Full Paper

Applied
Organometallic
Chemistry

Received: 31 July 2007 Revised: 30 August 2007 Accepted: 3 June 2008

(www.interscience.com) DOI 10.1002/aoc.1435

Synthesis of a series of boronated unnatural cyclic amino acids as potential boron neutron capture therapy agents

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New boronated unnatural cyclic amino acids, 1–6, were synthesized for potential use in neutron capture therapy. In order to understand the effect of molecular lipophilicity on the biological activity, different linkers were introduced between the boronic acid and 1-aminocycloalkanecarboxylic acid moieties. The key step in the syntheses was the preparation of a series of alkenyl-substituted cycloalkanones, which were subsequently converted to amino acids via the Bücherer–Strecker reaction. The introduction of the boronic acid function into hydrantoins 19–24 was realized by hydroboration reactions using diisopinocampheylborane (Ipc$_2$BH). The target boronated amino acids were modeled after 1-aminocyclobutanecarboxylic acid and 1-amino-3-boronocyclopentanecarboxylic acid, which have previously demonstrated high uptake in tumors. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: cyclic amino acids; boronic acids; neutron capture therapy; synthesis

Introduction

In the last decade, there has been considerable interest in boron neutron capture therapy (BNCT),[1] a binary approach for the treatment of cancer. BNCT is a particularly attractive therapy for patients with high-grade gliomas and metastatic brain tumors whose life expectancy is generally less than one year, even with aggressive treatments using surgery, radiation and chemotherapy. The potential use of boron compounds for the treatment of cancer is based upon the unique nuclear properties of the ^{10}B nucleus and its high capacity to absorb thermal neutrons. The resulting activated ^{11}B nucleus, generated by neutron capture, undergoes fission and releases an α-particle and a high-energy lithium-7 ion. The linear energy transfer (LET) of these heavily charged particles has a range of approximately one cell diameter and thus they are lethal to the cells in which they are generated. To minimize the damage to normal tissues, a highly tumor-selective, nontoxic boron-containing compound is critical for successful BNCT. It has been estimated that the concentration of ^{10}B necessary for effective BNCT is 15–30 µg of ^{10}B per gram of tumor tissue. In addition, the boron ratio should exceed 3 for both tumor : blood and tumor : normal tissue.[2] To date, a variety of molecules have been used to deliver boron to tumor cells. These include carbohydrates,[3] polyamines,[4] amino acids,[5] nucleosides,[6] antisense agents,[7] porphyrins[8] and peptides.[9] Boronic acid and polyhedral boron compounds are generally used as the boron carriers. In fact, one of the drugs currently in BNCT clinical trials is an amino acid, 4-dihydroxyborylphenylalanine (BPA).[10]

It is also known that 1-aminocycloalkanecarboxylic acids cross the blood–brain barrier[11] and that they are metabolically stable.[12] Positron emission tomographic (PET) investigations[13] using carbon-11 labeled 1-aminocyclobutanecarboxylic acid (ACBC) demonstrated that this amino acid localizes in tumors more avidly than BPA. For this reason we have focused on the synthesis of unnatural cyclic amino acids containing boronic acids[14] and carboranes[15] as the boron source. Remarkably, bio-distribution studies using 1-amino-3-boronocyclopentanecarboxylic acid, in mice-bearing melanoma tumors, resulted in tumor to normal tissue boron ratios in excess of 20:1.[16,17] Encouraged by the results of these studies, we prepared a series of novel boronated unnatural cyclic amino acids, **1**–**6**, for a bio-distribution study (Fig. 1) in an effort to understand the effect of molecular lipophilicity on the biological activity.

Materials and Methods

General methods

All reagents were used as received. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Column chromatography was performed using silica-gel (60 Å, 230–400 mesh, ICN Biomedicals GmbH, Eschwege, Germany). Analytical thin-layer chromatography was performed using 250 µm silica (Analtech, Inc., Newark, DE, USA) and compounds were visualized by phosphomolybdic acid.

^{1}H NMR and ^{13}C NMR spectra were recorded at 250.13 and 63.89 MHz, respectively. In cases where more than one isomer formed, we have reported the ^{13}C NMR of the major isomer. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra were referenced to TMS and measured with respect to the residual protons in the deuterated solvents. Microanalysis was performed by Atlantic Microlab Inc. (Norcross, GA, USA). HR-FAB-MS (M+1) were obtained on a ZABEQ instrument in a glycerol matrix.

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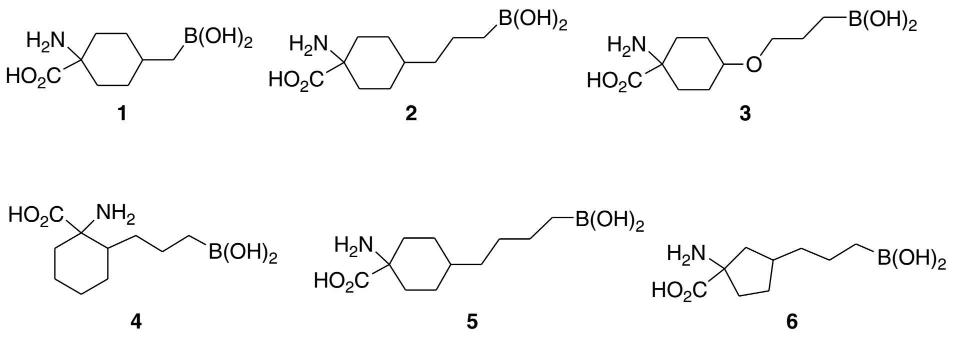


Figure 1. New boronated unnatural cyclic amino acids.

Synthesis of 8-methylene-1,4-dioxa-spiro[4,5]decane (14)

A 250 ml flask equipped with a magnetic stirring bar, a septum inlet, a reflux condenser and a nitrogen bubbler was charged with 1,4-cyclohexanedione monoethylene ketal, **13** (5.00 g, 32.0 mmol), and methyltriphenylphosphonium bromide (11.4 g, 32.0 mmol). The flask was flushed with nitrogen and then dry toluene (40 ml) was added. After stirring at room temperature for 30 min, the solution was cooled to 0 °C, and KOBu^t (3.59 g, 32.0 mmol) was added. The mixture was slowly warmed to room temperature, refluxed for 4 h, and then treated with water (40 ml) at room temperature. The organic layer was separated and dried over anhydrous $MgSO_4$. Analytically pure product was isolated by column chromatography (silica-gel, EtOAc-hexanes, 1 : 9) as a colorless liquid (4.50 g, 91%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.67 (s, 2H), 3.95 (s, 4H), 2.34–2.25 (m, 4H), 1.72–1.69 (m, 4H). ^{13}C NMR (63.9 MHz, $CDCl_3$): δ 147.1, 128.1, 108.1, 64.2, 35.7, 31.8. Anal calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.96; H, 9.10.

