Title of the Research Project

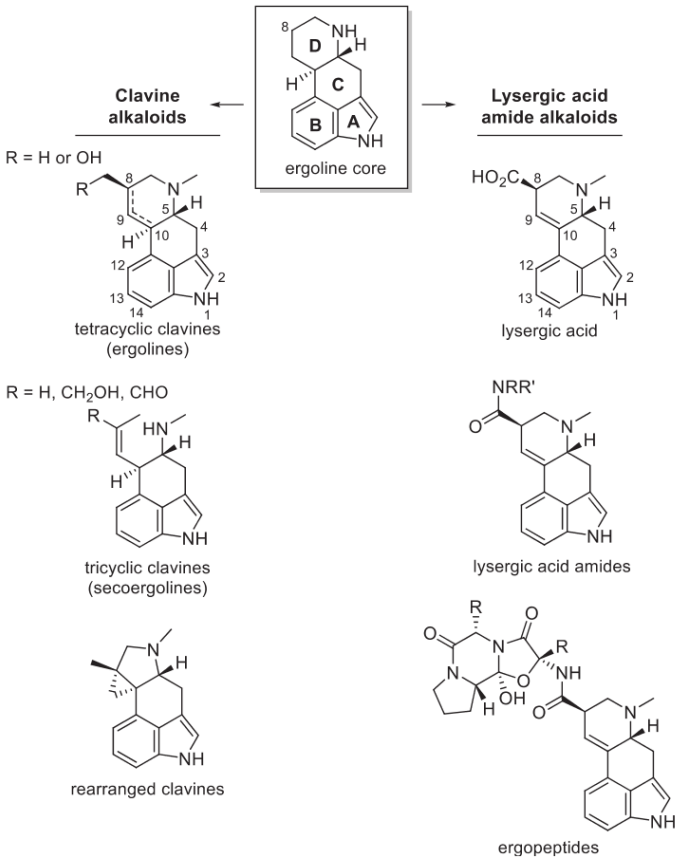
Natural Product-Assisted Hetero Diels-Alder for the Sinthesis of Ergoline Core

Research Area

CHIM/06; CHIM/08

General presentation of the project and State of the Art

Ergot Alkaloids represent an extremely interesting target for synthetic and medicinal chemists, both because of their complexity and of their pharmaceutical proprieties. *(1)*

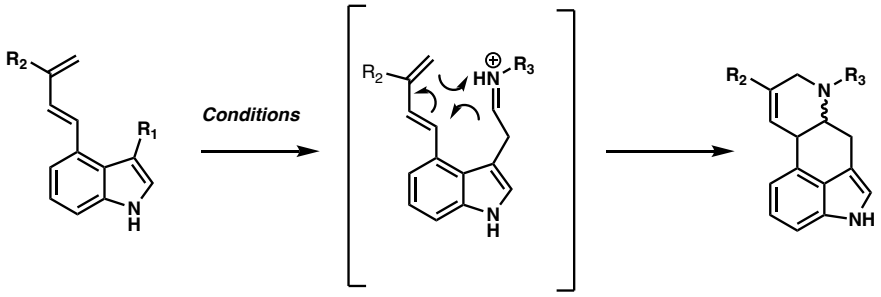


Scheme 1 Classification of *ergot* alkaloids.

Several attempts have been made to obtain these molecules, but few synthetic routes of the ergolinic core are reported in the current literature. *(2)*

This project focuses on a possible strategy to obtain the ergoline core throughout a rapid synthesis that allows the closure of C and D rings in a single step.
To reach this aim, a natural product-assisted [4+2] hetero-Diels-Alder approach via iminium generation has been selected: in fact, it is well known

that these kinds of reactions offer the advantage of being stereospecific, stereo- and regioselective, moreover their use in natural products total synthesis has been over-employed. *(3)*



Scheme 2: *single-step ring closure of C and D.*

The challenge to achieve this transformation is to win enantioselectivity over stereoselectivity: to this purpose, a Diels-Alder reaction could be performed by employing a natural product that can induce the formation of one enantiomer over another.

One possibility has been detected in using thioureas derived from Cinchona natural products, which could coordinate the iminium ion and yield an enantiomerically enriched product.
Another possibility is to perform the reaction into the presence of a Diels-Alderase enzyme: in fact, many studies have been carried out to demonstrate that there are several enzymes that can support these kinds of transformations, also for indole alkaloids. *(4)*

Scheme 3: *(a) General structure for Cinchona derivatives; (b) Example of Diels-Alderase enzyme.*

Research Objectives

This project's aims are three:
1 - To find a rapid sequence to obtain the intermediate A, either from thryptophan or 3-formyl-indole, which offer the possibility to functionalize the C-4 position quickly. *(5)*

