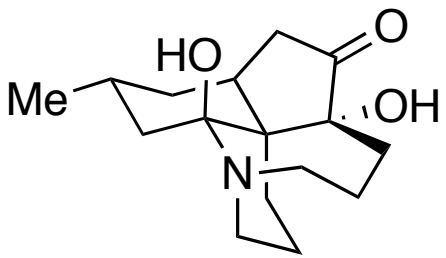
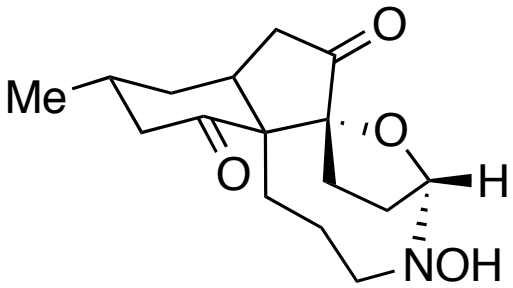
Total Synthesis of (±)-Alopecuridine and Its Biomimetic Transformation into (±)-Sieboldine A

Zhang, X.-M.; Tu, Y.-Q.; Zhang, F.-M.; Shao, H.; Meng, X . *Angew. Chem. Int. Ed*. **2011**, 50, ASAP



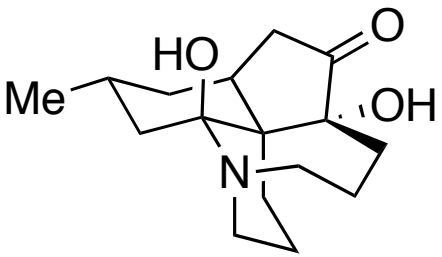
alopecuridine



sieboldine A

Eric E. Buck
Current Literature
April 9, 2011

Isolation and Background

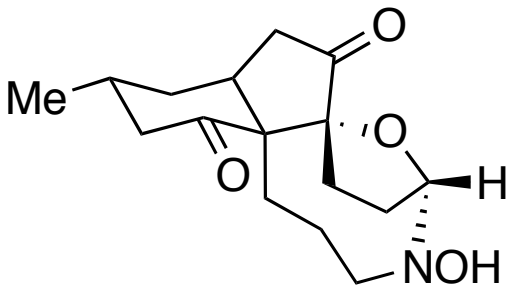


alopecuridine

- Alopecuridine was isolated from *L. alopecuroides* (foxtail club moss).
- There are 38 species in the genus *Lycopodiella*, which are found all over the world.
- *There is no known biological data associated with alopecuridine.*

Ayer, W. A.; Altenkirk, B.; Valverde-Lopez, S.; Douglas, B.; Raffauf, R. F.; Wiesbach, J. A. *Can. J. Chem.* **1968**, 46, 15-20
Ayer, W. A.; Altenkirk, B.; Fukazawa, Y. *Tetrahedron* **1974**, 30, 4213-4214

