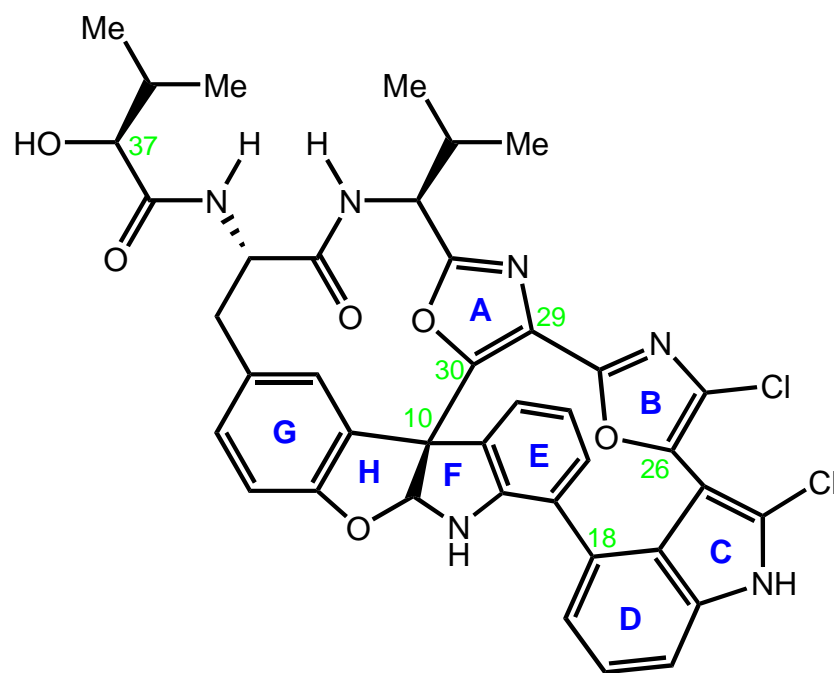
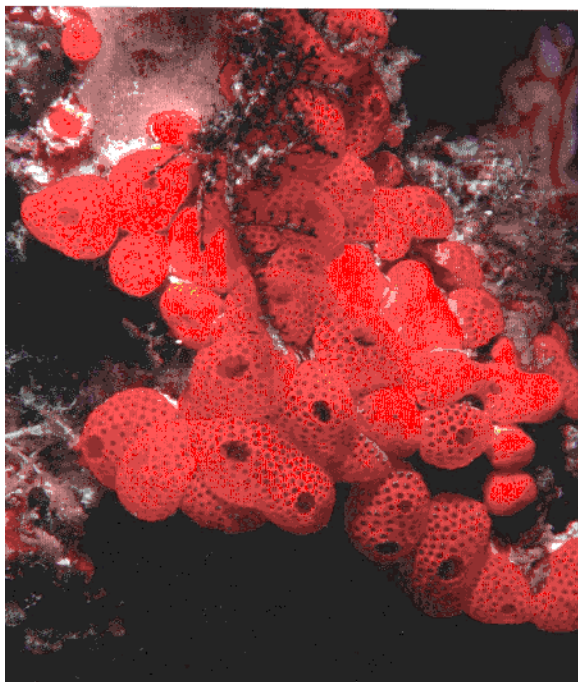


# Total Synthesis of Diazonamide A



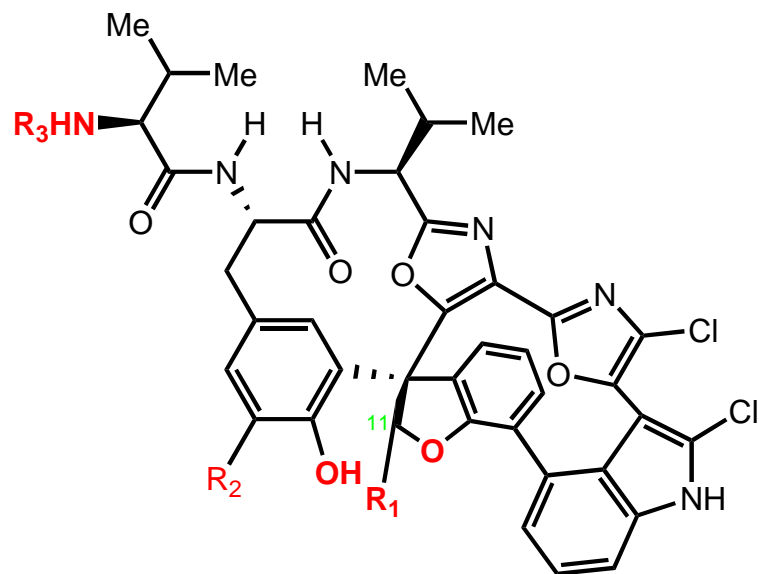
**Jennifer Moore**  
**Literature Group Meeting**  
**21 June 2005**

# Originally proposed structure of *Diazonamide A*

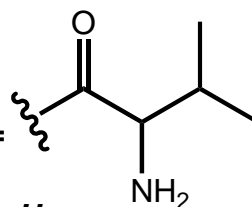


- Hexane extracts from lyophilized ascidian, *Diazona angulata*, Siquijor Island, **Philippines**
- Isolated by Fenical, Clardy, and co-workers in 1991
- Exhibits antimicrobial, cytotoxic, and antiviral activities
- Mean  $GI_{50}$ =4.9 nM against standardized panel of human cancer cell lines
- In vitro activity against HCT-116 human colon carcinoma, and B-16 murine melanoma cancer cell lines, with  $IC_{50}$ <15 ng/mL

# “Structure Determination”

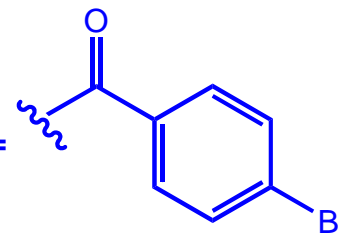


*Diazonamide A*: R<sub>1</sub> = OH, R<sub>2</sub> = H, R<sub>3</sub> =



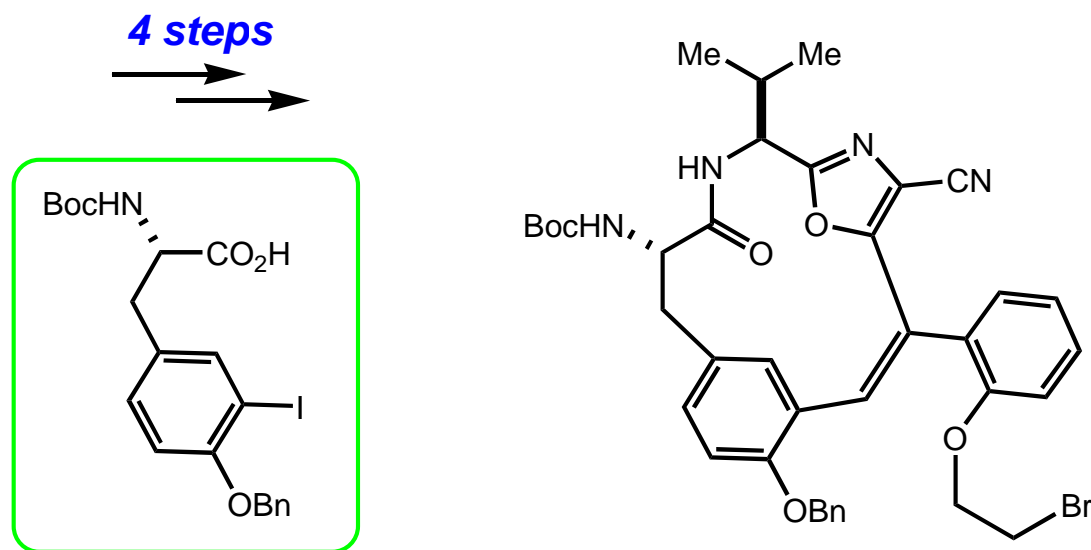
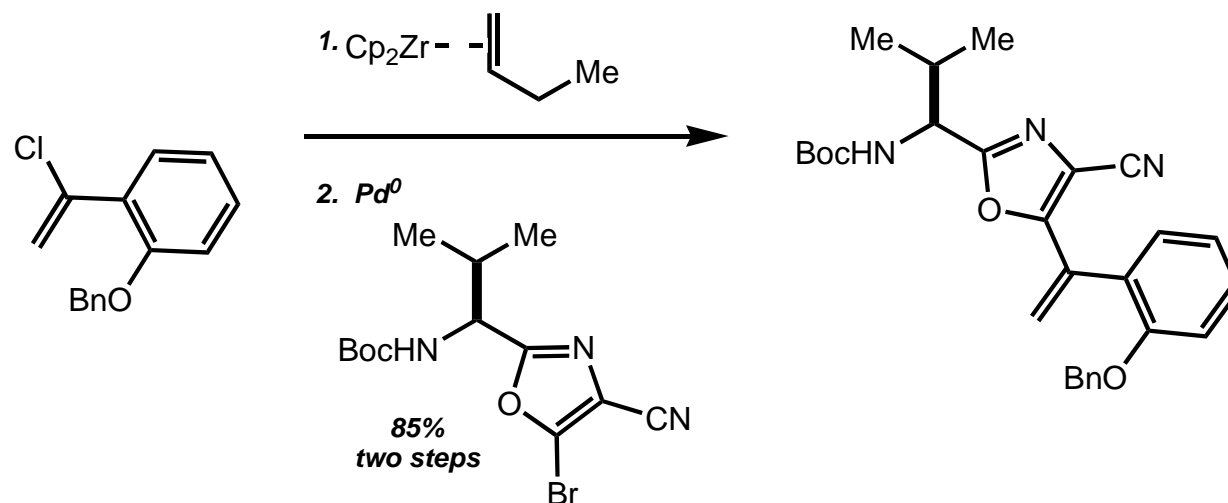
*Diazonamide B*: R<sub>1</sub> = OH, R<sub>2</sub> = Br, R<sub>3</sub> = H

*p*-bromobenzamide derivative: R<sub>1</sub> = O<sub>2</sub> (acetal), R<sub>2</sub> = Br, R<sub>3</sub> =

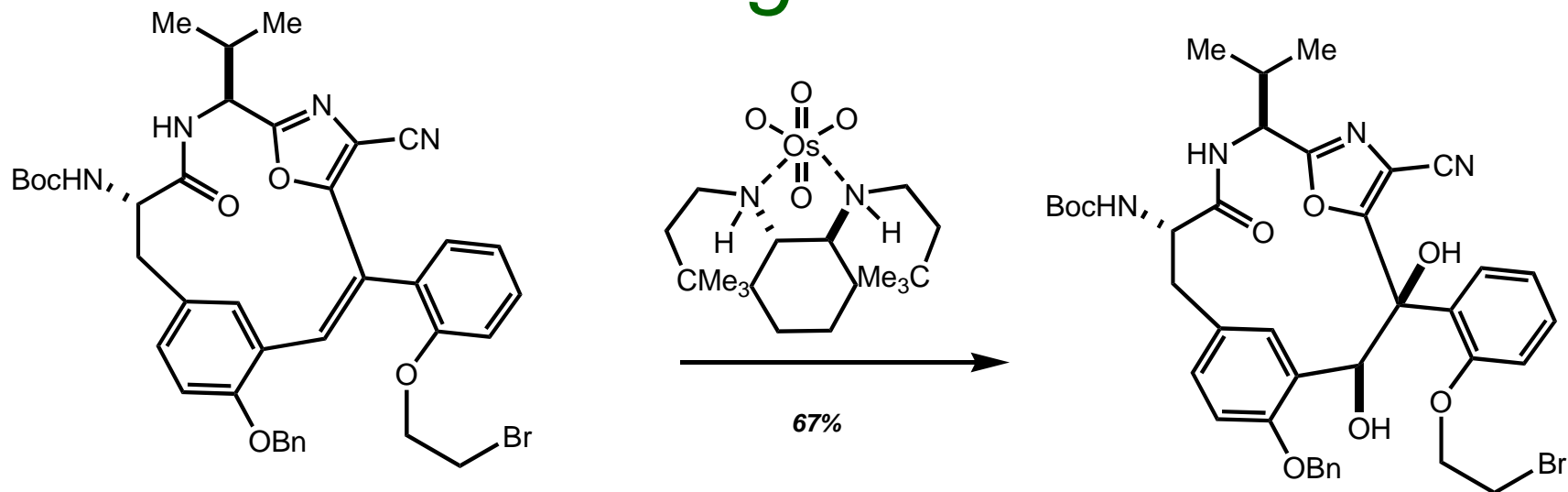


- <sup>1</sup>H NMR, <sup>13</sup>C NMR, HRFABM
- UV spectra – little evidence for unsaturation
- Single-crystal X-ray diffraction of *p*-bromobenzamide derivative of Diazonamide B
- Unable to obtain stereochemistry at C11

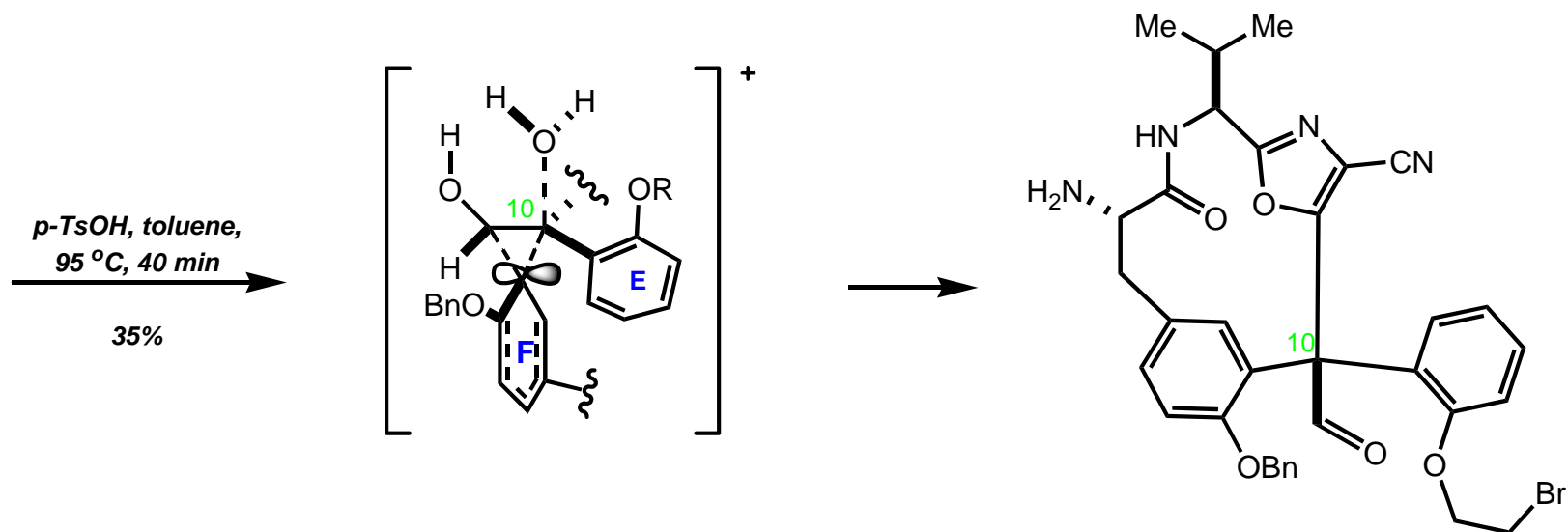
# Harran's Synthesis for Proposed Diazonamide A



