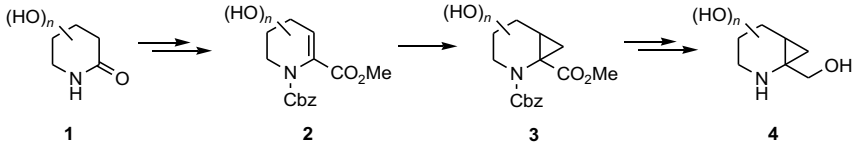
Abstract

The introduction of conformational restrictions into biologically active molecules is a commonly used strategy in drug design because locking the compound into its favourable binding conformation might enhance the potency and the selectivity, improve the pharmacokinetic profile and reduce the side effects.

Polyhydroxylated piperidines, also known as iminosugars, are potent inhibitors of many carbohydrate-processing enzymes what makes them potential antiviral, anticancer and antidiabetic agents in different therapeutic areas as well as in agrochemical science. Among many naturally occurring iminosugars, deoxynojirimycin, swainsonine and castanospermine have been used as the starting point in the drug development for many years but due to the lack of selectivity or potency only few compounds have been progressed beyond the discovery phase.

The main challenge in the development of the iminosugars as therapeutic agents is to overcome promiscuous inhibition by modulating the selectivity and the potency toward given biological target. It has already been demonstrated that the use of cyclopropane and cyclopentane as conformational restrictions can help and therefore, the development of new synthetic methods for the construction of conformationally restricted *N*-heterocycles is essential for achieving additional diversity. In this thesis, the methodologies for merging a piperidine core and other *N*-heterocycles with cyclopropane and cyclopentane rings were explored.

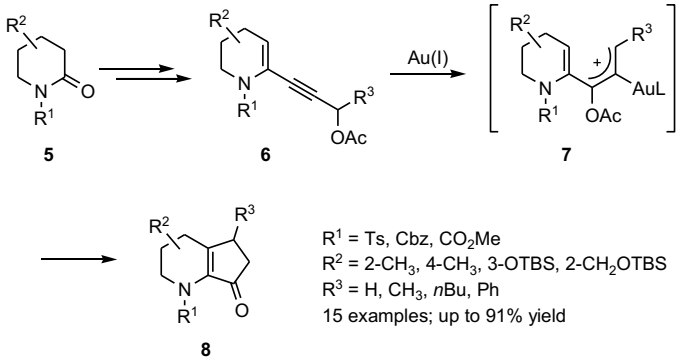
In general, the synthesis of cyclopropane-fused piperidine core **4** presented within this thesis is based on the OH-directed Simmons-Smith cyclopropanation of corresponding enecarbamate ester **2** (Scheme 1). The different hydroxylated enecarbamate esters could be prepared through a Pd-catalyzed methoxycarbonylation of valerolactam-derived enol phosphates. To this end, enantiopure 5-hydroxy-piperidin-2-one and 4,5-dihydroxy-piperidin-2-one were prepared according to a previously developed methodology from commercially available (*S*)-(+)-*γ*-hydroxymethyl-*γ*-butyrolactone and 2-deoxy-D-ribose, while racemic 5-hydroxy-6-hydroxymethyl-piperidin-2-one was prepared from *δ*-valerolactam.



Scheme 1. Synthesis of polyhydroxylated cyclopropane-fused piperidine core.

The fact that gold(I) catalysis has become a very powerful methodology for the construction of 5-membered rings, prompted us to explore the tandem gold(I)-catalyzed rearrangement/cyclization reactions of piperidine-derived enynyl acetates **6**, **9** and **14**.

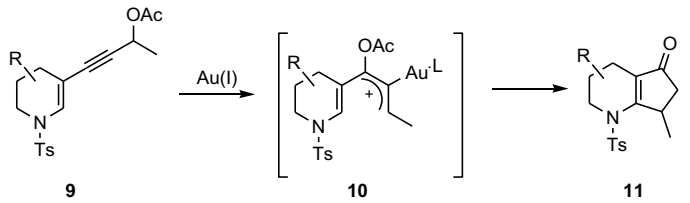
Among the explored methods, the tandem gold(I)-catalyzed [3,3]-rearrangement/Nazarov reaction of piperidine-derived enynyl acetates bearing a C-2 propargylic ester side-chain (**6**) was the most robust and reliable (Scheme 2). To understand the influence of the reaction conditions and substrate structural features the whole process was studied in details both experimentally and computationally. The scope and the limitations of the reaction were assessed by varying the substituents on the propargylic side-chain and on the piperidine ring as well as the *N*-heterocycle. Since the protected hydroxyl groups at C-5 and C-6 in substrate **6** were well tolerated in the gold(I)-catalyzed step, this method is then suitable for the synthesis of conformationally restricted iminosugars.



Scheme 2. Cyclopenta-fused piperidines **8** via gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization.

The shift of the propargylic ester side-chain from position C-2 to C-3 of the piperidine ring (Scheme 3)

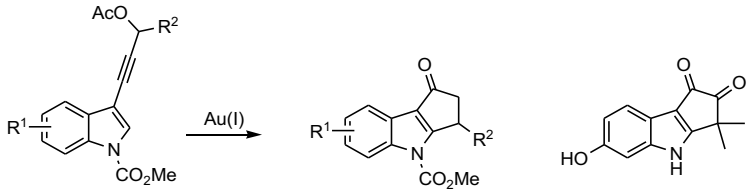
influenced the reactivity of intermediate **10** thus giving the corresponding cyclopenta-fused product with alternate position of C=O group on the five-membered ring, although in moderate yield.



9 **10** **11**

Scheme 3. Gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization of enynyl acetate **9**.

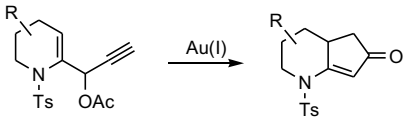
Instead, indole-derived enynyl acetates bearing a C-3 propargylic ester side-chain (**12**) provided 3,4-dihydro-cyclopenta[*b*]indol-1-ones (**13**) in excellent yields (15 examples, up to 84% yield). These cyclopenta[*b*]indoles possess a substitution pattern on the five-membered ring which allows an easy entry to the bruceollines and other naural products possessing the cyclopenta[*b*]indol-1-one nucleus.



12 **13** **Bruceolline H**

Scheme 4. Gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization of indole-derived enynyl acetate **12**.

Finally, modification of the propargylic moiety (**14**) allowed us the preparation of cyclopenta-fused compound with C=O group at the central position of the five membered ring (Scheme 5).



14 **15**

Scheme 5. Gold(I)-catalyzed Rautenstrauch rearrangement of enynyl acetate **14.**

All these pentannulated piperidines will be in future converted into novel polyhydroxylated conformationally restricted iminosugars and tested toward the suitable targets.