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SHORT COMMUNICATIONS

Synthesis of *meta*-Carboranyl-(*S*)-homocysteine Sulfoxide

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Abstract—New (*S*)-homocysteine derivatives containing a *meta*-carborane fragment were synthesized. *m*-Carboranyl-(*S*)-homocysteine sulfoxide was obtained as a mixture of diastereoisomers. The reduction of the side-chain carboxy group of *N*-*tert*-butoxycarbonyl-(*S*)-aspartic acid α-*tert*-butyl ester with sodium tetrahydridoborate was not accompanied by racemization.

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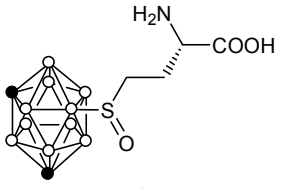
Amino acid derivatives containing polyhedral dicarba-*closo*-dodecaborane (carborane) fragments in the side chain and unsubstituted functional groups in the α-position are promising agents for boron neutron capture therapy (BNCT) of cancer. Amino acid derivatives are efficiently transported to tumor cells [1–4], and boron-containing amino acid and peptide derivatives are capable of selectively accumulating in tumors [5–8].

We previously synthesized a series of lysine, glutamine, and asparagine derivatives containing an *o*-carborane fragment in the side chain and free carboxy and amino groups in the α-position [9, 10]. In this work we were the first to synthesize *S*-(*m*-carboran-9-yl)-(*S*)-homocysteine sulfoxide [**1**, (2*S*)-2-amino-4-(1,7-dicarba-*closo*-dodecaboran-9-yl)sulfinylbutanoic acid] as a mixture of diastereoisomers.

Sulfur-substituted homocysteine and methionine derivatives are potent glutamine synthetase inhibitors [11, 12]. This enzyme is very important for the vital activity of *Mycobacterium tuberculosis*, so that it is the target of tuberculostatic agents [13, 14]. We believe that compound **1** could be used as a BNCT agent and also as a potential mycobacterial glutamine synthetase inhibitor.



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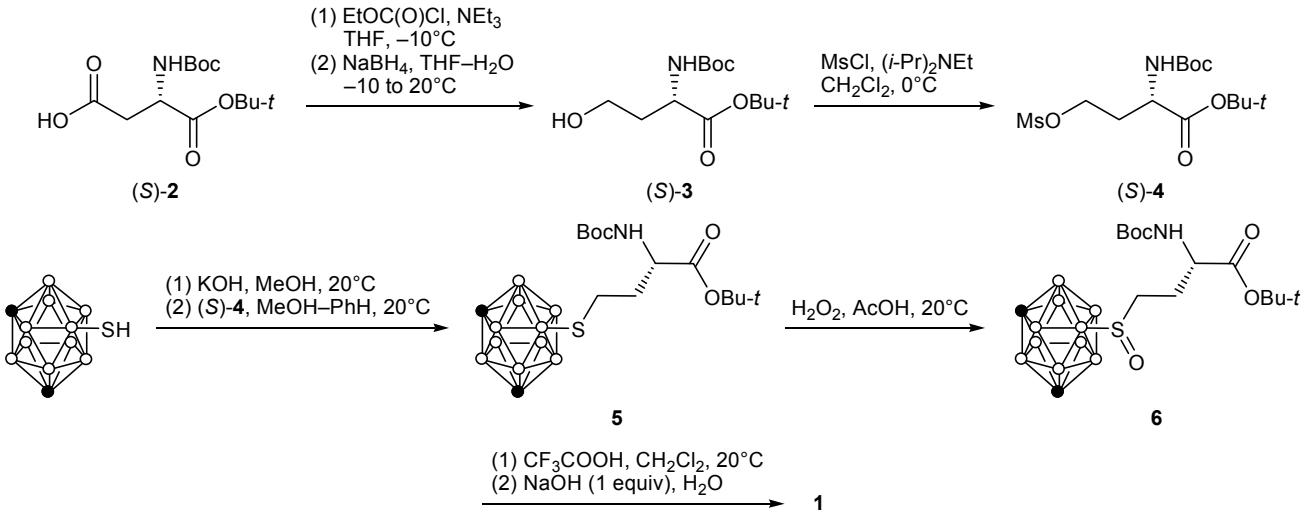
Hereinafter, light circles denote BH groups and boron atoms, and dark circles denote CH groups.

