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Expanding the Scope of Transaminase Triggered aza-Michael Chemistry for the Synthesis of High Value Targets

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PURPOSE OF THE ABSTRACT

The pyrrolidine scaffold is commonly found in natural products,[1] synthetic drugs,[2] and organocatalysts.[1] We propose a transaminase (TA) triggered intramolecular aza-Michael reaction (IMAMR), where a simple prochiral ketoenone undergoes regio- and stereo-selective amination to form a chiral secondary amine that spontaneously cyclises, affording disubstituted pyrrolidines (Figure 1). This work expands the scope of the biocatalytic intramolecular aza-Michael chemistry that has been previously reported by our group to synthesise 2,6-disubstituted piperidines[3]and cyclic β-enaminones.[4] The synthetic route to access the ketoenone substrates has been developed by employing a tandem ozonolysis-Wittig reaction (25 – 49% yields). The small ketoenone panel was converted to their corresponding chiral pyrrolidine products using a commercially available TA (10 – 57% yields). While the transamination reactions are highly selective, the spontaneous IMAMR results in the formation of diastereoisomers that were isolated as inseparable mixtures. Further chemoenzymatic steps are being investigated to isolate an enantio-enriched pyrrolidine product after the transamination reaction.

FIGURES

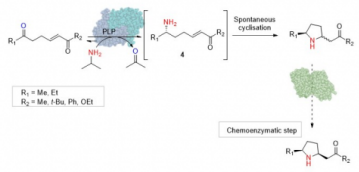

FIGURE 1

Figure 1.

FIGURE 2

KEYWORDS

Transaminase | Enzyme-triggered reaction | Pyrrolidines | Chemoenzymatic

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