Synthesis of Optically Active Hydroxyalkylbenzothiazepinones by Ring Transformation of 2-Alkylidenelactons with *o*-Aminothiophenol

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Dedicated to the memory of Professor Raymond N. Castle

A stereoselective synthesis of new optically active 3-(hydroxyalkyl)-2,3-dihydro-1,5-benzothiazepin-4-ones **4** and **7** was achieved by Michael-like addition of *o*-aminothiophenol to chiral α-alkylidenelactons **1** and **5** followed by ring chain transformation of the resulting adducts **3** and **6**.

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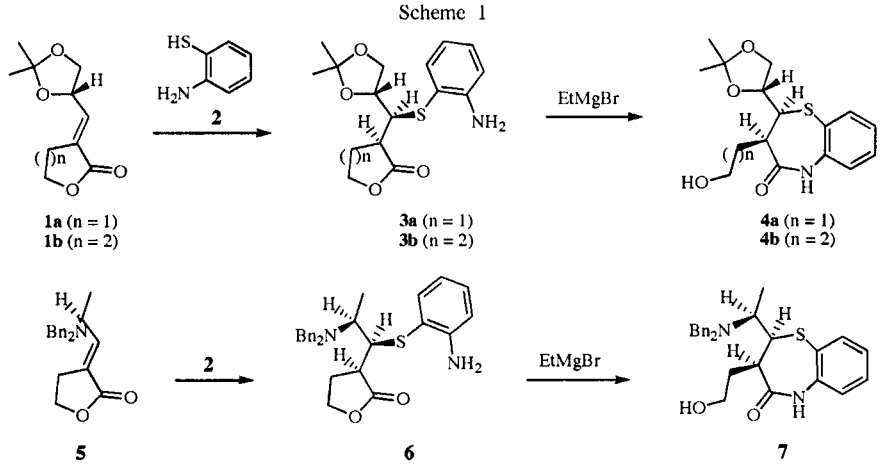
Partially saturated benzodiazepinones such as the antidepressive Thiazesim® [1] and the antihypertensive Diltiazem® [2,3] have found application as potent drugs. Both compounds are chiral and were also obtained as pure enantiomers. Analogues of these compounds have been synthesized as potential pharmacologically active compounds [4,5,6,7,8]. Racemic benzothiazepinones were obtained by reaction of cinnamic acid derivatives with *o*-aminothiophenol by two step procedures, *i. e.* at first Michael-like addition of the thiol function to the β-position followed by attack of the amino group at the carbonyl group [9,10]. Optically active 2-(α-hydroxyalkyl)-1,5-benzothiazepin-4-ones were obtained following the concept of ring chain transformation [11], *i. e.* by a reaction wherein a new ring is formed from a side chain and a new side chain is formed by opening a ring. In this known case, *o*-aminothiophenol was stereoselectively added to the C-C-double bond of butenolides *via* the sulfur atom; the resulting adducts were ring transformed by attack of the amino group at the lactone carbonyl carbon opening the lactone ring thus affording both the hydroxyalkyl side chain and the benzothiazepinone ring.

We report here the stereoselective synthesis of optically active 3-(ω-hydroxyalkyl)-2,3-dihydro-1,5-benzothiazepin-4-ones **4** and **7** by ring chain transformation of α-alkylidenelactones **1** and **5** with *o*-aminothiophenol. Unlike in the known case [11] where the Michael-system is part of the ring, the C-C-double bond of starting materials **1** and **5** is exocyclic. Such systems serve as building blocks in the stereoselective synthesis of heterocyclic products taking advantage from the fact that the chiral information in the side chain renders a stereoselective Michael-like addition of nucleophiles to the β-position [12,13].

The Michael-like addition of *o*-aminothiophenol to lactons **1** and **5** affording *o*-aminophenylthioalkyllactons **3** and **6** was investigated in ethanol and THF at various temperatures. The application of a high excess of *o*-aminothiophenol **2** in the presence of one equivalent of lithium *o*-aminothiophenolate in THF at temperatures between -78 °C and -20 °C turned out to be optimal with regard to the total yield and the diastereomeric ratios. Under conditions that are not optimal sometimes a third stereoisomer appeared, which however was not further investigated. The application of equimolar quantities of the reactants in ethanol left the starting materials unchanged even under reflux conditions. Increasing the amount of *o*-aminothiophenol to 3-5 equivalents gave products **3** and **6** but only in 51 to 66% yield and in low stereoselectivities. Diastereopure products **3a**, **3b** and **6** could be obtained

