Nine-Step Enantioselective Total Synthesis of (-)-Vincorine

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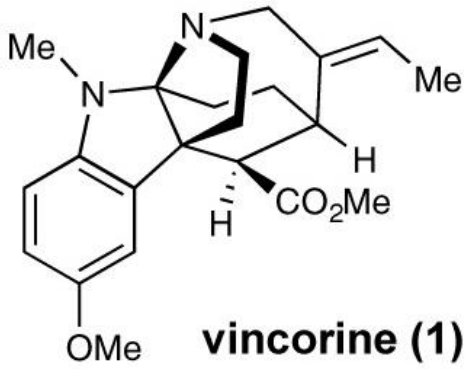


vincorine (1)

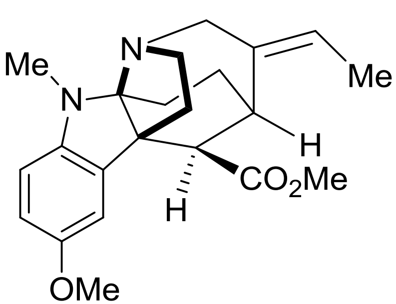
Joseph Salamoun

Wipf Group

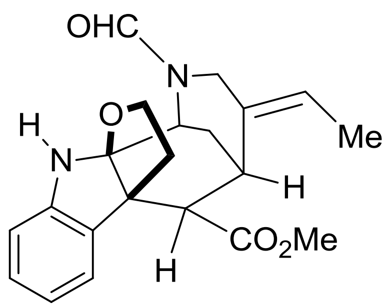
Current Lit. 05/11/13

Vincorine

- Isolated from *Alstonia vitiensis* in 1975.
- Indole alkaloids are of interest for cancer research and drug discovery.
- Belongs to the akuammiline alkaloid family.

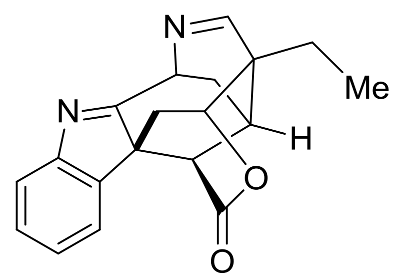


Vincorine



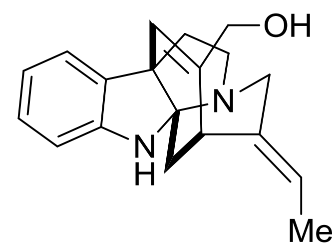
Aspidophylline A

See Liming's CL 06/18/11 for total synthesis.



Scholarisine A

See Filip's CL 02/18/12 for total synthesis.

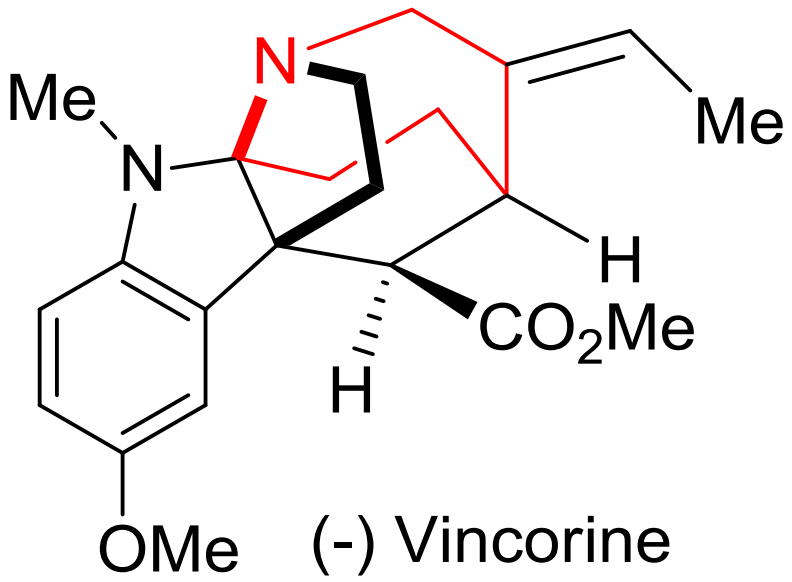


(+)-Minfiensine

See Kara's CL 11/12/09 for total synthesis.

