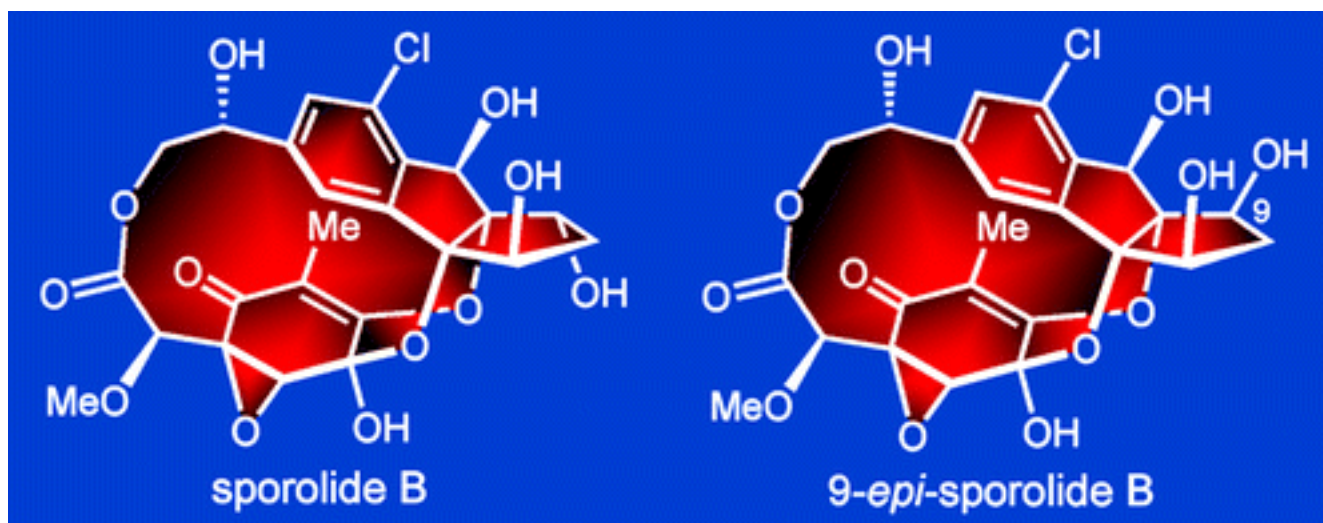
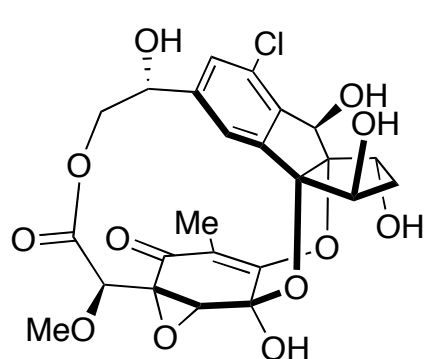


## Total Synthesis of Sporolide B and 9-*epi*-Sporolide B

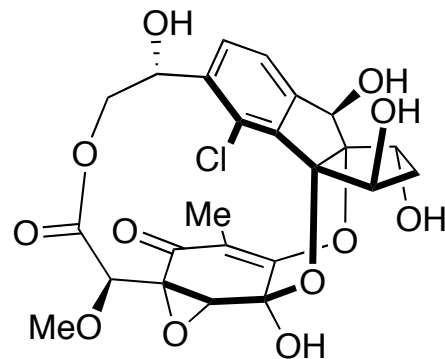


K.C.Nicolaou, Jianhua Wang, Yefeng Tang, and Lorenzo Botta  
*J. Am. Chem. Soc.* **2010**, *132*(32), 11350.

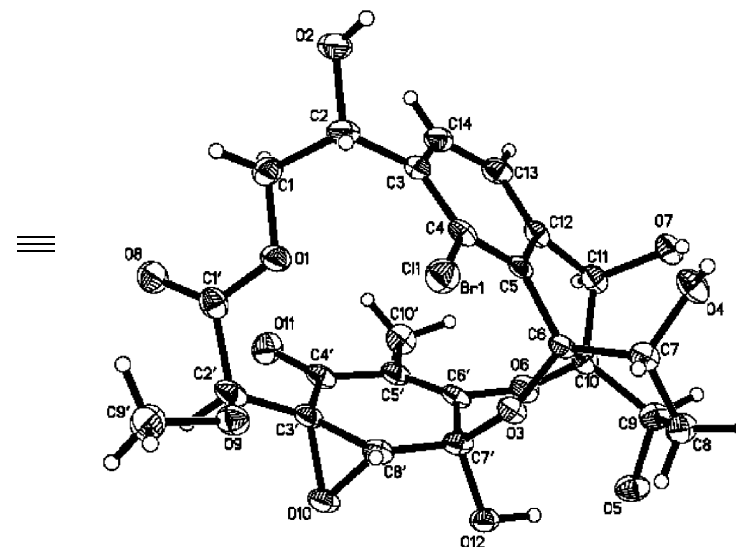
## Sporolide Isolation and Its Structural Determination



**Sporolide B**



**Sporolide A**



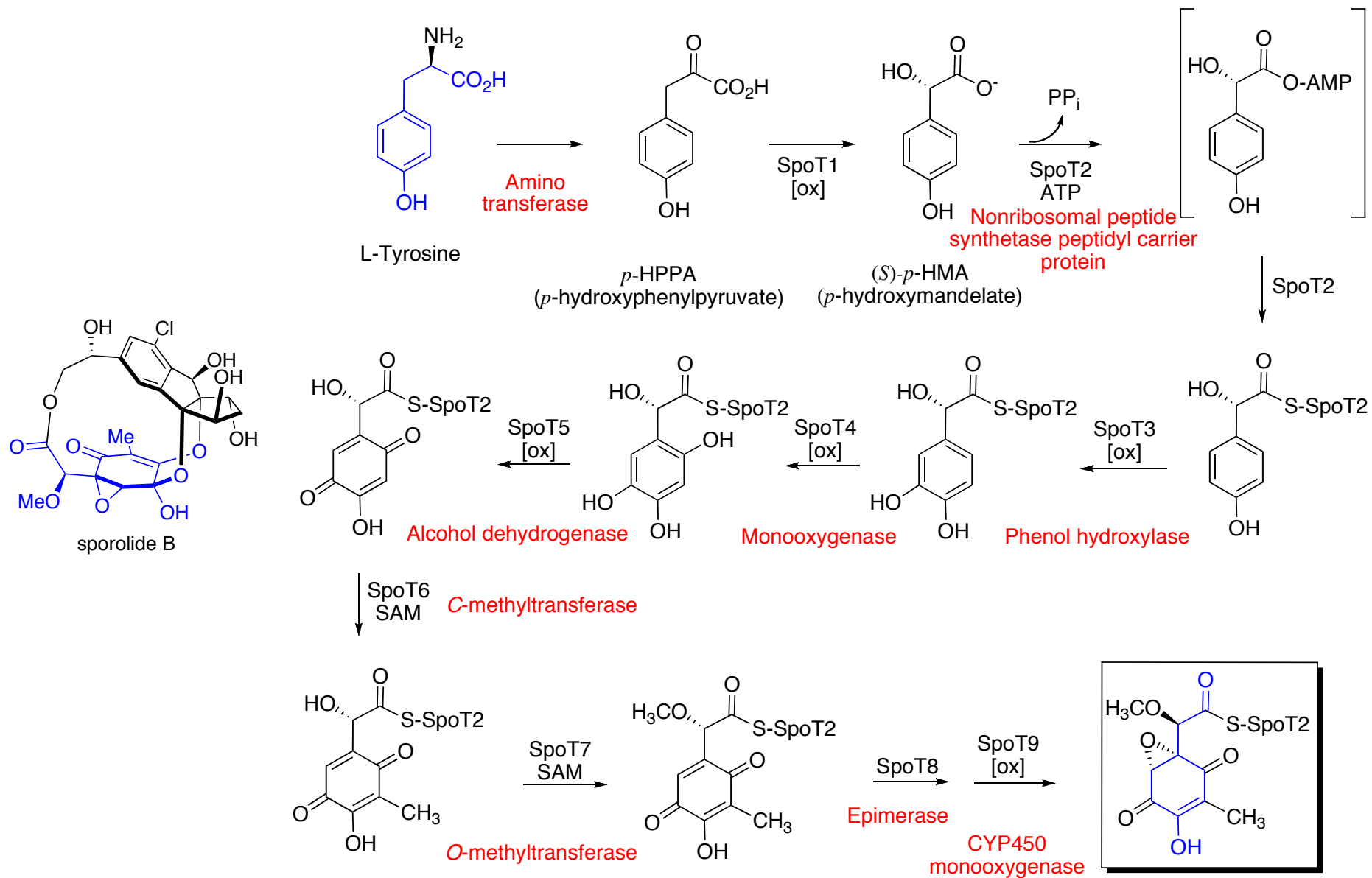
*Salinospora tropica* →



- no obvious biological activity
- intriguing molecular architecture
- 24-carbon polycyclic structure (cyclopenta[*a*]indene – cyclohexenone system)
- 10 stereocenters
- 13-membered ring

