Synthesis of a Potential Boron Neutron Capture Therapy Agent: 1-Aminocyclobutane-1-carboxylic Acid Bearing a Butylboronic Acid Side Chain

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Received 15 October 2003

Abstract: A novel boronated aminocyclobutanecarboxylic acid was synthesized for potential use in neutron capture therapy. The synthesis involves the preparation of tosylate **5**, which was then converted to an amino acid using Bucherer–Strecker methodology. The molecule was modeled after the unnatural amino acid, 1-aminocyclobutane-1-carboxylic acid, which has shown high uptake in brain tumors.

Key Words: amino acids, neutron capture therapy, boronic acid, synthesis, cyclobutanecarboxylic acid

Boron neutron capture therapy[1] (BNCT) is dependent on the selective deposition of ^{10}B in tumor cells. Irradiation by thermal neutrons then results in a fission reaction, which releases highly energetic particles that destroy the cells. To date, a variety of molecules have been used to deliver boron to tumor cells. These include carbohydrates,[2] polyamines,[3] amino acids,[4] nucleosides,[5] antisense agents,[6] porphyrins,[7] and peptides.[8] In recent years, encouraging results have been obtained using 4-dihydroxyborylphenylalanine (BPA) as the tumor specific boronated agent.[9]

It is believed that the amino acids are preferentially taken up by growing tumor cells. Positron emission tomography (PET) investigations[10] carried out at The University of Tennessee using carbon-11 labeled 1-aminocyclobutane-1-carboxylic acid (ACBC) demonstrated that this amino acid localizes in tumors more avidly than BPA. Very recently, Goodman reported that ^{18}F labeled 1-amino-3-(fluoromethyl)cyclobutanecarboxylic acid also localizes in tumors.[11]

Prompted by the hypothesis that incorporation of bond rotation restriction in bioactive peptides can augment the biopotency, selectivity and metabolic stability,[12] the synthesis of conformationally restricted 1-aminocyclobutane-1-carboxylic acids has attracted much attention in recent years.[13] Encouraging results have been reported.[12,13a] For example, the introduction of a 3-(aminomethyl)- or 3-(hydroxymethyl)aminocyclobutanecarboxylic acid into the antitumor peptide Tuftsin significantly increased resistance to enzymatic hydrolysis.

We have focused our efforts on the synthesis of boronated ACBC derivatives. Carborane[14] and phenylboronic acid[15] ACBC derivatives were prepared previously. In a continuation of our studies, we have now synthesized a novel butylboronic substituted amino acid **1** (Figure 1).

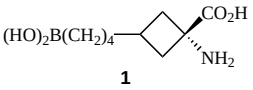

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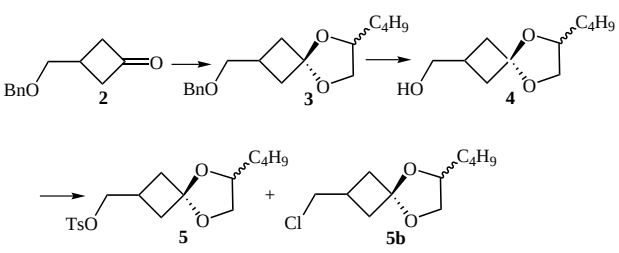
Figure 1 Structure of amino acid **1**

The synthesis of **1** is initiated utilizing 3-benzyloxymethylcyclobutanone (**2**) (Scheme 1). The reaction of **2** with hexane-1,2-diol produces the corresponding ketal **3** in high yield.[16] The choice of the diol is critical to the synthetic strategy.[17] Not only is the hexanediol ketal less volatile and easier to handle than the ethanediol ketal but it is more stable in the subsequent deprotection reaction. Since ketal **3** exists in the spiro configuration and contains two chiral centers, diasteromers are formed. The ratio of diasteromers is essentially 1:1. In the ^{13}C NMR spectrum of ketal **3**, the resonances of the carbons at the spiro core are clearly differentiated. The spectral differences are also apparent in **4**, **5** and **6**. The hydrogenation of ketal **3** (10% Pd/C) proceeds smoothly in methanol at room temperature and produces **4** after simple filtration and removal of solvent. Treatment of **4** with *p*-toluenesulfonyl chloride at 0 °C, followed by slow warming to room temperature,[18] affords tosylate **5** in moderate yield (65%). Significant quantities (28% based on alcohol **4**) of chloride **5b** are also formed. Chlorination of in situ generated tosylate is a common side reaction in tosylate preparations.[19] We discovered that the formation of **5b** can be completely eliminated by keeping the reaction temperature at 0 °C which increased the yield of **5** to 94%.



