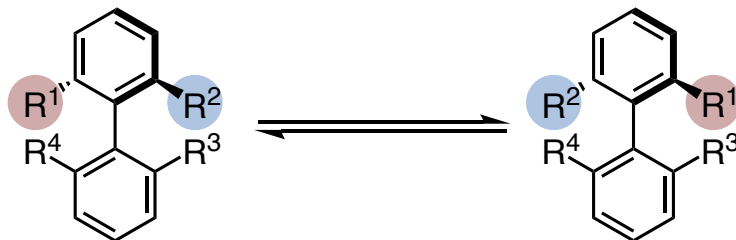


Atroposelective Syntheses of Natural Products: Synthesis of Diazonamide A

Jen Crawford
Synthesis Club
07/31/2018

Axial Chirality



0 – 20 kcal/mol

20 – 30 kcal/mol

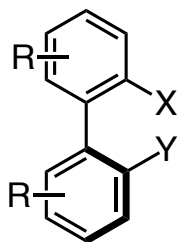
>30 kcal/mol

Free rotation

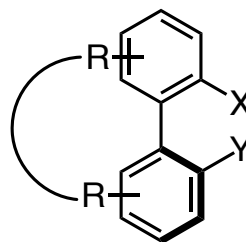
Atropisomers
(interconversion)

Atropisomers
(no interconversion)

Two major classes

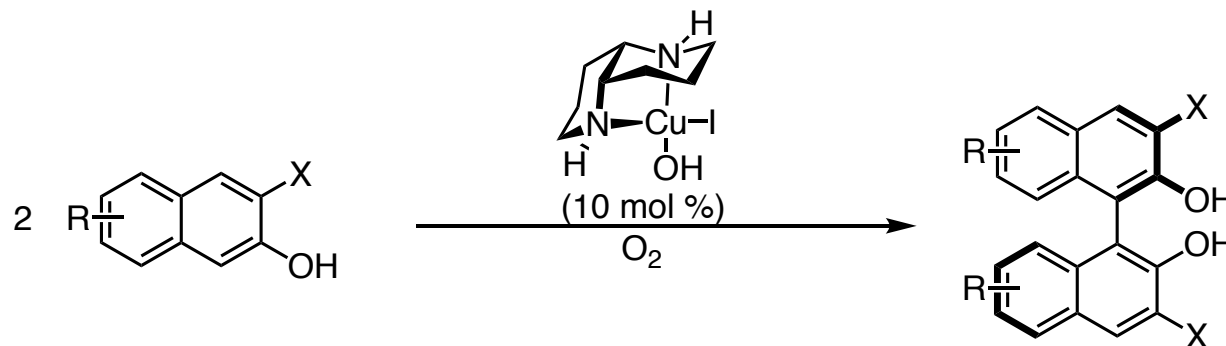
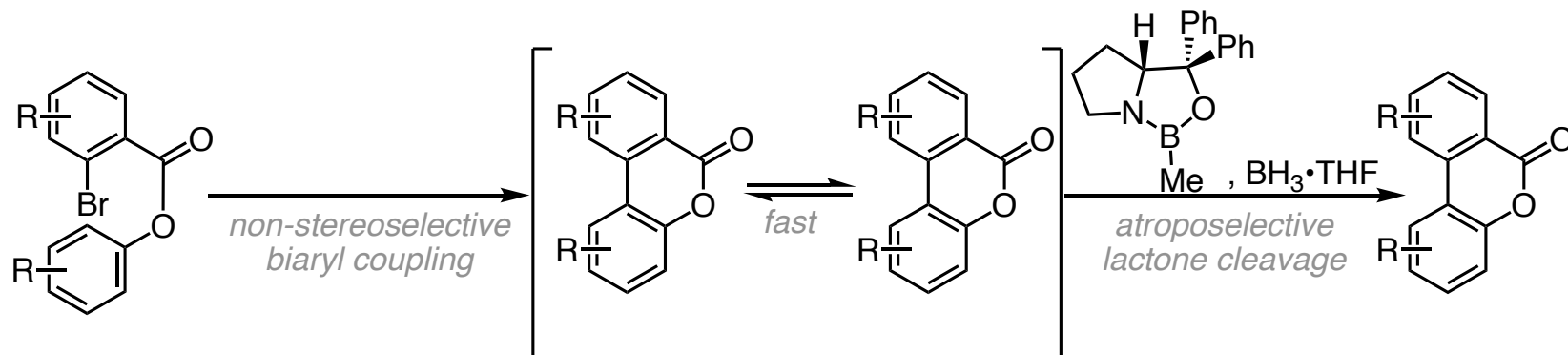
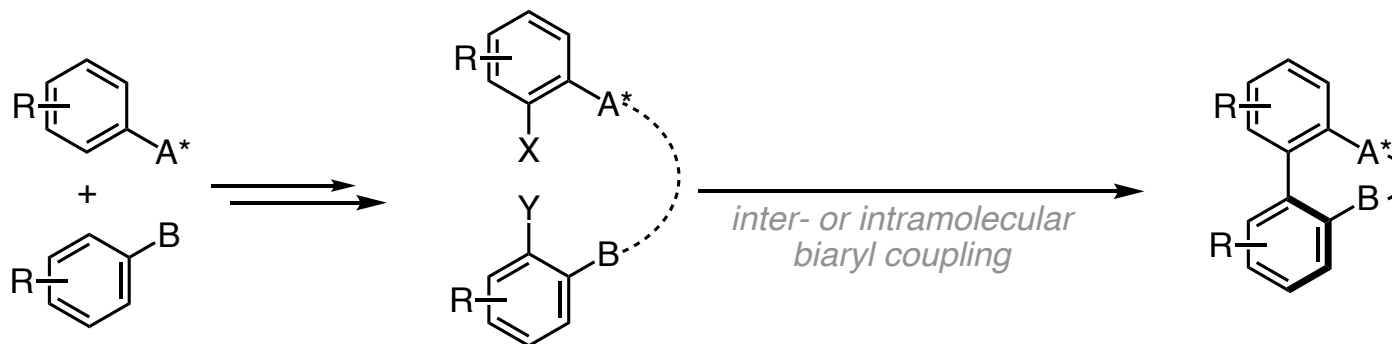


