Syntheses of 1-Amino-3-[2-(7-(2-hydroxyethyl)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl)ethyl]cyclobutanecarboxylic Acid and Its *nido*-Analogue: Potential BNCT Agents

Rajiv R. Srivastava and George W. Kabalka*

Departments of Chemistry and Radiology, University of Tennessee, Knoxville, Tennessee 37996-1600

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The syntheses of unnatural amino acids, 1-amino-3-[2-(7-(2-hydroxyethyl)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl)ethyl]cyclobutanecarboxylic acid (**2**) and its *nido* analog 1-amino-3-[2-(7-(2-hydroxyethyl)-1,7-dicarba-*nido*-dodecaboran(12)-1-yl)ethyl]cyclobutanecarboxylic acid (**3**) were achieved. The key steps in the syntheses of **2** and **3** involved the sequential dialkylation of *m*-carborane and an intramolecular ethoxide ion mediated cage degradation process.

Introduction

Boron neutron capture therapy (BNCT) was first proposed as a potential cancer therapy in 1936[1] but the successful application of BNCT to the treatment of cancer still presents a challenge in medical research. An early attempt to cure cancer using this protocol was unsuccessful[2−5] due to vascular damage caused by the nonselective uptake of the boronated agent resulting in a high boron concentration in the blood. Encouraging results obtained in Japan[6] using sodium mercaptoundecahydrodecaborate ($Na_2B_{12}H_{11}SH$, BSH) and 4-(dihydroxyboryl)phenylalanine (BPA) has led to a resurgence of interest in BNCT. The Japanese data suggest that BNCT can play an important role in cancer therapy (especially in the treatment of glioblastoma multiforme where conventional chemotherapy and radiation therapy have had little success).

Boron neutron capture therapy (BNCT) is a binary therapy which is dependent on the selective deposition of boron-10 in the tumor prior to irradiation by slow (thermal) neutrons.[7] The interaction of a boron-10 atom with a thermal neutron produces an α-particle and a high energy lithium-7 ion. The linear energy transfer (LET) of these heavy charged particles (^4He and ^7Li) has a range of one cell diameter and thus they are lethal to the cells in which they are generated. To minimize damage to normal tissues, the quantity of boron in the tumor (≈30 μg ^{10}B/g of tumor) must exceed that in the surrounding normal tissues by a factor exceeding 3.[7−9] A variety of carrier molecules have been used to deliver boron to the tumor cells. These include carbohydrates,[10−12] amino acids,[13−16] nucleosides,[17,18] antisence agents,[19] porphyrins,[20] antibodies,[21,22] and liposomes.[23] While these carrier molecules are being developed, BSH and BPA are being used clinically for the treatment of brain tumors and malignant melanoma in human patients.[6,24,25]

Boron-containing amino acid derivatives[13−16] have been examined as potential agents for BNCT. It is believed that amino acids are preferentially taken up by growing tumor cells. In fact, the only drug (BPA) currently in clinical trials in the United States is an amino acid.[26] Carboranyl analogues of phenylalanine[15,16] have also been synthesized and are currently being evaluated as potential BNCT agents.

We recently reported the synthesis of an unnatural alicyclic, boron-containing α-amino acid, 1-amino-3-[2-(1,7-dicarba-*closo*-dodecaboran(12)-1-yl)ethyl]cyclobutanecarboxylic acid, **1** (*closo*-*m*-carboranyl-ACBC).[27] This molecule was modeled after 1-aminocyclobutanecarboxylic acid (ACBC) which is known to be preferentially retained in intracerebral tumors.[28,29] This property makes boronated ACBC analogues promising candidates

