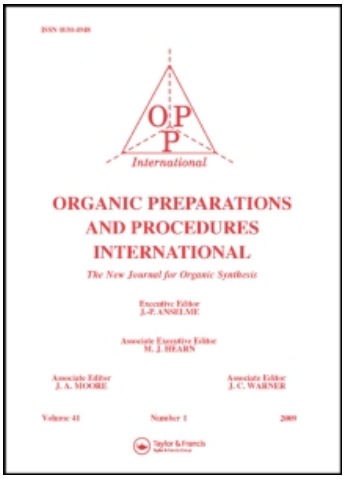

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AN IMPROVED SYNTHESIS OF (*S*)- OR (*R*)-N-Boc-PROTECTED 1,5-BENZOTHIAZEPINE DERIVATIVES

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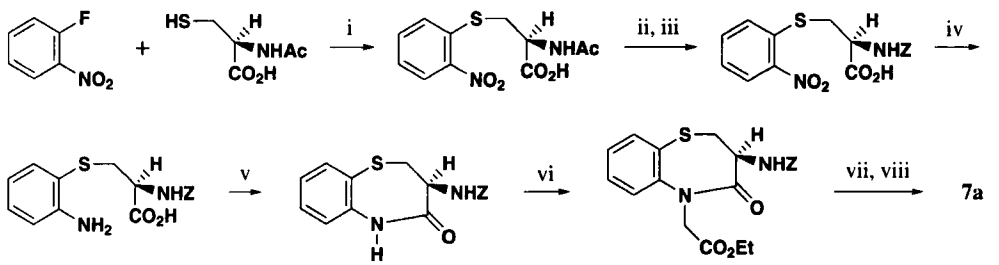
1,5-benzothiazepine derivatives are important lead compounds in medicinal chemistry. They were used not only as constrained dipeptide mimetics in protease inhibitors[1,2,3] but also in G-protein-coupled receptor antagonists.[4,5] Our group was particularly interested in the (*S*)-3-amino-5-carboxylmethyl-2,3-dihydro-1,5-benzothiazepine-4(5*H*)-one (D-BT) moiety. It has been shown that its introduction into bradykinin analogues lead to potent bradykinin B_2 receptor agonists[6,7] and bradykinin B1 receptor antagonists.[8,9] The previous synthesis of these motifs[1] started with the condensation of Ac-Cys-OH and 1-fluoro-2-nitrobenzene (*Scheme 1*). However, the use of an acetyl protecting group required rather drastic conditions (*e.g.* H_2SO_4, reflux) for removal. In our bradykinin program, we



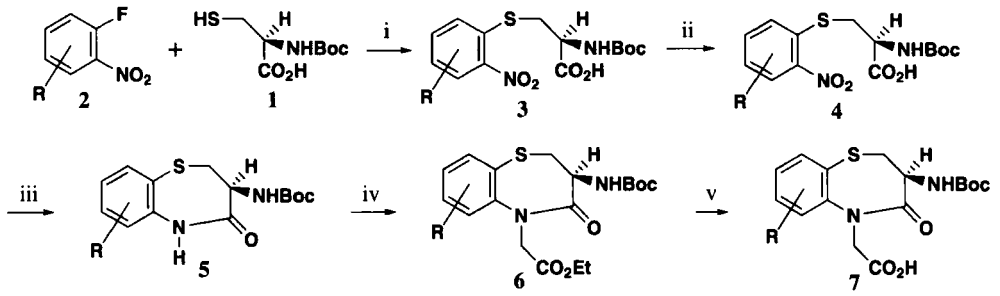
i) $NaHCO_3$, EtOH-H_2O ii) H_2SO_4, NH_4OH iii) ZCl, NaOH iv) Zn, NH_4Cl, MeOH
v) $Me_2N(CH_2)_3N{=}C{=}N{-}Et$. HCl, DMF vi) $BrCH_2CO_2Et$, KOH, n-Bu_4NBr, THF
vii) 33% HBr in AcOH viii) Boc_2O, 1N NaOH, dioxane

Scheme 1

used a 1,5-benzothiazepine derivative with a Boc protecting group which is removed at room temperature by a TFA treatment. In our first attempts, we only adapted the described strategy (*Scheme 1*)

which required some additional steps of deprotection and protection (steps ii, iii, vii and viii) to afford the Boc-protected derivative **7a**.

We now report a modification of this procedure by direct use of Boc-(L or D)-Cys-OH instead of Ac-(L or D)-Cys-OH for the preparation of Boc-D-BT-OH, Boc-L-BT-OH as well as various aryl-substituted derivatives (*Scheme 2*). Therefore, the new synthetic pathway lead to the N-Boc-protected-1,5-benzothiazepine derivatives (**7a-c**) in five steps as shown in *Scheme 2*.[10] The



a) R = H b) R = CH_3 c) R = CF_3

i) $NaHCO_3$, EtOH-H_2O ii) Zn, NH_4Cl, MeOH iii) BOP, $NaHCO_3$,DMF
iv) $BrCH_2CO_2Et$, KOH, *n*-Bu_4NBr, THF v) NaOH, EtOH

Scheme 2

aromatic nucleophilic substitution of the *o*-fluoronitrobenzene (**2a**) and its aryl-substituted analogues (**2b-c**) with Boc-D-Cys-OH (**1**) was achieved according to the conditions described by Slade *et al.*[1] to lead to intermediates **3a-c** in very high yield (92-98%). The nitro group of the resulting compounds was then reduced by zinc dust in quantitative yield to give **4a-c**. Under these conditions we never observed partial deprotection of the acid-labile Boc group with formation of side-products. Intermediates **4a-c** were then cyclized in DMF at a 10 mM concentration, with benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP)[11] as coupling reagent in the presence of sodium bicarbonate as "insoluble base"[12] to yield **5a-c**. Alkylation of the lactam nitrogen with ethyl bromoacetate gave the corresponding protected 1,5-benzothiazepine derivatives **6a-c** which were then hydrolyzed to lead to the final compounds **7a-c**. The yield for the total synthesis of **7a** (52%) was nearly triple that obtained (18%)[13] with the synthetic strategy described by Slade *et al.*[1]

In conclusion, we have described a convenient and higher-yielding synthesis in 5 steps of (*S* and *R*)-3-(*tert*-butyloxycarbonylamino]-5-carboxylmethyl-2,3-dihydro-1,5-benzothiazepine-4(5*H*)-one (Boc (L or D)-BT-OH. This route was also successfully applied to the preparation of their methyl and new trifluoromethyl aryl-substituted analogues.

