Synthesis of novel carboranyl derivatives of α-amino acids

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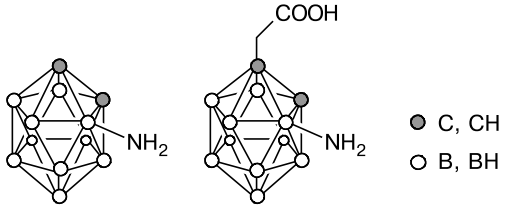
New routes to *closo*-carboranyl derivatives of L-lysine and L-glutamic acid with free α-NH_2 groups were proposed.

Key words: carboranes, amino acids, C- and N-protecting groups, amides.

Boron neutron capture therapy (BNCT) is a modern approach to cancer treatment that is under intensive development. This is based on capturing thermal neutrons by ^{10}B nuclei followed by fission of radioactive ^{11}B isotopes emitting α particles, which cause local damage to the target cells. This results in selective death of cells containing boron compounds. Intensive relevant investigations in the last decade were aimed at searching for new BNCT agents.[1—4] In this respect, dicarba-*closo*-dodecaborane (carborane) derivatives are very promising. Essential requirements to BNCT agents include selective delivery to tumor cells and the ability to be retained and accumulate in these cells. In previous attempts at designing such agents, carborane-containing derivatives of biomolecules (nucleosides,[5—7] porphyrins,[8,9] amino acids,[10—12] *etc.*[1,2]) were used. Carborane derivatives containing amino and/or carboxy groups, including 3-amino-1,2-dicarba-*closo*-dodecaborane (**1**)[13] and 2-(3-amino-1,2-dicarba-*closo*-dodecaboran-1-yl)acetic acid (**2**)[14] are promising objects for the synthesis of novel BNCT agents



1 **2**

Amino acids and peptides are essential components of proliferating malignant cells. The mechanisms of active transport are most efficient for L-amino acid derivatives containing free carboxy and α-amino groups.[15,16]

Recent investigations showed that tumor cells are characterized by increased and selective uptake of folic acid.[17—19] The highest affinity for folate receptors is exhibited by folic acid derivatives with the modified γ-carboxy group of the L-glutamic acid fragment and the free α-carboxy group.[19—22]

Targeted introduction of carborane residues into amino acids containing additional functional groups (*e.g.*, lysine or glutamic acid) can be an important step in the preparation of promising BNCT agents and thus is of considerable interest.

The goal of the present work was to develop methods for the synthesis of carborane-containing derivatives of L-lysine and N^{γ}-(1,2-dicarba-*closo*-dodecaboran-3-yl)-L-glutamic acid.

Results and Discussion

We used (1,2-dicarba-*closo*-dodecaboran-1-yl)acetic acid (**3**) and N-protected (3-amino-1,2-dicarba-*closo*-dodecaboran-1-yl)acetic acids **4** (see Ref. 14) and **5** (see Ref. 23) as the starting carborane-containing reagents for the preparation of carboranyl derivatives of L-lysine (Scheme 1). The starting L-lysine derivative used was N^{α}-TFA-L-lysine methyl ester (**6**), because the N^{α}-TFA and COOMe protecting groups can simultaneously be removed under mild conditions without destruction of the *closo*-carborane cage. Earlier, in the synthesis of *N*-[(3-amino-1,2-dicarba-*closo*-dodecaboran-1-yl)acetyl] derivatives of amino acids, we have found that *closo*-carboranes withstand basic hydrolysis under mild conditions.[23]

Coupling of carboranylacetic acids **3**—**5** with compound **6** at room temperature using *N*,*N*´-dicyclohexylcarbodiimide (DCC) in the presence of 1-hydroxybenzotriazole (HOBt) in DMF gave compounds **7**—**9** in 60—80% yields (see Scheme 1). Compounds **8** and **9** containing the fragments of planar-chiral carboranes **4** and **5** were obtained as mixtures of diastereomers.

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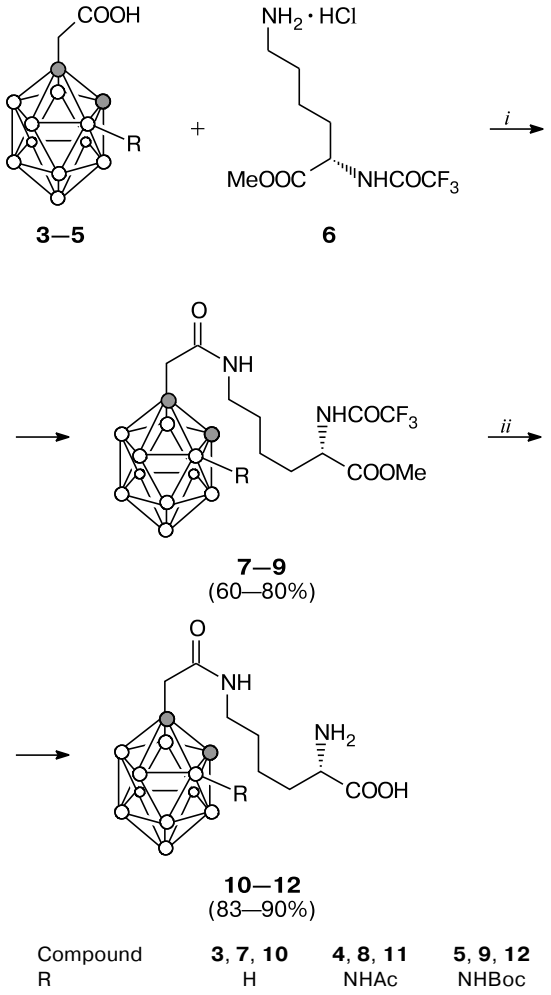
Scheme 1



