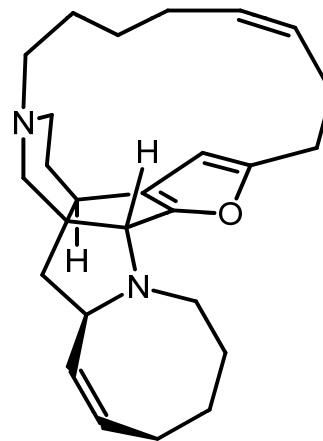
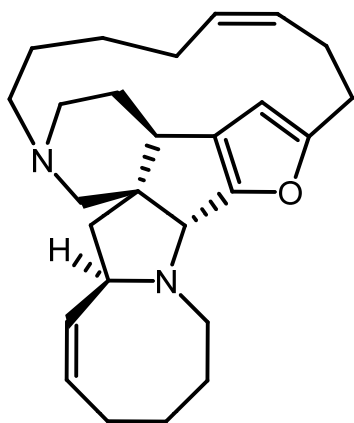
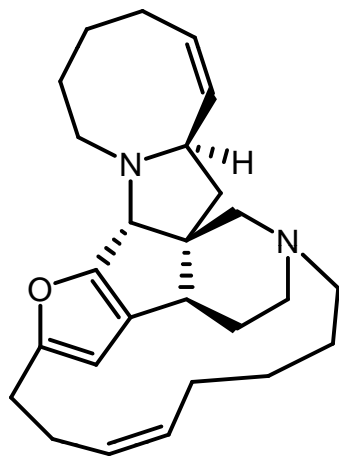


# ***Total Syntheses of Nakadomarin A***



# ***Nakadomarin A: The Facts***

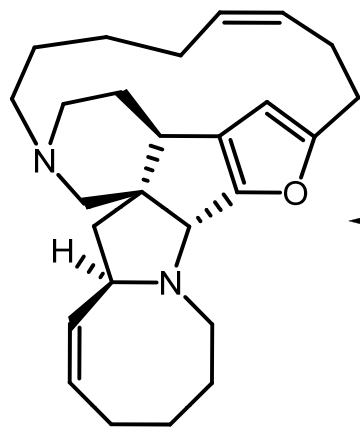


- Isolated in 1997 from an *Amphimedon* sea sponge by Kobayashi off the coast of the Kerama Islands, Okinawa
- Only member of the manzamine family containing a furan ring
- Bioactivity includes anticancer, antifungal and antibacterial
- Limited availability: 6 mg isolated from 1 kg of wet sponge
- Initially the absolute stereochemistry was unknown

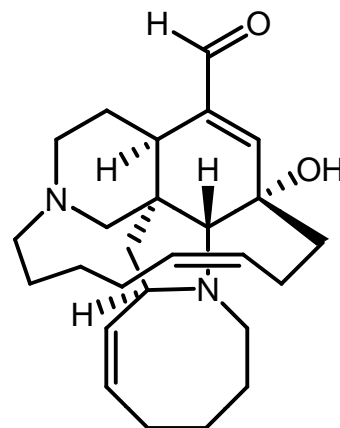
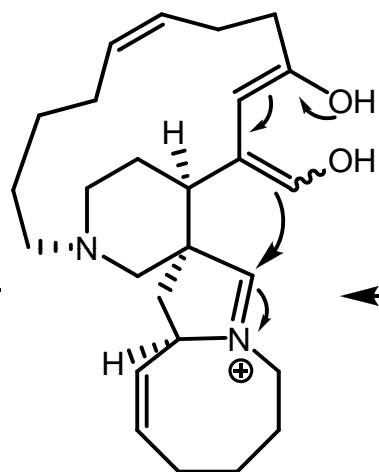
## ***Structural Features:***

- Tetracyclic core contains fused 6/5/5/5 ring system
- 3 different heterocycles
- 4 stereogenic centers, 1 quaternary
- Z-olefin

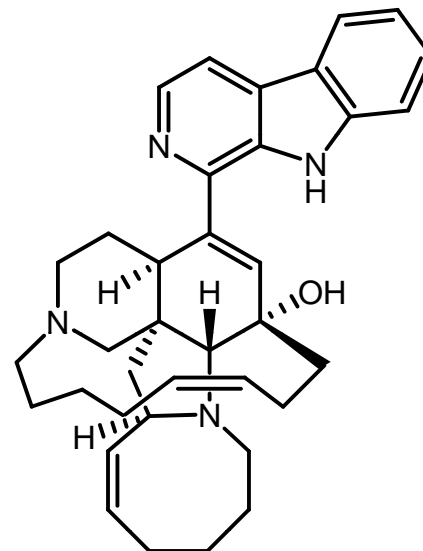
# Nakadomarin A: Proposed Biosynthesis



**(-)-Nakadomarin A**



**Ircinal**



**Manzamine A**

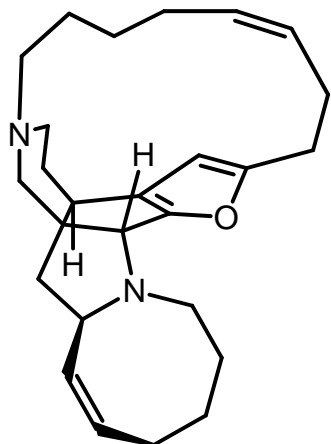
## Completed Syntheses:

(+)-Nakadomarin: Nagata, Nakagawa and Nishida 2003  
Young and Kerr 2007

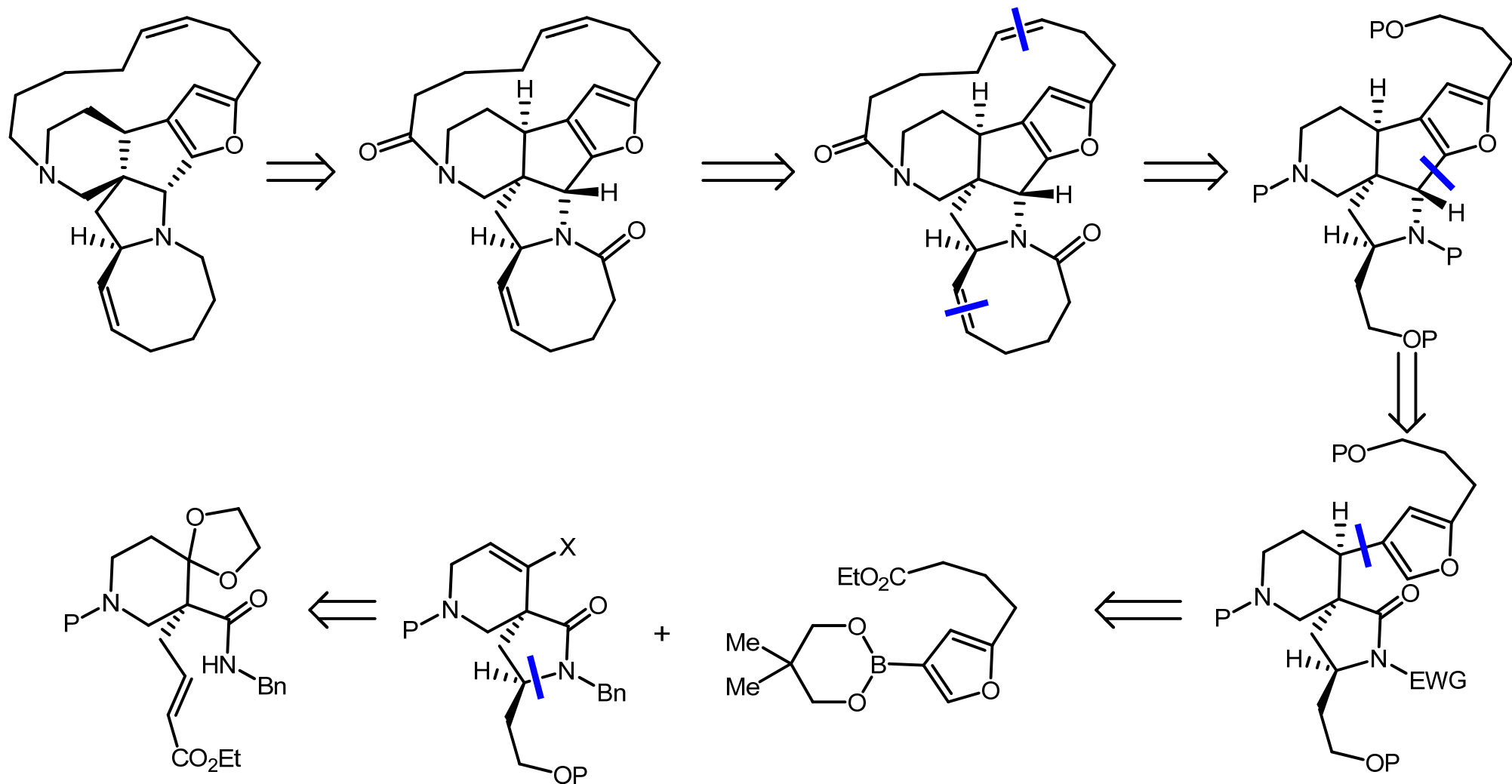
(-)-Nakadomarin: Ono, Nakagawa and Nishida 2004

