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Synthesis of *ortho*-Carboranyl Derivatives of (*S*)-Asparagine and (*S*)-Glutamine

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Abstract—(*S*)-Asparagine and (*S*)-glutamine *ortho*-carboranyl derivatives with free amino and carboxy groups in the α-position were synthesized. By an example of N^{γ}-(1,2-dicarba-*closo*-dodecarboran-3-yl)-(*S*)-glutamine it was demonstrated that the developed synthetic approach carboranyl derivatives of amino acids allowed the preparation of optically pure isomers.

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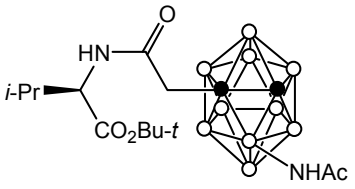
Dicarba-*closo*-dodecarboranes (carboranes) are molecules of icosahedral structure including ten boron atoms and two carbon atoms. Introduction of different substituents at carbon atoms or boron atoms opens a synthetic route to compounds of various structures [1, 2]. Carborane moieties are used as building blocks in designing the molecular devices, liquid crystals, and nanomaterials [3–6]. The introduction of carborane fragments in the structures of biomolecules [7–10], including natural amino acids [11–14], is an important way to novel bioactive compounds, as well as reagents for boron neutron capture therapy of cancer.

Derivatives of polyfunctional amino acids with free α-amino and α-carboxy groups are especially promising for creation of new pharmaceuticals (pharmaceutical agents) [15–18]. Compounds capable to self-organization into ordered nanostructures exhibiting piezoelectric properties were found among amino acids and their derivatives. Amide 1 obtained from [3-(acetylamino)-*o*-carboran-1-yl]acetic acid and natural amino acid valine has piezoelectric coefficient exceeding that of classic inorganic piezoelectrics [19].

We have obtained derivatives of (*S*)-asparagine **2** and (*S*)-glutamine **3** with a fragment of *o*-carborane and free α-amino acid groups, which allows using these compounds as analogs of α-amino acids (Scheme 1).

Biological and physical properties of chiral compounds significantly depend on stereoisomeric composition and optical purity. N^{γ}-Carboranylglutamine was previously obtained as salt of trifluoracetic acid [14], however the free amino acid was not isolated from salt and its enantiomeric purity was not determined.



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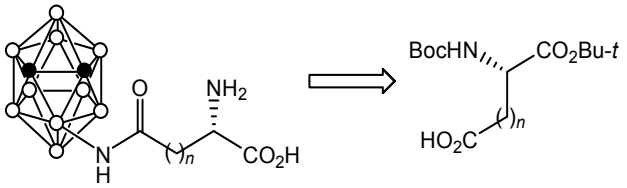
Hereinafter: ○ are BH groups and B atoms, ● are CH groups and C atom.

The most convenient precursors for *N*-carbonyl amino acids **2** and **3** are α-*tert*-butyl amino esters **4** and **5**. To obtain esters **4** and **5** with protected α-functional groups we carried out esterification of readily available monomethyl esters of (*S*)-aspartic acid (**6**) or (*S*)-

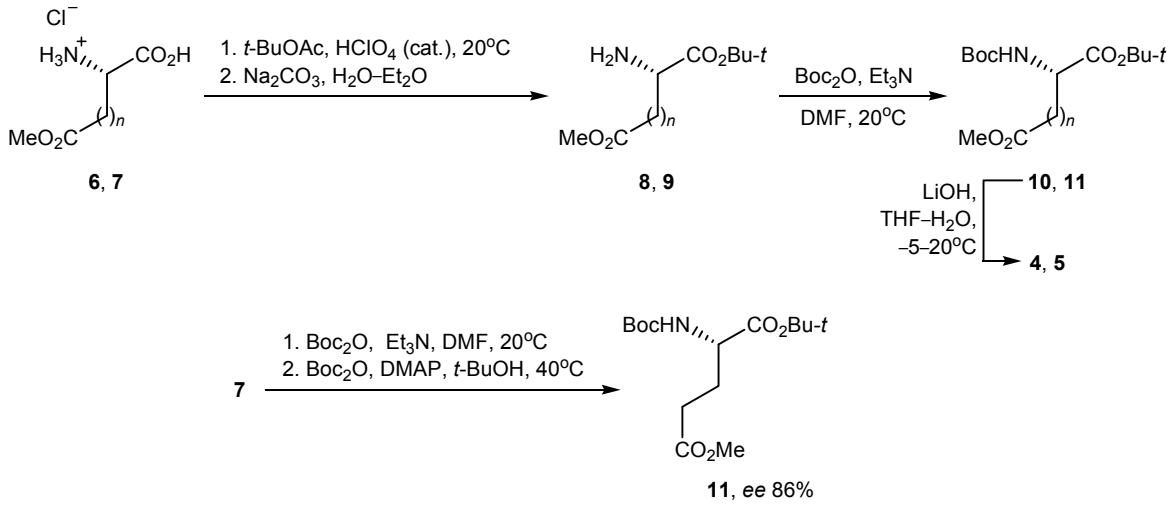
Scheme 1.



