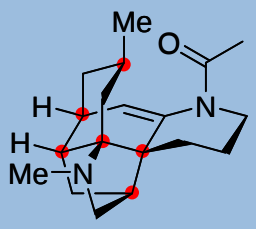
Concise Synthesis of (+)-Fastigiatine

R. A. Samame, C. M. Owens, S. D. Rychnovsky, Chem. Sci. **2016**, *7*, 188.



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26.01.2017, Journal Club

Autors

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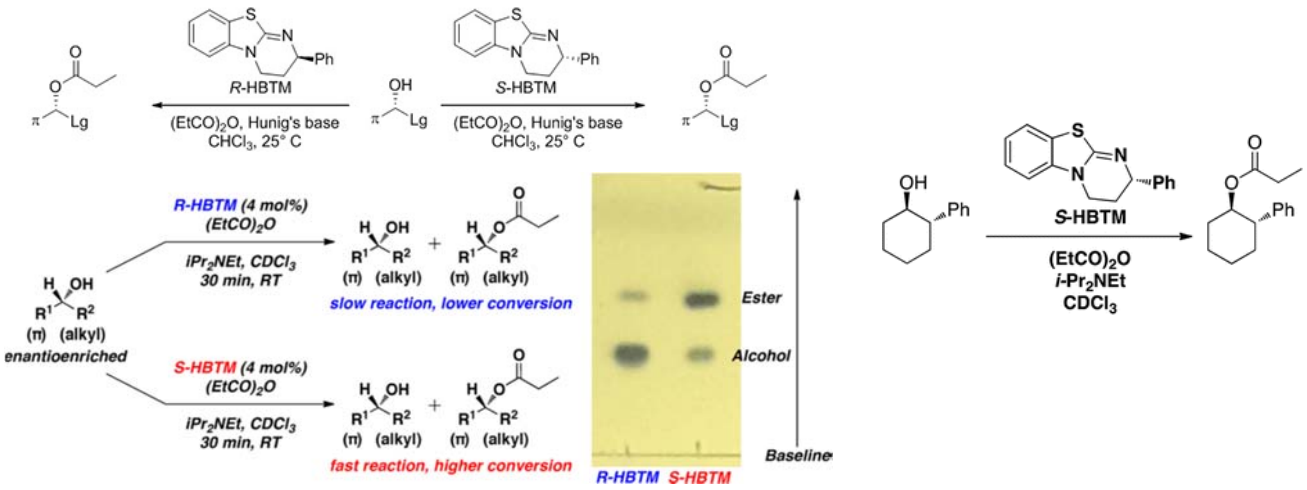
  - Postdoc: Harvard University and Yale University
  - Faculty Member: University of Minnesota
  - Professor: University of California, Irvine

- Total synthesis
- Synthetic method
  - Synthesis of substituted pyridines
  - Competing Enantioselective Conversion (CEC) method
- Chemical Biology

Competing Enantioselective Conversion

- Kinetic resolution agents to establish absolute configuration based on targeted reactivity
  - fastest-reacting enantiomer is identified
  - comparison with an established mneumonic