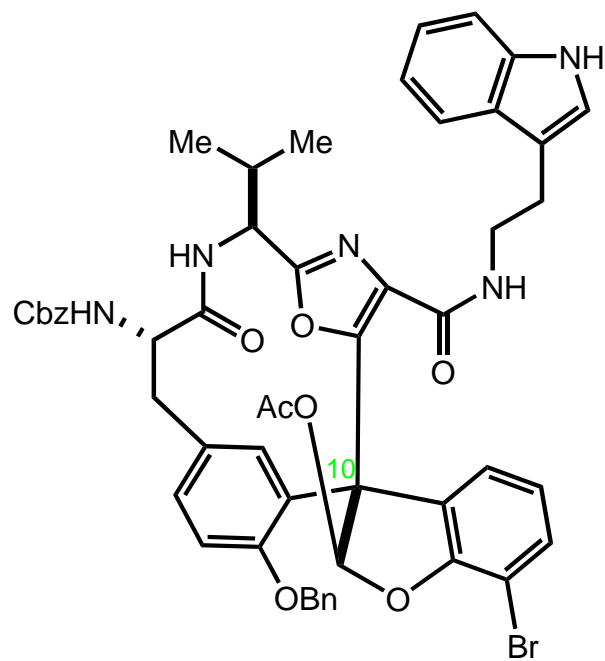
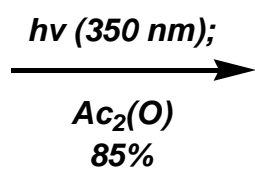
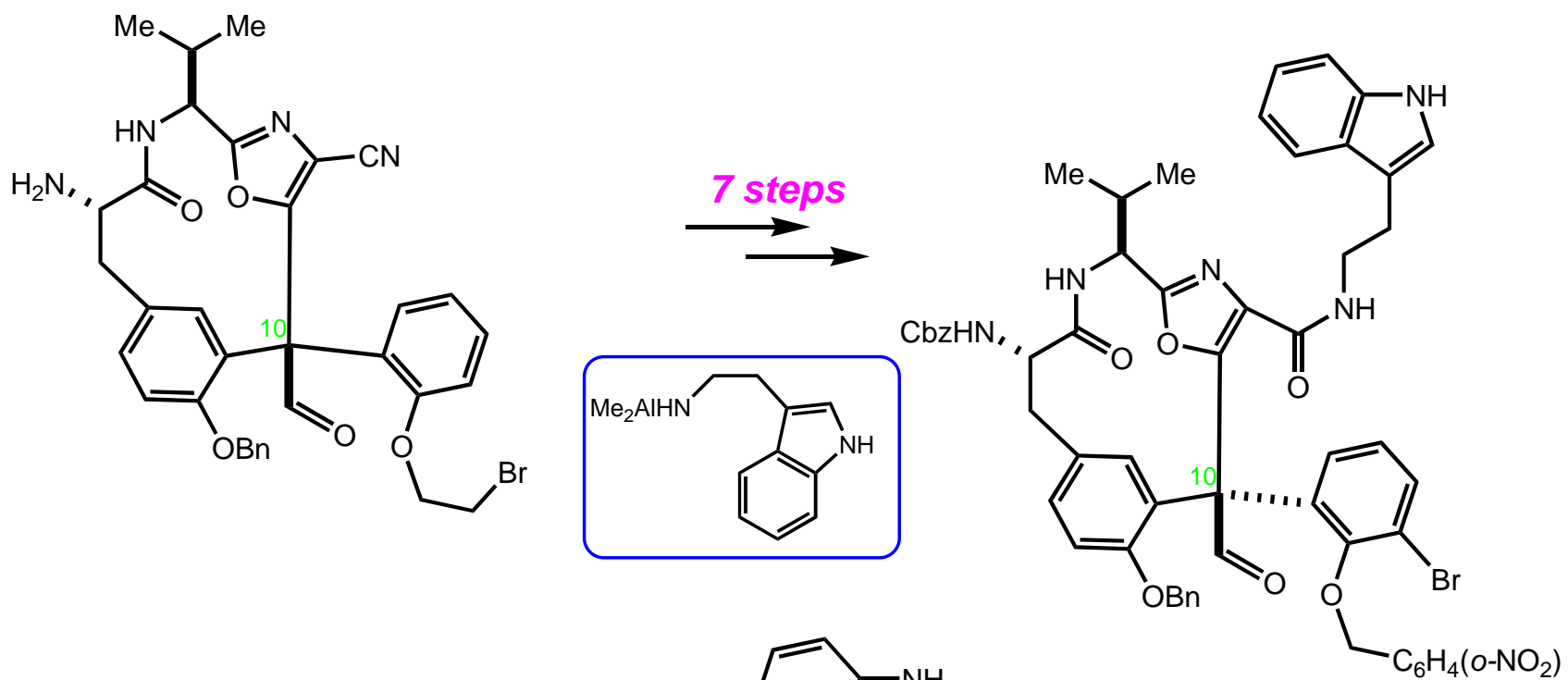
# Pinacol Ring-Contraction



*diastereofacial selectivity 97:3*



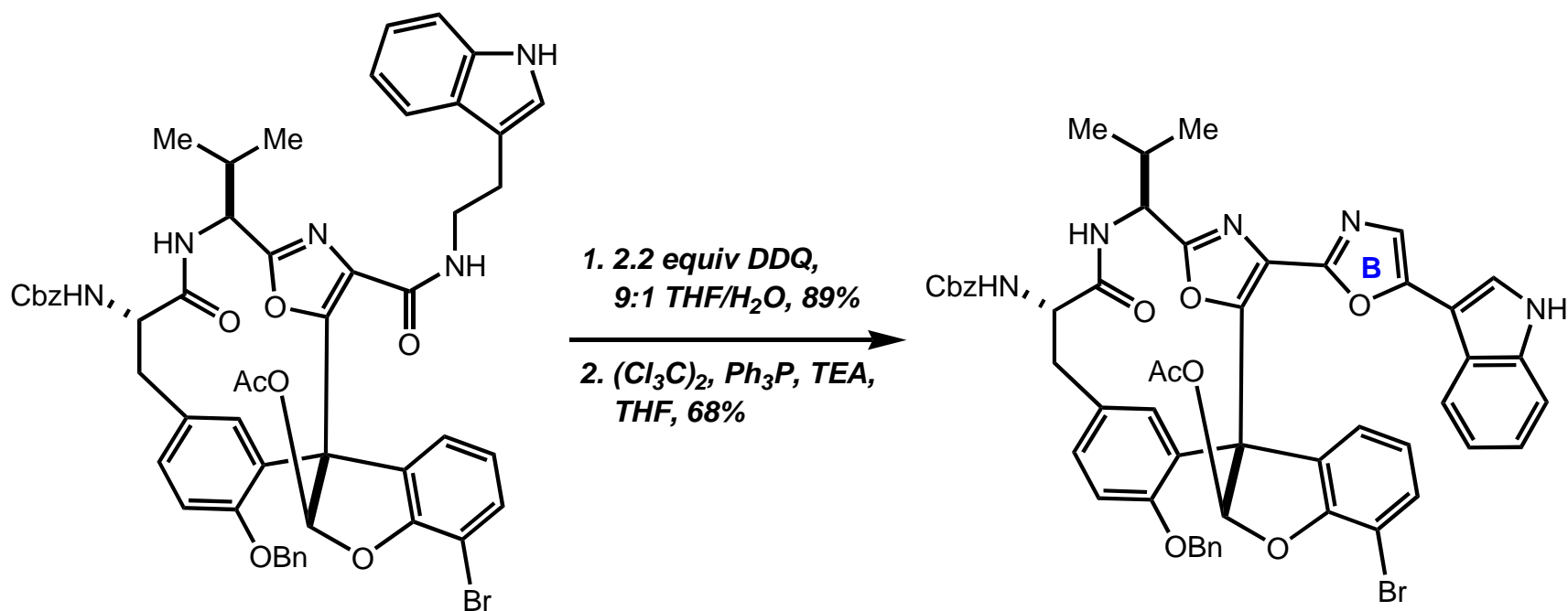
*single isomer*



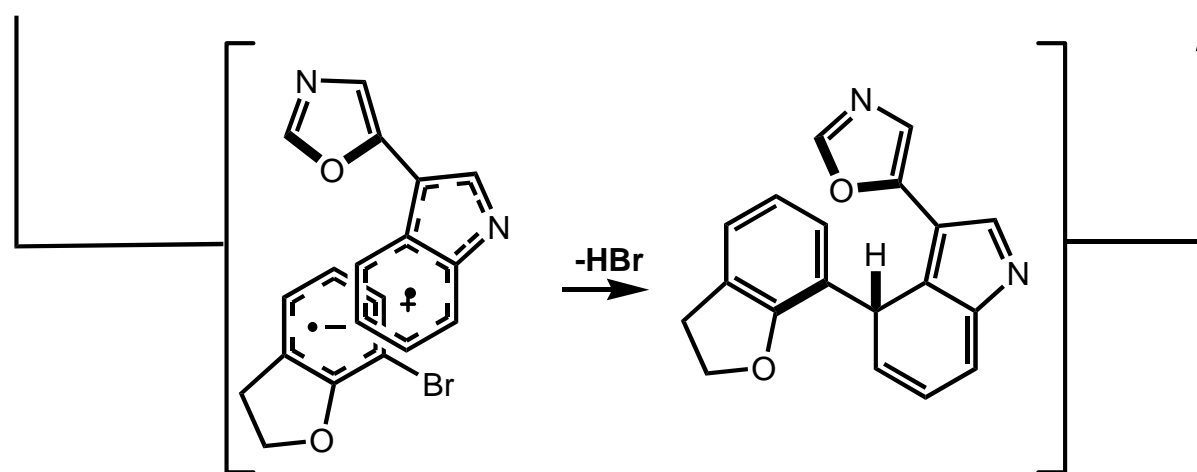
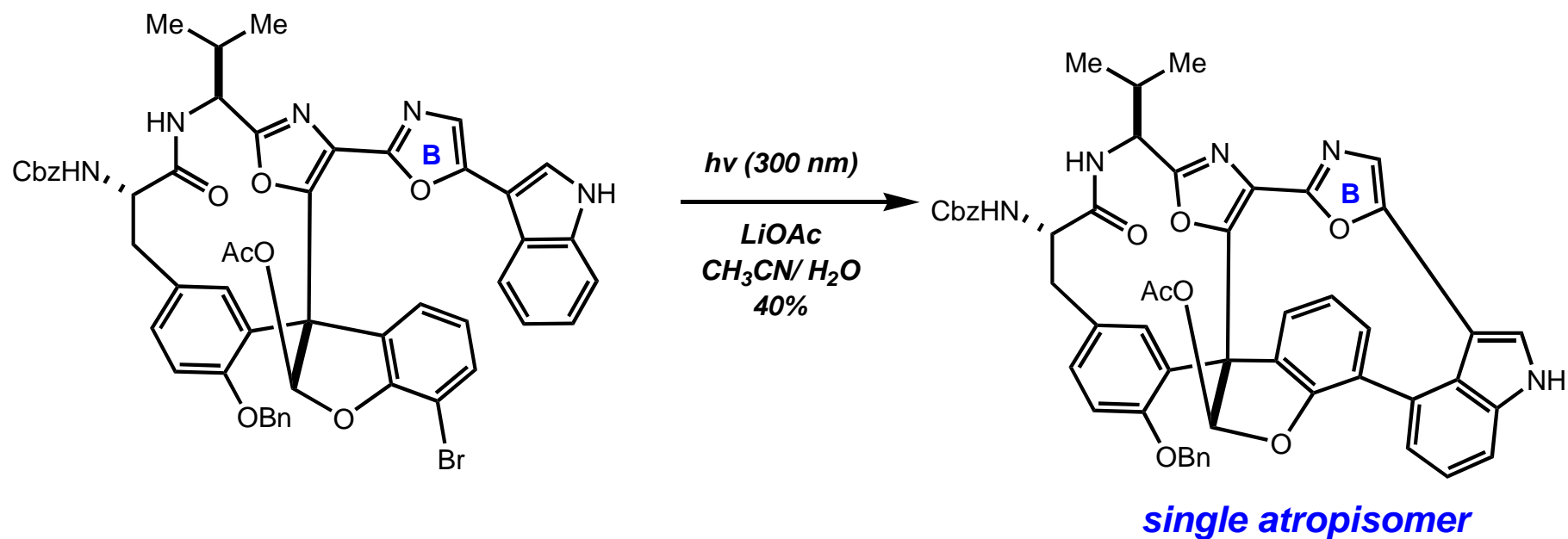
*single diastereomer*

Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, 40, 4765

# Robinson-Gabriel cyclodehydration

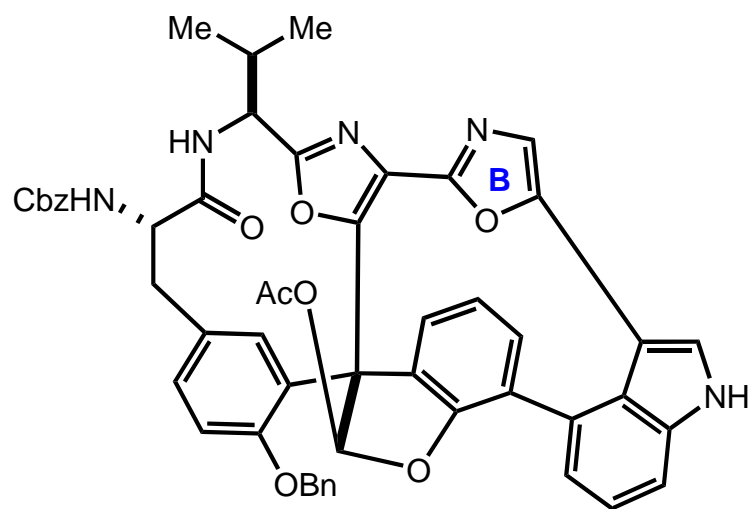


# Witkop-type cyclization

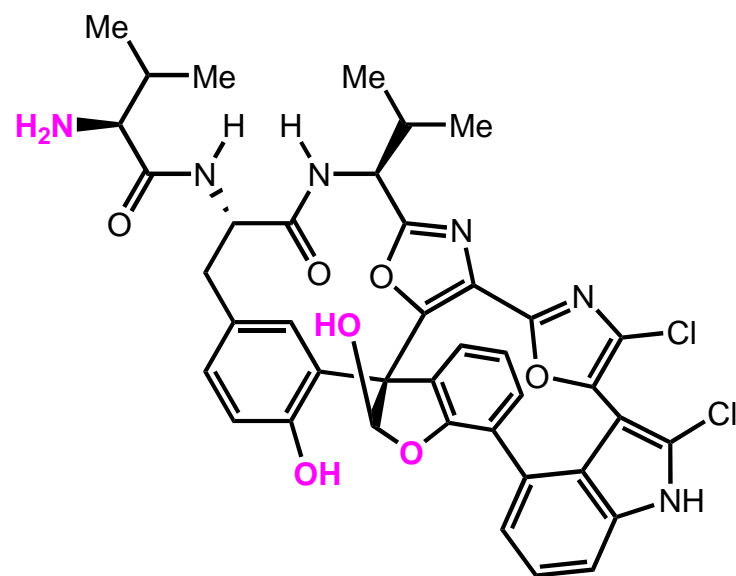


Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4765  
Witkop, B. J. *Am. Chem. Soc.* **1966**, *88*, 3941

Oopps!



4 steps

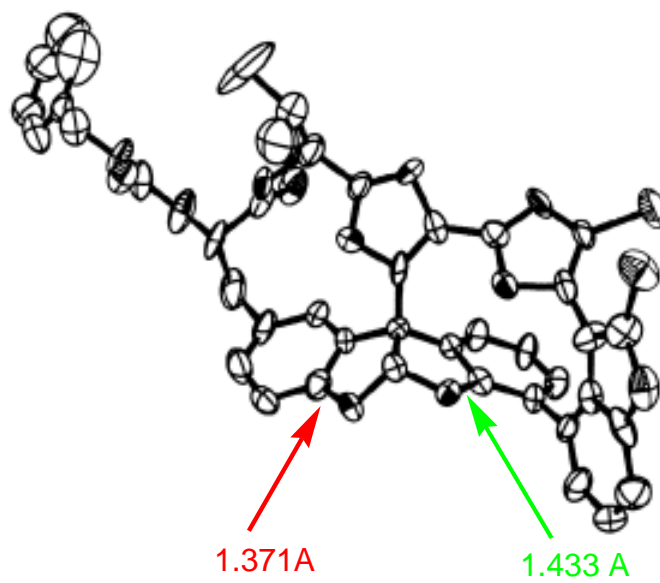
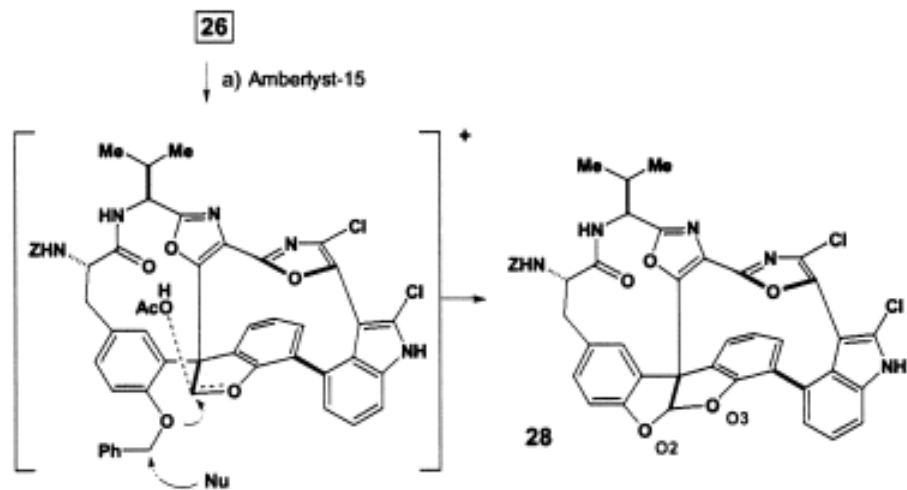


