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Rapid synthesis of the core scaffold of crinane and haemanthamine through a multi-component approach

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ABSTRACT

A rapid synthesis of the core structures of crinane and haemanthamine has been developed, enabled by a multicomponent approach. This work constitutes a formal synthesis of crinane and sets the stage for access to both families of natural products and key analogues. A key highlight of the approach is the modularity of the core synthesis, overcoming existing challenges for these scaffolds and providing a path to explore site-selective oxidation to expand the scope of molecules accessible from common intermediates.

Introduction

The Amaryllidaceae plant family has a legacy of antitumor properties from very early use as an herbal treatment for uterine tumors to current isolation and exploration of the alkaloids responsible for their potency towards a variety of ailments [1]. Amaryllidaceae alkaloids represent a diverse class of molecules that often contain significant structural variation frequently due to highly divergent biosynthetic paths from early common intermediates [2]. Examples of this divergence have led to five major alkaloid structural types, two of which are the crinine alkaloids represented by crinane (**1**) and haemanthamine (**2a**) and the tazettine alkaloids represented by pretazettine (**3**) and tazettine (**4**) (Fig. 1a) [3,4]. One key intermediate of this pathway is 4-*O*-methylnorbelladine originating from the precursors L-tyrosine and L-phenylalanine [2]. Tang and co-workers, inspired by the biosynthetic pathway, accessed crinane through a transition metal catalyzed dearomative cyclization [5]. Although biomimetic, this route provided no access to higher oxidation levels within the pyrrolidine core necessary to access many oxygenated members of this class. A more prominent focus for the synthesis of these molecules has been towards the hydroindole core present within numerous crinane alkaloids (Fig. 1a). Three representative examples established early on for accessing this core were by Stevens utilizing a Robinson annulation [6,7], Tsuda utilizing a 4 + 2 cycloaddition [8,9] and Martin and Campbell utilizing a conjugate addition (Fig. 1b) [10]. Stemming from these pioneering efforts, various other groups employed similar strategies to access the hydroindole core, although there remains a lack of mild and modular approaches to access the core scaffold of these natural products [11–18].

In our research program we have been interested in both the crinine and tazettine classes of amaryllidaceae alkaloids due to their challenging synthetic scaffolds as well as their bioactivity. Furthermore, the co-crystallization of haemanthamine with the p53 binding site provides an opportunity for rational Structure Activity Relationship (SAR) design [19]. With this new information, there is a need to access the crinane scaffold in a modular approach to facilitate analogue generation [20]. When considering the biosynthetic origins of these natural products, their proposed biogenetic pathway suggests a common precursor for a number of highly complex molecules such as tazettine, augustamine, plicamine, gracilamine, mesembrine, and galasine which all originate from a *N*,6-seco-crinane. Furthermore, this biosynthetic intermediate is proposed to spawn from crinane itself [4]. Three common approaches to this intermediate have been established; however, there are currently no multicomponent approaches to the crinane alkaloids that focus on modularity and the ability to conduct pinpoint modifications for SAR studies. With regard to crinane alkaloids, a common theme is the construction of a hydroindole core that is then subjected to Pictet-Spengler conditions yielding the bridged natural product core. Due to the well precedented literature for this strategy, we envisioned the same Pictet-Spengler

