A new synthesis of D-lysergic acid, with Photoredox Catalysis as a key step.

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1. Research objectives

The proposed research is a new strategy for the synthesis of D-lysergic acid, which is a natural product. A new approach based on photocatalysis is proposed as a key step, never been used for the synthesis of ergot alkaloids; this will allow to the synthesis of Ergot alkaloids via new bond formation protocols that are not easily accessible under thermal control.

2. Introduction

The Ergot alkaloids are a class of natural products known for their pharmacologically privileged molecular structure. For the chemists, the Ergot alkaloid family offers the highest level of challenges and rewards. Spiked with isolated as well as connected stereogenic carbons and complex heterocyclic and carbocyclic ring systems, the lore of Ergot alkaloids and their potent physiological properties span millennia of human history, folk medicine, and occultism, as well as decades of pharmacology, pharmaceutical, medicinal and synthetic organic chemistry.[1] Albert Hofmann's discovery of lysergic acid diethylamide (LSD) a chemically derived ergot alkaloid, is one of the most potent agonists for the 5-HT_2A serotonergic receptor (Kd = 0.33 nM).[2] As a result, several natural ergot alkaloids were discovered and unnatural analogs were synthesized, and some were used to treat an array of deseases, including Alzheimer's and Parkinson's disease. The key active pharmaceutical ingredient (API) of these ergoline-derivatives comes from D-lysergic acid (DLA).

3. Biosynthesis

The Ergot alkaloids are produced by several filamentous fungi from the *Ascomycota phylum*, but most notably from the parasitic fungus—*Claviceps purpurea*.[4] All ergot alkaloids are derived from L-tryptophan and share a common set of early biosynthetic steps enzymes-mediated that form the ergoline C-ring.[5] The most important steps are the addition of Dimethylallyl pyrophosphate on C(4) of the tryptophane and the formation of the intermediate **C** via decarboxylative radical coupling (fig.1).