Synthesis of 4-methylenecyclohexanone (7)

To a 100 ml round-bottomed flask equipped with a stirring bar was added 8-methylene-1,4-dioxa-spiro[4,5] decane, **14** (2.23 g, 14.48 mmol), $CeCl_3{\bullet}7H_2O$ (2.70 g, 7.24 mmol), NaI (1.09 g, 7.24 mmol), acetone (15.0 ml) and aqueous HCl (2 M, 5.0 ml). The mixture was stirred for 10 h at room temperature and then extracted with Et_2O (5 × 20 ml). The ether layer was separated and dried over anhydrous $MgSO_4$. After solvent removal, the product was purified by column chromatography (silica-gel, EtOAc-hexanes, 1 : 20) as colorless liquid (0.99 g, 62%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.89 (s, 2H), 2.55–2.50 (m, 4H), 2.46–2.40 (m, 4H). ^{13}C NMR (63.9 MHz, $CDCl_3$): δ 212.4, 144.1, 110.5, 41.3, 32.8. Anal calcd for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 76.24; H, 9.08.

Synthesis of 4-hydroxy-1,4-dioxaspiro[4,5]decane (15)

1,4-Cyclohexanedione monoethylene ketal, **13** (21.0 g, 134.5 mmol) was dissolved in absolute ethanol (50 ml). $NaBH_4$ (2.54 g, 67.2 mmol) was added in five portions at 0 °C and then the mixture warmed to room temperature and stirred for another 3 h. The excess ethanol was removed under reduced pressure, the residue hydrolyzed with water (50 ml) and extracted into ether (3 × 25 ml). The combined organic phase was dried over anhydrous $MgSO_4$. Column chromatography (silica-gel, EtOAc-hexanes, 1 : 3) afforded compound **15** as a colorless liquid (21.0 g, 99%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.94 (s, 4H), 3.79 (br, 1H), 1.89–1.77 (m, 4H), 1.67–1.56 (m, 4H). ^{13}C NMR (63.9 MHz, $CDCl_3$): δ 108.2, 68.0, 64.2, 31.9, 31.5. Anal. calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.51; H, 8.84.

Synthesis of 8-tosyl-1,4-dioxaspiro[4,5]decane (16)

Compound **15** (3.0 g, 19.0 mmol), tosyl chloride (3.62 g, 19.0 mmol) and pyridine (3 ml) were added to a 250 ml flask at 0 °C. The reaction flask was sealed and stored at 0 °C overnight. The mixture was extracted with ethyl acetate (3 × 20 ml), washed with saturated aqueous $CuSO_4$ solution (20 ml) to remove the pyridine, and dried over anhydrous $MgSO_4$. The product was purified by flash chromatography (silica-gel, EtOAc-hexanes, 2 : 3) to obtain a white solid (5.69 g, 96%); m.p. 68–69 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.79 (d, 2H, $J = 8.7$ Hz), 7.56 (d, 2H, $J = 8.7$ Hz), 4.62 (br, 1H), 3.94–3.87 (m, 4H), 2.44 (s, 3H), 1.85–1.77 (m, 5H), 1.57–1.50 (m, 3H). ^{13}C NMR (63.9 MHz, $CDCl_3$): δ 144.4, 134.2, 129.6, 127.3, 107.1, 78.7, 64.1, 30.4, 28.9, 21.4. Anal. calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45. Found: C, 57.60; H, 6.33.

Synthesis of 8-allyl-1,4-dioxaspira[4,5]decane (17)

Tosylate **16** (3.0 g, 9.60 mmol) in THF (30 ml) was charged to a 150 ml round-bottomed flask equipped with a magnetic stirring bar the solution was cooled to 0 °C in a ice bath. Allyl magnesium bromide (9.60 mmol, 9.60 ml of a 1.0 M solution in ethyl ether) was added dropwise with stirring at 0 °C. After refluxing overnight, the reaction solution was hydrolyzed with saturated aqueous solution of ammonium chloride (30 ml). The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 20 ml). The combined organic layers were dried over anhydrous $MgSO_4$, concentrated and purified by flash column chromatography (silica-gel, EtOAc-hexanes, 1 : 10) to afford the product as a colorless liquid (1.52 g, 86%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.86–5.70 (m, 1H), 5.01–4.95 (m, 2H), 3.93 (s, 4H), 2.04–1.97 (m, 2H), 1.75–0.97 (m, 9H). ^{13}C NMR (63.9 MHz, $CDCl_3$): δ 137.2, 115.5, 108.9, 64.1, 40.6, 36.1, 34.4, 29.8. Anal. calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.36; H, 9.76.

Synthesis of 4-allylcyclohexanone (8)

Compound **17** (1.00 g, 5.49 mmol) was dissolved in acetone (20 ml) in a 100 ml round-bottomed flask equipped with a magnetic stirring bar. Aqueous HCl (4 M, 5 ml) was added and the solution stirred overnight at room temperature. The reaction was then extracted with pentane (3 × 20 ml). The organic layers were combined, dried over anhydrous $MgSO_4$. The solvent was evaporated at 40 °C and the product purified by flash column chromatography (silica-gel, Et_2O-petane, 1 : 10) to obtain colorless liquid (0.62 g, 82%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.89–5.73 (m, 1H), 5.08–5.01 (m, 2H), 2.11–1.97 (m, 2H), 1.86–1.33 (m, 9H). ^{13}C NMR (63.9 MHz, $CDCl_3$): δ 211.9, 136.5, 116.2, 40.6, 39.8, 35.8, 32.2. Anal. calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.11; H, 10.05.

Synthesis of the ethylene ketal of 4-allyloxycyclohexanone (18)

Compound **15** (12.0 g, 75.9 mmol) was placed in a 250 ml round-bottomed flask and dissolved in dry THF (100 ml) at 0 °C. Sodium hydride (2.0 g, 83.3 mmol) was added in four portions. The reaction mixture was allowed to stir at room temperature for 2 h. Allyl bromide (9.20 g, 75.9 mmol) was added via a syringe at room temperature. After stirring at room temperature overnight, the solvent was removed; the residue was hydrolyzed with water (20 ml) and extracted with ether (3 × 25 ml). The ether layer was combined, dried over anhydrous $MgSO_4$, concentrated under reduced pressure and the residue purified by column chromatography (silica-gel, EtOAc-hexanes, 1 : 4) to afford compound **18** as a colorless liquid (15.0 g, 85%). ^1H NMR ($CDCl_3$, 250 MHz): δ 6.00–5.84 (m, 1H), 5.31–5.12 (m, 2H), 3.98 (d, 2H, $J = 5.4$ Hz), 3.94 (s, 4H), 3.48–3.43 (m, 1H), 1.88–1.50 (m, 8H). ^{13}C NMR ($CDCl_3$, 63.9 MHz): δ 135.4, 116.2, 108.4, 74.1, 68.9, 64.2, 31.3, 28.5. Anal. calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.52; H, 8.98.

