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Tricarboranyl Pentaerythritol-Based Building Block

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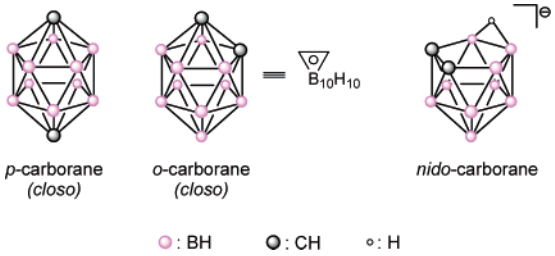
A new tricarborane building block based on pentaerythritol was prepared for applications in boron neutron capture therapy (BNCT). Its X-ray single-crystal structure revealed a high degree of steric congestion. To enable the attachment of the building block to other moieties, a succinimidyl linker has been introduced at the focal point, and a generation-2 hexacarborane-containing dendron carrying 60 boron atoms has been prepared using a 2,2-bis(hydroxymethyl)-propionic acid core.

Introduction

Boron-rich compounds are important in applications involving neutron capture, such as electron microscopy[1] and boron neutron capture therapy (BNCT) of cancer.[2] In the latter, bringing a sufficient number of boron atoms to cancer cells ($\geq 10^9$ ^{10}B atoms/cell $\approx 20-35$ μg ^{10}B/cell) is critical.[3,4] In this respect, polyhedral boranes and carboranes (Chart 1) with their high kinetic stability, high boron content, and ease of derivatization[2,4] have received much attention.[3−12] *o*-Carborane (Chart 1) is particularly attractive because it is easily prepared from decaborane.[13−15]

To further increase the boron content in boron-rich compounds, multiple carboranes have been attached to a porphyrin framework[4,16] or incorporated into macromolecules. To the latter end, dendrimers, albeit harder to prepare than linear polymers, are attractive because of their low polydispersity index (∼1.0) and reproducible pharmacokinetic behavior.[17−19] Several dendrimers carrying multiple carboranes have been prepared in the past for use in BNCT.[20−29,40]

Chart 1



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We are exploring the synthesis of boron-containing *dendrons* (i.e., dendritic wedges), in which carboranyl moieties are attached to the exterior of the dendron,[30] leaving its focal point free to be connected to targeting and/or imaging modules. Herein, we describe the synthesis and properties of a pentaerythritol derivative containing three *o*-carboranyl units and its incorporation into a more complex structure.

Experimental Section

General. All solvents were obtained from Mallinckrodt Chemicals or Fisher Scientific as reagent grade, except for hexanes and ethyl acetate that were of technical grade. THF was dried by distillation on benzophenone sodium under nitrogen, and dichloromethane was dried by distillation over calcium hydride under nitrogen. Toluene was dried over molecular sieves. All other solvents were used without further purification.

Pentaerythritol (98%), *tert*-butyldimethylsilyl chloride (TBDMSCl, 98%), propargyl bromide (80 wt % in toluene), and sodium hydride (NaH, 60% dispersion in mineral oil) were purchased from Acros Organics. Imidazole (99%), succinic anhydride (99%), DOWEX 50W-X2 ion-exchange resin, and 2,2,2-trichloroethanol (99%) were purchased from Aldrich. Decaborane ($B_{10}H_{14}$), tetra-*n*-butylammonium fluoride (TBAF, 1 M solution in THF), 1-*n*-butyl-3-methylimidazolium chloride (ionic liquid (IL), 99%), and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 99%) were obtained from Alfa Aesar. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) was purchased from Advanced ChemTech. Zinc dust (99%) was obtained from Fisher, and 4-(dimethylamino)-pyridine (DMAP, 99%) was from Fluka. Acetonide-2,2-bis(methoxy)-propionic acid,[31] 2,2,2-trichloroethyl-2,2-bis(methylol)propionate,[32] and 4-(dimethylamino)pyridinium 4-toluenesulfonate (DPTS)[33] were prepared as previously reported.

All reactions were followed by TLC using Merck silica gel $60F_{254}$ on aluminum plates. Solvent systems are reported as v:v mixtures. Compounds were visualized using a potassium permanganate or bromocresol green stain. Silicycle silica gel (Ultrapure, 230−400 mesh) was used for flash chromatography separations. NMR spectra were recorded at ambient temperature on a Varian XL-300 equipped with a 5 mm Varian Broadband Probe 30−120 MHz or a Varian Inova-400. Chemical shifts (δ) are relative to the solvent signals for both ^{1}H and ^{13}C NMR recordings, while $B(OEt)_3$ was used as an external standard for ^{11}B NMR (δ 18.10). CI and EI mass spectrometry were performed using a Finnigan MAT 95, ESI MS was performed using a Micromass Quattro II, and MALDI-TOF MS was performed at the Mass Spectrometry Facility, Department of Chemistry, University of Arizona, using a Bruker Reflex-III MALDI-TOF. IR spectra were collected using a Perkin-Elmer-FT-1600-IR spectrometer.

X-ray Crystallography. X-ray crystallographic data were collected from a colorless plate shaped crystal (0.35 × 0.30 × 0.08 mm) mounted on a glass fiber with traces of viscous oil and then transferred to a Nonius Kappa CCD diffractometer equipped with Mo Kα radiation (λ = 0.71073 Å). Ten frames of data were collected at 150(1) K with an oscillation range of 1 deg/frame and an exposure time of 20 s/frame. Indexing and unit cell refinement based on all observed reflection from those 10 frames indicated a monoclinic *P* lattice. A total of 11434 reflections (Θ_{max} = 25.36°) were indexed, integrated, and corrected for Lorentz, polarization, and absorption effects using DENZO−SMN and SCALEPAC.[34] Post-refinement of the unit cell gave a = 12.9440(9) Å, b = 20.1061(13) Å, c = 14.4164(9) Å, and V = 3673.7(4) Å^3. Axial photographs and systematic absences were consistent with the compound having crystallized in the monoclinic space group $P2_1/c$. The structure was solved by a combination of direct methods and heavy atom using SIR 97 software (Release 1.02). All of the non-hydrogen atoms were refined with anisotropic displacement coefficients. Hydrogen atoms were assigned isotropic displacement coefficients U(H) = 1.2U(C) or 1.5U(Cmethyl), and their coordinates were allowed to ride on their respective carbons using SHELXL97 software (Release 97-2). The weighting scheme employed was $w = 1/[\sigma^2(F_o^2) + (0.1164P)^2 + 2.6748P]$ where $P = (F_o^2 + 2F_c^2)/3$. The refinement converged to R1 = 0.0888, wR2 = 0.2106, and S = 1.027 for 3576 reflections with $1 > 2\sigma(I)$, and R1 = 0.1683, wR2 = 0.2579, and S = 1.027 for 6731 unique reflections and 467 parameters. The maximum Δ/σ in the final cycle of the least-squares was 0, and the residual peaks on the final difference Fourier map ranged from −0.276 to 0.467 e/Å^3. Scattering factors were taken from the International Tables for Crystallography, Volume C.[35,36]