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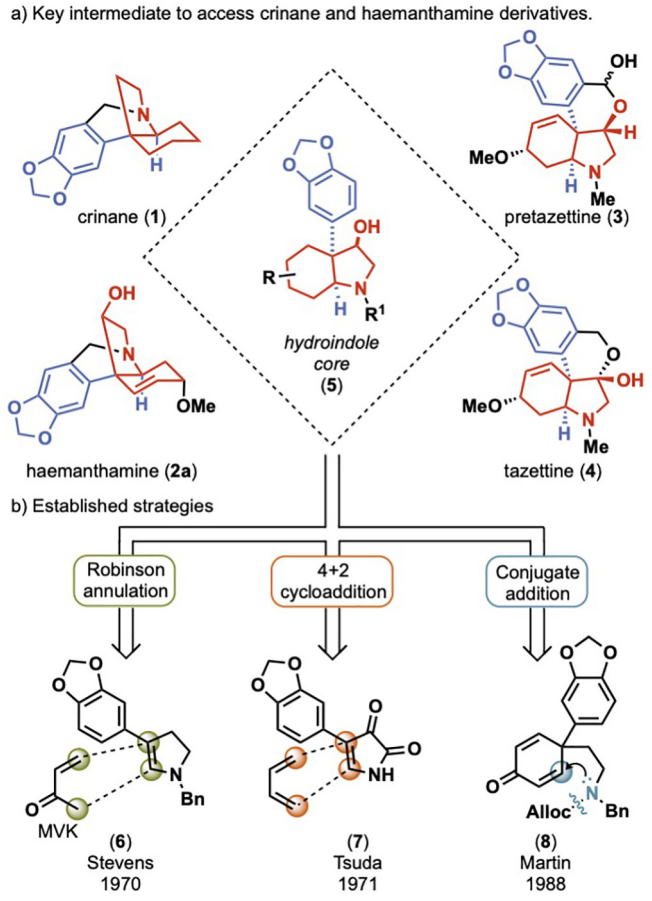


Fig. 1. Relevance and synthetic strategies currently employed to access the 3-hydroxy-hydroindoline core.

transformation of the haemanthamine core **2b** leading to 3-hydroxy-*cis*-hydroindoline **9** (Fig. 2a). This intermediate was envisioned to be easily accessed from our previously reported convergent approach to hydroindoline scaffolds enabled through a functionalized multicomponent product (**10**) that would allow for an intramolecular 6-*exo-tet* cyclization to access (**11**) (Fig. 2b). We planned for this to provide the foundation to access the haemanthamine core in a modular fashion to enable analogue generation and SAR studies. Herein, we report our approach to dihydro-demethoxyhaemanthamine and a formal synthesis of crinane.

Results and discussion

We initially sought to improve our reported approach to the arylpyruvic acid methyl ester multicomponent fragment. Previously we had made this fragment from an Erlenmeyer reaction followed by prolonged acid hydrolysis to yield pyruvic acid **13** followed by alkylation with methyl iodide. Our revised route begins from commercially available piperonal (**12**). We performed an Erlenmeyer reaction utilizing a modified protocol from Buck and Ide yielding azlactone **13** under neat heating conditions [21]. This azlactone was then subject to hydrolysis with 6 M HCl(aq). Our original approach to access these aryl pyruvic acids required heating at reflux for reaction times greater than 18 h. In our revised protocol we accomplish the same transformation by subjecting **13** to microwave irradiation for 15 min at 130 °C yielding **14** in an equivalent yield to our previous approach. Although low yielding, it is noteworthy that no chromatographic purification is necessary for the synthesis of **14** from piperonal (**12**) over two steps (Scheme 1). Subsequent methanolysis of **14** provided **15** in good yield.

With fragment **15** and aldehyde **16** derived from 1,5-pentane diol available *via* our previously published protocol [22], we then utilized these key fragments for the synthesis of pyrrolidinedione **18**, with a modified procedure utilizing activated 3 Å molecular sieves and slow addition of commercially available 2,4-dimethoxybenzylamine (**17**) which drastically improved our overall yield of **18** compared to that previously reported [22]. With **18** in hand we employed a 6-*exo-tet* cyclization yielding **19** in good yield as a single diastereomer [22]. We were able to accomplish a stereoselective reduction of this substrate with an excess of $LiAlH_4$ at room temperature providing the kinetic product (**20**) with no observation of the other diastereomer. We then proceeded to deprotect the 2,4-dimethoxybenzyl (Dmb) group utilized in our initial multicomponent reaction. Initially, we explored trifluoroacetic acid at room temperature and at reflux, however no desired product **21** was observed [23]. We then moved to more forcing conditions utilizing microwave irradiation. To our delight, we obtained **21** with clean conversion. Upon removal of trifluo-

