

# Studies toward the synthesis of *Welwitindolinones*

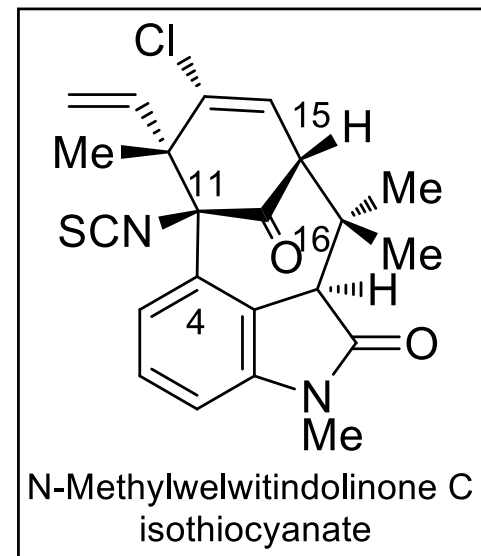
Dong group at UT Austin

Xuan Zhou

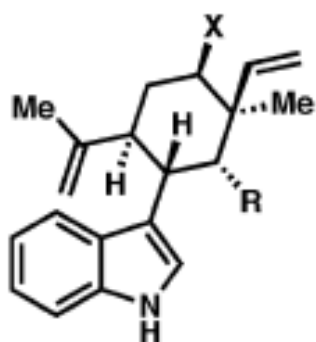
May 08, 2013

# Contents

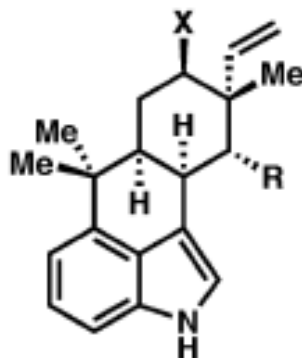
1. Background of *Welwitindolinones*
2. Studies toward synthesis of *Welwitindolinones*
3. Total synthesis of *Welwitindolinones*
4. Acknowledgement



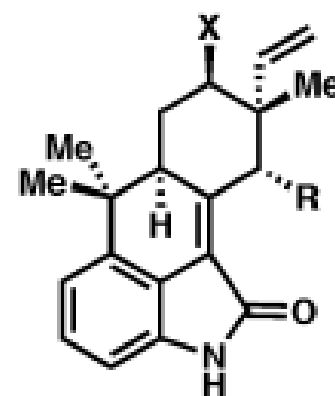
# Hapalindole-type natural products



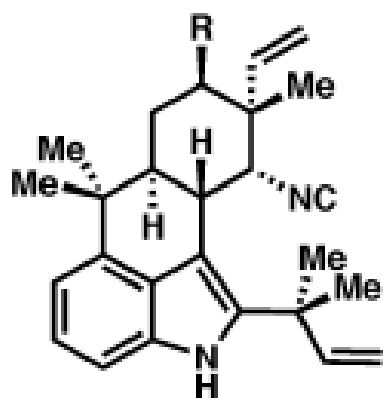
R=NC, X=H: 12-*epi*-hapalindole C<sup>2f</sup>  
 R=NCS, X=H: 12-*epi*-hapalindole D<sup>2f</sup>  
 R=NC, X=Cl: 12-*epi*-hapalindole E<sup>2f</sup>  
 R=NCS, X=Cl: 12-*epi*-hapalindole F<sup>2f</sup>



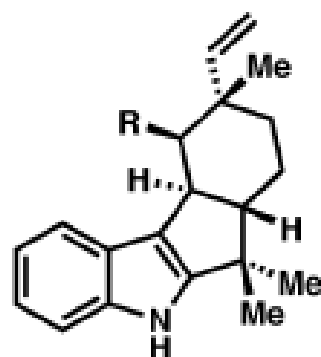
R=NC, X=Cl: hapalindole A<sup>1</sup>  
 R=NCS, X=Cl: hapalindole B<sup>1</sup>  
 R=NC, X=H: hapalindole J<sup>2a</sup>  
 R=NCS, X=H: hapalindole M<sup>2a</sup>  
 R=NCS, X=OH: hapalindole O<sup>2a</sup>



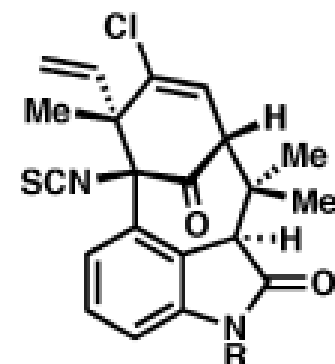
R=NC, X=Cl: anhydrohapaloxindole A<sup>2c</sup>  
 R=NCS, X=Cl: anhydrohapaloxindole B<sup>2j</sup>  
 R=NCS, X=H: anhydrohapaloxindole M<sup>2j</sup>



R=Cl: ambigaine A<sup>2d</sup>  
 R=H: ambigaine H<sup>2k</sup>



R=NC: fischerindole U isonitrile<sup>2f</sup>  
 R=NCS: fischerindole U isothiocyanate<sup>2f</sup>

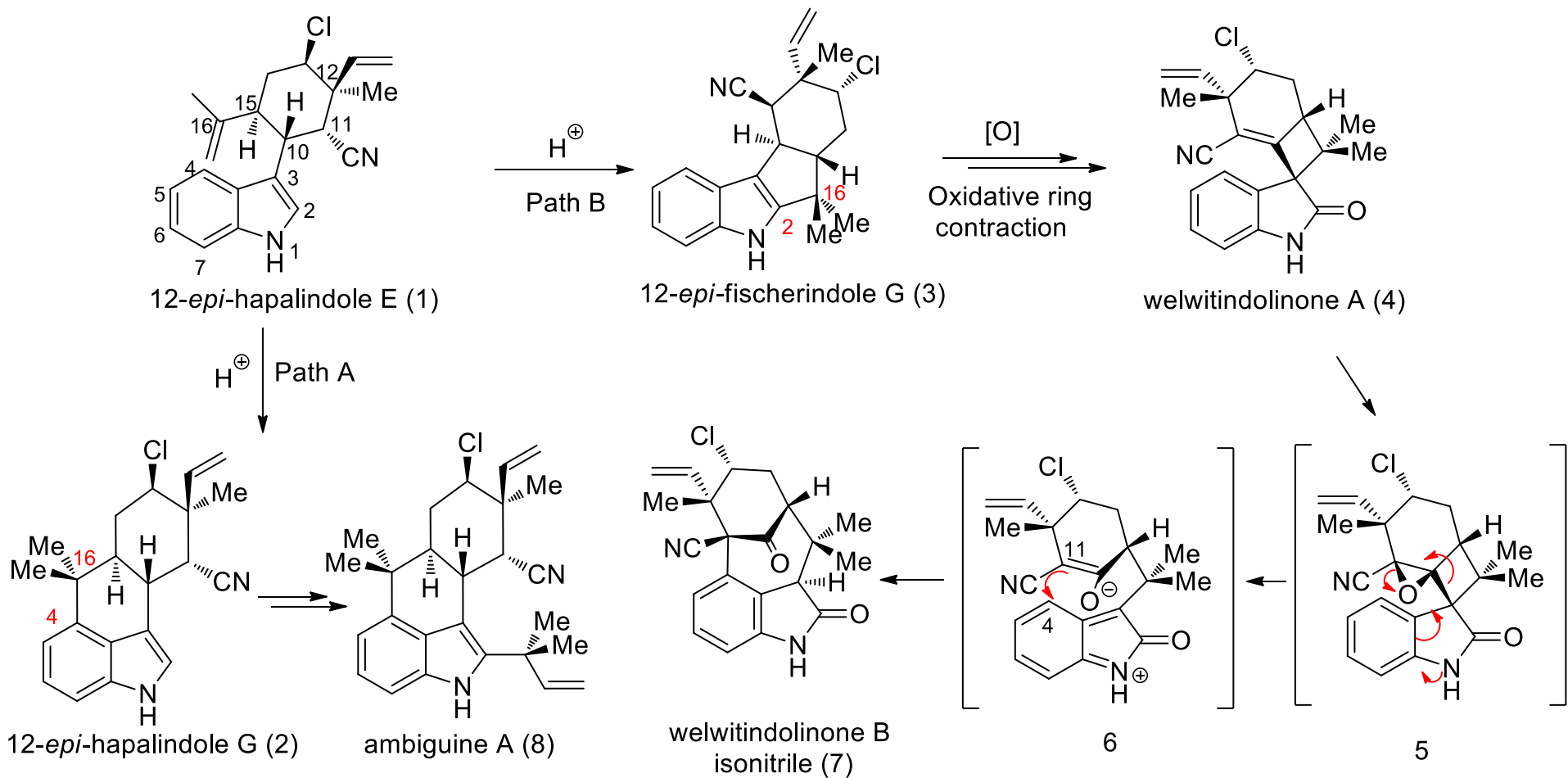


R=H: welwitindolinone  
 C isothiocyanate<sup>2f</sup>  
 R=Me: *N*-Me-welwitindolinone  
 C isothiocyanate<sup>2f</sup>

Moore, R. E., *et. al. J. Am. Chem. Soc.* **1984**, *106*, 6456-6457

Baran, P. S., *et. al. J. Am. Chem. Soc.* **2008**, *130*, 17938-17954

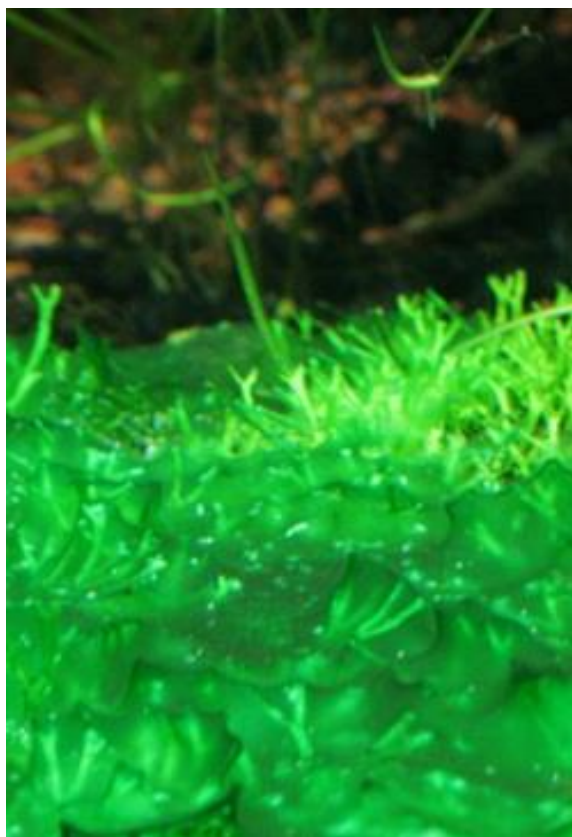
# Biosynthetic proposal of hapalindole –type alkaloids



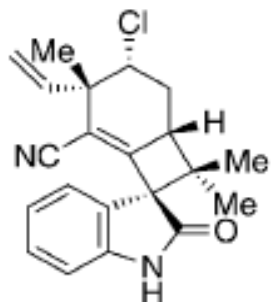
Moore, R. E., *et. al. J. Am. Chem. Soc.* **1994**, *116*, 9935

Baran, P. S., *et. al. J. Am. Chem. Soc.* **2008**, *130*, 17938-17954

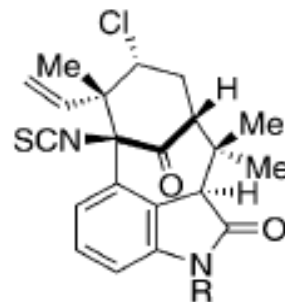
# Welwitindolinone natural products



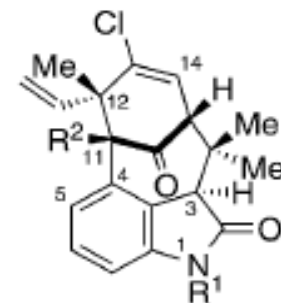
Blue green alga



Welwitindolinone A  
isonitrile (1)



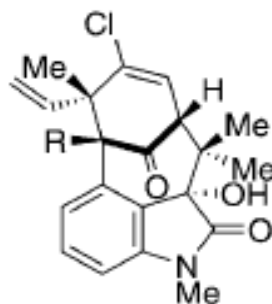
Welwitindolinone B  
isothiocyanate  
(R = H, 2)



Welwitindolinone C  
isothiocyanate  
(R<sup>1</sup> = H, R<sup>2</sup> = NCS, 4)

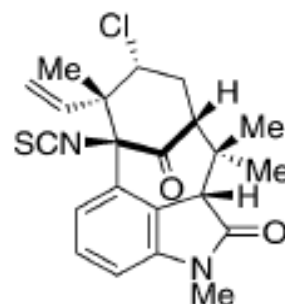
*N*-Methylwelwitindolinone B  
isothiocyanate  
(R = Me, 3)

*N*-Methylwelwitindolinone C  
isothiocyanate  
(R<sup>1</sup> = Me, R<sup>2</sup> = NCS, 5)

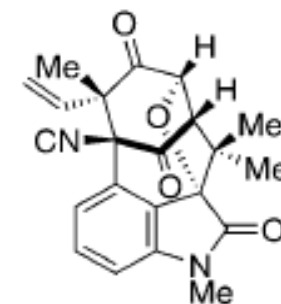


3-Hydroxy-*N*-methyl-  
welwitindolinone C  
isothiocyanate (R = NCS, 7)

3-Hydroxy-*N*-methyl-  
welwitindolinone C  
isonitrile (R = NC, 8)

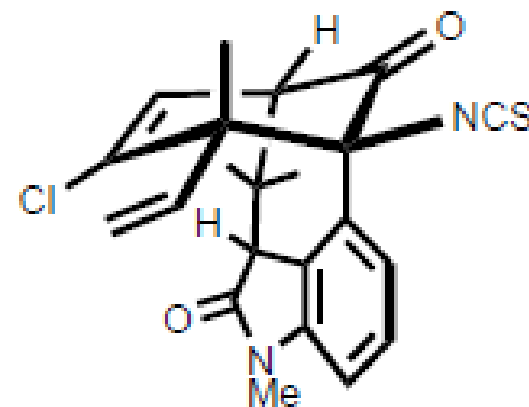
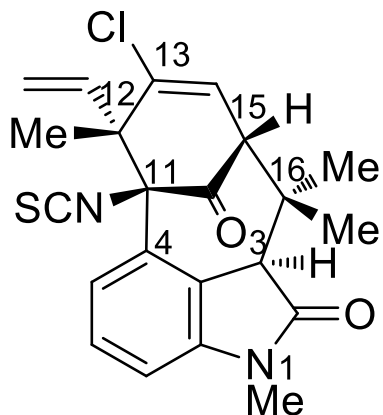
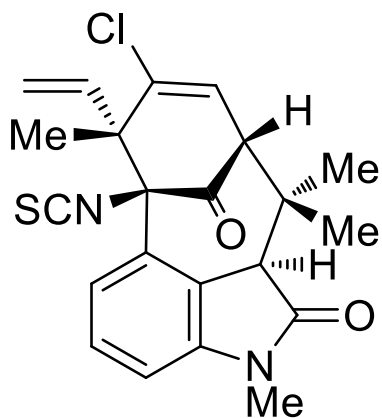


3-*epi*-Welwitindolinone  
B isothiocyanate (9)



*N*-Methylwelwitindolinone  
D isonitrile (10)

