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New types of potential BNCT agents, *o*-carboranyl aminoalcohols

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ABSTRACT

o-Carboranyl aminoalcohols were synthesized using a standard Mannich reaction, and were tested for their anticancer properties using an in vitro test for CT26 cancer cells. The polar periphery of the aminoalcohols benefited from the high boron uptake in CT26 cancer cells with low toxicity, indicating their potential as BNCT agents.

As part of an ongoing study into the development of new types of boron neutron capture therapy (BNCT) agents,[1] an *o*-carborane framework was fully utilized both as a boron carrier[2] and as a synthetic template to produce a biologically active unit.[3] It has been reported that biological properties of BNCT are improved when polar functional groups, such as alcohol, are properly organized. Yamamoto et al. demonstrated that cascade polyol[4] units resulted in good water solubility, low cytotoxicity, and high cellular uptake of MACB$(OH)_2$ and MACB$(OH)_4$.[5]

In this study, the bis(hydroxyethyl)aminomethylphenol unit was introduced into *o*-carborane as a multi-functional group to improve the biological properties. The amine nitrogen of the *o*-bis(hydroxyethyl)amine unit coordinated to the phenolic hydrogen through an intra-molecular hydrogen bond.[6] This potential secondary 'N···H–O' bonding can organize two polar functional groups, *o*-bis(hydroxyethyl)amine and phenol, resulting in enhanced biological properties. This multi-functional group showed higher boron uptake and lower cytotoxicity to CT26 cancer cells.

The required precursor **1** was prepared using two different methods (Scheme 1): In Method A,[7] the hydroxylation of H_2SO_4 and an aqueous $NaNO_2$ to 4-*o*-carboranylaniline was observed, whereas in Method B[8] the demethylation of BBr_3 to 4-*o*-carboranylanisole was observed.

Method A: Synthesis of *o*-carboranylphenol **1** (Scheme 1): 4-*o*-carboranylnitrobenzene was obtained from commercially available *o*-carborane in quantitative yield. The hydrogenation of 4-*o*-carboranylnitrobenzene with $Pd/C/H_2$ gave 4-*o*-carboranylaniline in 95% yield. The NH_2 unit was converted to the OH (43%) using H_2SO_4 and an aqueous $NaNO_2$ solution.[9]

Method B: Lithiation of the *o*-carborane group with *n*-BuLi gave lithio-*o*-carborane, which was treated with CuCl, pyridine, and 4-iodoanisole to give 4-*o*-carboranylanisole (80%). The conversion of 4-*o*-carboranylanisole to 4-*o*-carboranylphenol **1** (91%) was achieved by BBr_3 in CH_2Cl_2.[9]

The general synthetic strategy for the preparation of 4-*o*-carboranyl-2-[bis(methyl propionato)aminomethyl]phenol (**2**),[10] 4-*o*-carboranyl-2-[bis(ethyl propionato)aminomethyl]phenol (**3**),[11] *N*-[(5-*o*-carboranyl-2-hydroxyphenyl)methyl]iminodiacetic acid (**4**),[12] 4-*o*-carboranyl-2-[bis(methoxyethyl)aminomethyl]phenol (**5**),[13] *N*-[(5-*o*-carboranyl-2-hydroxyphenyl)methyl]amino diethanol (**6**),[14] 4-*o*-carboranyl-2,6-bis{2-[bis(methoxyethyl)aminomethyl]} phenol (**7**),[15] and 7,16-bis[(5-*o*-carboranyl-2-hydroxyphenyl)aminomethyl]-1,4,10,13-tetraoxadiazacyclooctadecane (**8**)[16] was developed using the Mannich reaction[17] (see Supplementary data for details). The hydroxyl proton in the –O*H* unit of **2**–**8** was removed via an intramolecular N···H–O hydrogen bonding interaction. Compound **1** was then treated with methyl or ethyl iminodiacetate in toluene to generate the bis(methyl propionato)- and bis(ethyl propionato)aminomethyl-substituted intermediates **2** and **3** in 21% and 71% yields, respectively (Scheme 2).

