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Synthesis, NMR, and X-ray Crystallographic Analysis of *C*-Hydrazino-*C*-Carboxycarboranes: Versatile Ligands for the Preparation of BNCT and BNCS Agents and ^{99m}Tc Radiopharmaceuticals

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Protected hydrazine derivatives of *ortho*-, *meta*-, and *para*-carboranes were synthesized in good to excellent yields by reacting the mono-lithio salts of the respective carboranes with di-*tert*-butyl azodicarboxylate (DBAD). Subsequent deprotonation of the remaining carborane CH group, followed by the addition of CO_2(g), resulted in the formation of bifunctional *C*-hydrazino-*C*-carboxycarboranes in good to excellent overall yields. Crystal structures of the monosubstituted *ortho*-carborane, 1-[(*N*,*N*′((*tert*-butyloxy)carbonyl)hydrazino)]-1,2-dicarba-*closo*-dodecaborane (**8**) [$a = 21.213(6)$ Å, $b = 10.498(3)$ Å, $c = 9.866(2)$ Å, $\alpha = \gamma = 90°$, $\beta = 90.529(4)°$] and the bifunctional *para*-carborane 1-[(*N*,*N*′((*tert*-butyloxy)carbonyl)hydrazino)]-1,12-dicarba-*closo*-dodecaborane-12-carboxylic acid (**3**) [$a = 12.744(10)$ Å, $b = 12.875(9)$ Å, $c = 14.767(9)$ Å, $\alpha = \beta = \gamma = 90°$] were obtained. Intermolecular hydrogen bonding was a dominant packing feature in both structures. The reported compounds represent a unique class of bifunctional carboranes that can be used in peptidomimetic research and as synthons to prepare novel radiopharmaceuticals and boron neutron capture therapy/boron neutron capture synovectomy (BNCT/BNCS) agents.

Introduction

Carboranes are versatile synthons, which have been used to prepare catalysts,[1] polymers,[2] pharmaceuticals,[3] radiopharmaceuticals,[4] and a range of unique inorganic complexes.[5] Carborane derivatives have also been extensively employed to construct boron delivery vehicles for boron neutron capture therapy (BNCT), an experimental cancer treatment technique, because of the cluster's high boron content and its stability in vivo.[6] For similar reasons, functionalized carboranes have also been used in boron neutron capture synovectomy (BNCS), which is a treatment modality for rheumatoid arthritis currently under investigation as an alternative to radiation synovectomy.[7] Continued exploitation of carboranes for medicinal chemistry and material science research will require the development of new and more efficient methods for preparing functionalized carboranes.

Bifunctional carboranes, which are readily adaptable for use in a wide range of biological and material science

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(1) (a) Larsen, A. S.; Holbrey, J. D.; Tham, F. S.; Reed, C. A. *J. Am. Chem. Soc.* **2000**, *122*, 7264. (b) Pindado, G. J.; Lancaster, S. J.; Thornton-Pett, M.; Bochmann, M. *J. Am. Chem. Soc.* **1998**, *120*, 6816. (c) Reed, C. A. *Acc. Chem. Res.* **1998**, *31*, 133. (d) Curtis, M. A.; Finn, M. G.; Grimes, R. N. *J. Organomet. Chem.* **1998**, *550*, 469. (e) Blandford, I.; Jeffery, J. C.; Jelliss, P. A.; Stone, F. G. A. *Organometallics* **1998**, *17*, 1402. (f) Felekidis, A.; Goblet-Stachow, M.; Liegeois, J. F.; Pirotte, B.; Delarge, J.; Demonceau, A.; Fontaine, M.; Noels, A. F.; Chizhevsky, I. T.; Zinevich, T. V.; Bregadze, V. I.; Dolgushin, F. M.; Yanovsky, A. I.; Struchkov, Yu. T. A. *J. Organomet. Chem.* **1997**, *536*/*537*, 405. (g) Chizhevsky, I. T.; Yanovsky, A. I.; Struchkov, Y. T. *J. Organomet. Chem.* **1997**, *536*/*537*, 51. (h) Teixidor, F.; Flores, M. A.; Viñas, C.; Kivekäs, R.; Sillanpää, R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2251. (i) Chizhevsky, I. T.; Pisareva, I. V.; Petrovskii, P. V.; Bregadze, V. I.; Dolgushin, F. M.; Yanovsky, A. I.; Struchkov, Yu. T.; Hawthorne, M. F. *Inorg. Chem.* **1996**, *35*, 1386. (j) Belmont, J. A.; Soto, J.; King, R. E., III; Donaldson, A. J.; Hewes, J. D.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1989**, *111*, 7475.

(2) (a) McLemore, D. K.; Dixon, D. A.; Strauss, S. H. *Inorg. Chim. Acta* **1999**, *294*, 193. (b) Ivanova, S. M.; Ivanov, S. V.; Miller, S. M.; Anderson, O. P.; Solntsev, K. A.; Strauss, S. H. *Inorg. Chem.* **1999**, *38*, 3756. (c) Jiang, W.; Chizhevsky, I. T.; Mortimer, M. D.; Chen, W.; Knobler, C. B.; Johnson, S. E.; Gomez, F. A.; Hawthorne, M. F. *Inorg. Chem.* **1996**, *35*, 5417. (d) Arterburn, J. B.; Wu, Y.; Quintana, W. *Polyhedron* **1996**, *15*, 4355. (e) Plešek, J. *Chem. Rev.* **1992**, *92*, 269.

(3) (a) Endo, Y.; Iijima, T.; Yamakoshi, Y.; Fukasawa, H.; Miyaura, C.; Inada, M.; Kubo, A.; Itai, A. *Chem. Biol.* **2001**, *8*, 341. (b) Yamamoto, K.; Endo, Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2389.

(4) Hawthorne, M. F.; Maderna, A. *Chem. Rev.* **1999**, *99*, 3421.