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(1) Locher, G. L. *Am. J. Roentgenol. Radiat. Ther.* **1936**, *36*, 1.
(2) Sweet, W. H. *N. Engl. J. Med.* **1951**, *245*, 875.
(3) Sweet, W. H. N.; Javid, M. *J. Neurosurg.* **1952**, *9*, 200.
(4) Asbury, A. K.; Ojeann, R. G.; Nielsen, S. L.; Sweet, W. H. N. *J. Neuropathol. Exp. Neurol.* **1972**, *31*, 278−303.
(5) Sweet, W. H. N. Proceedings of First International Symposium on Neutron Capture Therapy, Brookehaven National Laboratory Report No. 51730, 1983; p 376.
(6) Hatanaka, H.; Nakagawa, Y. *Int. J. Radiat. Oncol. Biol. Phys.* **1994**, *28*, No. 5, 1061−1066.
(7) Barth, R. F.; Soloway, A. H.; Brugger, R. M. *Cancer Invest.* **1996**, *14*, No. 6, 534−550.
(8) Fairchild, R. G.; Bond, V. P. *Int. J. Radiat. Oncol. Biol. Phys.* **1985**, *11*, 831.
(9) Zamenhof, R. G.; Kalend, A. M.; Bloomer, W. D. *J. Natl. Cancer Inst.* **1992**, *84*, 1290−91.
(10) Tjarks, W.; Anisuzzaman, A. K. M.; Liu, L.; Soloway, A. H.; Barth, R. F.; Perkins, D. J.; Adams, D. M. *J. Med. Chem.* **1992**, *35*, 1628−1633.
(11) Maurer, J. L.; Berchier, F.; Serino, A. J.; Knobler, C. B.; Hawthorne, M. F. *J. Org. Chem.* **1990**, *55*, 838−843.
(12) Maurer, J. L.; Serino, A. J.; Hawthorne, M. F. *Organometallics* **1988**, *7*, 2519−2524.
(13) Fauchere, J. L.; Leukart, O.; Eberle, A.; Schwyzer, R. *Helv. Chim. Acta* **1979**, *62*, 1382−1395.
(14) Radel, P. A.; Kahl, S. B. *J. Org. Chem.* **1996**, *61*, 4582−4588.
(15) Malmqist, J.; Sjoberg, S. *Tetrahedron* **1996**, *52*, 9207−9208.
(16) Yong, J.-H.; Barth, R. F.; Wyzlic, I. M.; Soloway, A. H.; Rotaru, J. H. *Anticancer Res.* **1995**, *15*, 2033−2038.
(17) Anisuzzaman, A. K. M.; Alan, F.; Soloway, A. H. *Polyhedron* **1990**, *9*, 891−892.
(18) Goudgaon, N. M.; Kattan, Fulcrand-E. G.; Liotta, D. C.; Schinazi, R. F. *Nucleosides Nucleotides* **1994**, *13*, 849.
(19) Yamamoto, Y.; Seko, T.; Nemoto, H. *J. Org. Chem.* **1989**, *54*, 4734−4736.
(20) Kattan, Fulcrand-E. G.; Lesnikowski, Z. J.; Yao, S.; Tanious, F.; Wilson, W. D.; Schinazi, R. F. *J. Am. Chem. Soc.* **1994**, *116*, 7494−501.
(21) Kahl, S. B.; Koo, M.-S. *J. Chem. Soc., Chem. Commun.* **1990**, 1769−1771.
(22) Chen, C−J.; Kane, R. R.; Primus, F. J.; Szalai, G.; Hawthorne, M. F.; Shively, J. E. *Bioconjugate Chem.* **1994**, *5*, 557−564.
(23) Shelly, K.; Feakes, D. A.; Hawthorne, M. F.; Schmidt, P. G.; Krisch, T. A.; Bauer, W. F. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 9039.
(24) Kageji, T.; Nakagawa, Y.; Kitamura, K.; Matsumoto, K.; Hatanaka, H. *J. Neuro-Oncol.* **1997**, *33*, 117−130.
(25) Coderre, J. A.; Elowitz, E. H.; Chadha, M.; Bergland, R.; Capala, J.; Joel, D. D.; Liu, H. B.; Slatkin, D. N.; Chanana, A. D. *J. Neuro-Oncol.* **1997**, *33*, 141−152.
(26) Coderre, J.; Rubin, P.; Freedman, A.; Hansen, J.; Wooding, T. S.; Joel, D.; D. V. M.; Gash, D. *Int. J. Rad. Oncol. Biol. Phys.* **1994**, *28*, No. 5, 1067−1077.
(27) Srivastava. R. R.; Singhous, R. R.; Kabalka, G. W. *J. Org. Chem.* **1997**, *62*, 4476.

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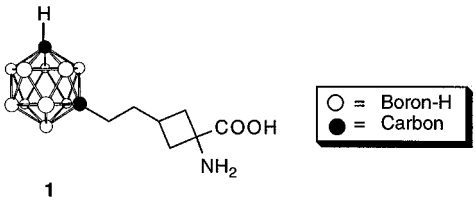

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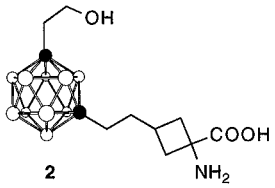
for BNCT. We are primarily interested in the *m*-carborane cage as the boron source because of its chemical stability. Carboranes can form *nido*-derivatives upon reaction with a variety of bases;[30] this can be advantageous for obtaining water soluble carboranes[19,21,31] (*nido* carboranes are water soluble). Although some *nido*-carborane derivatives have been found to be nontoxic in in vitro studies,[32] the ionic nature of the cage can be problematic in in vivo studies because it may react with proteins resulting in nonspecific binding to biological materials.[33,34] In a recent study it has been found that, some *o*-carboranyl amino acids degrade spontaneously in an intramolecular process in aqueous medium at a pH around the isoelectric point.[35] These findings raise serious questions concerning the in vivo stability of *o*-carboranyl-based BNCT agents. To address the problem of in vivo stability and to have better understanding of in vivo biodistribution and toxicity of *closo*- and *nido*-carboranyl cages, we decided to synthesize 1-amino-3-[2-(7-(2-hydroxyethyl)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl)ethyl]cyclobutanecarboxylic acid (**2**), and its *nido* analogue 1-amino-3-[2-(7-(2-hydroxyethyl)-1,7-dicarba-*nido*-dodecaboran(12)-1-yl)ethyl]cyclobutanecarboxylic acid (**3**).