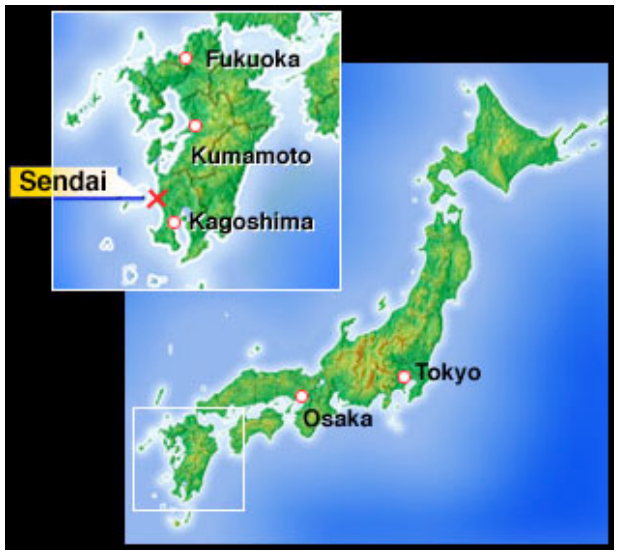
Isolation and Background



sieboldine A

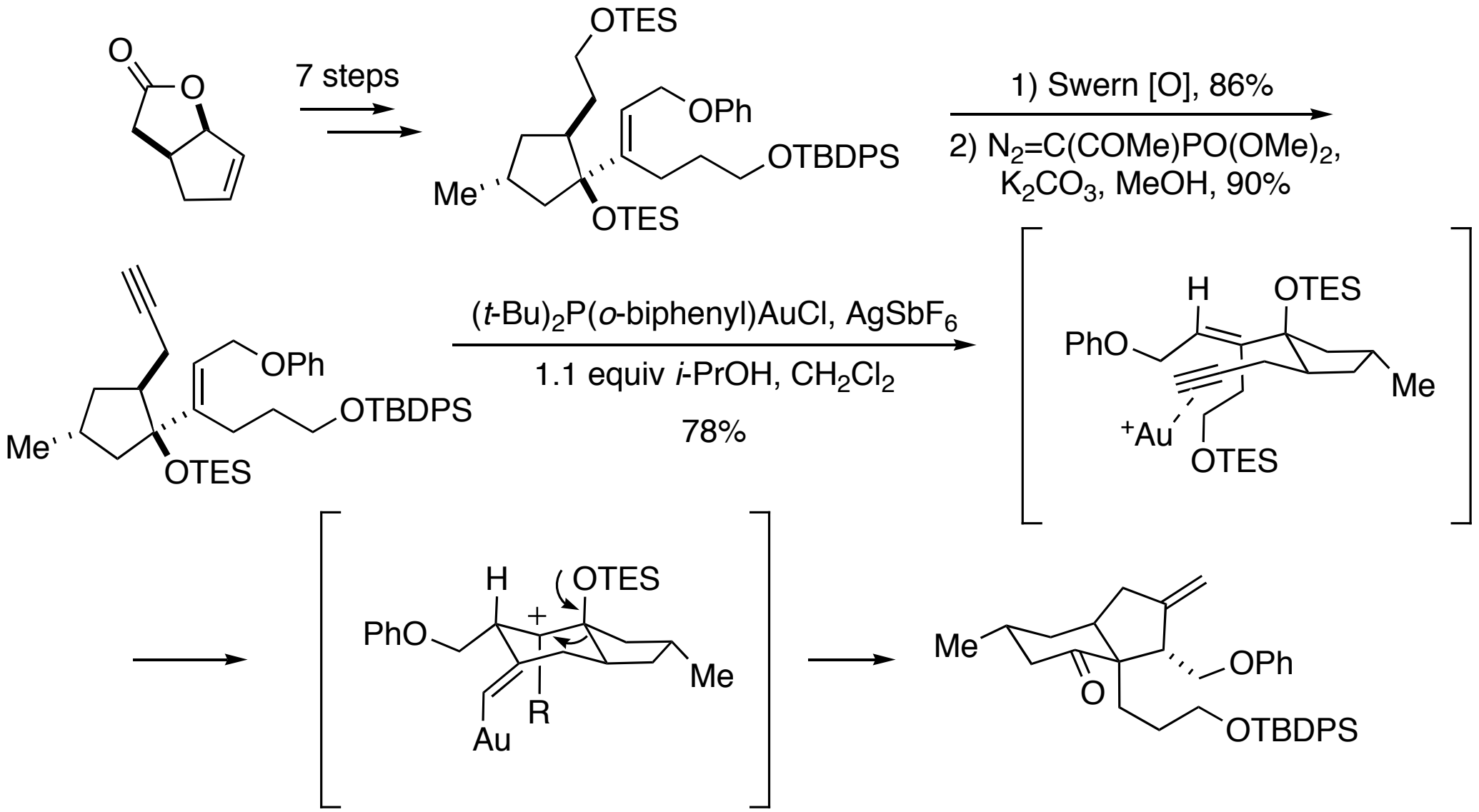
- Sieboldine A was isolated from the club moss *L. sieboldii* collected in Kagoshima.

- Inhibits acetylcholinesterase (IC_{50} = 2.0 μM) and is cytotoxic against murine lymphoma L1210 cells (IC_{50} = 5.1 μg/mL. (Below: *Lycopodium Cernuum*)



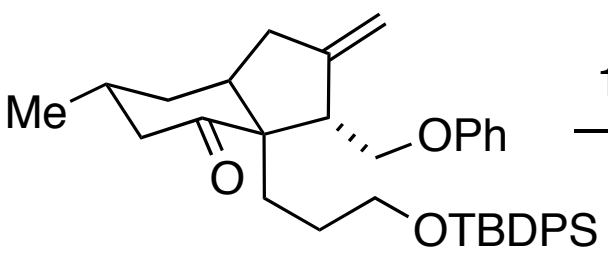
Hirasawa, Y.; Morita, H.; Shiro, M.; Kobayashi, J. *Org. Lett.* **2003**, 5, 3991-3993

Overman's Synthesis of (+)-Sieboldine A



Canham, S. M.; France, D. F.; Overman, L. E. *J. Am. Chem. Soc.* **2010**, 132, 7876-7877