2,2-Bis-hydroxymethyl-2-(*tert*-butyldimethylsilyloxymethyl)-propan-1,3-diol (2). To a solution of pentaerythritol **1** (5.00 g, 36.72 mmol) in anhydrous DMF (235 mL) was added imidazole (2.67 g, 38.65 mmol) followed by the slow dropwise addition of a solution of *tert*-butyldimethylchlorosilane (2.94 g, 19.59 mmol) in anhydrous DMF (15 mL). The solution was stirred at room temperature (RT) for 24 h under nitrogen, partially concentrated in vacuo, poured in water (100 mL), and extracted with EtOAc (3 × 100 mL). The combined organic phases were partially concentrated in vacuo, washed with water (3 × 100 mL), dried over Na_2SO_4, and concentrated. The resulting yellow oil was purified by flash chromatography (hexanes:EtOAc 50:50) to give **2** as a colorless oil that solidified on standing (2.98 g, 61% on the basis of the reagent added). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.70 (d, J = 5.6 Hz, 6H, CH_2OH), 3.65 (s, 2H, CH_2OSi), 3.03 (t, J = 5.6 Hz, 3H, OH), 0.90 (s, 9H, $C(CH_3)_3$), 0.08 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (90.6 MHz, $CDCl_3$, δ): 66.0, 64.7, 45.3, 26.0, 18.3, −5.5. IR (film): ν 3373, 2953, 2928, 2856. MS (CI): m/z = 251.2 $[M + H]^+$.

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2,2-Bis(prop-2-ynyloxymethyl)-3-(prop-2-ynyloxy)-2-(*tert*-butyldimethylsilyloxymethyl)propane (3). A solution of **2** (1.50 g, 6.00 mmol) in anhydrous THF (150 mL) was cooled to 0 °C under nitrogen. Sodium hydride (60%, 0.96 g, 24.00 mmol) was added in three portions. After stirring for 15 min, propargyl bromide (80%, 4.01 mL, 36.00 mmol) was added dropwise over 1 h, and the reaction was allowed to warm to room temperature and was stirred for 12 h. After quenching the excess sodium hydride with NH_4Cl, the solvent was evaporated in vacuo. The crude material was taken in diethyl ether (100 mL) and poured in water (100 mL). The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2 × 100 mL). The combined organic layers were partially concentrated in vacuo, washed with water (2 × 100 mL) and then brine, dried over Na_2SO_4, and concentrated. The resulting yellow oil was purified by flash chromatography (hexanes: EtOAc 100:0 increasing by 2% EtOAc every 100 mL) to give **3** as a yellow sticky oil that solidified on standing (1.80 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.12 (d, $J = 2.3$ Hz, 6H, $CH_2C{\equiv}CH$), 3.57 (s, 2H, CH_2OSi), 3.50 (s, 6H, CH_2O), 2.40 (t, $J = 2.3$ Hz, 3H, CH), 0.89 (s, 9H, $C(CH_3)_3$), 0.04 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (90.6 MHz, $CDCl_3$, δ): 80.3, 74.2, 69.1, 61.6, 58.9, 45.8, 26.1, 18.4, −5.4. IR (film): ν 3292, 2919, 2850, 2118, 1094. MS (CI): $m/z = 365.2$ $[M + H]^+$.

2,2-Bis[(1′,2′-dicarba-*closo*-dodecaboran-1′-yl)oxymethyl]-3-[(1′,2′-dicarba-*closo*-dodecaboran-1′-yl)oxy]-2-(*tert*-butyldimethylsilyloxymethyl)propane (4). Silyl ether **3** (1.86 g, 5.11 mmol) was dissolved in toluene (25 mL). Decaborane(14) (2.26 g, 18.52 mmol) was added to the solution followed by 1-butyl-3-methylimidazolium chloride (1.94 g, 11.11 mmol). The reaction mixture was heated to 120 °C for 3 h under nitrogen with vigorous stirring, after which the solution was allowed to cool to room temperature. The solvent was removed in vacuo, giving a bright yellow oil. The oil was taken in Et_2O (60 mL), and the organic layer was washed with 1 M NaOH (3 × 45 mL), water (45 mL), then dried over Na_2SO_4, and concentrated. The resulting oil was purified by flash chromatography (hexanes:EtOAc 98:2 increasing by 3% EtOAc every 200 mL) to give **4** as a pale yellow oil that solidified on standing (0.95 g, 26%, 64% per alkyne). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.84 (s, 6H, CH_2CB_{10}) 3.72 (bs, 3H, $C_{cage}H$), 3.45 (s, 2H, CH_2OSi), 3.36 (s, 6H, CH_2O), 0.89 (s, 9H, $C(CH_3)_3$), 0.04 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (90.6 MHz, $CDCl_3$, δ): 73.0, 72.8, 70.1, 60.9, 58.2, 46.9, 26.0, 18.4, −5.5. ^{11}B NMR ($CDCl_3$, 192 MHz, δ): −3.68, −5.69, −10.30, −12.81, −14.15. IR (film): ν 2953, 2926, 2856, 2589, 1104. MS (CI): $m/z = 719.7$ $[M + H]^+$.

