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Synthesis of a water soluble boron neutron capture therapy agent: 1-amino-3-[2-(7-{3-[2-(2-hydroxymethyl-ethoxy)-1-(2-hydroxy-1-hydroxymethyl-ethoxymethyl)ethoxy]propyl}-1,7-di-carba-*closo*-dodecaboran-1-yl)ethyl]cyclobutanecarboxylic acid

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Dedicated to Professor Sheldon Shore on the occasion of his 70th birthday.

Abstract

A water soluble boronated amino acid containing a cascade polyol, 1-amino-3-[2-(7-{3-[2-(2-hydroxymethyl-ethoxy)-1-(2-hydroxy-1-hydroxymethyl-ethoxymethyl)ethoxy]propyl}-1,7-di-carba-*closo*-dodecaboran-1-yl)ethyl]cyclobutanecarboxylic acid, has been developed. The key step in the synthesis is the alkylation of 3-[2-(1,7-dicarba-*closo*-dodecarboran-1-yl)ethyl]cyclobutanone hemithioketal with toluene-4-sulfonic acid 3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxymethyl)ethoxy]propyl ester which gave the required precursor ketone which was then converted to the title amino acid via a Bücherer–Strecker synthesis followed by hydrogenolysis to remove the benzyl protecting groups.

Keywords: BNCT; Polyol; Amino acid; Carborane

1. 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 modern medical research. Early attempts to cure cancer using BNCT were unsuccessful, due to vascular damage caused by the nonselective uptake of the boronated agents [2,3]. Encouraging results obtained in Japan [4] using sodium mercaptoundecahydrodecaborate ($Na_2B_{12}H_{11}SH$, BSH) and 4-dihydroxyborylphenylalanine (BPA) has led to a resurgence of interest in BNCT. Current clinical trials suggest that BNCT can play an important role in cancer 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 [5]. 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 (^{4}He and ^{7}Li) has a range of approximately 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 of ^{10}B g^{-1} of tumor) must exceed that in the surrounding normal tissues by at least a factor of three [6,7]. A variety of carrier molecules have been used to deliver boron to the tumor cells. These include carbohydrates [8–10], amino acids [11–14], nucleosides [15,16], antisense agents [17], porphyrins [18], antibodies [19,20], and liposomes [21].

Boron-containing amino acid derivatives have been examined as potential agents for BNCT [22–24]. It is believed that amino acids are preferentially taken up by

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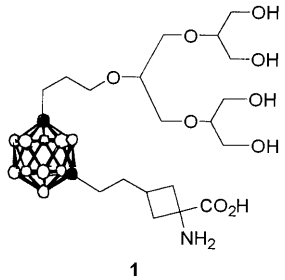
growing tumor cells. In fact, the only drug (BPA) currently in clinical trials in the US is an amino acid [25]. Carboranyl analogues of phenylalanine [15,16] have also been synthesized and are currently being evaluated as potential BNCT agents.

Relatively large cellular concentrations of boron are required for successful BNCT which makes it imperative that the carrier molecules be non-toxic. For this reason, we have focused our efforts on a cyclic α-amino acid, 1-aminocyclobutanecarboxylic acid (ACBC), as a boron carrier. This unnatural amino acid is non-toxic and is preferentially retained in intracerebral tumors. In fact, carbon-11 labeled ACBC is used for imaging brain tumors at the University of Tennessee Medical Center [26,27].

Recently we reported the syntheses of a *meta*-carborane-containing ACBC derivative and a less lipophilic *nido*-analogue [28,29]. The *nido* derivative provided good water-solubility but the ionic character of the cage has always been problematic in in vivo studies because it leads to non-specific protein binding [30,31]. However, *closo-meta*-carboranyl-ACBC and its less lipophilic analogue, the hydroxyethyl derivative, are extremely hydrophobic and therefore their in vivo uses are limited. In order to increase the water solubility of *meta*-carboranyl-ACBC, we decided to introduce polyol substituents. We wish to report the syntheses of a water soluble polyol (of the cascade type) containing a *meta*-carboranyl-ACBC derivative, 1-amino-3-[2-(7-{3-[2-(2-hydroxymethyl-ethoxy)-1-(2-hydroxy-1-hydroxymethyl - ethoxymethyl) - ethoxy]propyl} - 1,7 - dicarba - *closo* - dodecaboran - 1 - yl)ethyl]cyclobutanecarboxylic acid (**1**).