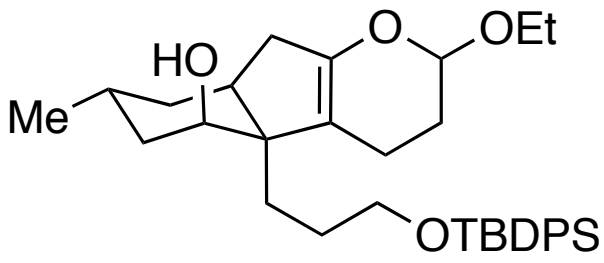
Overman's Synthesis of (+)-Sieboldine A



1) Ozonolysis; Me_2S; DBU 86%

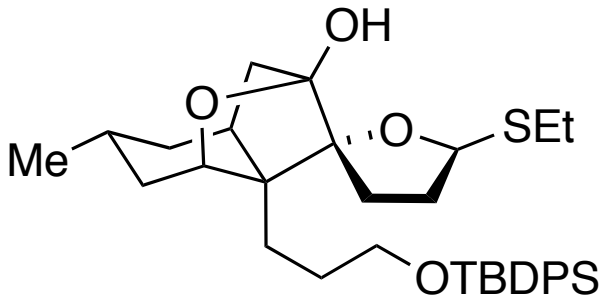
2) 10 mol% $Eu(fod)_3$, ethyl vinyl ether, 86%