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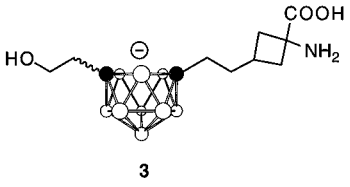

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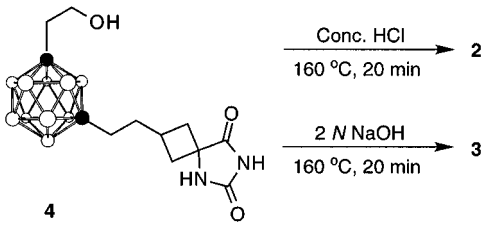
Results and Discussion

Syntheses of **2** and **3** involved dialkylation of *m*-carborane and formation of *nido*-*m*-carboranyl cage (for **3**). While the sequential dialkylation of the *m*-carborane cage is an extension of our earlier findings, successful monoalkylation of *m*-carborane and synthesis of 1-amino-3-[2-(1,7-dicarba-closo-dodecaboran(12)-1-yl)ethyl]cyclobutanecarboxylic acid,[27] the synthesis of *nido*-*m*-carboranyl based BNCT agents have never been reported. Earlier studies of the syntheses of *nido*-*m*-carboranes, especially dialkylated *m*-carborane cages, used high temperature, long reaction times, and strong bases, and

Scheme 1



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the reactions were carried out in an autoclave.[36] The severity of these reaction conditions decreased interest in *nido*-*m*-carboranyl based BNCT agents. In our strategy, we chose to incorporate the ethoxide ion as part of the carborane cage which could lead to an intramolecular cage degradation process. We found that the intramolecular reaction is fast compared to the intermolecular reaction, and we successfully synthesized the *nido*-*m*-carboranyl cage under relatively mild conditions.

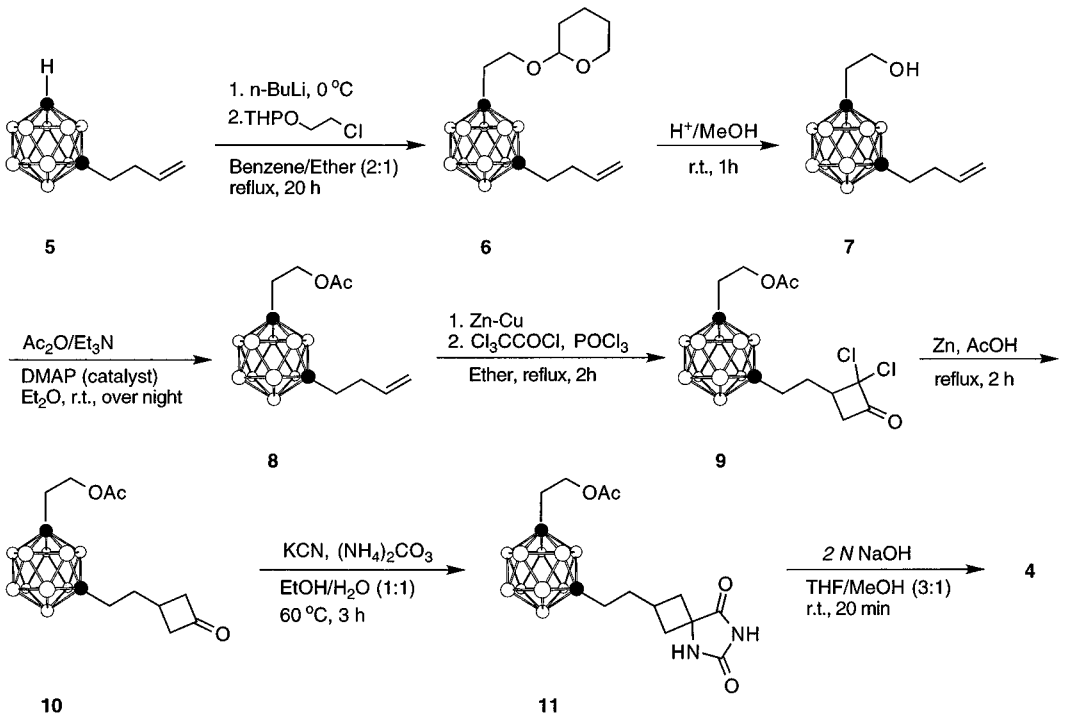
m-Carboranyl aminocyclobutanecarboxylic acids **2** and **3** were synthesized from a common intermediate, hydroxyhydantoin **4** (Scheme 1). The synthesis of **4** was accomplished in seven steps (Scheme 2). The synthesis was initiated by the sequential dialkylation of *m*-carborane. 4-*m*-Carboranyl-1-butene (**5**) was synthesized according to the literature procedure.[27] When **5** was reacted with an equimolar quantity of butyllithium in a mixture of ether and benzene (1:2 ratio), followed by reaction with tetrahydro-2-(2-chloroethoxy)-2*H*-pyran, 4-[7-(2-tetrahydropyranyloxy)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl]-1-butene (**6**) was formed in high yield. The tetrahydropyranyl protected alcohol was deprotected under acidic condition to obtain 4-[7-(2-hydroxyethyl)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl]-1-butene (**7**) also in high yield. Alcohol **7** was acetylated with acetic anhydride using triethylamine as base in the presence of a catalytic amount of 4-(dimethylamino)pyridine to obtain 4-[7-(2-acetoxyethyl)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl]-1-butene (**8**). Alkene **8** was subjected to a 2 + 2 cycloaddition with dichloroketene which was generated in situ via the reaction of trichloroacetyl chloride with phosphorus oxychloride in the presence of a Zn−Cu couple.[37] The crude product **9** obtained from the ketene addition was subjected to reductive dechlorination with Zn and acetic acid.[38] The resultant 3-[2-(7-(2-acetoxyethyl)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl)ethyl]cyclobutanone (**10**) was reacted with ammonium carbonate and potassium cyanide in a pressure tube.[39] Hydantoin **11** was formed in excellent yield. In the next step, **11** was treated with base for a short period of time to generate hydroxyhydantoin **4**. Acid hydrolysis of **4** generated **2** whereas base hydrolysis afforded **3**.

