Synthesis of a Macrocyclic Marine Natural Product Analog

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INTRODUCTION

Marine natural products Aerucyclamide B (**1**)[1] and Dendroamide A (**2**),[2] Figure 1, are bioactive hexacyclopeptides alternating in hydrophobic and hydrophilic (Thr and Cys) amino acids. The side chains of these polar amino acids are heterocyclized to form azole rings.

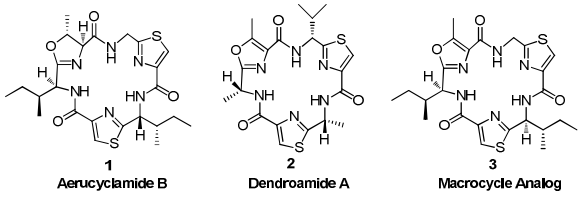


Figure 1. Aerucyclamide B, Dendroamide and Macrocycle analog

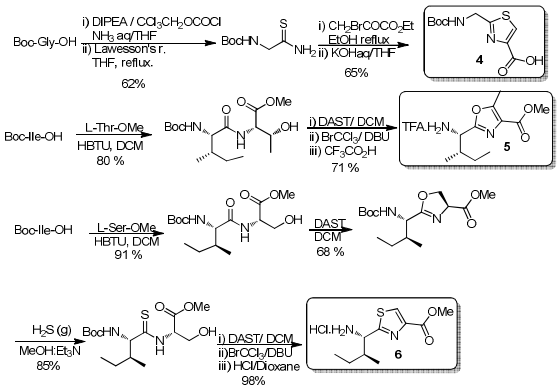
The oxidation state of heterocyclic rings can enforce different conformations on macrocycles and this has been shown to result in very different affinities for metal ions and consequently different biological activity.[2]

As part of our search for candidates for antiparasitic new drugs,[3] we embarked in the synthesis of macrocycles analogs of these marine natural products. In the present work, we present the synthesis of the macrocycle **3** which is more stable, cheaper and easier to prepare than Aerucyclamides.

RESULTS AND DISCUSSION

Our planed synthesis of **3** began with the construction of three heterocyclic building blocks, **4**, **5** and **6**, Scheme 1.

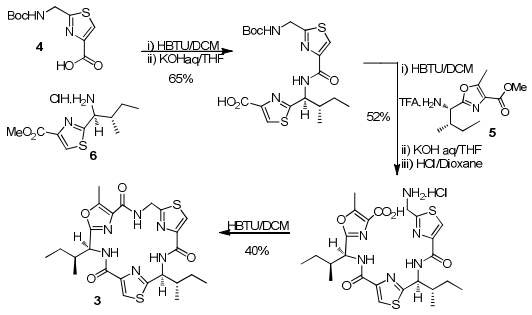
Scheme1. Synthesis of heterocyclic building blocks **4**, **5, 6**.



Thiazole **4** was obtained by Hantszch reaction from the Boc-Gly thioamide and bromopyruvate. Cyclodehydration, oxidation and deprotection processes using DAST, $BrCCl_3$/DBU, and TFA respectively allowed us to obtain oxazole **5** from dipeptide Boc-Ile-Thr-OMe in 71% overall yield. In a similar way, thiazole **6** was prepared from Boc-Ile-Ser-OMe thioamide in 98% yield.

The macrocycle **3** was obtained by successive coupling reaction of **4**, **6** and **5** using HBTU as is showed in Scheme 2.

Scheme 2. Synthesis of macrocycle **3**



CONCLUSION

The macrocyclic analog of marine natural products (**3**), was obtained by a convergent strategy from three heterocyclic building blocks. The processes could be used for the construction of others natural product analogs. Biological evaluation of the obtained compounds is currently in progress.

ACKNOWLEDGEMENTS

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