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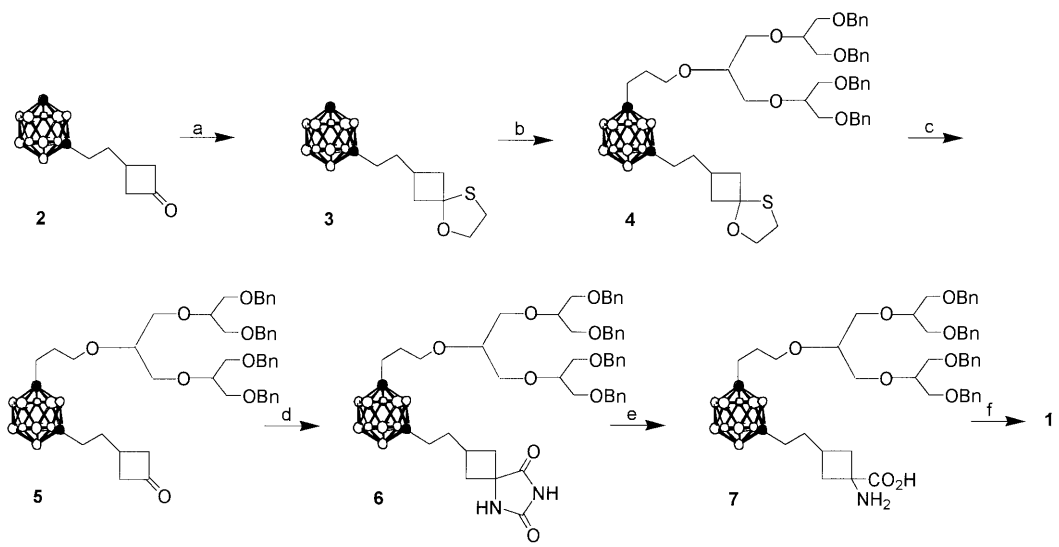
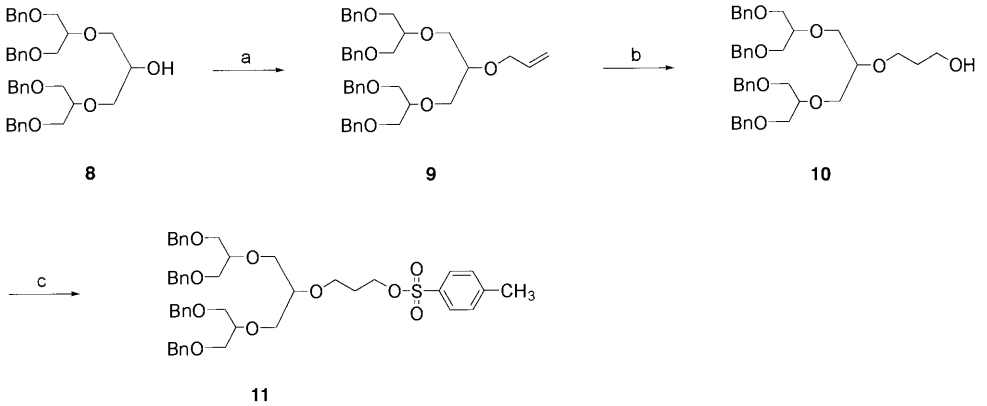
2. Results and discussion

The key synthetic step in the formation of the title compound is the preparation of the benzyl protected *meta*-carboranylcyclobutanone **5** (Scheme 1). Ketone **5** was prepared by coupling the lithium salt of the *meta*-carboranyl-cyclobutanone hemithiol ketal **3** with the polyol tosylate **11**. Hemithiol ketal **3** was obtained by refluxing the *meta*-carboranyl-cyclobutanone **2** with mercaptoethanol in the presence of a catalytic amount of *p*-toluenesulfonic acid. Tosylate **11** was prepared from cascade polyol **8** in three steps (Scheme 2). The benzyl protected polyol **8** was allylated at the secondary hydroxyl position. Alkene **9**, thus obtained, was subjected to hydroboration followed by oxidation to obtain primary alcohol **10** which was then converted to the desired tosylate **11** by the action of *p*-toluenesulfonic acid in pyridine. In the next step, the hemithiol ketal group in **4** was removed by the action of mercuric chloride in tetrahydrofuran containing aqueous sodium



