

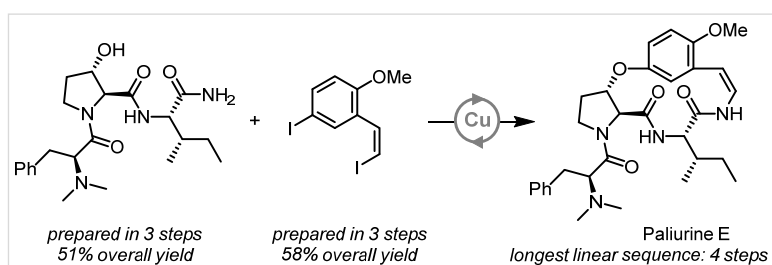
TOTAL SYNTHESIS OF PALIURINE E: A HIGHLY CONVERGENT “BLOCK” APPROACH

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Improved efficiency is one of the main concerns of modern natural product synthesis. Catalytic reactions, reduced number of steps and convergent approaches can indeed bring rapid accesses to complex scaffolds with various biological activities and facilitate their structural modification in a diversity-oriented approach. Among natural products, macrocyclic ones represent an interesting subclass and various strategies have been reported over the years for their preparation.^[1] As a challenging alternative, assembling macrocyclic natural products via an unprecedented “block” approach that would chemoselectively couple two fragments of equal complexity in a single step could enable the design of shorter synthetic routes.

With this strategy in mind, the cyclopeptide alkaloid paliurine E was selected as potential target.^[2] From a retrosynthetic perspective, this 13-membered cycle, previously synthesized by our group using 15- and 14-steps sequences,^[3] could be assembled via a key challenging copper(I)-catalyzed inter-/intra- molecular double cross-coupling between two simple bifunctional precursors. The synthesis and the coupling of these two fragments will be described.



[1] For representative examples, see: (a) K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, P. Bertinato *J. Am. Chem. Soc.* **1993**, *115*, 4419. (b) A. B. Smith III, J. Barbosa, W. Wong, J. L. Wood *J. Am. Chem. Soc.* **1996**, *118*, 8316.

[2] For a review on cyclopeptide alkaloids, see: N. H. Tan, J. Zhou, *Chem. Rev.* **2006**, *106*, 840.

[3] (a) M. Toumi, F. Couty, G. Evano *Angew. Chem. Int. Ed.* **2007**, *46*, 572. (b) M. Toumi, F. Couty, G. Evano *J. Org. Chem.* **2008**, *73*, 1270. (c) M. Toumi, V. Rincheval, A. Young, D. Gergeres, E. Turos, F. Couty, B. Mignotte, G. Evano *Eur. J. Org. Chem.* **2009**, 3368.