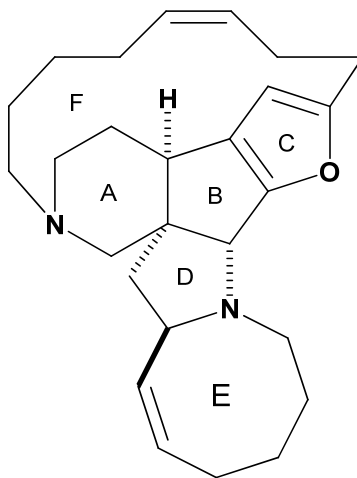


Burke Group Literature Seminar

May 30, 2008

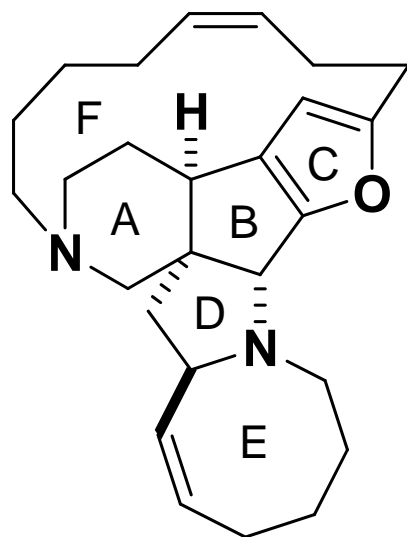
6pm, RAL 433

Synthesis of Nakadomarin A



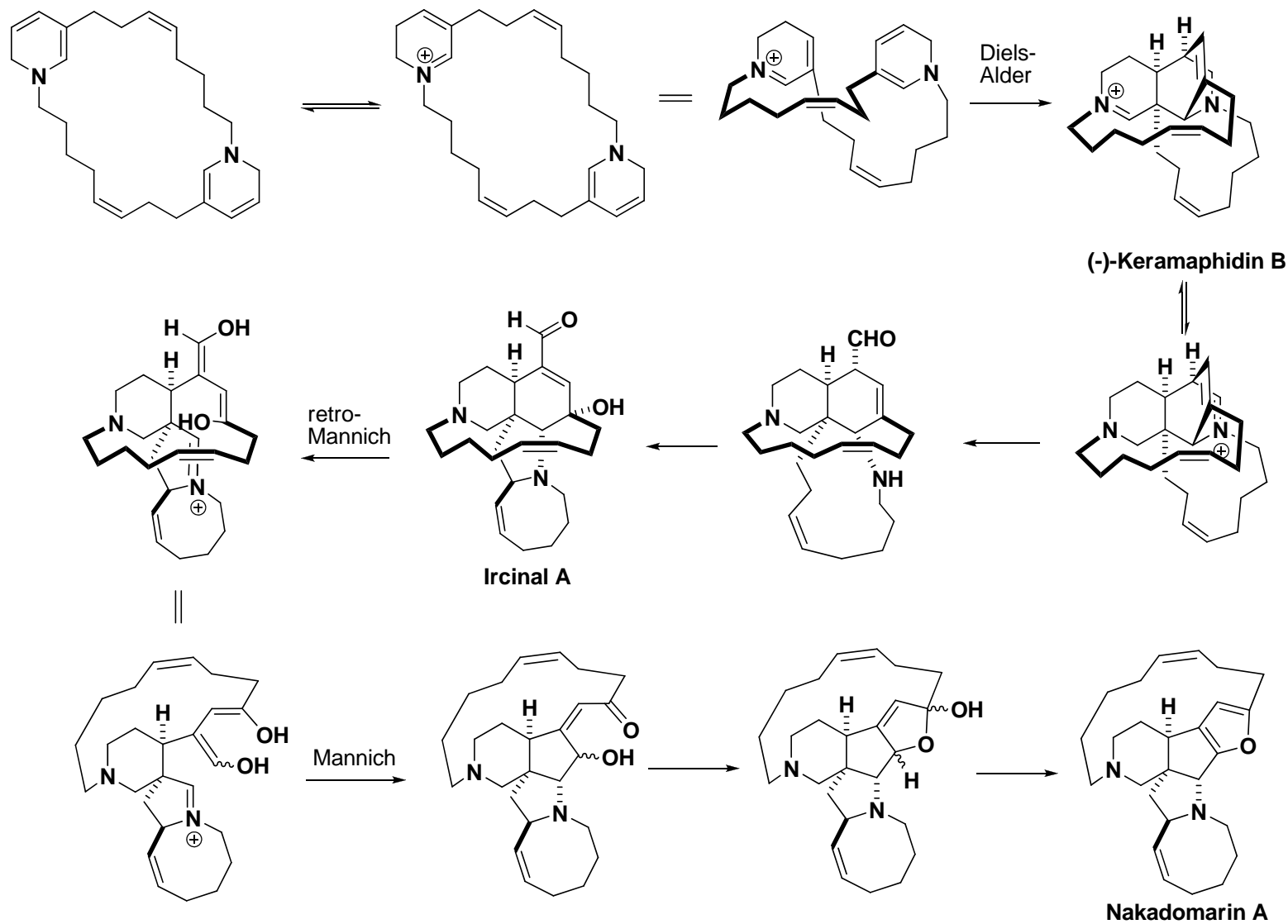
1. (a) Nagata, T.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8345. (b) Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484. (KCG, LMJ, SGB, BW)
2. Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020. (DSP, DS, BEU)
3. (a) Young, I.S.; Williams, J.L.; Kerr, M.A. *Org. Lett.* **2005**, *7*, 953. (b) Young, I.S.; Kerr, M.A. *J. Am. Chem. Soc.* **2007**, *129*, 1465. (TMA, ID, HCT, SJL)
4. (a) Nilson, M.G.; Funk, R.L. *Org. Lett.* **2006**, *8*, 3833. (b) Deng, H.; Yang, X.; Tong, Z.; Li, Z.; Zhai, H. *Org. Lett.* **2008**, *10*, 1791. (c) Ahrendt, K.A.; Williams, R.M. *Org. Lett.* **2004**, *6*, 4539. (DMK, EPG, PW, EMW)

Nakadomarin A



- Cytotoxicity against murine lymphoma L1210 cells (IC_{50} 1.3 $\mu\text{g}/\text{mL}$)
- Inhibitory activity against cyclin dependent kinase 4 (IC_{50} 9.9 $\mu\text{g}/\text{mL}$)
- Antifungal activity against *Trichophyton mentagrophytes* (MIC 23 $\mu\text{g}/\text{mL}$)
- Antibiotic activity against Gram-positive bacterium *Corynebacterium xerosis* (MIC 11 $\mu\text{g}/\text{mL}$)

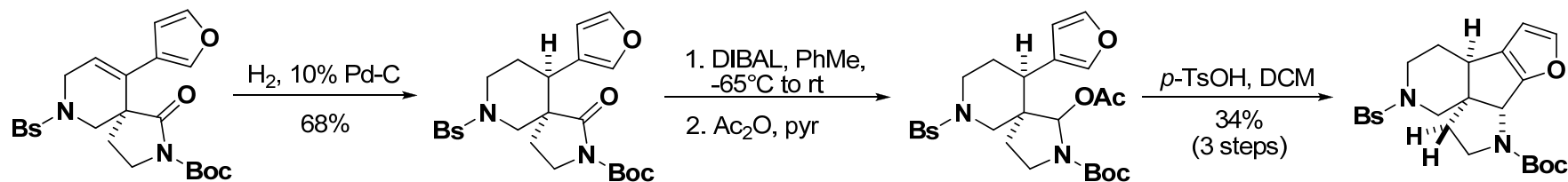
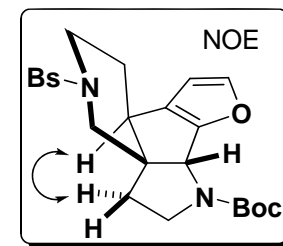
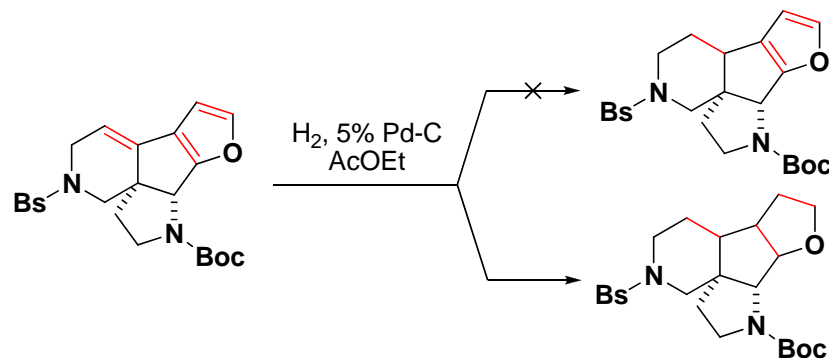
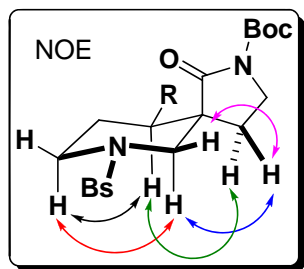
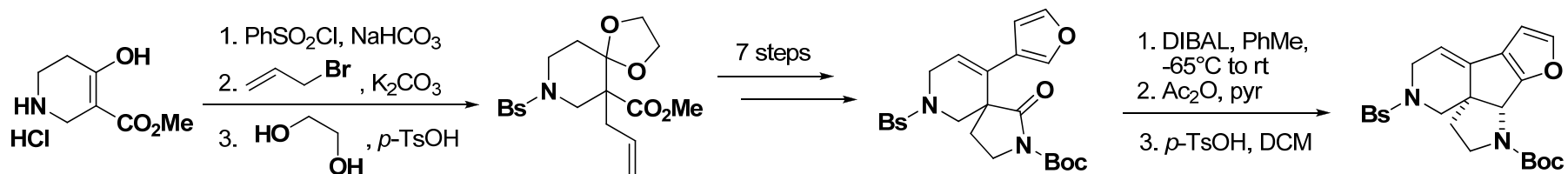
Proposed Biosynthesis