EXPERIMENTAL SECTION

Mps were determined with a Büchi apparatus and are uncorrected. Optical rotations were measured with a Perkin Elmer, model 241 polarimeter. NMR spectra were recorded with a Bruker DRX 400 spectrometer. Data are reported as follows: chemical shifts (δ) are in ppm with respect to TMS, multi-

plicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (J) in Hz. HPLC analyses were performed with a Waters 510 instrument with variable detector; Column: Symmetry shield (Waters) C_{18}: 50 x 4.6 mm; 100 Å; 3.5 µM; 1mL/min; detection 214 nm, gradient H_2O / CH_3CN / 0.1% TFA 20→95 (15 min). The ESI mass spectra were recorded with a platform II quadrupole mass spectrometer (Micromass, Manchester, UK) fitted with an electrospray source.

(S or R)-S-(2-Nitroaryl)-N-(*tert*-butyloxycarbonyl)cysteine (3a-c). General Procedure.- To a mixture of (S or R)-N-(*tert*-butyloxycarbonyl)cysteine (S)-**1** or (R)-**1** (1.99 g, 9.0 mmol) and sodium bicarbonate (2.18 g, 26.0 mmol) in 16 mL of water was added slowly compound **2** (9.0 mmol, 1 eq) in 20 mL of ethanol. The reaction was refluxed for 6 h and then stirred overnight at room temperature. The ethanol was evaporated under vacuum and the resulting aqueous solution was diluted with water (20 mL), washed with ether (3x 20 mL), acidified with 1N HCl solution (pH 2-3) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford the expected compound (S)-**3** or (R)-**3**.

(S)-S-(2-Nitrophenyl)-N-(*tert*-butyloxycarbonyl)cysteine [(S)-3a] prepared from (S)-N-(*tert*-butyloxycarbonyl)cysteine (S)-**1** (1.99 g, 9.0 mmol) and 1-fluoro-2-nitrobenzene (**2a**) (1.27 g, 9.0 mmol). Obtained as a yellow solid (3.02 g, 98%), mp. 53-54°; $[\alpha]_D^{20}$ = -75 (c 1.5, CH_3OH); HPLC: t_R = 9.6 min; ^{1}H NMR ($CDCl_3$): conformer I (37%): δ 1.42 (s, 9H, ($(CH_3)_3C$), 3.30 (m(br), 1H, S-*H*CH), 3.62 (m(br),1H, S-*H*CH), 4.57 (m(br), 1H, NH-C*H*-CO), 7.05 (br, 1H, N*H*), 7.34 (d, J = 8.0 Hz, 1H, Ar-*H*), 7.60 (s, 1H, Ar-*H*), 8.21 (d, J = 8.0 Hz, 1H, Ar-*H*); conformer II (63%): δ 1.46 (s, 9H, $(CH_3)_3C$), 3.42 (m(br), 1H, S-*H*CH), 3.62 (m(br),1H, S-*H*CH), 4.69 (m(br), 1H, NH-C*H*-CO), 5.46 (d, J = 6.5 Hz, 1H, N*H*), 7.32 (d, J = 8.0 Hz, 1H, Ar-*H*), 7.60 (s, 1H, Ar-*H*), 8.17 (d, J = 8.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): conformer I: δ 28.50 ($(CH_3)_3C$), 36.25 (S-CH_2), 53.51 (N-*C*H-CO), 81.16 ($(CH_3)_3C$), 125.74, 126.63, 127.44, 134.08 (Ar-*C*H), 136.41, 147.12 (Ar-*C*), 157.10 (N-*C*O-O), 174.09 (*C*OOH); conformer II: δ 28.67 ($(CH_3)_3C$), 35.28 (S-CH_2), 52.85 (N-*C*H-CO), 81.34 ($(CH_3)_3C$), 125.93, 126.44, 128.15, 134.08 (Ar-*C*H), 135.73, 147.50 (Ar-*C*), 155.84 (N-*C*O-O), 174.54 (*C*OOH); ESI-MS *m/z*: 243.1, 286.9, 343.0 [(M+H)$^+$], 685.5 [(2M+H)$^+$].

Anal. Calcd for $C_{14}H_{18}N_2O_6S$: C, 49.11; H, 5.30; N, 8.18. Found C, 49.27; H, 5.42; N, 8.02

(R)-S-(2-Nitrophenyl)-N-(*tert*-butyloxycarbonyl)cysteine [(R)-3a] prepared from (R)-N-(*tert*-butyloxycarbonyl)cysteine (R)-**1** (1.99 g, 9.0 mmol) and 1-fluoro-2-nitrobenzene (**2a**) (1.27 g, 9.0 mmol). Obtained as a yellow solid (2.96 g, 96%), mp. 52-53°; $[\alpha]_D^{20}$ = + 74 (c 1.5, CH_3OH); other analytical data are identical to those of the S enantiomer.

Anal. Calcd for $C_{14}H_{18}N_2O_6S$: C, 49.11; H, 5.30; N, 8.18. Found C, 49.30; H, 5.38; N, 8.10

(S)-S-(5-Methyl-2-nitrophenyl)-N-(*tert*-butyloxycarbonyl)cysteine [(S)-3b] prepared from (*S*)-N-(*tert*-butyloxycarbonyl)cysteine (S)-**1** (1.99 g, 9.0 mmol) and 3-fluoro-4-nitrotoluene (**2b**) (1.39 g, 9.0 mmol). Obtained as a yellow solid (3.05 g, 95%), mp. 96-98°; $[\alpha]_D^{20}$ = -64 (c 1.0, CH_3OH); HPLC: t_R = 10.2 min; ^{1}H NMR ($CDCl_3$): conformer I (34%): δ 1.31 (s, 9H, ($(CH_3)_3C$), 2.38 (s, 3H, CH_3-Ar-C), 3.16 (m, 1H, S-*H*CH), 3.48 (dd, J = 4.6 Hz and 13.3 Hz, 1H, S-*H*CH), 4.49 (m, 1H, NH-C*H*-CO),

7.01 (d, J = 8.3 Hz, 1H, Ar-*H*), 7.08 (d, J = 7.6 Hz, 1H, N*H*), 7.19 (s, 1H, Ar-*H*), 8.02 (d, J = 8.3 Hz, 1H, Ar-*H*); conformer II (66%): δ 1.37 (s, 9H, $((CH_3)_3C)$, 2.38 (s, 3H, CH_3-Ar-C), 3.31 (dd, J = 6.3 Hz and 13.3 Hz, 1H, S-*H*CH), 3.48 (dd, J = 4.6 Hz and 13.3 Hz, 1H, S-*H*CH), 4.60 (m, 1H, NH-C*H*-CO), 5.25 (d, J = 7.6 Hz, 1H, N*H*), 7.01 (d, J = 8.3 Hz, 1H, Ar-*H*), 7.26 (s, 1H, Ar-*H*), 8.02 (d, J = 8.3 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): conformer I: δ 22.12 (CH_3-Ar-C), 28.47 ($(CH_3)_3C$), 36.48 (S-CH_2), 53.32 (N-*C*H-CO), 81.19 ($(CH_3)_3C$), 126.49, 126.74, 127.36 (Ar-*C*H), 136.71, 144.68, 145.64 (Ar-*C*), 157.27 (N-*C*O-O), 174.41 (*C*OOH); conformer II: δ 22.12 (CH_3-Ar-C), 28.67 ($(CH_3)_3C$), 35.18 (S-CH_2), 52.71 (N-*C*H-CO), 81.36 ($(CH_3)_3C$), 126.58, 126.74, 128.05 (Ar-*C*H), 135.83, 145.04, 145.65 (Ar-*C*), 155.84 (N-*C*O-O), 175.16 (*C*OOH); ESI-MS *m/z*: 257.0, 301.0, 357.0 [(M+H)$^+$], 713.3 [(2M+H)$^+$].