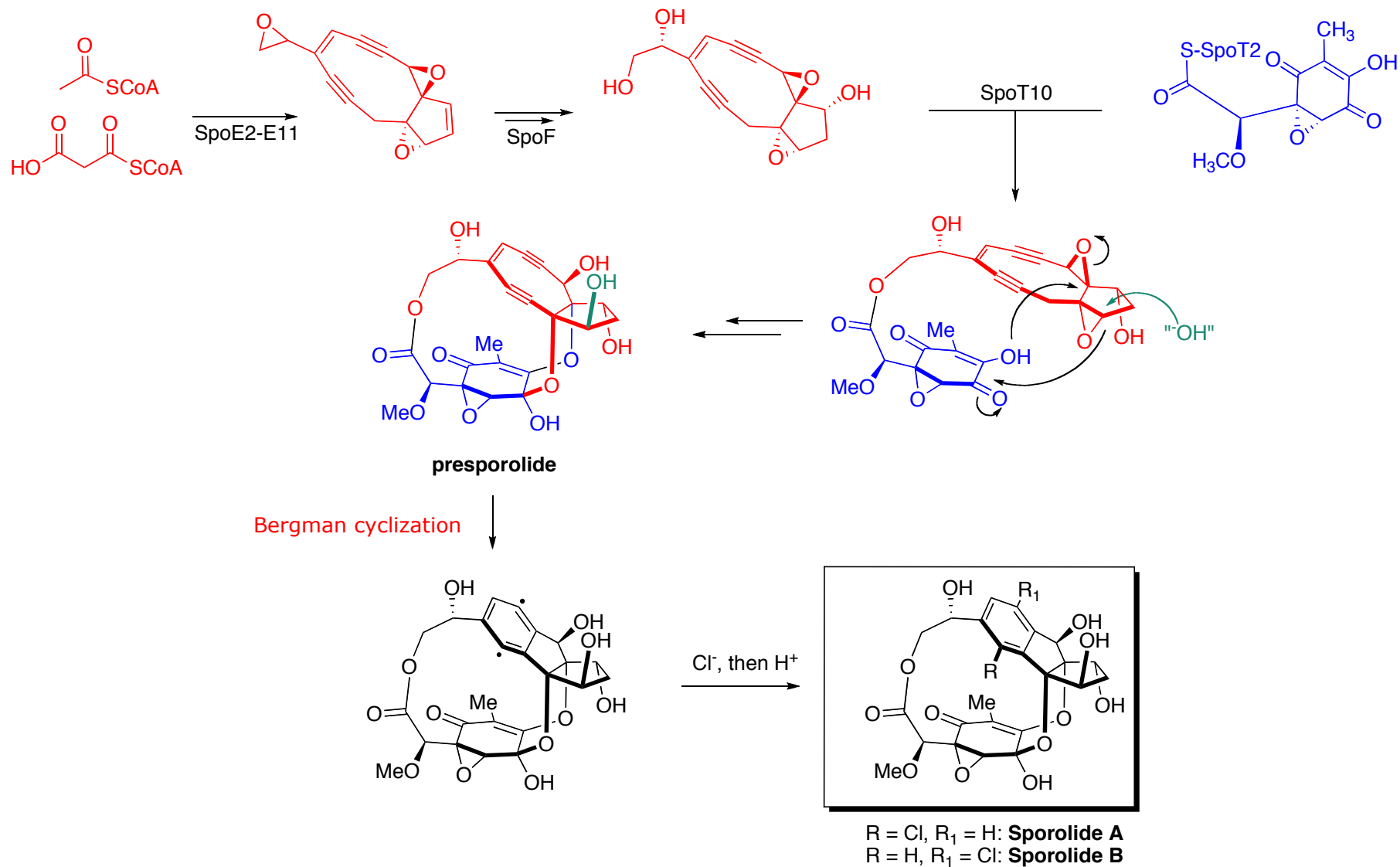
(a) Bunchan, G.O.; Williams, P.G.; Feling, R.H.; Kauffman, C.A.; Jensen, P.R.; Fenical, W. *Org. Lett.* **2005**, 7, 2731. (b) Nicolaou, K.C.; Tang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2009**, 48, 3449. (c) Nicolaou, K.C.; Wang, J.; Tang, Y.; Botta, L. *J. Am. Chem. Soc.* **2010**, 132, 11350. (d) <http://www.aquapreneur.com/2008/01/11/scripps-jgi-sequence-marine-bacterium-s-tropica/comment>

# Unraveling the Biosynthesis of Sporolide: From L-Tyrosine toward Sporolide



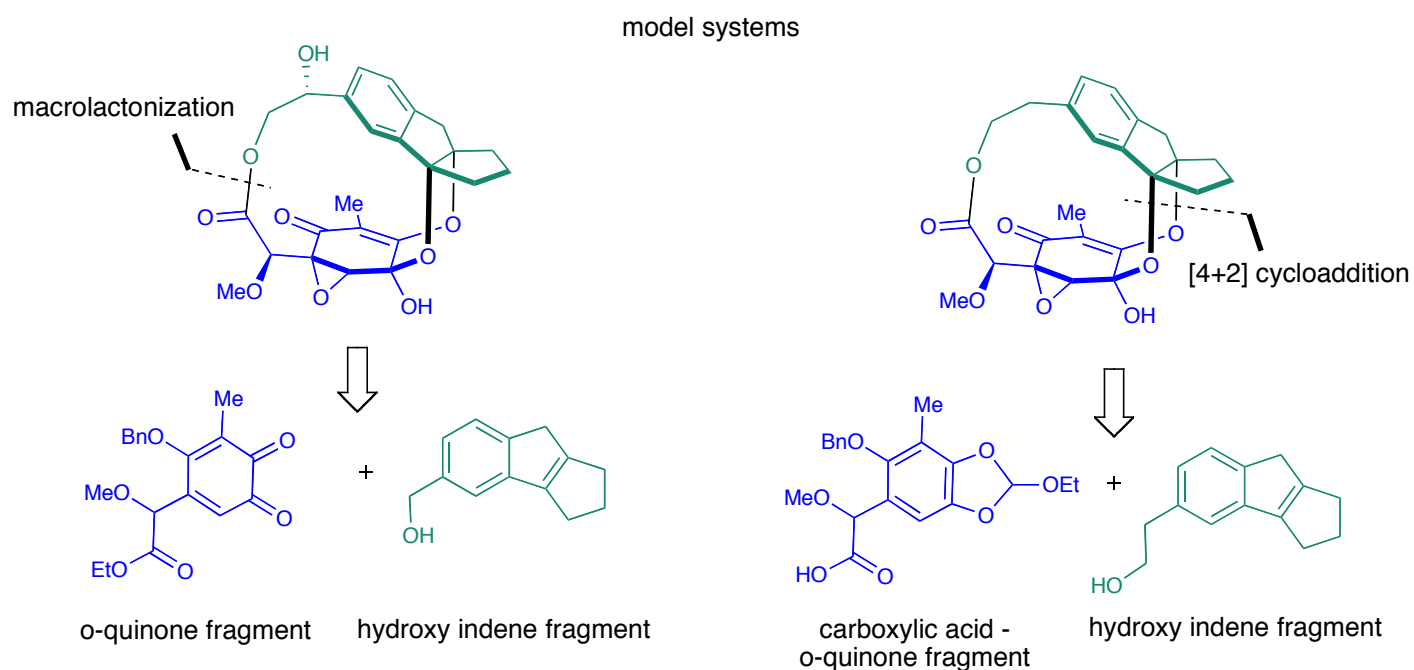
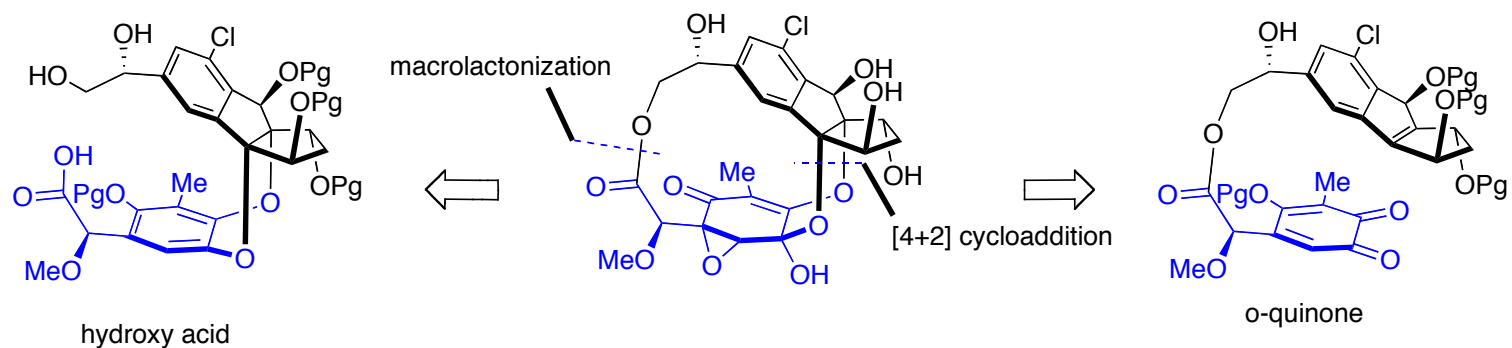
(a) McGlinchey, R.P.; Nett, M.; Moore, B.S. *J. Am. Chem. Soc.* **2008**, *130*, 2406. (b) Nett, M.; Moore, B.S. *Pure Appl. Chem.* **2009**, *81*, 1075.