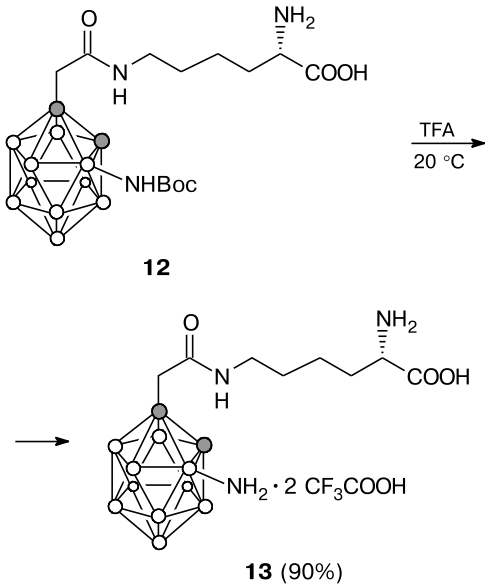
Reagents and conditions: *i*. DCC, HOBt, NEt_3, DMF; *ii*. 1) KOH/H_2O—acetone, 0 °C; 2) H^+.

Treatment of derivatives **7**—**9** with KOH in aqueous acetone at 0 °C smoothly afforded the corresponding compounds **10**—**12** in 83—90% yields. According to ^1H NMR data, the protecting groups were completely removed from the lysine residue and no deboronation products (*nido*-derivatives) were formed: the spectra of the compounds showed no signal at δ −2.3—2.5 characteristic of the bridging B—H—B proton in *nido*-carboranes.[24]

Introduction of *closo*-carborane fragments is known to make biomolecules substantially more lipophilic and less soluble in water.[1,2,7] That is why the synthesis of carboranyl derivatives with the maximum number of polar groups is of particular interest, *e.g.*, compounds containing amino acid **2** with a free amino group in position 3 of the carborane cage.

Treatment of compound **12** with trifluoroacetic acid (TFA) at room temperature according to a standard procedure afforded N^{ε}-(3-amino-1,2-dicarba-*closo*-dodecaboran-1-yl)acetyl-L-lysine trifluoroacetate (**13**) (Scheme 2), which is highly hygroscopic and unstable on storage. When stored at room temperature for a week, compound **13** underwent partial decomposition (TLC) into unidentified products.

Scheme 2

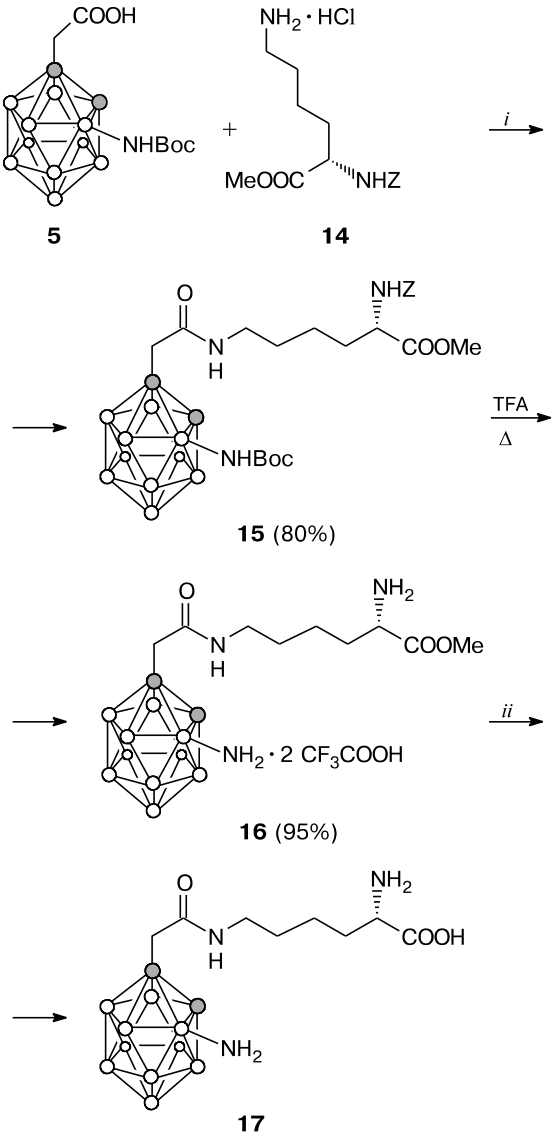


For the synthesis of free N^{ε}-(3-amino-1,2-dicarba-*closo*-dodecaboran-1-yl)acetyl-L-lysine, we developed an alternative approach (Scheme 3). Coupling of racemic *N*-Boc-amino acid **5** with N^{α}-benzyloxycarbonyl(Z)-L-lysine methyl ester (**14**) in the presence of DCC and HOBt gave amide **15** as a mixture of diastereomers (HPLC on silica gel).

