A novel approach to the synthesis of amino acids based on cobalt bis(dicarbollide)

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A novel approach to the synthesis of boron-containing amino acids based on ring opening of cyclic oxonium derivatives of polyhedral boron hydrides under the action of the terminal functional groups of natural amino acids was proposed. This approach was successfully implemented for the synthesis of cobalt bis(dicarbollide) — tyrosine conjugate.

Key words: cobalt complexes, carboranes, oxonium compounds, amino acids, tyrosine, boron neutron capture therapy of cancer.

Boron neutron capture therapy (BNCT) of cancer is a binary method for cancer treatment, wherein the reaction of two components that are virtually harmless for health affords highly toxic products damaging the cancer cell. The method is based on selective accumulation of the non-radioactive ^{10}B isotopes in the cancer cells followed by their treatment with a flux of thermal neutrons. The irradiation results in the formation of high-energy fission products having short free-path lengths comparable with the cell size, which allows selective destruction of tumor cells with the surrounding healthy tissue being virtually nonaffected.[1—3]

One of the main requirements for BNCT is the availability of the boron-containing medicines that can be accumulated selectively in the tumor tissue at the concentrations sufficient for the intracellular nuclear reaction to proceed (20—35 μg of ^{10}B per 1 g of tumor). In particular, amino acids, peptides, and nucleotides can be used as molecules carrying out the targeted delivery of boron to a tumor.

Since BNCT is a complex set of activities associated with the use of neutron beam from a nuclear reactor, this therapy is applied for treatment of the tumors that cannot be treated using conventional procedures, primarly, for treatment of highly-malignant brain gliomas.[4] In this connection, an additional prerequisite for selective delivery of boron-containing drugs is its penetration through the blood-brain barrier (BBB).[5] One of the possible ways for overcoming the BBB is the use of membrane transport systems located in the plasma membrane.[6] The amino-acid transporter LAT1 (large neutral amino acid transporter 1) is an example of such systems, which are capable of transferring efficiently L-amino acids with the aromatic or branched side chain (tyrosine, phenylalanine, tryptophan, histidine, valine, leucine, and isoleucine) through the BBB.[7—9] It has been shown that a number of clinically used drugs — mimetics of tyrosine (levodopa, thyroxine, triiodothyroxine, melphalan),[9—11] as well as some compounds being potential diagnostic or therapeutic agents (*O*-6-^{18}F-fluoro-3-methyllevodopa,[12] 2-amino-3-{4-[2-(3-benzoylphenyl)propionyloxy]phenyl}propionic acid[13]) can penetrate through the BBB with the aid of the amino-acid transporter LAT1. In the present work, we describe the synthesis of boron-containing derivatives of tyrosine that contain the cobalt bis(dicarbollide) fragment in the side chain.

Results and Discussion

Owing to the combination of high chemical stability, low toxicity, good water solubility (in the form of sodium salts), and sufficiently high lipophilicity, cobalt bis(dicarbollide) [3,3′-Co(1,2-$C_2B_9H_{11})_2]^-$ derivatives[14] attract ever increasing attention as a basis for the design of medicines for BNCT. Earlier,[15] we have proposed a method for functionalization of cobalt bis(dicarbollide) by opening of its cyclic oxonium derivative [8-O($CH_2CH_2)_2$O-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] (**1**), which has become over the past years a classical method for the preparation of its organic and bioorganic derivatives.[16]

This approach has been used earlier for the preparation of the first amino acid based on cobalt bis(dicarbollide) by Sorenson′s method by opening of the oxonium ring of compound **1** with diethyl acetamidomalonate.[15] In the present work, we decided to use the phenolic group of tyrosine for opening of the oxonium ring. The tyrosine molecule has three nucleophilic reaction sites: phenolic,