## Unraveling the Biosynthesis of Sporolide: End Game



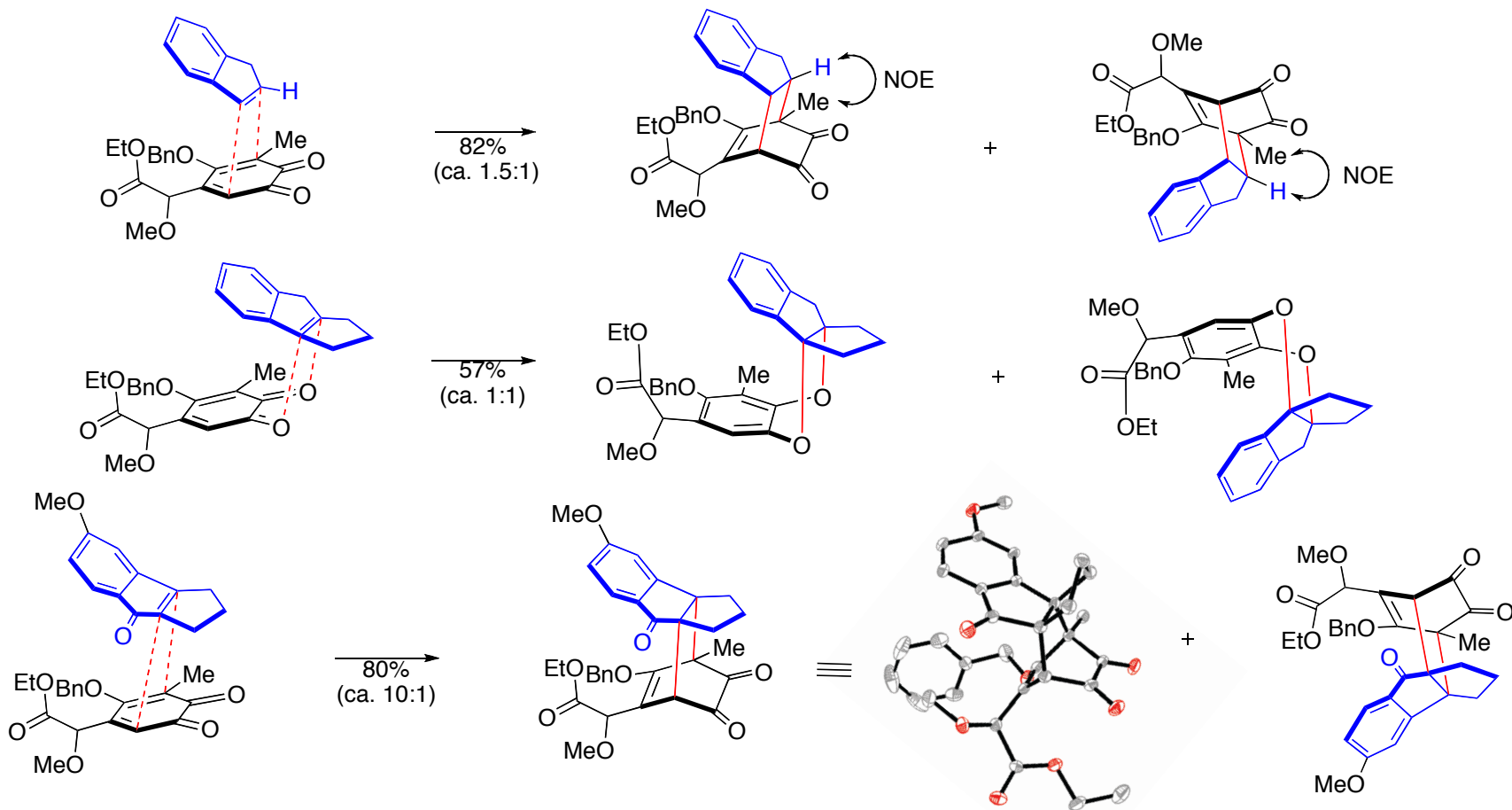
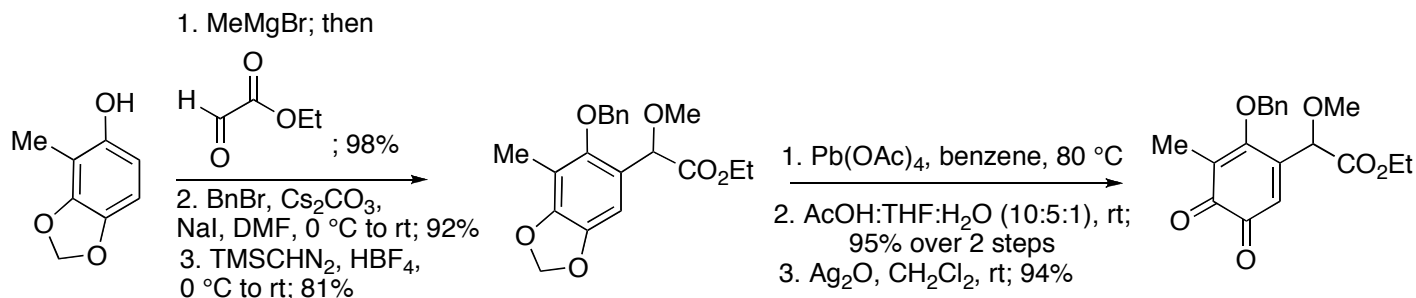
(a) McGlinchey, R.P.; Nett, M.; Moore, B.S. *J. Am. Chem. Soc.* **2008**, *130*, 2406. (b) Nett, M.; Moore, B.S. *Pure Appl. Chem.* **2009**, *81*, 1075. (c) Van Lanen, S.G.; Oh, T.J.-; Liu, W.; Pienkowski, E.W.; Shen, B. *J. Am. Chem. Soc.* **2007**, *129*, 13082. (d) Liu, W.; Christenson, S.D.; Standage, B.; Shen, B. *Science* **2002**, *297*, 1170.