Anal. Calcd for $C_{15}H_{20}N_2O_6S$: C, 50.55; H, 5.66; N, 7.86. Found C, 50.24; H, 5.80; N, 7.72

(R)-S-(5-Methyl-2-nitrophenyl)-N-(*tert*-butyloxycarbonyl)cysteine [(R)-3b] prepared from (R)-N-(*tert*-butyloxycarbonyl)cysteine (R)-**1** (1.99 g, 9.0 mmol) and 3-fluoro-4-nitrotoluene (**2b**) (1.39 g, 9.0 mmol). Obtained as a yellow solid (3.10 g, 96%), mp. 97-98°; $[\alpha]_D^{20}$ = + 66 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

Anal. Calcd for $C_{15}H_{20}N_2O_6S$: C, 50.55; H, 5.66; N, 7.86. Found C, 50.34; H, 5.78; N, 7.75

(S)-S-(4-Trifluoromethyl-2-nitrophenyl)-N-(*tert*-butyloxycarbonyl)cysteine [(S)-3c] prepared from (*S*)-N-(*tert*-butyloxycarbonyl)cysteine (*S*)-**1** (1.99 g, 9.0 mmol) and 4-fluoro-3-nitrobenzotrifluoride (**2c**) (1.88 g, 9.0 mmol). Obtained as a yellow solid (3.40 g, 92%), mp. 82-83°; $[\alpha]_D^{20}$ = -60 (c 1.0, CH_3OH); HPLC: t_R = 11.7 min; ^{1}H NMR ($CDCl_3$): conformer I (38%): δ 1.46 (s, 9H, $((CH_3)_3C)$, 3.36 (dd, J = 8.6 Hz and 12.7 Hz, 1H, S-*H*CH), 3.63 (m, 1H, S-*H*CH), 4.61 (m, 1H, NH-C*H*-CO), 7.21 (d, J = 7.1 Hz, 1H, N*H*), 7.67 (d, J = 8.5 Hz, 1H, Ar-*H*), 7.84 (d, J = 8.5 Hz, 1H, Ar-*H*); 8.52 (s, 1H, Ar-*H*), conformer II (62%): δ 1.46 (s, 9H, $((CH_3)_3C)$, 3.48 (dd, J = 5.8 Hz and 13.5 Hz, 1H, S-*H*CH), 3.70 (dd, J = 4.6 Hz and 13.5 Hz, 1H, S-*H*CH), 4.74 (m, 1H, NH-C*H*-CO), 5.47 (d, J = 7.1 Hz, 1H, N*H*), 7.76 (d, J = 8.5 Hz, 1H, Ar-*H*), 7.84 (d, J = 8.5 Hz, 1H, Ar-*H*), 8.48 (s, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): conformer I: δ 28.49 ($(CH_3)_3C$), 36.33 (S-CH_2), 53.23 (N-*C*H-CO), 83.63 ($(CH_3)_3C$), 123.26 (q, J = 273 Hz, CF_3), 123.83 (Ar-*C*H), 127.5 (q, J = 32 Hz, *C*-CF_3), 127.60, 130.17 (Ar-*C*H), 141.97, 146.23 (Ar-*C*), 157.18 (N-*C*O-O), 173.66 (*C*OOH); conformer II: δ 28.61 ($(CH_3)_3C$), 34.99 (S-CH_2), 52.80 (N-*C*H-CO), 81.58 ($(CH_3)_3C$), 123.26 (q, J = 273 Hz, CF_3), 123.80 (Ar-*C*H), 127.50 (q, J = 32 Hz, *C*-CF_3), 128.19, 130.20 (Ar-*C*H), 141.47, 146.46 (Ar-*C*), 155.81 (N-*C*O-O), 173.94 (*C*OOH); ESI-MS *m/z*: 311.0, 354.7, 410.5 [(M+H)$^+$], 821.5 [(2M+H)$^+$].

Anal. Calcd for $C_{15}H_{17}F_3N_2O_6S$: C, 43.90; H, 4.18; N, 6.83. Found C, 44.02; H, 4.49; N, 6.47

(R)-S-(4-Trifluoromethyl-2-nitrophenyl)-N-(*tert*-butyloxycarbonyl)cysteine [(R)-3c] prepared from (R)-N-(*tert*-butyloxycarbonyl)cysteine (R)-**1** (1.99 g, 9.0 mmol) and 4-fluoro-3-nitrobenzotrifluoride (**2c**) (1.88 g, 9.0 mmol). Obtained as a yellow solid (3.40 g, 92%), mp. 81-82°; $[\alpha]_D^{20}$ = + 57 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

Anal. Calcd for $C_{15}H_{17}F_3N_2O_6S$: C, 43.90; H, 4.18; N, 6.83. Found C, 43.98; H, 4.39; N, 6.54

(S or R)-S-(2-Aminoaryl)-N-(*tert*-butyloxycarbonyl)cysteine [(4a-c)]. General Procedure.- To a

solution of compound (*S*)-**3 or** (*R*)-**3** (8.80 mmol) and ammonium chloride (0.96 g, 17.60 mmol, 2 equiv) in 120 mL of methanol were added 10 equivalents of zinc dust (11.37 g, 175.0 mmol). After stirring at room temperature for two hours, the mixture was heated at 75° for two more hours. The reaction mixture was then directly filtered through celite and the celite was washed with boiling methanol (2 x 100 mL). The combined filtrates were partially concentrated under vacuum (50 mL) and the residue was allowed to stand overnight at room temperature. Solid salts were eliminated by filtration, then CH_2Cl_2 (100 mL) and water (100 mL) were added to the filtrate. The resulting organic phase was washed with water (3 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the expected compound (*S*)-**4** or (*R*)-**4** that was used without further purification in the following step.