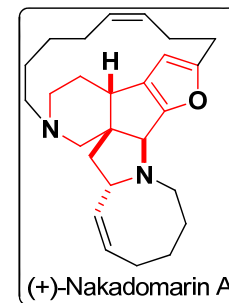
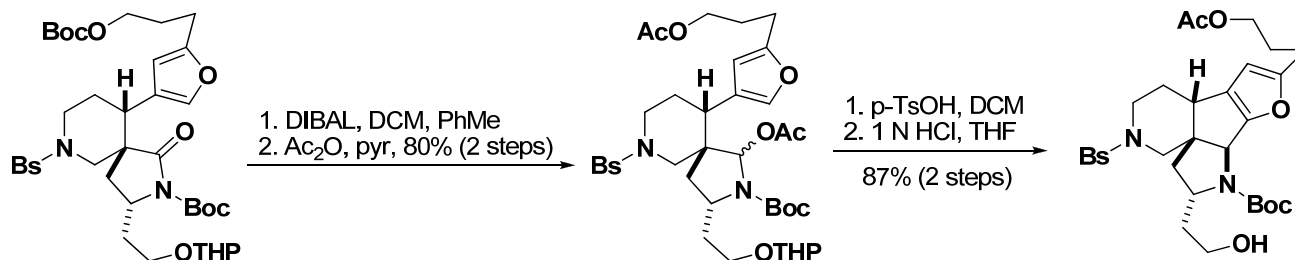
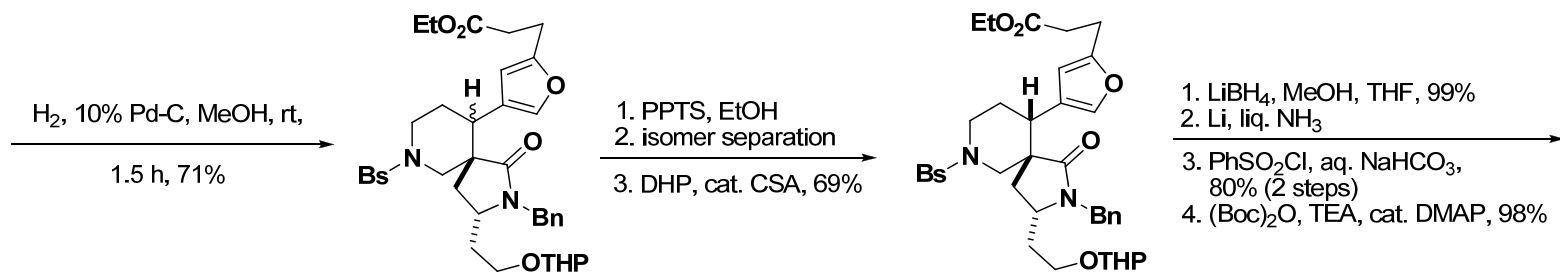
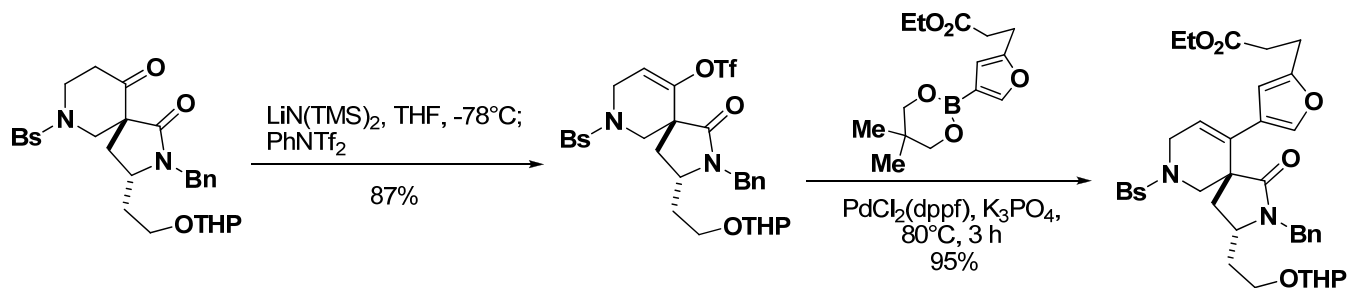
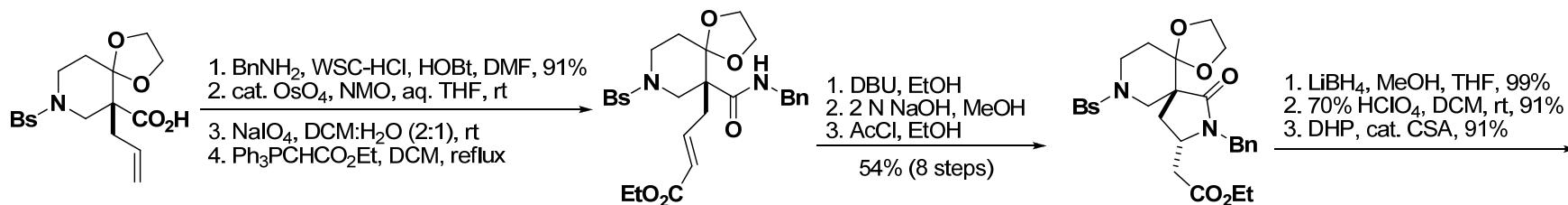
Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9239.

Baldwin, J.E.; Whitehead, R.C. *Tetrahedron Lett.* **1992**, *33*, 2059.

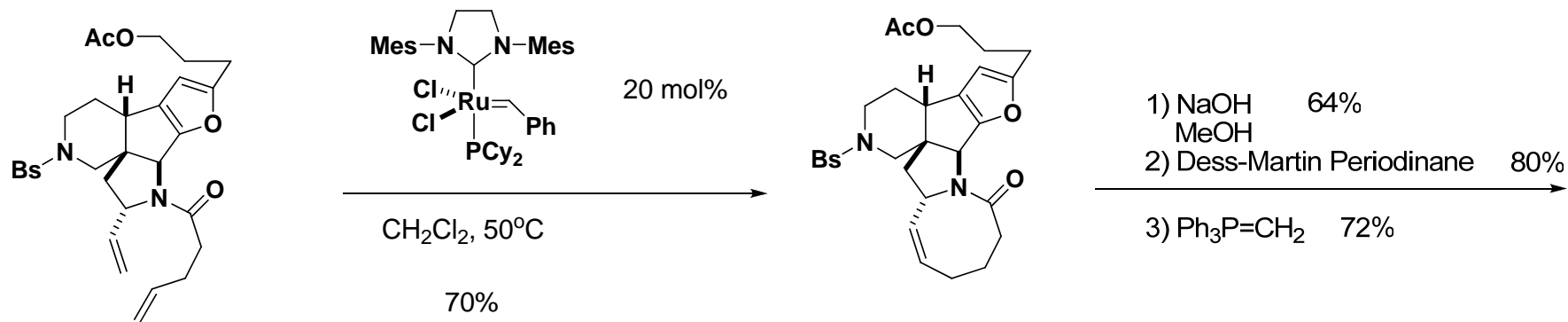
Selective Hydrogenation Model Study



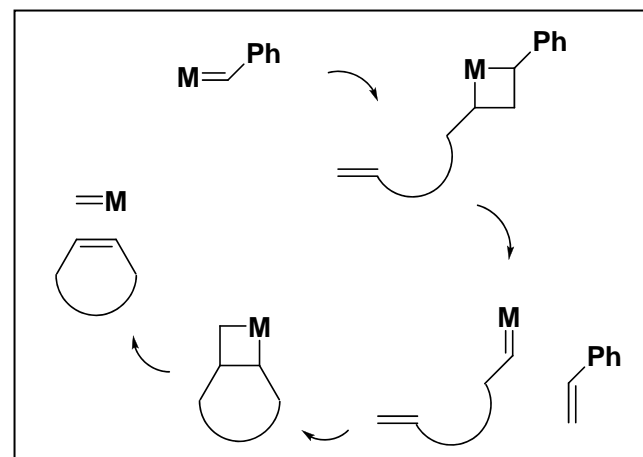
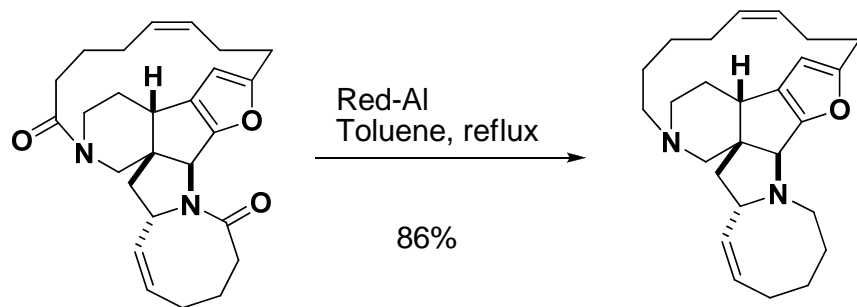
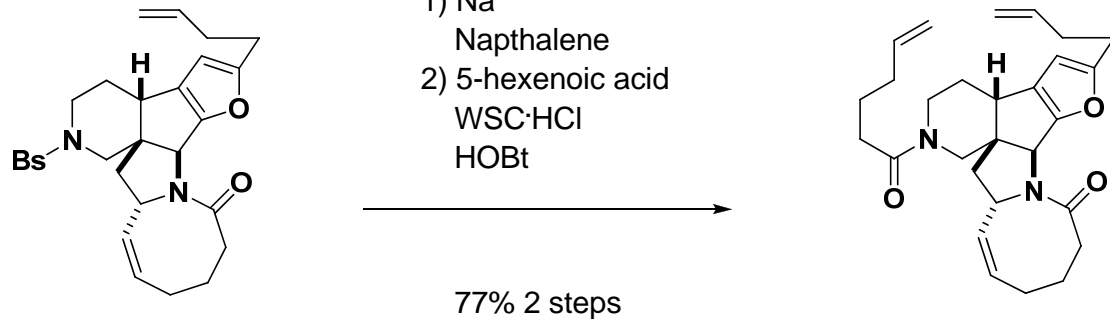
A, B, C, D Tetracyclic Core Construction