Synthesis of 4-allyloxycyclohexanone (9)

The procedure paralleled that described for compound **16**. Compound **18** (2.2 g, 11.1 mmol), acetone (25 ml), aqueous HCl (4 ml, 2 M), $CeCl_3•7H_2O$ (2.0 g, 5.5 mmol) and NaI (0.82 g, 5.5 mmol) were utilized. Compound **9** was purified by column chromatography (silica-gel, EtOAc–hexanes, 1 : 4) and isolated as a colorless liquid (1.65 g, 97%). ^1H NMR ($CDCl_3$, 250 MHz): δ 6.03–5.88 (m, 1H), 5.35–5.17 (m, 2H), 4.08–4.05 (m, 2H), 3.81–3.74(m, 1H), 2.86–2.53 (m, 2H), 2.32–2.21 (m, 2H), 2.16–2.04 (m, 2H), 2.01–1.92 (m, 2H). ^{13}C NMR ($CDCl_3$, 63.9 MHz): δ 211.0, 134.9, 116.5, 72.1, 69.1, 37.1, 30.4. Anal. calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.05; H, 9.00.

Synthesis of 3-allylcyclohexanone (11)

Cyclohexenone (2.00 g, 21.0 mmol) and $TiCl_4$ (21 ml of 1.0 M CH_2Cl_2 solution, 21.0 mmol) were dissolved in CH_2Cl_2 (15 ml) in a 250 ml round-bottomed flask equipped with a magnetic stirring bar at −78 °C. Freshly distilled allylsilane (2.62 g, 22.9 mmol) was added dropwise with stirring at −78 °C. After stirring at room temperature for 3 h, the solution was hydrolyzed (20 ml of H_2O), extracted with Et_2O (3 × 20 ml), the combined organic fractions dried over anhydrous $MgSO_4$, and the product purified by flash column chromatography (silica-gel, EtOAc-hexanes, 1 : 10) to afford a colorless liquid (2.43 g, 84%). ^1H NMR (250 MHz, $CDCl_3$): δ 5.83–5.67 (m, 1H), 5.06–5.00 (m, 2H), 2.39–2.29 (m, 2H), 1.86–1.33 (m, 11H). ^{13}C NMR (63.9 MHz, $CDCl_3$): δ 211.9, 135.6, 116.7, 47.6, 41.2, 40.7, 38.6, 30.7, 25.0.

Synthesis of 3-allylcyclopentanone (12)

The procedure paralleled that described for compound **11** using cyclopentenone (2.00 g, 24 mmol) to afford compound **12** as a colorless liquid (2.3 g, 79%). ^1H NMR (250 MHz, $CDCl_3$): δ 5.81–5.74 (m, 1H), 5.09–5.02 (m, 2H), 2.54–2.10 (m, 5H), 1.90–1.63 (m, 2H), 1.62–1.52 (m, 2H). ^{13}C NMR (63.9 MHz, $CDCl_3$): δ 219.4, 136.2, 116.4, 44.6, 39.5, 38.3, 36.6, 28.9.

Synthesis of the hydantoin of 4-methylenecyclohexanone (19)

A 50 ml Ace pressure tube was charged with compound **7** (0.50 g, 4.54 mmol), aqueous ethanol (50% ethanol in water, 10 ml), potassium cyanide (1.20 g, 18.5 mmol) and ammonium carbonate (2.70 g, 28.4 mmol). The reaction vessel was sealed and heated at 60 °C (oil bath) for 4 h. A pale-yellow precipitate formed. The reaction tube was cooled to room temperature and carefully opened in a fume hood. The solvent was removed under reduced pressure and the product was obtained by column chromatography over silica-gel using EtOAc as the eluting solvent (white solid, 0.79 g, 97%); m.p. 210–212 °C. ^1H NMR (250 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.50 (s, 1H), 4.68 (s, 2H), 2.27–2.24 (m, 4H), 1.67–1.61 (m, 4H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 178.0, 156.3, 146.2, 108.4, 61.6, 34.5, 29.3. Anal. calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.85; H, 6.64; N, 15.43.

Synthesis of the hydantoin of 4-allylcyclohexanone (20)

The synthesis was carried out as described for compound **19**. A solution of 4-allylcyclohexanone, **8**, (0.35 g, 3.62 mmol), aqueous ethanol (50% ethanol in water, 10 ml), potassium cyanide (0.71 g, 10.9 mmol) and ammonium carbonate (1.72 g, 18.1 mmol) was sealed and heated at 60 °C (oil bath) for 4 h. The product was purified by column chromatography over silica-gel using EtOAc as the eluting solvent (white solid, 0.59 g, 78%); m.p. 212–214 °C. ^1H NMR (250 MHz, DMSO-d_6): δ 10.50 (s, 1H), 8.41 (s, 1H), 5.79–5.72 (m, 1H), 5.00–4.54 (m, 2H), 1.99–1.62 (m, 11H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 178.6, 156.3, 137.0, 115.8, 62.2, 40.8, 35.6, 33.0, 27.0. Anal. calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.25; H, 7.66; N, 13.42.

Synthesis of the hydantoin of 4-allyloxycyclohexanone (21)

The synthesis was carried out as described for compound **19**. A solution of 4-allyloxycyclohexanone, **9** (1.11 g, 7.25 mmol), aqueous ethanol (50% ethanol in water, 15 ml), potassium cyanide (0.94 g, 14.5 mmol) and ammonium carbonate (3.48 g, 36.2 mmol) was sealed and heated at 60 °C (oil bath) for 5 h. The product was purified by column chromatography over silica-gel using EtOAc as the eluting solvent (white solid, 1.40 g, 86%); m.p. 164–165 °C. ^1H NMR ($CDCl_3$, 250 MHz): δ 10.57(s, 1H), 8.40 (s, 1H), 5.95–5.79 (m, 1H), 5.26–5.08 (m, 2H), 3.97–3.91 (m, 2H), 3.30 (m, 1H), 1.93–1.28 (m, 8H). ^{13}C NMR ($CDCl_3$, 63.9 MHz): δ 178.4, 156.3, 135.9, 115.8, 74.9, 68.0, 61.3, 31.5, 26.8. Anal. calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.79; H, 7.10; N, 12.38.

Synthesis of the hydantoin of 2-allylcyclohexanone (22)

The synthesis was carried out as described for compound **19**. A solution of 2-allylcyclohexanone, **10** (1.0 g, 7.24 mmol), aqueous ethanol (50% ethanol in water, 20 ml), potassium cyanide (1.41 g, 21.72 mmol) and ammonium carbonate (3.44 g, 36.2 mmol) was sealed and heated at 60 °C (oil bath) for 4 h. The product was purified by column chromatography over silica-gel using EtOAc as the eluting solvent (white solid, 1.20 g, 80%); m.p. 195–197 °C. ^1H NMR (250 MHz, DMSO-d_6): δ 10.30 (s, 1H), 7.97 (s, 1H), 5.81–5.63 (m, 1H), 4.97–4.93 (m, 2H), 1.95–1.12 (m, 11H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 177.7, 156.6, 135.2, 115.5, 65.6, 39.9, 34.3, 25.9, 24.3, 20.4. Anal. calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.32; H, 7.65; N, 13.32.