# Structure analysis of N-Methylwelwitindolinone C isothiocyanate



N-Methylwelwitindolinone C  
isothiocyanate

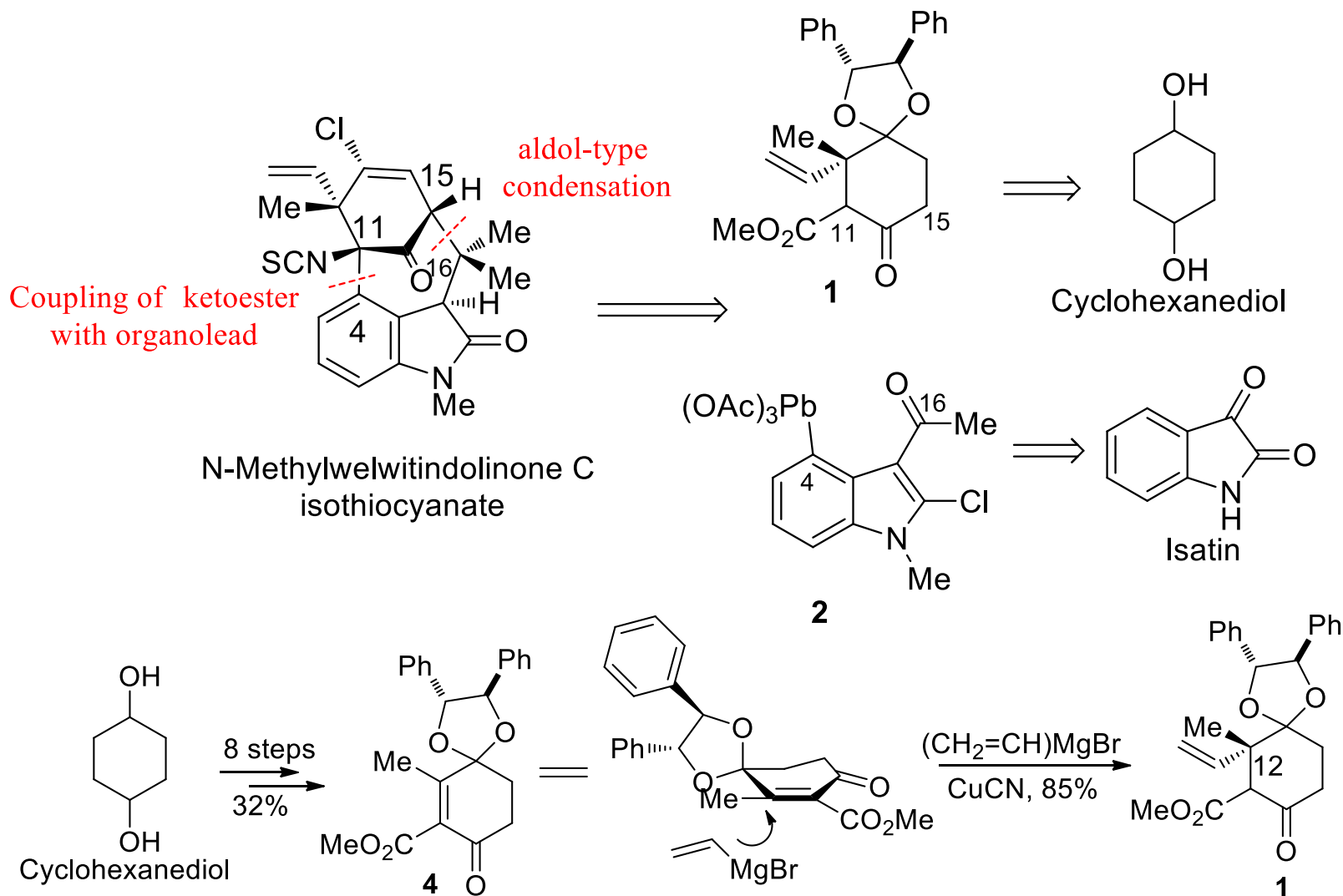
## Biological activity:

Exhibit biological activity against drug-resistant cancer cells.

## Synthesis challenge

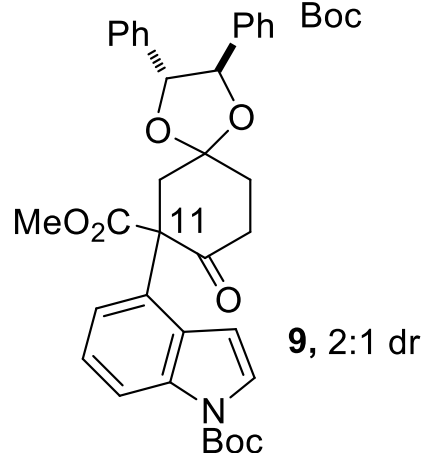
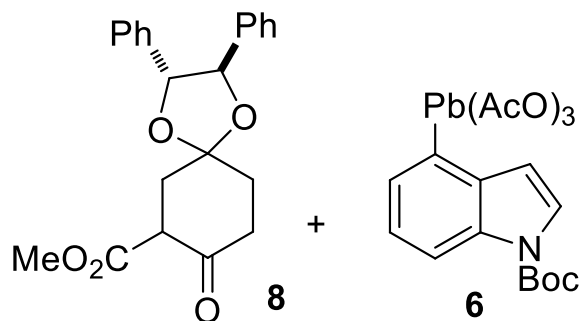
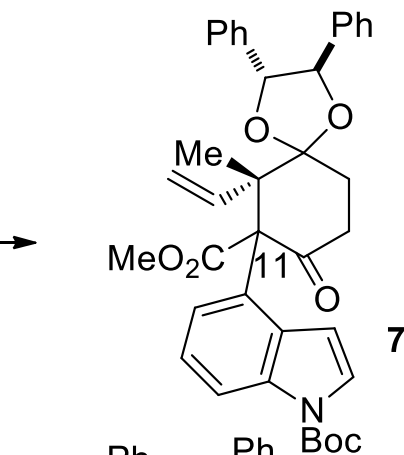
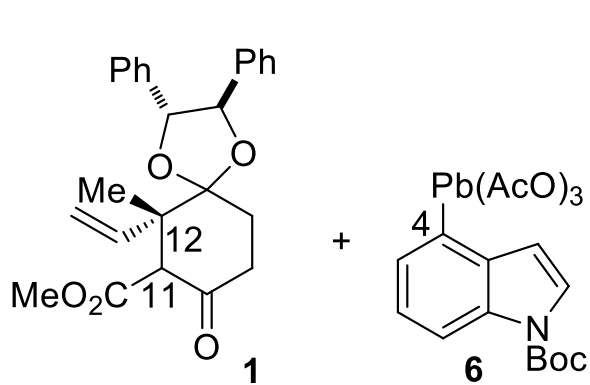
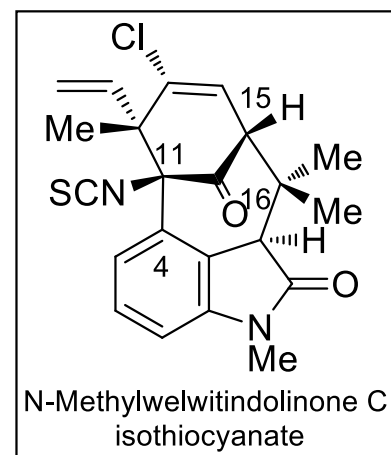
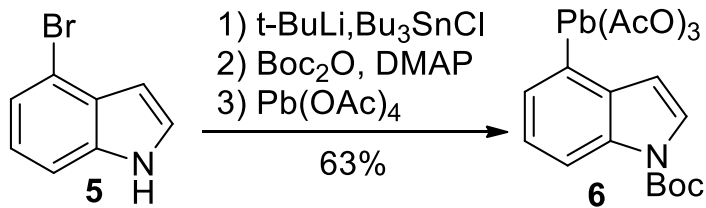
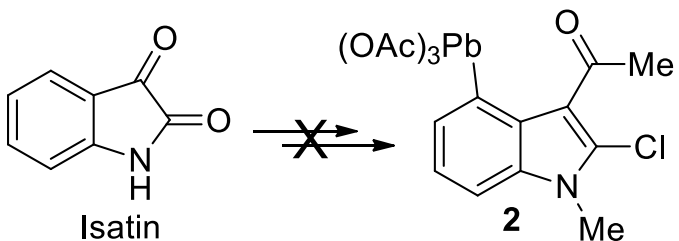
- Bicyclo[4.3.1]-decane ring system
- Contains four stereogenic centers
- Highly substituted C11-C12-C13 array
- Sensitive vinyl chloride, bridgehead isothiocyanate, gem-dimethyl substituent

# Konopelski's synthesis to NMWCI



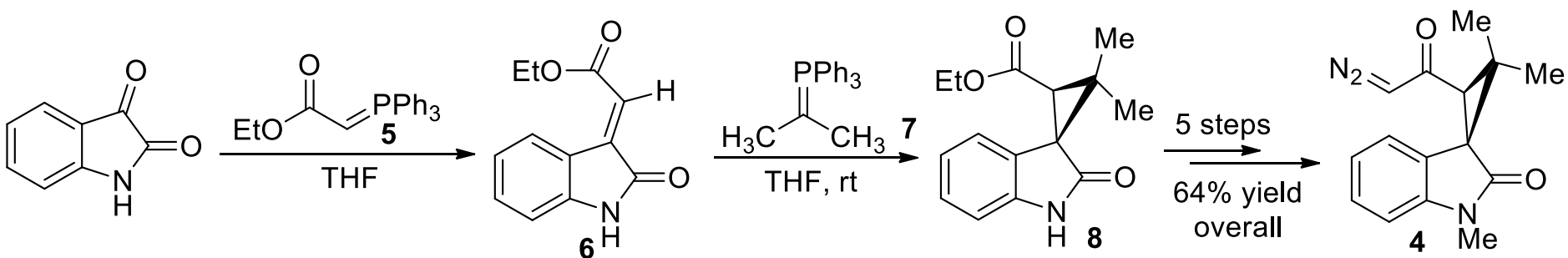
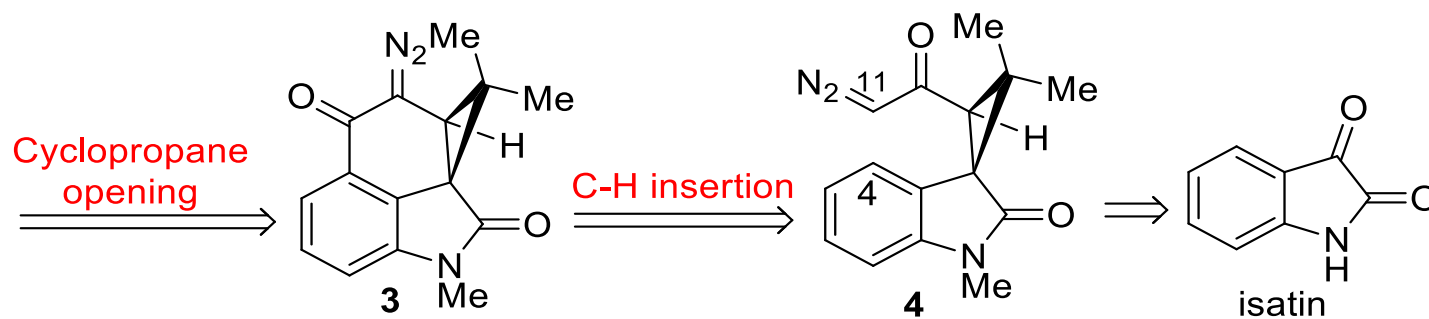
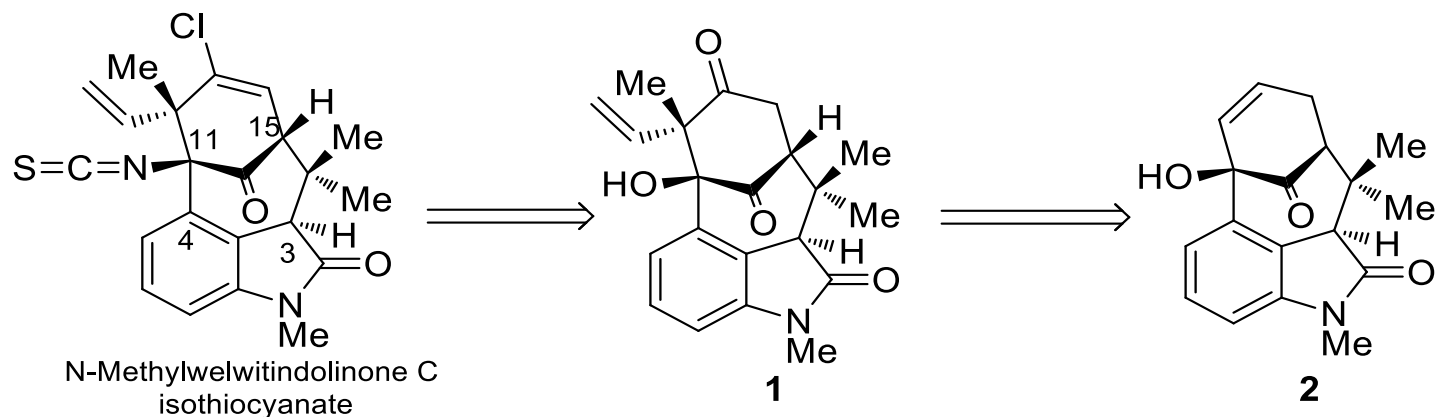
Konopelski, J. P., *et. al. synlett.* **1998**, 1105-1108

