## Development of One-Pot Sequential Cyclizations and Photocatalyzed Decarboxylative Radical Cyclization: Application Towards Aspidospermatan Alkaloids

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Abstract: There is an undeniable thirst from organic chemists and from the pharmaceutical industry to access complex alkaloids with short syntheses. While medicinal chemists are interested in the fascinating wide range of biological properties of alkaloids, synthetic chemists are rather interested in finding new routes to access these challenging natural products of often low availability from nature. To synthesize complex polycyclic cores of natural products, reaction cascades or sequences performed one-pot offer a neat advantage over classical methods for their rapid increase in molecular complexity in a single operation. In counterpart, reaction cascades need to be run on substrates bearing all the required functional groups necessary for the key cyclizations. Chemoselectivity is thus a major issue associated with such a strategy, in addition to diastereocontrol and regiocontrol for the overall transformation. In the pursuit of synthetic efficiency, our research group developed an innovative one-pot transformation of linear substrates into bi- and tricyclic adducts applied to the construction of Aspidospermatan-type alkaloids. The latter is a rich class of indole alkaloids bearing a unique bridged azatricyclic core. Despite many efforts toward the synthesis of members of this family, efficient and versatile synthetic routes are still coveted. Indeed, very short, non-racemic approaches are rather scarce: for example, in the cases of aspidospermidine and aspidospermine, syntheses are all fifteen steps and over. We envisaged a unified approach to access several members of the Aspidospermatan alkaloids family. The key sequence features a highly chemoselective formamide activation that triggers a Vilsmeier-Haack cyclization, followed by an azomethine ylide generation and intramolecular cycloaddition. Despite the high density and variety of functional groups on the substrates (electron-rich and electron-poor alkenes, nitrile, amide, ester, enol ether), the sequence generated three new carbon-carbon bonds and three rings in a single operation with good yield and high chemoselectivity. A detailed study of amide, nucleophile, and dipolar ophile variations to finally get to the successful combination required for the key transformation will be presented. To complete the indoline fragment of the natural products, we developed an original approach. Indeed, all reported routes to Aspidospermatan alkaloids introduce the indoline or indole early in the synthesis. In our work, the indoline needs to be installed on the azatricyclic core after the key cyclization sequence. As a result, typical Fischer indolization is not suited since this reaction is known to fail on such substrates. We thus envisaged a unique photocatalyzed decarboxylative radical cyclization. The development of this reaction as well as the scope and limitations of the methodology, will also be presented. The original Vilsmeier-Haack and azomethine ylide cyclization sequence as well as the new photocatalyzed decarboxylative radical cyclization will undoubtedly open access to new routes toward polycyclic indole alkaloids and derivatives of pharmaceutical interest in general.

**Keywords:** Aspidospermatan alkaloids, azomethine ylide cycloaddition, decarboxylative radical cyclization, indole and indoline synthesis, one-pot sequential cyclizations, photocatalysis, Vilsmeier-Haack Cyclization

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