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applications, are particularly rare. Kahl and co-workers recently reported the synthesis of carboranes containing both amino and carboxylic acid residues.[8] These versatile compounds can be coupled to biomolecules through one or both of the carboxy and amino groups making them interesting amino acid analogues for peptidomimetic research. We were interested in developing a new class of bifunctional carboranes that, like the amino carboxycarboranes, could be readily linked to biomolecules but that could also be labeled with a range of different radionuclides. These compounds could be used to prepare targeted radiopharmaceuticals and novel BNCT and BNCS agents, whose bulk distribution could be readily evaluated by radioimaging. The ability to visualize the distribution of BNCT agents using positron emission tomography (PET) in animal models of cancer has been shown to have a number of advantages compared to the conventional method of measuring boron uptake in isolated tissue samples.[4,9] Herein, we report the synthesis and characterization of *C*-hydrazino-*C*-carboxy derivatives of *ortho*-, *meta*-, and *para*-carborane as a new class of bifunctional carborane ligands. These compounds have the appropriate functionalities to be linked to biomolecules and to be labeled with a range of different radionuclides including ^{99m}Tc, the most widely used radionuclide in diagnostic medicine.[10]

Experimental Section

Materials and General Procedures. All commercial reagents were used as supplied. THF and Et_2O were distilled under nitrogen from sodium and benzophenone while CH_2Cl_2 was distilled from CaH_2. *Ortho*- and *para*-carboranes were purchased from Katchem Ltd. (Czech. Rep.), while *meta*-carborane was purchased from Dexsil Corp. (Hamden, CT). CO_2(g), which was generated by sublimation of CO_2(s), was passed through a column of Drierite prior to its addition to a reaction. Analytical TLC was performed on silica gel 60-F_{254} (Merck). Boron compounds were visualized with 0.1% $PdCl_2$ in hydrochloric acid (3.0 M), which upon heating gave dark brown spots.[11] Hydrazine derivatives were visualized using a ninhydrin solution, which consisted of 0.3% of ninhydrin in *n*-butanol containing 3% acetic acid.

NMR spectroscopy experiments were performed on Bruker Avance AV300 and DRX500 spectrometers. TMS and BF_3-Et_2O were used as internal standards for ^{1}H and ^{11}B spectra, respectively. For NMR assignments, b refers to broad signals, s refers to singlets, and m refers to multiplets. Electrospray mass spectrometry experiments were performed on a Fisons Platform quadrupole instrument. Samples were dissolved in 50:50 CH_3CN/H_2O, and for compounds run in negative ion detection mode, one drop of 0.10 M NH_4OH was added. Microanalyses were performed by Guelph Chemical Laboratories (Guelph, Ontario, Canada). IR spectra were run on a Bio-Rad FTS-40 FTIR spectrometer.

Structure Determination by X-ray Crystallography. Single-crystal X-ray diffraction data was collected with a Bruker SMART-1K CCD detector on a P4/RA diffractometer equipped with an Oxford Cryostream cooling system. The diffraction experiments were carried out with graphite-monochromated Mo Kα X-radiation (λ = 0.71753 Å). Single crystals of compounds **3** and **8** were mounted on the tips of glass fibers. Accurate cell parameters were determined at 173 K from a refinement of the setting angles (χ, ϕ, and 2θ) obtained from a chosen number of centered reflections in reciprocal space (maximum $2\theta = 54.45°$ for compound **8** and $2\theta = 46°$ for compound **3**) using the SMART[12] software. The SAINT[13] program was used to integrate the raw frame data, and the structures were solved by direct methods and refined by full-matrix least squares on F^2 for structure solution using the SHELXTL PLUS package.[14] Corrections were made to the integrated diffraction spots by applying Lorentz and polarization corrections. The SADABS[15] program was used for the application of a decay correction, and an empirical absorption correction based on redundant reflections. For compound **8**, thermal restraints were added during least-squares refinement in order to correct for nonpositive definites and to refine atomic positions anisotropically. Non-hydrogen atoms were refined with anisotropic atomic displacement parameters. All hydrogen atoms were assigned except for the *tert*-butyl groups (C3A to C5A and C3B to C5B) in compound **8**, where hydrogen atoms were added as fixed contributors at calculated points with isotropic thermal parameters, based on the carbon atom to which they were bonded. A noncentrosymmetric space group *Cc* was selected over the centrosymmetric space group ($C2_1/c$) for **8** because of the absence of any center of symmetry in the unit cell. Crystallographic data for both structures are presented in Table 1.

Synthesis of 1-[(*N*,*N*′((*tert*-Butyloxy)carbonyl)hydrazino)]-1,12-dicarba-*closo*-dodecaborane, 2. *n*-BuLi (0.38 mL, 0.61 mmol, 1.6 M in diethyl ether) was added dropwise to 1,12-dicarba-*closo*-dodecaborane (0.088 g, 0.61 mmol) in ether (10 mL) over 5 min with stirring under an argon atmosphere. The reaction mixture, which was maintained at 0 °C for 45 min, was subsequently added

(5) (a) Westerhausen, M.; Gückel, C.; Schneiderbauer, S.; Nöth, H.; Hosmane, N. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1902. (b) Patmore, N. J.; Mahon, M. F.; Steed, J. W.; Weller, A. S. *J. Chem. Soc., Dalton Trans.* **2001**, *3*, 277. (c) Vyakaranam, K.; Li, S.; Zheng, C.; Hosmane, N. S. *Inorg. Chem. Commun.* **2001**, *4*, 180. (d) Rockwell, J. J.; Herzog, A.; Peymann, T.; Knobler, C. B.; Hawthorne, M. F. *Curr. Sci.* **2000**, *78*, 405. (e) Li, F.; Shelly, K.; Knobler, C. B.; Hawthorne, M. F. *Inorg. Chem.* **1999**, *38*, 4926. (f) Hardie, M. J.; Raston, C. L. *Eur. J. Inorg. Chem.* **1999**, 195. (g) Peymann, T.; Herzog, A.; Knobler, C. B.; Hawthorne, M. F. *Angew Chem., Int. Ed.* **1999**, *38*, 1061. (h) Teixidor, F.; Gomez, S.; Lamrani, M.; Viñas, C.; Sillanpaeae, R.; Kivekäs, R. *Organometallics* **1997**, *16*, 1278. (i) Rousseau, R.; Lee, S.; Canadell, E.; Teixidor, F.; Viñas, C.; Stibr, B. *New J. Chem.* **1996**, *20*, 277. (j) Zheng, Z.; Knobler, C. B.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1995**, *117*, 5105. (k) Chari, S. L.; Chiang, S.-H.; Jones, M., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 3138.

(6) Soloway, A. H.; Tjarks, W.; Barnum, A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515.

