Synthesis of Carboranyl Amino Acids, Hydantoins, and Barbiturates

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Received August 24, 1995[⊗]

The syntheses of three novel boronated hydantoins, 5-(*o*-carboran-1-ylmethyl)hydantoin, **14**, the tetraphenylphosphonium salt of 7-(hydantoin-5-ylmethyl)dodecahydro-7,8-dicarba-*nido*-undecaborate, **15**, 5-(*o*-carboran-1-ylmethyl)-2-thiohydantoin, **16**, and two new barbiturates, 5,5-bis(but-2-ynyl)barbiturate, **18**, and 5,5-bis[(2-methyl-*o*-carboran-1-yl)methyl]barbiturate, **20**, are described. Hydantoins **14**−**16** were synthesized from *o*-carboranylalanine (Car, **13**). The detailed syntheses of Car and two other carborane-containing amino acids, *O*-(*o*-carboran-1-ylmethyl)tyrosine (CBT, **5a**) and *p*-(*o*-carboran-1-yl)phenylalanine (CBPA, **5b**), presented earlier as a communication,[16] are also described. Hydantoin **14** and barbiturates **18** and **20** were tested for their potential anticonvulsant activity. Initial qualitative screening showed moderate activities for hydantoin **14** and barbiturate **18**. Barbiturate **20** had no activity. Compound **14** appeared to be nontoxic at doses of 300 mg/kg (mice, ip) and 50 mg/kg (rats, oral). However, **18** was very toxic under similar conditions.

Introduction

o-, *m*-, and *p*-carboranes are slightly distorted icosahedral structures that consist of ten boron atoms and two carbon atoms; the latter are in either the 1,2- (*o*), 1,7- (*m*), or 1,12- (*p*) positions.[1] They are highly lipophilic (i.e., the hydrophobic parameter, π, for *o*-carborane is $+4.20$[2]) with an extraordinary chemical and thermal stability. It is possible to carry out a variety of chemical reactions on the C-substituents of carboranes without degrading the cage. Many carborane-containing compounds have been synthesized but little is known about their toxicity or metabolic fate. However, LD_{50} values of 1400 mg/kg (oral, rats) and 1000 mg/kg (subcutaneous, mice) for *m*-carborane indicate a generally low toxicity for the boron cluster itself.[3] Despite the large number of carborane-containing compounds that have been synthesized, their medical use, with only few exceptions,[4] has been largely limited to their potential as boron neutron capture therapy (BNCT) agents.[5] Leukart et al.[6] recognized that the volume of the *o*-carborane cage was only slightly larger than the volume occupied by a phenyl ring, rotating about its C_1-C_4 axis. Therefore, they synthesized L-*o*-carboranylalanine (L-Car)[6] to replace phenylalanine in biologically-active peptides. L-Car was used to replace aromatic residues in tripeptide inhibitors of α-chymotrypsin[7] and in [Leu[5]]-enkephalin.[8] Studies showed that Car may bind to the hydrophobic Phe recognition site of α-chymotrypsin to give a strongly inhibitory tripeptide and to the opiate receptors in rat brain extracts in which [Car[4],Leu[5]]-enkephalin showed an affinity 3 times higher than the natural peptide [Leu[5]]-enkephalin.[7,8] Carboranyl analogues of angiotensin II ([Sar[1],Car[8]]AT and des-Arg[9]-bradykinin ([Car[5]]-des-Arg[9]-bradykinin) showed a decreased activity but significantly prolonged duration of action compared with their phenylalanine-containing counterparts.[9,10] The authors assumed that the prolonged duration of action was related to the enhanced lipophilicity of the peptides containing the hydrophobic carborane cage. These results led to more useful syntheses of *o*-carboranylalanine as the D- and L-forms,[11−14] L-form,[15] and the racemic mixture.[16] The detailed synthesis of Car **13** and two other carborane-containing amino acids, *O*-(*o*-carboran-1-ylmethyl)tyrosine (CBT, **5a**) and *p*-(*o*-carboran-1-yl)phenylalanine[17] (CBPA, **5b**), presented earlier as a communication,[16] are described in this paper.

Aryl-containing hydantoins and barbiturates have been widely used as anticonvulsant drugs. However, toxicological studies revealed important side effects, e.g. teratogenicity and hypersensitivity, stemming from the formation of highly reactive metabolic intermediates, such as arene oxides.[18,19] Replacement

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1996.

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S0020-1669(95)01122-0 CCC: $12.00

of the aromatic function with a carborane moiety having comparable 3-dimensional space and increased metabolic stability and lipophilicity might yield compounds with improved therapeutic efficacy. Also, related CNS depressants were shown not only to enter the brain rapidly but to achieve concentration differentials between primary brain tumors and normal brain of 4:1.[20,21] Therefore, carboranyl hydantoins and barbiturates might be considered as potential agents for BNCT.

Zakharkin et al.[22] investigated the sedative effect of a number of C-substituted *closo*- and *nido*-carboranes and found high activity for compounds possessing a side chain amino function with no other specific structural characteristics. These results and the availability of *o*-carboranylalanine[16] prompted the synthesis of novel boronated hydantoins and barbiturates.

In 1970, the first carboranyl hydantoins and barbiturates were described. Brattsev et al.[23] synthesized boron-containing barbiturate and thiobarbiturate compounds by the condensation of barbituric or thiobarbituric acids with carboranyl aldehydes. Zakharkin et al.[24] synthesized 5-(*o*-carboranylmethyl)barbiturate, from *o*-carboranylmethyl malonic ester and urea, as well as the first boronated hydantoin, 5-(methyl-*o*-carboranylmethyl)hydantoin. The latter was formed by the action of potassium cyanide and ammonium carbonate on the bisulfite derivative of methylcarboranylacetaldehyde. Recently, Kazantsev et al.[25] described the synthesis of carboranylthiohydantoins by the reaction of benzylidene-2-thiohydantoins with 1-isopropyl-2-lithio-*o*-carboranes. To our knowledge, none of these compounds were evaluated with respect to their anticonvulsant activity or for their potential as BNCT agents.

Experimental Section

FT-NMR spectra (proton and carbon) were obtained at The Ohio State University Chemical Instrument Center using a Bruker AM500 (carbon and proton) and in the College of Pharmacy at OSU using a Bruker AC250 (proton spectra). Chemical shifts (δ) are reported in ppm downfield from an internal tetramethylsilane standard. Coupling constants (J) are reported in hertz. IR spectra were recorded on a RFX 40 FT-IR spectrometer (Laser Precision Corp.). The spectra were in accordance with the proposed structures. Melting points were determined on a Fisher-Johns melting point apparatus and are reported uncorrected. Mass spectra were obtained at The Ohio State University Chemical Instrument Center on Finnigan MAT-900 mass spectrometer. HPLC was performed by use of Rainin HPLC System with Dynamax Model UV-1 detector. Column Dynamax-60A 8 μm C_8, 25 cm × 4.6 mm, with a guard module Dynamax-60A 8 μm C_8, 1.5 cm × 4.6 mm, was applied. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN; Atlantic Microlab, Inc., Norcross, GA; and Analytische Laboratorien, Gummersbach, Germany. Silica gel 60-F_{254} glass plates (Merck) were used for TLC. Compound visualization was achieved with UV light (254 nm), iodine, and spraying with 0.06% $PdCl_2$/% HCl (boron) and subsequent heating at 120 °C for 10−15 min. Silica gel 60 (70−230 mesh ASTM, Merck) was used for column chromatography. Reagent grade solvents were used for reactions and chromatography. Toluene and THF were distilled from sodium.