# Konopelski's synthesis to NMWCI

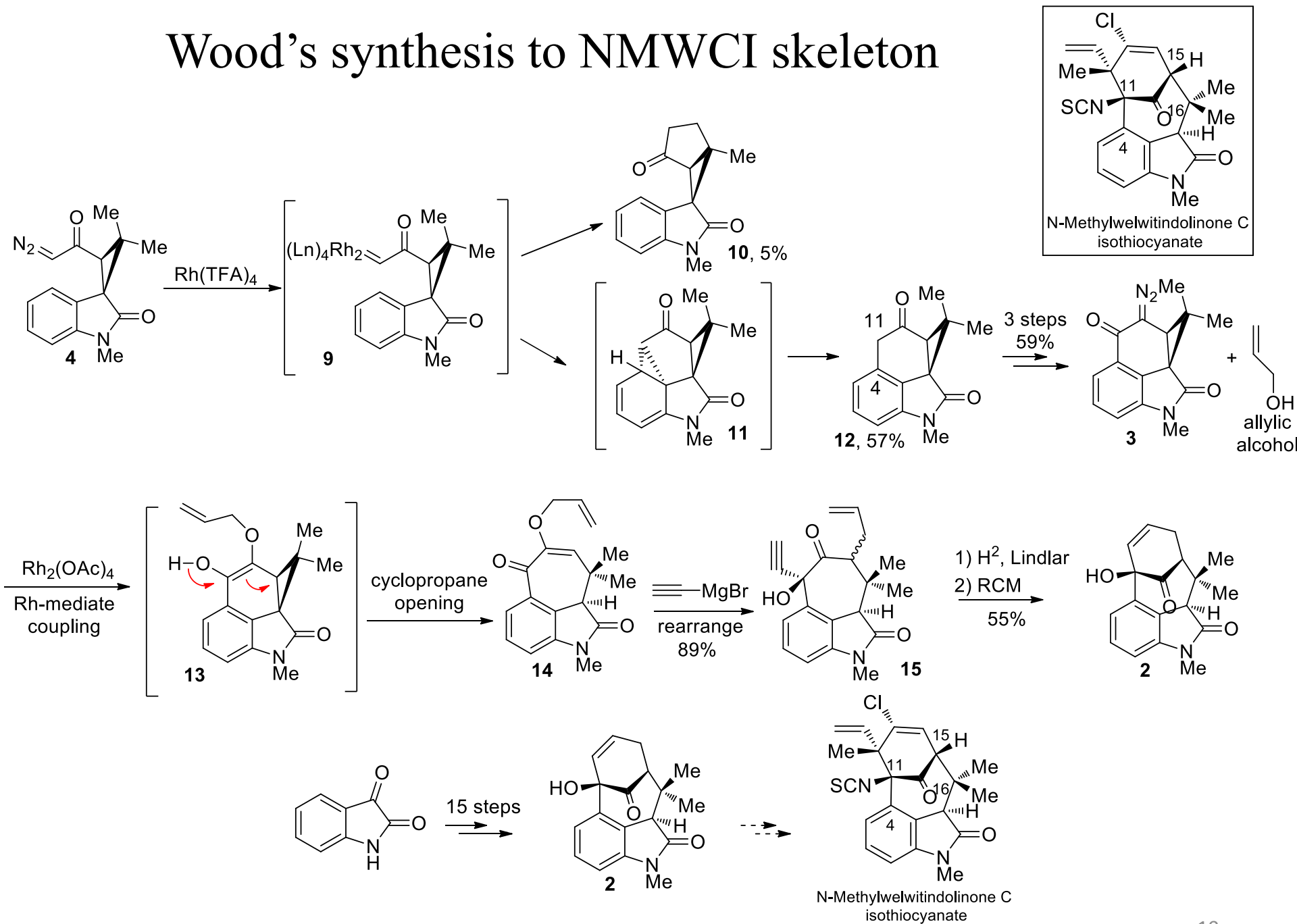




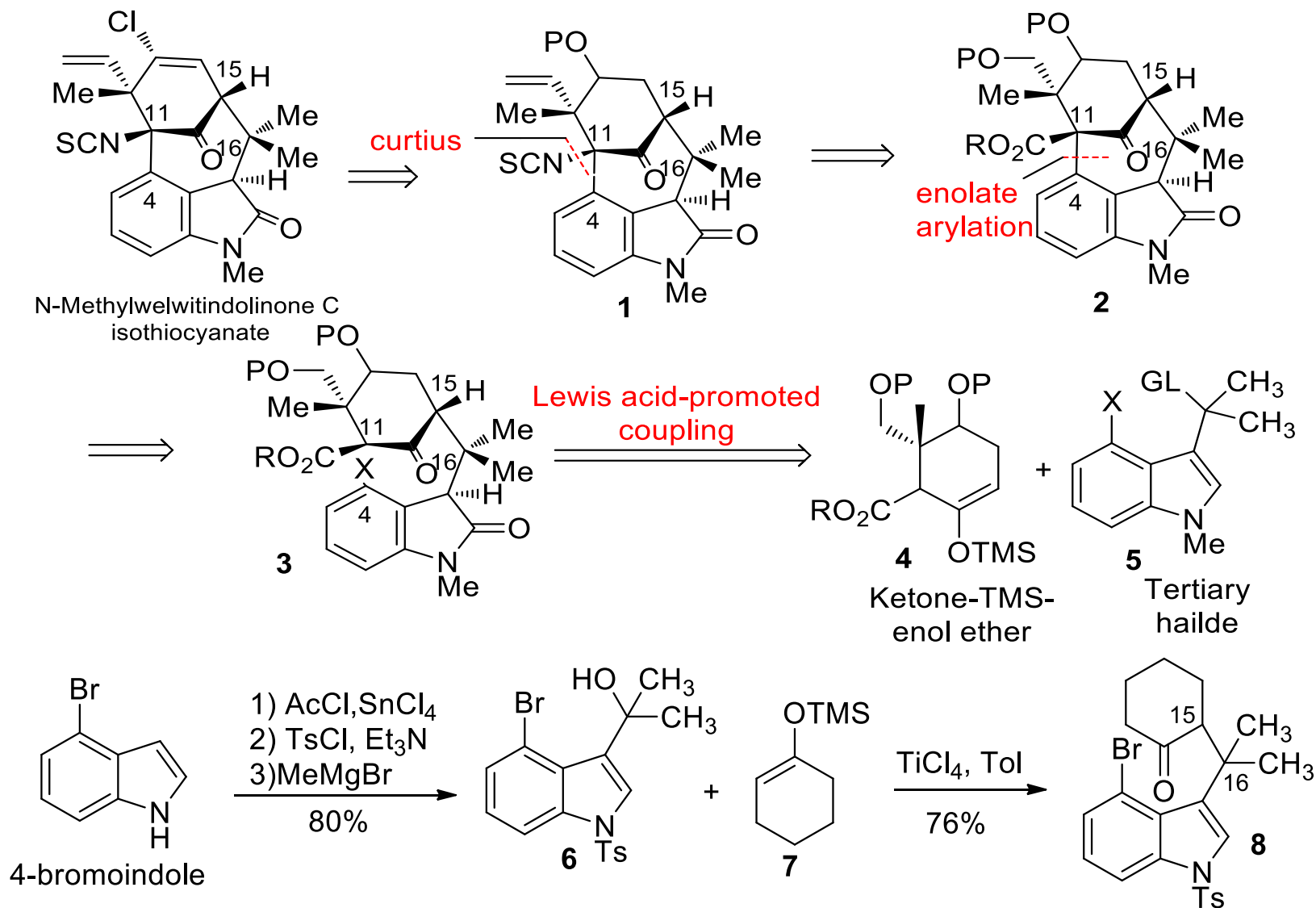
# Wood's synthesis to NMWCI skeleton



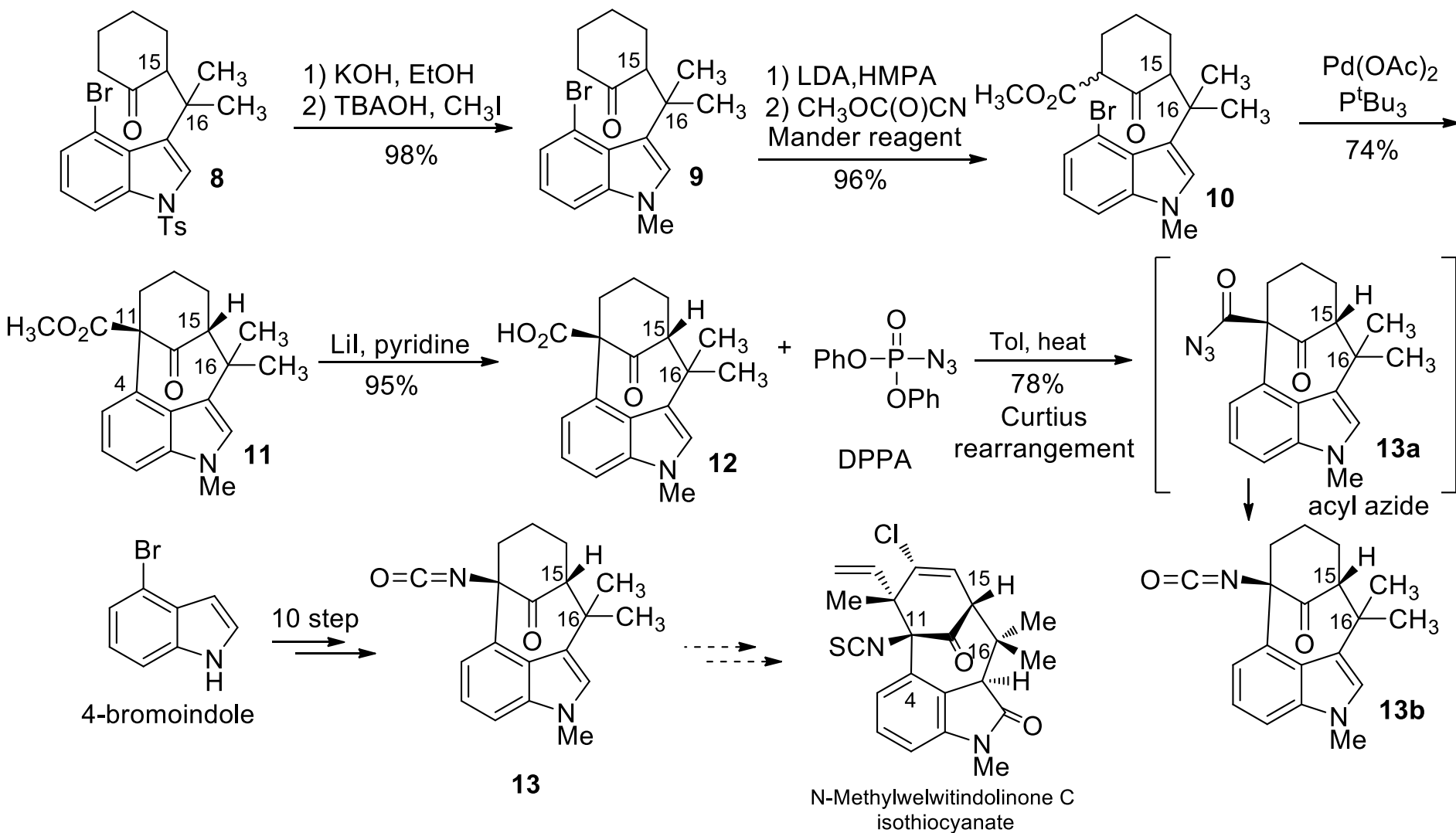
# Wood's synthesis to NMWCI skeleton



# Rawal's synthesis to NMWCI skeleton

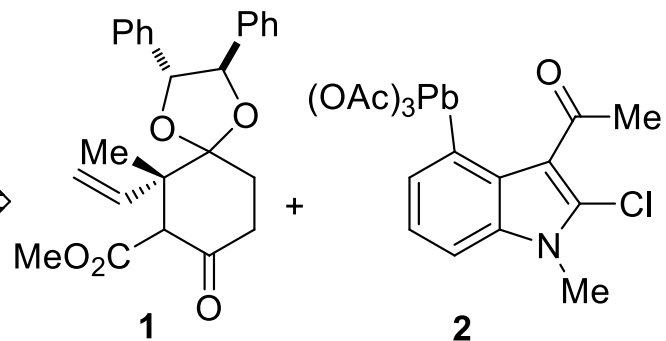
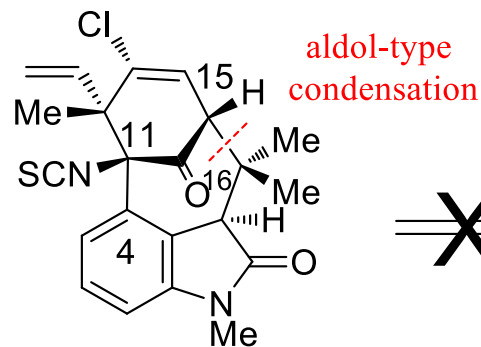


# Rawal's synthesis to NMWCI skeleton

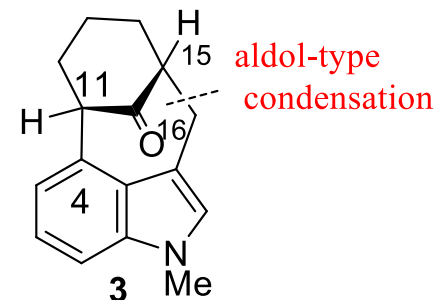


# Simpkins's work to NMWCI skeleton

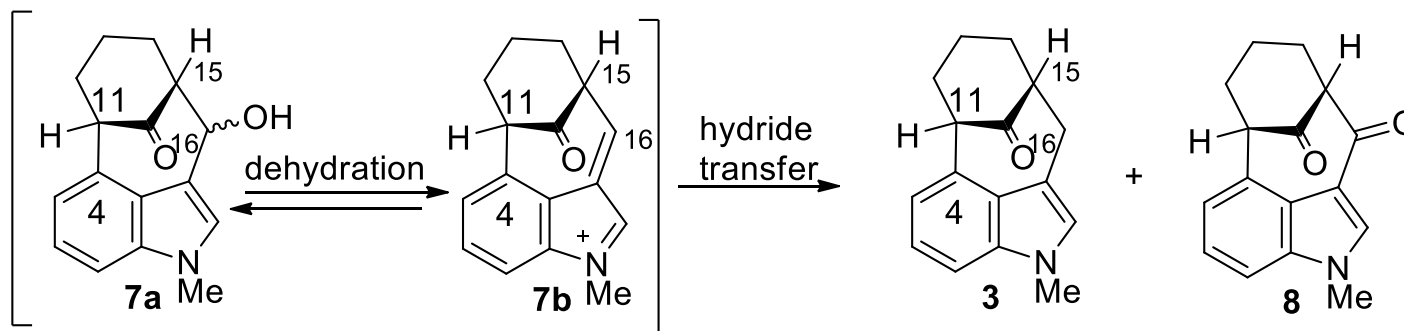
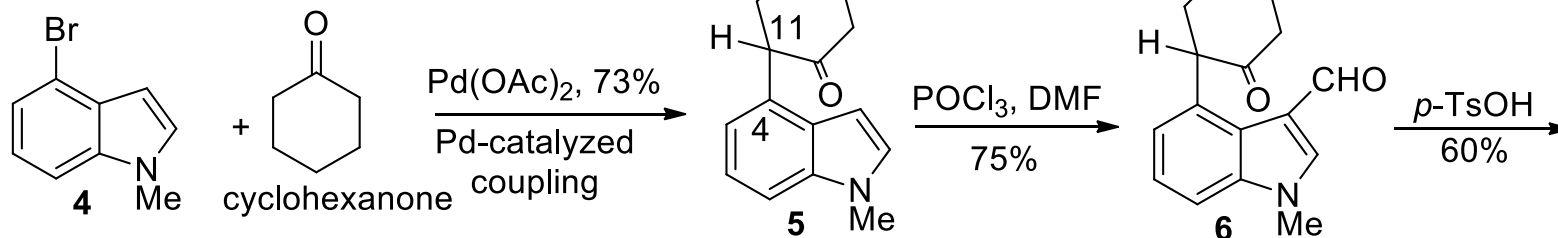
Konopelski's work



Simpkins's work

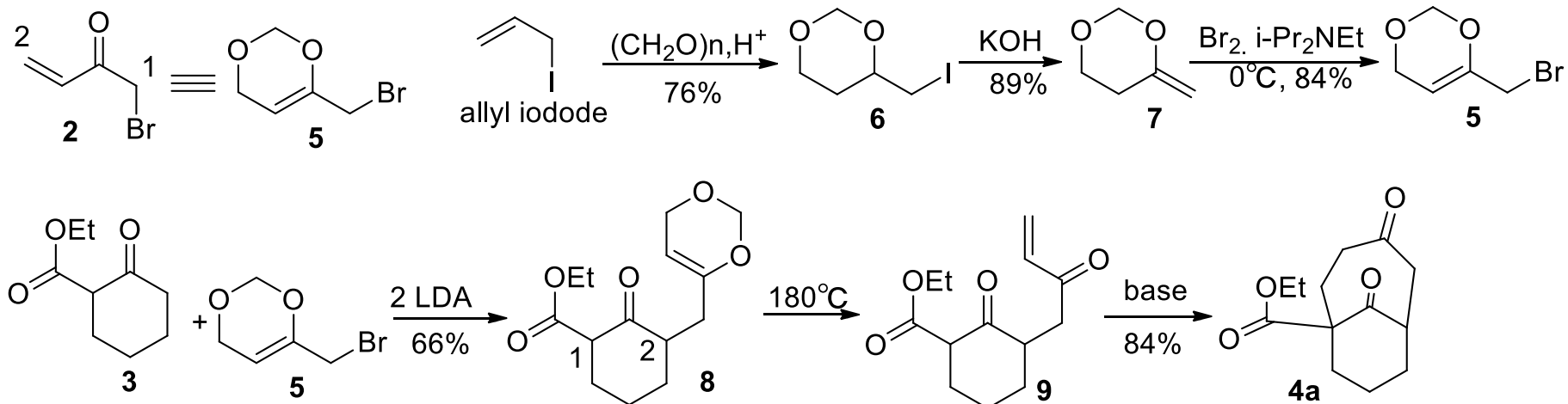
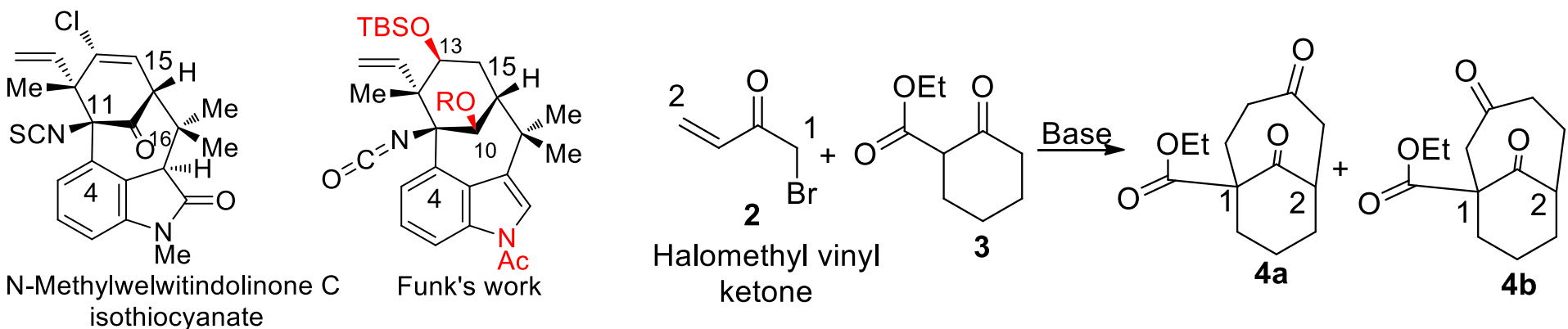