(S)-S-(2-Aminophenyl)-N-(*tert*-butyloxycarbonyl)cysteine [(S)-4a] prepared from compound (*S*)-**3a** (3.01 g, 8.80 mmol). Obtained as an off-white solid (2.75 g, 100%) after silica gel chromatography (CH_2Cl_2-CH_3OH, 9:1) Rf = 0.34; mp. 65-66°; $[\alpha]_D^{20}$ = + 43 (c 1.0, CH_3OH); HPLC: t_R = 6.0 min; ^1H NMR ($CDCl_3$): δ 1.26 (s, 9H, ($(CH_3)_3C$), 3.06 (m(br), 1H, S-*H*CH), 3.14 (m(br),1H, S-*H*CH), 4.28 (m(br), 1H, NH-C*H*-CO), 5.46 (br, 2H, NH_2), 5.79 (br, 1H, N*H*), 6.60 (t, $J_1 = J_2$ = 7.4 Hz, 1H, Ar-*H*), 6.66 (d, J = 7.4 Hz, 1H, Ar-*H*), 7.01 (t, $J_1 = J_2$ = 7.4 Hz, 1H, Ar-*H*), 7.31 (d, J = 7.4 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 28.70 ($(CH_3)_3C$), 38.28 (S-CH_2), 55.18 (N-*C*H-CO), 80.46 ($(CH_3)_3C$), 116.57 (Ar-*C*H), 118.65 (Ar-*C*), 120.13, 130.50, 136.89 (Ar-*C*H), 147.86 (Ar-*C*), 156.12 (N-*C*O-O), 176.55 (*C*OOH); ESI-MS *m/z*: 212.8, 256.8, 312.9 [(M+H)$^+$], 621.3 [(2M+H)$^+$].

(R)-S-(2-Aminophenyl)-N-(*tert*-butyloxycarbonyl)cysteine [(R)-4a] prepared from compound (R)-**3a** (3.01 g, 8.80 mmol). Obtained as an off-white solid (2.75 g, 100%) after silica gel chromatography (CH_2Cl_2-CH_3OH, 9:1) Rf = 0.34; mp. 62-64°; $[\alpha]_D^{20}$ = -40 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

(S)-S-(5-Methyl-2-aminophenyl)-N-(*tert*-butyloxycarbonyl)cysteine [(S)-4b] prepared from compound (*S*)-**3b** (3.13 g, 8.80 mmol). Obtained as an off-white solid (2.87 g, 100%) after silica gel chromatography (CH_2Cl_2-CH_3OH, 9:1) Rf = 0.30; mp. 105-107°; $[\alpha]_D^{20}$ = + 28 (c 1.0, CH_3OH); HPLC: t_R = 6.2 min; ^1H NMR (DMSO-d_6): δ 1.44 (s, 9H, ($(CH_3)_3C$), 2.18 (s, 3H, CH_3), 2.95 (dd, J = 9.3 Hz and 12.8 Hz, 1H, S-*H*CH), 3.13 (dd, J = 3.8 Hz and 12.8 Hz, 1H, S-*H*CH), 4.00 (m, 1H, NH-C*H*-CO), 5.19 (s, 2H, NH_2), 6.73 (d, J = 8.4 Hz, 1H, N*H*), 6.67 (d, J = 8.1 Hz, 1H, Ar-*H*), 6.90 (d, J = 8.1 Hz, 1H, Ar-*H*), 7.14 (s, 1H, Ar-*H*); ^{13}C NMR (DMSO-d_6): δ 20.74 (CH_3), 29.09 ($(CH_3)_3C$), 38.34 (S-CH_2), 55.33 (N-*C*H-CO), 78.50 ($(CH_3)_3C$), 115.28 (Ar-*C*H), 116.73 (Ar-*C*), 125.69 (Ar-*C*), 130.90, 136.51 (Ar-*C*H), 148.01 (Ar-*C*), 156.04 (N-*C*O-O), 176.12 (*C*OOH); ESI-MS *m/z*: 226.7, 270.7, 327.1 [(M+H)$^+$].

(R)-S-(5-Methyl-2-aminophenyl)-N-(*tert*-butyloxycarbonyl)cysteine [(R)-4b] prepared from compound (R)-**3b** (3.13 g, 8.80 mmol). Obtained as an off-white solid (2.87 g, 100%) after silica gel chromatography (CH_2Cl_2-CH_3OH, 9:1) Rf = 0.30; mp. 106-107°; $[\alpha]_D^{20}$ = -29 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

(S)-S-(4-Trifluoromethyl-2-aminophenyl)-N-(*tert*-butyloxycarbonyl)cysteine [(S)-4c] prepared from compound (*S*)-**3c** (3.61g, 8.80 mmol). Obtained as an off-white solid (3.35 g, 100%) after silica

gel chromatography (CH_2Cl_2-CH_3OH, 9:1) Rf = 0.31; mp. 135-136°; $[\alpha]_D^{20}$ = + 34 (c 1.0, CH_3OH); HPLC: t_R = 10.5 min; ^1H NMR (DMSO-d_6): δ 1.35 (s, 9H, ($(CH_3)_3C$), 3.01 (dd, J = 8.8 Hz and 13.2 Hz, 1H, S-*H*CH), 3.21 (dd, J = 3.8 Hz and 13.2Hz, 1H, S-*H*CH), 3.98 (m, 1H, NH-C*H*-CO), 5.74 (s, 2H, NH_2), 6.65 (d, J = 8.1 Hz, 1H, N*H*), 6.77 (d, J = 7.6 Hz, 1H, Ar-*H*), 6.99 (s, 1H, Ar-*H*) 7.42 (d, J = 7.6 Hz, 1H, Ar-*H*); ^{13}C NMR (DMSO-d_6): δ 29.00 ($(CH_3)_3C$), 37.40 (S-CH_2), 55.23 (N-*C*H-CO), 78.61 ($(CH_3)_3C$), 110.75, 112.83 (Ar-*C*H), 122.06 (Ar-*C*), 125.21 (q, J = 272 Hz, CF_3), 129.92 (q, J = 32 Hz, *C*-CF_3), 135.28 (Ar-*C*H), 150.12 (Ar-*C*), 159.94 (N-*C*O-O), 175.90 (*C*OOH); ESI-MS *m/z*: 280.8, 324.8, 380.7 [(M+H)$^+$].

(R)-S-(4-Trifluoromethyl-2-aminophenyl)-N-(*tert*-butyloxycarbonyl)cysteine [(R)-4c] prepared from compound (R)-**3c** (3.61g, 8.80 mmol). Obtained as an off-white solid (3.35 g, 100%) after silica gel chromatography (CH_2Cl_2-CH_3OH, 9:1) Rf = 0.31; mp. 135-137°; $[\alpha]_D^{20}$ = -31 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

(S or R)-3-(*tert*-Butyloxycarbonylamino)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (5a-c). General Procedure.- To a solution of compound (*S*)-**4** or (*R*)-**4** (8.80 mmol) in DMF (60 mL) were added BOP (3.89 g, 8.8 mmol) and $NaHCO_3$ (3.69 g, 44.0 mmol, 5 equiv). The reaction mixture was stirred overnight at room temperature. The DMF was evaporated under vacuum and the solid residue was dissolved in 100 mL of CH_2Cl_2 . The CH_2Cl_2 phase was washed with 1N HCl solution (2 x 100 mL) and with a saturated sodium bicarbonate solution (2 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford compound (*S*)-**5** or (*R*)-**5** which can be directly used in the following step.