3) DIBAL-H

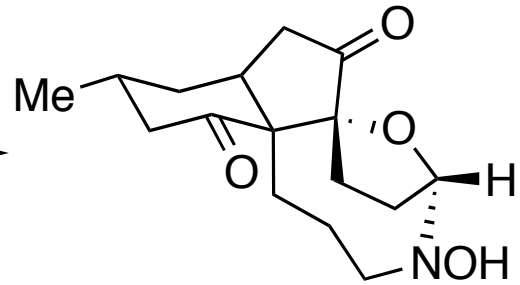


DMDO; BF_3•OEt_2, EtSH

53%



6 steps

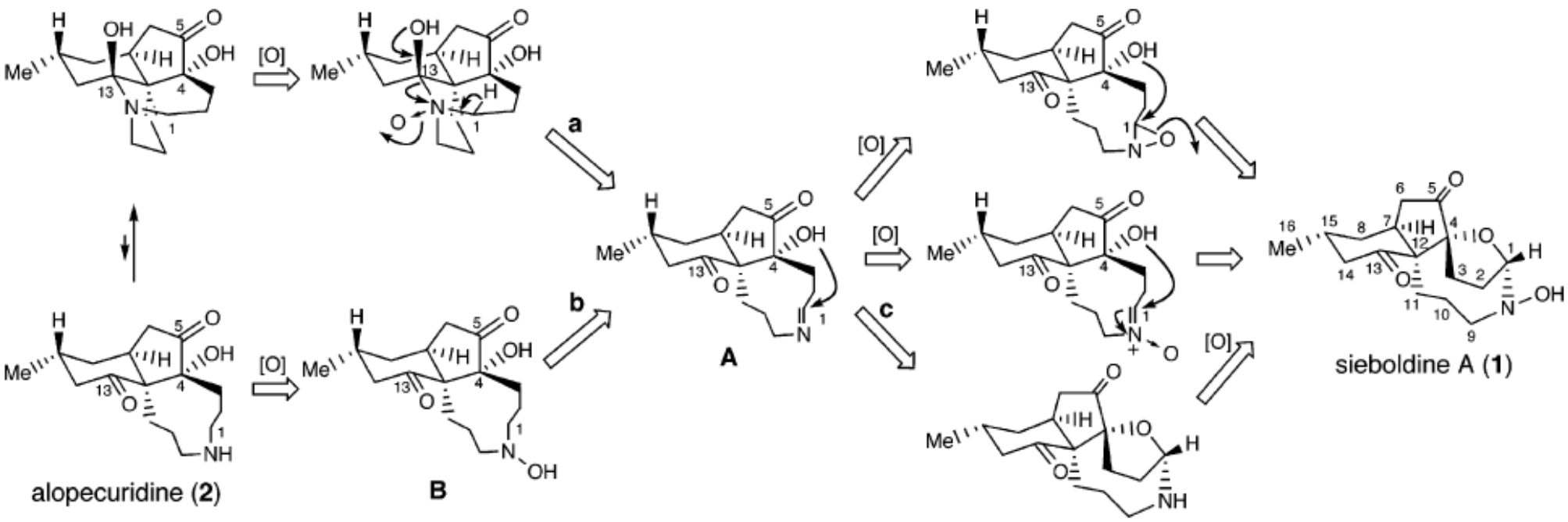


sieboldine A

20 steps, 5.5 %

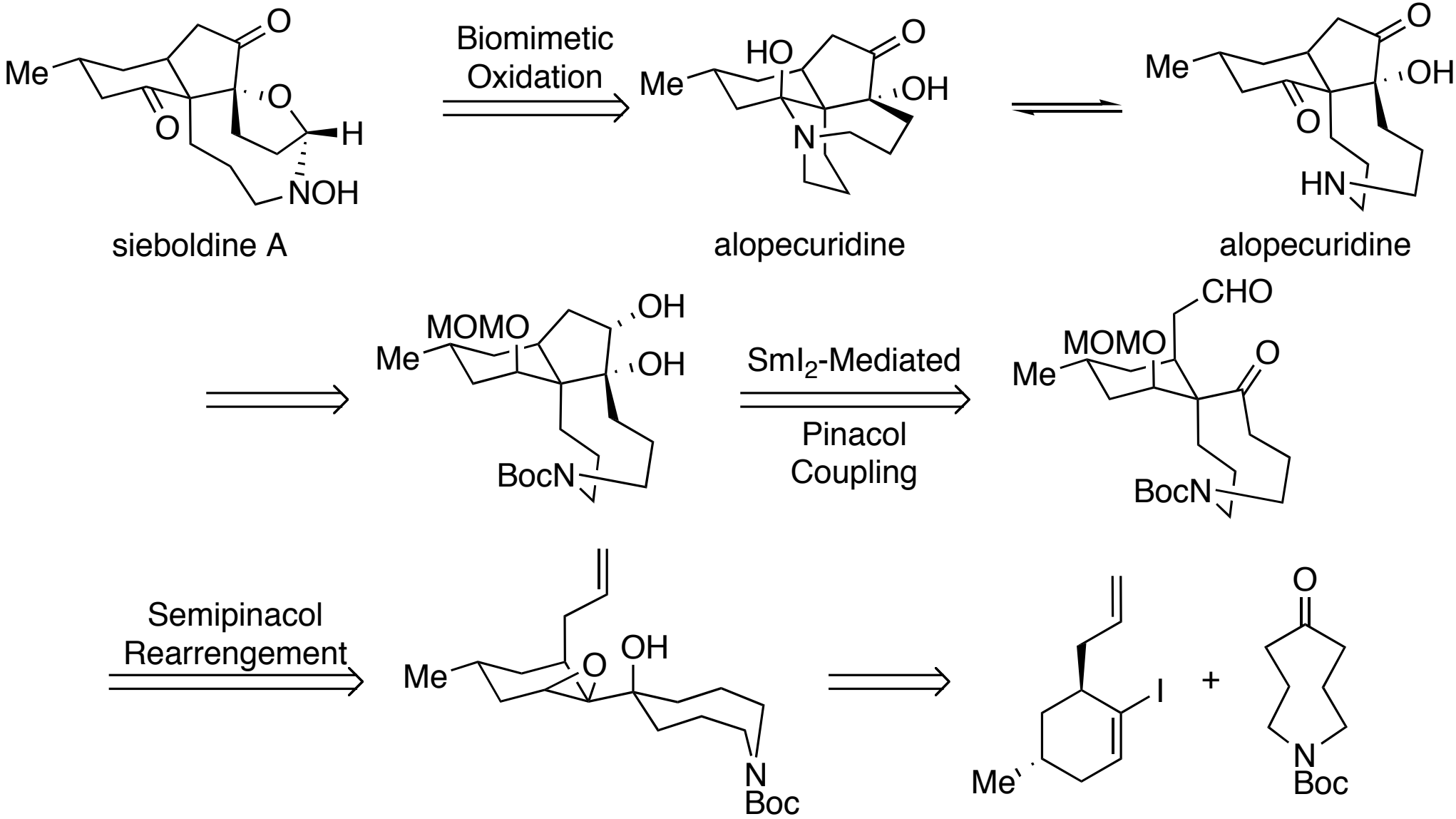
Canham, S. M.; France, D. F.; Overman, L. E. *J. Am. Chem. Soc.* **2010**, 132, 7876-7877

Kobayashi's Proposed Biomimetic Pathway for Sieboldine A



Hirasawa, Y.; Morita, H.; Shiro, M.; Kobayashi, J. *Org. Lett.* **2003**, 5, 3991-3993