(7) (a) Yanch, J. C.; Shortkroff, S.; Shefer, R. E.; Johnson, S.; Binello, E.; Gierga, D.; Jones, A. G.; Young, G.; Vivieros, C.; Davison, A.; Sledge, C. *Med. Phys.* **1999**, *26*, 364. (b) Watson-Clark, R. A.; Banquerigo, M. L.; Shelly, K.; Hawthorne, M. F.; Brahn, E. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 2531.

(8) Kasar, R. A.; Knudsen, G. M.; Kahl, S. B. *Inorg. Chem.* **1999**, *38*, 2936.

(9) (a) Imahori, Y.; Ueda, S.; Ohmori, Y.; Sakae, K.; Kusuki, T.; Kobayashi, T.; Takagaki, M.; Ono, K.; Ido, T.; Fujii, R. *Clin. Cancer Res.* **1998**, *4*, 1825. (b) Ishiwata, K.; Shiono, M.; Kubota, K.; Yoshino, K.; Hatazawa, J.; Ido, T.; Honda, C.; Ichihashi, M.; Mishima, Y. *Melanoma Res.* **1992**, *2*, 171. (c) Kabalka, G. W.; Smith, G. T.; Dyke, J. P.; Reid, W. S.; Longford, C. P. D.; Roberts, T. G.; Reddy, N. K.; Buonocore, E.; Hubner, K. F. *J. Nucl. Med.* **1997**, *38*, 1762.

(10) Dilworth, J. R.; Parrott, S. J. *Chem. Soc. Rev.* **1998**, *27*, 43.

(11) Wellum, G. R.; Tolpin, E. I.; Andersen, L. P.; Sneath, R. *J. Chromatogr.* **1975**, *103*, 153.

(12) *SMART*, version 4.05; Siemens Energy and Automotive Analytical Instrumentation: Madison, WI, 53719, 1999.

(13) *SAINT*, version 4.05; Siemens Energy and Automotive Analytical Instrumentation: Madison, WI, 53719, 1996.

(14) Sheldrick, G. M. *SHELXTL*, Release 5.03; Siemens Crystallographic Research Systems: Madison, WI, 53719, 1994.

(15) Abrams, M. J.; Juweid, M.; tenKate, C. I.; Schwartz, D. A.; Hauser, M. M.; Gaul, F. E.; Fuccello, A. J.; Rubin, R. H.; Strauss, H. W.; Fischman, A. J. *J. Nucl. Med.* **1990**, *31*, 2022.

Table 1. Crystallographic Data for Compounds **3** and **8**

	compound **3**	compound **8**
empirical formula	$C_{13}H_{30}B_{10}N_2O_6$	$C_{12}H_{30}B_{10}N_2O_4$
fw	418.49	374.48
T	173(2) K	173(2) K
wavelength	0.71073 Å	0.71073 Å
cryst syst	orthorhombic	monoclinic
space group	$P2_12_12_1$	*Cc*
unit cell dimensions	$a = 12.744(10)$ Å	$a = 21.213(6)$ Å
	$b = 12.875(9)$ Å	$b = 10.498(3)$ Å
	$c = 14.767(9)$ Å	$c = 9.866(2)$ Å
	$\alpha = 90°$	$\alpha = 90°$
	$\beta = 90°$	$\beta = 90.529(4)°$
	$\gamma = 90°$	$\gamma = 90°$
V	2423(3) Å^3	2197.0(10) Å^3
Z	4	4
D(calcd)	1.147 Mg/m^3	1.132 Mg/m^3
abs coeff	0.077 mm^{-1}	0.071 mm^{-1}
F(000)	880	792
cryst size	0.22 × 0.05 × 0.03 mm^3	0.06 × 0.18 × 0.30 mm^3
θ range for data collection	2.10−22.99°	1.92−27.47°
index ranges	$-14 \le h \le 13$, $-14 \le k \le 14$, $-16 \le l \le 16$	$-27 \le h \le 27$, $-13 \le k \le 12$, $-12 \le l \le 12$
reflns collected	15460	9224
independent reflns	3373 [*R*(int) = 0.1314]	4119 [*R*(int) = 0.0331]
completeness to θ	22.99° 100.0%	27.47° 99.1%
abs correction	empirical	empirical
refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
data/restraints/params	3373/0/329	4119/9/288
GOF on F^2	1.046	1.093
final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0714, wR2 = 0.1000	R1 = 0.0768, wR2 = 0.2116
R indices (all data)	R1 = 0.1207, wR2 = 0.1125	R1 = 0.0890, wR2 = 0.2196
absolute structure param	3.5(18)	−1.3(19)
extinction coeff	0.0031(6)	0.0035(10)
largest diff peak and hole	0.175 and −0.207 e·Å^{-3}	0.303 and −0.258 e·Å^{-3}

dropwise to a solution of di-*tert*-butyl azodicarboxylate (DBAD) (0.154 g, 0.67 mmol) in ether (3 mL) under argon. The reaction was stirred for 2.5 h at room temperature whereupon the solvent was removed by rotary evaporation leaving a white solid. Distilled water (10 mL) was added and the solution acidified through the dropwise addition of 1 M HCl (pH = 5). The heterogeneous solution was extracted with ethyl acetate (3 × 10 mL), the organic layers were combined and dried over $MgSO_4$, and the solvent was removed by rotary evaporation affording a white solid. The product was purified by silica gel chromatography (gradient elution; 100% petroleum ether to 50% diethyl ether in petroleum ether; 5% intervals) and by recrystalization from petroleum ether affording a fine white powder (0.207 g, 91%). TLC R_f (1:9 ether/pet. ether) = 0.55; mp 153−155 °C; ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.294, 1.330, 1.364, 1.932 (s, CH_3), 1.30−2.90 (b, BH), 3.276, 3.446 (bs, CH), 7.752, 8.192 (bs, NH); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 27.32, 27.69 (CH_3), 57.93 (CH), 80.12, 80.65, 82.02 ($C(CH_3)_3$), 97.0 (CN), 151.47 (NCO), 154.53 (NHCO); ^{11}B{^{1}H} NMR (acetone-d_6, 96.3 MHz) δ −12.02, −16.41; IR (KBr, cm^{-1}) 3321, 2982, 2934, 2630, 1743, 1726; MS/ESI 373.3 [M − H]$^-$ with the expected isotopic distribution. Anal. Calcd for $C_{12}B_{10}H_{30}N_2O_4$: C, 38.49; H, 8.07; N, 7.48. Found: C, 39.92; H, 8.11; N, 8.17.