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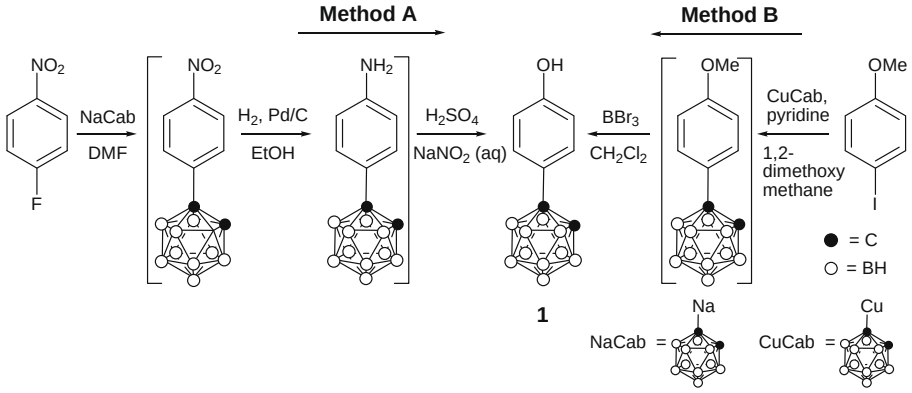


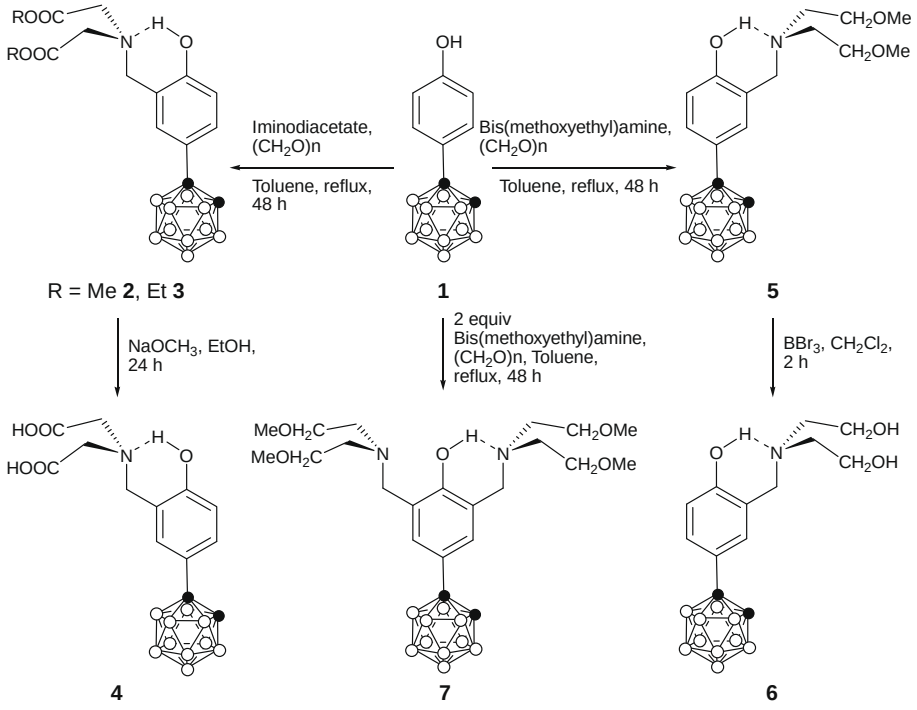
Scheme 1. Synthesis of *o*-carboranylphenol **1**.

The ^{1}H NMR spectrum showed resonances at 4.93/4.66 (**2**) and 3.95/3.55 ppm (**3**) due to the methylene protons in the NC*H*$_2$ and NC*H*$_2$C(=O) unit, respectively. Compound **3** was further treated with 3 equiv of NaOCH$_3$ to generate the deethylated compound **4** in 63% yield (Scheme 2). No signal corresponding to the ethyl proton in the OC*H*$_2$C*H*$_3$ unit was observed in the ^{1}H NMR spectrum of compound **4**, and the resonance due to the methylene proton in the NC*H*$_2$C(=O) unit was shifted downfield.