Mamatas-Kalamaras, S.; Sevenet, T.; Thal, C.; Potier, P. Phytochemistry, **1975**, *14*, 1637.

The Challenge



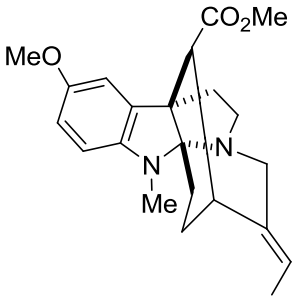
(-) Vincorine

- Contains a pentacyclic caged structure.
- Installation of a strained seven-membered azepanyl ring system (red).
- Enantioselective synthesis.

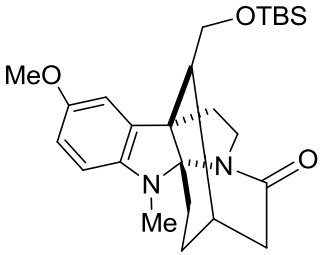
Previous Syntheses

- Total synthesis of Vincorine completed by:
  - Qin group, 31 steps, racemic, 1% overall yield
    - J. Am. Chem. Soc. 2009, 131, 6013-6020
  - Ma group, 18 steps, 5% overall yield
    - J. Am. Chem. Soc. 2012, 134, 9126-9129
  - MacMillan group, 9 steps, 9% overall yield
    - Title Paper, 2013

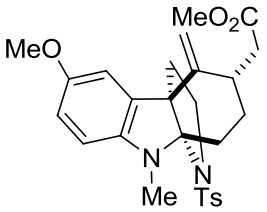
Key Steps from Qin Group

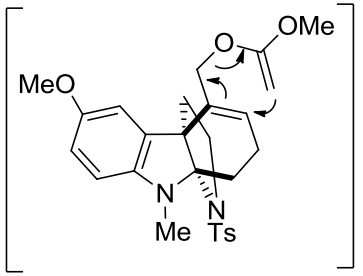


(±)-Vincorine

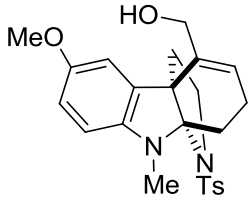


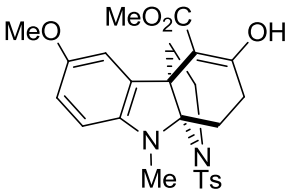
Condensation of carboxylic acid and amine with Mukaiyama's reagent to form lactam.