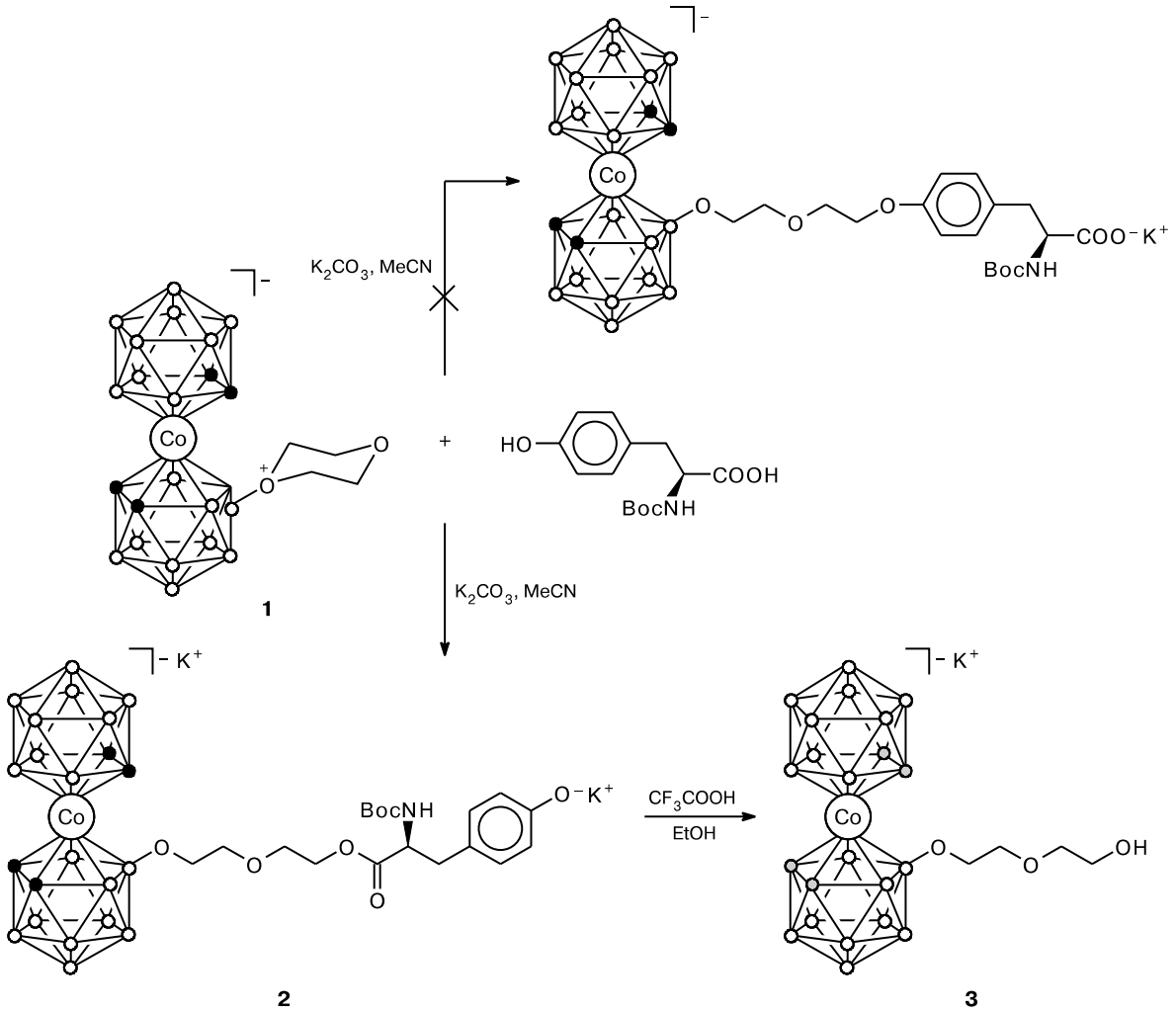
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2246—2251, December, 2010.

amino, and carboxylic groups. Opening of cyclic oxonium derivatives of polyhedral boron hydrides under the action of the phenolate anion and amines is well known[16] and a few examples of opening of the oxonium ring of compound **1** under the action of the carboxylate anion have been described.[17] Selective opening of the oxonium ring requires the use of protective groups, the protection of amino group being obligatory, since cyclic oxonium derivatives react with the amino groups of the amino acid esters in the absence of bases.[16a] However, we have found earlier that the reaction of compound **1** with *p*-hydroxybenzoic acid in the presence of K_2CO_3 in acetonitrile proceeds selectively at the hydroxyl group.[18] Therefore, we first studied the reaction of compound **1** with *N*-Boc-L-tyrosine. We found that the reaction in acetonitrile in the presence of K_2CO_3 proceeds selectively to form ester **2**, *i.e.*, the dioxane ring-opening product, under the action of the carboxylate anion (Scheme 1).

The structure of compound **2** was established by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectrum of compound **2** contains the signals for the protons of the CH groups of cobalt bis(dicarbollide) at δ 4.13 and 4.09, the signals for the aromatic ring at δ 7.06 and 6.75, the signals for the methylene protons of tyrosine in the region of δ 3.06—2.86, the signal for the CH group of tyrosine at δ 4.35, and the signal for the *tert*-butyl group at δ 1.35. The signals for the open dioxane ring appear as a set of multiplets in the region of δ 4.23—3.56. The downfield shift of one of the signals for the opened dioxane ring (the signal at δ 4.23) evidences the ester formation. The ^{13}C NMR spectrum displays a signal at δ 172.6, which corresponds to the carbonyl of the ester group.

An additional confirmation of the structure of compound **2** is its acid hydrolysis to the corresponding alcohol **3**, whose synthesis has been described earlier.[15]

Scheme 1



Thus, the protection of the carboxyl group was the prerequisite for opening of the oxonium ring with the phenolate anion of tyrosine.[19] Indeed, the reaction of compound **1** with the ethyl ester of *N*-trifluoroacetyl-L-tyrosine in acetonitrile in the presence of K_2CO_3 affords the target product **4** in high yield (Scheme 2).

