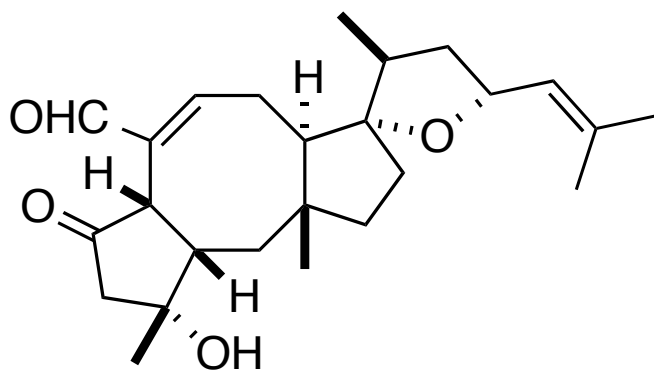


# Convergent Total Synthesis of (+)-Ophiobolin A

Tsuna, K.; Noguchi, N.; Nakada, M. *Angew. Chem. Int. Ed.* **2011**, 50, ASAP



(+)-ophiobolin A



*Eric E. Buck*  
*Current Literature*  
*October 8, 2011*

# Background and Bioactivity of (+)-Ophiobolin A

- Isolated from the culture broth of the pathogenic plant fungus *Ophiobolus miyabeanus* (among others) in 1958. The picture right is the effect of this fungus on rice plants.



- The absolute structure was elucidated through X-ray analysis of a derivative.

- Induces apoptotic cell death in the L1210 cell line.

- Inhibits calmodulin-activated cyclic nucleotide phosphodiesterase through interaction with the  $\epsilon$ -amino lysine group of calmodulin and the aldehyde function of ophiobolin A.

- Shows potent ( $IC_{50}$  62.5 to 125 nM) cytotoxicity against several cancer cell lines.

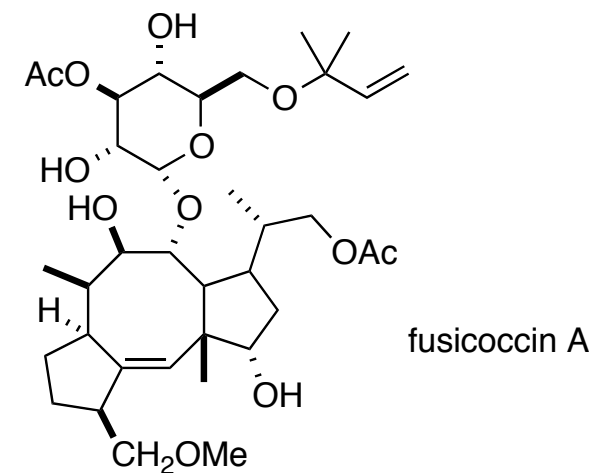
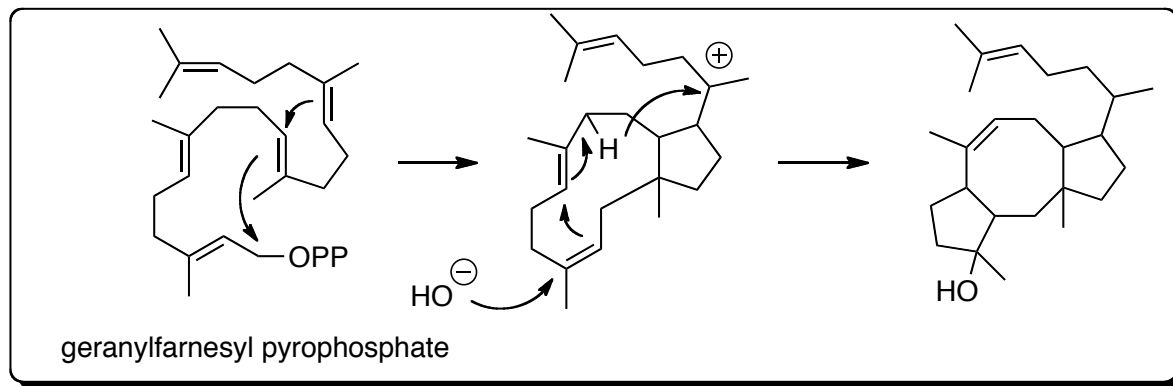
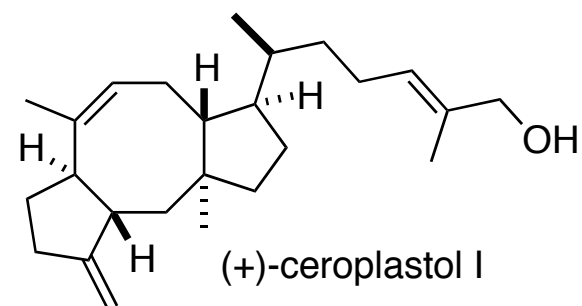
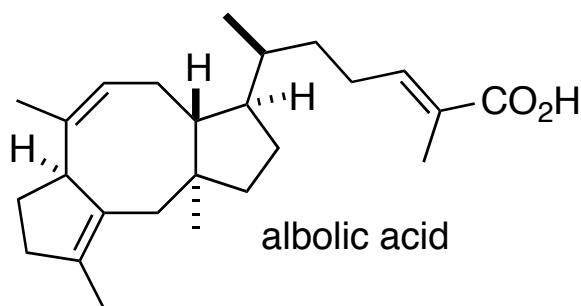
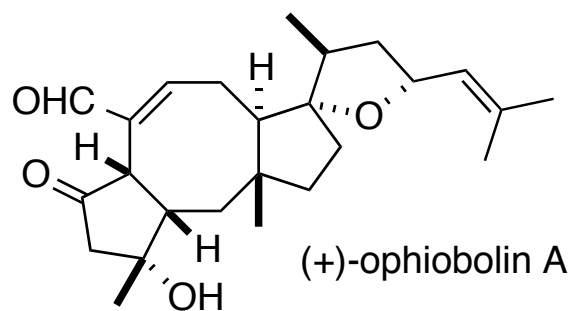
Shen, X.; Krasnoff, S. B.; Lu, S.; Dunbar, C. D.; O'Neal, J.; Turgeon, B. G.; Yoder, O. C.; Gibson, D. M.; Hamann, M. T. *J. Nat. Prod.* **1999**, 62, 895-897

Leung, P. C.; Taylor, W. A.; Wang, J. H.; Tipton, C. L. *J. Bio. Chem.* **1984**, 259, 2742-2747