Synthesis of 1-[(*N*,*N*′((*tert*-Butyloxy)carbonyl)hydrazino)]-1,12-dicarba-*closo*-dodecaborane-12-carboxylic Acid, 3. *n*-BuLi (0.35 mL, 0.57 mmol; 1.6 M in hexanes) was added dropwise to compound **2** (0.090 g, 0.246 mmol) dissolved in ether (8 mL), which had been cooled to 0 °C. The reaction, which became heterogeneous, was permitted to proceed for 2 h at 0 °C, whereupon the temperature was lowered to −78 °C and THF (2 mL) added to solubilize the precipitate. CO_2 was bubbled into the solution for 2 h after which the mixture was permitted to warm to room temperature and the solvent removed under vacuum. Distilled water (5 mL) was added and the pH adjusted to between 3 and 4 using HCl (1.0 M). The resulting precipitate was extracted into ethyl acetate (3 × 10 mL), and the organic layers were combined, dried over anhydrous $MgSO_4$(s), and evaporated leaving a yellow oil. The oil was suspended in petroleum ether affording a white crystalline powder, which was collected by filtration and further washed with petroleum ether (5 × 10 mL). The product was purified by silica gel chromatography (100% CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2) and isolated as a white crystalline solid (95 mg, 92%). TLC R_f (1:4 CH_3OH/CH_2Cl_2) = 0.65; mp 180 °C (decomp); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.226, 1.262, 1.303 (s, CH_3), 1.005−3.330 (b, BH), 8.735, 9.127 (bs, NH); ^{13}C NMR (DMSO-d_6, 125.77 MHz) δ 27.43, 27.70, 27.93 (CH_3), 75.47 (CCO_2H), 79.89, 80.12, 82.04 ($C(CH_3)_3$), 94.02 (CN), 150.80, 151.04 (BocC(O)), 153.92, 154.23 (BocC(O)), 163.14 (CO_2H); ^{11}B{^{1}H} NMR (DMSO-d_6, 96.3 MHz) δ −13.20, −15.74 (broad multiplet); IR (KBr, cm^{-1}) 3408, 3309, 2621, 1722, 1630; MS/ESI 417.3 [M − H]$^-$, 373.3 [M − CO_2H] $^-$ with the expected isotopic distribution. Anal. Calcd for $C_{13}H_{30}B_{10}N_2O_6$: C, 37.31; H, 7.23; N, 6.69. Found: C, 36.88; H, 7.06; N, 6.23.

One Pot Synthesis of 3. MeLi (4.98 mL, 6.93 mmol, 1.4 M in diethyl ether) was added dropwise over 5 min to a solution of 1,12-dicarba-*closo*-dodecaborane (1.00 g, 6.93 mmol) in ether (125 mL) cooled to 0 °C under an argon atmosphere. After stirring for 45 min, the solution was added dropwise over 15 min to a solution of DBAD (1.59 g, 6.93 mmol) in ether (100 mL). The reaction was permitted to warm to room temperature and stirred under an inert atmosphere for an additional 2.5 h. The reaction was again cooled to 0 °C and *n*-BuLi (4.33 mL, 6.93 mmol, 1.6 M in hexanes) added dropwise. After 45 min, approximately 75 mL of ether was evaporated from the reaction vessel (vacuum) and replaced with dry THF (75 mL). The solution was cooled to −72 °C and CO_2 bubbled into the stirring solution for 3 h. The heterogeneous solution was permitted to warm to room temperature and the solvent removed by rotary evaporation. Distilled water (100 mL) was added and the solution acidified with HCl (1.0 M) to ∼pH = 3. The resulting precipitate was extracted into ethyl acetate (3 × 100 mL), and the organic layers were combined, dried over $MgSO_4$, and evaporated leaving a yellow oil. The oil was suspended in petroleum ether (100 mL) and the resulting precipitate collected by filtration and washed with petroleum ether (4 × 100 mL). After silica gel chromatography (gradient elution: 100% CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2), the major fraction, a clear colorless oil, was again suspended in petroleum ether (100 mL) and the resulting precipitate washed with petroleum ether (4 × 100 mL) affording the product as a white crystalline solid (2.44 g, 84%).

Synthesis of 1-Hydrazino-12-hydroxycarbonyl-1,12-dicarba-*closo*-dodecaborane, 4. A 1:1 (v/v) mixture of triisopropylsilane and H_2O (1 mL) was added to compound **3** (0.47 g, 1.14 mmol) under nitrogen at room temperature followed by the gradual addition of TFA (19 mL) with stirring. The reaction proceeded for 4 h at which time the solvent was removed under reduced pressure yielding a clear oily residue. The residue was redissolved in a solution of 0.1% TFA in H_2O (50 mL) and lyophilized at −50 °C yielding a fine white powder (0.375 g, >99%). TLC R_f (3:7 CH_3OH/CH_2Cl_2) = 0.56; mp 153−154 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.9−3.5 (b, BH), 6.00−8.30 (b, NH); ^{13}C NMR (DMSO-d_6,

125.77 MHz) δ 73.71 (CCO_2H), 98.65 (CNH), 168.46 (CO_2H); IR (KBr, cm^{-1}) 3660, 3243, 2960, 2612, 1712, 1665, 1299; MS/ESI 219.4 $[M + H]^+$ with the expected isotopic distribution.