*Diazonamide A ???*

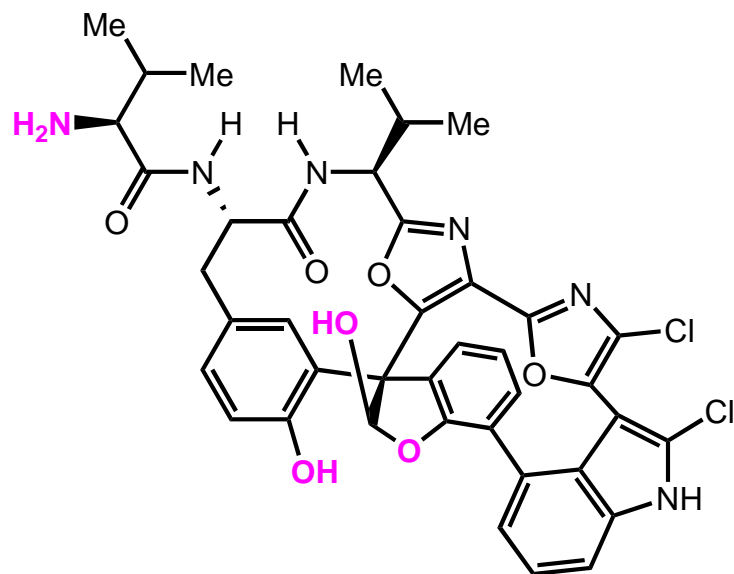


**Harran**

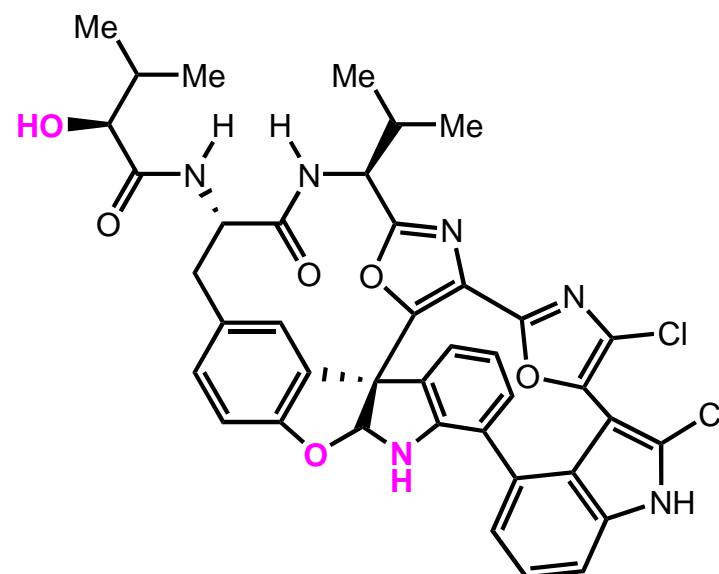
# X-Ray structure proposed Diazonamide A



# Diazonamide A



*Initially Proposed Structure of Diazonamide A*



*Revised Structure of Diazonamide A*

- *Re-evaluated crystal structure*
- *Acid digests do not produce valine;  $-OH \Rightarrow -NH_2$*
- *Protonated N has been mistaken for O*

# *Efforts toward the Total Synthesis of Diazonamide A*

## Total Syntheses



**Nicolaou**  
**“2002, 2003”**



**Harran**  
**2003**

## Contributions



**Fu**

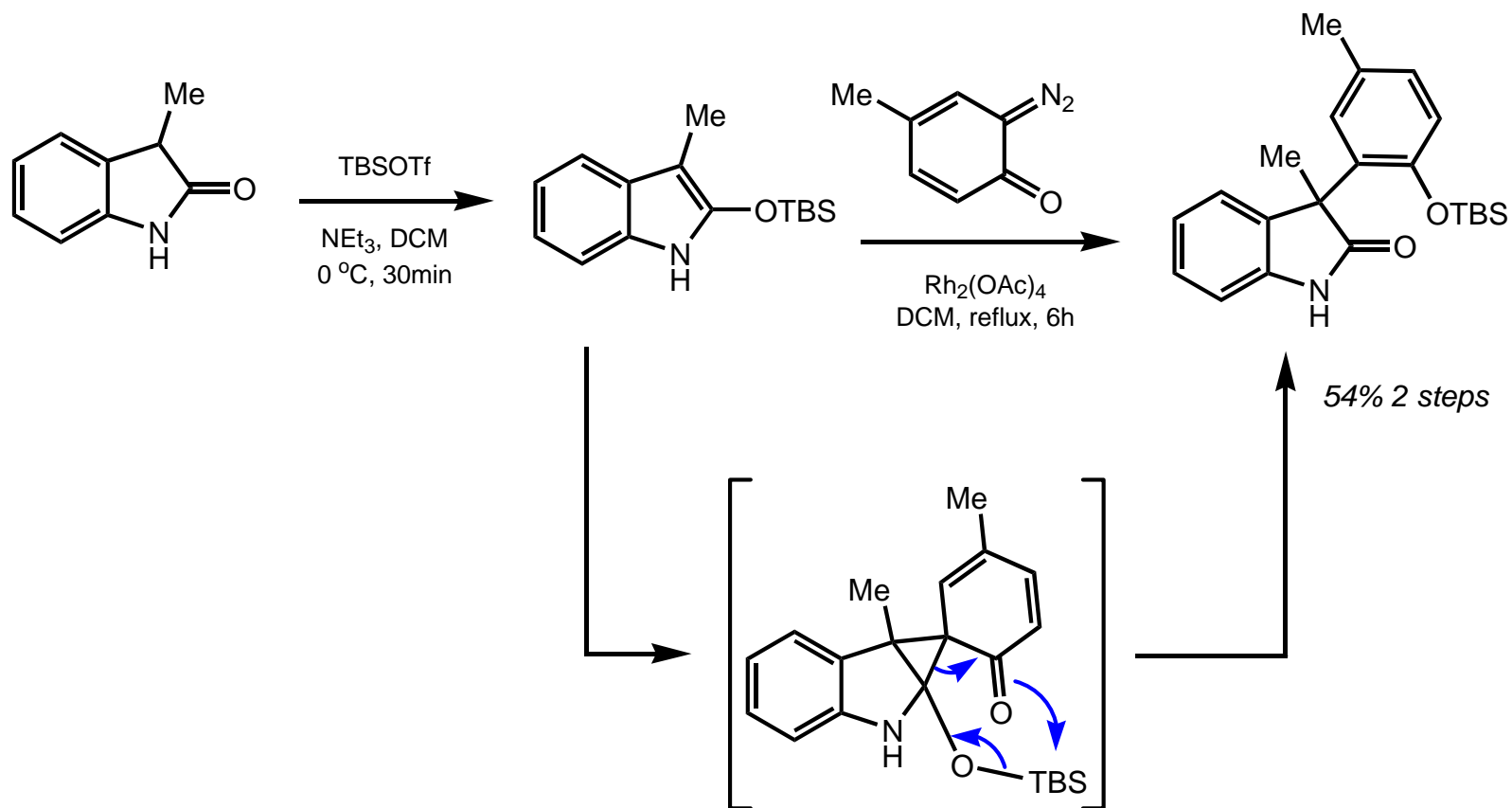


**Wood**

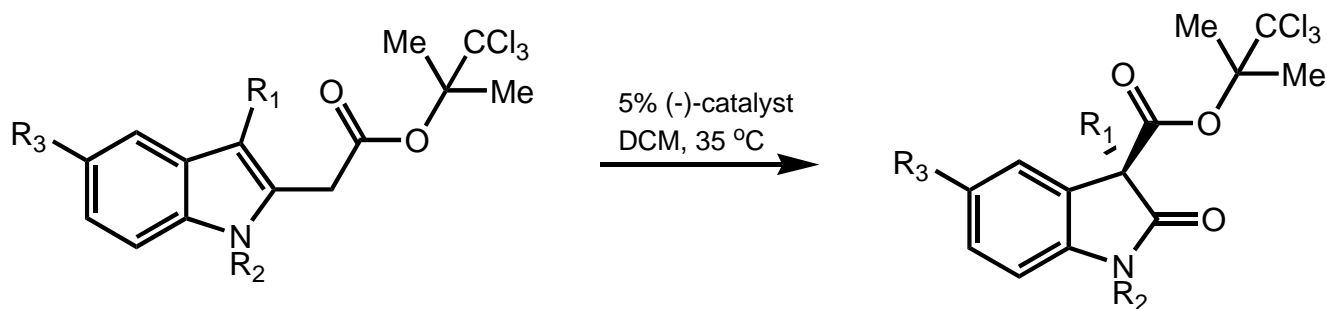


**Vedejs**

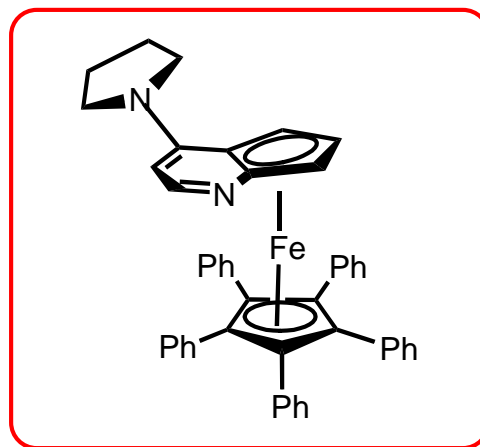
# Rhodium-catalyzed synthesis of oxindole



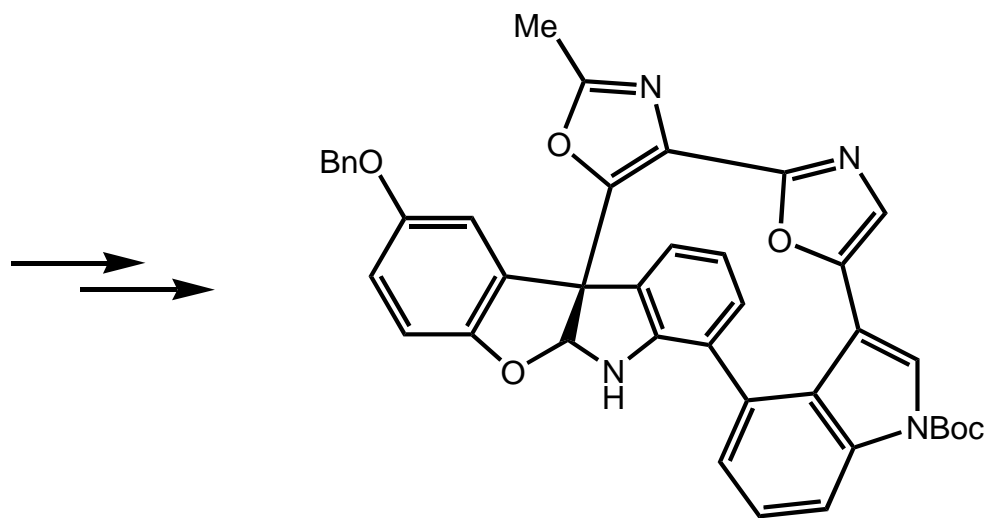
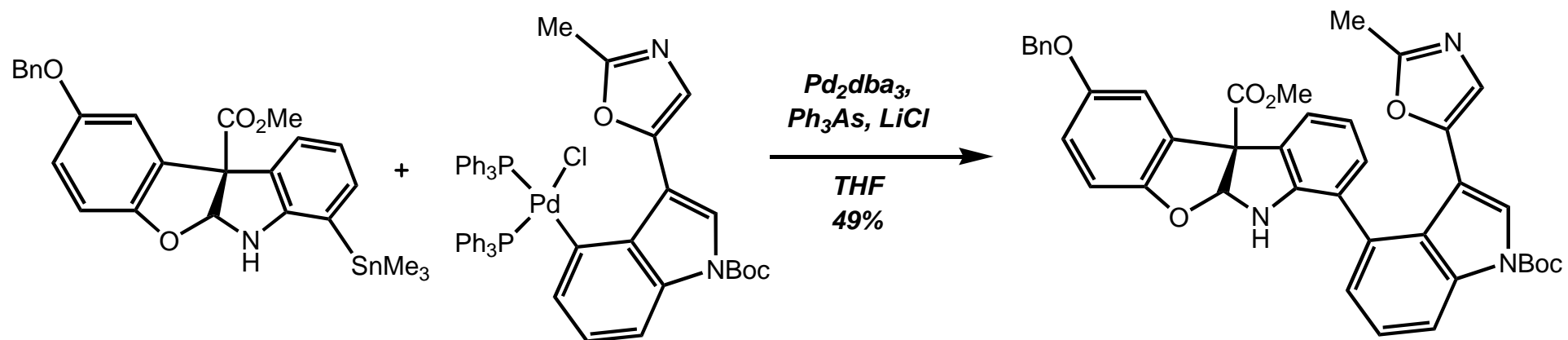
# Catalytic Enantioselective Synthesis of Oxindole



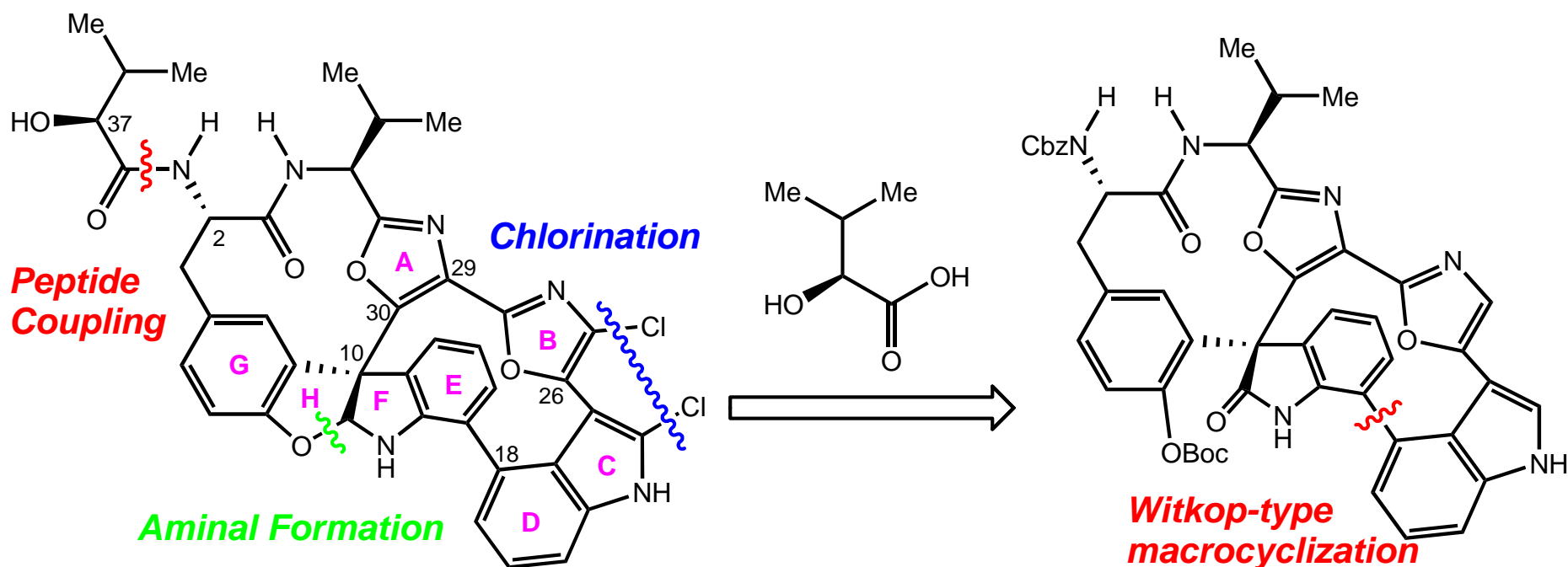
88-91 % yield  
93-99% ee

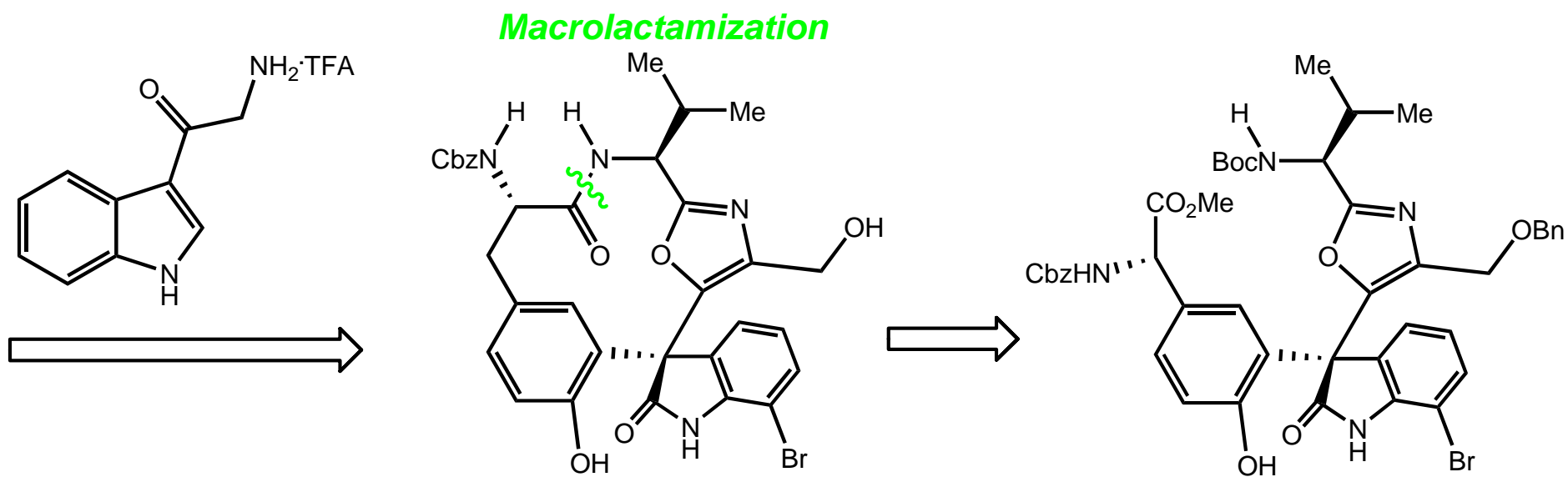
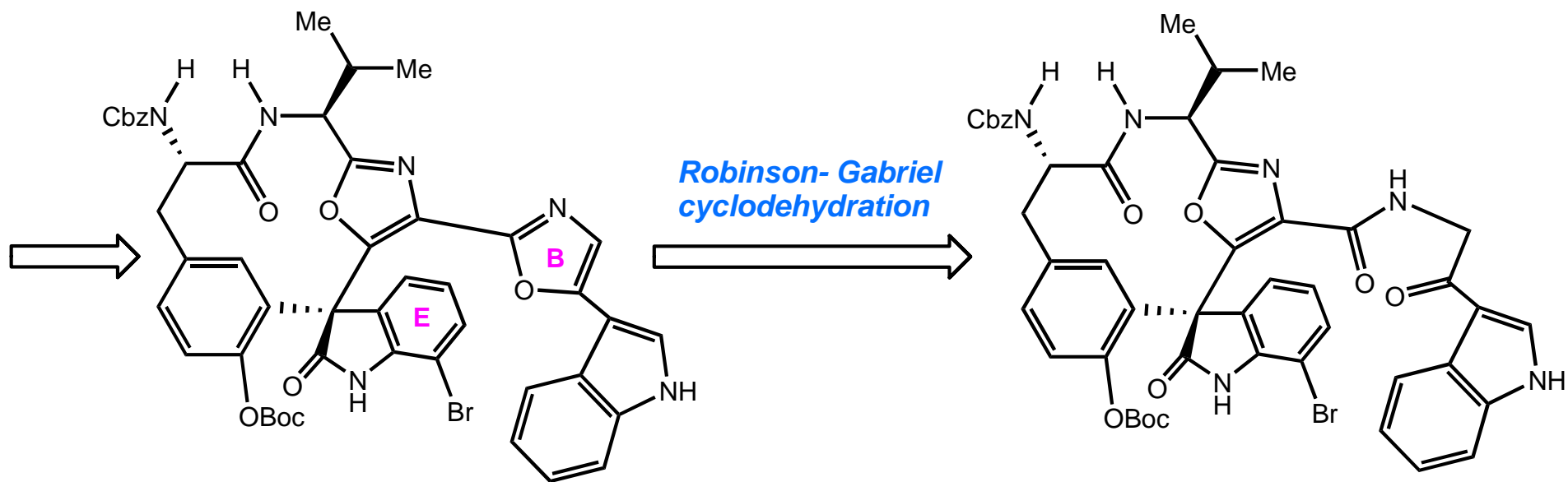