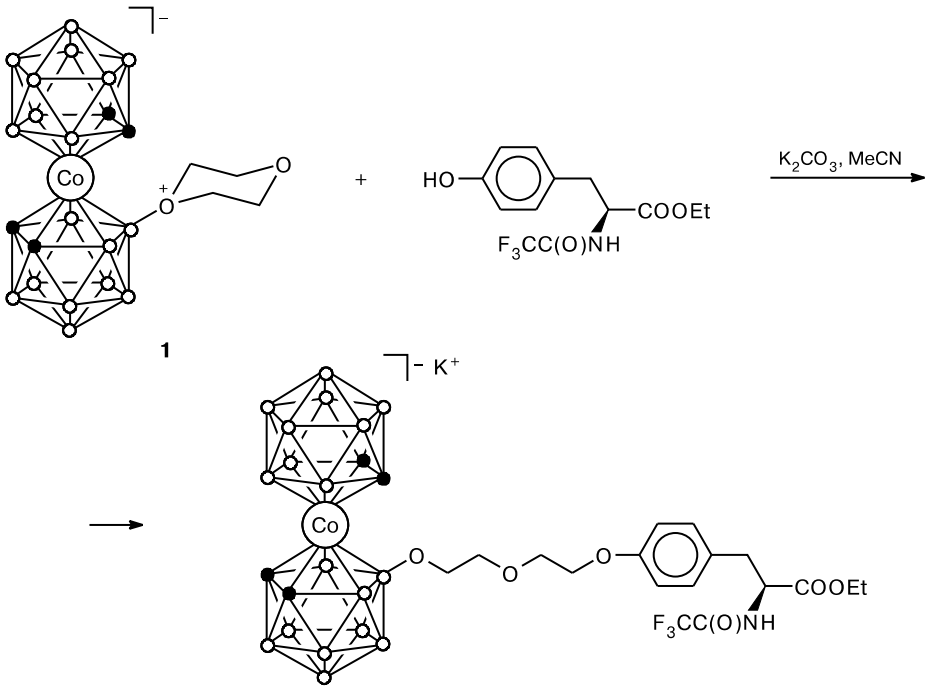
The ^{1}H NMR spectrum of compound **4** contains the signals for the protons of the aromatic ring at δ 7.16 and 6.87, the protons of the methylene group of tyrosine in the region of δ 3.22—2.98, the CH group of tyrosine at δ 4.66, and the ethyl group at δ 4.13 and 1.18, as well as the signal for the protons of the CH groups of cobalt bis(dicarbollide) at δ 4.20 and the signals for the protons of the open dioxane ring in the region of δ 4.08—3.56. The ^{13}C NMR spectrum contains the signals for the carbon atoms of the trifluoroacetyl group as quartets at δ156.6 ($J_{C,F}$ = 37 Hz) and 116.0 ($J_{C,F}$ = 287 Hz). Unfortunately, all our attempts to remove the protecting groups under mild conditions were unsuccessful and the use of drastic conditions (long-term boiling with hydrochloric acid in ethanol) results in decomposition of the metallocarborane skeleton.

In the search for the tyrosine derivatives with easily removable protecting groups, we prepared (4*S*)-3-*tert*-butoxycarbonyl-4-(4-hydroxybenzyl)-5-oxazolidinone by the reaction of *N*-Boc-L-tyrosine with paraformaldehyde in the presence of *p*-toluenesulfonic acid by analogy with the derivative of L-4-iodophenylalanine described earlier.[20] The reaction of the oxazolidinone with compound **1** in acetonitrile in the presence of K_2CO_3 affords the protected boron-containing tyrosine **5** (Scheme 3). The ^{1}H NMR spectrum of compound **5** contains the signals for the protons of the aromatic ring in the region of δ 7.1—6.9, the protons of the methylene group in the region of δ3.14—3.03 and the CH and CH_2 groups of oxazolidin-5-one at δ 5.26 and 4.45, and the protons of the *tert*-butyl group at δ 1.51, as well as the signal for the protons of the CH groups of the cobalt bis(dicarbollide) fragment at δ 4.26 and the signals for the protons of the open dioxane ring in the region of δ 4.13—3.59. The IR spectrum of compound **5** contains the bands typical of oxazolidin-5-one at 1802 cm^{-1} and the *tert*-butoxy group at 1716 cm^{-1}.

The treatment of compound **5** with a solution of NaOH in aqueous ethanol at room temperature results in the hydrolysis of the aminal-acetal fragment to form salt **6** (see Scheme 3). In the ^{1}H NMR spectrum of compound **6**, the signal for the CH_2 group of the oxazolidin-5-one ring disappears, and the disappearance of the characteristic band of oxazolidin-5-one at 1802 cm^{-1} and the appearance of the band of carboxylate anion at 1697 cm^{-1} are observed in the IR spectrum. Subsequent treatment of compound **6** with a solution of HCl in ethanol results in the removal of the Boc group to form the boron-containing tyrosine **7** isolated in the neutral *N*-protonated form (see Scheme 3).

