Synthesis of a novel planar-chiral *nido*-carborane amino acid

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The deboronation of enantiomers of planar-chiral benzyl (3-formamido-1,2-dicarba-*closo*-dodecaboran-1-yl)acetate gave the individual (R_P)- and (S_P)-enantiomers (*ee* > 98%) of a new amino acid containing a *nido*-carborane fragment, (3-ammonio-7,8-dicarba-*nido*-undecaboran-7-yl)acetic acid. Chiral HPLC methods for the analysis of enantiomeric purity of this compound was developed.

Key words: carborane, planar chirality, amino acid, deboronation.

Boron neutron capture therapy (BNCT) is a high-tech modern method of cancer treatment based on the combined effect of two components on tumor cells: thermal neutrons and a drug containing ^{10}B isotopes. The capture of a neutron by the isotope ^{10}B results in the emission of high-energy α-particles, which locally damage the cells with accumulated boron-containing compounds.

Derivatives of 1,2-dicarba-*closo*-dodecaborane (*closo*-carborane) are currently being actively studied as potential sources of boron. The carborane molecule has a polyhedral structure and contains 10 boron atoms. Its derivatives are characterized by high stability, lipophilicity, and low toxicity and have a unique property of "three-dimensional aromaticity". Compounds based on 7,8-dicarba-*nido*-undecaborane (*nido*-carborane) obtained by deboronation of the corresponding *closo*-carborane derivatives have similar properties; however, the presence of a negatively charged *nido*-carborane moiety provides better solubility in aqueous media.[1]

Derivatives of biologically active compounds containing fragments of carboranes are of considerable interest for modern medicinal chemistry,[2—4] primarily for use in BNCT.[5—12] Carboranyl derivatives of amino acids and peptides occupy an important place among potential agents for BNCT.[13—17]

Earlier, we have developed methods for the preparation of *closo*-carborane-containing analogs of amino acids and peptides[18—20] and derivatives of polyfunctional amino acids containing a *closo*-carborane moiety in the side chain.[21—23] Among the chiral carboranyl derivatives of natural amino acids, there are compounds with high piezoelectric activity.[20,24]

Polar *nido*-carborane derivatives have a high potential for the use in BNCT, among which one can find water-soluble compounds with a high boron content.[1,25—27] In addition, *nido*-carborane derivatives can be a basis for catalysts,[28—30] luminescent materials,[31,32] and molecular switches.[33]

In the present work, we for the first time obtained (3-ammonio-7,8-dicarba-*nido*-undecaboran-7-yl)acetic acid (**1**) in enantiomerically pure form. This amino acid possesses the unique property of planar chirality, since its molecule contains three different substituents at one carborane face, and exists in the form of (R_P)- and (S_P)-enantiomers (Fig. 1).

Chiral derivatives of carborane are of particular interest, for example, for the development of new catalysts and materials.[20,28,29] Earlier, we have developed synthetic approaches to some enantiopure 1-substituted derivatives of 3-amino-*closo*-carborane.[34—36] Thus, we used diastereoselective acylation with (*S*)-naproxen acyl chloride[37] and *N*-protected (*S*)-amino acyl chlorides to separate the enantiomers of planar-chiral 3-aminocarborane derivatives.[38,39]

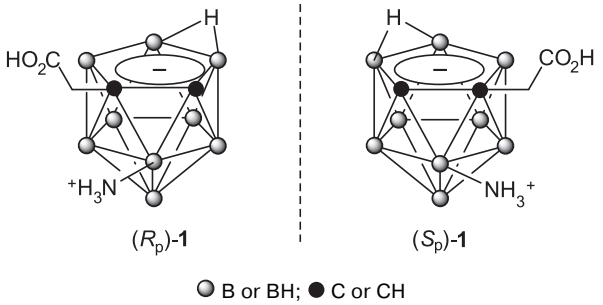

Fig. 1. The structures of (R_P)- and (S_P)-enantiomers of (3-ammonio-7,8-dicarba-*nido*-undecaboran-7-yl)acetic acid (**1**).