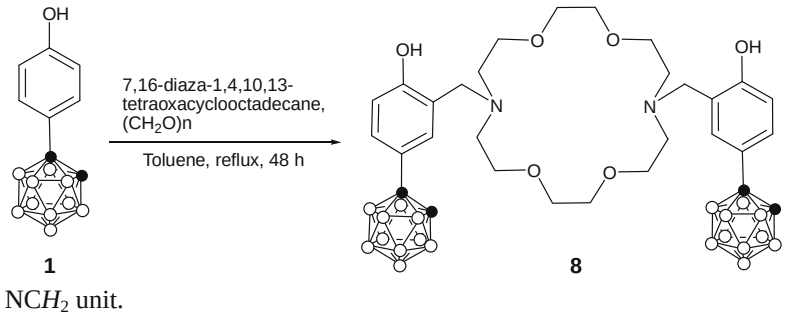
A similar synthetic protocol was used in the preparation of 4-*o*-carboranyl-2-[bis(methoxyethyl)aminomethyl]phenol **5**, as shown is Scheme 2. The addition of bis(methoxyethyl)amine and paraformaldehyde to a toluene solution of compound **1** resulted in the formation of 2-bis(methoxyethyl)aminomethyl-substituted intermediate **5** in 67% yield (Scheme 2). The ^{1}H NMR spectrum of compound **5** showed peaks at 2.77 and 3.50 ppm due to the ethyl protons in the NC*H*$_2$C*H*$_2$O unit, and at 3.89 ppm due to the methylene protons in the NC*H*$_2$ unit. Compound **5** was further treated with 3 equiv of BBr$_3$ to generate the demethylated compound **6** in 74% yield (Scheme 2). In the ^{1}H NMR spectrum of compound **6**, there was no signal corresponding to the methyl proton in the OC*H*$_3$ unit or the ethyl proton in the NC*H*$_2$C*H*$_2$O unit.

A similar synthetic protocol was used for the preparation of 4-*o*-carboranyl-2,6-bis[bis(2-methoxyethyl)aminomethyl]phenol **7**, as shown in Scheme 2. The addition of bis(methoxyethyl)amine and paraformaldehyde to a toluene solution of compound **1** resulted in the formation of bis[2-(methoxyethyl)aminomethyl] substituted compound **7** in 48% yield (Scheme 2). The ^{1}H NMR spectrum of compound **7** showed peaks at 2.73 and 3.48 ppm due to the ethyl protons in the NC*H*$_2$C*H*$_2$O unit, and at 3.77 ppm due to the methylene protons in the NC*H*$_2$ unit.

In addition, as a surrogate of a secondary amine, the *o*-carboranyl phenol **1** was incorporated into the 7,16-diaza-1,4,10,13-tetraoxacyclooctadecane to generate a new type of *o*-carboranyl aza-crown ether **8** (11%) (Scheme 3). The ^{1}H NMR spectrum of compound **8** showed resonances at 2.81 (NC*H*$_2$CH$_2$O), 3.66 (NCH$_2$C*H*$_2$O), and 4.05 (OC*H*$_2$C*H*$_2$O) ppm due to the ethyl protons in the C*H*$_2$C*H*$_2$ unit, and at 3.86 ppm due to the methylene protons in the NC*H*$_2$ unit.



Scheme 2. Synthesis of functionalized *o*-carboranylphenol derivatives **2**–**7**.



Scheme 3. Synthesis of *o*-carboranyl aza-crown ether derivative **8**.