N-Methylwelwitindolinone C  
isothiocyanate



Simpkins, N.S., *et. al. Org.lett.* **2005**, 7,3421-3424

# Funk's work to NMWCI skeleton

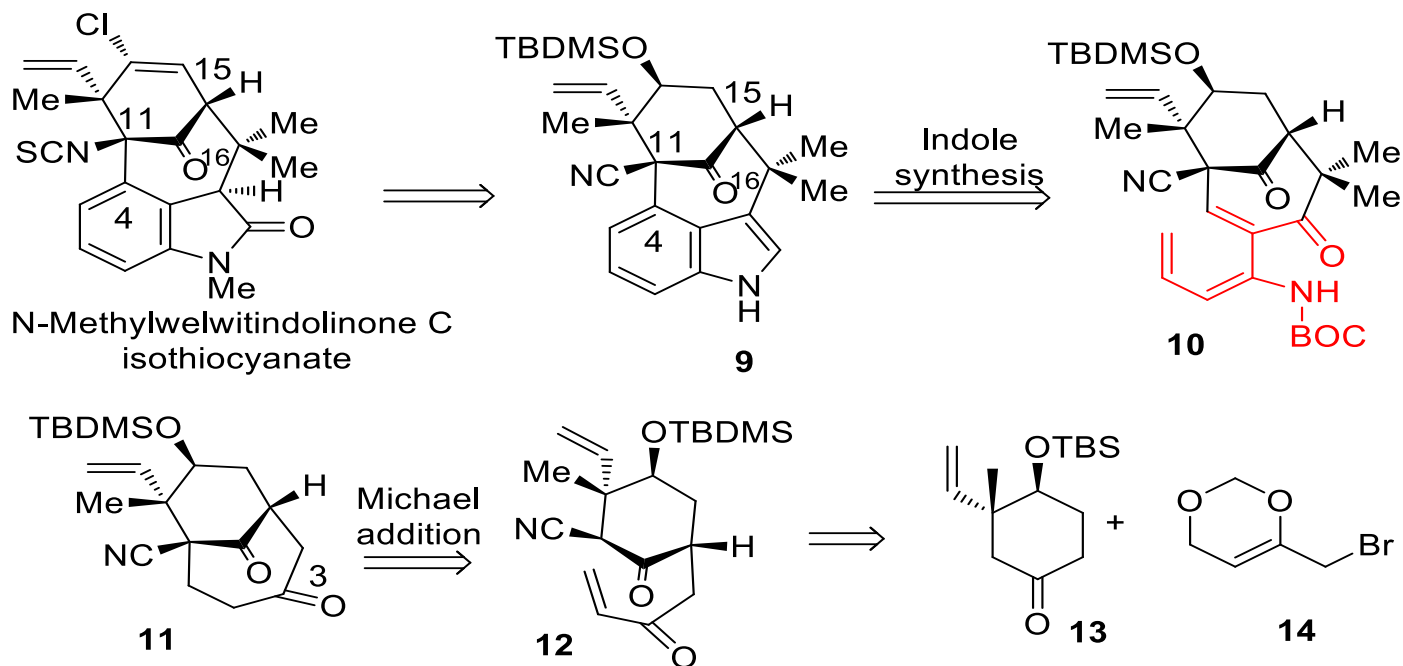
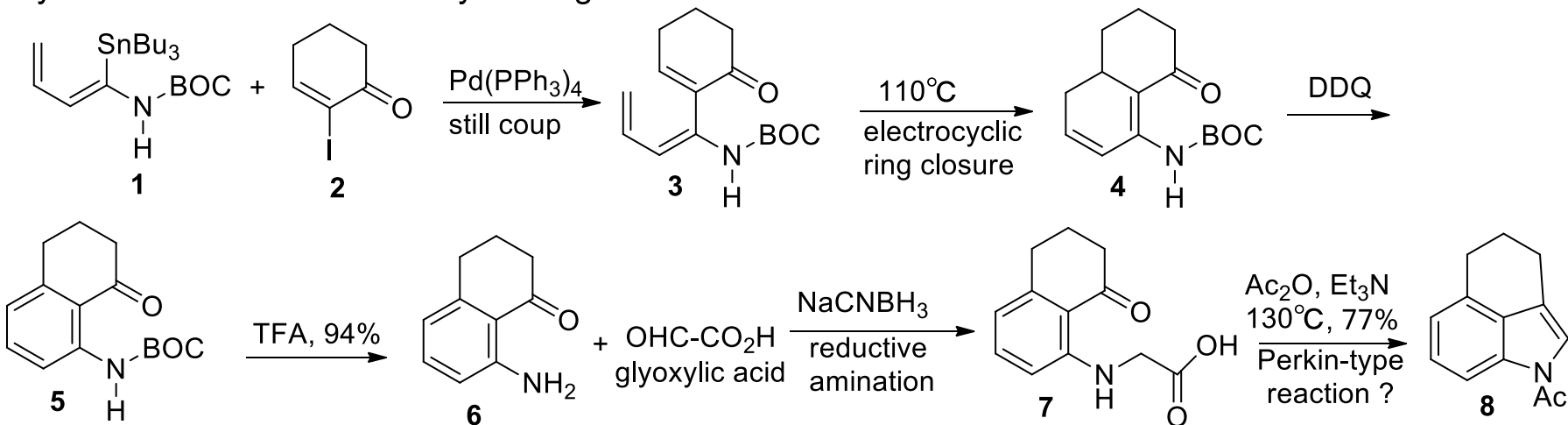


Funk, P. L., et al. *J. Am. Chem. Soc.* **2002**, *124*, 754-755

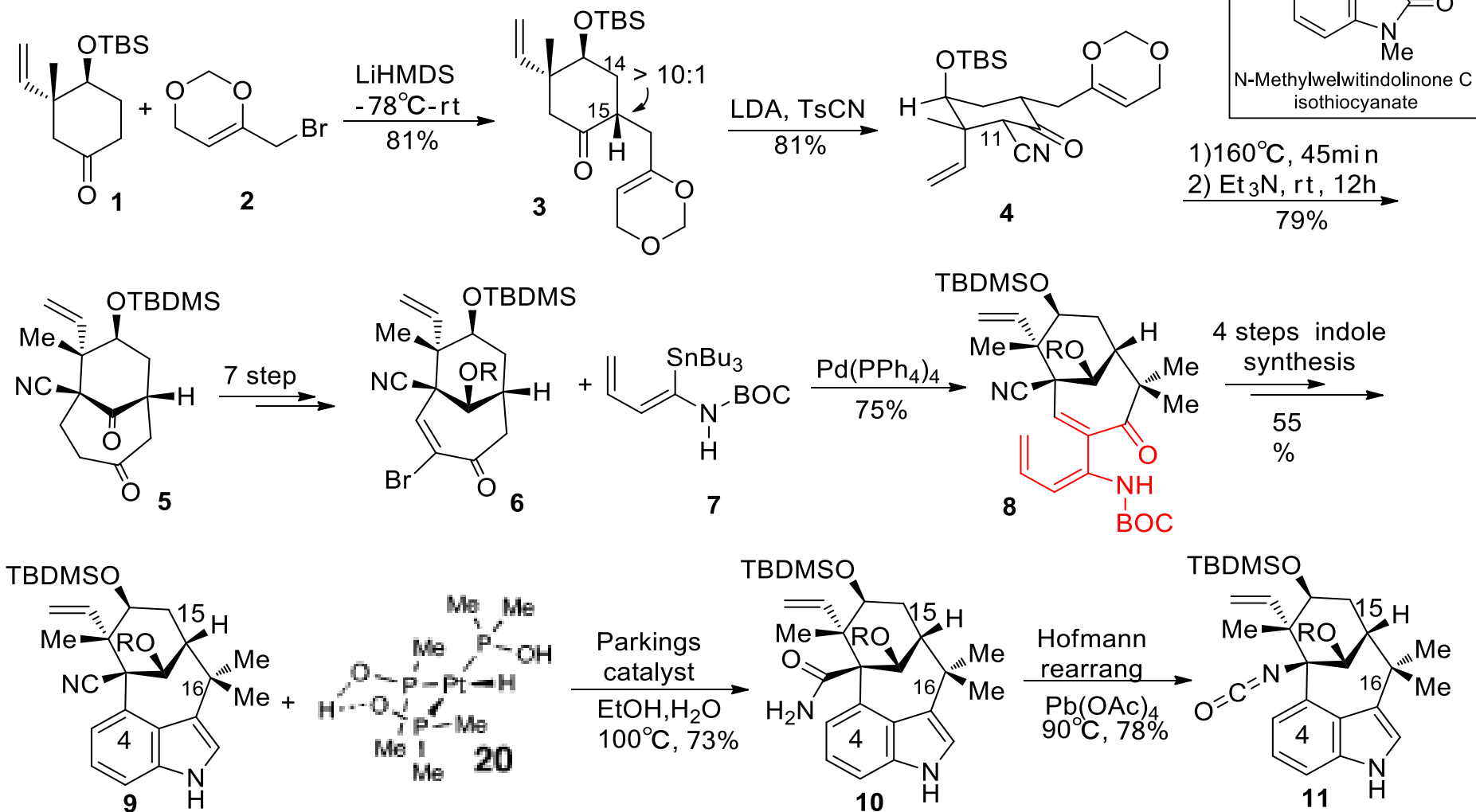
Funk, R. L., et al. *Org. Lett.* **2006**, *8*, 2643-2645

# Funk's work to NMWCI skeleton

Synthesis indole via Electrocyclic ring closure



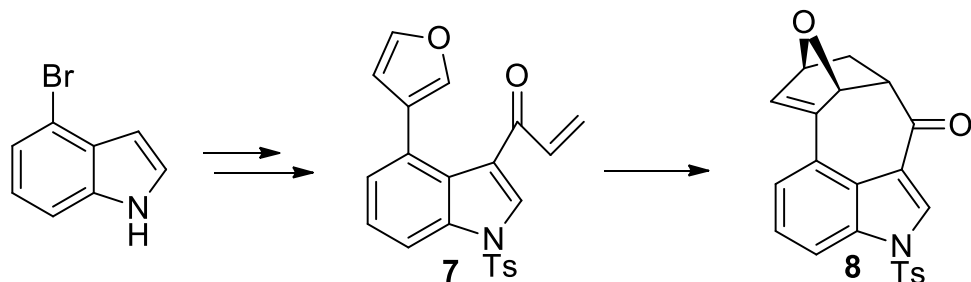
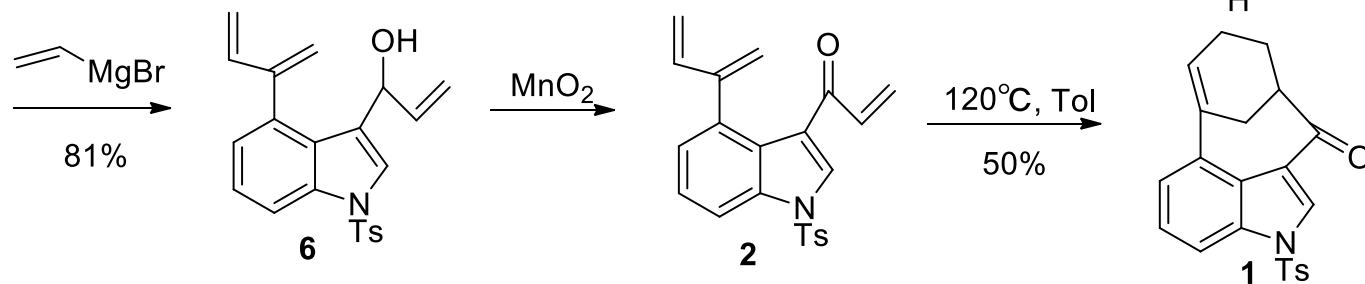
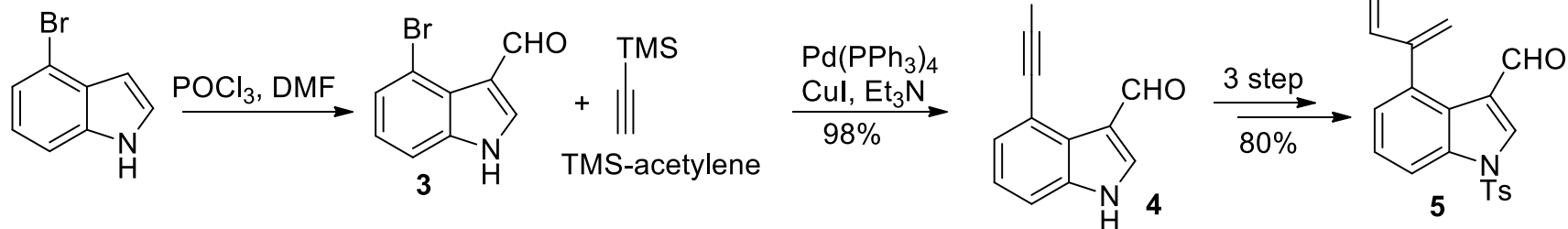
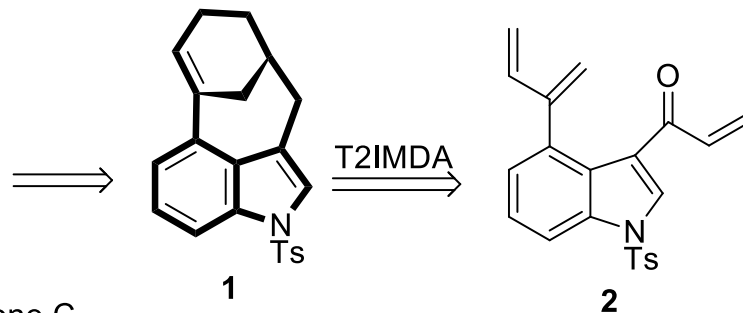
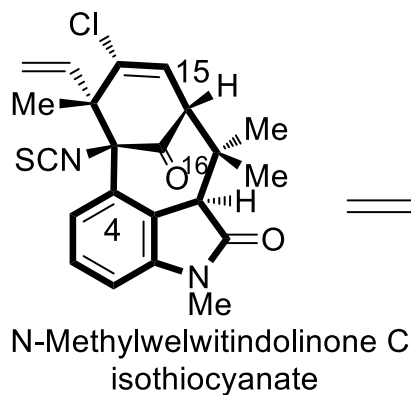
# Funk's work to NMWCI skeleton