2,2-Bis[(1′,2′-dicarba-*closo*-dodecaboran-1′-yl)oxymethyl]-3-[(1′,2′-dicarba-*closo*-dodecaboran-1′-yl)oxy]propan-1-ol (5). Compound **4** (400 mg, 0.56 mmol) was dissolved in methanol (10 mL), and DOWEX 50WX2-200(H) (washed with methanol, approximately 400 mg) was added. The solution was vigorously stirred at 50 °C under nitrogen for 12 h, after which time it was allowed to cool to room temperature. Following removal and washing of the resin with small amounts of methanol, the filtrate was evaporated to give a yellow solid that was dissolved in a mixture of hexanes: EtOAc (50:50) and run through a short plug of silica gel (eluting with hexanes:EtOAc 50:50 then pure EtOAc). The solvent was removed in vacuo, yielding **5** as a light white solid (330 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.87 (s, 6H, CH_2CB_{10}) 3.75 (bs, 3H, $C_{cage}H$), 3.60 (s, 2H, CH_2OH), 3.44 (s, 6H, CH_2O). ^{13}C NMR (90.6 MHz, acetone-d_6, δ): 75.2, 74.0, 71.3, 61.3, 61.2, 47.7. ^{11}B NMR ($CDCl_3$, 192 MHz, δ) −3.43, −5.44, −9.96, −12.14, −13.48. IR (film): ν 3390, 2877, 2590, 1124. MS (CI): $m/z = 606.7$ $[M + H]^+$.

2,2-Bis[(1′,2′-dicarba-*closo*-dodecaboran-1′-yl)oxymethyl]-3-[(1′,2′-dicarba-*closo*-dodecaboran-1′-yl)oxy]propanoic Acid (6). CrO_3 (273 mg, 2.73 mmol) in 5.5 M H_2SO_4 (1.4 mL) was added over a period of 30 min to a solution of alcohol **5** (320 mg, 0.546 mmol) in acetone (25 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 4 h under nitrogen. After evaporation of the solvent in vacuo, the crude material was taken in water (40 mL) and extracted with EtOAc (3 × 45 mL). The combined organic phases were washed with water (2 × 40 mL) and brine, dried over Na_2SO_4, and concentrated. The resulting pale-green solid was dissolved in a mixture of hexanes: EtOAc (50:50) and run through a short plug of silica gel (eluting with hexanes:EtOAc 50:50 and then pure EtOAc). After removal of the solvent in vacuo, **6** was isolated as a light-white solid (316 mg, 96%). ^{1}H NMR (300 MHz, CD_3OD, δ): 4.31 (bs, 3H, $C_{cage}H$) 3.85 (s, 6H, CH_2CB_{10}), 3.56 (s, 6H, CH_2O). ^{13}C NMR (90.6 MHz, CD_3OD, δ): 174.7, 74.8, 73.8, 70.6, 60.9, 54.4. ^{11}B NMR (192 MHz, CD_3OD, δ): −3.51, −5.36, −9.88, −12.14, −13.48. IR (film): ν 3428, 2918, 2850, 2591, 1710, 1126. MS (ESI, negative): $m/z = 618.6$ $[M - H^+]^-$.

[*n*Bu$_4$N]$_3$[2,2-Bis[(7′,8′-dicarba-*nido*-undodecaboran-7′-yl)-oxymethyl]-3-[(7′,8′-dicarba-*nido*-undodecaboran-7′-yl)oxy]propanoic Acid] (6a). Acid **6** (327 mg, 0.528 mmol) was dissolved in dry THF (10 mL), and a solution of TBAF in THF (1 M, 3.96 mL, 3.96 mmol) was added dropwise over a period of 30 min. The reaction mixture was brought to reflux and vigorously stirred for 24 h under nitrogen, after which the solution was allowed to cool to room temperature and the solvent was removed in vacuo. The resulting yellow oil was taken in an acetone and EtOAc mixture (30 mL, 50:50), washed with water (2 × 25 mL) and then brine, dried over Na_2SO_4, and concentrated to give a thick yellow oil. After dissolution in a boiling mixture of water and methanol (50: 50), a soft white solid precipitated upon cooling. It was rinsed with cold solvent and dried to yield the desired trianion **6a** (as a tetra-*n*-butylammonium salt, 651 mg, 93%). ^{1}H NMR (300 MHz, acetone-d_6, δ):[37] 3.64 (bs), 3.41 (m, $N(CH_2)_4$), 3.33 (s), 1.89 (bs, $C_{cage}H$), 1.81 (q, $J = 7.3$ Hz, CH_2), 1.44 (sex, $J = 7.3$ Hz, CH_2), 0.98 (t, $J = 7.3$ Hz, CH_3). ^{13}C NMR (90.6 MHz, acetone-d_6, δ): 173.7, 79.7, 69.6, 59.4, 53.9, 46.2, 24.4, 20.3, 13.9. ^{11}B NMR (192 MHz, acetone-d_6, δ): −10.9, −15.6, −17.5, −18.2 (br), −19.7, −23.1, −33.7, −37.9. IR (film): ν 3220, 2963, 2919, 1876, 2519, 1699, 1458, 1418, 1381, 1303, 1089. MS (ESI, negative): $m/z =$ 1071.3 $[M + 2n\text{Bu}_4N^+]^-$, 414.7 $[M + n\text{Bu}_4N^+]^{2-}$.

3-{[3-(1′,2′-Dicarba-*closo*-dodecaboran-1′-yl)oxy-2,2-bis((1′,2′-dicarba-*closo*-dodecaboran-1′-yl)oxymethyl)propoxy]carbonyl}-propanoic Acid (11) from Alcohol (5). A solution of alcohol **5** (100 mg, 0.166 mmol) in dry THF (20 mL) was cooled to 0 °C and vigorously stirred. Sodium hydride (60%, 21 mg, 0.498 mmol) was added, followed after 15 min by succinic anhydride (166 mg, 1.653 mmol). The reaction mixture was allowed to warm up to room temperature and then was refluxed for 12 h under nitrogen. After cooling, the solvent was removed in vacuo, and the resulting solid was taken in Et_2O (30 mL) and then poured in acidified water (30 mL, pH 5). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic phases were washed with water (2 × 30 mL) and then brine, dried over Na_2SO_4, and concentrated. The resulting pale-yellow oil was purified by flash chromatography ($CHCl_3$:MeOH 99:1 increasing by 2% MeOH every 100 mL) to give **11** as a white solid (100 mg, 86%). ^{1}H NMR (300 MHz, acetone-d_6, δ): 4.67 (bs, 3H, $C_{cage}H$), 4.15 (s, 2H, $CH_2OC(O)$), 4.03 (s, 6H, CH_2CB_{10}), 3.59 (s, 6H, CH_2O), 2.59 (m, 4H, CH_2CH_2).^{13}C NMR (90.6 MHz, acetone-d_6, δ): 174.0, 172.6, 74.8, 73.3, 70.8, 63.2, 60.9, 46.1, 29.2, 29.2. ^{11}B

NMR (192 MHz, acetone-d_6, δ): −3.34, −5.27, −9.71, −11.80, −13.23. IR (film): ν 3367, 2921, 2851, 2588, 1738, 1714, 1125. MS (ESI, negative): m/z = 704.7 $[M - H^+]^-$.