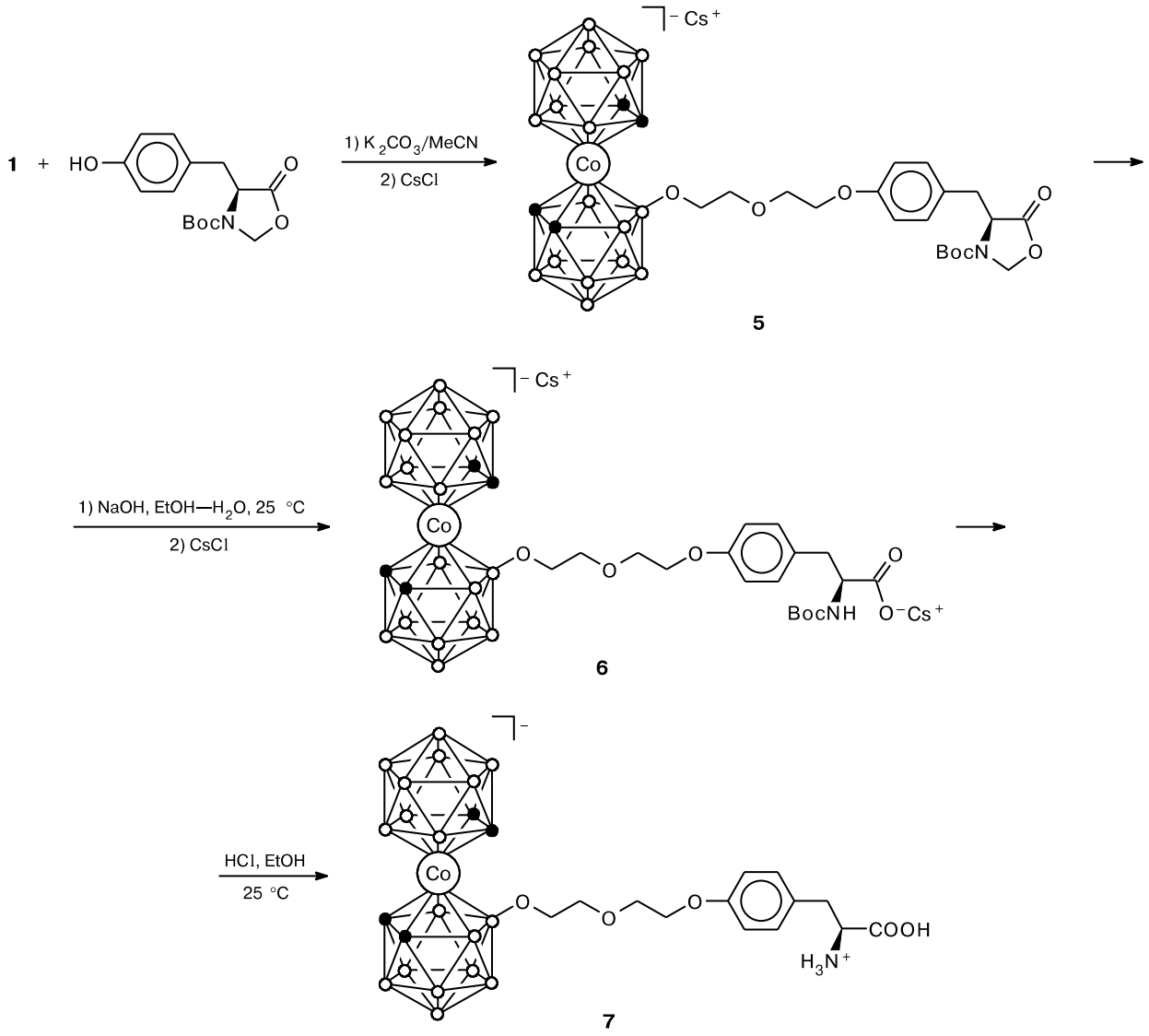
The approach described above can be used for the preparation of boron-containing derivatives of other amino

Scheme 2



1 **4**

Scheme 3



acids having the terminal functional groups that can act as nucleophiles (serine, cysteine, lysine, *etc.*).

The reaction of the dioxane derivative **1** with *N*-Boc-L-serine and ethyl ester of *N*-Boc-L-serine in acetonitirle in the presence of K_2CO_3 results in opening of the oxonium ring under the action of carboxyl or alkoxyl groups to form compounds **8** and **9**, respectively (Scheme 4). At the same time, the lower acidity of the alcoholic hydroxy group compared to the phenolic one is the cause of lower yield of the target product **9**, which requires further optimization of the synthesis conditions.

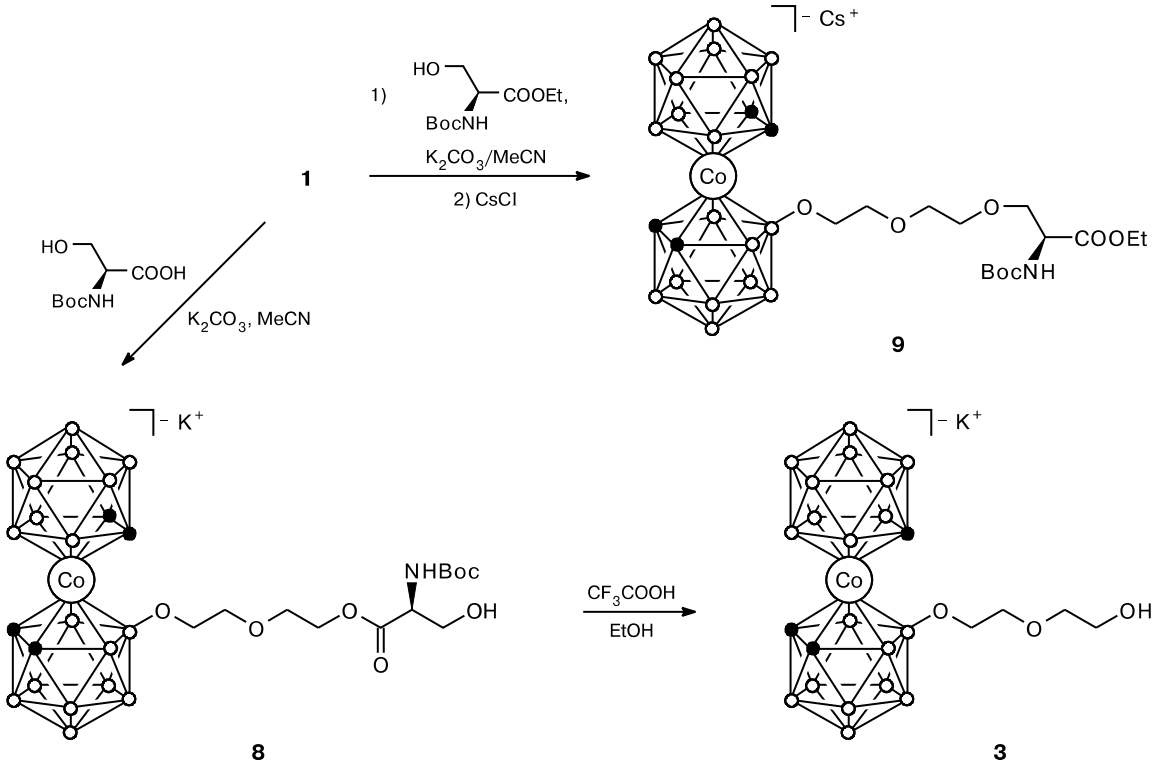
Thus, we proposed a novel approach to the synthesis of boron-containing amino acids, which is based on the ring opening of the cyclic oxonium derivatives of polyhedral boron hydrides under the action of the terminal functional groups of natural amino acids.