***p*-[(3-Prop-1-ynyl)oxy]toluene (6).** A 2.4 g (60.0 mmol) quantity of sodium hydride (60% dispersion in mineral oil) was slowly added to an ice-cooled solution of 5.4 g (50.0 mmol) of *p*-cresol in 45 mL of dry DMF. The mixture was stirred for 50 min at 0 °C until hydrogen evolution had ceased. Then, 5.4 mL (60.0 mmol) of proparagyl bromide was slowly added to the ice-cooled solution, and the solution was stirred for an additional 5 h and allowed to warm to room temperature. The reaction mixture was concentrated and filtered to remove the NaBr. The filtrate was evaporated to dryness. The resulting yellow oil was purified by column chromatography (hexanes/ethyl acetate, 4:1, v/v). **6**: yield 5.3 g (73%) of light yellow oil; R_f 0.73 (hexanes/ethyl acetate, 4:1, v/v); MS (FAB^+, 3-NBA) *m*/*z* 149 (M + 3H); ^{1}H-NMR ($CDCl_3$) δ 2.33 (s, 3H, $-CH_3-$), 2.53 (t, 1H, $-C{\equiv}CH$, $J_{1,3\text{-propynyl}} = 2.4$), 4.69 (d, 2H, $-CH_2C{\equiv}CH$), 6.92, 7.14 (2d, 4H, aromat, $J = 8.5$); ^{13}C-NMR ($CDCl_3$) δ 20.41 (q, CH_3), 55.86 (t, CH_2), 75.24 (d, CH), 78.80 (d of t, $-CH_2CCH$), 114.79, 129.86 (2d, aromat), 130.81, 155.44 (2s, aromat). Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.23; H, 6.91.

***p*-[(*o*-Carboran-1-ylmethyl)oxy]toluene (7).** A solution of 1.8 g (12.2 mmol) of *p*-[(3-prop-1-ynyl)oxy]toluene (**6**) and 2.5 g (12.2 mmol) of decarborane−acetonitrile in 50 mL of dry toluene was heated for 5 h at 90 °C. The progress of the reaction was checked by TLC (hexanes/ethyl acetate, 4:1, v/v). Following evaporation of the toluene, the remaining residue was purified on a silica gel column (hexanes/ethyl acetate, 10:1, v/v). **7**: yield 2.4 g (75%) of white crystals; R_f 0.52 (hexanes/ethyl acetate, 10:1, v/v); mp 109−110 °C; MS (FAB^+, 3-NBA) *m*/*z* 264 (M); ^{1}H-NMR ($CDCl_3$) δ 1.6−2.8 (br, m, 10H, BH), 2.29 (s, 3H, $-CH_3$), 4.06 (br s, 1H, carborane H), 4.36 (s, 2H, $-CH_2-$), 6.73, 7.09 (2d, 4H, aromat, $J = 8.5$); ^{13}C-NMR ($CDCl_3$) δ 20.49 (q, CH_3), 57.74 (d, CH), 69.74 (t, CH_2), 71.72 (s, carborane−*C*−), 114.66, 130.24 (2d, aromat), 132.12, 155.08 (2s, aromat). Anal. Calcd for $C_{10}H_{20}B_{10}O$: C, 45.43; H, 7.63. Found: C, 45.74; H, 7.77.

***p*-[(*o*-Carboran-1-ylmethyl)oxy]benzyl Bromide (1a).** A solution of 370 μL (7.2 mmol) of Br_2 in 5 mL of carbon tetrachloride was added dropwise to a solution of 1.9 g (7.0 mmol) of *p*-[(*o*-carboran-1-ylmethyl)oxy]toluene (**7**) in 30 mL of carbon tetrachloride. The reaction mixture was stirred and heated for 4 h at 50 °C. The progress of the reaction was monitored by TLC (hexanes/ethyl acetate, 6:1, v/v). Following evaporation of the solvent, the remaining residue was purified by column chromatography (hexanes/ethyl acetate, 6:1, v/v). **1a**: yield 1.9 g (79%) of white crystals; R_f 0.52 (hexanes/ethyl acetate, 6:1, v/v); mp 78−79 °C; MS (FAB^+, 3-NBA) *m*/*z* 343 (M); ^{1}H-NMR ($CDCl_3$) δ 1.6−2.8 (br, m, 10H, BH), 4.05 (br s, 1H, carborane H), 4.40 (s, 2H, $-CH_2O-$), 4.46 (s, 2H, $-CH_2Br$), 6.81, 7.36 (2d, 4H, $J = 8.7$, aromat); ^{13}C-NMR ($CDCl_3$) δ 32.95 (t, $-CH_2Br$), 57.76 (d, CH), 69.27 (t, $-CH_2O$), 71.29 (s, carborane−*C*−), 115.00, 130.71 (2d, aromat), 132.20, 156.98 (2s, aromat). Anal. Calcd for $C_{10}H_{19}B_{10}OBr$: C, 34.99; H, 5.58. Found: C, 35.25; H, 5.47.

Phase-Transfer Alkylation of [(Diphenylmethylene)amino]acetonitrile with *p*-[(*o*-Carboran-1-ylmethyl)oxy]benzyl Bromide (1a). To a solution of 1.2 g (3.5 mmol) of *p*-[(*o*-carboran-1-ylmethyl)oxy]-benzyl bromide (**1a**) and 0.8 g (3.5 mmol) of [(diphenylmethylene)-amino]acetonitrile (**2**) in 25 mL of acetonitrile were added 2.9 g (21.0 mmol) of anhydrous potassium carbonate and 0.34 g (1.1 mmol) of tetra-*n*-butylammonium bromide, and the solution was refluxed under argon for 5 h. The progress of the reaction was monitored by TLC (hexanes/ethyl acetate, 6:1, v/v). The reaction mixture was cooled to room temperature and filtered to remove the solid, which was washed with dichloromethane. The filtrate and washings were combined and concentrated. The remaining residue was purified by a column chromatography (hexanes/ethyl acetate, 6:1, v/v) and recrystallized from hexanes/ethyl acetate (6:1). **3a**: yield 1.2 g (71%) of white crystals; R_f 0.33 (hexanes/ethyl acetate, 6:1, v/v); mp 94−96 °C; MS (FAB^+, 3-NBA) *m*/*z* 483 $(M + H)^+$; ^{1}H-NMR ($CDCl_3$) δ 1.5−2.9 (br m, 10H, BH), 3.12, 3.19 (d of AB_q, 2H, $-CH_2CH-$, $J_{AB} = 13.6$, $J_{BX} = 7.6$, $J_{AX} = 6.2$), 4.04 (br s, 1H, carborane H), 4.35 (dd, 1H, $-CHCH_2-$, $J_{AX} = 6.3$, $J_{BX} = 7.6$), 4.37 (s, 2H, $-CH_2O-$), 6.7−7.8 (m, 14H, aromat); ^{13}C-NMR ($CDCl_3$) δ 40.27 (t, $-CH_2CH-$), 54.88 (d, $-CHCH_2-$), 57.76 (d, H*C*− of carborane), 69.32 (t, $-CH_2O-$), 71.46 (s, $-CH_2C-$ of carborane), 119.10 (s, $-CN$), 114.81−156.37 (aromat), 173.33 (s, $-N{=}CPh_2$). Anal. Calcd for $C_{25}H_{30}B_{10}N_2O$: C, 62.22; H, 6.27; B, 22.40; N, 5.80. Found: C, 62.06; H, 6.45; B, 22.25; N, 5.62.