*non bridged axially chiral
biaryl natural products*



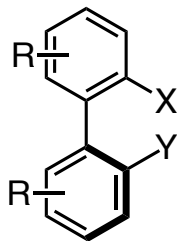
*bridged axially chiral
biaryl natural products*

Methods to Set Biaryl Atropaxes

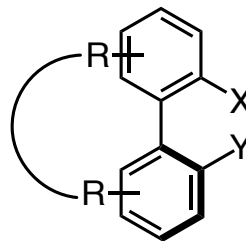


Atropaxes in Biaryl Natural Products

Two major classes



*non bridged axially chiral
biaryl natural products*

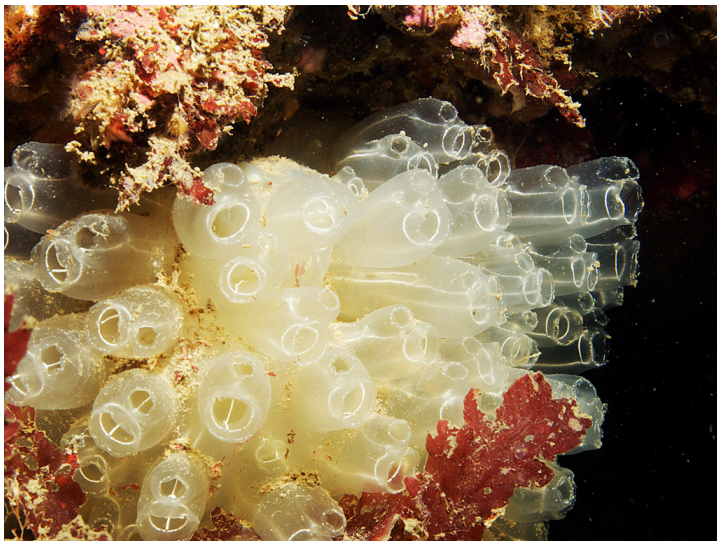


*bridged axially chiral
biaryl natural products*

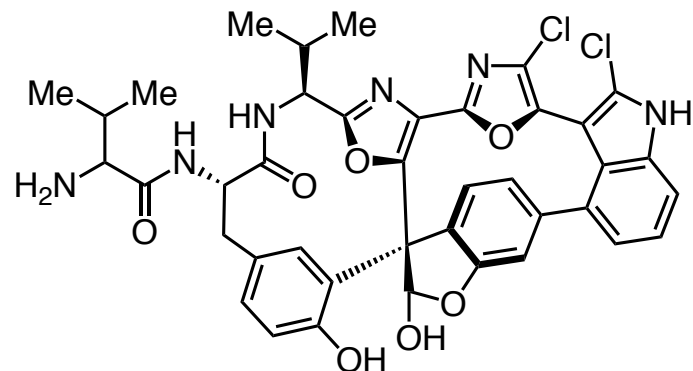
Synthetic Challenges

- Interconversion through rotation, not through bond breaking/making
- Challenging stereochemistry to set
- Frequently accompanies rigid, complex natural products

Diazonamide A



Original structure



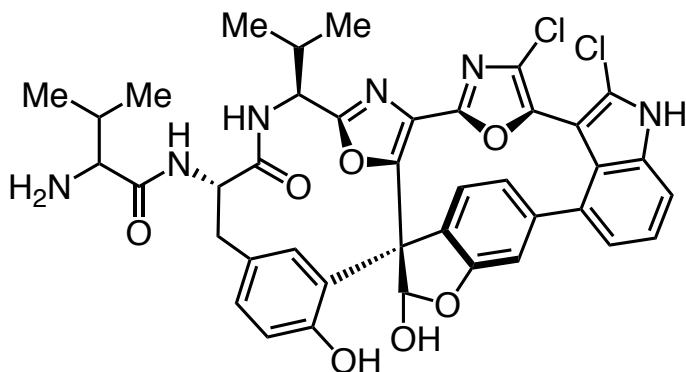
Isolated from *Diazona angulata*
Assigned in 1991 by Clardy & Fenical

