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Synthesis of a boronated amino acid as a potential neutron therapy agent: 1-amino-3-[(dihydroxyboryl)ethyl]-cyclobutanecarboxylic acid

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Abstract—A novel boronated aminocyclobutanecarboxylic acid was synthesized in 10 steps for potential use in neutron capture therapy. The molecule was modeled after the unnatural amino acid 1-aminocyclobutanecarboxylic acid, which has shown high uptake in brain tumors.

Boron neutron capture therapy[1] (BNCT) is a cancer treatment that involves the irradiation of tumors containing boron-10 with low-energy neutrons. The resulting excited boron-11 nucleus then undergoes a prompt fission and releases high energy α-particles and lithium-7 ions. The linear energy transfer (LET) of these heavy charged particles has a range of approximately one cell diameter, thus they are only lethal to the cells in which they are generated. The clinical success of BNCT depends on two factors: (1) selective delivery of a sufficient quantity of nontoxic boron-10 containing compounds to the tumor and (2) a neutron flux sufficient to achieve the prerequisite nuclear reaction. BNCT is an attractive modality for the treatment of patients with high-grade gliomas and metastatic brain tumors whose life expectancy is generally less than 1 year despite aggressive treatments using surgery, and radio- and chemotherapy. To date, a variety of molecules[2–8] have been used to deliver boron to tumor cells. Encouraging results have been obtained using 4-dihydroxyborylphenylalanine (BPA) and sodium mercaptoundecahydrododecaborate (BSH) as the tumor specific boronated agent, and both are being used in clinical trials.[9]

It is believed that amino acids are preferentially taken up by growing tumor cells. Positron emission tomography (PET) investigations[10] using carbon-11 labeled 1-aminocyclobutanecarboxylic acid (ACBC) demonstrated that this amino acid localizes in tumors more avidly than BPA. Recently, Goodman reported that fluorine-18 labeled 1-amino-3-(fluoromethyl)cyclobutanecarboxylic acid and its derivatives also localize in tumors.[11] Prompted by the hypothesis that incorporation of bond rotation restriction in bioactive peptides can augment biopotency, selectivity and metabolic stability,[12] the synthesis of conformationally restricted 1-aminocyclobutane-1-carboxylic acids (ACBCs) has attracted attention in recent years.[13]

We have focused our efforts on the synthesis of boronated ACBC derivatives.[14,15] Two novel 3-butylboronic and 3-methylboronic substituted ACBC derivatives were synthesized for in vivo biodistribution evaluation.[16] To complete a structure–activity relationship study (by adjusting the lipophilicity of the compounds), we prepared a 3-ethylboronic substituted ACBC **1** (Fig. 1).

The synthesis of **1** starts from but-3-enyloxymethylbenzene[17] as shown in Scheme 1. The 3-substituted

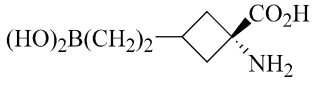

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Figure 1.

Keywords: Boronic acid; Amine borane; Amino acid; Cyclobutane derivative.
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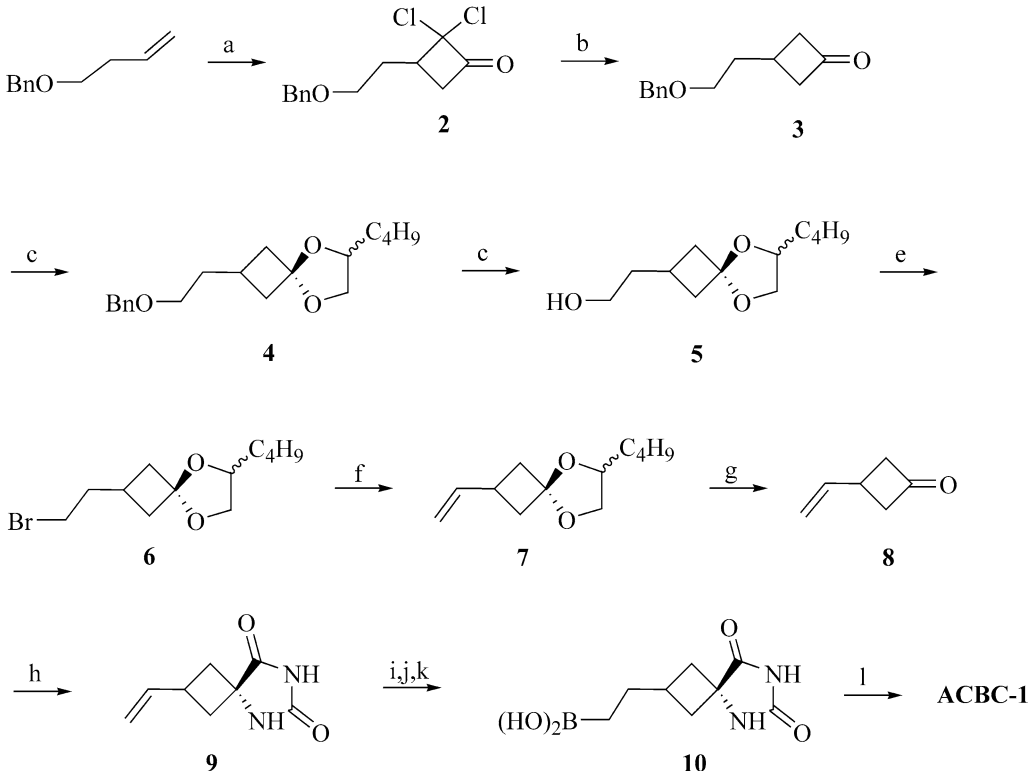