J. Org. Chem. **2013**, *78*, 4594. *Org. Lett.* **2013**, *15*, 5504.

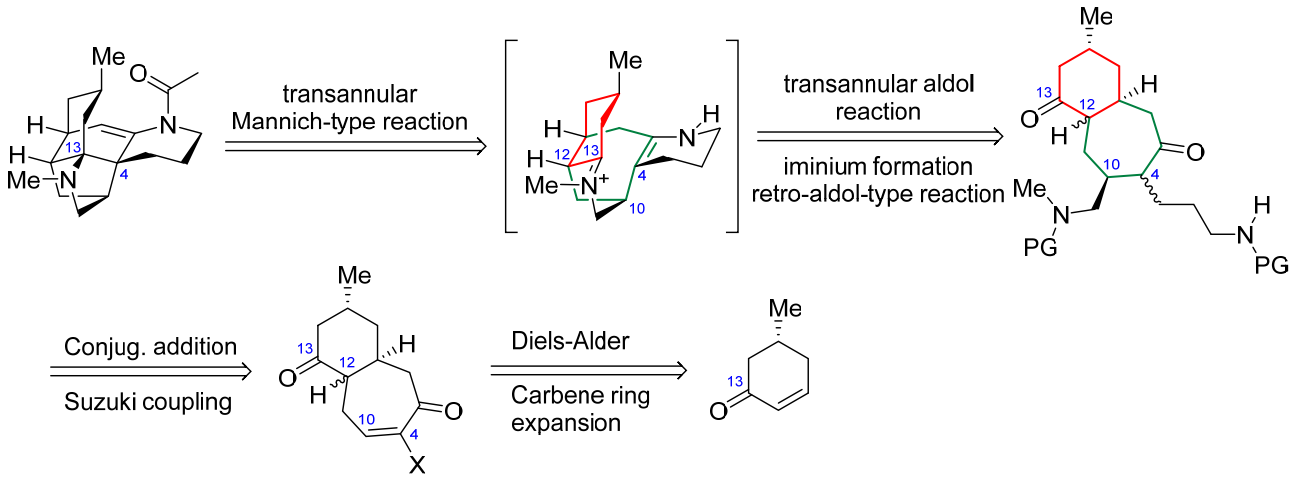
(+)-Fastigiatine

- Lycopodium alkaloids
  - Showing moderate anticancer activity

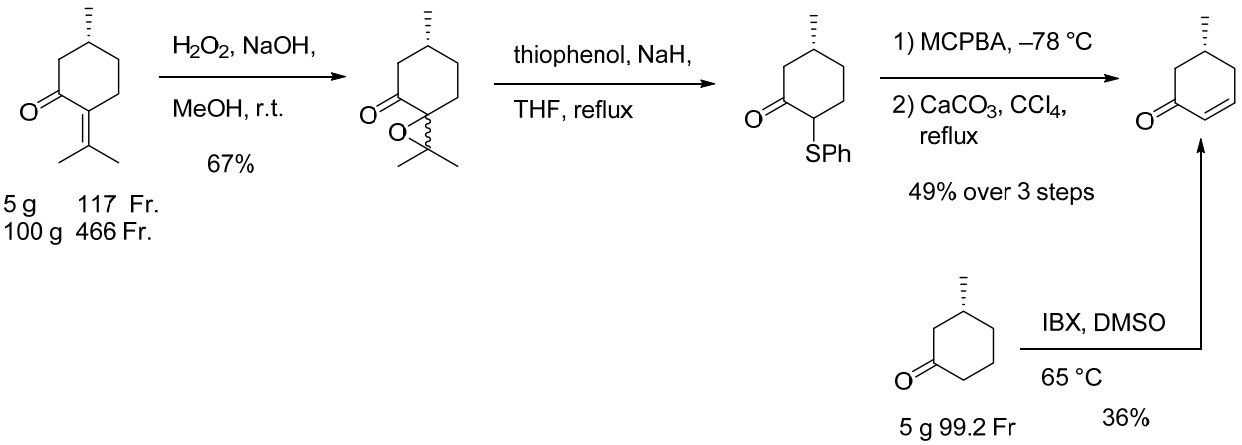
- Twice synthesized by Shair-group (15 and 19 steps)