Bioactivity

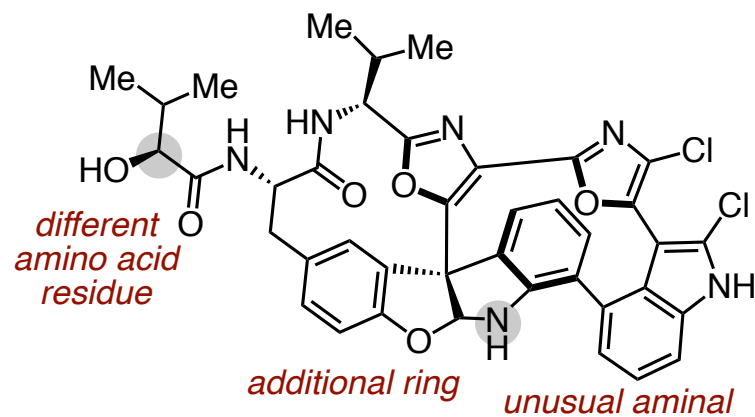
- Unusual antitumor activity, inhibits development of mitotic spindle
- Useful in cases where taxol-resistance has developed because different MOA
- Receptor is ornithine δ -amino-transferase $\rightarrow$ cancer selective therapeutic agent

Diazonamide A

Original structure



Revised structure

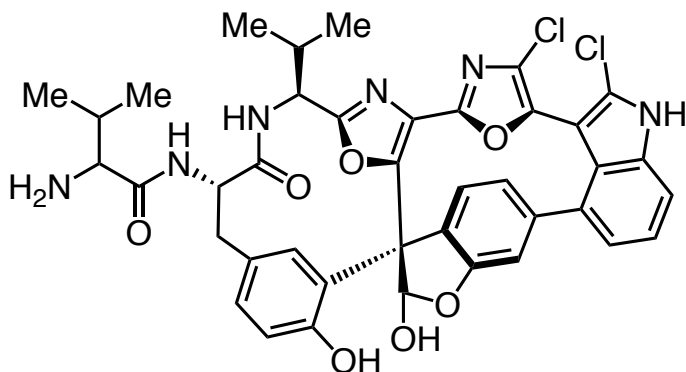


Synthetic Challenges

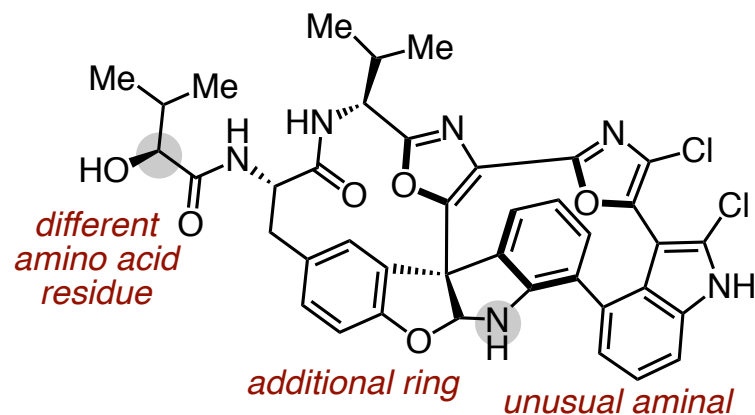
- Quaternary stereocenter at C10, joining two macrocycles
- Large degree of unsaturation
- Rigid framework, atropaxis