Synthesis of the hydantoin of 3-allylcyclohexanone (23)

The synthesis was carried out as described for compound **19**. A solution of 3-allylcyclohexanone **11** (0.92 g, 6.7 mmol), aqueous ethanol (50% ethanol in water, 10 ml), potassium cyanide (1.08 g, 16.7 mmol) and ammonium carbonate (3.16 g, 33.3 mmol) was sealed and heated at 60 °C (oil bath) for 4 h. The product was purified by column chromatography over silica-gel using EtOAc as the eluting solvent (white solid, 1.31 g, 95%); m.p. 182–184 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.50 (s, 1H), 8.39 (s, 1H), 5.81–5.65 (m, 1H), 5.02–4.96 (m, 2H), 1.95–0.86 (m, 11H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 178.4, 156.3, 136.4, 116.3, 62.7, 40.7, 40.5, 32.9, 31.8, 30.9, 20.7. Anal. calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.37; H, 7.58; N, 13.27.

Synthesis of the hydantoin of 3-allylcyclopentanone (24)

The synthesis was carried out as described for compound **19**. A solution of 3-allylcyclopentanone, **12** (0.62 g, 5 mmol), aqueous ethanol (50% ethanol in water, 14 ml), potassium cyanide (0.65 g, 10.0 mmol) and ammonium carbonate (2.40 g, 25.0 mmol) was sealed and heated at 60 °C (oil bath) for 4 h. The product was purified by column chromatography over silica-gel using EtOAc as the eluting solvent (white solid, 0.63 g, 64%); m.p. 197–199 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 9.94 (s, 1H), 8.10 (s, 1H), 5.82–5.66 (m, 1H), 5.05–4.93 (m, 2H), 2.12–1.56 (m, 7H), 1.37–1.16 (m, 2H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 179.0, 158.2, 137.5, 115.6, 67.7, 42.5, 38.2, 36.7, 31.2, 30.6. Anal. calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.37; H, 7.53; N, 14.29.

Synthesis of boronohydantoin (25)

A dry 100 ml round-bottomed flask was charged with **19** (0.56 g, 3.10 mmol) and flushed with nitrogen. Freshly distilled THF (10 ml) was added and stirred until **19** was completely dissolved, then diisopinocampheylborane $(Ipc)_2BH$ (13 ml of 0.74 M solution in THF, 9.62 mmol) added dropwise at room temperature. The solution was allowed to stir overnight at room temperature. Freshly distilled acetaldehyde (0.84 g, 19.1 mmol) was added to the mixture at room temperature. After stirring for 6 h, the mixture was hydrolyzed with dilute aqueous HCl (2 M, 6 ml). The solvent was removed and the residue was subjected to column chromatography (silica-gel, MeOH–EtOAc, 1 : 10) to afford compound **25** as a white solid (0.60 g, 86%); m.p. 231–233 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.34 (s, 1H), 8.40 (s, 1H), 1.95–0.92 (m, 9H), 0.85–0.78 (m, 2H). ^{13}C NMR (63.9 MHz, DMSO–d_6): δ 178.7, 156.4, 60.9, 37.4, 32.3, 24.2, 23.8. HR-MS (FAB, glycerol matrix): calcd for $M + H + Gly - 2H_2O$; 283.1468. Found: 283.1471.

Synthesis of boronohydantoin (26)

The synthesis was carried out as described for compound **25**. Compound **20** (0.30 g, 1.44 mmol) and $(Ipc)_2BH$ (5.84 ml of a 0.74 M solution in THF, 4.32 mmol) was used. After stirring at room temperature overnight, acetaldehyde (0.38 g, 8.64 mmol) was added. The product was purified by column chromatography (silica-gel, MeOH–EtOAc, 1 : 10) to afford compound **26** as a white solid (0.30 g, 83%); m.p. 169–171 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.34 (s, 1H), 8.40 (s, 1H), 1.90–0.82 (m, 16H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 178.6, 156.4, 62.9, 40.8, 35.4, 26.5, 25.3, 21.5, 20.7. HR-MS (FAB, glycerol matrix): calcd for $M + H + Gly - 2H_2O$; 311.1781. Found: 311.1779.

Synthesis of boronohydantoin (27)

The synthesis was carried out as described for compound **25**. Compound **21** (0.50 g, 2.23 mmol) and $(Ipc)_2BH$ (8.64 ml of 0.74 M solution in THF, 6.69 mmol) was used. After stirring at room temperature overnight, acetaldehyde (0.60 g, 13.62 mmol) was added. The product was purified by silica-gel column chromatography (MeOH–EtOAc, 1 : 10) to afford **27** as a white solid (0.52 g, 87%); m.p. 168–170 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 10.56 (s, 1H), 8.38 (s, 1H), 3.44–3.42 (m, 1H), 3.34–3.23 (m, 2H), 1.88–1.38 (m, 10H), 0.58–0.52 (m, 2H). ^{13}C NMR ($CDCl_3$, 63.9 MHz): δ 178.4, 156.3, 75.1, 69.8, 61.4, 31.5, 28.2, 26.9, 24.8. HR-MS (FAB, glycerol matrix): calcd for $M + H + Gly - 2H_2O$; 327.1730. Found: 327.1724.

Synthesis of boronohydantoin (28)

The synthesis was carried out as described for compound **25**. Compound **22** (0.53 g, 2.55 mmol) and $(Ipc)_2BH$ (10.34 ml of a 0.74 M solution in THF, 7.65 mmol) were used. After stirring at room temperature overnight, acetaldehyde (0.67 g, 15.30 mmol) was added. The product was purified by silica-gel column chromatography (MeOH–EtOAc, 1 : 10) to afford compound **28** as a white solid (0.56 g, 86%); m.p. 143–145 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 9.93 (s, 1H), 8.19 (s, 1H), 1.89–0.80 (m, 13H), 0.51–0.40 (m, 2H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 178.5, 156.9, 66.3, 40.8, 35.0, 32.9, 26.2, 25.1, 21.6, 20.9. HR-MS (FAB, glycerol matrix): calcd for $M + H + Gly - 2H_2O$; 311.1781. Found: 311.1776.

Synthesis of boronohydantoin (29)

The synthesis was carried out as described for compound **25**. Compound **23** (0.53 g, 2.55 mmol) and $(Ipc)_2BH$ (10.3 ml of a 0.74 M Solution in THF, 7.65 mmol) was used. After stirring at room temperature overnight, acetaldehyde (0.67 g, 15.30 mmol) was added. The product was purified by silica-gel column chromatography (MeOH–EtOAc, 1 : 10) to afford compound **29** as a white solid (0.45 g, 69%); m.p. 162–164 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.50 (s, 1H), 8.37 (s, 1H), 1.68–0.79 (m, 15H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 178.5, 156.3, 62.8, 41.2, 33.1, 31.7, 31.4, 21.2, 20.8. HR-MS (FAB, glycerol matrix): calcd for $M + H + Gly - 2H_2O$; 311.1781. Found: 311.1782.