3-[*p*-((*o*-Carboran-1-ylmethyl)oxy]phenyl]-2-aminopropionitrile (4a). A 0.4 g (0.8 mmol) quantity of compound **3a** dissolved in

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5 mL of benzene was reacted with 15 mL of 6 N HCl. After 18 h of stirring at room temperature, the aqueous layer was adjusted to pH 8−9, and the organic layer was removed, dried ($MgSO_4$), and evaporated to dryness. The remaining residue was purified by column chromatography (chloroform/methanol, 6:1, v/v). **4a**: yield 235 mg (90%) of a yellow, hygroscopic glasslike compound; R_f 0.9 (chloroform/methanol, 6:1, v/v); MS *m/z* (FAB^+, 3-NBA) 319 $(M + H)^+$; ^{1}H-NMR ($CDCl_3$) δ 1.5−2.9 (br m, 10H, BH), 1.78 (br s, 2H, $-NH_2$) 3.00, 2.94 (d of AB_q, 2H, $-CH_2CH-$, $J_{AB} = 13.8$, $J_{BX} = 7.1$, $J_{AX} = 5.9$), 3.89 (t, 1H, $-CHCH_2-$, $J = 6.822, 6.128$), 4.07 (br s, 1H, carborane H), 4.40 (s, 2H, $-CH_2O-$), 6.83, 7.24 (2d, 4H, aromat, $J = 8.6$); ^{13}C-NMR ($CDCl_3$) δ 40.23 (t, $-CH_2CH-$), 44.71 (d, $-CHCH_2-$), 57.85 (d, HC− of carborane), 69.28 (t, $-CH_2O-$), 71.45 (s, $-C-$ of carborane), 115.08 (d, aromat), 121.34 (s, $-CN$), 129.03 (s, aromat), 131.00 (d, aromat), 156.61 (s, aromat). Since compound **4a** was hygroscopic, it was used directly in the formation of the amino acid **5a**.

***O*-(*o*-Carboran-1-ylmethyl)tyrosine (5a).** A 0.16 g (3.1 mmol) quantity of 3-[*p*-((*o*-carboran-1-ylmethyl)oxy)phenyl]-2-aminopropionitrile (**4a**) was reacted with 10 mL of 75% H_2SO_4 at 95 °C for 24 h. The mixture was cooled (ice−water bath) and filtered. The resulting yellow solid was washed with water and dried. The product was purified by reversed-phase flash chromatography (C_8, 40 μm, 60 Å, MeOH/H_2O, 9:1, v/v). **5a**: yield 115 mg (70%) of white solid; R_f 0.6 (*n*-BuOH/CH_3COOH/H_2O, 4:1:1, v/v/v); HPLC retention time 13.64 (Dynamax-60A 8 μm C_8, flow rate 0.75 mL/min, solvent system 25% H_2O/75% MeOH, injection pressure 0.91 kpsi); ninhydrin positive; mp 196−197 °C; MS (FAB^+, 3-NBA) *m/z* 338 $(M + H)^+$; ^{1}H-NMR (MeOH-d_4) δ 1.1−3.3 (br m, 10H, BH), 2.97−3.23 (d of AB_q, 2H, $-CH_2CH-$, $J_{AB} = 14.6$, $J_{BX} = 8.4$, $J_{AX} = 4.5$), 3.73 (dd, 1H, $-CHCH_2-$, $J_{AX} = 4.5$, $J_{BX} = 8.4$), 4.51 (s, 2H, $-CH_2O-$), carborane H overlapped by MeOH, 6.92, 7.24 (2d, 4H, aromat, $J = 8.6$). Anal. Calcd for $C_{12}H_{23}B_{10}NO_3$: C, 42.71; H, 6.87; N, 4.15; B, 32.04. Found: C, 42.45; H, 6.77; N, 4.00; B, 31.91.

***p*-(*o*-Carboran-1-yl)toluene (8).** A solution of 4.7 g (40.5 mmol) of 4-ethynyltoluene and 9.1 g (45.2 mmol) of a decaborane−acetonitrile complex in 200 mL of dry toluene was heated for 5 h at 90 °C. The progress of the reaction was monitored by TLC (hexanes/ethyl acetate, 10:1, v/v). Following evaporation of the toluene, the residue was purified on a silica gel column (hexanes/ethyl acetate, 10:1, v/v). **8**: yield 6.6 g (70%) of white crystals; R_f 0.53 (hexanes/ethyl acetate, 10:1, v/v); subl 133−134 °C/760 mm Hg; MS (FAB^+, 3-NBA) *m/z* 235 $(M + H)^+$; ^{1}H-NMR ($CDCl_3$) δ 1.2−3.6 (br m, 10H, BH), 2.34 (s, 3H, $-CH_3$), 3.92 (br s, 1H, carborane H), 7.13, 7.36 (2d, 2H, aromat, $J = 8.3$). Anal. Calcd for $C_9H_{18}B_{10}$: C, 46.13; H, 7.74; B, 46.13. Found: C, 45.95; H, 7.63; B, 46.03.

***p*-(*o*-Carboran-1-yl)benzyl Bromide (1b).** To an ice-cooled solution of 0.26 g (1.1 mmol) of *p*-(*o*-carboran-1-yl)toluene (**8**) in 10 mL of carbon tetrachloride irradiated with a 600-W photolamp was added dropwise with stirring a solution of 60 μL (1.2 mmol) of bromine in 3 mL of carbon tetrachloride. The reaction was complete in 15 min. Following evaporation of the solvent, the residue was isolated on a silica gel column (hexanes/ethyl, acetate 10:1, v/v) and contained **1b** (major) and *p*-(*o*-carboran-1-yl)benzaldehyde (**9**). **1b**: yield 257 mg (77%) of white crystals; R_f 0.36 (hexanes/ethyl acetate, 10:1, v/v), mp 110−112 °C; MS (FAB^+, 3-NBA) *m/z* 312 $(M - H)^+$; ^{1}H-NMR ($CDCl_3$) δ 1.2−3.6 (br m, 10H, BH), 3.94 (br s, 1H, carborane H), 4.44 (s, 2H, $-CH_2-$), 7.36, 7.46 (2d, 4H, aromat, $J = 8.5$). Anal. Calcd for $C_9H_{17}B_{10}Br$: C, 34.51; H, 5.47; B, 34.51. Found: C, 34.34; H, 5.28; B, 34.58. **9**: yield 21 mg (5%) of white crystals; R_f 0.13 (hexanes/ethyl acetate, 10:1, v;v); mp 126 °C; MS (FAB^+, 3-NBA) *m/z* 248 (M); ^{1}H-NMR ($CDCl_3$) δ 1.0−3.3 (br m, 10H, BH), 4.03 (br s, 1H, carborane H), 7.66, 7.86 (2d, 4H, aromat, $J = 8.5$), 10.04 (s, 1H, −CHO). Anal. Calcd for $C_9H_{16}B_{10}O$: C, 43.53; H, 6.49; B, 43.53. Found: C, 43.50; H, 6.29; B, 43.26.

Phase-Transfer Alkylation of [(Diphenylmethylene)amino]-acetonitrile with *p*-(*o*-Carboran-1-yl)benzyl Bromide (1b). To a solution of 0.24 g (0.76 mmol) of *p*-(*o*-carboran-1-yl)benzyl bromide (**1b**) and 0.17 g (0.76 mmol) of [(diphenylmethylene)amino]acetonitrile (**2**) in 10 mL of acetonitrile were added 0.63 g (2.86 mmol) of anhydrous potassium carbonate and 0.07 g (0.23 mmol) of tetrabutylammonium bromide. The reaction mixture was refluxed under argon for 4 h, and progress was followed by TLC (hexanes/ethyl acetate, 10:1, v/v). The mixture was cooled to room temperature and filtered. The solid was washed with dichloromethane, and the filtrates were combined and concentrated. The residue was purified by column chromatography (hexanes/ethyl acetate, 10:1, v/v) and crystallized from ethyl acetate/hexanes, 1:5. **3b**: yield 202 mg (59%) of white crystals; R_f 0.24 (hexanes/ethyl acetate, 10:1, v/v); mp 162−163 °C; MS (FAB^+, 3-NBA) *m/z* 453 $(M + H)^+$; ^{1}H-NMR ($CDCl_3$) δ 1.7−3.3 (br m, 10H, BH), 3.15, 3.22 (d of AB_q, 2H, $-CH_2CH-$, $J_{AB} = 13.5$, $J_{BX} = 7.6$, $J_{AX} = 6.0$), 3.92 (br s, 1H, carborane H), 4.37, 4.38 (dd, 1H, $-CHCH_2-$, $J = 7.5$), 6.8−7.8 (m, 14H, aromat); ^{13}C-NMR ($CDCl_3$) δ 40.40 (t, $-CH_2CH-$), 54.39 (d, $-CHCH_2-$), 60.07 (d, HC− of carborane), 75.94 (s, $-C-$ of carborane), 118.82 (s, $-CN$), 127.07−138.044 (aromat), 173.57 (s, $-N{=}CPh_2$). Anal. Calcd for $C_{24}H_{28}N_2B_{10}$: C, 63.69; H, 6.24; N, 6.19; B, 23.89. Found: C, 63.47; H, 6.18; N, 6.02; B, 23.68.

