 3.66 (dd, 1H, J_1=9.2, J_2=3.0) CH-S; 3.76 (d, 1H, J=6.3) CH-CO-O; 4.63 (m, 1H) CH-O; 7.14-7.18 (m, 3H) CH_{arom}; 7.23 (m, 1H) CH_{arom}; ^{13}C NMR: -3.6 (CH_3-Si); -3.5 (CH_3-Si); 18.3 ($\underline{C}(CH_3)_3$); 20.7 ($\underline{C}H_3$-CH); 25.8 (($\underline{C}H_3)_3C$); 44.9 (CH-S); 46.8 ($\underline{C}$H-CO-O); 49.2 (CH_3-O); 83.6 (CH-O); 96.0 (C_{qu}-O-Si); (125.8; 126.4; 127.8; 129.2) (CH_{arom}); 132.2 (C_{qu}-S); 135.9 ($\underline{C}_{qu}$-CO-O); 171.1 (CO-O); Anal. calc. for $C_{19}H_{28}O_4SSi$ (380.62): C, 59.95; H, 7.43; S, 8.42; found: C, 60.37; H, 7.29; S, 8.48.

(3a*S/R*, 6*R/S*, 6a*S/R*)-6-Methyl-hexahydro-thieno[2,3-c]furan-3,4-dione (7a) (racemic mixture)

5 ml of 10% aqueous HCl were added dropwise to a solution of 0.646 g (2 mmol) of the silylated hemiacetal **6a** (diastereomeric mixture) in 10 ml ethanol. After 24 h stirring at 40°C the solvent was evaporated in vacuum and the remainder purified by column chromatography (silica gel; $CHCl_3$/methanol 95:5). Yield: 80 %, m.p. 106-108°C, ^1H NMR: 1.42 (d, 3H, J=6.5) CH_3-CH-O; 3.42 (d, 2H, J=1) CH_2-S; 3.66 (d, 1H, J=8) CH-CO; 3.95 (dd, 1H, J_1=8, J_2=3) CH-S; 4.55 (m, 1H) CH-O; ^{13}C NMR: 20.7 ($\underline{C}H_3$-CH); 38.2 (CH_2); 47.9 ($\underline{C}$H-CO-O); 54.6 (CH-S); 81.9 (CH-O); 167.9 (CO-O); 201.4 (CO); Anal. calc. for $C_7H_8O_3S$ (172.21): C, 48.81; H, 4.69; S, 18.62; found: C, 48.75; H, 4.58; S, 17.98.

***Crystal Structure Analysis of* 7a:** Crystal data: $C_7H_8O_3S$, M_r = 172.19, monoclinic, space group $P2_1/c$, a = 13.866 (4), b = 7.779 (3), c = 7.386 (3) Å, β = 103.83 (2)°, V = 773.6 Å^3, Z = 4, D_x = 1.478 Mg m^{-3}, λ(Mo Kα) = 0.71073 Å, μ = 0.37 mm^{-1}, T = -100°C. Data collection and reduction: A colorless tablet 0.7 x 0.6 x 0.15 mm was mounted in inert oil. Data were collected to $2\Theta_{max}$ 50° on a Siemens P4 diffractometer. Of 1619 measured data, 1362 were unique (R_{int} 0.019). Structure solution and refinement: The structure was solved by direct methods and refined anisotropically on F^2 using all reflections (program SHELXL-93, G.M. Sheldrick, University of Göttingen). Hydrogen atoms were included as rigid methyls or with a riding model The final $wR(F^2)$ was 0.097 for 101 parameters, conventional $R(F)$ 0.039. S = 1.13, max. Δ/σ < 0.001; max $\Delta\rho$ 0.33 e Å^{-3}. [10]

(3a*S/R*, 6*R/S*, 6a*S/R*)-3a,6-Dimethyl-hexahydro-thieno[2,3-c]furan-3,4-dione (8) (racemic mixture)

