Synthesis of (±)-Actinophyllic Acid and Analogs:

Applications of Cascade Reactions and Diverted Total Synthesis

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Martin, S. F. *et al.*
J. Am. Chem. Soc. **2013**, *135*, 12984.

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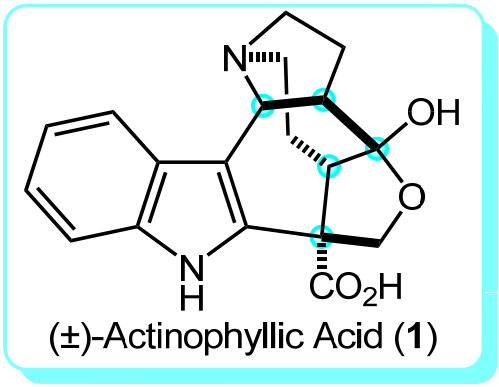
Contents

- Introduction of (±)-Actinophyllic Acid
- Martin's Method for Synthesis of (±)-Actinophyllic Acid
- Overman's Method for Synthesis of (±)-Actinophyllic Acid
- Summary of the Two Methods

Introduction



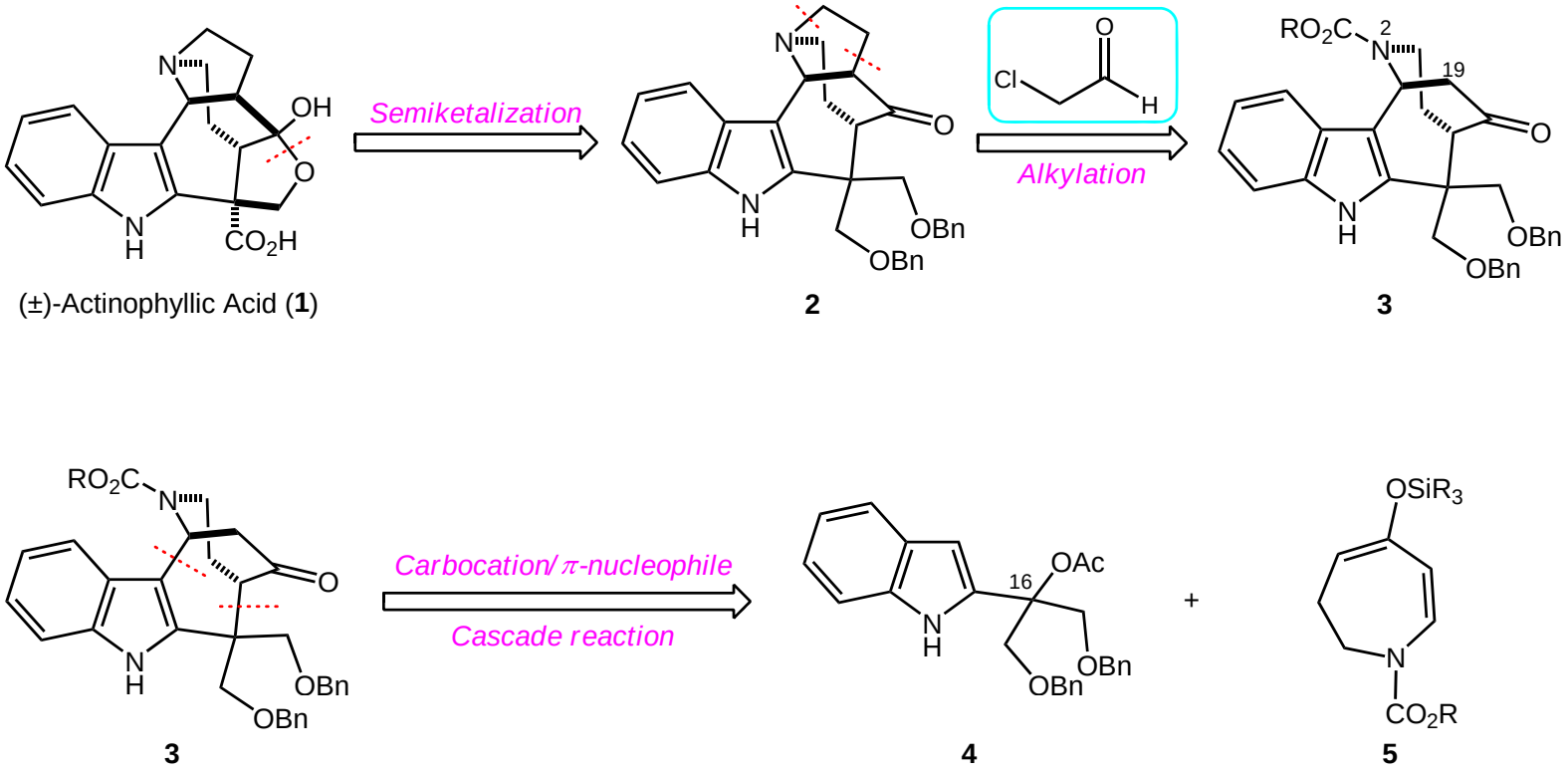
(±)-Actinophyllic Acid (**1**)

Characters:

- Six rings, indole alkaloid;
- Five contiguous stereocenters;
- 1-azabicyclo[4.4.2]dodecane and 1-azabicyclo[4.2.1]nonane.