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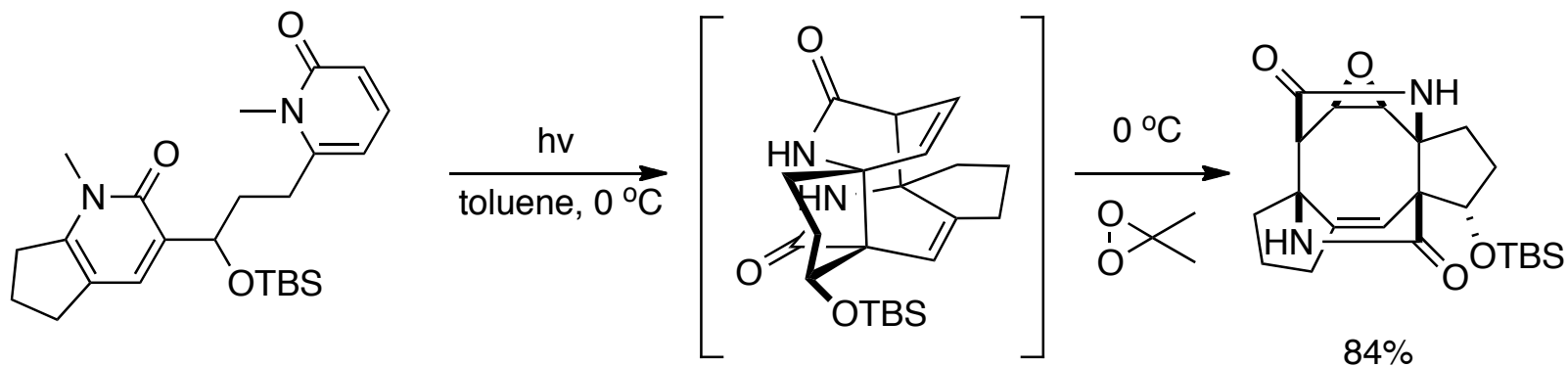
Fujiwara, H.; Matsunaga, K.; Kumagai, H.; Ishizuka, M.; Ohizumo, Y. *Pharm. Pharmacol. Commun.* **2000**, 6, 427-431

# Biosynthesis of (+)-Ophiobolin A and Related Family Members

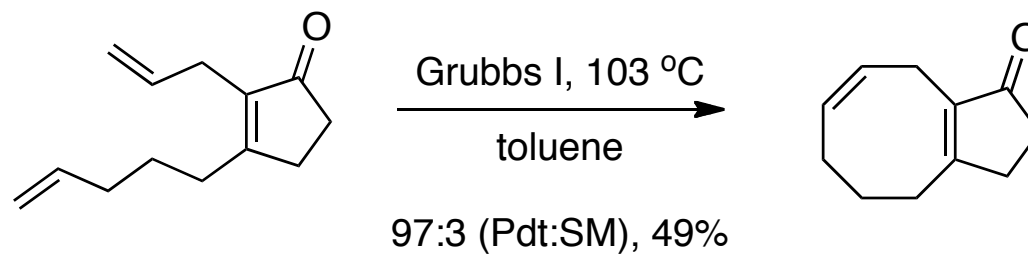


Canonica, L.; Fiechi, A.; M. Galli Kienle; Ranzi, B. M.; Scala, A.; Salvatori, T.; Pella, E. *Tetrahedron Lett.* **1967**, 35, 3371-3376

# Recent Efforts Towards the 5,8,5 Ring System

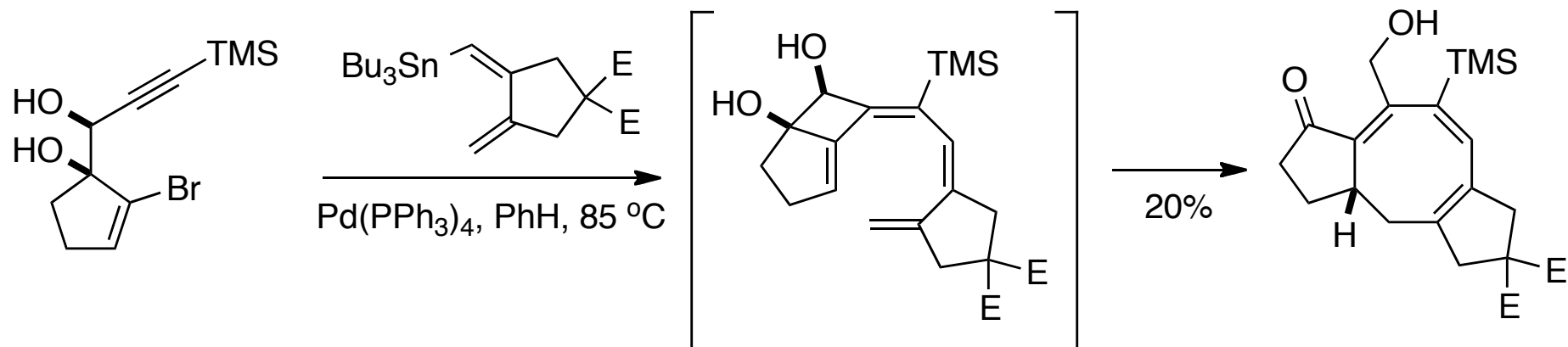


McGee, Jr., K. F.; Al-Tel, T. H.; Sieburth\*, S. M. *Synthesis* **2001**, 8, 1185-1191



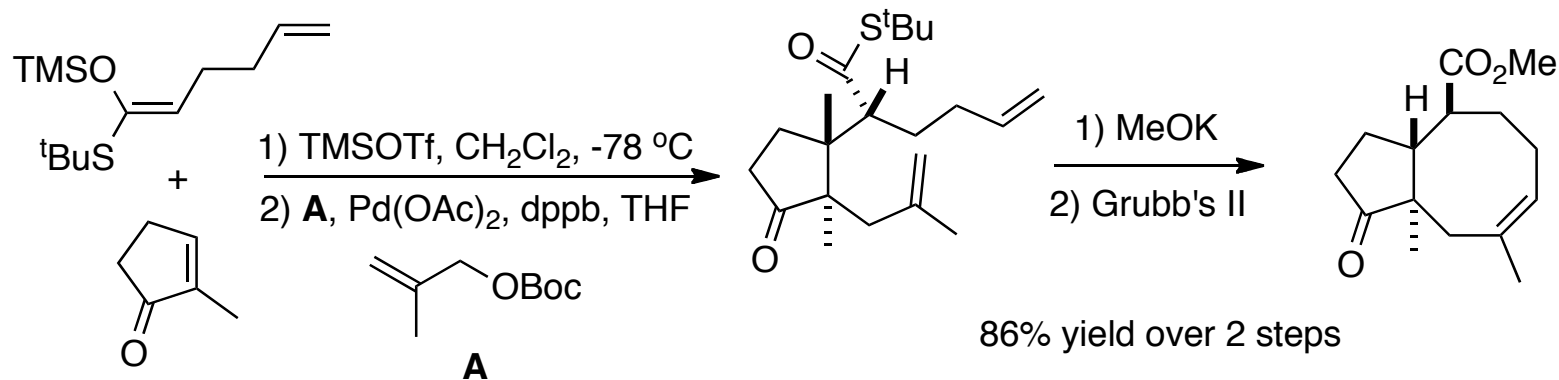
Ruprah, P. K.; Cros, J-P.; Pease, J. E.; Whittingham, W. G.; Williams\*, M. J. *Eur. J. Org. Chem.* **2002**, 3145-3152

