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Total Synthesis of Mersicarpine through a Cationic Cyclization Approach

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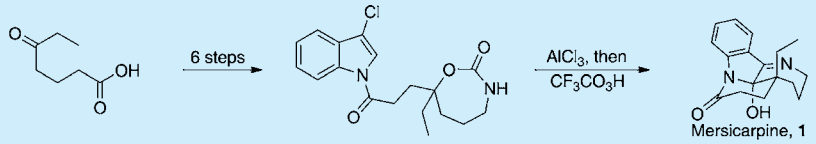
Supporting Information



ABSTRACT: A concise total synthesis of mersicarpine is achieved by exploiting a cyclic carbamate for generation of a tertiary carbocation. The key step involves intramolecular Friedel−Crafts alkylation with this carbocation for the construction of a quaternary carbon center and a subsequent oxidation and cyclization cascade for the formation of a seven-membered cyclic imine. The chemistry allowed for a rapid one-pot synthesis of mersicarpine from a simple intermediate using straightforward chemical operations.

Mersicarpine (**1**, Figure 1) is a structurally intriguing monoterpene indole alkaloid isolated from the *Kopsia*

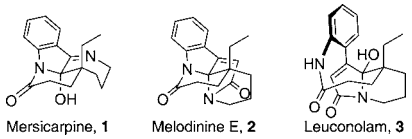


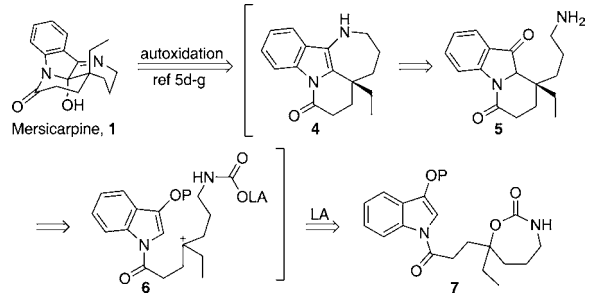
Figure 1. Molecular structures of mersicarpine, melodinine E, and leuconolam.

species of plants by Kam and co-workers in 2004.[1] Other than the indoline moiety, this unusual tetracyclic natural product possesses an atypical seven-membered cyclic imine and a δ-lactam around a fully substituted hemiaminal stereogenic center. Adjacent to the hemiaminal is a synthetically challenging all-carbon quaternary center. Biosynthetically, mersicarpine shares the same biogenetic origin as melodinine E,[2] **2**, and leuconolam,[3] **3**, from vincadifformine.[4] It was proposed that leuconolam is a biosynthetic precursor of melodinine E which further produces mersicarpine through skeleton rearrangement and the loss of two carbons in the form of acetic acid.[1]

The unique structural feature of mersicarpine as well as its interesting biosynthetic relationship to other alkaloids has prompted many elegant solutions to the total synthesis of this molecule.[5] To date, two total syntheses and four formal syntheses have been reported. Kerr and co-workers disclosed the first total synthesis of mersicarpine in 2008 based on an elegant malonic radical addition to indole for the construction of the all-carbon quaternary center.[5a] A late stage key intermediate in their synthesis inspired two formal total syntheses from both Zard's[5b] and Han's[5c] groups. Fukuyama and co-workers accomplished the first asymmetric total synthesis of (−)-mersicarpine.[5d] The autoxidation of a tetracyclic azepinoindole they observed also facilitated two other asymmetric syntheses achieved by the groups of Tokuyama[5e,f] and Zhu.[5g]

Driven by our continuous interest in the total synthesis of mersicarpine,[6] we conceived an appealing cationic polycyclization strategy toward this target (Scheme 1). Given that

Scheme 1. Original Synthetic Design of a Cationic Polycyclization Strategy towards Mersicarpine



compound **4** has been reported to be an advanced intermediate leading to mersicarpine through autoxidation and subsequent reduction,[5d−g] we considered it as a primary synthetic target. Presumably, compound **4** would be readily transformed from **5** through an enamine forming reaction. We envisioned that **5** could be made through an intramolecular Friedel−Craft alkylation[7] in a reactive cationic intermediate **6** if the protecting group on oxygen tends to fall off under the reaction conditions. To produce the critical cationic species, we decided to take advantage of the carbamate functionality in **7**. We assumed that

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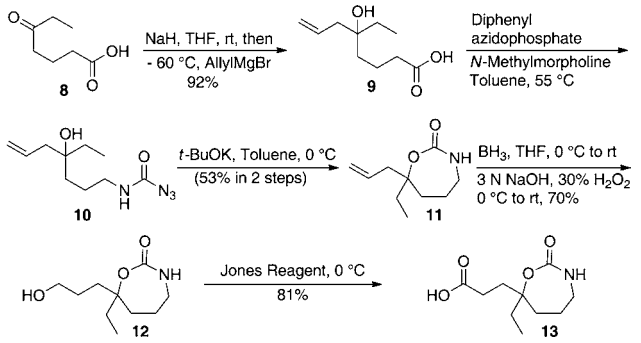
7 would produce **6** upon treatment with a Lewis acid to trigger a facile Friedel–Craft cyclization to form the δ-lactam. Subsequent loss of carbon dioxide and acidity adjustment of the reaction media will generate a free amine in **5** for further cyclization. What is worth noting is that although the carbamate functionality has been widely used as protecting groups in alkaloid chemistry, a tertiary carbocation derived from a carbamate during deprotection of amines has hardly been used for major bond forming reactions. This new application of cyclic carbamate has the potential to facilitate a one-pot synthesis of mersicarpine directly from 7 owing to the consecutive reaction cascade.

