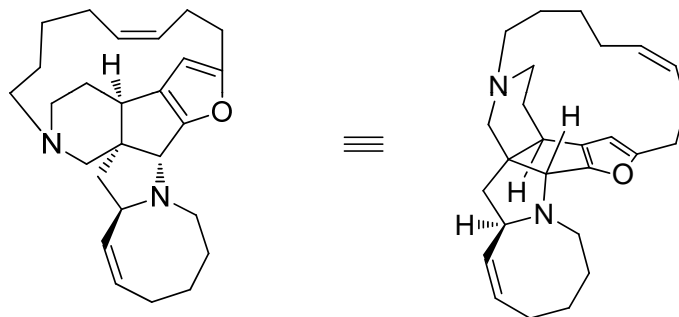


# Total Synthesis of (-)-Nakadomarin A

Nilson, M. G.; Funk, R. L. *Org. Lett.* **2010**, ASAP.



**Chad Hopkins**

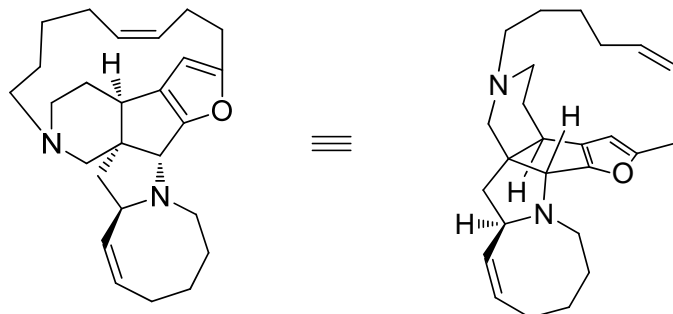
**Wipf Group Literature Presentation**

**10-23-10**

## Isolation and Biological Activity



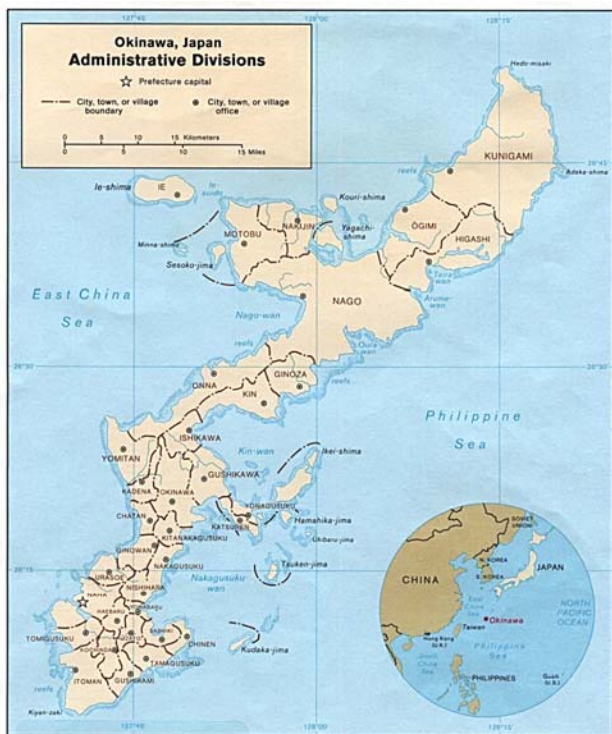
<http://www.reefclub.or.kr>



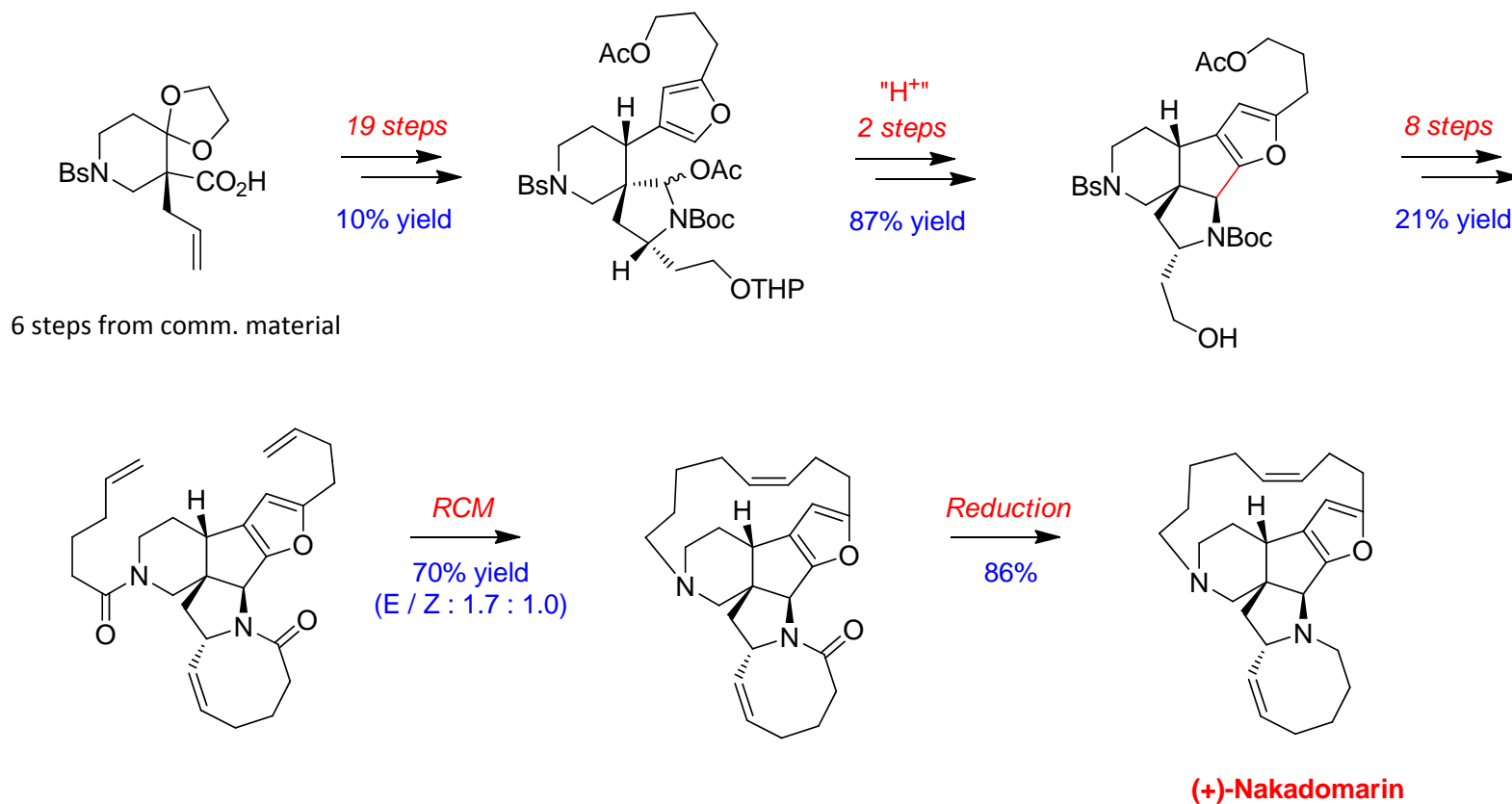
**(-)-Nakadomarin A**

- Isolated in 1997 from the marine sponge *Amphimedon* sp. collected off the coast of the Kerama Islands, Okinawa (1 kg of sponge yielded 6.0 mg or 0.0018% of (-)-Nakadomarin A).
- Structure assigned by 1-D/2-D NMR, HRMS (EI), and Macromodel (v 5.0, Pseudo Monte Carlo, MM2 FF H<sub>2</sub>O)