## Initial Retrosynthetic Considerations and Model Studies: Plan A or Plan B

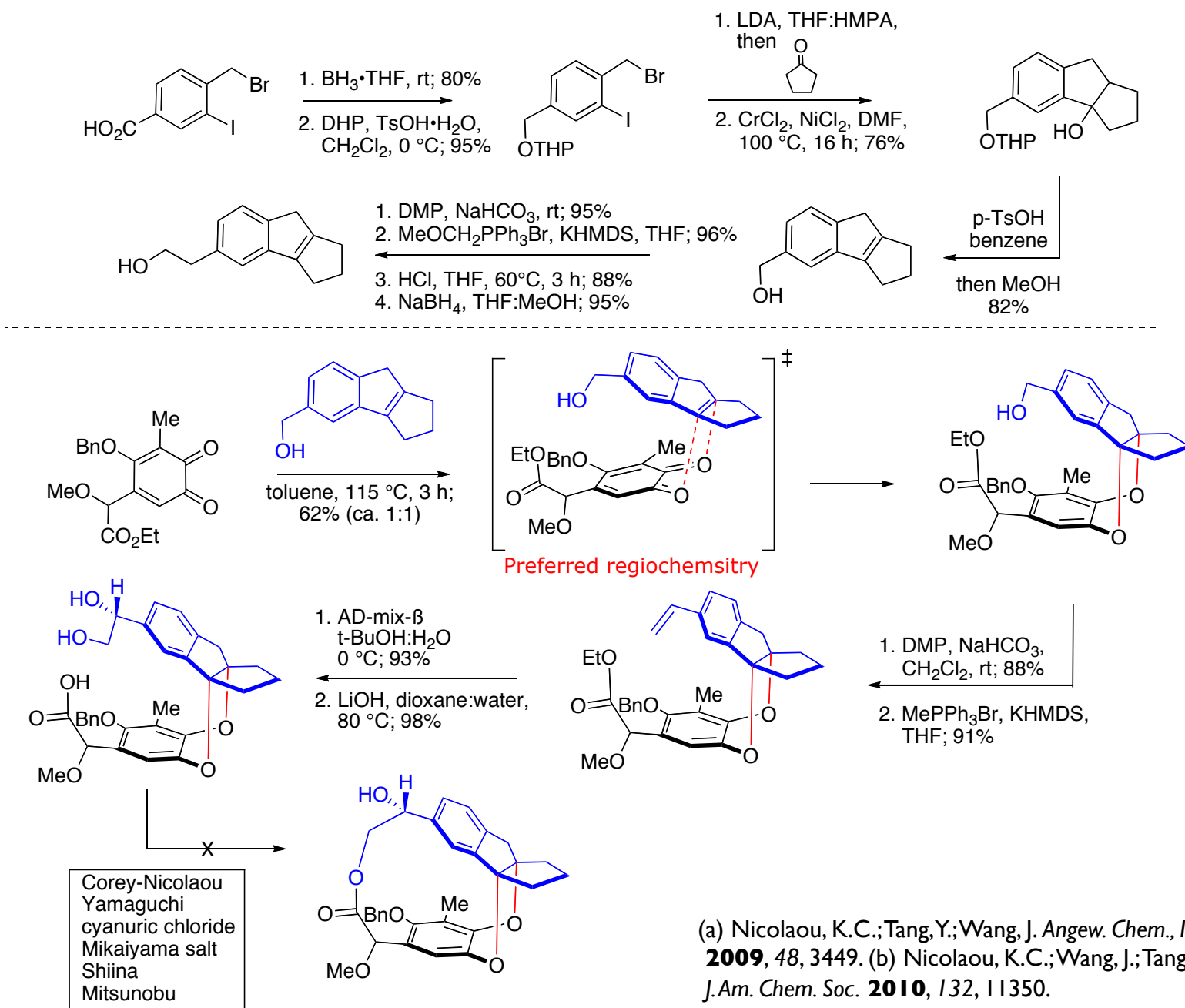


(a) Nicolaou, K.C.; Tang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3449. (b) Nicolaou, K.C.; Wang, J.; Tang, Y.; Botta, L. *J. Am. Chem. Soc.* **2010**, *132*, 11350. (c) Aly, A.A.; Ehrhardt, S.; Hopf, H.; Dix, I.; Jones, P.G. *Eur. J. Org. Chem.* **2006**, 335.

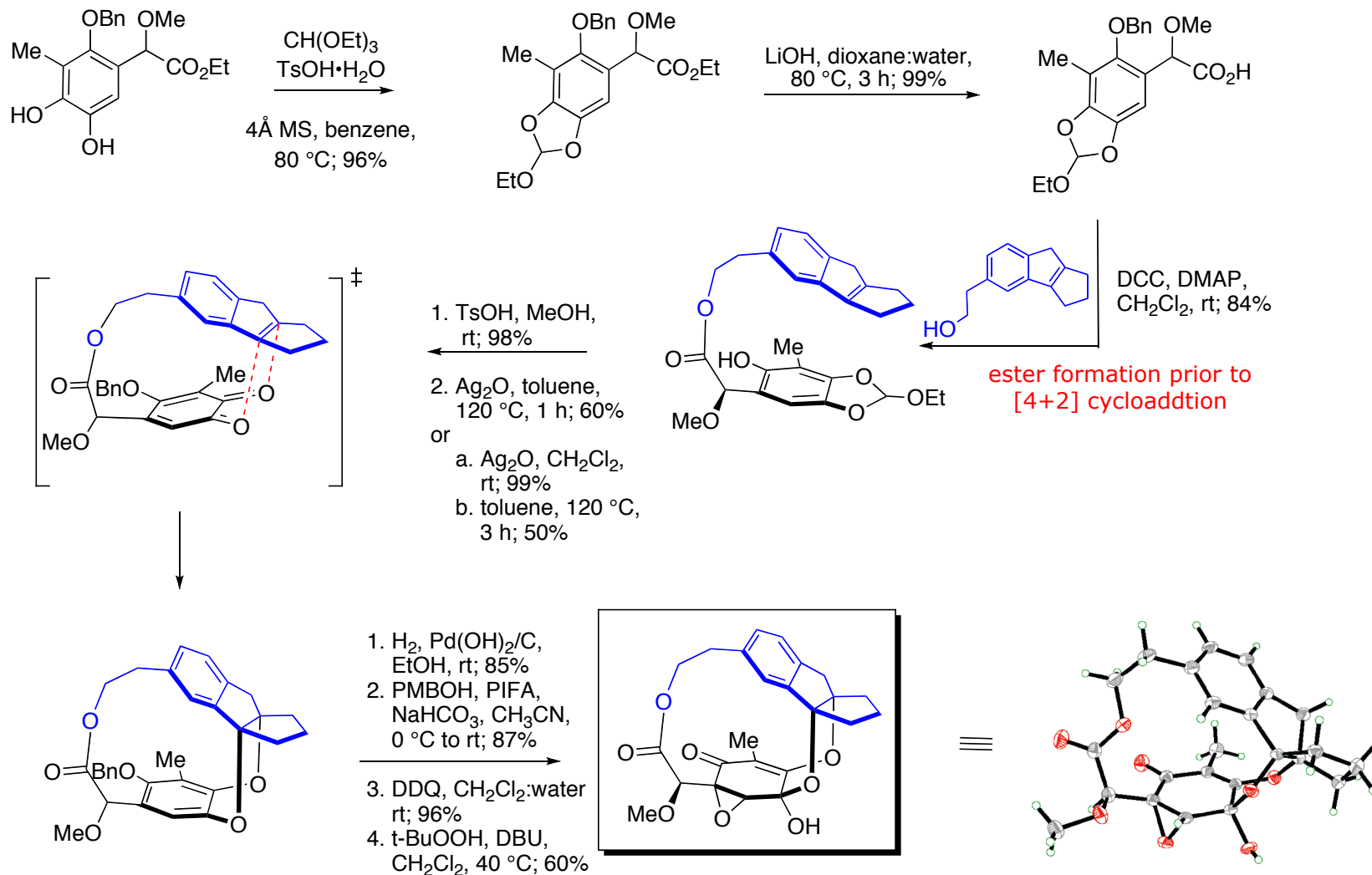
# Synthesis of *o*-Quinone and Its Reaction with Indene Derivatives: [4+2] Cycloaddition