***p*-(*o*-Carboran-1-yl)phenylalanine (5b).** A 0.28 g (0.62 mmol) quantity of **3b** dissolved in 10 mL of benzene was hydrolyzed with 15 mL of 6 N HCl. After the mixture was stirred for 17 h at room temperature, the organic layer was removed and the aqueous layer was extracted with ether. The combined organic solutions were dried and evaporated to dryness. The residue was purified by column chromatography (chloroform/methanol, 10:1, v/v), yielding 80 mg of the corresponding aminonitrile. This was immediately reacted with 15 mL of 70% H_2SO_4 at 95 °C for 24 h. The mixture was cooled (ice−water bath) and filtered, and the resulting yellow solid was washed with water, dried under vacuum, and purified by reversed-phase flash chromatography (C_8, 40 μm, 60 Å, MeOH/H_2O, 8.5:1.5, v/v). **5b**: yield 150 mg (79% total yield of hydrolysis) of white solid; R_f 0.56 (*n*-BuOH/CH_3COOH/H_2O, 4:1:1, v/v/v); HPLC retention time 6.7 (Dynamax-60A 8 μm C_8, flow rate 0.63 mL/min, solvent system 15% H_2O/85% MeOH, injection pressure 0.75 kpsi); ninhydrin positive; mp 200−201 °C; MS (FAB^+, 3-NBA) *m/z* 308 $(M + H)^+$; ^{1}H-NMR (MeOH-d_4) δ 1.2−3.3 (br m, 10H, BH), 3.04, 3.27 (d of AB_q, 2H, $-CH_2-$, $J_{AB} = 14.5$, $J_{BX} = 8.3$, $J_{AX} = 4.7$), 3.78 (dd, 1H, $-CHCH_2-$), 5.11 (br s, 1H, carborane H), 7.32, 7.53 (2d, 4H, aromat, $J = 8.4$). Anal. Calcd for $C_{11}H_{21}NO_2B_{10}$: C, 42.98; H, 6.89; N, 4.56; B, 35.17. Found: C, 42.68; H, 6.67; N, 4.41; B, 35.20.

2-[(Diphenylmethylene)amino]pent-4-ynenitrile (10). To a solution of 6.7 g (30.5 mmol) of [(diphenylmethylene)amino]acetonitrile (**2**) in 300 mL of acetonitrile were added 50.4 g (365.0 mmol) of anhydrous potassium carbonate and 5.9 g (18.2 mmol) of tetra-*n*-butylammonium bromide. Propargyl bromide (6 mL, 67.3 mmol) was added dropwise to the refluxing solution under argon for 3 h. The reaction mixture was carefully monitored by TLC (hexanes/ethyl acetate, 6:1, v/v). The reaction mixture was cooled to room temperature and filtered to remove the solid, which was washed with dichloromethane. The filtrate and washings were combined and concentrated, and the residue was purified by column chromatography (hexanes/ethyl acetate, 10:1, v/v). **10**: yield 5.0 g (63.5%) of light yellow crystals; R_f 0.50 (hexanes/ethyl acetate, 6:1, v/v); mp 93−93.5 °C; MS (FAB^+, 3-NBA) *m/z* 259 $(M + H)^+$; ^{1}H-NMR ($CDCl_3$) δ 2.095 (t, 1H, $HC{\equiv}C-$, $J_{1,3\text{-propynyl}} = 2.6$), 2.78, 2.90 (d of AB_q, 2H, $-CH_2-$, $J_{AB} = 16.6$, $J_{BX} = 6.7$, $J_{AX} = 7.4$, $J_{1,3\text{-propynyl}} = 2.6$), 4.40 (t, 1H, $-HCCH_2-$, $J = 7.05$), 7.25−7.81 (m, 10H, aromat); ^{13}C-NMR ($CDCl_3$) δ 25.43 (t, $-CH_2-$), 52.25 (d, $-CHCH_2-$), 72.05 (d, $HC{\equiv}C-$), 78.24 (s, $-C{\equiv}CH$), 118.30 (s, −CH), 127.56, 128.26, 129.09, 129.21, 129.56, 130.06, 131.42, 132.40 (8d, aromat), 134.95, 138.27 (2s, aromat), 174.36 (s, $-N{=}CPh_2$). Anal. Calcd for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.44; H, 5.51; N, 10.73.

3-(*o*-Carboran-1-yl)-2-[(diphenylmethylene)amino]propionitrile (11). A solution of 4.4 g (17.0 mmol) of 2-[(diphenylmethylene)amino]pent-4-ynenitrile (**10**) and 3.8 g (18.7 mmol) of the decaborane−acetonitrile complex in 70 mL of dry toluene was heated for 4 h at 90 °C. The progress of the reaction was followed by TLC (hexanes/ethyl acetate, 6:1, v/v). After evaporation of the toluene, the residue was purified on a silica gel column (hexanes/ethyl acetate, 10:1, v/v). **11**: yield 2.4 g (36%) of yellow glasslike compound; R_f 0.21 (hexanes/ethyl acetate, 10:1, v/v); MS (FAB^+, 3-NBA) *m/z* 377 $(M + H)^+$; ^{1}H-NMR ($CDCl_3$) δ 1.5−2.8 (br m, 10H, BH), 2.905, 2.95 (d of AB_q, 2H, $-CH_2-$, $J_{AB} = 15.3$, $J_{BX} = 6.9$, $J_{AX} = 6.0$), 3.81 (br s, 1H, HC− of carborane), 4.34 (t, 1H, $-CH-$), 7.21−7.62 (m, 10H, aromat); ^{13}C-NMR ($CDCl_3$) δ 42.220 (t, $-CH_2-$), 51.576 (d, $-HCHC_2-$),

60.193 (d, H*C*− of carborane), 70.710 (s, −*C*− of carborane), 117.808 (s, −*C*N), 126.515−137.682 (8d, 2s, aromat), 175.563 (s, −N═*C*Ph$_2$). Anal. Calcd for $C_{18}H_{24}N_2B_{10}\cdot{}^4/_3H_2O$: C, 53.98; H, 6.71; B, 26.99. Found: C, 54.06; H, 6.84; B, 26.60.

3-(*o*-Carboran-1-yl)-2-aminopropionitrile (12). A 2.0 g (5.3 mmol) quantity of 3-(*o*-carboran-1-yl)-2-[(diphenylmethylene)amino]-propionitrile (**11**) was dissolved in 80 mL of benzene, and the solution was stirred with 100 mL of 6 N HCl for 17 h at room temperature. The organic layer was removed, and the aqueous layer was extracted with ether (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), and the solvents were evaporated. The residue was purified by column chromatography (chloroform/methanol, 10:1, v/v). **12**: yield 1.0 g (92%) of white solid; R_f 0.5 (chloroform/methanol, 10:1, v/v); mp 112−113 °C; MS (FAB$^+$, 3-NBA) *m*/*z* 213 (M + H)$^+$; ^{1}H-NMR ($CDCl_3$) δ 1.5−2.8 (br m, 10H, BH), 2.62, 2.75 (d of AB_q, 2H, −CH_2−, J_{AB} = 15.4, J_{AX} = 5.04, J_{BX} = 8.98), 3.85 (dd, 1H, J_{BX} = 8.9895, J_{AX} = 5.07), 4.24 (br s, 1H, carborane H); ^{13}C-NMR ($CDCl_3$) δ 41.835 (t, −CH_2−), 42.380 (d, −*C*HCH_2−), 59.898 (d, H*C*− of carborane), 70.697 (s, −*C*− of carborane), 120.102 (s, −CN). Anal. Calcd for $C_5H_{16}N_2B_{10}$: C, 28.29; H, 7.60; N, 131.9; B, 50.92. Found: C, 28.45; H, 7.50; N, 13.14; B, 50.86.