Martin's Method

Proposed Retrosynthesis



(±)-Actinophyllic Acid (**1**) **2** **3**

3 **4** **5**

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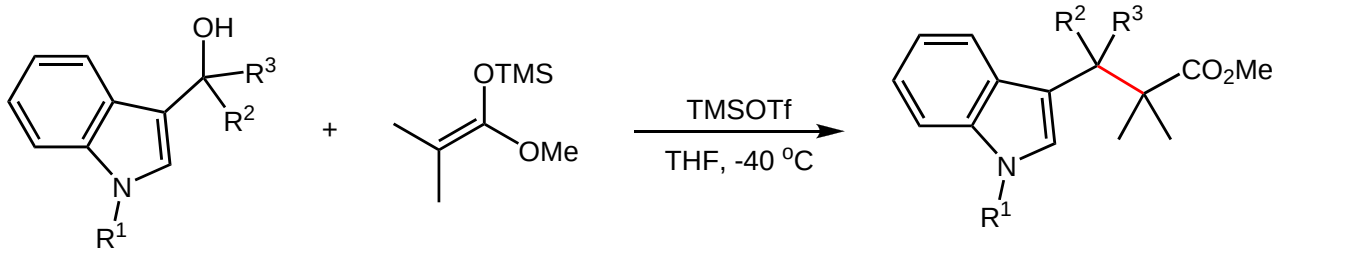
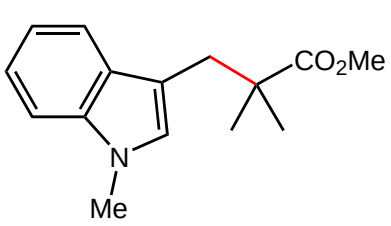
Synthesis of β-Heteroaryl Propionates





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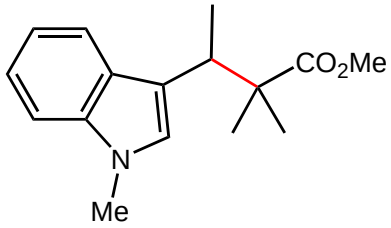

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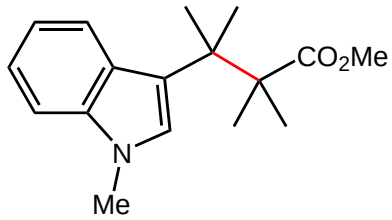

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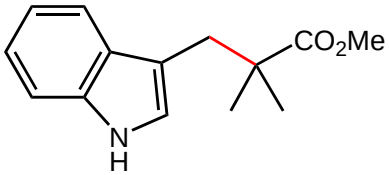

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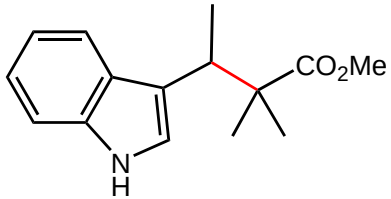

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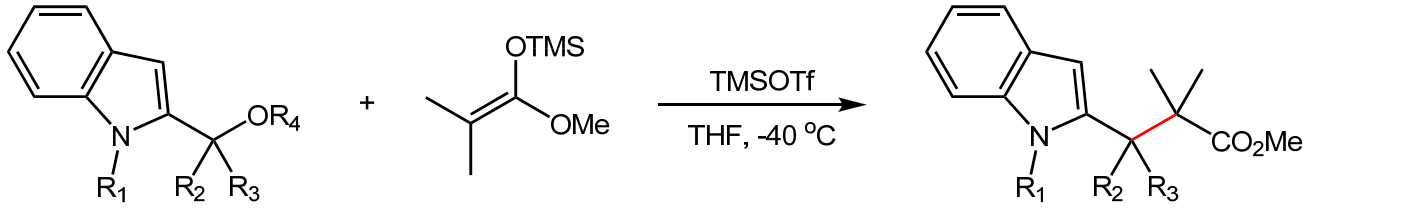
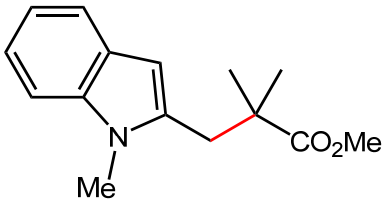
Synthesis of β-Heteroaryl Propionates





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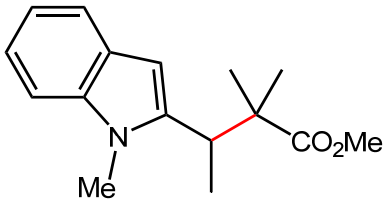

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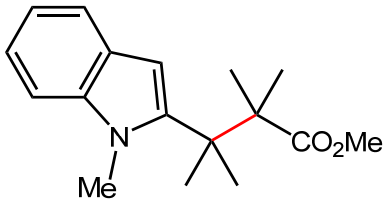

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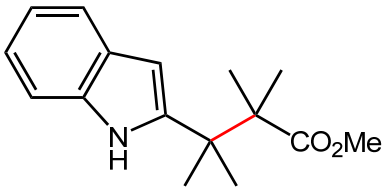

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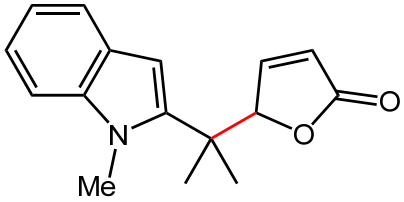