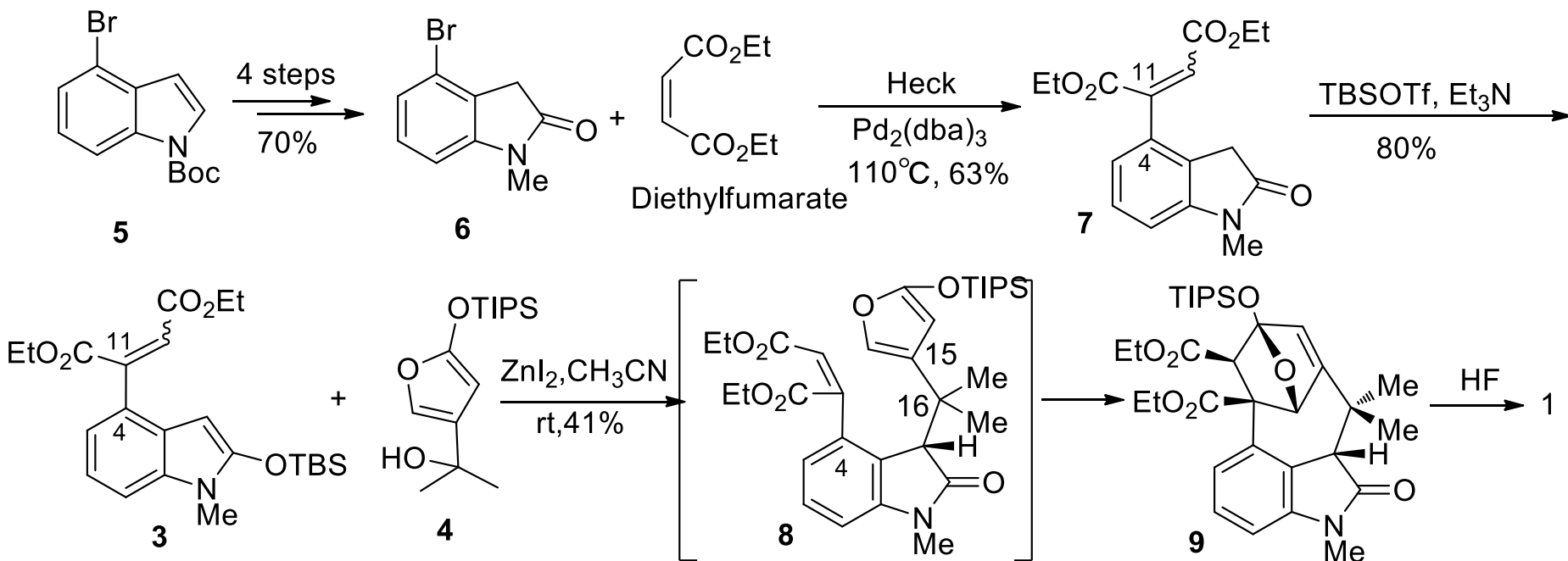
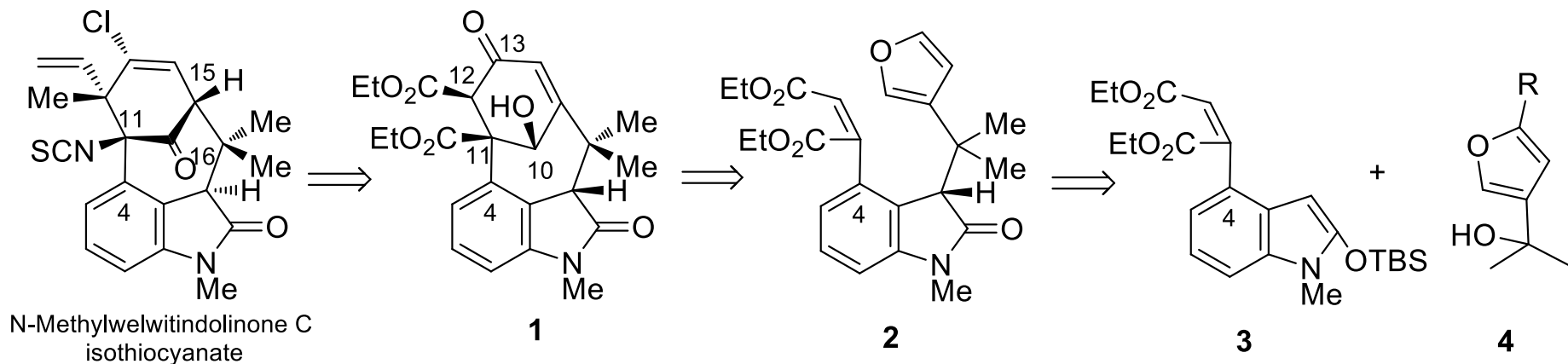
1 was converted to 11 through 18 steps



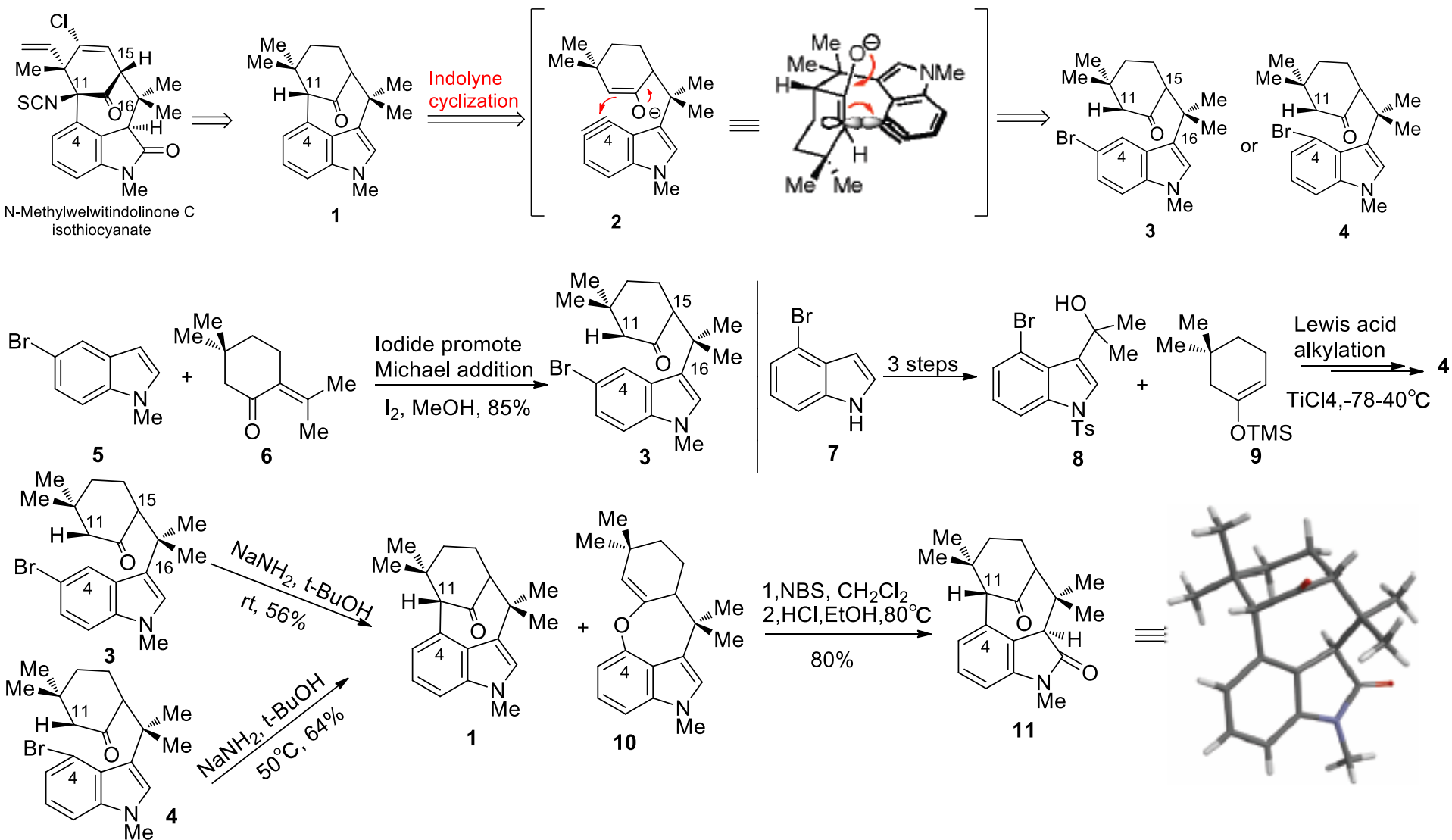
# Shea's work to NMWCI skeleton



# Shea's work to NMWCI intermediate

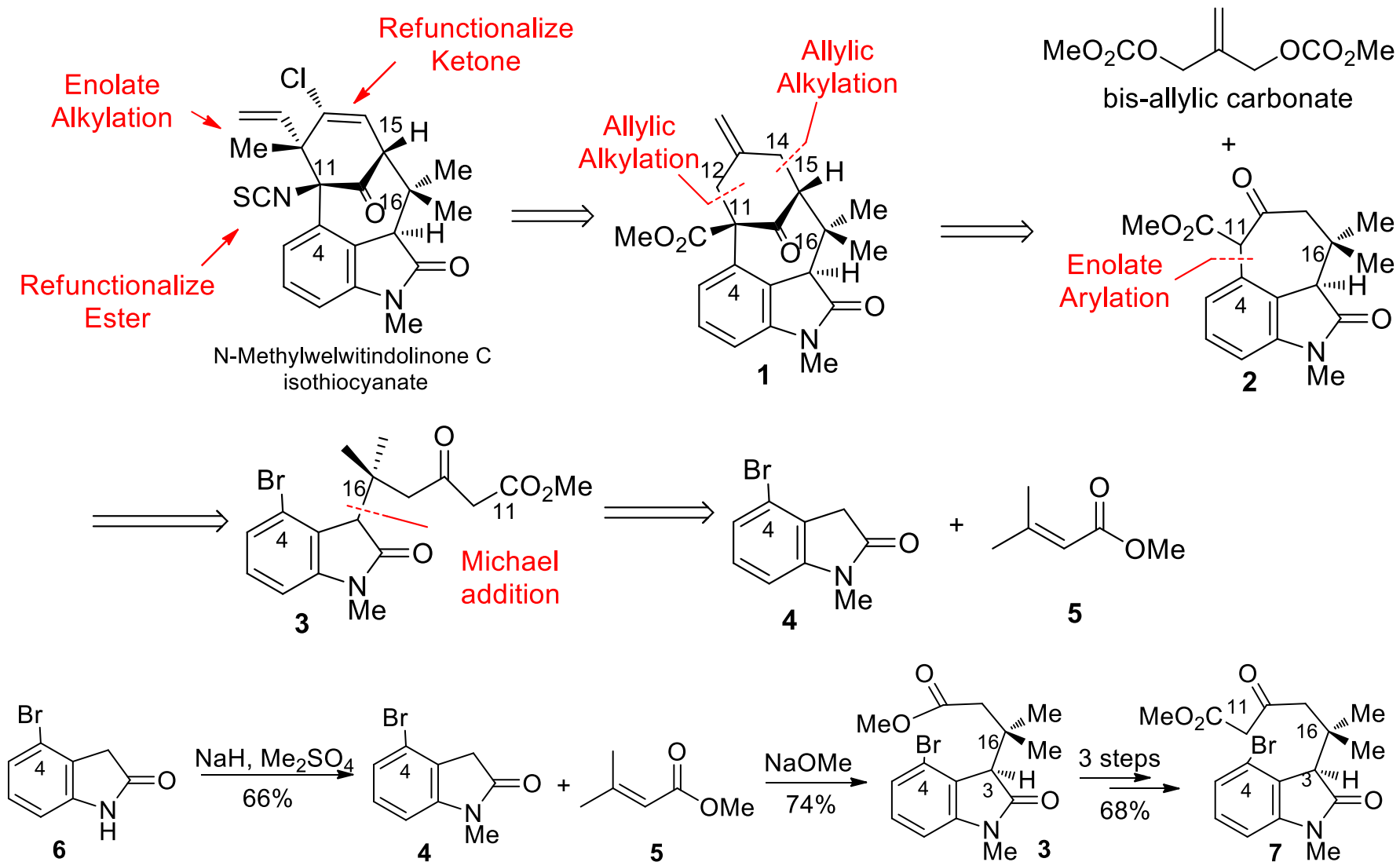


# Garg's work to NMWCI skeleton



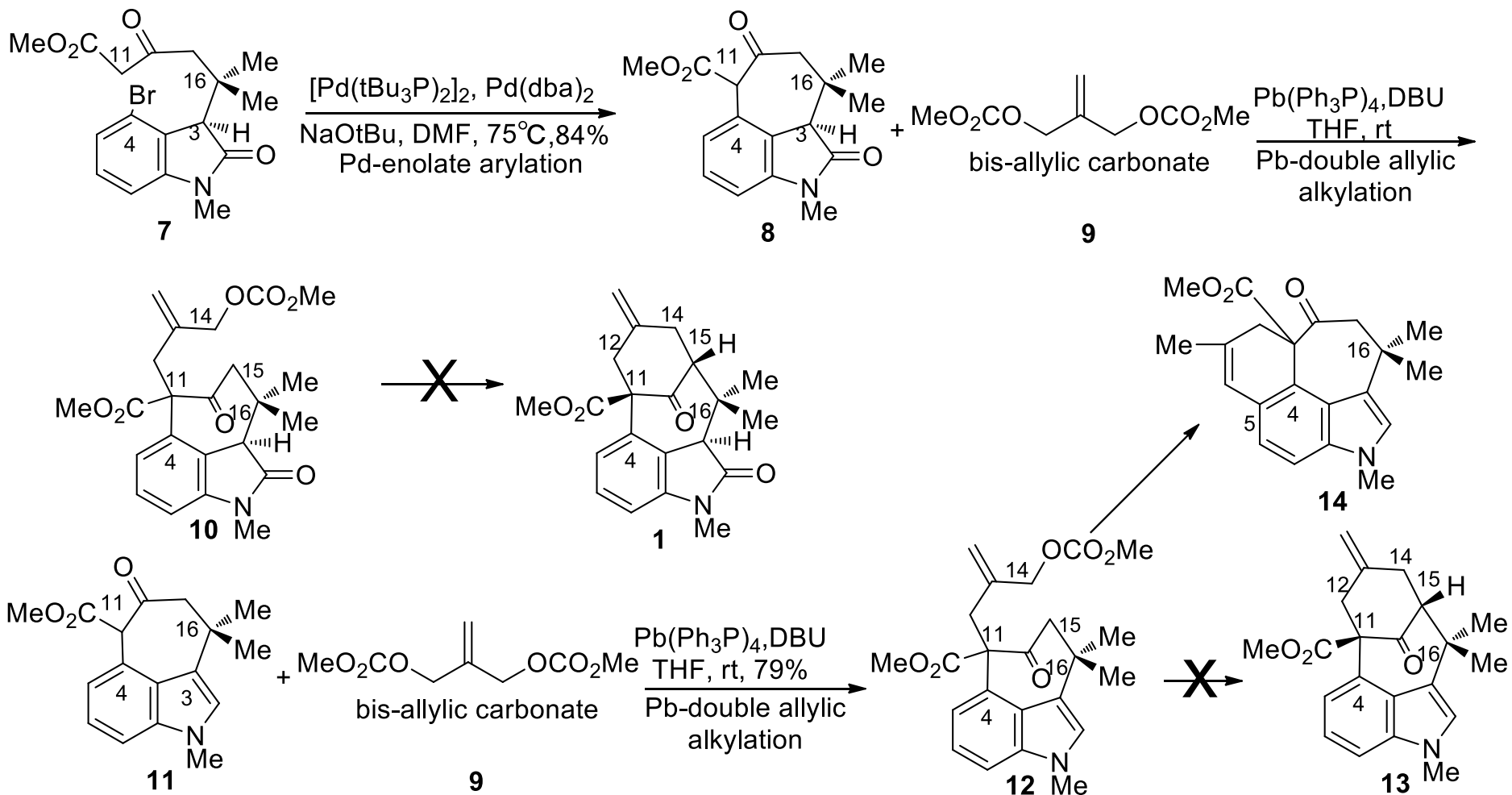
Garg, N.K., et al. *Org. Lett.* 2009, 11, 2349-2351