Reflux of compound **15** in TFA resulted in simultaneous removal of the protecting *N*-Boc and *N*-Z groups from the aminocarborane and lysine fragments, respectively. Elimination of the *N*-Z group under the action of TFA has been described earlier.[25—27] This method is preferred for the synthesis of methyl ester **16** from compound **15**. Hydrolysis of the *N*-Z group with TFA at room temperature was incomplete (60% conversion upon treatment for 1 day, ^1H NMR), while reflux in TFA for 40 min gave product **16** free of the starting compound and deboronation products (^1H NMR). Subsequent routine hydrolysis of the ester group afforded target compound **17** in 95% yield.

L-Glutamic acid γ-amide with 3-amino-1,2-dicarba-*closo*-dodecaborane (**1**) was synthesized from accessible γ-methyl L-glutamate (**18**). First, the N- and C^{α}-protecting groups (*N*-Boc and *tert*-butyl ester) were successively introduced into compound **18**; they can simultaneously be removed under mild conditions. The *N*-Boc group was introduced into compound **18** under the action of Boc_2O in the presence of triethylamine in DMF (Scheme 4).

Scheme 3



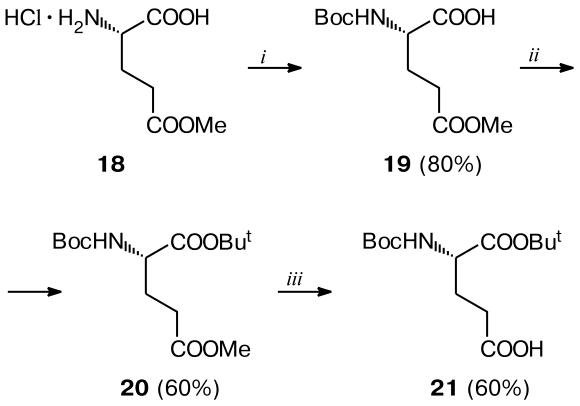
Reagents and conditions: *i*. DCC, HOBt, NEt_3, DMF; *ii*. 1) KOH/H_2O—acetone, 0 °C; 2) H^+.

tert-Butyl ester **20** was obtained by activation of the carboxy group of the amino acid followed by a reaction with Bu^tOH.[28] With Boc_2O as an activating agent, the yield of compound **20** was 60%, while the use of DCC was less efficient: the target product was isolated by flash chromatography in ~40% yield.

Hydrolysis of γ-methyl ester **20** with NaOH in aqueous acetone at reduced temperature was accompanied by partial (7—15%) hydrolysis of the *tert*-butyl ester (^{1}H NMR). Compound **21** was isolated by flash chromatography on silica gel in 60% yield.

Amide **22** was obtained by coupling of 3-aminocarborane **1** with α-*tert*-butyl *N*-Boc-L-glutamate (**21**) using

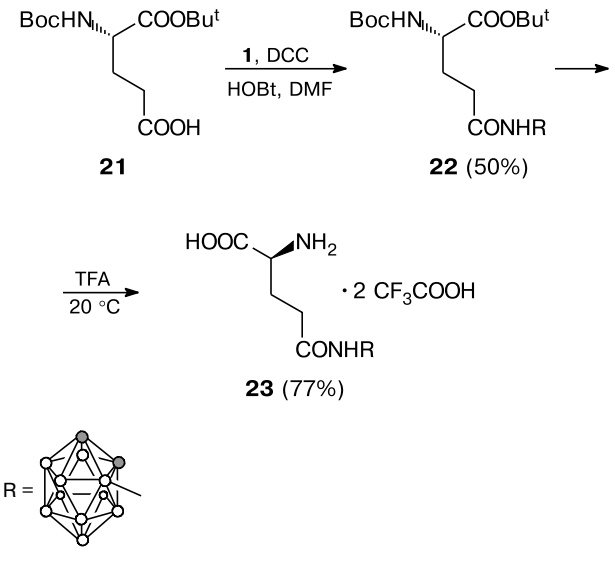
Scheme 4



Reagents and conditions: *i*. Boc_2O, NEt_3, DMF; *ii*. Boc_2O, Py/DMAP, Bu^tOH; *iii*. $NaOH/H_2O$—acetone.

the carbodiimide method. The best results (50% yield) were obtained using DCC and HOBt in DMF (Scheme 5). The N- and C-protecting groups were removed by treating amide **22** with TFA at room temperature for 5 h. No deboronation of the *closo*-carborane fragment with the formation of *nido*-derivatives occurred under these conditions (^{1}H NMR). The yield of compound **23** was 77%. *N*$^\gamma$-(1,2-dicarba-*closo*-dodecaboran-3-yl)-L-glutamine (**23**) can be used as starting material for the synthesis of the corresponding folic acid γ-amide.

Scheme 5



Thus, we obtained for the first time *closo*-carboranyl derivatives of natural L-amino acids with free α-functional groups and developed methods for the targeted synthesis of *N*$^\gamma$-(1,2-dicarba-*closo*-dodecaboran-3-yl)-L-glut-

amine, N^{ε}-(3-acetylamino-1,2-dicarba-*closo*-dodecaboran-1-yl)acetyl-L-lysine, and a compound with an additional free amino group at the B(3) atom of the carborane cage. The structures of all the products were confirmed by ^{1}H NMR and GC-MS data. The compounds obtained are promising BNCT agents and can serve as precursors for more complex carborane-containing molecules.

