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A Powerful Enantioselective Organocatalytic Approach to the Total Synthesis of Madangamine Alkaloids

"POWORMAD"

A Powerful Enantioselective Organocatalytic Approach to the Total Synthesis of Madangamine Alkaloids

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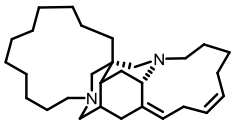
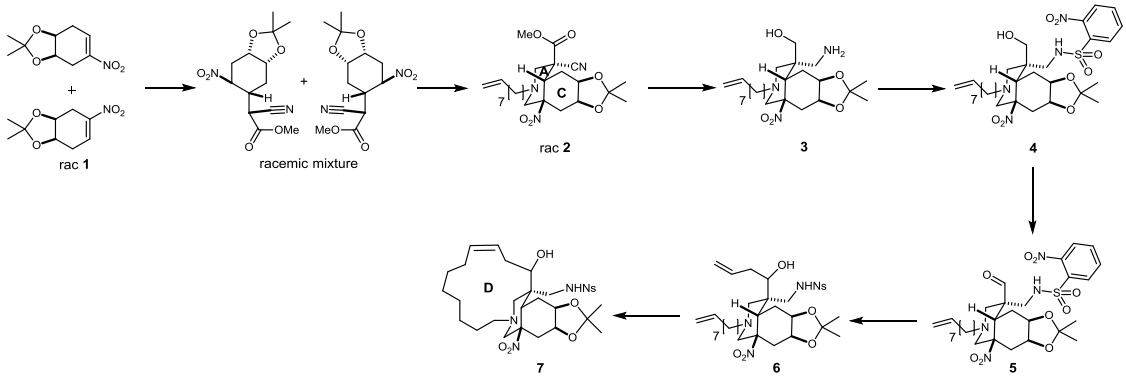
INTRODUCTION

Our proposal is based on the development of the first successful total synthesis of a madangamine alkaloid. We believe that Madangamine D will be an excellent first target, because this saturated macrocycle offers several synthetic possibilities.



RESULTS

Our retrosynthetic plan devised for the synthesis of the AC azabicyclic core of the madangamine alkaloids was based on the key nitro olefin Michael addition and nitro-Mannich lactamization steps to give the right diastereomer **rac 2**. The synthesis has been performed starting from the racemic nitroolefin **1**.

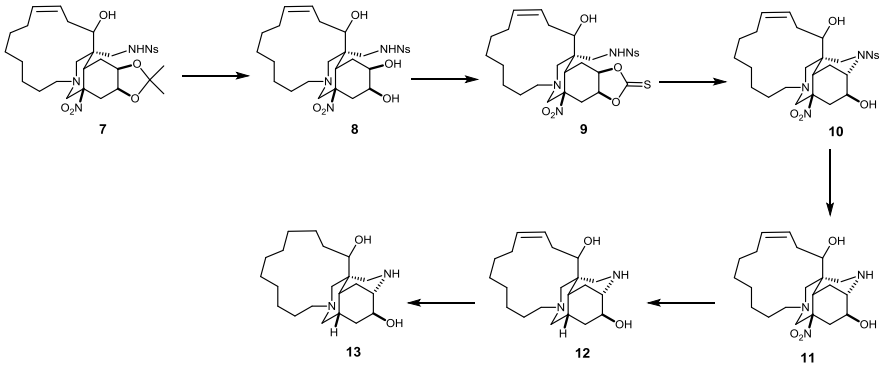


Reduction and tosylation of rac **2** led to compound **4** in good yield over 2 steps, and the following oxidation smoothly produced the aldehyde **5**.

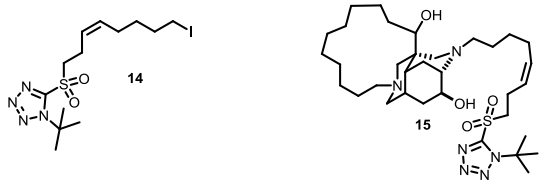
In order to obtain the macrocycle D necessary for the synthesis of the Madangamine D, an allylic group was introduced on the aldehyde **5**, followed by RCM employing 10 mol % of Grubbs

Hoveyda 2nd generation catalyst to give the ACD tricycle **7**. The use of 10 mol % of catalyst was possible only carrying out the reaction at low pressure (16 mbar).

Tetracycle **10** has been achieved in three steps: acetal group on compound **8** was converted into tiocarbonate **9**, followed by cyclisation to give **10**. Subsequently the nosyl and nitro group on compound **10** were removed, and hydrogenation of the double bond on **12** led to the advanced amino alcohol **13**.



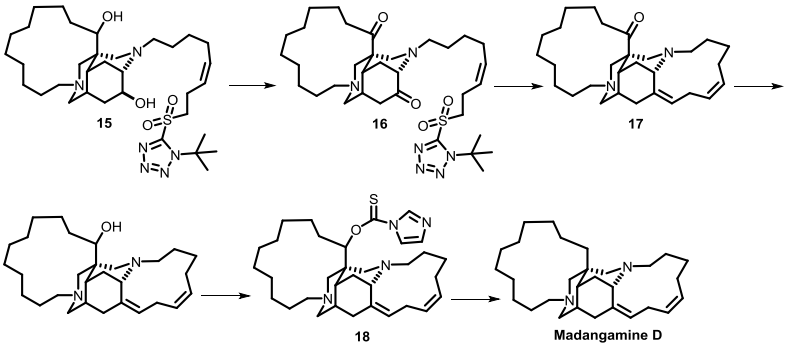
In order to achieve the last cyclisation to Madangamine D, the appropriate fragment **14** was synthesized. Unfortunately any attempts to coupling the iodide **14** with the tetracycle **13** resulted in very low yields of **15** (about 10 %).



Other coupling reactions, which were carried out by changing the iodide group of **19** to aldehyde or carboxylic acid, produced no reaction or only trace of the desired product.

PROSPECTIVES

We prospect that, at this stage, only few steps divide Madangamine D from the compound **15**.



The last key step will be the intramolecular Julia-Kocienski to give the compound **17** (the carbonyl group on the six membered ring is plausibly more accessible), and the other carbonyl group can be removed via tiocompound **18**, allowing to achieve the first total synthesis of a member of the madangamines family.