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Chiral 1,4-Diazepinones and 1,4-Thiazepinones by Diastereoselective Ring Chain Transformation of α,ß-Unsaturated Lactones or Lactams

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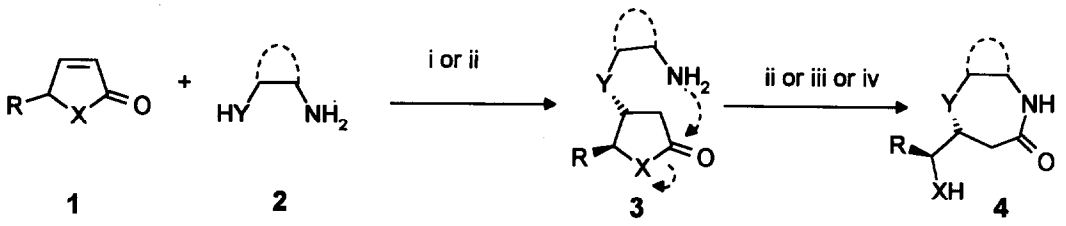
Abstract: Butenolides or α,ß-unsaturated lactams **1** react with 1,2-diamines, cysteamine or 2-aminothiophenol by addition and ring transformation giving new chiral, hydrogenated or partly hydrogenated 7-(α-hydroxyalkyl) and 7-(α-aminoalkyl)-1,4-diazepin-5-ones and 1,4-thiazepin-5-ones **4**.

Recently effective stereoselective syntheses of chiral α-hydroxyalkylpyrazolidinones [1,2] and isoxazolidinones [3] were found by ring chain transformation of butenolides such as **1** (X = O) or pentenolides with hydrazines or hydroxyl amines as 1,2-binucleophiles. Analogously 7-acyl-1,4-benzodiazepin-5-ones were obtained by reaction of 3-hydroxybutenolides with 1,2-diaminobenzenes as 1,4-binucleophiles.[4] In the latter case inseparable mixtures of diastereomers were obtained, no diastereomeric ratios were reported. Unlike butenolides and pentenolides α,ß-unsaturated lactams have not yet been submitted to ring chain transformations. We now report the extension of this ring transformation concept to the synthesis of chiral 7-(α-hydroxyalkyl)-1,4-diazepinones and 1,4-thiazepinones on one hand as well as to corresponding α-aminoalkyl heterocycles by the application of generally less reactive α,ß-unsaturated lactams **1** (X = NBoc) on the other hand. The anticipated 1,4-benzothiazepinones might gain practical interest, since a number of pharmaceuticals were found in this class of compounds. [4, 5]

The reaction of 1,2-diaminoethane hydrate, cysteamine or 2-aminothiophenol as 1,4-binucleophiles **2** with butenolides **1** (X = O) or α,ß-unsaturated lactams **1** (X = NBoc) in water, aqueous methanol or basic aqueous methanol (Methods E-G) gives the expected ring chain transformation to seven-embered rings **4** by primary nucleophilic addition to the ß-position of **1** affording **3** and subsequent formation of a C-Y bond while the C-X bond is cleaved. Intermediates **3** were only isolated in reactions with 2-aminothiophenol in DMF (Method A). These addition products **3** can be transformed to seven-embered rings **4** without changing the diastereomeric ratio by subsequent treatment with aqueous NaOH in methanol (Method B) or with $AlMe_3$ (Method C). In case of the N-Boc-aminomethyl substituted benzothiazepinone **4b** (X = NBoc) Method C also affords the corresponding N-acetylaminomethyl benzothiazepinone **4c** as by-product, which probably had derived from the reaction of $AlMe_3$ with the Boc moiety. This side reaction can be circumvented if EtMgBr was used as cyclization reagent (Method D). It is worth mentioning that the known synthesis of 1,4-diazepin-5-ones by reaction of 1,2-diamines with α,ß-unsaturated carboxylic acids follows a reversed reaction sequence i. e. at first formation of an amide and subsequent addition to the C-C double bond.[6] Regioisomers of the intermediates **3** or of the 1,4-thiazepin-5-ones **4** (Y = S) were not observed in our investigations. This is in accordance with the known reaction of o-aminothiophenol or 1-amino-2-mercaptoalkanes with substituted α,ß-unsaturated carboxylates giving 1,4-thiazepin-5-one rather than 1,4-thiazepin-7-ones. [7,8] The primary addition of **2** to **1** is stereoselective (see Table 1).



i DMF, r. t., 6 h ii H_2O/MeOH/OH^-, 80°C iii $AlMe_3/CH_2Cl_2$, 0 - 20°C, 1 h
iv EtMgBr/THF, r. t.