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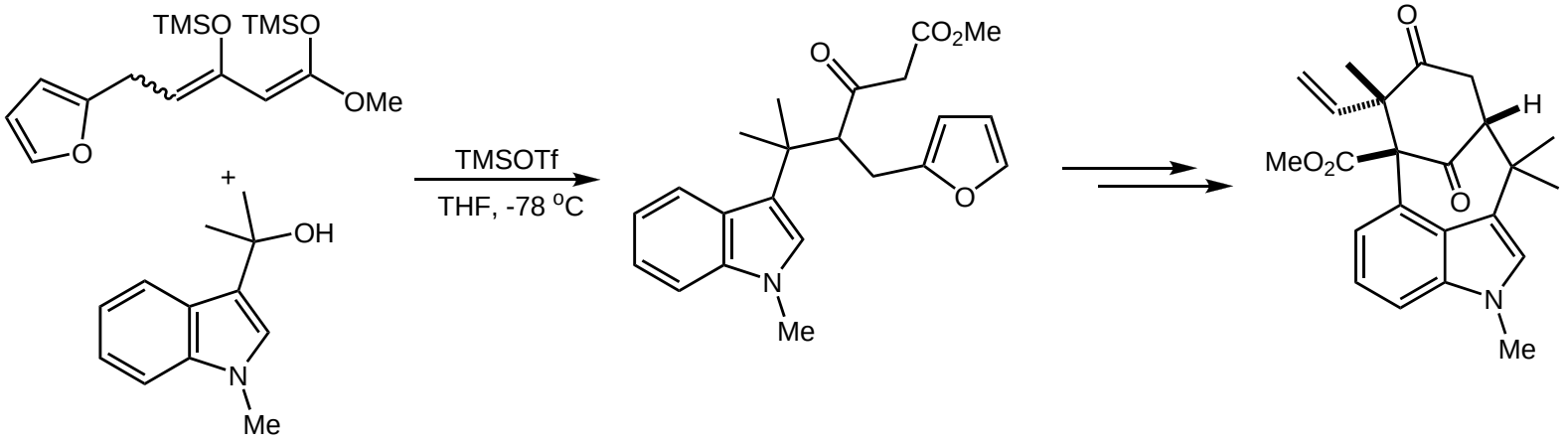
Synthesis of *β*-Heteroaryl Propionates



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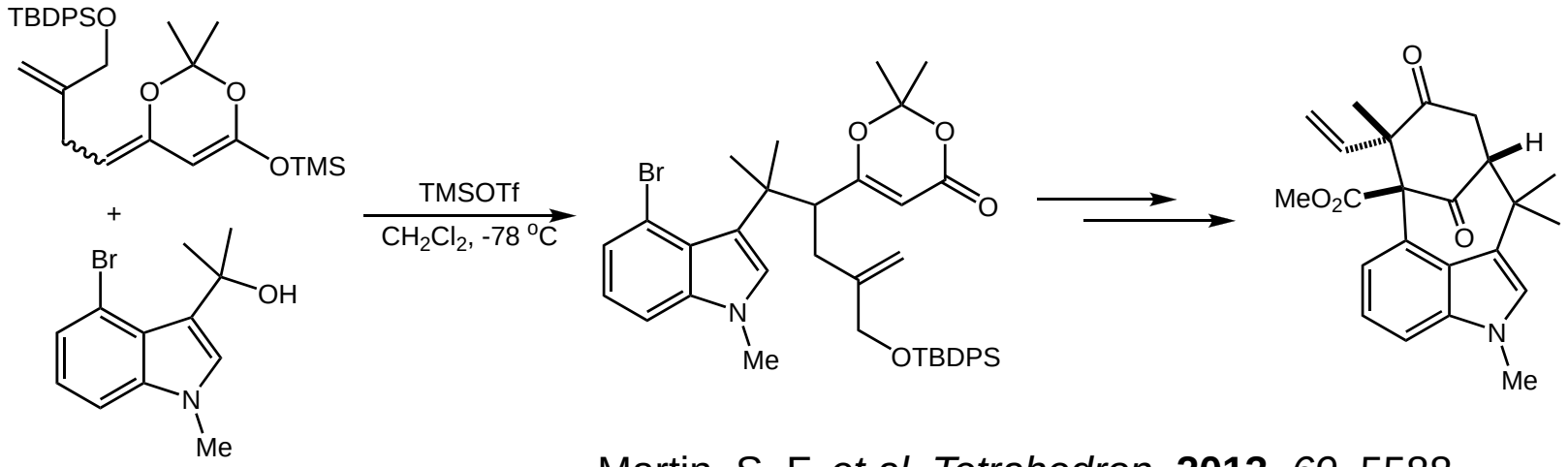
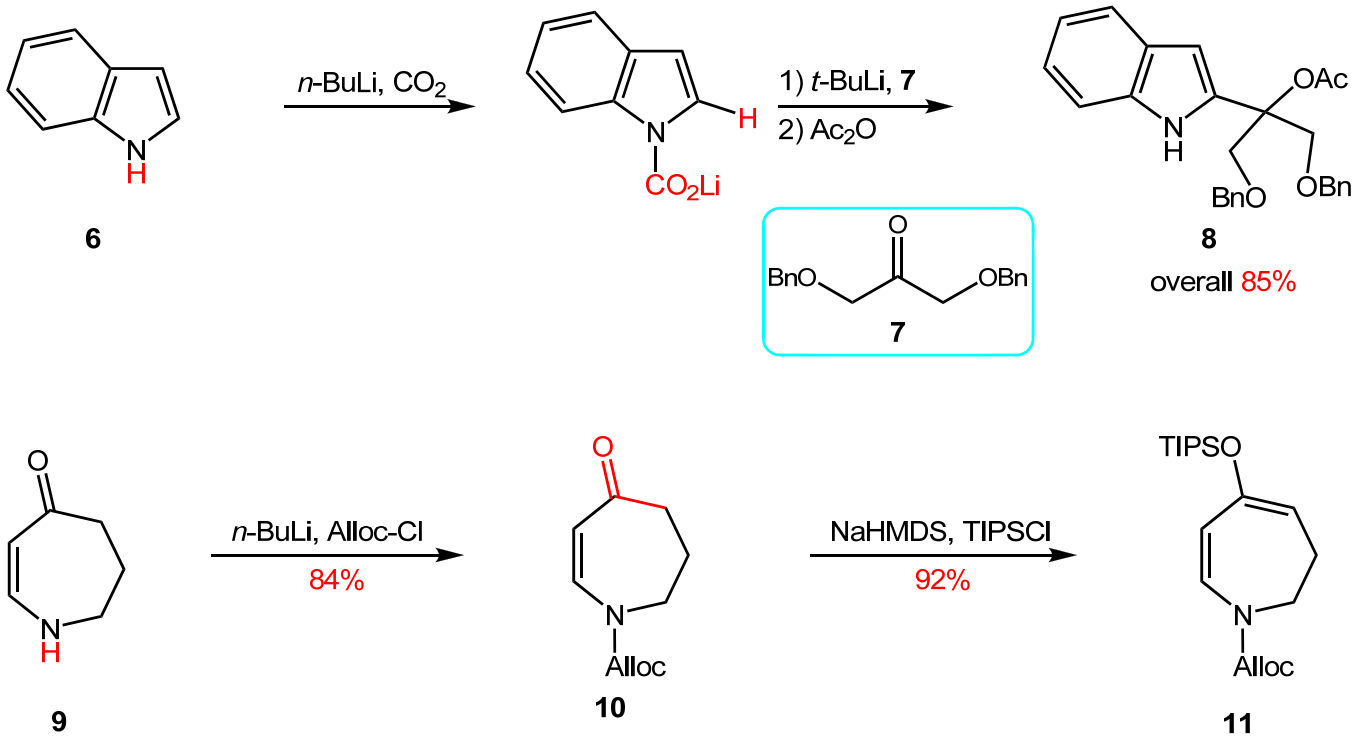


