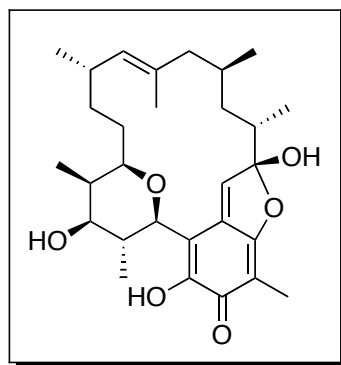


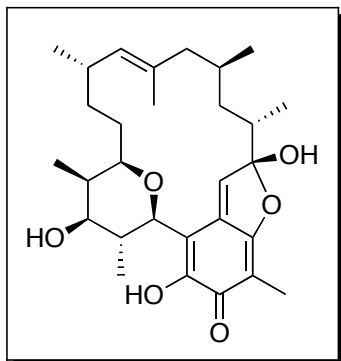
# Total Synthesis of Kendomycin Featuring Intramolecular Dötz Benzannulation

Kyosuke Tanaka, Masahito Watanabe, Kodai  
Ishibashi, Hiroshi Matsuyama, Yoko Saikawa,\* and  
Masaya Nakata\*

OL, ASAP



Presented by: Jared Hammill  
Wipf Group Cur. Lit. 3/27/10



# Isolation & Activity

- 1996 by Funahashi et al. from *Streptomyces violaceoruber*
- Absolute Stereochem determined by X-ray in 2000 by Zeeck et al.
- Potent antibacterial (Gram  $\pm$ , MRSA) and cytotoxic activity

Table 3 Cytotoxic activity of 1 and 2 (in  $\mu\text{mol l}^{-1}$ )

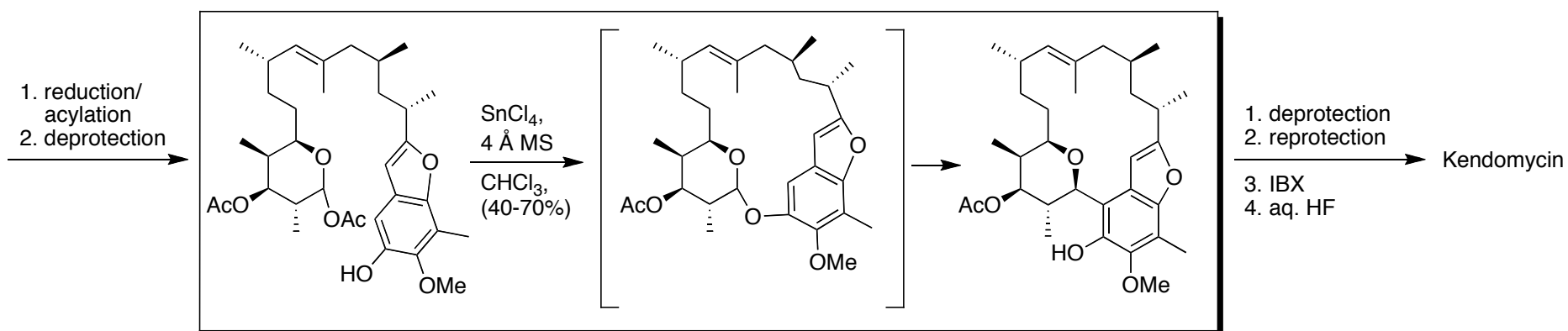
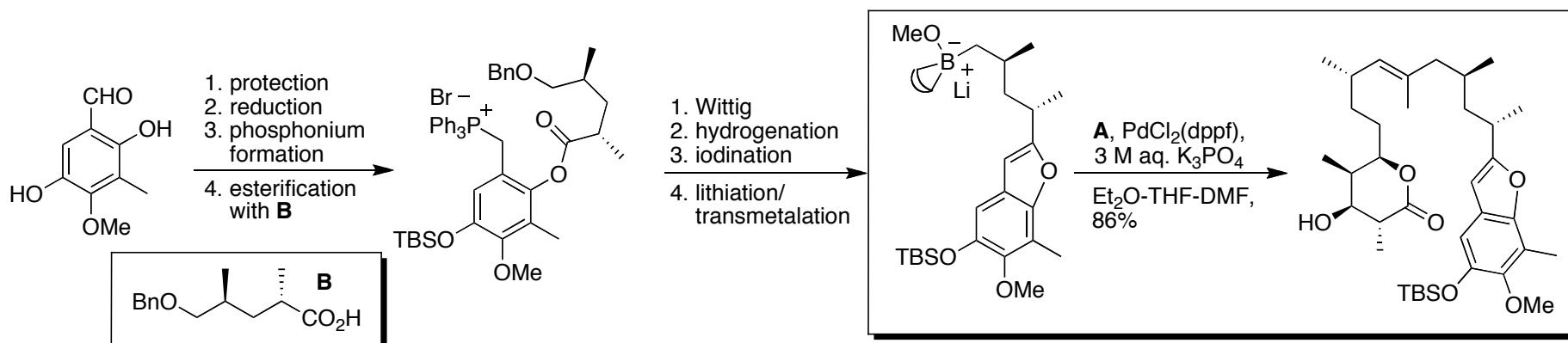
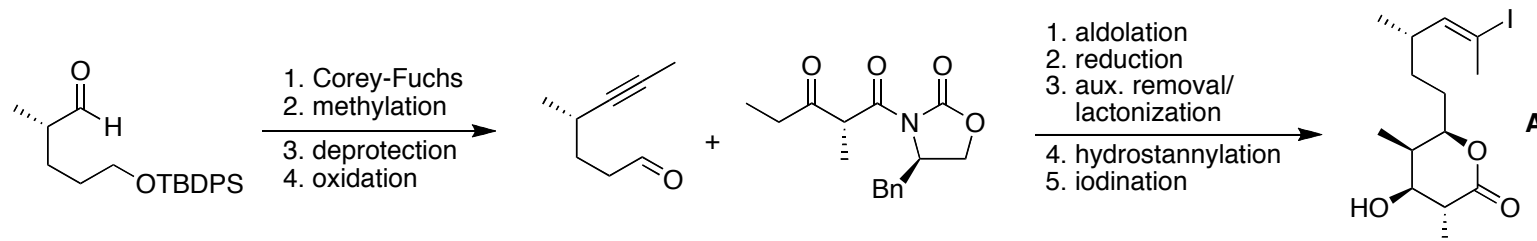
Compound	HMO2 <sup>a</sup>		HEP G2 <sup>b</sup>		MCF7 <sup>c</sup>	
	GI <sub>50</sub> <sup>d</sup>	TGI <sup>e</sup>	GI <sub>50</sub>	TGI	GI <sub>50</sub>	TGI
1	<0.1	0.2	<0.1	0.2	<0.1	0.5
2	0.1	0.4	0.8	48	0.2	0.6
Doxorubicin	<0.1	0.1	0.3	1.0	<0.1	0.2
Cisplatin	0.2	1.5	0.5	5.0	0.1	10

<sup>a</sup> Stomach adenocarcinoma. <sup>b</sup> Hepatocellular carcinoma. <sup>c</sup> Breast adenocarcinoma. <sup>d</sup> 50% growth inhibition. <sup>e</sup> Total growth inhibition.

