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The Selective Reduction of a Morita-baylis-hillman Adduct-derived Ketones Using Various Ketoreductase Enzyme Preparations

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Abstract : The preparation of enantiopure Morita-Baylis-Hillman (MBH) adducts remains a challenge in organic chemistry. MBH adducts are highly functionalised compounds which act as key intermediates in the preparation of compounds of medicinal importance. MBH adducts are prepared in racemic form by reacting various aldehydes and activated alkenes in the presence of DABCO. Enantiopure MBH adducts can be obtained by employing Enzymatic kinetic resolution (EKR). This technique has been successfully demonstrated in our group, amongst others, using lipases in either hydrolysis or transesterification reactions. As these methods only allow 50% of each enantiomer to be obtained, our interest grew in exploring other enzymatic methods for the synthesis of enantiopure MBH adducts where, theoretically, 100% of the desired enantiomer could be obtained.Dehydrogenase enzymes can be employed on prochiral substrates to obtain optically pure compounds by reducing carbon-carbon double bonds or carbonyl groups of ketones. Ketoreductases have been used historically to obtain enantiopure secondary alcohols on an industrial scale. Ketoreductases are NAD(P)H-dependent enzymes and thus require nicotinamide as a cofactor. This project focuses on employing ketoreductase enzymes to selectively reduce ketones derived from Morita-Baylis-Hillman (MBH) adducts in order to obtain these adducts in enantiopure form.Results obtained from this study will be reported. Good enantioselectivity was observed using a range of different ketoreductases, however, reactions were complicated by the formation of an unexpected by-product, which was characterised employing single crystal x-ray crystallography techniques. Methods to minimise by-product formation are currently being investigated.

Keywords : ketoreductase, morita-baylis-hillman, selective reduction, x-ray crystallography
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