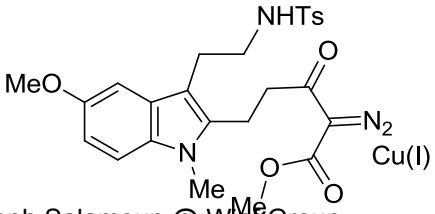
Johnson-Claisen Rearrangement





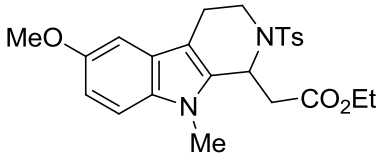
1:5 ratio of ketone:enol isomers

Cu(I) catalyzed cyclization



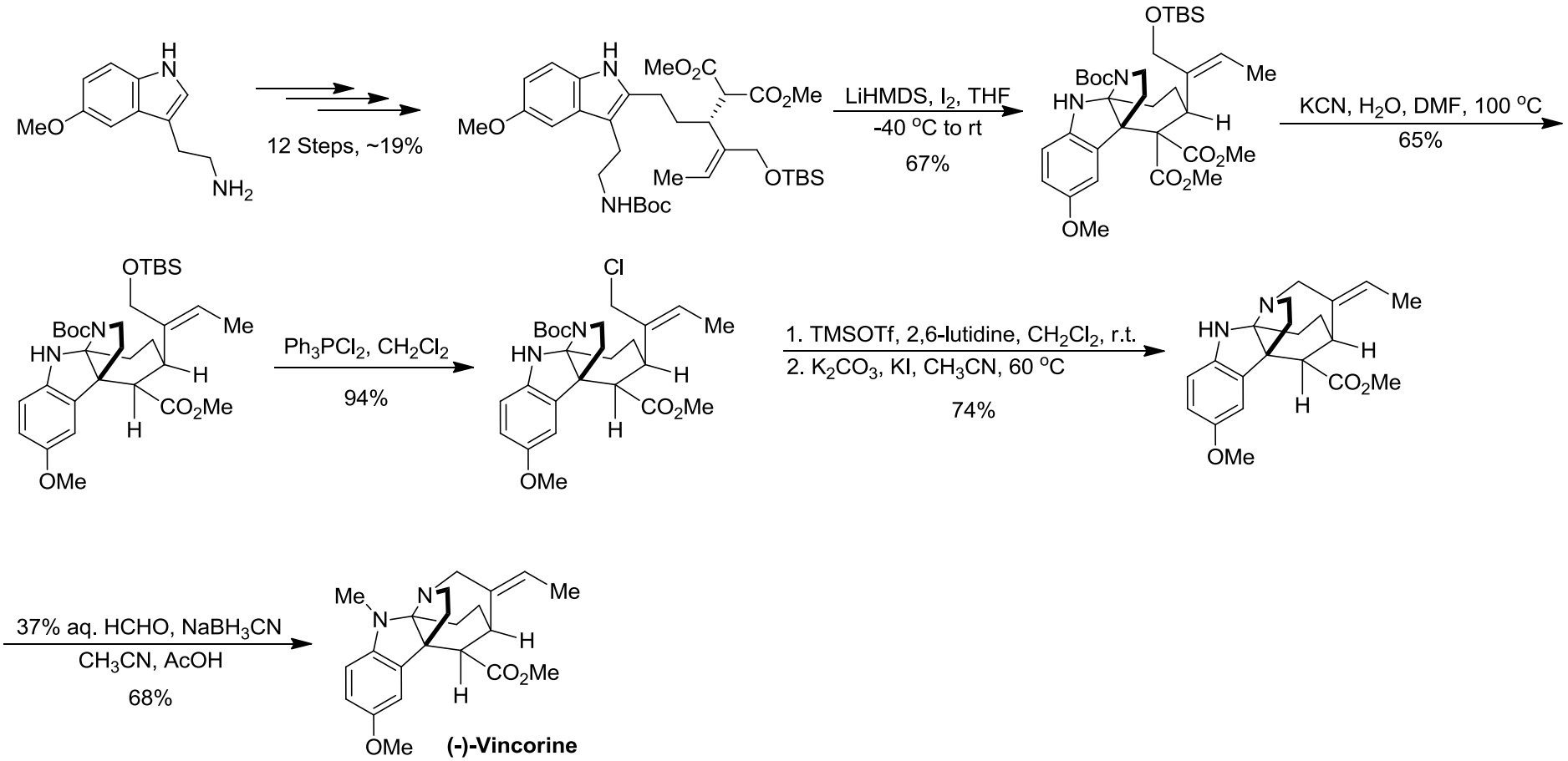
Formation of keto-ester with Meldrum's Acid

Regitz Diazo Transfer



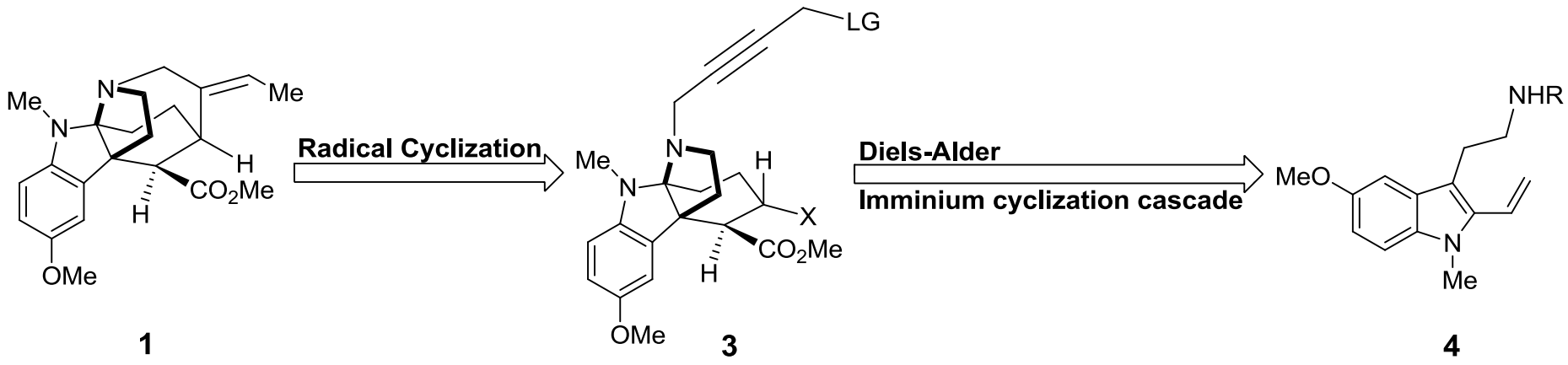
Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009,** 131, 6013.