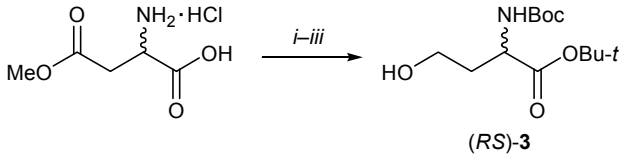
By analogy with the previously reported procedure [15], the reduction of *N*-Boc-(*S*)-aspartic acid α-*tert*-butyl ester (*S*)-**2** afforded Boc-(*S*)-homoserine *tert*-butyl ester (*S*)-**3** without loss of enantiomeric purity (Scheme 1). According to the HPLC data (chiral stationary phase), the *ee* value of (*S*)-**3** was 98% [in comparison to racemate (*RS*)-**3**]. Protected homoserine (*RS*)-**3** was prepared starting from racemic aspartic acid methyl ester through the same reaction sequence as in the synthesis of (*S*)-**3** [10, 15] (Scheme 2).

Sulfonylation of (*S*)-**3** and subsequent nucleophilic substitution gave *m*-carboranylhomocysteine derivative **5** in an overall yield of 47% (Scheme 1). Analogous approach to homocysteine derivatives was described in [16, 17]. By oxidation of **5** with hydrogen peroxide in acetic acid at 20°C we obtained sulfoxide **6**, and deprotection of the latter by the action of trifluoroacetic acid afforded *m*-carboranyl-(*S*)-homocysteine sulfoxide **1** which was isolated in a moderate yield after purification by preparative reversed-phase chromatography. Some signals in the NMR spectra of Boc-amino acid *tert*-butyl esters were doubled due to the presence of stable conformers. Compounds **1** and **6** possess an asymmetric sulfur atom, and they were iso-

Scheme 1.



Scheme 2.



Reagents and conditions: *i*: (1) *t*-BuOAc, $HClO_4$, 20°C; (2) Boc_2O, NEt_3, DMF, 20°C; *ii*: LiOH, THF–H_2O, 0–20°C; *iii*: (1) EtOCOCl, NEt_3, THF, –10°C; (2) $NaBH_4$, THF–H_2O, –10 to 20°C.

lated as mixtures of diastereoisomers distinguishable by NMR and HPLC.

***tert*-Butyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-hydroxybutanoate (*S*)-3.** A solution of 0.65 g (2.25 mmol) of *N*-Boc-(*S*)-aspartic acid α-*tert*-butyl ester [10] in 5 mL of THF was cooled to –10°C, 0.24 mL of ethyl chloroformate and 0.35 mL of triethylamine were added, and the mixture was stirred for 30 min at –10°C. The precipitate was filtered off, a solution of 0.18 g (4.73 mmol) of sodium tetrahydridoborate in 5 mL of water was added to the filtrate, and the mixture was stirred for 22 h at 20°C. The mixture was then acidified with 1 M aqueous HCl to pH 3 and extracted with ethyl acetate (3×10 mL). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate (2×15 mL) and brine (2×15 mL), dried over Na_2SO_4, and evaporated, and the residue was purified by flash chromatography using hexane–ethyl acetate (85:15 to 70:30) as eluent. Yield 0.46 g (70%), colorless oily material, $[\alpha]_D^{20} = -14.7°$ (c = 0.63, EtOH); published data: $[\alpha]_D^{25} = -39.9°$ (c = 1.0, EtOH) [18], –37.5° (c = 1, EtOH) [15]; *ee* 98%. HPLC (Chiralcel OD-H, hexane–*i*-PrOH–CF_3CO_2H, 10:1:0.02), τ = 8.4 min. The ^1H and ^{13}C NMR spectra of (*S*)-**3** were identical to those reported in [18].

***N*-*tert*-Butoxycarbonyl-(*RS*)-aspartic acid α-*tert*-butyl ester (*RS*)-2** was synthesized as described in [10] for (*S*)-**2** [10] from (*RS*)-aspartic acid β-methyl ester [19]. White powder, mp 111°C. The ^1H and ^{13}C NMR spectra were identical to those of (*S*)-**2** [10].

***tert*-Butyl (2*RS*)-2-(*tert*-butoxycarbonylamino)-4-hydroxybutanoate (*RS*)-3** was synthesized as described above for (*S*)-**3** from 0.32 g (1.11 mmol) of (*RS*)-**2**. Yield 0.21 g (70%), colorless oily material. HPLC (Chiralcel OD-H, hexane–*i*-PrOH–CF_3CO_2H, 10:1:0.02): $\tau_{(R)\text{-}3}$ = 7.3 min, $\tau_{(S)\text{-}3}$ = 8.4 min. The ^1H and ^{13}C NMR spectra were identical to those of (*S*)-**3**.