Y. Funahashi, N. Kawamura, T. Ishimaru, JP Patent, 08231551A2960910, 1996 [Chem. Abstr. 1997, 126, 6553]

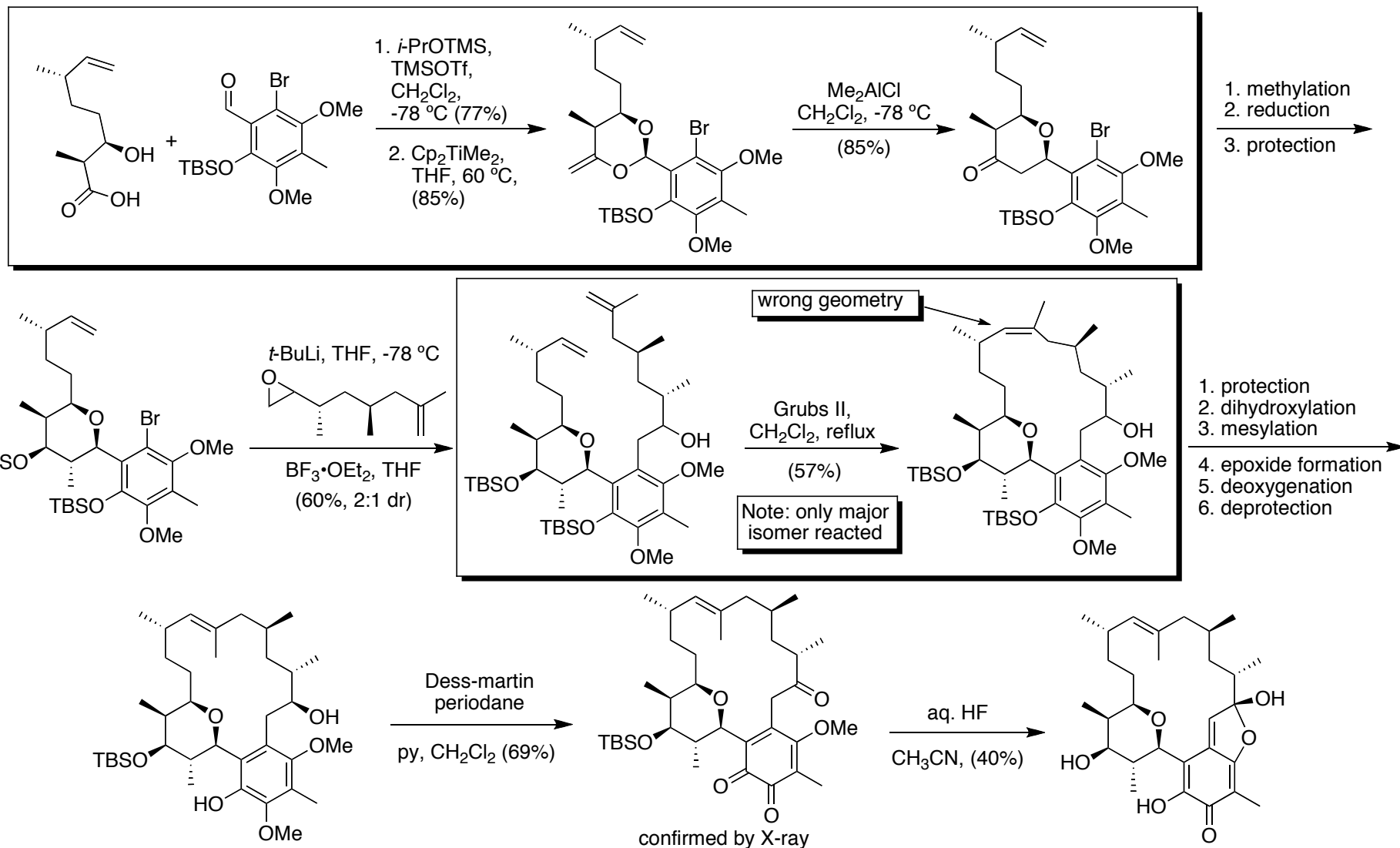
H. B. Bode, A. Zeeck, J. Chem. Soc. Perkin Trans. 1 2000, 323; H. B. Bode, A. Zeeck, J. Chem. Soc. Perkin Trans. 1 2000, 2665