Title Paper: Retrosynthesis



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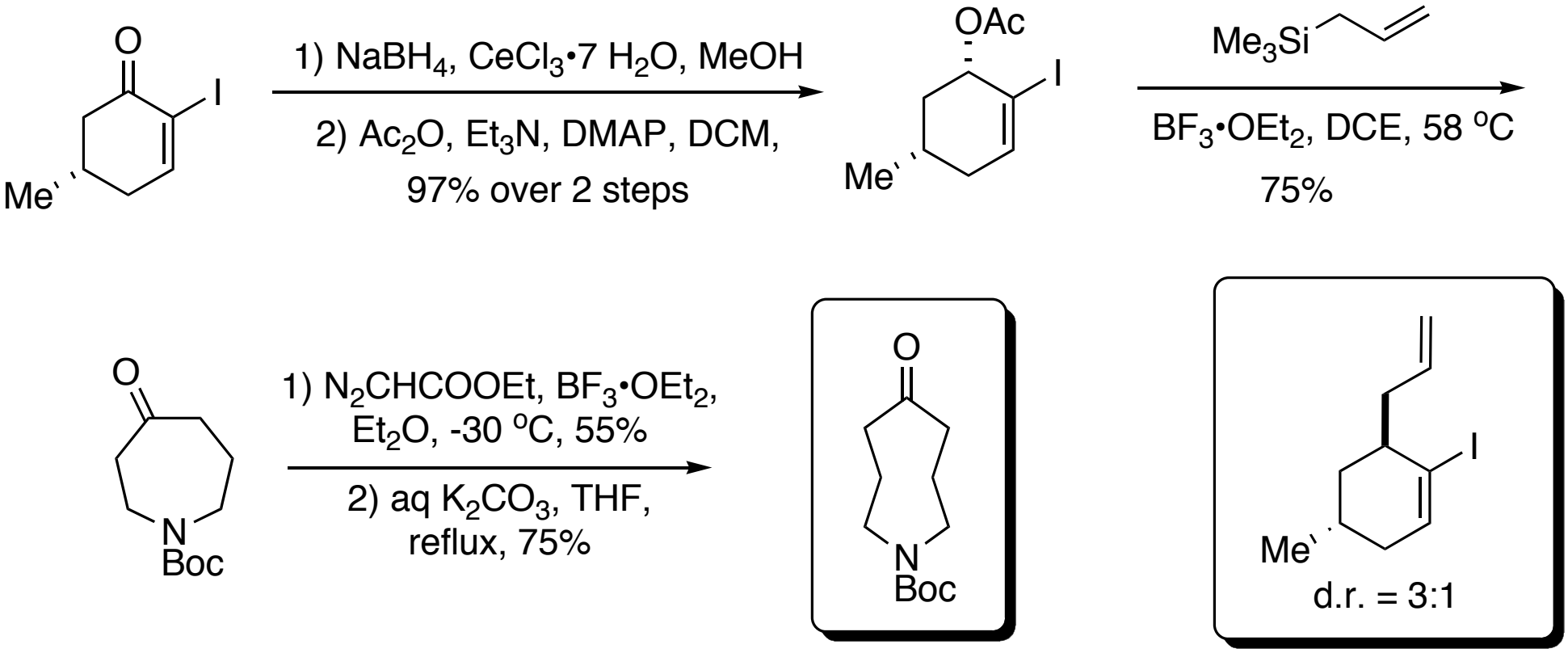
Title Paper: Synthesis of Intermediates