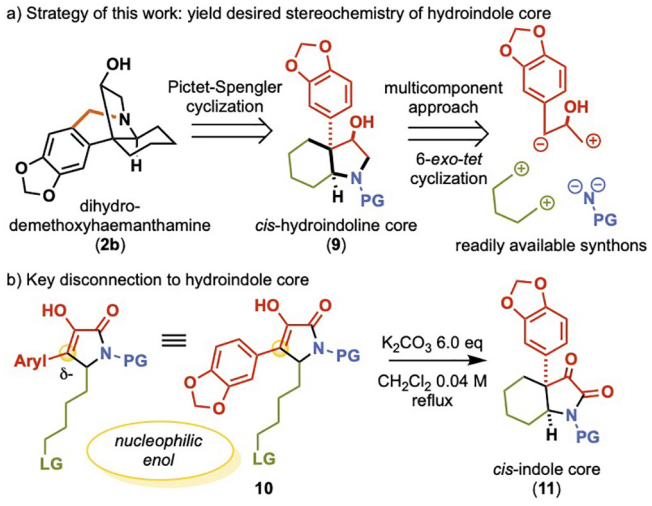
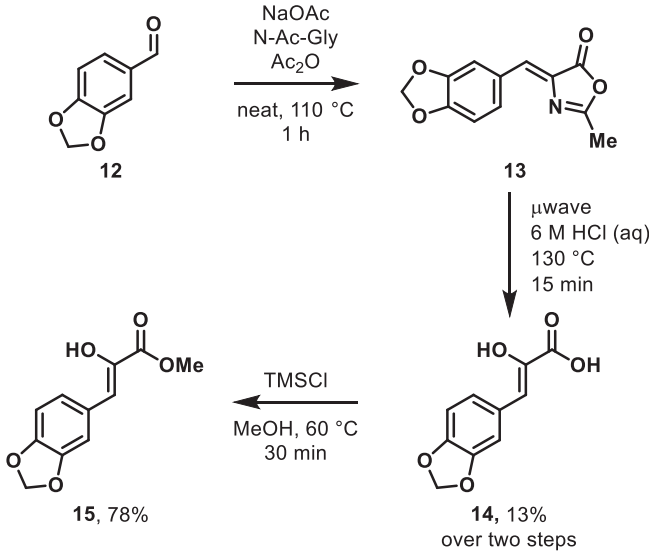


Fig. 2. a) Retrosynthetic approach; b) current multicomponent 6-*exo-tet* cyclization.

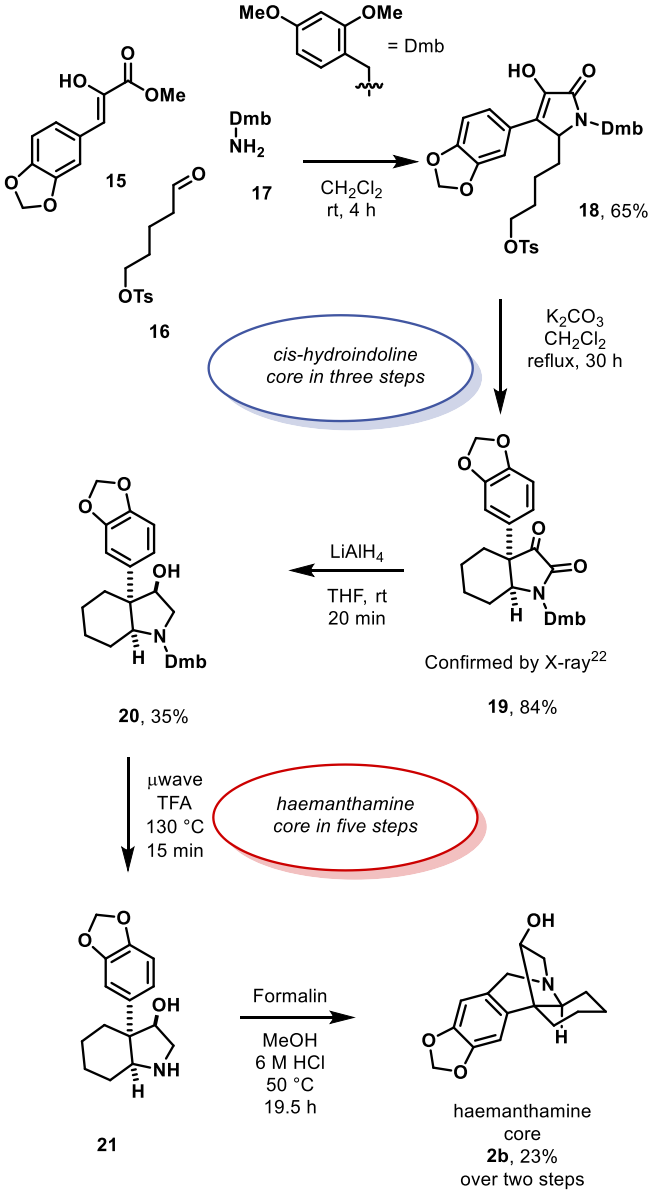


Scheme 1. Preparation of pyruvic acid methyl ester **15**.

