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Quick access to the core of mersicarpine through an S_NAr strategy

Zining Li, Guangxin Liang *

State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, 94 Weijin Road, Tianjin 300071, China

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ABSTRACT

A quick access to the core of dihydroindole alkaloid mersicarpine was developed based on straightforward transformations from readily available and inexpensive starting materials. The synthetic route features an aldol reaction, a Beckmann rearrangement for the synthesis of the δ-lactam, an intramolecular S_NAr strategy for indoxyl heterocycle formation, and in situ autoxidation of indoxyl intermediate. The new strategy offered an alternative approach for the formation of an oxidized indoxyl moiety, which could potentially have a wider application in the total synthesis of indole alkaloids containing apparent or masked indoxyl moieties.

Introduction

Mersicarpine (**1**; Fig. 1) is a structurally intriguing dihydroindole alkaloid isolated from the *Kopsia* species of plants by Kam and co-workers in 2004.[1] This tetracyclic natural product possesses an unusual 7-membered cyclic imine fused with both an indoline and a δ-lactam around a fully substituted hemiaminal stereogenic center adjacent to a quaternary carbon center. Interestingly, the *Kopia* species also contains a number of other challenging carbon frameworks such as arboloscine (**2**; Fig. 1) and rhazinilam (**3**; Fig. 1). The synthetically daunting structural features of this class of molecules together with their biosynthetic relationship have made them appealing synthetic targets and attracted a lot of attention among synthetic community.[2]

The first total synthesis of mersicarpine was reported by Kerr and co-workers in 2008 (Scheme 1).[2a] They employed an elegant malonic radical cyclization induced by Mn(III) to introduce the quaternary carbon center in **5**. The key intermediate **6** was oxidized to form the required oxidation state for the indoline heterocycle and subsequent deprotection and cyclization afforded the natural product.

Based on Kerr's synthetic intermediate **6**, both Zard and Han achieved the formal total synthesis of mersicarpine in 2009 and 2012, respectively. To construct **6**, Zard and co-workers used an efficient radical addition and cyclization cascade;[2b] while Han and co-workers applied a cationic approach to build the quaternary carbon center from silyl vinyl ether and tertiary alcohol.[2e]

The first asymmetric total synthesis of (−)-mersicarpine was accomplished by Fukuyama and co-workers (Scheme 2).[2c] Taking advantage of optically pure starting material **8** and Eschenmoser-Tanabe fragmentation, they successfully prepared the chiral building block **9** for indole formation through a Sonogashira coupling and a gold(III) catalyzed cyclization sequence. Hydrogenation of **11** followed by S_N2 reaction afforded the unstable intermediate **12**, which produced (−)-mersicarpine upon autoxidation.

Tokuyama and co-workers reported an alternative route for the total synthesis of (−)-mersicarpine utilizing the same starting material **8** (Scheme 3).[2d] Their synthesis featured a Fischer indole synthesis and an elegant DIBAL-H mediated reductive ring-expansion reaction for construction of the azepinoindole core in the molecule. Going through the same intermediate **12** and autoxidation as in Fukuyama's synthesis, they completed a rather concise synthesis of (−)-mersicarpine.

Noticing that the previous work all generated the indoline moiety from indole itself, we decided to explore a new strategy. Herein, we report our different approach for forming the indoline heterocycle and δ-lactam in the target molecule. In our retrosynthetic analysis (Scheme 4), we envisioned that autoxidation of the intermediate **16** would provide the required tertiary hydroxyl group because it has long been known that indoxyl could readily be autoxidized.[3] To prepare indoxyl **16**, we proposed an intramolecular nucleophilic aromatic substitution reaction (S_NAr) from substrate **17**.[4] The δ-lactam required for the substitution in **17** could be produced through a Beckmann rearrangement on the tosylated oxime **18**.[5] The carbonyl precursor **19** in principle could be assembled through a domino Michael/aldol reaction sequence from three readily available components **20**, **21**, and **22**.

* Corresponding author.
E-mail address: lianggx@nankai.edu.cn (G. Liang).