Synthesis of boronohydantoin (30)

The synthesis was carried out as described for compound **25**. Compound **24** (0.58 g, 3.0 mmol) and $(Ipc)_2BH$ (12.16 ml of a 0.74 M solution in THF, 9.0 mmol) were used. After stirring at room temperature overnight, acetaldehyde (0.79 g, 18.0 mmol) was added. The product was purified by silica-gel column chromatography (MeOH–EtOAc, 1 : 10) to afford compound **30** as a white solid (0.63 g, 87%); m.p. 120–122 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 9.94 (s, 1H), 8.18 (s, 1H), 1.99–1.12 (m, 13H), 0.59–0.47 (m, 2H). ^{13}C NMR (63.9 MHz, DMSO-d_6): δ 179.7, 158.2, 67.7, 43.7, 40.4, 38.5, 38.0, 36.9, 31.2, 23.1. HR-MS (FAB, glycerol matrix): calcd for $M + H + Gly - 2H_2O$; 269.1311. Found: 269.1322.

Synthesis of 1-amino-4-boronomethylcyclohexanecarboxylic acid (1)

Boronohydantoin **25** (0.42 g, 2.00 mmol) was placed in a 50 ml Ace pressure tube along with a solution of aqueous hydrogen chloride (12 M, 3 ml). The tube was sealed and then heated at

130 °C (oil bath) for 48 h. After cooling to room temperature, the tube was carefully opened. The mixture was decolorized with charcoal (0.2 g) and filtered. The solvent was removed under reduced pressure to afford a pale-yellow solid (0.37 g, 93%), which decomposed when heated above 238 °C. ^{1}H NMR (250 MHz, D_2O): δ 2.09–1.58 (m, 9H), 1.17–0.88 (m, 2H). ^{13}C NMR (63.9 MHz, D_2O): δ 172.7, 56.8, 46.5, 30.1, 21.2, 17.8. HR-MS (FAB, glycerol matrix): calcd for M + H + Gly − $2H_2O$; 258.1515. Found: 258.1516.

Synthesis of 1-amino-4-boronopropylcyclohexanecarboxylic acid (2)

The synthesis was carried out as described for **1**. Boronohydantoin **26** (0.51 g, 2.00 mmol) and aqueous hydrogen chloride (12 M, 3 ml) were sealed and then heated at 130 °C (oil bath) for 48 h. A pale-yellow solid (0.44 g, 96%) was obtained after workup, which decomposed when heated above 252 °C. ^{1}H NMR (250 MHz, D_2O): δ 2.09–1.58 (m, 13H), 1.17–0.84 (m, 2H). ^{13}C NMR (63.9 MHz, D_2O): δ 172.7, 56.8, 36.5, 30.1, 23.7, 21.2, 17.8. HR-MS (FAB, glycerol matrix): calcd for M + H + Gly − $2H_2O$; 286.1828. Found: 286.1829.

Synthesis of 1-amino-4-[3-boronopropoxy]cyclohexane carboxylic acid (3)

Hydantoin **27** (0.42 g, 1.54 mmol) was placed in a 50 ml Ace pressure tube along with a solution of aqueous sodium hydroxide (2 M, 4 ml). The tube was flushed with argon and sealed. The reaction vessel was heated at 160 °C (oil bath) for 40 min. After cooling to room temperature, the tube was carefully opened in a fume hood. The reaction mixture was diluted with water and acidified with aqueous HCl (2 M) to pH = 4. The pale-yellow, clear aqueous solution was decolorized with charcoal (0.2 g) and filtered. The solvent was removed under reduced pressure to give a white solid. The solid was extracted with dry methanol (2 × 10 ml) to remove NaCl. The crude product was purified via column chromatography (silica-gel, methanol) to afford **3** (as the HCl salt) as a pale-yellow solid (0.33 g, 88%) which decomposed when heated above 247 °C. ^{1}H NMR (D_2O, 250 MHz): δ 3.67–3.52 (m, 3H), 2.34–1.62 (m, 10H), 0.82–0.76 (m, 2H). ^{13}C NMR (D_2O, 62.9 MHz): δ 173.7, 77.3, 72.4, 51.6, 31.6, 30.6, 28.3, 26.4. HR-MS (FAB, glycerol matrix): calcd for M + H + Gly − $2H_2O$; 302.1777. Found: 302.1769.

Synthesis of 1-amino-2-boronopropylcyclohexanecarboxylic acid (4)

The synthesis was carried out as described for **1**. Boronohydantoin **28** (0.51 g, 2.0 mmol) and aqueous hydrogen chloride (12 M, 3 ml) were sealed in an Ace tube and then heated at 130 °C (oil bath) for 48 h. A pale-yellow solid (0.42 g, 92%) was obtained after workup, decomposed when heated above 261 °C. ^{1}H NMR (250 MHz, D_2O): δ 2.04–0.99 (m, 13H), 0.83–0.63 (m, 2H). ^{13}C NMR (63.9 MHz, D_2O): δ 177.3, 59.9, 36.8, 30.9, 23.4, 21.3, 18.1. HR-MS (FAB, glycerol matrix): calcd for M + H + Gly − $2H_2O$; 286.1828. Found: 286.1826.

Synthesis of 1-amino-3-boronopropylcyclohexanecarboxylic acid (5)

The synthesis was carried out as described for **1**. Boronohydantoin **29** (0.51 g, 2.0 mmol) and aqueous hydrogen chloride (12 M, 3 ml) were sealed in an Ace tube and then heated at 130 °C (oil bath) for 48 h. A pale-yellow solid (0.39 g, 86%) was obtained after workup, which decomposed when heated above 255 °C. ^{1}H NMR (250 MHz, D_2O): δ 1.78–0.93 (m, 13H), 0.79–0.66 (m, 2H). ^{13}C NMR (63.9 MHz, D_2O): δ 176.5, 57.9, 36.4, 30.9, 23.3, 21.1, 18.0. HR-MS (FAB, glycerol matrix): calcd for M + H + Gly − $2H_2O$; 286.1828. Found: 286.1819.

Synthesis of 1-amino-3-boronopropylcyclopentanecarboxylic acid (6)

The synthesis was carried out as described for boronated amino acid **1**. Boronohydantoin **30** (0.48 g, 2.0 mmol) and aqueous hydrogen chloride (12 M, 3 ml) were sealed and then heated at 130 °C (oil bath) for 48 h. A white solid (0.36 g, 84%) was obtained after workup which decomposed when heated above 244 °C. ^{1}H NMR (250 MHz, D_2O): δ 2.03–1.01(m, 11H), 0.73–0.55 (m, 2H). ^{13}C NMR (63.9 MHz, D_2O): δ 178.0, 67.3, 45.3, 42.7, 41.2, 38.8, 34.3, 23.4, 16.1. HR-MS (FAB, glycerol matrix): calcd for M + H + Gly − $2H_2O$; 272.1672. Found: 272.1666.