Scheme 1. Synthesis of cascade polyl-containing *meta*-carbonyl ACBC: Reaction condition: (a) $HO(CH)_2SH$, TsOH, C_6H_6; (b) BuLi, THF, **11**; (c) $HgCl_2$, 0.1 N NaOH, THF; (d) KCN, $(NH_4)_2CO_3$, aqueous EtOH (50% solution in H_2O); (e) 2 N NaOH; (f) H_2, Pd–C, MeOH.



Scheme 2. Synthesis of *p*-toluene sulfonate derivative of cascade polyol. Reaction condition: (a) allyl bromide, NaH, DMF; (b) (i) $(c\text{-}C_6H_{11})_2BH$, THF (ii) *p*-TsCl, pyridine.

hydroxide to generate ketone **5** which was reacted with ammonium carbonate and potassium cyanide in a pressure tube. Hydantoin **6** was formed in good yield. The hydantoin was then hydrolyzed with sodium hydroxide at 160°C (oil bath) to generate amino acid **7**. Removal of the benzyl groups from **7** was achieved by hydrogenolysis in the presence of palladium on activated carbon to afford the desired product, 1-amino-3-[2-(7-{3-[-(2-hydroxymethyl-ethoxymethyl)-1-(2-hydroxy-1-hydroxymethyl-ethoxymethyl)ethoxyl]-propyl}-1,7-di-carba-*closo*-dodecaboran-1-yl)ethyl]-cyclobutanecarboxylic acid (**1**), which was found to readily dissolve in water (>60 g l^{-1}).

3. Conclusions

A water soluble, boron containing amino acid, 1-amino-3-[2-(7-{3-[2-(2-hydroxymethyl-methylethoxy)-1-(2-hydroxy-1-hydroxymethyl-ethoxymethyl)ethoxy]propyl}-1,7-dicarba-*closo*-dodecaboran-1-yl)ethyl]cyclobutanecarboxylic acid was prepared. A cascade polyol was attached to the carboranyl portion of the amino acid to impart water solubility. This agent is being evaluated as a potential BNCT agent.

4. Experimental

4.1. General methods

All solvents were reagent grade. Tetrahydofuran and diethyl ether were distilled from sodium benzophenone ketyl; benzene was distilled from calcium hydride; all were stored under nitrogen. All other chemicals (Aldrich Chemical Co., Milwaukee, WI) were used as received.

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

Melting points are uncorrected. Infrared (Bio-Rad FTS-7) spectra were obtained either neat or as Nujol mulls. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC250 at 250.13 and 62.89 MHz, respectively. In cases where more than one isomer was formed, we report the ^{13}C-NMR of the major isomer. ^{11}B-NMR (^{1}H-decoupled) spectra were obtained on a Bruker AMS-400 at 128.38 MHz. Chemical shifts for ^{1}H- and ^{13}C-NMR spectra were determined using the residual protons in the deuterated solvents and referenced to $Si(CH_3)_4$. Microanalysis were performed by Galbraith Laboratories Inc, Knoxville, TN. HR-FABMS [M + 1] were obtained in a glycerol matrix using a ZAB-EQ mass spectrometer. Positive ion electrospray mass spectra (ES^+) were obtained in instances where satisfactory elemental analyses were obtained for compounds containing carbon and hydrogen but where boron values exceeded acceptable limits (not uncommon for boron cages).

4.2. Synthesis of 3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxy-methyl)ethoxy]propene (*9*)

A solution of 2-[2-allyloxy(1,3-dibenzyloxy-2-propyloxy)-2-propanol (**8**) [32] (4.80 g, 6.73 mmol) in anhydrous DMF (15 ml) was allowed to react with sodium hydride (1.08 g, 60% in mineral oil, 26.9 mmol). After the mixture was stirred at room temperature (r.t.) for