2,2-Bis(prop-2-ynyloxymethyl-3-(prop-2-ynyloxy)propan-1-ol (7). Silyl ether **3** (750 mg, 2.057 mmol) was dissolved in dry THF (40 mL). Cooling to 0 °C was followed by the dropwise addition of a solution of TBAF in THF (1 M, 10.29 mL, 10.286 mmol) over a period of 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 3 h under nitrogen, after which time the solvent was removed in vacuo to give an oil that was taken in Et_2O (50 mL) and washed with water (2 × 50 mL) and then brine. The organic layer was then dried over Na_2SO_4 and concentrated. The resulting yellow oil was purified by flash chromatography (hexanes:EtOAc 80:20) to yield **7** as a pale-yellow oil (430 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.13 (d, J = 2.3 Hz, 6H, $CH_2C{\equiv}CH$), 3.69 (bs, 2H, CH_2OH), 3.56 (s, 6H, CH_2O), 2.46 (bs, 1H, OH), 2.43 (t, J = 2.3 Hz, 3H, CH). ^{13}C NMR (90.6 MHz, $CDCl_3$, δ): 79.8, 74.7, 70.3, 65.1, 59.0, 44.9. IR (film): ν 3446, 3289, 2917, 2878, 2117, 1092. MS (CI): m/z = 251.1 $[M + H]^+$.

3-{[2,2-Bis(prop-2-ynyloxymethyl)-3-(prop-2-ynyloxy)propoxy]carbonyl}propanoic Acid (8). To a solution of alcohol **7** (410 mg, 1.639 mmol) in dry THF (30 mL) was added succinic anhydride (1312 mg, 13.112 mmol) and DMAP (801 mg, 6.556 mmol). The mixture was refluxed for 5 h under nitrogen, after which time it was allowed to cool to room temperature, and the solvent was removed in vacuo. The resulting oil was taken in Et_2O (50 mL) and poured in acidic water (50 mL, pH 5). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with water (2 × 50 mL) and then brine, dried over Na_2SO_4, and concentrated. The crude mixture was purified by flash chromatography ($CHCl_3$:MeOH 100/0 increasing by 2% MeOH every 100 mL) to afford **8** as a pale-yellow oil (544 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.16 (s, 2H, $CH_2OC(O)$), 4.10 (d, J = 2.4 Hz, 6H, $CH_2C{\equiv}CH$), 3.51 (s, 6H, CH_2O), 2.67 (m, 4H, CH_2CH_2), 2.42 (t, J = 2.4 Hz, 3H, CH). ^{13}C NMR (90.6 MHz, $CDCl_3$, δ): 178.4, 171.9, 79.9, 74.5, 68.8, 64.0, 58.8, 41.2, 29.1. IR (film): ν ∼3400, 3287, 2955, 2922, 2884, 2856, 2117, 1733, 1715, 1094. MS (ESI, negative): m/z = 349.1 $[M - H^+]^-$.

2,2,2-Trichloroethyl-3-{[2,2-bis(prop-2-ynyloxymethyl)-3-(prop-2-ynyloxy)propoxy]carbonyl}propionate (9). Acid **8** (520 mg, 1.485 mmol) was dissolved in dry CH_2Cl_2 (15 mL). Trichloroethanol (277 mg, 178 μL, 1.850 mmol) was added to the solution, followed by DPTS (55 mg, 0.185 mmol) and then DCC (381 mg, 1.850 mmol). The reaction mixture was stirred at room temperature for 18 h under nitrogen and then poured in water (15 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were washed with water (2 × 15 mL) and then brine, dried over Na_2SO_4, and concentrated. The crude mixture was purified by flash chromatography (hexanes:EtOAc 90:10 increasing by 2.5% EtOAc every 80 mL) to yield **9** as a yellow oil (647 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.76 (s, 2H, CH_2CCl_3), 4.17 (s, 2H, $CH_2OC(O)$), 4.11 (d, J = 2.5 Hz, 6H, $CH_2C{\equiv}CH$), 3.52 (s, 6H, CH_2O), 2.76 (m, 4H, CH_2CH_2), 2.42 (t, J = 2.4 Hz, 3H, CH). ^{13}C NMR (120.8 MHz, $CDCl_3$, δ): 171.6, 170.9, 95.0, 80.0, 74.5, 74.3, 68.8, 64.0, 58.9, 44.2, 29.1. IR (film): ν 3288, 2958, 2927, 2885, 2120, 1739, 1095. MS (CI): m/z = 483.0 $[M + H]^+$.

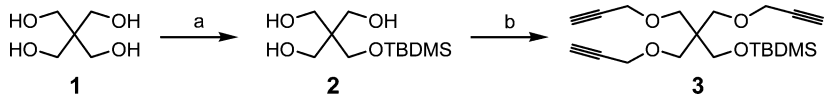
2,2,2-Trichloroethyl-3-{[2,2-Bis[(1′,2′-dicarba-*closo*-dodecaboran-1′-yl)oxymethyl]-3-[(1′,2′-dicarba-*closo*-dodecaboran-1′-yl)oxy]propoxy]carbonyl}propionate (10). A mixture of **9** (613 mg, 1.278 mmol) and decaborane(14) (586 mg, 4.791 mmol) was dissolved in toluene. 1-Butyl-3-methylimidazolium chloride (503 mg, 2.875 mmol) was added, and the reaction mixture was heated to 120 °C for 3 h under nitrogen while stirring vigorously, after which time it was allowed to cool to room temperature. The solvent was removed in vacuo to give a bright yellow oil that was taken in Et_2O (40 mL). The organic layer was washed with 1 M NaOH (3 × 40 mL) and then with water (2 × 30 mL), dried over Na_2SO_4, and concentrated. The resulting oil was purified by flash chromatography (hexanes:EtOAc 80:20 increasing by 2.5% EtOAc every 250 mL) to yield **10** as a thick white oil (144 mg, 13.5%, 51% per alkyne). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.76 (s, 2H, CH_2CCl_3), 4.10 (s, 2H, $CH_2OC(O)$), 3.85(s, 6H, CH_2CB_{10}), 3.77 (bs, 3H, $C_{cage}H$), 3.41 (s, 6H, CH_2O), 2.83 (m, 2H, CH_2CH_2), 2.65 (m, 2H, CH_2CH_2). ^{13}C NMR (120.8 MHz, $CDCl_3$, δ): 171.6, 171.2, 94.8, 74.4, 73.0, 72.6, 70.0, 62.5, 58.4, 45.4, 28.8, 28.8. ^{11}B NMR (192 MHz, $CDCl_3$, δ): −3.43, −5.44, −9.96, −12.14, −13.48. IR (film): ν 2957, 2923, 2881, 2590, 1743, 1133. MS (CI): m/z = 837.6 $[M + H]^+$.

