Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Organometallic Chemistry 690 (2005) 2761–2765
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Synthesis of carborane analogues of γ-aminobutanoic acid

Valentina A. Ol'shevskaya [a,*], Rami Ayuob [a], Zhanna G. Brechko [a], Pavel V. Petrovskii [a], Elena G. Kononova [a], Galina L. Levit [b], Victor P. Krasnov [b], Valery N. Charushin [b], Oleg N. Chupakhin [b], Valery N. Kalinin [*,a]

[a] *A.N. Nesmeyanov Institute of Organoelement Compounds of RAS, Vavilova St., 28, Moscow 119991, Russia*
[b] *I.Ya. Postovsky Institute of Organic Synthesis of RAS (Ural Div.), S. Kovalevskoy St., 20, Ekaterinburg 620219, Russia*

Received 20 September 2004; accepted 13 January 2005
Available online 8 March 2005

Abstract

General method for preparation of high yields of novel *N*-protected carborane amino acid derivatives, 3-acylamino-1-carboxymethyl-2-R-*o*-carboranes (R = H, Me, Ph), is reported. The synthesis starts from readily available 3-amino-*o*-carboranes and includes the protection of amino group, introduction of carboxymethyl function to the carbon atom of polyhedron via the metallation of carborane CH bond with sodium amide in liquid ammonia, and treatment of corresponding sodium carboranes with sodium bromoacetate. Deprotection of *N*-acylated carborane amino acids is studied in acidic media. Depending on the procedure employed, *closo*- or *nido*-carborane amino acids were obtained.

Keywords: 3-Amino-*o*-carboranes; Amino acids; Protection; Deprotection; Acidic hydrolysis

1. Introduction

In the last decade, particular attention has been paid to biomedical applications of carboranes. Along with traditional use for boron neutron capture therapy (BNCT) and photodynamic therapy, at present the unique structural and chemical properties of polyhedral carboranes are used in preparation of inorganic pharmaceuticals, radio pharmaceuticals, and biological probes [1]. In this connection elaboration of general methods for synthesis of functionalized carboranes is still a key problem in spite of the four decades of progress in this branch of chemistry.

Recently, synthetic aspects and potential fields of application of boronated amino acids have been the subject of intensive research. To this end, known boronated amino acids analogues contain boron as component part of amino acids backbone or as a substituent in the side chain. These structurally diverse compounds can be used as a boron constituents for biomolecules such as peptides, porphyrins, etc. [2]. Moreover, boronated phenylalanine (BPA) is used in the clinic for BNCT. However, a major problem with BPA is its low solubility in water at physiological pH [3]. We believe that carborane amino acids bearing functional groups of opposite nature at boron and carbon atom of the polyhedron must be water soluble and biologically active. The first compound of this class have been synthesized by Kahl and co-workers [4].

We report here general strategy of synthesis of carborane amino acids with the amino group at boron at position 3 and carboxymethyl group at carbon atom of the polyhedron (A). These amino acids can be considered as boronated analogs of γ-aminobutanoic acid (B) with the second and third methylene groups replaced by carbon and boron (B^3) atoms of polyhedron, respectively (Fig. 1).

* Corresponding author.
E-mail address: olshevsk@ineos.ac.ru (V.A. Ol'shevskaya).

0022-328X/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2005.01.056

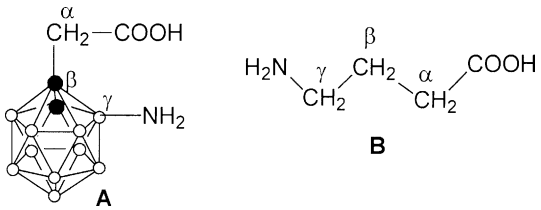


Fig. 1. 3-Amino-1-carboxymethyl-*o*-carborane (A) as a boronated analogue of γ-aminobutanoic acid (B).

γ-Aminobutanoic acid is an important metabolite in the central nervous system [5], therefore we assumed that this type of hydrophilic carborane amino acids can exhibit a broad spectrum of biological activities.