Martin, S. F. *et al*. *Tetrahedron* **2013**, *69*, 5588.

Synthesis of Key Intermediate 12



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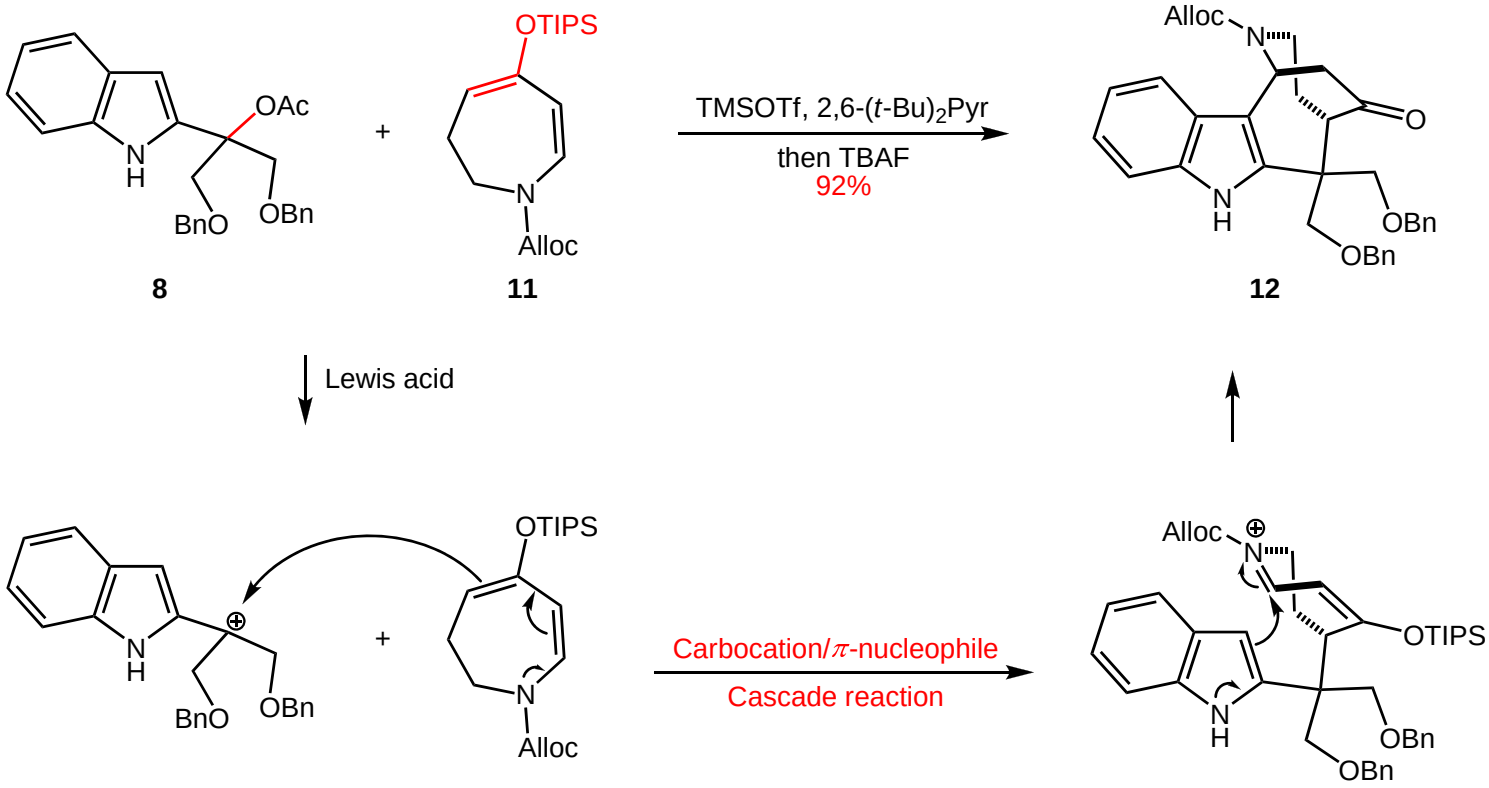
Synthesis of Key Intermediate 12



