Enantioselective Synthesis of *cis*- and *trans*-3-Hydroxypipecolic Acids by Addition of Metal Alkynyls to Serine Derivatives

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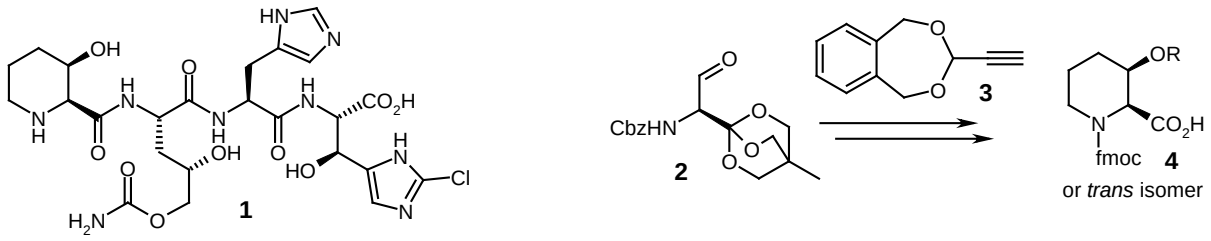
During the total synthesis of the tetrapeptidic natural product GE81112A **1** a major challenge was the synthesis of all four isomers of *cis* and *trans*-3-hydroxy pipecolic acid.[1] In our first approach, we used a nonselective pathway and separated the isomers via chiral chromatography. For the synthetic access to bigger quantities of **1** and its derivatives, a stereoselective synthesis of a Fmoc protected *cis*-(2*S*,3*R*)-3-hydroxy pipecolic acid **4**, ideally with a TIPS-protected hydroxyl function, would be key to success.

Herein we report the concise stereoselective synthesis of both orthogonally protected *cis* and *trans*-3-hydroxypipecolic acid starting from *ortho*-ester (OBO) protected serine aldehyde **2**. Utilizing metalated alkyne **3** as a nucleophile containing a masked aldehyde enabled us to perform a reduction - protecting group cleavage - piperidine formation cascade reaction under simple hydrogenation conditions in one pot and one step. Compared to other reported syntheses of protected 3-hydroxypipecolic acids our protocol displays a highly improved step efficiency. Furthermore, the OBO ester-based protecting group strategy represents an attractive stereoselective approach towards other *β*-hydroxy functionalized amino acid building blocks.



[1] G. Jürjens, S. M. M. Schuler, M. Kurz, S. Petit, C. Couturier, F. Jeannot, F. Nguyen, R. C. Wende, P. E. Hammann, D. N. Wilson, E. Bacqué, C. Pöverlein, A. Bauer, *Angew. Chem. Int. Ed*. **2018**, *57*, 12157-12161