Studies toward the synthesis of potencial artificial nucleases derived from trypargine

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INTRODUCTION

The ability to efficiently hydrolyze nucleic acids in a biomimetic non-destructive process with high selectivity has become important because one can find many applications in structural design of new probes and drug development. This molecular recognition is a common feature in biological systems, where some functional groups form supramolecular systems by non-covalent interactions. For example, the guanidinium group present in the active site of the *Staphylococcus* nuclease is used to recognize the phosphodiester group, accelerating its hydrolysis.[1]

Recently, our group has synthesized the alkaloid tetrahydro-β-carboline (S)-(-)-trypargine (**1**) that presents a side chain at C1 with a terminal guanidine residue.[2] Therefore, we decided to synthesize new derivatives of trypargine (**2** and **3**) in order to investigate their ability to recognize and trigger hydrolysis of phosphodiesters, such as DNA and RNA.

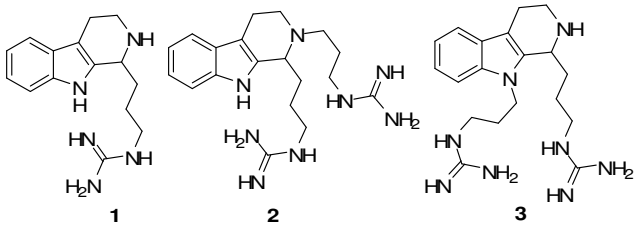
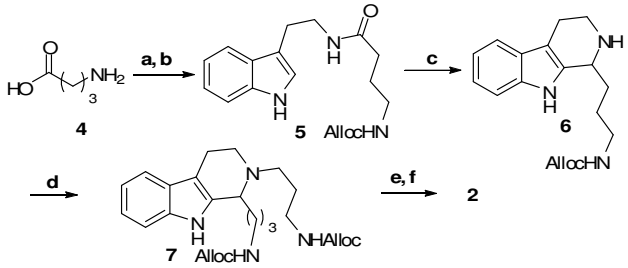


Figure 1. Trypargine (1) and analogues 2 and 3

RESULTS AND DISCUSSION

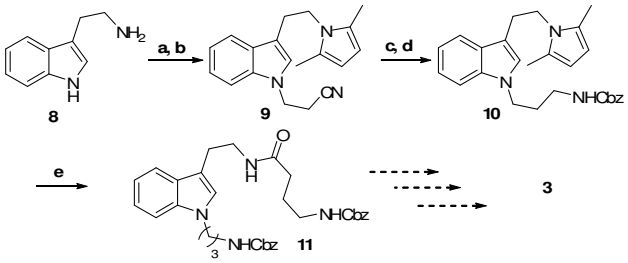
The synthesis of analogue **2** started with a three step procedure developed in our group, to build intermediate **6**.[2] Selective alkylation led to compound **7**, which was deprotected with Pd/C and triethylsilane, providing the free diamine which was subjected to guanylation conditions (Scheme 1).

Analogue **3** was prepared by protecting tryptamine **8** in the form of a 2,5-dimethylpyrrol prior to Michael addition to acrylonitrile, leading to compound **9**. Reduction of the nitrile gave the corresponding amine which was protected as a carbamate. Deprotection of the 2,5-dimethylpyrrol and coupling with Cbz-protected GABA, gave the advanced intermediate **11** in good yield over two steps (Scheme 2).



Reagents and conditions: a) Alloc-Cl, THF/ $NaHCO_3$ solution (1:1), r.t., 24 h, 83%; b) Tryptamine, EDC, HOBt, THF, r.t., 18 h, 97%; c) (1) $POCl_3$, PhMe/MeCN (7:3), reflux, 2 h; (2) $NaBH_4$, MeOH, 0 ºC-r.t., 4 h, 69%; d) allyl 3-bromopropylcarbamate, K_2CO_3, MeCN, r.t., 12h, 72%; e) Pd/C 10%, Et_3SiH, MeOH, r.t., 2 h, 45%; f) 1*H*-Pirazole carboxamidine, DIPEA, DMF, r.t., 24 h.

Scheme 1. Preparation of analogue 2



Reagents and conditions: a) 2,5-hexanedione, PhMe, reflux, 18h, 79%; b) Acrilonitrile, DBU, MeCN, 16 h, 50 ºC, 99%; c) $LiAlH_4$, THF, r.t., 7h, 68%; d) Cbz-Cl, THF/ Na_2CO_3 solution (1:2), r.t., 24 h, 95%; e) (1) $NH_2OH.HCl$, Et_3N, Isopropanol/H_2O (3:1), reflux, 5 h; (2) GABA-Cbz, EDC, HOBt, THF, r.t., 18 h, 52% (two steps).

Scheme 2. Preparation of analogue 3

Also, the study of interaction between trypargine **1** and bis(p-nitrophenyl)phosphate by calorimetric and NMR techniques is currently under investigation.

CONCLUSION

The synthetic route for the preparation of compound **2** has been well established, the deprotection of the Alloc group and final purification still requiring optimization. The strategy used for compound **3** is promising, with three steps remaining to achieve the target structure.

ACKNOWLEDGEMENTS

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REFERENCES

[1] a) Cowan, J. A. *Curr. Opin. Chem. Biol.* **2001**, *5*, 634; b) Schug, K. A.; Lindner, W. *Chem. Rev.* **2005**, *105*, 67.

[2] Pilli, R. A.; Rodrigues Jr., M. T. *J. Braz. Chem. Soc.* **2009**, *20*, 1434.