3-{[2,2-Bis[(1′,2′-dicarba-*closo*-dodecaboran-1′-yl)oxymethyl]-3-[(1′,2′-dicarba-*closo*-dodeca-boran-1′-yl)oxy]propoxy]carbonyl}-propanoic Acid (11) from Trichloroethyl Ester (10). Compound **10** (117 mg, 0.140 mmol) was dissolved in a mixture of acetic acid and THF (20 mL, 3:1). Zinc powder (55 mg, 0.840 mmol) was added over a period of 10 min, and the reaction mixture was vigorously stirred for 12 h under nitrogen. The insoluble residue was filtered off and washed with small amounts of THF, and the filtrate was poured in Et_2O (30 mL). The organic phase was washed with saturated aqueous sodium bicarbonate (30 mL), water (30 mL), and then brine, dried over Na_2SO_4, and concentrated. The resulting oil was taken in $CHCl_3$ and run through a short plug of silica gel (eluting with $CHCl_3$ then $CHCl_3$:MeOH 90:10). After removal of the solvent in vacuo, **12** was isolated as a light white solid (96 mg, 99%). ^{1}H NMR (400 MHz, CD_3OD, δ): 4.52 (bs, 3H, $C_{cage}H$), 4.14 (s, 2H, $CH_2OC(O)$), 3.94(s, 6H, CH_2CB_{10}), 3.49 (s, 6H, CH_2O), 2.62 (m, 4H, CH_2CH_2).

Hexacarboranyl-[G#2] Trichloroethyl Ester (13). Acid **11** (50.0 mg, 0.071 mmol) and diol **12** (8.6 mg, 0.032 mmol) were dissolved in a mixture of dry CH_2Cl_2 and THF (5 mL, 9:1). DPTS (9.5 mg, 0.032 mmol) was added followed by DCC (17.3 mg, 0.838 mmol). After stirring at room temperature for 4 days under nitrogen, the DCC−urea was filtered off and washed with small amounts of CH_2Cl_2. The solvent was removed in vacuo to give a white solid that was purified by flash chromatography (eluting with $CHCl_3$), yielding **13** as a light white solid (47.6 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.81 (s, 2H, CH_2CCl_3), 4.30 (s, 4H, $CH_{2\ bis-MPA}$), 4.09 (s, 4H, $CH_2OC(O)$), 3.86 (s, 12H, CH_2CB_{10}), 3.79 (bs, 6H, $C_{cage}H$), 3.41 (s, 12H, CH_2O), 2.66 (m, 4H, CH_2CH_2), 2.56 (m, 4H, CH_2CH_2), 1.37 (s, 3H, CH_3). ^{13}C NMR (120.8 MHz, $CDCl_3$, δ): 172.1, 171.8, 171.1, 94.8. 74.4, 73.0, 72.6, 70.1, 65.9, 58.6, 58.4, 46.1, 45.4, 29.9, 28.8, 17.9. ^{11}B NMR (192 MHz, $CDCl_3$, δ): −3.51, −5.52, −10.21, −12.81, −13.81. IR (film): ν 2917, 2850, 2592, 1742, 1133. MS (ESI, positive): m/z = 1531.4 $[M + Na]^+$.

Hexacarboranyl-[G#2] Acid (14). 13 (70 mg, 0.043 mmol) was dissolved in a mixture of glacial acetic acid and THF (20 mL, 2:1). Zinc powder (90 mg, 1.281 mmol) was added over a period of 10 min, and the reaction mixture was vigorously stirred for 18 h under nitrogen. The insoluble residue was filtered off, and the THF evaporated. The filtrate was then diluted with water (50 mL) and poured in Et_2O (50 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic phases were partially concentrated in vacuo, washed with dilute aqueous sodium bicarbonate (3 × 50 mL) and then water

Scheme 1 [a]



1 2 3

[a] Reagents and conditions: (a) TBDMSCl, imidazole, DMF, RT, 24 h. (b) NaH, propargyl bromide, THF, 0 °C to RT, 12 h.

(50 mL), dried over Na_2SO_4, and concentrated. The resulting oil was taken in $CHCl_3$ and run through a short plug of silica gel (eluting with $CHCl_3$ and then $CHCl_3$:MeOH 95:5). After removal of the solvent in vacuo, **14** was isolated as a light-white solid (62 mg, 96%).^{1}H NMR (300 MHz, acetone-d_6, δ): 4.64 (bs, 6H, $C_{cage}H$), 4.26 (s, 4H, $CH_{2\ bis-MPA}$), 4.15 (s, 4H, $CH_2OC(O)$), 4.03 (s, 12H, CH_2CB_{10}), 3.60 (s, 12H, CH_2O), 2.64 (m, 8H, CH_2CH_2), 1.28 (s, 3H, CH_3). ^{13}C NMR (90.6 MHz, acetone-d_6, δ): 174.3 172.6, 172.3, 74.6, 73.2, 70.7, 66.4, 63.3, 60.7, 46.6, 45.9, 29.4, 29.4, 18.1. ^{11}B NMR (192 MHz, acetone-d_6): δ −3.34, −5.19, −9.71, −11.80, −13.14. IR (film): ν 3346, 2918, 2850, 2588, 1738, 1128. MS (ESI, positive): m/z = 1662.2 $[M + Na]^+$.

Attempted Preparation of Dodecacarboranyl [G#3] Trichloroethyl Ester (15). Acid **14** (160.0 mg, 0.106 mmol) and diol **12** (12.8 mg, 0.048 mmol) were dissolved in a mixture of dry CH_2Cl_2 and THF (10 mL, 9:1). DPTS (14.2 mg, 0.048 mmol) was added followed by DCC (25.9 mg, 0.125 mmol). After stirring at room temperature for 5 days under nitrogen, the DCC−urea was filtered off and washed with small amounts of CH_2Cl_2. The solvent was removed in vacuo to give a pale-yellow solid that has been analyzed using MALDI-TOF MS.