Diazonamide A

Original structure



Revised structure

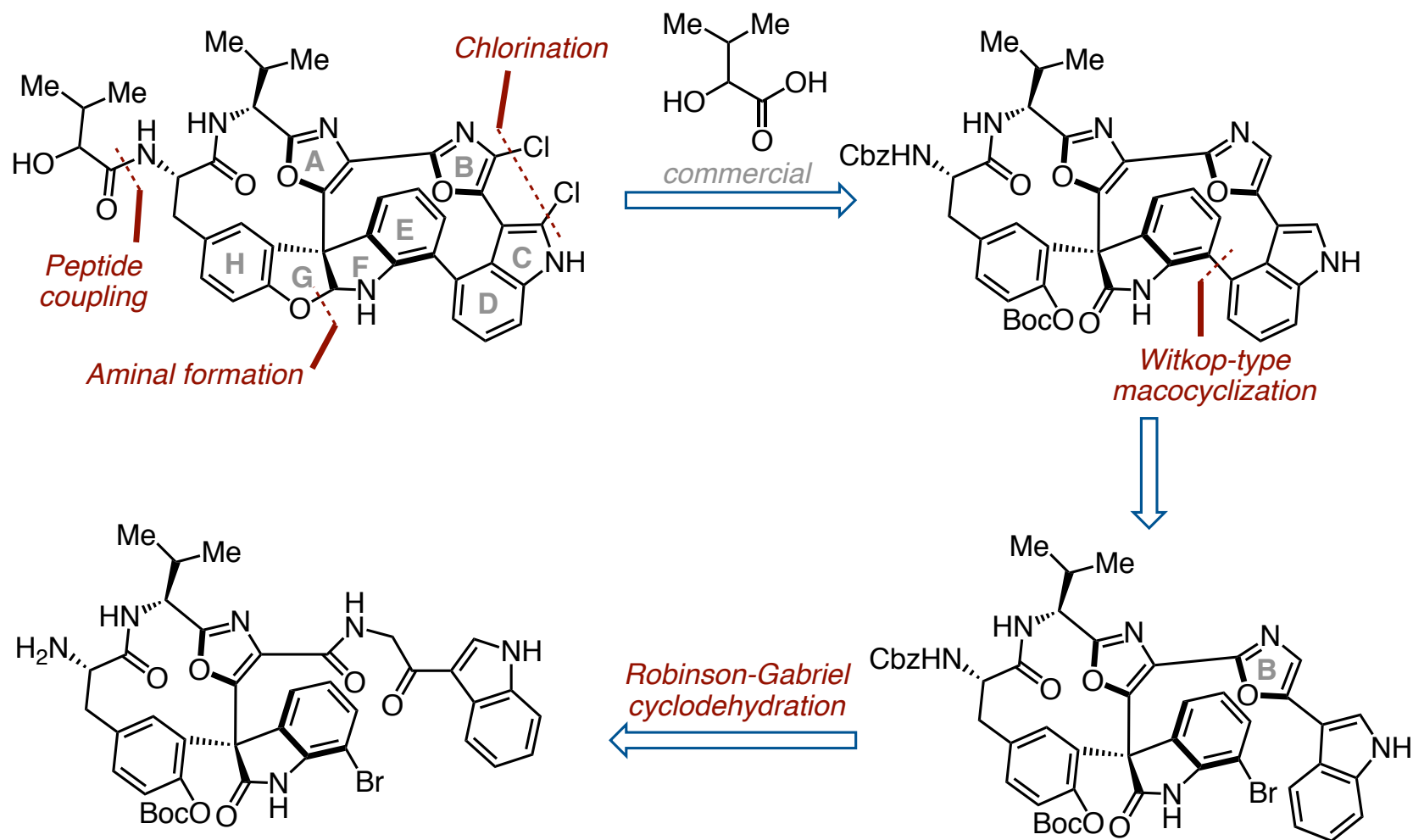


Successful Total Syntheses

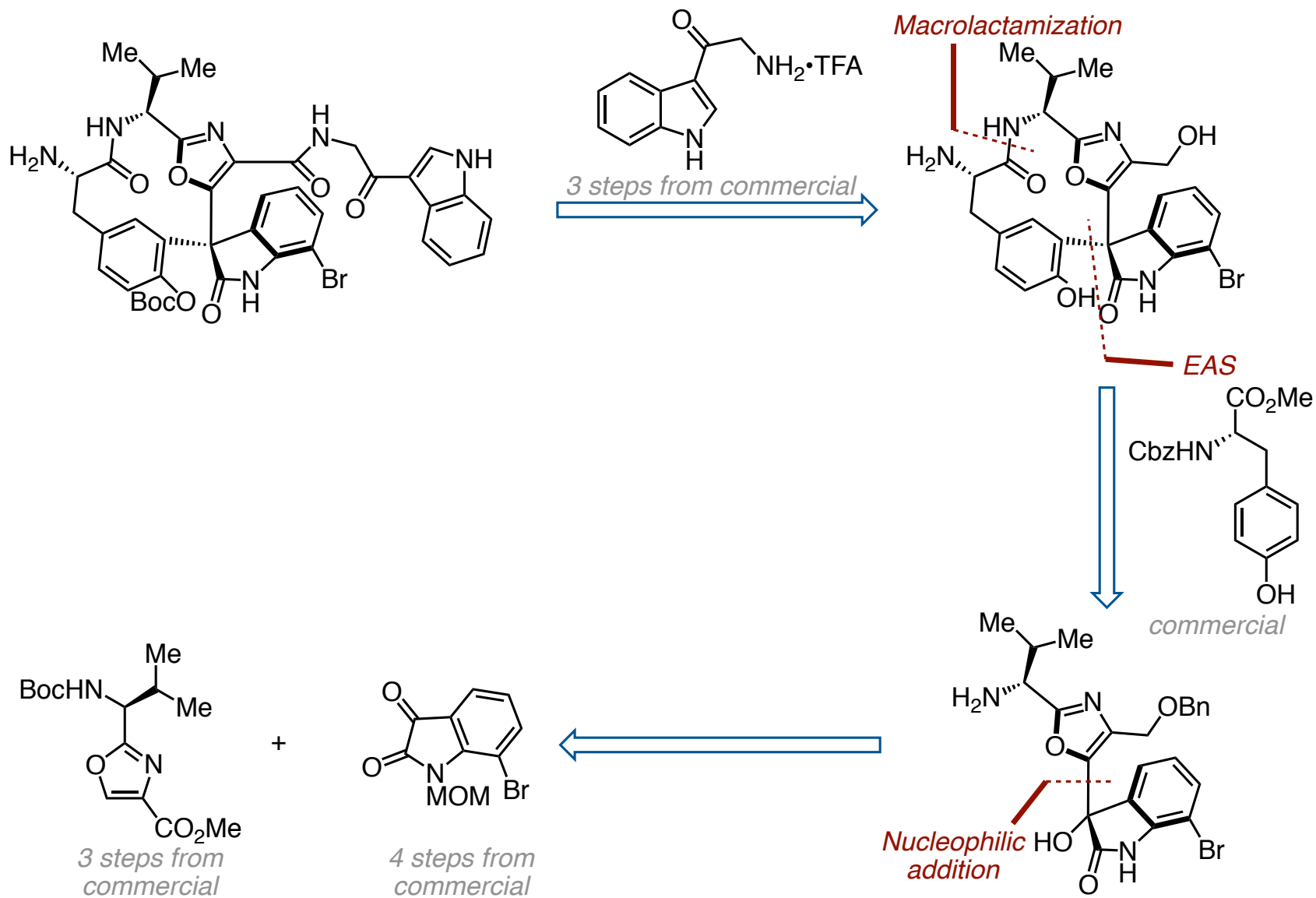
- One total synthesis of original structure (Harran)
- Four total syntheses of revised structure (Harran, Nicolau, MacMillan)
- Two formal syntheses (Magnus, Sammakia)