# Martin's work to NMWCI skeleton



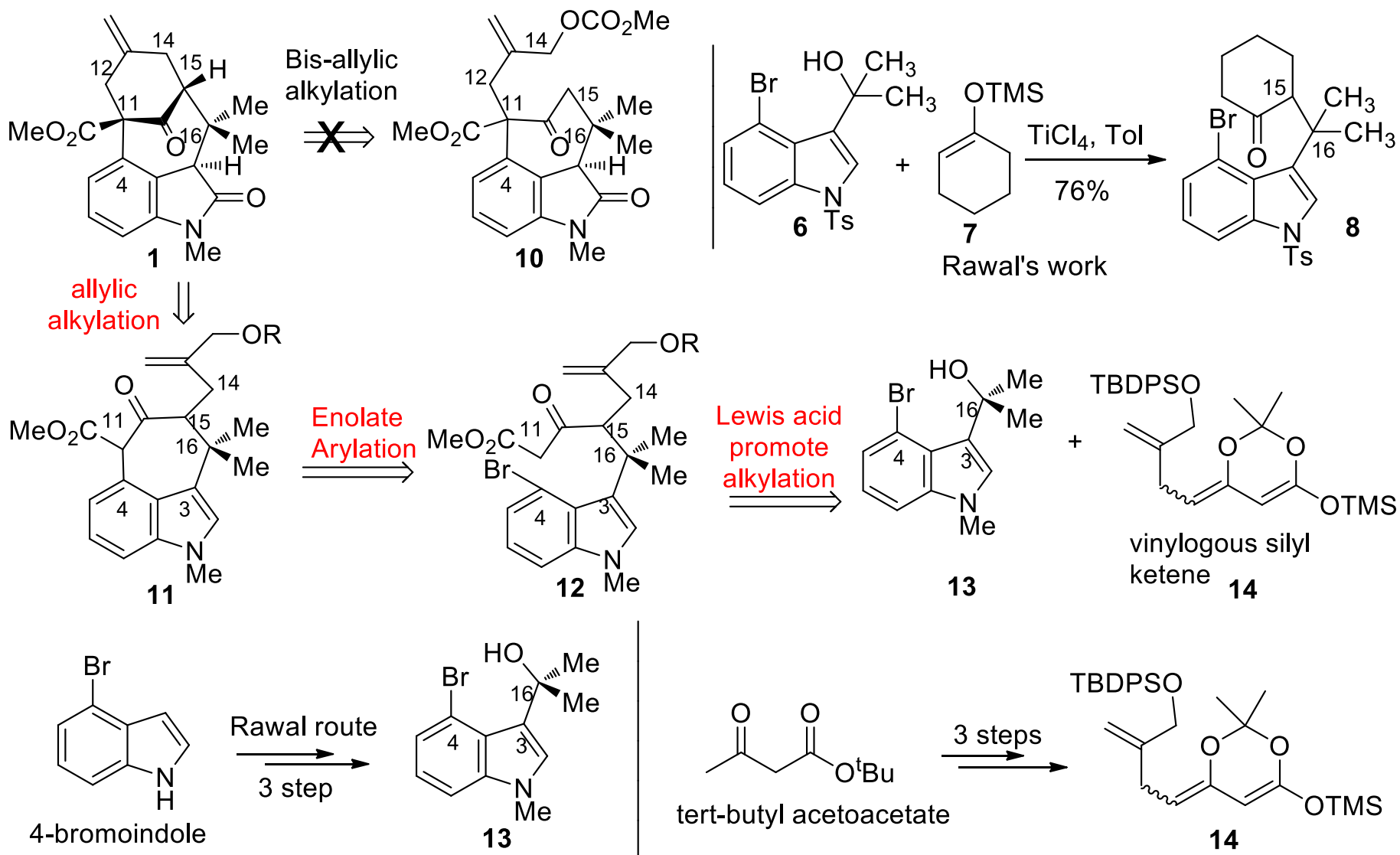
Martin, S.F., et al. *Org. Lett.* 2009, 11, 2349-2351

# Synthesis compound 1 through bis-allylic alkylation strategy

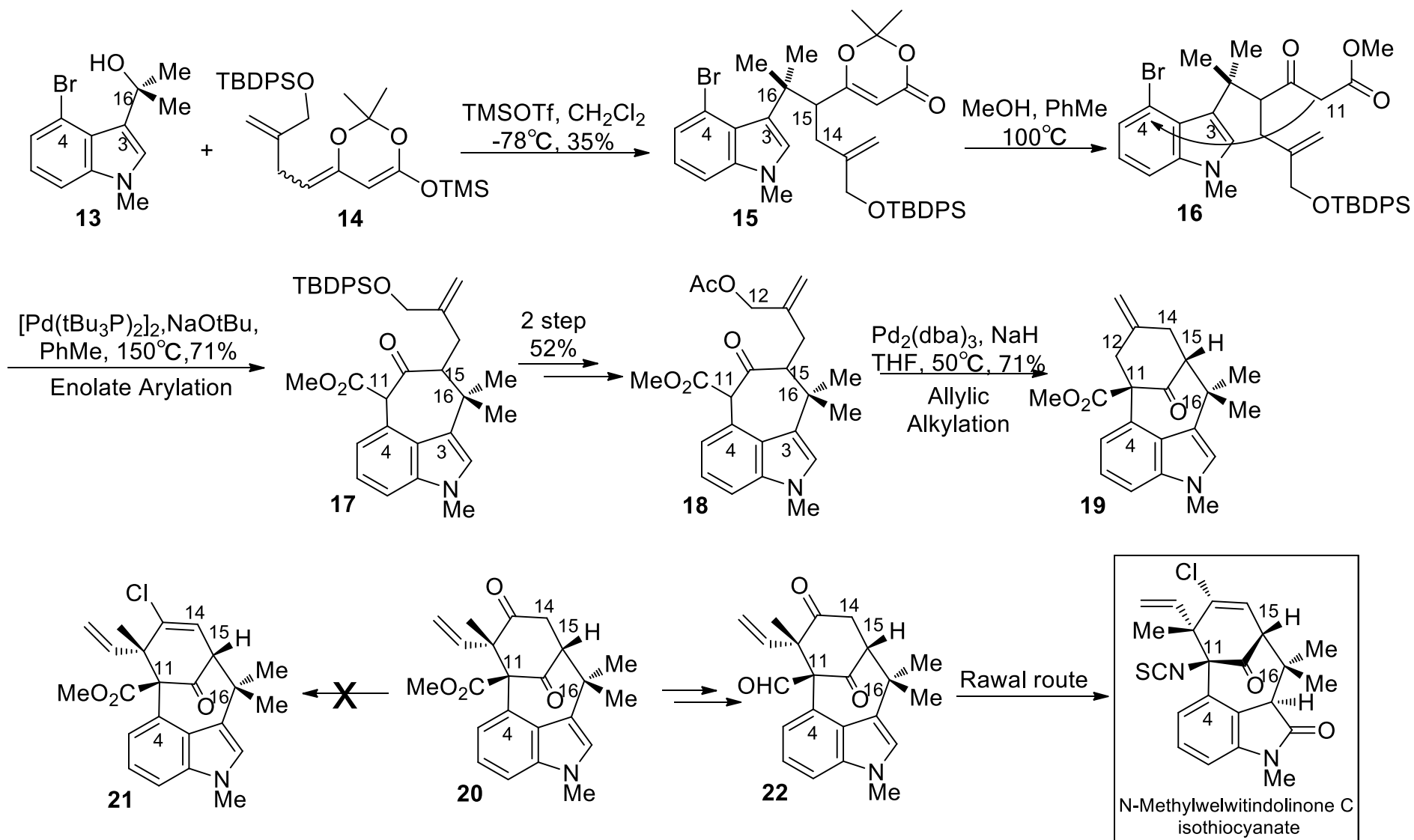


Martin, S.F., *et al.* *Org. Lett.* **2009**, *11*, 2349-2351

# Martin's new synthesis route to NMWCI skeleton



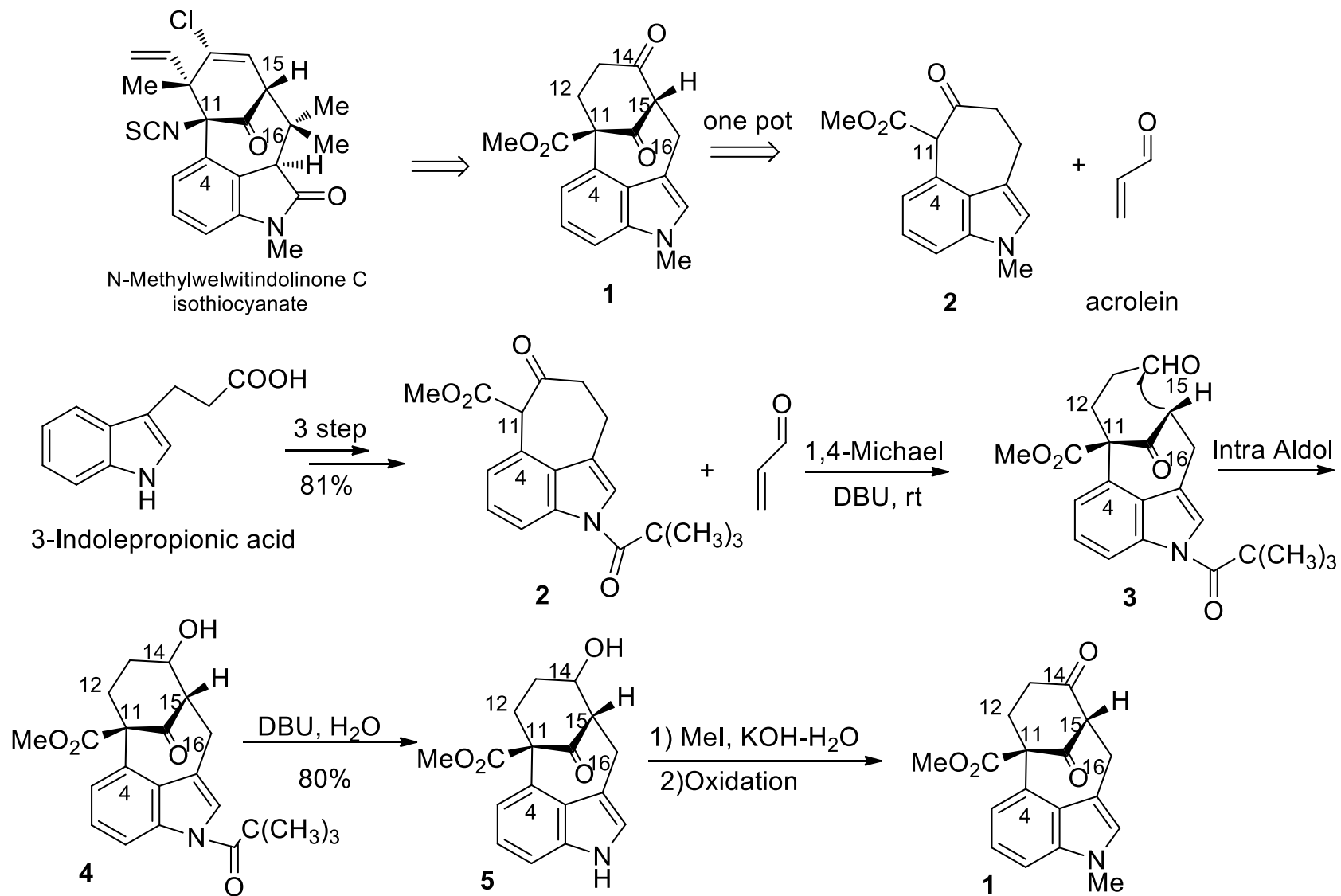
# Martin's formal synthesis of NMWCI



Martin, S.F., *et. al. Org.lett.* **2009**, *11*, 2349-2351

Martin, S.F., *et. al. Org.lett.* **2012**, *14*, 3834-3837

# Menendez's work to NMWCI skeleton

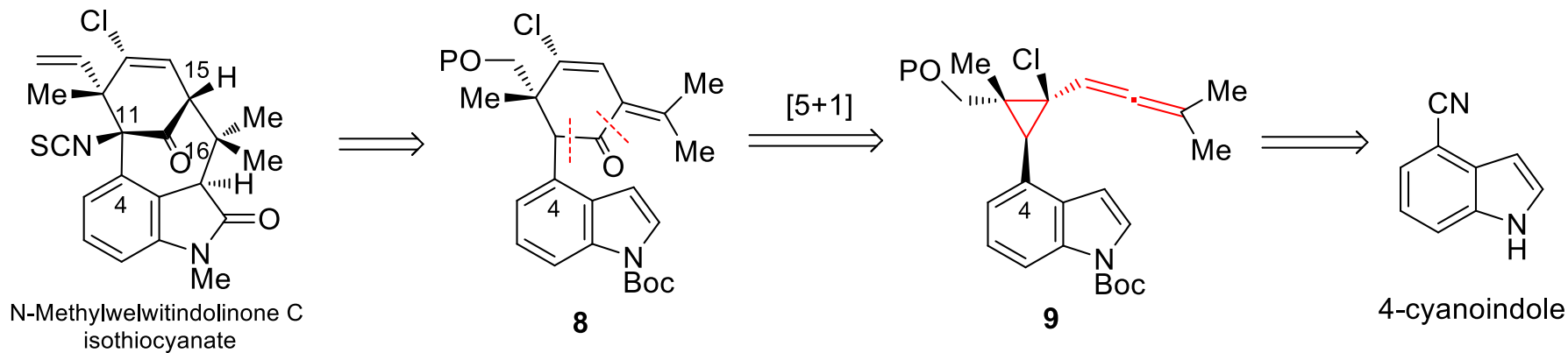
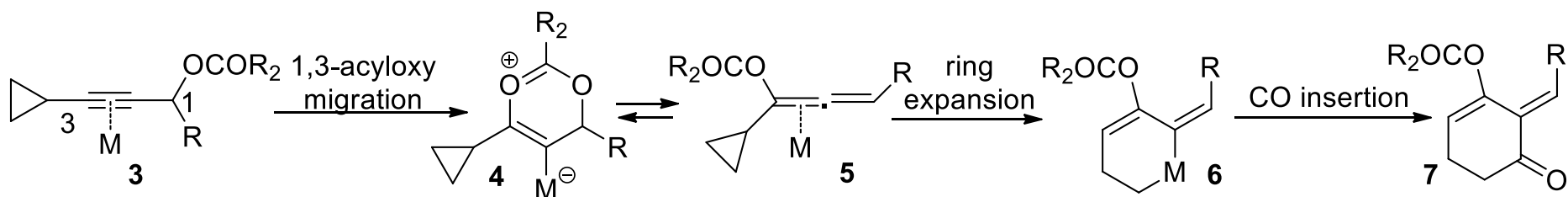
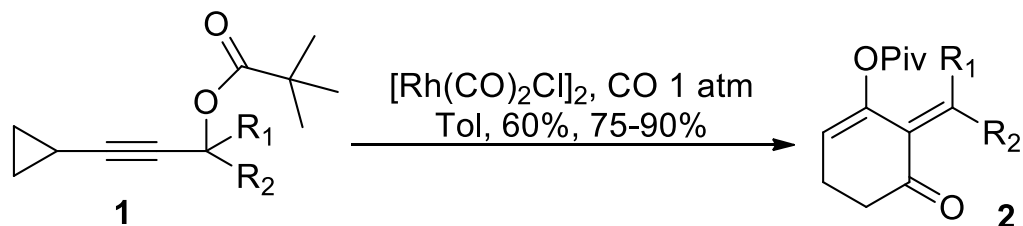