- Novel furan-containing hexacyclic alkaloid consisting of an unprecedented 8/5/5/5/15/6 ring system
- Cytotoxic against murine L1210 (mouse lymphoma, IC<sub>50</sub> 1.3  $\mu\text{g}/\text{mL}$  or 3.5  $\mu\text{M}$ )
- Demonstrated ant-fungal and anti-bacterial activity
- First asymmetric synthesis completed in 2004 by Nishida

Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236-9239.  
Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020-2023.



## First Synthesis of (+)-Nakadomarin (Nishida)



Longest Linear Sequence: 31 steps from chiral acid, 1.1% yield

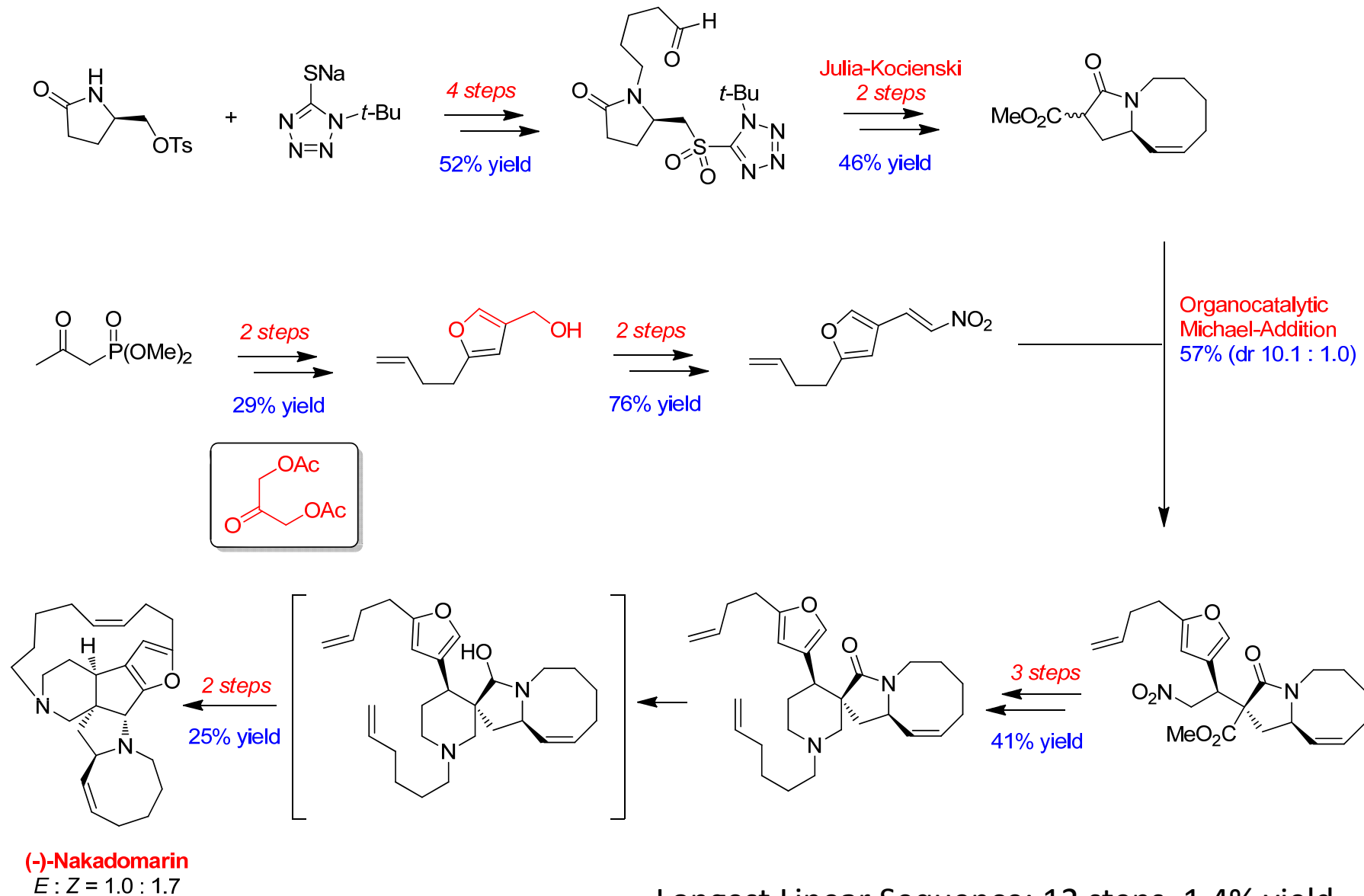
Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484-7485.