Conclusion

We report the first successful sequential dialkylation of *m*-carborane and the use of an intramolecular ethoxide ion mediated cage degradation strategy to obtain a *nido*-*m*-carboranyl cage under relatively mild reaction conditions. It should be noted that previous reports on the synthesis of *nido*-*m*-carborane, especially dialkylated-*m*-

(28) Washburn, L. C.; Sun, T. T.; Byrd, B. L.; Hayes, R. L.; Butler, T. A. *J. Nucl. Med.* **1980**, *20*, No. 10, 1055.
(29) Hubner, K. F.; Smith, G. T.; Thie, J. A.; Buonocore, E. *J. Nucl. Med.* **1992**, *33*(5), Suppl. 922.
(30) Grimes, R. N. *Carborane*; Academic Press: New York and London, 1970.
(31) Kane, R. R.; Drechsel, K.; Hawthorne, M. F.; *J. Am. Chem. Soc.* **1993**, *115*, 8853−8854.
(32) Yong, J.-H.; Barth, R. F.; Rotaru, J. H.; Wyzlic, I. M.; Soloway, A. H. *Anticancer Res.* **1995**, *15*, 2039−2044.
(33) Tjarks, S. W.; Ketz, H.; Gabel, D. *Progress in Neutron Capture Therapy for Cancer*; B. J. Allen et al., Eds.; Plenum Press: New York, 1992.
(34) Pettersson, M. L.; Courel, M.-N.; Abraham, R.; Gabel, D.; Thellier, M.; Delpech, B. *J. Immunol. Meth.* **1990**, *126*, 95−102.
(35) Lindstrom, P.; Gogoll, A.; Rousell, P.; Sjoberg, S. Presented at Seventh International Symposium on Neutron Capture Therapy, Zurich, Switzerland, September, 1996.
(36) Hawthorne, M. F.; Young, D. C.; Garrett, P. M.; Owen, D. A.; Schwerin, S. G.; Tebbe, F. N.; Wegner, P. A. *J. Am. Chem. Soc.* **1968**, *90*, 862−868.
(37) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879−82.
(38) Jeff, P. W.; Molina, G.; Cass, M. W.; Cortese, N. A. *J. Org. Chem.* **1982**, *47*, 3871−75.
(39) Henze, H. R.; Speer, R. J. *J. Org. Chem.* **1942**, *7*, 522−523.

Scheme 2



carborane, required much harsher reaction condition[35] which severely limited the scope of those reactions. The syntheses of 1-amino-3-[2-(7-(2-hydroxyethyl)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl)ethyl]cyclobutanecarboxylic acid (**2**) and its *nido* analogue 1-amino-3-[2-(7-(2-hydroxyethyl)-1,7-dicarba-*nido*-dodecaboran(12)-1-yl)ethyl]-cyclobutanecarboxylic acid (**3**) were achieved, and the agents are being evaluated for potential use in BNCT.

Experimental Section

General Methods. All solvents were reagent grade and were distilled from appropriate drying agents under a nitrogen atmosphere prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl; benzene was distilled from calcium hydride and stored under nitrogen. *m*-Carborane was purchased from Boron Biologicals, Inc. (Raleigh, NC) and purified by sublimation. 4-*m*-Carboranyl-1-butene (**5**) was prepared according to the literature procedure.[27] All other chemicals were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used as received.

Column chromatography was performed using silica gel (60 Å, 230−400 mesh) obtained from Baxter Co. (McGaw Park, IL). Reverse-phase column chromatography was performed utilizing octadecyl functionalized silica gel obtained from Aldrich Chemical Co. (Milwaukee, WI). Analytical thin-layer chromatography was performed on 250 micron silica plates obtained from Analtech Inc. (Newark, DE) and were visualized by phosphomolybdic acid, palladium chloride, and silver nitrate solutions.

