SYNTHESIS OF *N*-[(3-AMINO-1,2-DICARBA-*closo*-DODECABORAN-1-YL)-ACETYL] DERIVATIVES OF α-AMINO ACIDS

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The *N*-[(3-amino-1,2-dicarba-*closo*-dodecaboran-1-yl)acetyl] derivatives of α-amino acids were prepared starting from *N*-protected (Ac, Form, Bz, and Boc) 3-amino-1-(carboxymethyl)-*o*-carboranes and alkyl esters of natural α-amino acids using the carbodiimide method of coupling and removing the ester groups. All the amides obtained were diastereoisomeric mixtures. Some diastereoisomers were separated and the assignment of the absolute configuration of aminocarborane fragments was performed by X-ray crystallography.

Keywords: Amides; *N*,*N*′-Dicyclohexylcarbodiimide; Amino acids; Carboranes; Diastereoisomeric resolution; HPLC; NMR spectroscopy; X-ray crystallography.

Recently, synthetic aspects and potential fields of biomedical application of polyhedral carboranes having the unique structural and chemical properties have been the subject of intensive research[1–3]. Among others, carboranes having dissimilar polar functional groups on the carbon or boron atoms of the icosahedral cage might be important synthons for the incorporation of carborane unit into various biologically active molecules, such as peptides, porphyrins, etc. The first carborane amino acids bearing the functional groups of the opposite nature at boron and carbon atoms of the polyhedron were synthesized by Kahl and co-workers[4].

A general high-yield method for the preparation of carboranyl derivatives of amino acids, 3-amino-1-(carboxymethyl)-2-R-*o*-carborane hydrochlorides

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(R = H, Me, Ph), was developed starting from the readily available 3-amino-*o*-carboranes[5]. Carborane amino acid **1** can be considered as a boronated analogue of γ-aminobutyric acid (GABA) with the second and the third methylene group replaced by carbon and boron atoms of polyhedron, respectively (Fig. 1).

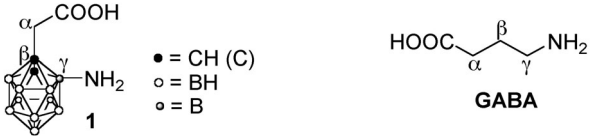
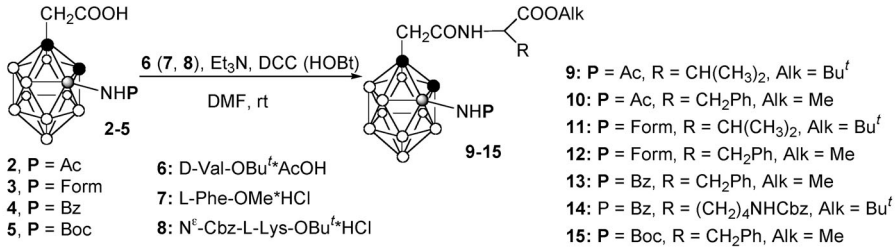


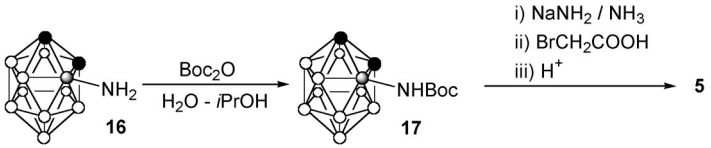
FIG. 1
Boronated analogues of γ-aminobutyric acid (BABA)

The purpose of the present work was the development of synthetic routes to *N*-[(3-amino-1,2-dicarba-*closo*-dodecaboran-1-yl)acetyl] derivatives of α-amino acids.



SCHEME 1

N-Protected 3-amino-1-(carboxymethyl)-*o*-carboranes **2**–**5** were used as starting materials for preparation of the target amides (Scheme 1). *N*-Acetyl-, *N*-formyl- and *N*-benzoyl-3-aminocarboranes (**2**, **3** and **4**, respectively) were obtained previously[5]. *N*-Boc derivative **5** was prepared by treatment of 3-amino-*o*-carborane **16** with Boc_2O in aqueous *i*-PrOH followed by introduction of 1-(carboxymethyl) fragment into *N*-Boc-3-amino-*o*-carborane **17** according to the described[5] procedure (Scheme 2).