Table 1: Synthesis of Adducts **3** and 1,4-Diazepin-5-ones **4** (Y = NH) and 1,4-Thiazepin-5-ones **4** (Y = S)

	X	R	Y		ratio of diastereomers
3a	O	Me (rac)	S		84 : 16
3b	NBoc	H	S		-
3c	NBoc	$CH_2OTBDMS$ (S)	S		84 : 16
4a	O	Me (rac)	S		84 : 16
4b	NBoc	H	S		-
4c	NCOMe	H	S		-
4d	NBoc	$CH_2OTBDMS$ (S)	S		89 : 11
4e	O	Me (rac)	S	$-CH_2CH_2-$	75 : 25
4f	O	CH_2OH (S)	S	$-CH_2CH_2-$	69 : 31
4g	O	CH_2OAc (S)	S	$-CH_2CH_2-$	76 : 24
4h	O	$CH_2OTrityl$ (S)	S	$-CH_2CH_2-$	81 : 19
4i	O	Me (rac)	NH	$-CH_2CH_2-$	93 : 7
4j	O	CH_2OH (S)	NH	$-CH_2CH_2-$	> 95 : 5
4k	NBoc	H	S	$-CH_2CH_2-$	-
4l	NBoc	$CH_2OTBDMS$ (S)	S	$-CH_2CH_2-$	90 : 10
4m	NBoc	H	NH	$-CH_2CH_2-$	-
4n	NBoc	$CH_2OTBDMS$ (S)	NH	$-CH_2CH_2-$	> 95 : 5

The diastereomeric ratios (see Table 1) were determined by ^{13}C-NMR spectroscopy from the crude reaction mixture. Further enrichment of the major isomer of compounds **3** was possible by column chromatography. According to known additions of other S- and N-nucleophiles to butenolides or α,ß-unsaturated lactams the primary nucleophilic addition must be mainly trans. [1-3,9,10] As compared with reactions of sulphur containing binucleophiles **2** (Y = S) the stereoselectivity of the reaction of **1** with 1,2-diaminoethane is higher, giving rise to just one detectable diastereoisomer **4** (starting from racemic **1**) or enantiomer **4** (starting from enantiomerically pure **1**) in most cases.

The yields of 7-(α-hydroxyalkyl) and 7-(α-aminoalkyl)-1,4-diazepin-5-ones **4** (Y = NH) and 1,4-thiazepin-5-ones **4** (Y = O) are modest (see Table 1). Usually a very polar by-product is formed which could not be isolated and characterized.

The results demonstrate that the ring chain transformation concept can also be successfully applied to the stereoselective synthesis of seven-embered α-hydroxyalkyl and α-aminoalkyl heterocycles. In these cases the N-Boc-protected α,ß-unsaturated lactams **1** (X = NBoc) exhibit similar synthetic utility like butenolides **1** (X = O).

Experimental Section

NMR spectra were recorded with Bruker AC 300. In case of diastereomeric mixtures only the spectra of the major isomer (trans addition) were reported. The splitting pattern are designated as follows: s (singlet), d (doublet), dd (double doublet), ddd (double double doublet), t (triplet), q (quartet), qd (quartet doublet), quint (quintet), m (multiplet), and br (broad). Mass spectra (70 eV) were recorded with HP 5995 A (Hewlett-Packard). Melting points are 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. Starting materials **1** (X = O) [11] and **1** (X = NBoc) [12] were synthesized according to known procedures.

General procedure for the preparation of adducts 3

Method A: A solution of 3 mmol of the lactam or lactone **1** and 0.44 g (3.5 mmol) of 2-amino-thiophenol in 5 ml of dry DMF was stirred at room temperature for 6 h. After evaporation of the solvent in vacuo the product **3** was purified by column chromatography on silica gel (hexane/ethyl acetate 1:1).

General procedures for the preparation of compounds 4

Method B: 0.7 ml of aqueous NaOH (0.25 m = 0.175 mmol) were added dropwise to a solution of 1 mmol of **3** in 6 ml of methanol. After heating to reflux for 12 h and evaporating of the solvent the product was purified by column chromatography on silica gel (chloroform/methanol 6:4).

Method C: In an argon atmosphere at 0 °C 0.18 mmol of $Al(CH_3)_3$ (0.2 m solution in hexane) were slowly added to a solution of 0.6 mmol of **3** in 6 ml of dry dichloromethane. After stirring (10 min at 0 °C, 60 min at room temperature) the reaction was quenched with 5 ml of 5% aqueous HCl. The resulting mixture was extracted with dichloromethane (3 x 20 ml), the organic layer was dried ($MgSO_4$). After

evaporation of the solvent the residue was purified by column chromatography on silica gel with chloroform/methanol (85:15).

