1- Asymmetric total synthesis of both Cycloclavin (-) and (+) enantiomers.

2- Research Area (ERC) PE5, (SSD) CHIM/08, CHIM/06

3- Cycloclavin is a substance of the family of clavine alkaloids, a subclass of ergot indole-containing molecules produced by several members of *clavicipitaceae* and *trichocomaceae* families of funghi [1].

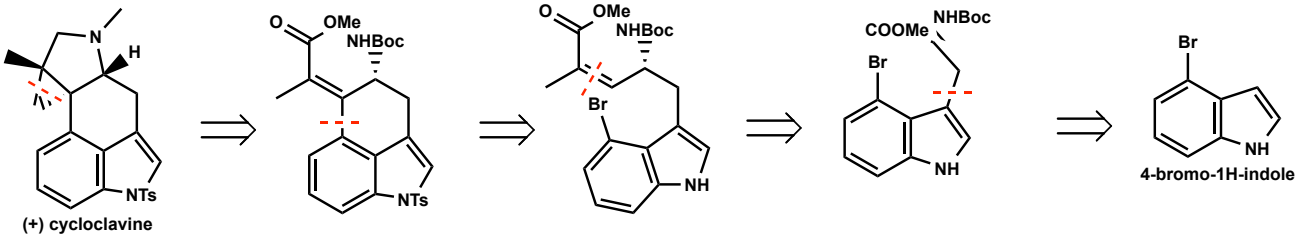
These molecules showed an important activity in important receptors like the one of serotonin, dopamine and alfa-adrenergic [2]. For this reason some of the natural or semisynthetic proline derivates are used as drugs for the treatment of diseases like Parkinson and iper-production of prolactin [10]. Cycloclavine was isolated in 1969 from the seeds of *ipomea hildebrandtii* and later from a funghi species of filamentous fungus, *Aspergillus japonicus*. A unique structural feature of cycloclavine is a pyrrolidine-fused cyclopropane in place of piperidine that is typical from other calcine and lysergic acid alkaloids, the presence of three contiguous stereocenters, out of which two are vicinal all-carbon quaternary stereocenters, poses a formidable synthetic challenge for the synthetic community.

In 2008 Szantay's group [3] reported the first total synthesis of (+-)-cycloclavine, in which intramolecular aldol condensation and cyclopropanation of the tetrasubstitued olefin were employed. During the years which follow only racemic synthesis have been reported, until 2016, where Wipf and McCabe [4] achieved the first total synthesis of unnatural (-)-cycloclavine via Rh-catalyzed enantioselective cyclopropanation of an unsubstituted alkene to reach a methylene-cyclopropane derivate. About the (+)-enantiomer, Cao's group [5] have reported an elegant total synthesis starting from substituted indoles. Subsequently a formal synthesis of both enantiomers was realised by Bisai and co-workers [6] based on a Heck coupling and a d- or l-proline catalyzed alfa-aminoxylation. Cao, Shi and co-workers [7] developed a ring-enlargement of benzocyclobutenone intermediate to develop a new pathway for the synthesis of (- cyclocavine) and (-)-5-epi-cyclocavine. Most recently McCabe and Wifp [2] reported the firs enantioslective total synthesis of (+)-cycloclavine based on rhodium-catalysed cyclopropanation of allene with a diazo propane active ester and aminolysis for the assembly of the precursor for the IAMDAMC reaction.

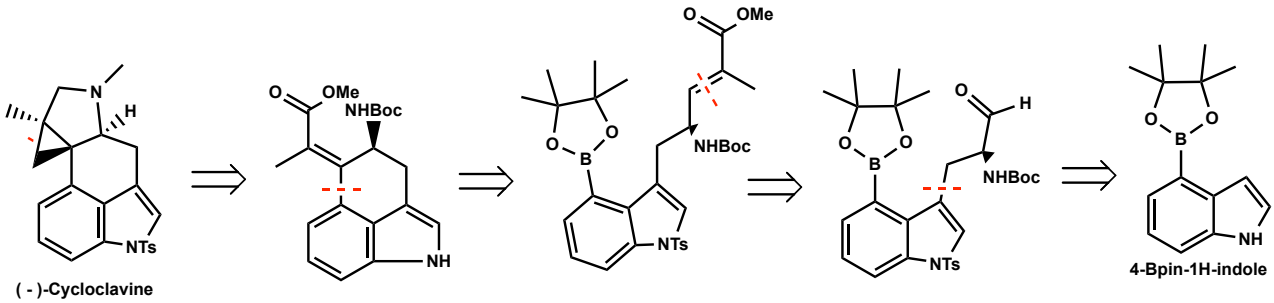
The high level of current interest in novel natural and unnatural alkaloids showed from the impressive publication surge and the growing number of different strategies of these synthetic approaches, in addition to the therapeutical potential of these molecules push the community to find a new pathway for an asymmetric total synthesis of both cyclocavin (-) and (+) enantiomers. For these reasons, I'm proposing a new synthetic approach for the asymmetric total synthesis of both the anantiomers of cycloclavin.