## Published Approaches:

Furstner 1999  
Magnus 2002  
Tius 2003  
Williams 2004  
Funk 2006

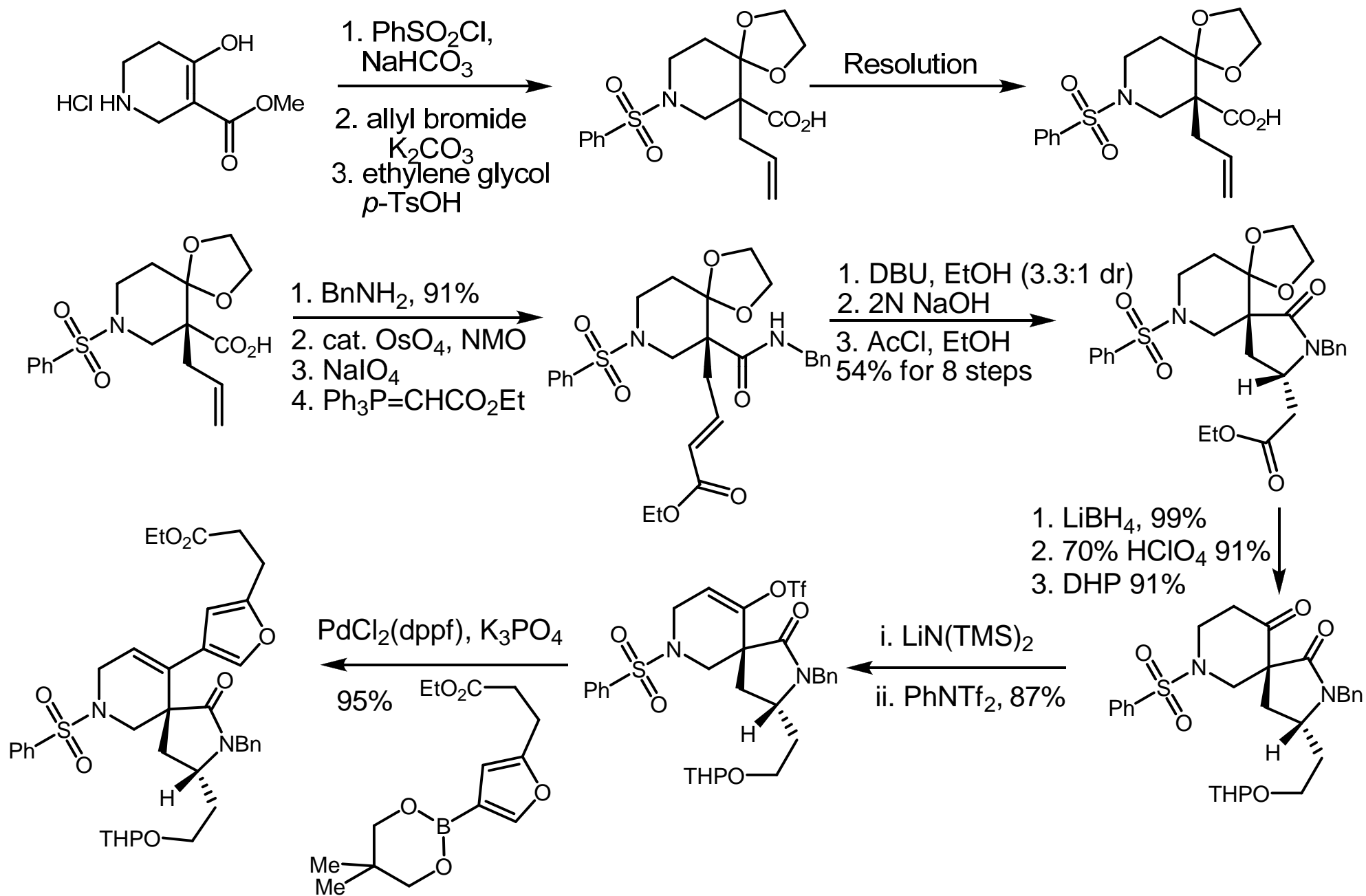


# Nakagawa's Retrosynthetic Analysis of Nakadomarin A

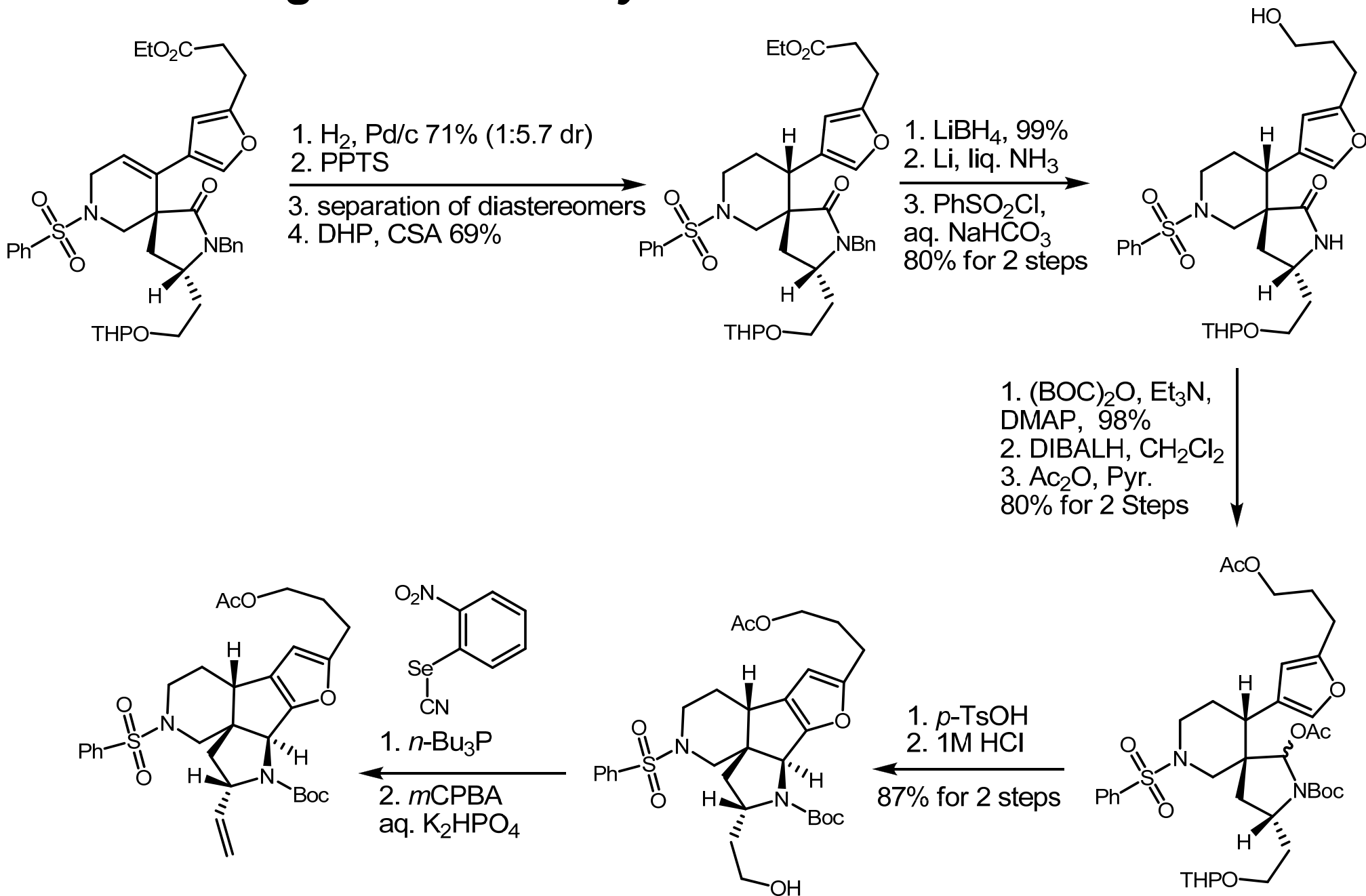


Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484-7485.

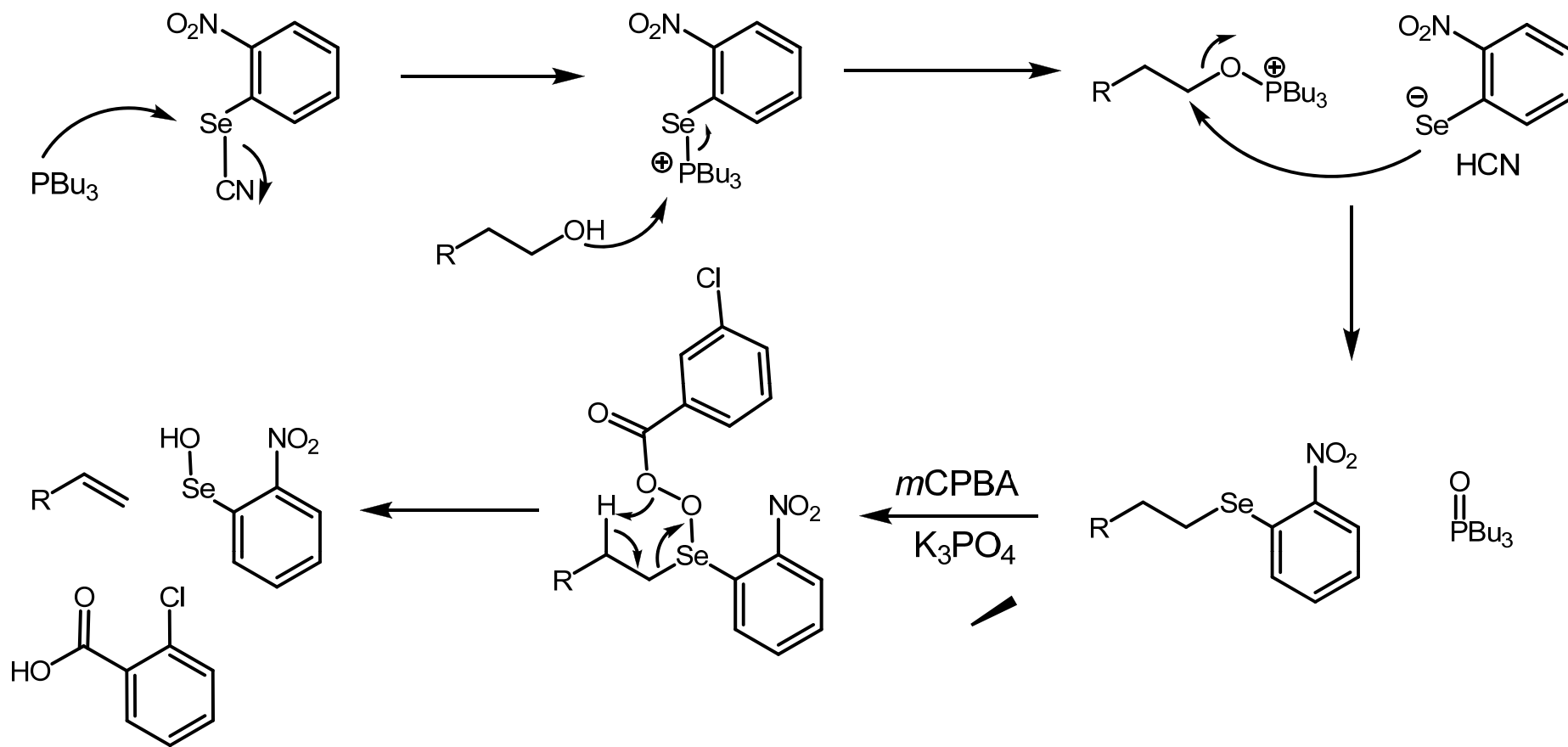
# Nakagawa's Total Synthesis of Nakadomarin A



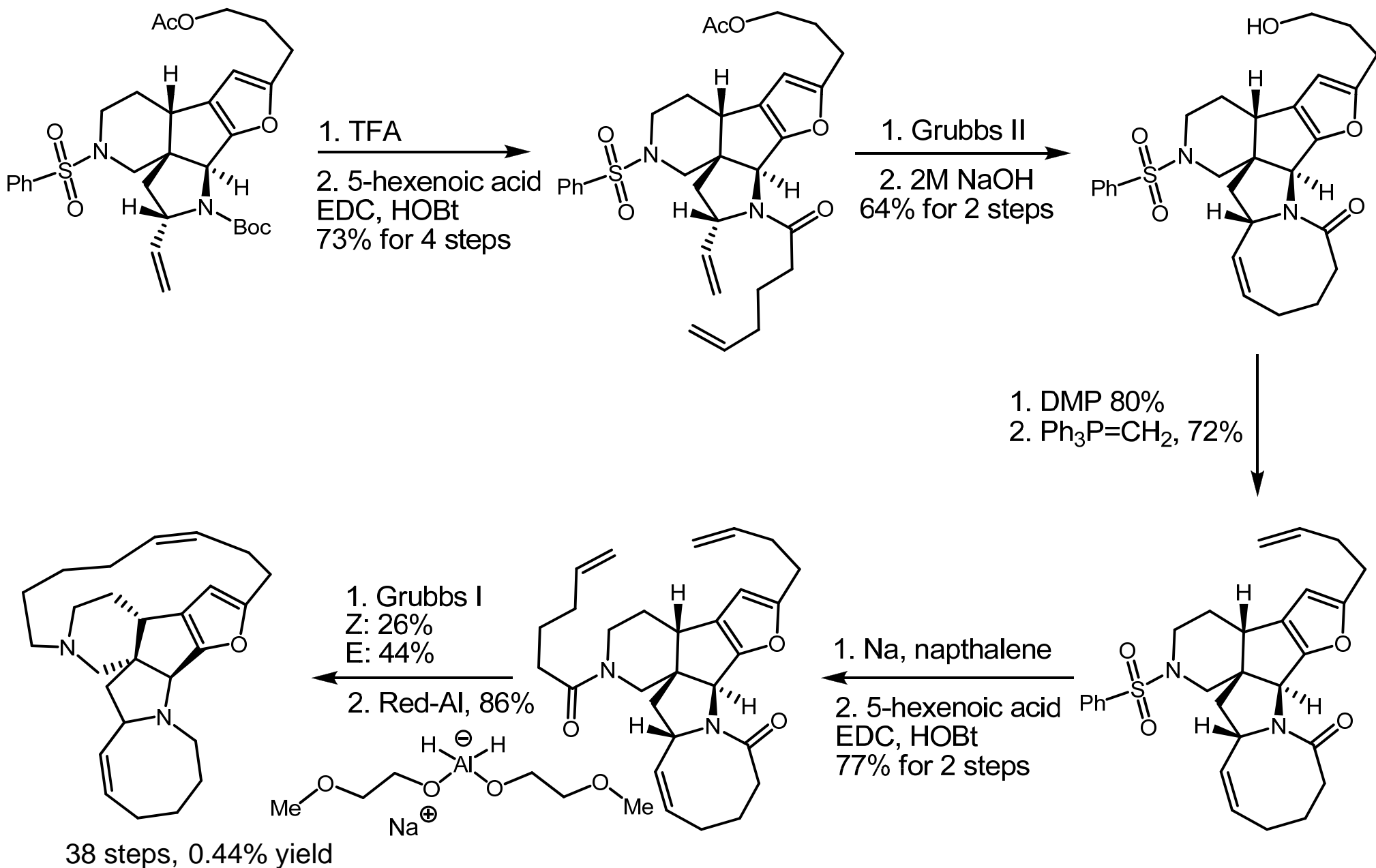
# Nakagawa's Total Synthesis of Nakadomarin A



