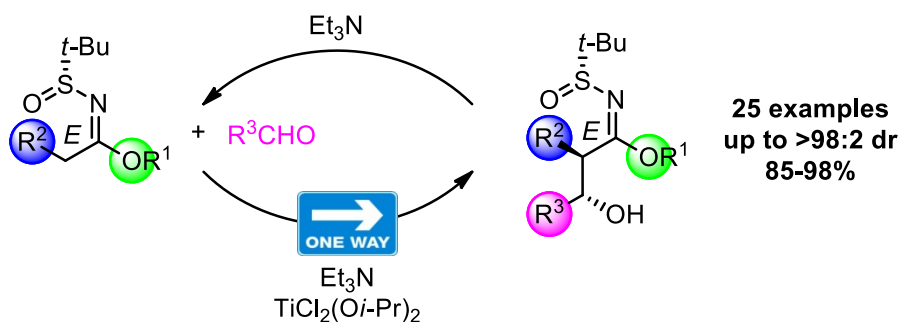


## 1. Final Publishable Summary Report

The EU funded project Metalk was primarily concerned with the development of new methodology, which could ultimately be used as a key step in a general synthetic route towards Lycorine-type alkaloids. To date around 500 of these alkaloids have been isolated and initial tests have shown that many members exhibit useful antitumoral, antibacterial, antifungal, antimalarial, antiviral, analgesic and AChE activities. They therefore have the potential to be interesting targets for the development of novel drugs. However, a comprehensive study of these interesting biological activities has been impeded by a lack of general synthetic studies towards these alkaloids.

Our synthetic approach relies on the development of new methodology to enable a flexible, versatile and general route to a variety of the Lycorine alkaloids. The critical step of this approach involves the unprecedented and challenging aldolisation of a suitable *N*-sulfinylimidate, installing, with appropriate stereocontrol, two contiguous stereocentres, which are present in a large number of the natural products. This was the focus of the Marie Curie Fellowship and during the course of this project, mild, efficient and highly diastereoselective conditions for this transformation were developed. A Lewis acid ( $\text{TiCl}_2(\text{O}i\text{-Pr})_2$ ) proved to be essential for the success of this reaction, enabling the innate and destructive reversibility of the reaction to be overcome. Under the optimised conditions, the diastereomerically and enantiomerically pure product could be isolated in excellent yields. A potential application of this methodology, highlighting its importance, was illustrated by the expedient and efficient synthesis of a potential neurotransmitter re-uptake inhibitor in four steps from the aldol product.



It was also possible to adapt and extend this developed methodology to the aldolisation reactions of both *N*-sulfonylimidates and *N*-thiosulfinylimidates (which had not been previously reported to date). In both cases, the transformation proceeded with high diastereoselectivity to give the corresponding  $\beta$ -hydroxyimides in excellent yields.

The long-term aim of the project is to incorporate the key methodology developed during the course of this research into a flexible approach towards the synthesis of different members of the Lycorine family of alkaloids. Access to a variety of these alkaloids would enable comprehensive studies of their significant biological activities and therefore determine whether they could be of interest as potential drug candidates. The nature of the

synthetic strategy would also enable a range of analogues to be synthesised, and evaluated in a similar manner. This research therefore, depending on the outcome of the biological studies could be of significant interest for the pharmaceutical industry.