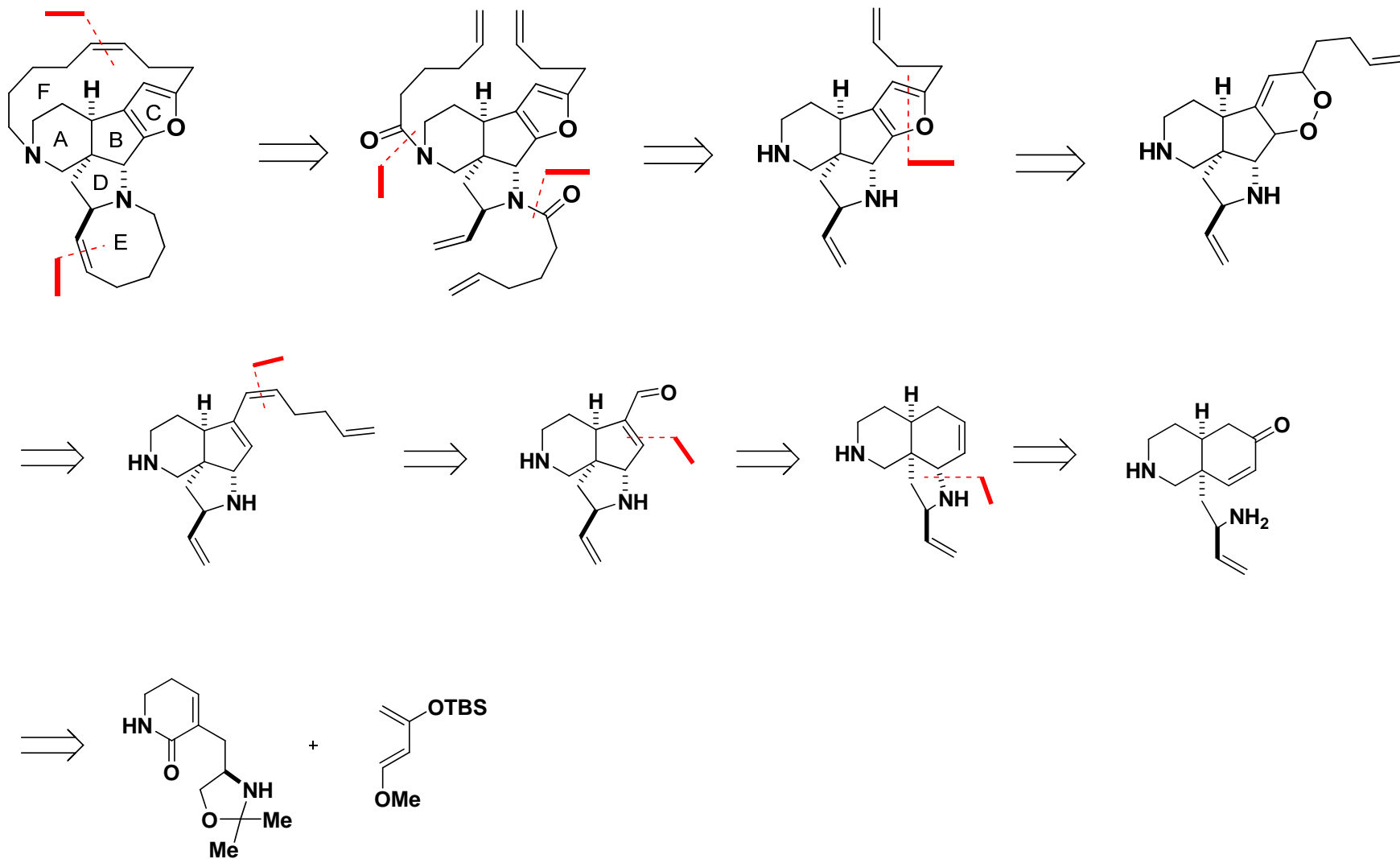
Nakadomarin A : Rings E and F



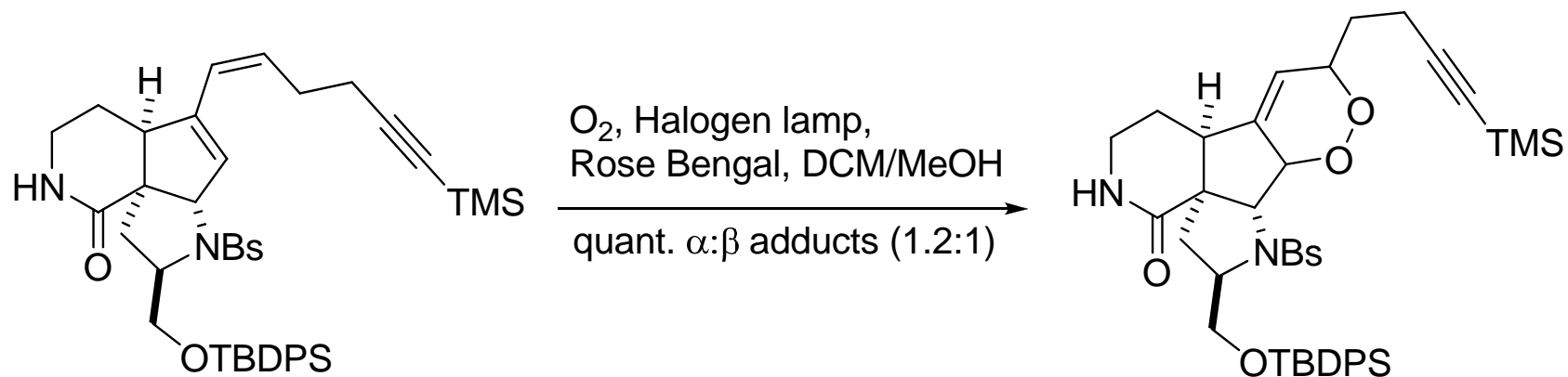
1) NaOH 64%
 MeOH
 2) Dess-Martin Periodinane 80%
 3) $\text{Ph}_3\text{P}=\text{CH}_2$ 72%



