Total synthesis of (±)-Preussin from an α,β-unsaturated diazoketone *via* the Stevens rearrangement

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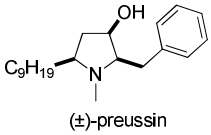
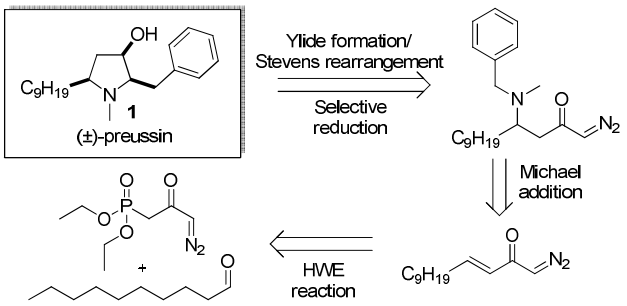
INTRODUCTION

Preussin is a pyrrolidine alkaloid that has been isolated from the fermentation broths of *Aspergillus ochraceus* and *Preussia* sp[1]. This compound exhibits antifungal, antibacterial and antitumor properties with potent growth-inhibitory and apoptosis-inducing effects on human cancer cells[2].



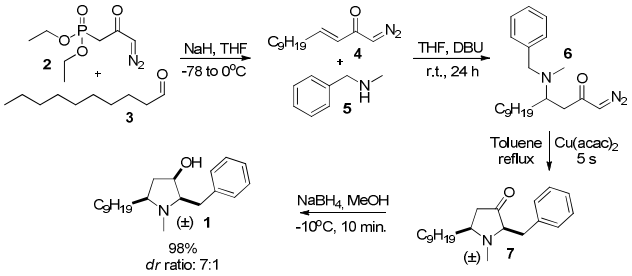
In this work, we employed the chemistry of α,β-unsaturated diazoketones and ammonium-ylides to synthesize (±)-Preussin **1** in just 3 steps from decanal as depicted in Scheme 1. The main transformation in the present strategy involves a stereoselective Stevens rearrangement from an ammonium ylide.



Scheme. 1. Strategy for the synthesis of (±)-Preussin.

RESULTS AND DISCUSSION

We started our work by preparing unsaturated diazoketone **4** in 92% yield from decanal **3**, employing the diazophosphonate **2**[3] (Scheme 2). Next, Michael addition in the presence of benzylmethylamine **5** and catalytic amount of DBU furnished adduct **6** in 97% yield. After the synthesis of **6**, we then evaluated its one-pot cyclization-Stevens rearrangement (via ammonium ylide) in order to obtain the dissubstituted pyrrolidinone **7**. After a deep study it was observed that $Cu(acac)_2$ as catalyst, in toluene under reflux, was the best option to perform this transformation (58% yield). Moreover, it is important to notice that only the desired *cis* isomer was observed after the Stevens rearrangement. Completion of the synthesis was then straightforward after the reduction of **7** with $NaBH_4$ in excellent yield and good stereoselectivity (98%; *dr* = 7:1).



Scheme 2. Synthesis of (±)-Preussin.

The one pot cyclization-Stevens rearrangement-reduction from diazoketone **4** could also be carried out, leading to preussin in 55% overall yield and with the same selectivity (*dr* : 7:1).

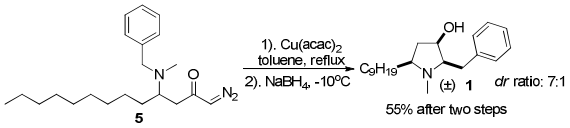


Fig. 2. Stevens rearrangement and ketone reduction one pot.

CONCLUSION

It was possible to synthesize (±)-Preussin in 3 steps from decanal with a global yield of 49%, employing the chemistry of α,β-unsatured diazoketones and the Stevens rearrangement as the key transformation.

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