Scheme 1 *Reagents and conditions*: (a) hexane-1,2-diol, PTSA, benzene, reflux; (b) H_2, 10% Pd/C, MeOH, r.t.; (c) TsCl, pyridine, 0 °C

SYNTHESIS 2003, No. 18, pp 2890–2893
Advanced online publication: 12.11.2003
DOI: 10.1055/s-2003-42479; Art ID: C14103SS
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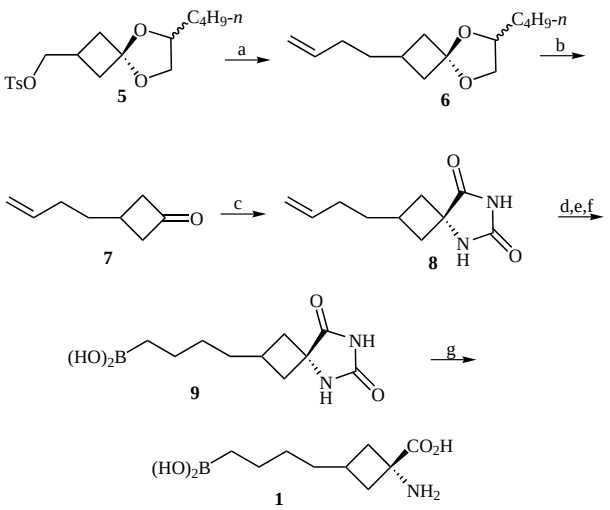
Tosylate **5** couples smoothly with allylmagnesium chloride to give alkene **6** in 89% isolated yield.[20] In the ^{13}C NMR spectrum of alkene **6**, four distinct resonances are visible for the two secondary cyclobutyl carbon atoms. The ketal group in **6** is removed using dilute hydrochloric acid in refluxing ethanol, which generates **7**. Ketone **7** is a highly volatile compound. Hydantoin **8** is prepared by reaction of **7** with potassium cyanide and ammonium carbonate in an Ace pressure tube at 60 °C for 8 hours (83% yield).[21] Hydantoin **8** is obtained in a 2.5:1 ratio of stereoisomers with the *cis*-isomer being the main product. The observed selectivity can be attributed to the steric interaction of the 3-butene substitutent during the formation of the hydantoin, i.e. during the addition of cyanide to the imino species.[22] The hydroboration of **9** is accomplished using 3 equivalents of diisopinocampheylborane (Ipc_2BH) in THF at room temperature.[23] The hydrolysis of **10** in the presence of hydrochloric acid (12 M) produces **1** in good yield (Scheme 2).



Scheme 2 *Reagents and conditions*: (a) allylmagnesium chloride, THF, r.t. to reflux; (b) 2 M HCl, EtOH, reflux; (c) $(NH_4)_2CO_3$, KCN, EtOH–H_2O, 60 °C; (d) $(Ipc)_2BH$, THF, 0 °C to r.t.; (e) MeCHO, THF, 0 °C to r.t.; (f) 2 M HCl, r.t.; (g) 12 M HCl, 150 °C

In conclusion, we have reported an eight-step synthesis of a novel 1-aminocyclobutane-1-carboxylic acid containing an alkylboronic acid substituent. The new agent is currently being evaluated as a BNCT agent.

3-Benzyloxymethylcyclobutanone (**2**) was prepared according to the literature procedure.[24] All reagents were used as received. Et_2O and THF were distilled from sodium benzophenone ketyl. Column chromatography was performed using silica gel (grade 60, 230–400 mesh, ICN Biomedicals GmbH, Eschwege, Germany). Analytical TLC was performed on 250 μm silica gel (Analtech, Inc., Newark, DE) and was visualized by phosphomolybdic acid, $PdCl_2$, and $AgNO_3$ solutions.

^1H NMR and ^{13}C NMR spectra were recorded at 250.13 and 62.89 MHz, respectively. In cases where more than one isomer formed, we have reported the ^{13}C NMR spectrum of the major isomer. Chemical shifts for ^1H NMR and ^{13}C NMR spectra were referenced to TMS and measured with respect to the residual protons in the deuterated solvents. Microanalyses were performed by Atlantic Microlab, Inc. Norcross, Georgia. HRMS-FAB (M + 1) spectra were obtained on a ZABEQ instrument in a glycerol matrix.