Retrosynthesis

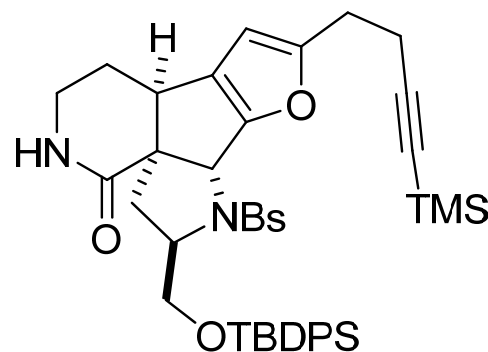


Furan Formation

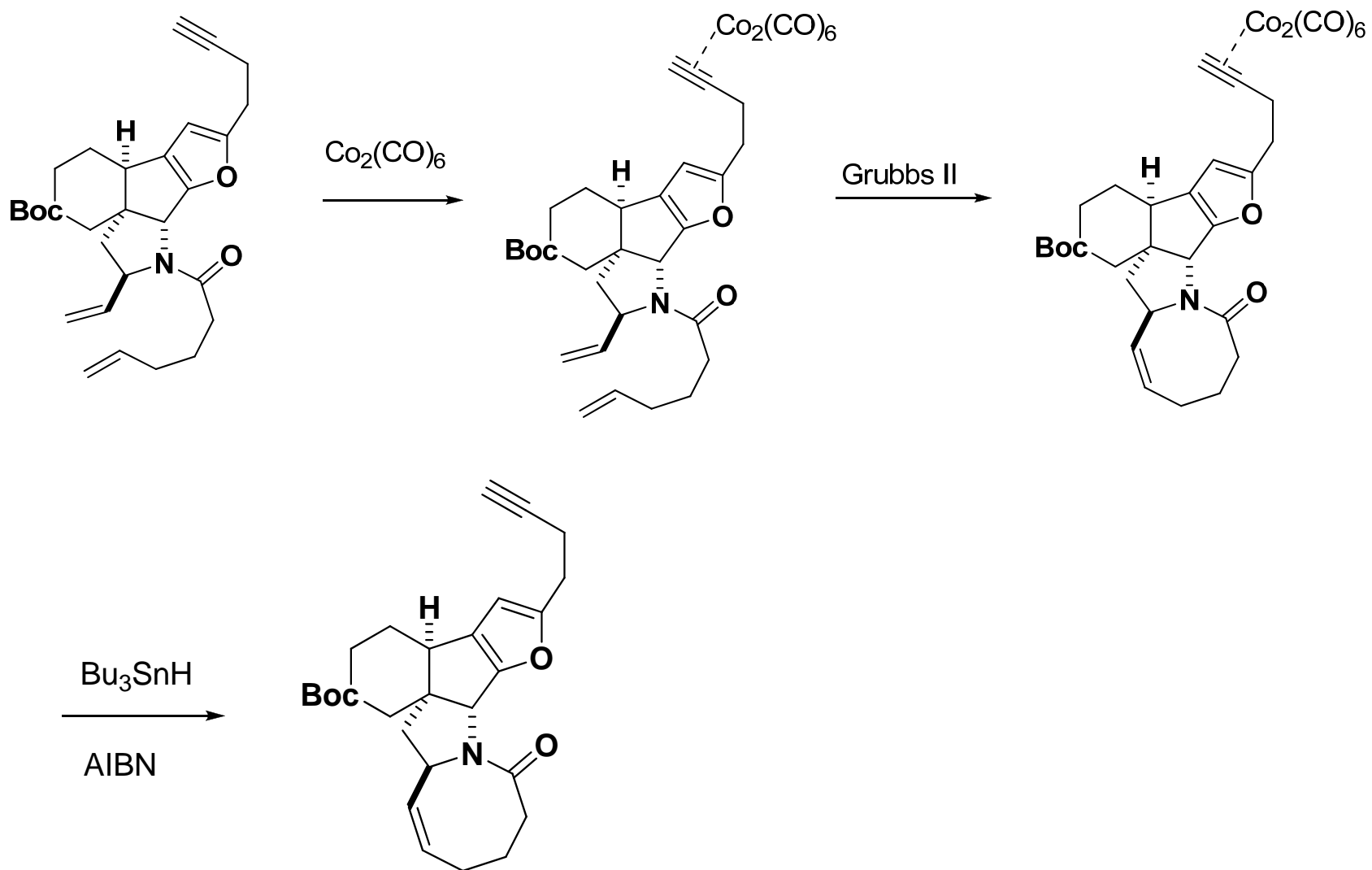


$tBuOK$, THF, $-78\text{ }^\circ\text{C}$;
HCl (6N), RT, 88% from α

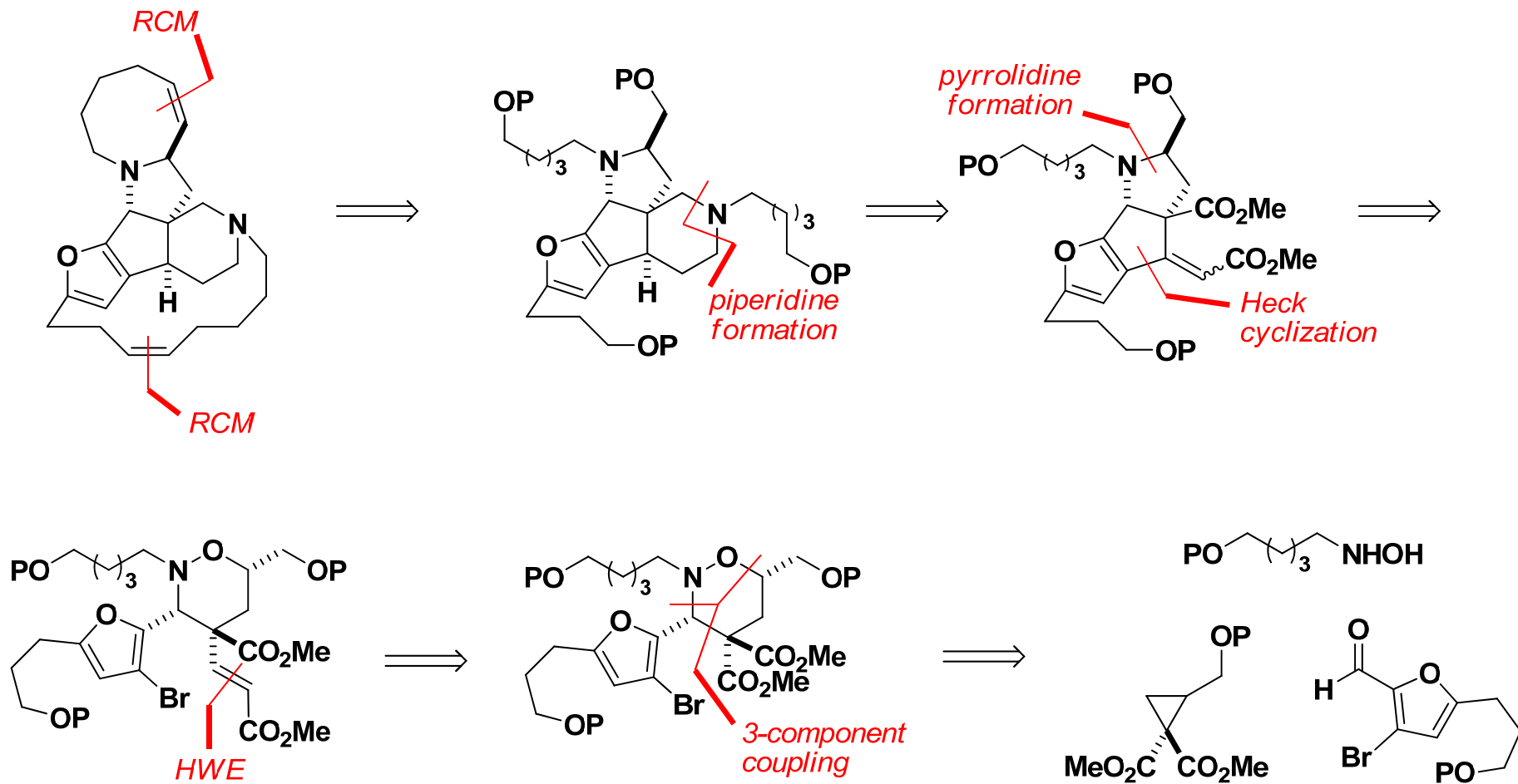
$tBuOK$, THF, $-30\text{ }^\circ\text{C}$;
HCl (6N), RT, 69% from β



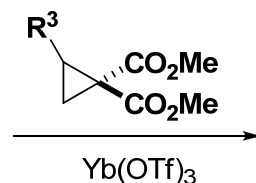
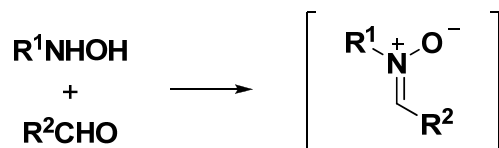
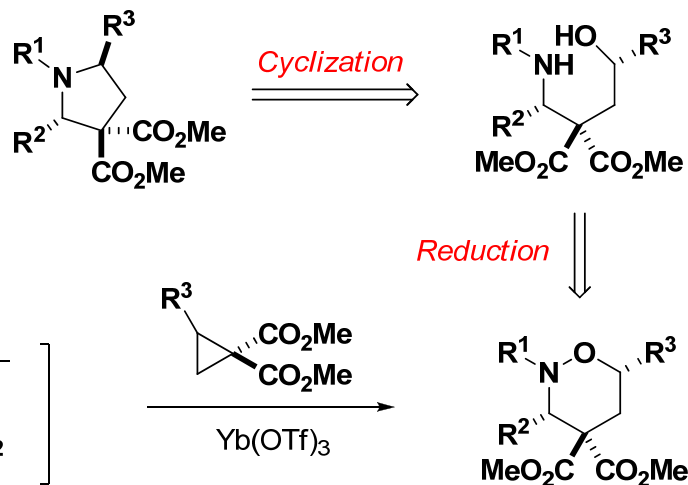
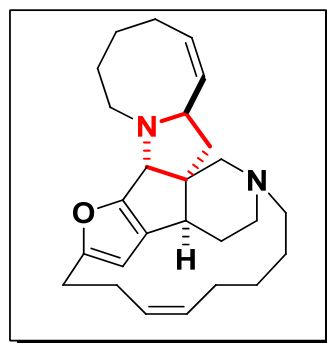
Ring Closing Metathesis



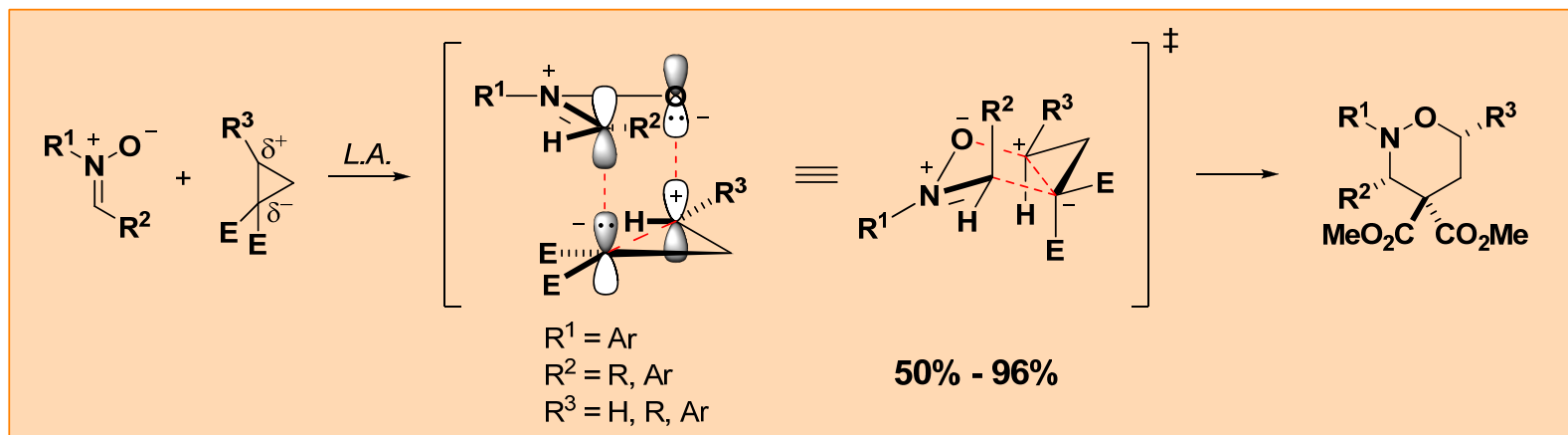
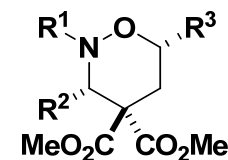
Kerr's Retrosynthesis