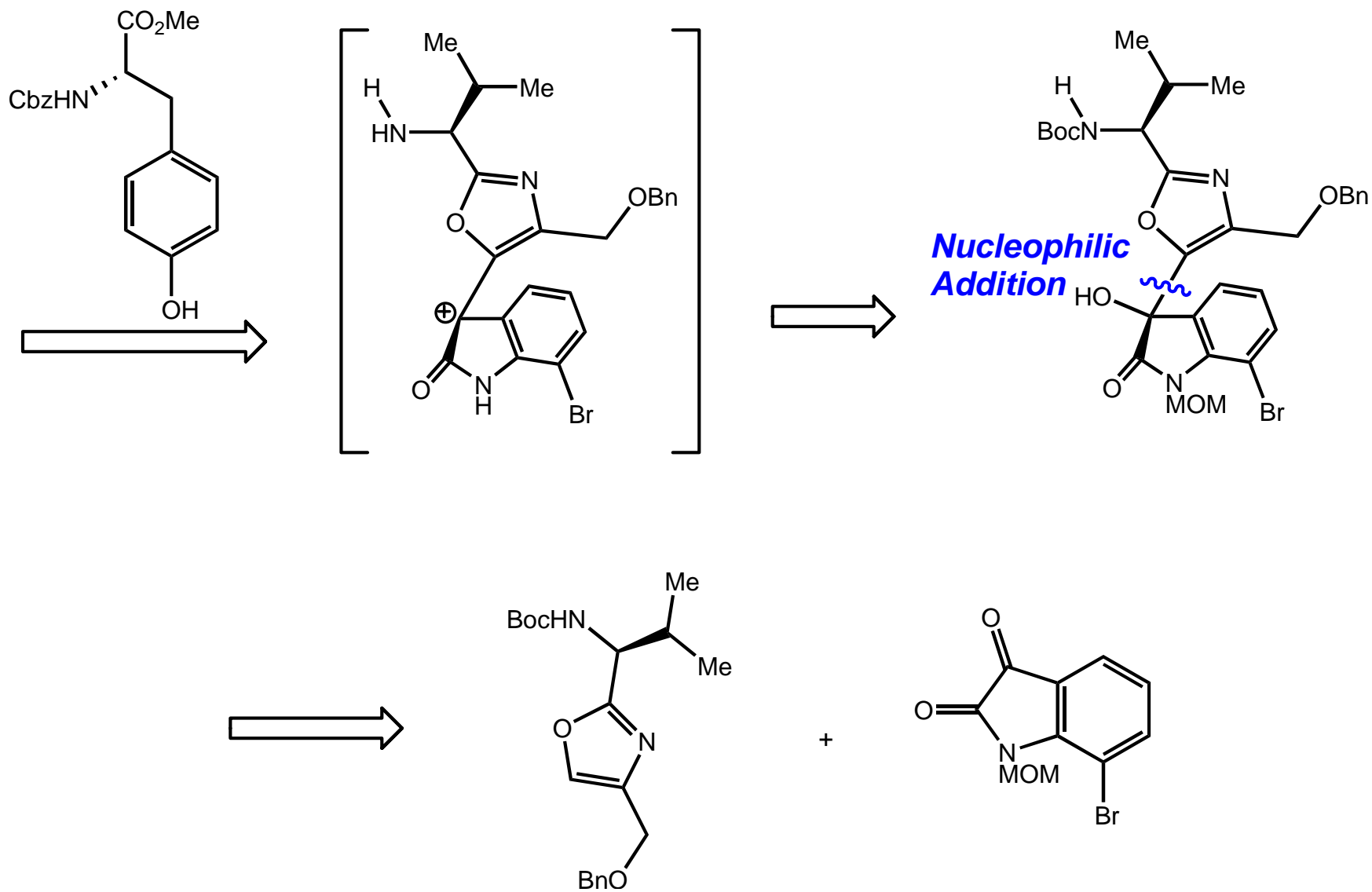
# Stille Coupling



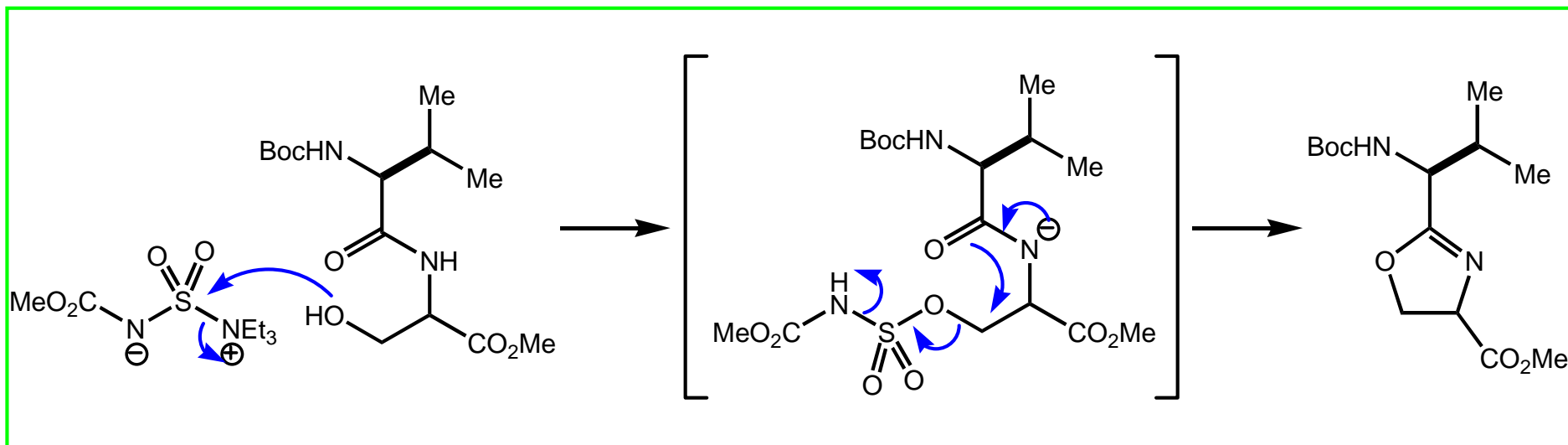
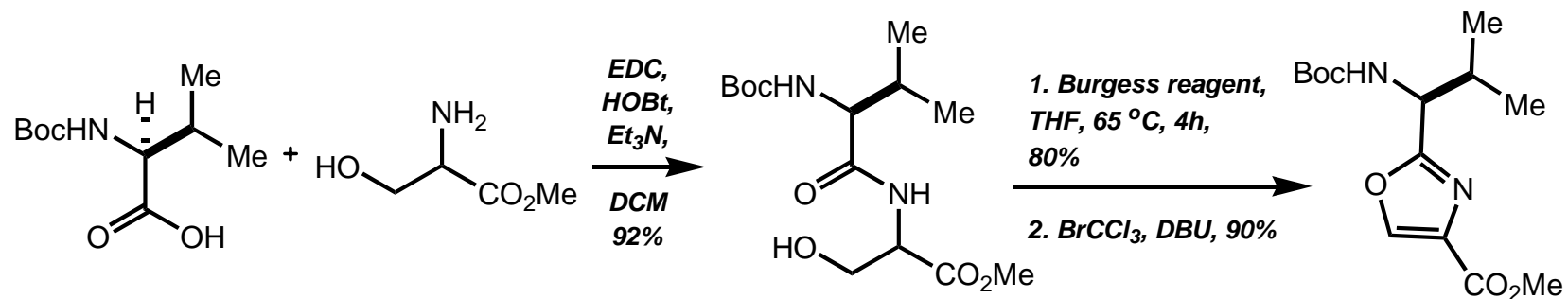
# Niclaou I: Retrosynthesis



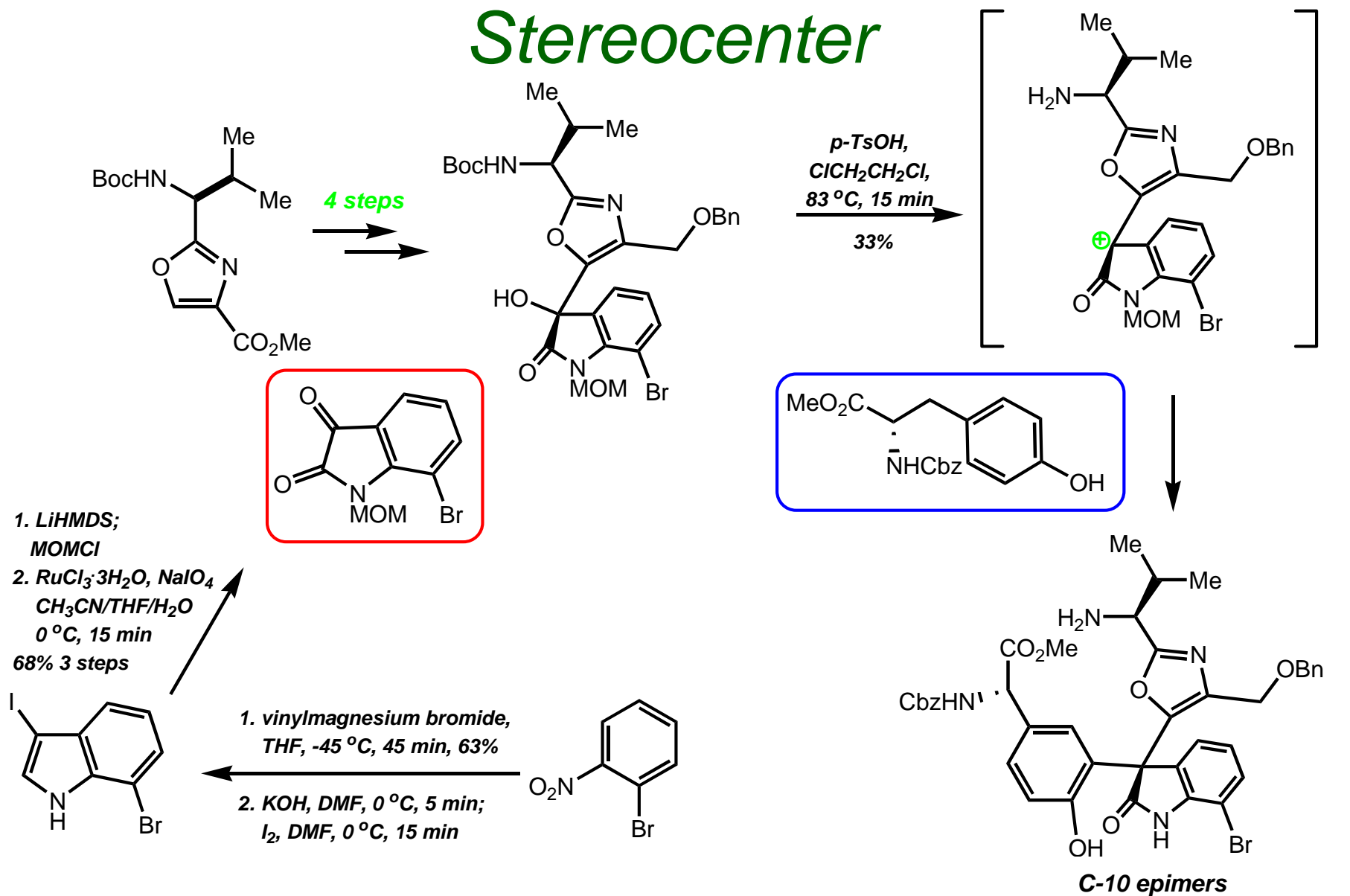




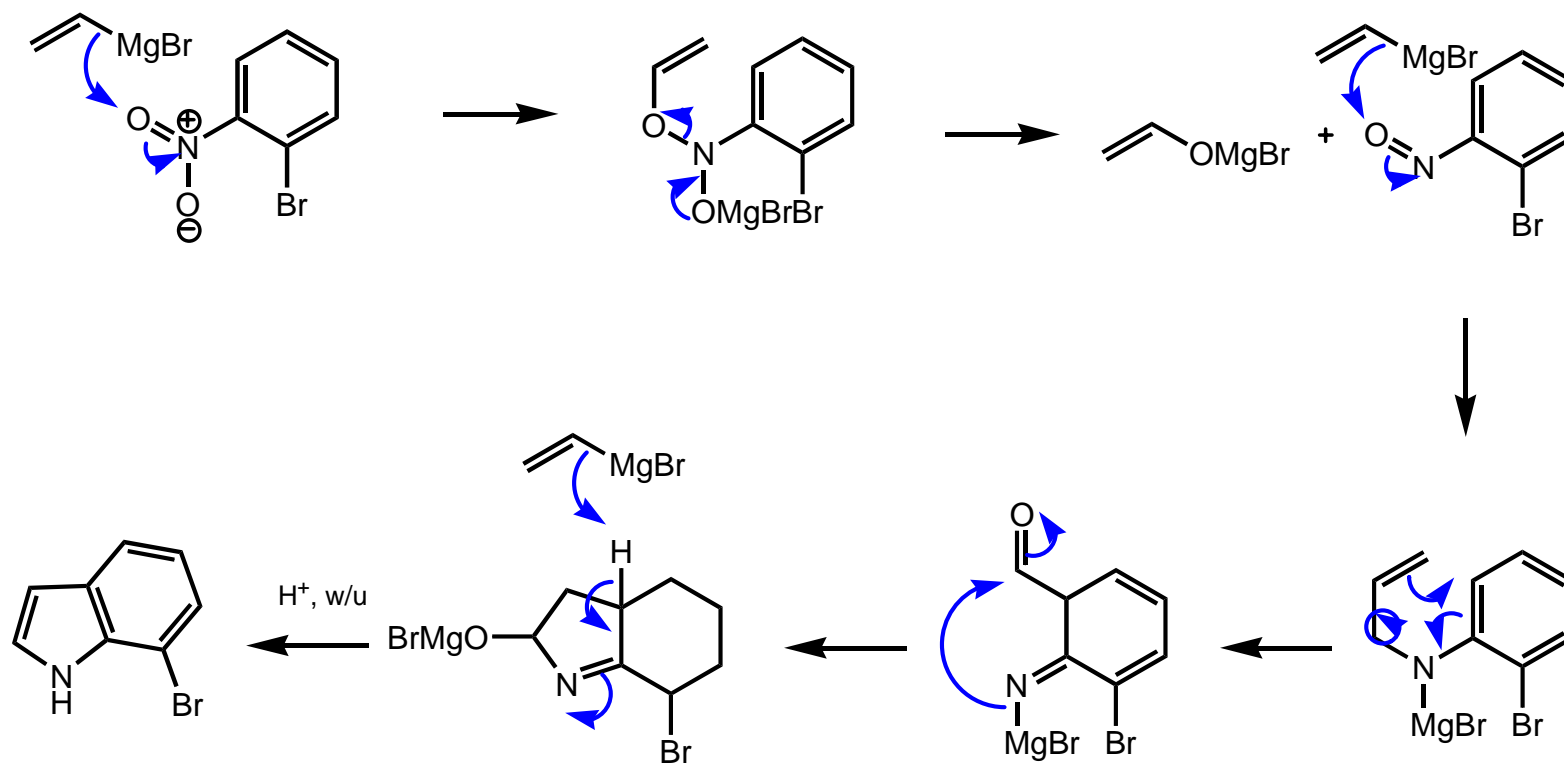
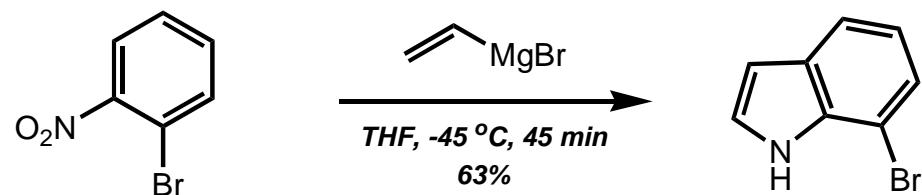
# Oxazole Formation