Method D: In an argon atmosphere at room temperature 1.4 ml of a 1 m solution of EtMgBr in THF were added to a solution of 0.185 g (0.6 mmol) **4b** in 25 ml of dry THF. After 3 h of stirring the reaction mixture was worked up like in Method C.

Method E: 2.5 mmol of lactone **1** and 0.193 g (2.5 mmol) of cysteamine or 0.195 g (2.5 mmol) of 1,2-diaminoethane monohydrate respectively were dissolved in 3 ml of water. The stirred solution was heated to 80 °C for 15 min. After further stirring at room temperature for 3 h the solvent was evaporated and the product was purified by column chromatography on silica gel.

Method F: The solution of 2.5 mmol of lactone **1** and 0.193 g (2.5 mmol) of cysteamine in 5 ml of dry methanol was stirred at room temperature for 48 h. Purification see method E.

Method G: 1 mmol of lactam **1** and 0.077 g (1 mmol) of cysteamine or 0.078 g (1 mmol) of 1,2-diaminoethane monohydrate were dissolved in 6 ml of methanol/water (~ 1:1) and heated to reflux for 10 h. After evaporation of the solvent the product was purified by column chromatography on silica gel.

trans (Major) and cis-4-(2-amino-phenylthio)-5-methyl-dihydro-furan-2-one (3a). Yield: 74%, oil, ^{1}H NMR (300 MHz, $CDCl_3$, TMS); δ / ppm; J / Hz: 1.36 (d, 3H, J = 6) CH_3; 2.53 (dd, 1H, J = 18, 9) CH_2-CO; 2.82 (dd, 1H, J = 18, 9) CH_2-CO; 3.36 (m, 1H) CH-S; 4.40 (br s, 2H) NH_2; 4.45 (m, 1H) CH-O; 6.70 (m, 2H) CH_{arom}; 7.24 (m, 2H) CH_{arom}. ^{13}C NMR (75 MHz, $CDCl_3$, TMS); δ / ppm: 19.3 (CH_3); 35.3 (CH_2-CO); 47.7 (CH-S); 81.4 (CH-O); 113.0 (C_{arom}); 115.3 (CH_{arom}); 118.7 (CH_{arom}); 131.4 (CH_{arom}); 137.7 (CH_{arom}); 149.4 (C_{arom}); 174.3 (C=O); Anal. calcd. for $C_{11}H_{13}NO_2S$: C, 59.16; H, 5.88; N, 6.27, found: C, 58.91; H, 6.14; N, 6.20.

4-(2-Amino-phenylthio)-N-Boc-pyrrolidin-2-one (3b). Yield: 80%, oil, ^{1}H NMR (300 MHz, $CDCl_3$, TMS); δ / ppm; J / Hz: 1.44 (s, 9H) t-Bu; 2.44 (dd, 1H, J = 17, 6) CH_2-CO; 2.82 (dd, 1H, J = 17, 7) CH_2-CO; 3.64 (m, 2H) CH-S, CH_2-N; 3.83 (m, 1H) CH_2-N); 4.34 (br s, 2H) NH_2; 6.64 (m, 2H) CH_{arom}; 7.11 (t, 1H, J = 7) CH_{arom}; 7.28 (d, 1H, J = 7) CH_{arom}. ^{13}C NMR (75 MHz, $CDCl_3$, TMS); δ / ppm: 28.0 (t-Bu); 37.3 (CH-S); 39.6 (CH_2-CO); 51.7 (CH_2-N; 83.2 ($\underline{C}(CH_3)_3$); 114.0 (C_{arom}); 115.2 (CH_{arom}); 118.6 (CH_{arom}); 131.2 (CH_{arom}); 137.5 (CH_{arom}); 149.4 (C_{arom}); 149.8 (O-C=O); 171.8 (C=O); Anal. calcd. for $C_{15}H_{20}N_2O_3S$: C, 58.42; H, 6.54; found: C, 58.58; H, 6.43.

