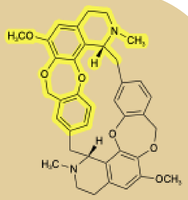
Synthesis of the Tetracyclic Core Found in the Natural Product Cissacapine

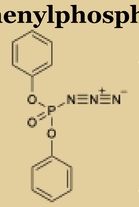
Jaylynn Jiang, Joel Pena & Thomas J. Osberger*
Department of Chemistry and Biochemistry, California State Polytechnic University, Pomona

Abstract:


Cissacapine

Cissampelos capensis, commonly known as "dawidjies" is the best known medicinal plant of the family Menispermaceae used by rural people in the western region of South Africa. The rhizomes are widely used in traditional medicine as a diuretic medicine and as a blood purifier. Other more prominent uses of rhizomes are diabetes, tuberculosis, stomach and skin cancers. Previous studies have identified variation of alkaloids found in different parts of the plant. Chemical structures of major alkaloids contains variations of a 6-6-x-6 tetracyclic ring. We were particularly interested in Cissacapine, a new alkaloid with antiplasmodial activity found in relatively high concentrations from the rhizomes of C. capensis with a 6-6-7-6 tetracyclic core. Despite the wide use of extracts of this plant in traditional medicine, the relationship between chemical structure and biological activity has not been directly established. Chemical synthesis of Cissacapine or the tetracyclic ring system has not been reported to-date, but synthesis of Cissacapine and its analogues would enable more comprehensive structure-activity relationships to be studied. Herein we present our progress towards the syntheis of the tetracyclic core of Cissacapine. Vanillin was used as the starting material to investigate the synthesis of the 6-6-7-6 tetracyclic ring. Alkylation of the phenol was attached onto a (2-bromo)benzyl group at the site where the seven membered ring would form. The aldehyde was then modified through several steps to a key nitrogen functional group. Additional steps are required to form the tetracyclic ring, and completion of the synthesis will enable the study of this ring system, which may be crucial to the medicinal properties of these plants.

Diphenylphosphoryl azide (DPPA)



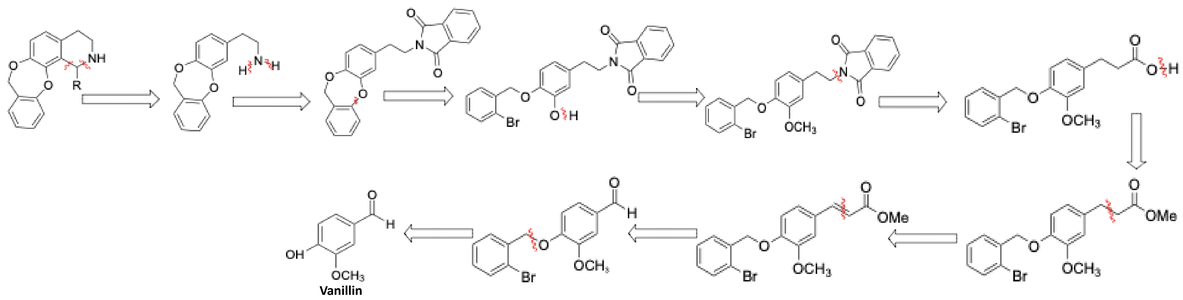
- One of the most employed methods in medicinal chemisty applications is the direct conversion of carboxylic acids using DPPA
- DPPA produces an amine, which we plan to protect as a phthalimide group

Acknowledgements

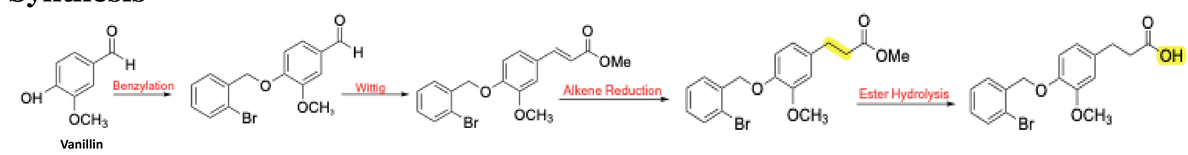
- Dr. Thomas J. Osberger and the CPP Obserger Research Team
- Cal Poly Pomona College of Science
- Chemistry and Biochemistry Department