2, **3** **4**, **5**

n = 1 (**2**, **4**), 2 (**3**, **5**).

Scheme 2.



n = 1 (**6**, **8**, **10**), 2 (**7**, **9**, **11**).

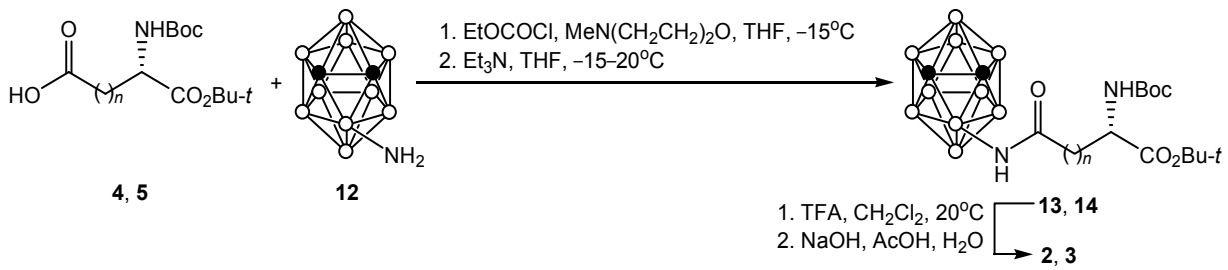
glutamic acid (**7**) followed by introduction of *N*-Boc groups with subsequent selective hydrolysis of methyl esters **10** and **11**. Amino diesters **8** and **9** were obtained from compounds **6** and **7** by treating with *tert*-butyl acetate in the presence of $HClO_4$. Compounds **8** and **9** are unstable in a free state, so in following transformations they were used directly after their isolation and purification. The introduction of Boc group into amino esters **8** and **9** and the hydrolysis of methyl esters **10** and **11** under mild alkaline conditions resulted in selectively protected amino acids **4** and **5** in 29 and 33% overall yield, respectively (Scheme 2).

Hardly available *tert*-butyl methyl *N*-Cbz-amino diesters were selected as the starting compounds in the published approach to the synthesis of compounds **4** and **5** [20]. Other synthetic routes to compounds **4** and **5** were also described; they distinguished by the nature of applied protecting groups and by the sequence of their introduction and removal [21–28]; the synthesis of compound **4** starting from protected puroglutamic acid was also described [29]. The comparison of values of specific rotation and melting points of compounds **4** and **5** and intermediate compounds **10** and **11** with the published data indicates that the synthesis of selectively protected amino acids **4** and **5** according to Scheme 2 was not accompanied by racemization.

An alternative sequence of protective groups introduction (first of Boc group followed by esterification with *tert*-butyl alcohol in the presence of DCC or Boc_2O/DMAP [27–31]) resulted in partial racemization of protected glutamic acid **9** (86% *ee* by polarimetry). Evidently, the partial racemization occured at the stage of *tert*-butyl ester formation from the Boc-amino acid [32].

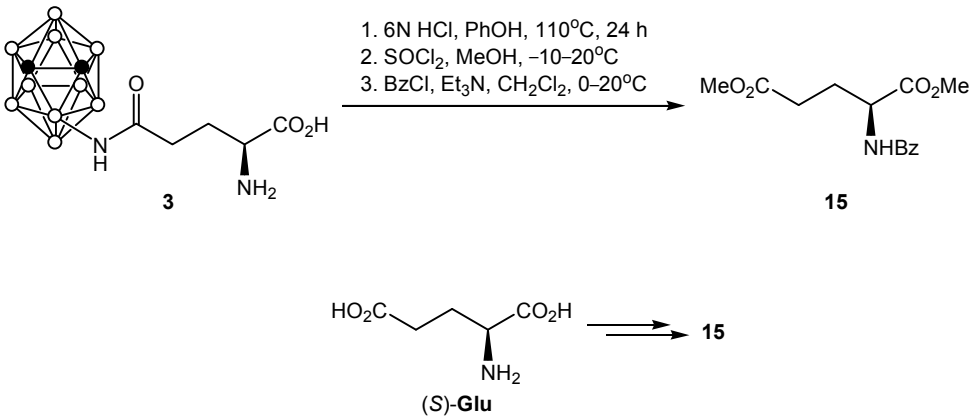
Coupling of *o*-carboran-3-amine **12** [33] and acids **4** and **5** by the method of mixed anhydrides resulted in *tert*-butyl esters **13** and **14** (77 and 69% yield respectively). After the removal of protecting groups in

Scheme 3.



n = 1 (**13**), 2 (**14**).

