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A Simple Enantioselective Route to Functionalized Indolizidines: Synthesis of (+)-Ipalbidine and (+)-Antofine

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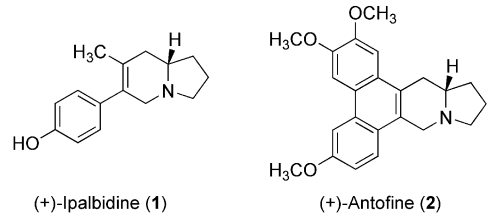
An efficient route to functionalized indolizidines from an enantiomerically enriched γ-nitro ketone is described. The nitro ketone is obtained by an organocatalytic, enantioselective ketone-nitro alkene Michael addition. Oxidative ring expansion of the nitro ketone and subsequent methanolysis provides a 8-nitro-4-oxooctanoate. This is stereoselectively transformed to the key, functionalized indolizidine intermediate which is readily converted to (+)-ipalbidine and (+)-antofine.

Introduction

The indolizidine motif is a prominent structural unit in numerous alkaloids[1] and also constitutes a major class of glycosidase inhibitors.[2] In addition, several indolizidines have an interesting biological profile which includes antibacterial, antiviral, antitumor and antidiabetic properties.[3] Aryl-substituted indolizidines are also of interest; either as bioactive natural products[4] or as peptidomimetics.[5] Accordingly, the synthesis of arylindolizidines continues to be intensely investigated and general synthetic strategies toward aryl-fused[6a–6c] or aryl-substituted indolizidines[6d–6h] as well as other, functionalized indolizidines have been reported.[7] Herein, we describe a concise and stereoselective synthesis of the arylindolizidine alkaloid (+)-ipalbidine (**1**, Figure 1),[8] a non-addictive analgesic[9] and oxygen free-radical scavenger,[10] and the phenanthroindolizidine alkaloid (+)-antofine (**2**),[11] the enantiomer of which has potent anticancer[12] and antiviral acitvity.[13] The syntheses of **1** and **2** are based on a readily available γ-nitro ketone precursor.



(+)-Ipalbidine (**1**) (+)-Antofine (**2**)

Figure 1. Arylindolizidine alkaloids synthesized in this study.

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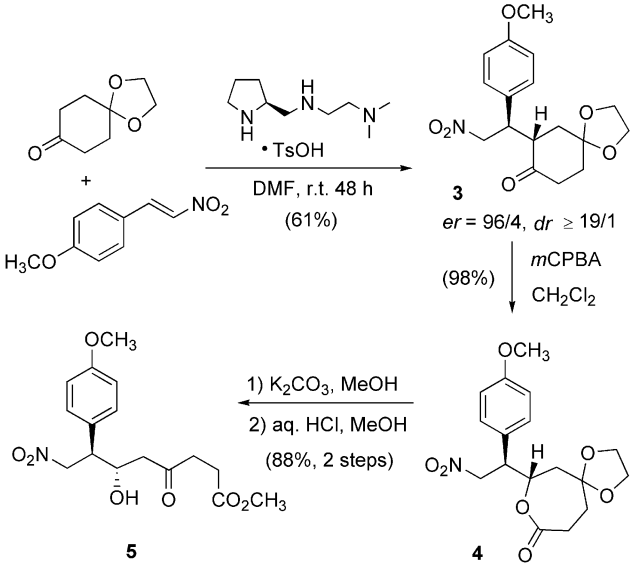
Our interest in indolizidines stems from our studies on the organocatalytic synthesis of γ-nitro ketones from cyclic ketones and 2-nitrovinylarenes via an enamine-based Michael addition reaction.[14] This reaction has been extensively studied and the development of new catalysts for the process continues at a remarkable pace.[15]

Undoubtedly, the full potential of the organocatalytic ketone–nitro alkene Michael reaction will be realized only when the γ-nitro ketone products are utilized in target oriented synthesis, but this has been relatively unexplored.[16] We therefore chose to examine the application of γ-nitro ketone **3** (Scheme 1) in the synthesis of ipalbidine and antofine.

Results and Discussion

Our studies began with the synthesis of the appropriate γ-nitro ketone starting material for (+)-ipalbidine (**1**).[8] The organocatalytic Michael addition of cyclohexane-1,4-dione monoethylene ketal and 4-methoxy-β-nitrostyrene employing our triamine salt catalyzed protocol[14a] provided the nitro ketone **3** in good yield and stereoselectivity (*er* = 96:4, *dr* >19:1). Baeyer–Villiger oxidation of **3** provided the lactone **4** in excellent yield (98%). Methanolysis of **4** and subsequent hydrolysis of the ketal generated the highly functionalized octanoate **5** (Scheme 1, 88% over two steps) that has all the required carbon atoms for the indolizidine framework.

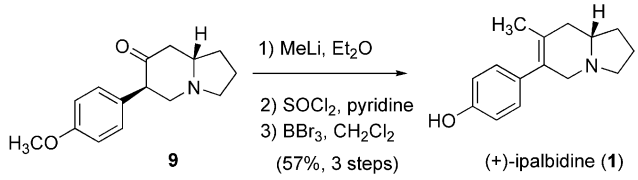
Partial reduction of the nitro group in **5** provided the nitrone **6** (Scheme 2) which was anticipated to be subject to stereoselective reduction due to a 1,3 disposition with the secondary alcohol stereocenter. Treatment of **6** with L-Selectride® or LAH at –78 °C resulted in reduction of the ester. Reduction with $NaBH_4$ was stereorandom and also led to reduction of the ester, indicating the need for a milder reducing agent. Accordingly, we examined Me_4NBH-



Scheme 1. Synthesis of a functionalized octanoate intermediate.