3-Benzyloxymethylcyclobutanone Ketal (3)

A 250 mL, three-necked, round-bottomed flask equipped with a Dean–Stark apparatus and a reflux condenser was charged with **2** (7.6 g, 40 mmol), hexane-1,2-diol (6.2 g, 44 mmol), and *p*-toluenesulfonic acid (500 mg) in benzene (150 mL). The reaction mixture was refluxed at 120 °C (oil bath) for 14 h and the progress of the reaction was monitored by TLC. After 14 h, the flask was cooled to r.t., and sat. aq $NaHCO_3$ (20 mL) was added. The mixture was transferred to a separatory funnel, washed sequentially with H_2O (15 mL) and then brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a colorless oil. The product was purified by column chromatography (hexane–EtOAc, 20:1) to yield 11.2 g (97%) of **3** as a colorless liquid.

^1H NMR (250 MHz, $CDCl_3$/TMS): δ = 7.25–7.41 (m, 5 H), 4.50 (s, 2 H), 3.90–4.02 (m, 2 H), 3.48 (d, *J* = 6.26 Hz, 2 H), 3.42 (dd, *J* = 12.3, 6.7 Hz, 1 H), 2.18–2.46 (m, 3 H), 2.05–2.17 (m, 2 H), 1.17–1.65 (m, 6 H), 0.90 (t, *J* = 6.49 Hz, 3 H).

^{13}C NMR (62.89 MHz, $CDCl_3$/TMS): δ = 138.4, 128.2, 127.5, 106.8, 106.7, 75.8, 75.5, 74.2, 72.8, 68.9, 68.6, 39.1, 38.7, 33.3, 33.0, 27.8, 24.7, 24.5, 22.6, 14.0.

MS: *m*/*z* = 290 (M^+), 169, 142, 100, 91.

Anal. Calcd for $C_{18}H_{26}O_3$ (290.41): C, 74.45, H, 9.02. Found: C, 74.23; H, 9.08.

3-Hydroxymethylcyclobutanone Ketal (4)

To a 100 mL round-bottomed flask fitted with a septum cap, ketal **3** (11.2 g, 38.6 mmol), 10% Pd/C (1.12 g), and MeOH (60 mL) were added. The air in the flask was removed under vacuum and H_2 was introduced using a H_2-filled balloon. After stirring for 24 h at r.t., the reaction mixture was filtered and the residual Pd/C was washed with MeOH. Concentration of the filtrate and washings under reduced pressure yielded the colorless product **4** (7.6 g, 99%).

^1H NMR (250 MHz, $CDCl_3$/TMS): δ = 3.93–4.05 (m, 2 H), 3.63 (d, *J* = 6.18 Hz, 2 H), 3.45 (dd, *J* = 12.4, 6.7 Hz, 1 H), 3.68 (s, 1 H), 2.23–2.47 (m, 3 H), 2.00–2.17 (m, 2 H), 1.16–1.64 (m, 6 H), 0.91 (t, *J* = 6.48 Hz, 3 H).

^{13}C NMR (62.89 MHz, $CDCl_3$/TMS): δ = 106.7, 106.5, 75.9, 75.7, 69.0, 68.8, 66.7, 66.6, 38.6, 38.5, 38.3, 33.3, 33.1, 27.8, 26.8, 26.6, 22.6, 13.9.

HRMS: *m*/*z* calcd for $C_{11}H_{20}O_3$ + 1: 201.1491; found: 201.1490.

Anal. Calcd for $C_{11}H_{20}O_3$ (200.28): C, 65.97; H, 10.07. Found: C, 65.44; H, 10.09.

Tosylate 5

A chilled solution of ketal **4** (7.4 g, 37 mmol) in pyridine (10 mL) was added via syringe to a solution of tosyl chloride (7.73 g, 40.7 mmol) in anhyd pyridine (10 mL) maintained at 0 °C. After stirring at 0 °C for 18 h under N_2, the reaction mixture was diluted with chilled Et_2O (50 mL), washed with aq $CuSO_4$ (3 × 20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual product was purified by column chromatography (hexane–EtOAc, 4:1) to yield a colorless liquid **5** (12.3 g, 94%).

^1H NMR (250 MHz, $CDCl_3$/TMS): δ = 7.78 (d, *J* = 8.20 Hz, 2 H), 7.34 (d, *J* = 8.20 Hz, 2 H), 4.04 (d, *J* = 5.79 Hz, 2 H), 3.84–4.03 (m, 2 H), 3.36–3.42 (m, 1 H), 2.45 (s, 3 H), 2.06–2.42 (m, 3 H), 1.94–2.04 (m, 2 H), 1.22–1.58 (m, 6 H), 0.90 (t, *J* = 6.79 Hz, 3 H).