Scheme 1



from the product mixtures obtained under optimal conditions by flash chromatography. They were further submitted to a ring chain transformation reaction to give benzothiazepinones **4** and **7**. Treatment with triethylamine hydrochloride [9], with molecular sieves in xylene [10] or with *p*-toluene sulfonic acid in ethanol [14] as well established methods for the formation of thiazepinones turned out to be unsuccessful in our cases. But treatment of **3** and **6** with excess of ethylmagnesium bromide in THF/diethyl ether gave the expected optically active 3-(ω-hydroxyalkyl)-2,3-dihydro-1,5-benzothiazepin-4-ones **4** and **7** in high yields.

Structures of products **3**, **4**, **6** and **7** were elucidated on the basis of X-ray crystal analysis of the adduct **3b** (see Figure 1) and spectroscopic data. Thus the X-ray crystal analysis revealed the formation of the stereoisomer **3b** which is *anti* with respect to the hydrogen atoms found at the chiral carbon atoms in the side chain of the lactone ring and proves for the attack of *o*-aminothiophenol **2** at **1a** from the *si*-side. The formation of stereoisomers **3** is in accordance with Houks model of the "inside alkoxy effect" [15], while the aminoethyl compound **5** followed the "antiperiplanar" effect giving the *syn*-product, as found before in other addition reactions with this reactant [16]. The protonation of the ring carbon atom occurred *trans* with respect to the incoming *o*-aminothiophenolate, which is in accordance with known results for the addition of thiophenolate to α-alkylidenelactones [17,18]. Since no reaction at the chiral centers occurred during the cyclisation of adducts **3** and **6** the configurations were maintained in the final ring transformation products **4** and **7**. The *cis*-configuration at the thiazepinone ring of all products **4a**, **4b** and **7** is in accordance with the observed J^3 (H, H)-coupling constants which range between 3.8 and 5.2 Hz and with NOE difference NMR-investigations demonstrating

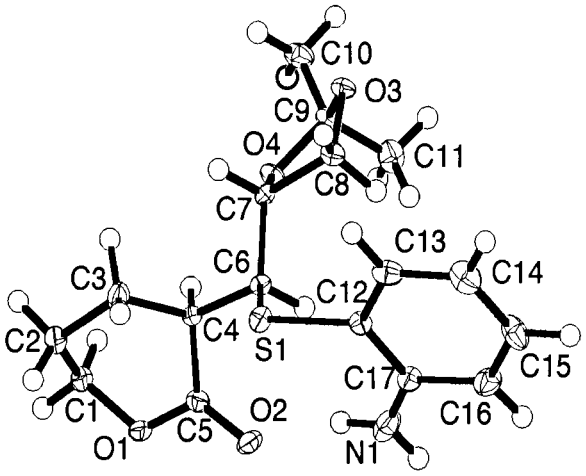


Figure 1. X-Ray Structural Analysis of **3b**.