(4R,5S) (Major) and (4S,5S)-4-(2-amino-phenylthio)-5-[(O-tert-butyldimethylsilyl)-hydroxymethyl]-N-Boc-pyrrolidin-2-one (3c). Yield: 70%, oil, $[\alpha]_D^{20}$= -92.4° (c = 2.4, methanol), ^{1}H NMR (300 MHz, $CDCl_3$, TMS); δ / ppm; J / Hz: -0.05 (s, 6H) Si-$(CH_3)_2$; 0.79 (s, 9H) t-Bu-Si; 1.49 (s, 9H) t-Bu-O; 2.34 (d, 1H, J = 18) CH_2-CO; 2.98 (dd, 1H, J = 18, 8) CH_2-CO; 3.56 (dd, 1H, J = 11, 2) CH_2-O;

3.69 (m, 1H) CH-S; 3.81 (dd, 1H, J = 11, 4) CH_2-O; 3.99 (m, 1H) CH-N; 4.37 (br s, 2H) NH_2; 6.68 (m, 2H) CH_{arom}; 7.13 (m, 1H) CH_{arom}; 7.32 (m, 1H) CH_{arom}. ^{13}C NMR (75 MHz, $CDCl_3$, TMS); δ / ppm: -5.6 (Si-$(CH_3)_2$); 18.1 (C_q-Si); 25.8 (($\underline{C}H_3)_3$C-Si); 28.1 (($\underline{C}H_3)_3$C-O); 39.2 (CH_2-CO); 40.9 (CH-S); 63.7 (CH_2-O); 64.2 (CH-N); 83.0 (C_q-O); 114.5 (C_{arom}); 115.1 (CH_{arom}); 118.6 (CH_{arom}); 131.1 (CH_{arom}); 137.3 (CH_{arom}); 149.3 (O-C=O); 149.9 (C_{arom}); 172.7 (C=O). Anal. calcd. for $C_{22}H_{36}N_2O_4SSi$: C, 58.36; H, 8.03; found: C, 58.14; H, 8.32.

2-(1-Hydroxyethyl)-3,5-dihydro-2H-benzo[b][1,4]-thiazepin-4-one (4a) (racemic mixture of diastereomers). Method B, yield: 75%, oil, ^1H NMR (300 MHz, DMSO-d_6, TMS); δ / ppm; J / Hz: 1.02 (d, 3H, J = 6) CH_3; 2.16 (dd, 1H, J = 16, 8) CH_2-CO; 2.45 (m, 1H) CH_2-CO; 3.17 (m, 1H) CH-S; 3.71 (m, 1H) CH-O; 5.61 (br s, 1H) OH; 6.42 (t, 1H, J = 7) CH_{arom}; 6.69 (d, 1H, J = 7) CH_{arom}; 6.98 (d, 1H, J = 7) CH_{arom}; 7.23 (d, 1H, J = 7) CH_{arom}. ^{13}C NMR (75 MHz, DMSO-d_6, TMS); δ / ppm: 20.3 (CH_3); 38.5 (CH_2-CO); 51.8 (CH-S); 67.4 (CH-O); 114.1 (CH_{arom}); 115.0 (C_{arom}); 115.6 (CH_{arom}); 129.4 (CH_{arom}); 136.6 (CH_{arom}); 150.3 (C_{arom}); 177.4 (C=O). Anal. calcd. for $C_{11}H_{13}NO_2S$: C, 59.16; H, 5.88; N, 6.27, found: C, 58.94; H, 5.98; N, 6.20.

2-(N-Boc-Aminomethyl)-3,5-dihydro-2H-benzo[b][1,4]-thiazepin-4-one (4b). Method C, yield: 65%, m.p. 172-173 °C, ^1H NMR (300 MHz, $CDCl_3$, TMS); δ / ppm; J / Hz: 1.38 (s, 9H) t-Bu; 2.36-2.62 (m, 2H) CH_2-CO; 3.07-3.41 (m, 2H) CH_2-N; 3.62 (m, 1H) CH-S; 4.50 (br s, 1H) NH; 4.81 (br s, 1H) NH; 6.59 (t, 1H, J = 7) CH_{arom}; 6.65 (d, 1H, J = 7) CH_{arom}; 7.07 (t, 1H, J = 7) CH_{arom}; 7.28 (d, 1H, J = 7) CH_{arom}. ^{13}C NMR (75 MHz, $CDCl_3$, TMS); δ / ppm: 28.3 (C($\underline{C}H_3)_3$); 37.0 (CH_2-CO); 51.8 (CH-S); 57.4 (CH_2-N); 79.4 ($\underline{C}(CH_3)_3$); 115.2 (CH_{arom}); 118.3 (CH_{arom}); 120.8 (C_{arom}); 130.8 (CH_{arom}); 137.7 (CH_{arom}); 145.2 (C_{arom}); 149.4 (O-C=O); 171.6 (C=O); Anal. calcd. for $C_{15}H_{20}N_3O_2S$: C, 58.42; H, 6.54; N, 9.08, found: C, 58.18; H, 6.79; N, 9.01.