Experimental

^1H, ^{11}B, $^{11}B\{^1H\}$, and ^{13}C NMR spectra were recorded on Bruker Avance 400 and Bruker Avance 600 spectrometers. Negative-ion electrospray ionization (ESI) mass spectra were recorded on a micrOTOF Q II (Bruker Daltonics) instrument. The course of reactions was monitored by TLC on Kieselgel 60 F245 (Merck) plates. Acetonitrile was dried by distillation over P_2O_5 and CaH_2. The dioxane derivative **1**, ethyl ester of *N*-trifluoroacetyl-L-tyrosine, and ethyl ester of *N*-Boc-L-serine were prepared according to the previously published procedures.[21,19,22]

(4*S*)-3-*tert*-Butoxycarbonyl-4-(4-hydroxybenzyl)-1,3-oxazolidin-5-one. A suspension of *N*-Boc-L-tyrosine (5.62 g, 20.0 mmol), paraformaldehyde (3.00 g, 100.0 mmol), and $TsOH \cdot H_2O$ (0.38 g, 2.0 mmol) in toluene (250 mL) was refluxed with vigorous stirring for 4 h with azeotropic distillation of

Scheme 4



water. The reaction mixture was cooled to room temperature and filtered. The filtrate was washed with 1 *M* $NaHCO_3$, dried with Na_2SO_4, and concentrated to dryness on a rotary evaporator to yield the white product (3.99 g, 68%). ^{1}H NMR ($CDCl_3$), δ: 7.00 (d, 2 H); 6.74 (d, 2 H); 5.20 (d, 1 H); 4.44 (s, 1 H); 4.29 (d, 1 H); 3.28 (d, 1 H); 3.08 (d, 1 H); 1.51 (s, 9 H). ^{13}C NMR ($CDCl_3$), δ: 172.2, 155.7, 151.8, 130.8, 126.1, 115.7, 82.4, 78.2, 56.7, 34.9, 28.3.

Dipotassium {2-[2-(uncosahydro-1′,1″,2′,2″-tetracarba-3′-*commo*-cobalta-*closo*-tricosaborato-8′-oxy)ethoxy]ethyl}[*N*-(*tert*-butoxycarbonyl)-L-tyrosinate] (2). To a solution of *N*-Boc-L-tyrosine (0.24 g, 0.85 mmol) in MeCN (15 mL), compound **1** (0.35 g, 0.85 mmol) and K_2CO_3 (1.17 g, 8.5 mmol) were added. The reaction mixture was refluxed for 1 h and then cooled to room temperature. The excess of K_2CO_3 was filtered off and the solvent was removed on a rotary evaporator to yield the orange oily product (0.60 g, 96%). ^{1}H NMR (acetone-d_6), δ: 7.06 (d, 2 H, *J* = 8.4 Hz); 6.75 (d, 2 H, *J* = 8.4 Hz); 6.18 (d, 1 H, NH, *J* = 7.6 Hz); 4.35 (m, 1 H); 4.23 (m, 2 H); 4.13 (s, 2 H, CH_{carb}); 4.09 (s, 2 H, CH_{carb}); 3.67 (m, 4 H); 3.56 (m, 2 H); 3.06—2.86 (m, 2 H); 1.35 (s, 9 H). ^{13}C{^{1}H} NMR (acetone-d_6), δ: 172.6, 156.7, 155.9, 130.3, 126.9, 115.4, 79.4, 72.2, 68.7, 68.5, 64.3, 55.5, 52.5, 46.7, 36.3, 28.0. ^{11}B NMR (acetone-d_6), δ: 23.3 (s, 1 B); 4.6 (d, 1 B); 0.4 (d, 1 B); −2.5 (d, 1 B); −4.46 (d, 2 B); −7.7 (d, 6 B); −17.3 (d, 2 B); −20.4 (d, 2 B); −22.0 (d, 1 B); −28.4 (d, 1 B). MS (ESI), *m/z*: 690 $[M]^-$.