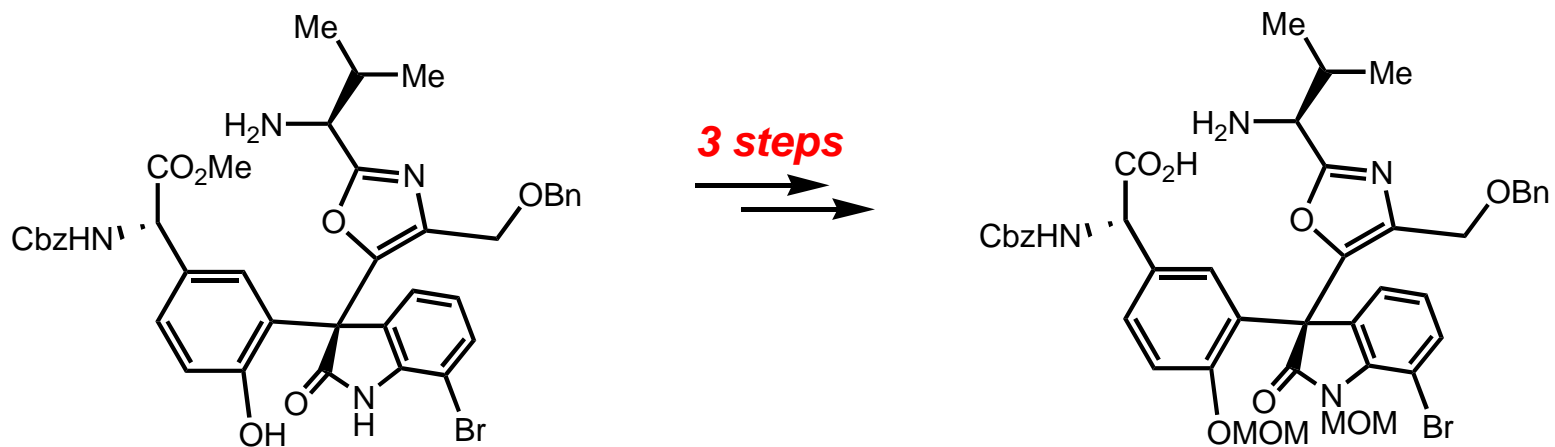


# Formation of Quaternary Stereocenter

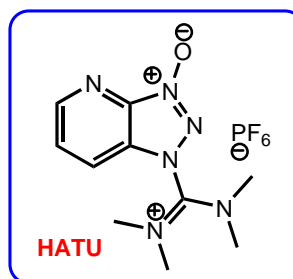


# Bartoli Indole Synthesis

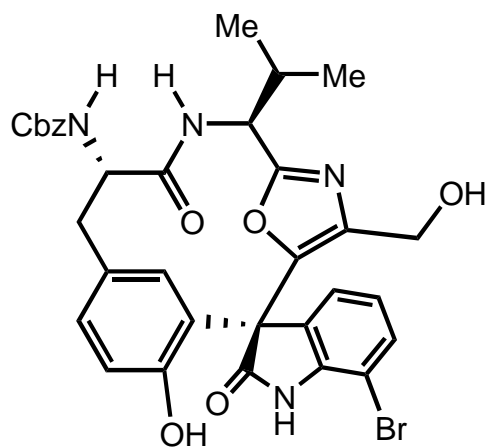




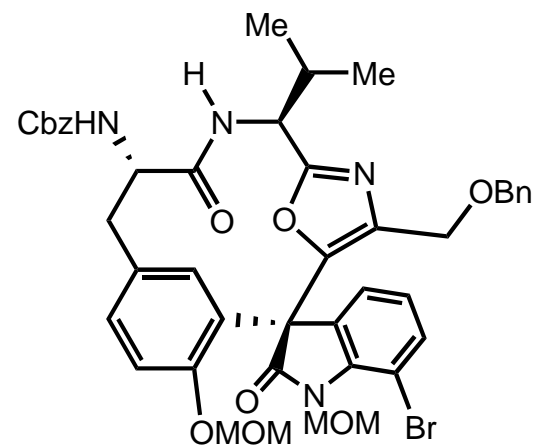
**3 steps**



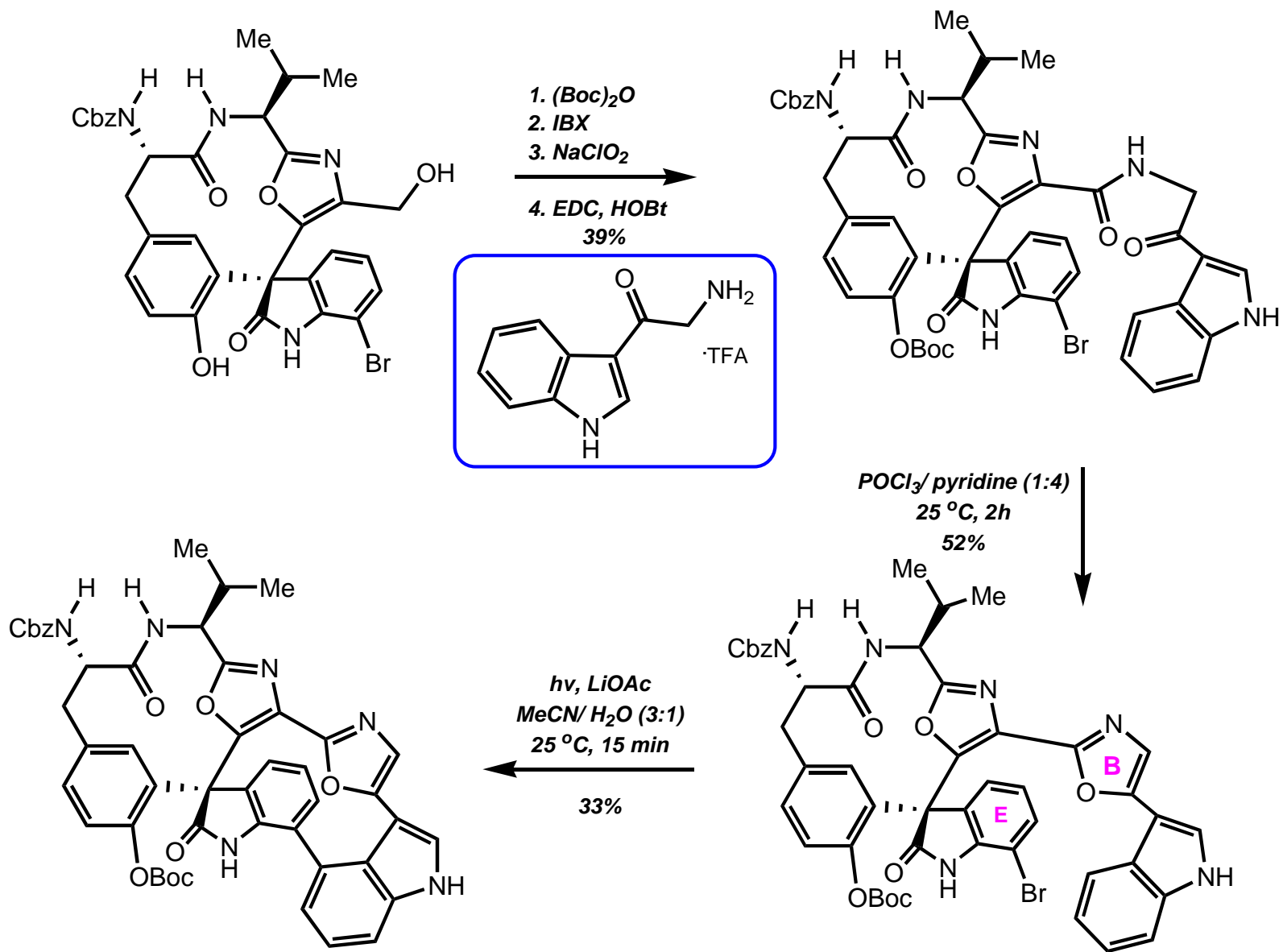
**HATU, collidine**  
**DMF, DCM**  
**25 °C, 12 h**  
**36%**



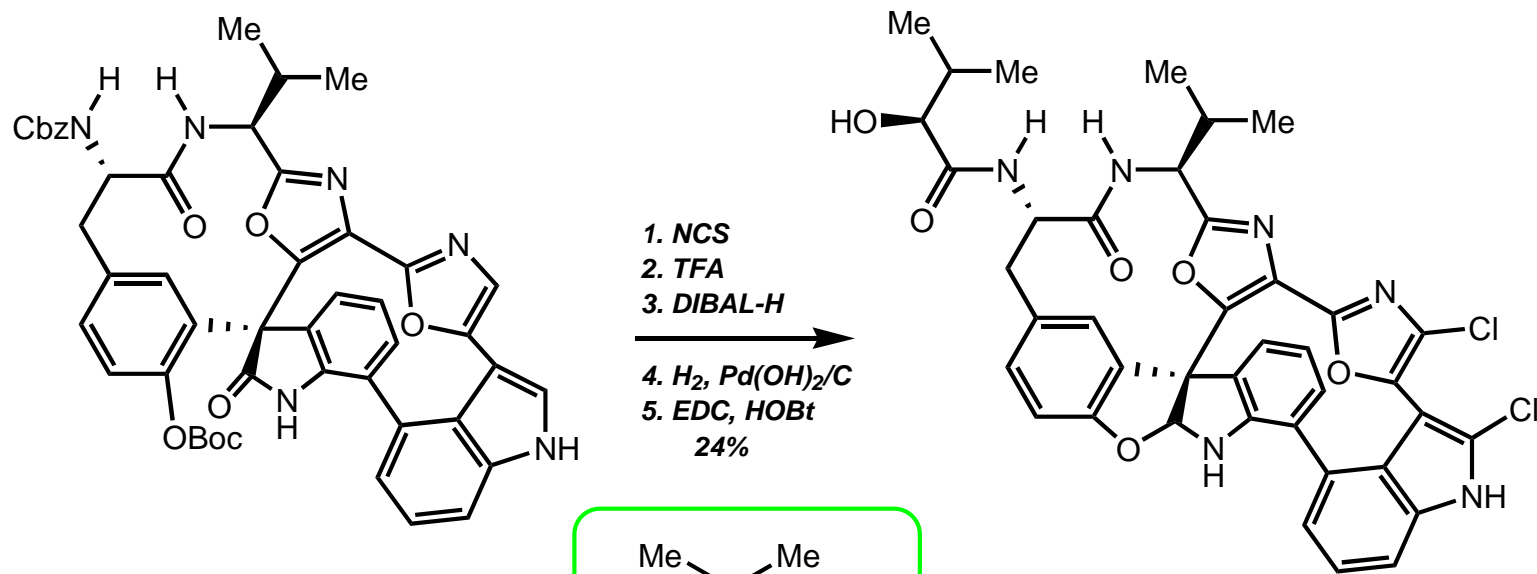
***BCl<sub>3</sub>; NaOH***



**Only one C-10 epimer cyclized**



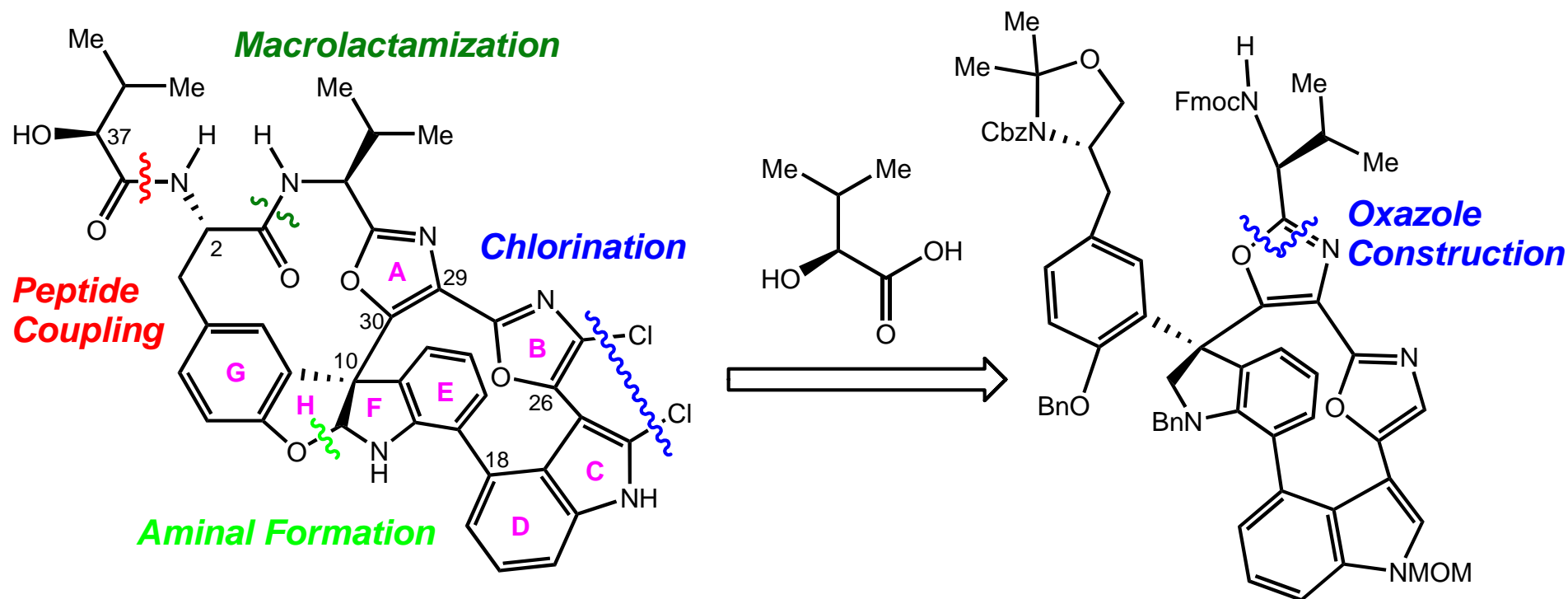
# Final Steps...