## Construction of the Indene and Unsuccessful Macrolactonization



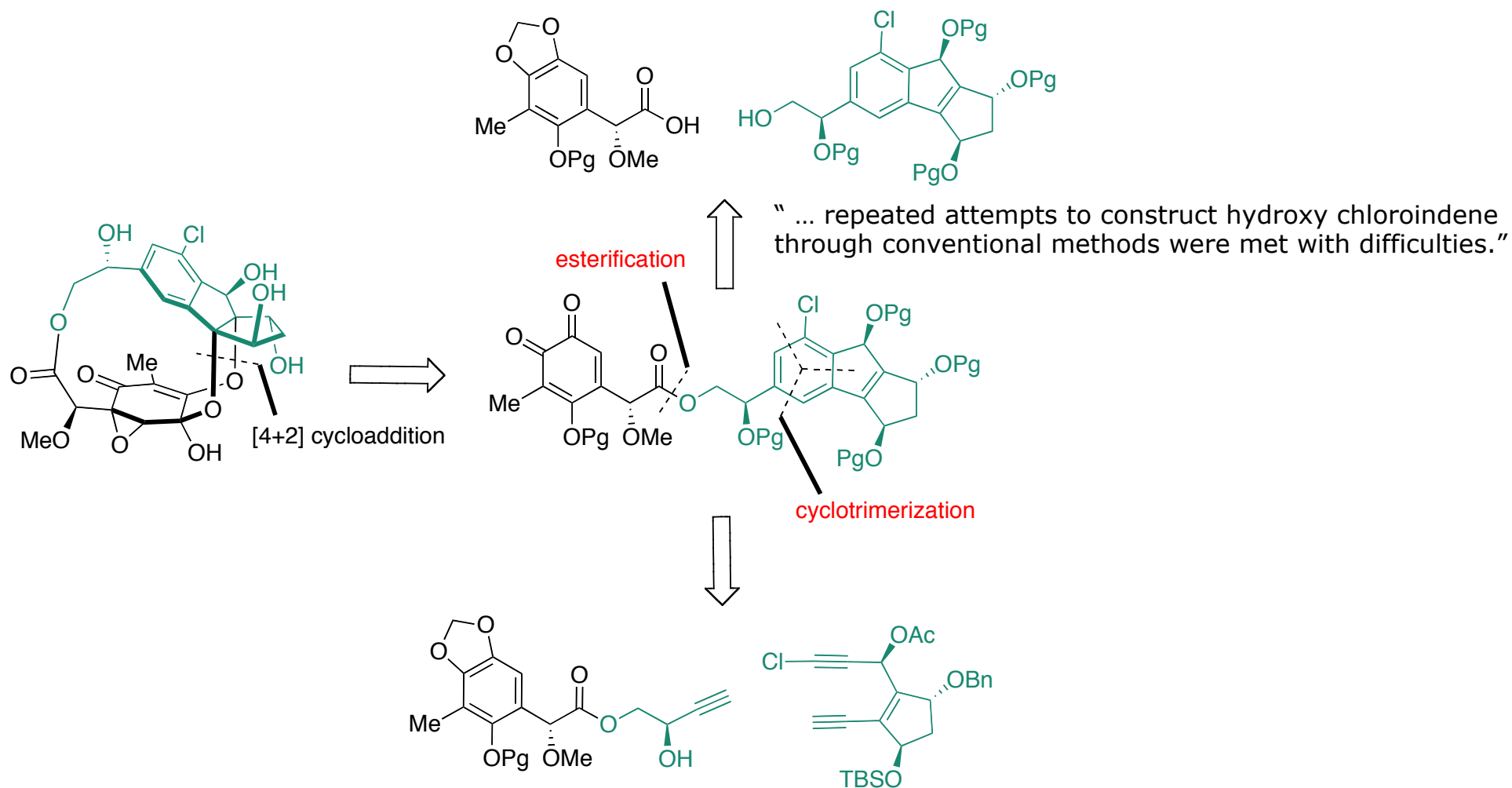
## The Proof of Concept: Successful Synthesis of Sporolide Model System



(a) Nicolaou, K.C.; Tang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3449. (b) Nicolaou, K.C.; Wang, J.; Tang, Y.; Botta, L. *J. Am. Chem. Soc.* **2010**, *132*, 11350.

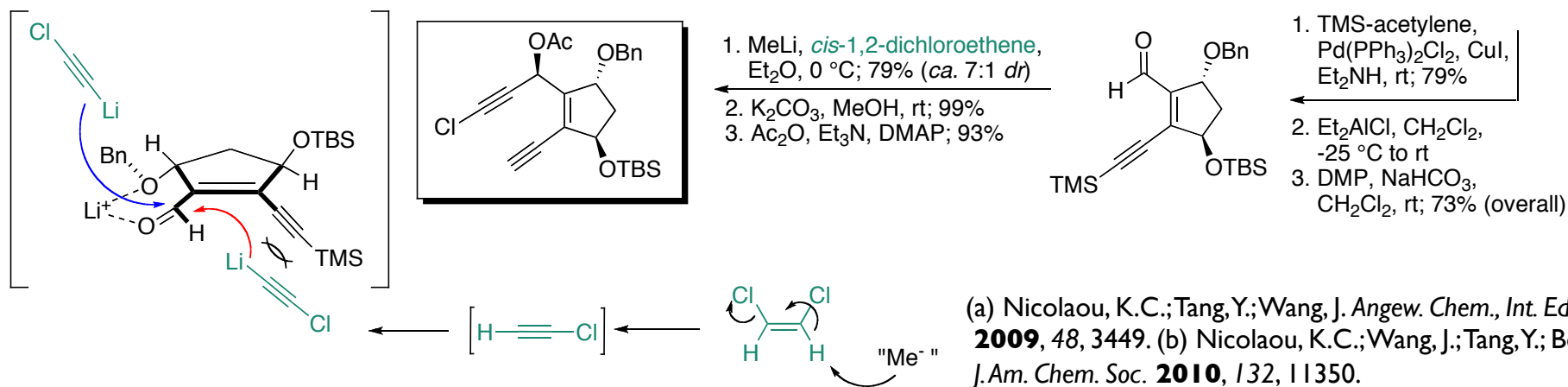
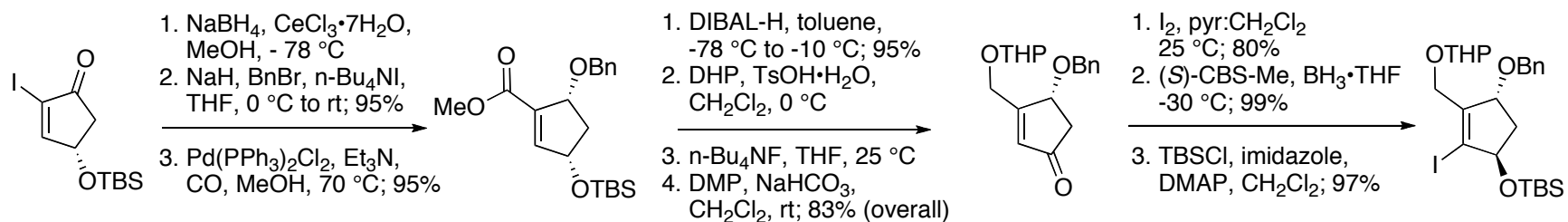
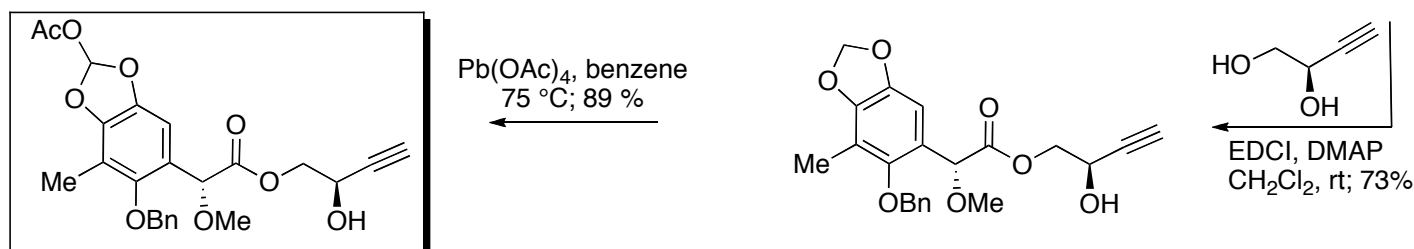
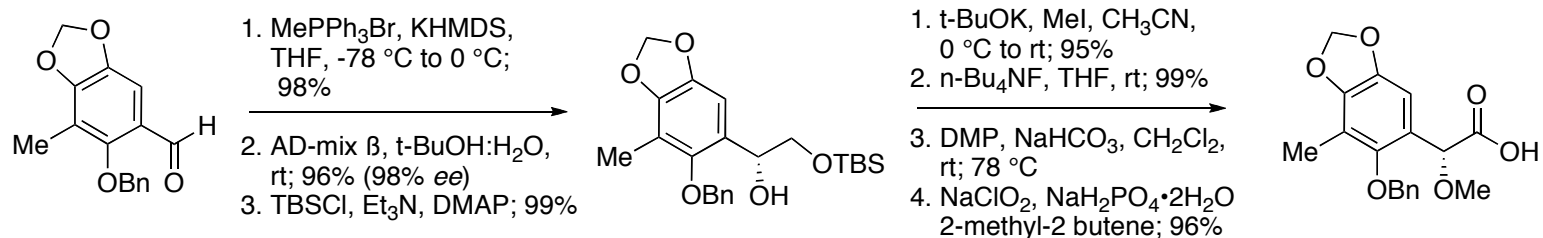