To investigate the aforementioned strategy, we devised a rapid synthesis of **13** bearing the desired carbamate functionality commencing from a readily available compound **8** (Scheme 2).[8] After the carboxylic acid was inactivated

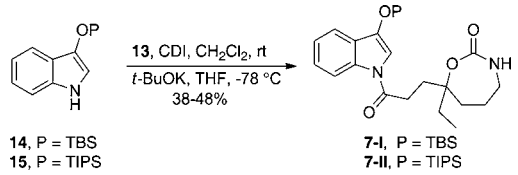
Scheme 2. Preparation of the Intermediate 13



through deprotonation by sodium hydride, **8** was converted to **9** upon treatment with an allyl Grignard reagent. Initially, we anticipated that **11** could be produced from **9** in a single step upon its conversion to an acyl azide. More specifically, the acyl azide was expected to undergo a Curtius rearrangement[9] to generate an isocyanate intermediate which could be captured by the tertiary alcohol to produce **11** directly. However, when we carried out the reaction with 1 equiv of diphenyl azidophosphate in the presence of *N*-methylmorpholine in toluene,[10] the reaction could not go to completion and **10** was isolated as a major product in nearly 40% yield. Presumably, the azide ion dissociated from diphenyl azidophosphate in the presence of *N*-methylmorpholine reacted with the isocyanate intermediate faster than the tertiary hydroxyl group. Only when we used 2.5 equiv of diphenyl azidophosphate did the reaction achieve completeness. We then achieved the synthesis of **11** from **9** in an overall yield of 53% through an additional step under basic conditions. Hydroboration–oxidation[11] of **11** followed by Jones oxidation on **12** afforded the desired intermediate **13** in good yield.

Originally, we assumed that a silyl protecting group would easily fall off after the key Friedel–Crafts alkylation reaction occurs, which could facilitate the transformation from 7 to **4**. Although in low yield, we managed to prepare two substrates bearing TBS (**7-I**) and TIPS (**7-II**) from **14** and **15**,[12] respectively, using CDI to activate **13** (Scheme 3). However, neither **14** nor **15** gave the desired product upon treatment with a variety of Lewis acids or Brønsted acids. In most cases, the substrates decomposed under the reaction conditions. We reasoned that the acid-sensitive indole moiety in **7-I** and **7-II** could not survive activation of the carbamate under acidic

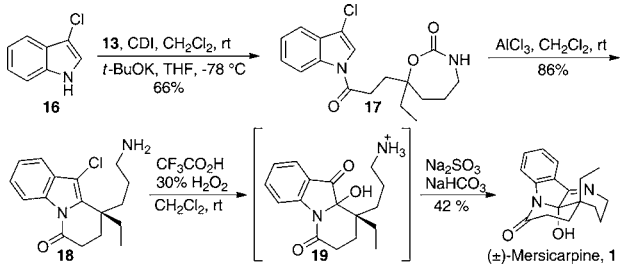
Scheme 3. Syntheses of Substrates for Cationic Polycyclization



conditions. As a result, the essential intermediate **6** was not obtained in the reaction sequence.

In view of the fact that the current indole moiety in **7-I** and **7-II** was excessively labile under acidic conditions, we switched to a new substrate carrying a more robust indole moiety to explore the Friedel–Craft alkylation reaction. Chloroindole **16** (Scheme 4) was chosen owing to its stability under both basic

Scheme 4. Total Synthesis of Mersicarpine



and acidic reaction conditions showcased in our total synthesis of isatisine A.[13] Indeed, the use of **16** in the coupling reaction resulted in the production of **17** in 66% yield, significantly higher than the yield of reactions using **14** and **15**. More importantly, the key Friedel–Crafts alkylation reaction was fulfilled by using the new substrate which eventually led to our total synthesis of mersicarpine. The natural product was isolated in 25% yield after **17** was sequentially treated with aluminum trichloride, a mixture of trifluoroacetic acid and hydrogen peroxide, and sodium sulfite/sodium bicarbonate for acidity optimization. To evaluate the efficiency of the Friedel–Crafts alkylation, we closely monitored the reaction and observed that it went to completion in 5 min with the product **18** isolated in 86% yield. Upon oxidation of **18** and acidity optimization, mersicarpine was produced in 42% yield. Notably, the ^{1}H NMR data of our synthetic sample did not match those reported for the natural material. The same observation by Kerr and co-workers was reported in their first total synthesis of mersicarpine. Through a careful titration experiment, they claimed that the ^{1}H NMR spectra of mersicarpine are very sensitive to solvent acidity, which caused variation in the ^{1}H NMR resonances.[5a] By using Kerr's protocol, we obtained both ^{1}H and ^{13}C NMR data of our synthetic sample and found they were in agreement with those acquired in base-washed $CDCl_3$ by Kerr and co-workers, which verified the identity of our synthetic sample.[14]

In summary, we have achieved a short synthesis of mersicarpine based on a cationic cyclization strategy. A new application of the carbamate functionality enabled production of a carbocation species bearing a masked amine. An intramolecular Friedel–Crafts alkylation of chloroindole with the carbocation species fulfilled the facile construction of an all-carbon quaternary center in mersicarpine. With subsequent oxidation and optimization of acidity, the synthetic sequence

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rapidly expanded the molecular complexity, leading to a one-pot transformation of **17** to mersicarpine through simple chemical operations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and procedures, compound characterization data, copies of ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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