Scheme 4.



the amino acid fragment by treating with TFA followed by neutralization with equimolar amount of NaOH we smoothly obtained N^{β}-(*o*-carboranyl)-(*S*)-asparagine **2** and N^{γ}-(*o*-carboranyl)-(*S*)-glutamine **3**. Compounds **2** and **3** are poorly soluble in water and precipitated from aqueous solutions at pH 5–6 as hydrates (according to the elemental analysis data) (Scheme 3).

To confirm the optical purity of (*S*)-glutamine derivative **3** we converted it into dimethyl *N*-benzoyl-(*S*)-glutamate **15** that was analyzed by HPLC on a chiral stationary phase. Dimethyl ester **15** was obtained as a result of acidic hydrolysis of compound (*S*)-**3** [34] and subsequent treatment of the formed (*S*)-glutamic acid with thionyl chloride in methanol and benzoyl chloride in methylene chloride. Reference compounds for HPLC analysis of amino acids (*S*)-**15** and (*RS*)-**15** were specially synthesized from an enantiomerically pure (*S*)-glutamic acid and a racemate (Scheme 4).

Enantiomeric excess (*ee*) of compound **15** obtained from carborane **3** was 97.6% (according to HPLC data on a chiral stationary phase). The treatment of enantiomerically pure (*S*)-glutamic acid similarly to compound **3** also resulted in diester **15**, 97.6% *ee*.

Thus, for the first time we synthesized (1,2-dicarba-*closo*-dodecarboran-3-yl) derivatives of (*S*)-asparagine and (*S*)-glutamine. The applied approach to the synthesis of asparagine and glutamine derivatives with free α-amino and α-carboxy groups allows the preparation of enantiomerically pure derivatives of amino acids with an *ortho*-carboranyl substitutent in the side chain. The obtained carboranyl derivatives of amino acids may be applied to the production of piezoelectric materials, and also as potential reagents for boron neutron capture therapy of cancer.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on Bruker DRX-400 (400 and 100 MHz respectively) and Bruker Avance 500 (500 and 125 MHz respectively) spectrometers, TMS as an internal reference. Melting points were measured on a Stuart SMP3 apparatus (Barloworld Scientific, Great Britain). Specific rotation, deg·mL/(g·dm), was determined on a Perkin Elmer Model 341 polarimeter, solution concentration g/100 mL. Elemental analysis was carried out on a Perkin Elmer 2400 II CHNS automatic analyzer. High resolution mass spectra were registered on a Bruker maXis impact HD instrument, electrospray ionization (ESI) in positive ions mode, carrier gas (nitrogen) flow rate 4 L/min, pressure in nebulizer 0.4 bar, pin voltage 4.5 kV.

Enantiomeric composition of compound **15** was determined by the chiral HPLC on a Knauer Smart-line -1100 instrument (Knauer Wissen-schaftliche Geräte, Germany), Chiralcel OD-H column, 5 μm (Daicel Corp., Japan), detection at 230 nm, mobile phase hexane–MeOH–*i*-PrOH, 10 : 0.8 : 0.2, elution rate 1.0 mL/min. For flash column chromatography Silica gel 60 0.063–0.040 mm (Alfa Aesar, Great Britain) was used; for TLC, Sorbfil plates (Imid, Russia). TLC detection of compounds **2–5** and **8–11** was performed with 0.2% ninhydrin in acetone; of compounds **13** and **14**, with Denigés' reagent; of compound **15**, with UV irradiation.

β-Methyl (*S*)-asparagine hydrochloride [35], γ-methyl (*S*)-glutamate hydrochloride [36], and dimethyl (*S*)-glutamate hydrochloride [37] were obtained by known methods.

Diesters 8 and 9. General procedure. *tert*-Butyl acetate (82 mL) was added to a solution of hydrochloride of methyl ester **6** or **7** (12.2 mmol) in 2.45 mL of 58% $HClO_4$ at vigorous stirring. The mixture was stirred at room temperature for 72 h, then poured into cooled (5°C) mixture of 270 mL of 10% Na_2CO_3 solution and 40 mL of Et_2O. The organic layer was separated, the reaction products were extracted from the aqueous layer with Et_2O (2 × 70 mL). Combined organic layers were washed with 10% solution of Na_2CO_3 (2 × 100 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (eluent CH_2Cl_2–MeOH, 98 : 2).