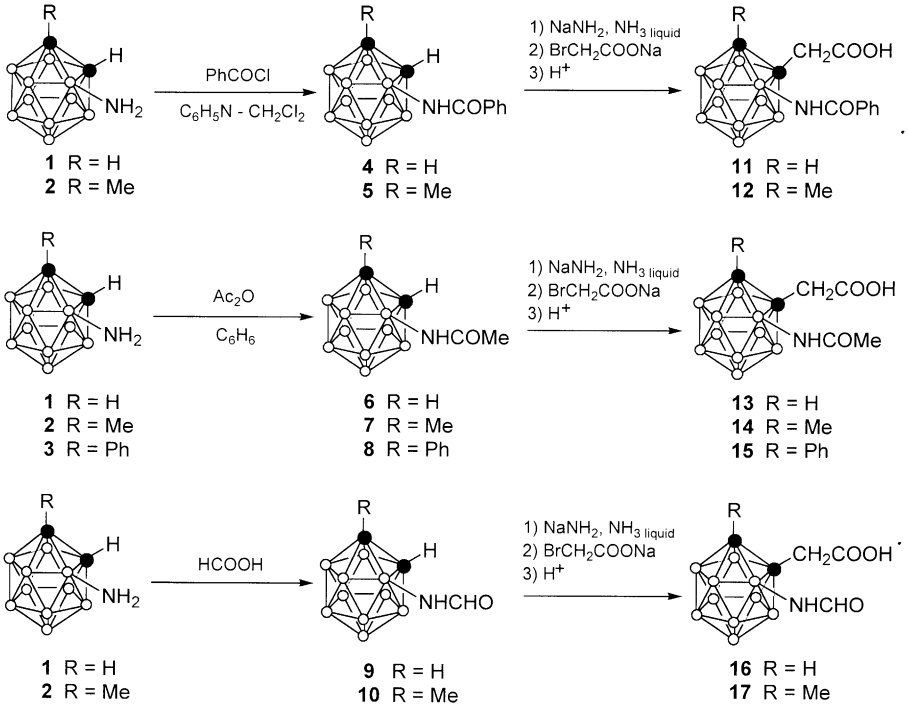
2. Results and discussion

Carboranyl amino acids were synthesized starting from readily available 3-amino-*o*-carborane (**1**) and its 1-R-substituted derivatives (**2**, R = Me; **3**, R = Ph) [6].

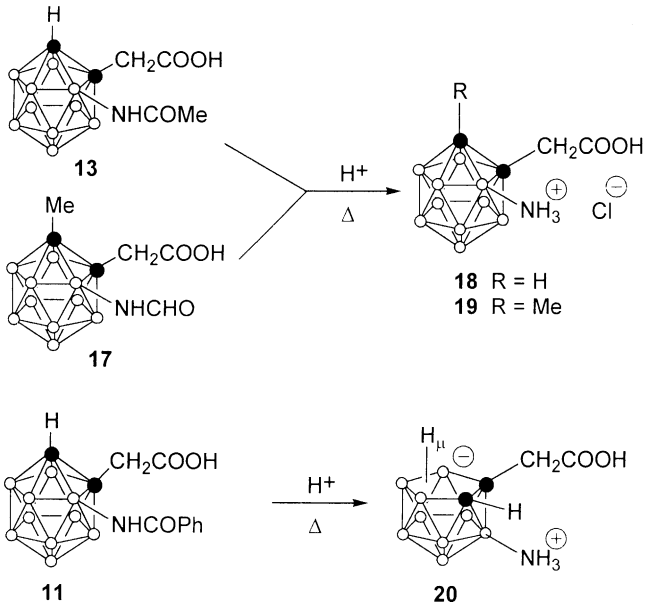
The strategy was to introduce the carboxymethyl group to the carbon atom of the polyhedron by metallating the carborane CH bonds in *N*-protected carboranylamines (**4**–**10**) with sodium amide in liquid ammonia followed by treatment of corresponding sodium carboranes with sodium salt of bromoacetic acid. Subsequent treatment of the reaction mass with water and acidification led to previously unknown 3-benzoyl – (**11**, **12**), 3-acetyl- (**13**–**15**), 3-formyl-substituted (**16**, **17**) C-carboranylacetic acids in 80–95% yields (Scheme 1). Introduction of a substituent into position 1 of 3-substituted *o*-carboranes makes these molecules chiral [7]. Therefore, the carborane amino acids obtained exist as corresponding pairs of enantiomers. The structure of carborane amino acids obtained in this work was confirmed by IR, ^{1}H and ^{11}B NMR spectroscopy. The IR spectral data for compounds **11**, **12**, **13**, **14**, **15**, **16** and **17** show the expected NH and OH stretches at ranges 3307–3349 cm^{-1} and at 2915–2940 cm^{-1}, respectively. Peaks at 2601–2616 cm^{-1}, typical of BH stretches, coupled with peaks at 1726–1730 cm^{-1} and 1634–1674 cm^{-1} due to the carbonyl groups of COOH and CONH units, respectively support the formation of compounds **11**, **12**, **13**, **14**, **15**, **16** and **17**.