Experimental

The starting compounds 3-amino-1,2-dicarba-*closo*-dodecaborane (**1**) and (1,2-dicarba-*closo*-dodecaboran-1-yl)acetic acids **3**—**5** were prepared according to known procedures.[13,14,23] Other reagents are commercially available. Melting points were determined on a Boetius instrument; optical rotation was measured on a Perkin-Elmer M 341 polarimeter. ^{1}H NMR spectra were recorded on a Bruker DRX-400 instrument (400 MHz) in DMSO-d_6 with $SiMe_4$ as the internal standard. Mass spectra were recorded on a Shimadzu LCMS-2010 instrument fitted with a quadrupole analyzer for positive or negative ions (APCI or ESI, acetonitrile—water as a mobile phase). HPLC analysis was carried out on a Merck-Hitachi chromatograph on a Hibar pre-packed RT250-4 LiChrosorb Si-60 column (4×250 mm, 5 μm) with hexane—Pr^iOH (10 : 1) as an eluent (elution rate 1 mL min^{-1}, L-4000A Intelligent Pump instrument, UV detection at λ = 220 nm, an L-4000A UV detector, a D-2500A Chromato-Integrator).

***N*$^{\varepsilon}$-[(3-R-1,2-Dicarba-*closo*-dodecaboran-1-yl)acetyl]-*N*$^{\alpha}$-trifluoroacetyl-L-lysine methyl ester (7—9) (general procedure).** Compound **6** (0.205 g, 0.7 mmol), NEt_3 (0.098 mL, 0.7 mmol), HOBt (0.109 g, 0.7 mmol), and DCC (0.145 g, 0.7 mmol) were added to a solution of 3-R-2-(1,2-dicarba-*closo*-dodecaboran-1-yl)acetic acid (**3**, **4**, or **5**) (0.7 mmol) in DMF (7 mL). The reaction mixture was stirred at room temperature for 24 h and poured into water (25 mL). The product was extracted with AcOEt. The organic layer was dried with $MgSO_4$ and concentrated to dryness. The residue was treated with acetone (4 mL); the precipitate of *N*,*N*′-dicyclohexylurea was filtered off and the filtrate was concentrated to dryness. The residue was purified by flash chromatography on silica gel in benzene—AcOEt.

***N*$^{\varepsilon}$-[(1,2-Dicarba-*closo*-dodecaboran-1-yl)acetyl]-*N*$^{\alpha}$-trifluoroacetyl-L-lysine methyl ester (7).** Yield 60%, colorless crystals, m.p. 138—140 °C, $[\alpha]_D^{20}$ −12.8 (*c* 1, MeOH). ^{1}H NMR, δ: 9.81 (d, 1 H, $N^{\alpha}H$, *J* = 7.4 Hz); 8.23 (t, 1 H, $N^{\varepsilon}H$, *J* = 5.5 Hz); 5.11 (s, 1 H, CH of carborane); 4.31 (ddd, 1 H, C(2)H, *J* = 9.5 Hz, *J* = 7.4 Hz, *J* = 5.1 Hz); 3.67 (s, 3 H, COOMe); 3.09 (s, 2 H, CO—CH_2—carborane); 3.03 (m, 2 H, C(6)H_2); 1.8 (m, 2 H, C(5)H_2); 1.4 (m, 2 H, C(3)H_2); 1.3 (m, 2 H, C(4)H_2); 1.2—2.8 (m, 10 H, 10 BH). MS (ESI), *m*/*z* (I_{rel} (%)): 440 [M − H]$^-$ (100); 475 [M + Cl]$^-$ (26); 460 [M + H_2O + H]$^+$ (100); 442 [M + H]$^+$ (7). Calculated for $C_{13}H_{27}B_{10}F_3N_2O_4$: M = 440.48.

***N*$^{\varepsilon}$-[(3-Acetylamino-1,2-dicarba-*closo*-dodecaboran-1-yl)acetyl]-*N*$^{\alpha}$-trifluoroacetyl-L-lysine methyl ester (8).** Yield 69%, colorless crystals, m.p. 66—68 °C. ^{1}H NMR, δ: 9.81 (d, 1 H, $N^{\alpha}H$, *J* = 7.3 Hz); 8.37 (s, 1 H, NH—carborane); 8.21 (t, 1 H, $N^{\varepsilon}H$, *J* = 5.3 Hz); 5.24 (s, 1 H, CH of carborane); 4.31 (ddd, 1 H, C(2)H, *J* = 9.4 Hz, *J* = 7.3 Hz, *J* = 5.1 Hz); 3.67 (s, 3 H, COOMe); 3.04 (m, 2 H, C(6)H_2); 2.14 (d, 1 H, CO—CH_A—carborane, *J* = 14.5 Hz); 2.84 (d, 1 H, CO—CH_B—carborane, *J* = 14.5 Hz); 1.97 (s, 3 H, COMe); 1.77 (m, 2 H, C(5)H_2); 1.4 (m, 2 H, C(3)H_2); 1.3 (m, 2 H, C(4)H_2); 1.4—2.8 (m, 9 H, 9 BH). MS (ESI), *m*/*z* (I_{rel} (%)): 497 [M − H]$^-$ (100); 533 [M + Cl]$^-$ (43); 498 [M + H]$^+$ (57); 519 [M + Na]$^+$ (75). Calculated for $C_{15}H_{30}B_{10}F_3N_3O_5$: M = 497.53.