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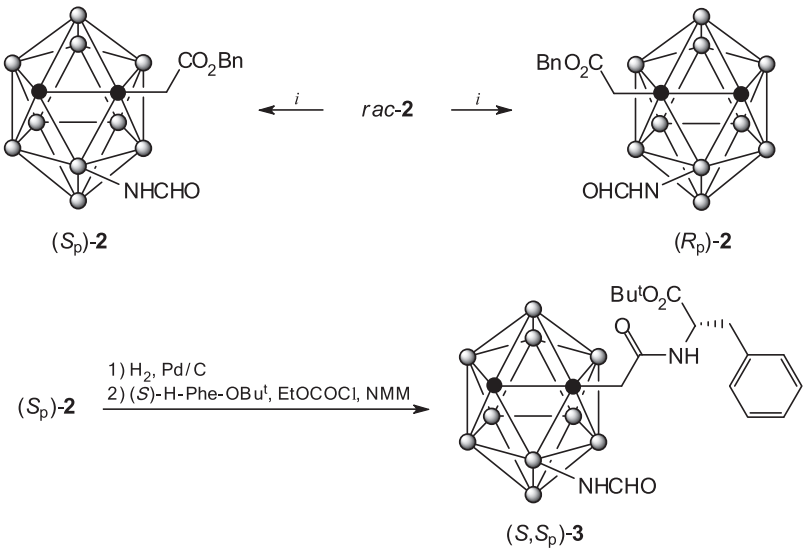
Scheme 1



○ B or BH; ● C or CH

i. Preparative chiral HPLC.

NMM is *N*-methylmorpholine.

We successfully selected the conditions for the separation of racemate **2** using preparative HPLC on a chiral stationary phase (CSP) and obtained individual enantiomers (R_P)-**2** and (S_P)-**2** (*ee* > 99%) (Scheme 1).[40] The configurations of compounds (R_P)-**2** and (S_P)-**2** were assigned based on the X-ray diffraction data of amide (S,S_P)-**3** obtained by the transformations of compound (S_P)-**2**.

We carried out the removal of the formyl group from enantiomerically pure compounds (R_P)-**2** and (S_P)-**2** using the method we proposed earlier[40] (Scheme 2). Treatment of the resulting amino esters (R_P)-**4** and (S_P)-**4** with cesium fluoride in benzyl alcohol led to a mixture of planar-chiral deboronation products **5** and **6** with a predominance of the target amino esters **5**. The preparative yields of compounds (R_P)-**5** and (S_P)-**5** were 64 and 55%, respectively, calculated on *closo*-carboranylamino ester **4**. Benzyl esters (R_P)-**6** and (S_P)-**6** were isolated in 20% yields. When the deboronation was carried out in ethanol, the process was complicated by transesterification and led to difficult-to-separate mixtures of compounds.

The structure of the planar-chiral amino ester (R_P)-**5** was confirmed by X-ray diffraction data (Fig. 2). Crystals of compound (R_P)-**5** belong to the chiral space group $P2_12_12_1$, the unit cell includes four structurally independent molecules. The geometry of the icosahedral *nido*-carborane cage of the molecule is slightly distorted, similarly as it is in the case of 1-unsubstituted 3-ammonio-7,8-dicarba-*nido*-undecaborane.[41] The main molecular packing motif of compound (R_P)-**5** is the alternation of layers formed by the *nido*-carborane clusters and the phenyl fragments and oriented parallel to the *a*0*b* plane (Fig. 3).