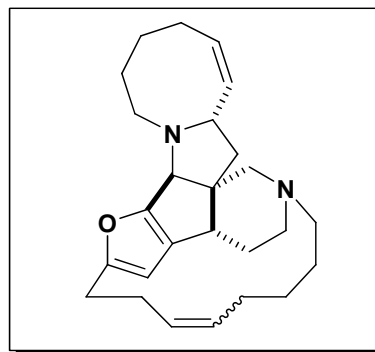
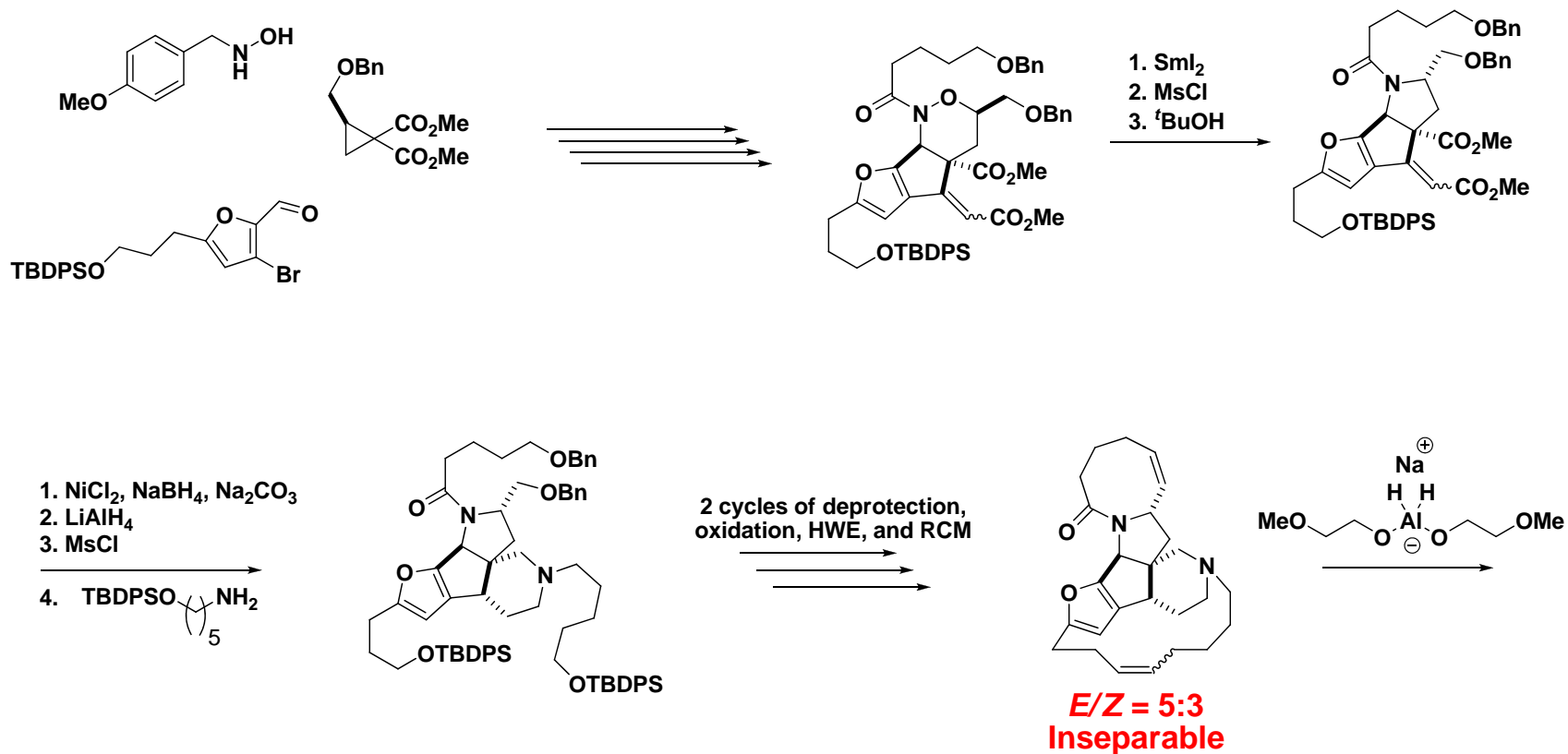
Pyrrolidines via Nitronne/Cyclopropane Homo [3+2] Dipolar Cycloaddition



Reduction

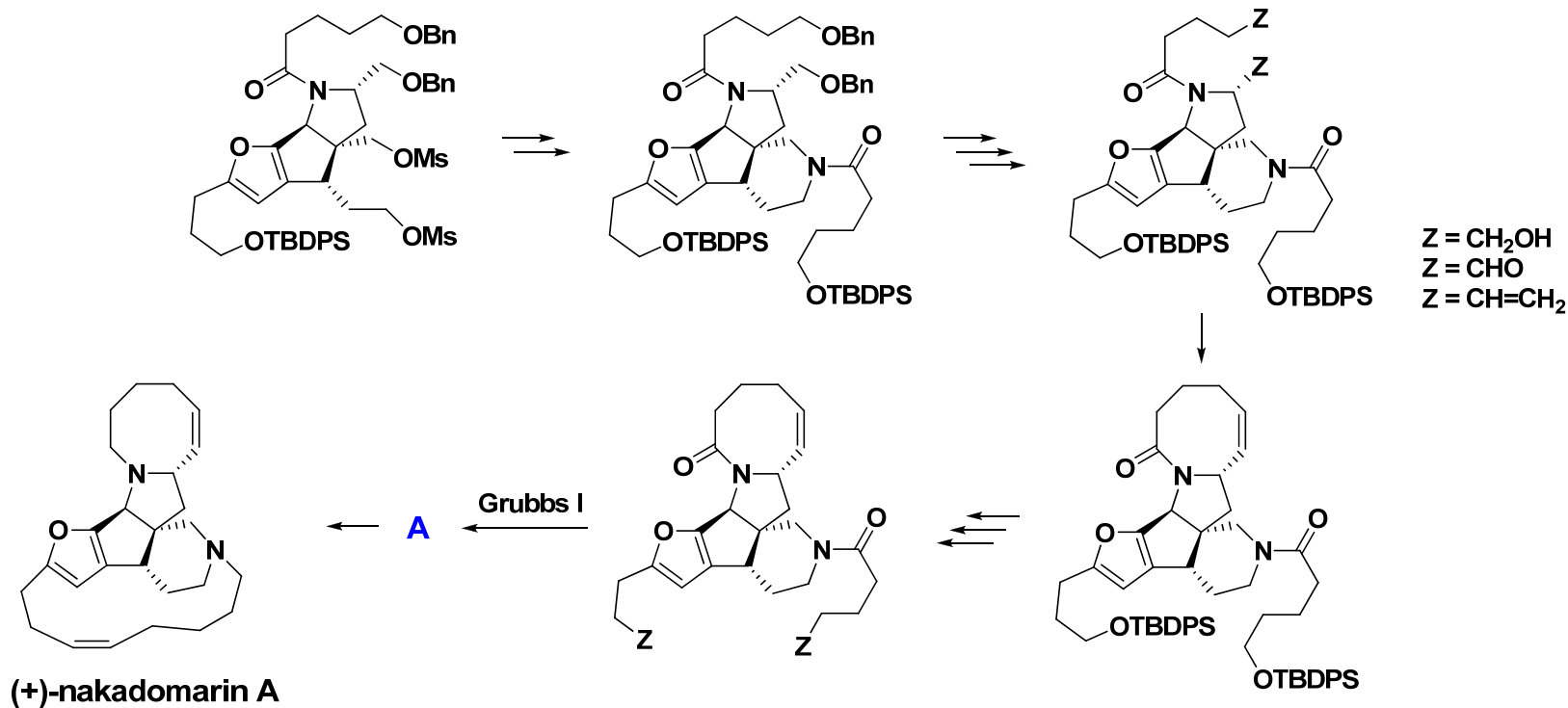
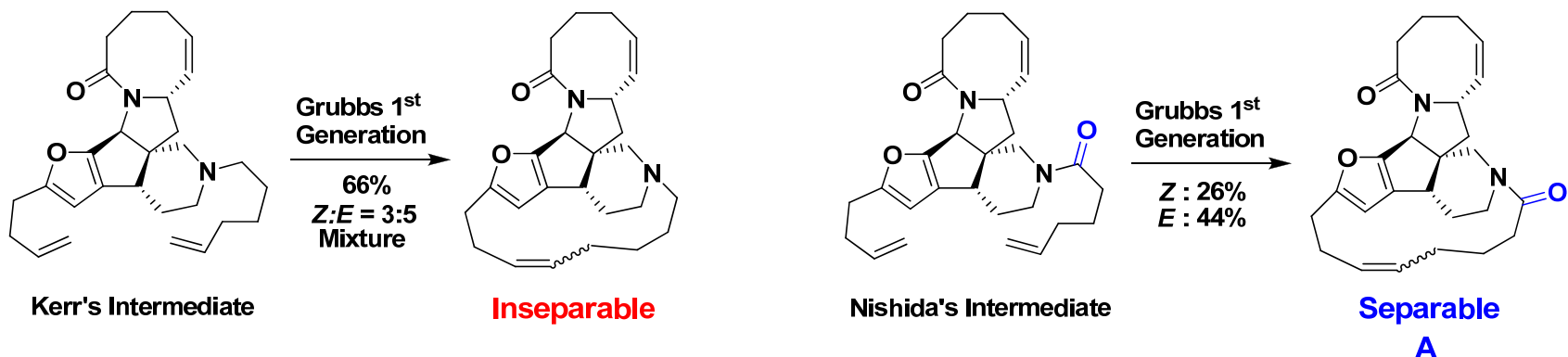