For Nishida's synthesis of (-)-Nakadomarin, see: Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020-2023.

For Kerr's synthesis of (+)-Nakadomarin, see: Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465-1469.

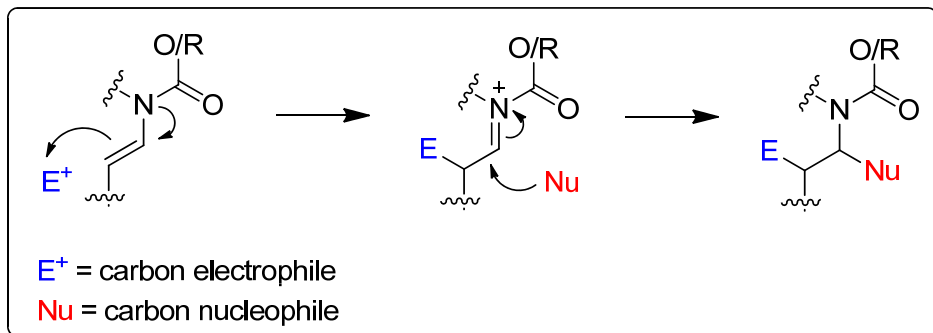
Kerr's Longest Linear Sequence: 29 steps from D-mannitol, RCM for 15-membered ring gave a  $E : Z = 1.5 : 1.0$

## Synthesis of (-)-Nakadomarin (Dixon)

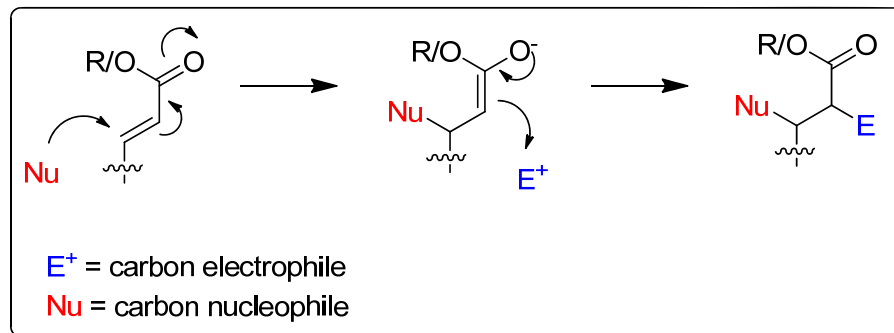


Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632-16633.

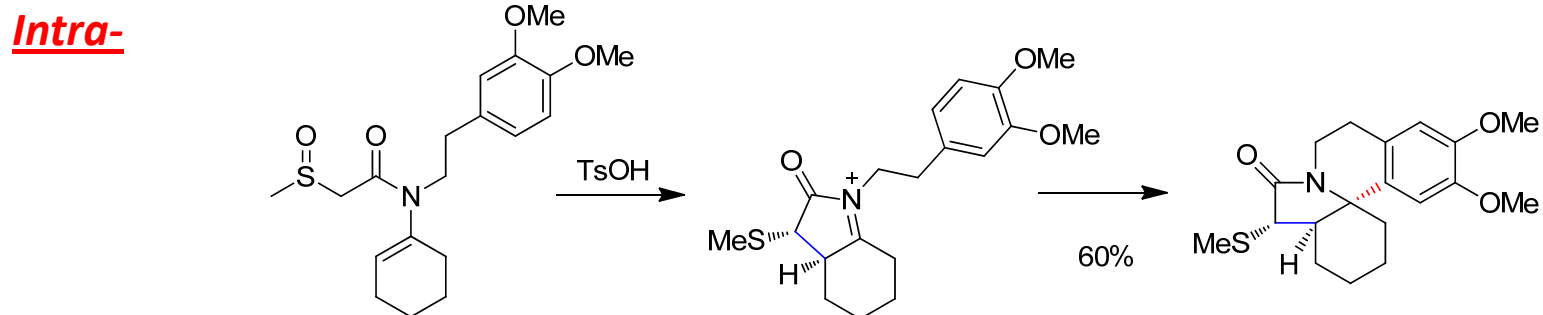
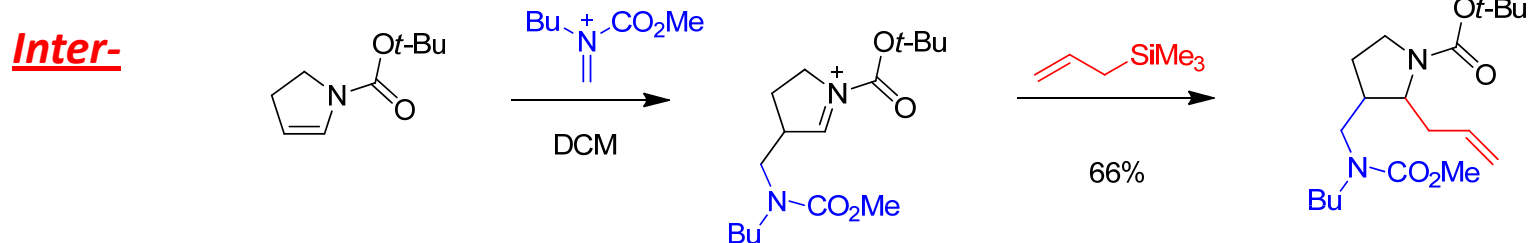
## Vicinal Difunctionalization



For a review on tandem vicinal difunctionalization involving *N*-acyliminium ions, see: Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, T. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431-1628.