0.5 h, allyl bromide (2.83 ml, 32.3 mmol) was added and solution stirred overnight at r.t. The reaction mixture was then diluted with ether (100 ml), washed successively with water (3 × 10 ml), brine (10 ml) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue dried under vacuum (0.1 mmHg) for 1 h to yield **9** as a yellow oil (4.60 g), which was used in the next step without further purification; $R_f = 0.65$ (30% ethyl acetate in hexane). ^{1}H-NMR ($CDCl_3$): δ 7.29 (m, 20H), 5.87 (m, 1H), 5.21 (dt, 1H, $J = 17.5, 6.4$), 5.08 (dt, 1H, $J = 12.5, 6.4$), 4.50 (s, 8H), 4.11 (d, 2H, $J = 6.4$), 3.80–3.50 (m, 15H). ^{13}C-NMR ($CDCl_3$): δ 138.29, 135.32, 128.26, 127.47, 116.42, 78.64, 77.61, 73,29, 71.21, 70.36, 70.10; IR (neat) 3063, 3029, 2906, 2863, 1495, 1453, 1365, 1306, 1257, 1205, 1101, 1027, 997, 921,738, cm $^{-1}$. Anal. Calc. for $C_{40}H_{48}O_7$: C, 74.97; H, 7.55. Found: C, 74.92; H, 7.68%.

4.3. Synthesis of 3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxy-methyl)ethoxy]propan-1-ol ***(10)***

A 50 ml round-bottomed flask equipped with an Ar filled balloon was charged with BH_3·THF (11.1 ml, 10.1 mmol). While keeping the flask at 0°C (ice bath), cyclohexene (2.10 ml, 20.2 mmol) was added via a syringe over a period of 10 min. The solution was stirred for an additional 1 h. Alkene **9** (3.20 g, 5.00 mmol) was added to the flask and the resulting mixture was stirred under an argon atmosphere for 12 h at r.t. The reaction mixture was cooled in an ice-bath and then the organoborane carefully oxidized using a mixture of water (10 ml) and sodium perborate tetrahydrate (4.60 g, 30.0 mmol). Volatiles were removed under reduced pressure and the residue extracted with ether (3 × 40 ml), the ether solutions washed with brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to obtain a faint yellow oil. The product was purified by column chromatography using silica gel (30–50% ethyl acetate in hexane) to obtain **10** as a colorless oil (3.42 g, 79% yield based on **9**); $R_f = 0.186$ (30% ethyl acetate in hexane). ^{1}H-NMR ($CDCl_3$): δ 7.29 (m, 20H), 4.50 (s, 8H), 3.85–3.45 (m, 19H), 2.95 (brs, 1H), 1.74 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ 138.22, 128.31, 127.58, 78.62, 73.32, 70.30, 70.14, 69.06, 61.24, 31.40; IR (neat) 3477, 3087, 3063, 3030, 2914, 2867, 1584, 1495, 1452, 1366, 1273, 1205, 1100, 1027, 911, 740, 713 cm $^{-1}$. Anal. Calc. for $C_{40}H_{50}O_8$: C, 72.92; H, 7.65. Found: C, 72.10; H, 7.58%.

4.4. Synthesis of toluene-4-sulfonic acid 3-[2-(2-benyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxymethyl)ethoxy]propyl ester ***(11)***

A 25 ml round-bottomed flask was charged with alcohol **10** (1.56 g, 2.37 mmol), pyridine (5 ml) and cooled to 0°C (ice bath), *p*-toluenesulfonyl chloride (0.679 g, 3.56 mmol) was added and the solution stirred for 6 h while maintaining the bath temperature at 0°C. TLC indicated the disappearance of the starting alcohol. The reaction mixture was poured into a mixture of Et_2O (150 ml), ice (20 g) and HCl (5.3 ml). The ether solution was separated, washed with ice water (3 × 20 ml) and dried over anhydrous magnesium sulfate. Solvents were removed under reduced pressure and residue was purified by chromatography (30% EtOAc in hexane) to give **11** as a colorless oil (1.57 g, 82% yield); $R_f = 0.30$ (35% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$): δ 7.74 (d, 2H, $J = 8.2$), 7.37–7.08 (m, 22H), 4.49 (s, 8H), 4.08 (t, 2H, $J = 6.3$), 3.74–3.39 (m, 17H), 2.38 (s, 3H), 1.80 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 144.50, 138.26, 133.22, 129.73, 128.28, 127.79, 127.52, 78.46, 73.27, 70.24, 70.08, 69.91, 65.70, 29.58, 21.53. The tosylate was used without further purification.

