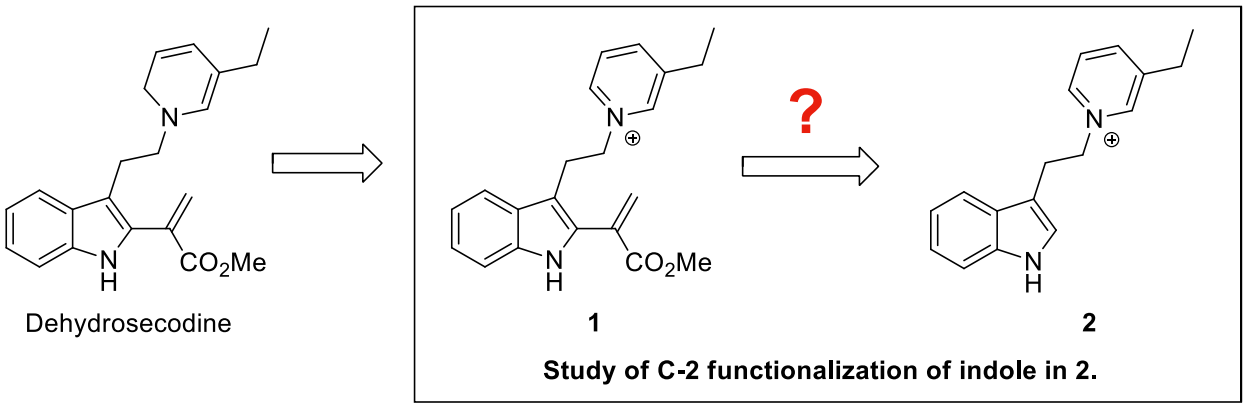
Group : Biomimetic Catalysis and Synthesis
Project : **C2-Functionalization of Tryptamine Based Pyridinium Salts: Streamlined Synthetic Approach toward Dehydrosecodine**
Supervisors : Yifei Zhou, Fedor Miloserdov, Han Zuilhof

Keywords. Organic Synthesis, Indole Alkaloids, Transition Metal Catalysis

Introduction. Dehydrosecodine is a common biological intermediate to different families of indole alkaloids, and compounds of this type were successfully employed as intermediates in biomimetic organic synthesis of a variety of natural products.[1] The development of dehydrosecodine chemistry is particularly important, because it can be used for the biomimetic synthesis of natural compounds, that are applied in cancer treatment.[2] In particular, indole alkaloids of family vinca are widely used as tubulin inhibitors for chemotherapy. However, up to date there is no general synthetic method that would allow to achieve substituted dehydrosecodines in a unified manner, and this project aims to contribute to the solution of this problem.

One of the first and the most straightforward synthetic approaches to dehydrosecodine was developed in 1979 by Kutney.[3] The synthesis involved the reduction of tryptamine derived pyridinium salt **1** as the key step. Although this synthetic route represented a breakthrough at that time, the length of their synthesis of the pyridinium intermediate **1** (7-10 steps) and the lack of the derivatization prevented further practical utilization of the "pyridinium salt" approach.

Goal. In this work we will reinvestigate the "pyridinium salt" approach to dehydrosecodine using the modern arsenal of synthetic tools. The study will focus on the C2-functionalization of tryptamine based pyridinium salts **2**, which are readily available in 2 steps from tryptamine and substituted pyridines.[4] Different Ti-, Re- and Au-catalyzed reactions[5] will be tested in order to achieve the C-2 functionalization of indole unit in **2**, leading to **1** and its derivatives. Depending on the project progress, the reduction of **1** into dehydrosecodine and its radical-mediated in-situ conversion into natural product-like indole alkaloids will be studied.[6]



Topics to be studied. The project is focused on the organic synthesis. The work will involve the synthesis and isolation of organic compounds; analysis of reactions outcome; rational-based reaction design and optimization of chemical transformations, including transition-metal catalyzed processes. Ultimately, the synthesis of natural product-like organic molecules will be performed.

Techniques to be used. General organic synthesis techniques, including work under inert atmosphere, Schlenk-line techniques, catalysis with transition metal complexes, TLC, column chromatography, crystallization, NMR, GC-MS.

Contact details. Han Zuilhof, room Helix 7.031, email: han.zuilhof@wur.nl

[1] Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nature Chem.*, **2014**, *6*, 57-64.
[2] Lee, C.-T.; Huang, Y.-W.; Yang, C.-H.; Huang, K.-S. *Curr. Top. Med. Chem.* **2015**, *15*, 1491-1500.
[3] a) Kuthey, J. P. et al. Can. J. Chem. 1979, 289-299; b) Leeson, P. D. *J. Chem. Soc. Perk. Trans. I* **1984**, 2125-2128.
[4] Gnecco, D.; Juárez, J.; Galindo, A.; Marazano, C.; Enríquez, R. G. *Synth. Commun.* **1999**, *29*, 281-287.
[5] a) Dong, H.-M. et al. *Adv. Synth. Catal.* **2007**, *349*, 1597-1603; b) Xia, D. et al. *Org. Lett.* **2012**, *14*, 588-591; c) C. Ferrer et al. *Chem. Eur. J.* **2007**, *13*, 1358-1373.
[6] Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. *Chem. Rev.* **2016**, *116*, 8912-9000.