Melting points were measured on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained either neat or as Nujol mulls and were recorded on a Bio-Rad FTS-7 instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 250 at 250.13 and 62.89 Mz, respectively. ^{11}B NMR (^{1}H-decoupled) spectra were obtained on a Bruker AMX-400 at 128.38 Mz. Chemical shifts for ^{1}H and ^{13}C NMR spectra were referenced to $Si(CH_3)_4$ and measured with respect to the residual protons in the deuterated solvents. In the case of ^{11}B NMR, chemical shifts were measured with reference to external $BF_3{\cdot}OEt_2$. Resonances observed upfield of the reference ($BF_3{\cdot}OEt_2$) were assigned negative chemical shift values. Microanalysis were performed by Galbraith Laboratories Inc., Knoxville, TN. HR-FAB-MS (M + 1) were obtained on a ZAB-EQ instrument in a glycerol matrix. Positive ion electrospray mass spectra (ES+) were recorded on a VG Quattro II spectrometer in instances where satisfactory elemental analyses were obtained for carbon and hydrogen but where boron values exceeded acceptable limits (not uncommon for boron cages).[40]

4-[7-(2-Tetrahydropyranyloxy)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl]-1-butene (6). A three-necked, round-bottomed flask equipped with an addition funnel, reflux condenser, and argon balloon was charged with 4-*m*-carboranyl-1-butene (**5**) (25 mmol, 5.0 g) in a mixture of benzene (100 mL) and ether (50 mL). The reaction mixture was cooled to 0 °C, butyllithium (30 mmol, 19 mL of 1.6 M solution in hexane) was added via a syringe over a period of 10 min, and the mixture was allowed to stir at room temperature for 30 min. The reaction mixture was then cooled to 0 °C and to it was added a solution of 2-(2-chloroethoxy)tetrahydro-2*H*-pyran (30 mmol, 5.0 g) in a mixture of benzene (10 mL) and ether (5 mL) over a period of 5 min. The reaction mixture was then refluxed at 90 °C in an oil bath for 18 h, cooled to room temperature, and quenched with water (2.0 mL). The solution was transferred to a separatory funnel and washed successively with water (2 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator. After drying at 50 °C at 0.2 mmHg, a colorless liquid (10 g) was obtained. The crude product was purified by column chromatography using silica gel (30 × 4 cm, 5% ethyl acetate in hexane) to yield **6** as a colorless liquid (6.4 g, 78% yield); R_f = 0.72 (10% ethyl acetate in hexane, thin-layer chromatography); ^{1}H NMR ($CDCl_3$) δ 5.53 (m, 1 H), 4.84 (m, 2 H), 4.40 (br s, 1 H), 3.68 (m, 1H), 3.57 (m, 1 H), 3.36 (m, 1 H), 3.19 (m, 1 H), 2.09 (t, J = 7.19 Hz, 2 H), 1.92 (m, 4 H), 1.74−1.29 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 136.07, 115.67, 98.84, 75.44, 72.67, 65.87, 62.23, 36.42, 36.00, 33.69, 30.46, 25.29, 19.33; ^{11}B ($CDCl_3$) δ −4.22 (2 B), −8.25 (6 B), −10.42 (2 B); IR (neat) 3077, 2938, 2969, 2793, 2589, 1641, 1440, 1352, 1196, 1200, 1169, 1136, 1125, 1074, 1035, 988, 972, 907, 871, 815, 737 cm^{-1}. Anal. Calcd for $C_{13}H_{30}B_{10}O_2$: C, 47.86; H, 9.26; B, 33.11. Found: C, 48.28; H, 9.39; B, 32.08.

(40) (a) Gomez, F. A.; Hawthorne, M. F. *J. Org. Chem.* **1992**, *57*, 1384−1390. (b) Tebbe, F. N.; Garrett, P. M.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1968**, *90*, 869−879.

4-[7-(2-Hydroxyethyl)-1,7-dicarba-*closo*-dodecaboran-(12)-1-yl]-1-butene (7). A 100 mL round-bottomed flask was charged with 4-[7-(2-tetrahydropyranyloxy)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl]-1-butene (**6**) (23 mmol, 7.6 g) in methanol (50 mL), and then concentrated hydrochloric acid (0.5 mL) was added. The solution was stirred at room temperature, and the progress of the reaction was monitored by thin-layer chromatography. After 1 h stirring at room temperature, solvent was removed under reduced pressure using a rotary evaporator and the residue taken up into ethyl acetate (100 mL) and washed with water (2 × 20 mL) and then brine (1 × 20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator. The reaction yielded a viscous material (6.9 g) which was purified by column chromatography using silica gel (22 × 4 cm, 8% ethyl acetate in hexane) to yield **7** as a viscous material (5.2 g, 93% yield). The compound solidified at room temperature: $R_f = 0.34$ (10% ethyl acetate in hexane, thin-layer chromatography); mp 41 °C; ^{1}H NMR (CD_3OD) δ 5.69 (m, 1 H), 4.98 (m, 2 H), 3.51 (t, $J = 7.28$ Hz, 2 H), 2.11 (m, 6 H); ^{13}C (CD_3OD) δ 137.50, 116.24, 77.08, 74.33, 61.68, 40.15, 37.41, 35.03; ^{11}B (CD_3OD) δ −4.28 (2 B), −8.26 (6 B), −10.45 (2 B); IR (neat) 3298, 3081, 2949, 2924, 2851, 2592, 1642, 1455, 1376, 1293, 1181, 1046, 988, 917, 736 cm^{-1}. Anal. Calcd for $C_8H_{22}B_{10}O$: C, 39.65; H, 9.15; B, 44.60. Found: C, 39.98; H, 8.49; B, 44.59.