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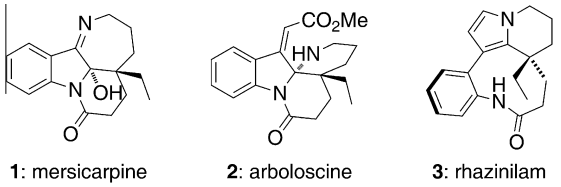
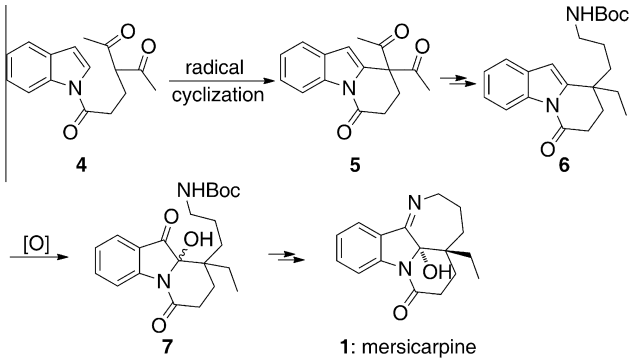
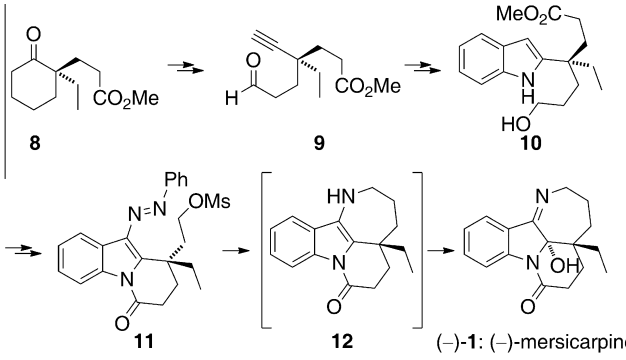


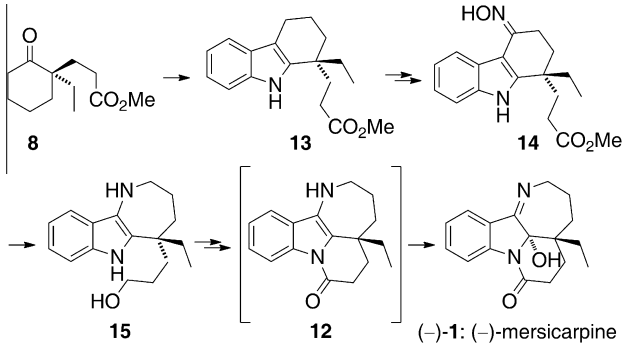
Figure 1. Mersicarpine and biosynthetically related indole alkaloids from *Kopsia* species.



Scheme 1. First total synthesis of mersicarpine by Kerr and co-workers. Boc = *tert*-butoxycarbonyl.

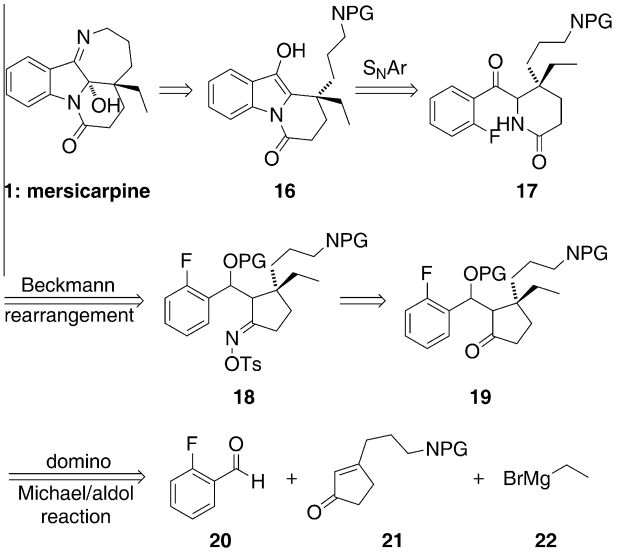


Scheme 2. First total synthesis of (–)-mersicarpine by Fukuyama and co-workers.