Table 1
Bond lengths [Å] and angles [°] for **3b**

Bond lengths		angles	
C(1)-O(1)	1.458(3)	O(1)-C(1)-C(2)	109.74(16)
C(1)-C(2)	1.502(3)	C(1)-C(2)-C(3)	111.4(2)
C(2)-C(3)	1.528(3)	C(2)-C(3)-C(4)	112.44(17)
C(3)-C(4)	1.532(3)	C(5)-C(4)-C(3)	111.39(18)
C(4)-C(5)	1.509(3)	C(5)-C(4)-C(6)	112.57(17)
C(4)-C(6)	1.541(3)	C(3)-C(4)-C(6)	114.59(15)
C(5)-O(2)	1.199(3)	O(2)-C(5)-O(1)	118.2(2)
C(5)-O(1)	1.348(2)	O(2)-C(5)-C(4)	126.12(18)
C(6)-C(7)	1.516(3)	O(1)-C(5)-C(4)	115.68(19)
C(6)-S(1)	1.8439(18)	C(7)-C(6)-C(4)	110.81(16)
C(7)-O(4)	1.439(2)	C(7)-C(6)-S(1)	110.88(11)
C(7)-C(8)	1.526(3)	C(4)-C(6)-S(1)	109.23(14)
C(8)-O(3)	1.422(3)	O(4)-C(7)-C(6)	108.78(14)
C(9)-O(3)	1.429(2)	O(4)-C(7)-C(8)	102.68(16)
C(9)-O(4)	1.435(3)	C(6)-C(7)-C(8)	115.83(16)
C(9)-C(10)	1.504(3)	O(3)-C(8)-C(7)	102.62(14)
C(9)-C(11)	1.505(3)	O(3)-C(9)-O(4)	104.88(15)
C(12)-C(17)	1.397(3)	O(3)-C(9)-C(10)	108.89(17)
C(12)-C(13)	1.400(3)	O(4)-C(9)-C(10)	109.31(17)
C(12)-S(1)	1.781(2)	O(3)-C(9)-C(11)	110.17(16)
C(13)-C(14)	1.368(4)	O(4)-C(9)-C(11)	109.78(18)
C(14)-C(15)	1.364(4)	C(10)-C(9)-C(11)	113.45(19)
C(15)-C(16)	1.382(3)	C(17)-C(12)-C(13)	120.3(2)
C(16)-C(17)	1.417(3)	C(17)-C(12)-S(1)	122.04(15)
C(17)-N(1)	1.345(3)	C(13)-C(12)-S(1)	117.28(17)
		C(14)-C(13)-C(12)	122.0(2)
		C(15)-C(14)-C(13)	118.2(2)
		C(14)-C(15)-C(16)	121.9(2)
		C(15)-C(16)-C(17)	120.8(2)
		N(1)-C(17)-C(12)	122.8(2)
		N(1)-C(17)-C(16)	120.4(2)
		C(12)-C(17)-C(16)	116.72(18)
		C(5)-O(1)-C(1)	117.07(16)
		C(8)-O(3)-C(9)	105.70(14)
		C(9)-O(4)-C(7)	109.51(13)
		C(12)-S(1)-C(6)	104.14(9)

the proximity of the two hydrogen atoms attached to the 7-membered ring. Under the conditions employed a competing reaction of the Grignard reagent at the carbonyl carbon atom was not observed; an epimerisation at the carbon atom next to the carbonyl group did not occur either.

In summary, an efficient synthesis of new optically active 3-(α-hydroxyalkyl)-1,5-benzothiazepin-4-ones **4** and **7** was developed. It once more demonstrates the usefulness of the ring chain transformation concept and the possibility of stereofacial differentiation in the addition of nucleophiles to α-alkylidenelactons with substitutents that are not conformationally fixed in the side chain.

EXPERIMENTAL

Melting points were determined on a Boetius hot-stage apparatus and are uncorrected. The ^1H nmr and ^{13}C nmr spectra were recorded o a Bruker AC 300 spectrometer, using tetramethylsilane as internal standard. X-Ray crystal analysis was performed on a STOE Ipds Diffraktometer (Mo-K_α irradiation). Elemental analyses

Table 2

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **3b** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)				
C(2)	(3)	12438(2)	-357(1)	27(1)
C(3)	2477(3)	11169(2)	-643(1)	27(1)
C(4)	1951(3)	9935(2)	-204(1)	31(1)
C(5)	2680(2)	10190(2)	397(1)	17(1)
C(6)	4400(3)	10638(2)	354(1)	22(1)
C(7))	2394(2)	8848(2)	831(1)	16(1)
C(8)	676(2)	8793(2)	1015(1)	16(1)
C(9)	243(3)	7512(2)	1448(1)	20(1)
C(10)	-551(3)	9812(2)	1847(1)	19(1)
C(11)	-2019(3)	10798(2)	1879(1)	31(1)
C(12)	504(3)	9982(2)	2369(1)	32(1)
C(13)	3514(3)	5775(2)	1096(1)	19(1)
C(14)	2684(3)	4370(2)	1161(1)	29(1)
C(15)	3093(3)	3284(2)	1571(1)	37(1)
C(16)	4324(3)	3615(2)	1932(1)	36(1)
C(17)	5177(3)	4987(2)	1885(1)	33(1)
N(1)	4810(3)	6104(2)	1451(1)	23(1)
O(1)	5663(3)	7424(2)	1403(1)	36(1)
O(2)	4745(2)	11751(2)	-41(1)	28(1)
O(3)	5460(2)	10107(2)	637(1)	31(1)
O(4)	-998(2)	8213(1)	1773(1)	20(1)
S(1)	310(2)	10201(1)	1330(1)	21(1)
3425	2998(1)	6984(1)	495(1)	22(1)

of the final products **4** and **7** were determined by the microanalytical laboratory of Humboldt-University Berlin. Intermediates **3** and **6** were not purified and characterized by elemental analysis but were further used as isolated from flash chromatography. Starting materials were prepared as reported [12].