***tert*-Butyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-(methanesulfonyloxy)butanoate (*S*)-4.** A solution of 0.4 g (1.38 mmol) of (*S*)-**3** in 10 mL of methylene chloride was cooled to 0°C, 0.12 mL (1.53 mmol) of methanesulfonyl chloride and 0.72 mL (4.15 mmol) of ethyl(diisopropyl)amine were added, and the mixture was stirred for 2 h at 0°C. The mixture was washed with a 10% solution of citric acid (3×10 mL) and water (2×10 mL), the organic phase was dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography using hexane–ethyl acetate (6:4 to 1:1) as eluent. Yield 0.44 g (89%), white powder, mp 87–90°C, $[\alpha]_D^{20} = +12.0°$ (c = 0.51,

$CHCl_3$); published data [20]: mp 85–87°C, $[\alpha]_D^{20}$ = +11.6° (*c* = 1.03, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.45 s (9H, *t*-Bu), 1.48 s (9H, *t*-Bu), 2.00–2.10 m and 2.25–2.38 m (1H each, 3-H), 3.03 s (3H, $MeSO_2$), 4.25–4.36 m (2H, 4-H), 5.16 d (1H, NH, *J* = 6.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 27.94 (3C), 28.27 (3C), 32.21, 37.28, 50.90, 66.13, 80.11, 82.77, 155.35, 170.77. Found, %: C 47.72; H 7.83; N 4.12; S 9.31. $C_{14}H_{27}NO_7S$. Calculated, %: C 47.58; H 7.70; N 3.96; S 9.07.

***tert*-Butyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-[(1,7-dicarba-*closo*-dodecaboran-9-yl)sulfanyl]-butanoate (5).** 1,7-Dicarba-*closo*-dodecaborane-9-thiol, 0.243 g (1.38 mmol), was added to a solution of 0.079 g (1.38 mmol) of potassium hydroxide in 3 mL of methanol, and the mixture was stirred under argon until it became homogeneous. A solution of 0.400 g (1.1 mmol) of (*S*)-**4** in 3 mL of benzene was then added, and the mixture was stirred for 1.5 h at 20°C. Ethyl acetate, 20 mL, was added, and the mixture was washed with a 5% solution of $NaHCO_3$ (3×15 mL), water (15 mL), and brine (15 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography using hexane–ethyl acetate (90:10 to 80:20) as eluent. Yield 0.317 g (53%), colorless oily material, $[\alpha]_D^{20}$ = +17.0° (*c* = 0.49, $CHCl_3$). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (a mixture of conformers **A** and **B** at a ratio of 8:2): 1.36 s (1.8H, *t*-Bu, **B**), 1.38 s (7.2H, *t*-Bu, **A**), 1.39 s (7.2H, *t*-Bu, **A**), 1.41 s (1.8H, *t*-Bu, **B**), 1.76–1.92 m (2H, 3-H), 1.00–3.20 m (9H, BH), 3.30–3.39 m (2H, 4-H), 3.83–3.90 m (0.2H, 2-H, **B**), 3.88–3.94 m (0.8H, 2-H, **A**), 4.09 br.s (2H, CH, carborane), 6.80 d (0.2H, NH, **B**, *J* = 7.5 Hz), 7.15 d (0.8H, NH, **A**, *J* = 7.9 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 27.57 (3C), 28.12 (3C), 28.61, 32.66, 53.31, 55.38 (2C), 77.98, 80.25, 155.44, 171.38. Found, %: C 41.42; H 8.32; N 3.23. $C_{15}H_{35}B_{10}NO_4S$. Calculated, %: C 41.55; H 8.14; N 3.23.