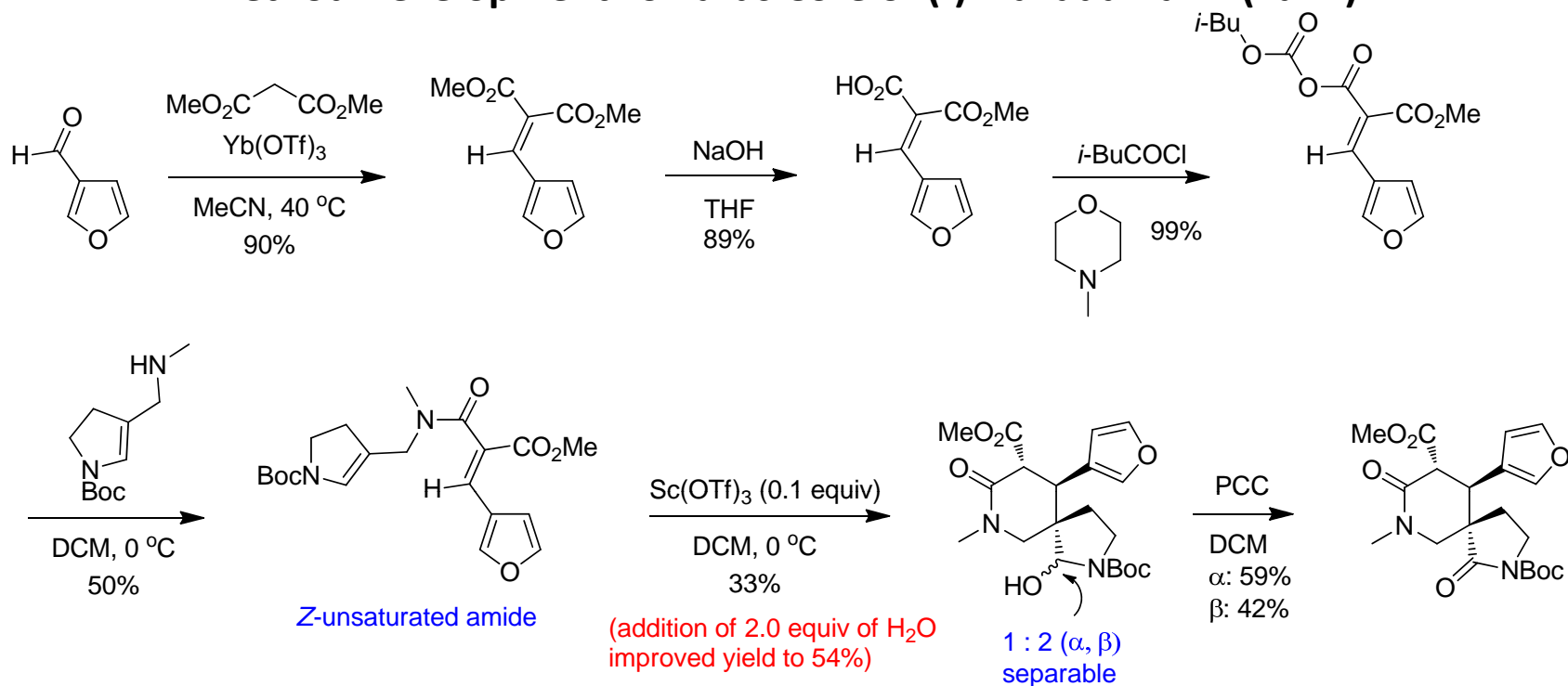


For a review on tandem vicinal difunctionalization involving  $\alpha,\beta$ -unsaturated carbonyls, see: Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225-295.



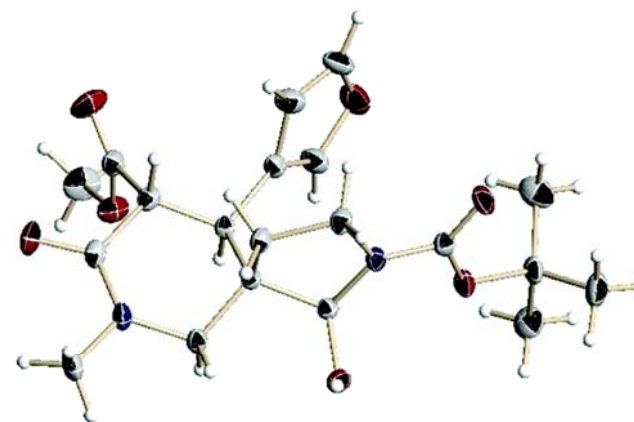
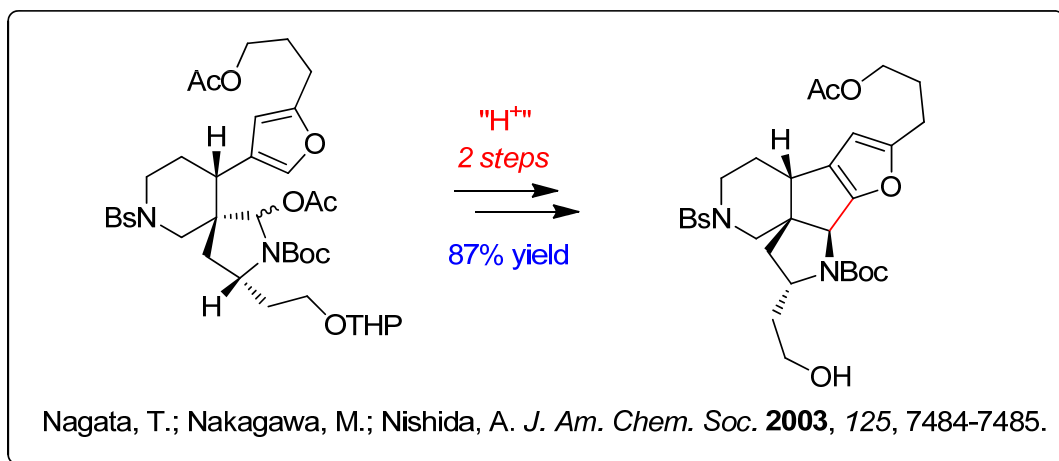
For a review on tandem vicinal difunctionalization involving *N*-acyliminium ions, see: Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, T. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431-1628.