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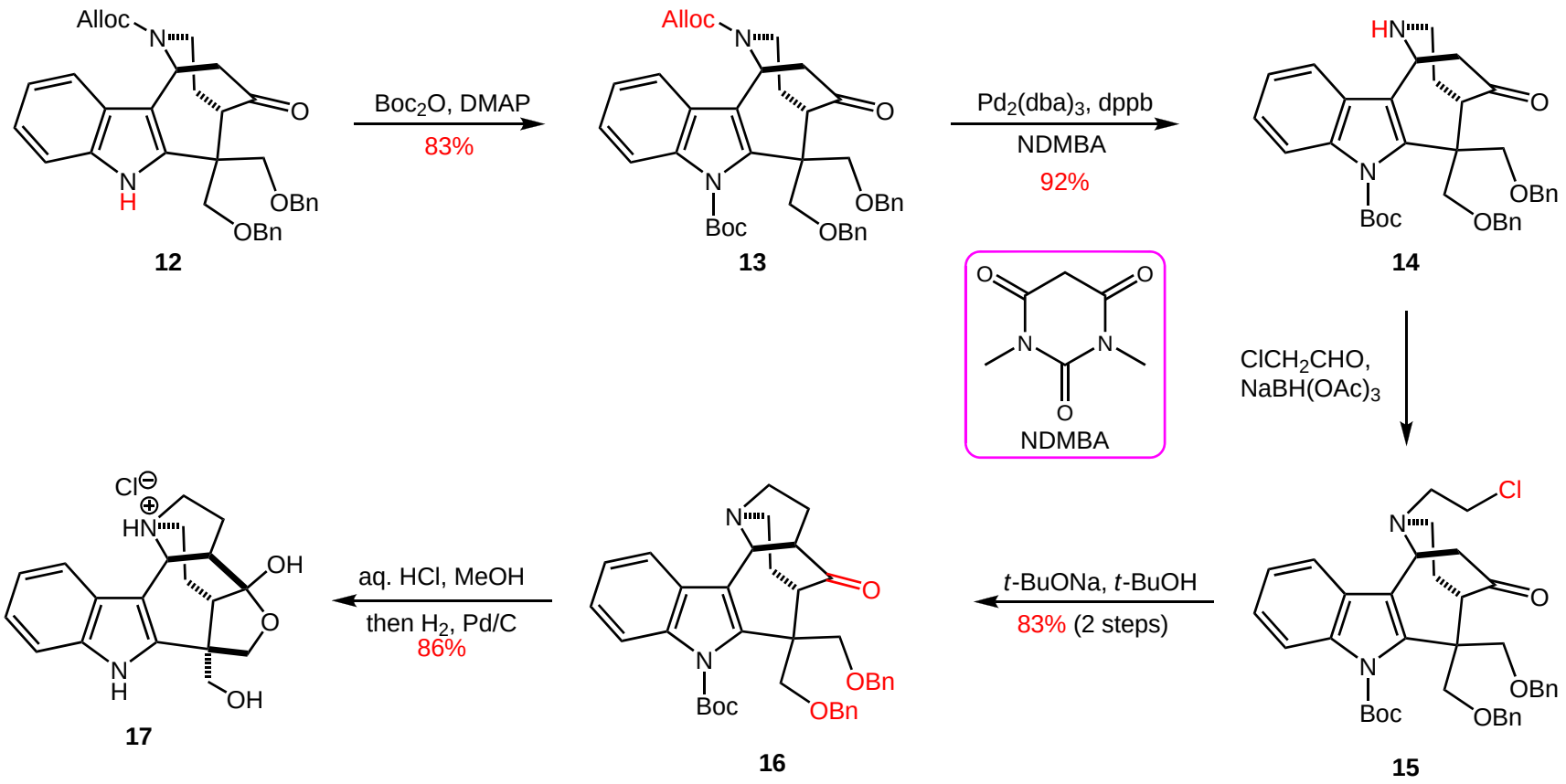
Completion of the Synthesis



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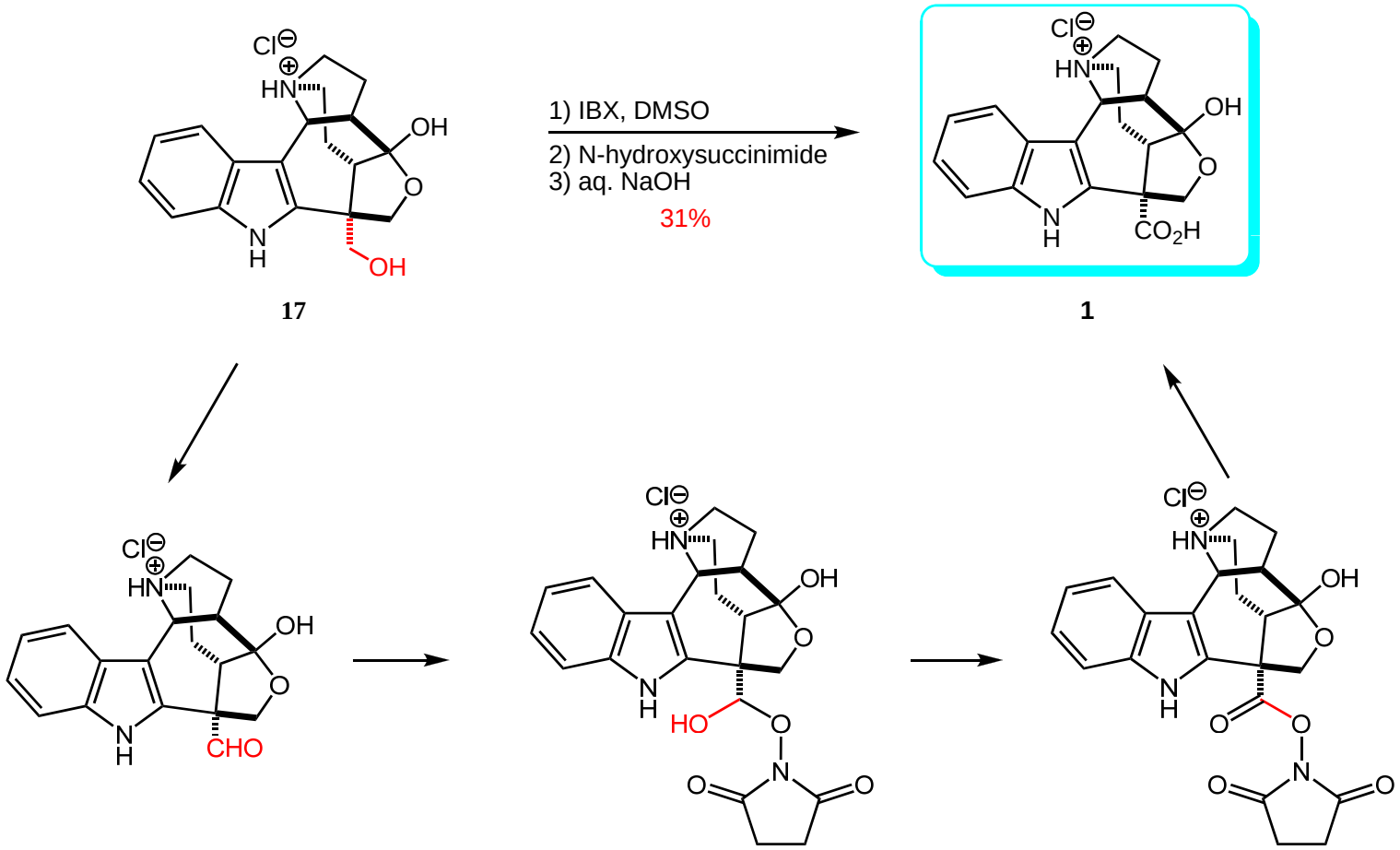