**Diazonamide A**

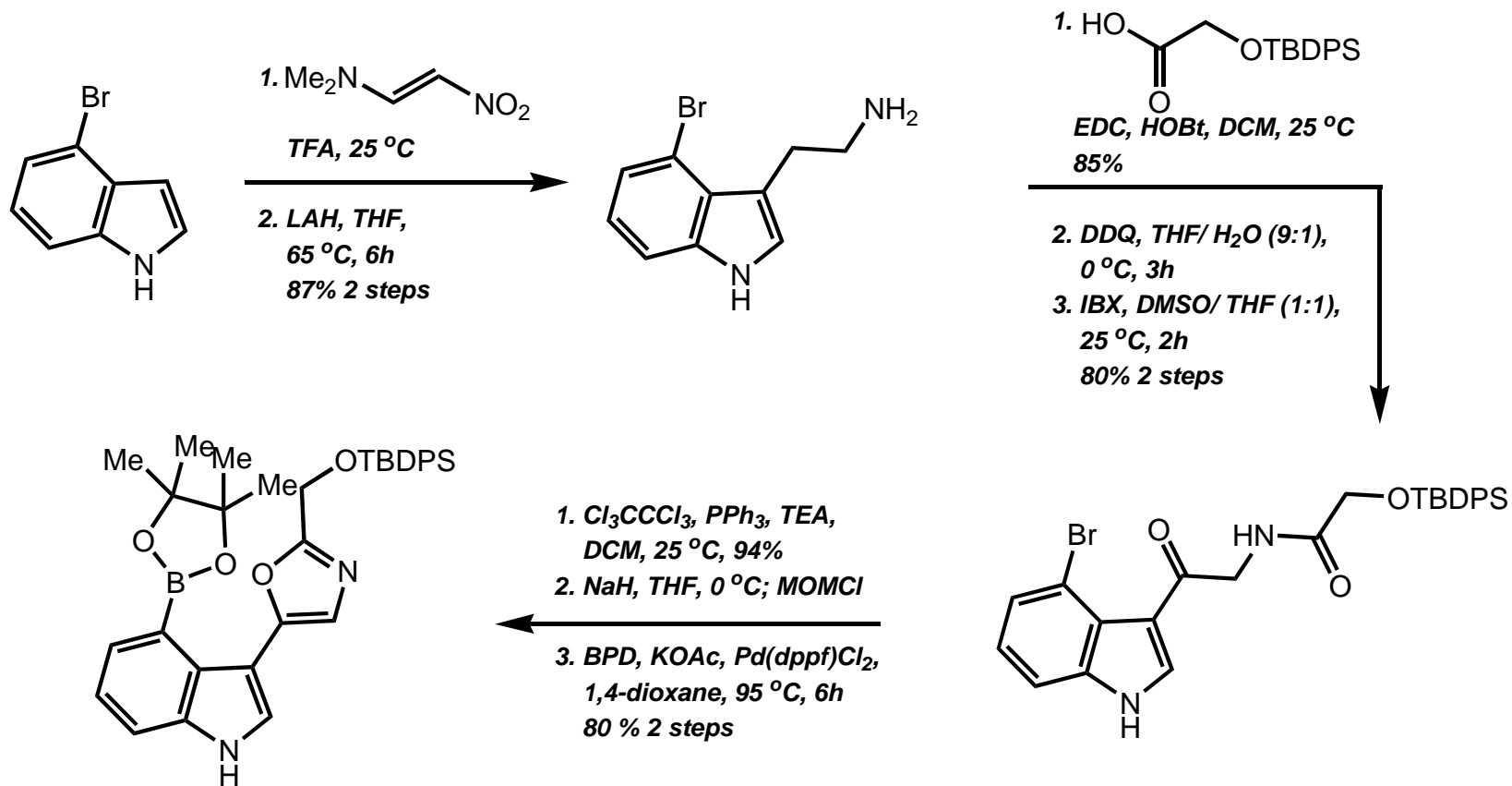
24 steps  
3.98 x 10<sup>-4</sup> % overall yield

# Nicolaou II: Retrosynthesis

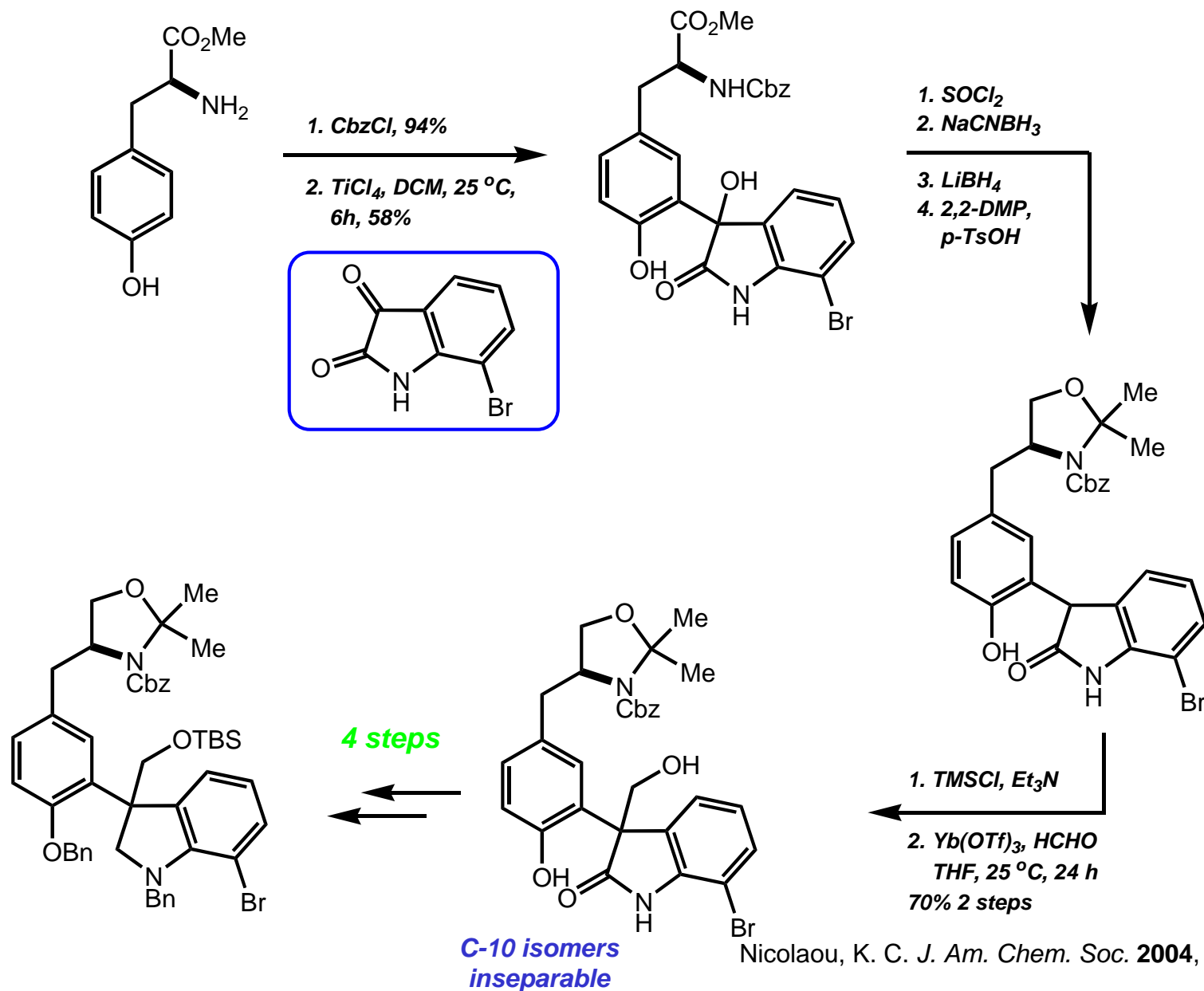




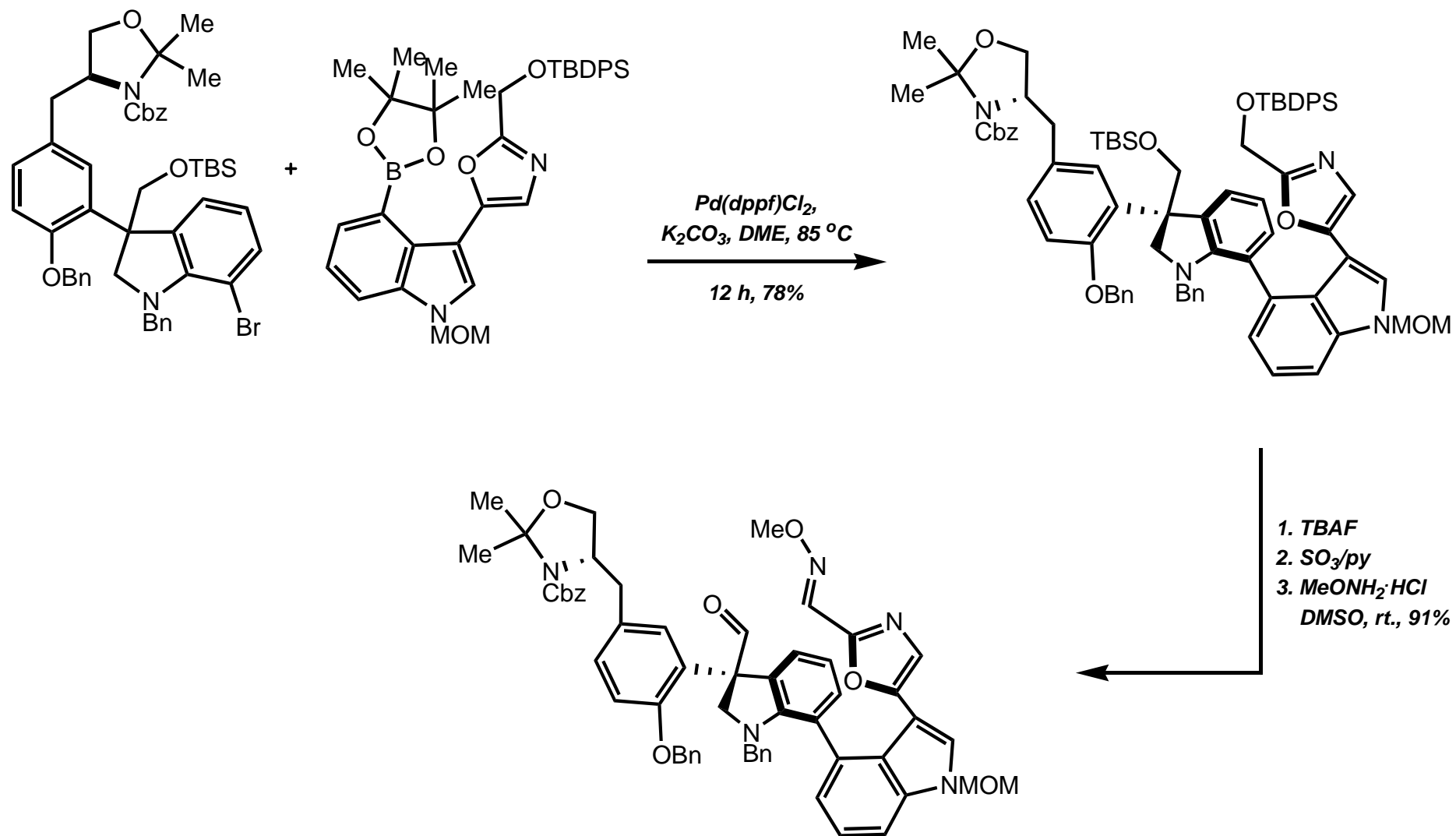
# Formation of aryl boronate

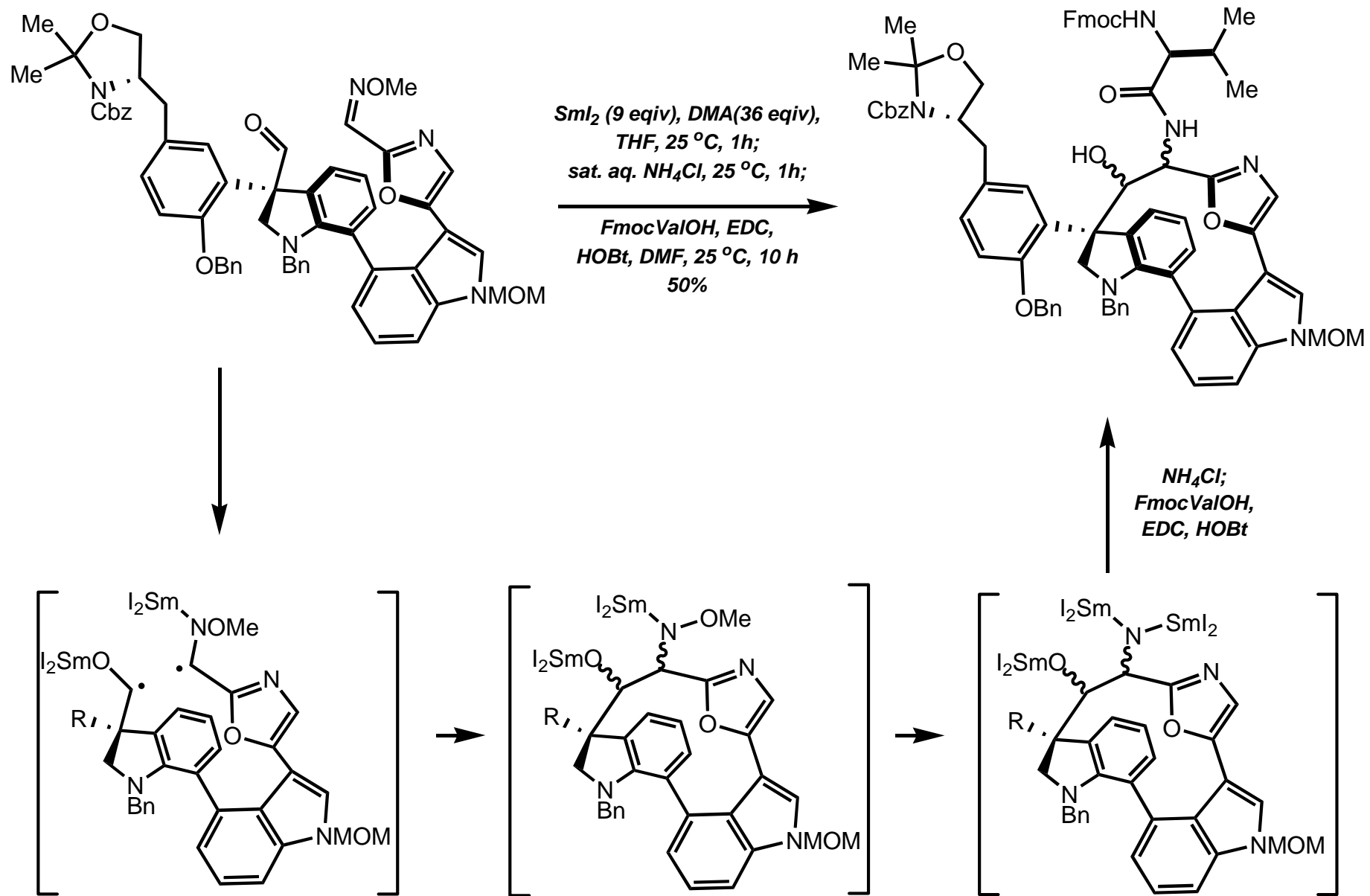


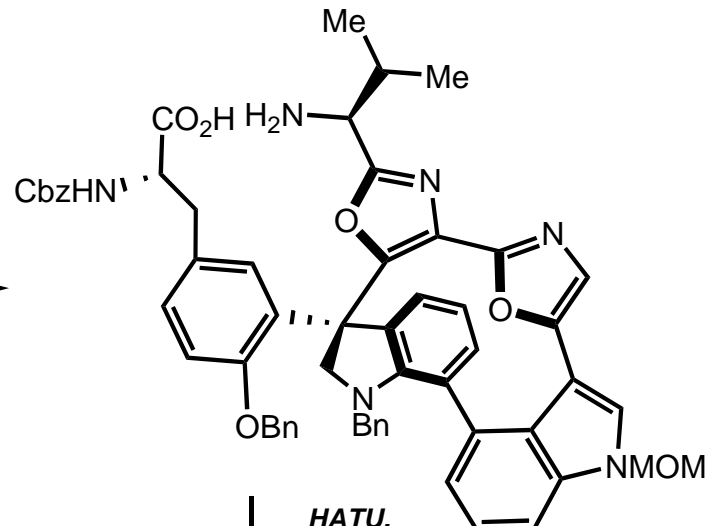
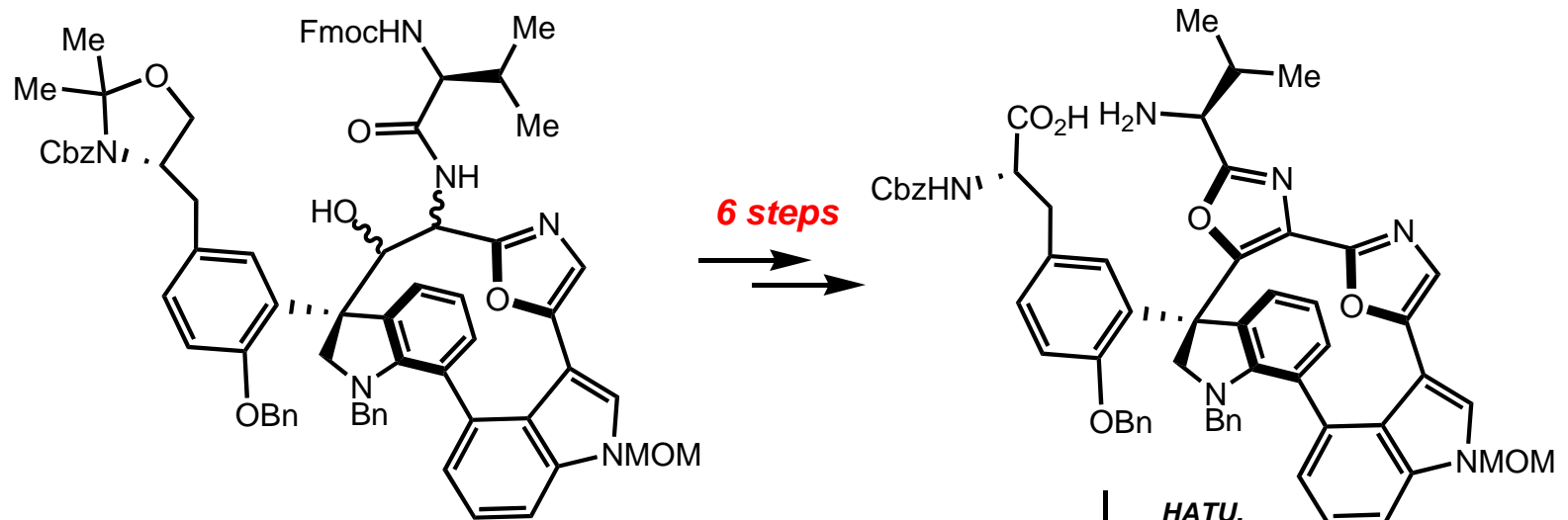
# Formation of aryl halide