α-*tert*-Butyl β-methyl (*S*)-aspartate (8). Yield 1.29 g (52%). Colorless oily substance. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 25°C), δ, ppm: 1.46 s (9H, *t*-Bu), 2.66 d.d (1H, H^{3B}, *J* 16.2, 7.2 Hz), 2.76 d.d (1H, H^{3A}, *J* 16.2, 4.9 Hz), 3.70 s (3H, CO_2Me), 3.71 d.d (1H, H^2, *J* 7.2, 4.9 Hz). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, 25°C), δ, ppm: 27.91 (3C), 39.03, 51.74, 51.83, 81.56, 171.74, 173.34. Mass spectrum: *m*/*z* 204.1233 $[M + H]^+$. $C_9H_{18}NO_4$. M_{calc} 204.1230.

α-*tert*-Butyl γ-methyl (*S*)-glutamate (9). Yield 1.35 g (51%). Colorless oily substance. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 25°C), δ, ppm: 1.47 s (9H, *t*-Bu), 1.77–1.88 m (1H, H^{3B}), 2.00–2.09 m (1H, H^{3A}), 2.47 t (2H, H^4, *J* 7.6 Hz), 3.35 dd (1H, H^2, *J* 8.2, 5.2 Hz), 3.68 s (3H, CO_2Me). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, 25°C), δ, ppm: 28.01 (3C), 29.82, 30.48, 51.62, 54.32, 81.22, 173.71, 174.87. Mass spectrum: *m*/*z* 218.1384 $[M + H]^+$. $C_{10}H_{20}NO_4$. M_{calc} 218.1387.

Diesters 10 and 11. General procedure. Boc_2O (1.94 g, 8.9 mmol) was added to a solution of 8.1 mmol of diester **8** or **9** and 1.13 mL (8.1 mmol) of Et_3N in 13 mL of DMF. The mixture was stirred at room temperature for 20 h, then 40 mL of EtOAc was added. The solution was washed with 10% solution of citric acid (3 × 30 mL) and over brine (2 × 30 mL), dried with Na_2SO_4, evaporated. The residue was purified by flash chromatography (eluent hexane–EtOAc, 85 : 15).

α-*tert*-Butyl β-methyl *N*-*tert*-butoxycarbonyl-(*S*)-aspartate (10). Yield 1.82 g (74%). Colorless powder, mp 51.5–53.5°C (52–54°C [38], 56–58°C [20]), $[\alpha]_D^{20}$ +17.0 (*c* 1.0, $CHCl_3$) {$[\alpha]_D^{20}$ +16.7 (*c* 0.026, $CHCl_3$) [38]}. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 25°C), δ, ppm: 1.45 s (9H, *t*-Bu), 1.46 s (9H, *t*-Bu), 2.77 d.d (1H, H^{3B}, *J* 16.6, 5.0 Hz), 2.95 d.d (1H, H^{3A}, *J* 16.6, 4.4 Hz), 3.69 s (3H, CO_2Me), 4.43–4.47 m (1H, H^2), 5.43 d (1H, NH, *J* 7.4 Hz). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, 25°C), δ, ppm: 27.87 (3C), 28.30 (3C), 36.98, 50.56, 51.79, 79.86, 82.31, 155.41, 169.95, 171.33. Found, %: C 55.46; H 8.48; N 4.46. $C_{14}H_{25}NO_6$. Calculated, %: C 55.43; H 8.31; N 4.62.

α-*tert*-Butyl γ-methyl *N*-*tert*-butoxycarbonyl-(*S*)-glutamate (11). Yield 2.21 g (86%). Colorless powder, mp 63.5–65.0°C (62–63.5°C [20], 65–67°C [39]), $[\alpha]_D^{20}$ –28.5 (*c* 1.1, MeOH) {$[\alpha]_D^{25}$ –25.0 (*c* 1.0, MeOH) [20]; –28.2 (*c* 1.52, MeOH) [40]}. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 25°C), δ, ppm: 1.44 s (9H, *t*-Bu), 1.47 s (9H, *t*-Bu), 1.87–1.96 m (1H, H^{3B}), 2.11–2.20 m (1H, H^{3A}), 2.32–2.47 m (2H, H^4), 3.68 s (3H, CO_2Me), 4.18–4.23 m (1H, H^2), 5.07 d (1H, NH, *J* 7.5 Hz). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, 25°C), δ, ppm: 27.97 (3C), 28.11, 28.30 (3C), 30.11, 51.71, 53.40, 79.75, 82.17, 155.36, 171.29, 173.30. Found, %: C 56.92; H 8.78; N 4.34. $C_{15}H_{27}NO_6$. Calculated, %: C 56.77; H 8.57; N 4.41.