Synthesis of 1-[(*N*,*N*′((*tert*-Butyloxy)carbonyl)hydrazino)]-1,7-dicarba-*closo*-dodecaborane, 5. *n*-BuLi (5.00 mL, 6.93 mmol; 1.39 M in hexanes) was added to 1,7-dicarba-*closo*-dodecaborane (1.00 g, 6.93 mmol) in dry diethyl ether (125 mL) at 0 °C under argon. After 45 min, the solution containing the anion was added slowly to DBAD (3.19 g, 13.86 mmol) in dry diethyl ether (100 mL). The reaction was subsequently heated under reflux for 2.5 h whereupon it was cooled to room temperature and quenched by the addition of water (10 mL). Diethyl ether was removed under reduced pressure and the mixture extracted with ethyl acetate (100 mL), which in turn was washed with water (1 × 100 mL), 0.1 M HCl (2 × 100 mL), and brine (2 × 100 mL). The organic layers were combined and dried over $MgSO_4$, and the solvent was concentrated under reduced pressure. The product, an amorphous white solid (1.94 g, 75%), was further purified by silica gel chromatography (gradient elution; from petroleum ether to 1:9 ethyl acetate/petroleum ether). TLC R_f (1:9 ethyl acetate/pet. ether) = 0.36; mp 143−144 °C; ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.242, 1.280 (s, CH_3), 1.198−2.87 (b, BH), 3.541, 4.445 (bs, CH), 8.056, 8.503 (bs, NH); ^{13}C NMR (acetone-d_6, 125.77 MHz) δ 27.22, 27.57 (CH_3), 53.12 (CH), 80.22, 80.78, 82.30, 82.51 ($C(CH_3)_3$), 89.37 (CN), 151.70, 151.87 (BocC(O)), 154.25, 154.50 (BocC(O)); ^{11}B{^{1}H} NMR (acetone-d_6, 96.3 MHz) δ −4.79, −11.27, −12.97, −15.68; IR (KBr) 3317, 3061, 2972, 2607, 1739, 1722.1; MS/ESI 373.3 $[M - H]^{-1}$. Anal. Calcd for $C_{12}B_{10}H_{30}N_2O_4$: C, 38.49; H, 8.07; N, 7.48. Found: C, 38.91; H, 8.42; N, 7.47.

Synthesis of 1-[(*N*,*N*′((*tert*-Butyloxy)carbonyl)hydrazino)]-1,7-dicarba-*closo*-dodecaborane-7-carboxylic Acid, 6. *n*-BuLi (1.75 mL, 2.80 mmol) was added dropwise over a period of 5 min to **5** (0.50 g, 1.34 mmol) in dry THF (100 mL) under argon at 0 °C for 45 min. The temperature of the reaction was subsequently lowered to −78 °C, and dry CO_2(g) was bubbled into the solution with rigorous stirring. After 3.5 h, the reaction was allowed to warm to room temperature and acidified with 1 M HCl (pH = 3). The solvent was removed under reduced pressure and the yellowish residue redissolved in ethyl acetate (50 mL) and extracted with brine (3 × 50 mL). The organic phase was dried over $MgSO_4$ and evaporated to dryness. The resulting yellow oil was further purified by flash chromatography through silica gel (gradient elution; from CH_2Cl_2 to 5:95 CH_3OH/CH_2Cl_2) yielding an amorphous solid (0.41 g, 73%). TLC R_f (1:4 CH_3OH/CH_2Cl_2) = 0.57; mp 156−159 °C; ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.353, 1.391, 1.430 (s, CH_3), 0.95−4.25 (b, BH), 8.064, 8.507 (bs, NH); ^{13}C NMR (acetone-d_6, 125.77 MHz) δ 27.21, 27.55 (CH_3), 70.12 (CCO_2H), 80.45, 81.09, 82.66, 82.84 ($C(CH_3)_3$), 89.12 (CN), 151.81, 154.52 (BocC(O)), 161.80 (CO_2H); ^{11}B{^{1}H} NMR (acetone-d_6, 96.3 MHz) δ −4.36, −8.90, −10.52, −12.76; IR (KBr) 3317, 3185, 2986, 2939, 2617, 1753, 1721; MS/ESI 373.3 $[M - H]^-$, 835.5 $[2M - H]^-$. Anal. Calcd for $C_{13}B_{10}H_{30}N_2O_6$: C, 37.31; H, 7.23; N, 6.69. Found: C, 36.96; H, 7.61; N, 6.20.

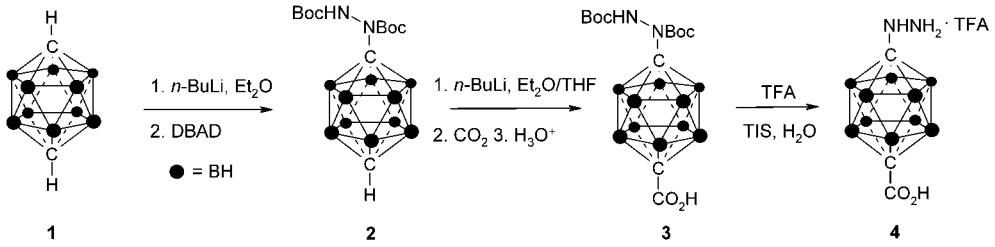
Synthesis of 1-[(*N*,*N*′((*tert*-Butyloxy)carbonyl)hydrazino)]-1,2-dicarba-*closo*-dodecaborane, 8. MeLi (4.70 mL, 6.53 mmol, 1.39 M in diethyl ether) was added dropwise over 5 min to a solution of 1,2-dicarba-*closo*-dodecaborane (1.00 g, 6.93 mmol) in ether (125 mL) at 0 °C. The reaction was maintained at 0 °C for an additional 45 min, at which time the solution was added dropwise over 15 min to a solution of DBAD (4.00 g, 17.37 mmol) in ether (100 mL) under argon atmosphere. After the complete addition of the carborane, the reaction heated to reflux for 2.5 h, at which point the reaction was quenched with the addition of water (100 mL). The solvent was removed by rotary evaporation and the resulting solution acidified through dropwise addition of HCl (1.0 M) affording a white precipitate. The solution was extracted with ethyl acetate (3 × 100 mL), the organic layers were combined and dried over $MgSO_4$, and the solvent was removed by rotary evaporation. Residual water was removed by the addition and subsequent evaporation of 9:1 $CHCl_3$/toluene mixtures (5 × 50 mL). Excess DBAD was removed by triturating the yellow solid with cold pentane (5 × 50 mL), leaving a colorless solid, which was further purified by silica gel chromatography (gradient elution; 100% hexanes to 1:3 diethyl ether/hexanes). The main product isolated from the column was recrystallized from petroleum ether affording a white solid (2.01 g, 84%). TLC R_f (1:5 diethyl ether/pet. ether) = 0.38; mp 171−174 °C (decomp); ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.391, 1.422 (s, CH_3), 0.91−3.1 (b, BH), 5.084, 5.233 (bs, CH), 8.241, 8.808 (bs, NH); ^{13}C NMR (acetone-d_6, 125.77 MHz) δ 27.08, 27.46 (CH_3), 63.86 (CH), 81.12, 83.80 ($C(CH_3)_3$), 87.44 (CN), 151.69 (NCO), 155.01 (NHCO); ^{11}B{^{1}H} NMR ($CDCl_3$, 96.3 MHz) δ −3.51, −5.00, −7.43, −11.03, −12.66, −15.05; IR (KBr, cm^{-1}) 3321, 3077, 2612, 1754, 1719; MS/ESI 373.3 $[M - H]^-$ with the expected isotopic distribution. Anal. Calcd for $C_{12}B_{10}H_{30}N_2O_4$: C, 38.49; H, 8.07; N, 7.48. Found: C, 38.10; H, 8.12; N, 7.40.