Table 1
Effects of *o*-carboranyl aminoalcohol derivatives on CT26 cells viability and intracellular accumulation

Compd	Viability IC_{50}[a] (mM)	Accumulated boron concn[b] (ppm)
2	0.682 ± 0.018	0.020 ± 0.017
3	0.031 ± 0.004	0.520 ± 0.046
4	0.242 ± 0.015	0.497 ± 0.116
6	0.195 ± 0.001	0.190 ± 0.017
7	0.567 ± 0.016	0.600 ± 0.150
BPA	1.303 ± 0.018	0.233 ± 0.142

[a] CT26 cells (5×10^3 cells) were incubated for 3 days in the presence of various concentrations of **2**–**4**, **6**, and **7** or BPA, and the viability was determined by MTT assay.

[b] CT26 cells (5×10^5 cells) were incubated for 3 h in the presence of **2**–**4**, **6**, and **7** or BPA (10 ppm). After three washes, the accumulated boron concentrations were determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES). Values are the mean ± s.d. from three samples.

The biological activities, including the cytotoxicity and intracellular accumulation of the *o*-carboranyl aminoalcohol derivatives, were next investigated. As shown in Table 1, compounds **2**, **4**, **6**, and **7** exhibited low cytotoxicity, with IC_{50} values (the half maximal inhibitory concentration) in the range of 0.195–0.682 mM. Furthermore, the accumulated boron concentration of compounds **3**, **4**, and **7** was higher than that of *p*-boronophenylalanine (BPA). Among the *o*-carboranyl aminoalcohol derivatives tested, compound **7** appeared to be a good candidate agent based on the three essential requirements for BNCT, good water solubility, low cytotoxicity, and high boron uptake. Moreover, compounds **2**–**7** formed a six-membered ring through intramolecular hydrogen bonding, as shown in Scheme 2. These proposed structures for compounds **2**–**7** are supported by the ^{1}H NMR data. The hydrogen bonds might be expected to prolong the physiological activity by retarding the formation of a quaternary ammonium salt.[6] The greater stability of these compounds as a free base compared with the other types of tertiary amine units might be related to the hydrogen-bonded structure.

In conclusion, new types of *o*-carboranyl aminoalcohol derivatives **2**–**8** with higher boron uptake were prepared. In particular, compounds **2** and **7** showed lower toxicity over a wide range of boron concentrations up to 250 mg boron mL^{-1}.