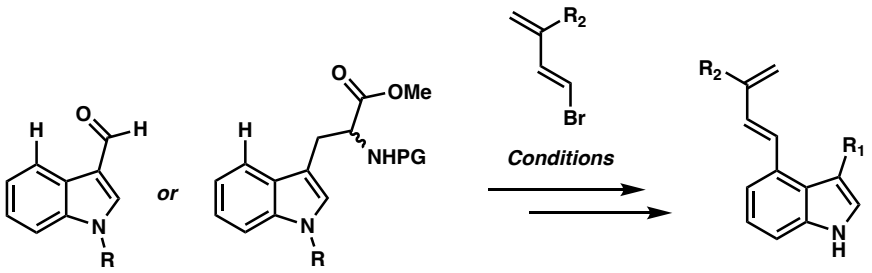
2 - To demonstrate the possibility of obtaining the ergoline core via an asymmetric hetero-Diels-Alder reaction employing natural products.
This second aim could also be useful to elucidate a possible biosynthetic pathway that nature involves to afford Ergot Alkaloids, because of the lack of knowledge in this field.

3 - To demonstrate the possibility to late-stage functionalize the ergoline core.

Methodology and Expected Results

1 - Functionalization of the indolic core
- C(4)-H transition metal-catalyzed prenylation of 3-formyl-indole, *(5)*. The aldehyde placed in C-3 position has the dual role of (a)-acting as a directing group for the metal catalyst and (b)-offer the possibility of a simple manipulation in the direction of the intermediate of interest.
The idea is to try to introduce various substituted prenyl units, that would later undergo Diels-Alder reaction to give the ergolinic core.

- C(4)-H transition metal-catalyzed prenylation of N-Tf or N-Ns protected tryptophans as reported by Jia and co-workers. *(6)* The utility of (C-4 prenylated tryptophan will be illustrated later, as well as the utility of the N-protecting groups also for the following transformation).



Scheme 4: *Direct C4-H functionalization of indole core.*

The idea is to try to introduce various substituted prenyl units, that would later undergo Diels-Alder reaction to give the ergolinic core, which could eventually be manipulated later.

2 - Aldehyde homologation at C-3 position
- Wittig reaction on the aldehyde introducing a methoxy group. The so obtained enol will hopefully tautomerize to yield the homologous aldehyde.

- Matteson homologation to afford the homologous aldehyde. *(7)*

3-Iminium generation and natural product assisted Hetero-Diels-Alder

- From tryptophan: Radical-polar crossover via decarboxylation of the carboxylic moiety.

The so-generated iminium, would hopefully undergo Diels-Alder reaction to give the desired product. *(8)*

- From aldehyde: Reaction with an amine. The so generated iminium ion would face the same destiny indicated above with tryptophan. Many amines could be selected to undergo this transformation, but to drive the equilibrium in favor of the imine versus the conjugated enamine, amines with electron withdrawing substituents should be selected.

To perform these reactions in an asymmetric fashion, natural products will be added in the reaction mixture.

Thioureas and Diels-Alderase are of particular interest in this reaction for two main reasons: (a) they would induce the formation of only one enantiomer over another and (b) by coordinating the positively charged nitrogen atom, they would help drive the imine-enamine equilibrium in favor of the former.

4-Simple late-stage functionalization of ergoline core

- Oxidation of C-8' in ergoline core. Mild oxidants would be chosen.

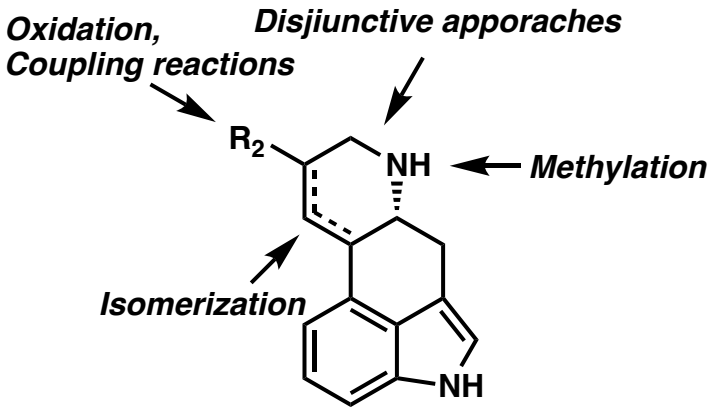
The possibility to involve enzymes because of regiochemistry issues would be considered.

- Transition Metal-catalyzed C-8/C-9 double bond isomerization.

- Late stage methylation of the aliphatic nitrogen.

- (After C-8' oxidation) Coupling reaction at the carboxylic moiety to afford ergopeptides.

- Disjunctive approach to open selectively the D ring and obtain chanoclavine derivatives. (*9*)



Scheme 5: *Late stage functionalization of the tetracyclic core.*

Feasibility

All the performed reactions performed would be conducted employing cheap or recyclable reagents and starting materials. All transition metals involved will be used in catalytic loads to minimize the waste.
Dividing the project in three parts (Indole C-4 functionalization, Diels-Alder, Late stage functionalization) will enable to focus on one single goal at a time.

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