## Forays toward Sporolide B: Successful but not Successful



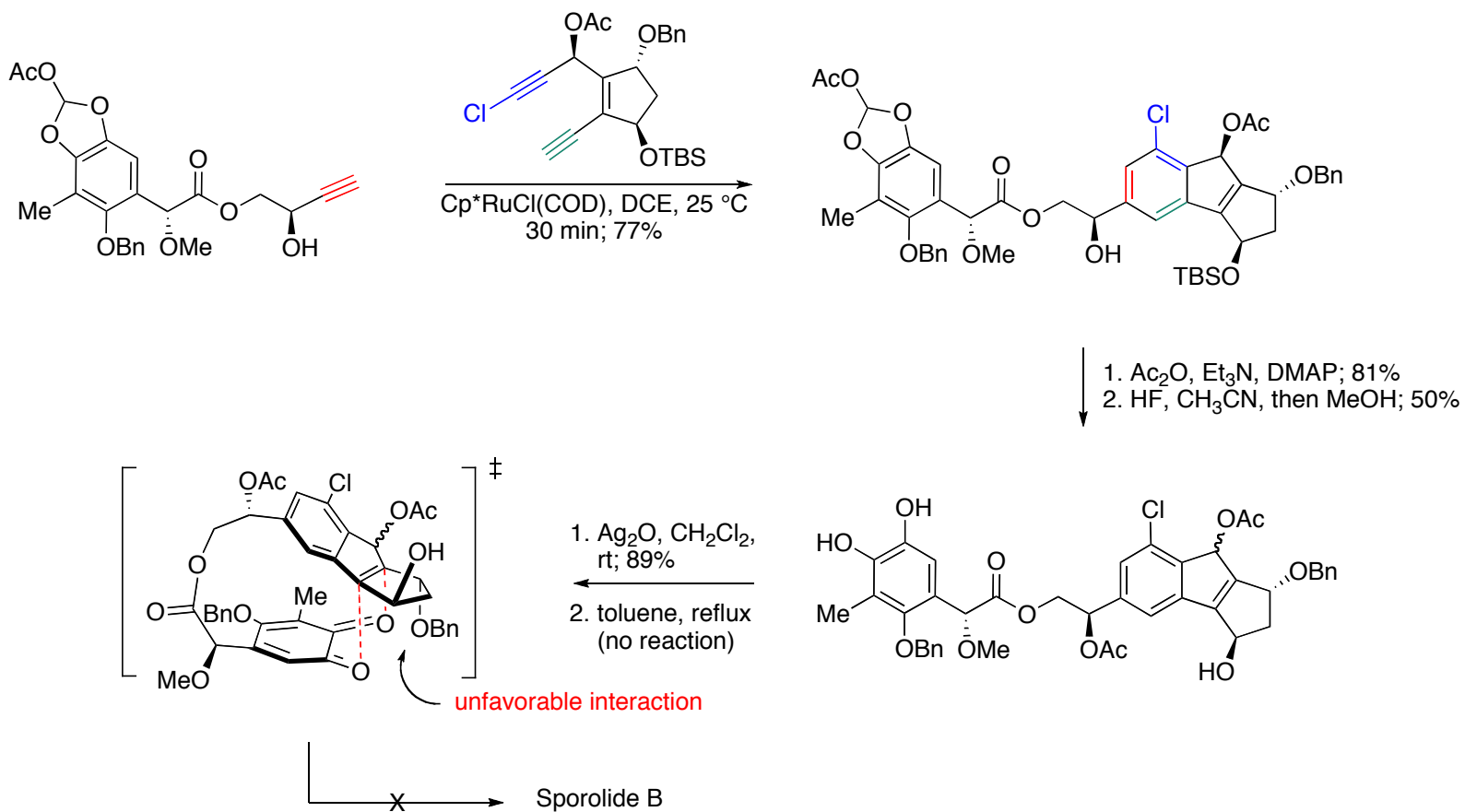
(a) Nicolaou, K.C.; Tang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2009**, 48, 3449. (b) Nicolaou, K.C.; Wang, J.; Tang, Y.; Botta, L. *J. Am. Chem. Soc.* **2010**, 132, 11350.

## Construction of the Cyclotrimerization Precursors: Toward the Indene Motif



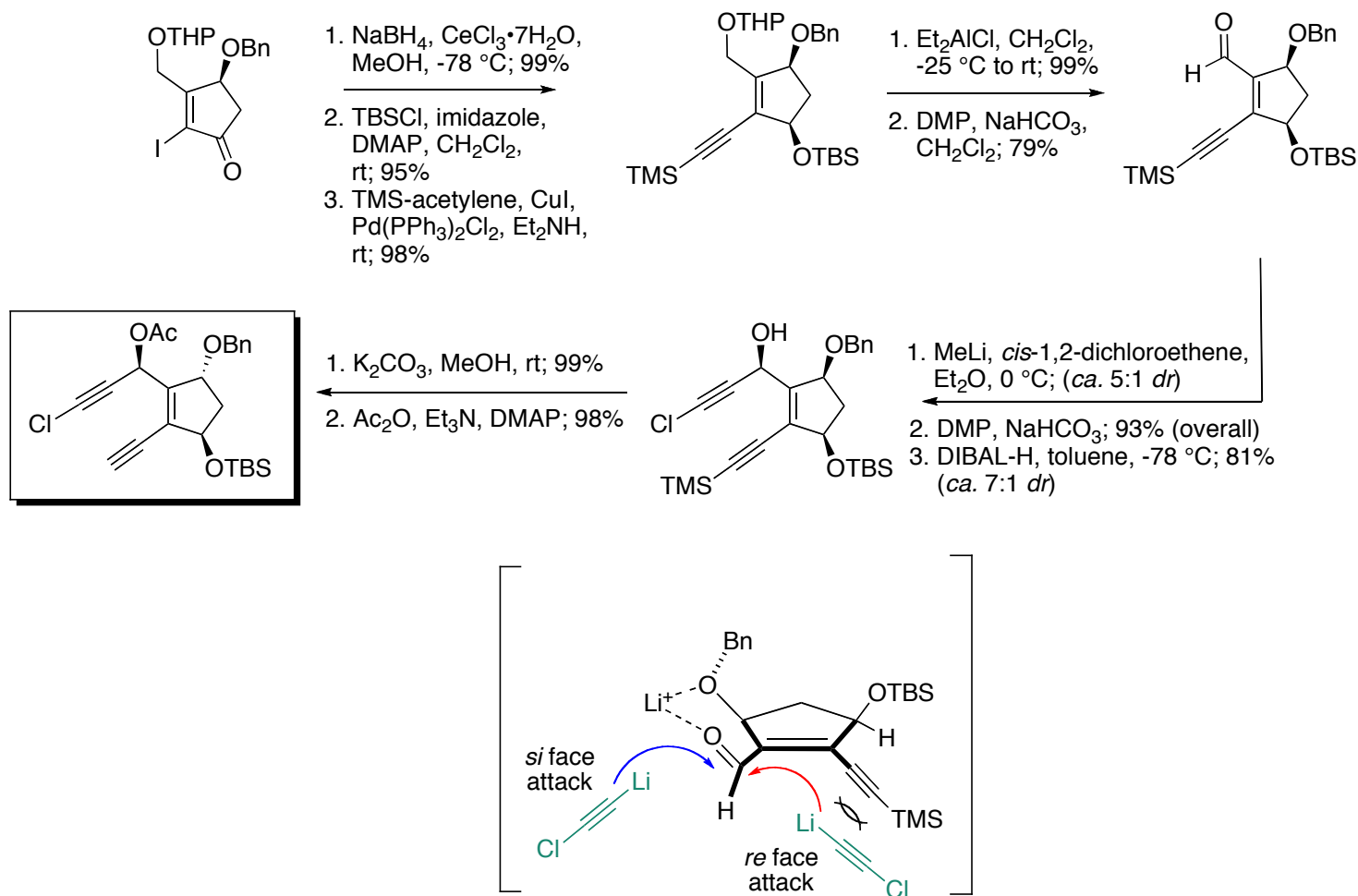
(a) Nicolaou, K.C.; Tang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3449. (b) Nicolaou, K.C.; Wang, J.; Tang, Y.; Botta, L. *J. Am. Chem. Soc.* **2010**, *132*, 11350.