# 1<sup>st</sup> Enantioselective Synthesis: Lee



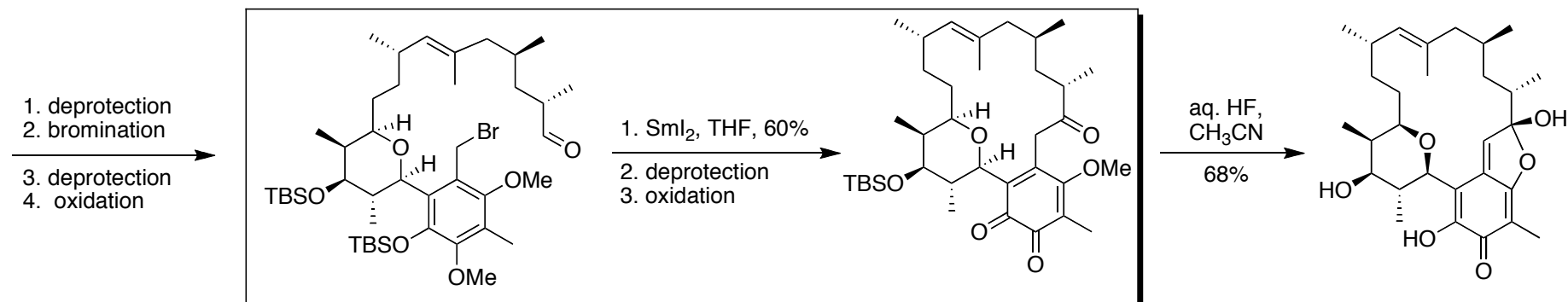
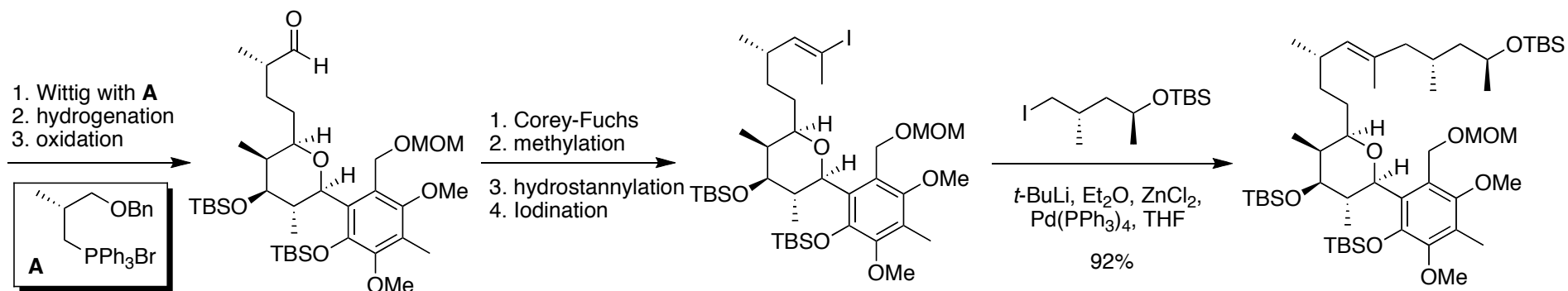
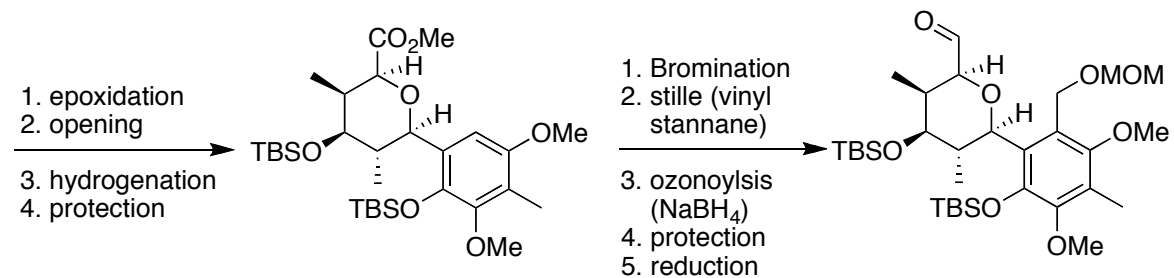
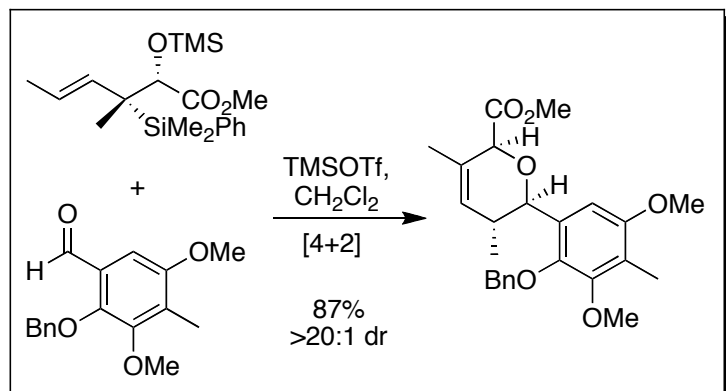
Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720–14721.

# Smith's approach



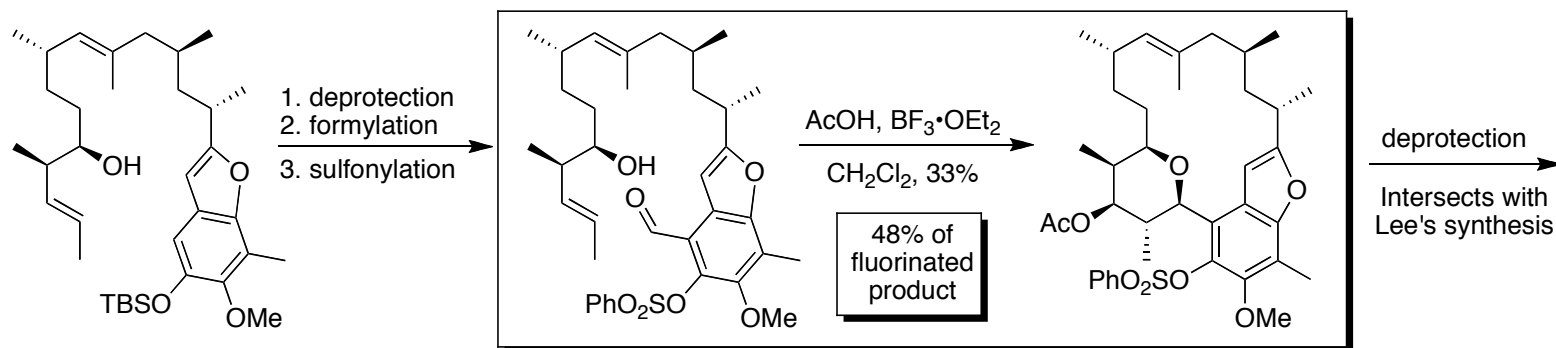
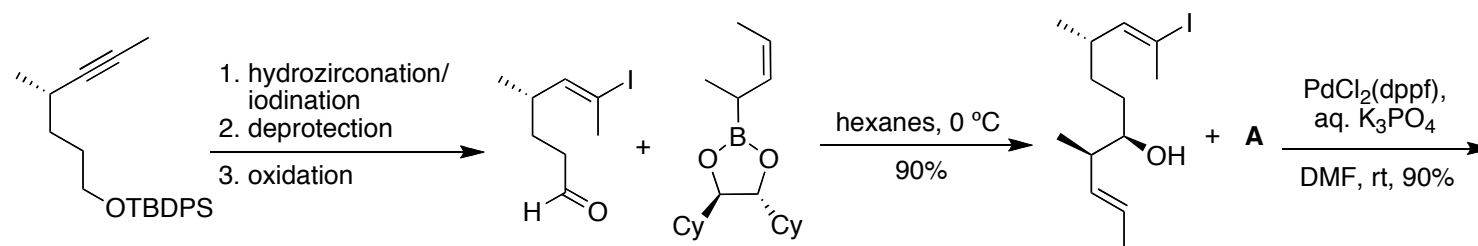
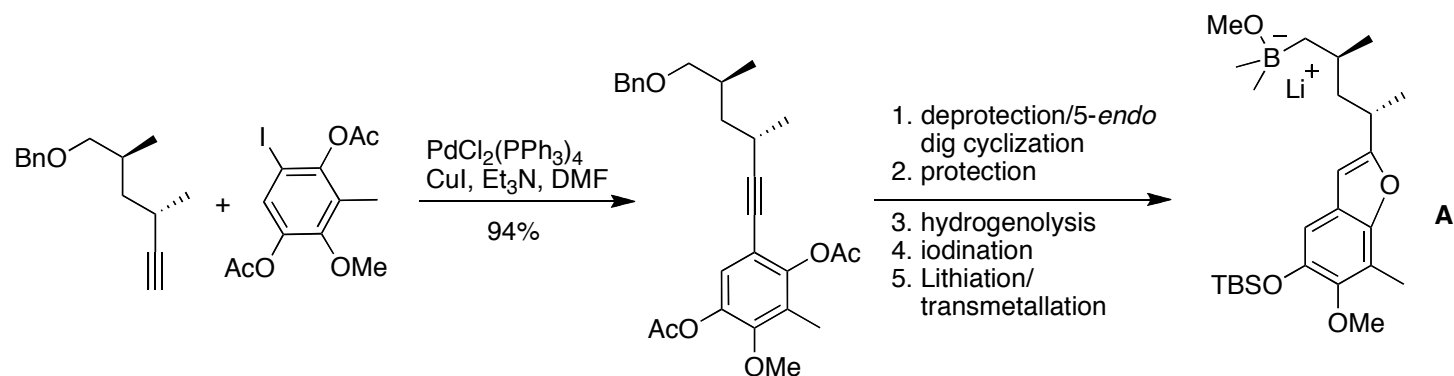
Smith, A. B., III.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948–6949.  
 Smith, A. B., III.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292–5299