## Method Development Towards Core of (-)-Nakadamarin (Funk)



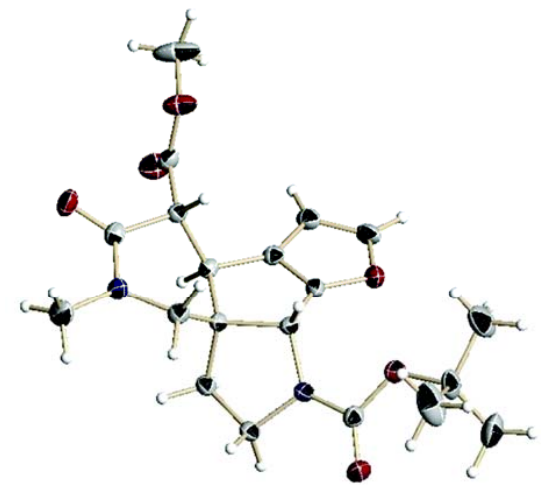
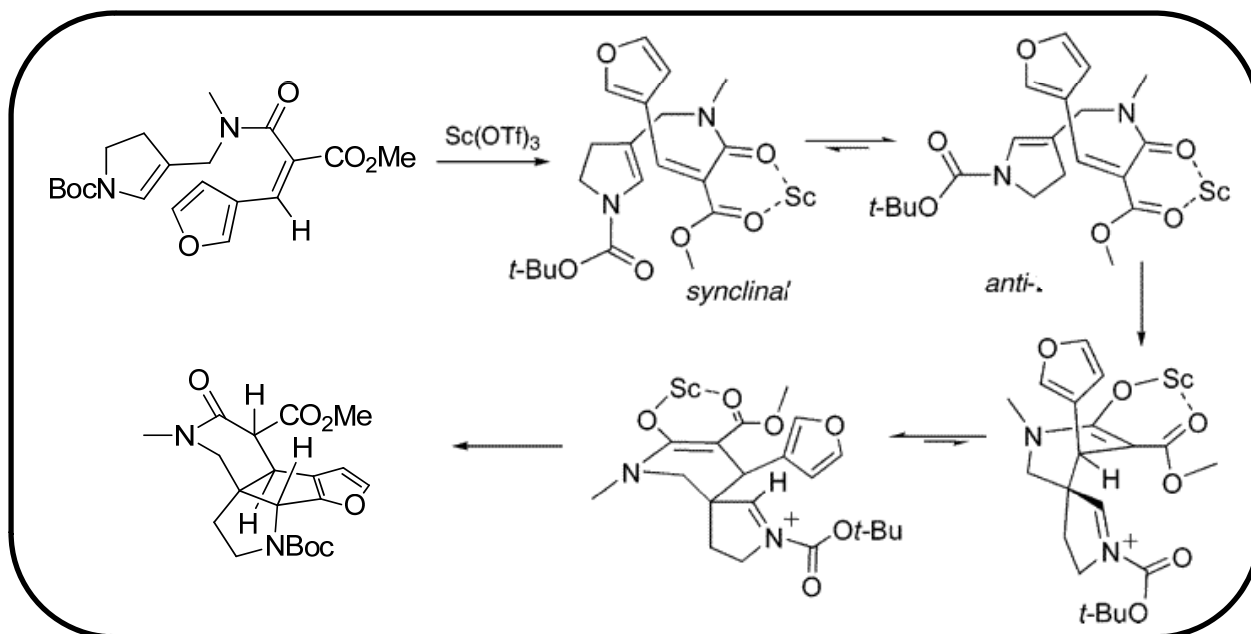
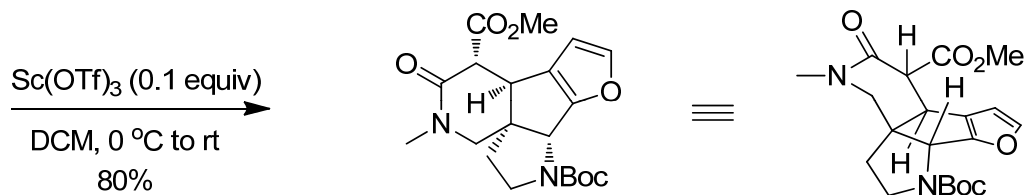
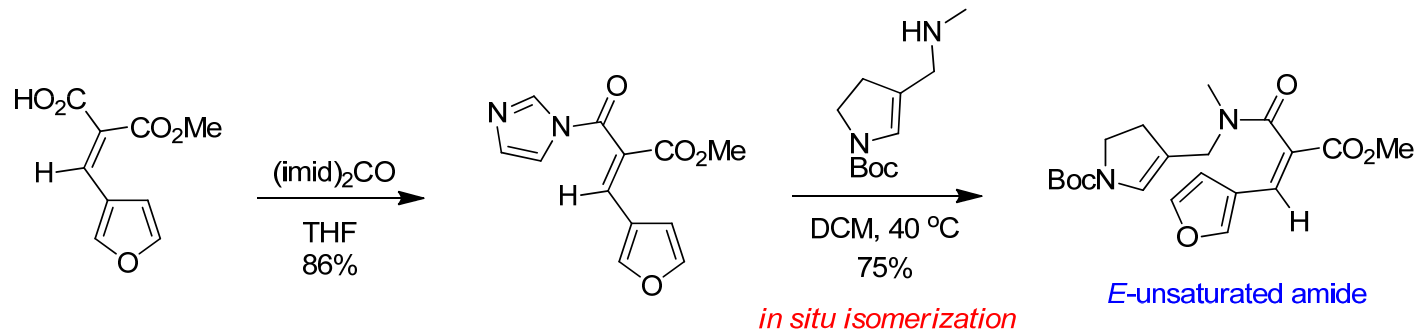
Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833-3836.