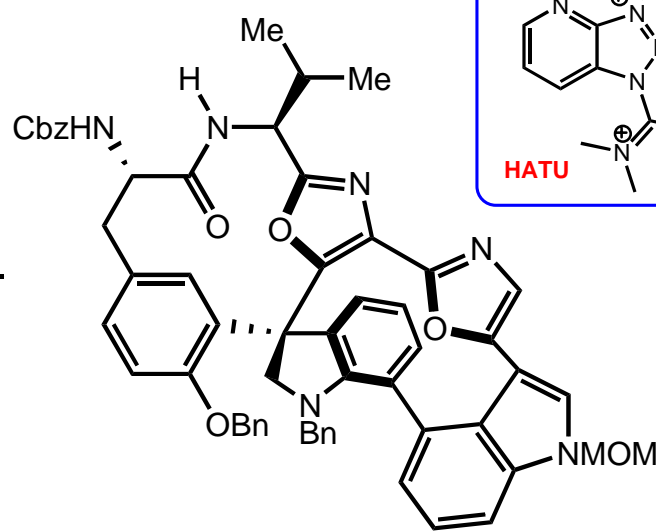
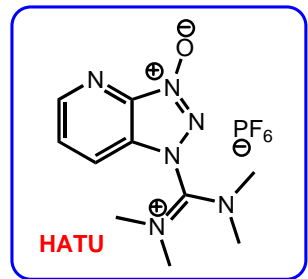
# Suzuki Coupling





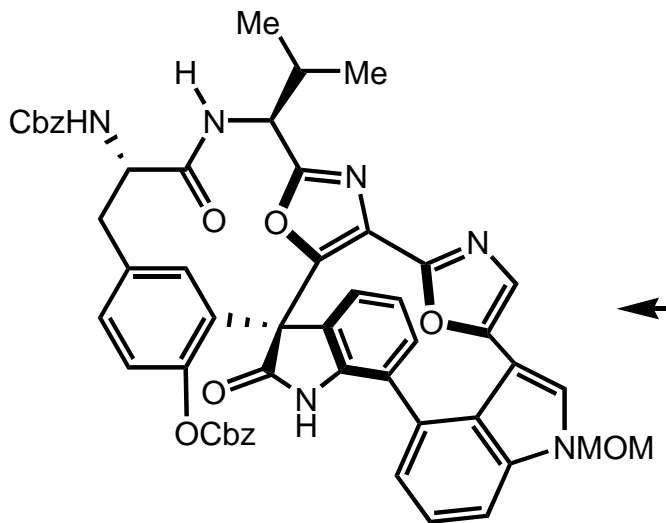


HATU,  
2,4,6-collidine  
DMF, DCM

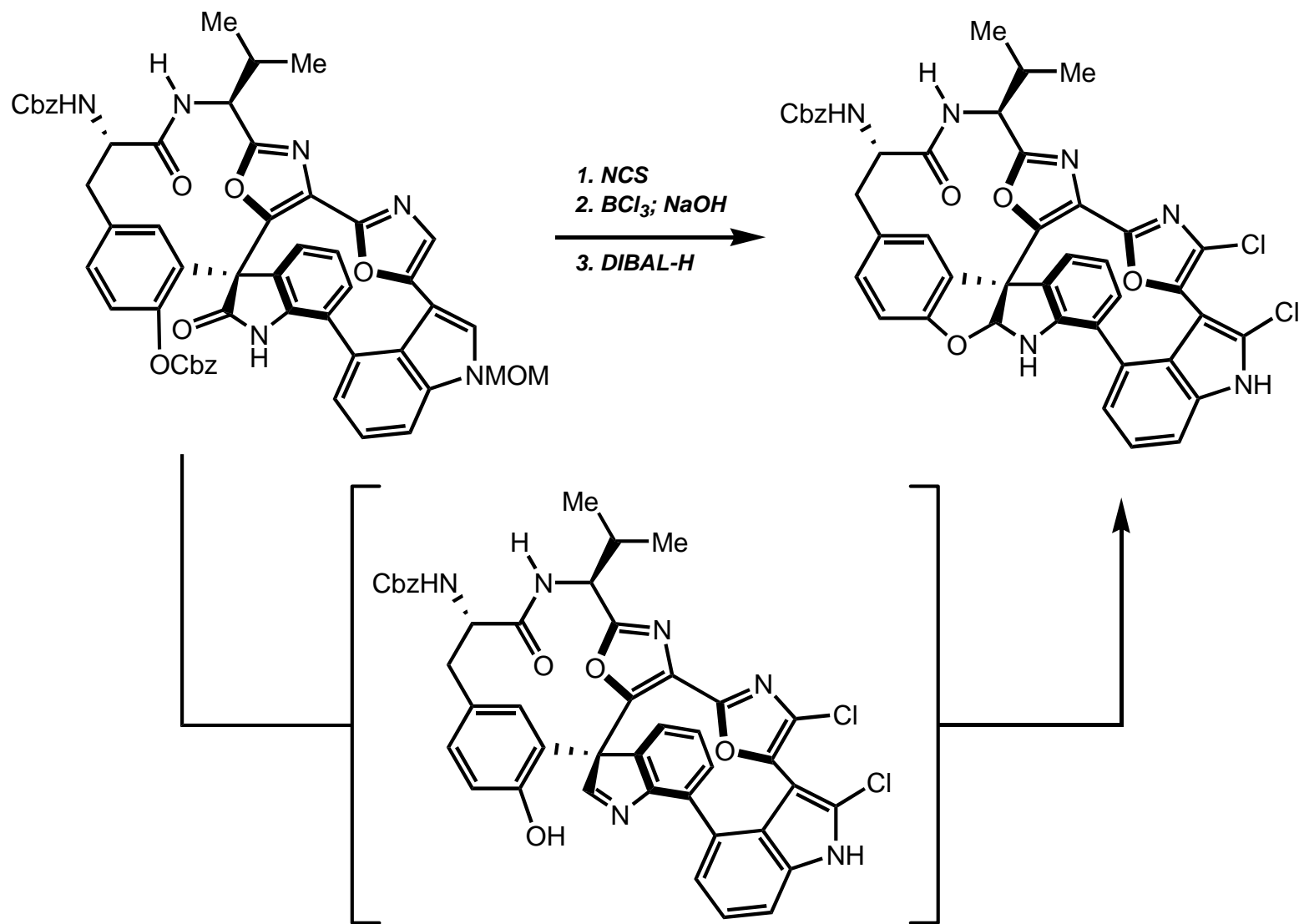


1.  $H_2$ , Pd(OH)<sub>2</sub>/C,  
EtOH, 25 °C, 12h  
2. CbzCl

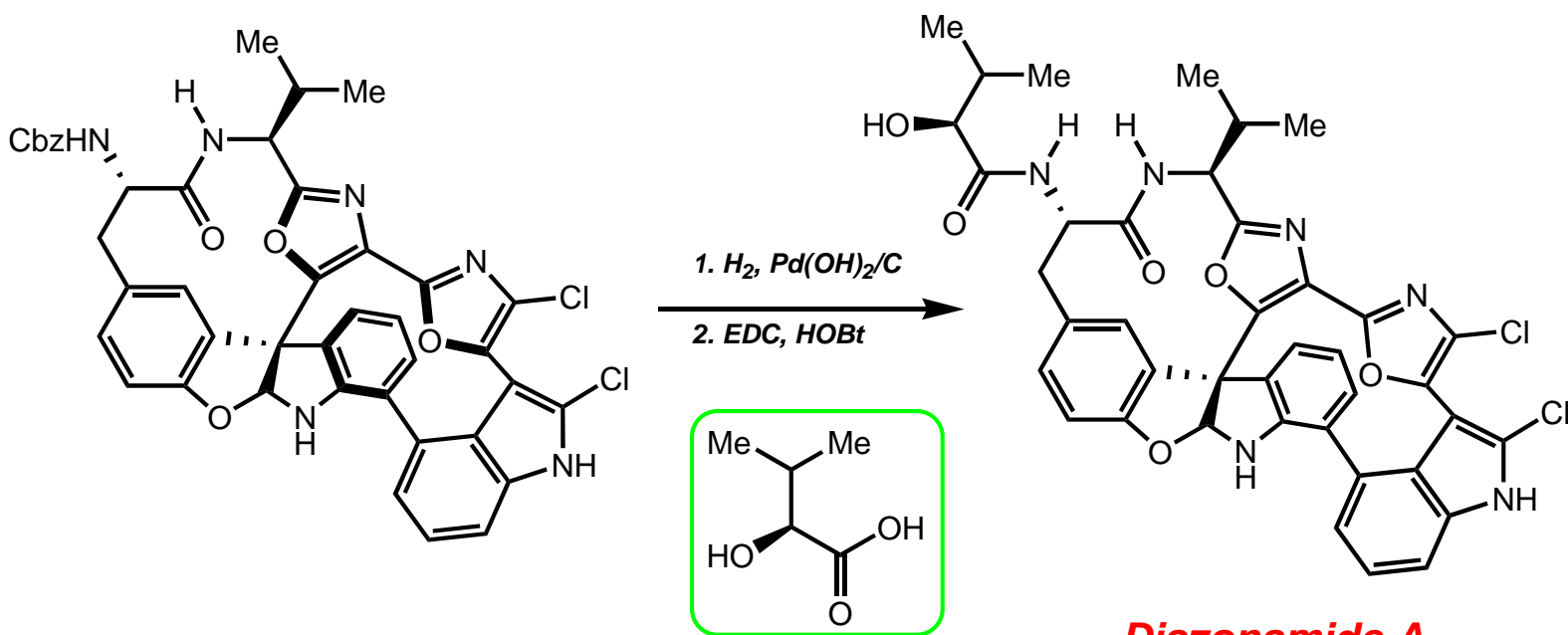
35% 2 steps



**C-10 epimers  
resolved**



# Final Steps...

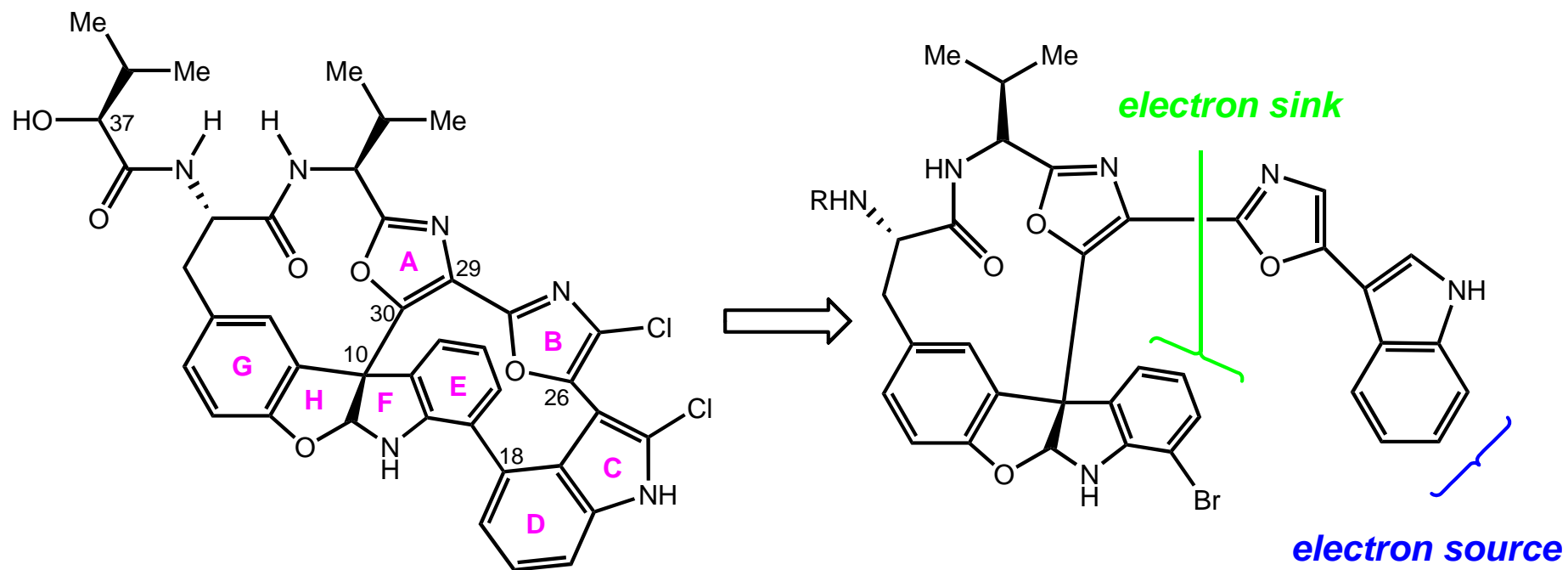


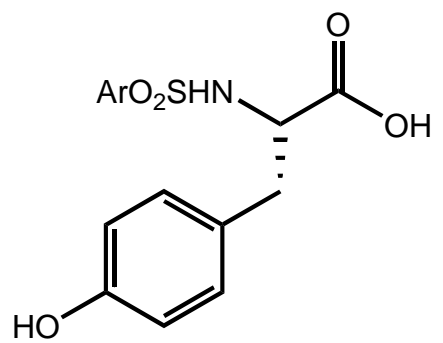
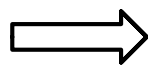
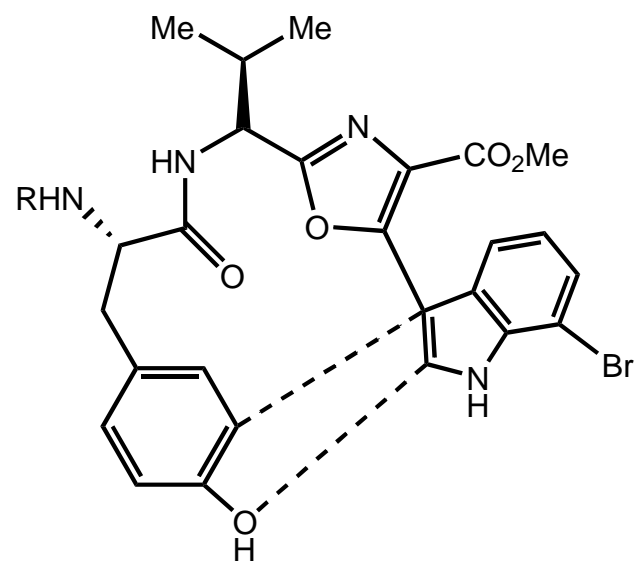
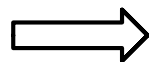
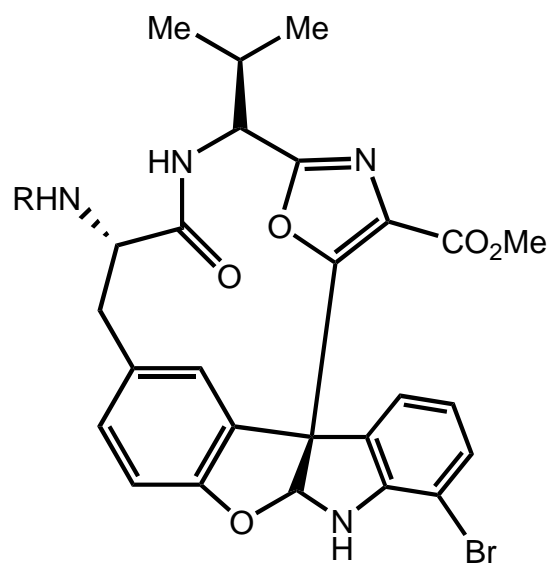
**Diazonamide A**

**31 steps**

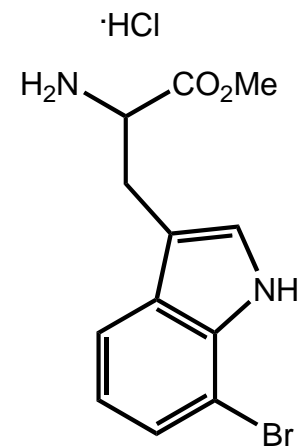
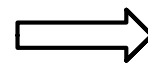
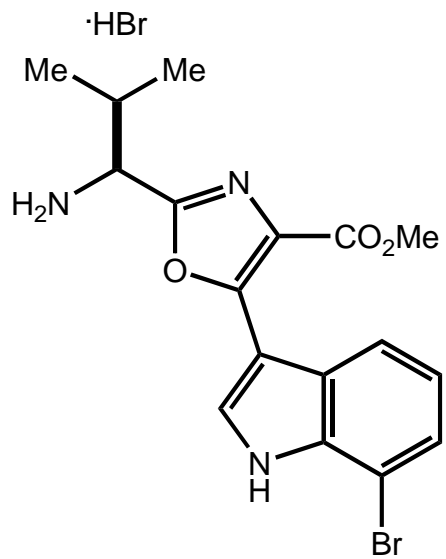
**$1.44 \times 10^{-4}$  % overall yield**

