

Leggans Group: Tryptamine Derivatives and Indole Alkaloid Natural Product Syntheses

Background and Significance

The field of complex natural products is growing increasingly more sophisticated, with technological advances being made in the screening and evaluation of these molecules and structural details of their interaction, with biological targets becoming more accessible. The importance and opportunities for providing unique solutions to complex biological problems have consequently grown, and a powerful complement to the examination of the natural products themselves is the preparation and subsequent examination of key partial structures and structural derivatives containing deep-seated modifications. Future progress in the field of natural product synthesis depends upon the development of dependable synthetic strategies and the development of new synthetic methodology to not only prepare natural products, but also key partial structures and analogs incorporating deep-seated structural changes.

Broadly, the research goals of my group are to develop synthetic routes using methodology studies to synthesize small molecules and biologically active natural products in a multi-disciplinary, collaborative environment. Emphasis is placed upon the total synthesis of biologically active natural products, the development of new synthetic methods, heterocyclic chemistry, and bioorganic and medicinal chemistry. In addition to natural product synthesis, my group has a keen interest in studying the natural products structural activity relationship (SAR) and the effect that selective structural modification has on their medicinal properties.

Project 1: Column-Free Syntheses of Tryptamine Derivatives and N-Substituted Tryptamine Derivatives

Tryptamine is an indole alkaloid found in animals, fungi, and plants and is structurally similar to the amino acid tryptophan, from which it derives its name. The tryptamine structural skeleton is found in many monoterpene alkaloids, such as the *Corynanthe*, *Iboga*, and *Aspidosperma* alkaloids (Figure 1). Due to the pharmacological activity and the inherent structural complexity of many monoterpene alkaloids, they have attracted considerable synthetic interest throughout the years. Many of the synthetic strategies have involved using tryptamine and its derivatives as a precursor.

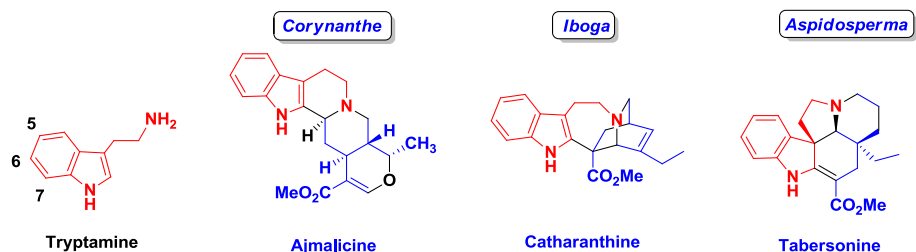
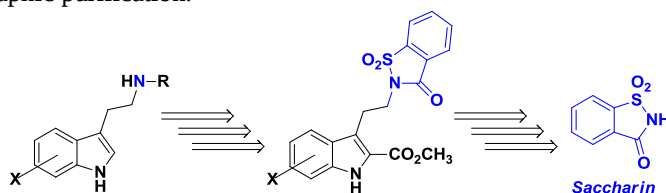


Figure 1. Tryptamine and Monoterpene Indole Alkaloids

Tryptamine is commercially available through a variety of suppliers; however, when the indole ring of tryptamine is functionally substituted, the commercial availability of the resulting derivatives decreases while their cost increases, especially with 6-substituted tryptamine derivatives. Recent investigations in our group have shown that tryptamine derivatives can be synthesized in a column-free method using phthalimide as precursor.

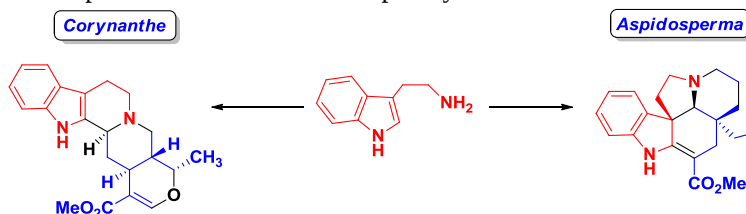
This project aims to expand the scope of synthesizing tryptamine derivatives with phthalimide and then apply this methodology towards the synthesis of *N*-substituted tryptamine derivatives using saccharin (Scheme 1) without the use of column chromatographic purification.