No furan trapping of acyliminium ion observed, cis vs. trans



X-Ray of  $\beta$ -hemiaminal

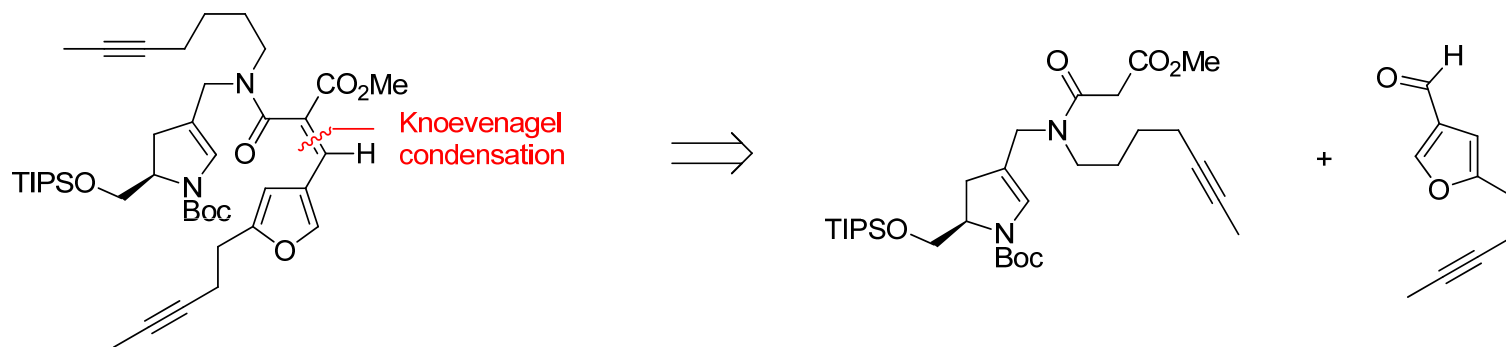
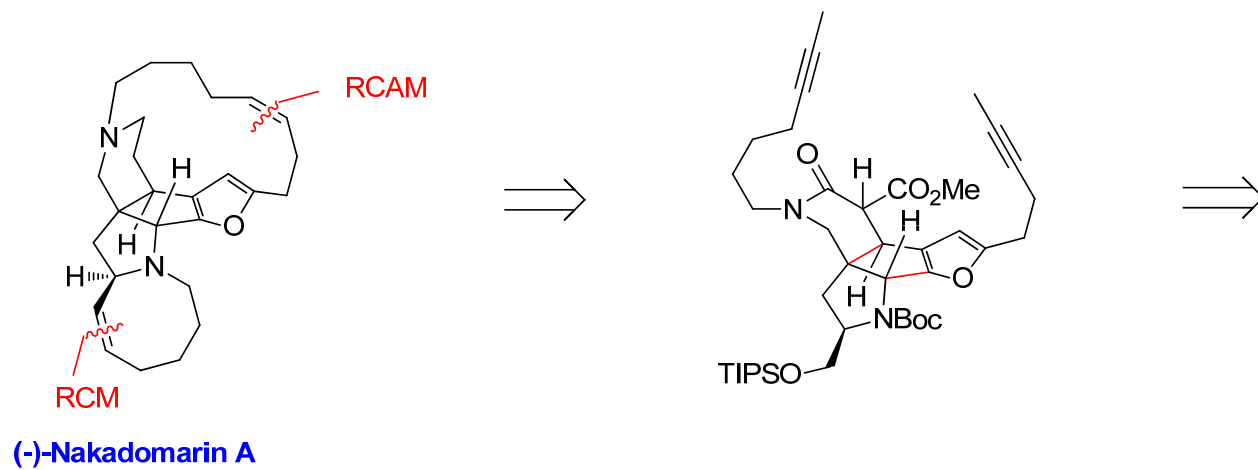
## Method Development Towards Core of (-)-Nakadamarin (Funk)