Potassium ethyl *O*-{2-[2-(uncosahydro-1′,1″,2′,2″-tetracarba-3′-*commo*-cobalta-*closo*-tricosaborato-8′-oxy)ethoxy]ethyl}-*N*-trifluoroacetyl-L-tyrosinate (4). To a solution of ethyl ester of *N*-trifluoroacetyl-L-tyrosine (0.10 g, 0.32 mmol) in MeCN (15 mL), compound **1** (0.13 g, 0.32 mmol) and K_2CO_3 (0.44 g, 3.20 mmol) were added. The reaction mixture was heated for 2.5 h to 60 °C and then cooled to room temperature. The excess of K_2CO_3 was filtered off, the solvent was removed on a rotary evaporator, and the resulted residue was chromatorgraphed on a silica gel column (the eluent was MeCN : CH_2Cl_2 (1 : 4)) to yield the orange oily product (0.21 g, 89%). ^{1}H NMR (acetone-d_6), δ: 8.69 (d, 1 H, *J* = 8.0 Hz); 7.16 (d, 2 H, *J* = 8.6 Hz); 6.87 (d, 2 H, *J* = 8.6 Hz); 4.66 (m, 1 H); 4.20 (s, 4 H, CH_{carb}); 4.13 (q, 2 H, *J* =7.2 Hz); 4.08 (t, 2 H, *J* = 4.8 Hz); 3.78 (t, 2 H, *J* = 4.8 Hz); 3.62 (m, 2 H); 3.56 (m, 2 H); 3.22—2.98 (m, 2 H); 1.18 (t, 3 H, *J* = 7.2 Hz). ^{13}C{^{1}H} NMR (acetone-d_6), δ: 169.9, 158.1, 156.6 ($J_{C,F}$ = 37 Hz); 130.2, 128.5, 114.4, 116.0 ($J_{C,F}$ = 287 Hz); 72.0, 69.3, 68.4, 67.5, 61.3, 54.5, 54.0, 46.5, 35.6, 13.5. ^{11}B{^{1}H} NMR (acetone-d_6), δ: 23.2 (s, 1 B); 4.3 (d, 1 B); 0.4 (d, 1 B); −2.5 (d, 1 B); −4.4 (d, 2 B); −8.0 (d, 6 B); −17.3 (d, 2 B); −20.4 (d, 2 B); −21.8 (d, 1 B); −28.5 (d, 1 B).

Cesium salt of (4*S*)-3-*tert*-butoxycarbonyl-4-(4-{2-[2-(uncosahydro-1′,1″,2′,2″-tetracarba-3′-*commo*-cobalta-*closo*-tricosaborato-8′-oxy)ethoxy]ethoxy}benzyl)-1,3-oxazolidin-5-one (5). To a solution of compound **1** (0.30 g, 0.73 mmol) in MeCN (10 mL), (4*S*)-3-*tert*-butoxycarbonyl-4-(4-hydroxybenzyl)-1,3-oxazolidin-5-one (0.21 g, 0.78 mmol) and K_2CO_3 (1.08 g, 7.80 mmol) were added. The reaction mixture was stirred for 22 h at room temperature. The excess of K_2CO_3 was filtered off and the solvent was removed on a rotary evaporator. The resulted residue was dissolved in acetone and an excess of an aqueous solution of CsCl was added. The formed oily precipitate was chromatographed on a silica gel column (the eluent was CH_2Cl_2 : CH_3CN (10 : 1)) to obtain the orange product (0.51 g,

94%). ^{1}H NMR (acetone-d_6), δ: 7.1—6.9 (m, 4 H); 5.26 (m, 1 H); 4.45 (m, 2 H); 4.26 (s, 4 H, CH_{carb}); 4.13 (t, 2 H, J = 5.0 Hz); 3.82 (t, 2 H, J = 5.0 Hz); 3.64 (t, 2 H, J = 5.0 Hz); 3.59 (t, 2 H, J = 5.0 Hz); 3.44—3.19 (m, 1 H); 3.03 (d, 1 H, J = 14 Hz); 1.51 (s, 9 H). ^{11}B NMR (acetone-d_6), δ: 23.3 (s, 1 B); 4.6 (d, 1 B); 0.5 (d, 1 B); −2.5 (d, 1 B); −4.4 (d, 2 B); −7.2 (d, 6 B); −17.3 (d, 2 B); −20.4 (d, 2 B); −22.0 (d, 1 B); −28.4 (d, 1 B). ^{13}C{^{1}H} NMR (acetone-d_6), δ: 172.2, 158.1, 151.6, 130.8, 127.6, 114.7, 81.0, 77.9, 72.2, 69.3, 68.4, 67.5, 56.3, 53.2, 46.5, 35.2, 27.6. IR, ν/cm^{-1}: 2552, 1802, 1716.

Dicesium *N*-(*tert*-butoxycarbonyl)-*O*-{2-[2-(uncosahydro-1′,1″,2′,2″-tetracarba-3′-*commo*-cobalta-*closo*-tricosaborato-8′-oxy)ethoxy]ethoxy}-L-tyrosinate (6). To a solution of compound **5** (0.16 g, 0.20 mmol) in MeOH (10 mL), a 2 *M* aqueous solution of NaOH was added. The reaction mixture was stirred for 1 h at room temperature and then acetone (40 mL) was added. The organic layer was separated. The procedure was repeated twice. The organic phases were combined, concentrated to 10 mL on a rotary evaporator, and then treated with an excess of an aqueous solution of CsCl. The formed orange precipitate was filtered off and dried to yield the product (0.13 g, 86%). ^{1}H NMR (acetone-d_6), δ: 7.17 (d, 2 H, J = 8.3 Hz); 6.84 (d, 2 H, J = 8.3 Hz); 6.08—5.94 (m, 1 H); 4.22 (s, 4 H, CH_{carb}); 4.09 (t, 2 H, J = 4.6 Hz); 3.80 (t, 2 H, J = 4.6 Hz); 3.68 (t, 2 H, J = 4.6 Hz); 3.60 (t, 2 H, J = 4.6 Hz); 3.22—3.12 (m, 2 H); 1.40 (s, 9 H). ^{11}B NMR (acetone-d_6), δ: 23.4 (s, 1 B); 4.9 (d, 1 B); 0.5 (d, 1 B); −2.4 (d, 1 B); −4.4 (d, 2 B); −7.1 (d, 6 B); −17.1 (d, 2 B); −20.3 (d, 3 B); −28.5 (d, 1 B). IR, ν/cm^{-1}: 2547 (ν_{BH}); 1715 ($\nu_{C=O}$); 1697 ($\nu_{C=O}$).