2-(N-Acetylaminomethyl)-3,5-dihydro-2H-benzo[b][1,4]-thiazepin-4-one (4c). Method C, yield: 20% (as by-product of **4b**), m.p. 124-126°C, ^1H NMR (300 MHz, DMSO-d_6, TMS); δ / ppm; J / Hz: 1.79 (s, 3H) CH_3CO; 2.16 (dd, 1H, J = 12, 11) CH_2CO; 2.43 (dd, 1H, J = 12, 6) CH_2CO; 3.17 (t, 2H, J = 6) $\underline{CH_2}$-NH; 3.69 (m, 1H) CH-S; 7.17 (m, 2H) CH_{arom}; 7.40 (m, 1H) CH_{arom}; 7.50 (m, 1H) CH_{arom}; 8.09 (t, 1H, J = 6) $\underline{NH}COCH_3$; 9.9 (br, 1H) NH. ^{13}C NMR (75 MHz, DMSO-d_6, TMS); δ / ppm: 22.6 ($\underline{C}H_3$); 37.4 ($\underline{C}H_2CO$); 44.5 ($\underline{C}H_2NH$); 49.0 (CH-S); 123.0 (CH_{arom}); 124.4 (CH_{arom}); 125.5 (C_{arom}); 130.1 (CH_{arom}); 135.6 (CH_{arom}); 142.6 (NC_{arom}); 169.6 ($\underline{C}O$-CH_3); 171.3 (C=O).

(αS,2R) (Major) and (αS,2S)-2-[(1-(N-Boc-amino-2-(O-tert-butyl-dimethylsilyl)-hydroxyethyl]-3,5-dihydro-2H-benzo[b][1,4]thiazepin-4-one (4d). Method C, yield: 77%, m.p. = 115-116 °C, $[\alpha]_D^{20}$ = +190.0 (c = 0.95, methanol), ^1H NMR (300 MHz, $CDCl_3$, TMS); δ / ppm; J / Hz: 0.05 (s, 3H) Si-CH_3; 0.06 (s, 3H) Si-CH_3; 0.87 (s, 9H) t-Bu-Si; 1.36 (s, 9H) t-Bu-O; 2.56 (d, 1H, J = 12) CH_2-CO; 2.69 (dd, 1H, J = 12, 4) CH_2-CO; 3.61 (m, 2H) CH_2-O, CH-S; 3.81 (m, 1H) CH-N; 4.26 (m, 1H) CH_2-O; 4.94 (br s, 1H) NH-CO; 7.10 (m, 2H) CH_{arom}; 7.34 (m, 1H) CH_{arom}; 7.53 (d, 1H, J = 7)

CH_{arom}; 8.34 (br s, 1H) NH-CO. ^{13}C NMR (75 MHz, $CDCl_3$, TMS); δ / ppm: -5.5 (Si-CH_3); -5.4 (Si-CH_3); 18.3 (C_q-Si); 25.9 (($\underline{C}H_3)_3C$-Si); 28.3 (($\underline{C}H_3)_3C$-O); 36.7 (CH_2-CO); 49.9 (CH-S); 56.0 (CH-N); 62.7 (CH_2-O); 79.6 (C_q-O); 122.9 (CH_{arom}); 124.8 (C_{arom}); 126.4 (CH_{arom}); 130.2 (CH_{arom}); 136.2 (CH_{arom}); 141.6 (C_{arom}); 155.5 (O-C=O); 173.6 (C=O); Anal. calcd. for $C_{22}H_{36}N_2O_4SSi$: C, 58.37; H, 8.02; N, 6.19, found: C, 58.01; H, 8.30; N, 6.12.

7-(1-Hydroxyethyl)-[1,4]-thiazepan-5-one (4e) (racemic mixture of diastereomers). Method D, eluent: chloroform/methanol 95:5, yield: 32%, m.p. 137-139 °C, ^1H NMR (300 MHz, DMSO-d_6, TMS); δ / ppm; J / Hz: 1.11 (d, 3H, J = 6) CH_3, 2.72 (m, 5H) CH_2-CO, CH_2-S, CH-S; 3.38 (m, 2H) CH_2-NH; 3.59 (m, 1H) CH-O; 4.84 (d, 1H, J = 5) OH; 7.57 (t, 1H, J = 2) NH. ^{13}C NMR (75 MHz, DMSO-d_6, TMS); δ / ppm: 21.0 (CH_3), 30.4 (CH_2-CO); 41.4 (CH_2-S); 43.6 (CH_2-N); 44.7 (CH-S); 68.9 (CH-O); 174.7 (C=O); Anal. calcd. for $C_7H_{13}NO_2S$: C, 47.97; H, 7.49; N, 7.99, found: C, 47.94; H, 7.43; N, 7.89.

