Application of Ugi Consecutive Protocol in the Synthesis of a Peptoid Analogue of Verticilide

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INTRODUCTION

Peptoids are non-natural molecules being capable to mimic the natural structure of peptides. These mimetics are based on oligo-*N*-substituted glycine backbones which exhibit proteolytic stability and wide range of biological activities.

Verticilide **1** is a cyclic depsipeptide that exhibits insecticidal activity and was isolated from the culture broth of *Verticilium sp.* FK-1033[1] (Figure 1).

In order to apply the microwave-assisted synthesis of peptoids via Ugi reactions developed by our groups,[2] we decided to perform the synthesis of a peptoid analogue of Verticilide (Figure 1).

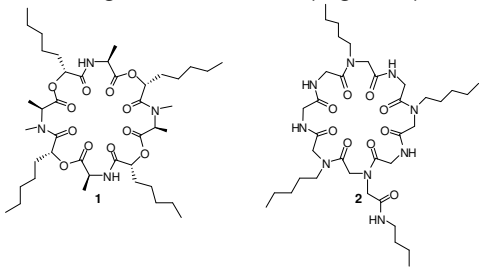
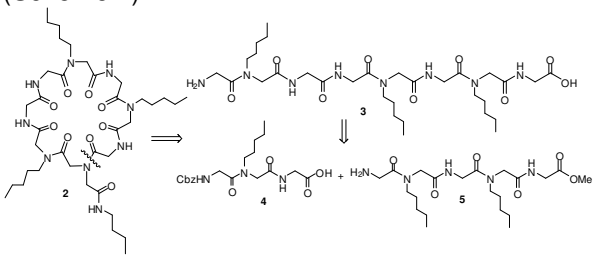


Figure 1. Verticilide (**1**) and its peptoid analogue (**2**).

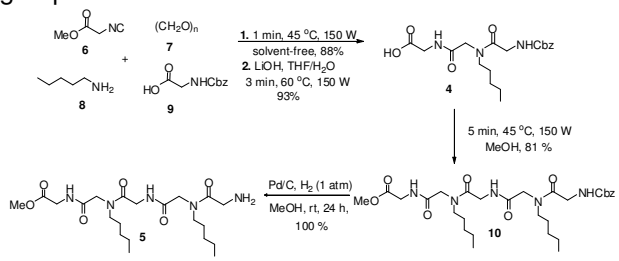
RESULTS AND DISCUSSION

A convergent strategy is being used for the synthesis of **2**. The retrosynthetic analysis shows that the cyclic octapeptoid **2** can be obtained by macrocyclization of acyclic substrate **3**, which can be assessed by the coupling of fragments **4** and **5** (Scheme 1).



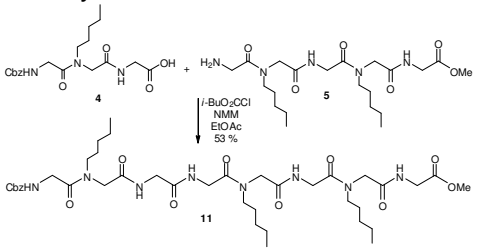
Scheme 1. Retrosynthetic analysis of cyclic octapeptoid **2**.

Peptoid **4** was easily prepared by an Ugi 4-component reaction (U-4CR) followed by a hydrolysis reaction (Scheme 2). Tetrapeptoid **5** was prepared using the fragment **4** in a second Ugi reaction followed by removal of the *Cbz* protecting group (Scheme 2). Both peptoids were obtained using a protocol previously established by our group.[2b]



Scheme 2. Synthesis of peptoid **4** and tetrapeptoid **5**.

Coupling of fragments **4** and **5** were performed using the mixed anhydride approach to give the acyclic heptapeptoid **11** in moderate yield (53%) (Scheme 3). Subsequent ester hydrolysis and removal of the *Cbz* protecting group reactions followed by macrocyclization involving Ugi three-component four-center reaction (U-3C4CR) are in progress in our laboratory.



Scheme 3. Synthesis of acyclic heptapeptoid **11**.

CONCLUSION

A fast and concise synthetic route allowed the synthesis of peptoid **4**, tetrapeptoid **5** and acyclic heptapeptoid **11** by Ugi consecutive reactions.

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REFERENCES

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