Adducts **3** and **6**.

General Procedure.

A 1.6 *M* solution of BuLi (0.16 ml, 0.1 mmol) in dry THF was slowly added to a solution of *o*-aminothiophenol **2** (1.25 g, 10 mmol) in dry THF (10 ml) with stirring at 0 °C during 5 minutes. After further stirring at 0 °C for 30 minutes the solution was cooled to -78 °C. A solution of α-alkylidene lactone **1** or **5** (1 mmol) in dry THF (5 ml) was slowly added at -78 °C. After the addition was complete the mixture was allowed to warm up to room temperature overnight and was then treated with 2 *M* aqueous NaOH (10 ml). The resulting mixture was extracted with CH_2Cl_2 (3 x 30 ml). The combined extracts were intensively washed with 2 *M* NaOH (10 ml). After drying the organic phase with Na_2SO_4 the solution was concentrated and the remainder was purified by flash chromatography. Diastereomeric ratios (d. r.) were determined from the crude products.

(*3R*)-3-{(*S*)-[2-Aminophenylthio]-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-methyl}-dihydro-3*H*-furan-2-one (**3a**).

The compound was obtained from **1a** as colorless crystals, mp 129-131 °C, yield 94%; d. r. = 73:23, R_f = 0.37 (hexane/ethyl acetate, 7:3), R_f of the minor diastereomer 0.27.

^{1}H nmr ($CDCl_3$): δ 1.24 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 2.30 (m, 2H, OCH_2CH_2), 3.21 (m, 1H, $CHCH_2O$), 3.33 (m, 1H, CHS), 3.49 (q, 1H, *J* = 2.9Hz, CHC=O), 3.92 (m, 1H, $CHCH_2O$), 4.16 (m, 2H, OCH_2CH_2), 4.39 (m, 1H, OCH), 4.55 (s, 2H, NH_2), 6.56 (m, 2H, CH-arom.), 7.0-7.3 (m, 2H, CH-arom.); ^{13}C nmr ($CDCl_3$): δ 23.9 (CH_2), 25.5 (CH_3), 26.6 (CH_3), 41.5 (*C*H), 48.4 (*C*H), 66.8 (CH_2), 68.4 (CH_2), 78.6 (*C*H), 109.0 (C_q), 112.9, 115.2, 118.0, 130.9, 136.9, 149.0 (*C*-arom.), 178.4 (*C*=O)

(*3R*)-3-{(*S*)-[2-Aminophenylthio]-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-methyl}-tetrahydro-2*H*-pyran-2-one (**3b**).

The compound was obtained from **1b** as colorless crystals, mp. 141-143 °C, yield 91%; d. r. = 82:18, R_f = 0.32 (hexane/ethyl acetate, 7:3), R_f of the minor diastereomer 0.24. ^{1}H nmr ($CDCl_3$): δ 1.22 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.86 (m, 2H, CH_2CHC=O), 1.91 (m, 1H, CH_2CH_2O), 2.10 (m, 1H, CH_2CH_2O), 3.08 (m, 1H, $CHCH_2O$), 3.25 (m, 1H, CHS), 3.75 (m, 1H, CHC=O), 3.86 (m, 1H, $CHCH_2O$), 4.17 (m, 1H, OCH), 4.34 (m, 1H, CH_2CH_2O), 4.59 (s, 2H, NH_2), 6.53 (m, 2H, CH-arom.), 7.0-7.28 (m, 2H, CH-arom.); ^{13}C nmr ($CDCl_3$): δ 20.7 (CH_2), 22.7 (CH_2), 25.7 (CH_3), 26.7 (CH_3), 42.4 (*C*H), 50.0 (*C*H), 68.7 (CH_2), 69.6 (CH_2), 77.5 (*C*H), 108.7 (C_q), 113.4, 115.1, 117.8, 130.7, 136.8, 149.1, (*C*-arom.), 172.9 (*C*=O).

X-Ray Structure Determination of Compound **3b**.