Key Steps from Ma Group



Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, 134, 9126.

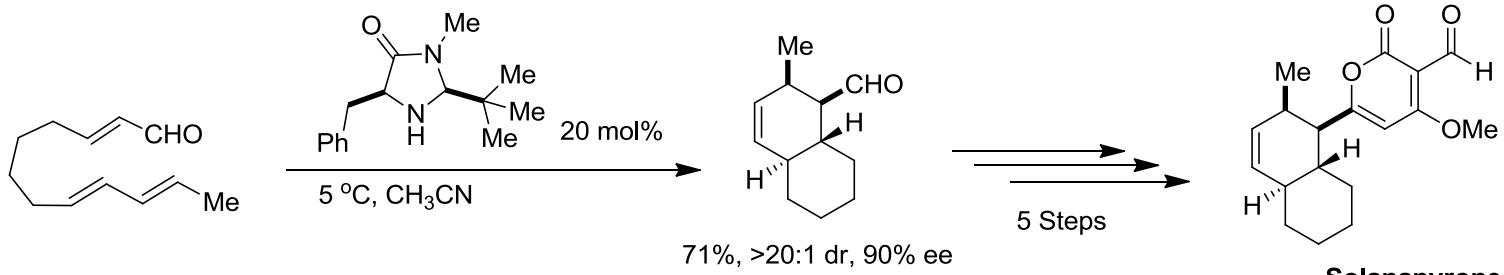
MacMillan's Strategy



dx.doi.org/10.1021/ja402953s

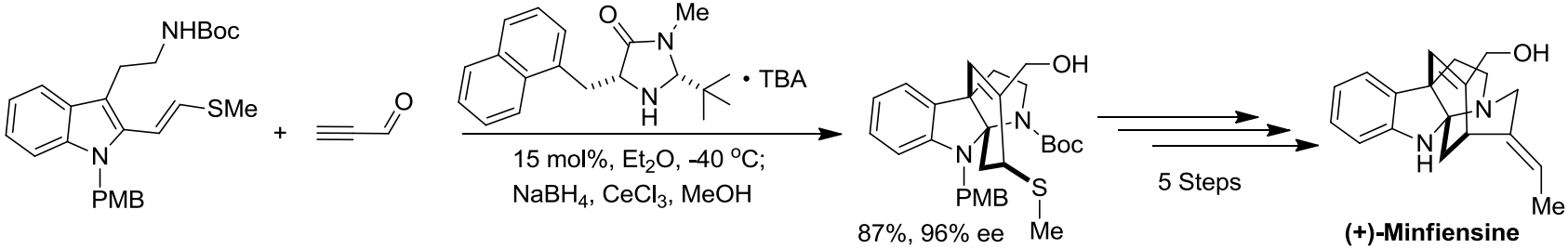
MacMillan's Earlier Methodology

Total Synthesis of Solanapyrone D, 2005 (9 steps)



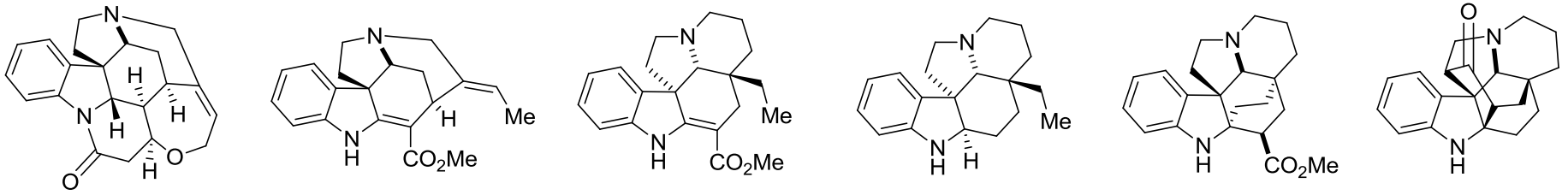
Wilson, R. M.; Jen, W.S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, 127, 11616.