# Panek's Synthesis



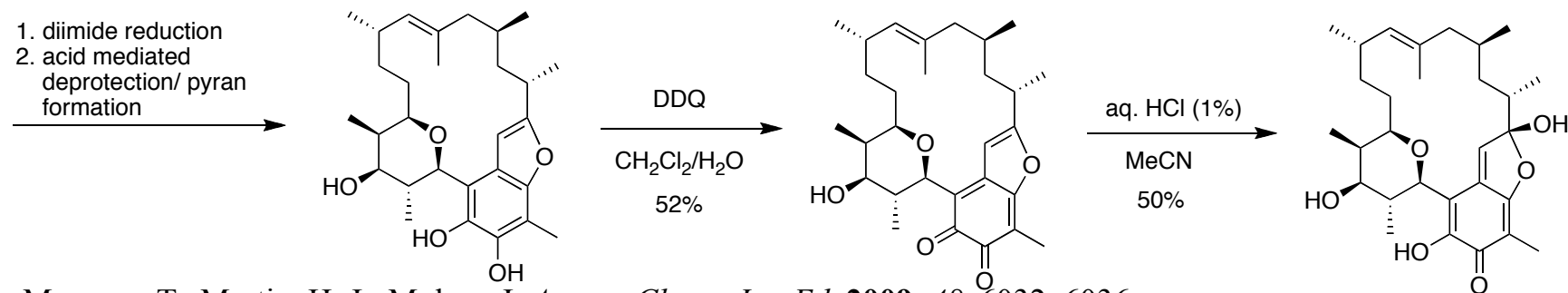
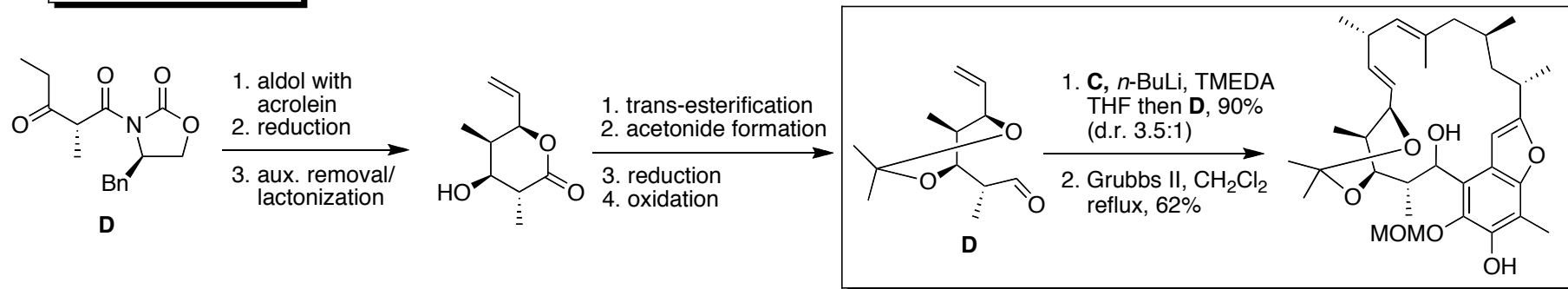
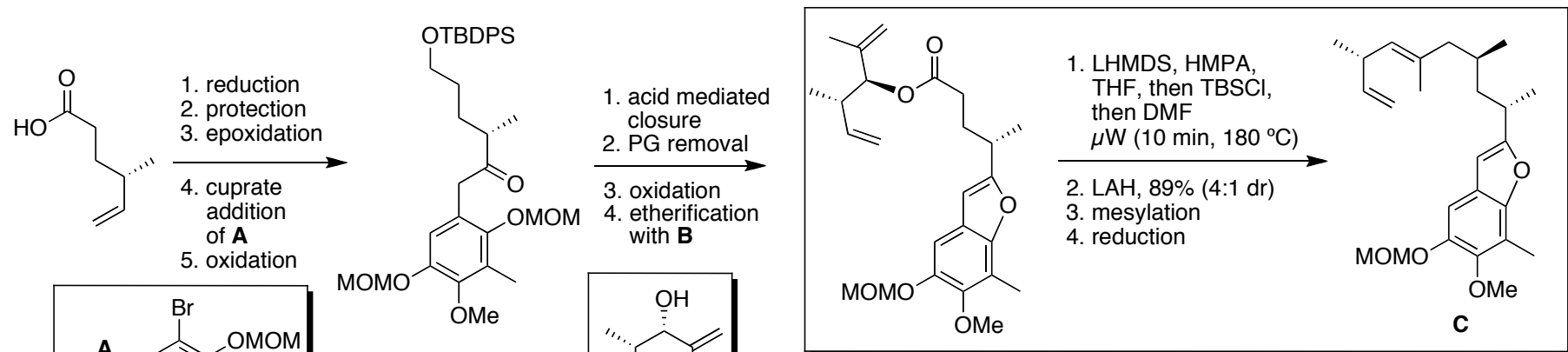
Lowe, J. T.; Panek, J. S. *Org. Lett.* **2008**, *10*, 3813–3816