(S)-3-(*tert*-Butyloxycarbonylamino)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one [(S)-5a] prepared from compound (*S*)-**4a** (2.75 g, 8.80 mmol). Obtained as a white solid (1.94 g, 75%) after silica gel chromatography (CH_2Cl_2-diethyl ether 8:2) Rf = 0.65; mp. 175-176°; $[\alpha]_D^{20}$ = + 274 (c 1.0, CH_3OH); HPLC: t_R = 8.7 min; ^1H NMR ($CDCl_3$): δ 1.33 (s, 9H, ($(CH_3)_3C$), 2.28 (t, $J_1 = J_2$ = 11.4 Hz, 1H, S-*H*CH), 3.75 (dd, J = 6.6 Hz and 11.4 Hz, 1H, S-*H*CH), 4.41 (m, 1H, NH-C*H*-CO), 5.61 (d, J = 7.8 Hz, 1H, N*H*Boc), 7.06 (d, J = 6.8 Hz, 1H, Ar-*H*), 7.10 (t, $J_1 = J_2$ = 6.8 Hz, 1H, Ar-*H*), 7.28 (t, $J_1 = J_2$ = 6.8 Hz, 1H, Ar-*H*), 7.53 (d, J = 6.8 Hz, 1H, Ar-*H*), 8.45 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 28.71 ($(CH_3)_3C$), 39.66 (S-CH_2), 50.80 (N-*C*H-CO), 80.60 ($(CH_3)_3C$), 124.17 (Ar-*C*H), 127.14 (Ar-*C*), 127.65, 130.49, 135.79 (Ar-*C*H), 140.44 (Ar-*C*), 155.02 (N-*C*O-O), 172.88 (*C*ONH); ESI-MS *m/z*: 195.1, 238.9, 295.0 [(M+H)$^+$], 611.1 [(2M+Na)$^+$].

Anal. Calcd for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52. Found C, 57.12; H, 6.21; N, 9.58

(R)-3-(*tert*-Butyloxycarbonylamino)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one [(R)-5a] prepared from compound (R)-**4a** (2.75 g, 8.80 mmol). Obtained as a white solid (1.81 g; 70%) after silica gel chromatography (CH_2Cl_2-diethyl ether 8:2) Rf = 0.65; mp. 174-176°; $[\alpha]_D^{20}$ = -270 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

Anal. Calcd for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52. Found C, 57.15; H, 6.20; N, 9.60

(S)-3-(*tert*-Butyloxycarbonylamino)-2,3-dihydro-8-methyl-1,5-benzothiazepin-4(5H)-one [(S)-5b] prepared from compound (S)-**4b** (2.87 g, 8.80 mmol). Obtained as a white solid (2.03 g, 78%) after silica gel chromatography (CH_2Cl_2-diethyl ether 8:2) Rf = 0.70; mp. 104-106°; $[\alpha]_D^{20}$ = + 219 (c 1.0,

CH_3OH); HPLC: t_R = 10.1 min; ^1H NMR ($CDCl_3$): δ 1.33 (s, 9H, ($(CH_3)_3C$), 2.24 (s, 3H, CH_3-Ar-C.), 2.85 (t, $J_1 = J_2$ = 11.2 Hz, 1H, S-*H*CH), 3.72 (dd, J = 6.6 Hz and 11.2 Hz, 1H, S-*H*CH), 4.38 (m, 1H, NH-C*H*-CO), 5.61 (d, J = 7.7 Hz, 1H, N*H*Boc), 6.93 (d, J = 8.0 Hz, 1H, Ar-*H*), 7.05 (d, J = 8.0 Hz, 1H, Ar-*H*), 7.33 (s, 1H, Ar-*H*), 8.27 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 21.13 (CH_3-Ar-C), 28.70 ($(CH_3)_3C$), 39.47 (S-CH_2), 50.74 (N-*C*H-CO), 80.52 ($(CH_3)_3C$), 124.03 (Ar-*C*H), 126.83 (Ar-*C*), 131.05 (Ar-*C*H and Ar-*C*), 136.14 (Ar-*C*), 137.64 (Ar-*C*H), 155.02 (N-*C*O-O), 172.84 (*C*ONH); ESI-MS *m/z*: 209.0, 252.8, 309.2 [$(M+H)^+$], 639.4 [$(2M+Na)^+$].

Anal. Calcd for $C_{15}H_{20}N_2O_3S$: C, 58.42; H, 6.54; N, 9.08. Found C, 57.95; H, 6.70; N, 8.88

(R)-3-(*tert*-Butyloxycarbonylamino)-2,3-dihydro-8-methyl-1,5-benzothiazepin-4(5H)-one [(R)-5b] prepared from compound (R)-**4b** (2.87 g, 8.80 mmol). Obtained as a white solid (2.06 g, 79%) after silica gel chromatography (CH_2Cl_2-diethyl ether 8:2) Rf = 0.70; mp. 103-105°; $[\alpha]_D^{20}$ = -215 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

Anal. Calcd for $C_{15}H_{20}N_2O_3S$: C, 58.42; H, 6.54; N, 9.08. Found C, 58.15; H, 6.66; N, 8.92

(S)-3-(*tert*-Butyloxycarbonylamino)-2,3-dihydro-7-trifluoromethyl-1,5-benzothiazepin-4 (5H)-one [(S)-5c] prepared from compound (*S*)-**4c** (3.35 g, 8.80 mmol). Obtained as a white solid (2.23 g, 70%) after silica gel chromatography (CH_2Cl_2-diethyl ether 8:2) Rf = 0.74; mp. 234-235°; $[\alpha]_D^{20}$ = + 195 (c 1.0, CH_3OH); HPLC: t_R = 11.4 min; ^1H NMR ($CDCl_3$): δ 1.34 (s, 9H, ($(CH_3)_3C$), 2.95 (t, $J_1 = J_2$ = 11.2 Hz, 1H, S-*H*CH), 3.77 (dd, J = 6.6 Hz and 11.2 Hz, 1H, S-*H*CH), 4.41 (m, 1H, NH-C*H*-CO), 5.50 (d, J = 7.7 Hz, 1H, N*H*Boc), 7.19 (s, 1H, Ar-*H*), 7.37 (d, J = 8.0 Hz, 1H, Ar-*H*), 7.68 (d, J = 8.0 Hz, 1H, Ar-*H*), 8.47 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 28.66 ($(CH_3)_3C$), 39.47 (S-CH_2), 50.69 (N-*C*H-CO), 80.94 ($(CH_3)_3C$), 120.98 (Ar-*C*H), 123.64 (q, J = 273 Hz, CF_3), 123.99 (Ar-*C*H), 131.89 (Ar-*C*), 132.65 (q, J = 33 Hz, *C*-CF_3), 136.26 (Ar-*C*H), 140.92 (Ar-*C*), 155.00 (N-*C*O-O), 172.57 (*C*ONH); ESI-MS *m/z*: 262.8, 307.0, 363.1 [$(M+H)^+$], 725.3 [$(2M+H)^+$], 747.3 [$(2M+Na)^+$].