***N*$^{\varepsilon}$-{[3-(*tert*-Butoxycarbonylamino)-1,2-dicarba-*closo*-dodecaboran-1-yl]acetyl}-*N*$^{\alpha}$-trifluoroacetyl-L-lysine methyl ester (9).** Yield 80%, colorless crystals, m.p. 59—62 °C. ^{1}H NMR, δ: 9.82 (d, 1 H, $N^{\alpha}H$, *J* = 7.4 Hz); 8.24 (t, 1 H, $N^{\varepsilon}H$, *J* = 5.4 Hz); 7.53 (s, 1 H, NH—carborane); 5.05 (s, 1 H, CH of carborane); 4.31 (ddd, 1 H, C(2)H, *J* = 9.6 Hz, *J* = 7.3 Hz, *J* = 5.0 Hz); 3.67 (s, 3 H, COOMe); 3.02 (m, 2 H, C(6)H_2); 2.98 (d, 1 H, CO—CH_A—carborane, *J* = 14.5 Hz); 2.85 (d, 1 H, CO—CH_B—carborane, *J* = 14.5 Hz); 1.77 (m, 2 H, C(5)H_2); 1.40 (m, 2 H, C(3)H_2); 1.40 (s, 9 H, $COOCMe_3$); 1.3 (m, 2 H, C(4)H_2); 1.4—2.5 (m, 9 H, 9 BH). MS (ESI), *m*/*z* (I_{rel} (%)): 480 [M − Bu^tOH − H]$^-$ (100); 456 [M − Bu^t − CO_2 + 2H]$^+$ (100); 579 [M + Na]$^+$ (97). Calculated for $C_{18}H_{36}B_{10}F_3N_3O_6$: M = 555.61.

***N*$^{\varepsilon}$-[(3-R-1,2-Dicarba-*closo*-dodecaboran-1-yl)acetyl]-L-lysine (10—12) (general procedure).** A 1 *M* solution of KOH (1.2 mL) was added dropwise at 0 °C to a stirred solution of compound **7**, **8**, or **9** (0.5 mmol) in acetone (4 mL). The reaction mixture was stirred at 10 °C for 16 h, diluted with water (5 mL), and washed with Et_2O. The aqueous layer was separated and acidified with 1 *M* HCl to pH 5.5. The product was extracted with AcOEt. The organic layer was dried with $MgSO_4$ and concentrated. The residue was dissolved in EtOH, the solution was filtered, and the filtrate was concentrated to dryness.

***N*$^{\varepsilon}$-[(1,2-Dicarba-*closo*-dodecaboran-1-yl)acetyl]-L-lysine (10).** Yield 90%, colorless crystals, m.p. 184—185 °C (decomp.), $[\alpha]_D^{20}$ +2.10 (*c* 1, MeOH). ^{1}H NMR, δ: 8.46 (t, 1 H, $N^{\varepsilon}H$, *J* = 5.3 Hz); 7.3—8.0 (br.s, 3 H, $N^{\alpha}H_3^+$); 5.23 (s, 1 H, CH of carborane); 4.56 (m, 1 H, C(2)H); 3.23 (t, 2 H, C(6)H_2, *J* = 5.5 Hz); 3.13 (s, 2 H, CO—CH_2—carborane); 3.02 (m, 2 H, C(3)H_2); 1.7 (m, 2 H, C(5)H_2); 1.4 (m, 2 H, C(4)H_2); 1.2—2.8 (m, 10 H, 10 BH). MS (ESI), *m*/*z* (I_{rel} (%)): 330 [M − H]$^-$ (100); 320 [M − B]$^-$ (40); 331 [M + H]$^+$ (100). Calculated for $C_{10}H_{26}B_{10}N_2O_3$: M = 330.44.

***N*$^{\varepsilon}$-[(3-Acetylamino-1,2-dicarba-*closo*-dodecaboran-1-yl)-acetyl]-L-lysine (11).** Yield 90%, colorless crystals, m.p. 149—152 °C. ^{1}H NMR, δ: 8.56, 8.53 (both s, 1 H, NH—carborane); 8.44 (t, 1 H, $N^{\varepsilon}H$, *J* = 4.8 Hz); 5.24 (s, 1 H, CH of carborane); 3.48 (m, 1 H, C(2)H); 3.01 (m, 2 H, C(6)H_2); 2.90 (d, 1 H, CO—CH_A—carborane, *J* = 14.5 Hz); 3.00 (d, 1 H, CO—CH_B—carborane, *J* = 14.5 Hz); 1.98 (s, 3 H, COMe); 1.73 (m, 2 H, C(3)H_2); 1.25—1.45 (m, 4 H, $(CH_2)_2$); 1.2—2.6 (m, 9 H, 9 BH). MS (APCI), *m*/*z* (I_{rel} (%)): 386 [M − H]$^-$ (100); 388 [M + H]$^+$ (100). Calculated for $C_{12}H_{29}B_{10}N_3O_4$: M = 387.49.