Synthesis of 1-[(*N*,*N*′((*tert*-Butyloxy)carbonyl)hydrazino)]-1,2-dicarba-*closo*-dodecaborane-2-carboxylic Acid, 9. *n*-BuLi (1.75 mL, 2.80 mmol, 1.6 M in hexanes) was added dropwise over a period of 5 min to a solution of compound **8** (0.50 g, 1.34 mmol) in 5:1 THF/ether (60 mL) at 0 °C. After 45 min, the temperature was lowered to −78 °C and CO_2 bubbled into the solution for 3.5 h. The temperature was allowed to warm to room temperature and the solvent removed in vacuo. Water (50 mL) was added and the solution acidified by dropwise addition of HCl (1.0 M) until a precipitate appeared (pH = 3). The solution was extracted with ethyl acetate (3 × 50 mL), and the organic layers were combined, dried over $MgSO_4$, and evaporated leaving a colorless oil. Suspension of the oil in a 4:1 mixture of pentane/ether afforded a white precipitate, which was washed with the pentane/ether mixture (4 × 50 mL) leaving the product as a white solid (371 mg, 65%). TLC R_f (1:9 CH_3OH/CH_2Cl_2) = 0.14; mp 131 °C (decomp); ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.438, 1.472 (s, CH_3), 1.220−2.810 (b, BH), 8.335, 8.904 (s, NH); ^{13}C NMR (acetone-d_6 + 2 drops of DMSO-d_6, 50.3 MHz) δ 27.50, 27.80, 27.95 (CH_3), 63.57, 64.76 (CCO_2H), 80.90, 81.16, 83.79 ($C(CH_3)_3$), 87.83 (CN), 151.74 (BocC(O)), 154.00 (CO_2H), 155.04 (BocC(O)); ^{11}B{^{1}H} NMR (acetone-d_6, 96.3 MHz) δ −3.58, −6.20, −11.05, −13.49; IR (KBr) 3380, 2578, 1713, 1650. MS/ESI: 835.5 $[2M - H]^-$, 417.3 $[M - H]^-$, 408.4 $[M - B]^-$, 373 $[M - CO_2H]^-$ with the expected isotopic distribution. Anal. Calcd for $C_{13}H_{30}B_{10}N_2O_6$: C, 37.31; H, 7.23. Found: C, 34.33; H, 7.59.

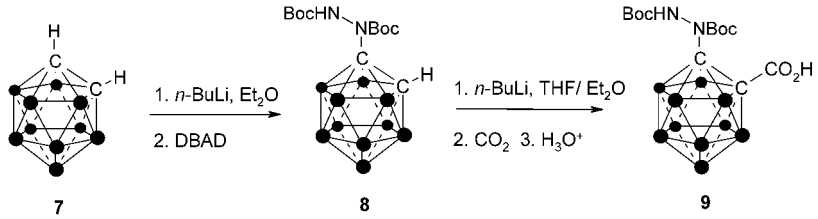
Results and Discussion

Synthesis and Characterization. We report herein a general and robust method for the preparation of *C*-hydrazino-*C*-carboxycarboranes from *ortho*-, *meta*-, and *para*-carborane (Schemes 1 and 2). In addition to being able to be linked to biomolecules, the reported compounds have the capacity to bind ^{99m}Tc because they are analogues of the hydrazinonicotinamide (HYNIC) ligand,[15] which has been used extensively to prepare technetium radiopharmaceuticals.[16] It should also be possible to label these unique synthons with ^{18}F, a common isotope used in PET, by converting the hydrazine group to a diazonium ion.[17]

Scheme 1



Scheme 2



The *para*-carborane hydrazine derivative, **2** (Scheme 1), was prepared by deprotonation of the appropriate carborane with *n*-BuLi at 0 °C followed by adding the solution of the anion to an ethereal solution of di-*tert*-butyl azodicarboxylate (DBAD).[18] Acid work up, followed by chromatographic purification, resulted in the isolation of the protected hydrazine, **2**, in excellent yield (91%). IR of the product clearly indicated the presence of the Boc groups (ν_{CO} = 1743, 1726 cm^{-1}) and the carborane BH vertices (ν_{BH} = 2630 cm^{-1}). The ^{11}B NMR, which exhibited a pair of doublets, is consistent with the proposed structure, while the electrospray mass spectrum exhibited the expected *m*/*z* values and isotopic distributions.

The addition of 2 equiv of *n*-BuLi to **2** resulted in the deprotonation of the remaining carborane CH group, and subsequent treatment with dry CO_2 resulted, after mild acidic workup, in the formation of **3**. Any reaction at the deprotonated amide would result in the formation of a carbamic acid, which would readily decompose, to give the desired product, upon workup. The electrospray mass spectrum of the main reaction product exhibited the *m*/*z* value and isotopic distribution expected for **3** while the ^{13}C spectrum clearly indicated the presence of three carbonyl groups, corresponding to the two carbamates and one carboxylic acid.

Compound **3** was also prepared in a one-pot procedure, by reacting the monoanion of *para*-carborane with DBAD followed by the addition of another equivalent of base and excess CO_2. It was necessary in this procedure to add some dry THF to help solubilize the lithium salt of **2**, which is only sparingly soluble in ether at low temperatures (−72 °C). Using the one-pot procedure, compound **3** was isolated in 84% yield, which is comparable to the overall yield for the two-step procedure.