Total Synthesis of Minfiensine, 2009 (9 steps, 21% overall yield)



Jones, S. B.; Simmons, B; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, 131, 13606.

Total Synthesis of Six Natural Products, 2011



(-)-Strychnine, 12 steps, 6.4% overall yield.

(-)-Akuammicine, 10 steps, 10% overall yield.

(+)-Vincadifformine, 11 steps,8.9% overall yield.

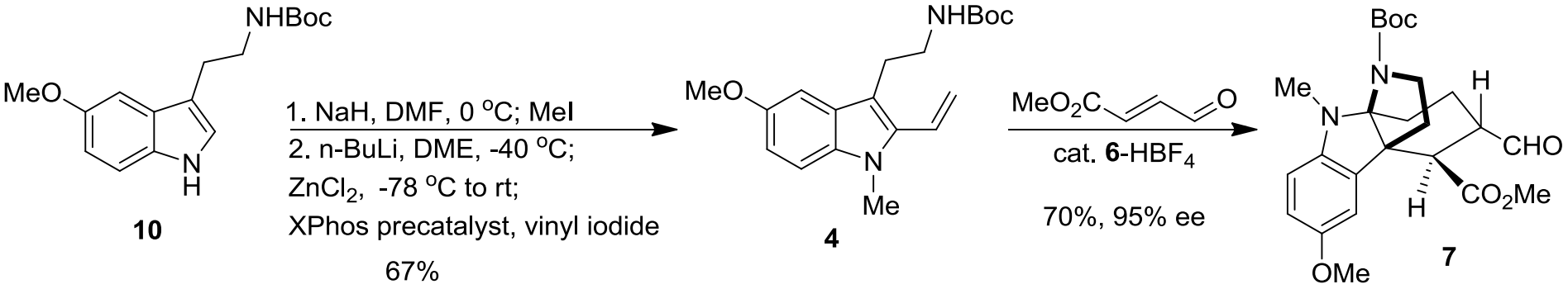
(+)-Aspidospermidine, 9 steps, 24% overall yield.

(-)-Kopsinine, 9 steps, 14% overall yield.