***N*$^{\varepsilon}$-{[3-(*tert*-Butoxycarbonylamino)-1,2-dicarba-*closo*-dodecaboran-1-yl]acetyl}-L-lysine (12).** Yield 83%, colorless crystals, m.p. 163—165 °C. ^{1}H NMR, δ: 8.44 (m, 1 H, $N^{\varepsilon}H$); 7.2—8.3 (br.s, 3 H, $N^{\alpha}H_3^+$); 7.56 (s, 1 H, NH—carborane); 5.09 (s, 1 H, CH of carborane); 3.26 (m, 1 H, C(2)H); 3.01 (m, 2 H, C(6)H_2); 3.02 (d, 1 H, CO—CH_A—carborane, *J* = 14.6 Hz); 2.91 (d, 1 H, CO—CH_B—carborane, *J* = 14.6 Hz); 1.6—1.7 (m, 2 H, C(3)H_2); 1.40 (s, 9 H, $COOCMe_3$); 1.25—1.4 (m, 4 H, $(CH_2)_2$); 1.2—2.6 (m, 9 H, 9 BH). MS (APCI), *m*/*z* (I_{rel} (%)): 444 [M − H]$^-$ (100); 446 [M + H]$^+$ (100). Calculated for $C_{15}H_{35}B_{10}N_3O_5$: M = 445.57.

***N*$^{\varepsilon}$-{[3-Amino-1,2-dicarba-*closo*-dodecaboran-1-yl]acetyl}-L-lysine bis(trifluoroacetate) (13).** A solution of compound **12**

(125 mg, 0.28 mmol) in TFA (2.5 mL) was stirred at room temperature for 19 h. The reaction mixture was concentrated to dryness and the residue was triturated with hexane. The yield of compound **13** was 0.137 g (89%), colorless crystals, m.p. 128—132 °C (decomp.). ^{1}H NMR, δ: 8.27 (m, 1 H, $N^{\varepsilon}H$); 8.16—8.30 (m, 3 H, $N^{\alpha}H_3^+$); 4.45 (s, 1 H, CH of carborane); 3.87 (m, 1 H, C(2)H); 3.03 (m, 2 H, $C(6)H_2$); 3.08 (d, 1 H, $CO—CH_A$—carborane, J = 14.6 Hz); 2.97 (d, 1 H, $CO—CH_B$——carborane, J = 14.6 Hz); 1.7—1.8 (m, 2 H, $C(3)H_2$); 1.3—1.4 (m, 4 H, $(CH_2)_2$); 1.0—2.6 (m, 9 H, 9 BH). MS (ESI), m/z (I_{rel} (%)): 335 $[M - B]^-$ (71), 447 $[M + CF_3COOH - B]^-$ (62); 346 $[M + H]^+$ (100). Calculated for $C_{10}H_{27}B_{10}N_3O_3$: M = 345.45.

N^{α}-Benzyloxycarbonyl-N^{ε}-{[3-(*tert*-butoxycarbonylamino)-1,2-dicarba-*closo*-dodecaboran-1-yl]acetyl}-L-lysine methyl ester (15). Compound **14** (0.232 g, 0.7 mmol), NEt_3 (0.098 mL, 0.7 mmol), HOBt (0.109 g, 0.7 mmol), and DCC (0.145 g, 0.7 mmol) were added to a solution of compound **5** (0.222 g, 0.7 mmol) in DMF (7 mL). The reaction mixture was stirred at room temperature for two days. The precipitate of *N*,*N*′-dicyclohexylurea was filtered off, the filtrate was poured into water (35 mL), and the product was extracted with AcOEt. The organic layer was dried with $MgSO_4$ and concentrated to dryness. The residue was dissolved in AcOEt (5 mL), the solution was filtered through a short column of silica gel, and the eluate was concentrated to dryness. The yield of compound **15** was 0.334 g (80%), oil. HPLC data: τ_{R_1} = 8.28 min, τ_{R_2} = 10.26 min. ^{1}H NMR, δ: 8.22 (t, 1 H, $N^{\varepsilon}H$, J = 5.6 Hz); 7.72 (d, 1 H, $N^{\alpha}H$, J = 7.8 Hz); 7.52 (br.s, 1 H, NH-carborane); 7.3—7.4 (m, 5 H, Ph); 5.05 (br.s, 1 H, CH of carborane); 5.03 (s, 2 H, $PhC\underline{H}_2O$); 4.00 (m, 1 H, C(2)H); 3.63 (s, 3 H, COOMe); 2.92—3.09 (m, 2 H, $C(6)H_2$); 3.00 (d, 1 H, $CO—CH_A$—carborane, J = 14.5 Hz); 2.85 (d, 1 H, $CO—CH_B$—carborane, J = 14.5 Hz); 1.63 (m, 2 H, $C(3)H_2$); 1.40 (s, 9 H, $COOCMe_3$); 1.2—1.4 (m, 4 H, $(CH_2)_2$); 1.4—2.5 (m, 9 H, 9 BH). MS (ESI), m/z (I_{rel} (%)): 630 $[M + Cl]^-$ (100); 584 $[M - B]^-$ (23); 616 $[M + Na]^+$ (100); 495 $[M - Bu^t - CO_2 + 2H]^+$ (23). Calculated for $C_{24}H_{43}B_{10}N_3O_7$: M = 593.73.