X-Ray of tetracycle

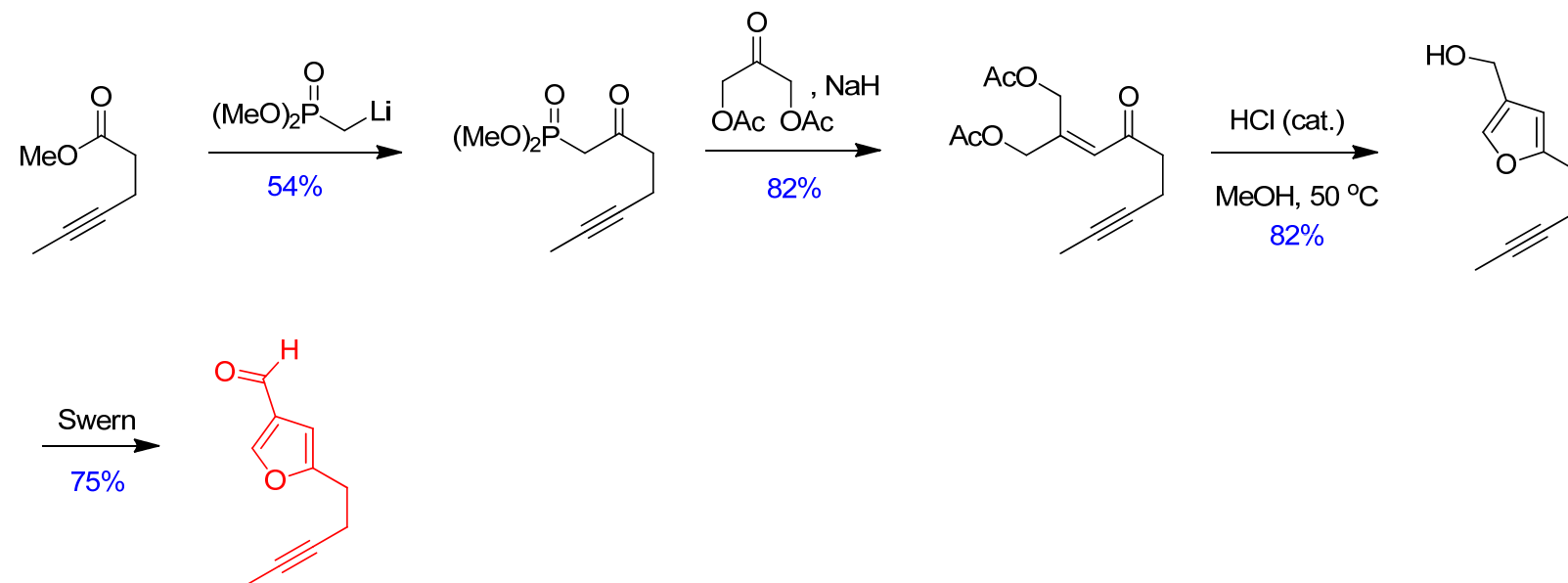
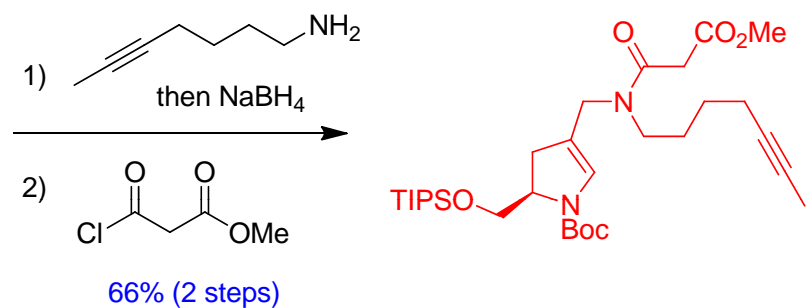
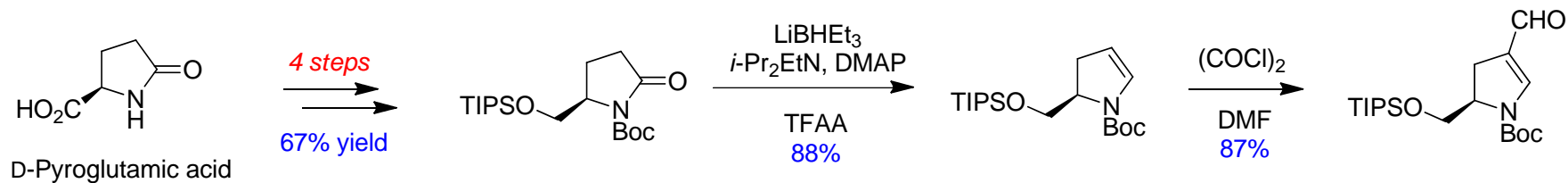
Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833-3836.