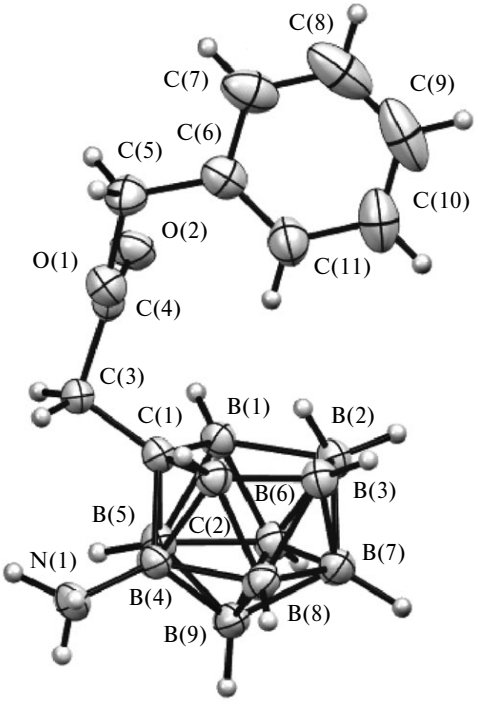
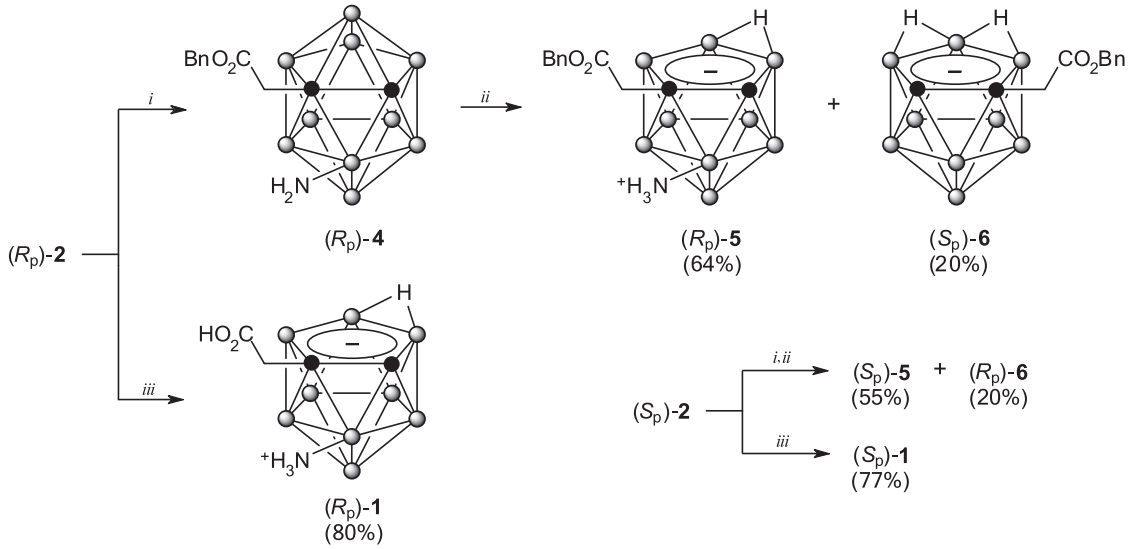


Fig. 2. A general view of the molecule (R_P)-**5** represented by thermal vibration ellipsoids with a 50% probability.

Scheme 2



Reagents and conditions: *i*. AcCl, BnOH (see Ref. 40); *ii*. CsF (3 equiv.), HCl (2 equiv.), BnOH, 80 °C; *iii*. 1) CsF, EtOH, Δ; 2) HCl/AcOH.

The deboronation of compounds (R_P)-**2** and (S_P)-**2** containing a formamido group at the atom B(3) under the action of CsF proceeded with a higher regioselectivity than in the case of B(3)-amino derivatives **4**. Treatment of enantiomerically pure formamido esters **2** with cesium fluoride in ethanol and the subsequent removal of the protective groups using a mixture of concentrated hydrochloric acid and acetic acid allowed us to obtain free amino acids (R_P)-**1** and (S_P)-**1** in up to 80% total yield (see Scheme 2). Similarly, racemic amino acid (R_PS_P)-**1** was synthesized starting from racemic compound **2**.