## Toward Sporolide B: Successful but not Successful Attempts



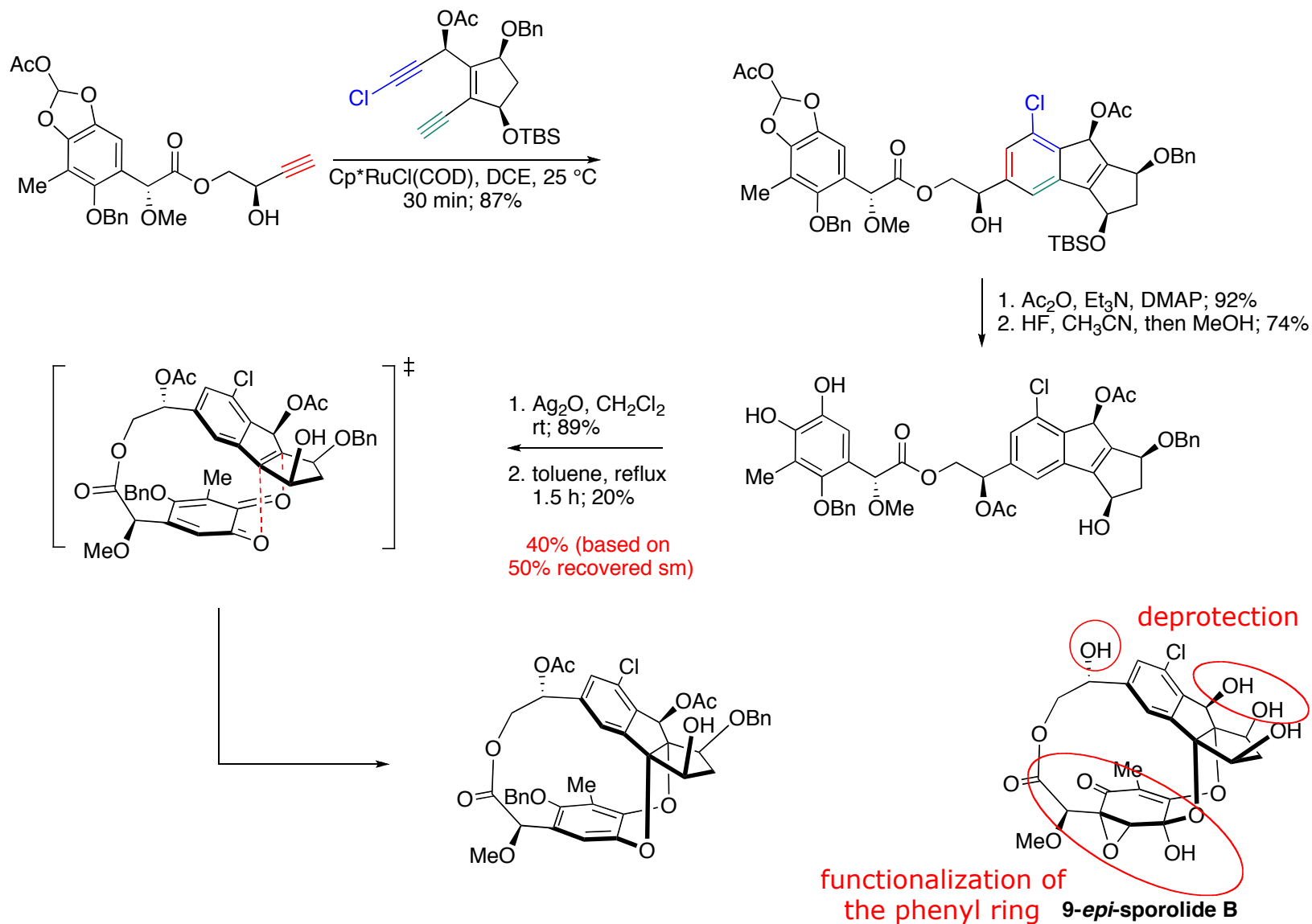
(a) Nicolaou, K.C.; Tang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2009**, 48, 3449. (b) Nicolaou, K.C.; Wang, J.; Tang, Y.; Botta, L. *J. Am. Chem. Soc.* **2010**, 132, 11350. For Ru-catalyzed cyclotrimerization, see: (c) Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* **2000**, 549. (d) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, 125, 12143.

## Toward *epi*-Sporolide B: Synthesis of 9-*epi*-Chloro Ene diene



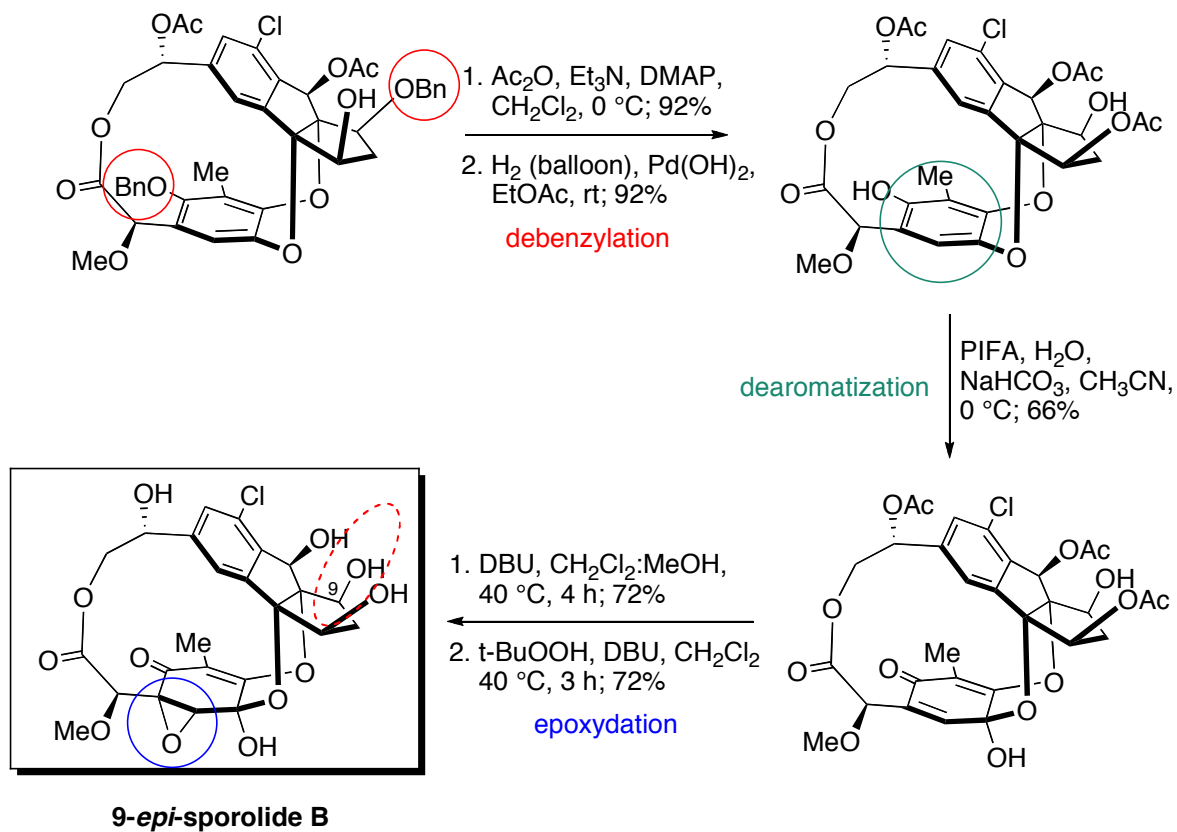
(a) Nicolaou, K.C.; Wang, J.; Tang, Y.; Botta, L. *J. Am. Chem. Soc.* **2010**, *132*, 11350.