Compound **3b** ($C_{27}H_{23}NO_4S$, M = 337.4) formes orthorhombic crystals in the space group P 21 21 21 with a = 8.4661(11) Å, b = 8.5523(12) Å, c = 23.031(5) Å, α = 90°, β = 90°, γ = 90°, V = 1667.5 (6) $Å^3$, Z = 4, D_c = 1.344 g/cm^3, λ(MoKα) = 0.71073 Å, μ = 0.077 mm^{-1}, F(000) = 720, T = 180(2)K. Data collection and reduction: A colorless crystal 0.57 x 0.47 x 0.23 mm was used to collect 7304 reflections of which 2697 were unique [R(int) = 0.0350] in the range of 2.54° < Θ < 25.24°. The structure was refined on F^2 using SHELX, the final residuals were $wR_{2\ (all)}$ = 0.0652, $R_{1\ (all)}$ = 0.0363 and $R_{1\ (obs)}$ = 0.0295. The maximum and minimum peaks in the final difmap were 0.285 and -0.162 e/$Å^3$, respectively.

Full details of the structure determination have been deposited at the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 138111. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

(*3R*)-3-[(1*S*, 2*S*)-1-(2-Aminophenylthio)-2-(2-dibenzylamino)-propyl]-dihydro-3*H*-furan-2-one (**6**).

The compound was obtained from **5** as colorless waxy material, yield 97%; d. r. = 91:9, R_f = 0.28 (hexane/ethyl acetate, 8:2), R_f of the minor diastereomer 0.24. ^{1}H nmr ($CDCl_3$): δ 1.16 (d, 3H, *J* = 6.9 Hz, CH_3), 2.12 (m, 1H, CH_2CH_2O), 2.34 (m, 1H, CH_2CH_2O), 2.93 (m, 1H, CHS), 2.99 (m, 1H, $CHCH_3$), 3.44 (d, 2H, *J* = 14 Hz, CH_2N), 3.68 (d, 2H, *J* = 14 Hz, CH_2N), 3.93 (m, 1H, CHC=O), 4.03 (m, 1H, CH_2CH_2O), 4.28 (m, 1H, CH_2CH_2O), 4.30 (s, 2H, NH_2), 6.46-7.23 (m, 10H, CH-arom.); ^{13}C nmr ($CDCl_3$): δ 12.6 (CH_3), 25.0 (CH_2), 41.3 (*C*H), 50.4 (*C*H), 54.6 (2xCH_2), 57.2 (*C*H), 66.6 (CH_2), 114.8, 115.2, 118.1, 126.9, 128.3, 128.8, 130.4, 136.9, 139.6, 149.0, (*C*-arom.), 178.8 (*C*=O).

3-(α-Hydroxyalkyl)-1,5-benzothiazepin-4-ones **4** and **7**.

General Procedure.

A 1 *M* solution of ethylmagnesium bromide in diethylether (2 ml) was slowly added to a solution of the adduct **3** or **6** (0.5 mmol) in dry THF (20 ml) under stirring at 0 °C. The mixture was allowed to warm up to room temperature under stirring over 1.5 hours. The mixture was combined with a solution of saturated NH_4Cl and 25%

aqueous NH_3 (9:1, 5 ml) and 5 g Na_2SO_4 were added. After 5 minutes the resulting suspension was filtered with suction through a layer (about 3 cm) of celite/Na_2SO_4 1:1. The layer is scavenged with ethyl acetate (30 ml) and CH_2Cl_2 (30 ml). The combined organic phases were dried with Na_2SO_4. After evaporation of the solvent the remainder was purified by flash chromatography.

(2*S*,3*R*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-(2-hydroxyethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**4a**).

This compound was obtained from **3a** as colorless waxy material, yield 86%, $[\alpha]_D^{20}$ = -123° ($CHCl_3$), R_f = 0.41 ($CHCl_3$/methanol, 9:1). ^1H nmr ($CDCl_3$): δ 1.28 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.72 (m, 1H, CH_2CH_2OH), 1.97 (s, 1H, OH), 2.22 (m, 1H, CH_2CH_2OH), 3.00 (dd, 1H, *J* = 5.2 Hz, 4.1, CHS), 3.52 (m, 2H, CH_2CH_2OH), 3.98 (m, 2H, $CHCH_2O$), 4.06 (m, 1H, CHC=O), 4.42 (q, 1H, *J* = 6.5 Hz, CHO), 7.0-7.52 (m, 4H, CH-arom.), 8.26 (s, 1H, NHC=O); ^{13}C nmr ($CDCl_3$): δ 25.5 (CH_3), 26.4 (CH_3), 31.8 (CH_2), 41.2 (*C*H), 55.7 (*C*H), 61.0 (CH_2), 66.0 (CH_2), 75.6 (*C*H), 109.1 (C_q), 123.1, 126.4, 126.8, 129.8, 135.1, 140.6 (*C*-arom.), 174.1 (*C*=O).