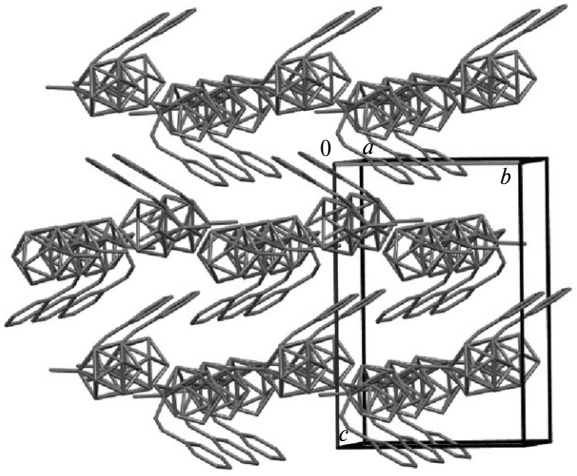


Fig. 3. A fragment of the molecular packing of (R_P)-**5** (hydrogen atoms are omitted).

The structure and purity of the compounds **1**, **5**, and **6** were confirmed by the NMR spectroscopy and high-resolution mass spectrometry data. The ^{1}H, ^{11}B, and ^{13}C NMR spectra contain signals for hydrogen (δ_H 1.7—1.9), boron (δ_B −36÷−38), and carbon atoms (δ_C 47—48), which are in the resonance range of the *nido*-carborane cluster. The ^{1}H NMR spectra also exhibit a signal at δ −2.3÷−2.6, which is characteristic of the bridging proton B—H—B located at the "open" face of *nido*-carborane. It was found that deboronation and removal of protective groups are not accompanied by racemization. The HPLC on CSP showed that enantiomeric purity of amino esters (R_P)-**5** and (S_P)-**5** was >98%. The absence of racemization in the synthesis of individual enantiomers of *nido*-carborane amino acids **1** was confirmed based on the analysis of compound (R_P)-**1** by HPLC on CSP in comparison with racemate **1**.

In conclusion, we for the first time proposed approaches to the preparation of (R_P)- and (S_P)-enantiomers of planar-chiral *nido*-carborane amino acid **1** and its benzyl ester **5**. Single crystals of the enantiomerically pure planar-chiral derivative of *nido*-carborane (R_P)-**5** were obtained. The *nido*-carborane amino acid derivatives are of interest as building blocks for the preparation of enantiopure carborane-containing derivatives of biomolecules, as well as chiral ligands.

Experimental

Benzyl (3-formamido-1,2-dicarba-*closo*-dodecaboran-1-yl)-acetates (R_PS_P)-**2**, (R_P)-**2**, and (S_P)-**2** and benzyl (3-amino-1,2-dicarba-*closo*-dodecaboran-1-yl)acetates (R_P)-**4** and (S_P)-**4** were

obtained according to the known procedures.[40] The other reagents were commercially available. The solvents were purified and dried using standard procedures.

^{1}H, ^{11}B, and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (500, 160, and 125 MHz, respectively) in DMSO-d_6 at 25 °C using $SiMe_4$ as an internal standard (δ 0.00 in the ^{1}H and ^{13}C NMR spectra) and $BF_3 \cdot Et_2O$ as an external standard (δ 0.00 in the ^{11}B NMR spectra). The ^{11}B and ^{13}C NMR spectra were recorded using broadband proton decoupling. Melting points of compounds were measured on a Stuart SMP3 apparatus (Barloworld Scientific, UK). The optical rotation was measured on a Perkin-Elmer M341 polarimeter (Perkin-Elmer Instruments, USA). Specific rotation is expressed in (deg mL) (g dm)$^{-1}$, solution concentration in g (100 mL)$^{-1}$. Elemental analysis was performed on a PerkinElmer 2400 II automatic CHNS-O analyzer. High-resolution mass spectra (HRMS) were recorded on a Bruker maXis Impact HD instrument, using electrospray ionization (ESI) in the negative ion mode; the carrier gas (nitrogen) flow rate was 4 L min^{-1}, the pressure in the nebulizer was 0.4 bar, the needle voltage was 4.5 kV. HPLC analysis was carried out on a Knauer Smartline-1100 chromatograph (Knauer Wissenschaftliche Geräte, Germany) on a Chiralcel OD-H column (250×4.6 mm, sorbent 5 μm) (Daicel Corp., Japan); detection at a wavelength of 220 nm; the eluent flow rate was 1 mL min^{-1}. The mobile phase was hexane—Pr^{i}OH, 2 : 1 (for compound **5**) or hexane—Pr^{i}OH—CF_3CO_2H, 2 : 1: 0.02 (for compound **1**). Flash column chromatography was carried out on Silica gel 60 (0.040—0.063 mm) (Alfa Aesar, UK). Sorbfil plates (Imid Ltd., Russia) were used for TLC. UV light (254 nm) and iodine vapors were used for visualization.