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9. *4-o-Carboranylphenol (**1**). Method A*: 4-fluoronitrobenzene (0.98 g, 7.0 mmol) in 10 mL of dry DMF was added to a stirred solution of *o*-carborane (1.0 g, 7.2 mmol) and NaH (0.24 g, 1.2 mmol) in 20 mL of dry DMF, at 0 °C, through a cannula over a period of 30 min. The reaction mixture was maintained at 0 °C for 10 min, and warmed slowly to room temperature. After stirring for an additional 1 h, the reaction mixture was quenched by adding 15 mL of an aqueous 10% HCl solution. The crude 4-*o*-carboranylnitrobenzene was extracted with AcOEt (20 mL × 2). The organic layer was washed with distilled H_2O (20 mL × 2) and brine, dried over $MgSO_4$, and then concentrated. The residue was purified by flash column chromatography (EA–*n*-hexane, 1:4, R_f = 0.53) to give 1.6 g (90%) of 4-*o*-carboranylnitrobenzene. 4-*o*-carboranylnitrobenzene and catalytic amounts of 10% Pd/C in EtOH (100 mL) were then stirred under H_2 until more hydrogen had been consumed. The mixture was filtered through a Celite® pad and the solvent was evaporated off using a rotary evaporator. The residue was purified by flash column chromatography (EA–*n*-hexane, 1:4, R_f = 0.34) to give 1.2 g (95%) of 4-*o*-carboranylaniline. Finally, $NaNO_2$ (0.4 g, 0.6 mmol) in 10 mL of distilled H_2O was added to a stirred solution of 4-*o*-carboranylaniline (1.2 g, 5.0 mmol) in 5 mL of aqueous 1 M H_2SO_4 solution at 0 °C. The reaction mixture was maintained at 0 °C for 45 min, and then heated to 95 °C for 15 min. The reaction mixture was cooled to room temperature and treated with a 50% (w/w) aqueous $NaHCO_3$ solution. The crude product was extracted with AcOEt (15 mL × 2). The organic layer was washed with distilled H_2O (10 mL × 2) and brine, and dried over $MgSO_4$. The residue was purified by flash column chromatography (EA–*n*-hexane, 1:2, R_f = 0.38) to give 0.52 g (43%) of 4-*o*-carboranylphenol **1**. *Method B*: A 2.5 M *n*-BuLi (0.38 mL, 0.90 mmol) solution was added dropwise to a stirred solution of *o*-carborane (0.14 g, 0.9 mmol) in 15 mL of 1,2-dimethoxymethane at 0 °C. The mixture was stirred for 30 min. CuCl (0.9 g, 10.0 mmol) was then added in one portion, and the mixture was stirred at room temperature for 2 h. Pyridine (6 mL, 76.0 mmol) and 4-iodoanisole were added in a single portion, and the resulting mixture was heated under reflux for 48 h. After cooling, the insoluble materials were removed by filtration through a Celite® pad. The filtrate was washed with a 2 N HCl solution, distilled H_2O, and brine, and then dried over $MgSO_4$. The residue was purified by flash column chromatography (EA–*n*-hexane, 1:4, R_f = 0.47) to give 1.9 g (80%) of 4-*o*-carboranylanisole. Finally, a 1 M solution of BBr_3 in CH_2Cl_2 (10 mL, 10 mmol) was added dropwise to a stirred solution of 4-*o*-carboranylanisole (1.8 g, 7.0 mmol) in 40 mL of CH_2Cl_2 at 0 °C. The mixture was stirred for 2 h at room temperature, and then quenched with ice water. The crude product was extracted with CH_2Cl_2 (20 mL × 2). The organic layer was washed with distilled H_2O (15 mL × 2) and brine, and then dried over $MgSO_4$. The residue was purified by flash column chromatography (EA–*n*-hexane, 1:2, R_f = 0.38) to give 1.5 g (91%) of 4-*o*-carobranylphenol **1**. Mp 89–91 °C; Anal. Calcd for $C_8H_{16}B_{10}O$: C, 40.66; H, 6.82. Found: C, 40.82; H, 6.91—IR (KBr pellet, cm^{-1}) ν(B–H) 2571, ν(O–H) 3323; ^{1}H NMR ($CDCl_3$) δ 5.01 (s, 1H, Cab–*H*), 6.81–6.83 (d, *J* = 6.9 Hz, 2H, *Ar*), 7.45–7.47 (d, *J* = 6.9 Hz, 2H, *Ar*); ^{13}C NMR ($CDCl_3$) δ 61.6, 77.8 (*Cab*); 115.5, 124.5, 129.3, 159.0 (*Ar*).
10. *4-o-Carboranyl-2-[bis(methyl propionato)aminomethyl]phenol (**2**)*: Methyl iminoacetate (0.16 g, 0.9 mmol) and paraformaldehyde (0.04 g 1.4 mmol)

were added to a stirred solution of compound **1** (0.2 g, 0.8 mmol) in 10 mL of dry toluene. The reaction mixture was heated for 48 h. After cooling, the toluene solvent was removed using a rotary evaporator, and the residue was purified by flash column chromatography (EA–*n*-hexane, 1:2, R_f = 0.55) to give 0.07 g (21%) of compound **2**. Mp 84–86 °C; Anal. Calcd for $C_{15}H_{27}B_{10}NO_5$: C, 44.00; H, 6.65; N, 3.42. Found: C, 44.10; H, 6.61; N, 3.48—IR (KBr pellet, cm^{-1}) ν(C=O) 1735, ν(B–H) 2595, ν(O–H) 3292; ^{1}H NMR ($CDCl_3$) δ 4.66 (s, 4H, CH_2C(=O)), 4.93 (s, 2H, NCH_2), 5.13 (s, 1H, Cab–*H*), 5.37 (s, 6H, OCH_3), 6.82–6.83 (d, *J* = 8.7 Hz, 1H, *Ar*), 7.40–7.41 (d, *J* = 8.7 Hz, 1H, *Ar*), 7.60 (s, 1H, *Ar*); ^{13}C NMR ($CDCl_3$) δ 44.6 (CH_2C(=O)); 51.4 (OCH_3); 52.3 (NCH_2); 60.6, 77.6 (*Cab*); 111.6, 113.6, 115.6, 129.6, 134.4, 148.4 (*Ar*); 171.1 (*C*=O).