The ^{1}H NMR spectra of compounds **11**, **12**, **13**, **14**, **15**, **16** and **17** exibit singlets of NH protons that lie in the range δ 7.28–8.31. It should be noted that methylene protons in these compounds are magnetically inequivalent and manifest themselves as doublets. The expected signals of CH=O group protons in compounds **16** and **17** appeared as singlets at δ = 8.50 and 8.45 respectively. The ^{11}B NMR spectra confirmed the *closo*-carborane structure of compounds **11**, **12**, **13**, **14**, **15**, **16** and **17**.

We also studied deprotection of *N*-protected amino acids (**11**, **13**, **16**) in acidic media. It was found that removal of the acetyl and formyl protective groups from corresponding *N*-acyl-substituted amino acids (**13**, **16**) occurs more easily than from their benzoyl analog **11**. Deprotection of the acetyl and formyl derivatives by controlling the temperature and duration of the reaction resulted in relevant *closo*-amino acids characterized by



Scheme 1.



Scheme 2.

good solubility in water. Removal of the benzoyl protective group in compound **11** requires a prolonged reflux (about 40 h) in a mixture of acetic acid and 12 N hydrochloric acid. As a result, a *nido*-amino acid **20** is formed (Scheme 2).

Importantly, removal of benzoyl protective group in **11** did not occur under conditions identical to those for acetyl and formyl groups. Noteworthy is the fact of deboronation of compound **11** in acidic media. We hypothesize that at the initial step of deprotection process the proton migrates from carboxylic group to the amino group, so that betaine is formed. This *closo*-betaine is thermodynamically less stable than its *nido*-analog. We believe that stabilization of the system is achieved by removal of the boron atom from position 6 and simultaneous transformation of *closo*-betaine in the *nido*-zwitter-ione. This is associated with deboronation of *closo*-carborane structure into *nido*-7,8-dicarbaundecaborate, though this process is known to proceed under the action of bases.

The structure of novel carborane amino acids was confirmed by IR spectroscopy and elemental analyses.

3. Conclusions

In summary, we have elaborated a general high yield strategy for obtaining of *N*-protected carboranyl amino acid derivatives containing an amino group at the boron atom and a carboxymethyl group at a carbon atom of the carborane polyhedron. Water soluble *closo*- and *nido*-boronated amino acids were prepared by acidic hydrolysis of corresponding acyl-protected amino acids. These *o*-carborane derivatives can be attractive synthons in the generation of highly structured boronated peptides, lactams, amino alcohols, and other boronated biomolecules.

4. Experimental

4.1. General

Dry THF was obtained by distillation over sodium benzophenone ketyl. The identities of newly synthesized compounds were checked by TLC on Silufol UV 254 plates (Kavalier; Czech Republic), eluents–toluene for compounds **1**–**3** and toluene - ethyl acetate (1:1) for compounds **11**–**17**.