4.5. Synthesis of 3-[2-(1,7-di-carba-dodecaboran-1-yl)-ethyl]cyclobutanone hemithiol ketal ***(3)***

A 250 ml three-necked, round-bottomed flask equipped with a Dean–Stark apparatus and reflux condenser was charged with *closo*-3-[2-(1,7-di-carba-dodecaboran-1-yl)ethyl]cyclobutanone (**2**) (0.488 g, 2.03 mmol), mercaptoethanol (0.170 ml, 2.44 mmol), and *p*-toluenesulfonic acid monohydrate (0.020 g, 0.10 mmol) in benzene (100 ml). The reaction mixture was refluxed for 4 h and the reaction was monitored by thin layer chromatography (TLC). After 4 h, the contents of the flask were cooled to r.t. and neutralized with aqueous 0.1 N NaOH. The mixture was transferred to a separatory funnel, washed with water (3 × 20 ml), brine (1 × 20 ml), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield a colorless oil. The crude material was purified using a silica gel column to obtain **3** as a white solid (0.576 g, 94% yield): m.p. 48–50°C; $R_f = 0.52$ (30% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$): δ 4.01 (m, 2H), 3.06 (m, 2H), 2.90 (s, 1H), 2.53 (m, 2H), 2.20–1.75 (m, 5H), 1.52 (m, 2H); ^{13}C-NMR ($CDCl_3$): δ 89.92, 75.99, 69.42, 54.81, 44.58, 36.39, 34.79, 33.66, 25.97; IR (Nujol) 2926, 2860, 2601, 1458, 1916, 1375, 1271, 1253, 1139, 1057, 1008, 940, 830, 727 cm $^{-1}$. Anal. Calc. for $C_{10}H_{24}B_{10}OS$: C, 39.97; H, 8.05. Found: C, 40.02; H, 8.14%.

4.6. Synthesis of 3-[2-(7-{3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxymethyl)ethoxy]propyl}-1,7-di-carba-closo-dodecaboran-1-yl)ethyl]cyclobutanone hemithiol ketal ***(4)***

A 100 ml three-necked, round-bottomed flask, fitted with an argon filled balloon, was charged with 3-[2-(1,7-di-carba-*closo*-dodecaboran-1-yl)ethyl]cyclobutanone

hemithiol ketal (**3**) (0.568 g, 1.89 mmol) in THF (10 ml). The flask was cooled to 0°C in an ice bath. Butyllithium (2.08 mmol, 1.30 ml of 1.60 M solution in hexane) was added dropwise via a syringe. The resultant solution was stirred at 0°C for 30 min and then at r.t. for 1 h. The solution was cooled to 0°C and then a solution of toluene-4-sulfonic acid 3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxymethyl)ethoxy]propyl ester (**11**) (1.57 g) in THF (2 ml) was added dropwise via a syringe. The reaction mixture was allowed to stir overnight (during which time the bath temperature was allowed to come to r.t.) and then it was refluxed for 1 h. The reaction was quenched with saturated aqueous ammonium chloride solution and then transferred to a separatory funnel. The product was extracted into ether (100 ml) and the organic layer was washed sequentially with water (2×20 ml), brine (2×20 ml), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a thick oil (1.40 g). The product was purified by column chromatography using silica gel (25% EtOAc in hexane) to obtain **4** as a semi-solid (1.12 g, 83% yield) along with the recovery of unreacted hemithiol ketal **3** (0.19 g, 33% yield); $R_f = 0.476$ (20% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$): δ 7.30 (m, 20H), 4.50 (s, 8H), 4.00 (dt, 2H, $J = 2.5$, 6.1), 3.76–3.47 (m, 15H), 3.43 (dt, 2H, $J = 12.3$, 6.1), 2.52 (m, 2H), 2.20–1.68 (m, 5H), 1.55 (m, 4H). ^{13}C-NMR ($CDCl_3$): δ 138.27, 128.31, 127.53, 90.80, 78.62, 78.42, 75.72, 75.38, 70.36, 70.14, 69.39, 69.20, 44.57, 36.33, 34.80, 33.72, 33.64, 30.46, 26.97; IR (neat) 3062, 3030, 2922, 2863, 2595, 1783, 1739, 1495, 1453, 1369, 1254, 1176, 1101, 1028, 737, 698 cm^{-1}. Anal. Calc. for $C_{50}H_{12}B_{10}O_8S$: C, 63.80; H, 7.71. Found: C, 64.06; H, 7.56%.