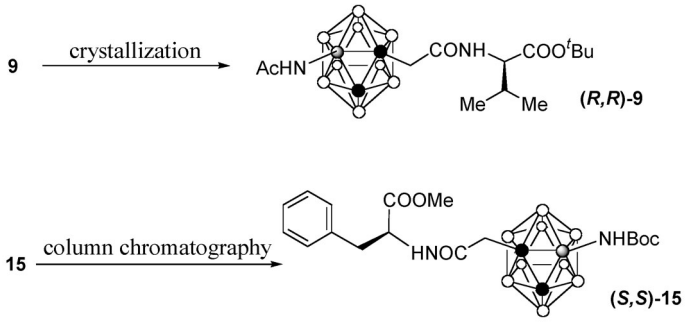
SCHEME 2

Coupling of *N*-protected carboranes **2**–**5** with alkyl esters of D-valine **6**, L-phenylalanine **7** and N^{ε}-Cbz-L-lysine **8** (Cbz = benzyloxycarbonyl) was carried out using various methods of activation of carboxylic group (mixed anhydrides, and carbodiimide). The best results (60–80% yields) were obtained while using *N*,*N*′-dicyclohexylcarbodiimide (DCC) in the presence of 1-hydroxybenzotriazole (HOBt) in DMF at room temperature.

Amides **9**–**15** were the mixtures of diastereoisomers, which were supported by ^{1}H NMR spectroscopy. The characteristic signals for distinguishing the diastereoisomers were the proton signals of alkyl (Me or *t*-Bu) ester groups. In the case of *N*-formyl derivatives **11** and **12** both diastereoisomers existed as *syn*/*anti* isomers due to the hindered rotation about the BN–CO bond, which resulted in doubling of some signals in ^{1}H NMR spectra recorded at ambient temperature.

The ratio of diastereoisomeric amides in **10**, **12**, **15** (containing the phenylalanine moiety) and compound **14** was also determined by UV-HPLC.

We managed to separate amides **9** and **15** into diastereoisomers. For convenience in the designation of the configuration of planar-chiral carboranes and their derivatives, we used the approach suggested for chiral 7,8-dicarba-*nido*-undecaboranes[6]. The observer looks onto the plane of $C^1R–C^2H–B^3NHX$ face of the carborane cage and then examines the positions of substituents according to the Cahn–Ingold–Prelog rule. Fractional crystallization of the diastereoisomeric mixture of **9** (Scheme 3) resulted in (*R*,*R*)-diastereoisomer ((*R*,*R*)-**9**; de 92% according to ^{1}H NMR) in 45% yield. Flash column chromatography (silica gel, benzene–ethyl acetate) of the diastereoisomeric mixture of **15** (Scheme 3) gave (*S*,*S*)-diastereoisomer ((*S*,*S*)-**15**; de 60% according to UV-HPLC) as a fast eluting diastereoisomer in 20% yield.



SCHEME 3

Absolute configuration in carborane fragments of (*R*,*R*)-**9** and (*S*,*S*)-**15** was determined by X-ray crystallography taking into account the known configuration of D-valine and L-phenylalanine moieties, respectively (Figs 2 and 3).

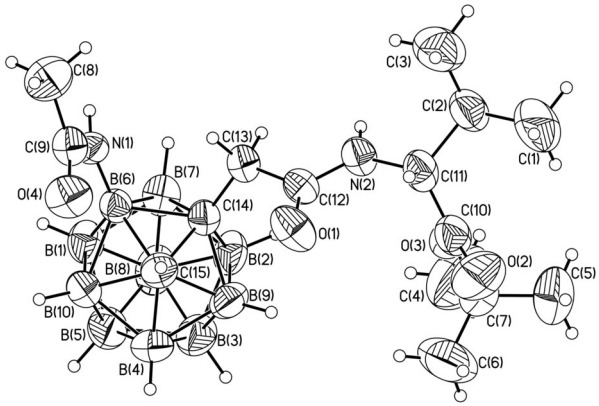


FIG. 2
X-ray structure of compound (*R*,*R*)-**9**

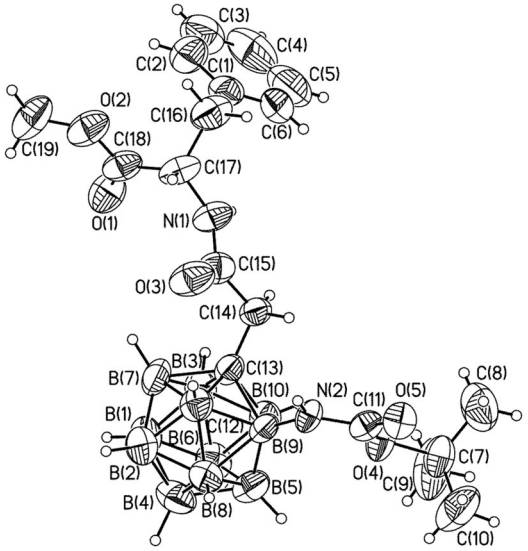
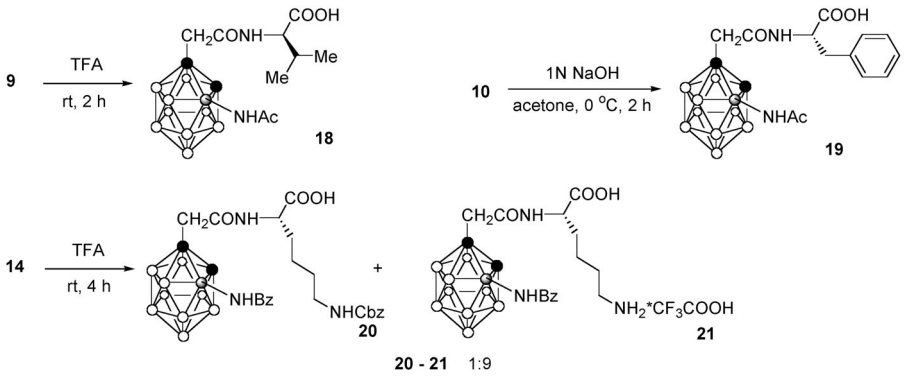