11. *4-o-Carboranyl-2-[bis(ethyl propionato)aminomethyl]phenol* (**3**): Ethyl iminoacetate (1.5 mL, 8.6 mmol) and paraformaldehyde (0.23 g, 8.7 mmol) were added to a stirred solution of compound **1** (1.0 g, 4.2 mmol) in 30 mL of dry toluene. The reaction mixture was heated for 48 h. After cooling, the toluene solvent was removed using a rotary evaporator and the residue was purified by flash column chromatography (EA–*n*-hexane, 1:4, R_f = 0.75) to give 1.3 g (71%) of compound **3**. Mp 68–70 °C; Anal. Calcd for $C_{17}H_{31}B_{10}NO_5$: C, 46.67; H, 7.14; N, 3.20. Found: C, 46.65; H, 7.10; N, 3.18—IR (KBr pellet, cm^{-1}) ν(C=O) 1736, ν(B–H) 2595, ν(O–H) 3317; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, *J* = 7.3 Hz, 6H, OCH$_2$*C*H$_3$), 3.55 (s, 4H, CH_2C(=O)), 3.95 (s, 2H, NCH_2), 4.18 (q, *J* = 7.3 Hz, 4H, OCH_2), 5.04 (s, 1H, Cab–*H*), 6.75–6.77 (d, *J* = 8.7 Hz, 1H, *Ar*), 7.33 (s, 1H, *Ar*), 7.42–7.44 (d, *J* = 8.7 Hz, 1H, *Ar*); ^{13}C NMR ($CDCl_3$) δ 13.6 (OCH$_2$*C*H$_3$); 53.8 (CH_2(C=O)); 55.2 (OCH_2CH$_3$); 60.6 (NCH_2); 61.5, 77.7 (*Cab*); 116.3, 122.5, 124.1, 128.7, 129.3, 159.2 (*Ar*); 170.8 (*C*=O).

12. *N-[(5-o-Carboranyl-2-hydroxyphenyl)methyl]iminodiacetic acid* (**4**): NaOCH_3 (0.15 g, 2.7 mmol) and distilled H_2O were added to a stirred solution of compound **3** (0.4 g, 0.9 mmol) in 10 mL of EtOH at 0 °C. The reaction mixture was maintained for 24 h. The solvent was evaporated using a rotary evaporator, and the product was extracted with excess acetone. The crude product was purified by flash column chromatography to give 0.22 g (63%) of compound **4**. Mp 105–107 °C; Anal. Calcd for $C_{13}H_{23}B_{10}NO_5$: C, 40.93; H, 6.08; N, 3.67. Found: C, 40.98; H, 6.11; N, 3.69—IR (KBr pellet, cm^{-1}) ν(C=O) 1777, ν(B–H) 2594, ν(O–H) 3353; ^{1}H NMR ($CDCl_3$) δ 3.28 (s, 4H, CH_2C(=O)), 4.78 (s, 2H, NCH_2), 5.54 (s, 1H, Cab–*H*), 7.57–7.59 (d, *J* = 8.7 Hz, 1H, *Ar*), 7.42–7.44 (d, *J* = 8.7 Hz, 1H, *Ar*), 7.93 (s, 1H, *Ar*); ^{13}C NMR ($CDCl_3$) δ 53.7 (CH_2(C=O)); 55.7 (NCH_2), 62.6, 77.1 (*Cab*); 116.5, 125.0, 131.6, 133.2, 158.5, 166.5 (*Ar*); 166.9 (*C*=O).

