Formation of Amino Acid-derived Cyclopropanols

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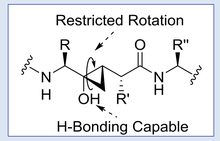
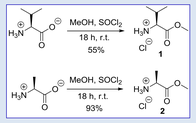


Figure 1: Cyclopropanol isosteres that can potentially inhibit aspartyl protease.

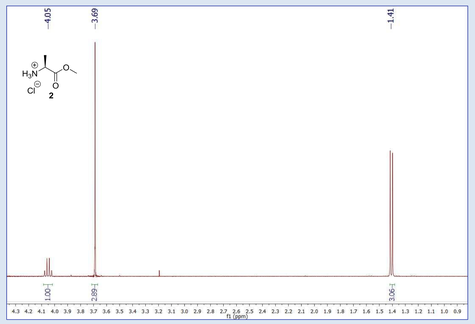
Introduction:

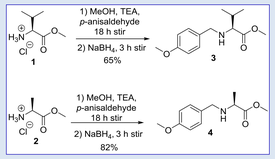
Peptide isosteres are used in peptidomimetics to mimic naturally occurring peptides for inhibition of protease. Protease are enzymes in the body that catalyse hydrolysis of peptide bonds into smaller polypeptides or amino acids.[1] By incorporating unnatural amide mimics into the peptide's backbone, the likelihood of this degradation decreases.[2] This method can be useful in inhibition of the human immunodeficiency virus (HIV) aspartyl protease since without this protease, the HIV virus could not reproduce. Inhibition of the HIV aspartyl protease has been shown by an isosteric replacement of the hydrolytic amide linkage with functionalities including ketomethylene groups and hydroxyethylene groups. However, these isosteres lack conformational rigidity around the amide replacements which decreased their inhibition efficiency.[3] Zercher and coworkers have developed a novel class of peptide isosteres in which the amide linkages are replaced with cyclopropanol groups that possess the desired conformational rigidity as well as hydrogen bonding capabilities (**Figure 1**).[4] These factors may prove to be important for increased protease inhibition efficiency. Mower and Moran have successfully shown these compounds can be formed using β-diketones through a zinc mediated chain extension when incorporated into proline-derived systems.[4,5] The focus of this study was to expand this methodology to different amino acid starting material including L-alanine and L-valine.

Results and Discussion:

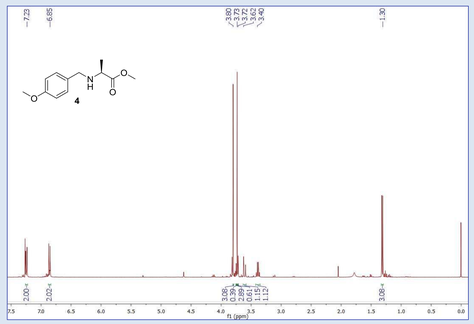


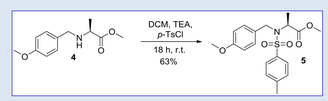
The first step in the preparation of β-diketone starting material was to form the methyl ester hydrochloride of the amino acid. The avoidance of the amino acid's zwitterionic character aided solubility and facilitated further synthetic manipulation.



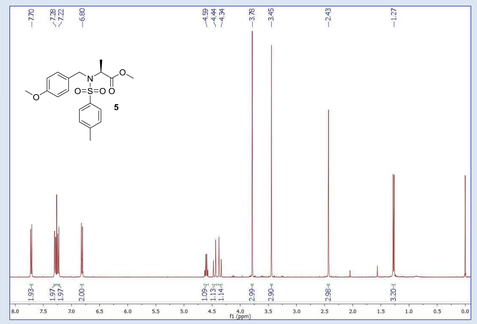


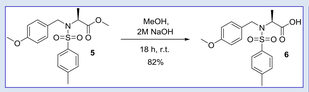
Di-protection of the amine was then performed in order to prevent participation in chemical reactions due to the basic and nucleophilic nature of the amine. The first protecting group added was *p*-methoxybenzyl (PMB).