Menendez, J.C., et al. *Org. Biomol. Chem.* **2010**, *8*, 4521-4523



# Tang's work to NMWCI skeleton

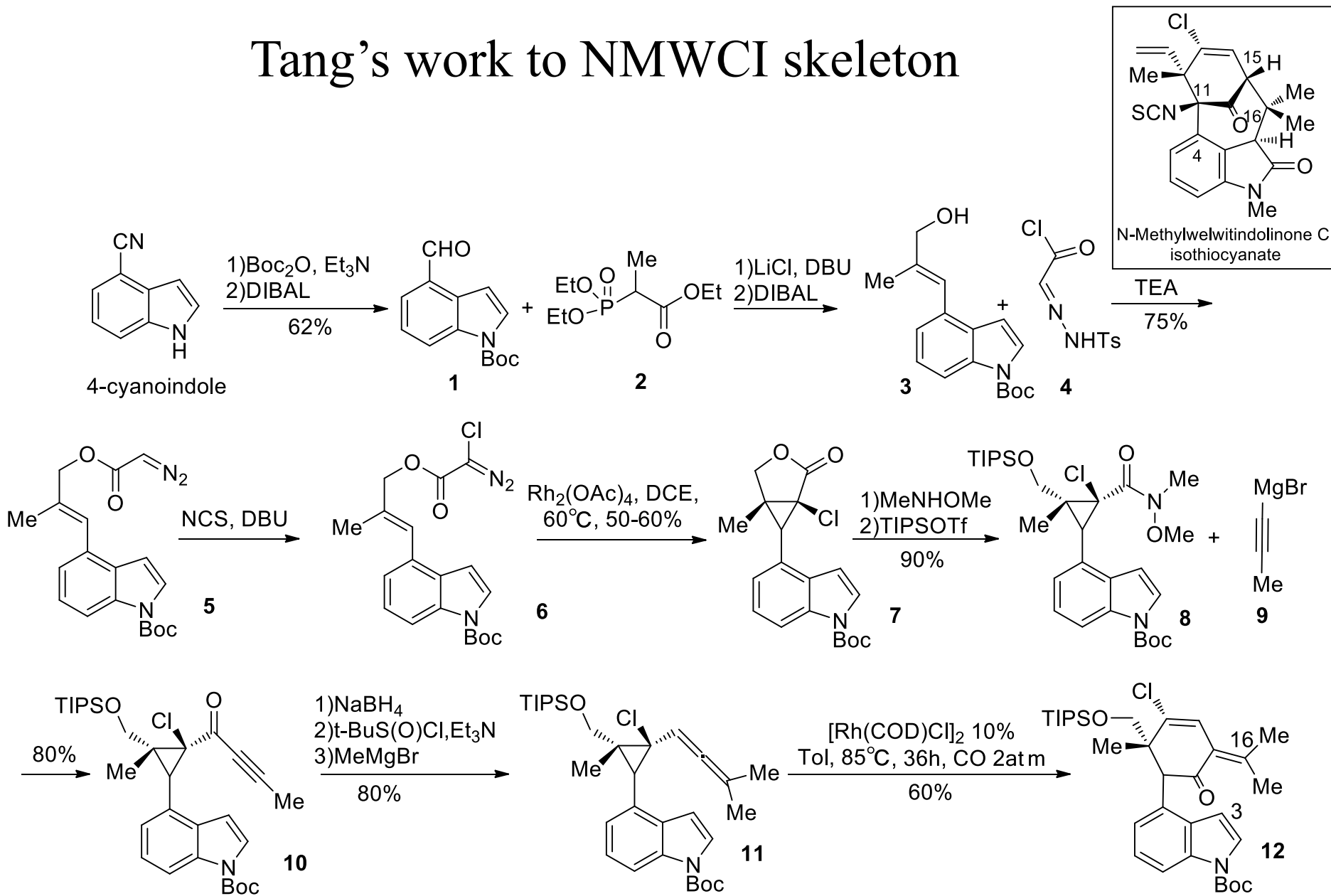
## Rhodium catalyzed [5+1] cycloaddition



Tang, W, et. al. *Angew. Chem., Int. Ed.* **2011**, 50, 1346-1348

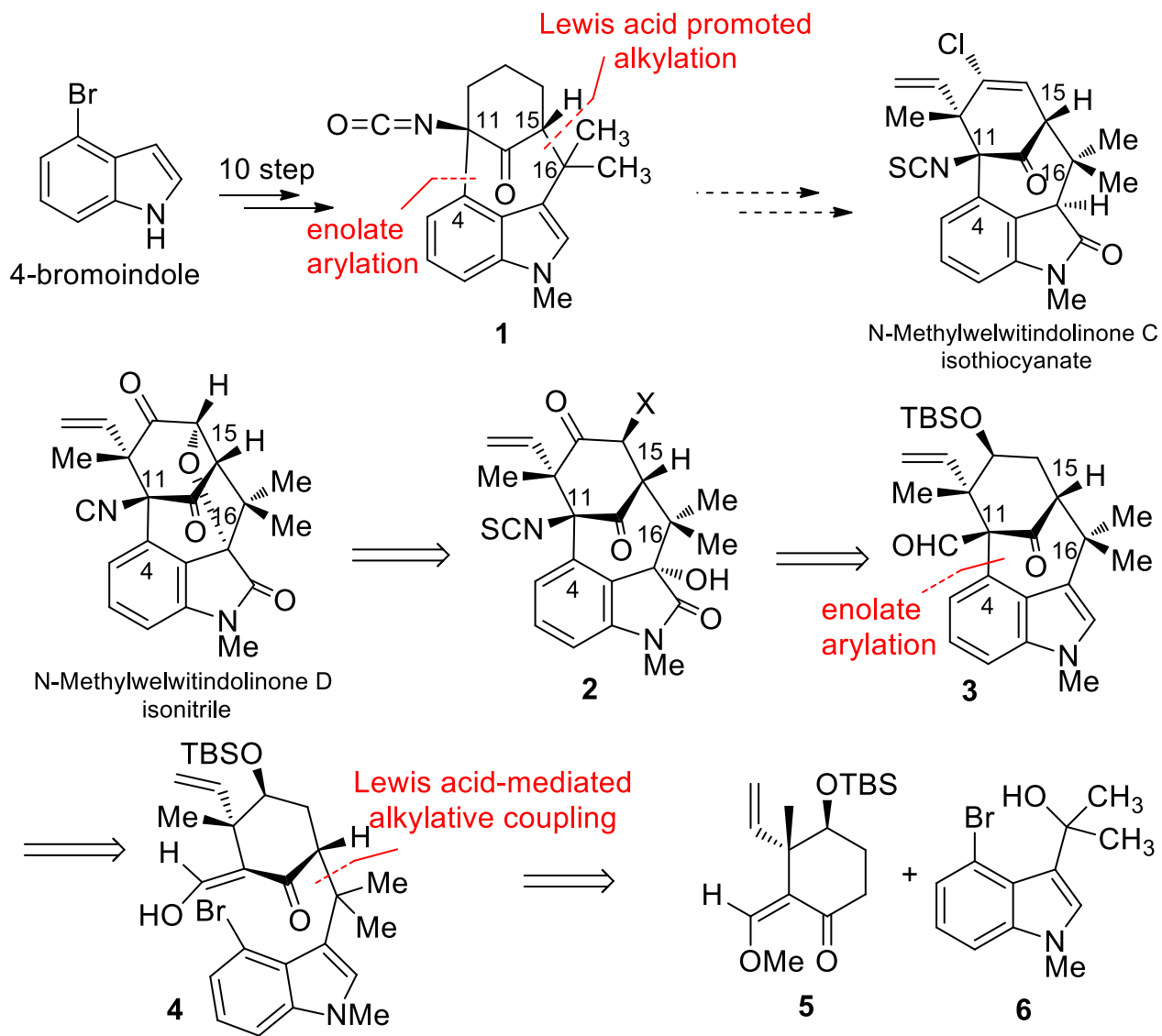
Tang, W, et. al. *Org. Lett.* **2012**, 14, 3756-3759

# Tang's work to NMWCI skeleton

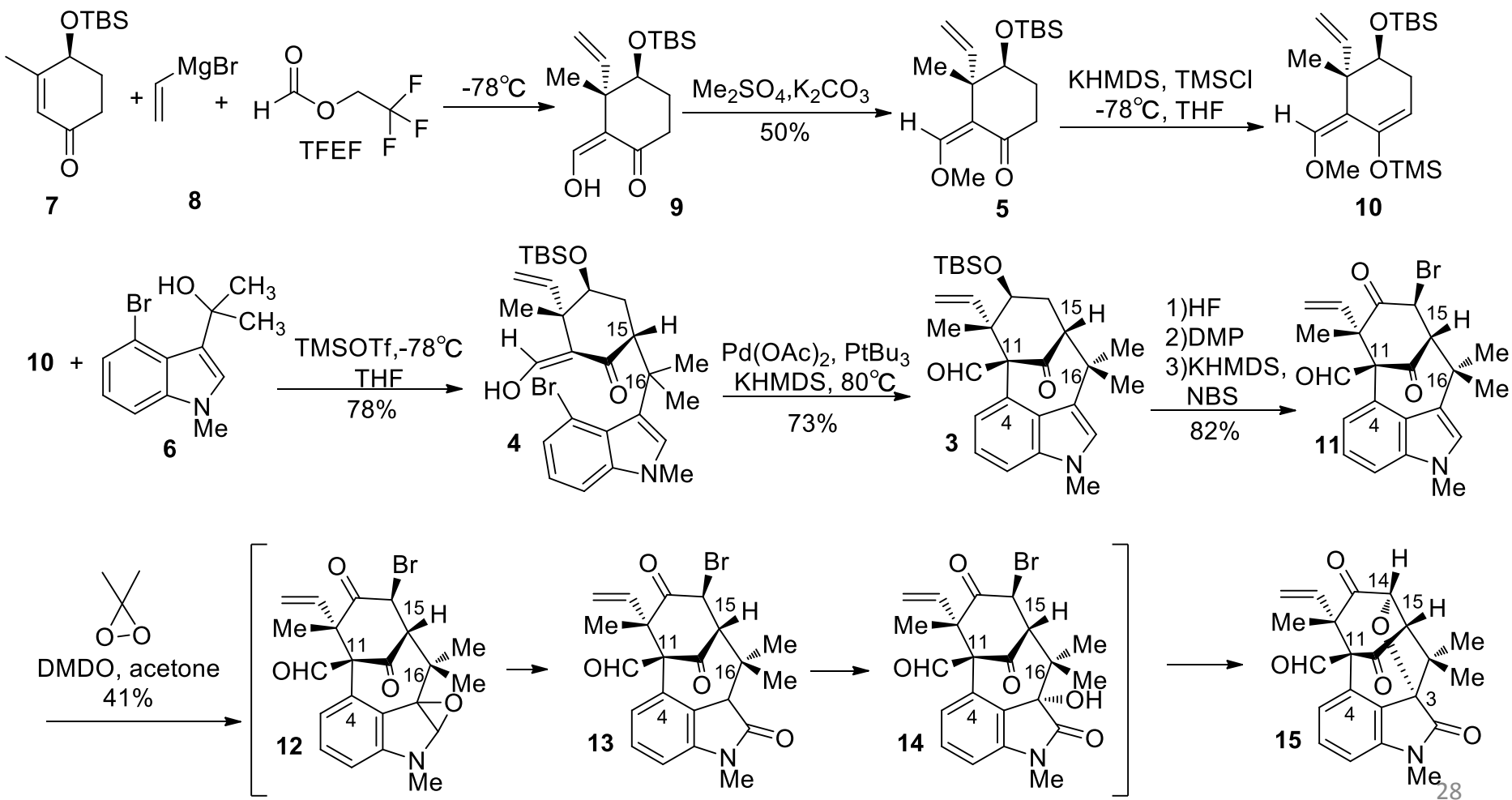
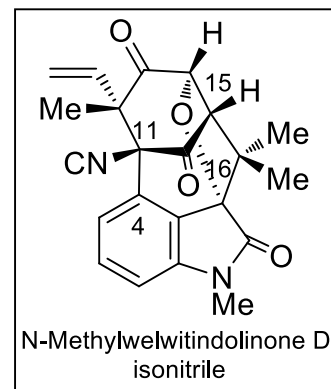


Tang, W, et. al. *Org.lett.* 2012, 14,3756-37597

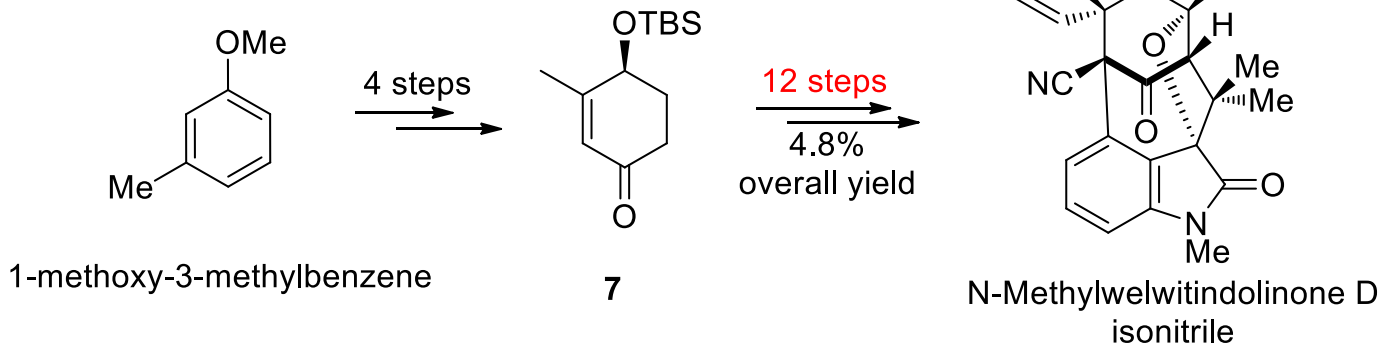
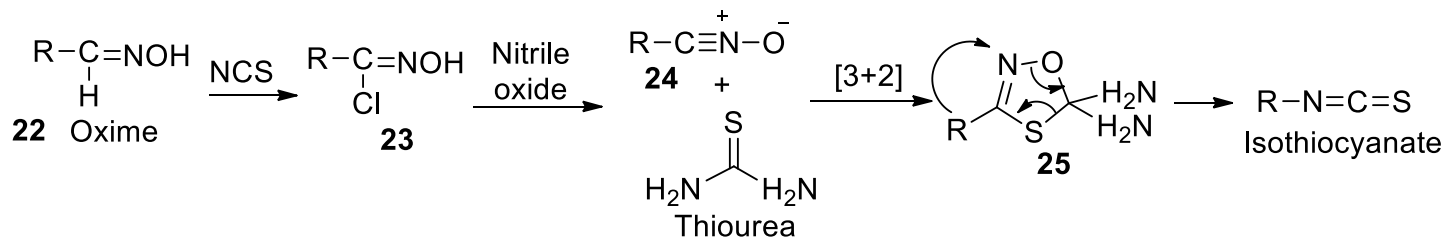
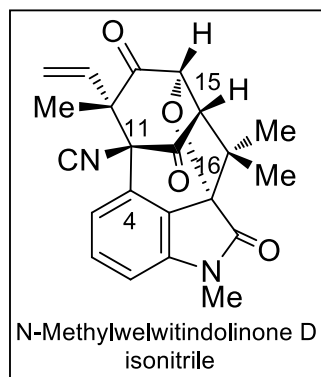
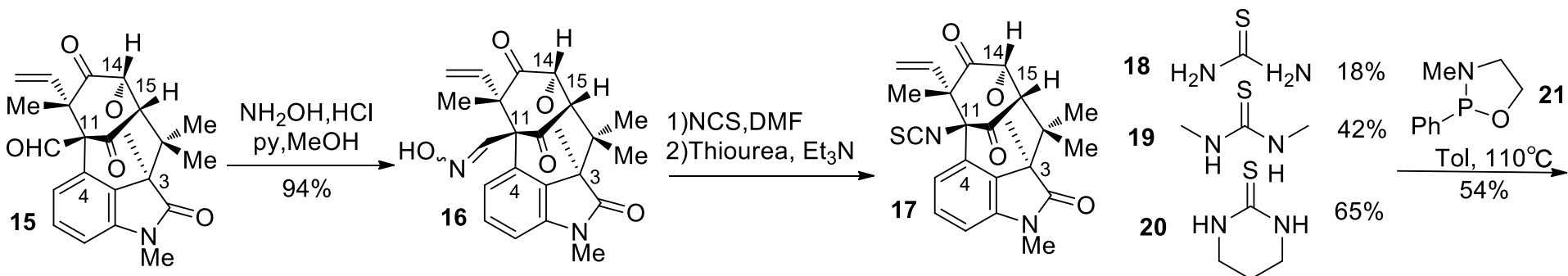
# Rawal's total synthesis of N-methylwelwitindolinone D Isonitrile