13. *4-o-Carboranyl-2-[bis(methoxyethyl)aminomethyl]phenol* (**5**): bis(methoxyethyl)amine (0.18 mL, 1.3 mmol) and paraformaldehyde (0.03 g, 1.3 mmol) were added to a stirred solution of compound **1** (0.21 g, 0.8 mmol) in 20 mL of dry toluene. The reaction mixture was heated for 48 h. After cooling, the toluene was removed using a rotary evaporator and the residue was purified by flash column chromatography (acetone, R_f = 0.12) to give 1.3 g (71%) of compound **5**. Mp 77–79 °C; Anal. Calcd for $C_{15}H_{31}B_{10}NO_3$: C, 47.22; H, 8.19; N, 3.67. Found: C, 47.25; H, 8.25; N, 3.63—IR (KBr pellet, cm^{-1}) ν(B–H) 2593, ν(O–H) 3291; ^{1}H NMR ($CDCl_3$) δ 2.77 (t, *J* = 5.5 Hz, 4H, NCH_2CH$_2$O), 3.26 (s, 6H, OCH_3), 3.50 (t, *J* = 5.5 Hz, 4H, NCH$_2$*C*H$_2$O), 3.89 (s, 2H, NCH_2), 5.04 (s, 1H, Cab–*H*), 6.67–6.68 (d, *J* = 8.7 Hz, 1H, *Ar*), 7.32 (s, 1H, *Ar*), 7.36–7.38 (d, *J* = 8.7 Hz, 1H, *Ar*); ^{13}C NMR ($CDCl_3$) δ 53.1 (NCH$_2$CH$_2$O); 57.3 (NCH_2); 57.9 (OCH_3); 61.6 (NCH$_2$*C*H$_2$O); 69.8, 77.9 (*Cab*); 115.9, 123.4, 123.7, 128.0, 128.3, 160.0 (*Ar*).

14. *N-[(5-o-Carboranyl-2-hydroxyphenyl)methyl]amino diethanol* (**6**): A 1 M solution of BBr_3 (1.8 mL, 1.8 mmol) was added to a stirred solution of compound **5** (0.2 g, 0.6 mmol) in 20 mL of CH_2Cl_2 at 0 °C through a syringe. The reaction temperature was maintained at 0 °C for 4 h. The reaction mixture was quenched by adding distilled H_2O (30 mL) and extracted with ethyl acetate (10 mL × 2). The combined organic layer was washed with distilled H_2O (15 mL × 2), dried with anhydrous sodium sulfate, and then concentrated in vacuo. The crude product was purified by flash column chromatography (ethylacetate–MeOH 5:1, R_f = 0.13) to give 0.13 g (74%) of compound **6**. Mp 126–128 °C; Anal. Calcd for $C_{13}H_{27}B_{10}NO_3$: C, 44.17; H, 7.70; N, 3.96. Found: C, 44.21; H, 7.73; N, 4.02—IR (KBr pellet, cm^{-1}) ν(B–H) 2593, ν(O–H) 3291; ^{1}H NMR ($CDCl_3$) δ 2.76 (t, *J* = 5.5 Hz, 4H, NCH_2CH$_2$O), 3.50 (t, *J* = 5.5 Hz, 4H, NCH$_2$*C*H$_2$O), 3.89 (s, 2H, NCH_2), 5.04 (s, 1H, Cab–*H*), 6.66–6.68 (d, *J* = 8.7 Hz, 1H, *Ar*), 7.31 (s, 1H, *Ar*), 7.36–7.38 (d, *J* = 8.7 Hz, 1H, *Ar*); ^{13}C NMR ($CDCl_3$) δ 55.2 (NCH_2); 60.0 (NCH$_2$CH$_2$O); 60.5 (*Cab*); 66.2 (NCH$_2$*C*H$_2$O); 77.5 (*Cab*); 112.3, 113.8, 115.2, 129.7, 134.5, 148.0 (*Ar*).