(4*S*)-8′-(2-{2-[4-(2-Ammonio-2-carboxyethyl)phenoxy]-ethoxy}ethoxy)uncosahydro-1′,1″,2′,2″-tetracarba-3′-*commo*-cobalta-*closo*-tricosaborate (7). To a solution of compound **6** (0.21 g, 0.31 mmol) in EtOH (8 mL), $SOCl_2$ (1 mL) was added dropwise The reaction mixture was stirred at room temperature for 27 h and concentrated to dryness on a rotary evaporator to yield the orange product (0.11 g, 70%). ^{1}H NMR (acetone-d_6), δ: 7.5 (d, 2 H, J = 8.6 Hz); 6.97 (d, 2 H, J = 8.6 Hz); 5.38 (m, 1 H); 4.31 (s+t, 6 H); 4.14 (t, 2 H, J = 4.8 Hz); 3.81 (t, 2 H, J = 4.8 Hz); 3.58 (m, 2 H); 3.53—3.15 (m, 2 H). ^{11}B NMR (acetone-d_6), δ: 22.8 (C, 1 B); 3.8 (d, 1 B); 0.3 (d, 1 B); −2.4 (d, 1 B); −4.2 (d, 2 B); −7.4 (d, 2 B); −8.3 (d, 4 B); −17.3 (d, 2 B); −20.4 (d, 2 B); −22.0 (d, 1 B); −28.4 (d, 1 B). IR, ν/cm^{-1}: 2558 (ν_{BH}), 1747 ($\nu_{C=O}$), 1726 ($\nu_{C=O}$).

Potassium {2-[2-(uncosahydro-1′,1″,2′,2″-tetracarba-3′-*commo*-cobalta-*closo*-tricosaborato-8′-oxy)ethoxy]ethyl}[*N*-(*tert*-butoxycarbonyl)-L-serinate] (8). To a solution of *N*-Boc-L-serine (0.14 g, 0.64 mmol) in MeCN (10 mL), compound **1** (0.26 g, 0.64 mmol) and K_2CO_3 (0.88 g, 6.40 mmol) were added. The reaction mixture was refluxed for 1 h and then cooled to room temperature. The excess of K_2CO_3 was filtered off, the solvent was removed on a rotary evaporator. The resulted residue was chromatographed on a silica gel column (the eluent was MeCN : CH_2Cl_2 (1 : 5)) to yield the orange oily product (0.40 g, 94%). ^{1}H NMR (acetone-d_6), δ: 6.16 (d, 1 H, J = 7.6 Hz); 4.39—4.21 (m, 2 H); 4.21—4.02 (m, 1 H); 4.15 (s, 2 H, CH_{carb}); 4.11 (s, 2 H, CH_{carb}); 3.95—3.78 (m, 2 H); 3.70 (t, 2 H, J = 4.6 Hz); 3.65 (m, 2 H); 3.55 (m, 2 H); 1.40 (s, 9 H). ^{13}C NMR (acetone-d_6), δ: 171.0, 155.6, 78.8, 71.9, 68.7, 68.4, 64.2, 62.3, 56.0, 53.7, 46.5, 27.7. ^{11}B NMR (acetone-d_6), δ: 23.2 (s, 1 B); 4.4 (d, 1 B); 0.4 (d, 1 B); −2.6 (d, 1 B); −4.5 (d, 2 B); −7.7 (d, 4 B); −17.3 (d, 2 B); −20.4 (d, 2 B); −22.1 (d, 1 B); −28.6 (d, 1 B). MS (ESI), m/z: 614 [M]$^-$.

Cesium ethyl-*N*-(*tert*-butoxycarbonyl)-*O*-{2-[2-(uncosahydro-1′,1″,2′,2″-tetracarba-3′-*commo*-cobalta-*closo*-tricosaborato-8′-oxy)ethoxy]ethyl}-L-serinate (9). To a solution of ethyl ester of *N*-Boc-L-serine (0.18 g, 0.79 mmol) in MeCN (5 mL), compound **1** (0.33 g, 0.79 mmol) and K_2CO_3 (1.09 g, 7.90 mmol) were added. The reaction mixtrure was refluxed for 4 h and cooled to room temperature, the excess of K_2CO_3 was filtered off, and the solvent was removed on a rotary evaporator. The resulted residue was dissolved in acetone and treated with an excess of an aqueous solution of CsCl. The formed precipitate was chromatographed on a silica gel column using a mixture of MeCN and CH_2Cl_2 as an eluent to yield the product (0.10 g, 18.6%). ^{1}H NMR (acetone-d_6), δ: 8.69 (d, 1 H, J = 8.0 Hz); 7.16 (d, 2 H, J = 8.6 Hz); 6.87 (d, 2 H, J = 8.6 Hz); 4.66 (m, 1 H); 4.20 (s, 4 H, CH_{carb}); 4.13 (q, 2 H, J = 7.2 Hz); 4.08 (t, 2 H, J = 4.8 Hz); 3.78 (t, 2 H, J = 4.8 Hz); 3.62 (m, 2 H); 3.56 (m, 2 H); 3.22—2.98 (m, 2 H); 1.18 (t, 3 H, J = 7.2 Hz). ^{11}B NMR (acetone-d_6), δ: 23.2 (s, 1 B); 4.3 (d, 1 B); 0.4 (d, 1 B); −2.5 (d, 1 B); −4.4 (d, 2 B); −8.0 (m, 6 B); −17.3 (d, 2 B); −20.4 (d, 2 B); −21.8 (d, 1 B); −28.5 (d, 1 B).