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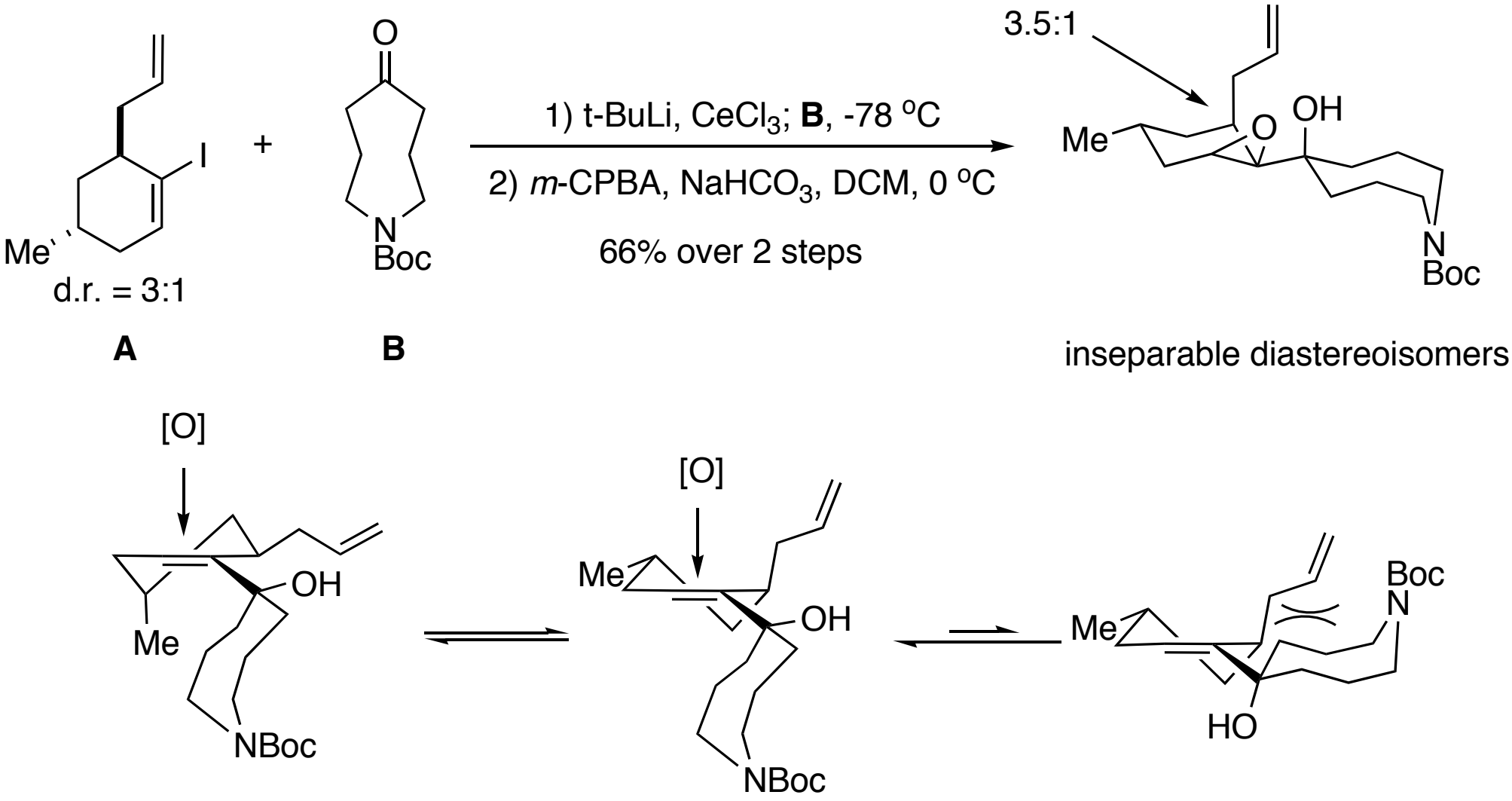
Title Paper: Addition and Epoxidation



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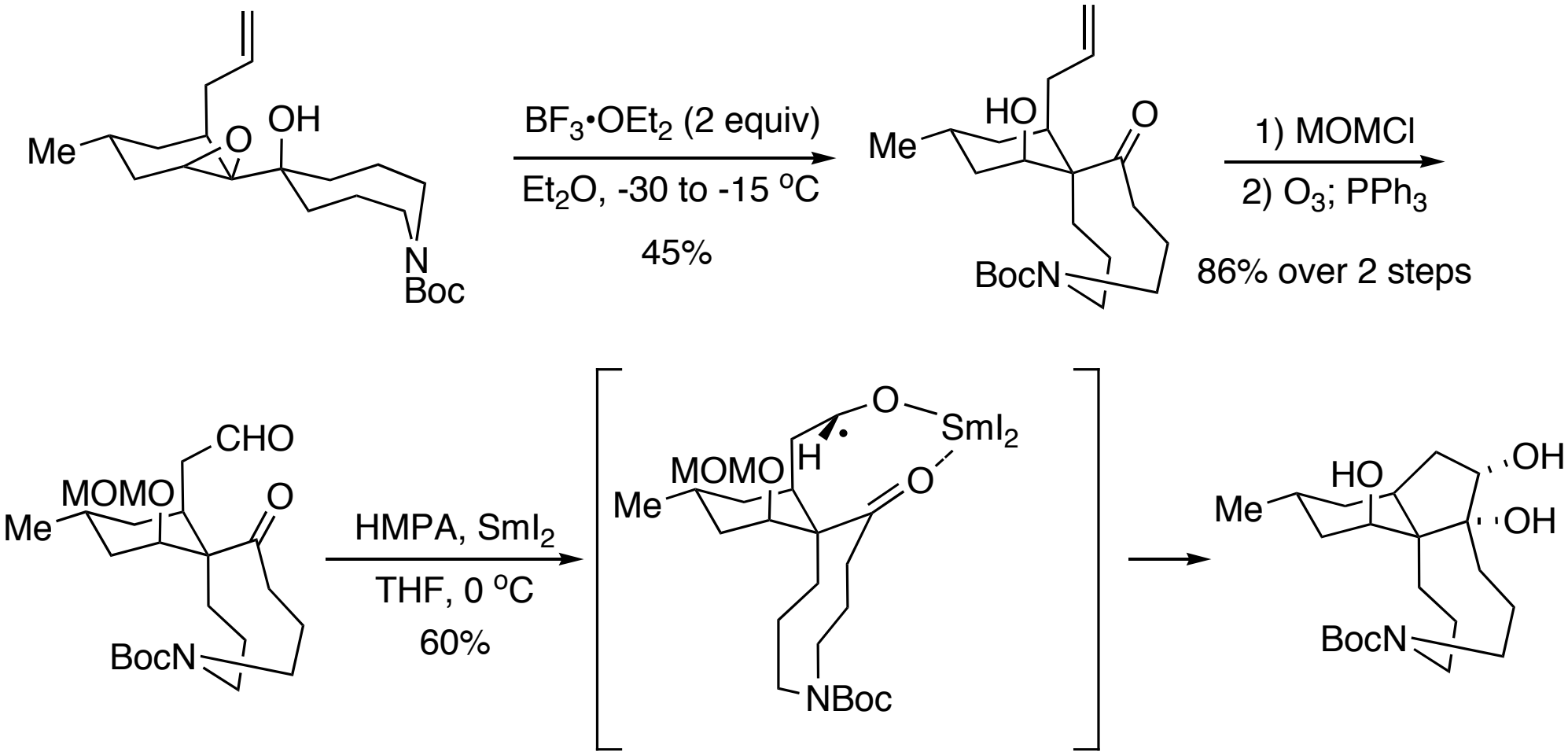
Title Paper: Semipinacol and Pinacol Rearrangement