15. *4-o-Carboranyl-2,6-bis{2-[bis(methoxyethyl)aminomethyl]}phenol* (**7**): bis(methoxyethyl)amine (0.18 mL, 1.3 mmol) and paraformaldehyde(0.03 g, 1.3 mmol) were added to a stirred solution of compound **1** (0.13 g, 0.5 mmol) in 20 mL of dry toluene. The reaction mixture was heated for 48 h. After cooling, the toluene solvent was removed using a rotary evaporator and the residue was purified by flash column chromatography (EA–*n*-hexane, 1:1, R_f = 0.05) to give 0.01 g (48%) of compound **7** as an oil. Anal. Calcd for $C_{22}H_{46}B_{10}NO_5$: C, 50.17; H, 8.80; N, 5.32. Found: C, 50.25; H, 8.87; N, 5.42—IR (KBr pellet, cm^{-1}) ν(B–H) 2595, ν(O–H) 3360; ^{1}H NMR ($CDCl_3$) δ 2.73 (t, *J* = 5.5 Hz, 8H, NCH_2CH$_2$O), 3.26 (s, 12H, OCH_3), 3.48 (t, *J* = 5.5 Hz, 4H, NCH$_2$*C*H$_2$O), 3.77 (s, 4H, NCH_2), 4.97 (s, 1H, Cab–*H*), 7.43 (s, 2H, *Ar*); ^{13}C NMR ($CDCl_3$) δ 53.7 (NCH$_2$CH$_2$O); 55.1 (NCH_2); 58.0 (OCH_3); 61.4 (*Cab*); 70.6 (NCH$_2$*C*H$_2$O); 78.4 (*Cab*); 123.3, 124.8, 127.0, 157.6 (*Ar*).

16. *7,16-Bis[(5-o-Carboranyl-2-hydroxyphenyl)aminomethyl]-1,4,10,13-tetraoxadiazacyclooctadecane* (**8**): 7,16-Diaza-1,4,10,13-tetraoxacyclooctadecane (0.16 g, 0.6 mmol) and paraformaldehyde(0.05 g, 1.6 mmol) were added to a stirred solution of compound **1** (0.3 g, 1.2 mmol) in 40 mL of dry toluene. The reaction mixture was heated for 48 h. After cooling, the toluene solvent was removed using a rotary evaporator and the residue was purified by flash column chromatography (EA, R_f = 0.24) to give 0.11 g (11%) of compound **8**. Mp 168–170 °C; Anal. Calcd for $C_{30}H_{58}B_{20}N_2O_6$: C, 47.47; H, 7.70; N, 3.69. Found: C, 47.52; H, 7.73; N, 3.74—IR (KBr pellet, cm^{-1}) ν(B–H) 2609, ν(O–H) 3380; ^{1}H NMR ($CDCl_3$) δ 2.81 (t, *J* = 5.5 Hz, 8H, NCH_2CH$_2$O), 3.66 (t, *J* = 5.5 Hz, 8H, NCH$_2$*C*H$_2$O), 3.86 (s, 4H, NCH_2), 4.05 (t, *J* = 7.4 Hz, 8H, OCH$_2$*C*H$_2$O), 5.04 (s, 1H, Cab–*H*), 6.68–6.70 (d, *J* = 8.3 Hz, 1H, *Ar*), 7.33 (s, 1H, *Ar*), 7.37–7.39 (d, *J* = 8.3 Hz, 1H, *Ar*); ^{13}C NMR ($CDCl_3$) δ 53.6 (NCH_2); 59.7 (NCH$_2$CH$_2$O); 61.6 (*Cab*); 68.6 (NCH$_2$*C*H$_2$O); 70.7 (OCH$_2$*C*H$_2$O); 77.9 (*Cab*); 116.0, 123.4, 123.7, 128.0, 128.3, 160.0 (*Ar*).

17. (a) Farrell, J. R.; Niconchuk, J.; Higham, C. S.; Bergeron, B. W. *Tetrahedron Lett.* **2007**, *48*, 8034; (b) Higham, C. S.; Dowling, D. P.; Shaw, J. L.; Cetin, A.; Zieglerb, C. J.; Farrell, J. R. *Tetrahedron Lett.* **2006**, *47*, 4419.