# Recent Efforts Towards the 5,8,5 Ring System



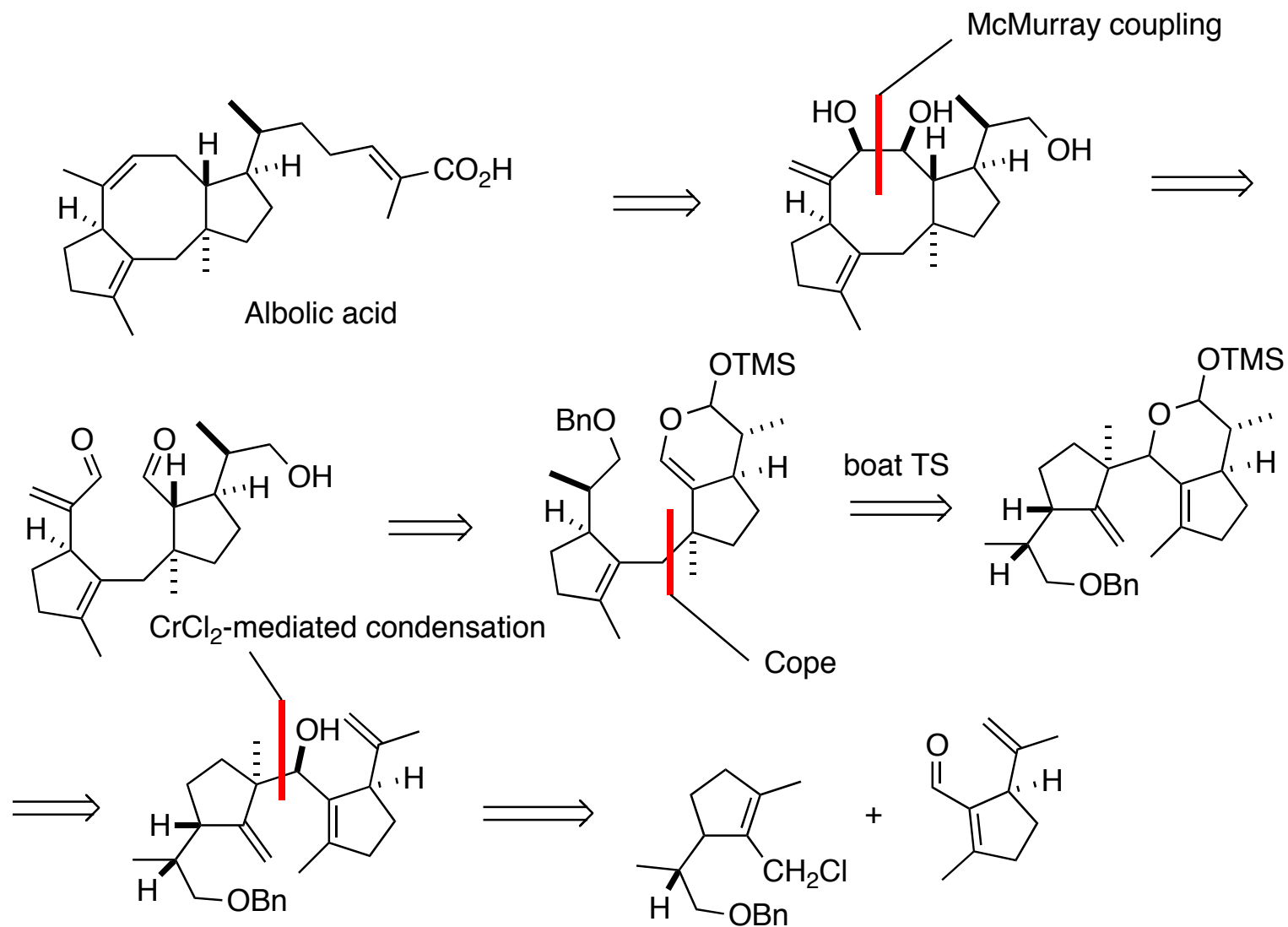
Salem, B.; Suffert\*, *J. Angew. Chem. Int. Ed.* **2004**, 43, 2826-2830

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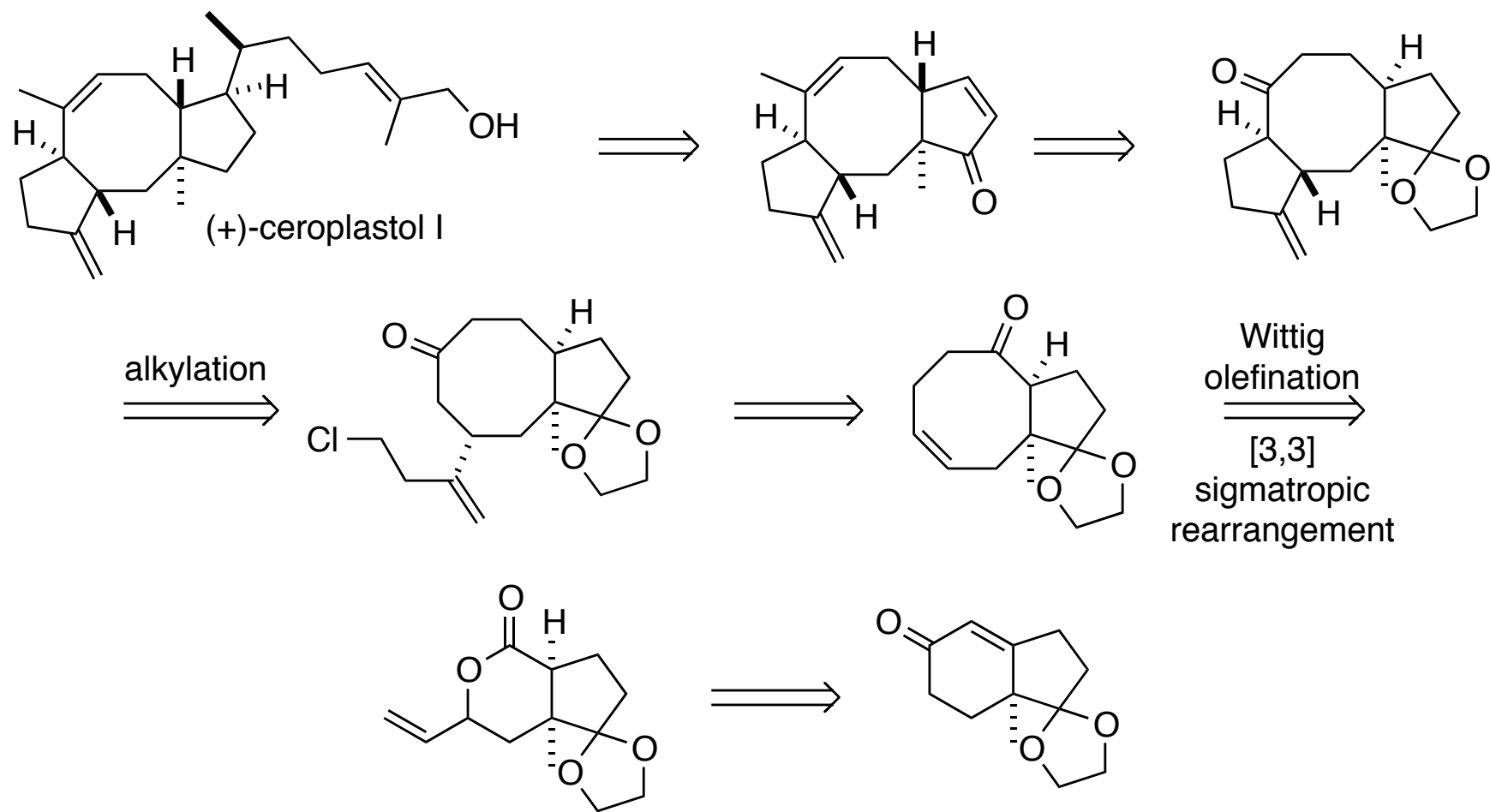
# Total Synthesis of Albolic Acid



Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, 354-356

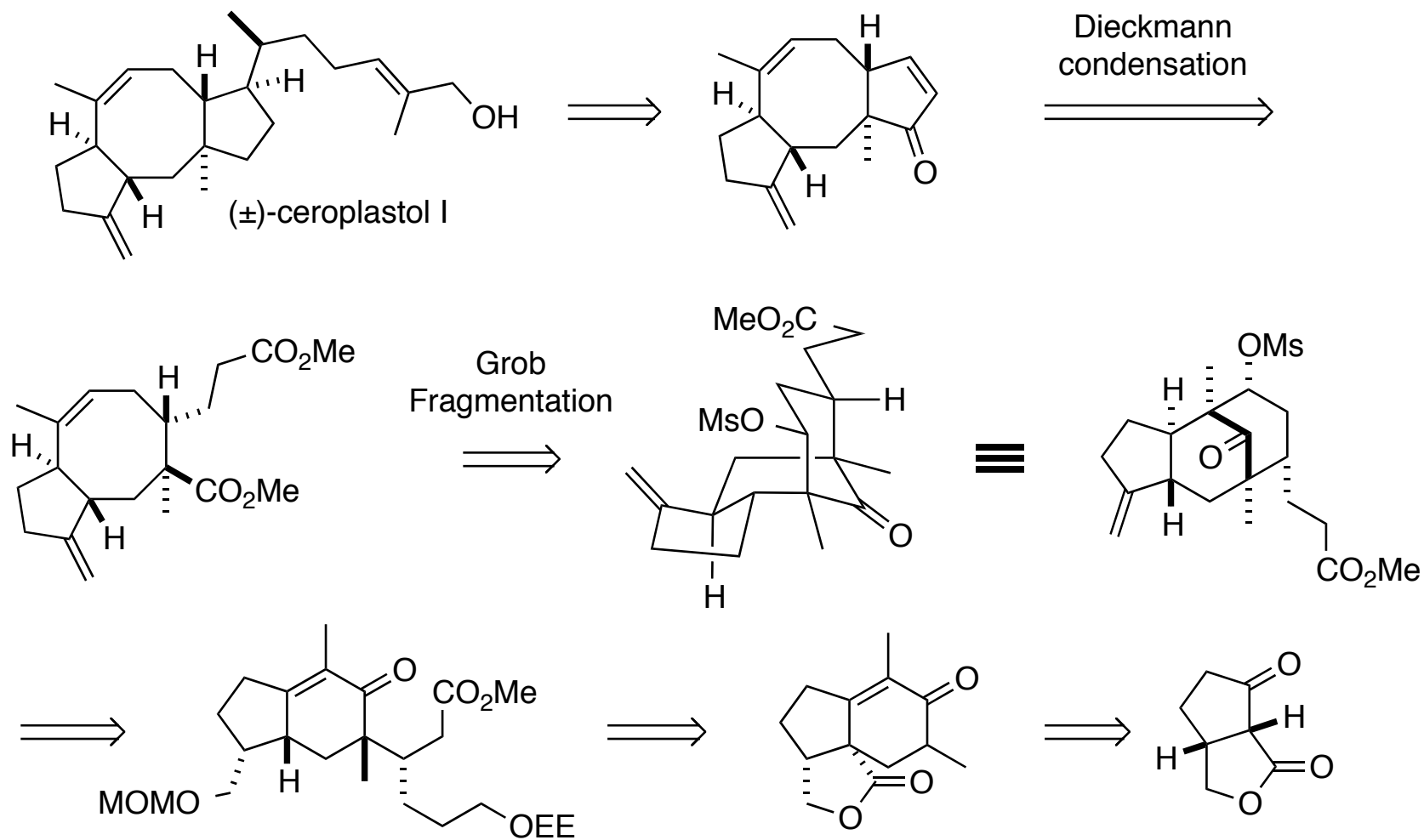
Kato, N.; Takeshita, H. *J. Chem. Soc. Perkin. Trans. I.* **1989**, 165-174