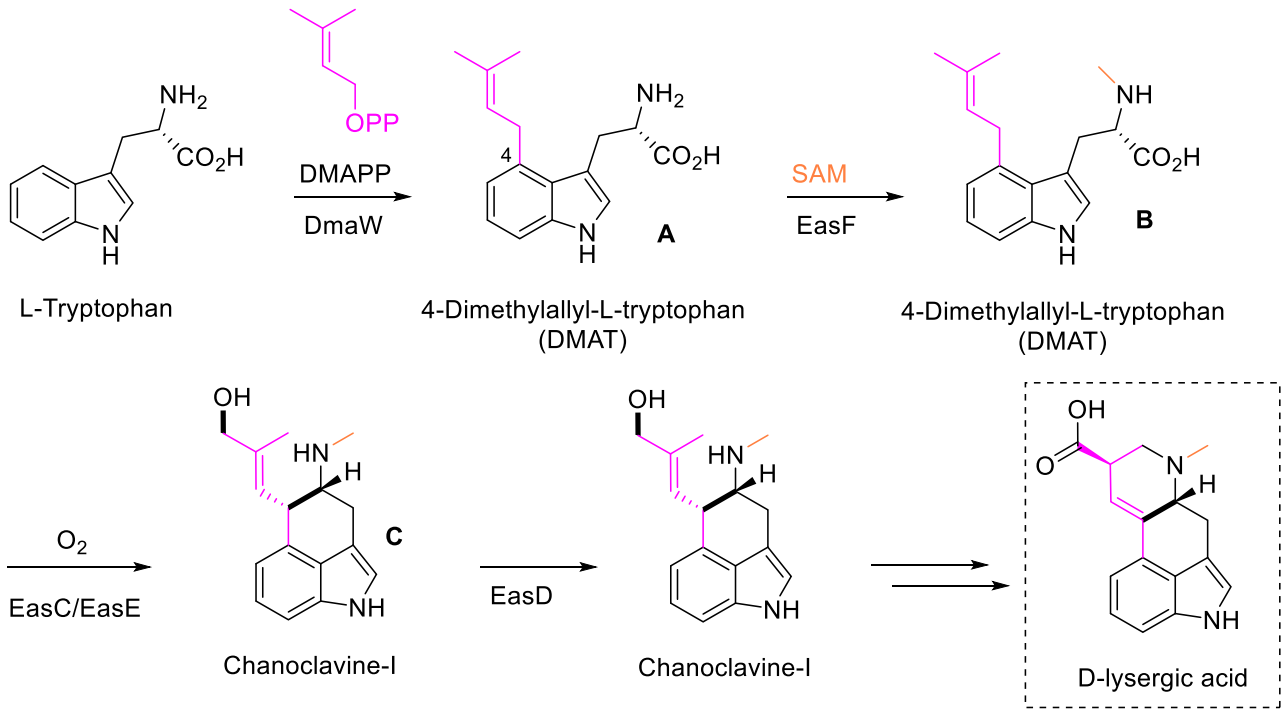

Figure 1- Biosynthesis D-lysergic acid

4. Reported synthesis

In the last decades, some works reported the total syntheses of lysergic acid, the shortest reported by Hendrickson,[6] (11 steps). However, this synthesis has led to problems with reproducibility, as reported by Nichols et al.,[7] the application of the reported reaction conditions led to decomposition of the starting material. Thus, the authors concluded that the Hendrickson synthesis "is not viable" unless the cyclization step was re-examined (fig.2a). Another important synthesis is from Jia et al.,[8] one of the key steps is a multicomponent reaction with (*R*)-*N*-tertbutanesulfinamide, allylbromide, an available aldehyde in the presence of $Ti(OEt)_4$ and indium metal led to homoallylic amine in 79% yield and a 7:1 dr. The second key step is a Heck cyclization reaction from the intermediate **A** to give the pure (+)-lysergic acid (fig.2b), with a total yield of 4.3%. In the literature there are other examples concerning the total synthesis of lysergic acid, however, a better synthesis of Jia has not yet been developed. Of note, a photocatalytic approach has never been used.[1]