Scheme 1. Reagents and conditions: (a) Cl_3CCOCl, $POCl_3$, Zn–Cu, Et_2O, reflux; (b) Zn, HOAc, 0 °C to reflux; (c) 1,2-hexanediol, PTSA, benzene, reflux; (d) H_2, Pd/C (10%), MeOH, rt; (e) CBr_4, PPh_3, CH_2Cl_2, rt; (f) NaOH (6 M), PEG-600, 90 °C; (g) HCl (2 M), EtOH, reflux; (h) $(NH_4)_2CO_3$, KCN, EtOH/H_2O (1:1), 60 °C; (i) $(Ipc)_2BH$, THF, 0 °C to rt; (j) CH_3CHO, THF, 0 °C to rt; (k) HCl (2 M), rt; (l) HCl (12 M), 160 °C.

cyclobutanone skeleton was constructed by a [2+2] cycloaddition reaction. Cyclobutanone **2** was obtained by the cycloaddition of but-3-enyloxymethylbenzene with dichloroketene, which was generated in situ from trichloroacetyl chloride in the presence of a zinc–copper couple and phosphorous oxychloride. Cyclobutanone **2** is unstable during silica gel column chromatography and the crude product was used directly in the next step. The reductive dechlorination of **2** with zinc in acetic acid[18] produced cyclobutanone **3** in 64% isolated yield (two steps).

In our previous work,[19] we found that cyclobutanone ethanediol ketals are somewhat unstable compared to the corresponding 1,2-hexanediol derivatives, which led us to prepare **3**. Another advantage of using 1,2-hexanediol is that intermediates **6** and **7** are less volatile. Since ketal **4** is a spiro compound and contains two stereogenic centers, diasteromers (in a 1:1 ratio) are formed. In the ^{13}C NMR spectrum of ketal **4**, the resonances of the carbons at the spiro core are clearly differentiated. These spectral differences are also apparent in intermediates **5** and **6**. Hydrogenation of ketal **4** (10% palladium on charcoal) in methanol at room temperature gave **5** in quantitative yield.

Bromination of **5** using CBr_4/PPh_3 in dichloromethane[20] at room temperature produced 3-(bromoethyl)cyclobutanone acetal, **6**, in 94% isolated yield. The dehydrobromination of **6** to generate the alkenyl group was realized using NaOH in PEG-600.[21] The ketal group in **7** was removed using dilute hydrochloric acid in refluxing ethanol, generating **8**. To avoid the loss of the highly volatile **8**, crude **8** was used directly for the Bücherer–Strecker reaction. Crude **8**, potassium cyanide and ammonium carbonate were sealed in an Ace pressure tube and heated at 60 °C for 9 h. The reaction produced hydantoin **9** in 83% isolated yield (two steps). Hydantoin **9** is formed in a 2.5:1 ratio of stereoisomers with the cis-isomer being the main product. The hydroboration of **9** was accomplished using 3.0 equiv of diisopinocampheylborane (Ipc_2BH) in THF at room temperature. The resultant diisocampheylborane product was readily converted to boronic acid **10** by reaction with acetaldehyde and then aqueous HCl according to the literature procedure.[22] Hydrolysis of **10** in the presence of hydrochloric acid (12 M) produced **1** in good yield.[23] This new agent is currently being evaluated as a BNCT agent.

Acknowledgements

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