# Total Synthesis of (+)-Ceroplastol I



Paquette, L. A.; Wang, T-Z.; Vo, N. *J. Am. Chem. Soc.* **1993**, 115, 1676-1683

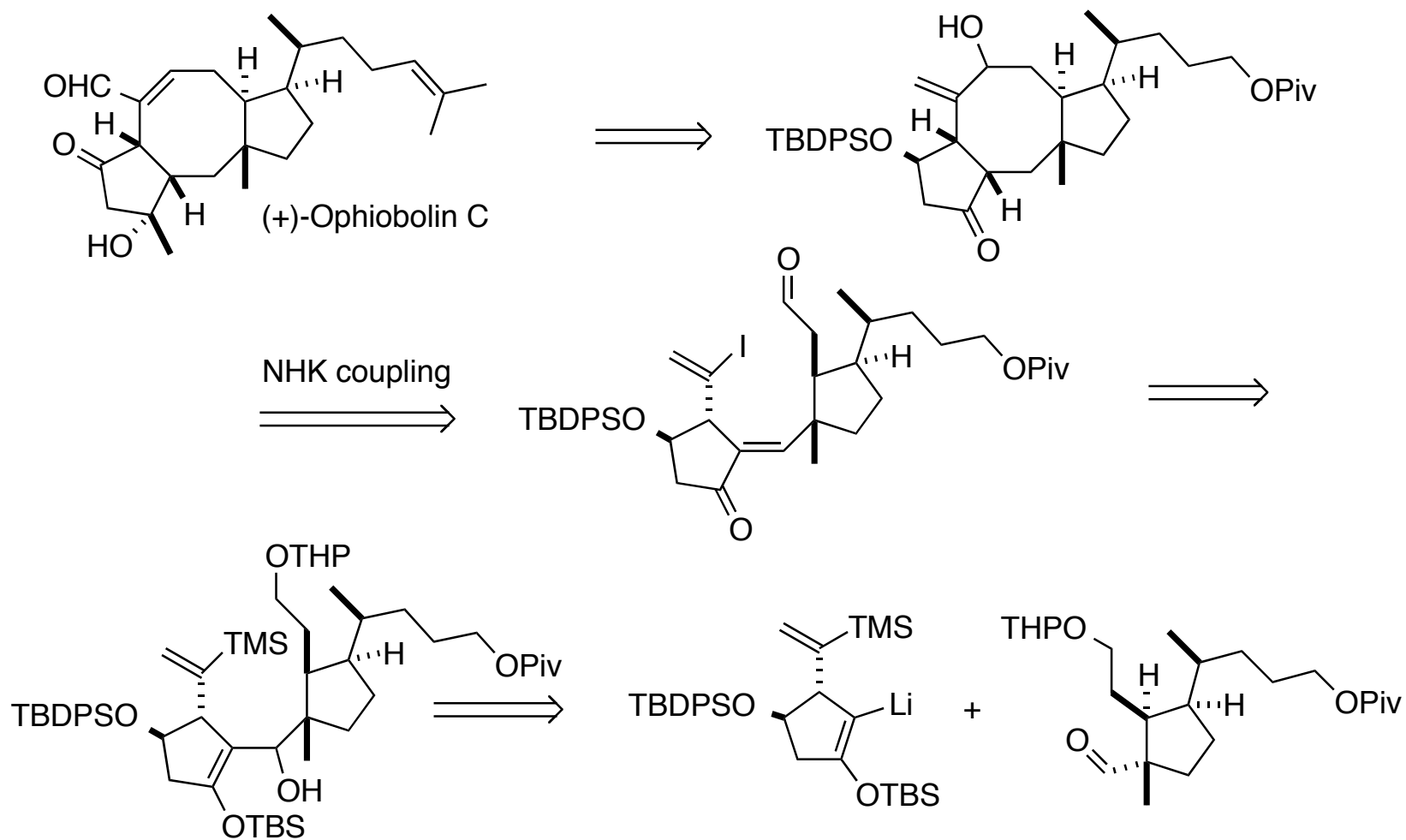
# Total Synthesis of (±)-Ceroplastol I



Boeckman, Jr., R. K.; Arvanitis, A.; Voss, M. E. *J. Am. Chem. Soc.* **1989**, 111, 2737-2739

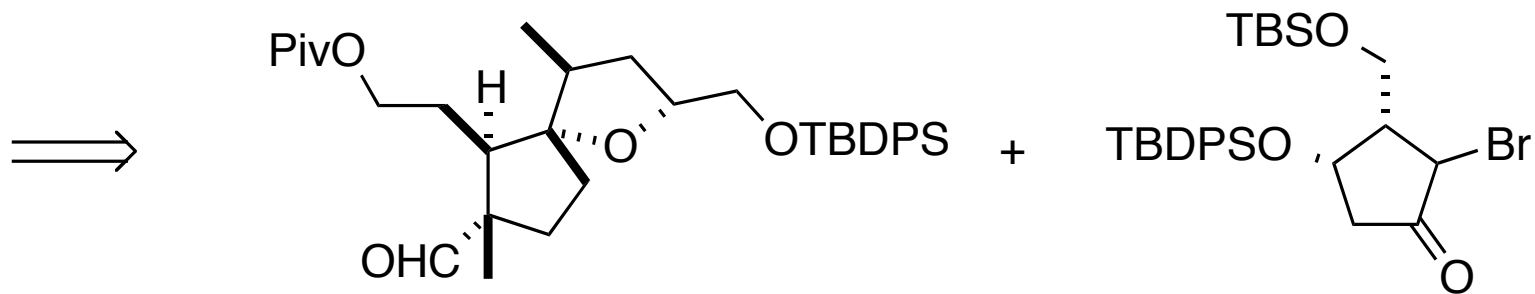
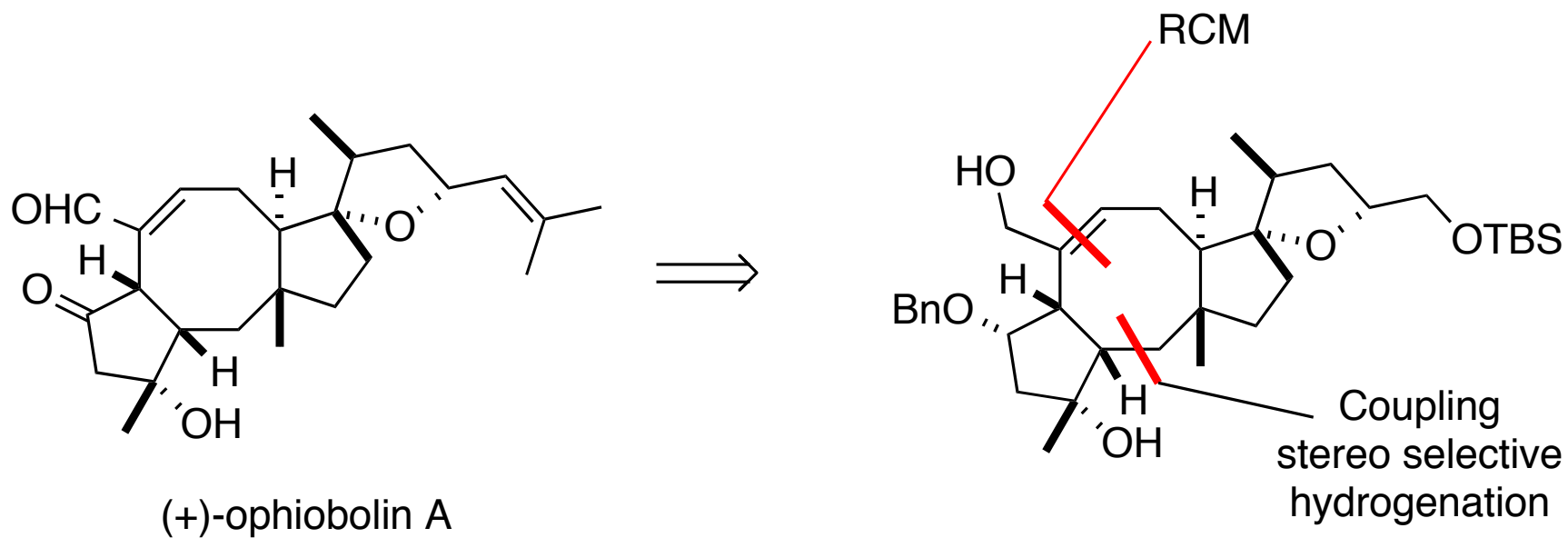


# Total synthesis of (+)-Ophiobolin C



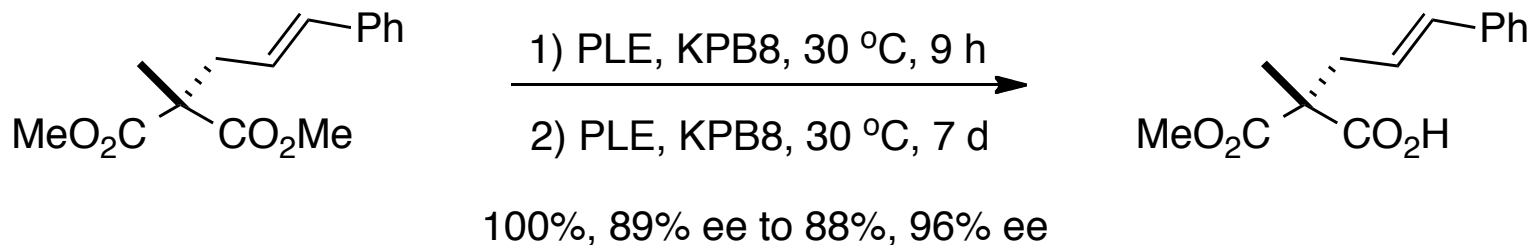
Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, 111, 2735-2737