Infrared spectra were recorded on UR-20 spectrometer as suspension in hexachlorobutadiene. ^{1}H NMR spectra (400.3 MHz) and ^{11}B NMR spectra (128.28 MHz) were recorded with a Bruker AMX-400 spectrometer in $[D]_6$ acetone. $Et_2O{\cdot}BF_3$ was used as the external standard for ^{11}B NMR. Proton chemical shifts were referenced to TMS. All signals are expressed in ppm (δ). Acylated amino derivatives **4**–**10** were prepared according to the literature procedures [6,8].

4.2. Preparation of N-acylated o-carborane amino acids 11–17. General procedure

A solution of corresponding 3-acylamino-*o*-carborane (10 mmol) in THF (25 ml) was added via syringe to a stirred mixture of $NaNH_2$ (30 mmol, for compounds **4**, **6** and **9**; 20 mmol, for compounds **5**, **7**, **8**, **10**) in liquid ammonia (50 ml) at −45 °C. The reaction mixture was stirred for 0.5 h at −50 °C. Then, sodium bromoacetate (4.8 g, 30 mmol for compounds **4**, **6** and **9**; 3.2 g, 20 mmol, for compounds **5**, **7**, **8**, **10**) was added and the mixture was stirred for another 1.5 h at −50 °C. 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 Na_2SO_4. The solvent was evaporated and the crude product was crystallized from ethyl acetate–heptane mixture to give corresponding *N*-acylamino-*o*-carborane amino acid derivatives **11**–**17** with 85–95% yield.

4.2.1. 3-Benzoylamino-1-carboxymethyl-o-carborane (11)

Obtained from compound **4** (3.0 g, 12 mmol), $NaNH_2$ (36 mmol) and sodium bromoacetate (5.8 g, 36 mmol) in 100 ml of liquid ammonia. Yield, 3.2 g (85%). M.p.: 198–199 °C. IR (cm^{-1}): 3332 (NH), 2942 (OH), 2608 (BH), 1730 (CO, COOH), 1634 (CO, CONH). ^{1}H NMR: 8.20 (s, 1H, NH), 7.61–7.46 (m, 5H, Ph) 5.63 (s, 1H, carborane CH), 3.57 (d, 1H, CH_2, J = 15.2 Hz), 3.42 (d, 1H, CH_2, J = 15.2 Hz). ^{11}B NMR: −3.51 (s, 1B, B^3), −5.19 (d, 2B, $B^{9,12}$,

J = 154 Hz), −9.24 (d, 1B, B^8, J = 165 Hz), −10.75 (d, 1B, B^{10}, J = 180 Hz), −12.32 (d, 2B, $B^{4,7}$, J = 171 Hz), −13.56 (d, 2B, $B^{5,11}$, J = 145 Hz), −14.04 (d, 1B, B^6, J = 138 Hz). Anal. Calc. for $C_{11}H_{19}B_{10}NO_3$: C, 41.12; H, 5.91; B, 33.67. Found: C, 41.52; H, 5.97; B, 33.98%.

4.2.2. 3-Benzoylamino-l-carboxymethyl-2-methyl-o-carborane (**12**)

Obtained from compound **5** (2.8 g, 10 mmol), $NaNH_2$ (20 mmol) and sodium bromoacetate (3.2 g, 20 mmol) in 100 ml of liquid ammonia. Yield, 3.0 g (89%). M.p.: 213–214 °C. IR (cm^{-1}): 3307 (NH), 2953 (OH), 2601 (BH), 1730 (CO, COOH), 1674 (CO, CONH). ^{1}H NMR: 8.44 (m, 2H, Ph), 8.31 (s, 1H, NH), 8.04–7.93 (m, 3H, Ph), 3.52 (d, 1H, CH_2, J = 14.8 Hz), 3.32 (d, 1H, CH_2, J = 14.8 Hz). ^{11}B NMR: −3.11 (s, 1B, B^3), −5.14 (d, 1B, B^9, J = 160 Hz), −6.41 (d, 1B, B^{12}, J = 158 Hz), −7.58 (d, 1B, B^8, J = 168 Hz), −9.71 (d, 2B, $B^{10,4(7)}$, J = 149 Hz), −10.67 (d, 2B, $B^{7(4),5}$, J = 162 Hz), −12.11 (d, 1B, B^{11}, J = 180 Hz), −13.73 (d, 1B, B^6, J = 159 Hz). Anal. Calc. for $C_{12}H_{21}B_{10}NO_3$: C, 42.98; H, 6.27; B, 32.26. Found: C, 43.15; H, 6.29; B, 32.02%.