## Synthesis of 9-*epi*-Sporolide B: "Almost There"



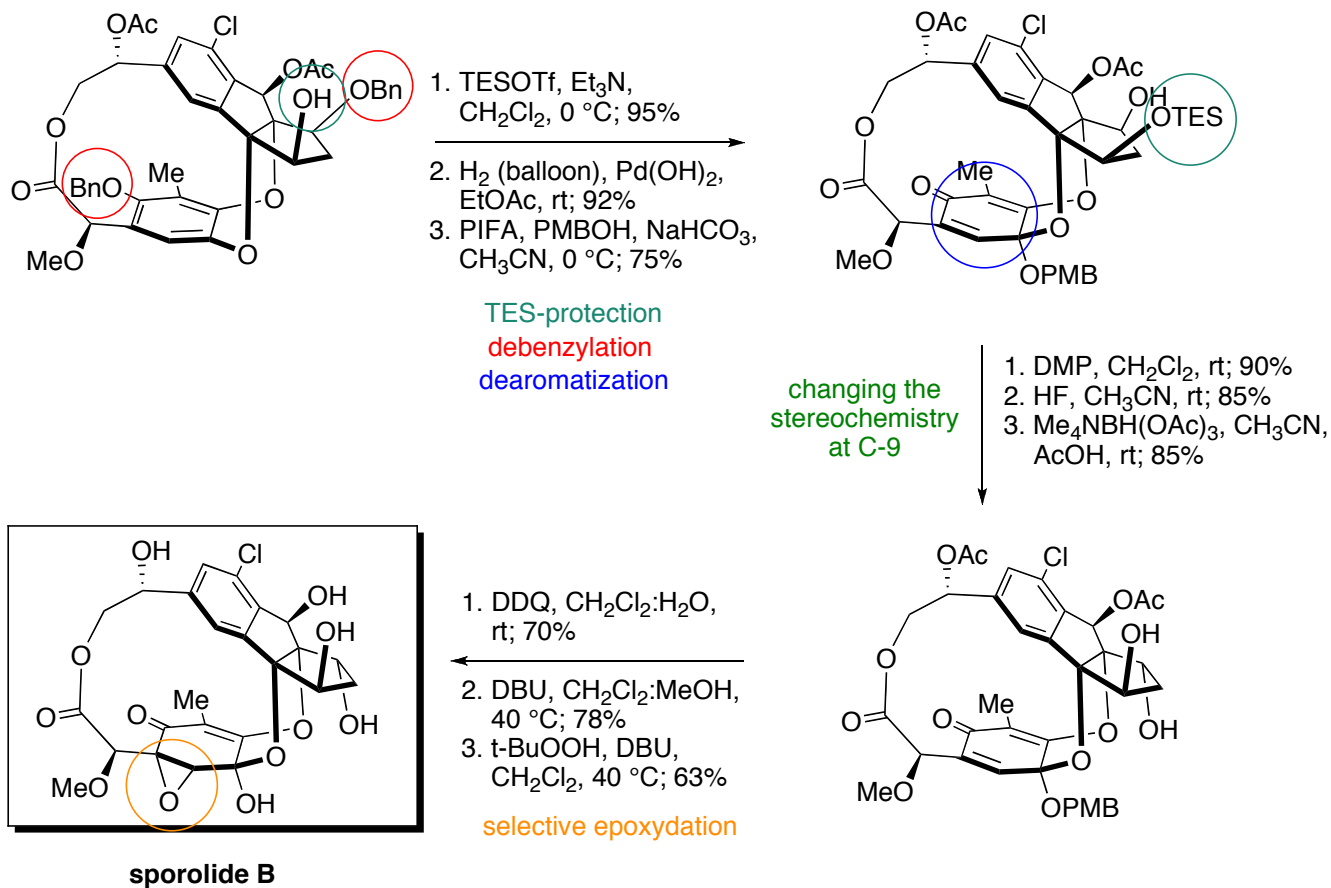
(a) Nicolaou, K.C.; Wang, J.; Tang, Y.; Botta, L. *J. Am. Chem. Soc.* **2010**, *132*, 11350.

## Synthesis of 9-*epi*-Sporolide B



(a) Nicolaou, K.C.; Wang, J.; Tang, Y.; Botta, L. *J. Am. Chem. Soc.* **2010**, *132*, 11350.

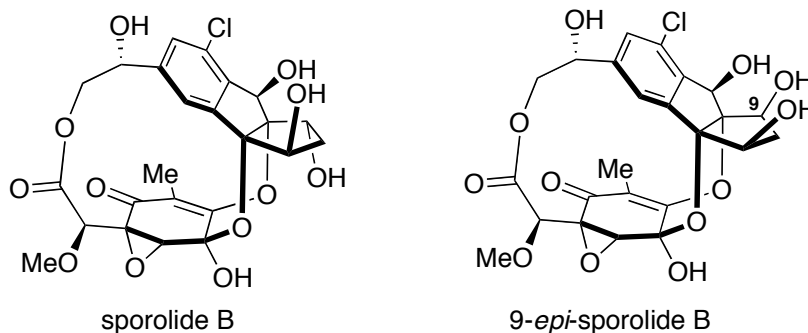
## Synthesis of Sporolide B: Mission Accomplished



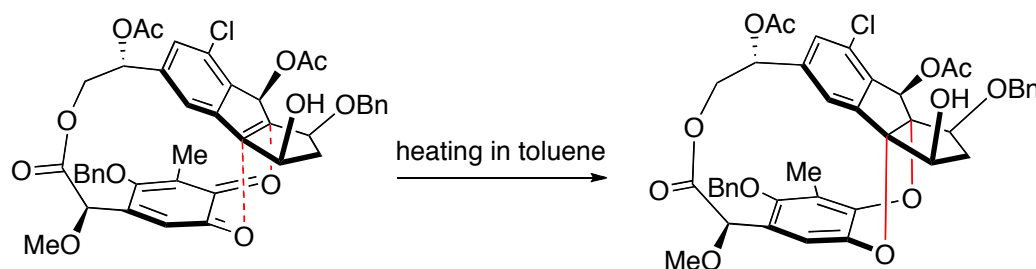
(a) Nicolaou, K.C.; Tang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3449. (b) Nicolaou, K.C.; Wang, J.; Tang, Y.; Botta, L. *J. Am. Chem. Soc.* **2010**, *132*, 11350.

## Conclusions: Total Synthesis of Sporolide B and Its Epimer in a Nutshell

- A stereocontrolled total synthesis of Sporolide B and 9-*epi*-Sporolide B has been achieved



- Key step: intramolecular hetero [4+2] cycloaddition of *o*-quinone onto tetrasubstituted alkene



- Ruthenium-catalyzed [2+2+2] cyclization (cyclootrimerization) has been used for the construction of the highly substituted chlorinated indene system

