New Approaches to Indoles and Indole Alkaloids

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INTRODUCTION

Second only to pyridines, indoles are among the most common aromatic scaffolds present in bioactive molecules. The 5-hydroxy indole moiety alone has currently >10,500 substructure hits Among the many indole-containing alkaloid scaffolds, ergot alkaloids comprise a notable group of natural products of great biological activities. The striking biological properties of indoles and challenging polycyclic molecular architectures and wide spectrum of physiological activities of indole derivatives have attracted organic chemists for decades. In spite of all the synthetic approaches published to date, there is still opportunity and need for novel synthetic strategies that can harness the unique chemical diversity of indole derivatives.

RESULTS AND DISCUSSION

We have previously shown that 4-mono- and 3,4-disubstituted indoles can be synthesized through an intramolecular Diels-Alder cycloaddition of furan (IMDAF) reaction. Recently, we have accomplished an extension of this procedure to the direct preparation of 5-hydroxy indoles. In addition, we have been able to demonstrate the utility of our indole methodology for the construction of the indole natural product cycloclavine. We were attracted to this compound as a synthetic target due to its unusual molecular scaffold, featuring the only cyclopropane-containing ergot alkaloid. Our 1st generation retrosynthetic plan for cycloclavine assumed that the stability of the cyclopropane moiety in the hydroindole intermediate **2** was sufficient to allow a thermal [4+2] process, and that dienone **3** could be obtained by a cascade TBS-de-protection-intramolecular S_N2-displacement (Figure 1). Indolinone **4** was be formed by *ortho*-alkylation of 3-aminophenol **5**. For the selective hydrogenation of cross-conjugated dienone **3**, we hoped that we could effect this conversion by taking advantage of Lewis-acidic reducing agents and the electron-donating properties of the β-amino substituent. While we were able to complete this 1st generation approach, it resulted in the preparation of a diastereomer–5-*epi*-cycloclavine–of the synthetic target. We were able to revise this analysis successfully, according to the pathway shown in Figure 2.

Figure 1. 1st Generation Analysis of Cycloclavine.

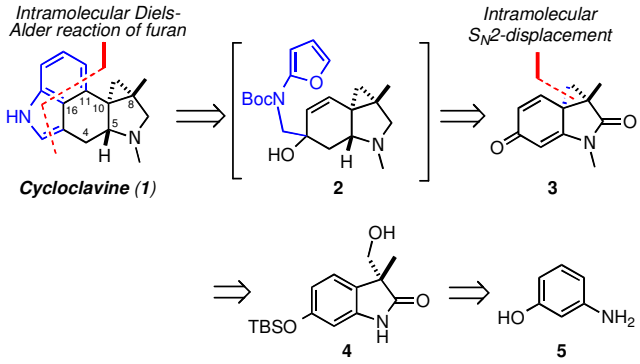
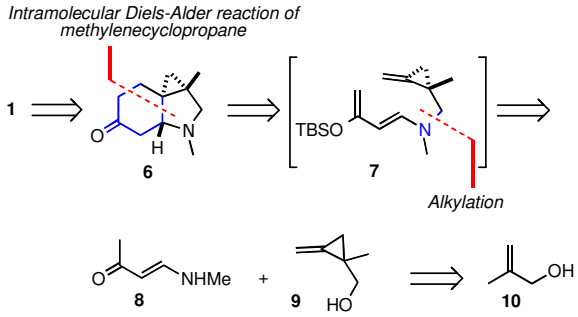


Figure 2. 2nd Generation Retrosynthetic Analysis.



CONCLUSION

As an extension of our new indole methodologies, we developed a novel synthetic route to the ergot alkaloid cycloclavine, proceeding in 14 steps and 1.2% overall yield. Noteworthy features of this work include the formation of the indole moieties through the allylic alcohol-IMDAF reaction, as well as the rapid synthesis of cycloclavine's indoline core through a novel and highly stereoselective intramolecular Diels-Alder reaction of a methylene-cyclopropane.

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REFERENCES

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