4.2.3. 3-Acetylamino-1-carboxymethyl-o-carborane (**13**)

Obtained from compound **6** (2.4 g, 12 mmol), $NaNH_2$ (36 mmol) and sodium bromoacetate (5.8 g, 36 mmol) in 100 ml of liquid ammonia. Yield, 2.85 g (92%). M.p.: 210–211 °C. IR (cm^{-1}): 3329 (NH), 2940 (OH), 2605 (BH), 1726 (CO, COOH), 1638 (CO, CONH). ^{1}H NMR: 7.76 (s, 1H, NH), 5.43 (s, 1H, carborane CH), 3.62 (d, 1H, CH_2, J = 15.2 Hz), 3.48 (d, 1H, CH_2, J = 15.2 Hz). ^{11}B NMR: −3.96 (s, 1B, B^3), −5.10 (d, 1B, B^9, J = 159 Hz), −5.59 (d, 1B, B^{12}, J = 160 Hz), −9.58 (d, 1B, B^8, J = 162 Hz), −10.95 (d, 2B, $B^{10,4(7)}$, J = 165 Hz), −12.54 (d, 2B, $B^{7(4),5(11)}$, J = 178 Hz), −13.97 (d, 1B, $B^{11,(5)}$, J = 158 Hz), −14.39 (d, 1B, B^6, J = 142 Hz). Anal. Calc. for $C_6H_{17}B_{10}NO_3$: C, 27.80; H, 6.64; B, 41.70. Found: C, 28.09; H, 6.60, B, 41.37%.

4.2.4. 3-Acetylamino-1-carboxymethyl-2-methyl-o-carborane (**14**)

Obtained from compound **7** (2.4 g, 11 mmol), $NaNH_2$ (22 mmol) and sodium bromoacetate (3.5 g, 22 mmol) in 100 ml of liquid ammonia. Yield, 2.70 g (90%). M.p.: 209–210 °C. IR (cm^{-1}): 3329 (NH), 2915 (OH), 2605 (BH), 1726 (CO, COOH), 1650 (CO, CONH). ^{1}H NMR: 7.38 (s, 1H, NH), 3.32 (d, 1H, CH_2, J = 14.8 Hz), 3.11 (d, 1H, CH_2, J = 14.8 Hz). ^{11}B NMR: −3.24 (s, 1B, B^3), −5.17 (d, 1B, B^9, J = 163 Hz), −6.53 (d, 1B, B^{12}, J = 158 Hz), −8.05 (d, 1B, B^8, J = 165 Hz), −10.14 (d, 3B, $B^{10,4,7}$, J = 170 Hz), −10.87 (d, 1B, $B^{5(11)}$, J = 159 Hz), −12.09 (d, 1B, $B^{11(5)}$, J = 148 Hz), −14.18 (d, 1B, B^6, J = 153 Hz). Anal. Calc. for $C_7H_{19}B_{10}NO_3$: C, 30.76; H, 6.96; B, 39.56. Found: C, 31.04; H, 7.03, B, 39.12%.