# Title Paper: Retrosynthesis

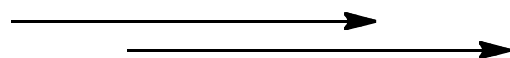


Noguchi, N.; Nakada, M. *Org. Lett.* **2006**, 8, 2039-2042  
Tsun, K.; Noguchi, N.; Nakada, M. *Angew. Chem. Int. Ed.* **2011**, ASAP

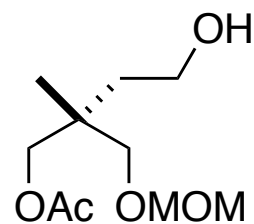
# Title Paper: The Prelude



step-wise oxidation state  
changes and FG protection

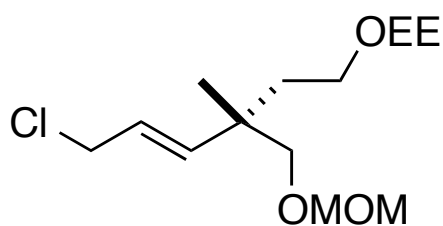


6 steps, 80% yield



1) protection  
2) Hydrolysis  
3) Swern [O]

4) HWE  
5) Reduction  
6) MsCl, LiCl



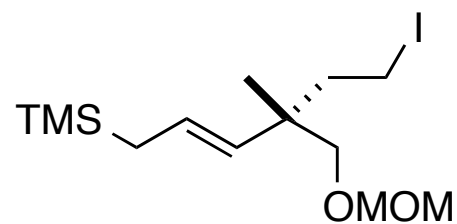
6 steps, 81% yield

1)  $\text{Me}_3\text{SiSiMe}_3$ , MeLi  
HMPA /  $\text{Et}_2\text{O}$



2) PPTs

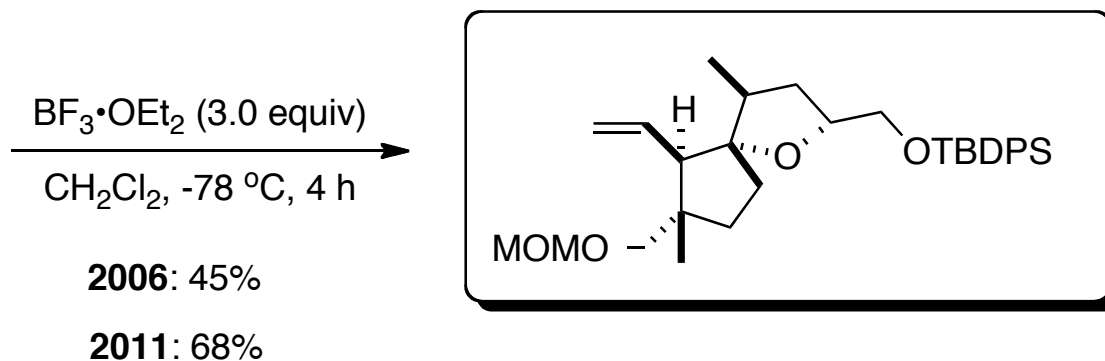
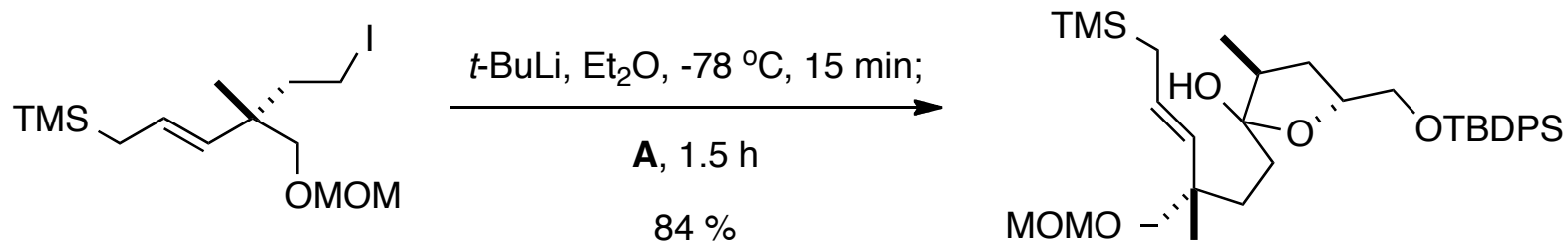
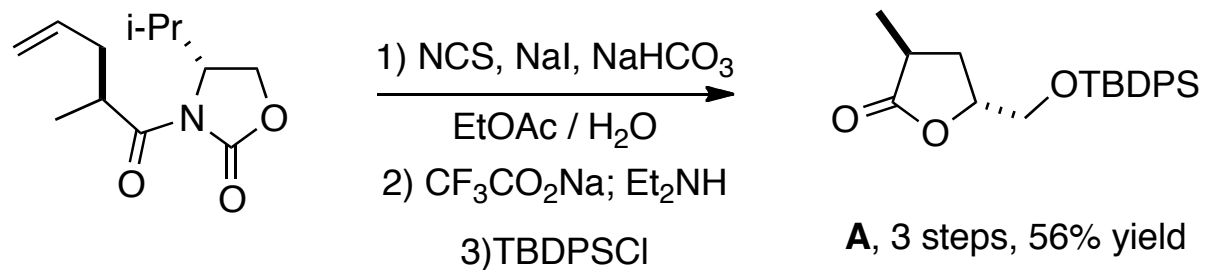
3)  $\text{PPh}_3$ ,  $\text{I}_2$ , imidazole