Kerr's Total Synthesis

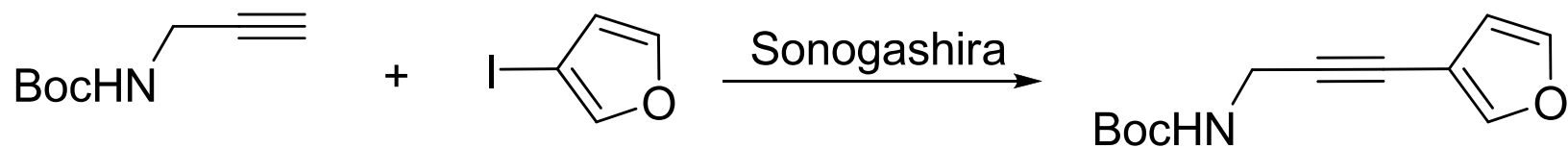


(+) - Nakadomarin A and inseparable *E* isomer

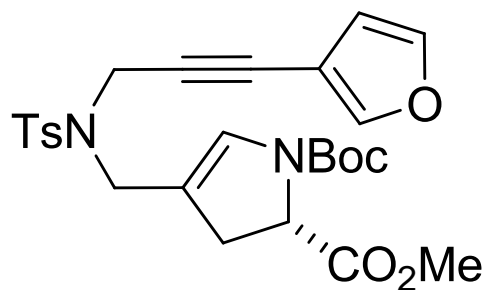
Completion of the Synthesis of Nakadomarin A



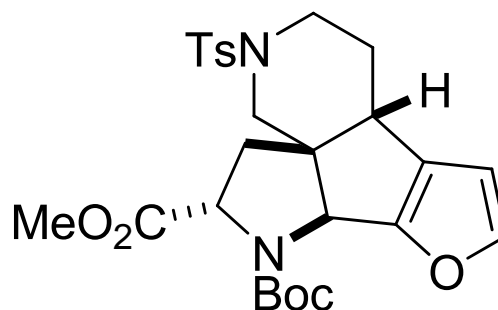
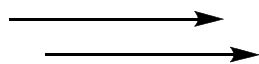
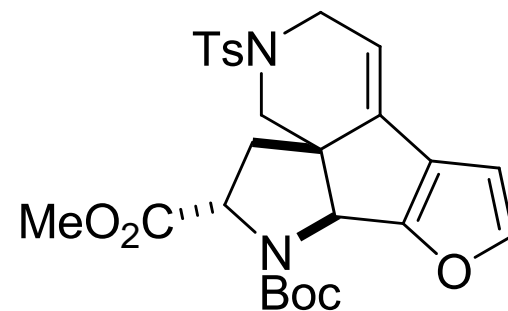
Zhai's Synthesis