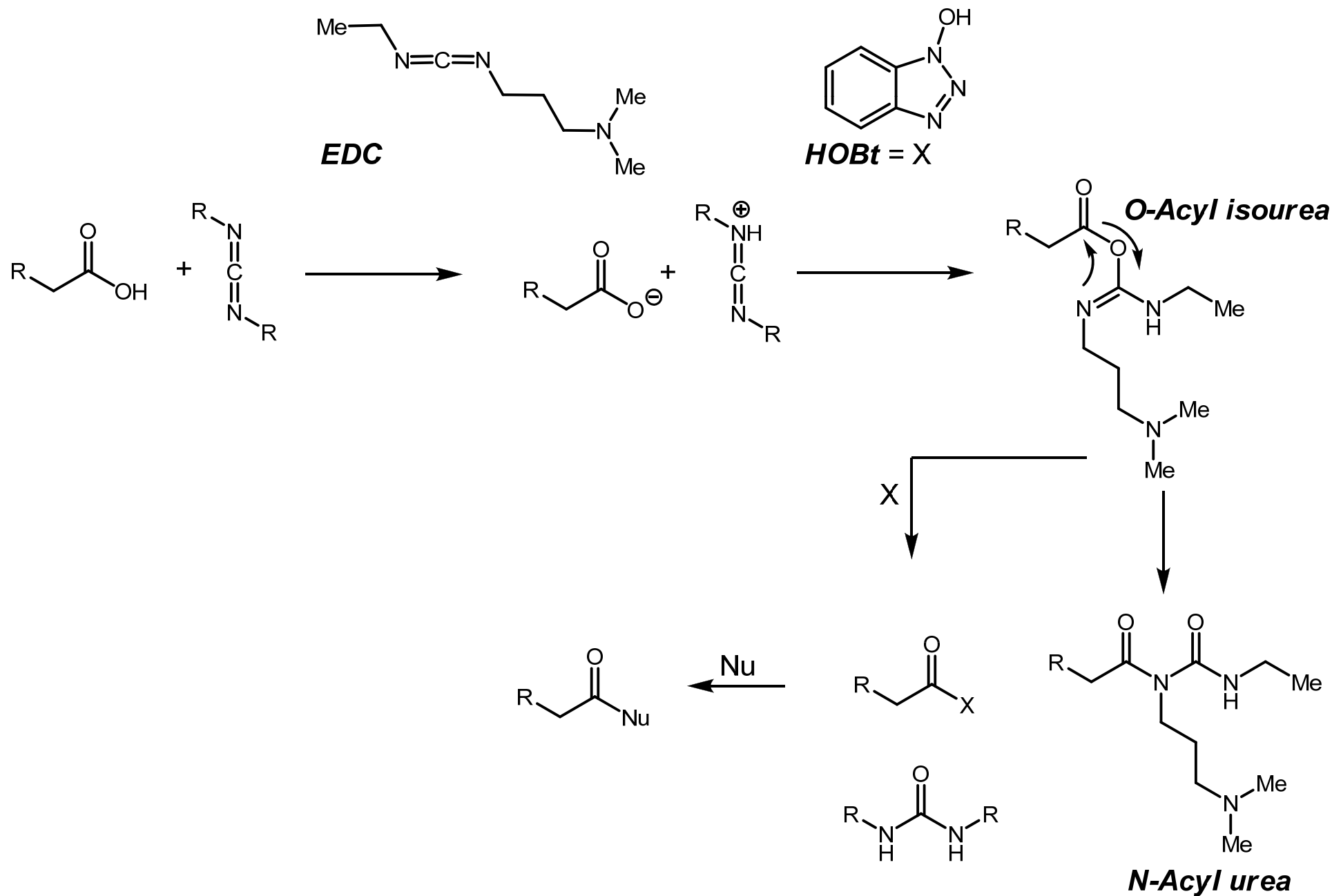
# Grieco Elimination



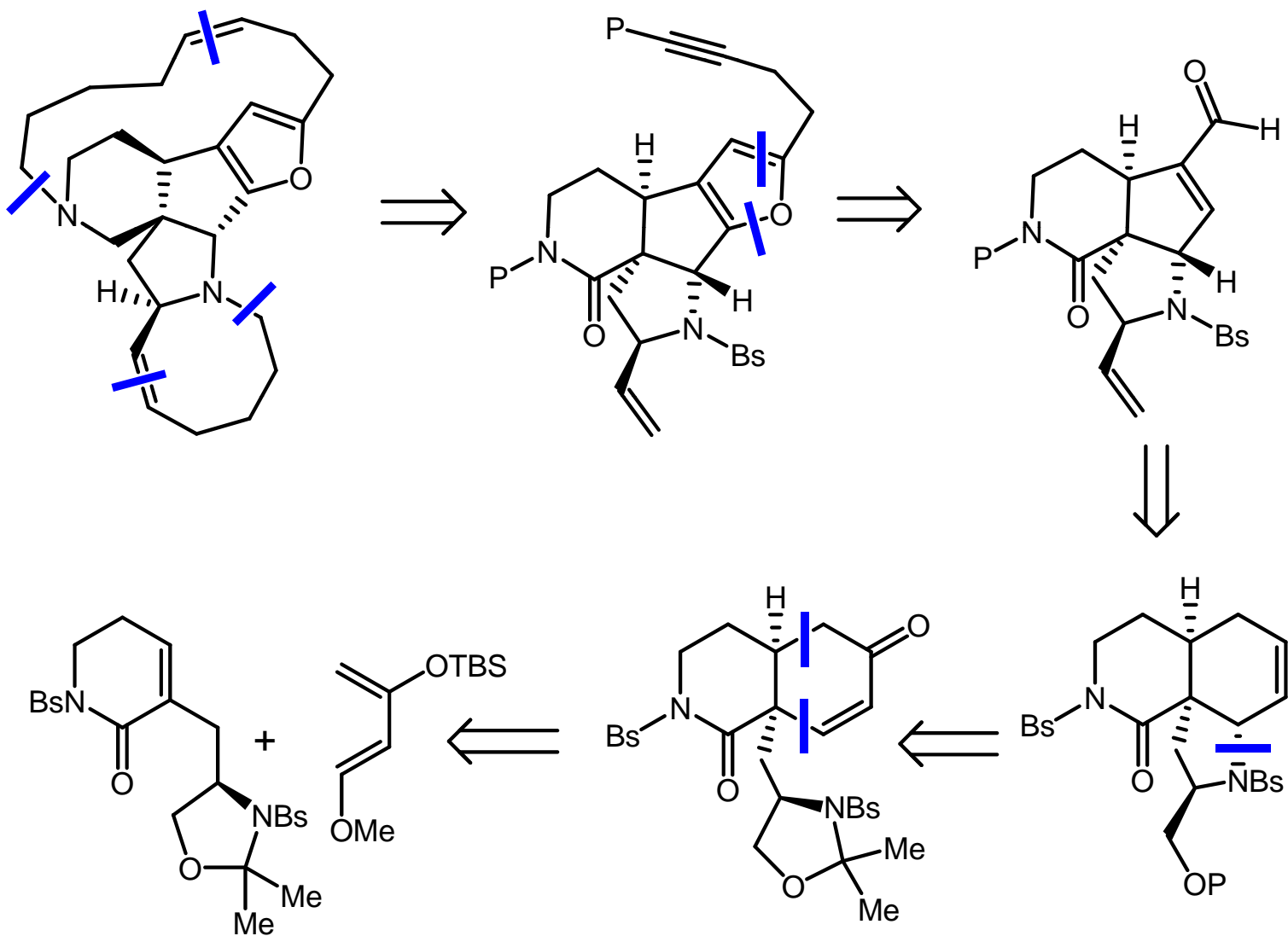
# Nakagawa's Total Synthesis of Nakadomarin A



# Acid Coupling with EDC and HOBt

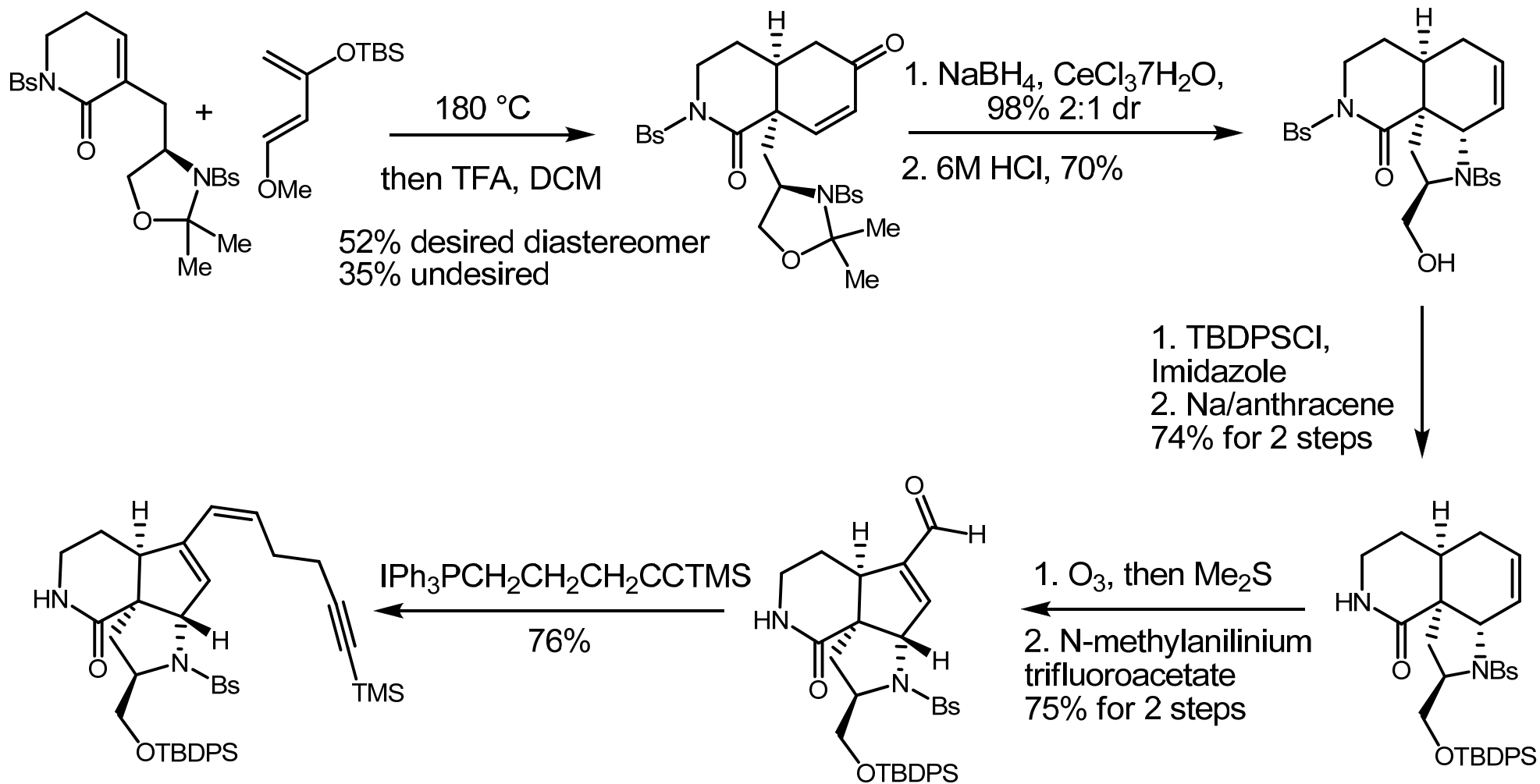


# Nakagawa's Retrosynthetic Analysis of (-)-Nakadomarin A

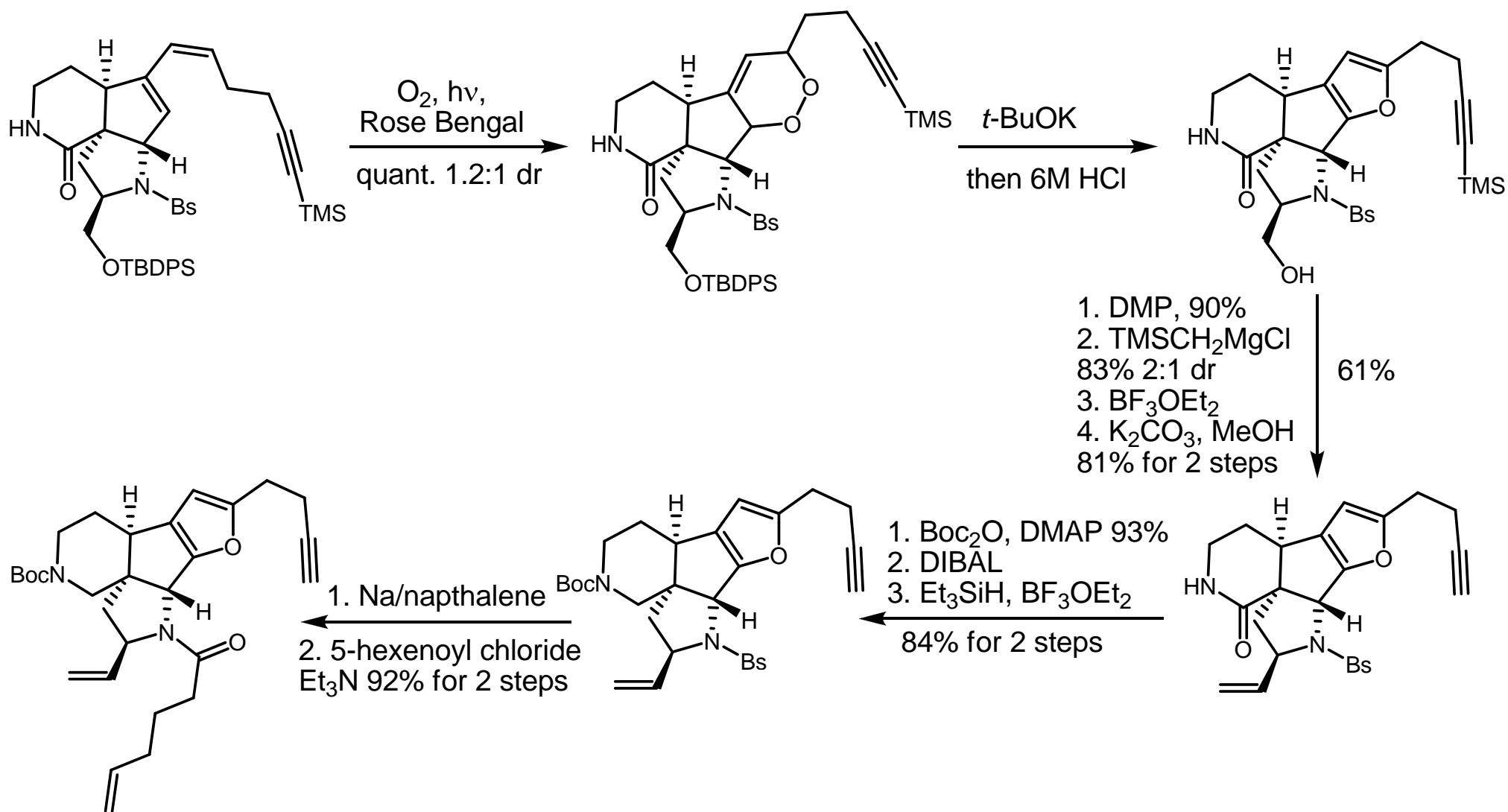


Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, 43, 2020-2023.