# Rychnovsky's synthesis



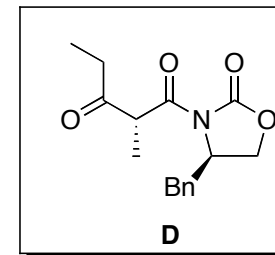
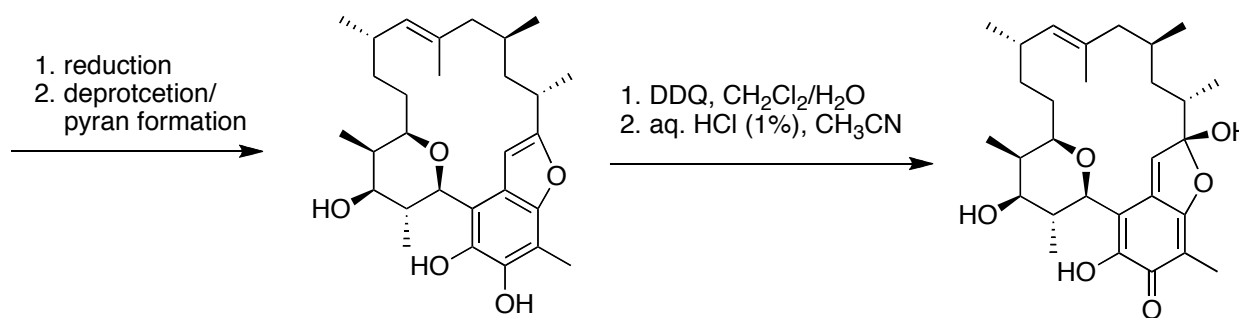
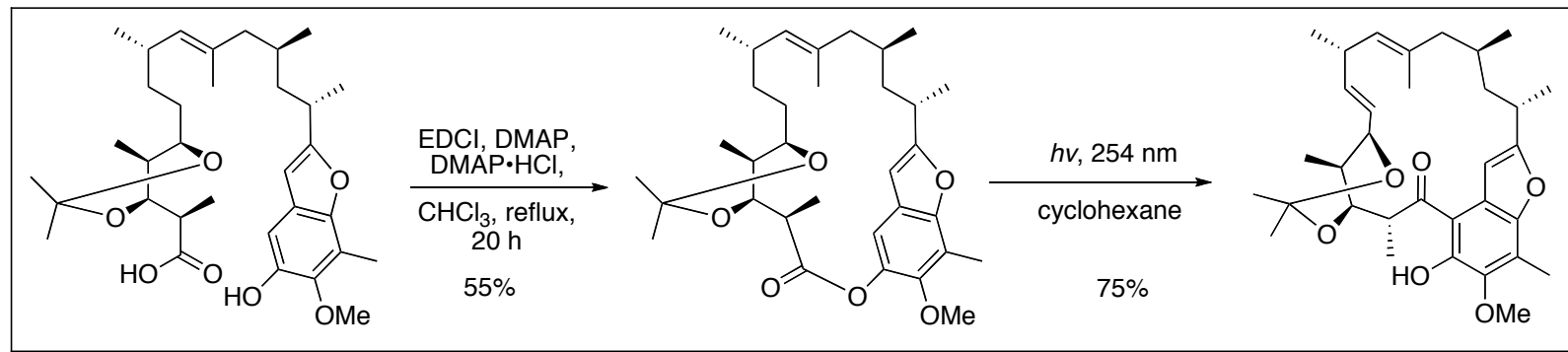
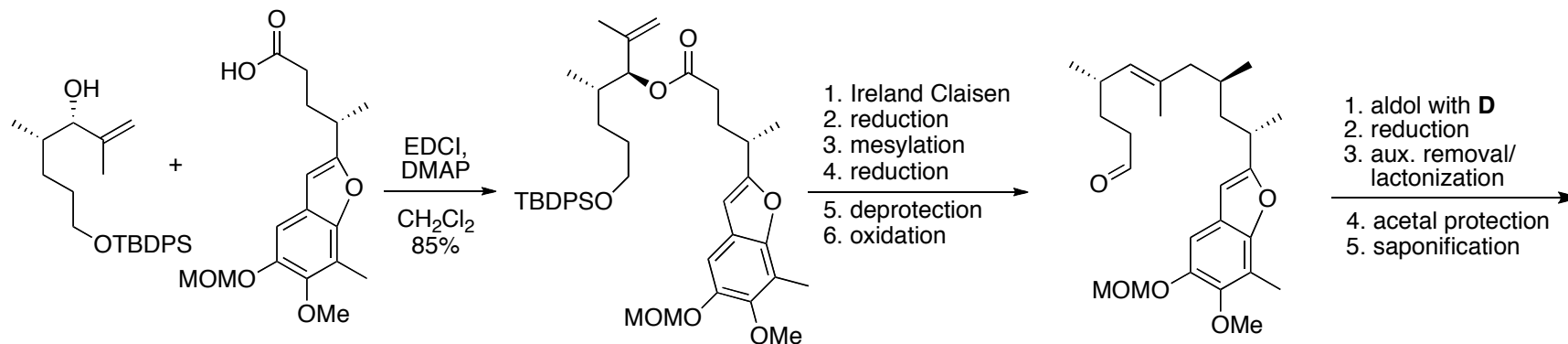
Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177–13181.