***tert*-Butyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-[(1,7-dicarba-*closo*-dodecaboran-9-yl)sulfinyl]-butanoate (6**, mixture of diastereoisomers**).** Compound **5**, 0.300 g (0.69 mmol), was dissolved in 1.3 mL of acetic acid, 0.26 mL of 30% hydrogen peroxide was added, and the mixture was stirred for 30 min at 20°C. The mixture was treated with 10 mL of methylene chloride, the organic layer was separated, and the aqueous layer was adjusted to pH 8 by adding $NaHCO_3$ and extracted with methylene chloride (3×10 mL). The combined extracts were washed with a 5% solution of $NaHCO_3$ (3×15 mL) and water (2×15 mL), dried over Na_2SO_4, and evaporated, and the residue was purified by flash chromatography using benzene–ethyl acetate (9:1 to 7:3) as eluent. Yield 0.215 g (65%), colorless amorphous powder. HPLC (Chiralcel OD-H, hexane–*i*-PrOH, 40:1), τ_1 = 13.6 min, τ_2 = 16.0 min. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (a mixture of diastereoisomers **A** and **B** at a ratio of 85:15): 1.36 s (1.35H, *t*-Bu, **B**), 1.38 s (7.65H, *t*-Bu, **A**), 1.40 s (7.65H, *t*-Bu, **A**), 1.42 s (1.35H, *t*-Bu, **B**), 1.95–2.20 m (2H, 3-H), 1.50–3.20 m (9H, BH), 2.58–2.87 m (2H, 4-H), 3.93–4.03 m (1H, 2-H), 4.32 br.s (2H, CH, carborane), 6.95 br.s (0.15H, NH, **B**), 7.28–7.36 m (0.85H, NH, **A**). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm (a mixture of diastereoisomers **A** and **B**): 25.81 (**A**), 26.43 (**B**), 27.56 (3C, **A**, **B**), 28.09 (3C, **A**, **B**), 48.13 (**A**), 48.32 (**B**), 52.96 (**A**), 53.56 (**B**), 56.53 (2C, **A**, **B**), 78.12 (**A**), 78.15 (**B**), 80.57 (**A**, **B**), 155.39 (**A**), 155.41 (**B**), 170.84 (**A**), 170.89 (**B**). Mass spectrum: *m*/*z* 456.3396 $[M + Li]^+$. $C_{15}H_{35}{}^{10}B_2{}^{11}B_8LiNO_5S$. Calculated: *M* + Li 456.3394.

(2*S*)-2-Amino-4-[(1,7-dicarba-*closo*-dodecaboran-9-yl)sulfinyl]butanoic acid (1, mixture of diastereoisomers**).** Trifluoroacetic acid, 1.5 mL, was added to a solution of 0.195 g (0.42 mmol) of compound **6** in 1.5 mL of methylene chloride, and the mixture was stirred for 4 h at 20°C. The mixture was evaporated, the residue was dissolved in 2 mL of methanol, a 2 N solution of NaOH was added to pH 6–7, the resulting solution was evaporated, and the residue was purified first by flash chromatography using chloroform–methanol (9:1 to 7:3) as eluent and then by preparative HPLC. Yield 0.072 g (55%), colorless powder, mp 260°C (decomp.). ^{1}H NMR spectrum (D_2O+DCl), δ, ppm (a mixture of diastereoisomers **A** and **B**): 1.70–3.40 m (9H, BH), 2.02–2.10 m (0.5H, 3-H, **A**), 2.11–2.17 m (1H; 3-H, **A**; 3-H, **B**), 2.20–2.27 m (0.5H, 3-H, **B**), 2.76–2.82 m (0.5H, 4-H, **A**), 2.84–2.92 m (1H; 4-H, **A**; 4-H, **B**), 2.93–3.01 m (0.5H, 4-H, **B**), 3.29–3.36 m (1H, 2-H, **A**, **B**), 4.32 br.s (2H, CH, carborane), 7.74 br.s (3H, NH_2, COOH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm (**A**/**B**): 26.65 (**A**), 27.06 (**B**), 48.23 (**A**), 48.48 (**B**), 52.86 (**A**), 53.22 (**B**), 56.54 (2C, **A**, **B**), 168.88 (**A**), 169.05 (**B**). Found, %: C 24.60; H 6.38; N 4.57. $C_6H_{19}B_{10}NO_3S$. Calculated, %: C 24.56; H 6.53; N 4.77.

The ^{1}H and ^{13}C NMR spectra were recorded at 25°C on a Bruker Avance 500 spectrometer (500 and 125 MHz, respectively) using tetramethylsilane as internal standard. The melting points were measured on a Stuart SMP3 melting point apparatus (Barloworld Scientific, UK). The optical rotations were determined with a Perkin Elmer Model 341 polarimeter. The

elemental analyses were obtained on a Perkin Elmer 2400 II automated CHNS-O analyzer. The high-resolution mass spectrum was recorded on a Bruker maXis impact HD instrument (electrospray ionization, positive ion detection; nebulizer gas nitrogen, flow rate 4 L/min, nebulizer pressure 0.4 bar; capillary voltage 4.5 kV). HPLC analysis of compounds **3** and **6** was performed on a Shimadzu LC-20 Prominence instrument (Japan) using a Chiralcel OD-H column, 250× 4.6 mm, grain size 5 μm (Daicel, Japan); detection at λ 220 nm; eluent flow rate 1.0 mL/min. Compound **1** was purified by preparative HPLC on a Reprosil-Pur C18-AQ column, 250×20 mm, 10 μm (Dr. Maisch, Germany); detection at λ 210 nm; eluent acetonitrile–water, 9:1, flow rate 10 mL/min. Silica gel 60 (0.063–0.040 mm, Alfa Aesar, UK) was used for column flash chromatography.

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