The procedure used to prepare **3** was repeated using *meta*-carborane, and as expected, 1,7-*C*-hydrazino-*C*-carboxycarborane was isolated in reasonable overall yield (55%). The synthesis of the *ortho*-carborane analogue, however, was particularly challenging because of the tendency of the monolithio *ortho*-carborane to disproportionate to *ortho*-carborane and its dianion,[19] which, in the reaction with DBAD, led to the formation of the disubstituted carborane. By maintaining the concentration of the reaction below 0.1 M,[20] the monosubstituted product (**8**, Scheme 2) was isolated preferentially in 84% yield. Again, the acid was prepared by deprotonation of **8** followed by treatment with CO_2. The carboxylation step involving *ortho*-carborane was lower yielding (65%) than for the other carborane isomers, which may be a consequence of steric hindrance issues. In addition, unlike the corresponding *meta* and *para* derivatives, compound **9** showed signs of degradation when left in solution. Initially, we felt that the decomposition was a result of the conversion of the *ortho*-carborane cage to the corresponding *nido* cluster, which has been shown to occur readily for other C-substituted *ortho*-carborane derivatives bearing electron-withdrawing substituents located α to the cage.[21] Closer analysis (NMR, MS, and TLC) indicated, however, that the compound was in fact decarboxylating. Loss of the carboxylic acid, which has been observed for other *ortho*-carboranyl acids,[19b] was much more rapid in DMSO than in acetone.

Removal of the carbamate protecting groups in the stable *meta* and *para* derivatives was readily accomplished through treatment of the appropriate carborane with trifluoroacetic acid (TFA), triisopropylsilane (TIS), and water or with TMSCl and phenol.[22] Using the former procedure, compound

(16) (a) Babich, J. W.; Solomon, H.; Pike, M. C.; Kroon, D.; Graham, W.; Abrams, M. J.; Tompkins, R. G.; Rubin, R. H.; Fischman, A. J. *J. Nucl. Med.* **1993**, *34*, 1964. (b) Bangard, M.; Behe, M.; Bender, H.; Guhlke, S.; Risse, J.; Grünwald, F.; Mäcke, H.; Biersack, H. *Eur. J. Nucl. Med.* **1998**, *25*, 837. (c) Liu, S.; Edwards, D. S.; Harris, A. R. *Bioconjugate Chem.* **1998**, *9*, 583.

(17) (a) Brown, F. C.; Bradsher, C. K.; Moser, B. F.; Forrester, S. *J. Org. Chem.* **1959**, *24*, 1056. (b) Frahn, J. L.; Illman, R. J. *Aust. J. Chem.* **1974**, *27*, 1361. (c) Popova, L. M.; Trishna, A. U.; Vershilov, S. V.; Ginak, A. I.; Maksimov, B. N. *J. Fluorine Chem.* **1999**, *96*, 51.

(18) (a) Zhang, L.; Tan, Z. *Tetrahedron Lett.* **2000**, *41*, 3025. (b) Demers, J. P.; Klaubert, D. H. *Tetrahedron Lett.* **1987**, *28*, 4933.

(19) (a) Zakharkin, L. I.; Grebennikov, A. V.; Kazantsev, A. V. *Izv. Akad. Nauk., Ser. Khim.* **1967**, *9*, 2077. (b) Grimes, R. N. *Carboranes*; Academic Press: New York, 1970.

(20) Nakamura, H.; Aoyagi, K.; Yamamoto, Y. *J. Organomet. Chem.* **1999**, *574*, 107.

(21) Schaeck, J. J.; Kahl, S. B. *Inorg. Chem.* **1999**, *38*, 204.

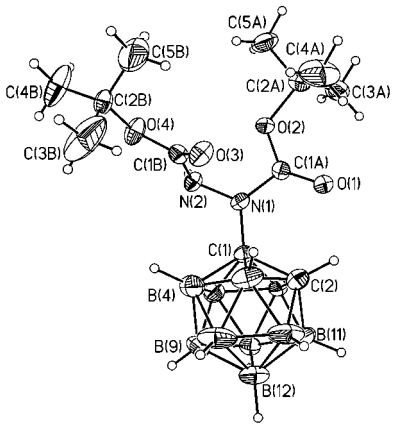


Figure 1. X-ray crystal structure of **8**. Thermal probability ellipsoids are drawn at the 50% probability level.

Table 2. Selected Bond Distances (Å) for Compounds **3** and **8**

bond	**3**	**8**	bond	**3**	**8**
N(1)−N(2)	1.374(5)	1.387(5)	C(2)−B(7)		1.752(9)
N(1)−C(1)	1.445(6)	1.441(5)	C(2)−B(11)		1.706(8)
N(1)−C(1A)	1.394(6)	1.409(5)	C(13)−O(5)	1.205(5)	
N(2)−C(1B)	1.351(5)	1.395(5)	C(13)−O(6)	1.315(5)	
C(1)−C(2)		1.668(6)	C(12)−B(7)	1.711(6)	
C(1)−B(3)	1.727(7)	1.728(6)	C(12)−B(8)	1.729(7)	
C(1)−B(4)	1.714(7)	1.737(7)	C(12)−B(9)	1.722(7)	
C(1)−B(5)	1.734(6)	1.704(6)	C(12)−B(10)	1.707(7)	
C(1)−B(6)	1.709(8)	1.729(6)	C(12)−B(11)	1.688(8)	
C(2)−B(3)		1.708(8)	C(12)−C(13)	1.512(6)	
C(2)−B(6)		1.753(8)			

Table 3. Selected Bond Angles (deg) for Compounds **3** and **8**

angle	**3**	**8**
N(2)−N(1)−C(1A)	118.9(4)	119.5(3)
C(1A)−N(1)−C(1)	123.3(4)	124.3(3)
O(1)−C(1A)−O(2)	126.9(4)	127.2(4)
N(1)−C(1)−C(2)		120.4(3)
N(2)−N(1)−C(1)	115.8(4)	116.1(3)
N(1)−N(2)−C(1B)	118.3(4)	117.1(3)
O(1)−C(1A)−N(1)	124.0(5)	123.4(4)
C(2)−C(1)−B(6)		62.1(3)
B(11)−C(12)−B(7)	63.4(4)	
O(5)−C(13)−O(6)	124.1(5)	
O(6)−C(13)−C(12)	112.8(4)	

4, for example, was isolated as the TFA salt in nearly quantitative yield. Our choice of Boc as the protecting group was done to facilitate the process of linking the bifunctional synthons to resin-bound targeting agents (peptides, carbohydrates, etc.), via the acid group, and to allow for simultaneous liberation of the hydrazine group and cleavage of conjugates from acid labile resin-linker systems.[23]