(αS,7R) (Major) and (αS,7S)-7-(1,2-dihydroxyethyl)-[1,4]-thiazepan-5-one (4f). Method D, eluent: chloroform/methanol 80:20, yield: 21%, m.p. 125-129 °C, $[\alpha]_D^{20}$= +10,8° (c=1, methanol); ^1H NMR (300 MHz, DMSO-d_6, TMS); δ / ppm; J / Hz: 2.50-3.00 (m, 5H) CH_2-CO, CH_2-S, CH-S; 3.25-3.60 (m, 5H) CH_2-N, CH-O, CH_2O; 4.61 (br s, 1H) OH; 4.93 (br s, 1H) OH; 7.54 (m, 1H) NH. ^{13}C NMR (75 MHz, DMSO-d_6, TMS); δ / ppm: 30.6 (CH_2-CO); 39.4 (CH-S); 40.4 (CH_2-S); 43.4 (CH_2-N); 63.1 (CH_2-O); 74.1 (CH-O), 174.8 (C=O); Anal. calcd. for $C_7H_{13}NO_3S$: C, 43.95; H, 6.86; N, 7.32, found: C, 44.03; H, 6.75; N, 7.13.

(αS,7R) (Major) and (αS,7S)-7-(2-acetoxy-1-hydroxyethyl)-[1,4]-thiazepan-5-one (4g). Method D, eluent: chloroform/methanol 80:20, yield: 32%, m.p. 75-80 °C, $[\alpha]_D^{20}$= +27.9 (c = 0.7, methanol) ^1H NMR (300 MHz, DMSO-d_6, TMS); δ / ppm; J / Hz: 2.04 (s, 3H) CH_3, 2.55 (m, 1H) CH_2-CO; 2.74-3.24 (m, 5H) CH_2-S, CH-S, CH_2CO; 3.58 (m, 3H) CH_2-N, OH; 3.92 (m, 1H) CH-O; 4.16 (dd, 1H, J = 11, 6), CH_2-O, 4.43 (dd, 1H, J = 11, 2) CH_2-O, 7.24 (m, 1H) NH. ^{13}C NMR (75 MHz, DMSO-d_6, TMS); δ / ppm: 21.0 (CH_3), 28.7 (CH_2-CO); 38.1 (CH-S); 41.3 (CH_2-S); 45.0 (CH_2-N); 66.3 (CH_2-O); 70.6 (CH-O), 171.2 (C=O), 176.9 (C=O); Anal. calcd. for $C_9H_{15}NO_4S$: C, 46.33; H, 6.49; N, 6.00, found: C, 46.98; H, 6.50; N, 6.10.

(αS,7R) (Major) and (αS,7S)-7-(1-hydroxy-2-trityloxy-ethyl)-[1,4]-thiazepan-5-one (4h). Method E, eluent: chloroform/methanol 90:10, yield: 44%, m.p. 65-70 °C, $[\alpha]_D^{20}$= +9,7° (c=1, methanol), ^1H NMR (300 MHz, DMSO-d_6, TMS); δ / ppm; J / Hz: 2.50-2.85 (m, 4H) CH_2-CO, CH_2-S; 2.95-3.10 (m, 3H) CH_2-N, CH-S; 3.35 (m, 2H) CH_2-O; 3.68 (quint, 1H, J = 5) CH-O; 5.25 (d, 1H, J = 5) OH; 7.20-7.45 (m, 15H) CH_{arom}; 7.56 (t, 1H, J = 2) NH. ^{13}C NMR (75 MHz, DMSO-d_6, TMS); δ / ppm: 30.4 (CH_2-CO); 39.9 (CH-S); 40.3 (CH_2-S); 43.2 (CH_2-N); 65.4 (CH_2-O); 72.4 (CH-O); 85.9 (C-O); 126.9 (CH_{arom}); 127.8 (CH_{arom}); 128.3 (CH_{arom}); 143.8 (C_{arom}); 174.4 (C=O); Anal. calcd. for $C_{26}H_{27}NO_3S$: C, 72.02; H, 6.29; N, 3.23, found: C, 71.84; H, 6.19; N, 3.20.