Retrosynthetic analysis

1) Analysis of (+) cyclocavine until starting materials.

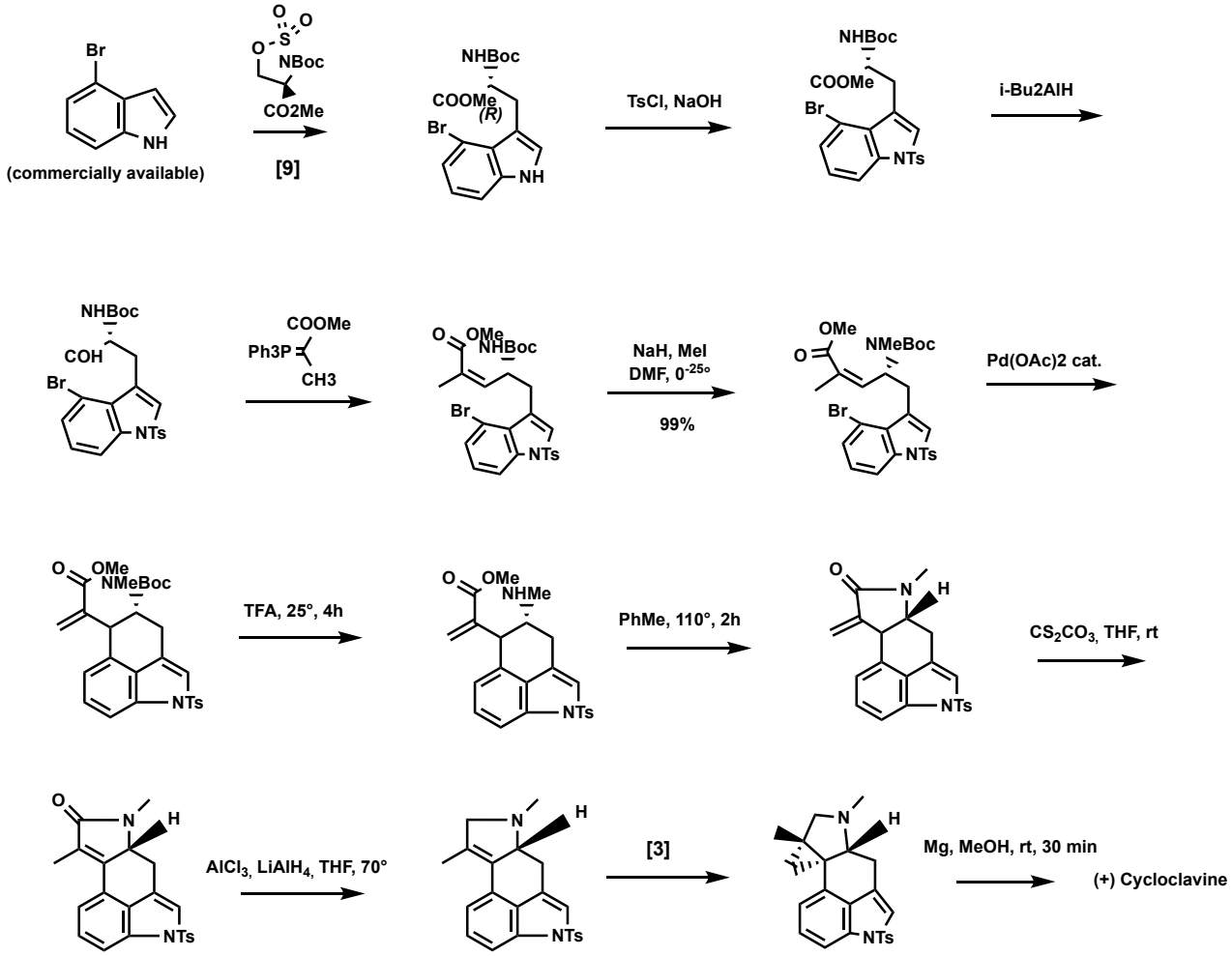


2) Analysis of (-) cyclocavine until starting materials.