J. Am. Chem. Soc. **2010**, *132*, 9594. *J. Am. Chem. Soc.* **2014**, *136*, 13442.

Retrosynthetic Analysis

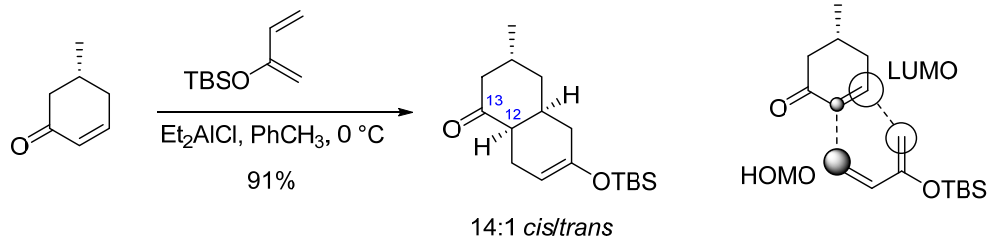


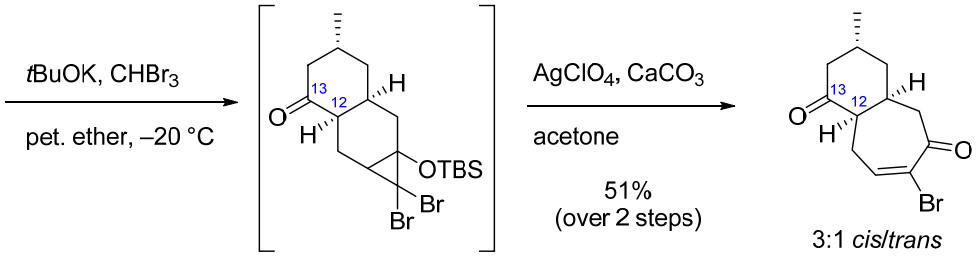
Forward Synthesis: Starting Material



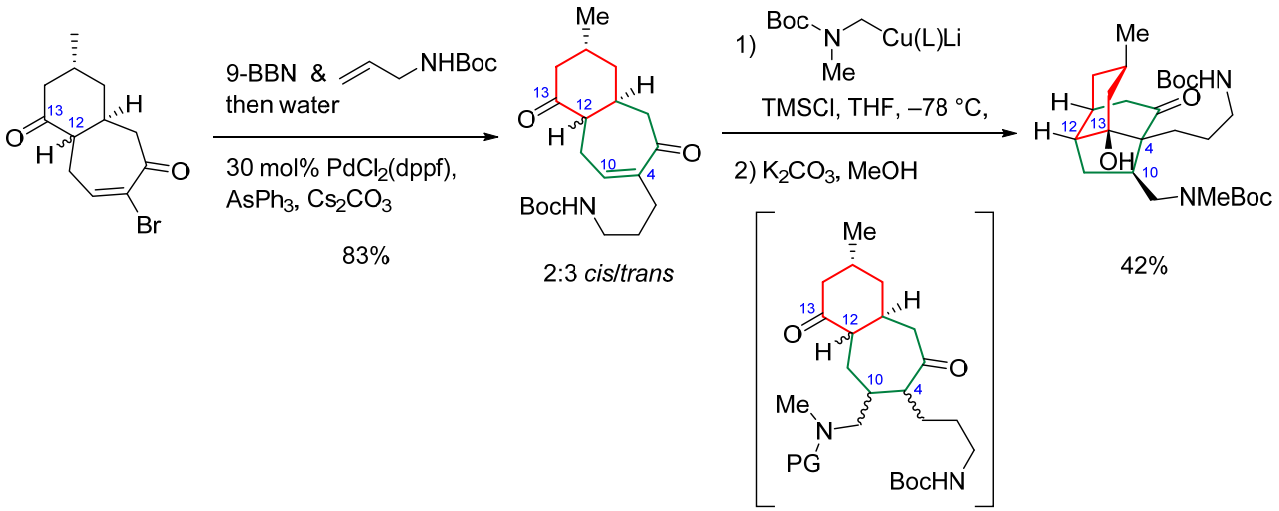
J. Org. Chem. **1984**, *49*, 2647. *Helv. Chim. Acta* **1978**, *61*, 2755.