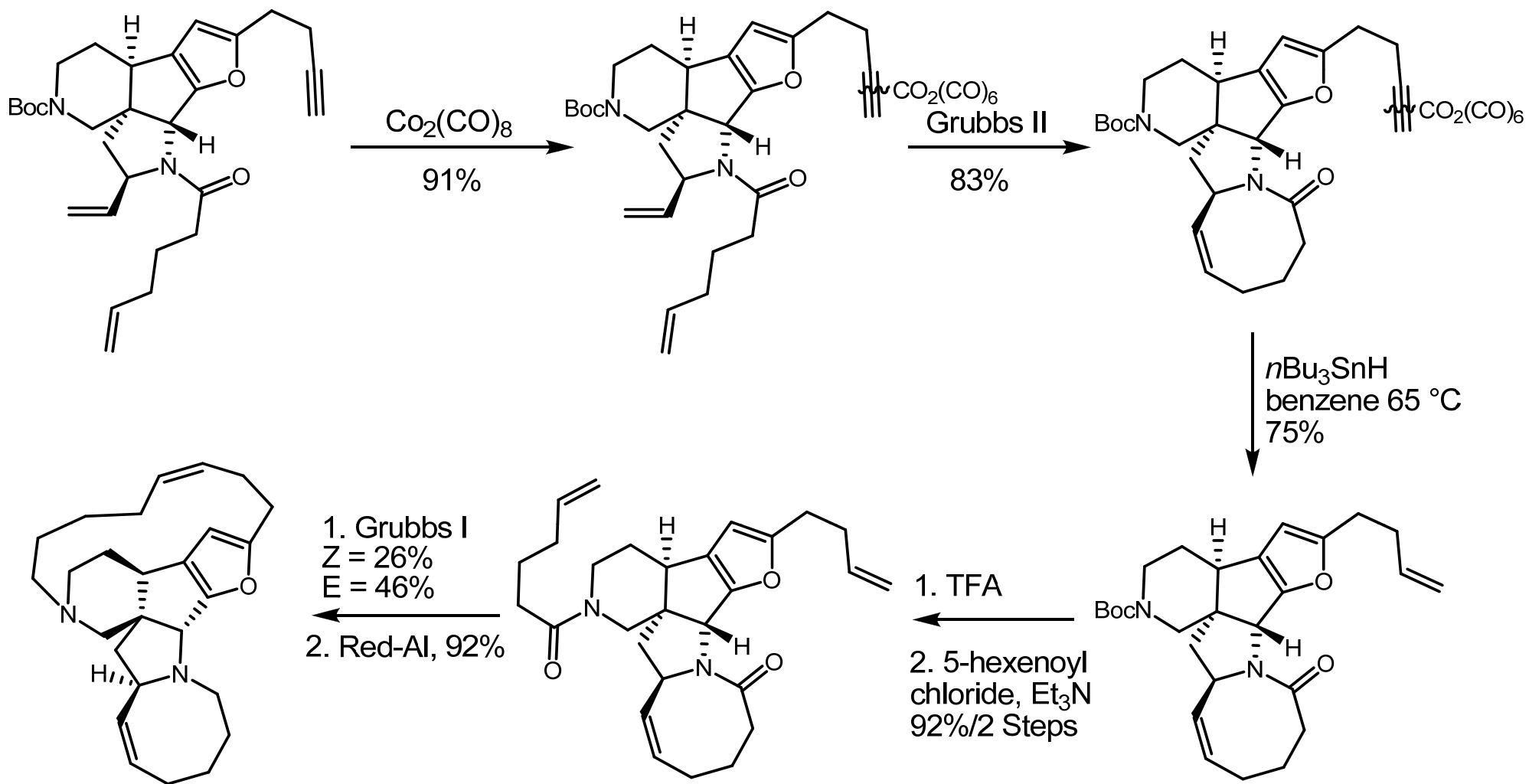
# Nakagawa's Retrosynthetic Analysis of (-)-Nakadomarin A



# Nakagawa's Retrosynthetic Analysis of (-)-Nakadomarin A

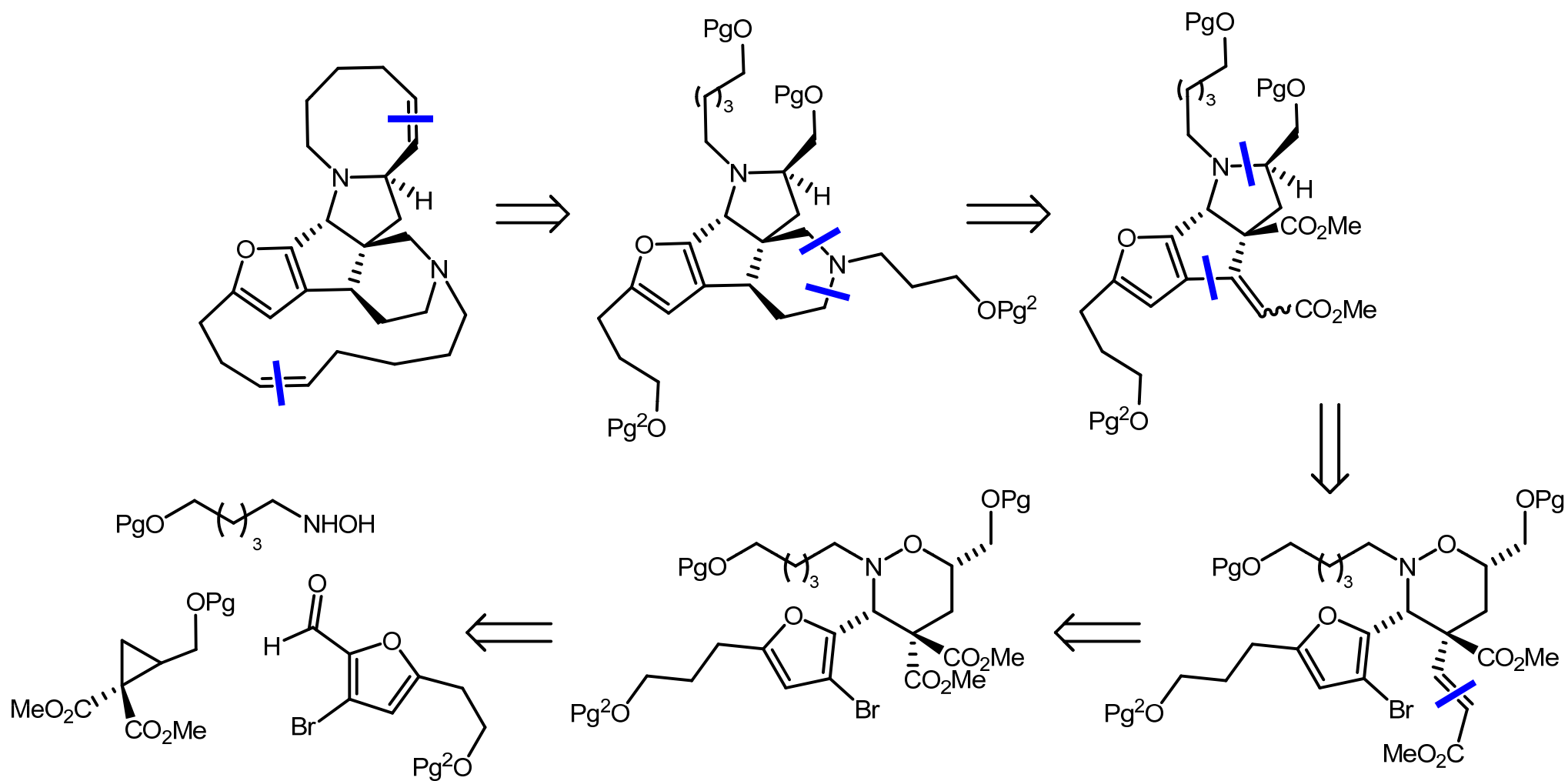


# Nakagawa's Retrosynthetic Analysis of (-)-Nakadomarin A



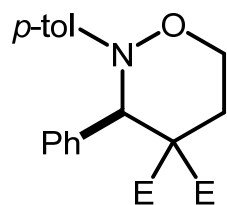
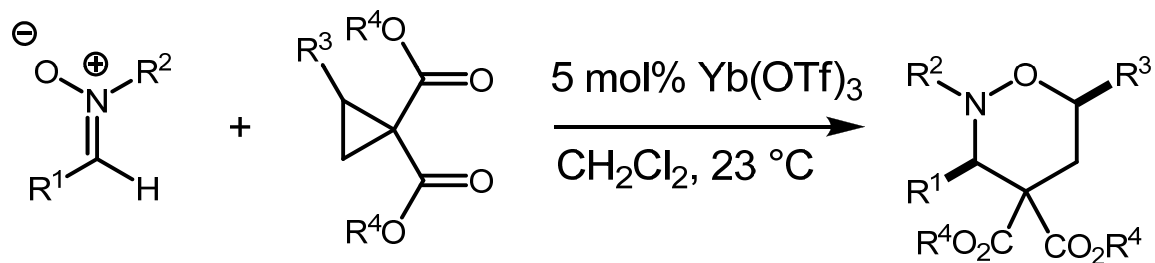
36 steps, 0.42% yield

# Kerr's Retrosynthetic Analysis of Nakadomarin A

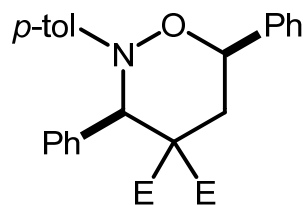


Young, I.; Kerr, M. *J. Am. Chem. Soc.* **2007**, *129*, 1465-1469.