## Retrosynthesis of (-)-Nakadamarin (Funk)



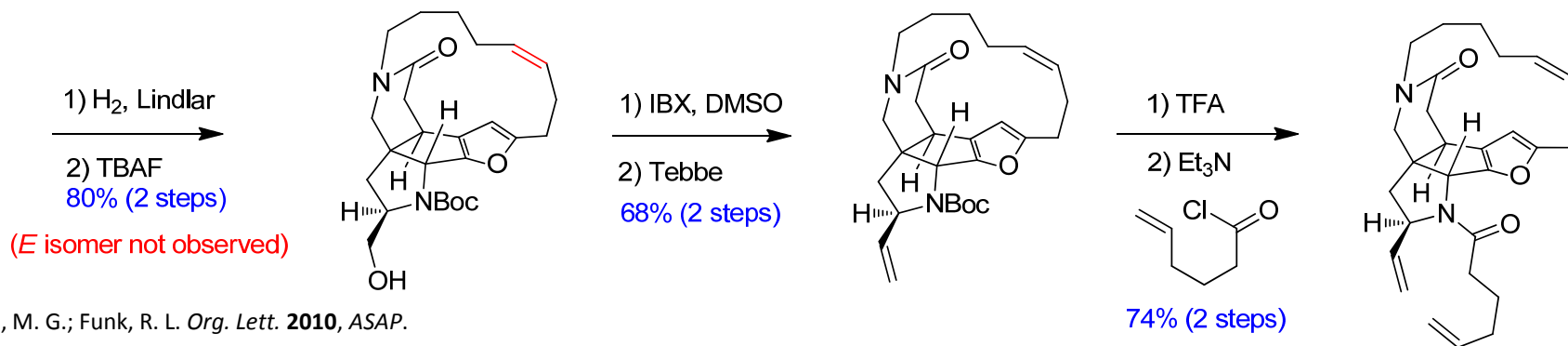
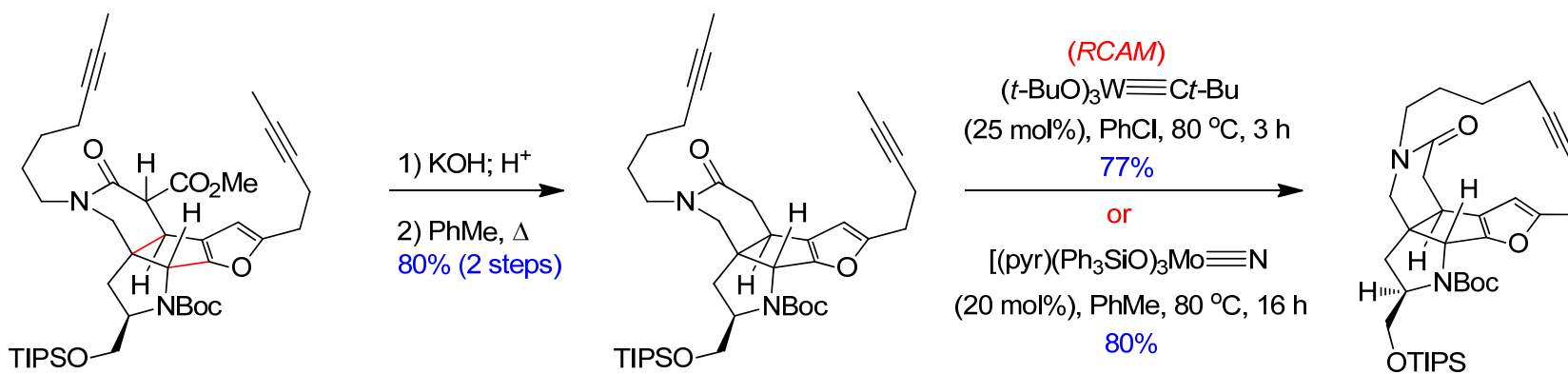
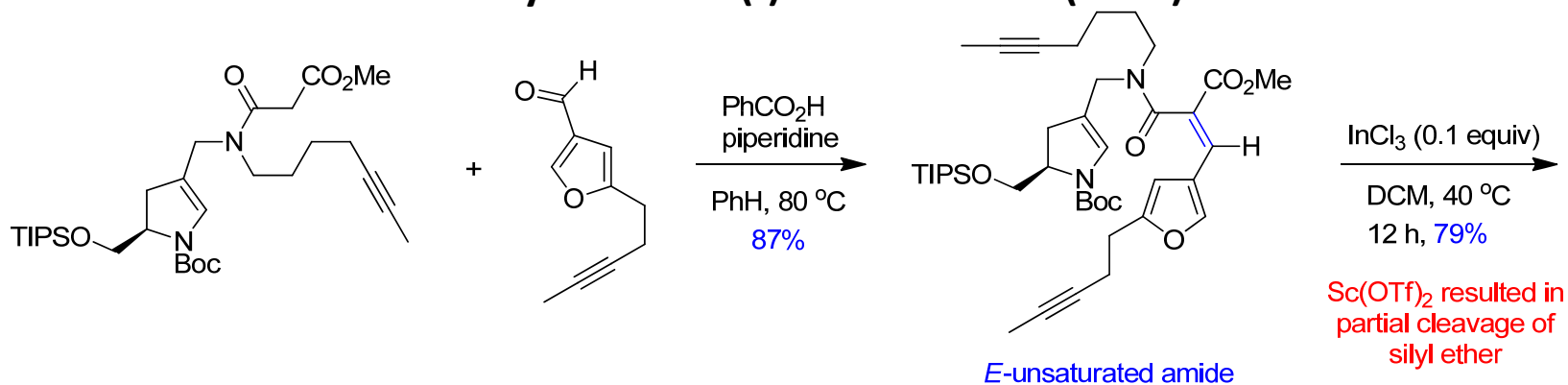


## Synthesis of (-)-Nakadamarin (Funk)



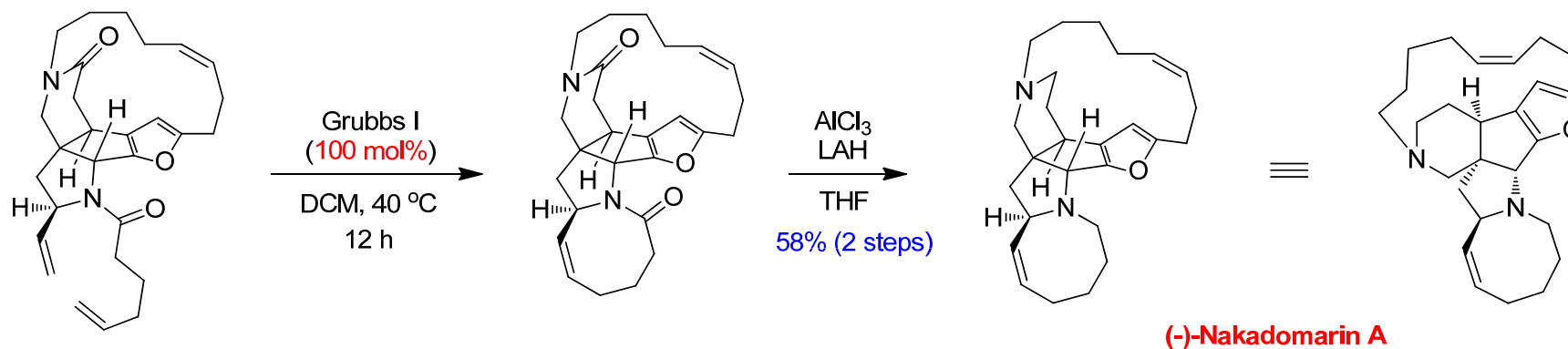
Nilson, M. G.; Funk, R. L. *Org. Lett.* **2010**, ASAP.

## Synthesis of (-)-Nakadamarin (Funk)



Nilson, M. G.; Funk, R. L. *Org. Lett.* **2010**, ASAP.

## End Game and Summary



- Enantioselective synthesis of (-)-Nakadomarin
- 21 steps (LLS), 3.5% overall yield from D-pyroglutamic acid
- Highest overall yielding synthesis to date
- Rapid assembly of tetracyclic core via a tandem enecarbamate Michael addition/furan *N*-acyliminium ion cyclization
- RCAM resolves olefin stereoselectivity issues with construction of 15-membered ring
- Cyclization of pyrrole analog of furan successful