***o*-Carboranylalanine (13).** A 0.42 g (2.0 mmol) quantity of 3-(*o*-carboran-1-yl)-2-aminopropionitrile (**12**) was reacted with 25 mL of 75% H_2SO_4 at 95 °C for 24 h. The mixture was cooled (ice−water bath), and the white solid was filtered off. The product was dissolved in water and neutralized with aqueous ammonia to pH 4.3−4.4. After cooling overnight, the crystalline amino acid was filtered off and dried under vacuum (0.5 mm). **13**: yield 416 mg (90%); R_f 0.64 (*n*-BuOH/CH_3COOH/H_2O, 4:1:1, v/v/v) [R_f lit.[7] 0.63]; MS (FAB$^+$, 3-NBA) *m*/*z* 232.3 (M + H)$^+$; ^{1}H-NMR (MeOH-d_4) δ 1.1−3.4 (br m, 10H, BH), 2.72, 3.13 (d of AB_q, 2H, −CH_2−, J_{AB} = 16.0, J_{BX} = 4.8, J_{AB} = 6.3), 3.94 (t, 1H, −CH−, J = 5.2), 4.81 (br s, 1H, carborane H); ^{13}C-NMR (MeOH-d_4) δ 39.97 (CH_2), 55.02 (CH), 63.62 (H*C*− of carborane), 74.30 (−*C*− of carborane), 171.78 (C÷xdbdO). Anal. Calcd for $C_5H_{17}NO_2B_{10}$: C, 25.96; H, 7.41; N, 6.06; B, 46.74. Found: C, 25.78; H, 7.30; N, 5.99; B, 46.50.

5-(*o*-Carboran-1-ylmethyl)hydantoin (14) and Tetraphenylphosphonium 7-(Hydantoin-5-ylmethyl)-D,L-dodecahydro-7,8-dicarba-*nido*-undecaborate (15). A solution of 1.0 g (4.32 mmol) of *o*-carboranylalanine (**13**) and 0.34 g (5.23 mmol) of sodium cyanate in 10 mL of water was refluxed with stirring until the components were completely dissolved (10−15 min). Then 3 mL of concentrated HCl was added, and the reaction mixture was stirred under flux for an additional 20−30 min, cooled to room temperature, and filtered. Crude 5-(*o*-carboran-1-ylmethyl)hydantoin (**14**) was washed three times with 20 mL of water, dried under vacuum (0.2 mm) over anhydrous calcium sulfate, and purified by column chromatography (hexane/ethyl acetate; 1:1, v/v). **14**: yield 685 mg (62%) of white powder; mp 226 °C; R_f 0.07 (hexane/ethyl acetate, 5:3, v/v); MS (FAB$^+$): *m*/*z* 257 (M + H)$^+$; ^{1}H-NMR (acetone-d_6) δ 1.5−3.1 (br m, 10H, BH), 2.75, 2.98 (d of AB_q, 2H, −CH_2−, $J_{A,B}$ = 15.8, $J_{A,H\text{-}5}$ = 8.9, $J_{B,H\text{-}5}$ = 3.2), 4.37−4.395 (m, 1H, CH), 4.815 (br s, 1H, carborane H), 7.14 (br s, 1H, H-1), 9.76 (br s, 1H, H-3); ^{13}C NMR (acetone-d_6) δ 41.386 (t, −CH_2−), 58.614 (d, CH), 63.550 (d, H*C*− of carborane), 74.185 (s, −*C*− of carborane), 157.475, 173.988 (2s, C═O). Anal. Calcd for $C_6H_{16}N_2O_2B_{10}$: C, 28.12; H, 6.29; N, 10.93. Found: C, 28.26; H, 6.38; N, 10.71.

A solution of 1.2 g (3.2 mmol) of tetraphenylphosphonium chloride in 10 mL of water was added to the combined filtrates. The resulting precipitate, consisting mainly of tetraphenylphosphonium 7-(hydantoin-5-ylmethyl)-D,L-dodecahydro-7,8-dicarba-*nido*-undecaborate (**15**), was filtered off, washed three times with 20 mL of water, dried under vacuum (0.2 mm) over anhydrous calcium sulfate, and purified by column chromatography (dichloromethane/methanol, 5:1, v/v). **15**: yield 580 mg (23%) of white powder; mp 238 °C; R_f 0.00 (hexane/ethyl acetate, 5:3, v/v); MS (FAB$^-$) *m*/*z* 246 [(M)$^-$ for the anion]; ^{1}H-NMR (acetone-d_6) δ −2.7 (br d, 1H, *nido*-carborane "extra" proton), −0.50 to 3.00 (br m, 9H, BH), 1.6−2.3 (m, 3H, −CH_2−, carborane H), 4.02 (apparent q[dd], ∼0.5H, H-5, $J_{B,H\text{-}5}$ = 3.3, $J_{A,H\text{-}5}$ = 9.2), 4.17 (apparent q[dd], ∼0.5H, H-5, $J_{B,H\text{-}5}$ = 2.6, $J_{A,H\text{-}5}$ = 9.9), 6.33 (br d, 1H, H-1), 7.85−7.90 (m, 20H, aromat), 9.39 (br s, 1H, H-3); ^{13}C NMR (acetone-d_6) δ 30.106, 30.260 (2d, CH), 42.8, 43.2 (2t, −CH_2−), 60.7, 61.7 (2s, −*C*− of carborane), 118.7, 119.4 (2s, aromat, Ph_4P^+), 131.3−136.4 (5d, aromat, Ph_4P^+), 198.5, 195.0 (2s, C═O). Anal. Calcd for $C_{30}H_{36}N_2O_2PB_6$: C, 61.61; H, 6.20; N, 4.79. Found: C, 61.43; H, 6.24; N, 4.73.

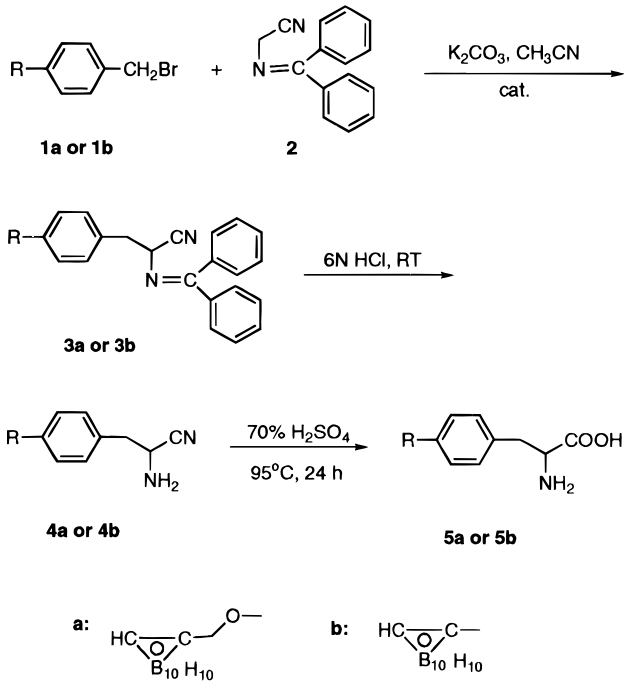
5-(*o*-Carboran-1-ylmethyl)-2-thiohydantoin (16). A solution of 0.10 g (0.43 mmol) of *o*-carboranylalanine (**13**) and 39.50 g (0.52 mmol) of ammonium thiocyanate was refluxed for 30 min in 5 mL of acetic anhydride/acetic acid (9:1, v/v). The solvents were evaporated, and the residue was stirred for 15 h at room temperature in 25 mL of acetone/10% aqueous HCl (3:2, v/v). Subsequently, the acetone was evaporated and the aqueous phase was extracted three times with 10 mL of ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by column chromatography (hexane/ethyl acetate, 5:3, v/v). **16**: yield 93 mg (79%) of white powder; mp 245 °C (subl under dec); R_f 0.43 (hexane/ethyl acetate, 5:3, v/v); MS (FAB$^-$) *m*/*z* 271 (M − H$^+$)$^-$; ^{1}H-NMR (acetone-d_6) δ 1.5−3.1 (br m, 10H, BH), 2.91, 3.025 (d of AB_q, 2H, −CH_2−, $J_{A,B}$ = 16.0, $J_{A,H\text{-}5}$ = 7.75, $J_{B,H\text{-}5}$ = 4.1), 4.57−4.59 (apparent q[dd], 1H, H-5, $J_{A,H\text{-}5}$ = 7.8, $J_{B,H\text{-}5}$ = 4.1), 4.82 (br s, 1H, carborane H), 8.905 (br s, 1H, H-1), 10.69 (br s, 1H, H-3); ^{13}C-NMR ($CDCl_3$) δ 40.050 (t, −CH_2−), 61.224 (d, CH), 63.513 (d, H*C*− of carborane), 73.745 (s, −*C*− of carborane), 174.505 (s, C═O), 184.450 (s, C═S). Anal. Calcd for $C_6H_{16}N_2OSB_{10}$: C, 26.46; H, 5.92; N, 10.29. Found: C, 26.80; H, 5.78; N, 10.29.