FIG. 3
X-ray structure of compound (*S*,*S*)-**15**

To prepare amides with free COOH groups we performed the removal of ester groups from amino acid moieties of the synthesized compounds using standard procedures (Scheme 4). Thus, *tert*-butyl ester was removed from the D-valine residue in amide **9** in trifluoroacetic acid (TFA) at room temperature. Removal of the methyl ester group from the L-phenylalanine moiety of amide **10** was carried out with 1 M aqueous NaOH in acetone under cooling. Compounds **18** and **19** were obtained in moderate yields (60–70%).



SCHEME 4

TFA treatment of amide **14**, containing the N^{ε}-Cbz-L-Lys-O*t*-Bu fragment, resulted (at room temperature for 2 h) not only in the cleavage of *tert*-butyl ester, but also in the removal of Cbz group from ε-NH_2 group of lysine (Scheme 4). According to ^{1}H NMR spectra the reaction product contained compounds **20** and **21** in the 1:9 ratio. Additional treatment with TFA at room temperature for 2 h did not lead to a change in the products ratio. Compound **21** as trifluoroacetate was isolated from the product mixture by flash column chromatography (silica gel, $CHCl_3$–MeOH) in 32% yield.

The structure of newly prepared compounds was confirmed by ^{1}H NMR, elemental analyses and mass spectra. It should be noted that in the APCI mass spectrum of compound **15** ($C_{19}H_{34}B_{10}N_2O_5$, M = 478.6), the molecular cluster ions were not detected, which is likely due to a high temperature of APCI probe (400 °C). At the same time, we observed the ions $[M - H - t\text{-BuOH}]^-$ 404 and $[M + H - COOt\text{-Bu}]^+$ 379, which was due to thermal decomposition of the parent compound.

In conclusion, coupling of *N*-protected 3-amino-1-(carboxymethyl)-*o*-carboranes and alkyl esters of natural amino acids carried out by the carbodiimide method results in the target amides. Removal of ester groups

from the amino acid moieties leads to the amides with free amino-acid COOH groups which can be subjected to further modifications.

EXPERIMENTAL

N-Acetyl-, *N*-formyl- and *N*-benzoyl-3-amino-1-(carboxymethyl)-1,2-dicarba-*closo*-dodecaboranes **2**–**4** were prepared according to the previously described procedure[5]. *tert*-Butyl D-valinate (**6**) was prepared as described previously[7]. All other reagents were commercial. Melting points were determined on a Boetius block and are uncorrected. Routine TLC monitoring of reaction mixtures was carried out using Sorbfil UV 254 (Russia) silica gel. Silica gel 60 (230–400 mesh) was used for flash chromatography. NMR spectra were recorded on a Bruker DRX 400 spectrometer operating at 400.13 MHz. DMSO-d_6 or $CDCl_3$ was used as the solvent. Proton chemical shifts are referenced to TMS and given in the δ-scale (ppm), coupling constants *J* in Hz. The capital letters A and B denote two protons bonded to the same carbon atom. Analytical UV-HPLC was performed on a Merck–Hitachi chromatograph with L-4000A intelligent pump, L-4000A UV detector, and D-2500A chromato-integrator with a Hibar pre-packed column RT250-4, LiChrosorb Si-60 (4 × 250 mm, 5 μm) column, with a flow rate of 1 ml/min, and by using a tunable UV set at 220 nm. Mixtures of hexane (solvent A) and *i*-PrOH (solvent B) were used as mobile phases. Microanalyses were carried out on a Perkin Elmer "CHN" PE 2400 (2nd) automated analyzer and were in good agreement with the calculated values. LCMS data were obtained by using a quadrupole Shimadzu LCMS-2010 system in negative (or positive) mode with an APCI probe installed with CH_3CN–H_2O as the solvent. The APCI probe temperature was set to 400 °C.