Compound (11). Scalemic sample. Boc_2O (5.70 g, 26.11 mmol) was added to a solution of 4.30 g (21.76 mmol) of γ-methyl (*S*)-glutamate hydrochloride and 4.57 g (54.40 mmol) of $NaHCO_3$ in a mixture of 22 mL of H_2O and 44 mL of 1,4-dioxane at 0°C. The reaction mixture was stirred at 0°C for 15 min, then at 20°C for 20 h and evaporated to half a volume. The mixture was diluted with 50 mL of 5% aqueous $NaHCO_3$ and washed with Et_2O (3 × 25 mL). The aqueous solution was acidified with citric acid to pH 3–4, the reaction products were extracted with EtOAc (3 × 50 mL). Organic layers were washed with brine (2 × 100 mL), dried over Na_2SO_4, evaporated. The obtained γ-methyl *N*-Boc-(*S*)-glutamate (4.21 g, 16.1 mmol) and 0.20 g (0.16 mmol) of 4-(dimethylamino)pyridine were dissolved in 22 mL of *tert*-butyl alcohol and a solution of 4.19 g (19.3 mmol) of Boc_2O in 12 mL of *tert*-butyl alcohol was added. The reaction mixture was stirred for 3 h at 40°C. A dark solution was evaporated, the residue was purified by flash chromatography (eluent hexane–EtOAc, from 95 : 5 to 80 : 20). Yield 2.71 g (41%). Colorless oily substance, solidifying at storage, 86% *ee*, $[\alpha]_D^{20}$ –24.6 (*c* 1.0, MeOH). Found, %: C 56.97; H 8.80; N 4.44. $C_{15}H_{27}NO_6$. Calculated, %: C 56.77; H 8.57; N 4.41.

Esters 4 and 5 *(general procedure)*. 0.2 N solution of LiOH (38 mL, 7.6 mmol) was added to a solution of 6.9 mmol of *N*-Boc-diester **10** or **11** in 38 mL of THF cooled to 0°C. The mixture was stirred at 0°C for 30 min, then for 20 h at room temperature. The solution was

evaporated by half, 20 mL of 5% aqueous solution of $NaHCO_3$ was added, the mixture was washed with Et_2O (2 × 15 mL). Aqueous layer was acidified with citric acid to pH 3–4, the reaction products were extracted with Et_2O (4 × 20 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, evaporated. The residue was recrystallized from a hexane–EtOAc, 85 : 15 mixture.

(*S*)-4-*tert*-Butoxy-3-(*tert*-butoxycarbonylamino)-4-oxobutanoic acid (4). Yield 1.52 g (76%). Colorless powder, mp 109.0°C (hexane–EtOAc) (97–98°C [21], 98–100°C [24], 97–99°C [28], 99–100°C [23], 104.8°C [25], 105–106°C [41], 106°C [20]), $[\alpha]_D^{20}$ –23.9 (*c* 1.0, MeOH) {$[\alpha]_D^{23.5}$ –23.6 (*c* 1.5, MeOH) [28]}. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 25°C), δ, ppm (conformers A and B, 8 : 2): 1.45 s (9H, *t*-Bu), 1.46 s (9H, *t*-Bu), 2.83 d.d (1H, H^{3B}, *J* 17.1, 4.1 Hz), 3.01 d.d (1H, H^{3A}, *J* 17.1, 4.2 Hz), 4.30 br.s [0.2H, H^2 (B)], 4.43–4.48 m [0.8H, H^2 (A)], 5.45 d [0.8H, NH (A), *J* 7.5 Hz], 5.93 br.s [0.2H, NH (B)]. ^{13}C NMR spectrum (125 MHz, $CDCl_3$, 25°C), d, ppm (conformers A and B): 27.83 (3C, A and B), 28.29 (3C, A and B), 36.85 (A and B), 50.36 (A), 51.73 (B), 80.11 (A), 81.33 (B), 82.56 (A and B), 155.51 (A), 155.84 (B), 169.58 (B), 169.78 (A), 174.74 (B), 176.25 (A). Found, %: C 53.76; H 8.14; N 4.78. $C_{13}H_{23}NO_6$. Calculated, %: C 53.97; H 8.01; N 4.84.