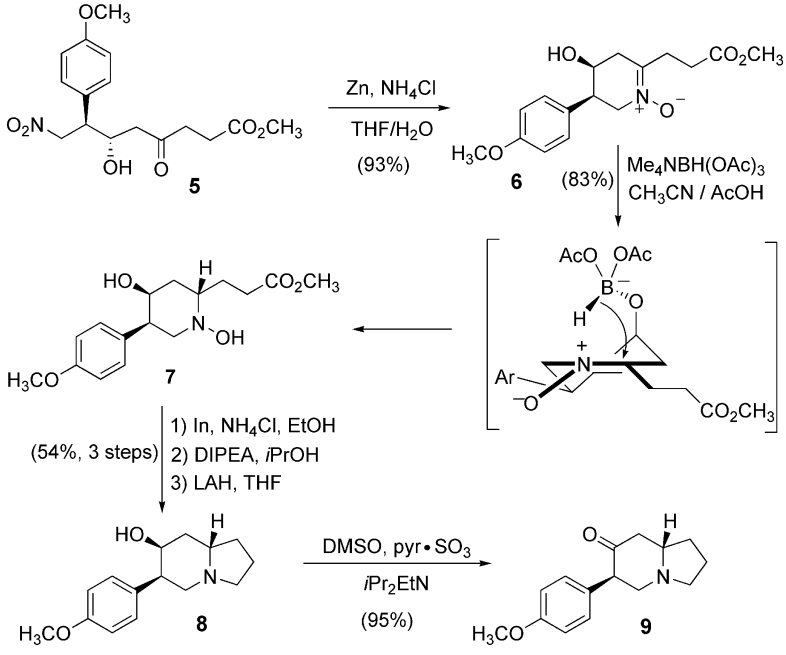
$(OAc)_3$, which gratifyingly provided the hydroxylamine **7** (83%) as a single diastereomer, presumably via a hydroxy-directed reduction (Scheme 2). At this stage, **7** was assigned the shown stereochemistry which was assumed to derive from an intramolecular, hydroxy-directed reduction of **6**.[17] Reduction of the N–O bond in **7** was achieved with indium metal to provide a mixture of the amino ester and the corresponding indolizidinone (**7a**) resulting from cyclization of the amino ester. This product mixture was treated with DIPEA in refluxing isopropyl alcohol to complete the lactamization. Reduction of the lactam (LAH) provided the indolizidine **8** (54% over 3 steps, Scheme 2). Comparison of the ^{1}H NMR spectroscopic data of **8** with that of the racemate[8f] established its relative stereochemistry, thereby confirming the stereochemistry of the reduction of **6** to **7**. Oxidation of **8** (DMSO, pyridine·SO_3) furnished the amino ketone **9**.[8b–8f] Notably, the conversion of **3** to **9** (9 steps, 18% overall yield) can be conducted without the purification of any intermediates.

The conversion of **9** to (+)-ipalbidine (**1**) was achieved by employing a modification[8c] of the Govindachari procedure[8d] described for the racemate. Thus, reaction of **9** with methyllithium and subsequent dehydration of the resulting tertiary alcohol provided ipalbidine methyl ether. This was demethylated with boron tribromide to provide (+)-ipalbidine (**1**, Scheme 3).

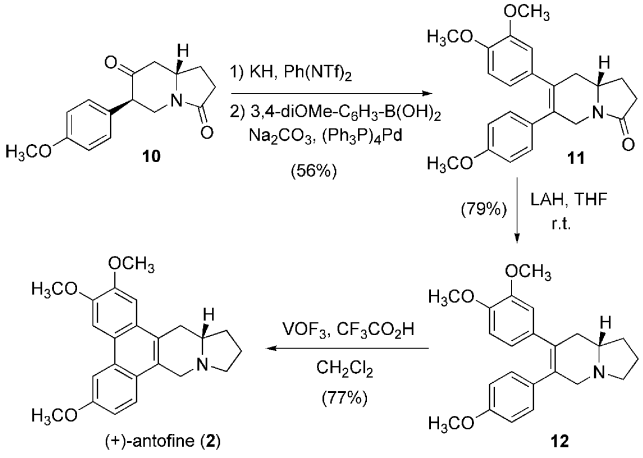


Scheme 3. Conversion of **9** to (+)-ipalbidine.

The synthesis of (+)-antofine was also completed from the lactam **7a** that was obtained as an intermediate in the preparation of the ketone **9**. Oxidation of **7a** (DMSO, pyridine·SO_3) provided the ketolactam **10** (Scheme 4). Conversion of **10** to the enol triflate followed by a Suzuki–Miyaura coupling[18] with (3,4-dimethoxyphenyl)boronic acid furnished the lactam **11**, which was reduced to secoantofine **12**. Oxidative biaryl coupling in **12** provided (+)-antofine (**2**, 77%).[11]



Scheme 2. Conversion of **5** to amino ketone **9**.



Scheme 4. Conversion of **10** to (+)-antofine.

Conclusions

In conclusion, an organocatalytic Michael-addition-based enantioselective synthesis of the indolizidine framework was developed. This approach has potential applications in the synthesis of congeners and analogs of the target alkaloids[1a] by a) variation in the ketone, nitrostyrene and the aryl cross-coupling partner, and b) embellishment of the propanoate side chain in **7**. The utility of our strategy is augmented by the large number of methods available for the stereoselective synthesis of a variety of γ-nitro ketones.[19] We are currently investigating the application of this methodology in the synthesis of other indolizidines, quinolizidines and functionalized piperidines.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for all compounds.

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