# Mulzer Synthesis



Magauer, T.; Martin, H. J.; Mulzer, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6032–6036

# Mulzer 2<sup>nd</sup> synthesis

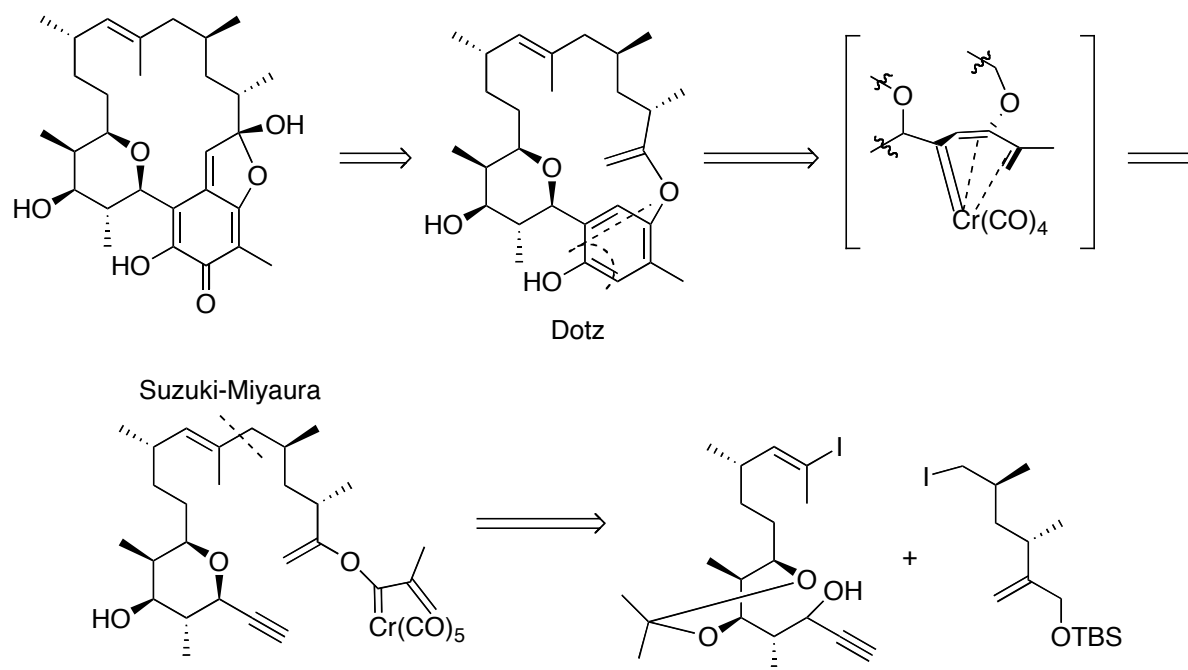


Magauer, T.; Martin, H. J.; Mulzer, J. *Chem. Eur. J.* **2010**, *16*, 507–519.



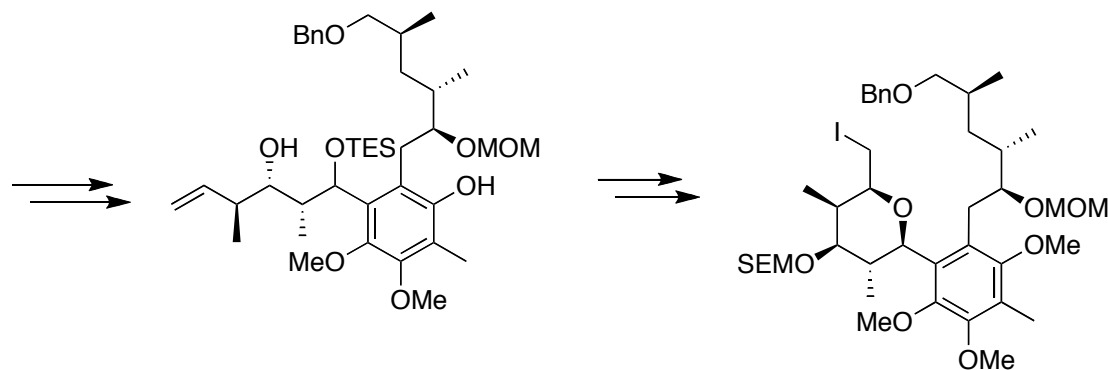
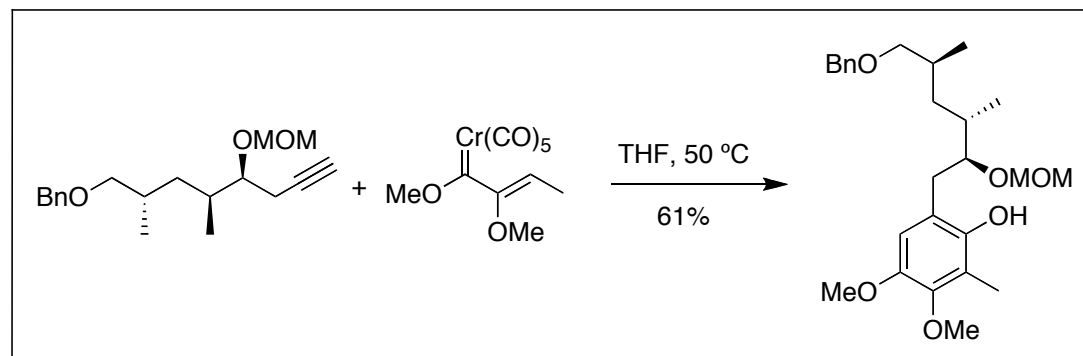
# Title Paper: Retrosynthesis

- Key Step: late stage intramolecular Dötz benzannulation/  
macrocyclization



Kyosuke Tanaka, Masahito Watanabe, Kodai Ishibashi, Hiroshi Matsuyama, Yoko Saikawa,\* and Masaya Nakata,  
*Org. Lett.*, **2010**, ASAP