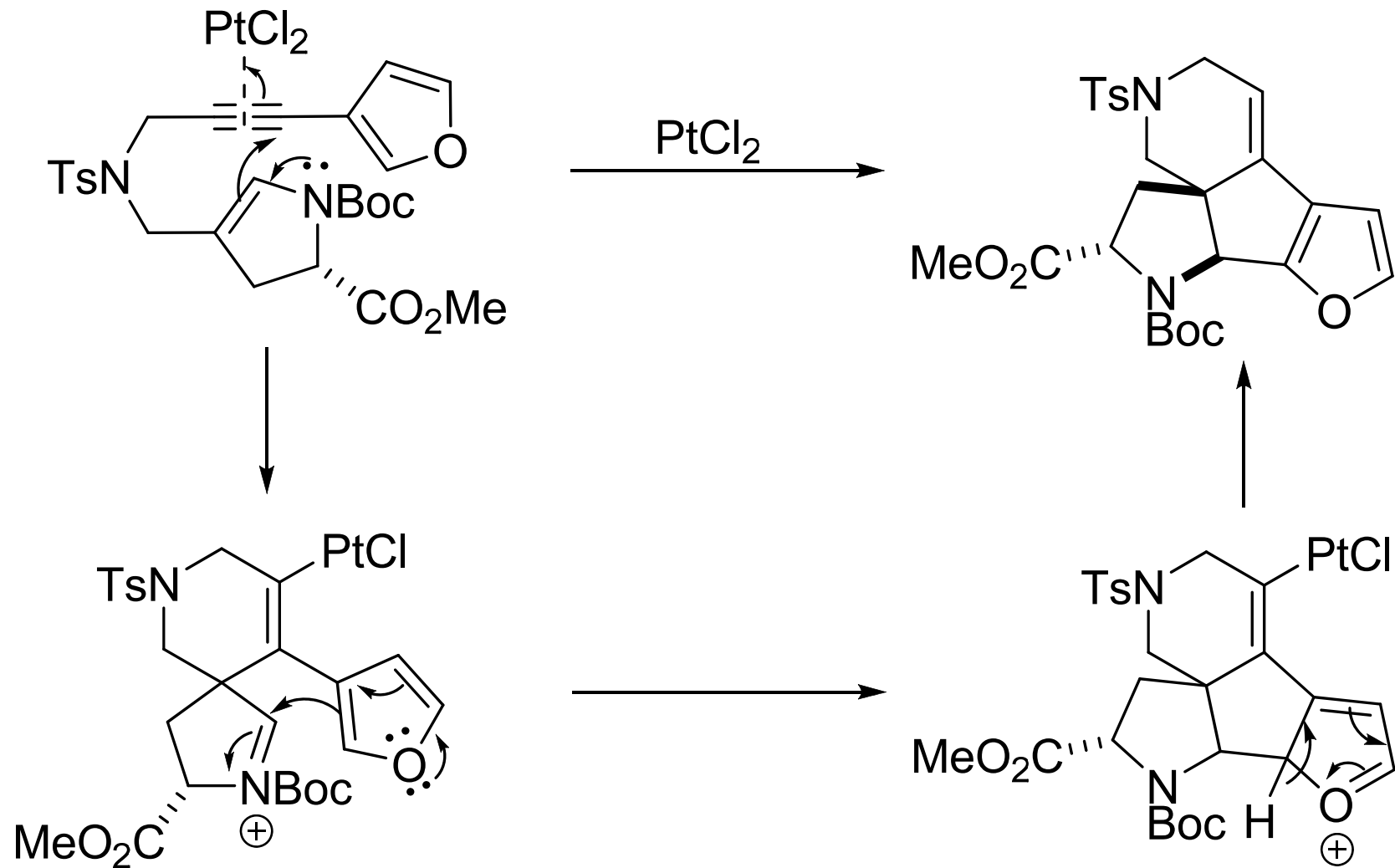
Reductive amination



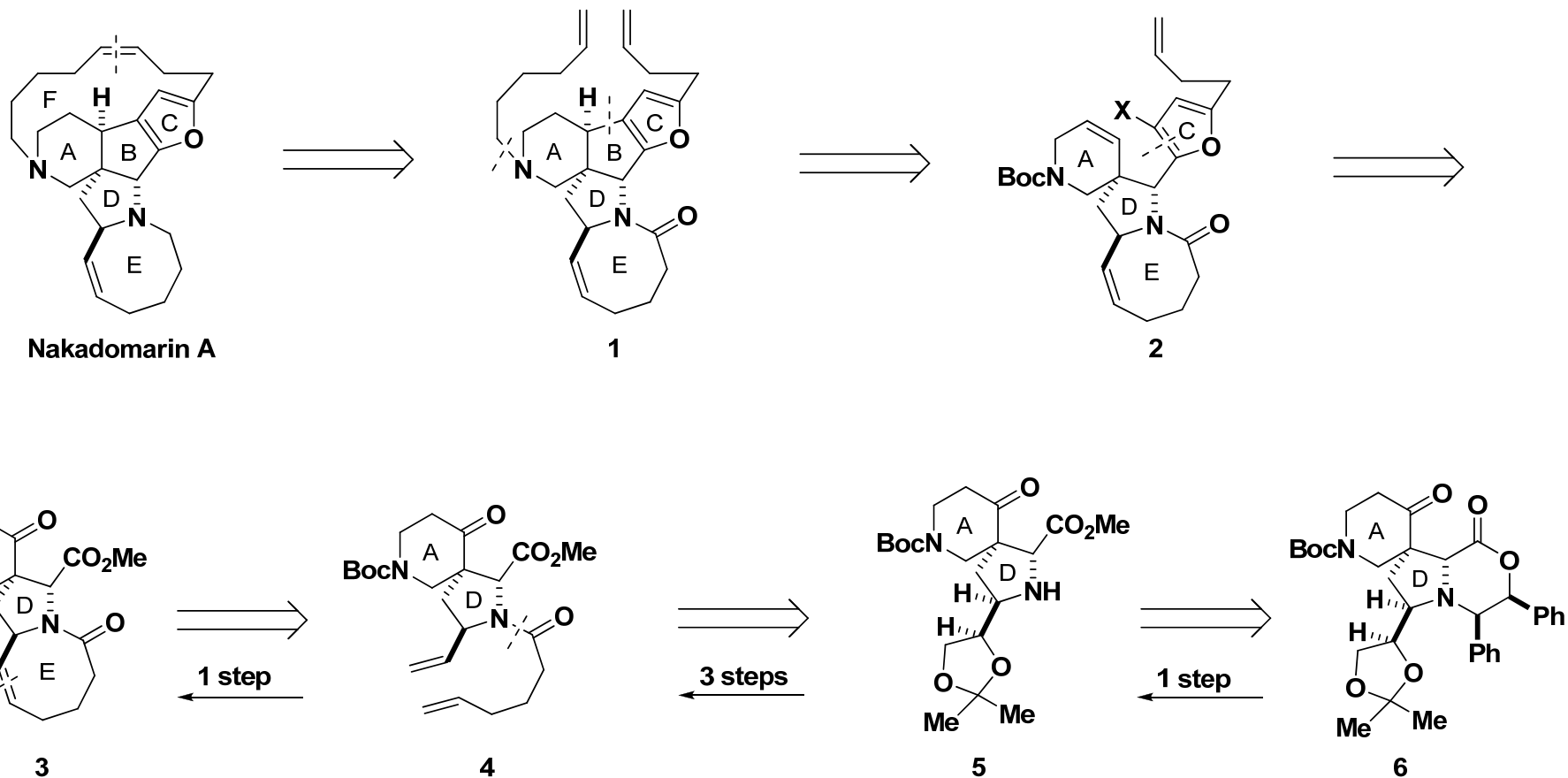
PtCl₂



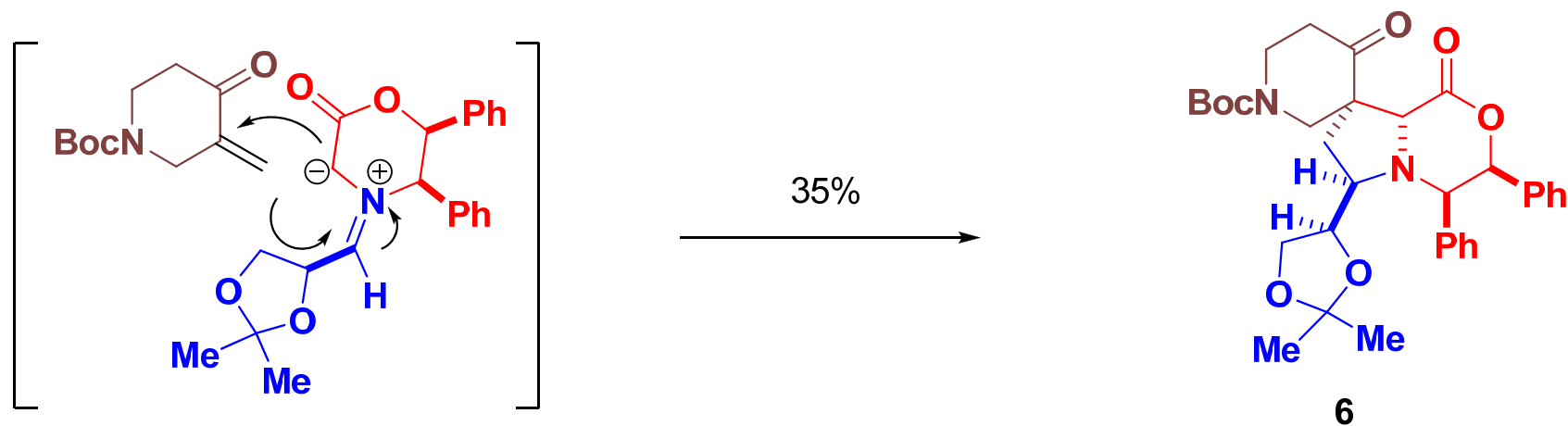
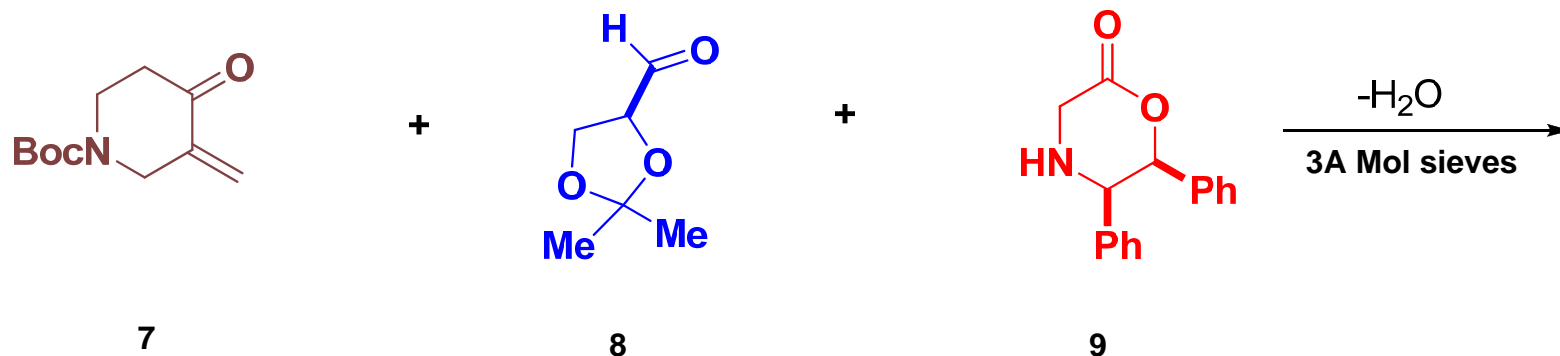
Zhai's Synthesis