Anal. Calcd. for $C_{16}H_{21}NO_4S$ (323.4): C, 59.42; H, 6.54; N, 4.33; S, 9.91. Found: C, 59.01; H, 6.22; N, 4.19; S, 9.78.

(2*S*,3*R*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-(3-hydroxypropyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**4b**).

This compound was obtained from **3b** as colorless waxy material, yield 82%, $[\alpha]_D^{20}$ = -110.8° ($CHCl_3$), R_f = 0.38 ($CHCl_3$/methanol, 9:1). ^1H nmr ($CDCl_3$): δ 1.26 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.48 (m, 1H, $CH_2CHC=O$), 1.99 (m, 1H, $CH_2CHC=O$), 2.39 (s, 1H, OH), 2.78 (m, 1H, CHC=O), 3.47 (m, 2H, CH_2CH_2OH), 4.03 (d, 2H, *J* = 6.4 Hz, $CHCH_2O$), 4.13 (t, 1H, *J* = 5.6 Hz, CHS), 4.41 (q, 1H, *J* = 6.4 Hz, CHO), 7.01-7.53 (m, 4H, CH-arom.), 8.61 (s, 1H, NHC=O); ^{13}C nmr ($CDCl_3$): δ 25.1 (CH_2), 25.4 (CH_3), 26.4 (CH_3), 31.2 (CH_2), 44.1 (*C*H), 55.7 (*C*H), 61.9 (CH_2), 65.5 (CH_2), 75.4 (*C*H), 108.8 (C_q), 123.1, 126.4, 127.0, 129.8, 135.2, 140.7 (*C*-arom.), 174.3 (*C*=O).

Anal. Calcd. for $C_{17}H_{23}NO_4S$ (337.4): C, 61.51; H, 6.87; N, 4.15; S, 9.50. Found: C, 61.28; H, 7.10; N, 3.89; S, 9.46.

(2*S*,3*R*)-2-[(1*S*)-1-(Dibenzylamino)-ethyl]-3-(2-hydroxyethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**7**).

This compound was obtained from **6** as colorless waxy material, $[\alpha]_D^{20}$ = -110.3° ($CHCl_3$), R_f = 0.23 ($CHCl_3$/methanol, 95:5). ^1H nmr ($CDCl_3$): δ 1.12 (d, 3H, *J* = 6.4 Hz, CH_3), 1.43 (m, 1H, CH_2CH_2OH), 1.74 (s, 1H, OH), 2.12 (m, 1H, CH_2CH_2OH), 3.01 (dt, 1H, *J* = 7.9 Hz, 3.8, CHS), 3.18 (dt, 1H, *J* = 6.5 Hz, 3.8, CHC=O), 3.28 (m, 2H, CH_2CH_2OH), 3.31 (d, 2H, *J* = 13.7 Hz, CH_2N), 3.75 (d, 2H, *J* = 13.7 Hz, CH_2N), 3.90 (q, 1H, *J* = 4.1 Hz, CHN), 6.85-7.50 (m, 4H, CH-arom.), 8.07 (s, 1H, NHC=O); ^{13}C nmr ($CDCl_3$): δ 12.4 (CH_3), 37.1 (CH_2), 42.5 (*C*H), 53.9 (2xCH_2), 57.0 (*C*H), 59.4 (*C*H), 61.5 (CH_2), 122.4, 125.7, 126.8, 128.0, 128.3, 128.6, 129.4, 130.6, 134.2, 139.0 (*C*-arom.), 174.3 (*C*=O).

Anal. Calcd. for $C_{27}H_{30}N_2O_2S$ (446.6): C, 72.61; H, 6.77; N, 6.27; S, 7.18. Found: C, 72.13; H, 6.63; N, 5.84; S, 6.75

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