roacetic acid by evaporation and basification of the trifluoroacetate salt to obtain **21** as the crude free-base, we directly subjected this substrate to Pictet-Spengler cyclization conditions with formalin and 6 M HCl at 50 °C yielding the final haemanthamine core (**2b**) in 23% over two steps (Scheme 2).

When considering the diastereoselectivity achieved upon reduction of **19** with $LiAlH_4$, we propose that the axial hydrogens create a steric repulsion causing the hydride source to deliver to the less sterically hindered peripheral face of the molecule providing the desired diastereomer (See Fig. 3).

Although a similar stereoselectivity was observed by Tsuda and co-workers with a related scaffold [8,9], we sought to further confirm the hydroxyl stereochemistry through NOE analysis. We initially confirmed the correct stereochemistry of **20** with the desired NOE interactions. Interestingly, we observed over a short time in $CDCl_3$, the full conversion of **2b** to the protonated iminium form (**2c**, Fig. 4b). Fortunately, stereochemical assignment of the hydroxyl could still be accomplished, which confirmed the desired stereochemistry of the hydroxyl group was obtained. With the confirmed stereochemistry, we have in fact synthesized (±)-dihydro-demethoxyhaemanthamine (**2b**). It is noteworthy that precursors **15** and **16** are both known compounds in the literature, but also commercially available upon demand, thus our route to the haemanthamine core is completed in five steps. Furthermore, Wildman and Fales have shown that **2b** can be readily converted to crinane by a deoxygenation sequence utilizing thionyl chloride followed by lithium aluminum hydride [24].



Scheme 2. Synthetic route to dihydro-demethoxyhaemanthamine.

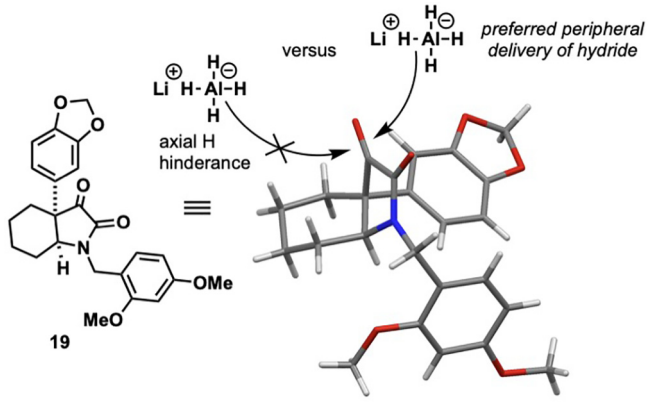


Fig. 3. Model showing the less sterically hindered face of **19**.

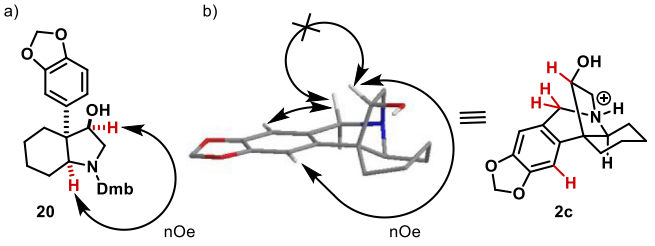


Fig. 4. Key NOE interactions of **20** and **2c** confirming the hydroxyl stereochemistry. 3D structure of **2b/c** generated with Chem3D 20.0.

Conclusion

In conclusion, we have presented a rapid approach to the crinane and haemanthamine core and a formal synthesis of crinane itself. This was accomplished through a highly convergent and modular multicomponent strategy that diastereoselectively constructs the natural product cores, which we plan to draw on for the synthesis of haemanthamine and pretazettine in due course. A highlight of the present study is the stereoselective installation of the quaternary center and hydroxyl group, overcoming many previous challenges in the synthesis of these natural product families.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153201.

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