Coupling of *N*-Protected 3-Amino-1-(carboxymethyl)-1,2-dicarba-*closo*-dodecaboranes and Alkyl Esters of Amino Acids. General Procedure

DCC (0.6 mmol) was added to a stirred solution of *N*-protected 3-amino-1-(carboxymethyl)-1,2-dicarba-*closo*-dodecaborane **2**–**5** (0.6 mmol), hydrochloride or acetate of alkyl ester of amino acid **6**–**8** (0.6 mmol), TEA (0.6 mmol), HOBt (0.6 mmol) in DMF (5 ml). The reaction mixture was stirred at room temperature for 18 h, and then poured into cold water (25 ml). The precipitate was filtered off and washed with water (2 × 5 ml). The crude product was treated with acetone (5 ml) at room temperature for 1 h. The precipitate of *N*,*N*′-dicyclohexylurea was filtered off, and the filtrate was evaporated to dryness under reduced pressure. Crystallization in a hexane–acetone mixture or flash column chromatography gave amides **9**–**15**.

tert-Butyl N-[(3-acetamido-1,2-dicarba-closo-dodecaboran-1-yl)acetyl]-(R)-valinate (**9**). Yield 60%. M.p. 210–214 °C (hexane–acetone). For $C_{15}H_{34}B_{10}N_2O_4$ (414.6) calculated: 43.46% C, 8.27% H, 6.76% N; found: 43.80% C, 8.43% H, 6.76% N. ^{1}H NMR (DMSO-d_6): 0.879 d and 0.884 d, *J* = 7.2, 6 H ($(CH_3)_2$); 1.41 s and 1.42 s, 9 H ($COO(CH_3)_3$); 1.978 s and 1.983 s, 3 H ($COCH_3$); 2.01 m, 1 H (CH-*i*Pr); 1.4–2.8 m, 9 H (9 × BH); 2.94 d, *J* = 14.5 and 2.96 d, *J* = 14.2, 1 H (CH_A); 3.11 d, *J* = 14.2 and 3.14 d, *J* = 14.5, 1 H (CH_B); 3.99 dd, *J* = 8.0, 6.0 and 4.03 dd, *J* = 8.5, 5.9, 1 H (C_αH-Val); 5.21 br s, 1 H (CH-carborane); 8.38 m, 2 H (2 × NH). LCMS (APCI): $[M - H]^-$ 414.

tert-Butyl N-[(R)-(3-acetamido-1,2-dicarba-closo-dodecaboran-1-yl)acetyl]-(R)-valinate ((*R*,*R*)-**9**). Diastereoisomeric mixture **9** (700 mg) was crystallized twice from a hexane–acetone mixture to afford (*R*,*R*)-diastereoisomer of amide **9** (106 mg, 15%). M.p. 231–232 °C. For

$C_{15}H_{34}B_{10}N_2O_4$ (414.6) calculated: 43.46% C, 8.27% H, 6.76% N; found: 43.76% C, 8.33% H, 6.70% N. ^{1}H NMR (DMSO-d_6): 0.880 d, J = 7.0 and 0.885 d, J = 6.6, 6 H ($(CH_3)_2$); 1.42 s, 9 H ($COO(CH_3)_3$); 1.978 s, 3 H ($COCH_3$); 2.00 m, 1 H (CH-*i*Pr); 1.4–2.8 m, 9 H (9 × BH); 2.96 d, J = 14.8, 1 H (CH_A); 3.11 d, J = 14.8, 1 H (CH_B); 3.99 dd, J = 8.2, 6.1, 1 H (C_αH-Val); 5.20 br s, 1 H (CH-carborane); 8.39 br s, 1 H (NH-carborane); 8.40 d, J = 8.1, 1 H (NH-Val).

Methyl N-[(3-acetamido-1,2-dicarba-closo-dodecaboran-1-yl)acetyl]-(S)-phenylalaninate (**10**). Yield 60%. M.p. 58–65 °C (hexane–acetone). For $C_{16}H_{28}B_{10}N_2O_4$ (420.5) calculated: 45.70% C, 6.71% H, 6.66% N; found: 46.09% C, 6.84% H, 6.80% N. ^{1}H NMR (DMSO-d_6): 1.94 s and 1.96 s, 3 H ($COCH_3$); 1.4–2.8 m, 9 H (9 × BH); 2.82–2.90 m, 2 H (CH_A-Phe and CH_A-carborane); 2.97–3.08 m, 2 H (CH_B-Phe and CH_B-carborane); 3.61 s and 3.62 s, 3 H (OCH_3); 4.48 m, 1 H (C_αH-Phe); 5.08 br s and 5.10 br s, 1 H (CH-carborane); 7.22 m, 3 H (Ph); 7.29 m, 2 H (Ph); 8.34 br s, 1 H (NH-carborane); 8.73 d, J = 8.3 and 8.74 d, J = 7.5, 1 H (NH-Phe). HPLC (A:B 5:1): τ_{R1} 9.80, τ_{R2} 11.27 min.