Results and Discussion

The key synthetic step in the preparation of the targeted amino acids **1–6** is the syntheses of the appropriate alkenyl-substituted cycloalkanones (Fig. 2). The intermediate ketones can be readily transformed into the target molecules using a modified Bücherer–Strecker reaction followed by a hydroboration sequence. Schemes 1–4 outline the preparation of the intermediate ketones.

Intermediate ketone **7** was prepared starting from 1,4-cyclohexanedione monoethylene ketal, **13**, (Scheme 1). In the presence of *tert*-BuOK, the Wittig reaction of ketal **7** and methylenetriphenylphosphorane proceeded readily to give compound **14** in 91% yield.[18] Unlike other ethylene ketal compounds, removal of the ethylene ketal group in **14** using dilute hydrochloric acid was sluggish. We then discovered that the reaction proceeded efficiently in the presence of $CeCl_3$•$7H_2O$ and NaI.[19]

The synthesis of alkenyl-substituted cyclohexanone **8** also started from ketal **13** (Scheme 2). Treatment of **13** with $NaBH_4$ produced alcohol **15** in quantitative yield.[20] The tosylation of **15** afforded tosylate **16** in high yield.[14a,21] To minimize a chlorination side reaction, the tosylation temperature was maintained at 0 °C.

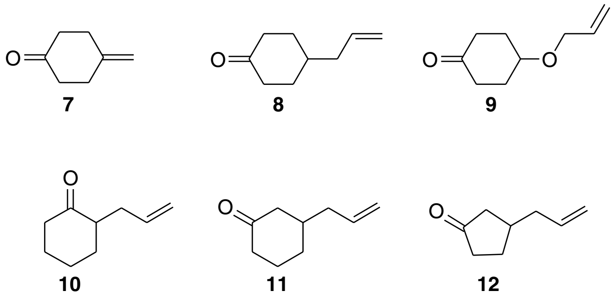
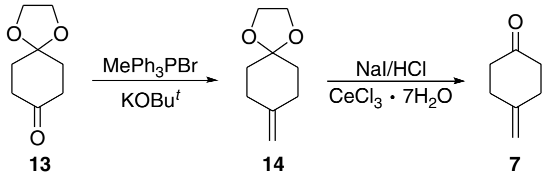
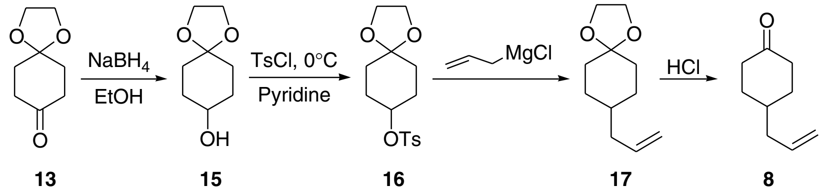


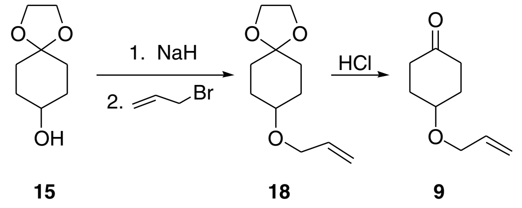
Figure 2. Intermediate alkenyl-substituted cycloalkanones.



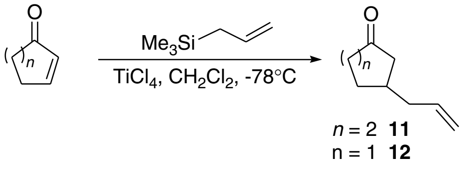
Scheme 1.



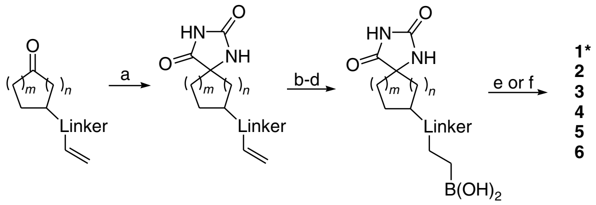
Scheme 2.



Scheme 3.



Scheme 4.



m	*n*	Linker		
1	2	none	**19**	**25**
1	2	CH_2	**20**	**26**
1	2	OCH_2	**21**	**27**
3	0	CH_2	**22**	**28**
2	1	CH_2	**23**	**29**
1	1	CH_2	**24**	**30**

*Compound **1** is prepared from 4-methylenecylenecyclohexanone, **7**

Reagents and conditions: (a) KCN, $(NH_4)_2CO_3$, EtOH/H_2O (1:1), 60 °C; (c) $(Ipc)_2BH$, THF, rt; (c) CH_3CHO, rt; (d) HCl (2 *M*), rt; (e) HCl (12 *M*), 130 °C; (f) NaOH (2*M*),160 °C.

Scheme 5.

Tosylate **16** coupled to allylmagnesium chloride to give alkene **17** in 86% isolated yield.[22] In the presence of dilute aqueous hydrochloric acid, the ethylene ketal group in **17** was readily removed in acetone at room temperature.

Introduction of an ether linker into a boronated amino acid should increase the lipophilicity of the molecule. The sequential treatment of alcohol **15** with sodium hydride and allyl bromide produced alkene **18** in 85% yield (Scheme 3). Removal of the ethylene ketal in **18** generated ketone **9** in good yield.

The Sakurai reaction, a $TiCl_4$-catalyzed reaction of an enone and allyltrimethylsiliane, was utilized to prepare intermediates **11** and **12**.[23] Starting from cyclohexenone and cyclopentenone, **11** and **12** were obtained in 84 and 79% isolated yields, respectively (Scheme 4).

The prerequisite ketone (2-allylcyclohexanone, **10**) required for the preparation of **4** was commercially available. With key intermediates ketones in hand, the corresponding hydantoins **19**–**24** were prepared using a modified Bücherer–Strecker reaction[24] (Scheme 5). In each case, two racemates were obtained. Although a detailed structural analysis has not been completed, the ^{13}C NMR spectra indicate that the racemate with the amino moiety *cis* to the linker group is the primary product.[25] The formation of the hydantoin boronates **25**–**30** from hydantoins **19**–**24** was realized by sequential treatment with diisopinocampheylborane (Ipc_2BH) and acetaldehyde.[26] The tolerance of the hydantoins in **19**–**24** to hydroboration is quite remarkable. According to the literature,[27] the NH functional group does not interfere in the hydroboration reactions. In our hands, large quantities of hydrogen gas were released during the hydroboration, which indicates reaction of the hydrogen in the NH group with Ipc_2BH.[28] Thus the use of 3.0 equivalents of Ipc_2BH was necessary for complete reaction. The hydrolysis of boronohydantoins **25, 26, 28, 29** and **30** using concentrated aqueous hydrochloric acid gave the desired boronated amino acids in good yields. The hydrolysis of **27** was carried out under basic conditions to protect the ether linkage.