Bis(but-2-ynyl)malonic Acid Diethyl Ester (17). To a cooled solution of 6 mL (39.5 mmol) of diethyl malonate in 44 mL of absolute ethanol was added with stirring a solution of 6.3 g (93.0 mmol) of sodium ethoxide in 200 mL of absolute ethanol. To this mixture was added a solution of 16.8 g (75.0 mmol) of 4-tosylbut-2-yne (R_f = 0.67, hexane/ethyl acetate, 5:3, v/v) in 100 mL of absolute ethanol. The addition occurred under cooled and anhydrous conditions. After 20 min of stirring at 0 °C, the reaction mixture was allowed to gradually warm to room temperature and then refluxed for 3 h. Ethanol was evaporated, and the residue was suspended in 150 mL of water. The suspension (pH 14) was extracted with diethyl ether, and the organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by column chromatography (hexane/ethyl acetate, 5:3, v/v). **17**: yield 9.3 g (89%) of a clear oil that crystallizes when stored in a refrigerator; bp 150 °C (3.2 mm); R_f 0.83 (hexane/ethyl acetate, 5:3, v/v); MS (FAB$^+$) *m*/*z* 265 (M + H)$^+$; ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, 6H, CH_2CH_3, J = 7.1), 1.72 (t, 6H, C≡C*C*H_3, J = 2.5), 2.87 (q, 4H, CH_2C≡C), 4.19 (q, 4H, CH_2-CH_3). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.33; H, 7.73.

5,5-Bis(but-2-ynyl)barbiturate (18). A solution of 7.5 g (28.4 mmol) of bis(but-2-ynyl)malonic acid diethyl ester (**17**), 1.9 g (28.4 mmol) of sodium ethoxide, and 1.7 g (28.4 mmol) of urea was refluxed in 200 mL of absolute ethanol for 12 h under anhydrous conditions. The reaction mixture was allowed to cool to room temperature, acidified with concentrated HCl to pH 2−3, and evaporated to dryness. The residue was suspended in 100 mL of water and extracted twice with 100 mL of ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by column chromatography (hexane/ethyl acetate, 5:3, v/v). **18**: yield 4.4 g (67%) of white crystals; mp 182 °C; R_f 0.35 (hexane/ethyl acetate, 5:3, v/v); MS (FAB$^+$) *m*/*z* 233 (M + H)$^+$; ^{1}H-NMR (DMSO-d_6) δ 1.72 (s, 6H, CH_3), 2.69, 2.70 (2s, 4H, CH_2), 12.7−13.3 (br s, 2H, N*H*). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.81; H, 5.31; N, 11.99.

5,5-Bis[(2-methyl-*o*-carboran-1-yl)methyl]barbiturate (20). A solution of 1.3 g (5.7 mmol) of 5,5-bis(but-2-ynyl)barbiturate (**18**) in 20 mL of 1,1,1,3,3,3-hexamethyldisilazane, 25 mL of THF, and 0.3 mL of chlorotrimethylsilane was refluxed under anhydrous conditions. Ammonia evolved and ammonium chloride precipitated in the reflux condenser. After 4 h, no further precipitation of ammonium chloride could be observed, and the mixture was cooled to room temperature. The solvents were thoroughly evaporated at 50 °C, and the waxlike residue was redissolved in 75 mL of anhydrous toluene. A 2.9 g (14.3 mmol) quantity of the decarborane−acetonitrile complex was added, and the reaction mixture was stirred for 12 h at 100 °C. Toluene was evaporated, and the residue was suspended in a mixture of 30 mL of MeOH, 60 mL of acetone, and 30 mL of 10% aqueous HCl. The suspension was refluxed for 3 h, the organic solvents were evaporated,

Scheme 1



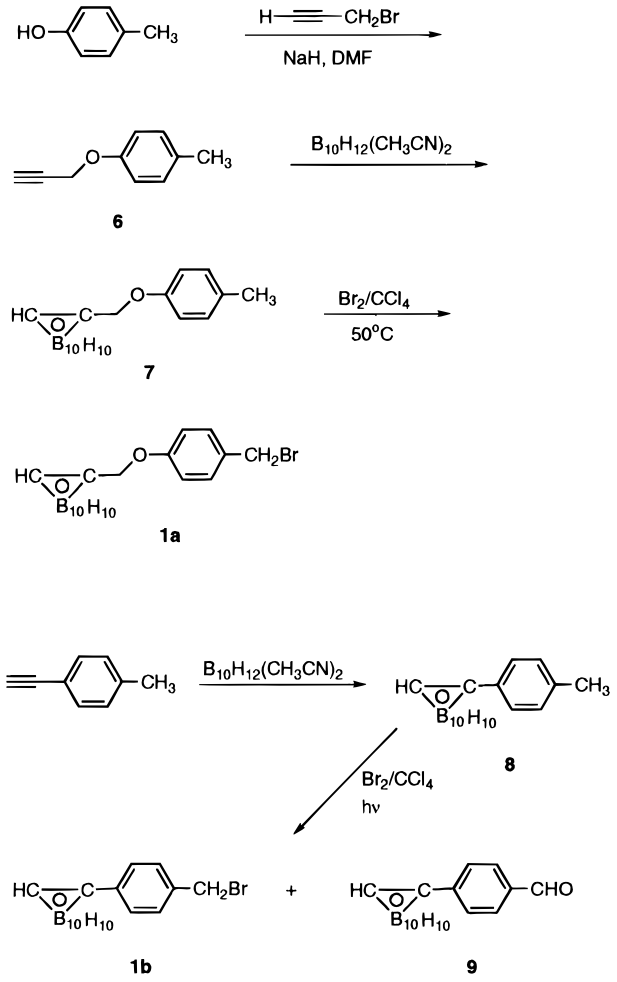
and the remaining aqueous phase was extracted three times with 50 mL of ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by column chromatography (hexane/ethyl acetate, 5:3, v/v). **20**: yield 720 mg (27%) of white powder; mp >300 °C; R_f 0.46 (hexane/ethyl acetate, 5:3, v/v); MS (FAB$^+$, 3-NBA, DMSO) *m*/*z* 469 (M + H)$^+$; ^{1}H-NMR (DMSO-d_6) δ 1.30−3.00 (br m, 20H, BH), 2.10 (s, 6H, CH_3), 3.05 (s, 4H, CH_2), 12.30 (br s, 2H, NH); ^{13}C-NMR (DMSO-d_6) δ 22.80 (q, CH_3), 43.11 (t, CH_2), 52.26 (s, C-5), 74.41 (s, CH_3C- of carborane), 78.98 (s, CH_2C- of carborane), 149.52 (s, C-4, C-6), 169.37 (s, C-2). Anal. Calcd for $C_{12}H_{32}N_2O_3B_{20}$: C, 30.76; H, 6.88; N, 5.98. Found: C, 31.03; H, 7.03; N, 5.71.