^{13}C NMR (62.89 MHz, $CDCl_3$/TMS): δ = 144.6, 133.0, 129.7, 127.8, 106.0, 105.0, 76.0, 75.7, 73.5, 69.0, 68.7, 38.7, 38.5, 38.3, 33.0, 32.9, 27.7, 23.9, 23.8, 22.6, 21.5, 13.9.

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MS: *m*/*z* = 355 (M + 1), 281, 176, 142, 100.

Anal. Calcd for $C_{18}H_{26}O_5S$ (354.47): C, 60.99; H, 7.39. Found: C, 60.98; H, 7.47.

When the reaction was carried out at r.t., **5b** was isolated as a by-product.

5b

^{1}H NMR (250 MHz, $CDCl_3$/TMS): δ = 3.93–4.04 (m, 2 H), 3.60 (d, *J* = 6.63 Hz, 2 H), 2.42–3.48 (m, 1 H), 2.40–2.53 (m, 3 H), 2.06–2.19 (m, 2 H), 1.28–1.62 (m, 6 H), 0.91 (t, *J* = 6.78 Hz, 3 H).

^{13}C NMR (62.89 MHz, $CDCl_3$/TMS):: δ = 105.8, 105.7, 76.0, 75.7, 69.0, 68.8, 49.1, 40.1, 40.0, 39.8, 33.2, 33.0, 27.8, 27.4, 27.3, 22.6, 13.8.

Anal. Calcd for $C_{11}H_{19}ClO_2$ (218.72): C, 60.40; H, 8.76. Found: C, 60.38; H, 8.59.

Alkene 6

A 250 mL, two-necked flask fitted with a reflux condenser, a magnetic stir bar, and a septum was flushed with N_2 and charged with **5** (10.6 g, 30 mmol) dissolved in anhyd THF (20 mL) at 0 °C. Allylmagnesium chloride (150 mmol, 75 mL of a 2 M solution in THF) was added drop-wise via syringe over a 30 min period. The stirring was continued at 0 °C for an additional 30 min, at which time the cooling bath was removed and the mixture was refluxed for 8 h. The mixture was stirred overnight at r.t., and then quenched with concd aq NH_4Cl (30 mL) and Et_2O (50 mL). Following the separation of the organic phase, the aqueous phase was extracted with Et_2O (3 × 30 mL), the combined organic phases were washed with brine (2 × 20 mL), and dried ($MgSO_4$). The crude product was purified by column chromatography (hexane–EtOAc, 50:1) to yield **6** as a colorless oil (5.98 g, 89%).

^{1}H NMR (250 MHz, $CDCl_3$/TMS): δ = 5.65–5.77 (m, 1 H), 4.83–4.95 (m, 2 H), 3.84–3.95 (m, 2 H), 3.35–3.41 (m, 1 H), 2.27–2.39 (m, 2 H), 1.78–1.98 (m, 5 H), 1.18–1.56 (m, 8 H), 0.83 (t, *J* = 6.62 Hz, 3 H).

^{13}C NMR (62.89 MHz, $CDCl_3$/TMS): δ = 138.5, 114.4, 106.7, 106.6, 75.8, 75.4, 69.0, 68.5, 41.8, 41.7, 41.6, 41.4, 35.7, 35.6, 33.5, 33.0, 32.0, 27.8, 24.8, 24.6, 22.6, 13.9.

MS: *m*/*z* = 224 (M^+), 209, 100, 82.

Anal. Calcd for $C_{14}H_{24}O_2$ (224.35): C, 74.95; H, 10.78. Found: C, 74.99, H, 10.85.

3-(But-3-enyl)cyclobutanone (7) (*Caution! Highly Volatile*)

A 100 mL, round-bottomed flask was charged with **6** (5.6 g, 25 mmol) dissolved in EtOH (150 mL) and aq 2 M HCl (5 mL). The mixture was refluxed overnight at which time the TLC indicated complete disappearance of the starting ketal. After cooling to r.t., the mixture was extracted with Et_2O (3 × 50 mL), the combined organic phases were dried ($MgSO_4$), and the solvent was removed by distillation. The residue was purified using silica gel chromatography (pentane–Et_2O, 30:1). The ketone **7** was obtained as a colorless liquid (2.79 g, 90%).

^{1}H NMR (250 MHz, $CDCl_3$/TMS): δ = 5.74–5.91 (m, 1 H), 4.97–5.08 (m, 2 H), 3.07–3.20 (m, 2 H), 2.65–2.74 (m, 2 H), 2.35–2.43 (m, 1 H), 2.11 (dd, *J* = 7.70, 6.86 Hz, 2 H), 1.69 (dd, *J* = 7.69, 6.86 Hz, 2 H).

^{13}C NMR (62.89 MHz, $CDCl_3$/TMS): δ = 208.7, 137.6, 115.1, 52.5, 35.5, 32.5, 23.4.