Anal. Calcd for $C_{15}H_{17}F_3N_2O_3S$: C, 49.72; H, 4.73; N, 7.73. Found C, 49.58; H, 4.67; N.7.73

(R)-3-(*tert*-Butyloxycarbonylamino)-2,3-dihydro-7-trifluoromethyl-1,5-benzothiazepin-4(5H)-one [(R)-5c] prepared from compound (R)-**4c** (3.35 g, 8.80 mmol). Obtained as a white solid (2.23 g, 70%) after silica gel chromatography (CH_2Cl_2-diethyl ether 8:2) Rf = 0.74; mp. 234-235°; $[\alpha]_D^{20}$ = -198 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

Anal. Calcd for $C_{15}H_{17}F_3N_2O_3S$: C, 49.72; H, 4.73; N, 7.73. Found C, 49.65; H, 4.63; N.7.67

(S or R)-3-(*tert*-Butyloxycarbonylamino)-5-(carboethoxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one [(6a-c)]. General Procedure.- To a mixture of compound (*S*)-**5** or (*R*)-**5** (6.0 mmol), potassium hydroxide (0.44 g, 7.8 mmol, 1.3 eq), tetrabutylammonium iodide (0.22 g, 0.6 mmol, 0.1 eq) in 30 mL of THF at 0° was added dropwise ethyl bromoacetate (1.0 mL, 9.0 mmol, 1.5 eq). The reaction mixture was stirred at the same temperature for 4 h and then stirred overnight at room temperature. THF was evaporated and the residue was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous phase was extracted again with ethyl acetate (2 x 100 mL) and the combined organic extracts were dried over Na_2SO_4. After concentration *in vacuo* the oily residue was purified by column chromatography on silica gel (hexane-AcOEt 7:3) to afford compound (*S*)-**6** or (*R*)-**6**.

(S)-3-(*tert*-Butyloxycarbonylamino)-5-(carboethoxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one [(S)-6a] prepared from compound (S)-**5a** (1.76 g, 6.0 mmol). Obtained as an oil (1.71g, 75%); $[\alpha]_D^{20}$ = + 223 (c 1.0, CH_3OH); HPLC: t_R = 10.9 min; ^1H NMR ($CDCl_3$): δ 1.22 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.31 (s, 9H, $((CH_3)_3C)$, 2.78 (t, $J_1 = J_2$ = 11.2 Hz, 1H, S-*H*CH), 3.70 (dd, J = 6.6 Hz and 11.2 Hz, 1H, S-*H*CH), 4.05 (d, J = 17.2 Hz, 1H, N-*H*CH), 4.17 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.39 (m, 1H, NH-C*H*-CO), 4.75 (d, J = 17.2 Hz, 1H, N-*H*CH), 5.51 (d, J = 7.5 Hz, 1H, N*H*Boc), 7.16 (t, $J_1 = J_2$ = 7.5 Hz, 1H, *H*-arom.), 7.26 (d, J = 7.5 Hz, 1H, Ar-*H*), 7.28 (t, $J_1 = J_2$ = 7.5 Hz, 1H, Ar-*H*), 7.56 (d, J = 7.5 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 15.38 (OCH_2CH_3), 28.86 ($((CH_3)_3C)$), 39.13 (S-CH_2), 51.12 (N-CH-CO), 51.77 (N-CH_2), 62.02 (OCH_2CH_3), 80.43 ($((CH_3)_3C)$), 124.64 (A*C*H), 128.00 (*C*-arom.), 128.32, 130.99, 136.03 (Ar-*C*H), 145.61 (Ar-*C*), 154.78 (N-*C*O-O), 169.09 ($COOCH_2CH_3$), 171.30 (*C*ONH); ESI-MS *m/z*: 280.8, 324.8, 380.9 [(M+H)$^+$], 761.6 [(2M+H)$^+$].

Anal. Calcd for $C_{18}H_{24}N_2O_5S$: C, 56.82; H, 6.36; N, 7.36. Found C, 56.18; H, 6.38; N, 7.05

(R)-3-(*tert*-Butyloxycarbonylamino)-5-(ethoxycarbonylmethyl)-2,3-dihydro-1,5-benzo-thiazepin-4(5H)-one [(R)-6a] prepared from compound (R)-**5a** (1.76 g, 6.0 mmol). Obtained as an oil (1.75g, 77%); $[\alpha]_D^{20}$ = -220 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

Anal. Calcd for $C_{18}H_{24}N_2O_5S$: C, 56.82; H, 6.36; N, 7.36. Found C, 56.35; H, 6.30; N, 7.08.

(S)-3-(*tert*-Butyloxycarbonylamino)-5-(ethoxycarbonylmethyl)-2,3-dihydro-8-methyl-1,5-benzothiazepin-4(5H)-one [(S)-6b] prepared from compound (S)-**5b** (1.85 g, 6.0 mmol). Obtained as an off-white solid (1.65 g, 70%), mp. 109-110°; $[\alpha]_D^{20}$ = + 181 (c 1.0, CH_3OH); HPLC: t_R = 11.8 min; ^1H NMR ($CDCl_3$): δ 1.22 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.32 (s, 9H, $((CH_3)_3C)$, 2.26 (s, 3H, CH_3-C-arom.), 2.76 (t, $J_1 = J_2$ = 11.1 Hz, 1H, S-*H*CH), 3.68 (dd, J = 6.7 Hz and 11.1 Hz, 1H, S-*H*CH), 4.03 (d, J = 17.2 Hz, 1H, N-*H*CH), 4.18 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.38 (m, 1H, NH-C*H*-CO), 4.73 (d, J = 17.2 Hz, 1H, N-*H*CH), 5.50 (d, J = 7.5 Hz, 1H, N*H*Boc), 6.98 (m, 2H, Ar-*H*), 7.36 (s, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 14.57 (OCH_2CH_3), 21.17 (CH_3-Ar-C), 28.70 ($((CH_3)_3C)$), 39.05 (S-CH_2), 51.11 (N-*C*H-CO), 51.71 (N-CH_2), 62.01 (OCH_2CH_3), 80.42 ($((CH_3)_3C)$), 124.41 (Ar-*C*H), 127.56 (Ar-*C*), 131.58, 136.49 (Ar-*C*H), 138.54, 149.90 (Ar-*C*), 154.80 (N-*C*O-O), 169.20 ($COOCH_2CH_3$), 171.36 (*C*ONH); ESI-MS *m/z*: 295.1, 338.9, 395.2 [(M+H)$^+$], 417.2 [(M+Na)$^+$], 789.4 [(2M+H)$^+$], 811.3 [(2M+Na)$^+$].

