Substrate-controlled Asymmetric Morita-Baylis-Hillman Reaction: an Approach to the Synthesis of Pyrrolizidinones and Pyrrolizidines

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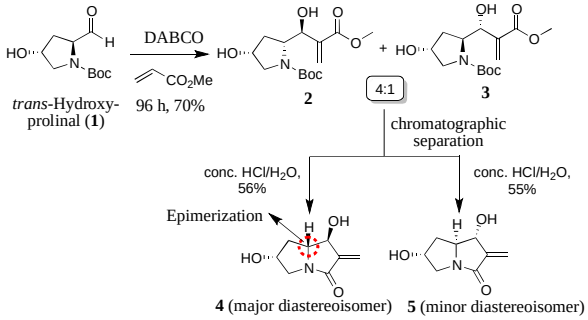
INTRODUCTION

The hexahydro-pyrrolizidine skeleton is a structural motif found in several biologically active compounds. The pyrrolizidinic alkaloids are a good example of compounds isolated from natural sources which exhibited this motif in their structures and remarkable biological effects.[1]

The biological relevance of these compounds justifies the development of new approach to them. We disclose herein a facile and fast approach to the synthesis of poly-hydroxylated pyrrolizidinones and pyrrolizidines using Morita-Baylis-Hillman adducts as substrate.[2]

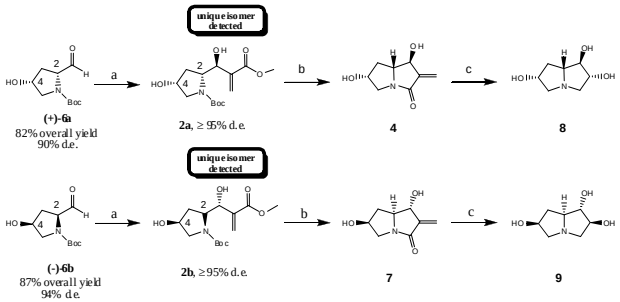
RESULTS AND DISCUSSION

In order to obtain our target compounds, we carried out a MBH reaction with substituted prolinal. So, (4*R*)-hydroxy-(2*S*)-prolinal (**1**) was submitted to a MBH reaction to give adducts **2** and **3,** as a mixture of diastereoisomers (4:1). After separation, both diastereoisomers were treated with concentrated HCl solution and water to provide hydroxylated pyrrolizidinones **4** and **5** (Scheme 1).



Scheme 1. Synthesis of pyrrolizidinones from MBH adducts

This result can only be explained if racemization had occurred during the Morita-Baylis-Hillman. Searching to understand this behaviour, we decided to determine if the hydroxyl group at C3 had some influence in this process. Both enantiomer of *cis*-hydroxy prolines (+)-**6a** and (-)-**6b** were used as substrate for another MBH reaction. In both cases, a unique diastereoisomer was detected. Most probably, an intramolecular hydrogen bond (only possible on the *cis*-isomer) can explain these results. The double bond of compound **7** and **4** were ozonolyzed, followed by *in situ* stereoselective reduction to provide pyrrolizidinones, as a sole product.



Scheme 2. Reagents and conditions: a) metyl acrylate, DABCO, 96 h, 70-76%; b) conc. HCl/H_2O, 55-60%. Proving the role displayed by hydroxyl group at C3. c) O_3, CH_2Cl_2:MeOH (8:2), -78 °C, 10 min; ii. $NaBH_4$, -78 °C to r.t., 4 h, 78%.) AlH_3 (17 equiv.) ($AlCl_3$:$LiAlH_4$, 1 mol/L), THF, reflux, 3 h, 75-80%; Synthesis of poly-hydroxylated pyrrolizidines.

Pyrrolizidinones were treated with AlH_3 to give poly-hydroxylated pyrrolizidines **8** and **9**, in 80 and 75% yield respectively. Compounds **8** and **9** were synthesized in 5 steps with an overall yield of 24 and 20%, respectively.

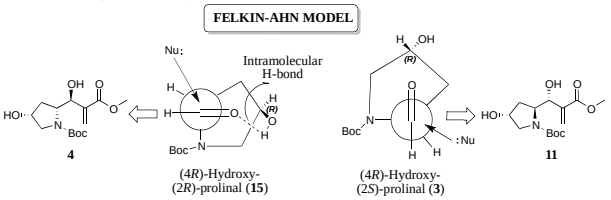


Figure 1. Rationalizing our results.

CONCLUSION

An asymmetric substrate-controlled Morita-Baylis-Hillman reaction allowed the synthesis pyrrolizidinones and pyrrolizidines in few steps and good overall yield.

ACKNOWLEDGEMENTS

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