Total Synthesis of Isoellipticine

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INTRODUCTION

The ellipticine (**1**), a member of pyridocarbazole family,[1] was firstly isolated at the end of 50's from the leaves of *Ochrosia elliptica*.[2] This alkaloid aroused interest in the pharmacologic area due its unique antitumor and anticancer properties.[3] More recently, studies indicate that this compound and its derivatives also show activity against HIV.[2] The isoellilpticine (**2**), a non-natural isomer of ellipticine (**1**), exhibits similar biological properties, however its preparation has been little explored.[4]

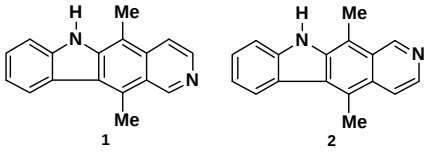
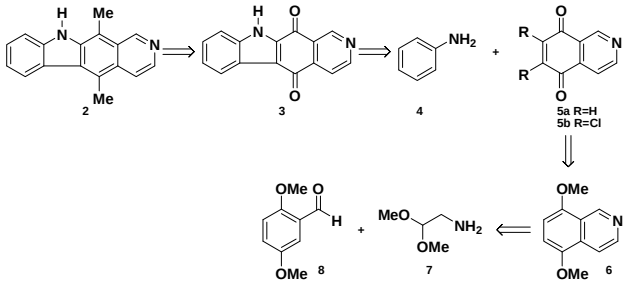


Figure 1. Strucutrue of ellipticne (**1**) and isoellipticine (**2**).

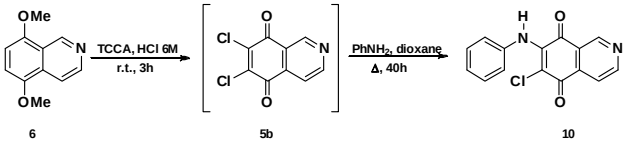
RESULTS AND DISCUSSION

The scheme 1 shows the applied retrosynthetic strategy. Originally, we intended to obtain **2** using **5a** as synthetic intermediate. Although it has been successfully prepared, **5a** showed reduced stability to be used in the following step.



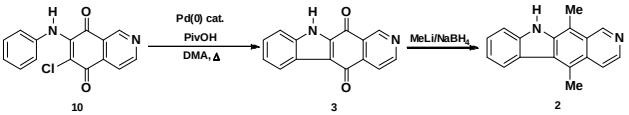
Scheme 1. Retrosynthetic strategy to obtain isoellipticine (**2**).

This inconvenient was circumvented applying an oxidation/halogenation step using TCCA/HCl for preparation of 6,7-dichloroisoquinoline-5,8-dione (**5b**). So, the dione **5b** was submitted directly to the oxidative amination step to furnish **10** and its regioisomer (10:1) in 67% yield, scheme 2.



Scheme 2. Preparation of 6-chloro-7-(phenilamino)-isoquinoline-5,8-dione (**10**).

The dione **10**, in sequence, was submitted to a palladium-catalyzed C-H activation, forming **3**. The total synthesis of isoellipticine (**2**) was achieved after the reaction of quinone **11** with MeLi followed by $NaBH_4$ reduction in ethanol under reflux, scheme 3.



Scheme 3. Preparation of isoellipticine (**2**).

CONCLUSION

It was possible to prepare 6-chloro-7-(phenylamino) isoquinoline-5,8-dione (**10**) in 6 steps and 58% yield using readily available starting materials. This substrate afforded the isoellipticine (**2**) after C-H activation and metilation/reduction reactions.

ACKNOWLEDGEMENTS

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