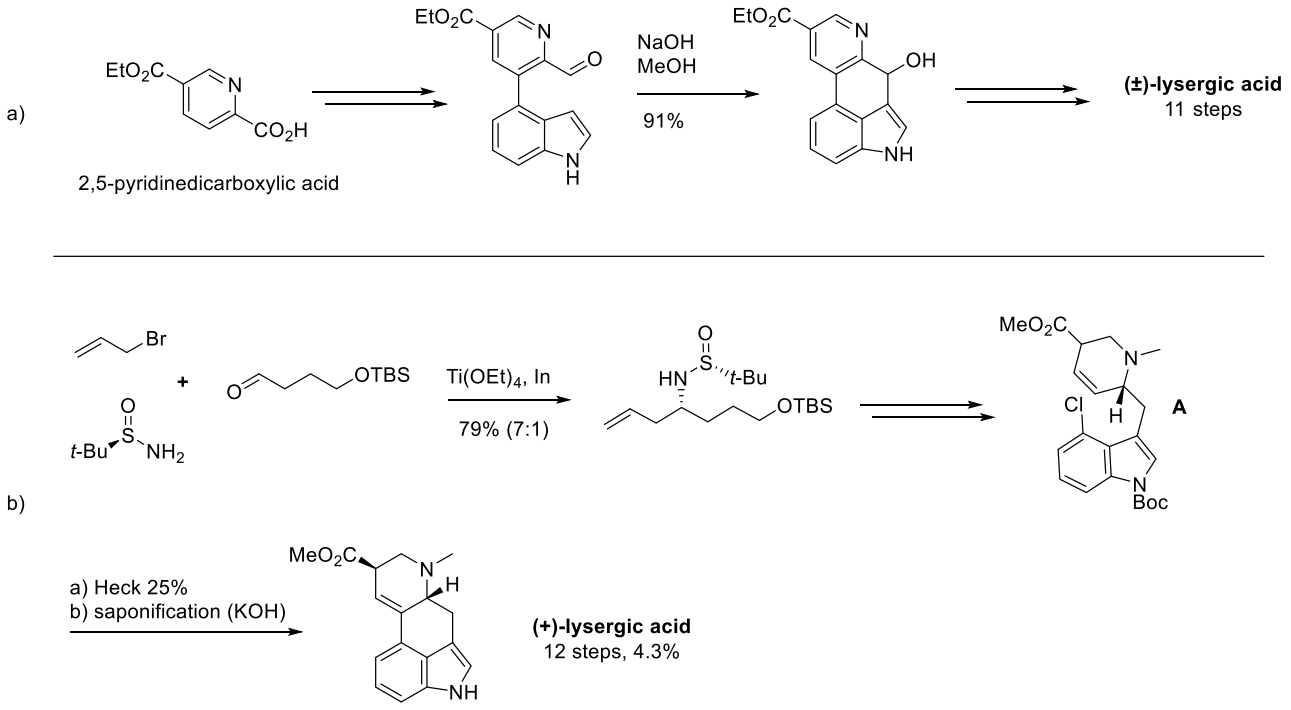

Figure 2- examples of total synthesis of lysergic acid

5. Proposed Total Synthesis

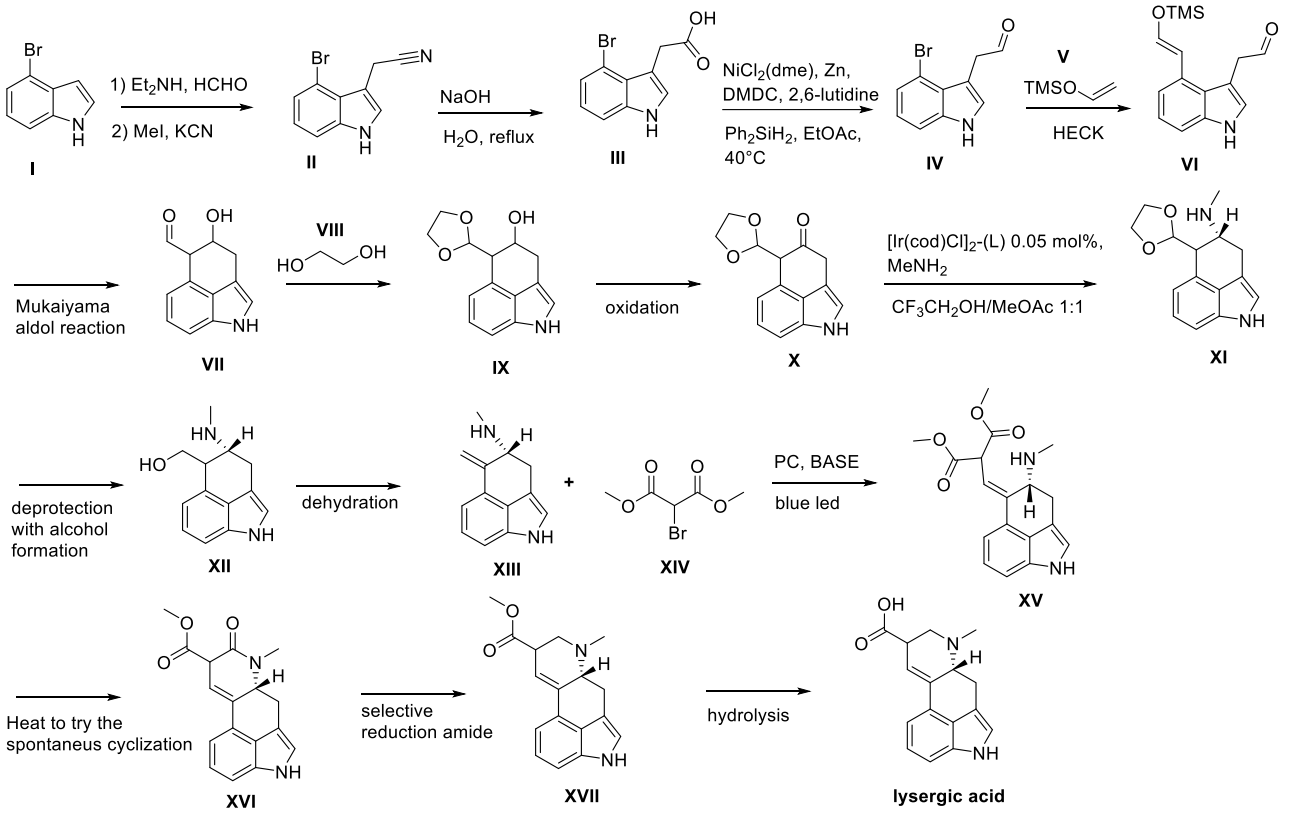

Figure 3- Steps for the total synthesis of Lysergic acid

Starting from the commercially available 4-bromoindole (fig.3), the intermediate **II** is synthesized following the methodology developed by Pérez-Alvarez et al.,[9,10] now the nitrile group can be easily hydrolysed with a base giving the intermediate **III**.[11] The carboxylic acid of the intermediate **III** is reduced to aldehyde by nickel catalyst, an activator of carboxylic (acid dimethyl decarbonate, DMDC), and lutidine as a base;[12] the functionalization with an aldehyde is fundamental for one of the key steps of this total synthesis. The intermediate reaction **IV** can undergo to Heck reaction with the commercially available protected vinyl alcohol **V** to give the required compound **VI**, this intermediate is necessary for the formation of the ring **C** via Mukaiyama aldol reaction (first key step). After the protection of the aldehyde through a cyclic acetal (**IX**) and the oxidation of the secondary alcohol to ketone, the intermediate **X** can undergo to an Iridium-catalyzed direct asymmetric reductive amination, this methodology was published in 2022 and allowed to synthesize enantiomerically enriched *N*-alkyl amines from ketones; for methylamine is reported 95% ee.[13] After a deprotection (**XII**) and dehydration (**XIII**), the compound **XIV** can be reduced by a photocatalyst to produce a very stable radical with the elimination of Br^- species, the radical undergoes Giese addition to **XIII**, while the base or heat could be useful for the formation of the alkene group (for a better explanation of the proposed mechanism see fig.4). Spontaneous cyclization could be promoted by heat, this is a critical step because there is an acid proton in the α-position of the two carbonyl groups. If the spontaneous cyclization does not occur, it may try to change the reagent in the previous step with one having two bromines in alpha to carbonyl groups to eliminate the problem of the α-H. After a selective reduction of the amide group,[14] the desired product is obtained with the hydrolysis of the ester group.