A fresh solution of LDA, prepared from 5 ml of THF and 0.2 ml (1.35 mmol) diisopropylamine and 1 ml of 1,6m n-BuLi in hexane at -78° C under argon, was added to a solution of 200 mg (1.16 mmol) of the thieno-furandione **7a** in about 20 ml of dry THF. The slightly colored solution was stirred at -78° for 30 min. With further stirring, 0.1 ml (1.5 mmol) MeI were added dropwise. The mixture was further stirred at -78° for 3h and at room temperature for 5 h. After removing the solvent under vacuum the residue was dissolved in dichloromethane and washed with saturated aqueous NH_4Cl solution. After extraction of the aqueous phase three times with dichloromethane, the combined extracts were dried over $NaSO_4$ and concentrated under vacuum. The remainder was purified by column chromatography (silica) with hexane/ethyl acetate 1:1. Yield: 49%, (dr: 95:5), ^1H NMR: 1.47 (d, 3H, J=6.0) CH_3-CH; 1.48 (s, 3H) CH_3-C_{qu}; 3.41 (d, 1H, J=6.3) CH-S, 4.42 (m, 1H) CH-O; ^{13}C NMR: 19.8 ($\underline{C}H_3$-C_{qu}); 19.9 ($\underline{C}H_3$-CH); 36.9 (CH_2-S); 55.0 (CH-S); 58.2(C_{qu}-CH_3); 81.3 (CH-O); 171.3 (CO-O); 204.3 (C=O).

(5*S*/*R*, α*R*/*S*)-6-(1-Hydroxyethyl)-tetrahydrothiophen-3-one (9) (racemic mixture)
5 ml 10% Aqueous HCl were added dropwise to a solution of 0.344 g (2 mmol) of thienofurandione **7a** in 10 ml ethanol. The mixture was stirred at 40° C for 24 h. After evaporating the solvent under vacuum the residue was purified by column chromatography (silica) chloroform/methanol 95:5. Yield: 58 mg, 20%, oil, ^{1}H NMR: 1.20 (d, 3H, J=6.0) CH_3-CH; 2.62 (d, 1H, J=7) CH_2-CO, 3.23 (d, 1H, J=17) S-CH_2, 3.33 (d, 1H, J=17), 3.41 (m, 1H) S-CH, 3.87 (m, 1H) CH-O; ^{13}C NMR: 20.8 ($\underline{C}H_3$-CH); 37.7 (CH_2); 40.2 (CH_2); 47.9 (S-CH); 70.3 (CH-O); 212.3 (CO); Anal. calc. for $C_6H_{10}O_2S$ (146.22): C, 49.28; H, 6.91; S, 21.93; found: C, 49.86; H, 6.95; S, 21.60.

(4*S*/*R*, α*R*/*S*)-3-Hydroxy-4-(1-hydroxyethyl)-4,6-dihydrothieno[3,4-c]pyrazole (10) (racemic mixture)
0.175 g (2.8 mmol) Hydrazine hydrate (80 % aqueous solution) were added to a solution of 344 mg (2 mmol) of thienofurandione **7a** in 10 ml methanol. After 24h stirring at room temperature the solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, chloroform/methanol 4:1). Yield: 282 mg, 76%, ^{1}H NMR: 0.96 (d, 3H, J=6.1) CH_3; 3.36 (d, 1H, J=7) S-CH_2; 3.41, (d, 1H, J=7); S-CH_2; 3.84 (m, 1H) S-CH; 4.16 (m, 1H) CH-O; ^{13}C NMR: 18.7 (CH_3); 27.5 (CH_2-S); 51.5 (CH-S); 70.0 (CH-O); 108.0 (C_{qu}=N); 150.4 ($\underline{C}$=C-OH); 153.3 (HO-C-NH); Anal. calc. for $C_7H_{10}N_2O_2S$ (186.25): C, 45.13; H, 5.42; N, 15.04; found: C, 44.98; H, 5.33; N, 14.44.

(3*R*, 7*S*, 7a*S*)-3-Ethyl-7-(2-aminophenylthio)-7a-methyl-tetrahydropyrrolo[2.1-b]-1,3-oxazol-5-one (12a)
A solution of 334 mg (2 mmol) pyrrolo[2,1-b]oxazolone **1c** and 0.44 g (3.5 mmol) 2-mercaptoaniline in 5 ml of dry DMF was stirred at room temperature for 6 h. The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel; hexane / ethyl acetate 1 : 1, r_f = 0.23). Yield: 397 mg, 68 % (dr: 80:20), m.p. 79°C, ^{1}H NMR: 0.95 (t, 3H, J=7) $\underline{C}H_3$-CH_2; 1.53 (s, 3H) CH_3; 1.62 (m, 2H) CH_2–CH_3; 2.38 (dd, 1H, J_1=17, J_2=1) CH_2-CO; 2.89 (dd, 1H, J_1=17, J_2=6.6) CH_2-CO; 3.78 (dd, 1H, J_1=6.6, J_2=1) CH-S; 3.90 (dd, 1H, J_1=8, J_2=4) CH_2-O; 4.05 (m, 1H) CH-N; 4.31 (dd, 1H, J_1=8, J_2=7) CH_2-O; 6.66 (m, 2H) CH_{arom}; 7.11 (m, 1H) CH_{arom}; 7.33 (m, 1H) CH_{arom}; ^{13}C NMR: 10.7 ($\underline{C}H_3$-CH_2); 25.9 (CH_3); 27.6 (CH_2-CH_3); 40.8 (CH_2-CO); 53.2 (CH-S); 56.2 (CH-N); 73.7 (CH_2-O); 99.6 (O-C_{qu}-N); 114.7 ($C_{qu/arom}$-S); 115.0 (CH_{arom}); 118.6 (CH_{arom}); 130.6 (CH_{arom}); 137.5 (CH_{arom}); 149.2 ($C_{qu/arom}$-N); 175.4 (CO); $[\alpha]_D^{22}$ = -78.1° (c=1, CH_3OH); Anal. calc. for $C_{15}H_{20}N_2O_2S$ (292.4): C, 61.61; H, 6.89; N, 9.58; found: C, 61.65; H, 6.73; N, 9.48.

