Studies aiming the synthesis of the indolizidine alkaloids (+)-Ipalbidine and (+)-Antofine

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INTRODUCTION

The indolizidine skeleton is present in a large number of compounds with interesting biological profiles. The (+)-ipalbidine **1** and (+)-antofine **2** have, among others, analgesic and anticancer properties, respectively. However, there are few short, divergent and enantioselective syntheses for these compounds.

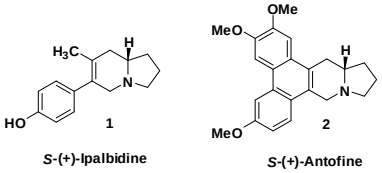
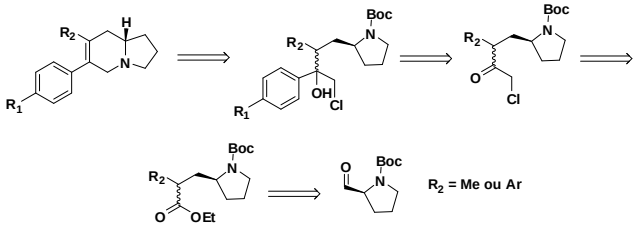


Figure 1. Structures of the target compounds.

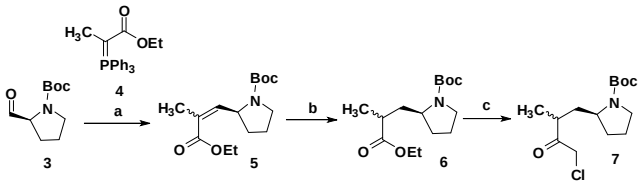
This work presents a new route to obtain the indolizidine skeleton present in these alkaloids, employing a cyclization reaction from α-chloroketones (R_1 = CH_3 (+)-Ipalbidine, R_2 = Ar, Phenanthroindolizidines), which can be easily prepared from (*S*)-prolinal (Scheme 1). The key steps of this strategy are: an olefination reaction (Wittig or Horner-Wadsworth-Emmons); the preparation of α-chloroketones; and converting them into the indolizidine skeleton.



Scheme 1. Retrosynthetic analysis strategy.

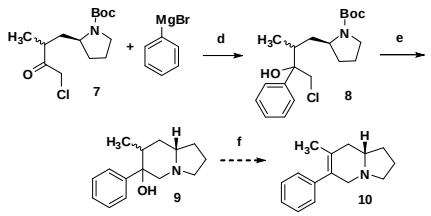
RESULTS AND DISCUSSION

Owing to its lower structural complexity, the studies were initiated by the synthesis of (+)-ipalbidine[1]. The α-chloroketone **8** was prepared from (*S*)-prolinal in 3 steps and with a 79% overall yield (scheme 2).



Scheme 2. a) DCM, r.t., 8 h (95%); b) Ni_2B, THF/MeOH, 0°C → r.t., 12 h (96%); c) LDA, $ClCH_2I$, THF, -78°C, 2 h (90%).

Initial studies aiming the cyclization reaction from α-chloroketones were fruitless. Considering that, we next evaluated the cyclization from α-chloroalcohols (installation of the aromatic ring prior to cyclization). In this study, phenyl magnesium Grignard was used as a model. After succeed in preparing α-chloroalcohol **8**, we then studied the cyclization reaction (scheme 3). The best results were achieved when we employed phenol and trimethylsilyl chloride, followed by purification on Dowex 50. In possession of compound **9**, it is now being converted into compound **10** by an elimination reaction[2].



Scheme 3. d) PhMgBr, Et_2O, -78°C→r.t., 10 h (60%); e) PhOH, TMSCl, DCM (yield under assessment); f) 25% H_2SO_4 reflux.

CONCLUSION

The strategy using α-chloroketones for the synthesis of indolizidine constitutes a new approach with reduced number of steps. This approach can be applied to obtain the (+)-ipalbidine, the (+)-antofine and other indolizidine alkaloids.

ACKNOWLEDGEMENTS

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