7-(1-Hydroxyethyl)-[1,4]-diazepan-5-one (4i) (racemic mixture of diastereomers). Method D, eluent: chloroform/methanol 60:40, yield: 43%, m.p. 135-142 °C, ^{1}H NMR (300 MHz, D_2O, TMS); δ / ppm; J / Hz: 1.16 (d, 3H, J = 6) CH_3; 2.42 (d, 1H, J = 14) CH_2-CO; 2.62-2.77 (m, 3H) CH_2-N, CH-N, CH_2-CO; 3.12 (ddd, 1H, J = 14, 5, 1) CH_2-N; 3.24 (ddd, 1H, J = 15, 5, 1.5) $\underline{CH_2}$-NH-CO; 3.41 (ddd, 1H, J = 15, 10, 1) $\underline{CH_2}$-NH-CO; 3.82 (qd, 1H, 6, 4) $\underline{CH}$-OH; ^{13}C NMR (75 MHz, D_2O, TMS); δ / ppm: 20.0 (CH_3); 42.0 (CH_2); 45.7 (CH_2); 50.6 (CH_2); 60.7 (CH-N); 72.8 (CH-O); 182.7 (C=O); Anal. calcd. for $C_7H_{14}N_2O_2$: C, 53.13; H, 8.94; N, 17.71, found: C, 53.02; H, 8.90; N, 17.54.

(αS,7R)-7-(1,2-Dihydroxyethyl)-[1,4]-diazepan-5-one (4j). Method D, eluent: chloroform/methanol 60:40, yield: 22%, m.p. 148-152 °C, $[\alpha]_D^{20}$= +12.7° (c = 1, methanol), ^{1}H NMR (300 MHz, D_2O, TMS); δ / ppm; J / Hz: 2.47 (d, 1H, J = 14) CH_2-CO, 2.72 (m, 2H) CH_2-CO, CH_2-N; 2.90 (dd, 1H, J = 10, 5) CH-N; 3.12 (dd, 1H, J = 14, 5) CH_2-N; 3.24 (ddd, 1H, J = 14, 5, 1) $\underline{CH_2}$-NH-CO; 3.40 (ddd, 1H, J = 15, 9, 1) $\underline{CH_2}$-NH-CO; 3.64 (m, 3H) CH_2-O, CH-O. ^{13}C NMR (75 MHz, D_2O, TMS); δ / ppm: 43.8 (CH_2-CO); 47.6 (CH_2-NH-CO); 52.2 (CH_2-N); 59.3 (CH-N); 78.7 (CH-O); 184.2 (C=O); Anal. calcd. for $C_7H_{14}N_2O_3$: C, 48.25; H, 8.12; N, 16.08, found: C, 48.00; H, 7.90; N, 15.96.

7-(N-Boc-Aminomethyl)-[1,4]-thiazepan-5-one (4k). Method F, eluent: chloroform/methanol 60:40, yield: 44%, m.p. 126-128 °C, ^{1}H NMR (300 MHz, DMSO-d_6, TMS); δ / ppm; J / Hz: 1.37 (s, 9H) t-Bu, 2.59 (m, 1H) CH_2-CO; 2.81 (m, 2H) CH_2-CO, CH-S; 2.98 (m, 2H) CH_2-S; 3.29 (m, 2H) CH_2-NH-Boc; 3.65 (m, 2H) CH_2-NH; 5.23 (br s, 1H) NH-Boc; 7.43 (br s, 1H) NH. ^{13}C NMR (75 MHz, DMSO-d_6, TMS); δ / ppm: 28.2 ($(\underline{C}H_3)_3C$), 28.8 (CH_2-CO); 36.8 (CH-S); 42.8 (CH_2-S); 43.3 (CH_2-NH-Boc); 79.3 (C_q-tBu); 155.7 (O-C=O); 175.8 (C=O); Anal. calcd. for $C_{11}H_{20}N_2O_3S$: C, 50.75; H, 7.74; N, 10.76, found: C, 51.04; H, 7.71; N, 10.54.