Anal. Calcd for $C_{19}H_{26}N_2O_5S$: C, 57.85; H, 6.64; N, 7.10. Found C, 57.88; H, 6.70; N, 6.99

(R)-3-(*tert*-Butyloxycarbonylamino)-5-(ethoxycarbonylmethyl)-2,3-dihydro-8-methyl-1,5-benzothiazepin-4(5H)-one [(R)-6b] prepared from compound (R)-**5b** (1.85 g, 6.0 mmol). Obtained as an off-white solid (1.53 g, 65%), mp. 110-111°; $[\alpha]_D^{20}$ = -182 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

Anal. Calcd for $C_{19}H_{26}N_2O_5S$: C, 57.85; H, 6.64; N, 7.10. Found C, 57.91; H, 6.69; N, 6.96

(S)-3-(*tert*-Butyloxycarbonylamino)-5-(carboethoxymethyl)-2,3-dihydro-7-trifluorome-thyl-1,5-benzothiazepin-4(5H)-one [(S)-6c] prepared from compound (*S*)-**5c** (2.17 g, 6.0 mmol). Obtained as an oil (1.93 g, 70%); $[\alpha]_D^{20}$ = + 164 (c 1.0, CH_3OH); HPLC: t_R = 11.9 min; ^1H NMR ($CDCl_3$): δ 1.24 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.32 (s, 9H, $((CH_3)_3C)$, 2.85 (t, $J_1 = J_2$ = 11.1 Hz, 1H, S-*H*CH), 3.72

(dd, J = 6.6 Hz and 11.1 Hz, 1H, S-*H*CH), 4.08 (d, J = 17.3 Hz, 1H, N-*H*CH), 4.20 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.38 (m, 1H, NH-C*H*-CO), 4.74 (d, J = 17.3 Hz, 1H, N-*H*CH), 5.50 (d, J = 7.5 Hz, 1H, N*H*Boc), 7.42 (d, J = 7.8 Hz, 1H, Ar-*H*), 7.52 (s, 1H, Ar-*H*), 7.70 (d, J = 8.0 Hz, 1H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ 14.53 (OCH_2CH_3), 28.68 ($(CH_3)_3C$), 38.94 (S-CH_2), 50.97 (N-CH-CO), 51.87 (N-CH_2), 62.31 (OCH_2CH_3), 80.78 ($(CH_3)_3C$), 121.60 (Ar-CH), 123.55 (q, J = 273 Hz, CF_3), 124.93 (Ar-CH), 133.05 (q, J = 33 Hz, C-CF_3), 136.63, 146.14 (Ar-C), 154.79 (N-CO-O), 168.77 ($COOCH_2CH_3$), 171.04 (CONH); ESI-MS *m/z*: 349.0, 392.9, 449.5 [$(M+H)^+$], 919.5 [$(2M+Na)^+$].

Anal. Calcd for $C_{19}H_{23}F_3N_2O_5S$: C, 50.89; H, 5.17; N, 6.25. Found C, 50.31; H, 5.29; N, 6.59

(R)-3-(*tert*-Butyloxycarbonylamino)-5-(carboethoxymethyl)-2,3-dihydro-7-trifluorome-thyl-1,5-benzothiazepin-4(5H)-one [(R)-6c] prepared from compound (R)-**5c** (2.17 g, 6.0 mmol). Obtained as an oil (1.87 g, 68%); $[\alpha]_D^{20}$ = -168 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

Anal. Calcd for $C_{19}H_{23}F_3N_2O_5S$: C, 50.89; H, 5.17; N, 6.25. Found C, 50.43; H, 5.21; N, 6.47

(S)-3-(*tert*-Butyloxycarbonylamino)-5-(carboxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (7a-c). General Procedure.- A mixture of (*S*)-**6** or (*R*)-**6** (5.0 mmol) in ethanol (20 mL) and a solution of 1N aqueous NaOH (6.0 mL, 6.0 mmol, 1.2 eq) was stirred at room temperature for 2 hours. The ethanol was then evaporated and the residue was diluted with water (100 mL). This aqueous phase was washed with ethyl acetate (100 mL), acidified with 1N HCl solution (pH 2) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were then dried over Na_2SO_4 and concentrated *in vacuo* to afford the expected compound (*S*)-**7** or (*R*)-**7**.

(S)-3-(*tert*-Butyloxycarbonylamino)-5-(carboxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one [(S)-7a] prepared from compound (*S*)-**6a** (1.90 g, 5.0 mmol). Obtained as a white solid (1.67 g, 95%), mp. 111-112°; $[\alpha]_D^{20}$ = + 230 (c 1.0, CH_3OH); HPLC: t_R = 8.6 min; ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9H, $((CH_3)_3C)$, 2.80 (t, $J_1 = J_2$ = 11.1 Hz, 1H, S-*H*CH), 3.70 (dd, J = 6.8 Hz and 11.1 Hz, 1H, S-*H*CH), 4.05 (d, J = 17.6 Hz, 1H, N-*H*CH), 4.39 (m, 1H, NH-C*H*-CO), 4.83 (d, J = 17.6 Hz, 1H, N-*H*CH), 5.62 (d, J = 7.8 Hz, 1H, N*H*Boc), 7.18 (t, $J_1 = J_2$ = 7.3 Hz, 1H, Ar-*H*), 7.30 (d, J = 7.3 Hz, 1H, Ar-*H*), 7.36 (t, $J_1 = J_2$ = 7.3 Hz, 1H, Ar-*H*), 7.56 (d, J = 7.3 Hz, 1H, Ar-*H*), 8.87 (br, 1H, CO_2H); ^{13}C NMR ($CDCl_3$): δ 28.70 ($(CH_3)_3C$), 39.06 (S-CH_2), 51.20 (N-CH-CO), 51.67 (N-CH_2), 80.67 ($(CH_3)_3C$), 124.75 (Ar-CH), 127.95 (Ar-C), 128.58, 131.20, 136.10 (Ar-CH), 145.46 (Ar-C), 154.95 (N-CO-O), 171.75 (CONH), 173.59 (CO_2H); ESI-MS *m/z*: 252.8, 296.8, 353.0 [$(M+H)^+$], 765.2[$(2M+H)^+$].