Results and Discussion

Our design of a boron-rich building block is based on a tetraol, pentaerythritol. It is a precursor of an AB_3-type building block, which would allow for a 50% increase in the number of boron clusters in a dendron as compared to a dendron constructed solely using AB_2-type building blocks. The use of such a terminus represents an efficient alternative to the synthesis of higher generation dendrons, a common way of increasing the number of outer-shell functional groups.[38]

There have been several recent reports describing the synthesis of molecules carrying neutral dicarbaboranes, mostly *p*- and *o*-carboranes (Chart 1).[29,39,40] The attachment of a *p*-carboranyl moiety requires a stepwise functionalization of two vertices of the costly *p*-$C_2B_{10}H_{12}$,[29] while *o*-carboranes can be introduced directly through insertion of alkynes into the much less expensive decaborane.[13−15] This reaction is substrate-dependent with variable reported yields and long reactions times (up to 4 days). However, its yield and reaction time have been recently shown to greatly improve in the presence of certain ionic liquids.[41]

Implementing the insertion reaction required the synthesis of a pentaerythritol derivative bearing three alkyne moieties and retaining a protected hydroxyl group necessary for further coupling of the boronated terminus. This was done through direct differentiation of the four equivalent hydroxyl groups of pentaerythritol using a stoichiometrically controlled monosilylation reaction (Scheme 1).[42] Initially, *tert*-butyldiphenylsilyl chloride or triisopropylsilyl chloride were employed, affording the desired monosilylated derivative in high yield (>85%). However, we found *tert*-butyldimethylsilyl ethers easier to cleave and prepared triol **2** in 61% yield through reaction of excess pentaerythritol with the corresponding silyl chloride in DMF. The triol **2** was then treated with excess sodium hydride followed by propargyl bromide in THF to afford the desired tripropargyl ether **3** in 82% yield.

The boron clusters were then installed through insertion of the terminal alkynes using a slight excess of decaborane in a biphasic mixture of toluene and the ionic liquid 1-butyl-3-methylimidiazolium chloride.[41] Refluxing the mixture for 3 h provided the desired tri-*o*-carboranyl silyl ether **4** in 26% yield (which represents 64% yield per alkyne). Both mono- and di-boronated products were isolated and resubmitted to the insertion conditions to afford the desired product in high yield. The silyl ether **4** was then quantitatively cleaved using DOWEX H^+ resin in methanol, and oxidation of the resulting alcohol **5** using Jones reagent afforded the tricarboranyl acid **6** in nearly quantitative yield (Scheme 2).

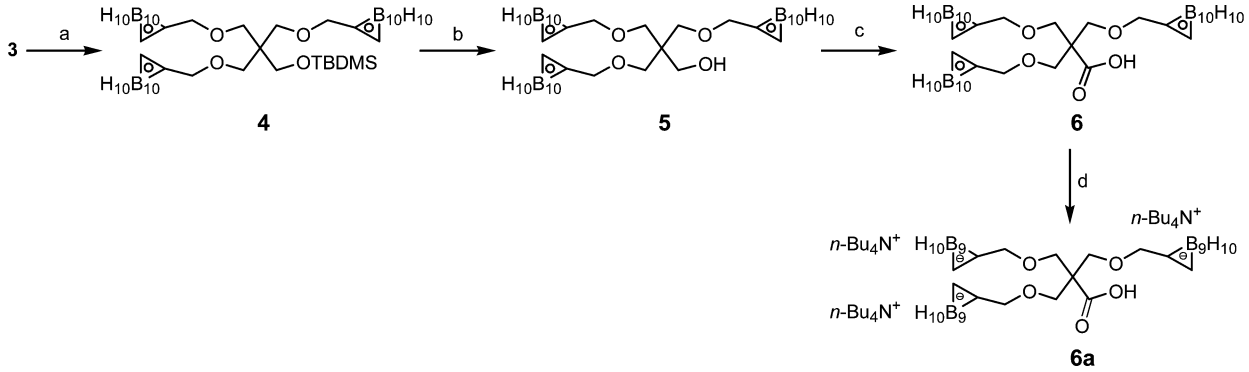
When fluoride ions were used to remove the silyl ether on **4**, they lead to deboronation.[43] Thus, upon addition of TBAF to a solution of **4** in THF, we observed both the cleavage of the TBDMS group and the deboronation of the three *closo*-carboranes to form the corresponding anionic *nido*-carborane cages. Jones oxidation appeared to be affected by the presence of tetra-*n*-butylammonium as complex inseparable mixtures were obtained under these conditions. However, refluxing acid **6** in THF in the presence of TBAF yielded the fully deboronated tri-*nido*-carboranyl acid **6a** (as a tetra-*n*-butylammonium salt) in almost quantitative yield.

Next, we explored the coupling of the tricarboranyl building block to the 2,2,2-trichloroethyl ester of 2,2-bis-(hydroxymethyl)propionic acid (bis-MPA) to prepare a higher generation dendron.[32] Unfortunately, the reaction was unsuccessful under standard coupling conditions (DCC, catalytic DPTS or EDC, catalytic DMAP) and only the starting materials were recovered. Further attempts at esterifying the acid under harsher conditions proved unsuccessful, often leading to the degradation of the carboranes. We discovered that even a methyl ester of **6** could not be obtained and LAH reduction of **6** also failed as well as reductions under more forcing conditions that led to degradation of the boron clusters. These observations suggest that the presence of three very bulky carboranes in close proximity to the carboxylic acid moiety renders it inaccessible to other reagents.

Further evidence of the steric congestion in **6** was found by X-ray crystallography. Crystals of **6** were obtained by

(41) Kusari, U.; Yuqi, L.; Bradley, M. G.; Sneddon, L. G. *J. Am. Chem. Soc.* **2004**, *126*, 8662−8663.
(42) Hanessian, S.; Prabhanjan, H.; Qiu, D.; Nambiar, S. *Can. J. Chem.* **1996**, *74*, 1731−1737.
(43) Fox, M. A.; Gill, W. R.; Herbertson, P. L.; MacBride, J. A. H.; Wade, K. *Polyhedron* **1996**, *15*, 565−571.

