CONCISE ENANTIOSELECTIVE TOTAL SYNTHESIS OF AZIMIC ACID AND RELATED ENTITIES

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Abstract - The purpose of this study is to accomplish the enantioselective synthesis of biologically relevant such as (-) Azimic Acid(a) and related analogues. The scheme is designed in such a way to have the minimum number of sequential steps to make a whole of the synthetic plan effective and efficient. The key steps of the synthesis are one-pot Lithium Aluminium Hydride (LAH) reduction and tert-Butyloxycarbonyl protection, Swern Oxidation, Gignard addition, Grubbs olefin metathesis.

I. INTRODUCTION

The piperidine entities are bioactive and thus found in numerous biologically relevant natural products as well as in medicinal and pharmaceutical agents[1].2,6-Disubstituted piperidin-3-ol alkaloids displaying attractive structural arrangement have shown interesting pharmacological activities.The macrocyclic dilactones azimine(l)[2] and carpaine (2)[3] belong to a small subgroup containing a 2,3,6-trisubstituted piperidine alkaloid, azimic acid (a) and carpamic (b) acids, whose total stereospecificsynthesis from D-glucose based on the concept of "chiral templates" [4] have been achieved byHanessian and coworkers.[5]We reported herein a concise total stereoselective synthesis of azimic acid (a)

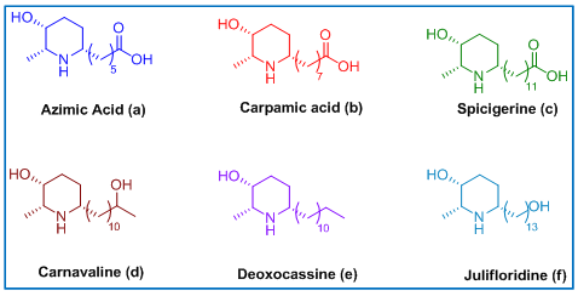
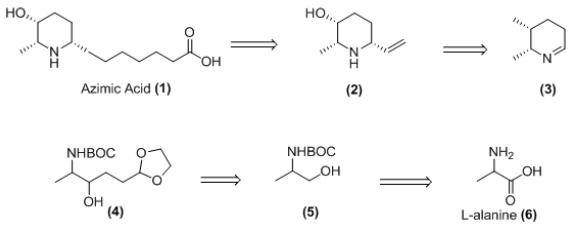


Figure 1: Biologically active 2,6-disubstituted piperidines targeted in this study

II. RETROSYNTHETIC PATHWAY

The desired Azimic Acidcan be synthesised from L-alanine,and the retrosynthetic pathway is given in the scheme below.

We envisaged that the synthesis of Azimic Acid could be accomplished through a key intermediate imine(3). Further,we comprehended that the imine (3) could further be obtained by deprotecting dioxolane and t-BOC groups from substrate (4). This would further result in formation of cyclic imine (3). The moiety (4) was obtained from (5) that was further synthesised from commercially available L-alanine (6) by carrying out in situ reactions of LAH reduction and BOC protection.



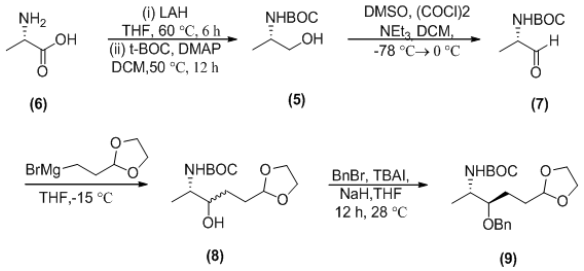
Scheme 1.

III. PROPOSED SYNTHETIC ROUTE

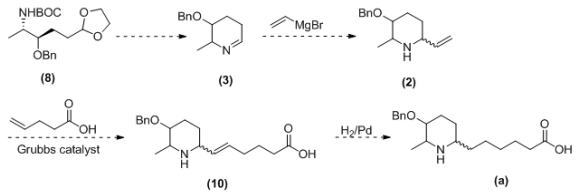
The synthetic forward plan for the synthesis of azimic acid and similar analogues is given in Scheme 2 and 3.

Our synthesis of Azimic Acid started from commercially available L-Alanine amino acid. To this one-pot synthesis was carried out in which acid functionality was reduced to alcohol and amine protection was carried out. Further, by Swern oxidation aldehyde (7) was obtained. The reaction of dioxolane magnesium bromide (2.5equiv) with aldehyde (7) afforded hydroxy oxolane moiety (8).

This was hydroxy group in (8)was protected by carrying out protection reaction with benzylbromide and sodium hydride in THF. Subjecting (8) to acidic condition may result in imine (3) formation, which may further on exposing to vinyl magnesium bromide may result in formation of (2). Grubbs coupling of (2) with pent-4-enoic acid may yield (10) that on further reduction by hydrogen palladium will result in Azimic acid (a).



Scheme 2.



Scheme 3.

IV. CONCLUSION

This project aims to develop a highly efficient stereoflexible total synthesis of (−)-Azimic Acid and similar entities from L-alanine.by exploiting the simple, classical and inexpensive methods. The methodology presented in this paper can be used for the synthesis of several other natural products of this class.

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