Synthesis of Proline Derivatives for Incorporation Into Phosphonamino Acid-Based Inhibitors of Metallo-β-Lactamase Enzymes

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Introduction

Antibiotics play a crucial role in modern healthcare. That role is threatened by perpetually evolving bacteria and the rapid rise of antibiotic resistance, making once successful treatments increasingly ineffective. Bacteria are able to produce ß-lactamase enzymes that hydrolyze ß-lactam antibiotics, such as penicillin, thereby inactivating them.[1] There are two super families of ß-lactamase enzymes, serine-dependent ß-lactamases and metallo-ß-lactamases (MBLs), but only serine-dependent ß-lactamases have clinically useful inhibitors.[2] The expression of MBLs is the most significant strategy by which pathogenic bacteria become resistant to currently known ß-lactam antibiotics.[3] Phosphonamino acids (Figure 1) are known to exhibit strong antibacterial and enzyme-inhibitory activity and were shown to successfully inhibit certain MBL activity.[4] The potential of phosphonamino acids as a clinically successful MBL inhibitor would be a major victory in the battle against antibiotic resistant bacteria.

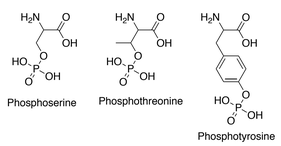


Figure 1. Examples of Phosphonamino Acids

The effectiveness of various phosphonamino acids can be tested, and later predicted, through structure-activity relationship (SAR). The objective of this research is to utilize synthetic organic chemistry in order to manufacture various proline derivatives (Figure 2), each with a modification to replace the carboxylic acid side change with a different substituent. These proline derivatives can then be built into phosphonamino acids in order to create a small library of compounds with MBL inhibition potential.

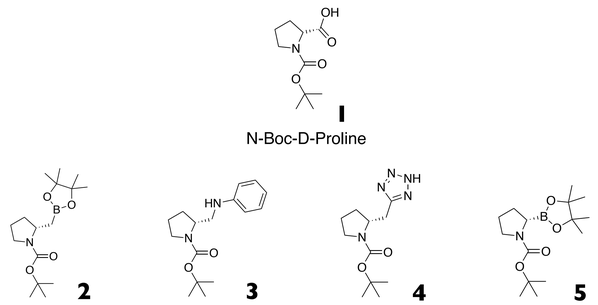
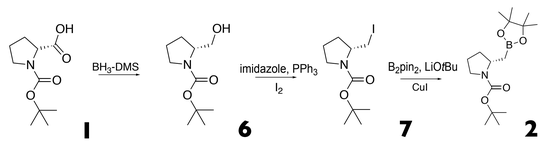
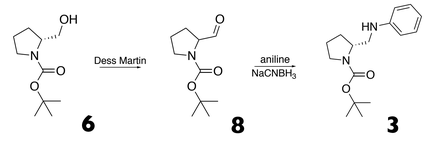


Figure 2. Target Derivatives of Boc-Protected D-Proline

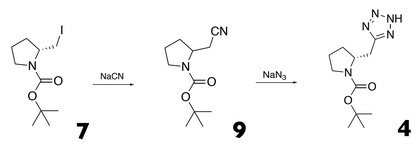
Methodology



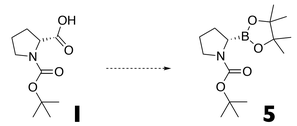
Scheme 1. Synthesis of (*R*)-2-(pinacolato)borylmethyl-*N*-*tert*-butoxycarbonyl-pyrrolidine[5]



Scheme 2. Synthesis of (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-[(phenylamino)methyl)]pyrrolidine[6]



Scheme 3. Synthesis of (2*R*)-*N*-(*tert*-butoxycarbonyl)-2-(tetrazolylmethyl)pyrrolidine[7,8]



Scheme 4. Synthesis of (*R*)-2-(pinacolato)boryl-*N*-*tert*-butoxycarbonyl-pyrrolidine[9]

Results

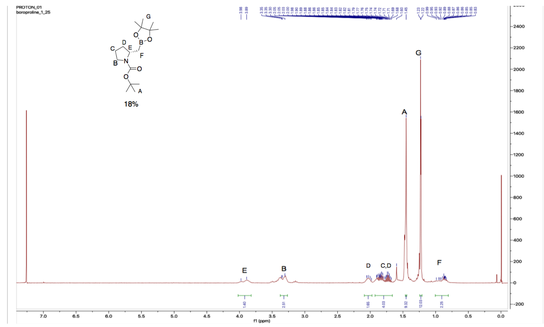


Figure 3. ^{1}H NMR spectrum of (*R*)-2-(pinacolato)borylmethyl-*N*-*tert*-butoxycarbonyl-pyrrolidine **2**

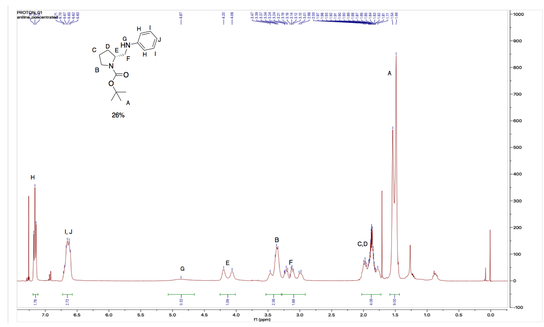


Figure 4. ^{1}H NMR spectrum of (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-[(phenylamino)methyl)]pyrrolidine **3**

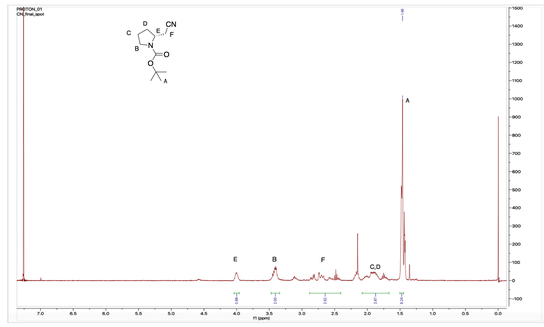


Figure 5. ^{1}H NMR spectrum of *tert*-butyl-(2*S*)-2-(cyanomethyl)pyrrolidine-1-carboxylate **9**

Conclusion

The boronate ester D-proline derivative **2** was successfully synthesized as well as the aniline D-proline derivative **3**.. The synthesis of the tetrazole D-proline derivative **4** is currently being done and the nitrile intermediate **9** has been synthesized but still needs to be purified. The synthesis of the boronate ester D-proline derivative **5** will be attempted via a decarboxylative borylation.

The successful syntheses need to be optimized in order to increase the yields of these reactions.

Future Work

Future work includes the incorporation of the target boronate ester D-proline derivative **2** and the target aniline D-proline derivative **3** into phosphonamino acid compounds.

Future work also includes the successful synthesis of the final two target D-proline derivatives, the tetrazole derivative **4** and the boronate ester derivative **5**.

Further down the line, once these proline derivatives have been successfully incorporated into larger phosphonamino structures, those compounds may be tested against metallo-ß-lactamase enzymes, such as NDM-1, in order to determine the inhibition capabilities of these compounds against the enzymes.

Work Cited

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