(*S*)-5-α-*tert*-Butoxy-4-(*tert*-butoxycarbonylamino)-5-oxopentanoic acid (5). Yield 1.57 g (75%). Colorless powder, mp 111–114°C (hexane–EtOAc) (103.5–105.5°C [29], 102–105°C [22], 108–111°C [24], 110–114°C [20]), $[\alpha]_D^{20}$ –30.6 (*c* 1.0, MeOH) {$[\alpha]_D^{20}$ –27.5 (*c* 0.6, MeOH) [24]; –30.2 (*c* 1.0, MeOH) [20]}. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 25°C), δ, ppm (conformers A and B, 8 : 2): 1.45 s (9H, *t*-Bu), 1.47 s (9H, *t*-Bu), 1.86–1.94 m (1H, H^{3B}), 2.13–2.22 m (1H, H^{3A}), 2.37–2.52 m (2H, H^4), 4.01–4.11 m [0.2H, H^2 (B)], 4.20–4.25 m [0.8H, H^2 (A)], 5.16 d [0.8H, NH (A), *J* 7.4 Hz], 5.60 br.s [0.2H, NH (B)]. ^{13}C NMR spectrum (125 MHz, $CDCl_3$, 25°C), δ, ppm (conformers A and B): 27.40 (B), 27.99 (3C, A and B), 28.12 (A), 28.30 (3C, A and B), 30.15 (A and B), 53.30 (A), 54.77 (B), 80.05 (A), 81.09 (B), 82.20 (B), 82.42 (A), 155.62 (A), 155.98 (B), 170.99 (B), 171.28 (A), 177.46 (B), 177.80 (A). Found, %: C 55.27; H 8.43; N 4.54. $C_{14}H_{25}NO_6$. Calculated, %: C 55.43; H 8.31; N 4.62.

***N*-(*ortho*-Carboran-3-yl)amides 13 and 14** *(general procedure).* Ethyl chloroformate (0.096 mL, 1.00 mmol) was added to solution of 1.00 mmol of protected amino acid **4** or **5** and 0.11 mL (1.00 mmol) of 4-methylmorpholine in 9 mL of THF cooled to –15°C. The mixture was stirred for 25 min at –15÷–10°C, then a solution of 0.23 mL (1.67 mmol) of triethyl-amine in 7.5 mL of THF and 0.13 g (0.83 mmol) of 3-amino-1,2-dicarba-*closo*-dodecarborane **12** were added. The reaction mixture was stirred for 20 h at 20°C, then evaporated. The residue was purified by flash chromatography (eluent benzene–EtOAc).

***tert*-Butyl (*S*)-2-(*tert*-butoxycarbonylamino)-4-[(1,2-dicarba-*closo*-dodecarboran-3-yl)-amino]-4-oxobutanoate (13).** Yield 0.28 g (77%). Colorless powder, mp 167.5–168.5°C (hexane–CH_2Cl_2), $[\alpha]_D^{20}$ +18.2 (*c* 0.7, CH_2Cl_2). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, 100°C), δ, ppm: 1.39 s (9H, *t*-Bu), 1.40 s (9H, *t*-Bu), 2.58 d.d (1H, H^{3B}, *J* 15.8, 6.9 Hz), 2.66 d.d (1H, H^{3A}, *J* 15.8, 5.7 Hz), 1.40–3.20 br.s (9H, BH), 4.20–4.34 m (1H, H^2), 4.83 s (2H, $CH_{carborane}$), 6.46 br.s (1H, NHBoc), 8.00 s (1H, BNH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, 25°C), δ, ppm: 27.54 (3C), 28.11 (3C), 38.33, 50.62, 56.98, 57.27, 78.15, 80.48, 155.13, 170.65, 173.52. Found, %: C 42.06; H 8.15; N 6.44. $C_{15}H_{34}B_{10}N_2O_5$. Calculated, %: C 41.84; H 7.96; N 6.51.