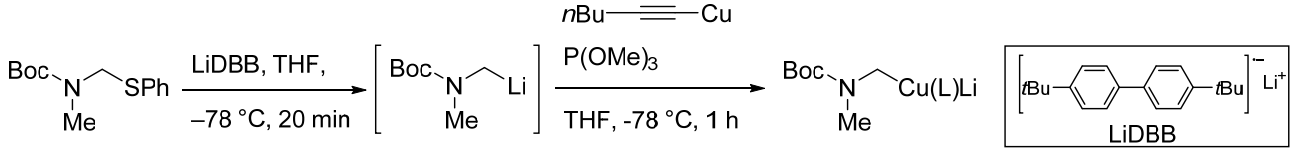
Forward Synthesis



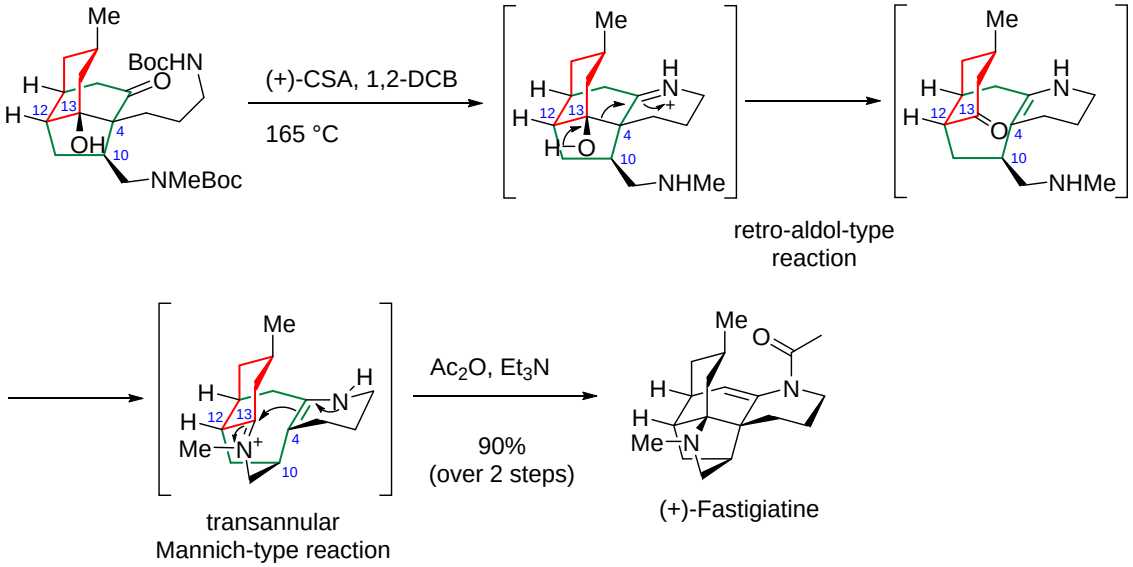


Forward Synthesis





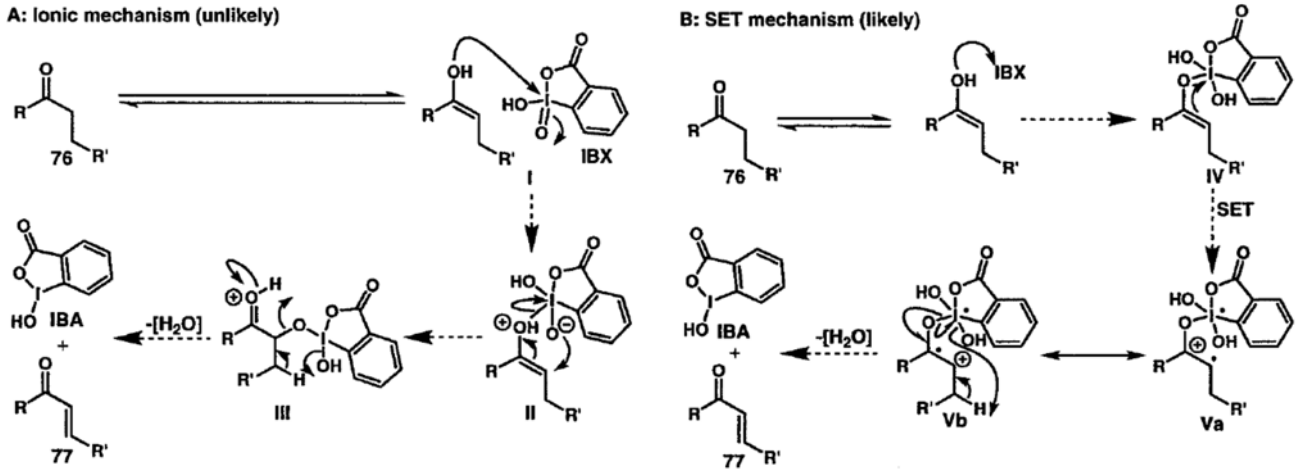
Forward Synthesis



Conclusion

- Synthesis of (+)-fastigiatine: 15% yield over 6 steps
- Lability at C12 was reestablished to the correct configuration by a transannular aldol reaction

IBX oxidation



J. Am. Chem. Soc. 2002, *124*, 2345.

Dibromo carbene ring expansion