(-)-Kopsanone, 11 steps, 10% overall yield

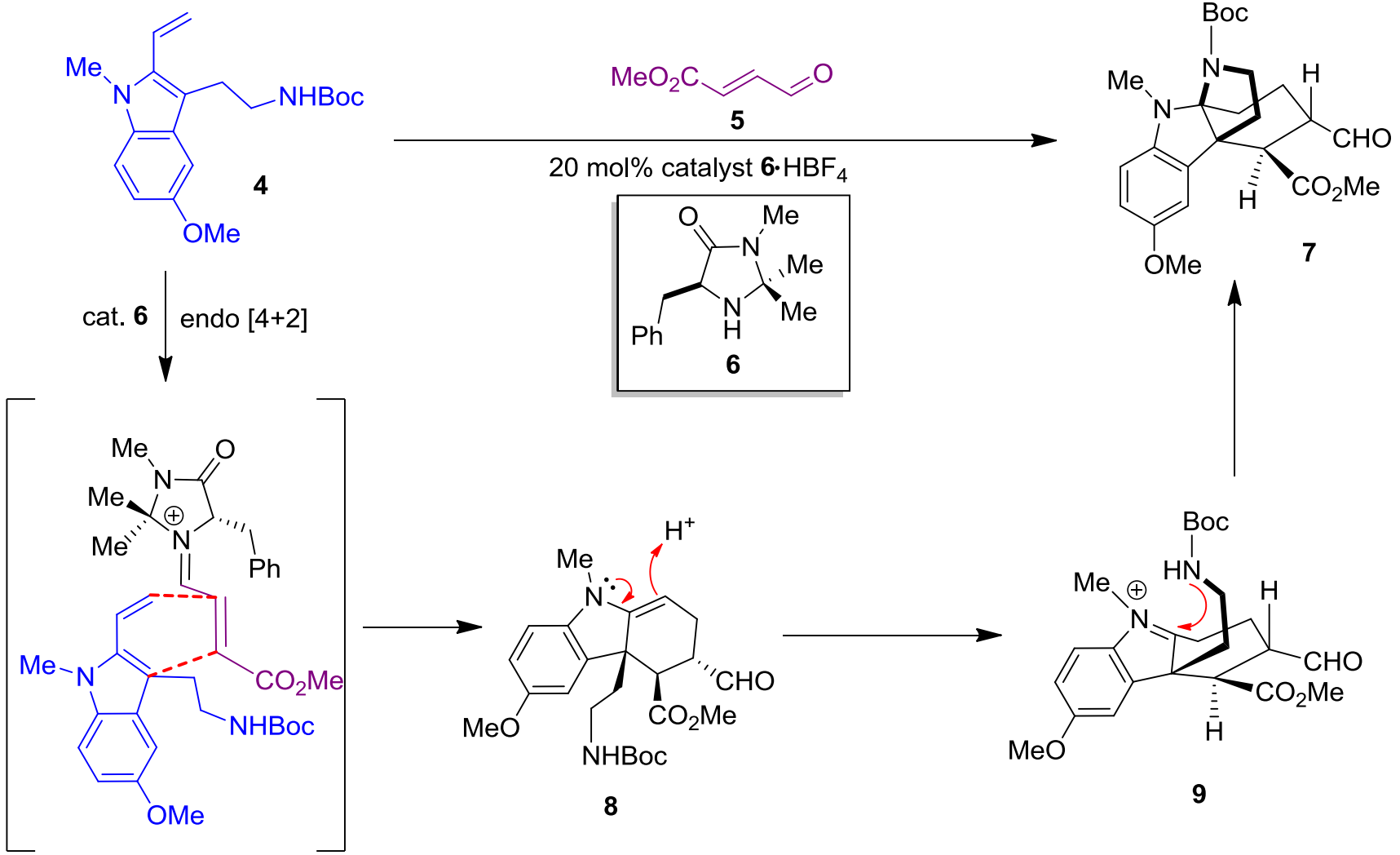
Jones, S. B.; Simmons, B; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, 475, 183.