Harran and coworkers *Angew. Chem. Int. Ed.* **2001**, *40*, 4765. Harran and coworkers, *Angew. Chem. Int. Ed.* **2003**, *42*, 4961.
Nicolau and coworkers *J. Am. Chem. Soc.* **2004**, *126*, 12888; Nicolau and coworkers *J. Am. Chem. Soc.* **2004**, *126*, 12897.
Magnus and coworkers, *J. Am. Chem. Soc.* **2007**, *127*, 12320. Sammakia and coworkers *Angew. Chem. Int. Ed.* **2010**, *49*, 2397.
Knowles, R. et al. *Chem. Soc.* **2011**, *2*, 308.

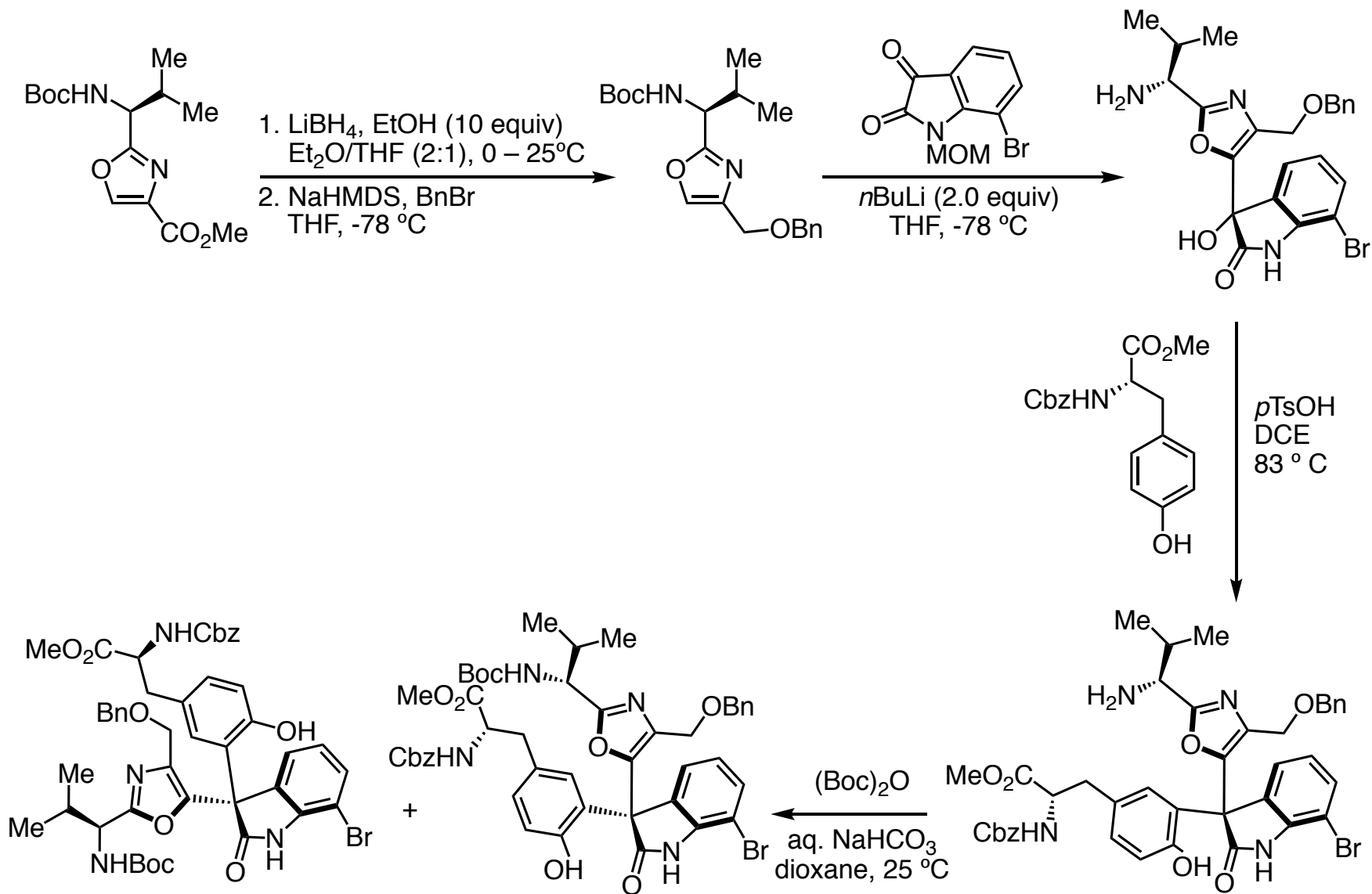
Retrosynthesis



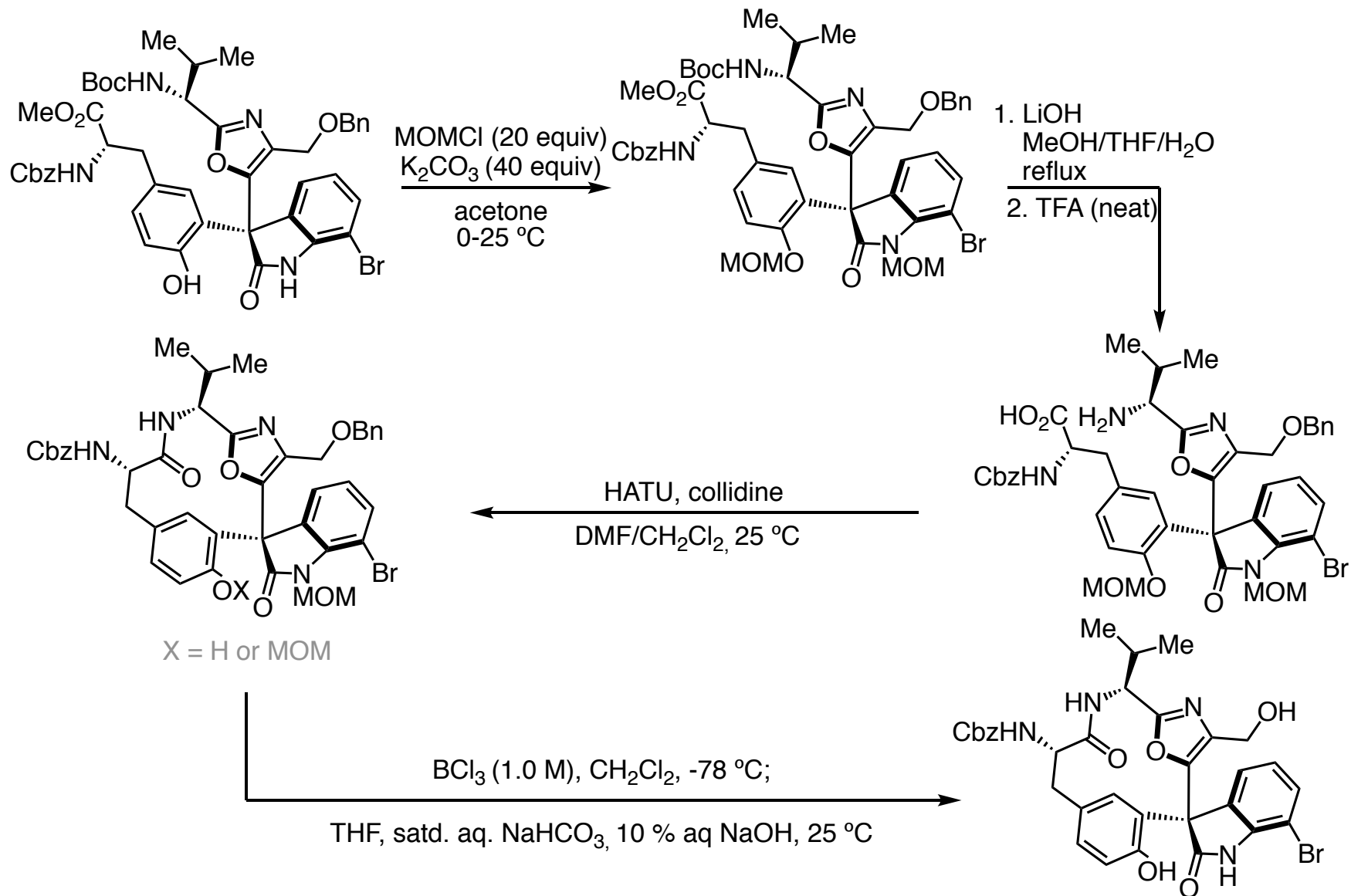
Retrosynthesis



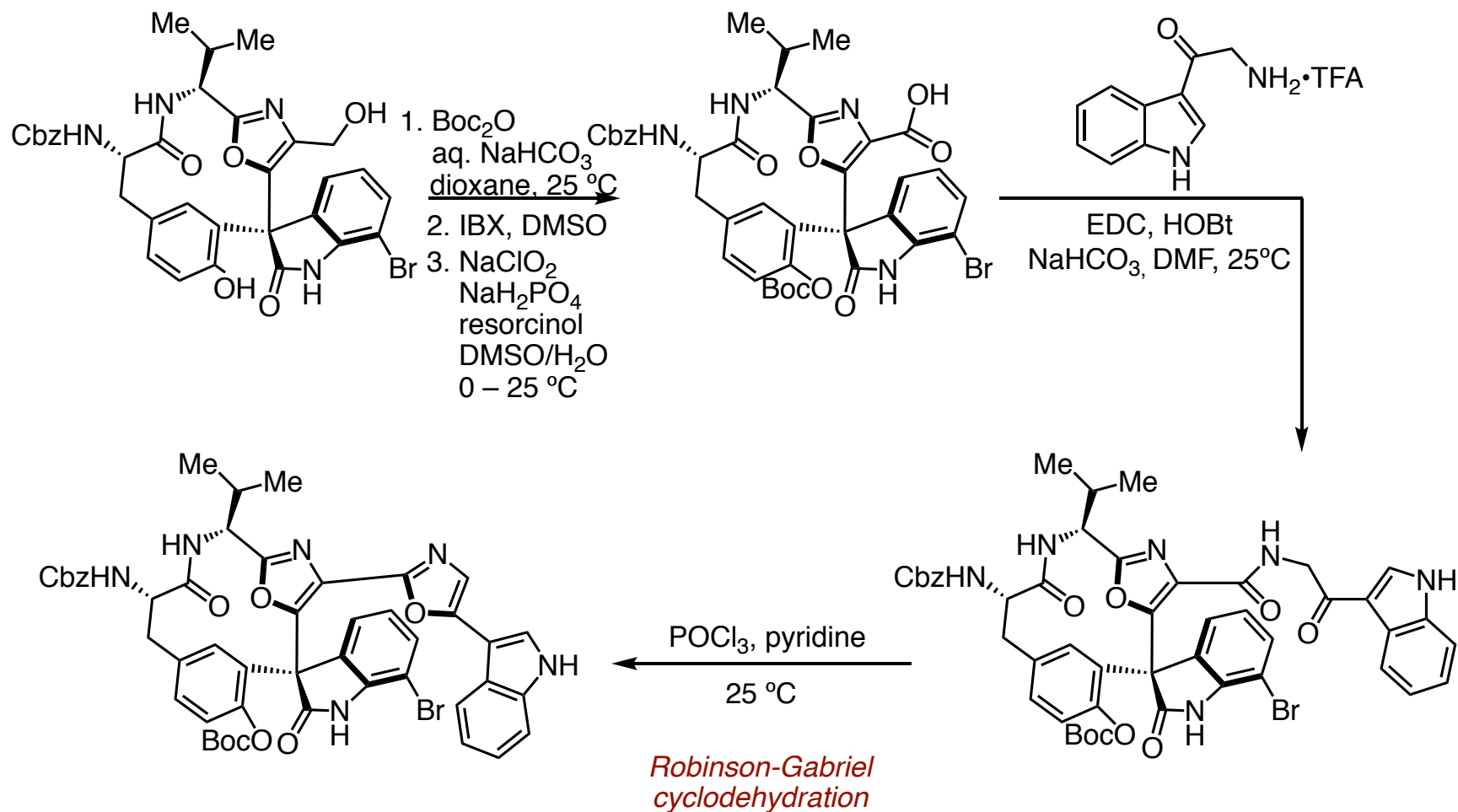
Nicolau's First Synthesis of Diazonamide A