Deboronation of compounds (R_P)-4 and (S_P)-4 (general procedure). Cesium fluoride (0.28 g, 1.83 mmol) and 35% HCl (d = 1.75 g mL^{-1}) (0.1 mL, 1.22 mmol) were added to a solution of benzyl (R_P)- or (S_P)-(3-amino-1,2-dicarba-*closo*-dodecaboran-1-yl)acetate (**4**) (0.19 g, 0.61 mmol) in BnOH (6.2 mL). The mixture was stirred at 80 °C (in a flask) for 12 h, followed by the addition of EtOAc (25 mL). The resulting solution was washed with water (3×20 mL) and concentrated *in vacuo*. The residue was treated with water (15 mL), followed by concentration (the procedure was repeated 4 times). The residue was subjected to flash chromatography using a mixture of $CHCl_3$—MeOH (95 : 5) for elution to obtain benzyl (R_P)- or (S_P)-(3-ammonio-7,8-dicarba-*nido*-undecaboran-7-yl)acetates (R_P)-**5** or (S_P)-**5**; further elution with 95% aqueous EtOH gave benzyl (S_P)- or (R_P)-(7,8-dicarba-*nido*-undecaboran-7-yl)acetates (S_P)-**6** or (R_P)-**6**.

Benzyl (R_P)-(3-ammonio-7,8-dicarba-*nido*-undecaboran-7-yl)acetate ((R_P)-5). The yield was 0.12 g (64%). A colorless powder, m.p. 214.6—216.5 °C; $[\alpha]_D^{22}$ −30.3 (*c* 0.6, MeOH); R_f = 0.38 ($CHCl_3$—MeOH, 95 : 5); *ee* 99%. HPLC, τ_R 8.5 min. ^{1}H NMR, δ: −2.37 (br.s, 1 H, BH); −0.70—2.30 (br.s, 8 H, 8 BH); 1.86 (s, 1 H, CH_{carb}); 2.45 (d, 1 H, $H_B(2)$, J = 16.6 Hz); 2.54 (d, 1 H, $H_A(2)$, J = 16.6 Hz); 5.12 (d, 1 H, C$\underline{H}_B$Ph, J = 12.6 Hz); 5.16 (d, 1 H, C$\underline{H}_A$Ph, J = 12.6 Hz); 7.24 (br.s, 3 H, NH_3^+); 7.32—7.43 (m, 5 H, Ph). ^{11}B NMR, δ: −9.22, −10.93 (2 B), −18.16 (2 B), −19.55, −22.64, −36.32, −37.62. ^{13}C NMR, δ: ~40 (the signal for the CH_2 group at carborane overlapping with the signal of DMSO-d_6); 47.01 (CH_{carb}); 52.60 (C_{carb}); 65.59 (CH_2O); 127.76 (2 *o*-C_{Ar}); 127.89 (*p*-C_{Ar}); 128.31 (2 *m*-C_{Ar}); 136.11 (*ipso*-C_{Ar}); 171.06 (C=O). Found (%): C, 44.85; H, 7.49; N 4.70. $C_{11}H_{22}B_9NO_2$. Calculated (%): C, 44.39; H, 7.45; N, 4.71. HRMS (ESI): found m/z 298.2433 [M − H]$^-$; calculated for $C_{11}H_{21}{}^{11}B_9NO_2$ 298.2432.

Benzyl (S_P)-(3-ammonio-7,8-dicarba-*nido*-undecaboran-7-yl)acetate ((S_P)-5). The yield was 0.10 g (55%). The product contains BnOH (7 mol.% according to ^{1}H NMR spectroscopy). A colorless powder, m.p. 188.7—193.0 °C; $[\alpha]_D^{22}$ +26.1 (*c* 0.6, MeOH); R_f = 0.38 ($CHCl_3$—MeOH, 95 : 5); *ee* 98%. HPLC, τ_R 12.0 min. The ^{1}H, ^{11}B, and ^{13}C NMR spectra are identical to those of compound (R_P)-**5**. HRMS (ESI): found m/z 298.2429 [M − H]$^-$; calculated for $C_{11}H_{21}{}^{11}B_9NO_2$ 298.2432.