*4.7. Synthesis of 3-[2-(7-{3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxymethyl)ethoxy]propyl}-1,7-dicarba-closo-dodecaboran-1-yl)ethyl]cyclobutanone (**5**)*

To a vigorously stirred solution of 3-[2-(7-{3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxymethyl)ethoxy]propyl}-1,7-dicarba-*closo*-dodecaboran-1-yl)ethyl]cyclobutanone hemithiol ketal (**4**) (0.912 g, 0.970 mmol) and $HgCl_2$ (0.276 g, 1.02 mmol) in THF (80 ml) was added aqueous 0.1 N NaOH (10 ml) via a syringe over a period of 30 min and the reaction monitored by TLC. After the reaction was complete, the THF was removed under reduced pressure and the residue extracted into Et_2O (3×30 ml). The ether solution was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain an oil. The product was purified by column chromatography using silica gel (10% MeOH in methylene chloride) to obtain **5** as a colorless oil (0.774 g, 91% yield); $R_f = 0.256$ (30% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$): δ 7.29 (m, 20H), 4.50 (s, 8H), 3.79–3.47 (m, 15H), 3.43 (t, 2H, $J = 6.1$), 3.10 (m, 2H), 2.57 (m, 2H), 2.19 (m, 1H), 1.93 (m, 4H), 1.57 (m, 4H). ^{13}C-NMR ($CDCl_3$): δ 206.67, 138.17, 128.22, 127.46, 78.54, 78.32, 75.79, 74.78, 73.21, 70.20, 70.23, 69.05, 52.24, 36.12, 35.48, 33.62, 30.38, 23.26; IR (neat) 3207, 3040, 2949, 2850, 2597, 1761, 1455, 1350, 1250, 1170, 1020, 778, 727, 643 cm^{-1}. Anal. Calc. for $C_{48}H_{68}B_{10}O_8$: C, 65.43; H, 7.78. Found, 64.63; H, 7.72%.

*4.8. Synthesis of the hydantoin of 3-[2-(7-{3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxymethyl)ethoxy]propyl}-1,7-di-carba-closo-dodecaboran-1-yl)ethy]cyclobutanone (**6**)*

A 35 ml Ace pressure tube was charged with 3-[2-(7-{3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxymethyl)ethoxy]-propyl}-1,7-di-carba-*closo*-dodecaboran-1-yl)ethyl]-cyclobutanone (**5**, 0.720 g, 0.817 mmol), potassium cyanide (0.106 g, 1.63 mmol), ammonium carbonate (0.314 g, 3.27 mmol), EtOH (4 ml), water (4 ml) and a stirring bar. The reaction vessel was sealed and heated at 80°C (oil bath) for 16 h. The reaction vial was then cooled to r.t. and carefully opened in a fume hood. The mixture was acidified using dilute aqueous hydrochloric acid and extracted with ether (150 ml). The ether layer was washed with brine (2×20 ml), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain an oil. The product was obtained by column chromatography using silica gel (10% methanol in methylene chloride) to obtain hydantoin **6** as a colorless oil (0.585 g, 73% yield); $R_f = 0.56$ (10% methanol in CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): δ 8.40 (brs, 1H), 7.30 (m, 20H), 6.33 (brs, 1H), 4.50 (s, 8H), 3.75–3.48 (m, 15H), 3.43 (t, 2H), $J = 6.1$), 260 (m, 2H), 2.27 (m, 1H), 195–1.70 (m, 6H), 1.65–1.40 (m, 4H). ^{13}C-NMR ($CDCl_3$): δ 177.28, 155.98, 138.26, 128.34, 127.58, 78.64, 78.44, 75.82, 75.05, 73.33, 70.36, 70.14, 69.18, 58.74, 38.94, 37.09, 34.19, 33.72, 30.48, 26.36; IR (neat) 3225, 3032, 2925, 2863, 2759, 2592, 1760, 1726, 1495, 1452, 1305, 1279, 1099, 738, 698 cm^{-1}. Anal. Calc. for $C_{50}H_{70}B_{10}N_2O_9$; C, 63.13; H, 7.41; N, 2.94. Found: C, 62.53; H, 7.45; N, 2.84%.