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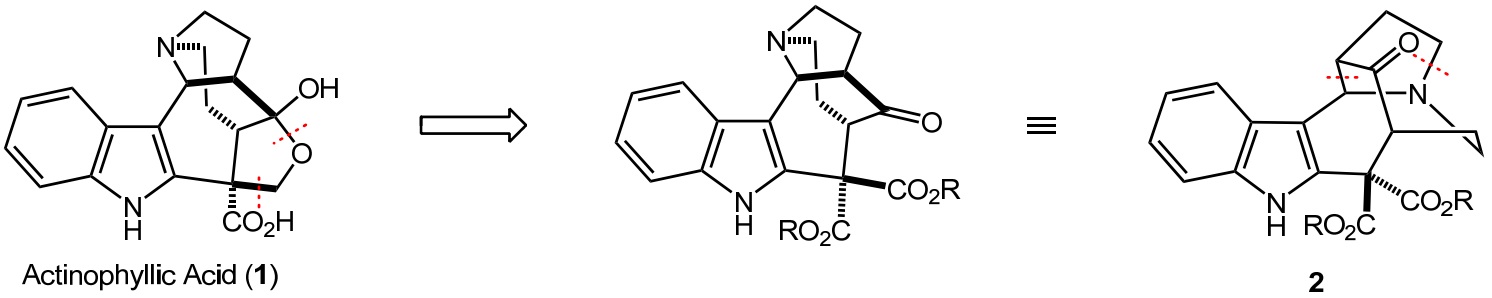
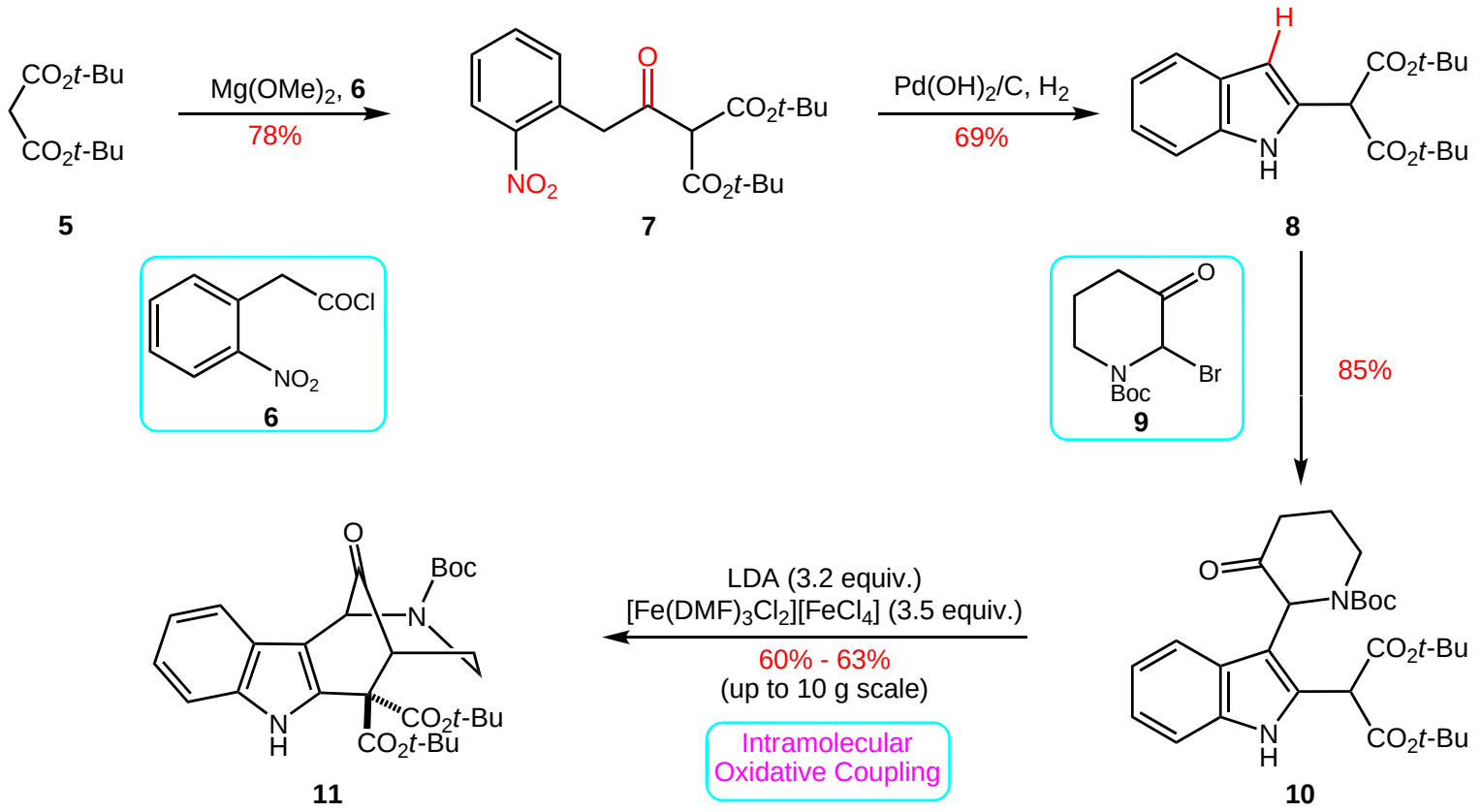
Overman's method