As anticipated, the introduction of different linker between the boronic acid and 1-aminocycloalkanecarboxylic acid moieties influenced the lipophilicities of the resulting boronated amino acids as reflected in their R_f values on thin-layer chromatography analysis. For example, the R_f value for **5**, which contains a butylboronic acid moiety, is 0.81 using a mixture of isopropanol : water : acetic acid (2 : 2:1), whereas **1** exhibits an R_f value of 0.18, reflecting the enhanced lipophilicity of **5** when compared with **1**.

Conclusion

We report the syntheses of several novel boronated unnatural cyclic amino acids starting from the readily available starting materials. The fructose complexes[29] of these new agents will be evaluated for use as BNCT agents.

Acknowledgment

The authors wish to thank the US Department of Energy and the Robert H. Cole Foundation for support of this research.

References

[1] For recent reviews, see J. F. Valliant, K. J. Guenther, A. S. King, P. Morel, P. Schaffer, O. O. Sogbein, K. A. Stephenson, *Coord. Chem. Rev.* **2002**, *232*, 173; b) M. F. Hawthorne, A. Maderna, *Chem. Rev.* **1999**, *99*, 3421; c) A. H. Soloway, W. Tjarks, B. A. Barnum, F. G. Rong, R. F. Barth, I. M. Codogni, J. G. Wilson, *Chem. Rev.* **1998**, *98*, 1515; d) M. F. Hawthorne, *Mol. Med. Today* **1998**, *4*, 174.

[2] R. G. Fairchild, V. P. Bond. *Int. J. Radiat. Oncol. Biol. Phys.* **1985**, *11*, 831; b) D. Gabel, S. Foster, R. G. Fairchild, *Radiat. Res.* **1987**, *111*, 14.

[3] A. V. Orlova, L. O. Kononov, B. G. Kimel, I. B. Sivaev, V. I. Bregadze, *Appl. Organometal. Chem.* **2006**, *20*, 416; b) M. E. El-Zaria, A. F. Genady, D. Gabel, *New J. Chem.* **2006**, *30*, 597; c) L. F. Tietze, U. Griesbach, I. Schuberth, U. Bothe, A. Marra, A. Dondoni, *Chem. Eur. J.* **2003**, *9*, 1296; d) L. F. Titze, U. Bothe, U. Griesbach, M. Nakaichi, T. Hasegawa, H. Nakamura, Y. Yamamoto, *Bioorg. Med. Chem.* **2001**, *9*, 1747; e) G. B. Giovenzana, L. Lay, D. Monti, G. Palmisano, L. Panza, *Tetrahedron* **1999**, *55*, 14123; f) J. L. Maurer, A. J. Serino, M. R. Hawthorne, *Organometallics* **1988**, *7*, 2519.

[4] M. E. El-Zaria, U. Doerfler, D. Gabel *J. Med. Chem.* **2002**, *45*, 5817; b) C. Bauce, D. Gabel, U. Doerfler, *Eur. J. Med. Chem.* **2002**, *37*, 649; c) B. Martin, F. Posseme, C. Le Barbier, F. Carreaux, B. Carboni, N. Seiler, J. P. Moulinoux, J. G. Delcros, *J. Med. Chem.* **2001**, *44*, 3653; d) J. C. Zhuo, J. Cai, A. H. Soloway, R. F. Barth, D. M. Adams, W. Ji, *J. Med. Chem.* **1999**, *42*, 1282.

[5] G. W. Kabalka, M. L. Yao, *Anti Cancer Agents Med. Chem.* **2006**, *6*, 111; b) S. Diaz, A. Gonzalez, S. G. de Riancho, A. Rodriguez, *J. Organometal. Chem.* **2000**, *610*, 25; c) P. Lindstroem, C. Naeslund, S. Sjoeberg, *Tetrahedron Lett.* **2000**, *41*, 751; d) H. Nakamura, M. Fujiwara, Y. Yamamoto, *J. Org. Chem.* **1998**, *63*, 7529; e) C. Malan, C. Morin, *J. Org. Chem.* **1998**, *63*, 8019; f) S. B. Kahl, R. A. Kasar, *J. Am. Chem. Soc.* **1996**, *118*, 1223; g) P. A. Radel, S. B. Kahl, *J. Org. Chem.* **1996**, *61*, 4582.

[6] Z. J. Lesnikowski, E. Paradowska, A. B. Olejniczak, M. Studzinska, P. Seekamp, U. W. Schuessler, D. Gabel, R. F. Schinazi, J. Plesek, *Bioorg. Med. Chem.* **2005**, *13*, 4168; b) W. Tjarks, *J. Organomet. Chem.* **2000**, *614–615*, 37; c) S. J. Hurwitz, L. Ma, A. Eleuteri, J. Wright, J. Moravek, R. F. Schinazi, *Nucleosides Nucleotides Nucleic Acids* **2000**, *19*, 691; d) J. Lin, B. R. Shaw, *Tetrahedron Lett.* **2000**, *41*, 6701; e) J. C. Zhou, A. H. Soloway, J. C. Beeson, W. Ji, B. A. Barnum, F. G. Rong, W. Tjarks, G. T. Jordan IV, J. Liu, S. G. Shore, *J. Org. Chem.* **1999**, *64*, 9566; f) A. H. Soloway, J. C. Zhuo, F. G. Rong, A. J. Lunato, D. H. Ives, R. F. Barth, *J. Organometal. Chem.* **1999**, *581*, 150.

[7] A. B. Olejiniczak, M. Koziolkiewcz, Z. J. Lesnikowski. *Antisense Nucleic Acid Drug Dev.* **2002**, *12*, 79; b) J. C. Zhuo, W. Tjarks, A. H. Soloway, J. Cai, J. Wang, R. F. Barth, D. M. Adams, S. Eriksson, A. J. Lunato, W. Ji, *Contemporary Boron Chemistry*, Special Publication. Royal Society of Chemistry: Cambridge, **2000**, pp. 127–130; c) El Fulcrand, G. Kattan, Z. J. Lesnikowski, S. Yao, F. Tanious, W. D. Wilson, R. F. Schinazi, *J. Am. Chem. Soc.* **1994**, *116*, 7494.

[8] A. K. Bandyopadhyaya, S. Narayanasamy, R. F. Bath, W. Tjarks, *Tetrahedron Lett.* **2007**, *48*, 4467; b) M. W. Renner, M. Miura, M. W. Easson, M. G. H. Vicente, *Anti Cancer Angents Med. Chem.* **2006**, *6*, 145; c) M. F. Isaac, S. B. Kahl, *J. Organometallic Chem.* **2003**, *680*, 232; d) A. Maderna, R. Huertas, M. F. Hawthorne, R. Luguya, M. G. H. Vicente. *Chem. Commun.* **2002**, 1784; e) M. G. H. Vicente, B. F. Edwards, S. J. Shetty, Y. Hou, J. E. Boggan, *Bioorg. Med. Chem.* **2002**, *10*, 481.

[9] E. Schirrmacher, R. Schirrmacher, C. Beck, W. Mier, N. Trautman, F. Rösch, *Tetrahedron Lett.* **2003**, *44*, 9143; b) D. Ivanov, W. W. Bachovchin, A. G. Redfield. *Biochemistry* **2002**, *41*, 1587; c) A. Leush, L. Jungblut, L. Moroder, *Synthesis* **1994**, 305.