4-[7-(2-Acetoxyethyl)-1,7-dicarba-*closo*-dodecaboran-(12)-1-yl]-1-butene (8). A 250 mL round-bottomed flask was charged with 4-[7-(2-hydroxyethyl)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl]-1-butene (**7**) (27 mmol, 6.5 g) in tetrahydrofuran (100 mL) solvent. Acetic anhydride (41 mmol, 3.9 mL) was added to the reaction mixture followed by the dropwise addition of triethylamine (41 mmol, 5.7 mL). A catalytic quantity of 4-(dimethylamino)pyridine (20 mg) was added to the solution. The reaction mixture was stirred overnight and then the solvent removed under reduced pressure using a rotary evaporator. The residue was taken up into ethyl acetate (100 mL) and washed with dilute hydrochloric acid (2 × 20 mL, 5% solution in water), water (2 × 20 mL), and then brine (1 × 20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator. The reaction yielded an oily material (6.4 g). The crude product was purified by column chromatography using silica gel (24 × 5 cm, 5% ethyl acetate in hexane) to yield **8** as a colorless oil (6.3 g, 82% yield): $R_f = 0.76$ (15% ethyl acetate in hexane, thin-layer chromatography); ^{1}H NMR (CD_3OD) δ 5.69 (m, 1 H), 5.05 (m, 2 H), 4.02 (t, $J = 6.56$ Hz, 2 H), 2.32 (t, $J = 6.67$ Hz, 2 H), 2.05 (m, 4 H), 2.02 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.16, 135.86, 115.69, 75.62, 71.86, 62.26, 35.88, 35.04, 33.61, 20.58; ^{11}B (CD_3OD) δ −4.23 (2 B), −8.16 (6 B), −10.46 (2 B); IR (neat) 3078, 2974, 2933, 2902, 2857, 2593, 1746, 1641, 1451, 1432, 1389, 1365, 1229, 1181, 1049, 987, 918, 737 cm^{-1}. Anal. Calcd for $C_{10}H_{24}B_{10}O_2$: C, 42.23; H, 8.51; B, 38.01. Found: C, 42.06; H, 8.14; B, 36.99.

3-[2-(7-(2-Acetoxyethyl)-1,7-dicarba-*closo*-dodecaboran-(12)-1-yl)ethyl]cyclobutanone (10). The synthesis of this compound was achieved in two steps. 2,2-Dichloro-3-[2-(7-(2-acetoxyethyl)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl)ethyl]cyclobutanone (**9**) was synthesized from **8**, and then the halo ketone was treated with zinc and acetic acid to yield **10**.

A 250 mL, three-necked, round-bottomed flask equipped with a reflux condenser and an argon balloon was charged with 4-[7-(2-acetoxyethyl)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl]-1-butene (**8**) (9.5 mmol, 2.7 g) and diethyl ether (50 mL). Freshly prepared Zn−Cu couple (57 mmol, 7.0 g) was added followed by trichloroacetyl chloride (21 mmol, 2.3 mL) and phosphorus oxychloride (21 mmol, 1.9 mL). After stirring the mixture at room temperature for 10 min, it was refluxed for 2 h under an argon atmosphere. After 2 h reflux, the mixture was cooled to room temperature and filtered through a pad of Celite. Additional ether (2 × 20 mL) was used to transfer the material. The solvent was removed under reduced pressure using a rotary evaporator, and the viscous material containing **9** was dried under high vacuum (0.2 mmHg at 50 °C).