N^{ε}-{[3-Amino-1,2-dicarba-*closo*-dodecaboran-1-yl]acetyl}-L-lysine methyl ester bis(trifluoroacetate) (16). A solution of compound **15** (0.300 g, 0.50 mmol) in TFA (5 mL) was refluxed for 40 min. The reaction mixture was concentrated to dryness and the residue was triturated with hexane and dried. The yield of compound **16** was 0.282 g (96%), oil. ^{1}H NMR, δ: 8.37 (br.s, 3 H, $N^{\alpha}H_3^+$); 8.29 (t, 1 H, $N^{\varepsilon}H$, J = 5.4 Hz); 4.52 (s, 1 H, CH of carborane); 4.03 (m, 1 H, C(2)H); 3.76 (s, 3 H, COOMe); 2.98—3.08 (m, 2 H, $C(6)H_2$); 3.09 (d, 1 H, $CO—CH_A$—carborane, J = 14.9 Hz); 3.00 (d, 1 H, $CO—CH_B$—carborane, J = 14.9 Hz); 1.77 (m, 2 H, $C(3)H_2$); 1.20—1.45 (m, 4 H, $(CH_2)_2$); 1.0—2.6 (m, 9 H, 9 BH). MS (ESI), m/z (I_{rel} (%)): 360 $[M + H]^+$ (100). Calculated for $C_{11}H_{29}B_{10}N_3O_3$: M = 359.48.

N^{ε}-{[3-Amino-1,2-dicarba-*closo*-dodecaboran-1-yl]acetyl}-L-lysine (17). A 1 *M* solution of KOH (1.7 mL) was added dropwise at 0 °C to a stirred solution of compound **16** (0.280 g, 0.48 mmol) in acetone (4.5 mL). The reaction mixture was stirred at 10 °C for 16 h, diluted with water (5 mL), and washed with Et_2O. The aqueous layer was separated and acidified with 1 *M* HCl to pH 4.0. The product was extracted with AcOEt. The organic layer was dried with $MgSO_4$ and concentrated. The residue was triturated with acetone. The yield of compound **17** was 0.158 g (95%), pale orange crystals, m.p. 72—74 °C (decomp.). ^{1}H NMR, δ: 8.28 (t, 1 H, $N^{\varepsilon}H$, J = 5.5 Hz); 8.24 (br.s, 3 H, $N^{\alpha}H_3^+$); 4.46 (s, 1 H, CH of carborane); 3.88 (m, 1 H, C(2)H); 2.95—3.09 (m, 2 H, $C(6)H_2$); 3.08 (d, 1 H, $CO—CH_A$—carborane, J = 14.5 Hz); 2.97 (d, 1 H, $CO—CH_B$—carborane, J = 14.5 Hz); 1.76 (m, 2 H, $C(3)H_2$); 1.3—1.4 (m, 4 H, $(CH_2)_2$); 1.0—2.6 (m, 9 H, 9 BH). MS (ESI), m/z (I_{rel} (%)): 335 $[M - B]^-$ (100); 345 $[M - H]^-$ (53); 347 $[M + H]^+$ (100). Calculated for $C_{10}H_{27}B_{10}N_3O_3$: M = 345.45.

γ-Methyl *N*-Boc-L-glutamate (19). Triethylamine (11.3 mL, 81.0 mmol) was added to a solution of γ-methyl L-glutamate hydrochloride (**18**) (8 g, 40.5 mmol) in DMF (20 mL). The precipitate that formed was filtered off. A solution of Boc_2O (17.7 g, 81.0 mmol) in Pr^iOH (15 mL) was added to the filtrate with stirring. The reaction mixture was kept for 24 h and diluted with water (150 mL). The solution was acidified with citric acid to pH ≈ 4. The product was extracted from the resulting oily liquid with AcOEt (4×45 mL). The extract was washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The yield of compound **19** was 8.46 g (80%), yellow oil. ^{1}H NMR, δ: 7.06 (d, 1 H, NH, J = 8.3 Hz); 3.7 (m, 1 H, C(2)H); 3.59 (s, 3 H, COOMe); 2.38 (m, 2 H, $C(4)H_2$); 1.98 (m, 1 H, $C(3)H_A$); 1.79 (m, 1 H, $C(3)H_B$); 1.39 (s, 9 H, $COOCMe_3$). MS (ESI), m/z (I_{rel} (%)): 262 $[M + H]^+$ (100). Calculated for $C_{11}H_{19}NO_6$: M = 261.04.