4.2.5. 3-Acetylamino-1-carboxymethyl-2-phenyl-o-carborane (**15**)

Obtained from compound **8** (2.77 g, 10 mmol), $NaNH_2$ (20 mmol) and sodium bromoacetate (3.2 g, 20 mmol) in 100 ml of liquid ammonia. Yield, 3.10 g (94%). M.p.: 227–224 °C. IR (cm^{-1}): 3349 (NH), 3040 (OH), 2603 (BH), 1730 (CO, COOH), 1643 (CO, CONH). ^{1}H NMR: 7.78–7.49 (m, 5H, Ph), 6.93 (s, 1H, NH), 3.08 (d, 1H, CH_2, J = 14.6 Hz), 3.02 (d, 1H, CH_2, J = 14.6 Hz). ^{11}B NMR: −2.85 (s, 1B, B^3), −4.30 (d, 1B, B^9, J = 142 Hz), −5.32 (d, 1B, B^{12}, J = 141 Hz), −7.85 (d, 1B, B^8, J = 163 Hz), −10.22 (d, 4B, $B^{10,4,7,5(11)}$, J = 160 Hz), −12.80 (d, 2B, $B^{11(5),6}$, J = 150 Hz). Anal. Calc. for $C_{12}H_{21}B_{10}NO_3$: C, 42.99; H, 6.27; B, 32.24. Found: C, 43.24; H, 6.47, B, 31.98%.

4.2.6. 1-Carboxymethyl-3-formylamino-o-carborane (**16**)

Obtained from compound **9** (3.74 g, 20 mmol), $NaNH_2$ (60 mmol) and sodium bromoacetate (9.7 g, 60 mmol) in 100 ml of liquid ammonia. Yield, 4.70 g (95%). M.p.: 178–179 °C. IR (cm^{-1}): 3296 (NH), 3060 (carborane CH), 2940 (OH), 2600 (BH), 1726 (CO, COOH), 1675 (CO, CONH). ^{1}H NMR: 8.50 (s, 1H, CHO), 7.25 (s, 1H, NH), 4.23 (s, 1H, carborane CH), 3.06 (d, 1H, CH_2, J = 14.5 Hz), 2.93 (d, 1H, CH_2, J = 14.5 Hz). ^{11}B NMR: −3.51 (s, 1B, B^3), −5.19 (d, 2B, $B^{9,12}$, J = 154 Hz), −9.24 (d, 1B, B^8, J = 165 Hz), −10.75 (d, 1B, B^{10}, J = 175 Hz), −12.32 (d, 2B, $B^{4,7}$ J = 171 Hz), −13.56 (d, 2B, $B^{5,11}$, J = 145 Hz), −14.04 (d, 1B, B^6, J = 143 Hz). Anal. Calc. for $C_5H_{15}B_{10}NO_3$: C, 24.48; H, 6.12; B, 44.13. Found: C, 24.56; H, 6.06, B, 43.87%.

4.2.7. 1-Carboxymethyl-3-formylamino-2-methyl-o-carborane (**17**)

Obtained from compound **10** (2.0 g, 10 mmol), $NaNH_2$ (20 mmol) and sodium bromoacetate (3.2 g, 20 mmol) in 100 ml of liquid ammonia. Yield, 2.3 g (90%). M.p.: 181–183 °C. IR (cm^{-1}): 3890 (NH), 2925 (OH), 2602 (BH), 1725 (CO, COOH), 1674 (CO, CONH). ^{1}H NMR: 8.45 (s, 1H, CHO), 7.25 (s, 1H, NH), 3.03 (d, 1H, CH_2, J = 14.6 Hz), 2.96 (d, 1H, CH_2, J = 14.6 Hz). ^{11}B NMR: −3.11 (s, 1B, B^3), −5.14 (d, 1B, B^9, J = 160 Hz), −6.41 (d, 1B, B^{12}, J = 158 Hz), −7.58 (d, 1B, B^8, J = 168 Hz), −9.71 (d, 2B, $B^{10,4(7)}$, J = 149 Hz), −10.67 (d, 2B, $B^{7(4),5}$, J = 162 Hz), −12.11 (d, 1B, B^{11}, J = 180 Hz), −13.73 (d, 1B, B^6, J = 159 Hz). Anal. Calc. for $C_6H_{17}B_{10}NO_3$: C, 27.80, H, 6.56, B, 41.70. Found: C, 27.56; H, 6.57, B, 42.04%.