The crude reaction mixture containing **9** was dissolved in glacial acetic acid (50 mL) along with zinc dust (5.0 g, excess). The reaction mixture was stirred at room temperature for 20 min and then refluxed for 2 h. TLC indicated the complete disappearance of the starting material. The reaction mixture was cooled to room temperature and filtered through a pad of Celite. Additional ethyl acetate (2 × 20 mL) was used to wash the Celite pad and transfer the material from the flask. The solvent was removed under reduced pressure using a rotary evaporator. The viscous mass was dissolved in ethyl acetate (100 mL) in a separatory funnel and then washed sequentially with water (2 × 20 mL), saturated sodium bicarbonate (2 × 20 mL), water (2 × 20 mL), and brine (1 × 25 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator. The reaction yielded a viscous material (2.1 g) which was purified by column chromatography using silica gel (20 × 4 cm, 10% ethyl acetate in hexane) to yield **10** as a colorless oily product (1.6 g, 53% overall yield based on acetoxy *m*-carboranyl alkene): $R_f = 0.37$ (15% ethyl acetate in hexane, thin-layer chromatography); ^{1}H NMR ($CDCl_3$) δ 3.83 (t, $J = 6.82$ Hz, 2 H), 2.94 (m, 2 H), 2.44 (m, 2 H), 2.05 (m, 3 H), 1.85 (s, 3 H), 1.76 (m, 2 H), 1.46 (m, 2 H); ^{13}C ($CDCl_3$) δ 206.49, 170.34, 75.31, 72.00, 62.27, 52.23, 36.12, 35.46, 35.06, 23.26, 20.65; ^{11}B NMR δ (CD_3OD) −4.17 (2 B), −8.13 (6 B), −10.33 (2 B); IR (neat) 2945, 2930, 2592, 1785, 1743, 1453, 1388, 1366, 1230, 1181, 1104, 1049, 737 cm^{-1}. Anal. Calcd for $C_{12}H_{26}B_{10}O_3$: C, 44.15; H, 8.03; B, 33.12. Found: C, 44.31; H, 7.55; B, 36.66. ES+ (M + H); obtained in MeOH−H_2O solvent mixture containing 1% formic acid). Calcd for $C_{12}H_{27}B_{10}O_3$: 326.3 (64%), 327.3 (100%), 328.3 (95%). Found: 326.1 (73%), 327.1 (100%), 328.1 (96%).

Hydantoin 11 of 3-[2-(7-(2-acetoxyethyl)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl)ethyl]cyclobutanone (10). A 15 mL Ace pressure tube was charged with **10** (0.31 mmol, 0.10 g), aqueous ethanol (6 mL of a 50% solution in water), potassium cyanide (0.67 mmol, 44 mg), and ammonium carbonate (1.5 mmol, 0.15 g). The reaction vessel was sealed and heated at 60 °C in an oil bath for 3 h. The reaction vial was then cooled to room temperature and the cap carefully unscrewed in a fume hood. The reaction mixture was quenched with aqueous acetic acid (2 mL of a 30% solution in water). The solvent was removed under reduced pressure using a rotary evaporator, and the resultant white solid was taken into ethyl acetate (50 mL) in a separatory funnel and washed sequentially with water (2 × 10 mL) and brine (1 × 10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. A white solid was obtained (0.12 g). The crude material was purified by column chromatography using silica gel (10 × 2 cm, 3% methanol in methylene chloride) to yield **11** as a white solid (97 mg, 80% yield): $R_f = 0.44$ (5% methyl alcohol in methylene chloride, thin-layer chromatography); mp 226−227 °C; ^{1}H NMR (CD_3OD) δ 4.02 (t, $J = 6.65$ Hz, 2 H), 2.54 (m, 2 H), 2.31 (t, $J = 6.59$ Hz, 2 H), 2.18 (m, 3 H), 2.02 (s, 3 H), 1.89 (m, 2 H), 1.56 (m, 1 H), 1.40 (m, 1 H); ^{13}C NMR (acetone-d_6) δ 178.76, 170.61, 156.19, 77.31, 62.95, 59.05, 39.17, 37.90, 35.96, 35.29, 34.89, 26.83, 20.67; ^{11}B NMR (acetone-d_6) δ −4.26 (2 B), −8.26 (6 B), −10.39 (2 B); IR (Nujol) 3201, 2951, 2926, 2851, 2591, 1758, 1737, 1460, 1376, 1305, 1229, 1046, 802, 763, 731 cm^{-1}. Anal. Calcd for $C_{14}H_{28}B_{10}N_2O_4$: C, 42.41; H, 7.12; B, 27.26; N, 7.07. Found: C, 42.60; H, 6.92; B, 29.09; N, 6.75. ES+ (M + H); obtained in MeOH−H_2O solvent mixture containing 1% formic acid) Calcd for $C_{14}H_{29}B_{10}N_2O_4$: 396.3 (64%), 397.3 (100%), 398.3 (96%). Found: 396.2 (68%), 397.2 (100%), 398.2 (96%).

Hydroxyhydantoin 4 of 3-[2-(7-(2-Hydroxyethyl)-1,7-dicarbadodecaboran(12)-1-yl)ethyl]cyclobutanone (10). A 50 mL round-bottomed flask was charged with **11** (0.13 mmol, 50 mg) in a mixture of tetrahydrofuran (3.0 mL) and methanol (1.0 mL). To the above reaction mixture was added aqueous sodium hydroxide (0.5 mL, 2 N NaOH). The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by thin-layer chromatography. After 20 min of stirring at room temperature, the mixture was neutralized by dilute hydrochloric acid and the solvent was