MS: *m*/*z* = 123 (M^+ – 1), 109, 80, 67.

Anal. Calcd for $C_8H_{12}O$ (124.18): C, 77.38; H, 9.74. Found: C, 77.29; H, 9.65.

Hydantoin 8

A 25 mL Ace pressure tube was charged with **7** (0.62 g, 5.0 mmol), aq EtOH (50%, 12.0 mL), KCN (650 mg, 10 mmol), and $(NH_4)_2CO_3$ (2.4 g, 25 mmol). The reaction vessel was sealed and heated at 60 °C (oil bath) for 8 h. A faint yellow precipitate formed. The reaction mixture was cooled to r.t. and the vessel carefully opened in a fume hood. The mixture was concentrated under reduced pressure and the solid obtained was purified by column chromatography (hexane–EtOAc,1:2) to afford **8** as a white solid (0.81 g, 83%).

^{1}H NMR (CD_3OD/TMS): δ = 5.65–5.81 (m, 1 H), 4.78–4.97 (m, 2 H), 2.47–2.55 (m, 2 H), 2.20–2.32 (m, 2 H), 1.84–1.98 (m, 3 H), 1.41–1.56 (m, 2 H).

^{13}C NMR (62.89 MHz, CD_3OD/TMS): δ = 181.1, 158.5, 139.5, 115.1, 60.0, 39.6, 37.6, 32.4, 27.6.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.83; H, 7.29; N, 14.13.

Boronohydantoin 9

Diisopinocampheylborane $(Ipc)_2BH$ was prepared according to the literature procedure.[23] A 100 mL round-bottomed flask was fitted with a septum, a magnetic stirring bar, and connected to a N_2 bubbler. The flask was flushed with N_2 and held at a positive static pressure of N_2. BH_3·THF (50 mmol, 50 mL, 1.0 M) was added slowly and the mixture stirred at 0 °C for 1 h. The reaction was left at 0 °C for 3 d to give the required crystalline product. Compound **8** (0.63 g, 3 mmol) was placed in a 150 mL round-bottomed flask and dissolved in THF (15 mL) at 0 °C. $(Ipc)_2BH$ (9 mmol) in THF (20 mL) was added drop-wise via a syringe. The mixture was allowed to warm to r.t. and stirred for 16 h. Freshly distilled acetaldehyde (12 mmol) was added and the mixture stirred for an additional 12 h. Excess acetaldehyde was removed under vacuum and the mixture was hydrolyzed with aq HCl (5 mL, 2 M). The mixture was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by column chromatography (MeOH) to afford **9** as a white solid (0.65 g, 85%).

^{1}H NMR (DMSO-d_6/TMS): δ = 8.52 (s, 1 H), 7.42 (s, 1 H), 2.47–2.58 (m, 2 H), 2.17–2.31 (m, 3 H), 1.04–1.48 (m, 6 H), 0.62 (t, *J* = 7.75 Hz, 2 H).

^{13}C NMR (62.89 MHz, DMSO-d_6/TMS): δ = 178.8, 155.9, 57.6, 38.3, 36.5, 29.5, 26.3, 24.1.

HRMS-FAB: *m*/*z* calcd for $C_{13}H_{22}BN_2O_5$ (M + H + gly – $2H_2O$; obtained in a glycerol matrix): 297.1624; found: 297.1618.

1-Amino-3-[4-(dihydroxyboryl)butyl]cyclobutanecarboxylic Acid (1)

Boronohydantoin **9** (446 mg, 1.5 mmol) was placed in a 25 mL Ace pressure tube along with 12 M HCl (4 mL). The tube was sealed and heated to 150 °C (oil bath) for 40 min. It was then cooled to r.t., carefully opened (Hood!), charcoal was added, and the mixture filtered through a pad of Celite. The Celite pad was washed with H_2O. Removal of the H_2O under reduced pressure gave a white solid (260 mg, 81%).

^{1}H NMR (D_2O/TMS): δ = 3.46–3.49 (m, 2 H), 2.47–2.68 (m, 2 H), 2.21–2.40 (m, 3 H), 1.09–1.43 (m, 6 H) 0.67 (m, 2 H).

^{13}C NMR (62.89 MHz, D_2O/TMS): δ = 180.2, 60.4, 42.3, 41.0, 34.9, 34.0, 29.6, 24.2.

HRMS: *m*/*z* calcd for $C_{12}H_{23}BNO_5$ (M + H + gly – $2H_2O$; obtained in a glycerol matrix): 272.1672; found: 272.1679.

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Acknowledgment

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

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