MacMillan's Synthesis



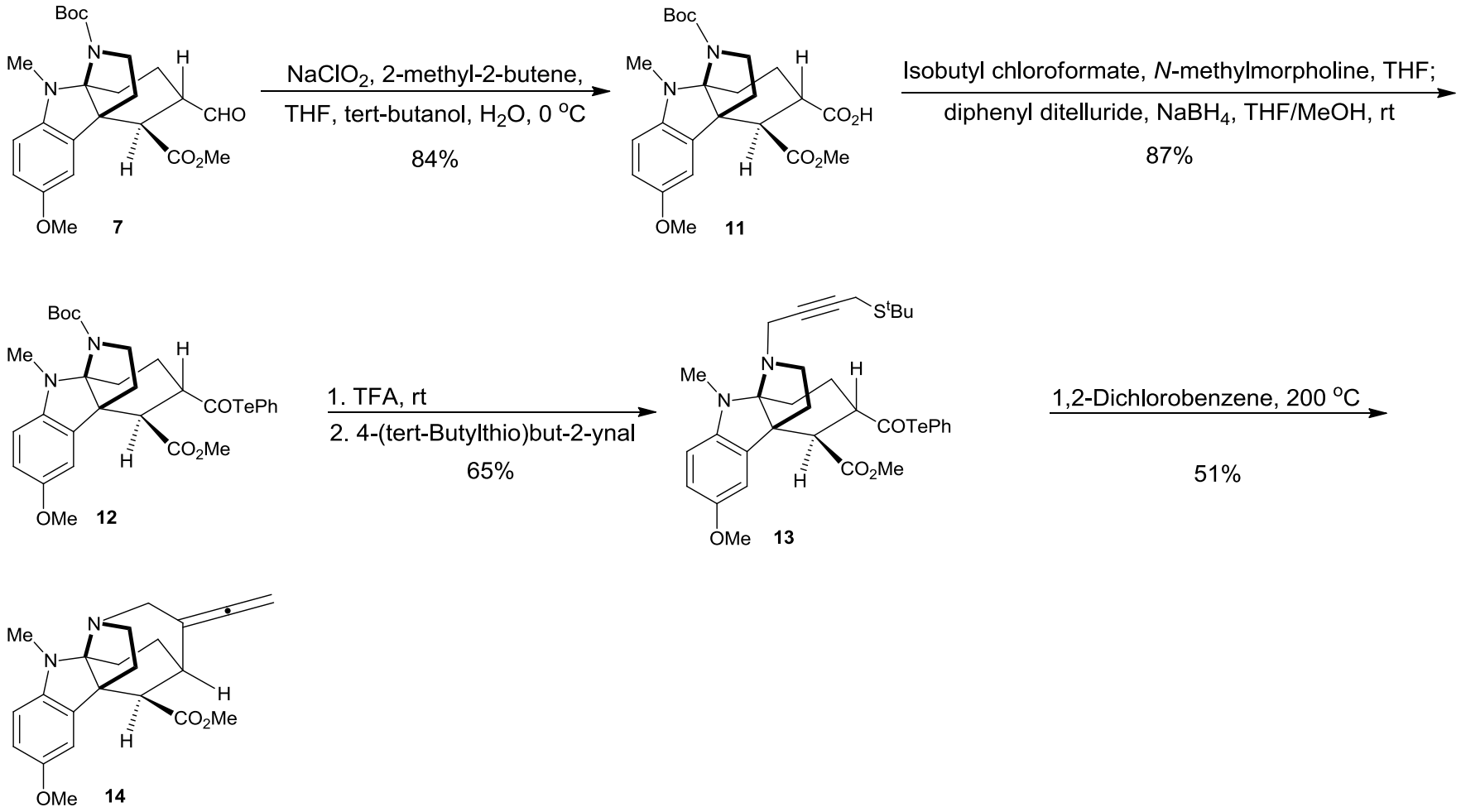
dx.doi.org/10.1021/ja402953s 5/3/2013

Enantioselective Organocatalytic Cascade



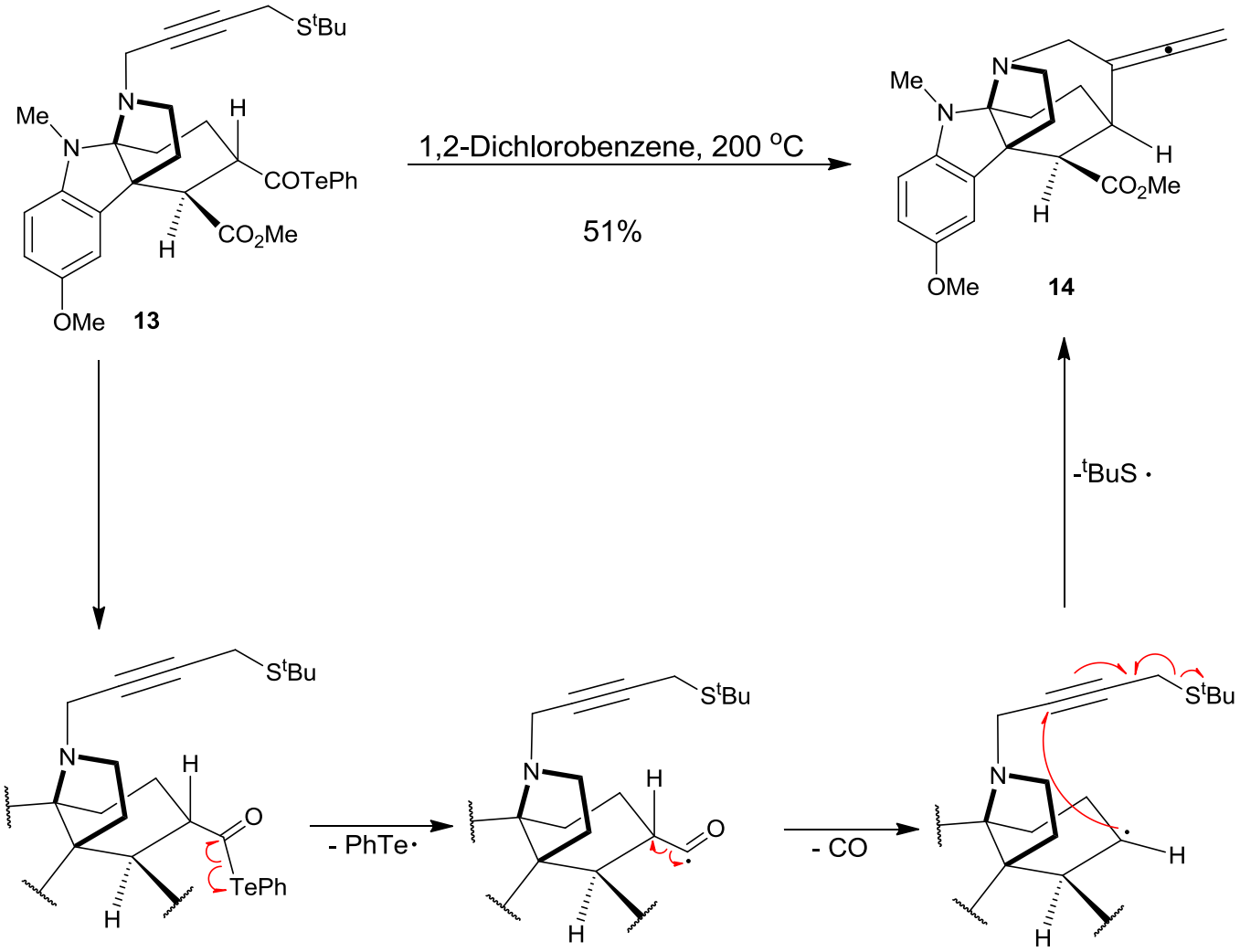
dx.doi.org/10.1021/ja402963s

MacMillan's Synthesis Cont'd

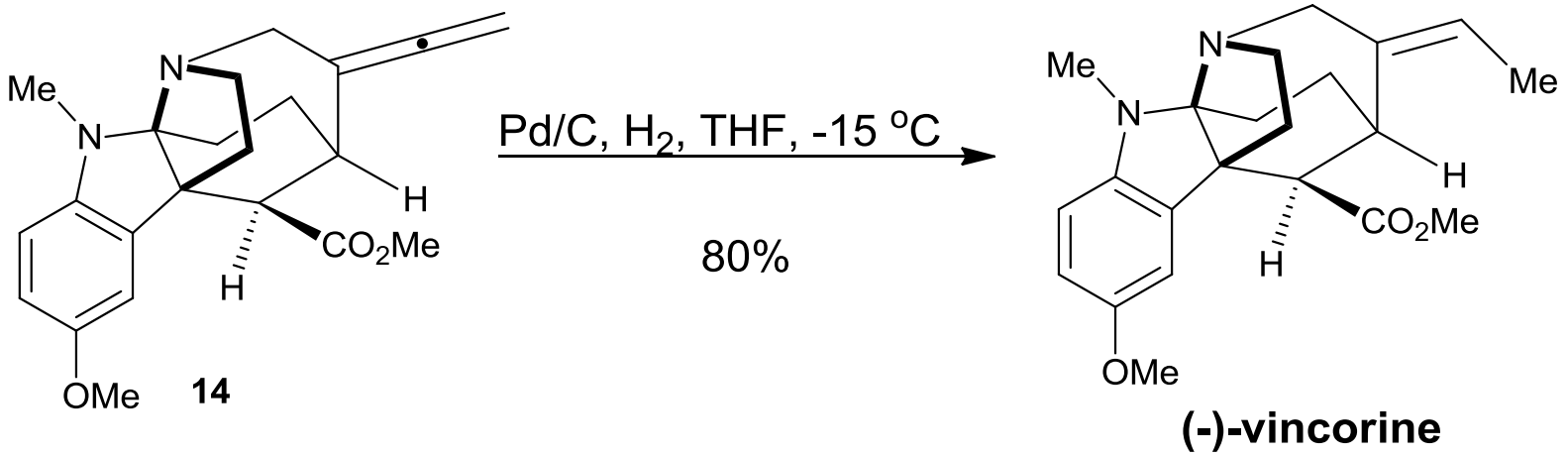


dx.doi.org/10.1021/ja402953s

Mechanism of Single-Electron Mediated Cyclization



MacMillan's Synthesis Cont'd



dx.doi.org/10.1021/ja402953s
5/3/2013

Conclusions

- 9 step, 9% overall yield, enantioselective synthesis.
- Stereoselective organocatalyzed Diels-Alder, iminium cyclization cascade sequence builds the tetracyclic core structure in one step.
- Seven member azepanyl ring constructed by single electron-mediated cyclization.