Scheme 2 [a]



[a] Reagents and conditions: (a) $B_{10}H_{14}$, IL, toluene, 120 °C, 3 h. (b) DOWEX 50W-X2, MeOH, 50 °C, 12 h. (c) CrO_3, H_2SO_4, acetone, 0 °C to RT, 12 h. (d) TBAF, THF, 0 °C to reflux, 24 h.

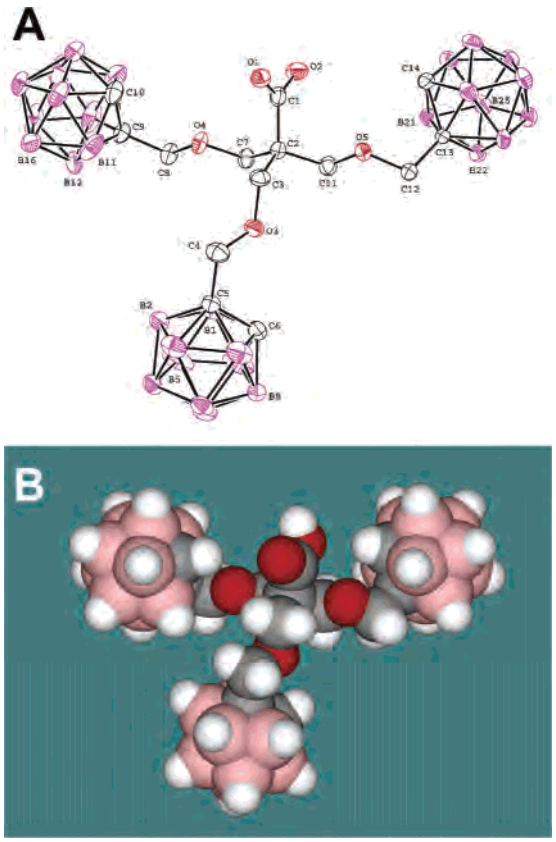


Figure 1. (A) X-ray crystal structure of the tricarboranyl acid **6**. (B) Space-filling model of **6** (boron atoms are pink, carbon atoms are gray, oxygen atoms are red, and hydrogen atoms are white).

slow evaporation of its water/methanol solution. The X-ray single-crystal structure of **6** (Figure 1A) and the corresponding space-filling model (Figure 1B) reveal that both faces of the carboxylic group are hindered by the bulky carboranes. The distance between hydrogen atoms attached to the cage carbon and the carbonyl carbon atom is only 3.5 Å. The carboxylic acid is rotated in such a way that its hydroxyl group is pointing toward the acidic hydrogen on one of the cage carbon atoms, placing it within a typical hydrogen bond distance of 2.7 Å. The approach to the carboxylic group of **6** is further hindered by the neopentyl-like structure of pentaerythritol. The structural data thus support the hypothesis that steric factors are responsible for the lack of reactivity of the carboxylic acid terminus in **6**.

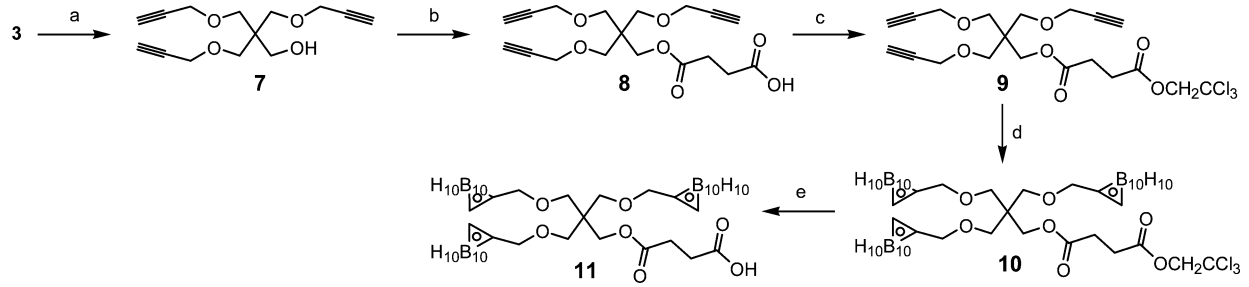
To avoid the steric congestion and to enable incorporation of **6** into higher generation bis-MPA-based dendrons, we decided to insert a linker between the quaternary carbon of the pentaerythritol backbone and the carboxylic group. Succinic anhydride was chosen for this purpose because it can easily be opened by nucleophiles,[44] such as the remaining hydroxyl group of **5**, placing the carboxylic acid five atoms away from the quaternary center.

The installation of the linker in the presence of the carboranes proved to be problematic because the pyridine derivatives used as acylation catalysts (DMAP, pyridine) acted as deboronation agents, yielding inseparable mixtures of the desired acid (carrying neutral *closo*-carboranes) and of partially deboronated *nido*-carboranyl acids. Thus, we decided to install the linker before performing the hydroboration reaction, and a new tri-alkyne substrate was synthesized. To this end, the TBDMS protecting group on **3** was removed using TBAF in THF, affording alcohol **7** in 83% yield (Scheme 3). The newly deprotected hydroxyl group was used in the nucleophilic opening of succinic anhydride, using DMAP as a stoichiometric base in THF and affording acid **8** in 95% yield. To enable the use of acid-sensitive decaborane,[2] **8** had to be protected before the hydroboration reaction could be performed. Thus, it was converted to the 2,2,2-trichloroethyl ester **9** in 90% yield through reaction with 2,2,2-trichloroethanol in dichloromethane in the presence of DCC and a catalytic amount of DPTS. Subsequent hydroboration of the three terminal alkynes under conditions similar to those described above afforded the desired tricarboranyl compound **10** in 14% yield (51% yield per alkyne). The protecting group was then quantitatively removed using zinc dust in a mixture of glacial acetic acid and THF to afford the desired boronated acid terminus with the linker (**11**, Scheme 3).