[10] R. F. Barth, W. Yang, R. T. Bartus, J. H. Rotaru, A. K. Ferketich, M. L. Moeschberger, M. M. Nawrocky, J. A. Coderre, E. K. Rofstad, *Int. J. Radiat. Oncol. Biol. Phys.* **2002**, *52*, 858; b) W. S. Kiger III, M. R. Palmer, K. J. Riley, R. G. Zamenhof, P. M. Busse, *Radiat. Res.* **2001**, *155*, 611; c) J. L. Mallesch, D. E. Moore, B. J. Allen, W. H. McCarthy, R. Jones, W. A. Stening, *Int. J. Radiat. Oncol. Biol. Phys.* **1994**, *28*, 1183.

[11] M. Aoyagi, G. W. Agranoff, L. C. Washburn, O. R. Smith, *J. Neurochem.* **1988**, *50*, 1220.

[12] C. Cativiela, M. D. Díaz-de-villegas, *Tetrahedron: Asymmetry* **2000**, *11*, 645; b) E. Gershonov, R. Granoth, E. Tzehoval, Y. Gaoni, M. Fridkin, *J. Med. Chem.* **1996**, *39*, 4833; c) M. Matrtín-vilà, C. Minguillón, R. M. Ortuno, *Tetrahedron: Asymmetry* **1998**, *9*, 4291; d) C. J. Koch, G. Höfner, K. Polborn, K. T. Wanner, *Eur. J. Org. Chem.* **2003**, *12*, 2233; e) Y. Gaoni, A. G. Chapman, N. Parvez, P. C. K. Pook, D. E. Jane, J. C. Watkins, *J. Med. Chem.* **1994**, *37*, 4288.

[13] K. F. Hubner, J. A. Thie, G. T. Smith, G. W. Kabalka, I. B. Keller, A. B. Cliefoth, S. K. Campbell, E. Buonocore, *Clin. Positron Imag.* **1998**, *1*, 165; b) R. F. Barth, W. Yang, R. T. Bartus, J. H. Rotaru, A. K. Ferketich, M. L. Moeschberger, M. M. Nawrocky, J. A. Coderre, E. K. Rofstad, *Int. J. Radiat. Oncol. Biol. Phys.* **2002**, *52*, 858.

[14] G. W. Kabalka, M. L. Yao, *Synthesis* **2003**, 2890; b) G. W. Kabalka, M. L. Yao, *Appl. Organometal. Chem.* **2003**, *17*, 398; c) R. R. Srivastava, R. Singhaus, G. W. Kabalka, *J. Org. Chem.* **1999**, *64*, 8495.

[15] B. C. Das, S. Das, G. Li, W. Bao, G. W. Kabalka, *Synlett* **2001**, 1419; b) B. C. Das, G. W. Kabalka, R. R. Srivastava, W. Bao, S. Das, G. Li, *J. Organometal. Chem.* **2000**, *614–615*, 255; c) R. R. Srivastava, R. Singhaus, G. W. Kabalka, *J. Org. Chem.* **1997**, *62*, 4476.

[16] G. W. Kabalka, B. C. Das, S. Das, *Tetrahedron Lett.* **2001**, *42*, 7145.

[17] G. W. Kabalka, Z. Z. Wu, M. L. Yao, N. Natarajan, *Appl. Radiat. Isotopes* **2004**, *61*, 1111.

[18] A. Frontier, S. J. Danishefsky, G. A. Koppel, D. Meng, *Tetrahedron* **1998**, *54*, 12721.

[19] E. Marcantoni, F. Nobili, G. Bartoli, M. Bosco, L. Sambri, *J. Org. Chem.* **1997**, *62*, 4183.

[20] C. Y. Cheng, S. C. Wu, L. W. Hsin, S. W. Tam, *J. Med. Chem.* **1992**, *35*, 2243.

[21] L. K. A. Blaehr, F. Björkling, M. J. Calverley, E. Binderup, M. Begtrup, *J. Org. Chem.* **2003**, *68*, 1367; b) G. A. Kraus, A. Melekhov, *Tetrahedron* **1998**, *54*, 11749.

[22] D. F. Taber, P. B. Deker, M. D. Gaul, *J. Am. Chem. Soc.* **1987**, *109*, 7488.

[23] H. Sakurai, A. Hosomi, J. Hayashi, *Org. Synth.* **1984**, *62*, 86; b) G. A. Molander, J. A. McKie, *J. Org. Chem.* **1991**, *56*, 4112.

[24] F. Alonso, I. Mico, C. Najera, J. M. Sansano, M. Jose, M. Yus, *Tetrahedron* **1995**, *51*, 10259; b) T. Rammeloo, C. Stevens, *Chem. Commun.* **2002**, 250.

[25] In our previous studies, syntheses of the boronated cyclobutyl- and cyclopentyl-based hydantoins using the Bücherer–Strecker reaction resulted primarily in the *cis* products, in which the amide fragment of the hydantoin was *cis* to the substituent on the ring (evidenced by an X-ray crystallographic study of one cyclopentyl derivative). The ^{13}C NMR of the *cis* racemate revealed that the resonances of the carbonyl carbons in the hydantoin ring appeared downfield of the corresponding *trans* racemate. (In the present study, all of the major products have ^{13}C resonances of the hydantoin carbonyls that appear downfield of the minor isomer.) See A. Naravane, Ph.D.Thesis, Synthesis of novel boronated amino acids for BNCT an alternate cancer therapy and use of microwaves in organic synthesis. The University of Tennessee, **2007**; b) G. Kabalka, A. Naravane, M. L. Yao, J. Coderre, Y. Chung, K. Riley, Synthesis and *in vivo* distribution of 1-amino-3-boronocyclopentanecarboxylic acids. Abstracts, *12th International Congress on Neutron Capture Therapy*, Takamatsu, Kagawa, 9–13 October, **2006**.

[26] A. Pelter, K. Smith, H. C. Brown, *Borane Reagents*. Academic Press: Burlington, MA, **1988**, p. 427.

[27] D. N. Butler, A. H. Soloway, *J. Am. Chem. Soc.* **1966**, *88*, 484.

[28] Although no details regarding gas evolution were noted in the earlier report focused on the hydroboration of *N*-alkenylureas and *N*-alkenyl-carbamates,[27] the authors did utilize excess BH_3•THF in their reactions. However, they make a strong case for the intermediacy of borane–amine complex, which then hydroborates the alkene to generate a monoalkylboronic acid. If, indeed, hydrogen gas was not evolved in the earlier studies, our observations may speak to the enhanced reactivity of dialkylborane reagents (when compared with borane itself) toward amide protons.

[29] B. K. Shull, D. E. Spielvogel, G. Head, R. Gopalaswamy, S. Sankar, K. Devito, *J. Pharm. Sci.* **2000**, *89*, 215.