***tert*-Butyl (*S*)-2-(*tert*-butoxycarbonylamino)-5-[(1,2-dicarba-*closo*-dodecarboran-3-yl)amino]-5-oxopentanoate (14).** Yield 0.25 g (69%). Colorless powder, mp 76–79°C, $[\alpha]_D^{20}$ –14.1 (*c* 0.74, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, 100°C), δ, ppm: 1.39 s (9H, *t*-Bu), 1.41 s (9H, *t*-Bu), 1.74–1.82 m (1H, H^{3B}), 1.90–1.97 m (1H, H^{3A}), 2.28 t (2H, H^4, *J* 7.6 Hz), 1.40–3.10 br.s (9H, BH), 3.84 d.d.d (1H, H^2, *J* 8.4, 8.3, 5.4 Hz), 4.86 s (2H, $CH_{carborane}$), 6.49 br.s (1H, NHBoc), 7.90 s (1H, BNH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, 25°C), δ, ppm: 26.04, 27.60 (3C), 28.11 (3C), 32.84, 53.72, 57.04, 57.13, 78.01, 80.24, 155.45, 171.51, 175.64. Found, %: C 43.23; H 8.42; B 24.50; N 6.05. $C_{16}H_{36}B_{10}N_2O_5$. Calculated, %: C 43.23; H 8.16; B 24.32; N 6.30.

Compounds 2 and 3 *(general procedure).* A solution of 0.30 mmol of protected derivative **13** or **14** in 2 mL of a mixture CH_2Cl_2–CF_3CO_2H, 1 : 1, was stirred for 4 h at 20°C, then evaporated. The residue was dried in a vacuum. The reaction product as a salt of trifluoroacetic acid was dissolved in 0.5 mL of MeOH, and a solution of 0.024 g (0.60 mmol) NaOH in 2.0 mL of H_2O was added. Acetic acid (17 μL, 0.3 mmol) was added to the

obtained solution. The residue was filtered, dried in a vacuum over P_2O_5.

***N*$^{\beta}$-(1,2-Dicarba-*closo*-dodecarboran-3-yl)-(*S*)-asparagine (2).** Yield 0.056 g (68%). Colorless powder, mp 168–169°C, $[\alpha]_D^{20}$ –21.1 (*c* 0.5, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, 25°C), δ, ppm: 2.82–2.88 m (1H, H^2), 3.46 br.s (2H, H^3), 1.30–3.90 br.s (9H, BH), 5.04 s (2H, $CH_{carborane}$), 6.20–8.60 br.s (3H, NH_2 and CO_2H), 8.98 s (1H, BNH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, 25°C), δ, ppm: 38.11, 50.46, 57.23, 57.55, 169.20, 174.60. Found, %: C 25.10; H 7.00; N 9.35. $C_6H_{18}B_{10}N_2O_3\cdot H_2O$. Calculated, %: C 24.65; H 6.90; N 9.58.

***N*$^{\gamma}$-(1,2-Dicarba-*closo*-dodecarboran-3-yl)-(*S*)-glutamine (3).** Yield 0.074 g (81%). Colorless powder, mp 164–166°C (decomp) (EtOH–H_2O), $[\alpha]_D^{20}$ –6.4 (*c* 0.44, MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, 25°C), δ, ppm: 1.78–1.93 m (2H, H^3), 2.34–2.40 m (2H, H^4), 3.20 t (1H, H^2, *J* 6.3 Hz), 1.50–2.70 br.m (9H, BH), 5.11 s (2H, $CH_{carborane}$), 7.60 br.s (3H, NH_2 and CO_2H), 8.67 s (1H, BNH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, 25°C), δ, ppm: 26.71, 33.15, 53.39, 57.35, 169.96, 176.22. Found, %: C 27.62; H 7.22; B 35.03; N 8.85. $C_7H_{20}B_{10}N_2O_3\cdot H_2O$. Calculated, %: C 27.44; H 7.24; B 35.29; N 9.14.

Dimethyl (*RS*)-glutamate hydrochloride. $SOCl_2$ (0.65 mL, 8.87 mmol) was added to 5.5 mL of methanol cooled to –10°C. The mixture was stirred for 15 min at –10°C, then 0.37 g (2.22 mmol) of (*RS*)-glutamic acid monohydrate was added. The reaction mixture was stirred at room temperature for 17 h. The solution was evaporated, the residue was treated with 12 mL of Et_2O. The precipitate was filtered off, dried in a vacuum over P_2O_5 and KOH. Yield 0.46 g (99%). Colorless powder, mp 156–157°C (149°C [42]). ^{1}H and ^{13}C NMR spectra are similar to the spectra of (*S*)-enantiomer [37]. Found, %: C 39.60; H 6.52; Cl 16.68; N 6.50. $C_7H_{14}ClNO_4$. Calculated, %: C 39.72; H 6.67; Cl 16.75; N 6.62.