Benzyl (S_P)-(7,8-dicarba-*nido*-undecaboran-7-yl)acetate ((S_P)-6). The yield was 0.034 g (20%). A yellowish amorphous compound. ^{1}H NMR, δ: −2.57 (br.s, 2 H, 2 BH); −0.70—2.30 (br.s, 9 H, 9 BH); 1.79 (s, 1 H, CH_{carb}); 2.37 (d, 1 H, $H_B(2)$, J = 15.7 Hz); 2.59 (d, 1 H, $H_A(2)$, J = 15.7 Hz); 5.08 (s, 2 H, C$\underline{H}_2$Ph); 7.30—7.42 (m, 5 H, Ph). HRMS (ESI): found m/z 283.2324 [M − H]$^-$; calculated for $C_{11}H_{20}{}^{11}B_9O_2$ 283.2323.

Benzyl (R_P)-(7,8-dicarba-*nido*-undecaboran-7-yl)acetate ((R_P)-6). The yield was 0.034 g (20%). A yellowish amorphous compound. ^{1}H NMR spectrum is identical to that of compound (S_P)-**6**. HRMS (ESI): found m/z 283.2322 [M − H]$^-$; calculated for $C_{11}H_{20}{}^{11}B_9O_2$ 283.2323.

(3-Ammonio-7,8-dicarba-*nido*-undecaboran-7-yl)acetic acid ((R_P)-1, (S_P)-1, and (R_PS_P)-1) (general procedure). Cesium fluoride (0.76 g, 4.98 mmol) was added to a solution of benzyl (R_P)- or (S_P)-(3-formamido-1,2-dicarba-*closo*-dodecaboran-1-yl)acetate (**2**) (0.56 g, 0.66 mmol) in EtOH (50 mL). The mixture was refluxed for 12 h and concentrated. The residue was dissolved in EtOAc (25 mL) and washed with water (3×20 mL); the organic layer was dried with Na_2SO_4 and concentrated. Acetic acid (7 mL) and 35% aq. HCl (d = 1.75 g mL^{-1}) (7 mL) were added to the residue. The mixture was stirred at 102—105 °C (a glycerin bath) for 16 h and concentrated *in vacuo*. Water (15 mL) and EtOAc (25 mL) were added to the residue. The organic layer was separated, washed with brine (3×25 mL), dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (eluent C_6H_6—EtOAc (85 : 15), then $CHCl_3$—MeOH (7 : 3)). The fractions containing the target compound were concentrated; the residue was dissolved in 50% aq. MeOH, strongly acidic sulfonate ion exchange resin Amberlite IR-120 (in H-form) (2 g) was added, the mixture was stirred for 30 min, then filtered and extracted with EtOAc (2×25 mL). The organic layer was dried with Na_2SO_4 and concentrated.

(R_P)-(3-Ammonio-7,8-dicarba-*nido*-undecaboran-7-yl)acetic acid ((R_P)-1). The yield was 0.275 g (80%). A colorless amorphous compound; $[\alpha]_D^{22}$ −25.4 (*c* 0.8, MeOH); R_f = 0.34 ($CHCl_3$—MeOH, 8 : 2); *ee* 99%. HPLC, τ_R 6.7 min. ^{1}H NMR, δ: −2.35 (br.s, 1 H, BH); −0.70—2.30 (br.s, 8 H, 8 BH); 1.84 (s, 1 H, CH_{carb}); 2.31 (d, 1 H, $H_B(2)$, J = 16.6 Hz); 2.39 (d, 1 H, $H_A(2)$, J = 16.6 Hz); 7.74 (br.s, 3 H, NH_3^+). ^{11}B NMR, δ: −9.68, −10.92 (2 B), −17.60, −19.01 (2 B), −22.88, −36.45, −37.67. ^{13}C NMR, δ: ~40 (the signal for CH_2 overlaps with that of DMSO-d_6); 47.67 (CH_{carb}); 52.88 (C_{carb}); 172.97 (CO_2H). HRMS (ESI): found m/z 208.1953 [M − H]$^-$; calculated for $C_4H_{15}{}^{11}B_9NO_2$ 208.1952.