Single-Crystal X-ray Analysis. Single crystals of compound **8** were obtained by slow evaporation of a $CDCl_3$ solution. The structure (Figure 1) is a distorted icosahedron in which the B−B bond lengths (average distance = 1.777(14) Å, range = 1.741(9) Å to 1.804 Å) and C−B bond lengths (average distance = 1.727(2) Å, range = 1.704(6) Å to 1.753(8) Å) are within expected values (Tables 2 and 3). Identification of the carbon atoms in the cage was achieved by noting the shorter C−C bond length (1.668(6) Å) relative to the elongated B−B bond distances. The N−N distance in **8** was unexceptional at 1.387(5) Å. In the packing of **8**, intermolecular H-bonding played a significant role in formation of the crystal lattice. Adjacent molecules along the *C*-axis pack such that the carbamate moieties align in a single direction. This motif arises as a consequence of an intermolecular H-bond, which forms between the carbamate N−H and a carbonyl oxygen atom on an adjacent molecule.

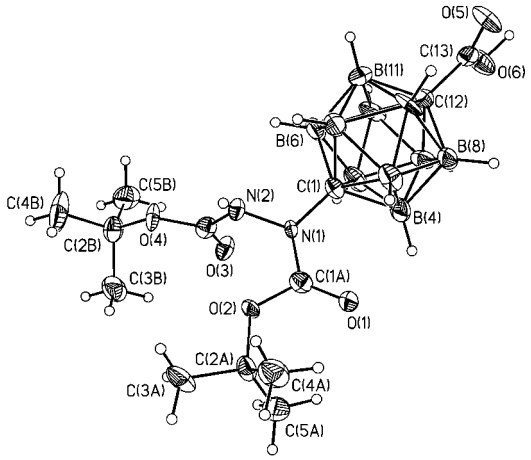


Figure 2. X-ray crystal structure of **3**. Thermal probability ellipsoids are drawn at the 50% probability level.

Single crystals of compound **3** were grown at room temperature from a mixture of 1:5 CH_3OH/CH_2Cl_2, and the structure is shown in Figure 2. Compound **3** was also a slightly distorted icosahedron having typical B−B bond lengths (average = 1.759(19) Å), ranging between 1.722(8) and 1.769(9) Å. The average C−B bond length for compound **3** was 1.719(16) Å, with a range 1.688(8)−1.734(6) Å. The N−N bond distance was 1.374(5) Å.

In the solid-state packing of compound **3**, intermolecular H-bonding was the dominant factor in directing the molecules to orient themselves in a helical sense in the unit cell. Because of this, compound **3**, an achiral molecule, packed in a chiral space group ($P2_12_12_1$) where the carboxylic acid group from one molecule was hydrogen bound to the carbamate NH of an adjacent molecule. The hydrophilic groups, which orient themselves at opposite ends of the pseudospherical carborane cage, mask the intermolecular cage interactions, which also play a role in the crystal packing of compound **8**. Alternating layers of carborane cages and carbamate groups form the backbone of the crystal lattice.

NMR Spectroscopy. The protected carborane derivatives exhibited surprisingly complex ^{1}H and ^{13}C NMR spectra. We determined that for each of the Boc protected compounds there were two predominant species that were observable on the NMR time scale at room temperature. There were, for example, two distinct ^{1}H resonances corresponding to the NH group in each of the reported compounds. These signals were assigned using HMBC experiments by noting correlations to the adjacent carbamate carbonyl group. Interestingly, despite the fact that resonances arising from the COOH group were clearly visible in the ^{13}C spectra of **3**, **6**, and **9**, we could not observe the carboxylic acid protons in the corresponding ^{1}H NMR spectra in either acetone or

(22) Kaiser, E., Sr.; Tam, J. P.; Kubiak, T. M.; Merrifield, R. B. *Tetrahedron Lett.* **1988**, *29*, 303.
(23) Wang, S.-S. *J. Am. Chem. Soc.* **1973**, *95*, 1328.

DMSO. Multiple resonances associated with the carbamate C(O) groups and especially the *tert*-butyl groups (both C and CH_3) were clearly visible in the ^{13}C NMR spectra of **2**, **3**, **5**, **6**, **8**, and **9**. These resonances were readily assigned again through HMBC and HSQC experiments.

It has been reported that exchange about the N−C(O) bonds (i.e., the cis and *trans* forms) in carbamates containing bulky substituents, like a carborane, can be observed on the NMR time scale.[24] Exchange in carbamates, unless there is a bulky substituent present, is typically a lower energy process compared to that for amides because of the reduced C−N bond order arising from the interaction of the carbonyl oxygen with the substituted oxygen atom.[25] The ^1H NMR of the deprotected carborane derivatives exhibited much simpler spectra, which corroborates our proposal that hindered rotation about the carbamate C−N bonds is most likely the source of the complexities observed in the NMR spectra of the reported compounds.

Concluding Remarks

Three *C*-hydrazino-*C*-carboxycarboranes were prepared in good-to-excellent overall yield using a novel synthetic strategy. Unlike the corresponding *meta* and *para* derivatives, the bifunctional *ortho*-carborane derivative **9** decomposed in solution via the loss of a carboxyl group. Notwithstanding, we are currently in the process of determining the ability of the hydrazine carboranes to coordinate to technetium and rhenium in addition to evaluating the optimal conditions for coupling the bifunctional derivatives to biomolecules having specificity for receptors found on tumors and inflamed synovial cells. Results of these studies will be reported in due course.

Acknowledgment. We would like to thank the National Sciences and Engineering Research Council (NSERC) of Canada for their financial support of this work.

Supporting Information Available: Relevant spectral data for compounds **2**, **3**, **5**, **6**, **8**, and **9** and crystallographic data for compounds **3** and **8** (tables of crystallographic details, non-hydrogen coordinates, bond distances and angles, anisotropic displacement parameters, hydrogen coordinates, and packing diagrams). This material is available free of charge via the Internet at http://pubs.acs.org.

IC0255048

(24) Rogers, M. T.; Woodbrey, J. C. *J. Phys. Chem.* **1962**, *66*, 540.
(25) Barker, R. H.; Vail, S. L.; Boudreaux, G. J. *J. Phys. Chem.* **1967**, *71*, 2228.