(αS,7R) (Major) and (αS,7S)-7-[1-(N-Boc)-amino-2-(O-tert-butyl-dimethylsilyl)-hydroxyethyl]-[1,4]-thiazepan-5-one (4l). Method F, eluent: chloroform/methanol 95:5, yield: 45%, oil, $[\alpha]_D^{20}$= +12.0° (c = 1, methanol), ^{1}H NMR (300 MHz, $CDCl_3$, TMS); δ / ppm; J / Hz: 0.00 (s, 6H) Si-$(CH_3)_2$; 0.83 (s, 9H) Si-C$(CH_3)_3$; 1.38 (s, 9H) O-C$(CH_3)_3$; 2.62-2.88 (m, 4H) CH_2-CO, CH_2-S; 3.04 (m, 1H) CH-S; 3.48-3.71 (m, 4H) CH_2-N, CH-N, CH_2-O; 3.91 (dd, 1H, J = 10, 3) CH_2-O; 4.95 (d, 1H, J = 9) NH-Boc; 6.90 (br s, 1H) NH.^{13}C NMR (75 MHz, $CDCl_3$, TMS); δ / ppm: -5.5 (Si-$(CH_3)_2$); 18.3 (Si-$\underline{C}(CH_3)_3$); 25.9 (Si-C$(\underline{C}H_3)_3$); 28.3 (O-C$(\underline{C}H_3)_3$); 30.4 (CH_2-S); 38.8 (CH-S); 42.1 (CH_2); 44.3 (CH_2); 54.9 (CH-N); 62.6 (CH_2-O); 79.6 (O-$\underline{C}(CH_3)_3$); 155.6 (O-C=O); 176.2 (C=O); Anal. calcd. for $C_{18}H_{36}N_2O_4S$: C, 53.43; H, 8.97; N, 6.92, found: C, 53.24; H, 8.81; N, 6.68.

7-(N-Boc-Aminomethyl)-[1,4]-diazepan-5-one (4m). Method F, eluent: chloroform/methanol 60:40, yield: 40%, oil, ^{1}H NMR (300 MHz, DMSO-d_6, TMS); δ / ppm; J / Hz: 1.36 (s, 9H) t-Bu, 2.17-3.19 (m, 10H) CH_2-CO, CH_2-NH, CH_2-NH-CO, CH_2-NH-Boc, CH-NH, NH; 6.91 (t, 1H, J = 5) NH-Boc;

7.58 (br s, 1H) NH-CO. ^{13}C NMR (75 MHz, CD_3OD, TMS); δ / ppm: 28.8 ($(\underline{C}H_3)_3C$), 43.2 (CH_2-CO); 44.5 (CH_2-N); 46.4 (CH_2-N); 49.9 (CH_2-NH-Boc); 54.8 (CH-N); 80.3 (C_q-tBu); 158.5 (O-C=O); 178.9 (C=O). $C_{11}H_{21}N_3O_3$, MS (m/z, (rel. int./%)): 244 (M^++1, 0.1), 126 (20, M^+-NH-Boc), 113 (100, M^+- CH_2-NH-Boc), 71 (96), 57 (30), hygroscopic substance, no satisfactory elemental analysis was obtained.

(αS,7R)-7-[1-(N-Boc)-Amino-2-(O-tert-butyl-dimethylsilyl)-hydroxyethyl]-[1,4]-diazepan-5-one (4n). Method F, eluent: chloroform/methanol 60:40, yield: 44%, oil, $[\alpha]_D^{20}$= 7.3° (c = 2.35, MeOH); ^1H NMR (300 MHz, $CDCl_3$, TMS); δ / ppm; J / Hz: 0.00 (s, 6H) Si-$(CH_3)_2$; 0.83 (s, 9H) Si-$C(CH_3)_3$; 1.38 (s, 9H) O-$C(CH_3)_3$; 2.49 (d, 1H, J = 14) CH_2-CO; 2.64 (m, 2H) CH_2-CO, CH_2-N; 2.94 (dd, 1H, J = 10, 6) CH_2-N; 3.07-3.46 (m, 3H) CH_2-NH-CO, CH-N; 3.46 (br s, 1H) NH; 3.71 (m, 4H) CH_2-N-Boc, CH_2-O; 5.38 (d, 1H, J = 8) NH-Boc; 7.06 (br s, 1H) NH. ^{13}C NMR (75 MHz, $CDCl_3$, TMS); δ / ppm: -5.6 (Si-CH_3); 18.1 (Si-$\underline{C}(CH_3)_3$); 25.8 (Si-$C(\underline{C}H_3)_3$); 28.4 (O-$C(\underline{C}H_3)_3$); 44.1 (CH_2); 45.8 (CH_2); 49.3 (CH_2); 54.6 (CH-N); 54.9 (CH-N); 62.4 (CH_2-O); 79.3 (O-$\underline{C}(CH_3)_3$); 155.5 (O-C=O); 177.2 (C=O). MS (m/z, (rel. int./%)): 388 (M^++1, 0.3), 202 (9), 128 (10), 113 (100), 71 (43), 57 (63); Anal. calcd. for $C_{18}H_{37}N_3O_4Si$: C, 55.76; H, 9.64; N, 10.84, found: C, 55.49; H, 9.70; N, 10.52.

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