4.2.8. 3-Ammonium-1-carboxymethyl-o-carborane hydrochloride (**18**)

3-Acetylamino acid (**13**) (1.3 g, 5.0 mmol) was heated in the mixture of AcOH (10 ml) and HC1 (10 ml) for 15 h at 60 °C. The reaction mixture was evaporated to dryness under reduced pressure. The crude product

was crystallized from water to afford hydrochloride **18** (1.1 g, 84%). IR (cm^{-1}): 2750–3650 (NH, OH), 2570 (BH), 1725 (CO). Anal. Calc. for $C_4H_{16}B_{10}ClNO_2$: C, 18.93; H, 6.31; B, 42.63; N, 5.52. Found: C, 19.23; H, 6.38; B, 42.38; N, 5.41%.

*4.2.9. 3-Ammonium-1-carboxymethyl-2-methyl-o-carborane hydrochloride (**19**)*

Following the procedure reported above for the preparation of compound **18** and starting with 3-formylamino acid **17** (1.25 g, 5 mmol) compound **19** (1.0 g, 79%) was obtained. IR (cm^{-1}): 2750–3650 (NH, OH), 2565 (BH), 1725 (CO). Anal. Calc. for $C_5H_{18}B_{10}C1NO_2$: C, 22.42; H, 6.73; B, 40.39; N, 5.23. Found: C, 22.75; H, 6.80; B, 39.98; N, 5.41%.

*4.2.10. 3-Ammonium-7-carboxymethyl-nido-7,8-dicarbaundecaborate (**20**)*

3-Benzoylamino acid **11**(1.6 g, 5 mmol) was refluxed in a mixture of AcOH (10 ml) and HCl (10 ml) for 40 h. The reaction mixture was evaporated to dryness under reduced pressure. Then, H_2O (15 ml) was added and the reaction mixture was cooled to 0 °C. The precipitated benzoic acid was filtered off. The solution was evaporated under the reduced pressure to dryness to give water soluble betaine **20** (0.79 g, 77%). IR (cm^{-1}): 2800–3600 (NH, OH), 2535 (BH), 1715 (CO). Anal. Calc. for $C_4H_{15}B_9NO$: C, 23.28; H, 7.27; B, 47.14; N, 6.79. Found: C, 23.75; H, 7.18; B, 46.98; N, 6.51%.

Acknowledgements

Supported by Division of General Chemistry and Material Science, Russian Academy of Sciences (Grant 591-07), Russian Foundation for Basic Research Grant 03-03-33091 and Russian Foundation for Basic Research/BNTS Austria Grant 03-03-20007.

References

[1] J.F. Valliant, K.J. Guenther, A.S. King, P. Morel, P. Schaffer, O.O. Sogbein, K.A. Stephenson, Coord. Chem. Rev. 232 (2002) 173.
[2] (a) C. Morin, Tetrahedron 54 (1994) 12521;
(b) A.H. Soloway, W. Tjarks, B.A. Barnum, F.-G. Rong, R.F. Barth, I.M. Codogni, J.G. Wilson, Chem. Rev. 98 (1998) 1515.
[3] J.L. Mallesch, D.E. Moore, B.J. Allen, W.H. McCarthy, R. Jones, W.A. Stenning, Int. J. Radiat. Oncol. Biol. Phys. 28 (1994) 1183.
[4] R.A. Kasar, G.M. Knudsen, S.B. Kahl, Inorg. Chem. 38 (1999) 2936.
[5] R. Tapi, in: L.L. Iversen, et al. (Eds.), Handbook of Psychopharmacology, Plenum, New York, 1975, pp. 1–58.
[6] L.I. Zakharkin, V.N. Kalinin, V.V. Gedymin, J. Organometal. Chem. 16 (1969) 371.
[7] V.P. Krasnov, G.L. Levit, V.N. Charushin, A.N. Grishakov, M.I. Kodess, V.N. Kalinin, V.A. Ol'shevskaya, O.N. Chupakhin, Tetrahedron: Asymmetry 13 (2002) 1833.
[8] L.I. Zakharkin, V.N. Kalinin, V.V. Gedymin, G.S. Dzarasova, J. Organometal. Chem. 23 (1970) 303.