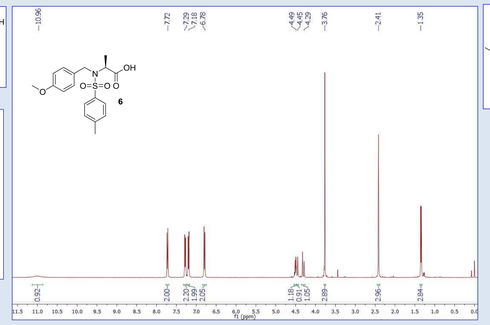


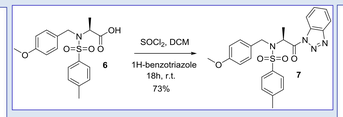
The second protecting group was added by using *p*-toluenesulfonyl chloride (*p*-TsCl). This reaction was successful when L-alanine derived products were used but caused many difficulties when L-valine was used. As a result, further research efforts focused mainly on L-alanine-derived products.



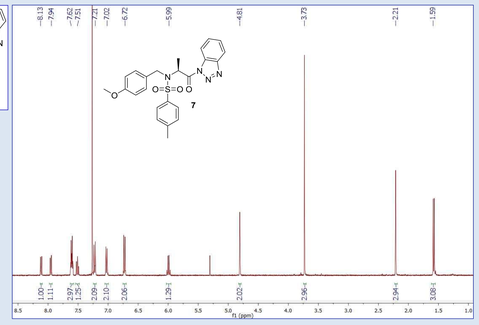


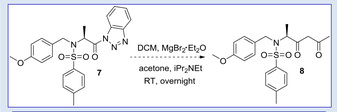
Once the di-protected product **5** was successfully prepared, the methyl group could be removed to form the carboxylic acid **6**. Further reactions were performed on the carboxylic acid functionality to form the desired β-diketone.



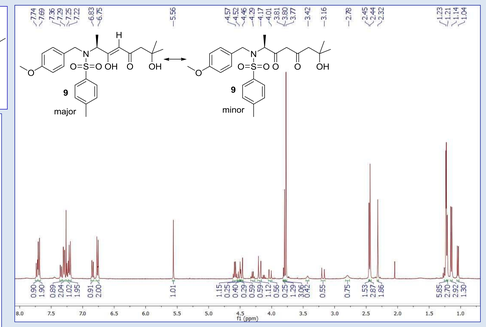


Acyl benzotriazole species are efficient acylating agents in the formation of β-diketones. So, the carboxylic acid **6** was first converted into the benzotriazole activated product **7** in order for the β-diketone to be prepared.

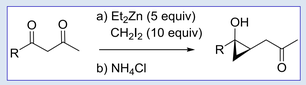




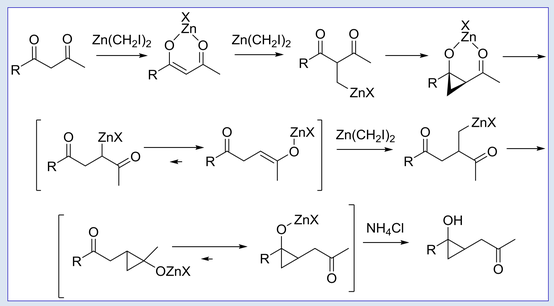
A soft enolization reaction was used in an attempt to prepare the β-diketone **8**. However, under the conditions initially chosen to perform this reaction, the targeted β-diketone was further transformed through an aldol reaction to form product **9** as a mixture of enol and keto forms, which was confirmed by NMR spectroscopy.



Zinc-Mediated Chain Extension-Cyclopropanation:



The tandem homologation-cyclopropanation reaction of a β-diketone



Proposed mechanism for the tandem homologation-cyclopropanation reaction of a β-diketone

Continuing and Future work:

- Rework conditions in the soft enolization reaction to form the desired amino acid-derived β-diketone **8**.
- Use the β-diketone starting material **8** to prepare the desired cyclopropanol product.
- Continue this research using L-valine amino acid.
- Determine stereochemistry of the major diastereomer of the cyclopropanol product.

Conclusion:

The successful production of β-diketone starting materials using proline as the amino acid has been demonstrated in work by Mower and Moran. Continuing this methodology using different amino acids was the basis of this research. Using L-alanine to derive β-diketone starting materials has shown to be more promising than when using L-valine. Knowledge gained in this study of primary amino acids will aid in the development of approaches to amino acid-derived β-diketones.

References:

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2. Brik, A.; Wong, C-H. *Org. Biomol. Chem.* **2003**, *1*, 5-14.
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4. Mower, M. B. S. Thesis. University of New Hampshire, 2012.
5. Moran, P. M. S. Thesis. University of New Hampshire, 2013.

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