Unnatural Beta-Amino Acids for the Synthesis of Anticancer Natural Products Dolostatin and Homodolostatin 16

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1. Introduction and Aims

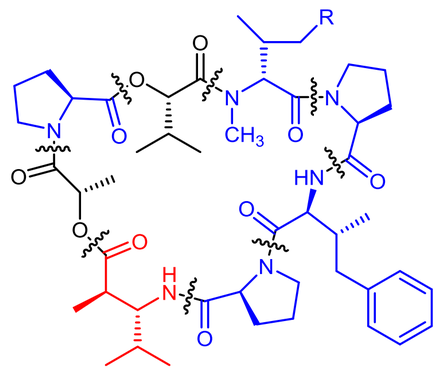
The aim of this project was to investigate synthesis routes to producing single enantiomers of β-amino acids. β-amino acids are less frequently found in natural products than their ubiquitous α–amino acid counterparts.

Figure 1: Examples of α- and β-amino acids

α-amino acid **β-amino acid**

Dolostatin and Homodolostatin 16 have β-amino acids in their backbones and are molecules of interest as they show anti-cancer activity. These natural products may be synthesised by starting from their β-amino acid precursors. The synthesis of the β-amino acids is made more complicated due to the multiple chiral centres. A viable synthetic route could allow them be synthesised on a large enough scale to be used as anti-cancer drugs

Figure 2: Dolostatin 16[1] (R=H) and Homodolostatin 16[2] (R=Me). α-amino acids (blue) and β–amino acids (red) amino acids displayed in the backbone



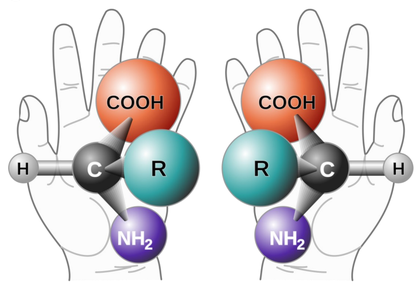
2. Chemistry background

There is a need for, cheap, reliable, synthetic routes to synthesising β-amino acids. Unlike α-amino acids, they can not be produced from natural resources on a commercial scale and have a limited range of functionality.

Chirality

Molecules can exhibit a property called chirality. Chiral molecules are asymmetric in such as way the structure and its mirror image are not superimposable. Achiral objects can be superimposed on their mirror image.

Figure 3: Examples of chiral objects[3]. A pair of hands and a chiral α-amino acid. They can not be rotated to superimpose on their mirror image



Molecules are desired as pure single enantiomers because the mirror images react differently with other chiral molecules, such as enzymes in the body.

Single enantiomers are difficult to make because it is synthetically challenging to only produce one enantiomer during a reaction. Separating enantiomers can be expensive because they have the same physical and chemical properties when reacting with achiral molecules, so chiral separating agents are needed.

3. Reactions

Reductive amination was chosen as the route to the β-amino esters. The β-keto esters and both enantiomers (R and S) of methyl benzylamine are commercially available .

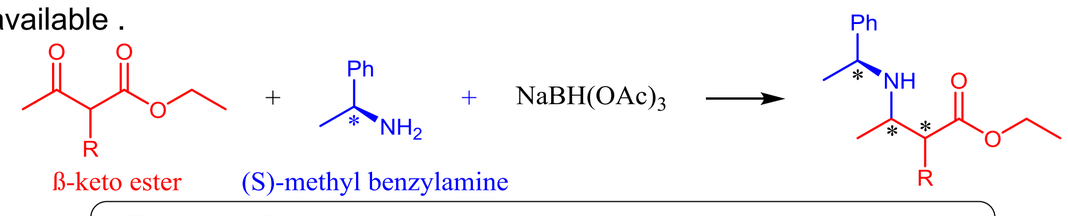


Figure 4: General reaction scheme for the reactive amination. Chiral centres are represented with (*)

Chiral molecules must be made using other chiral molecules. The chiral the amine was used to able to influence the chirality of the products three centres.

"Two pot" reactions

The first step in the synthesis was a condensation reaction between (S)-methyl benzyamine and the respective β-keto ester. The yields of the β-enamino esters **1** and **2** were 63% and 75%.

Figure 5: Reaction scheme for the condensation reaction[4,5] R=H (**1**) or Me (**2**)

The β-enamino esters **1** and **2** were reduced to the β-amino esters **3** and **4** with sodium triacetoxyborohydride in 1:1 acetonitrile/acetic acid, the yields were 58% and 89% respectively.

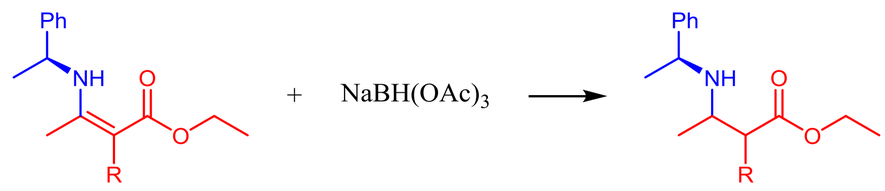


Figure 6: Reaction scheme for the reduction. R=H (**3**) or Me (**4**)

The H^1 spectrum of **3** revealed that the chiral molecules (diastereomers) were present in a 3:1 ratio. Unfortunately the diastereomers could not be separated.

The β-amino ester **3** was Boc protected to prevent oxidation when exposed to the air with a 53% yield.

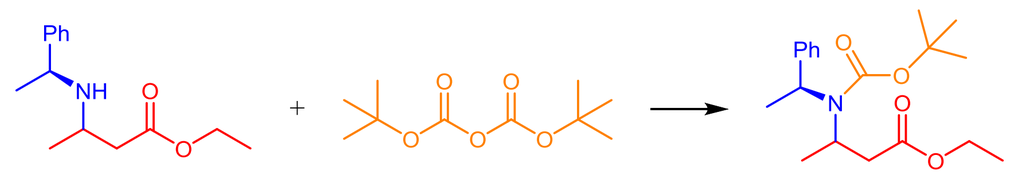


Figure 7: Reaction scheme for the Boc protection

Unfortunately the diastereomers could still not be separated .

Novel "One-pot" reactions

A search of the literature revealed that there was no known one-pot reductive aminations of β-keto esters. Different reaction conditions were tested, including varying the concentration of acetic acid and solvent).

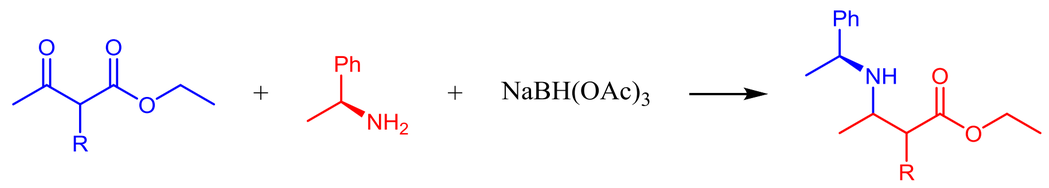


Figure 8: General reaction scheme for the "one-pot" reductive amination

The one-pot reactions worked but were low yielding and with long reaction times. It was found that the desired reaction went faster with higher concentrations of acetic acid and acetonitrile was preferred over THF.

4. Conclusions and Future Work

With the two-pot reductive amination reactions, we were able to synthesise the β-amino esters with some stereoselectivity.

Synthesis of more complex β-amino esters will be investigated and the different chiral molecules made will be separated by selective crystallisations of the HCl salts of the amines.

References

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