tert-Butyl N-[(3-formamido-1,2-dicarba-closo-dodecaboran-1-yl)acetyl]-(R)-valinate (**11**). Yield 70%. M.p. 144–146 °C (hexane–acetone). For $C_{14}H_{32}B_{10}N_2O_4$ (400.5) calculated: 41.98% C, 8.05% H, 6.99% N; found: 42.38% C, 8.55% H, 6.86% N. ^{1}H NMR (DMSO-d_6): 0.88 m, 6 H ($(CH_3)_2$); 1.41 s and 1.42 s, 9 H ($COO(CH_3)_3$); 2.02 m, 1 H (CH-*i*Pr); 1.4–2.8 m, 9 H (9 × BH); 3.02 m, 1 H (CH_A); 3.21 m, 1 H (CH_B); 4.02 m, 1 H (C_αH-Val); 5.04 br s and 5.22 br s, 1 H (CH-carborane); 8.28 br d, J = 2.0 and 8.60 br s, 1 H (COH); 8.36 br s, 1 H (NH-carborane); 8.39 d, 8.42 d, 8.48 d, 8.49 d, J = 8.3, 1 H (NH-Val). LCMS (APCI): $[M - H]^-$ 399.

Methyl N-[(3-formamido-1,2-dicarba-closo-dodecaboran-1-yl)acetyl]-(S)-phenylalaninate (**12**). Yield 70%. M.p. 68–72 °C. For $C_{15}H_{26}B_{10}N_2O_4$ (406.5) calculated: 44.32% C, 6.45% H, 6.89% N; found: 44.53% C, 6.70% H, 6.88% N. ^{1}H NMR (DMSO-d_6): 1.4–2.8 m, 9 H (9 × BH); 2.82–2.98 m, 2 H (CH_A-Phe and CH_A-carborane); 3.00–3.12 m, 2 H (CH_B-Phe and CH_B-carborane); 3.62 s and 3.63 s, 3 H (OCH_3); 4.98 m, 1 H (C_αH-Phe); 4.89 br s, 4.94 br s and 5.10 br s, 1 H (CH-carborane); 7.22 m, 3 H (Ph); 7.30 m, 2 H (Ph); 8.23 br d, 8.24 br d, J = 2.0 and 8.53 br s, 1 H (COH); 8.33 br s, 1 H (NH-carborane); 8.75 d, 8.76 d, 8.82 d, 8.83 d, J = 8.0, 1 H (NH-Phe). LCMS (APCI): $[M - H]^-$ 405. HPLC (A:B 5:1): τ_{R1} 7.46, τ_{R2} 8.50 min.

Methyl N-[(3-benzamido-1,2-dicarba-closo-dodecaboran-1-yl)acetyl]-(S)-phenylalaninate (**13**). Yield 60%. M.p. 171–173 °C. For $C_{21}H_{30}B_{10}N_2O_4$ (482.6) calculated: 52.27% C, 6.27% H, 5.80% N; found: 52.68% C, 6.77% H, 5.38% N. ^{1}H NMR (DMSO-d_6): 1.4–2.8 m, 9 H (9 × BH); 2.78–3.12 m, 4 H (CH_2-Phe and CH_2-carborane); 3.579 s and 3.584 s, 3 H (OCH_3); 4.43 m and 4.50 m, 1 H (C_αH-Phe); 5.20 br s and 5.25 br s, 1 H (CH-carborane); 7.13–7.28 m, 5 H (Ph); 7.51 m, 2 H (Ph); 7.60 m, 1 H (Ph); 7.96 m, 2 H (Ph); 8.65 br s, 1 H (NH-carborane); 8.75 d and 8.77 d, J = 7.3, 1 H (NH-Phe). LCMS (APCI): $[M - H]^-$ 482. HPLC (A:B 80:1): τ_{R1} 7.68, τ_{R2} 11.15 min.

tert-Butyl N^ε*-(benzyloxycarbonyl)-*N^α*-[(3-benzamido-1,2-dicarba-closo-dodecaboran-1-yl)acetyl]-(S)-lysinate* (**14**). Yield 57%. M.p. 57–58 °C. For $C_{29}H_{45}B_{10}N_3O_6$ (639.8) calculated: 54.44% C, 7.09% H, 6.57% N; found: 54.73% C, 7.21% H, 6.78% N. ^{1}H NMR (DMSO-d_6): 1.30 m, 2 H (CH_2-Lys); 1.36 s and 1.39 s, 9 H ($COOC(CH_3)_3$); 1.4–1.7 m, 4 H (CH_2-CH_2-Lys); 1.5–2.8 m, 9 H (9 × BH); 2.95 m, 2 H ($C_\varepsilon H_2$-Lys); 3.00 d and 3.03 d, J = 14.7, 1 H (CH_A-carborane); 3.137 d and 3.145 d, J = 14.7, 1 H (CH_B-carborane); 3.98 m and 4.05 m, 1 H (C_αH-Lys); 4.98 s and 4.99 s, 2 H (CH_2-Ph); 5.33 br s, 1 H (CH-carborane); 7.21 m, 1 H (N^εH-Lys); 7.33 m, 5 H (Ph); 7.50 m, 2 H (Ph); 7.59 m, 1 H (Ph); 7.97 m, 2 H (Ph); 8.53 d and 8.54 d,