# Harran: Retrosynthesis

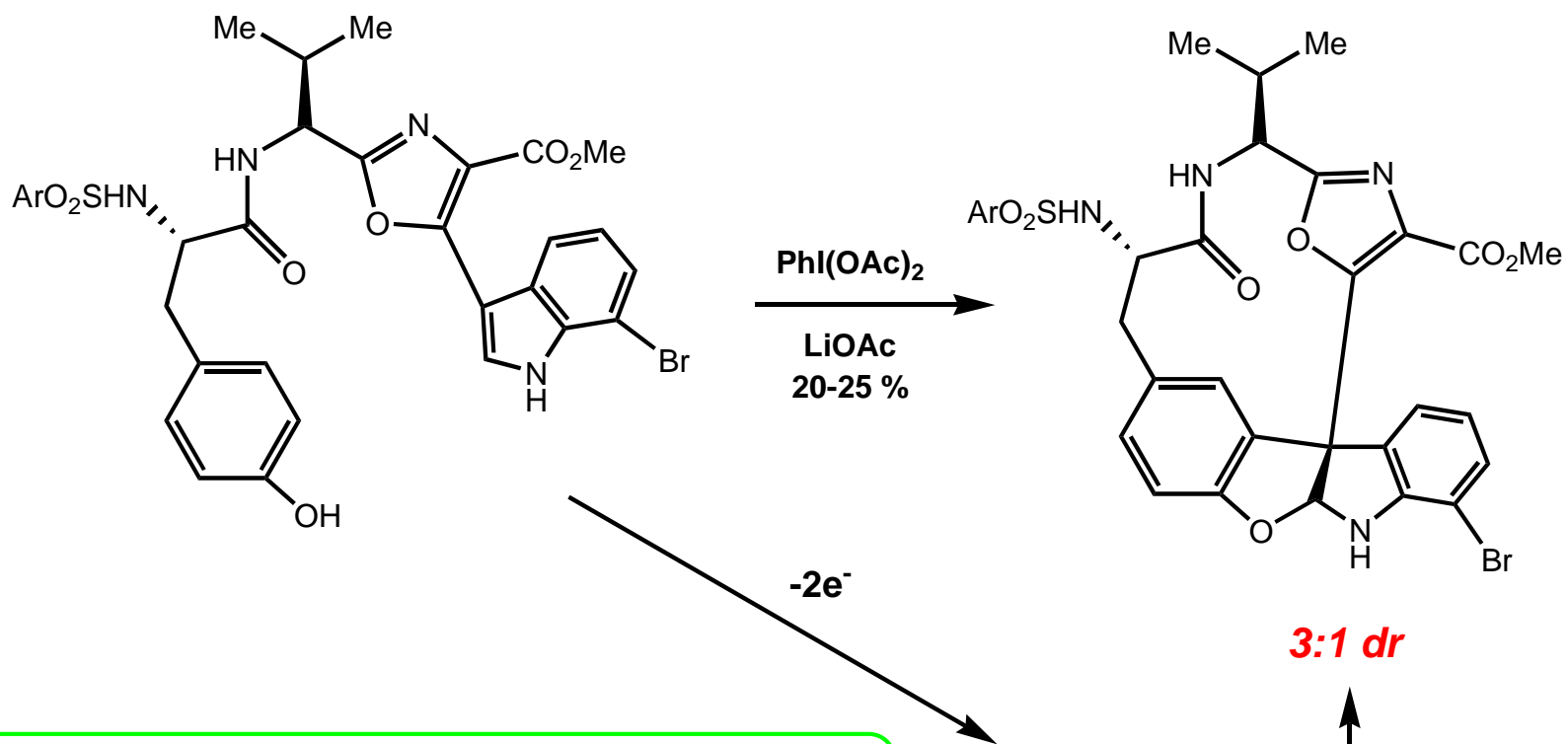




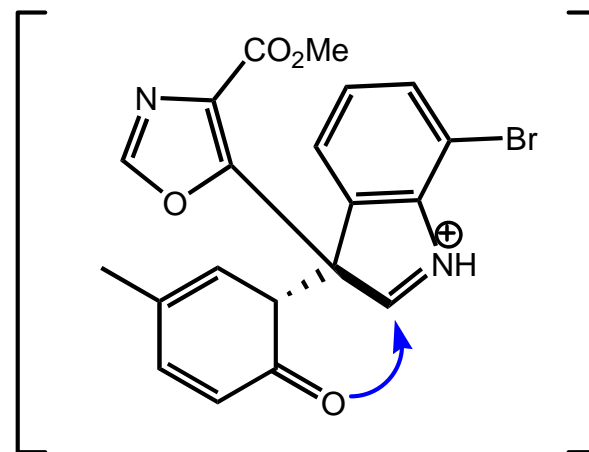
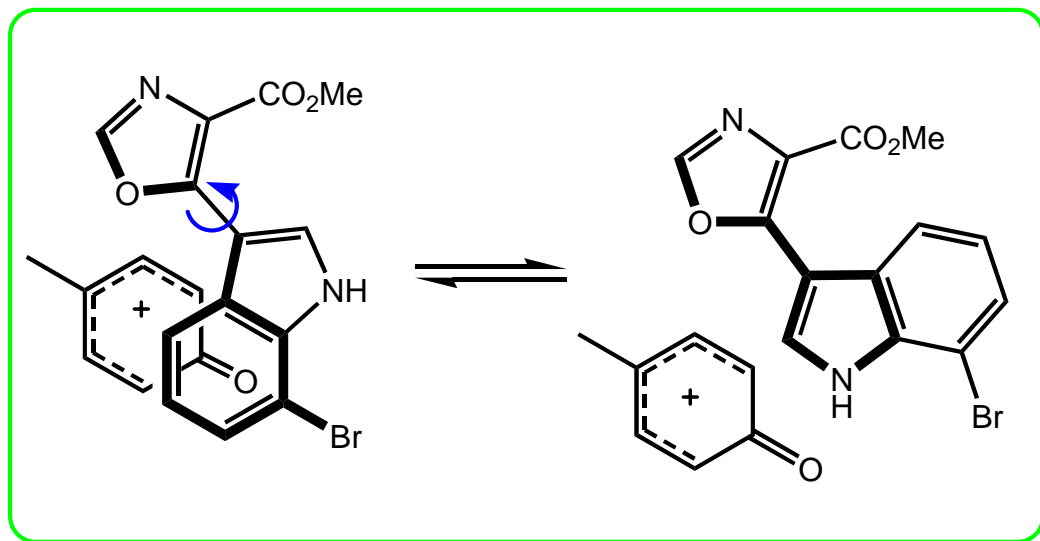
+

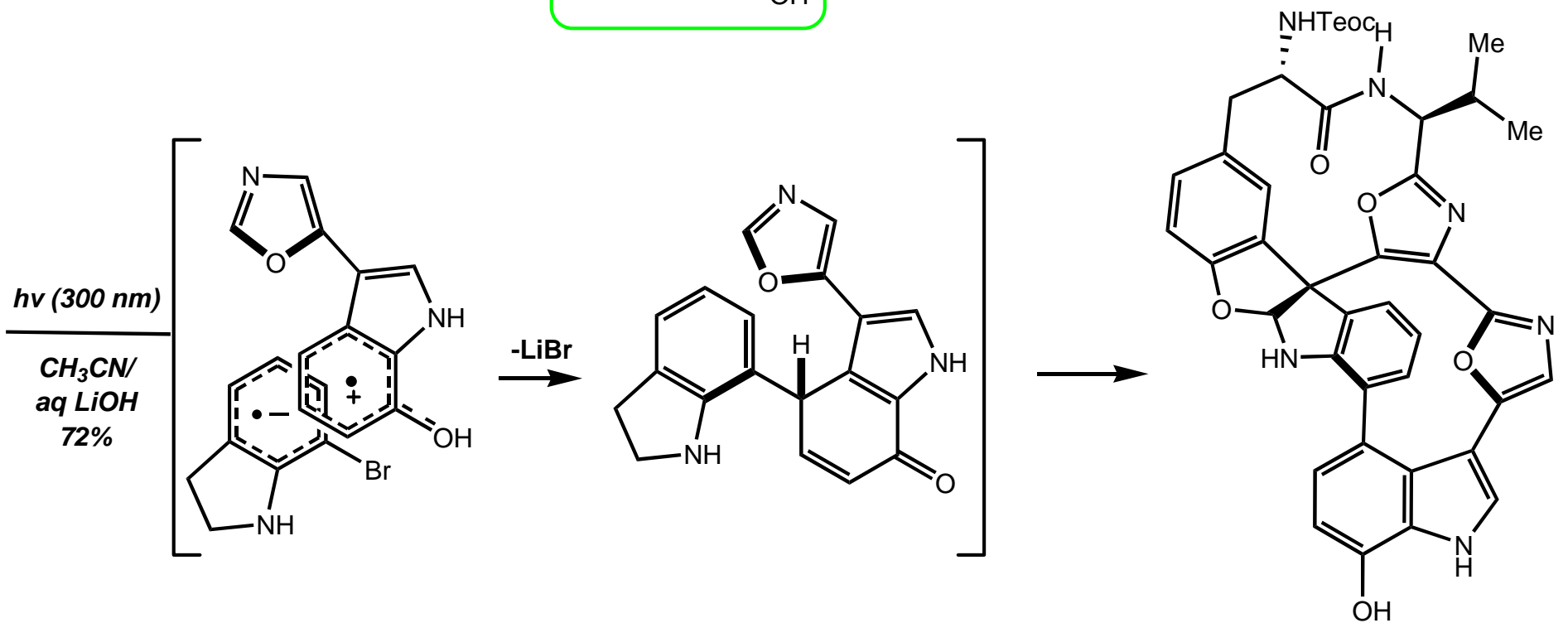
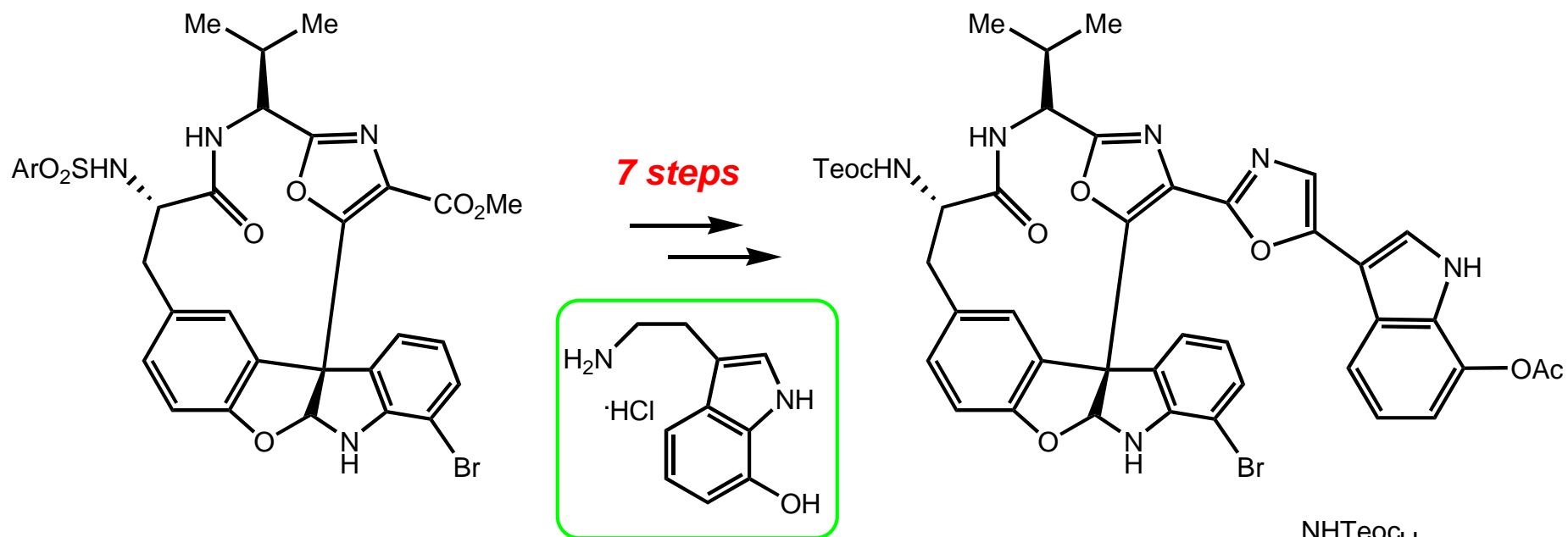






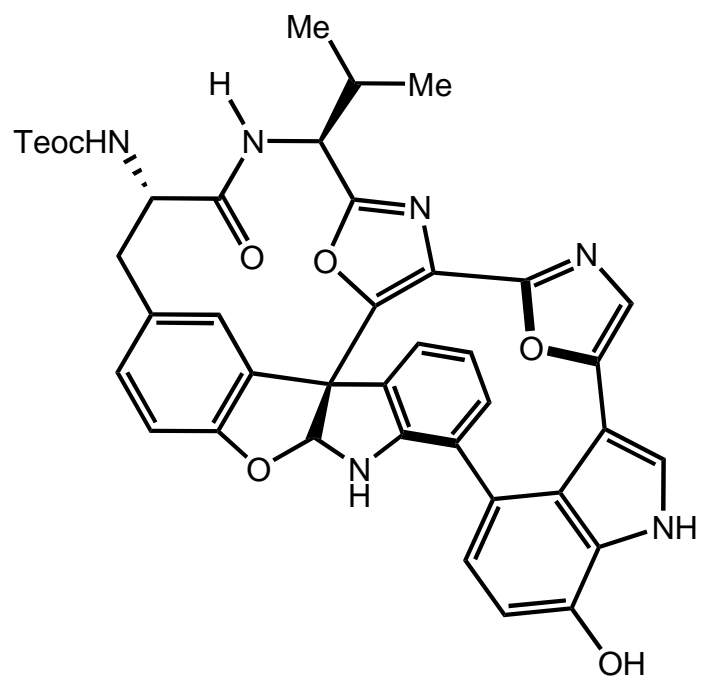
**3:1 dr**



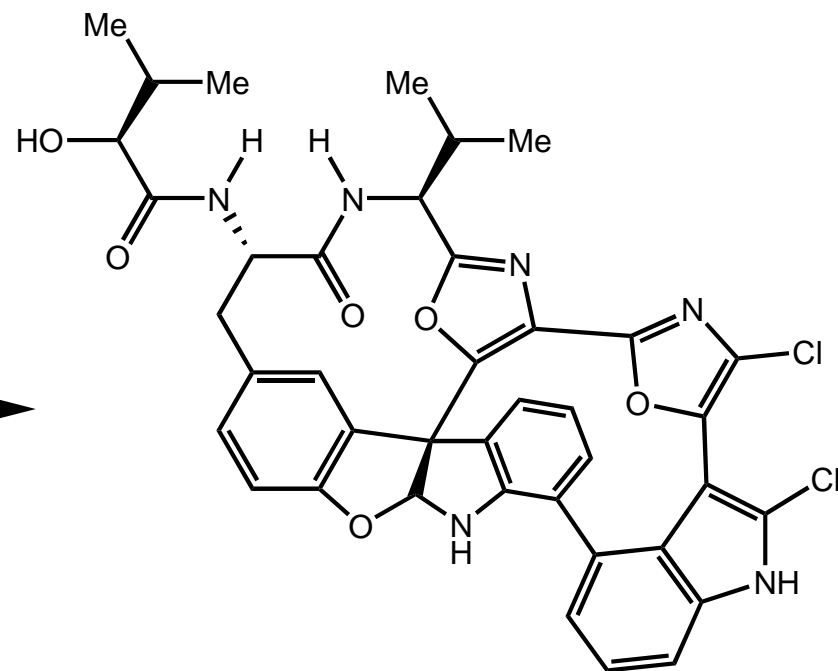


*single atropdiastereomer*

# Completion of *Diazonamide A*



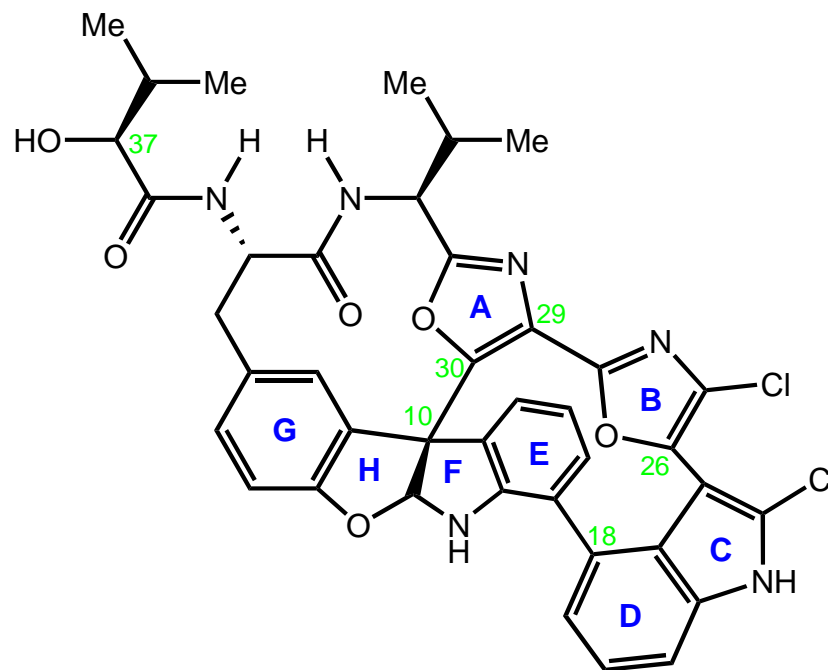
6 steps  
→  
→



***Diazonamide A***

19 steps  
.01 % overall yield

# Summary



**Nicolaou I**  
**2002**

**24 steps**

**$3.98 \times 10^{-4}$  % overall yield**

**Nicolaou II**  
**2003**

**31 steps**

**$1.44 \times 10^{-4}$  % overall yield**

**Harran**  
**2003**

**19 steps**

**.01 % overall yield**