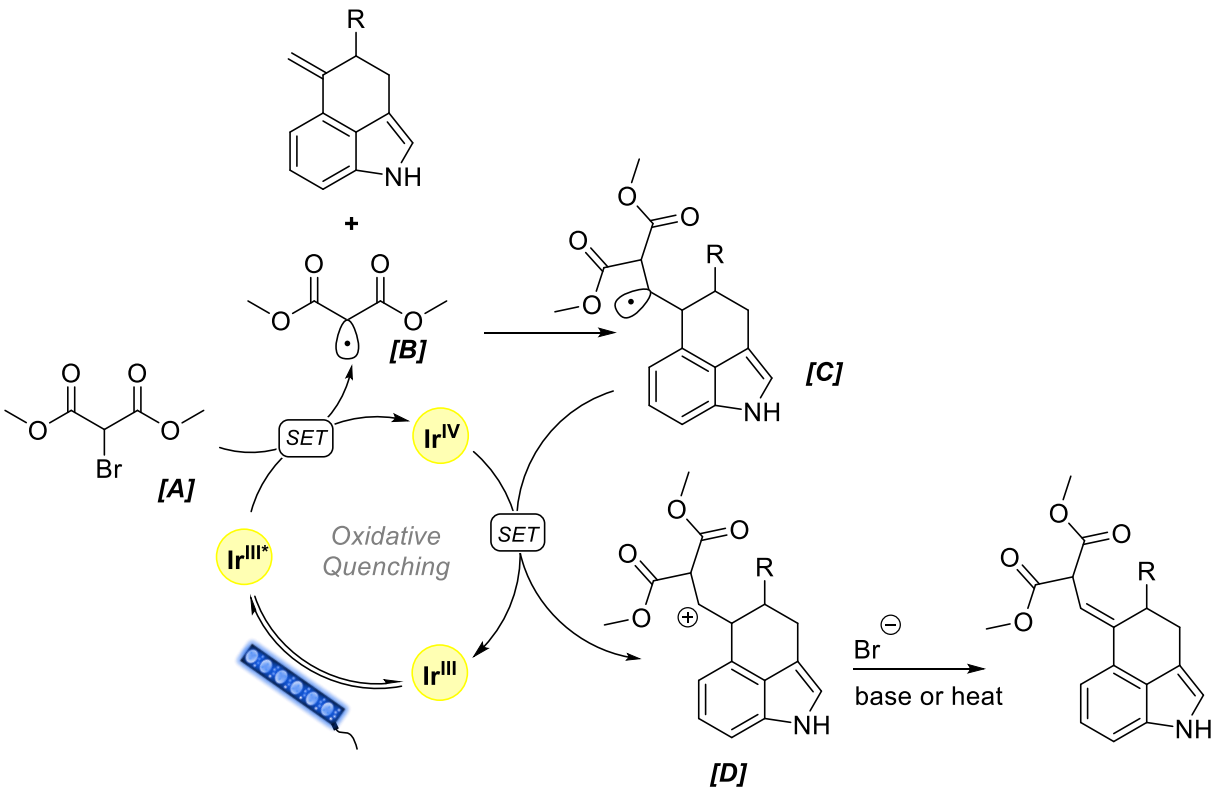

Figure 4- Proposed mechanism of Photocatalytic step

6. Methodology and Expected Results

Bibliographic research is fundamental for a research project both before starting and during the duration of the project. Another point that I consider fundamental for my research is the optimization of each step and the characterization of each intermediate through ^{1}H NMR, ^{13}C NMR, and spectroscopic characterizations because collecting data gradually allows the writing of each thesis easier. Optimizing each step (yields greater than 80% reported on other substrates) and overcoming some problems that could be encountered in the key steps, it is possible to obtain a better total synthesis of the lysergic acid, greener, higher yield and with the application of Photoredox catalysis, never applied in the synthesis of Ergot alkaloids.

7. Description of the research in the three-year period

I strongly believe in the feasibility of the project in three years; the initial phase will focus on the literature search (fig. 5). Within the first year, it is feasible to optimize the first key step (Mukaiyama). After the second year is possible to overcome the second key step, and in the third year to obtain lysergic acid. For the duration of the three years, the characterization and writing of the final thesis will be a fundamental part of my work. During the third year, it would be interesting to develop a new photocatalytic methodology for the functionalization of styrene.

	1st year	2nd year	3rd year
Literature search			
Reaction optimization			
1st key step Mukaiyama			
2nd key step Photoredox			
3rd key step ***D*** ring formation			
Characterization			
Thesis writing			

Figure 5- Gantt Chart for the proposed research project

8. Bibliography

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