J = 7.4, 1 H (N^{α}H-Lys); 8.68 br s and 8.70 br s, 1 H (NH-carborane). LCMS (APCI): $[M - H]^-$ 639. HPLC (A:B 30:1): τ_{R1} 32.00, τ_{R2} 34.11 min.

Methyl N-{[3-(tert-butoxycarbonamido)-1,2-dicarba-closo-dodecaboran-1-yl]acetyl}-(S)-phenylalaninate (**15**). Yield 60%. M.p. 143–145 °C. For $C_{19}H_{34}B_{10}N_2O_5$ (478.6) calculated: 47.68% C, 7.16% H, 5.85% N; found: 47.95% C, 7.20% H, 5.68% N. ^{1}H NMR (DMSO-d_6): 1.39 s and 1.40 s, 9 H ($COOC(CH_3)_3$); 1.4–2.8 m, 9 H (9 × BH); 2.86 m, 2 H (CH_A-Phe and CH_A-carborane); 3.05 m, 2 H (CH_B-Phe and CH_B-carborane); 3.62 s, 3 H (OCH_3); 4.50 m, 1 H (C_{α}H-Phe); 4.85 br s and 4.89 br s, 1 H (CH-carborane); 7.22 m, 3 H (Ph); 7.28 m, 2 H (Ph); 7.48 br s, 1 H (NH-carborane); 8.74 d, *J* = 7.6, 1 H (NH-Phe). LCMS (ESI): $[M + Na]^+$ 501, $[M + K]^+$ 517, $[M + Cu]^+$ 542. HPLC (A:B 40:1): τ_{R1} 9.65, τ_{R2} 12.06 min.

Methyl N-{[(S)-3-(tert-butoxycarbonamido)-1,2-dicarba-closo-dodecaboran-1-yl]acetyl}-(S)-phenylalaninate ((*S*,*S*)-**15**). Diastereoisomeric mixture **15** (107 mg) was subjected to flash column chromatography (silica gel, benzene–AcOEt) to afford (*S*,*S*)-diastereoisomer of amide **15** (14 mg, 13%) as a fast eluting isomer. HPLC (A:B 40:1): τ_{R1} 9.65 min, de 60%. M.p. 165–168 °C. For $C_{19}H_{34}B_{10}N_2O_5$ (478.6) calculated: 47.68% C, 7.16% H, 5.85% N; found: 47.93% C, 7.21% H, 5.68% N. ^{1}H NMR (DMSO-d_6): 1.39 s, 9 H ($COOC(CH_3)_3$); 1.4–2.8 m, 9 H (9 × BH); 2.84 d, *J* = 15.0, 1 H (CH_A-carborane); 2.87 dd, *J* = 14.0, 9.0, 1 H (CH_A-Phe); 3.04 d, *J* = 15.0, 1 H (CH_B-carborane); 3.05 dd, *J* = 14.0, 5.5, 1 H (CH_B-Phe); 3.62 s, 3 H (OCH_3); 4.48 ddd, *J* = 9.0, 8.0, 5.5, 1 H (C_{α}H-Phe); 4.89 br s, 1 H (CH-carborane); 7.20 m, 3 H (Ph); 7.24 m, 2 H (Ph); 7.48 br s, 1 H (NH-carborane); 8.76 d, *J* = 7.6, 1 H (NH-Phe). A mixture of diastereoisomers of amide **15** (58 mg, 54%) and (*R*,*S*)-diastereoisomer of amide **15** (10 mg, 9%, semisolid; de 94%, HPLC (A:B 40:1): τ_{R2} 12.06 min) were also collected.

N-(3-*tert*-Butoxycarbonamido)-1,2-dicarba-*closo*-dodecaborane (**17**)

A solution of Boc_2O (0.822 g, 3.77 mmol) in propan-2-ol (3 ml) was added dropwise to a stirred suspension of 3-amino-*o*-carborane **16** (0.300 g, 1.88 mmol) in water (3 ml) during 15 min. The mixture was stirred at room temperature for 20 h. The precipitate was filtered off, and washed successively with water and benzene. Compound **17** (0.297 g, 50%) was obtained. M.p. 147–149 °C. For $C_7H_{21}B_{10}NO_2$ (259.4) calculated: 32.42% C, 8.16% H, 5.40% N; found: 32.72% C, 8.26% H, 5.45% N. ^{1}H NMR ($CDCl_3$): 1.43 s, 9 H ($COOC(CH_3)_3$); 1.4–3.2 m, 9 H (9 × BH); 4.29 br s, 2 H (2 × CH); 4.81 br s, 1 H (NH).