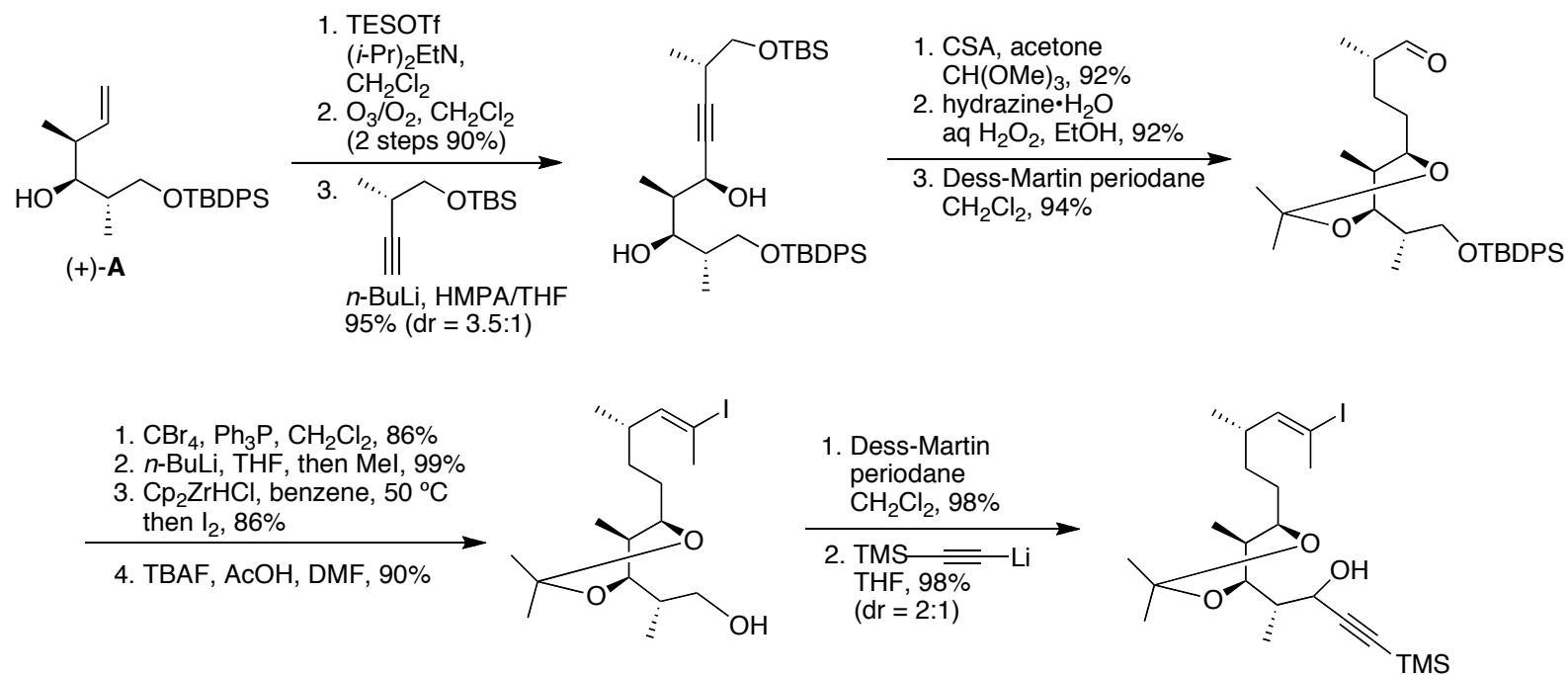
# Key Precedence



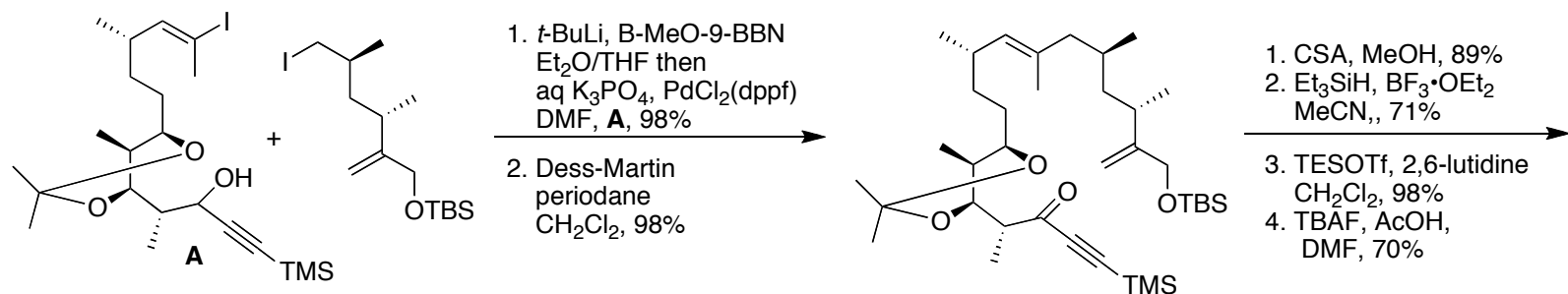
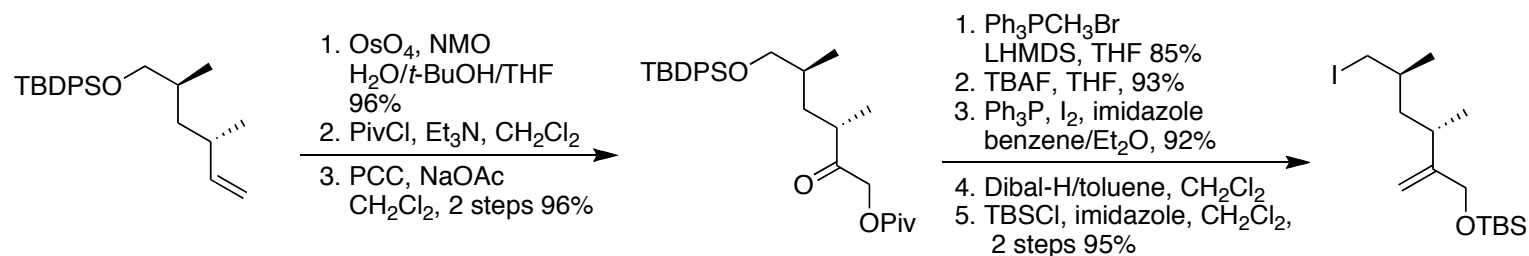
Interestingly the completion of the molecule was not described