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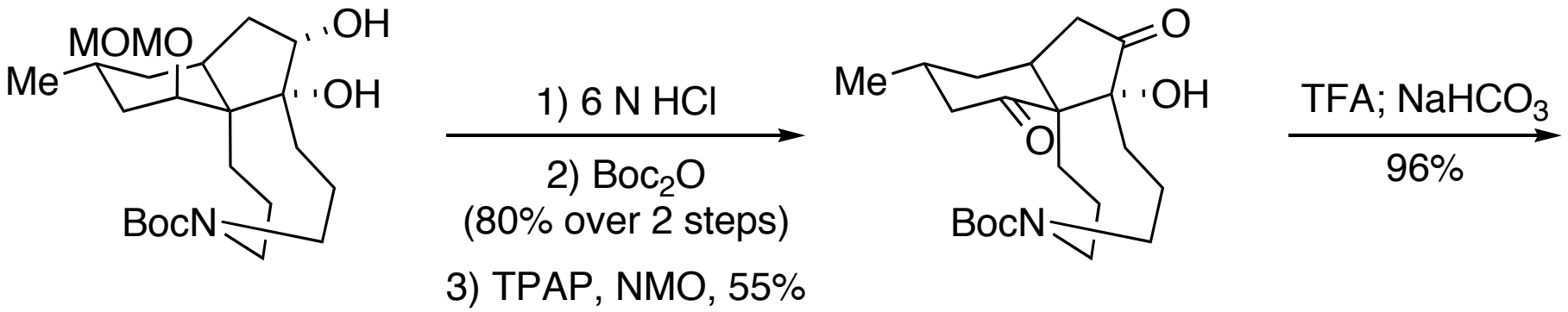
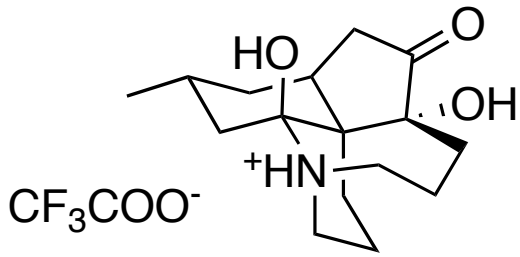
Title Paper: End Game Synthesis of Alopecuridine