Retrosynthesis Analysis



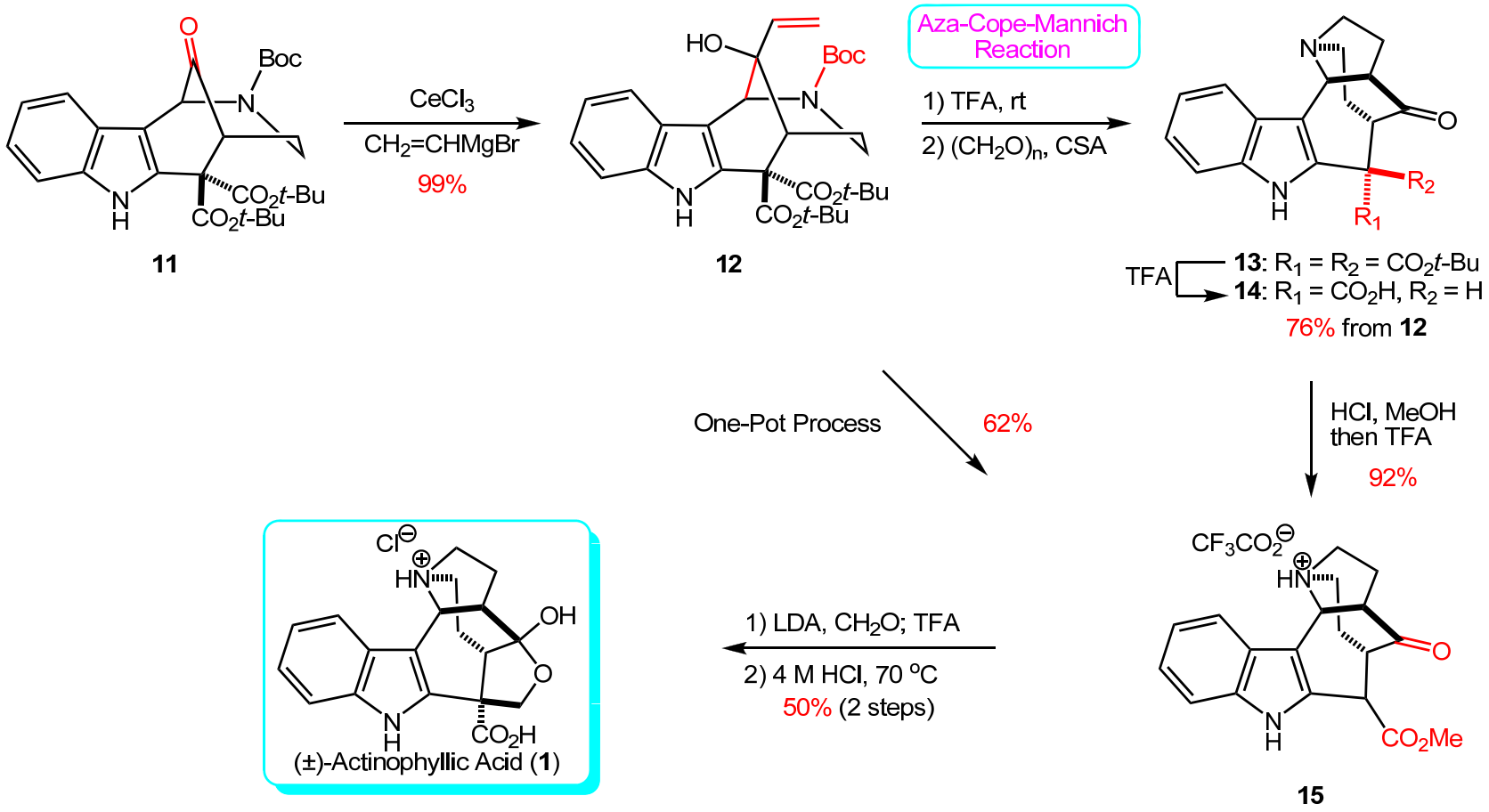
Overman, L. E. *et al. J. Am. Chem. Soc*. **2008**, *130*, 7568.

Synthesis of Tetracyclic Ketone 11



Overman, L. E. *et al. J. Am. Chem. Soc*. **2008**, *130*, 7568.