3 steps, 81% yield

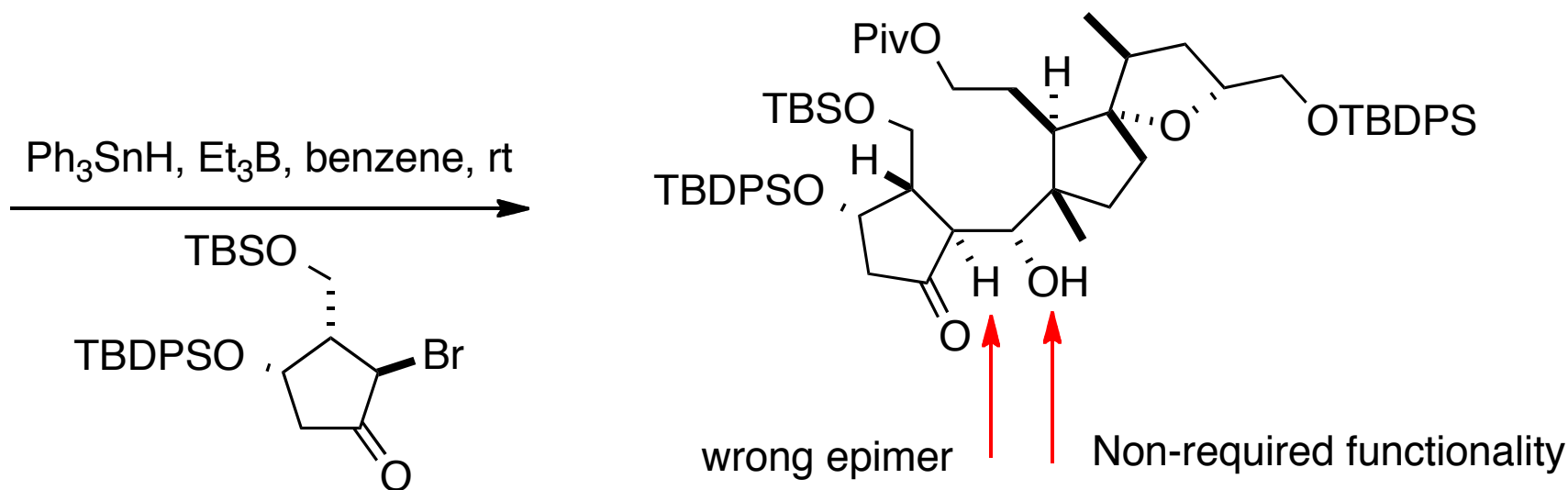
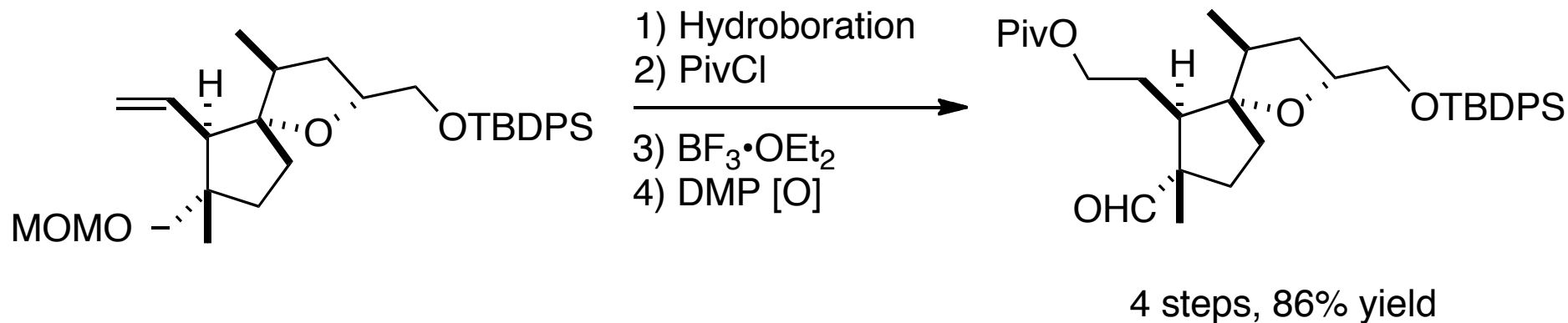
Noguchi, N.; Nakada, M. *Org. Lett.* **2006**, 8, 2039-2042

# Title Paper: The Prelude



Noguchi, N.; Nakada, M. *Org. Lett.* **2006**, 8, 2039-2042

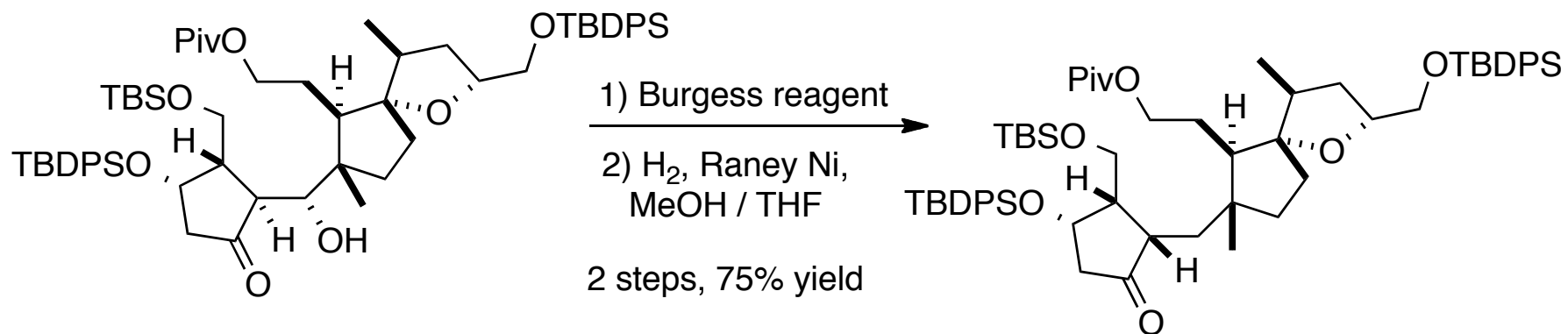
# Title Paper: Coupling the Two Pieces



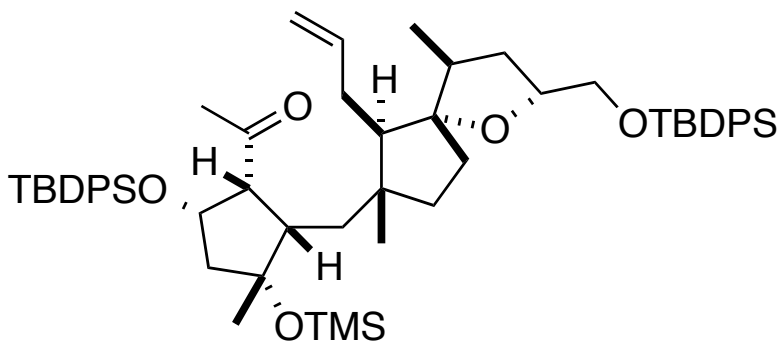
90% (83% from other Br-isomer)

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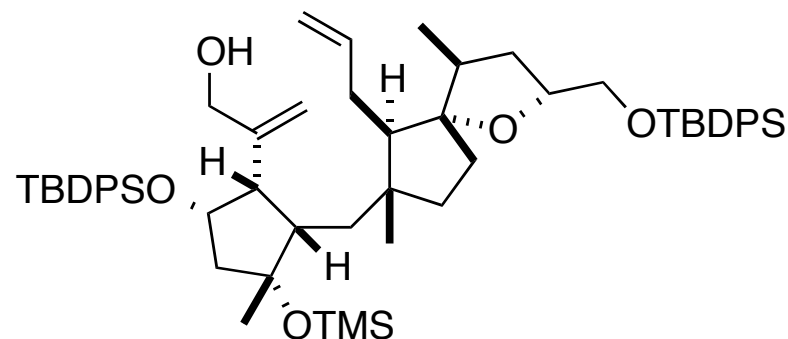
# Title Paper: Middle Game and Oxidation State Changes



- 1) MeLi
  - 2) Swern [O]
  - 3) Wittig
  - 4) PPTs
  - 5) IBX [O]
  - 6) MeLi
  - 7) DMP [O]
  - 8) TMSCl
- 8 steps, 75% yield