α-*tert*-Butyl γ-methyl *N*-Boc-L-glutamate (20). Pyridine (4.88 mL, 60.0 mmol), a solution of Boc_2O (19.6 g, 90.0 mmol) in Bu^tOH (45 mL), and DMAP (0.73 mg, 6.0 mmol) were added to a solution of compound **19** (15.7 g, 60.0 mmol) in Bu^tOH (30 mL). The reaction mixture was stirred for 24 h and diluted with water (200 mL). The product was extracted from the resulting oil with AcOEt (4×50 mL). The extract was washed with 10% $NaHCO_3$ and water and dried with $MgSO_4$. The solvent was removed under reduced pressure. The yield of compound **20** was 11.41 g (60%), yellow oil. ^{1}H NMR, δ: 7.15 (d, 1 H, NH, J = 7.8 Hz); 3.84 (ddd, 1 H, C(2)H, J = 9.0 Hz, J = 7.8 Hz, J = 5.2 Hz); 3.59 (s, 3 H, Me); 2.36 (m, 2 H, $C(4)H_2$); 1.92 (m, 1 H, $C(3)H_A$); 1.75 (m, 1 H, $C(3)H_B$); 1.39 (s, 9 H, CMe_3—Boc); 1.38 (s, 9 H, CMe_3—OBu^t). MS (ESI), m/z (I_{rel} (%)): 318 $[M + H]^+$ (100). Calculated for $C_{15}H_{27}NO_6$: M = 317.39.

α-*tert*-Butyl *N*-Boc-L-glutamate (21). A solution of compound **20** (1.3 g, 4.1 mmol) in acetone (15 mL) was cooled to −2 °C. A solution of NaOH (0.49 g, 12.3 mmol) in water (2 mL) was added. The reaction mixture was stirred at −2 °C for 1.5 h, diluted with water (70 mL), and washed with benzene. The aqueous layer was acidified with citric acid to pH ≈ 4 and the product was extracted with AcOEt (4×25 mL). The extract was washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel in chloroform—MeOH. The yield of compound **21** was 0.75 g (60%), colorless needle-like crystals, m.p. 154—156 °C. ^{1}H NMR, δ: 7.13 (d, 1 H, NH, J = 7.9 Hz); 3.82 (m, 1 H, C(2)H); 2.27 (m, 2 H, $C(4)H_2$); 1.86 (m, 1 H, $C(3)H_A$); 1.72 (m, 1 H, $C(3)H_B$); 1.39 (s, 9 H, CMe_3—Boc); 1.38 (s, 9 H, CMe_3—OBu^t). MS (ESI), m/z (I_{rel} (%)): 304 $[M + H]^+$ (100); 302 $[M - H]^-$ (100). Calculated for $C_{14}H_{25}NO_6$: M = 303.36.

***tert*-Butyl N^{α}-(*tert*-butoxycarbonyl)-N^{γ}-(1,2-dicarba-*closo*-dodecaboran-3-yl)-L-glutamate (22).** A solution of DCC (1.26 g, 6.09 mmol) in DMF (10 mL) was added to a solution of 3-aminocarborane (**1**) (0.97 g, 6.09 mmol), HOBt (0.82 g, 6.09 mmol), and compound **21** (1.85 g, 6.09 mmol) in DMF (20 mL). The reaction mixture was stirred at room temperature for 48 h and diluted with water (140 mL). The product was extracted

from the resulting oil with AcOEt (4×30 mL). The extract was washed with 10% $NaHCO_3$ and water and dried with $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel in chloroform—MeOH. The yield of compound **22** was 1.36 g (50%), colorless needle-like crystals, m.p. 167—169 °C. ^{1}H NMR, δ: 8.27 (s, 1 H, NH—carborane); 7.10 (d, 1 H, NH, J = 7.8 Hz); 5.06 (br.s, 2 H, 2 CH of carborane); 3.80 (m, 1 H, C(2)H); 3.0—1.3 (m, 10 H, 9 BH); 2.27 (m, 2 H, $C(4)H_2$); 1.88 (m, 1 H, $C(3)H_A$); 1.70 (m, 1 H, $C(3)H_B$); 1.40 (s, 9 H, CMe_3); 1.38 (s, 9 H, CMe_3). MS (ESI), m/z (I_{rel} (%)): 445 $[M + H]^+$ (100). Calculated for $C_{16}H_{36}B_{10}N_2O_5$: M = 444.58.

***N*$^{\gamma}$-(1,2-Dicarba-*closo*-dodecaboran-3-yl)-L-glutamine bis-(trifluoroacetate) (23).** A solution of compound **22** (1.36 g, 3.06 mmol) in TFA (5 mL) was stirred at room temperature for 5 h. The excess of TFA was removed under reduced pressure and the residue was triturated with hexane. The yield of compound **23** was 1.12 g (71%), yellow oil, $[\alpha]_D^{20}$ −3.96 (*c* 1, acetone). ^{1}H NMR, δ: 8.41 (s, 1 H, NH—carborane); 8.29 (br.s, 3 H, NH_3^+); 5.05 (br.s, 2 H, 2 CH of carborane); 3.94 (m, 1 H, C(2)H); 3.0—1.3 (m, 9 H, 9 BH); 2.40 (m, 2 H, $C(4)H_2$); 2.00 (m, 2 H, $C(3)H_2$). Found (%): C, 25.98; H, 4.46; N, 4.96; F, 21.55. $C_{11}H_{22}B_{10}N_2O_7F_6$. Calculated (%): C, 25.58; H, 4.29; N, 5.42; F, 22.07.

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