*4.9. Synthesis of 1-amino-3-[2-(7-{3-[-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxymethyl)ethoxy]propyl}-1,7-di-carba-closo-dodecaboran-1-yl)ethyl]cyclobutane-carboxylic acid (**7**)*

The hydantoin of 3-[2-(7-{3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxymethyl)ethoxy]propyl}-1,7-di-carba-*closo*-dode-

caboran-1-yl)ethyl]cyclobutanone (**6**), (0.310 g, 0.326 mmol) was placed in a 15 ml Ace pressure tube along with a solution of sodium hydroxide (4 ml of 2 N NaOH). The tube was sealed and then heated at 160°C (oil bath) for 3 h. It was then cooled to r.t. and carefully opened. The contents of the flask were washed with Et_2O (2×1 ml) and the aqueous suspension was neutralized with aqueous 0.5 N HCl. The solids obtained were dissolved in CH_2Cl_2 (100 ml) and washed with distilled water (3×10 ml). The solvent was removed under reduced pressure to obtain 1-amino-3-[2-(7-{3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy - 1 - benzyloxymethyl - ethoxymethyl)ethoxy]-propyl} - 1,7 - di - carba - *closo* - dodecaboran - 1 - yl)ethyl]-cyclobutane carboxylic acid (**7**) (0.252 g, 83%) as a semi-solid; $R_f = 0.62$ (isopropanol:water:AcOH in 10:10:0.5). ^{1}H-NMR ($CDCl_3$): δ 7.26 (brs, 20H), 4.67 (s, 8H), 3.75–3.30 (m, 17H), 2.70–1.40 (m, 13H). ^{13}C-NMR ($CDCl_3$): δ 175.34, 138.32, 128.31, 127.55, 78.60, 78.35, 77.20, 75.84, 73.27, 70.10, 69.17, 52.52, 37.80, 36.00, 33.70, 30.48; IR (Nujol) 3346, 2952, 2926, 2923, 2854, 2593, 2358, 1777, 1714, 1459, 1376, 1257, 1051, 739 cm^{-1}. Anal. Calc. for $C_{49}H_{71}B_{10}NO_9$: C, 63.54; H, 7.13; N, 1.51. Found: C, 62.68; H, 7.81; N, 1.50%.

*4.10. Synthesis of 1-amino-3-[2-(7-{3-[2-(2-hydroxymethyl-ethoxy)-1-(2-hydroxy-1-hydroxymethyl-ethoxymethyl)ethoxy]propyl}-1,7-dicarba-closo-dodecaboran-1-yl)ethyl]cyclobutanecarboxylic acid (**1**)*

1-Amino-3-[2-(7-{3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy) - 1 - (2 - benzyloxy - 1 - benzyloxymethyl-ethoxymethyl)ethoxy]propyl} - 1,7-di-carba-*closo*-dodecaboran-1-yl)ethyl]cyclobutanecarboxylic acid (**7**) (0.062 g), and 10% palladium on activated carbon (0.050 g) in MeOH (3 ml) were vigorously stirred under 1 atmosphere of hydrogen for 2 days in a 100 ml round-bottomed flask. The mixture was filtered through a pad of Celite® and washed with MeOH (3×10 ml). The colorless solution was concentrated to afford **1** as a semi-solid (0.33 g, 87% yield); $R_f = 0.49$ (isopropanol:water:AcOH in 10:10:0.5). ^{1}H-NMR (CD_3OD): δ 3.85–3.45 (m, 17H), 2.50–1.38 (m, 13H). ^{13}C-NMR (CD_3OD): δ 89.67, 81.90, 81.27, 78.08, 75.84, 69.05, 60.81 51.35, 37.90, 36.10, 34.03, 33.21, 29.91; IR (Nujol): 3362, 2952, 2923, 2854, 2725, 2597, 1777, 1618, 1459, 1376, 1079, 973, 724 cm^{-1}. Anal. Calc. for $C_{21}H_{47}B_{10}NO_9$: C, 44.59; H, 8.37, N, 2.48. Found: C, 44.54; H, 8.31; N, 2.45%.

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