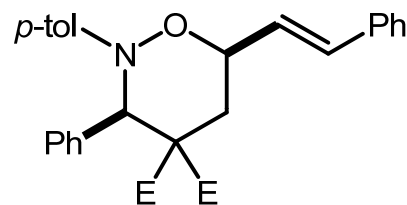
# Kerr's Synthesis of Nakadomarin A: Development of [3+2] Dipolar Cycloaddition



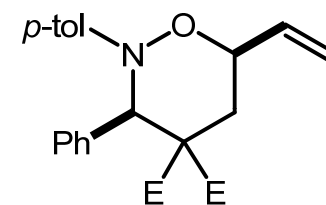
77%



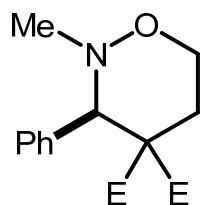
94%



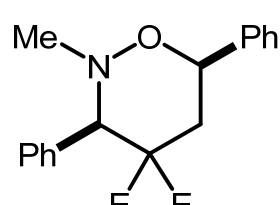
95%



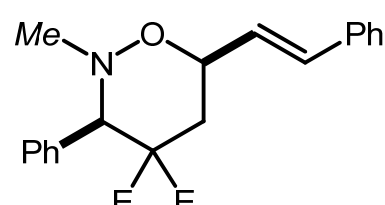
73%



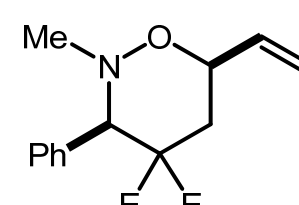
76%



84%

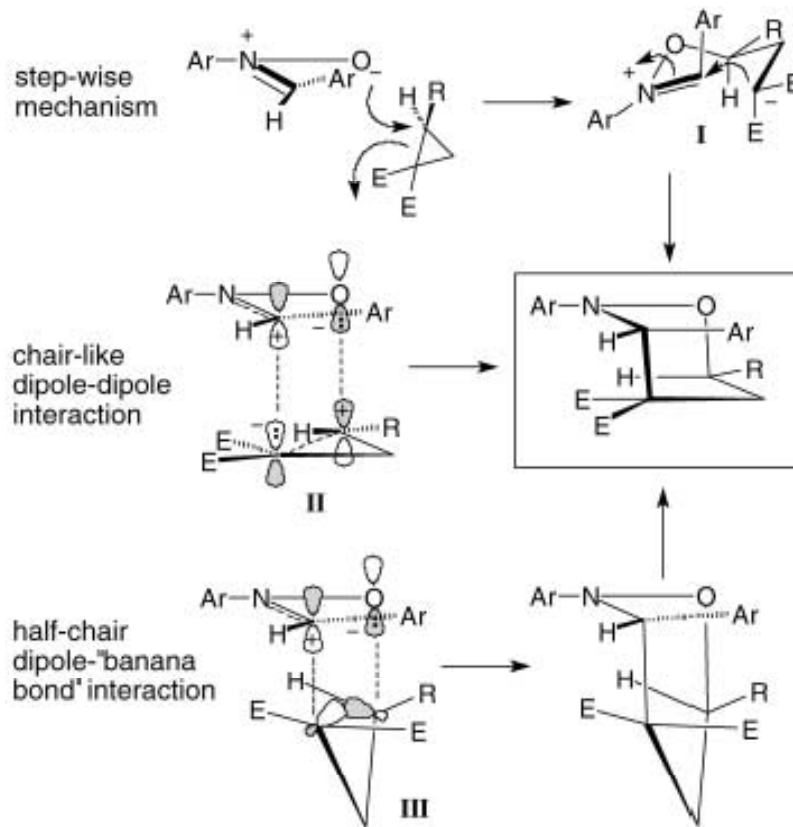
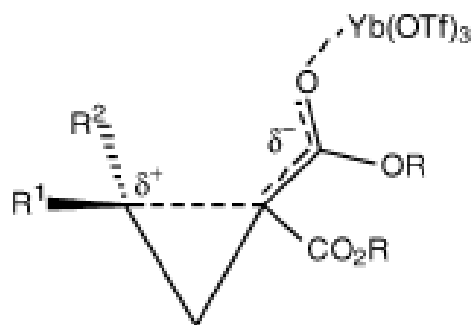
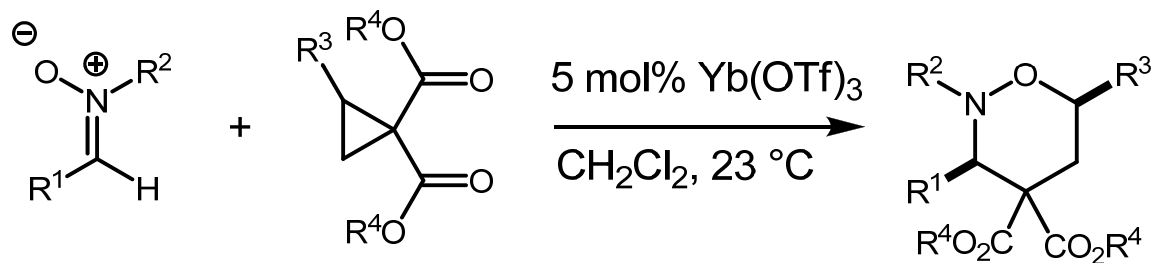


74%

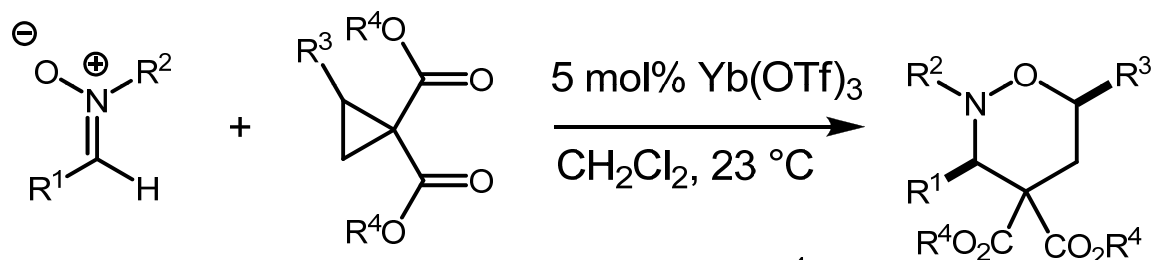


52%

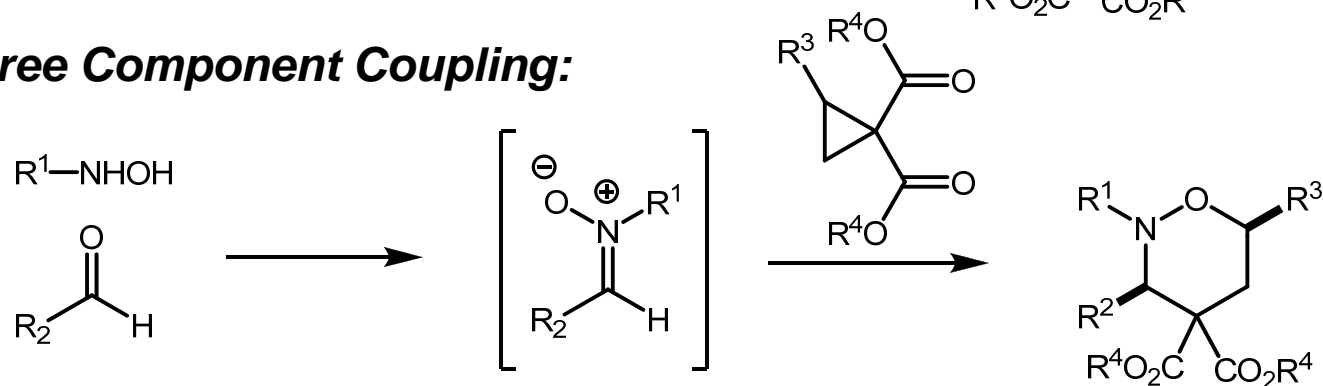
# Kerr's Synthesis of Nakadomarin A: Development of [3+2] Dipolar Cycloaddition



# Kerr's Synthesis of Nakadomarin A: Improvement of [3+2] Dipolar Cycloaddition

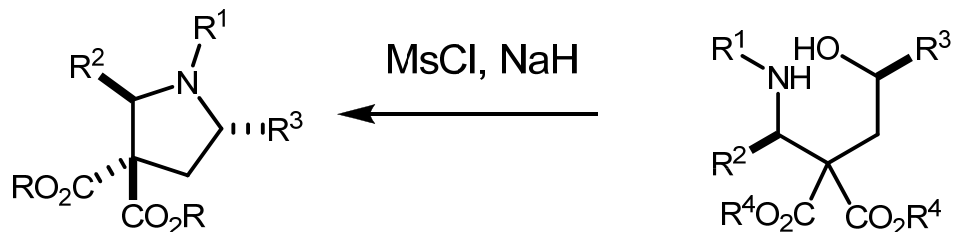


## Three Component Coupling:



**NO Bond Cleavage**

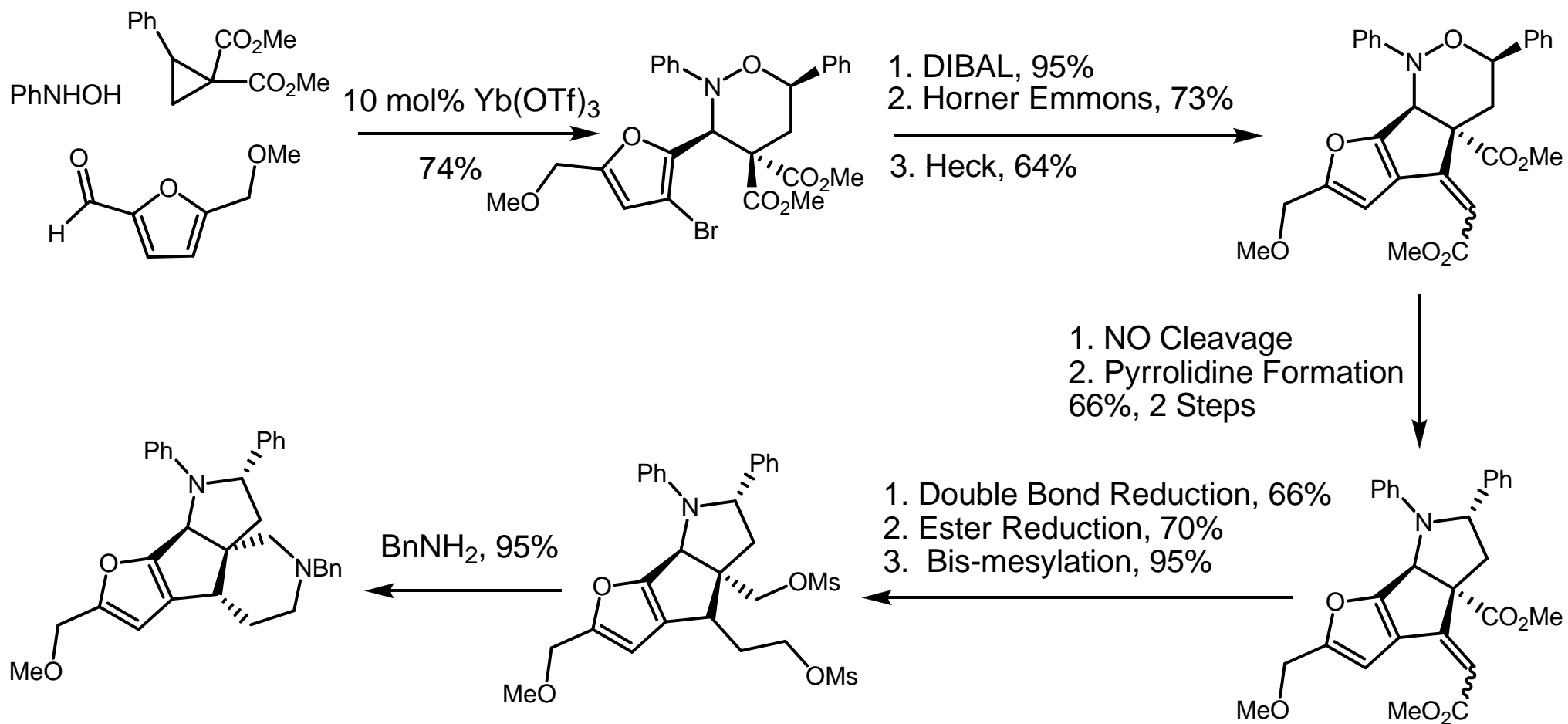
Sml<sub>2</sub>  
H<sub>2</sub> Pd/C  
Raney Nickel