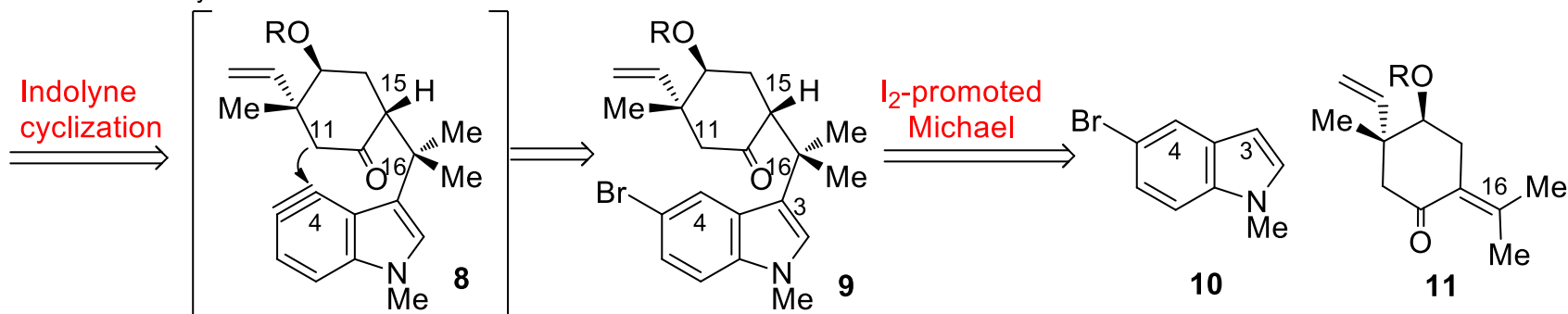
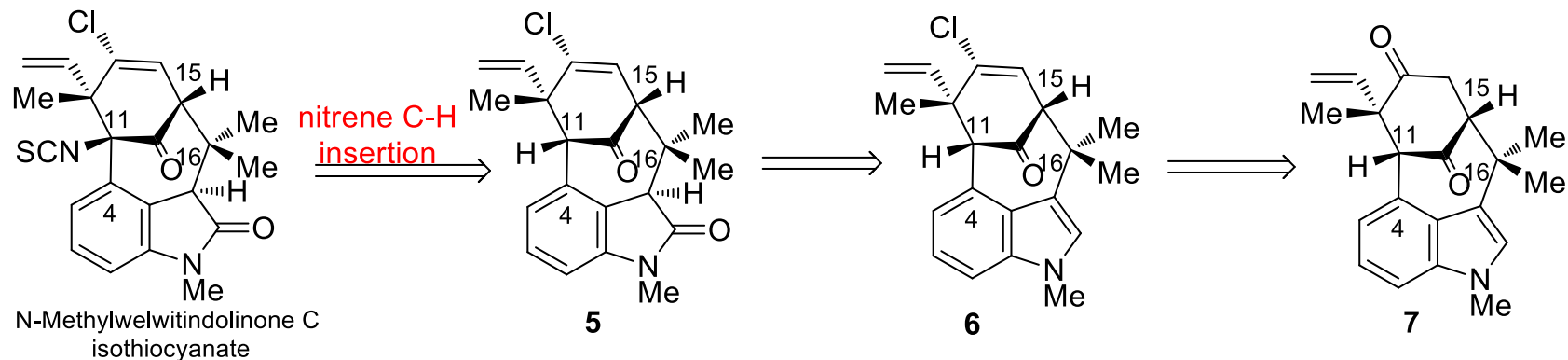
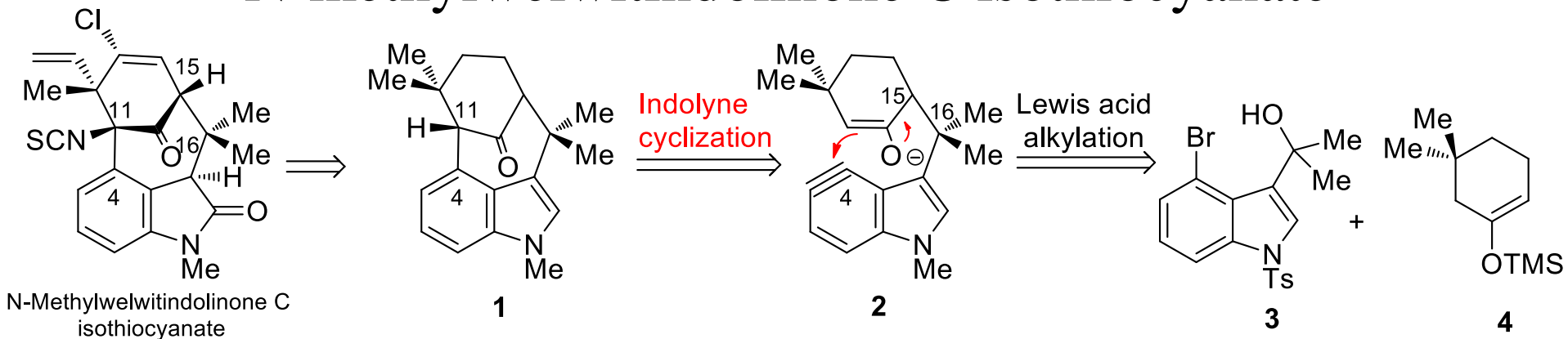
# Rawal's total synthesis of N-methylwelwitindolinone D Isonitrile



# Rawal's total synthesis of N-methylwelwitindolinone D Isonitrile

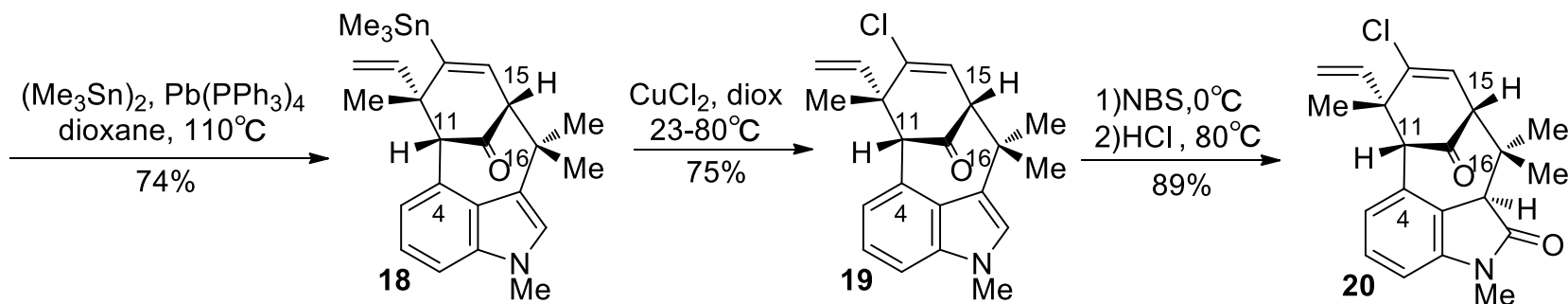
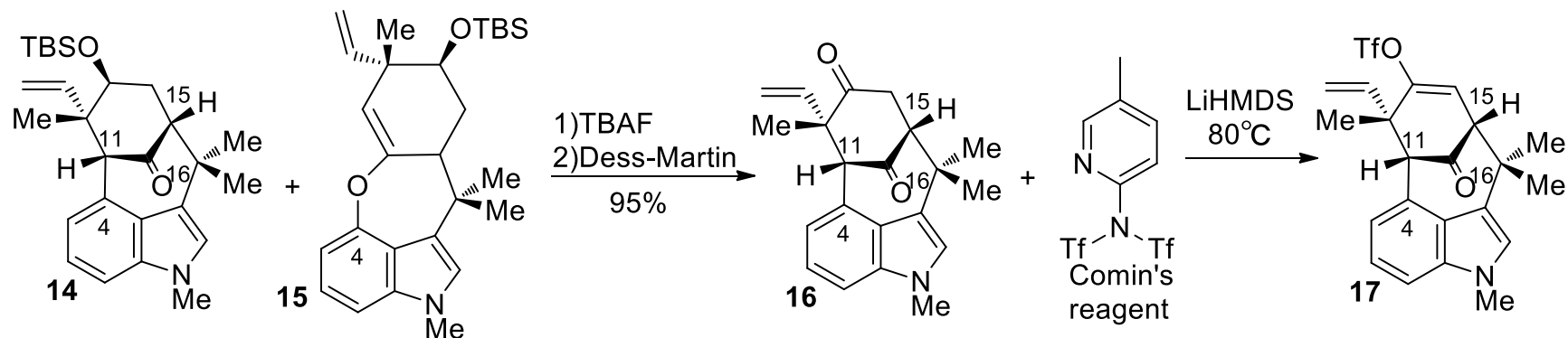
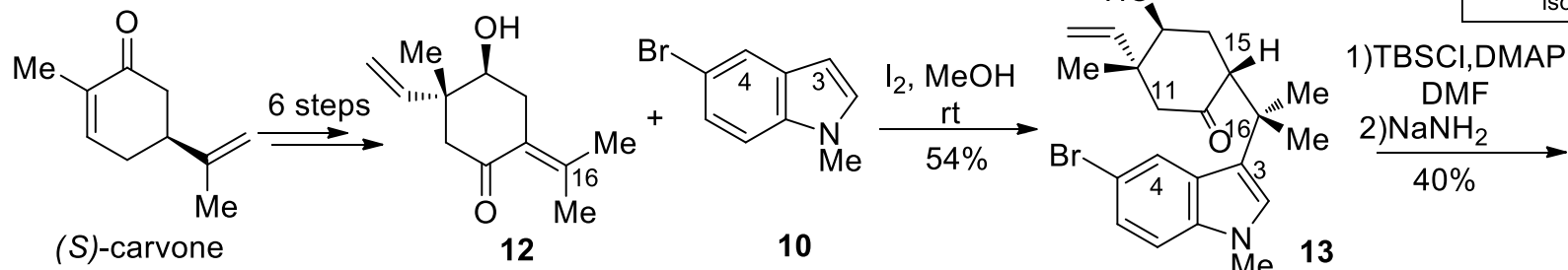
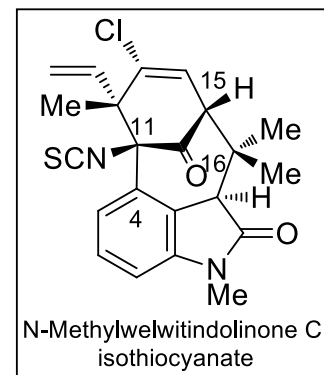


# Garg's total synthesis of N-methylwelwitindolinone C isothiocyanate

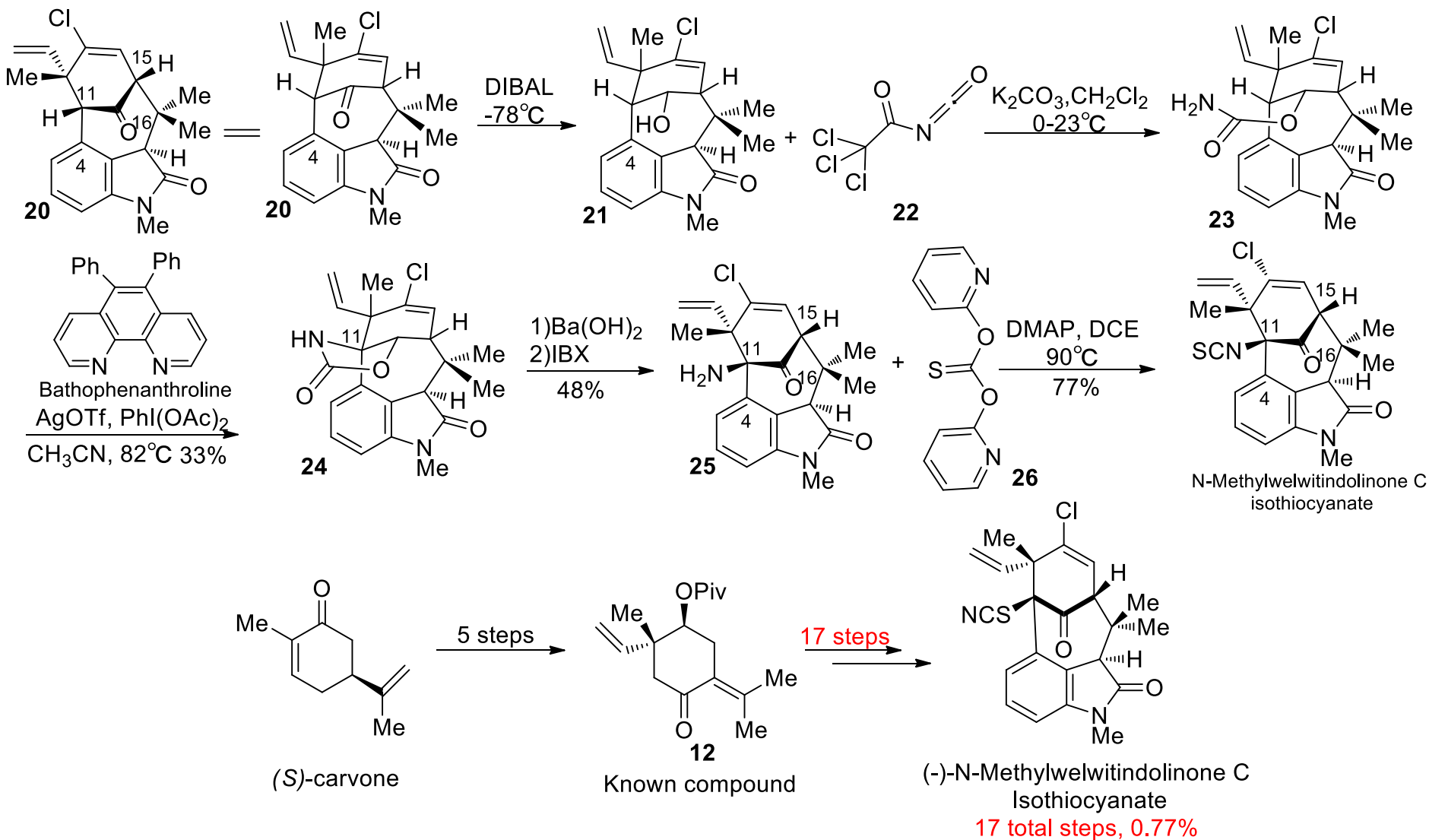


# Garg's total synthesis of

# N-methylwelwitindolinone C isothiocyanate



# Garg's total synthesis of N-methylwelwitindolinone C isothiocyanate





# Acknowledgement