This work was financially supported by the Russian Foundation for Basic Research (Projects Nos 08-03-00463, 09-03-00701, and 10-03-00698) and the Presidium of the Russian Academy of Sciences (Program "Development of methods for the preparation of chemical substances and design of new materials").

References

1. M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 950.
2. A. H. Soloway, W. Tjarks, B. A. Barnum, F.-G. Rong, R. F. Barth, I. M. Codogni, J. G. Wilson, *Chem. Rev.*, 1998, **98**, 1515.
3. (a) I. B. Sivaev, V. I. Bregadze, *Ross. Khim. Zh.*, 2004, 48(4), 109; (b) I. B. Sivaev, V. I. Bregadze, *Eur. J. Inorg. Chem.*, 2009, 1433.
4. R. F. Barth, J. A. Coderre, M. G. H. Vicente, T. E. Blue, S.-I. Miyatake, in *High-Grade Gliomas* (*Diagnosis and Treatment*), Humana Press, Totowa, NJ, 2007, p. 431.
5. N. Bodor, P. Buchwald, *Adv. Drug Delivery Rev.*, 1999, **36**, 229.
6. I. Tamai, A. Tsuji, *J. Pharm. Sci.*, 2000, **89**, 1371.
7. R. J. Boado, J. Y. Li, M. Nagaya, C. Zhang, W. M. Pardridge, *Proc. Natl. Acad. Sci. USA*, 1999, **96**, 12079.
8. R. Duelli, B. E. Enerson, D. Z. Gerhart, L. R. Drewes, *J. Cereb. Blood Flow Metab.*, 2000, **11**, 1557.
9. (a) Y. Kanai, H. Segawa, K.-i. Miyamoto, H. Uchino, E. Takeda, H. Endou, *J. Biol. Chem.*, 1998, 273, 23629; (b) O. Yanagida, Y. Kanai, A. Chairoungdua, D. K. Kim, H. Segawa, T. Nii, S. H. Cha, H. Matsuo, J. Fukushima, Y. Fukasawa, Y. Tani, Y. Taketani, H. Uchino, J. Y. Kim, J. Inatomi, I. Okayasu, K.-i. Miyamoto, E. Takeda, T. Goya, H. Endou, *Biochim. Biophys. Acta*, 2001, **1514**, 291.
10. P. Gomes, P. Soares-da-Silva, *Brain Res.*, 1999, **829**, 143.
11. G. J. Goldenberg, H. Y. Lam, A. Begleiter, *J. Biol. Chem.*, 1979, **254**, 1057.
12. (a) R. Bergman, J. Pietzsch, F. Fuechtner, B. Pawelke, B. Beuthien-Baumann, B. Johannsen, J. Kotzerke, *J. Nucl.*

Med., 2004, **45**, 2116; (b) C. Haase, R. Bergmann, F. Fuechtner, A. Hoepping, J. Pietzsch, *J. Nucl. Med.*, 2007, **48**, 2063.
13. M. Gynther, K. Laine, J. Ropponen, J. Leppänen, A. Mannila, T. Nevalainen, J. Savolainen, T. Järvinen, J. Rautio, *J. Med. Chem.*, 2008, **51**, 932.
14. I. B. Sivaev, V. I. Bregadze, *Collect. Czech. Chem. Commun.*, 1999, **64**, 783.
15. I. B. Sivaev, Z. A. Starikova, S. Sjöberg, V. I. Bregadze, *J. Organomet. Chem.*, 2002, **649**, 1.
16. (a) A. A. Semioshkin, I. B. Sivaev, V. I. Bregadze, *Dalton Trans.*, 2008, 977; (b) I. B. Sivaev, A. A. Semioshkin, V. I. Bregadze, *Appl. Radiat. Isotop.*, 2009, **67**, S91; (c) I. B. Sivaev, V. I. Bregadze, in *Boron Science: New Technologies and Applications*, Ed. N. S. Hosmane, CRC Press, 2011, in press.
17. P. Farras, F. Teixidor, R. Kivekäs, R. Sillanpää, C. Viñas, B. Grüner, I. Cisarova, *Inorg. Chem.*, 2008, **47**, 9497.
18. M. A. Grin, R. A. Titeev, O. M. Bakieva, D. I. Brittal, I. A. Lobanova, I. B. Sivaev, V. I. Bregadze, A. F. Mironov, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 2188 [*Russ. Chem. Bull.*, *Int. Ed.*, 2008, **57**, 2230].
19. A. Taurog, S. Abraham, I. L. Chaikoff, *J. Am. Chem. Soc.*, 1953, **75**, 3473.
20. H. Nakamura, M. Fujiwara, Y. Yamamoto, *Bull. Chem. Soc. Jpn*, 2000, **73**, 231.
21. F. Teixidor, J. Pedrajas, I. Rojo, C. Viñas, R Kivekäs, R. Sillanpää, I. B. Sivaev, V. I. Bregadze, S. Sjöberg, *Organometallics*, 2003, **22**, 3414.
22. D. Burg, J. Riepsaame, C. Pont, G. Mulder, B. van de Water, *Biochem. Pharm.*, 2006, **71**, 268.

Received November 1, 2010