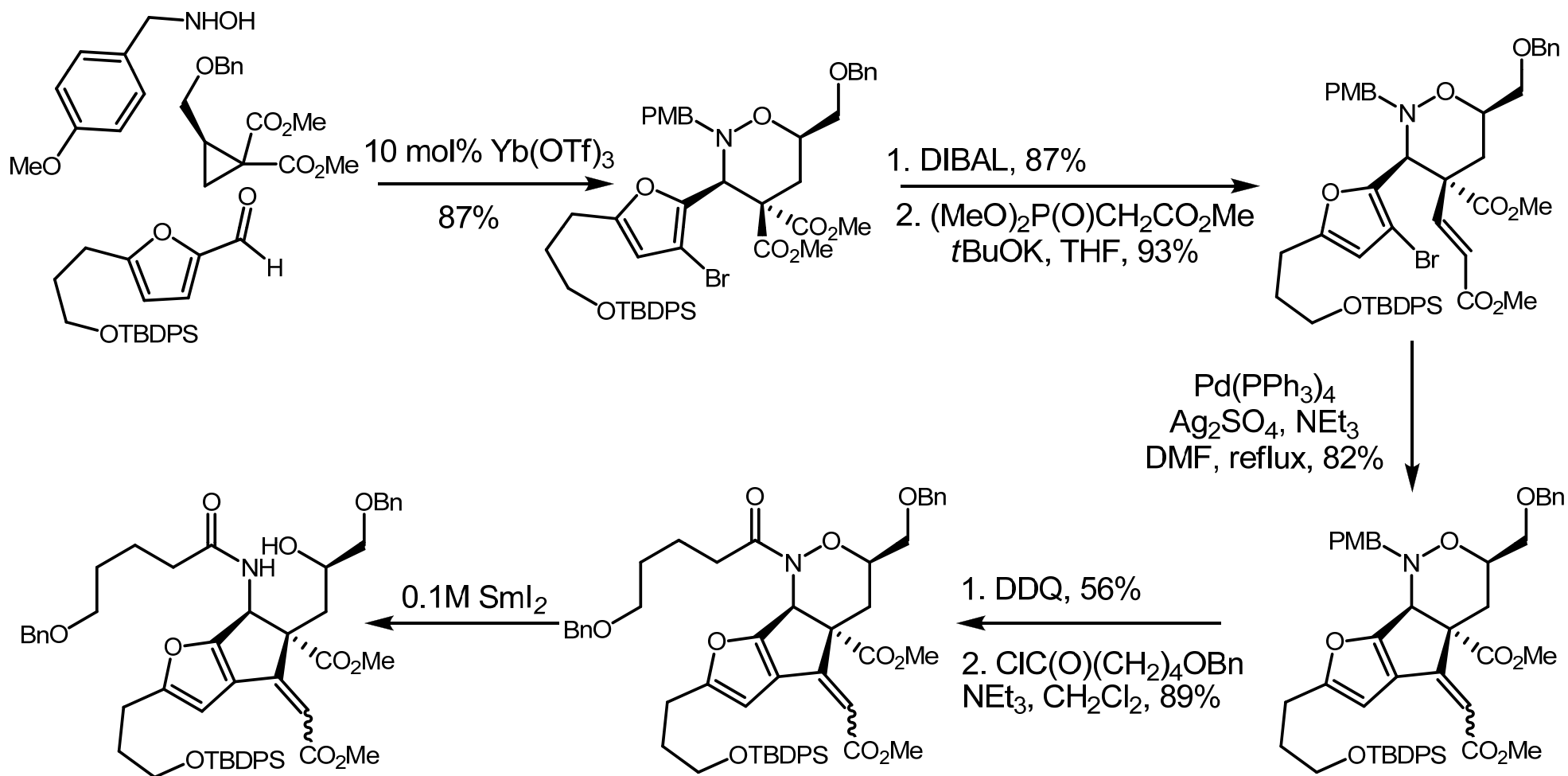
Young, I.; Kerr, M. *Org. Lett.* **2004**, 6, 139-141.

Young, I.; Williams, J.; Kerr, M. *Org. Lett.* **2005**, 7, 953-955.

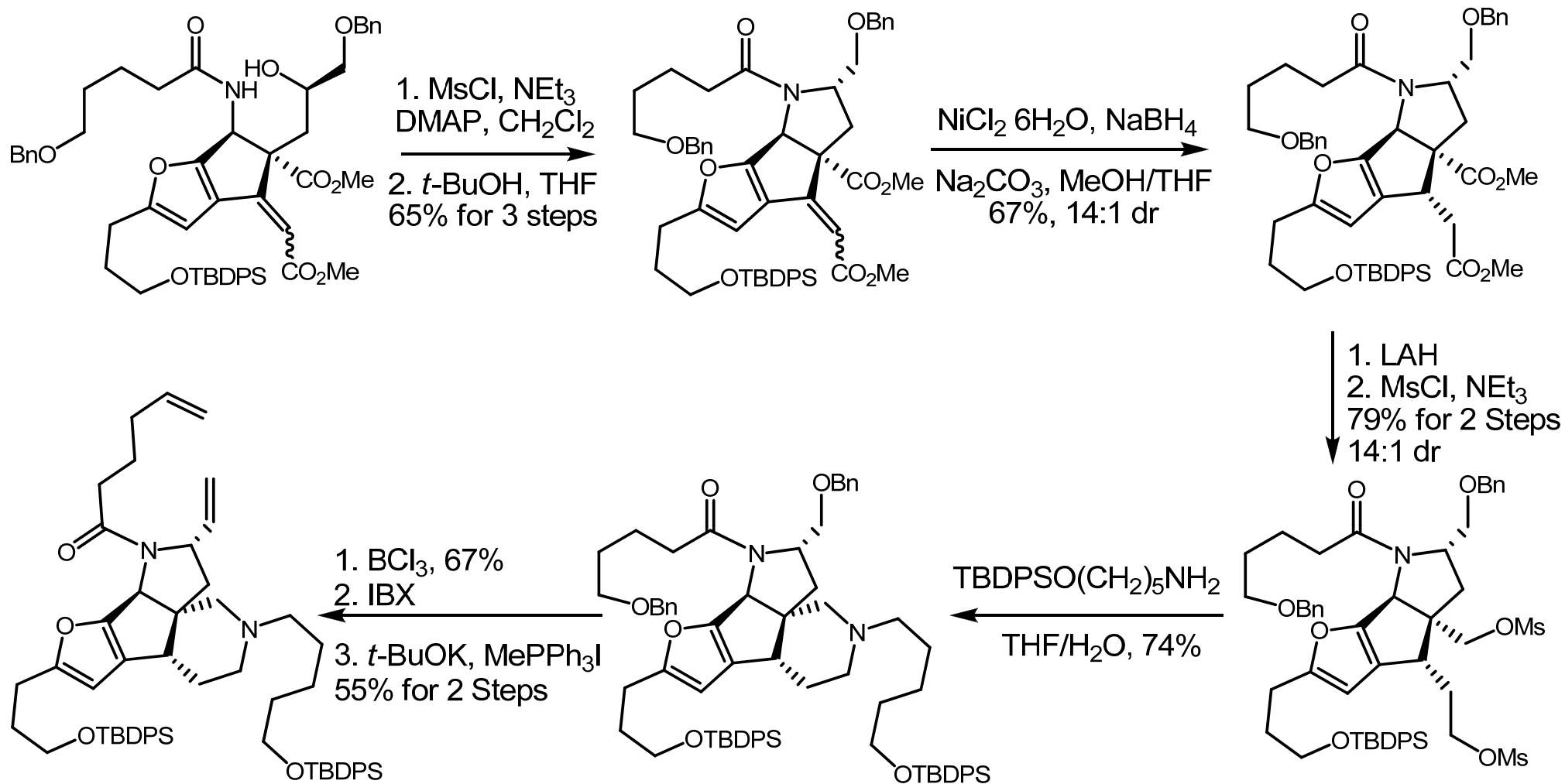
# Kerr's Synthesis of Nakadomarin A: Tetracyclic Core Model Studies