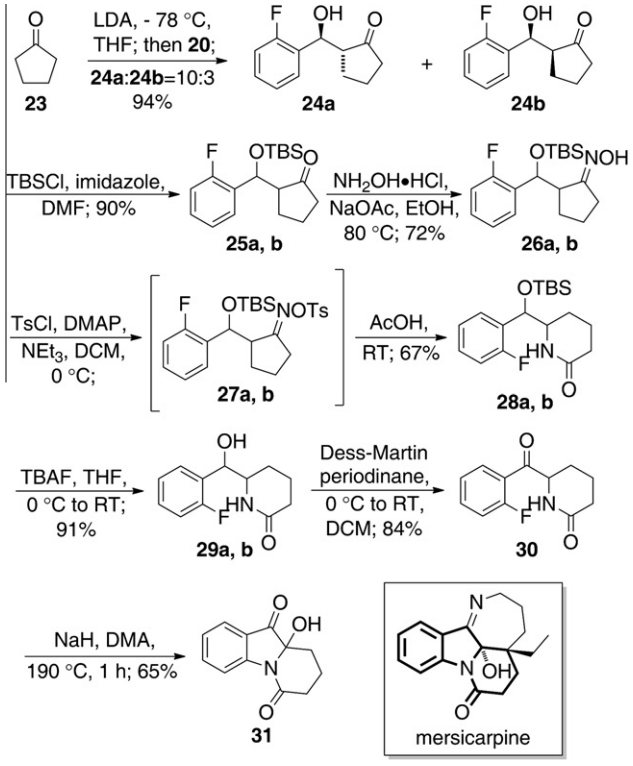


Scheme 3. Total synthesis of (–)-mersicarpine by Tokuyama and co-workers.

A simplified model system was designed to quickly investigate the S_NAr strategy for the formation of the indoxyl moiety (Scheme 5). The synthesis commenced with commercially available 2-fluoro-benzaldehyde **20** and cyclopentanone **23**. Aldol reaction mediated by LDA between these two compounds

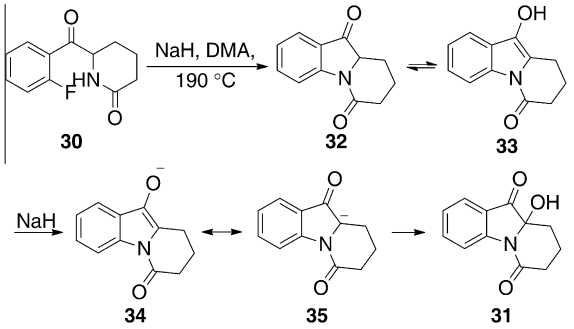


Scheme 4. Retrosynthetic analysis of mersicarpine. PG = protecting group, Ts = 4-toluenesulfonyl.



Scheme 5. A model study for the synthesis of the core of mersicarpine. DCM = dichloromethane, DMA = *N*,*N*-dimethylacetamide, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, RT = room temperature, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

produced **24a** and **24b** with a 10:3 diastereomeric ratio in 94% yield, which is typical for a traditional aldol reaction.[6] Given that one of the stereogenic centers would be eventually lost in the oxidation step; this pair of diastereomers was carried through the rest of the synthesis without separation. The aldol adducts **24a** and **24b** were then protected as *tert*-butyldimethylsilyl ether.[7] Oxime formation and subsequent activation of the oxime afforded the substrates **27a** and **27b** for the subsequent Beckmann



Scheme 6. Autoxidation of 32.

rearrangement.[5e] Due to the instability of the diastereomers, they were treated with AcOH at room temperature directly without purification. Under this condition, Beckmann rearrangement went smoothly to produce
δ-lactams **28a** and **28b** in good yield. Deprotection of the secondary alcohol and Dess-Martin oxidation[8] evenly gave the key intermediate **30** in excellent yield. By treating **30** with NaH in DMA and then heating the reaction mixture at 190 °C for 1 h, we were able to isolate **31**, the core of mersicarpine, in 65% yield. It is worth pointing out that the solvent DMA played a key part in this transformation. Substrate **30** refluxed in other solvents including DMF, DMSO, and dioxane all decomposed without producing identifiable products.

We assumed the overall transformation went through the S_NAr product **32**, which was autoxidized to give **31** (Scheme 6). Initially, we used 1.25 equiv of NaH in the reaction and assumed that the autoxidation of **32** went through a radical process similar to the autoxidation of intermediate **12** in Fukuyama's synthesis.[2c,9] But later on, we observed the same results when 2–4 equiv of NaH was applied in the reaction. Given that **32** would be deprotonated in the presence of excess NaH, it is suggested that the autoxidation could be an enolate oxidation process.[10]

In summary, starting from readily available and inexpensive starting materials, we have developed a concise synthesis of the core of mersicarpine based on straightforward transformations. Our approach features an aldol reaction, a Beckmann rearrangement for the synthesis of the δ-lactam, an intramolecular S_NAr strategy for indoxyl heterocycle formation, and in situ autoxidation of the indoxyl intermediate. The new strategy offered an alternative approach for the formation of an oxidized indoxyl moiety. Further application of this strategy to the total synthesis of indole alkaloids with apparent or masked indoxyl moieties is underway in our laboratory.

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Supplementary data

Supplementary data (detailed experimental analysis and spectral analysis including ^1H, ^{13}C, and HRMS) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.008.

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