Scheme 1. Retrosynthetic Analysis of *N*-Substituted Tryptamine Derivatives

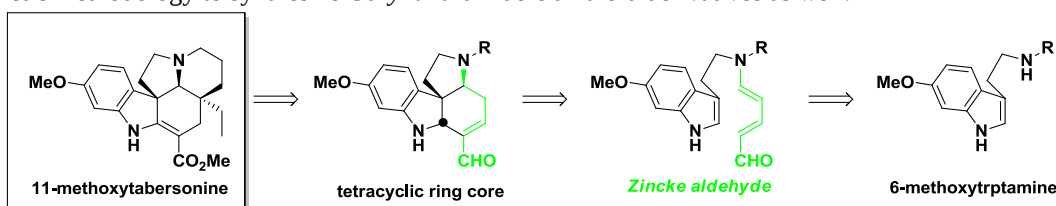
Project 2: Synthesis of Corynanthe and Aspidosperma Indole Alkaloids using Zincke Aldehydes

Indole alkaloids are well known for their antimitotic activity. There is great promise in their synthetic development due to their pharmaceutical importance and structural complexity.



Scheme 2. Indole Alkaloids Derived from Tryptamine

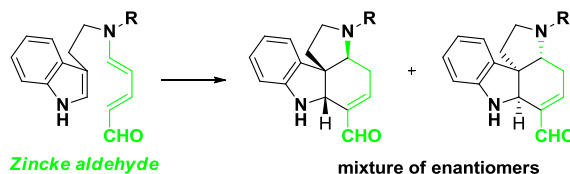
Recent investigations in our group have shown that the tetracyclic ring core exhibited in all *Aspidosperma* Indole alkaloid derivatives can be synthesized using the Zincke aldehyde created from using an *N*-substituted tryptamine derivatives; this project aims to synthesize the recently isolated melodinine natural products¹ (Scheme 3) and utilize this synthetic methodology to synthesize *Corynanthe* indole alkaloid derivatives as well.



Scheme 3. Retrosynthesis of 11-Methoxytabersonine

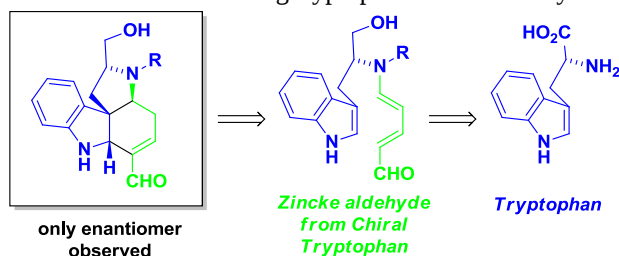
Project 3: Enantioselective Synthesis of Tetracyclic Ring Core using a Tryptophan Zincke Aldehyde Derivative

Zincke aldehydes have been shown to have a variety of synthetic applications by our group,² which includes producing the tetracyclic ring core in a highly diastereoselective manner; however, the development of a method that is diastereoselective as well as enantioselective using Zincke aldehydes to produce the tetracyclic ring core would be invaluable.



Scheme 4. Synthesis of Tetracyclic Ring Core Using Zincke Aldehyde

Tryptophan, the biological precursor of tryptamine, is commercially available in both of its chiral enantiomeric forms. Previous investigations have shown that introduction of a chiral center changes the enantioselectivity of a reaction to produce predominantly one enantiomer. This project aims to develop an enantioselective synthesis of the tetracyclic ring scaffold of tabersonine derivatives using tryptophan Zincke aldehyde derivatives (Scheme 5).



Scheme 5. Retrosynthesis of Tetracyclic Ring Core from Tryptophan

References

1. Liu, Y.; Li, Y.; Cai, X.; Li, X.; Kong, L.; Cheng, G.; Luo, X. *J. Nat. Prod.* **2012**, 75, 220-224.
2. (a) Michels, T. D.; Rhee, J. U.; Vanderwal, C.D. *Org. Lett.*, **2008**, 10, 4787-4790. (b) Steinhardt, S. E.; Silverston, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, 130, 7560-7561. (c) Vanderwal, C. D. *J. Org. Chem.* **2011**, 76, 9555-9567.