Results and Discussion

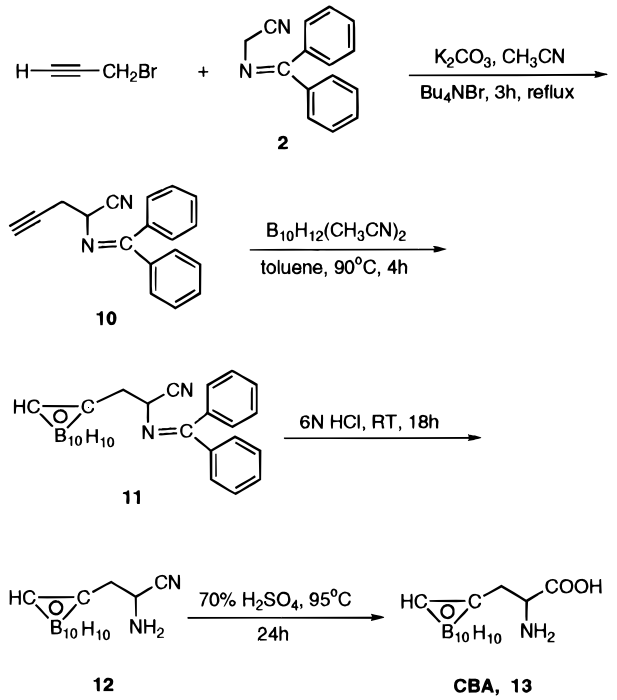
The reaction sequences for the syntheses of the amino acids *O*-(*o*-carboran-1-ylmethyl)tyrosine (CBT, **5a**) and *p*-(*o*-carboran-1-yl)phenylalanine (CBPA, **5b**) and of *o*-carboranylalanine (Car, **13**) are shown Schemes 1 and 3. Phase-transfer alkylation[26,27] of commercially available [(diphenylmethylene)amino]acetonitrile (**2**) with carborane-containing bromides **1a** and **1b**, followed by a two-step hydrolysis (6 N HCl, room temperature; 70% H_2SO_4, 95 °C) gave amino acids **5a** and **5b** in 77% and 71% yields, respectively. Strongly acidic conditions did not alter the carborane cage. The chemical structure of amino acids **5a** and **5b** was confirmed by elemental analysis, MS, and ^{1}H and ^{13}C NMR spectroscopy.

The synthesis of the carborane-containing bromides **1a** and **1b** is shown in Scheme 2. The O-alkylation of *p*-cresol with propargyl bromide gave *p*-[(3-prop-1-ynyl)oxy]toluene, **6**. Boronation of compound **6** with the bis(acetonitrile)−decaborane complex yielded the carboranyl derivative **7**, which was subsequently brominated with bromine in carbon tetrachloride. The major product of the bromination was *p*-[(*o*-carboran-1-ylmethyl)oxy]benzyl bromide (**1a**; 79%). A small amount of the dibromide (less than 5%) could be isolated. A similar approach has been applied in synthesizing the bromide **1b**. Boronation of commercially available 4-ethynyltoluene with the decaborane−acetonitrile complex gave *p*-(*o*-carboran-1-yl)-

Scheme 2



Scheme 3



toluene, **8**. However bromination of **8** under comparable conditions used in forming **1a** yielded, probably due to the presence of the carborane−phenyl conjugated system, the carborane-containing aldehyde **9**. Dropwise addition of a

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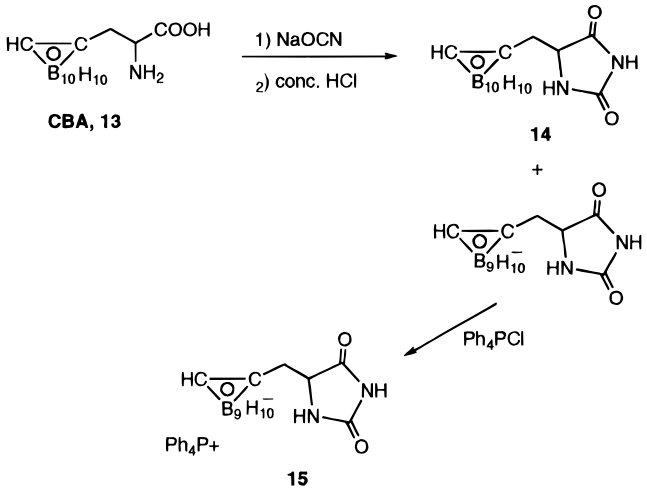
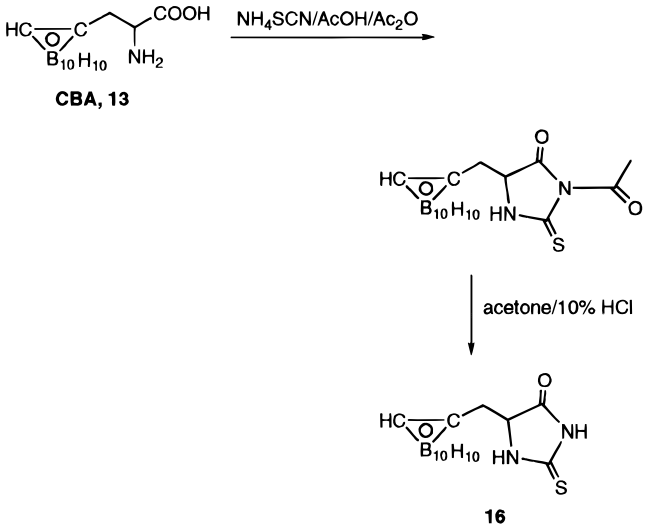
Scheme 4



Scheme 5



bromine solution to an irradiated, ice-cooled solution of **8** gave mainly the expected product, *p*-(*o*-carboran-1-yl)benzyl bromide, **1b** (77% yield), and only a small amount (5%) of **9**. The chemical structures of bromides **1a** and **1b**, as well as aldehyde **9**, were confirmed by elemental analysis, MS, and ^{1}H and ^{13}C NMR spectroscopy. This demonstrated that the photochemical bromination does not alter the carborane nucleus.

The synthesis of *o*-carboranylalanine (Car, **13**) is described in Scheme 3. The phase-transfer alkylation of compound **2** with propargyl bromide afforded derivative **10**. The reaction was monitored by TLC (hexanes/ethyl acetate, 6:1, v/v) to avoid the formation of the dialkylated product. Boronation of compound **10** with the decaborane−acetonitrile complex, followed by a two-step hydrolysis, gave *o*-carboranylalanine in 70% total yield.

The initial approach for synthesizing the carborane-containing hydantoins involved carboranyl ketones,[28−33] such as methyl-*o*-carboranyl methyl ketone, bis(methyl-*o*-carboranyl) ketone, bis(methyl-*o*-carboranyl) α-diketone, and bis(*o*-carboran-1-ylmethyl) ketone.[34] Unfortunately, the reactions of these ketones with potassium cyanide in the presence of ammonium carbonate (Bucherer−Berg reaction)[35−38] did not provide the desired cyclized products. The fact that the carboranyl ketones did not react and could be recovered almost quantitatively indicates that the physicochemical and electronic properties of the carborane cage may be responsible for this lack of reactivity and not its steric mass. Our second approach was to prepare hydantoins via amino acids.[35,39] The synthetic procedure utilized *o*-carboranylalanine (Car, **13**) and is presented in Scheme 4.