Anal. Calcd for $C_{16}H_{20}N_2O_5S$: C, 54.53; H, 5.72; N, 7.95. Found C, 54.29; H, 5.99; N, 7.57

(R)-3-(*tert*-Butyloxycarbonylamino)-5-(carboxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one [(R)-7a] prepared from compound (R)-**6a** (1.90 g, 5.0 mmol). Obtained as a white solid (1.70 g, 97%), mp. 110-112°; $[\alpha]_D^{20}$ = – 229 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

Anal. Calcd for $C_{16}H_{20}N_2O_5S$: C, 54.53; H, 5.72; N, 7.95. Found C, 54.23; H, 5.90; N, 7.62

(S)-3-(*tert*-Butyloxycarbonylamino)-5-(carboxymethyl)-2,3-dihydro-8-methyl-1,5-benzo-

thiazepin-4(5H)-one [(S)-7b] prepared from compound (S)-**6b** (1.97 g, 5.0 mmol), Obtained as a white solid (1.75 g, 96%), mp. 119-120°; $[\alpha]_D^{20}$ = + 199 (c 1.0, CH_3OH); HPLC: t_R = 9.7 min; ^1H NMR ($CDCl_3$): δ 1.32 (s, 9H, $((CH_3)_3C)$, 2.26 (s, 3H, CH_3-C-arom.), 2.77 (t, $J_1 = J_2$ = 11.2 Hz, 1H, S-*H*CH), 3.65 (dd, J = 6.7 Hz and 11.2 Hz, 1H, S-*H*CH), 4.02 (d, J = 17.5 Hz, 1H, N-*H*CH), 4.38 (m, 1H, NH-C*H*-CO), 4.80 (d, J = 17.5 Hz, 1H, N-*H*CH), 5.62 (d, J = 7.7 Hz, 1H, N*H*Boc), 7.15 (m, 2H, Ar-*H*), 7.36 (s, 1H, Ar-*H*), 8.56 (br, 1H, CO_2H); ^{13}C NMR ($CDCl_3$): δ 21.19 (CH_3-Ar-C), 28.70 ($(CH_3)_3C$), 38.95 (S-CH_2), 51.17 (N-*C*H-CO), 51.63 (N-CH_2), 80.61 ($(CH_3)_3C$), 124.50 (Ar-*C*H), 127.48 (Ar-*C*), 131.76, 136.50 (Ar-*C*H), 138.80, 142.74 (Ar-*C*), 154.95 (N-*C*O-O), 171.83 (*C*ONH), 173.64 (CO_2H); ESI-MS *m/z*: 311.1, 367.1 [$(M+H)^+$], 733.3[$(2M+H)^+$].

Anal. Calcd for $C_{17}H_{22}N_2O_5S$: C, 55.72; H, 6.05; N, 7.64. Found C, 55.63; H, 6.33; N, 7.17

(R)-3-(*tert*-Butyloxycarbonylamino)-5-(carboxymethyl)-2,3-dihydro-8-methyl-1,5-ben-zothiazepin-4(5H)-one [(R)-7b] prepared from compound (R)-**6b** (1.97 g, 5.0 mmol), Obtained as a white solid (1.71 g, 93%), mp. 120-121°; $[\alpha]_D^{20}$ = -203 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

Anal. Calcd for $C_{17}H_{22}N_2O_5S$: C, 55.72; H, 6.05; N, 7.64. Found C, 55.55; H, 6.27; N, 7.28

(S)-3-(*tert*-Butyloxycarbonylamino)-5-(carboxymethyl)-2,3-dihydro-7-trifluoromethyl-1,5-benzothiazepin-4(5H)-one [(S)-7c] prepared from compound (*S*)-**6c** (2.24 g, 5.0 mmol). Obtained as a white solid (1.68 g, 80%), mp. 126-127°; $[\alpha]_D^{20}$ = + 200 (c 1.0, CH_3OH); HPLC: t_R = 10.3 min; ^1H NMR ($CDCl_3$): δ 1.32 (s, 9H, $((CH_3)_3C)$, 2.87 (t, $J_1 = J_2$ = 11.2 Hz, 1H, S-*H*CH), 3.71 (dd, J = 6.6 Hz and 11.2 Hz, 1H, S-*H*CH), 4.10 (d, J = 17.6 Hz, 1H, N-*H*CH), 4.38 (m, 1H, NH-C*H*-CO), 4.79 (d, J = 17.6 Hz, 1H, N-*H*CH), 5.61 (d, J = 7.7 Hz, 1H, N*H*Boc), 7.44 (d, J = 8.0 Hz, 1H, Ar-*H*), 7.54 (s, 1H, Ar-*H*), 7.71 (d, J = 8.0 Hz, 1H, Ar-*H*), 9.64 (br, 1H, CO_2H); ^{13}C NMR ($CDCl_3$): δ 28.66 ($(CH_3)_3C$), 38.85 (S-CH_2), 51.03 (N-*C*H-CO), 51.78 (N-CH_2), 81.00 ($(CH_3)_3C$), 121.60 (Ar-*C*H), 123.51 (q, J = 273 Hz, CF_3), 125.25 (Ar-*C*H), 132.84 (Ar-*C*), 133.34 (q, J = 33 Hz, *C*-CF_3), 136.72 (Ar-*C*H), 145.96 (Ar-*C*), 154.95 (N-*C*O-O), 171.46 (*C*ONH), 173.57 (CO_2H); ESI-MS *m/z*: 364.9, 421.0[$(M+H)^+$], 841.5 [$(2M+H)^+$].

Anal. Calcd for $C_{17}H_{19}F_3N_2O_5S$: C 48.57, H 4.56, N 6.66. Found C, 47.95; H, 4.59; N 6.49

(R)-3-(*tert*-Butyloxycarbonylamino)-5-(carboxymethyl)-2,3-dihydro-7-trifluoromethyl-1,5-benzothiazepin-4(5H)-one [(R)-7c] prepared from compound (R)-**6c** (2.24 g, 5.0 mmol). Obtained as a white solid (1.72 g, 82%), mp. 126-128°; $[\alpha]_D^{20}$ = -202 (c 1.0, CH_3OH); other analytical data are identical to those of the S enantiomer.

Anal. Calcd for $C_{17}H_{19}F_3N_2O_5S$: C 48.57, H 4.56, N 6.66. Found C, 47.88; H, 4.61; N 6.45

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10. We have only described the synthesis of the D-benzothiazepine. The preparation of the L-analogues followed the same synthetic route starting from Boc-L-Cys-OH.

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13. This is the overall yield of H-LBT-OMe. We obtained the same total yield in our synthesis.