White, J. D.; Smits, H. *Org. Lett.* **2005**, *7*, 235-238

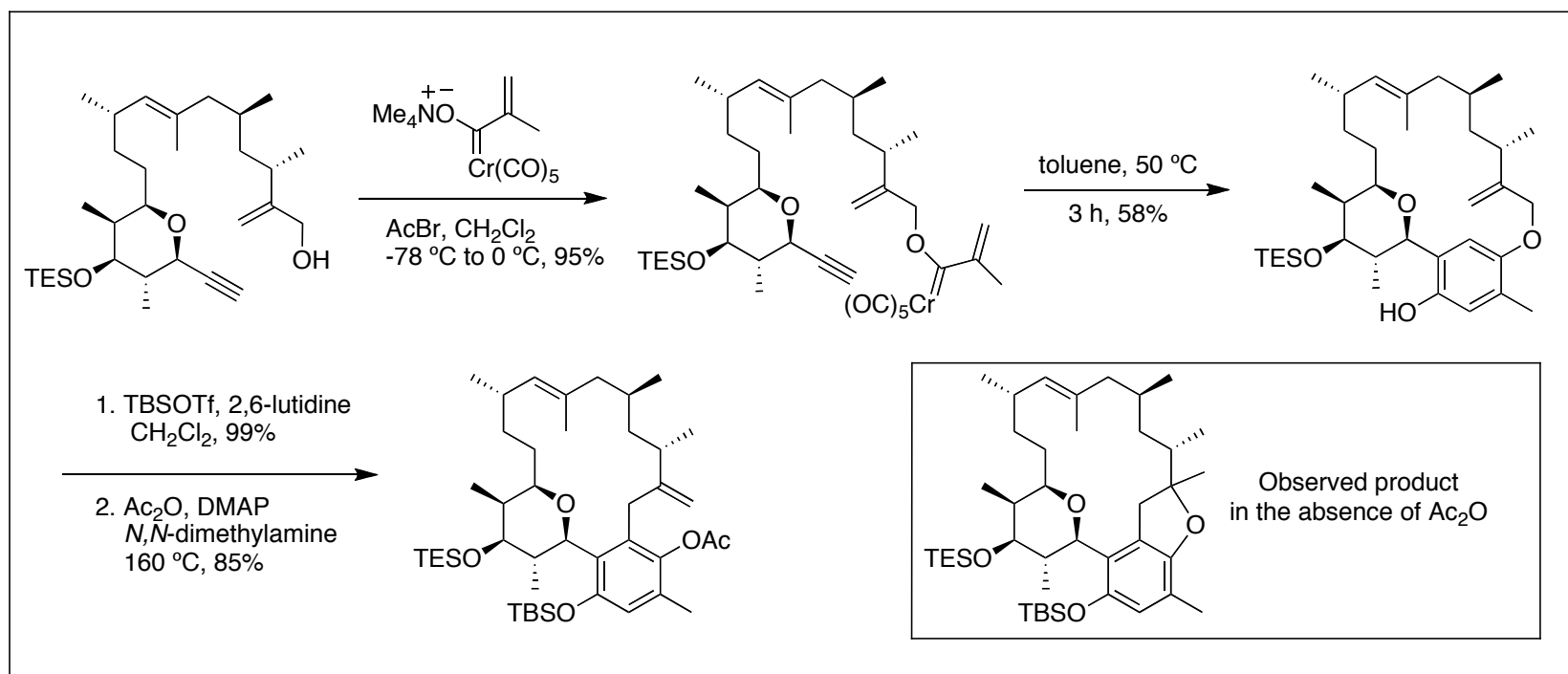
# Fragment 1



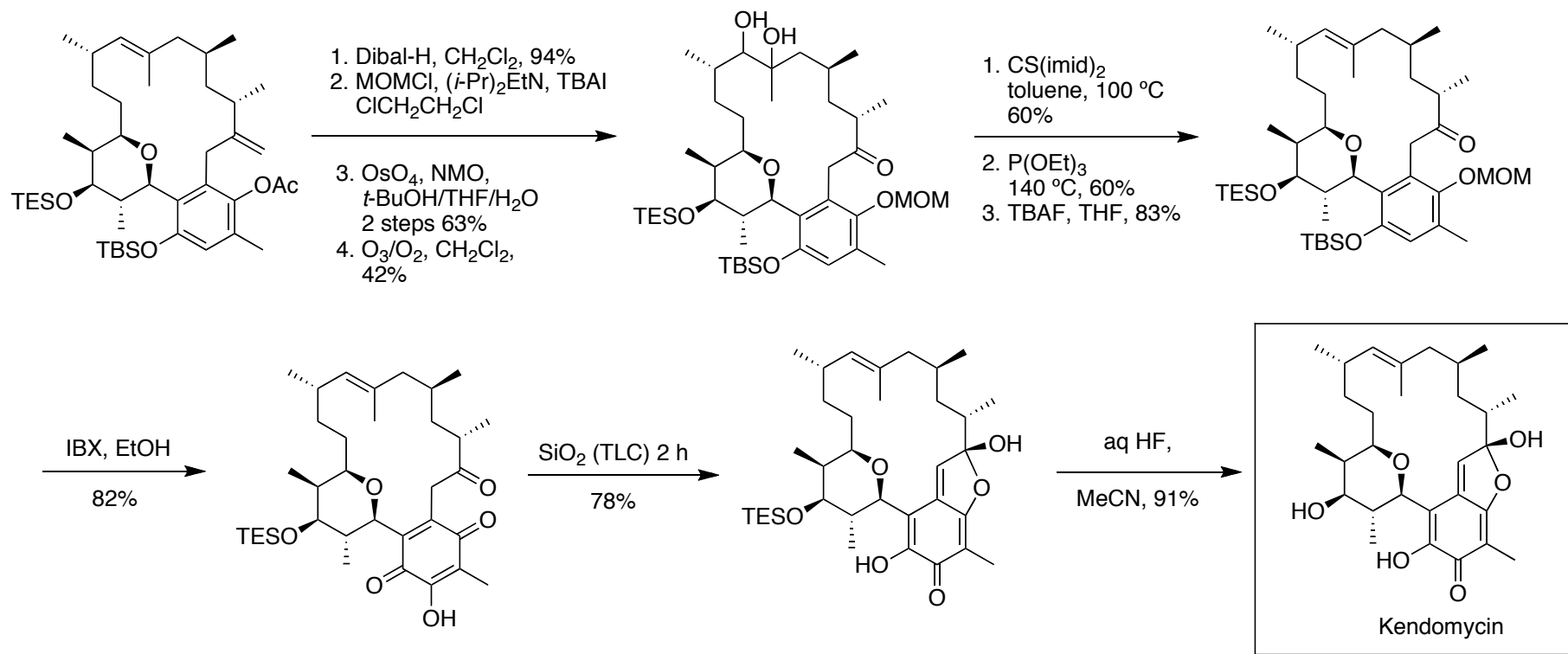
# Fragment 2 & Coupling



# Key Dötz & Claisen reactions



# End Game



# Conclusions

- The total synthesis Kendomycin was accomplished featuring several key steps:
  - Intramolecular Dötz benzannulation/macrocylation was utilized on a late stage intermediate
  - Subsequent Claisen rearrangement
  - Ortho oxidation and mild conversion from *p*-quinone to *p*-quinone methide on silica gel