5-(*o*-Carboran-1-ylmethyl)hydantoin (**14**) was formed in 62% yield by the reaction of Car (**13**) with sodium cyanate. In the residual aqueous filtrate, the *nido* analgoue, **15**, was isolated in approximately 23% yield. Partial degradation of Car under the reaction conditions with subsequent cyclization of *nido*-Car with sodium cyanate may be the basis for the formation of **15**. Sjoberg et al.[40] showed that *o*-carboranylalanine degrades spontaneously by an intramolecular process to a mixture of *nido* diastereomers in water and methanol solutions. Our studies confirm this self-degradation.[41] Proton and carbon-13 NMR spectra of **15** indicate the formation of a diastereoisomeric mixture of *nido*-hydantoin, **15**, in a 1:1 ratio. The proton NMR spectrum shows two apparent quartets [dd] at 4.02 and 4.17 ppm for 5-H, stemming from its coupling with protons on the methylene group attached at the 5-position of the hydantoin ring. The carbon-13 NMR spectrum also displays two sets of carbons for both diastereomeric *nido* forms. The basic degradation of 1-phenyl-*o*-carborane with formation of *nido* enantiomers was previously reported by Hawthorne et al.[42]

Car was also used to synthesize the corresponding thiohydantoin, **16**, by an analogous procedure[43−47] (Scheme 5) using ammonium thiocyanate in an acetic anhydride/acetic acid mixture. The corresponding *N*-acetyl derivative of **16** was also formed. The R_f values for the both thiohydantoin **16** and its 3-acetyl derivative are very close, requiring careful monitoring of the reaction by TLC. The 5-(*o*-carboran-1-ylmethyl)-2-thiohydantoin, **16**, was isolated in 79% yield.

The reaction sequence for the synthesis of carboranylbarbiturate **20** is shown in Scheme 6. The alkylation[48] of diethyl malonate with 4-tosylbut-2-yne[49] afforded bis(but-2-ynyl)-malonic acid diethyl ester, **17**. The reaction of **17** with urea[50] in the presence of sodium ethoxide in ethanol under anhydrous

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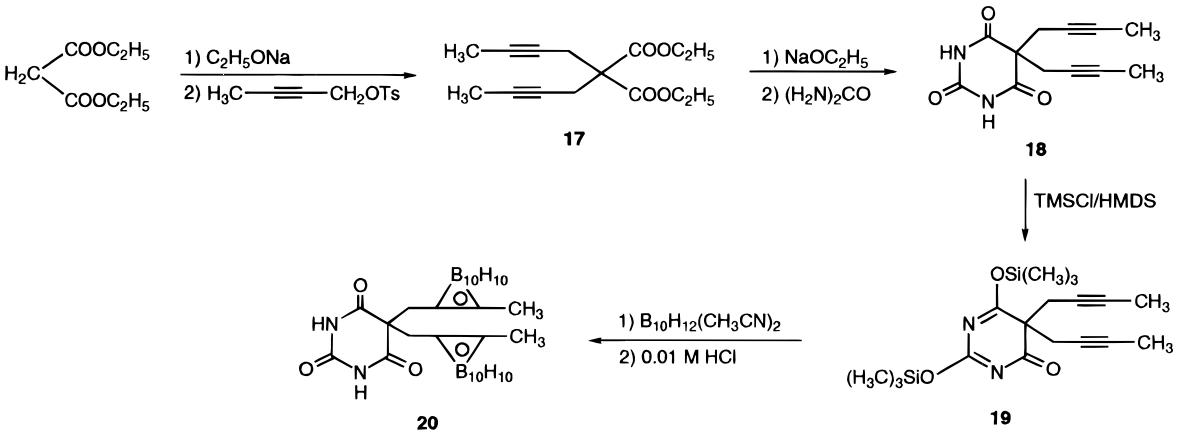
Scheme 6



conditions gave 5,5-bis(but-2-ynyl)barbiturate, **18** (67% yield). Excess of sodium ethoxide in the cyclization reaction should be avoided, since base, especially under refluxing conditions, causes ring opening between C-1 and C-6 and between C-3 and C-4 with the loss of urea.[51] The cyclized product, the acetylenic barbiturate **18**, was of interest *per se*, since compounds possessing the acetylenic function show hypnotic properties.[52]

It is well-known that acetylenes containing a free hydroxyl or amino group destroy decaborane and fail to give any carborane products.[1] To prevent such degradation, the imide functions of **18** were protected with trimethylsilyl groups (**19**) and the resulting compound was boronated by the usual procedure. The low yield (27%) of **20** can be explained by steric hindrance due to two carborane cages in close proximity at the 5-position. This conclusion is supported by the observation that the monoboronated product was the main product when the reaction was terminated after 4−5 h even in the presence of a 2.5 molar excess of the bis(acetonitrile)−decaborane complex. However, it is also conceivable that the trimethylsilyl protective groups are not optimal ones in this reaction. The chemical structures of barbiturates **18** and **20** were confirmed by elemental analysis, MS, and ^{1}H NMR.

Attempts to synthesize 5,5-bis(*o*-carboran-1-ylmethyl)barbiturate, using the procedure described in Scheme 6, were unsuccessful. The alkylation of diethyl malonate with propargyl bromide afforded bis(prop-1-ynyl)malonic acid diethyl ester, but cyclization of this ester with urea did not occur.

Pharmacology Studies

Initial evaluations of the anticonvulsant activities of the hydantoin **14** and barbiturates **18** and **20** were performed by the Antiepileptic Drug Development (ADD) Program, Epilepsy Branch, Neurological Disorders Program, National Institutes of Neurological Disorders and Stroke. The test procedures have been previously described.[53] The animals used in these studies were male Carworth Farms no. 1 (CF1) mice and male Sprague-Dawley rats. The compounds were suspended in 0.5% aqueous methylcellulose and were administered in mice intraperitoneally at three dosage levels (30, 100, and 300 mg/kg) and orally in rats (50 mg/kg). Two animal models were used to determine a compound's potential anticonvulsant activity: one evaluated the compound's ability to prevent seizure spread following maximal electroshock (MES); and the second measured its ability to raise the seisure threshold following the subcutaneous administration of pentylenetetrazole (sc Met). The hydantoin, **14**, showed activity in mice only at the maximal dose of 300 mg/kg and in rats after oral administration. There was no apparent toxicity at these levels. Barbiturate **18** showed activity in mice at dosages of 100 mg/kg and higher and in rats as well. However, this compound was toxic at these levels. Compound **20**, on the other hand, showed no anticonvulsant activity.

Conclusion

The compounds described here represent novel boron-containing amino acids,[1] hydantoins, and barbiturates. Amino acids **5a**, **5b**, and **13** were synthesized in good yields from readily available materials. *o*-Carboranylalanine (**13**) was used in the synthesis of three novel carboranyl hydantoins: *closo*-hydantoin (**14**), *nido*-hydantoin (**15**), and *closo*-thiohydantoin (**16**). Also two new barbiturates **18** (acetylenic) and **20** (carboranyl) were readily synthesized. Hydantoin **14** exhibited moderate activity in mice and rats without toxic effects. This warrants the synthesis and anticonvulsant screening of new carboranylhydantoins that more closely resemble the therapeutically used hydantoins Dilantin and Nirvanol. The biological evaluation of these compounds as potential boron carriers for BNCT is in progress and will be presented separately.

Acknowledgment. This research was supported by the U.S. Public Health Service (Grant R01 CA-53896) and the Department of Energy (Contracts DE-FG02-90ER60972 and DE-AC02-76CH00016). We wish to acknowledge Drs. H. J. Kupferberg and J. P. Stables of the Preclinical Pharmacology Section of the National Institute of Neurological Disorders and Strokes for anticonvulsant screening of compounds **14**, **18**, and **20**. We also wish to thank the Callery Chemical Co. for providing decaborane, Dr. C. E. Cottrell of the Campus Chemical Instrumentation Center of The Ohio State University for recording the ^{1}H NMR and ^{13}C NMR spectra on the Bruker AM500, and Dr. D. H. Chang of the Campus Chemical Instrumentation Center of The Ohio State University for recording the high-resolution mass spectra on the Finnigan MAT-900.

IC9511229

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