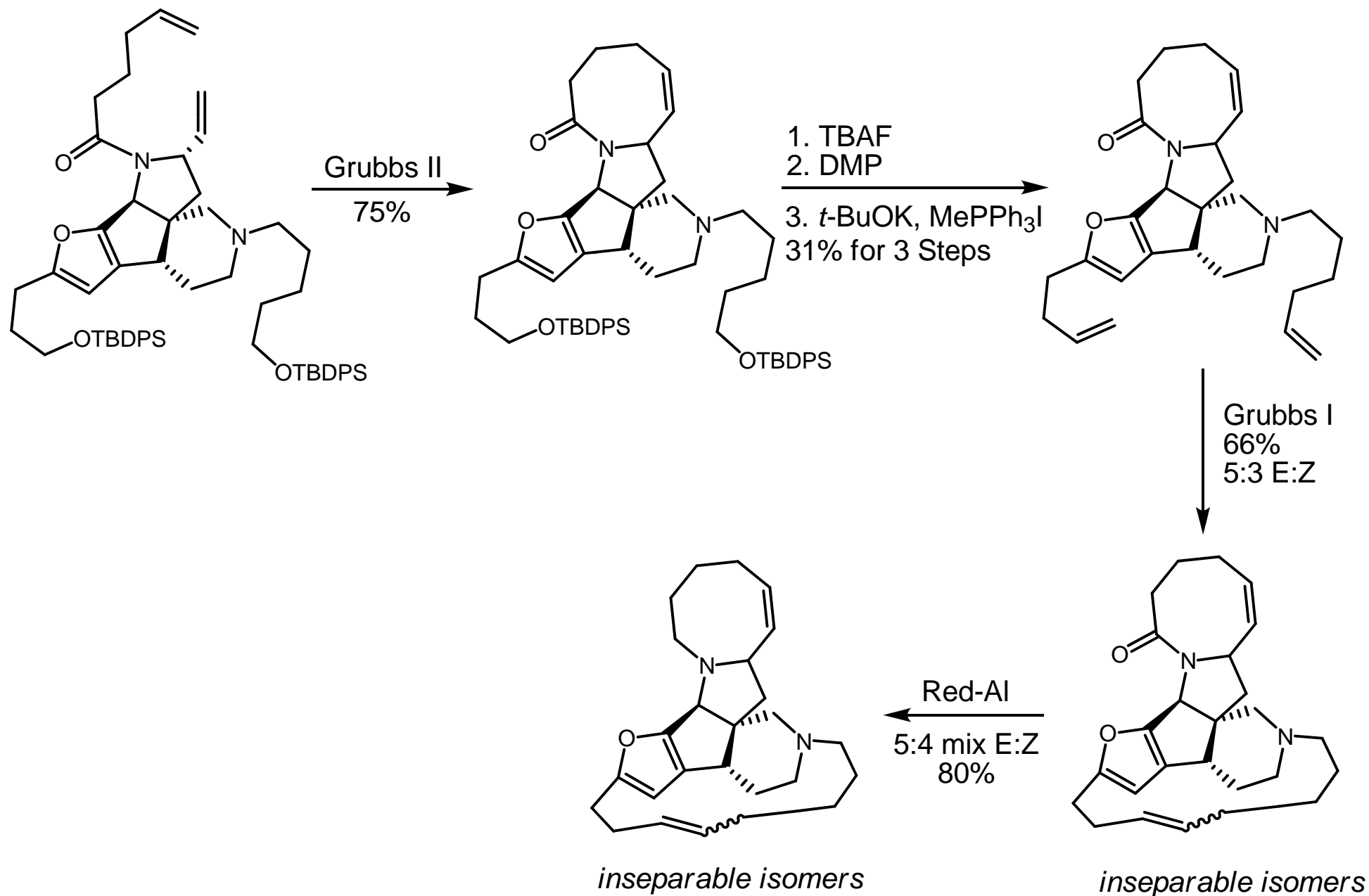
# Kerr's Synthesis of Nakadomarin A



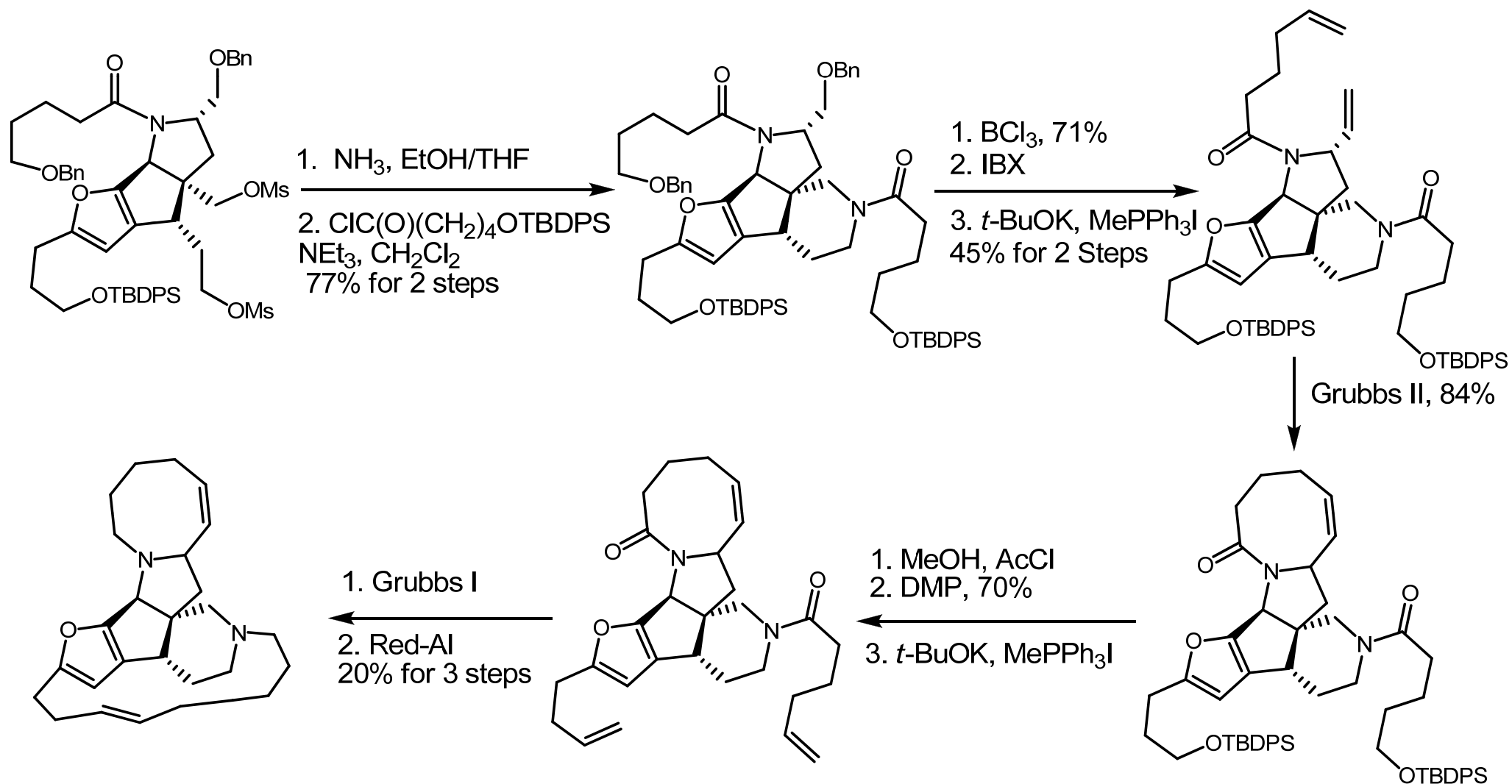
# Kerr's Synthesis of Nakadomarin A



# Kerr's Synthesis of Nakadomarin A



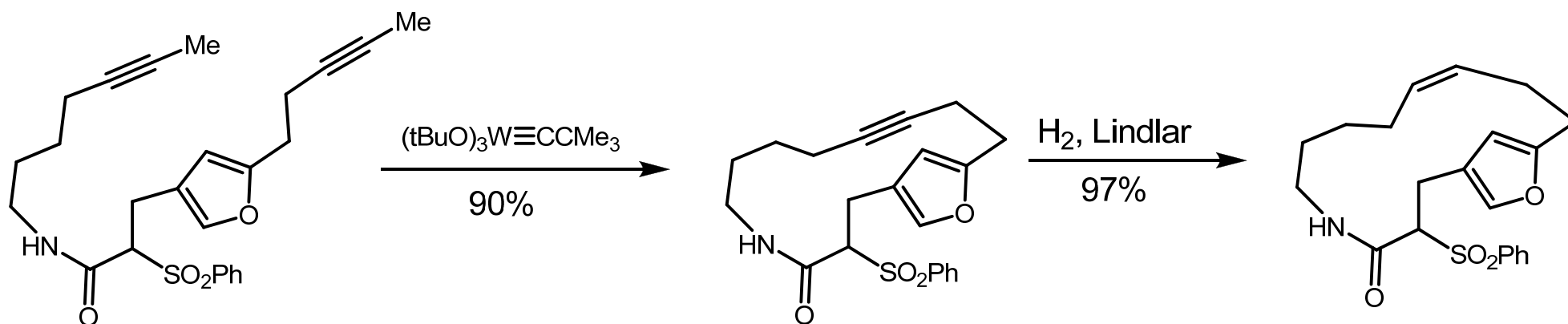
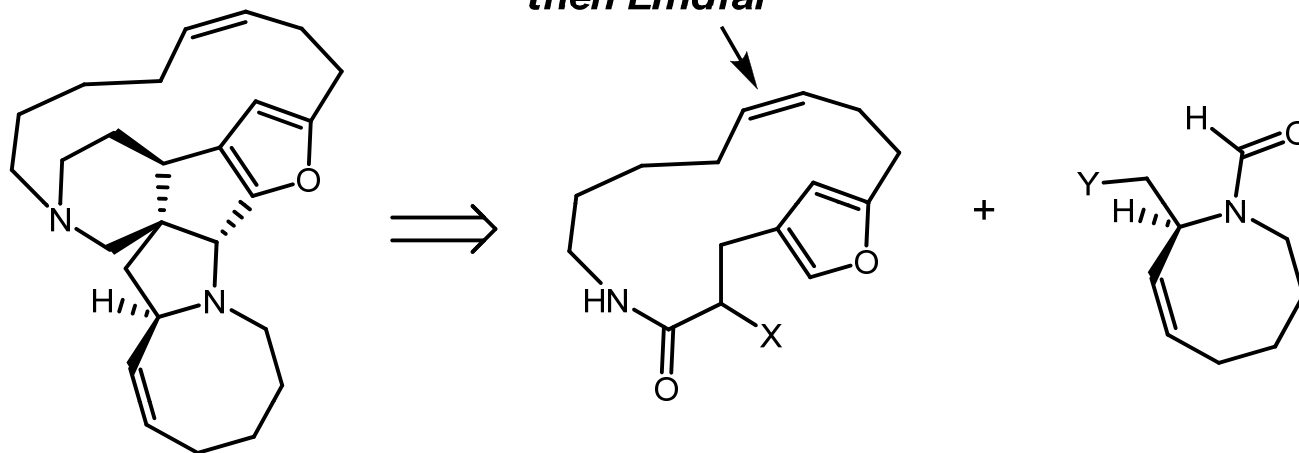
# Kerr's Synthesis of Nakadomarin A: Revised Endgame



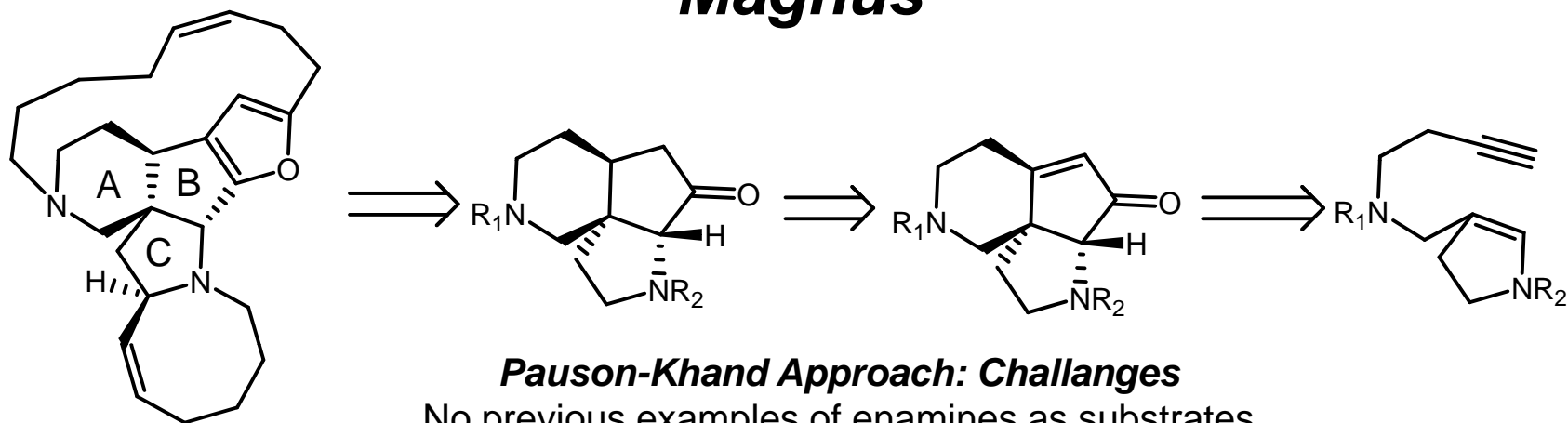
23 steps, 0.29% yield

# Approaches Toward Nakadomarin A: Furstner

*Diyne Metathesis  
then Lindlar*



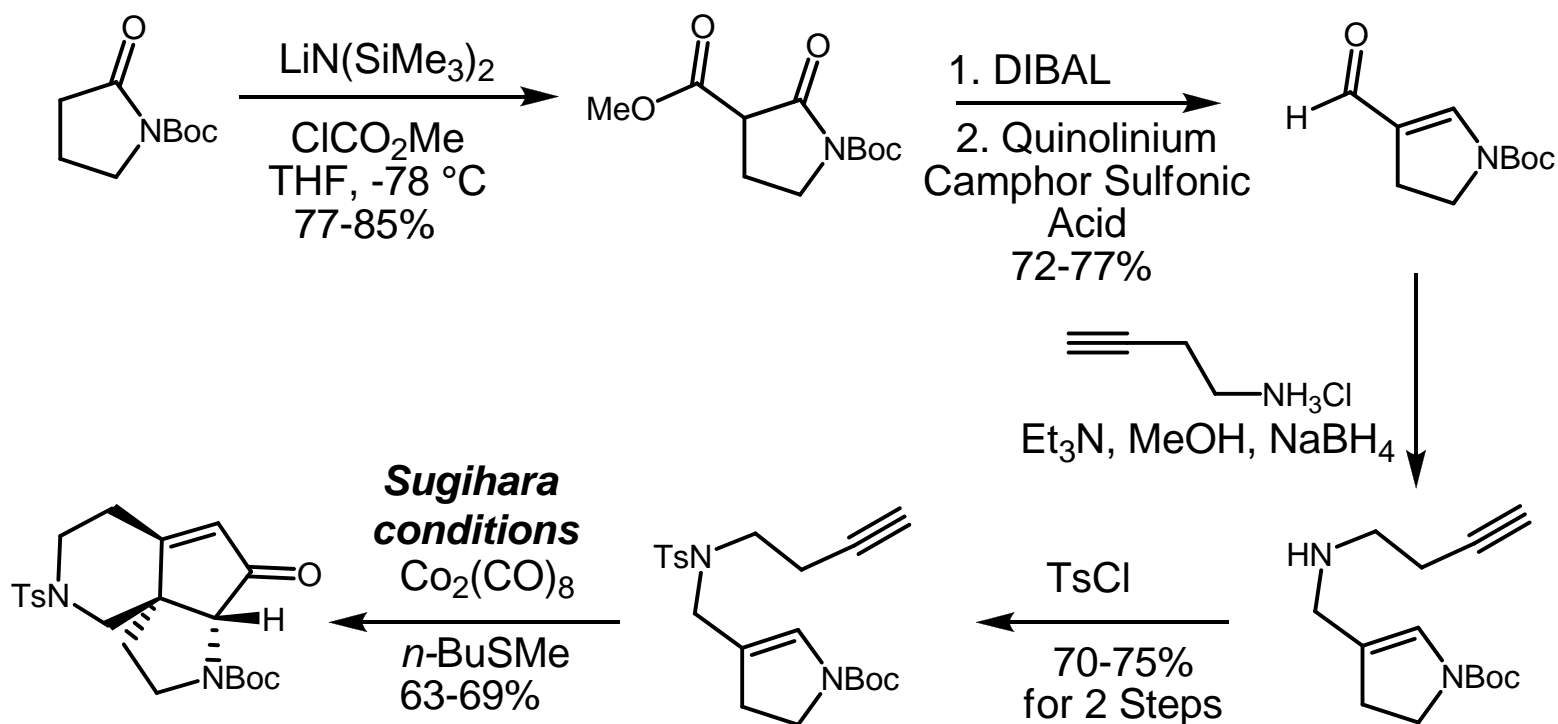
# Approaches Toward Nakadomarin A: Magnus