Completion of the Synthesis



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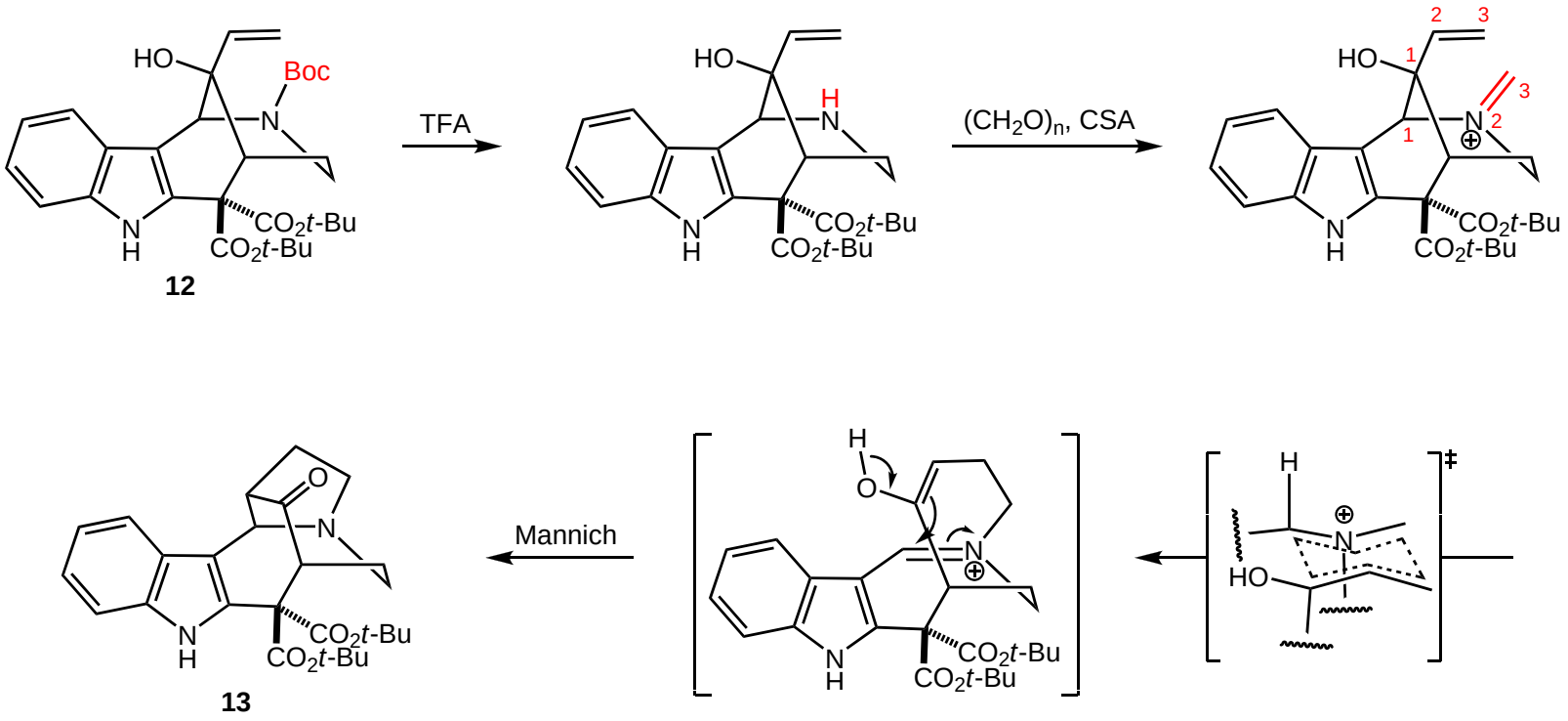
Aza-Cope-Mannich Reaction



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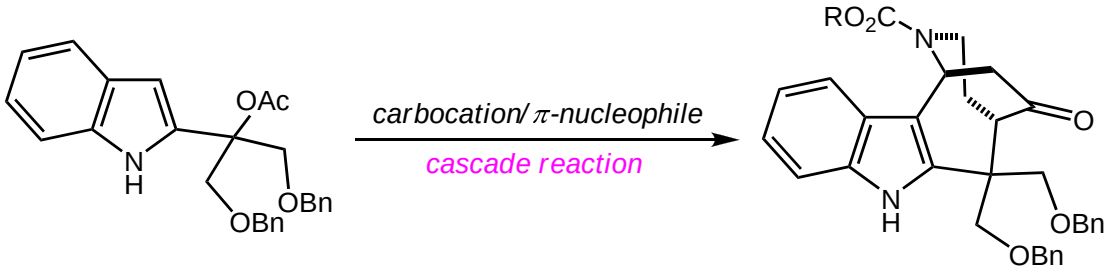
Summary

Martin's Method:



- Nine steps, 12% overall yield
- Cascade reaction of *N*-stablilized carbocations with π- nucleophile

Overman's Method:

- Seven steps, 8% overall yield, the first total synthesis
- Intramolecular oxidative coupling of ketone and malonate enolates
- Aza-Cope-Mannich rearrangement

Actinophyllic acid (**1**) is an indole alkaloid that was isolated in 2005 by Carroll and co-workers from the leaves of Alstonia actinophylla. Initially isolated on the basis of its biological activity as a potent inhibitor of carboxypeptidase U(CPU), **1** has possible therapeutic indications for the treatment of thrombotic diseases. We were first attracted to actinophyllic acid by its unique skeleton, which afforded an opportunity to develop novel chemistry. When we initiated our work toward **1**, we were aware of no other synthetic efforts in the area. However, since that time Overman and co-workers have published an elegant approach that culminated in syntheses of racemic and enantiomerically pure actinophyllic acid. Furthermore the groups of Wood, Taniguchi, and Maldonado have revealed alternate entries to this novel alkaloid.

A concise synthesis of (±)-actinophyllic acid (**1**) was achieved by a route that required only 10 chemical operations and the isolation of nine intermediates starting with readily available, known compounds. The synthesis features a novel cascade of reactions of *N*-stabilized carbocations with π-nucleophiles to create the tetracyclic core of actinophyllic acid in a single operation. Notably, some synthetic intermediates were diverted by refunctionalization and derivatization to furnish novel compounds that induce death in several cancer cell lines, whereas actinophyllic acid itself is inactive. Further optimization of the potency of these small molecules and mode-of-action studies are a focus of current efforts. The discovery of actinophyllic acid analogs that exhibit potentially promising anticancer activity validates the importance of developing alternative entries to complex natural products as a critical strategy for identifying compounds that would not otherwise be accessible for biological screening and evaluation.