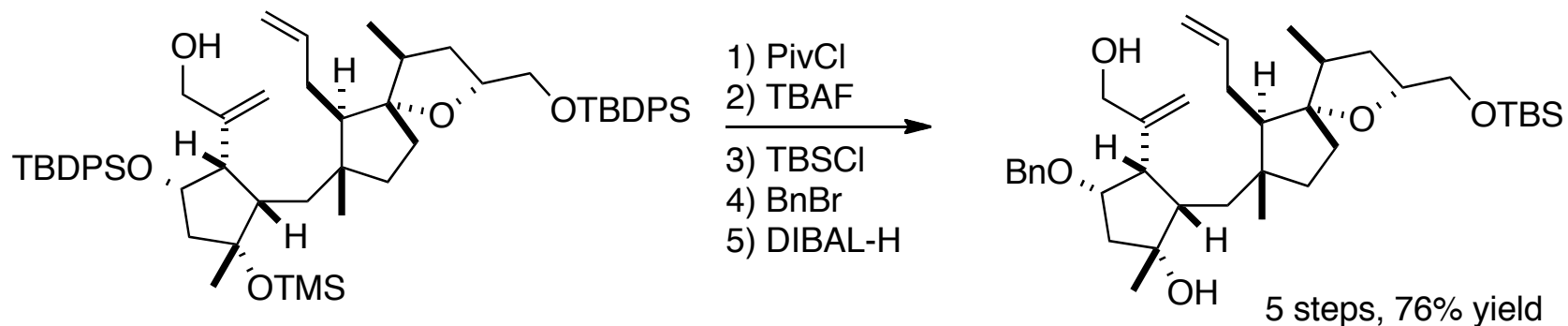


- 1) Comin's reagent, KHMDS
  - 2) Pd(PPh<sub>3</sub>)<sub>4</sub>, Et<sub>3</sub>N, CO (1 atm)
  - 3) DIBAL-H
- 3 steps, 47% yield

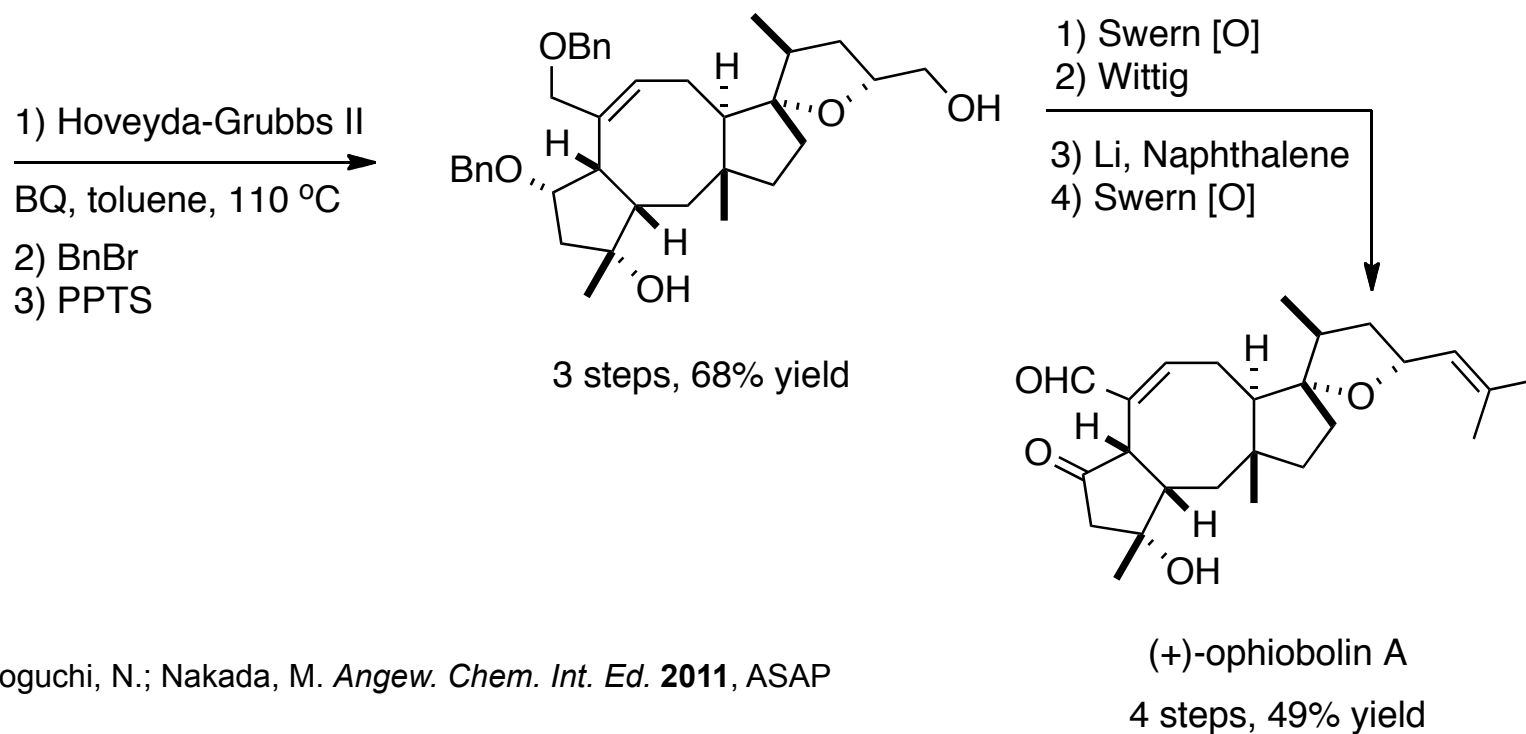


Tsuna, K.; Noguchi, N.; Nakada, M. *Angew. Chem. Int. Ed.* **2011**, ASAP

# Title Paper: Formation of B Ring and End Game



(Note: RCM did not work on this substrate)



Tsuna, K.; Noguchi, N.; Nakada, M. *Angew. Chem. Int. Ed.* **2011**, ASAP

# Summary

- The Nakada group finished the synthesis of (+)-Ophiobolin A in 57 steps (0.77 % overall yield) utilizing a key Reformatsky type reaction to couple the two 5-membered rings together and a RCM reaction to form the central B-ring.
- Other methods to construct the 5,8,5 core of this family of compounds included various RCM strategies, [4+4] photocycloaddition of pyridones, and a 4-exo-dig cyclocarbopalladation/  $8\pi$  electrocyclization strategy.
- The Takeshita group assembled albolic acid utilizing a key Cr (II) mediated coupling, cope rearrangement, and a McMurray coupling was used to for the B-ring.
- Boeckman Jr's group assembled the core of (+)-seroplastol I with a key [3,3]-sigmatropic rearrangement to establish the B-ring and a simple alkylation installed the A-ring.
- Through the use of a grob fragmentation to set the 8-membered B-ring and late stage Dieckmann condensation to install the C-ring, the Paquette group completed the total synthesis of ( $\pm$ )-seroplastol I.
- A vinyl lithium addition into a complex aldehyde brought rings A and C together in Kishi's synthesis of (+)-ophiobolin C. An NHK coupling finished the assembly of the B-ring.