alopecuridine•TFA

13 steps, 10.5% yield

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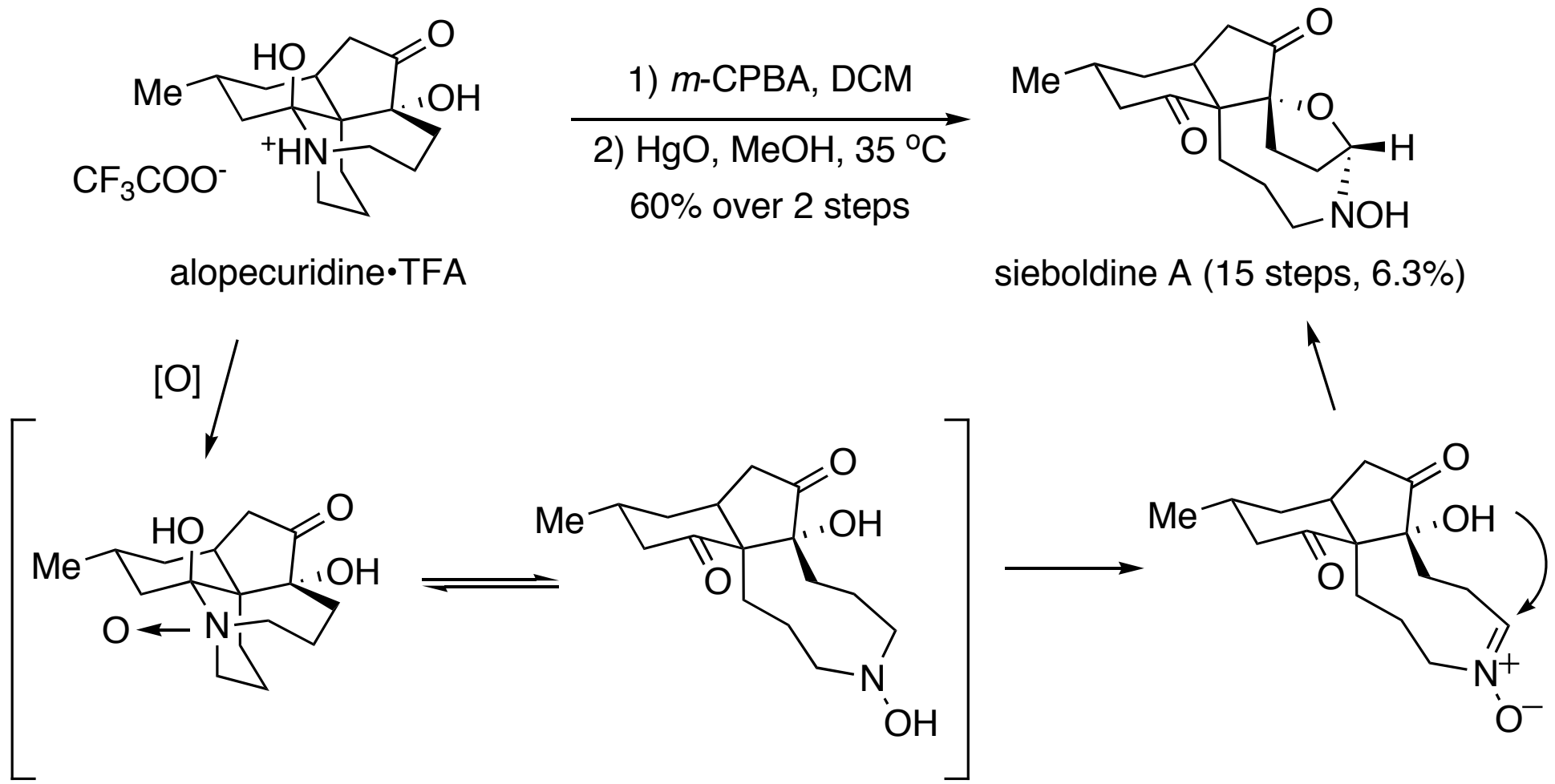
Title Paper: Biomimetic Transformation of Alopecuridine



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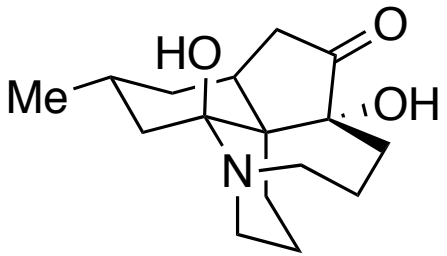
Summary

• Overman completed the first synthesis of (+)-sieboldine A in 20 steps (5.5% overall yield) with a key Au(I)-catalyzed cyclization and subsequent pinacol rearrangement.

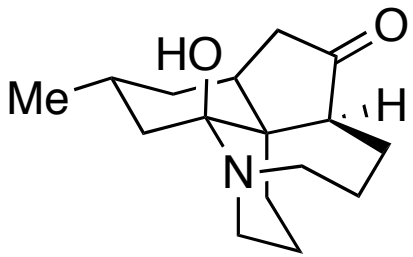
• The Tu group finished the first synthesis of (±)-alopecuridine in 13 steps (10.5% overall yield) utilizing a key semipinacol rearrangement to install the 9-membered ring and a pinacol rearrangement to install the 5-membered ring.

• (±)-Sieboldine A was completed in 2 additional steps from (±)-alopecuridine via an oxidative rearrangement that also validated Kobayashi's proposed biosynthesis.

• A natural sample of alopecuridine is no longer available and no known NMR spectroscopic data has been reported (crystal structure of acylated alopecuridine is reported). The author's NMR data is similar to fawcettimine hydrobromide.



alopecuridine



fawcettimine