N-(3-*tert*-Butoxycarbonamido)-1-(carboxymethyl)-1,2-dicarba-*closo*-dodecaborane (**5**)

A solution of compound **17** (0.259 g, 1 mmol) in THF (10 ml) was added via syringe to a stirred $NaNH_2$ (0.12 g, 3 mmol) in liquid ammonia (50 ml) at –45 °C. The reaction mixture was stirred at –50 °C for 0.5 h. Then, sodium bromoacetate (0.5 g, 3.1 mmol) was added and the mixture was stirred at –50 °C for 2.5 h. The liquid ammonia was evaporated and the residue was dissolved in water (50 ml) followed by acidification with 10% HCl at 0 °C. The solid product was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was crystallized from a heptane–ethyl acetate mixture to give compound **5** (0.168 g, 53%). M.p. 178–179 °C. For $C_9H_{23}B_{10}NO_4$ (317.4) calculated: 34.06% C, 7.30% H, 34.06% B, 4.41% N; found: 34.53% C, 7.50% H, 33.42% B, 4.18% N. ^{1}H NMR (DMSO-d_6): 1.40 s, 9 H ($COOC(CH_3)_3$); 1.3–3.0 m, 9 H (9 × BH); 3.08 d, *J* = 15.6, 1 H (CH_A); 3.19 d, *J* = 15.6, 1 H (CH_B); 5.08 br s, 1 H (CH); 7.62 br s, 1 H (NH); 13.06 br s, 1 H (COOH).

N-[(3-Acetamido-1,2-dicarba-*closo*-dodecaboran-1-yl)acetyl]-(*R*)-valine (**18**)

A solution of amide **9** (0.220 g, 0.531 mmol) in TFA (2.5 ml) was stirred at room temperature for 2 h. The reaction solution was evaporated to dryness under reduced pressure. The residue was dried over NaOH in vacuum and then crystallized from a hexane–acetone mixture to afford compound **18** (0.127 g, 67%). M.p. 115–120 °C. For $C_{11}H_{26}B_{10}N_2O_4$ (358.5) calculated: 36.86% C, 7.31% H, 7.82% N; found: 37.13% C, 7.51% H, 7.42% N. ^{1}H NMR (DMSO-d_6): 0.89 d, J = 6.8, 6 H ($(CH_3)_2$); 1.4–2.8 m, 9 H (9 × BH); 1.978 s and 1.984 s, 3 H ($COCH_3$); 2.05 m, 1 H (CH-*i*Pr); 2.94 d, J = 15.0 and 3.01 d, J = 14.7, 1 H (CH_A); 3.10 d, J = 14.7 and 3.19 d, J = 15.0, 1 H (CH_B); 4.09 dd and 4.12 dd, J = 8.3, 5.6, 1 H (C_αH-Val); 5.22 br s, 1 H (CH-carborane); 8.37 d, J = 8.3, 1 H (NH-Val); 8.38 br s, 1 H (NH-carborane).

N-[(3-Acetamido-1,2-dicarba-*closo*-dodecaboran-1-yl)acetyl]-(*S*)-phenylalanine (**19**)

To a stirred solution of amide **10** (0.566 g, 1.346 mmol) in acetone (4 ml) 1 M NaOH (3.25 ml) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then kept at +4 °C overnight, and extracted with diethyl ether (10 ml). The aqueous layer was acidified with concentrated HCl to pH 2–3 and then extracted with AcOEt (3 × 5 ml). Organic layers were dried with Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was crystallized from a hexane–acetone mixture to give compound **19** (0.323 g, 59%). M.p. 206–210 °C. For $C_{15}H_{26}B_{10}N_2O_4$ (406.5) calculated: 44.32% C, 6.45% H, 6.89% N; found: 44.78% C, 6.52% H, 6.58% N. ^{1}H NMR (DMSO-d_6): 1.4–2.8 m, 9 H (9 × BH); 1.94 s and 1.96 s, 3 H ($COCH_3$); 2.82 m, 2 H (CH_A-Phe and CH_A-carborane); 2.99 d and 3.00 d, J = 15.0, 1 H (CH_B-carborane); 3.05 dd and 3.09 dd, J = 8.7, 4.8, 1 H (CH_B-Phe); 4.42 m, 1 H (C_αH-Phe); 5.08 br s and 5.10 br s, 1 H (CH-carborane); 7.16–7.30 m, 5 H (Ph); 8.33 br s, 1 H (NH-carborane); 8.58 d, J = 8.5 and 8.59 d, J = 7.9, 1 H (NH-Phe). LCMS (APCI): $[M + H]^+$ 407.

