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Synthesis of novel boron containing unnatural cyclic amino acids as potential therapeutic agents

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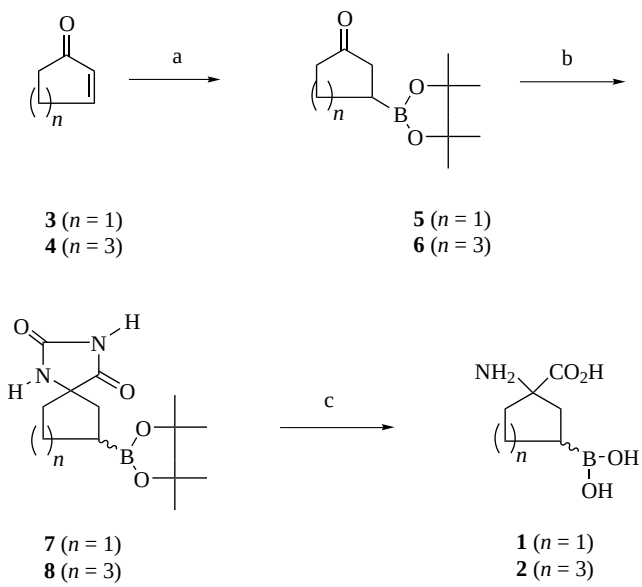
Abstract—Two boronated α-amino acids, 1-amino-3-boronocyclopentanecarboxylic acid and 1-amino-3-boronocycloheptanecarboxylic acid were prepared. The key step in the syntheses was the 1,4-boration of the α,β-unsaturated cyclic ketones using the bis-pinacolatodiboron ester to generate the boronated ketones which were then converted to the corresponding amino acids.

In the last decade, there has been considerable interest in boron neutron capture therapy (BNCT),[1] a binary approach to the treatment of cancer in which a compound containing boron-10 is selectively delivered to tumor tissues prior to irradiation by neutrons.[2] The interaction of a boron-10 atom with a thermal neutron produces an α-particle and a high energy lithium-7 ion. The linear energy transfer (LET) of these heavily charged particles have a range of approximately one cell diameter. To minimize damage to normal tissues, the quantity of boron in the tumor (~30 μg of ^{10}B per gram of tumor) must exceed that in the surrounding normal tissue by at least a factor of three.[3,4] The clinical success of BNCT depends on two factors: effective delivery of a sufficient quantity of boron to the targeted tumor and a neutron flux sufficient to achieve the prerequisite nuclear reaction while minimizing damage to healthy tissue. Early BNCT clinical trials were disappointing in that they failed to achieve either of these goals.[5] However, significant advances in the modification of the nuclear reactors and tumor seeking selective boron containing pharmaceuticals have been made in recent years.[6]

It is believed that amino acids are preferentially taken up by growing tumor cells. Clinical trials are now underway for the treatment of both Glioblastoma Multiforme (GBM)[7] and metastatic malignant melanoma (MM) utilizing a boron-containing amino acid, *para*-boronophenylalanine (BPA). Recent positron emission tomography (PET) investigations carried out at the University of Tennessee on BNCT patients using fluorine-18 labeled BPA and carbon-11 labeled 1-aminocyclobutanecarboxylic acid revealed that cyclic amino acids localize in GBM and MM tumors more avidly than BPA.[8] For this reason, we have focused our efforts on cyclic α-amino acids such as 1-aminocyclobutanecarboxylic acid (ACBC) as the boron carrier. We reported the syntheses of a *meta*-carborane containing ACBC derivative, a less liphophilic *nido*-analogue,[9] and



Scheme 1. *Reaction conditions*: (a) (i) CuCl, LiCl, KOAc, bis-pinacolatodiboron, DMF, N_2 atm.; (ii) H_2O (b) KCN, $(NH_4)_2CO_3$, EtOH:H_2O (1:1), 80°C; (c) 10 M HCl, 150°C, 15 h.

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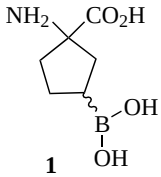
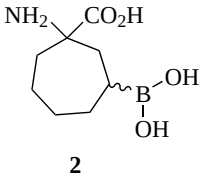
a solubilized *meta*-carborane derivative.[10] It is known that 1-aminocycloalkanecarboxylic acids cross the blood brain barrier (BBB).[11] We now wish to report the synthesis of a boronated aminocyclopentanecarboxylic acid **1**, and the more lipophilic seven-membered ring analogue **2**.



1



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The key synthetic step in the formation of the title compounds is the preparation of ketones **5** and **6** (Scheme 1) via addition of a diboron reagent to the corresponding α,β-unsaturated carbonyl compounds.[12] We were able to prepare compounds **5** and **6** via the boronation of cyclic alkenones **3** and **4** using bis-pinacolatodiboron in DMF.[13] Compound **5** was isolated in 70% yield while the yield of compound **6** was 82%. Compound **5** is thick liquid while compound **6** is a low melting solid. The corresponding ketones were allowed to react with ammonium carbonate and potassium cyanide in an Ace pressure tube at 80°C for 5 h.[14] The hydantoins **7** and **8** were formed in good yields. (The yield of **7** was 90% and the yield of **8** was 95%.) It is noteworthy that the hydantoins were difficult to hydrolyze. If milder conditions or shorter reaction times were employed, only the pinacol ester was hydrolyzed not the hydantoin.[15]

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13. Hydantoin **7** (0.14 g, 0.50 mmol) was placed in a 15 mL Ace pressure tube along with concentrated HCl (5 mL, 10 M). The tube was sealed and heated to 150°C (oil bath) for 15 h. It was then cooled to room temperature, carefully opened (Hood!), charcoal added, and the mixture passed through Celite. The Celite pad was washed successively with water. The filtrate and washes were combined and the water removed in vacuo to yield a diastereomeric mixture of **1** (0.079 g, 73%) as the solid hydrochloride: $R_f = 0.71$ (isopropanol:water:acetic acid; 1.0:1.0:0.5); solid turns brown at 256°C without melting; (major diastereomer) ^{1}H NMR (D_2O): δ 1.19–2.09 (broad m). ^{13}C NMR (D_20): δ 178.7, 67.2, 39.5, 34.63, 34.0, 26.1; ^{11}B NMR (D_2O): δ 31.8; HR-FAB-MS (M+H+gly-2H_2O; obtained in a glycerol matrix), calcd for $C_9HHH_{17}BNO_5$: 230.120, found 230.137.
14. Hydantoin **8** (0.15 g, 0.50 mmol) was placed in a 15 mL Ace pressure tube along with concentrated HCl (5 mL, 10 M), and the reaction carried out as described for **7** (Ref. 13) to obtain a diastereomeric mixture of **2** (0.084 g, 72%) as the solid hydrochloride: $R_f = 0.65$ (isopropanol:water: acetic acid; 1.0:1.0:0.5); solid turns brown at 248°C without melting; (major diastereomer) ^{1}H NMR (D_2O): δ 1.23–2.12 (broad m). ^{13}C NMR (D_20): δ 177.6, 66.1, 38.0, 37.1, 34.6, 33.3, 32.6, 24.6; ^{11}B NMR (D_2O): δ 30.9; HR-FAB-MS (M+H+gly-2H_2O; obtained in a glycerol matrix), calcd for $C_{11}HHH_{21}BNO_5$: 258.151, found 258.151.
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