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 Verticillium sp. (Figure 1). In order to apply the microwave-assisted synthesis of peptoids via Ugi reactions developed by our groups, 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.

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.


CONCLUSION

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

ACKNOWLEDGEMENTS

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

REFERENCES