N^2-[(3-Benzamido)-1,2-dicarba-*closo*-dodecaboran-1-yl)acetyl]-(*S*)-lysine Trifluoroacetate (**21**)

A solution of compound **14** (0.139 g, 0.218 mmol) in TFA (2 ml) was stirred at room temperature for 4 h. The solution was evaporated to dryness under reduced pressure. The residue was subjected to flash column chromatography (silica gel, $CHCl_3$–MeOH) to yield compound **21** (39 mg, 32%) as a slow-eluting compound. M.p. 160–162 °C. For $C_{17}H_{31}B_{10}N_3O_4 \cdot CF_3COOH$ (563.6) calculated: 40.49% C, 5.72% H, 10.11% F, 7.46% N; found: 40.09% C, 6.00% H, 9.80% F, 7.21% N. ^{1}H NMR (DMSO-d_6): 1.30 m, 2 H (CH_2-Lys); 1.50 m, 4 H (CH_2-CH_2-Lys); 1.4–2.8 m, 9 H (9 × BH); 2.69 m, 2 H ($C_\varepsilon H_2$-Lys); 3.03 d and 3.08 d, J = 14.3, 1 H (CH_A-carborane); 3.16 d and 3.21 d, J = 14.3, 1 H (CH_B-carborane); 3.87 m, 1 H (C_αH-Lys); 5.30 br s and 5.41 br s, 1 H (CH-carborane); 7.48 m, 2 H (Ph); 7.57 m, 1 H (Ph); 8.00 m, 2 H (Ph); 8.13 d and 8.20 d, J = 7.0, 1 H (N^αH-Lys); 8.97 br s and 9.13 br s, 1 H (NH-carborane). LCMS (APCI): $[M - H]^-$ 449.

X-ray Analysis

Data for compounds (*R*,*R*)-**9** and (*S*,*S*)-**15** were collected with an XCALIBUR-3 diffractometer with graphite-monochromated MoKα radiation. The structures were solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined aniso-

tropically. The hydrogen atoms involved in hydrogen bonding were located in electron density maps. The rest of the hydrogen atoms was placed in idealized positions and allowed to ride on the C atoms to which they are bonded. CCDC 661110 (for (*R*,*R*)-**9**) and 661111 (for (*S*,*S*)-**15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Crystal data for (*R*,*R*)-**9**: M_r = 414.54; 0.48 × 0.18 × 0.12 mm; colorless needle; T = 295 K; monoclinic; space group $P2_1$; a = 10.4977(3) Å, b = 9.3633(3) Å, c = 12.8510(5) Å; β = 92.277(3)°; V = 1262.17(7) Å^3; p_{calc} = 1.091 g cm^{-3}; θ_{max} = 26.38; R_1 = 3.92%.

Crystal data for (*S*,*S*)-**15**: M_r = 478.58; 0.33 × 0.24 × 0.12 mm; colorless prism; T = 295 K; monoclinic; space group $P2_1$; a = 7.3345(11) Å, b = 19.001(2) Å, c = 10.0993(10) Å; β = 103.402(10)°; V = 1369.2(3) Å^3; p_{calc} = 1.161 g cm^{-3}; θ_{max} = 26.37; R_1 = 4.16%.

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REFERENCES

1. Soloway A. H., Tjarks W., Barnum A., Rong F.-G., Barth R. F., Codogni I. M., Wilson J. G.: *Chem. Rev.* **1998**, *98*, 1515.
2. Valliant J. F., Guenther K. J., King A. S., Morel P., Schaffer P., Sogbein O. O., Stephenson K. A.: *Coord. Chem. Rev.* **2002**, *232*, 173.
3. Bregadze V. I., Sivaev I. B., Glazun S. A.: *Anti-Cancer Agents Med. Chem.* **2006**, *6*, 75.
4. Kasar R. A., Knudsen G. M., Kahl S. B.: *Inorg. Chem.* **1999**, *38*, 2936.
5. Olshevskaya V. A., Ayuob R., Brechko Zh. G., Petrovskii P. V., Kononova E. G., Levit G. L., Krasnov V. P., Charushin V. N., Chupakhin O. N., Kalinin V. N.: *J. Organomet. Chem.* **2005**, *690*, 2761.
6. Brunner H., Apfelbacher A., Zabel M.: *Eur. J. Inorg. Chem.* **2001**, 917.
7. Krasnov V. P., Levit G. L., Bukrina I. M., Demin A. M., Chupakhin O. N., Yoo J. U.: *Tetrahedron: Asymmetry* **2002**, *13*, 1911.