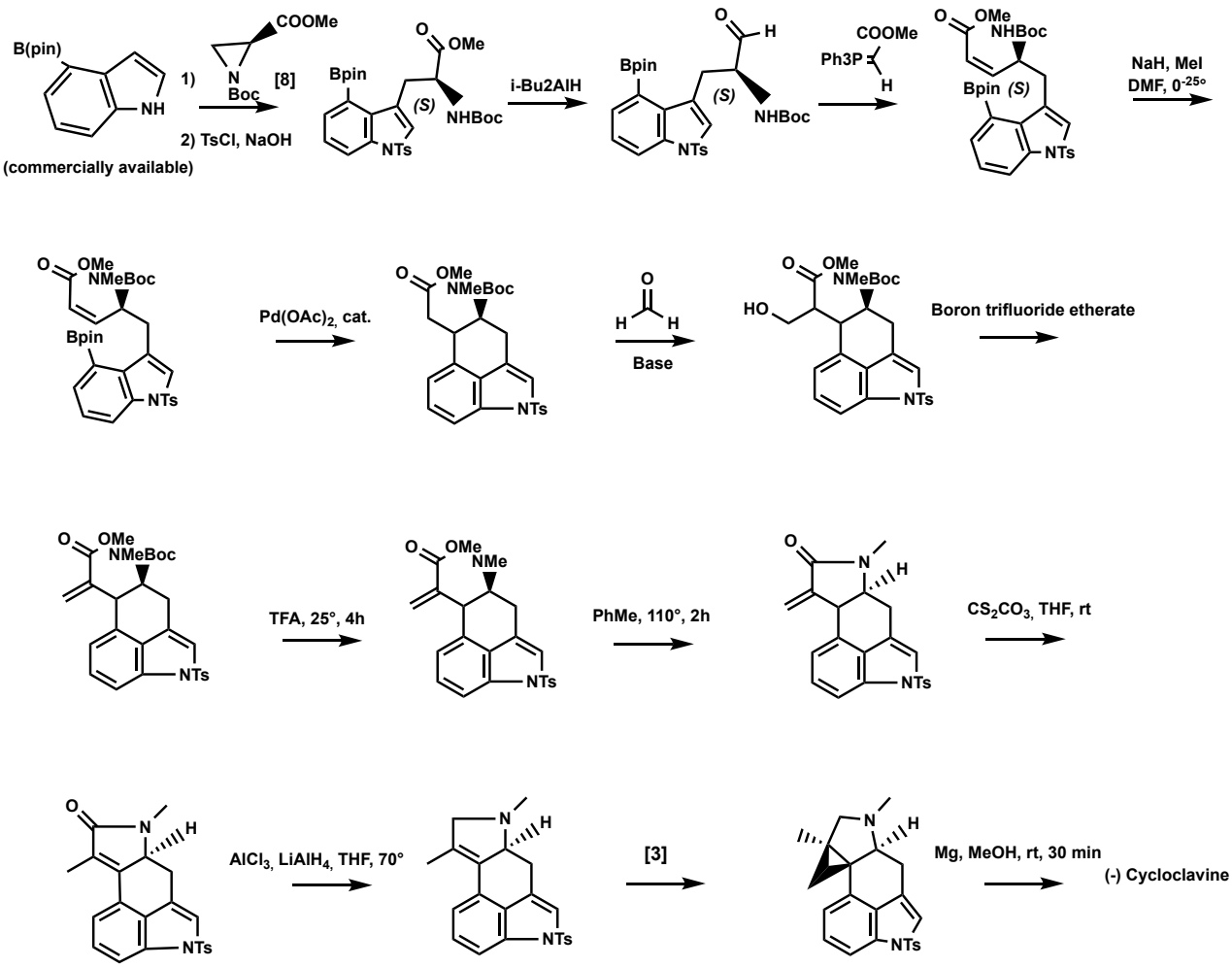


The Retrosynthetic analysis show the possibility to complete both the reaction passing by similar synthetic pathway by changing the starting materials.

Proposed synthesis



1) Proposed Synthesis: In the first step [9] we use cyclic sulfamidates derived from enantiopure d-serine to react whit 4-Bromo indole to obtain enantiopure bromotryptophans. In this proposed synthesis the key of the pathway is the Heck-type cross coupling reaction, using a Pd catalysis and forming the third ring of the scaffold. The cyclopropanation io already knows. [3]



2) Proposed synthesis of (-) cycloclavine.
The Lewis acid-promoted aziridine amino acid ring opening with 4-boronated indole is already reported [8], otherwise in that case the cross coupling is made by using Br at the place of B(pin) in the cross coupling reaction. The cyclopropanation io already knows. [3]

4- The objective of this research is reach to a new and efficient way for the synthesis enantiomerically pure of both cycloclavine (-) (+) enantiomers, emergent molecules of high interest for his property and receptor's activity which is generating attention in the scientific community.

5- We will see the positive points and negative ones to improve this methodology and find a better pathway. Specifically we will star with a retro synthesis analysis, and fixing the key points to elaborate the synthetic strategy. Subsequently, we will check if starting materials are commercially available and if possible, buy them, if not, we will make it by ourselves (including the study for best synthetic pathway and optimization of the process), after that, we will start the asymmetric synthesis of cycloclavine using the studied process (synthesis, purification and analysis). This point will need optimization and/or some changes in the studied methodology, so it will take time. The expected results are the complete synthesis of both enantiomers, with a good %ee and a good overall yield (maybe 20%).

6- Bibliography

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7- First year we will study the bibliography, generating the better synthetic pathway, synthesis and optimization of starting material and star with the first step of total synthesis of (+) Cycloclavine.

Second year, we will go ahead with the synthesis and conclusion of (+) enantiomer and start with the other one (including starting materials).

Third year, we will end the synthesis of (-) enantiomer and evaluating of the better option between publication and other.