(3*R*, 7*S*, 7a*S*) 3-Ethyl-7-(2-aminoethylthio)-7a-methyl-tetrahydropyrrolo[2.1-b]-1,3-oxazol-5-one (12b) and Bis-adduct 13. A. solution of 334 mg (2 mmol) of the pyrrolo[2,1-b]oxazolone **1c** and 0.162 g 2-mercaptoethylamine in 5 ml of methanol / water (1 : 3) was stirred at room temperature for 8 h. The solvent was evaporated and the remaining oil was submitted to column chromatography (silica gel; chloroform / methanol 6:4) affording **12b** as an inseparable diastereomeric mixture (r_f = 0.24) and **13** (r_f =0.7).
12b: Yield: 258 mg, 53 %, oil, (dr: 82:18, not separable), ^{1}H NMR: 0.90 (t, 3H, J= 7) $\underline{C}H_3$-CH_2; 1.45 (s, 3H,) CH_3; 1.59 (m, 2H) $C\underline{H}_2$–CH_3; 2.56 (dd, 1H, J_1=16, J_2=13) CH_2-CO; 2.77 (dd, 1H J_1=16, J_2=8) CH_2-CO; 2.84 (t, 2H, J=6) CH_2-S; 3.10 (t, 2H, J=6) CH_2-N; 3.44 (dd, 1H, J_1=13, J_2=8) CH-S; 3.85 (m, 2H,) CH_2-O, CH-N;

4.16 (dd, 1H, J_1=8, J_2=6) CH_2-O; 5.41 (sb, 2H) NH_2; ^{13}C NMR: 10.8 ($\underline{C}H_3$-CH_2); 21.7 (CH_3); 27.4 ($\underline{C}H_2$-CH_3); 31.9 (CH_2-S); 39.8 (CH_2-N); 41.1 (CH_2-CO); 50.7 (CH-S); 56.1 (CH-N); 72.9 (CH_2-O); 101.1 (O-Cqu-N); 173.6 (CO); $[\alpha]_D^{22}$ = -102° (c=1.1, CH_3OH); Anal. calc. for $C_{11}H_{20}N_2O_2S$ (244.3): C, 54.07; H, 8.25; N, 11.46; found: C, 54.00; H, 8.50; N, 11.12.

13: Yield: 19 %, (dr: 80:20), oil, ^{1}H NMR: 0.89 (t, 3H, J= 7) $C\underline{H}_3$-CH_2; 0.91 (t, 3H, J= 7) $C\underline{H}_3$-CH_2; 1.41 (s, 3H,) CH_3; 1.48 (s, 3H,) CH_3; 1.59 (m, 4H) 2 $C\underline{H}_2$–CH_3; 2.17 (d, 1H, J=16) CH_2-CO; 2.31 (dd, 1H, J_1=17, J_2=1.5) CH_2-CO; 2.64 (m, 5H) S-$(CH_2)_2$, CH_2-CO; 3.08 (dd, 1H, J_1=17, J_2=7) CH_2-O; 3.14 (d, 1H, J=5) CH-S; 3.45 (dd, 1H, J_1=7, J_2=1.5) CH-NH; 3.79 (m, 2H) CH_2-O; 3.92 (m, 2H) 2 CH-N; 4.04 (dd, 1H, J_1=8, J_2=6.5) CH_2-O; 4.19 (dd, 1H, J_1=8, J_2=7) CH_2-O; ^{13}C NMR: 10.7 (2 $\underline{C}H_3$-CH_2); 25.7 (CH_3); 26.5 (CH_3); 27.1 ($\underline{C}H_2$-CH_3); 27.2 ($\underline{C}H_2$-CH_3); 32.3 (CH_2-S); 40.3 (CH_2-CO); 40.8 (CH_2-CO); 46.1 (CH_2-NH); 50.7 (CH-S); 56.1 (CH-N); 56.3 (CH-N); 63.0 (CH-NH); 73.1(2 CH_2-O); 99.8 (O-Cqu-N); 100.3 (O-Cqu-N); 175.1 (CO); 176.4 (CO); Anal. calc. for $C_{20}H_{33}N_3O_4S$ (411.6): C, 58.36; H, 8.08; N, 10.21; found: C, 58.64; H, 7.87; N, 9.78.