## Pauson-Khand Approach: Challenges

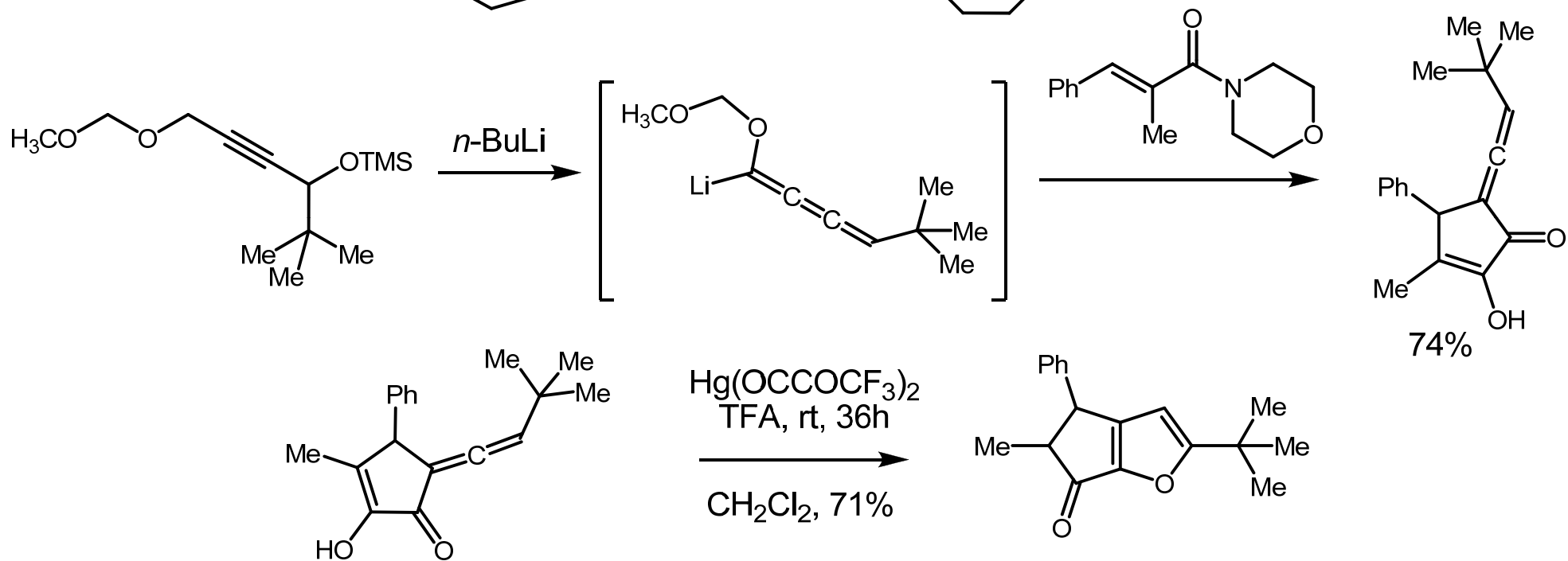
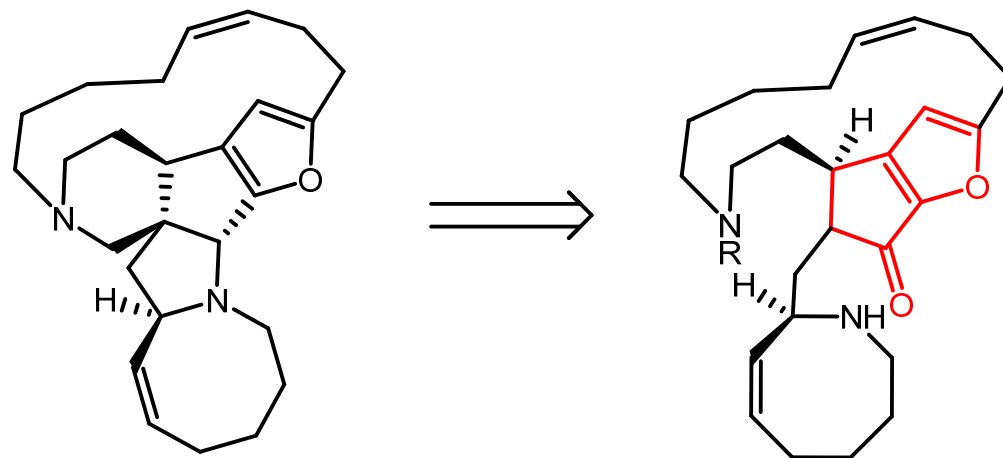
No previous examples of enamines as substrates

Creates a quaternary center



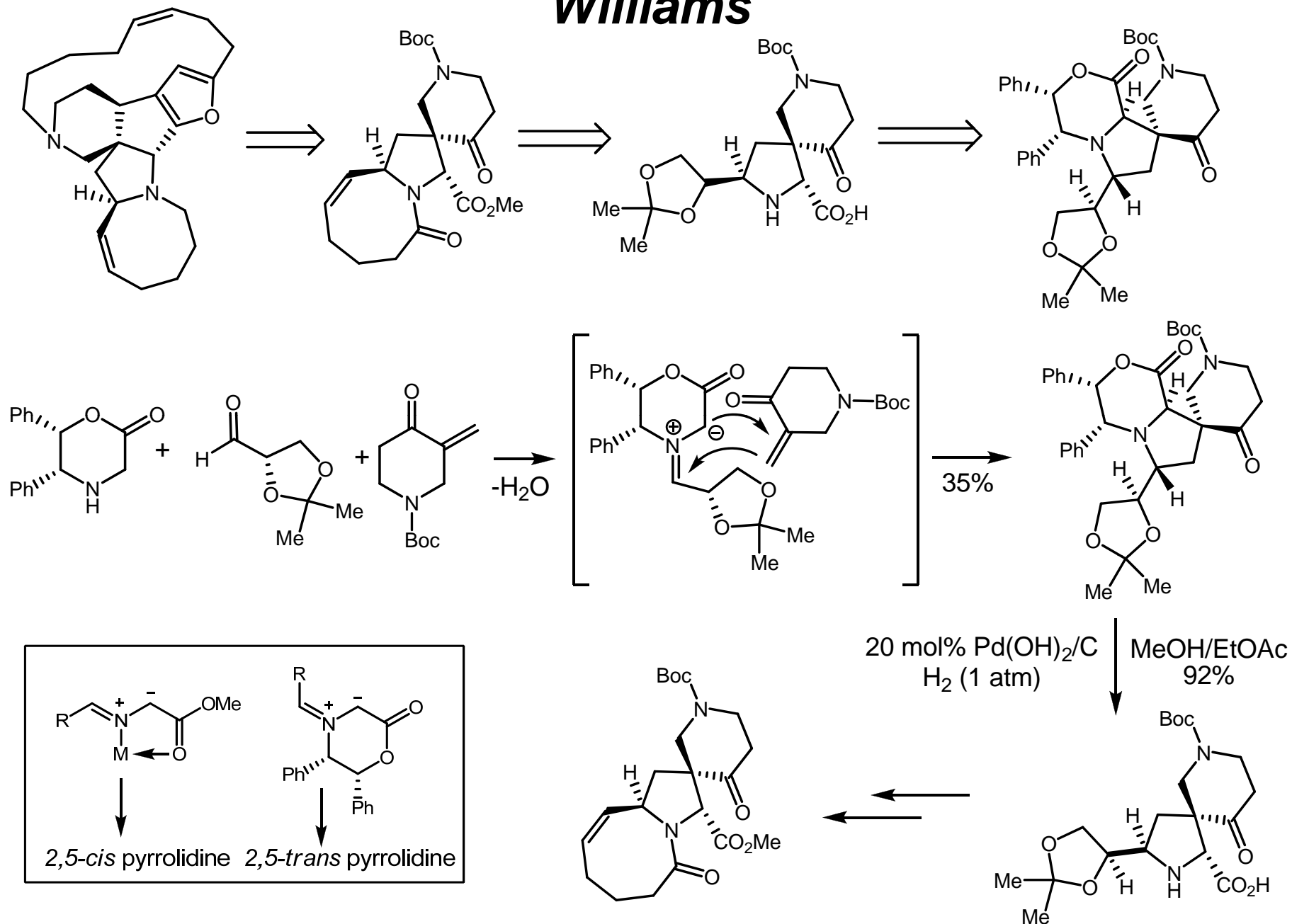
Magnus, P.; Fielding, M.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, 43, 947-950.

# Approaches Toward Nakadomarin A: Tius



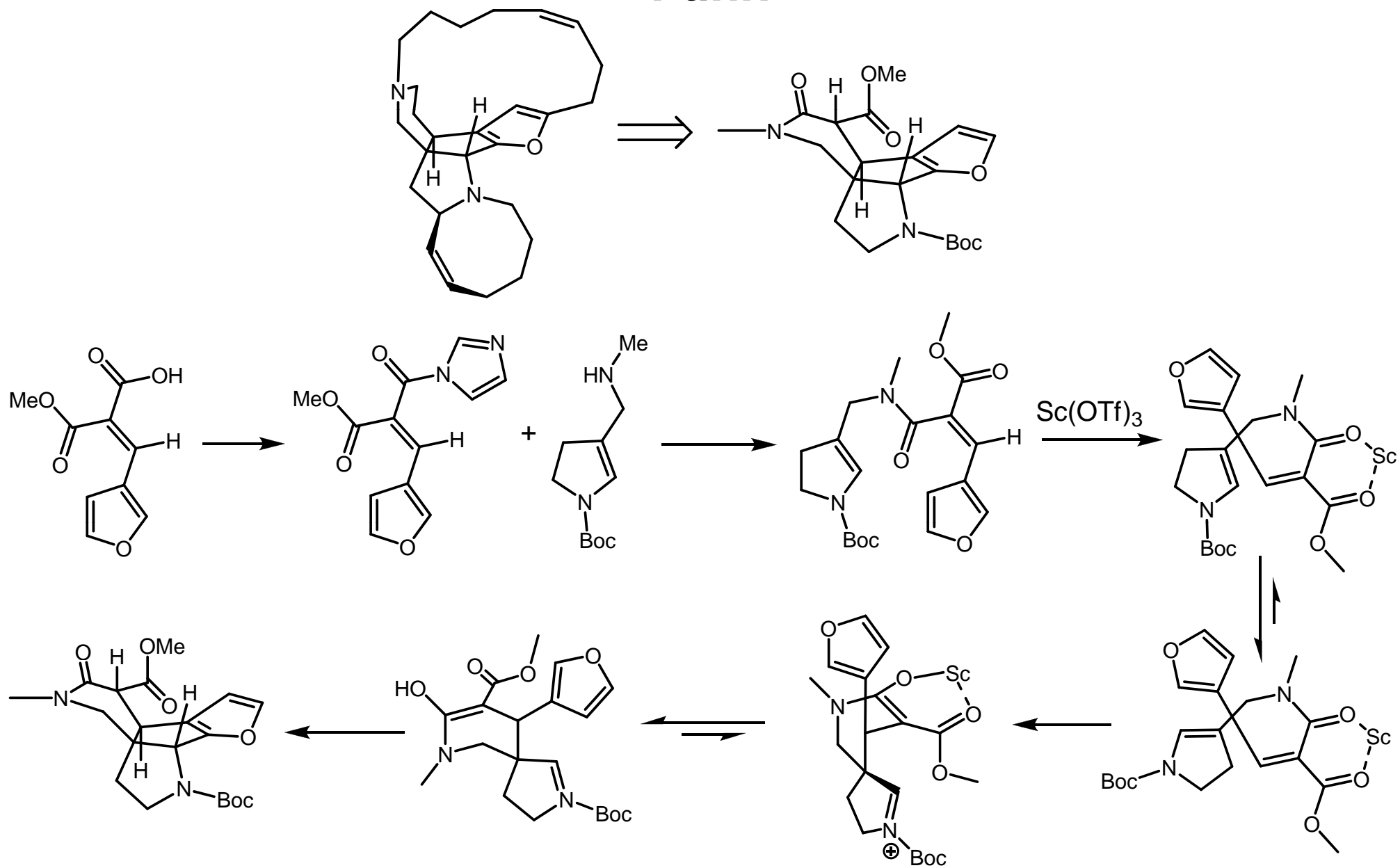
LecLerc, E.; Tius, M. *Org. Lett.* **2003**, *5*, 1171-1174

# Approaches Toward Nakadomarin A: Williams



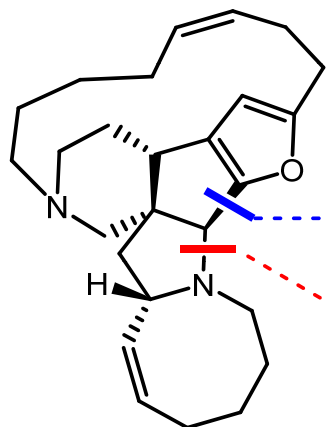
Ahrendt, K.; Williams, R. *Org. Lett.* **2004**, *6*, 4539-4541.

# Approaches Toward Nakadomarin A: Funk



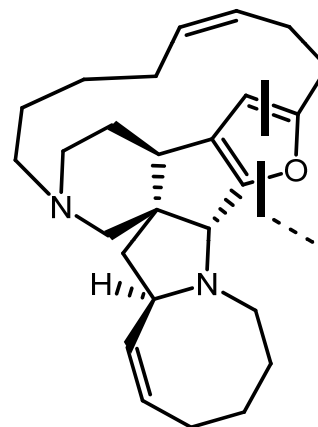
Nilson, M.; Funk, R. *Org. Lett.* **2006**, *8*, 3833-3836.

# Syntheses of Nakadomarin A: Summary

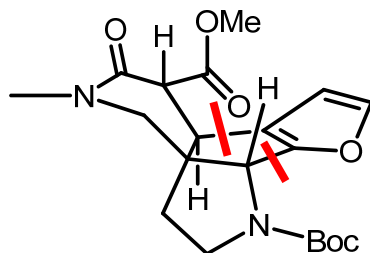


**Nakagawa and Nishida:**  
Addition to iminium

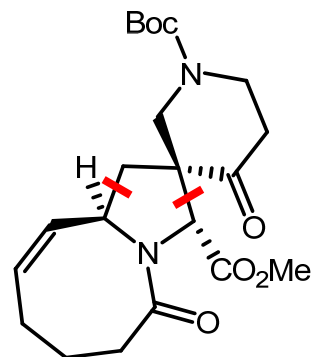
**Young and Kerr:**  
[3+2] to oxarine  
then intramolecular  
substitution



**Nakagawa and Nishida:**  
Singlet oxygen addition



**Funk:** Iminium Ion Addition



**Williams:** 1,3 Dipolar Cycloaddition