(S_P)-(3-Ammonio-7,8-dicarba-*nido*-undecaboran-7-yl)acetic acid ((S_P)-1). The yield was 0.265 g (77%). A colorless amorphous compound; $[\alpha]_D^{22}$ +27.3 (*c* 0.7, MeOH); R_f = 0.34 ($CHCl_3$—MeOH, 8 : 2). The ^{1}H, ^{11}B, and ^{13}C NMR spectra are identical to those of compound (R_P)-**1**. HRMS (ESI): found m/z 208.1953 [M − H]$^-$; calculated for $C_4H_{15}{}^{11}B_9NO_2$ 208.1952.

(R_PS_P)-(3-Ammonio-7,8-dicarba-*nido*-undecaboran-7-yl)-acetic acid ((R_PS_P)-1). The yield was 0.270 g (80%). A colorless amorphous compound; $R_f = 0.34$ ($CHCl_3$—MeOH, 8 : 2). HPLC, τ_R min: 6.7 ((R_P)-**1**) (50%), 10.2 ((S_P)-**1**) (50%). The ^1H, ^{11}B, and ^{13}C NMR spectra are identical to those of compound (R_P)-**1**. HRMS (ESI): found *m/z* 208.1953 $[M - H]^-$; calculated for $C_4H_{15}{}^{11}B_9NO_2$ 208.1952.

X-ray diffraction study of compound (R_P)-**5** was carried out on a Xcalibur 3 X-ray diffractometer (Oxford Diffraction, UK) with a CCD detector following the standard procedure (λ(Mo-Kα), graphite monochromator, ω-scan technique, $T = 295(2)$ K). The crystal used for the analysis was obtained by crystallization from EtOH—H_2O (5 : 1). Data collection and processing was carried out using the CrysAlis software package.[42] The structure was solved by the direct method using the SHELXS-97 software and refined using the SHELXL-97 software[43] with anisotropic (isotropic for hydrogen atoms) displacement parameters. Some of the hydrogen atoms were solved by the direct method and refined independently in the isotropic approximation, the rest of the hydrogen atoms were positioned geometrically and included in the refinement in the riding model. Note that, despite the crystallization of the molecule in the chiral space group $P2_12_12_1$, the insufficient anomalous scattering of the crystal when using λ(Mo-Kα) did not allow us to independently confirm the configuration of the molecule.

The X-ray diffraction data including atomic coordinates, geometrical parameters, and structural factors were deposited with the Cambridge Crystallographic Data Center (CCDC 2042220).

Compound (R_P)-5, $C_{11}H_{22}B_9NO_2$, M 297.58; the crystal size 0.46×0.29×0.13 mm, a colorless prism. Orthorhombic crystal system, $a = 10.2092(9)$ Å, $b = 10.2767(10)$ Å, $c = 15.4907(13)$ Å; $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; $V = 1625.2(2)$ Å^3; space group $P2_12_12_1$; $Z = 4$ ($Z' = 1$); $d_{calc} = 1.216$ g cm^{-3}; $\mu = 0.070$ mm^{-1}; $3.986° < \theta < 28.235°$. The completeness for $\theta \le 26.00°$ was 99.1%. It was collected 7171 reflections, out of which 4277 were independent ($R_{int} = 0.0420$), 2894 reflections were with $I > 2\sigma(I)$; S on F^2 1.009. The final refinement factors R_1 ($I > 2\sigma(I)$) 0.0617, wR_2 ($I > 2\sigma(I)$) 0.1355; $R_1 = 0.0983$ (for all reflections), $wR_2 = 0.1737$ (for all reflections).

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This work does not involve human participants and animal subjects.

The authors declare that there is no conflict of interest.

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