(6a*R*, 9a*S*, α*R*)-7-(1-Hydroxymethyl-propyl)-6a-methyl-pyrrolo[3,2-b]-1,4-benzothiazinone 16. 0.8 g (0.7 mmol) trifluoroacetic acid were added to a solution of 0.204 g (0.7 mmol) of the aminophenylthiopyrrolo[2,1-b]-1,3-oxazol-5-one **12a** in 7 ml of dry methanol. After refluxing the solution for 3 h the solvent was removed under vacuum and the residue was purified by column chromatography (silica gel; hexane / ethyl acetate 1 : 1). Yield: 0.12 g, 59 % (dr: 80:20), ^{1}H NMR: 0.89 (t, 3H, J=7) $C\underline{H}_3$-CH_2; 1.46 (m, 2H) CH_2CH_3; 1.66 (s, 3H) CH_3; 2.38 (dd, 1H J_1=17, J_2=5) CH_2-CO; 2.79 (dd, 1H, J_1=17, J_2=8) CH_2-CO; 3.16 (m, 1H) CH-S; 3.56 (dd, 1H, J_1=8, J_2=5) CH_2-OH; 3.75 (m, 1H) CH-N; 3.96 (dd, 1H, J_1=8, J_2=5); 4.28 (sb, 1H) NH; 4.51 (sb, 1H) OH; 6.62 (m, 1H) CH_{arom}; 6.8 (m, 1H) CH_{arom}; 7.04 (m, 1H) CH_{arom}; 7.19 (m, 1H) CH_{arom}; ^{13}C NMR: 11.3 ($\underline{C}H_3$-CH_2); 21.5 ($\underline{C}H_2$-CH_3); 27.8 (CH_3); 37.5 (CH_2-CO); 44.0 (CH-S); 56.6 (CH-N); 64.1 (CH_2-OH); 79.7 (N-Cqu-N); 116.5 (CH_{arom}); 118.6 (Cqu/arom-S); 120.8 (CH_{arom}); 127.4 (CH_{arom}); 128.9 (CH_{arom}); 141.0 (Cqu/arom-N); 172.9 (CO); Anal. calc. for $C_{15}H_{20}N_2O_2S$ (292.4): C, 61.62; H, 6.89; N, 9.59; found: C, 61.76; H, 6.85; N, 9.52.

***Crystal Structure Analysis of* 16:**

Crystal data: $C_{15}H_{20}N_2O_2S$, M_r = 292.39, orthorhombic, space group $P2_12_12_1$, a = 8.9704 (7), b = 11.3391 (9), c = 14.1161 (9) Å, V = 1435.8 Å^3, Z = 4, D_x = 1.353 Mg m^{-3}, μ = 0.23 mm^{-1}, T = -100°C. Data collection and reduction: Pale yellow irregular crystal 0.9 x 0.8 x 0.5 mm, 3583 data, 3306 unique (R_{int} 0.011). Structure solution and refinement: $wR(F^2)$ 0.070 for 188 parameters, $R(F)$ 0.025, S 1.04, max. Δρ = 0.21 e Å^{-3}. N-H refined freely, O-H as rigid group; absolute configuration parameter x = 0.02 (5) [H.D. Flack *Acta Cryst.* **1983**, *A39*, 876]. All other details as for **6a**. [10]

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9. Further investigation of the cyclization of the adduct **3a** to **6a** revealed that the diastereselectivity can be enhanced if the reaction was performed in dioxane at 5°C followed by stirring at room temperature for 24h.
10. Full details of the structure determination have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Germany. Any request for this material should quote a full literature citation and the reference number CSD 405097 (for **7a**) and 405098 (for **16**).

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