Esters 15 *(general procedure).* Benzoyl chloride (0.26 mL, 2.20 mmol) was added to a mixture of 0.31 g (1.46 mmol) of dimethyl glutamate hydrochloride, 6 mL of CH_2Cl_2, and 0.82 mL (5.86 mmol) of Et_3N, cooled to 0°C, the mixture was stirred for 2 h at room temperature, then 15 mL of CH_2Cl_2 was added and the reaction mixture was washed successively with 1N HCl (3 × 12 mL), brine (2 × 12 mL), 5% solution of $NaHCO_3$ (2 × 12 mL), and water (2 × 12 mL). The organic layer was dried over $MgSO_4$, evaporated. The residue was purified by flash chromatography on silica gel (eluent hexane–EtOAc, 7 : 3).

Dimethyl *N*-benzoyl-(*S*)-glutamate [(*S*)-15]. Yield 0.37 g (91%). Colorless powder, mp 81–83°C (79–80°C [43]), $[\alpha]_D^{20}$ +21.0 (*c* 0.97, $CHCl_3$), 99.6% *ee*. HPLC: $\tau_{(R)\text{-}15}$ 16.8 min (0.2%), $\tau_{(S)\text{-}15}$ 24.8 min (99.8%). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, 25°C), δ, ppm: 2.12–2.20 m (1H, H^{3B}), 2.30–2.37 m (1H, H^{3A}), 2.42–2.56 m (2H, H^4), 3.66 s (3H, OMe), 3.79 s (3H, OMe), 4.81–4.85 m (1H, H^2), 7.02 d (1H, NH, *J* 6.9 Hz), 7.44–7.47 m (2H, Ph), 7.51–7.54 m (1H, Ph), 7.82–7.83 m (2H, Ph). Found, %: C 60.30; H 6.07; N 4.75. $C_{14}H_{17}NO_5$. Calculated, %: C 60.21; H 6.14; N 5.02.

Dimethyl *N*-benzoyl-(*RS*)-glutamate [(*RS*)-15]. Yield 0.38 g (92%). Colorless oily substance solidifying at storage, mp 64–66°C. HPLC: $\tau_{(R)\text{-}15}$ 16.8 min (50%), $\tau_{(S)\text{-}15}$ 24.8 min (50%). ^{1}H NMR spectrum was identical to that of compound (*S*)-**15**. Found, %: C 60.42; H 5.98; N 4.78. $C_{14}H_{17}NO_5$. Calculated, %: C 60.21; H 6.14; N 5.02.

Hydrolysis of compound 3. A solution of 0.064 g (0.21 mmol) of compound **3** in 15.3 mL of 6 N HCl, containing 0.1% of phenol was incubated for 24 h in a sealed flask at 110–115°C. The solution was evaporated, the residue was dried in a vacuum over P_2O_5 and KOH. The hydrolyzate was dissolved in 3.0 mL of MeOH, and 155 μL (2.09 mmol, 10 equiv) of $SOCl_2$ was added at –5–0°C. The mixture was stirred for 15 min at –5–0°C and for 18 h at room temperature, then evaporated and dried in a vacuum over P_2O_5 and KOH. The obtained residue was dissolved in 4.0 mL of CH_2Cl_2, 310 μL (2.20 mmol, 10.5 equiv) of Et_3N and 97 μL (0.84 mmol, 4 equiv) of benzoyl chloride was added to this solution at 0°C. The mixture was stirred at room temperature for 2 h. CH_2Cl_2 (10 mL) was added to the solution and the mixture was washed successively with 1 N HCl (3 × 8 mL), brine (2 × 8 mL), 5% solution of $NaHCO_3$ (2 × 8 mL), water (2 × 8 mL). The organic layer was dried over $MgSO_4$, evaporated. The residue was purified by flash chromatography (eluent hexane–EtOAc, 7 : 3). Yield 0.058 g (99%). Yellowish oily substance, 97.6% *ee*. HPLC: $\tau_{(R)\text{-}15}$ 16.8 min (1.2%), $\tau_{(S)\text{-}15}$ 24.8 min (98.8%).

Control experiment was performed similarly using 0.088 g (0.59 mmol) of (*S*)-glutamic acid (*ee* ≥ 99.6%), 44 mL of 6N HCl with 0.1% of phenol, 8.1 mL of MeOH, 0.43 mL (5.95 mmol) of $SOCl_2$, 10.5 mL of CH_2Cl_2, 0.87 mL (6.24 mmol) of Et_3N, 0.28 mL (2.38 mmol) of benzoyl chloride. Yield 0.16 g (99%).

Yellowish oily substance, 97.6% *ee*. HPLC: $\tau_{(R)\text{-}\mathbf{15}}$ 16.8 min (1.2%), $\tau_{(S)\text{-}\mathbf{15}}$ 24.8 min (98.8%).

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