Unsatisfied with the low hydroboration yield and the impossibility to recover partially reacted products, we reinvestigated the installation of the linker in the presence of the carboranyl units. Since nitrogen-containing bases, even weakly nucleophilic, lead to deboronation of the carboranes, we considered the opening of succinic anhydride with the hydroxyl group of tricarboranyl alcohol **5** in the presence of

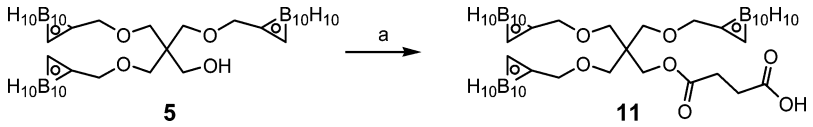
(44) Farcy, N.; De Muynck, H.; Madder, A.; Hosten, N.; De Clercq, P. J. *Org. Lett.* **2001**, *3*, 4299−4301.

Scheme 3 [a]



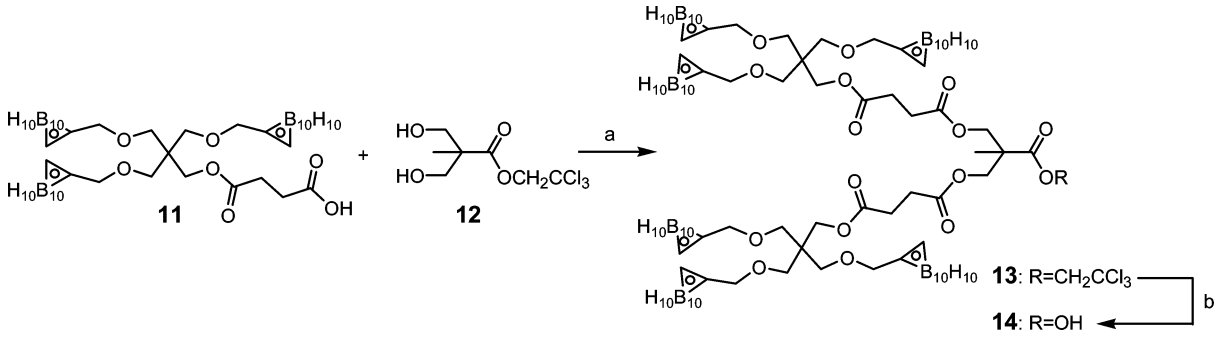
[a] Reagents and conditions: (a) TBAF/THF, 0 °C to RT, 12 h. (b) Succinic anhydride, cat. DMAP, THF, reflux, 5 h. (c) 2,2,2-Trichloroethanol, DCC, cat. DPTS, CH_2Cl_2, RT, 18 h. (d) $B_{10}H_{14}$, IL, toluene, 120 °C, 3 h. (e) Zn, AcOH/THF, RT, 12 h.

Scheme 4 [a]



[a] Reagents and conditions: (a) succinic anhydride, NaH, THF, 0 °C to reflux, 5 h.

Scheme 5 [a]



[a] Reagents and conditions: (a) DCC, DPTS, CH_2Cl_2/THF, RT, 4 days. (b) Zn, AcOH/THF, RT, 18 h.

catalytic amounts of base. We found this primary alcohol with neopentyl-like structure to be a very poor nucleophile since in the presence of DMAP or pyridine only deboronation products have been observed, while no reaction occurred in the presence of 2,6-lutidine. However, the nucleophilic ring opening proceeded well when the corresponding alkoxyde (prepared using excess NaH) was refluxed in THF in the presence of a large excess of succinic anhydride. Under these conditions, the desired tricarboranyl acid **11** was isolated in 96% yield (Scheme 4) and no deboronation was observed.

With the new tricarboranyl building block in hand, we proceeded to incorporate it in a bis-MPA based dendron. A convergent strategy[45] was chosen in which the dendron is grown inward, starting from the boronated "terminus" molecule and proceeding toward a focal point. The implementation of the convergent growth required a protection of the carboxylic acid moiety of bis-MPA during the coupling step between its two hydroxyl groups and the boronated acid. Subsequent deprotection would regenerate an acid at the focal point of the dendron, which could in turn be coupled to another molecule of acid-protected bis-MPA to produce the next generation dendron. Thus, we converted bis-MPA to its 2,2,2-trichloroethyl ester **12** (using the previously described high-yielding DCC coupling[32]) because the conditions used to remove this protecting group are compatible with the polyester structure.

Treating **12** with a slight excess of the boronated acid **11** in dichloromethane in the presence of DCC and a stoechiometric amount of DPTS resulted in the formation of the desired diester **13** in 90% yield (Scheme 5). The protecting group was then quantitatively removed using zinc dust in a mixture of glacial acetic acid and THF, affording the hexacarboranyl generation-1 acid **14** in nearly quantitative yield (Scheme 5). The outstanding yield obtained in the coupling reaction confirms that steric factors were responsible for the lack of reactivity of the building block **6** (without the linker).

Next, we attempted the preparation of a higher generation dendron (containing 12 carboranyl units) by coupling **14** to protected bis-MPA **12**. This reaction did not proceed under the conditions used in the couplings described above, and only the starting materials were recovered. After 6 days of reflux in 1,2-dichloroethane this reaction produced an inseparable mixture whose mass spectrometry revealed the presence of a monosubstituted product (MALDI-TOF, $m/z = 1779.9$ $[M + Na]^+$) where only one of the two hydroxyl groups in **12** reacted with **14**. It is likely that the close proximity of the hydroxyl groups in **12** prevents the second bulky molecule of **14** from reacting once the monoester has been formed.

(45) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638−7647.

Conclusions

We prepared a new tricarborane-containing building block based on pentaerythritol and its *nido*-carboranyl trianion analogue. The X-ray crystallography of the neutral tricarborane derivative revealed a highly sterically hindered structure. The low reactivity of this compound resulting from its steric congestion could be overcome by installing a linker in order to attach this moiety to other molecules. We successfully used a succinimidyl linker to attach the tricarboranyl building block to 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) to prepare a hexacarborane-containing dendron carrying 60 boron atoms. We are presently working on the preparation of higher generation dendrons containing the described building block, on the attachment of the dendrons to targeting and imaging moieties for use in BNCT, and on the synthesis of polyanionic analogues of the building block and corresponding dendrons.

Acknowledgment. This work has been funded in part by the University of Utah Funding Incentive Seed Grant. We are grateful to Prof. Bogdan Olenyuk (University of Arizona) for fruitful collaboration. We would like to thank Laura Parke, Cornelia Pfaffenroth, and Olga Schelepina for their help at the early stages of this project.

Supporting Information Available: Tables listing detailed crystallographic data, atomic positional and thermal parameters, and bond lengths and angles for the tricarborane acid **6** and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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