removed under reduced pressure using a rotary evaporator. The residue was taken up into ethyl acetate (50 mL) and washed with water (2 × 10 mL) and then brine (1 × 10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to yield a white solid (52 mg). The crude material was purified by column chromatography using silica gel (10 × 2 cm, 5% methanol in methylene chloride) to yield **4** (32 mg, 72% yield): $R_f = 0.39$ (5% methyl alcohol in methylene chloride, thin-layer chromatography); mp 259 °C; ^{1}H NMR (CD_3OD) δ 3.51 (t, $J = 6.98$ Hz, 2 H), 2.54 (m, 2 H), 2.23 (m, 5 H), 1.88 (m, 2 H), 1.65 (m, 1 H), 1.48 (m, 1 H); ^{13}C NMR (CD_3OD) δ 180.97, 158.45, 77.23, 74.34, 61.65, 59.73, 40.12, 39.20, 38.27, 37.88, 35.35, 27.32; ^{11}B NMR (CD_3OD) δ −4.25 (2 B), −8.28 (8 B, with a shoulder at −10 ppm); IR (Nujol) 3191, 3029, 2949, 2851, 2593, 2376, 2285, 1760, 1733, 1459, 1417, 1376, 1305, 1282, 1047, 765, 724, 642 cm^{-1}. Anal. Calcd for $C_{12}H_{26}B_{10}O_3N_2$: C, 40.66; H, 7.39; B, 30.50; N, 7.90. Found: C, 40.33; H, 7.07; B, 30.13; N, 7.76.

1-Amino-3-[2-(7-(2-hydroxyethyl)-1,7-dicarba-*closo*-dodecaboran(12)-1-yl)-ethyl]cyclobutanecarboxylic Acid (2). Hydroxyhydantoin **4** (0.28 mmol, 0.10 g) was placed in a 15 mL Ace pressure tube along with concentrated hydrochloric acid (5.0 mL). The reaction mixture was heated to 160 °C in an oil bath for 20 min. It was then cooled in an ice bath and opened carefully. The reaction mixture was concentrated under reduced pressure using a rotary evaporator. The white solid obtained was purified by column chromatography using silica gel (22 × 2 cm, 8% water in acetonitrile containing 1% acetic acid) to yield **2** (71 mg, 76% yield): $R_f = 0.32$ (10% water in acetonitrile containing 1% acetic acid; thin-layer chromatography); mp compound turns brown (without melting) at 160 °C; ^{1}H NMR (CD_3OD) δ 3.49 (t, $J = 7.5$ Hz, 2 H), 2.56 (m, 1 H), 2.42 (t, $J = 7.6$ Hz, 2 H), 2.34 (m, 1 H), 2.16 (m, 1H), 1.87 (m, 4H), 1.57 (m, 2H); ^{13}C NMR (CD_3OD) δ 176.76, 77.54, 74.26, 61.65, 54.69, 42.64, 40.36, 38.26, 37.50, 35.26, 29.06; ^{11}B NMR (CD_3OD) δ −7.5 (2B), −11.9 (8B, with a shoulder at −13.9); IR (Nujol) 3384, 3136, 2953, 2852, 2593, 1714, 1596, 1461, 1376, 1281, 1183, 1021, 734 cm^{-1}. HR−FAB-MS (M + H; obtained in glycerol matrix) Calcd for $C_{11}H_{28}B_{10}NO_3$: 330.308. Found: 330.309.

1-Amino-3-[2-(7-(2-hydroxyethyl)-1,7-dicarba-*nido*-dodecaboran(12)-1-yl)ethyl]cyclobutanecarboxylic Acid (3). Hydroxyhydantoin **4** (0.23 mmol, 80 mg) was placed in a 15 mL Ace pressure tube along with a solution of sodium hydroxide (2.0 mL of 2N NaOH). The reaction mixture was heated to 160 °C in an oil bath for 20 min. It was then cooled to room temperature and opened carefully. TLC indicated disappearance of the starting hydantoin. The reaction mixture was acidified using concentrated hydrochloric acid, and the volatiles were removed under reduced pressure using a rotatory evaporator. The white solid obtained was purified by column chromatography using octadecyl functionalized silica gel (22 × 2 cm, 50% methanol in water) to yield **3** (30 mg, 42% yield): $R_f = 0.68$ (butanol, water, and acetic acid in a ratio of 10:1:0.5; thin-layer chromatography); mp compound turns brown (without melting) at 228 °C; ^{1}H NMR (CD_3OD) δ 3.68 (t, $J = 8.24$ Hz, 2 H), 2.66 (m, 3 H), 2.39 (m, 2 H), 2.0−1.51 (m, 6 H); ^{13}C NMR (acetone-d_6, major peaks) δ 172.24, 65.53, 55.39, 49.29, 45.12, 42.43, 40.62, 39.09, 37.14, 36.43, 20.41; ^{11}B NMR (D_2O) δ −0.93 (3B), −15.5 (2B), −20.1 (2B), −32.5 (2B, top of the peak split into doublet at −32.1, and −32.96); IR (Nujol) 3653, 3175, 2943, 2850, 2695, 2515, 2366, 2335, 1703, 1461, 1376, 1201, 1083, 722 cm^{-1}. HR−FAB-MS (M + H; obtained in glycerol matrix) Calcd for $C_{11}H_{27}B_9NO_3$: 319.287. Found: 319.289.

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