Synthesis of Cyclic Pentadepsipeptoids Analogues of Sansalvamide A by Combination of Ugi and Passerini Reactions

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Keywords: Ugi/Passerini reaction, peptoids and Sansalvamide A.

INTRODUCTION

Sansalvamide A (San A, **1**) is a natural product isolated from a marine fungus (*Fussarium ssp.*).[1] This cyclic depsipeptide exhibits a potent anticarcinogenic activity on multiple cancer cell lines.[1b]

In continuing our research on the synthesis of peptoids with potential pharmacological activity,[2] we decided to perform the synthesis of cyclic depsipeptoids analogues of San A (**2a-b**, Figure 1) based on a strategy previously developed in our group,[2a] by combination of Ugi and Passerini reactions. To the best of our knowledge, the synthesis of cyclic depsipeptoids has not yet been explored.

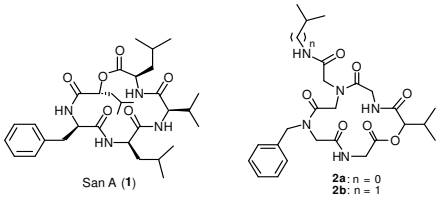
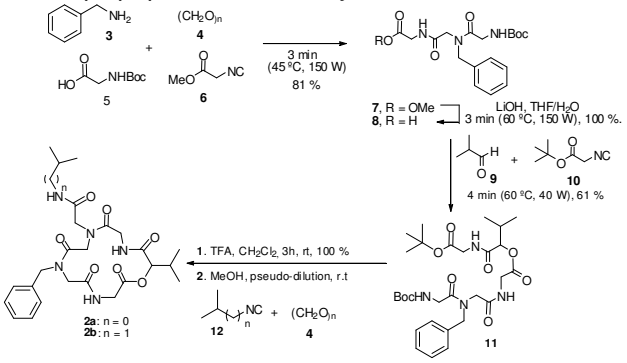


Figure 1. Sansalvamide A (**1**) and its depsipeptoid analogues (**2**).

RESULTS AND DISCUSSION

The aim of our study was to develop a general strategy for the synthesis of cyclic pentadepsipeptoids, as shown in Scheme 1. This strategy is based on: (a) formation of a peptoid via Ugi reaction; (b) ester hydrolysis; (c) formation of an acyclic tetradepsipeptoid scaffold in the Passerini reaction; (d) deprotection of the amine/acid and (e) a macrocyclization step via Ugi reaction.

Peptoid **7** was prepared in 81% yield by an Ugi 4-component reaction (U-4CR) using benzylamine **3**, paraformaldehyde **4**, N-*Boc*-glycine **5** and methyl isocyanoacetate **6** (Scheme 1) using microwave (MW) irradiation for 3 min (45 °C, 150 W). Peptoid **7** was hydrolyzed after basic treatment (LiOH, THF/H_2O) to give the corresponding acid in quantitative yield. Acid **8** was employed in a Passerini reaction with isobutyraldehyde **9** and *tert*-butyl isocyanoacetate **10**, under μW irradiation for 4 min (60 °C, 40 W) affording the acyclic tetradepsipeptoid **11** in 61% yield.



Scheme 1. Synthesis of cyclic pentadepsipeptoid analogues of San A (**2a-b**).

Removal of the *Boc* protecting group and ester hydrolysis were achieved after treatment of compound **11** with TFA in CH_2Cl_2 giving the amino acid in quantitative yield. Subsequent macrocyclization reactions involving Ugi three-component four-center reaction (U-3C4CR) using the obtained amino acid with paraformaldehyde and isopropyl/isobutyl isocyanide to give the target cyclic pentadepsipeptoid are in progress in our laboratory.

CONCLUSION

A fast and general synthetic route was developed for the synthesis of cyclic pentadepsipeptoids via consecutive multicomponent reactions.

ACKNOWLEDGEMENTS

IQ-UnB, Capes, CNPq and FINEP-CT INFRA nº 0970/01.

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