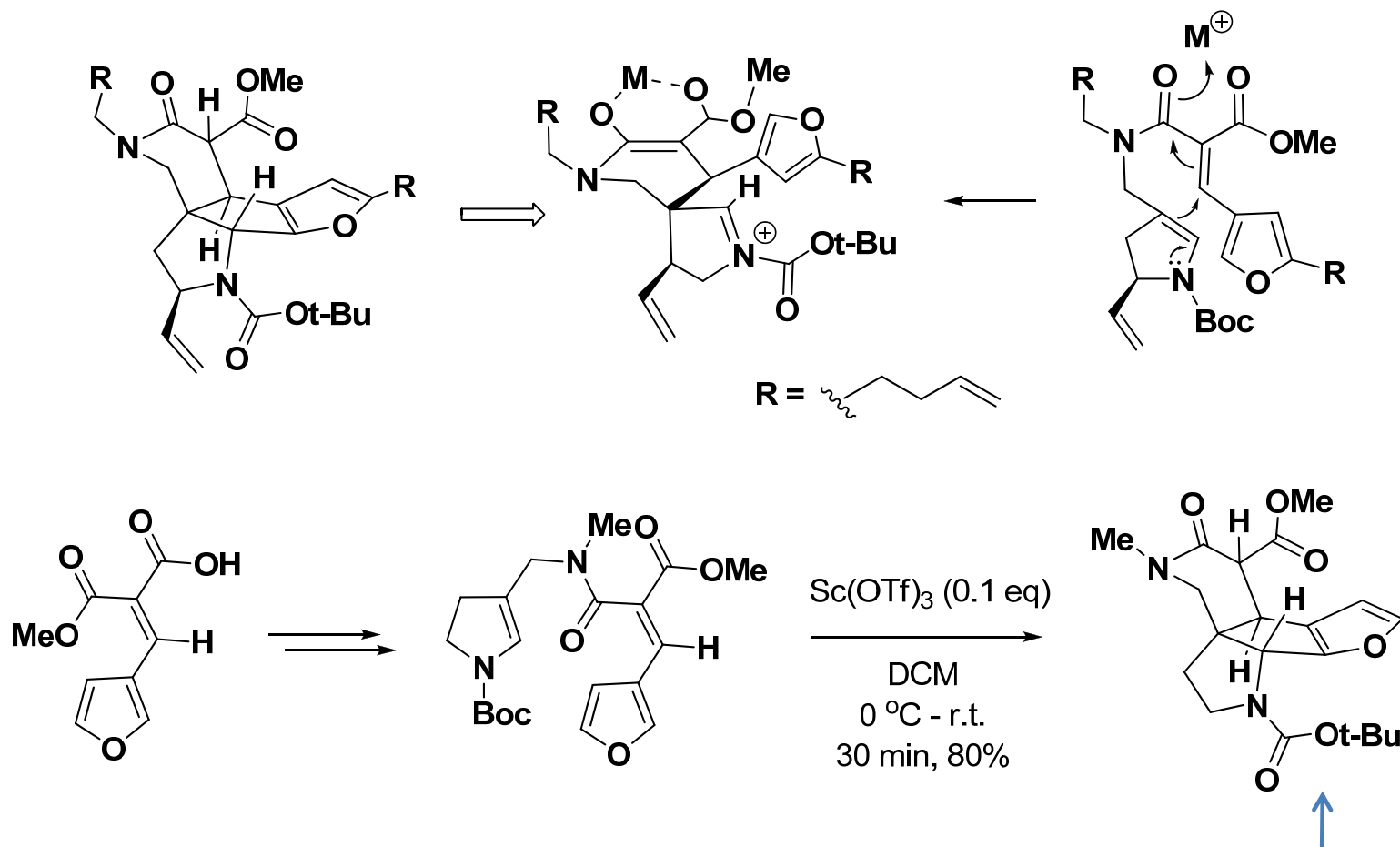
Williams' Retrosynthesis



Azomethine Ylide [1,3]-Dipolar Cycloaddition

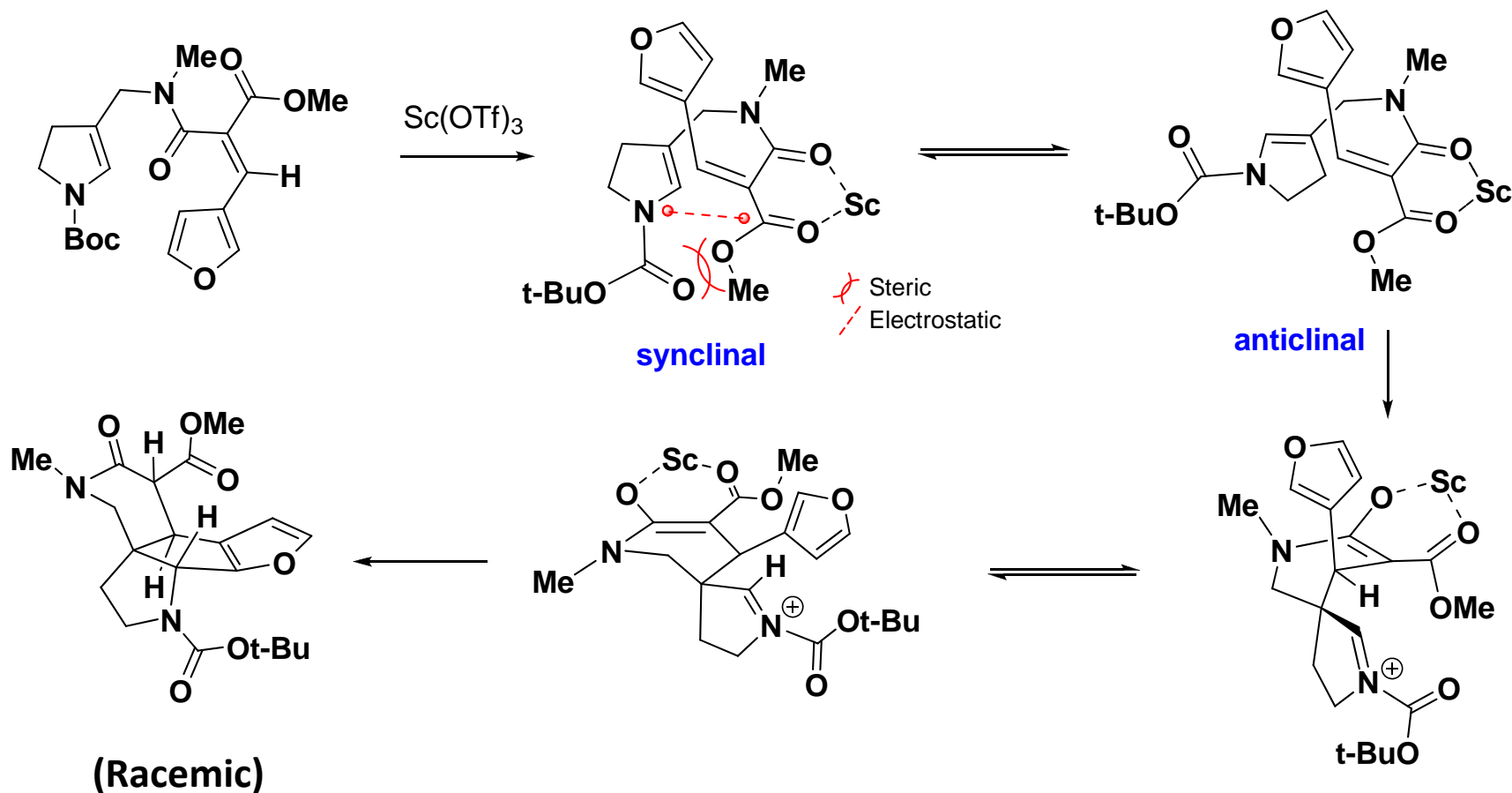


Funk's Retro- and Forward Synthesis



Stereochemistry confirmed by X-Ray Structure

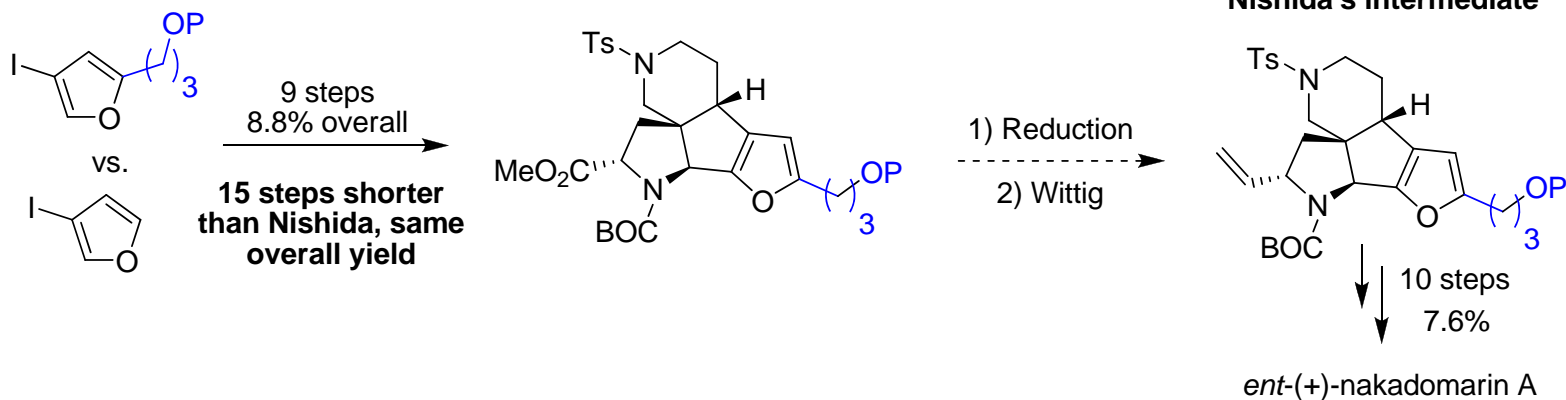
Stereochemical Rational



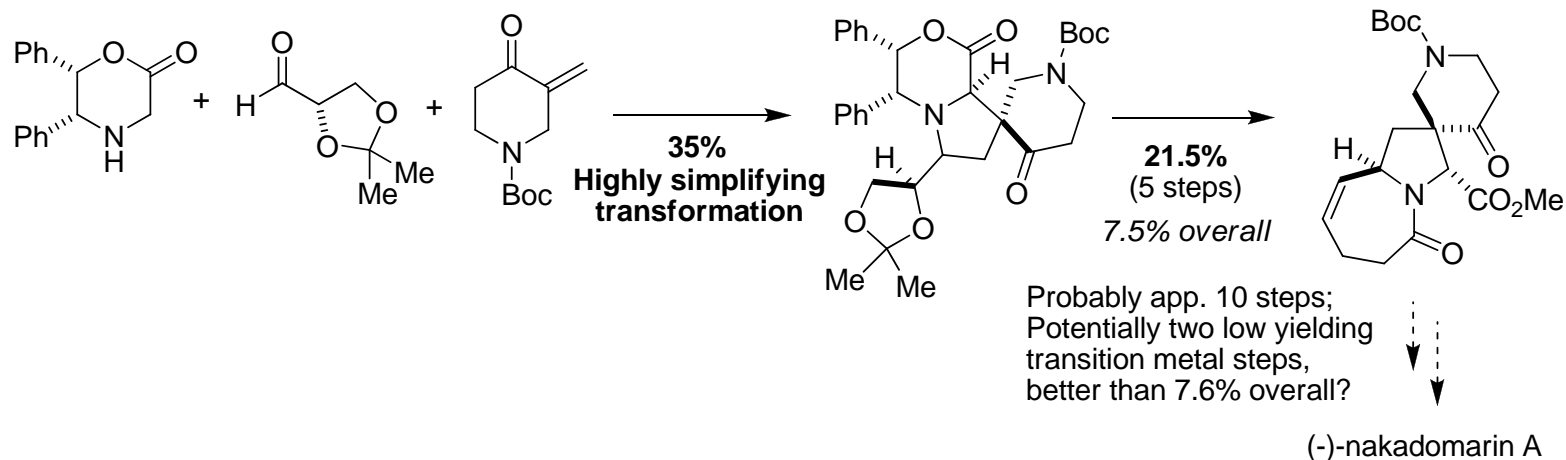
Evaluation of Approaches

Deng, Yang, Tong, Li and Zhai, Org. Lett. 2008

change starting material:



Ahrendt and Williams, Org. Lett. 2004



Evaluation of Approaches

Nilson and Funk, Org. Lett. 2006