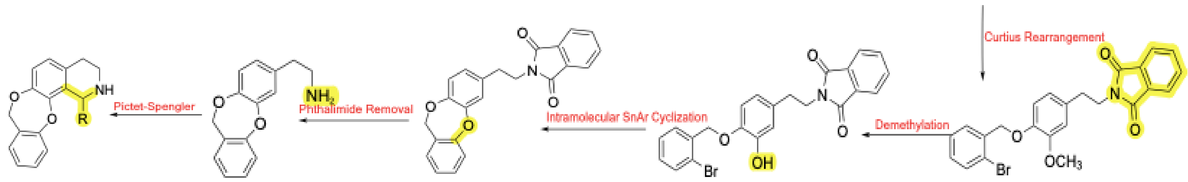
Synthetic Approaches and Results

Retrosynthetic Analysis

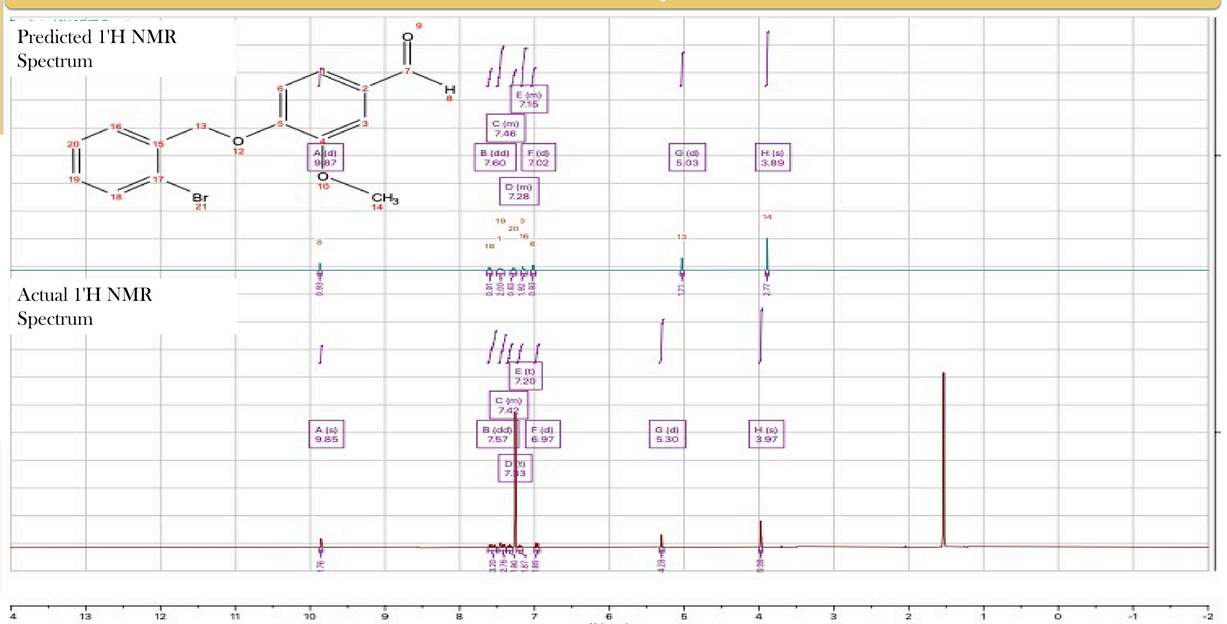


Synthesis

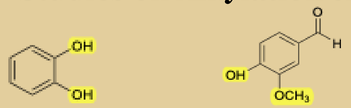




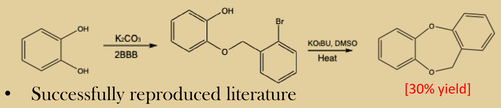
NMR Analysis



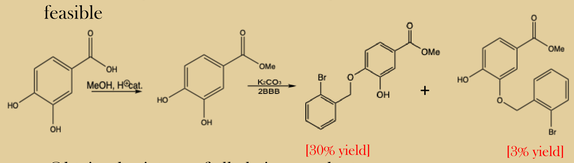
Studies on Alkylation & Cyclization


Catechol Vanillin

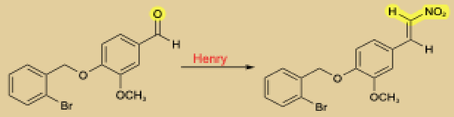
- Mixture of benzylation occurred on both 1,2 carbons
- Harder to distinguish the different ethers
- Vanillin used for better benzylation efficiency; benzylation will only occur at hydroxyl group



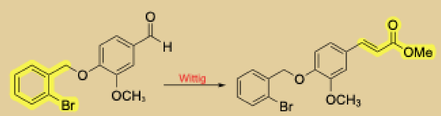
- Successfully reproduced literature
- Confirms key intramolecular SnAr cyclization is feasible



- Obtained mixture of alkylation products
- Selective for 4-hydroxy alkylation
- Sought less complex mixture



- Poor yield in the reaction of benzylaldehyde with nitromethane [23.5% yield]
- Attempts on larger scale were not reproducible



- Used Wittig reaction instead
- Through Curtius rearrangement, carboxylic acid is transformed into amine

Sources

1. Singha, Raju, et al. "KotBu Mediated Efficient Approach for the Synthesis of Fused Heterocycles via Intramolecular o-/n-Arylations." *RSC Advances*, vol. 5, no. 62, 2015, pp. 50174–50177., https://doi.org/10.1039/c5ra07532g.

2. Yamada, Koichiro, et al. "Studies on 1,2,3,4-Tetrahydroisoquinoline Derivatives. I. Syntheses and .Beta.-Adrenoceptor Activities of Positional Isomers of Trimetoquinol with Respect to Its 6,7-Dihydroxyl Groups." *Chemical and Pharmaceutical Bulletin*, vol. 29, no. 3, 1981, pp. 744–753., https://doi.org/10.1248/cpb.29.744.