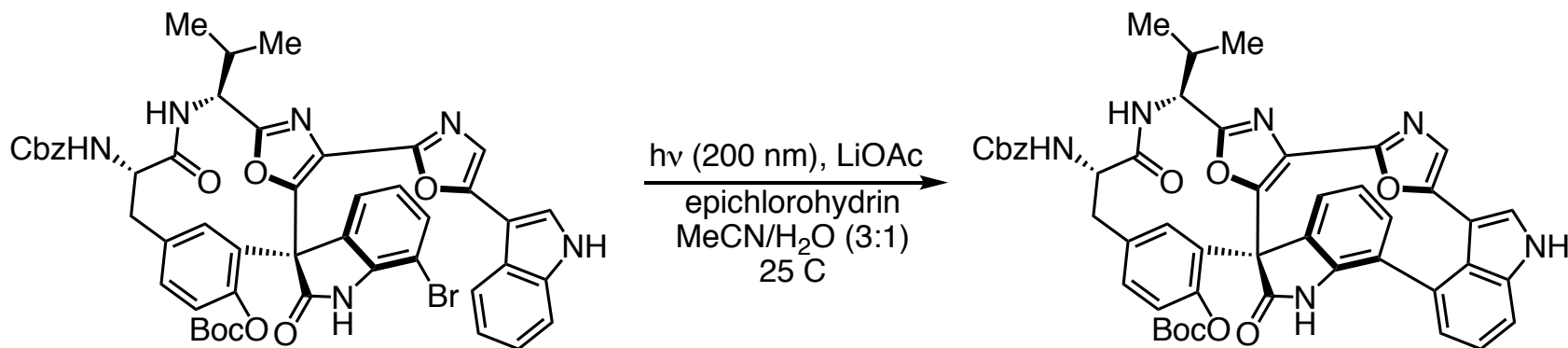
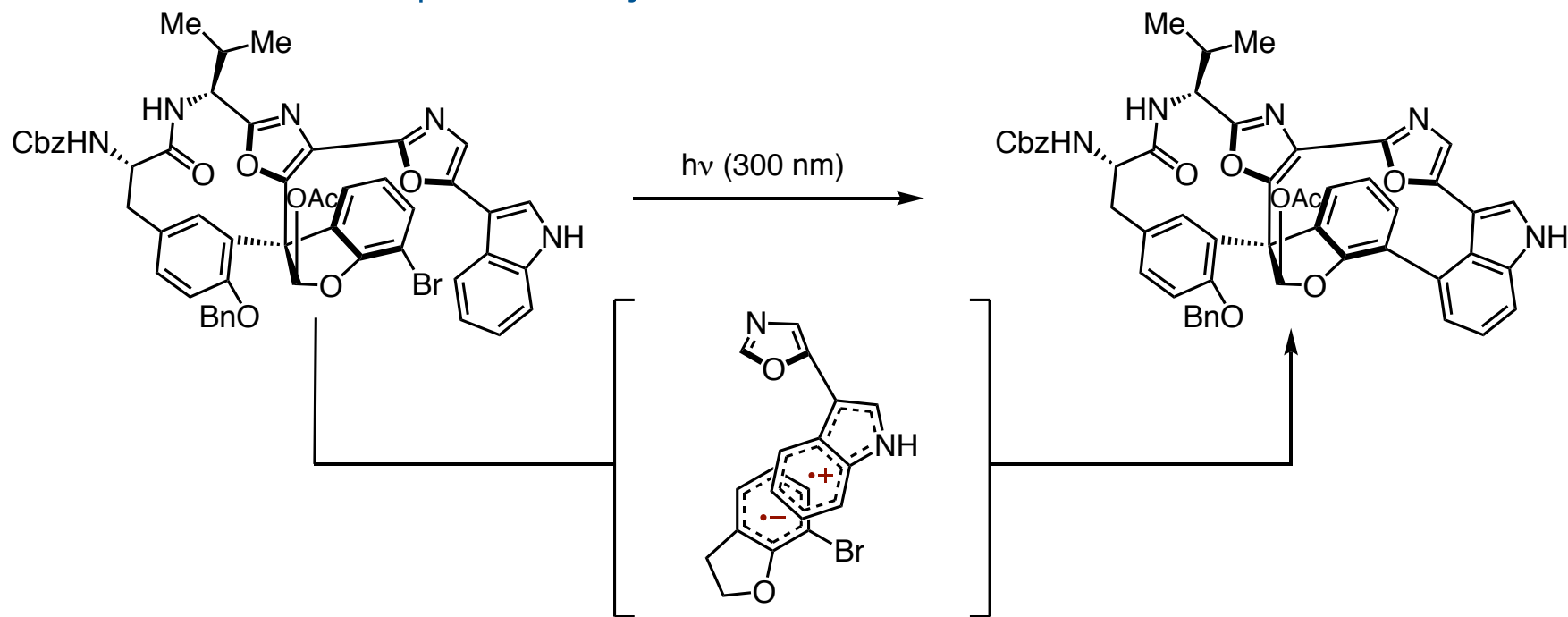
Nicolau's First Synthesis of Diazonamide A



Nicolau's First Synthesis of Diazonamide A



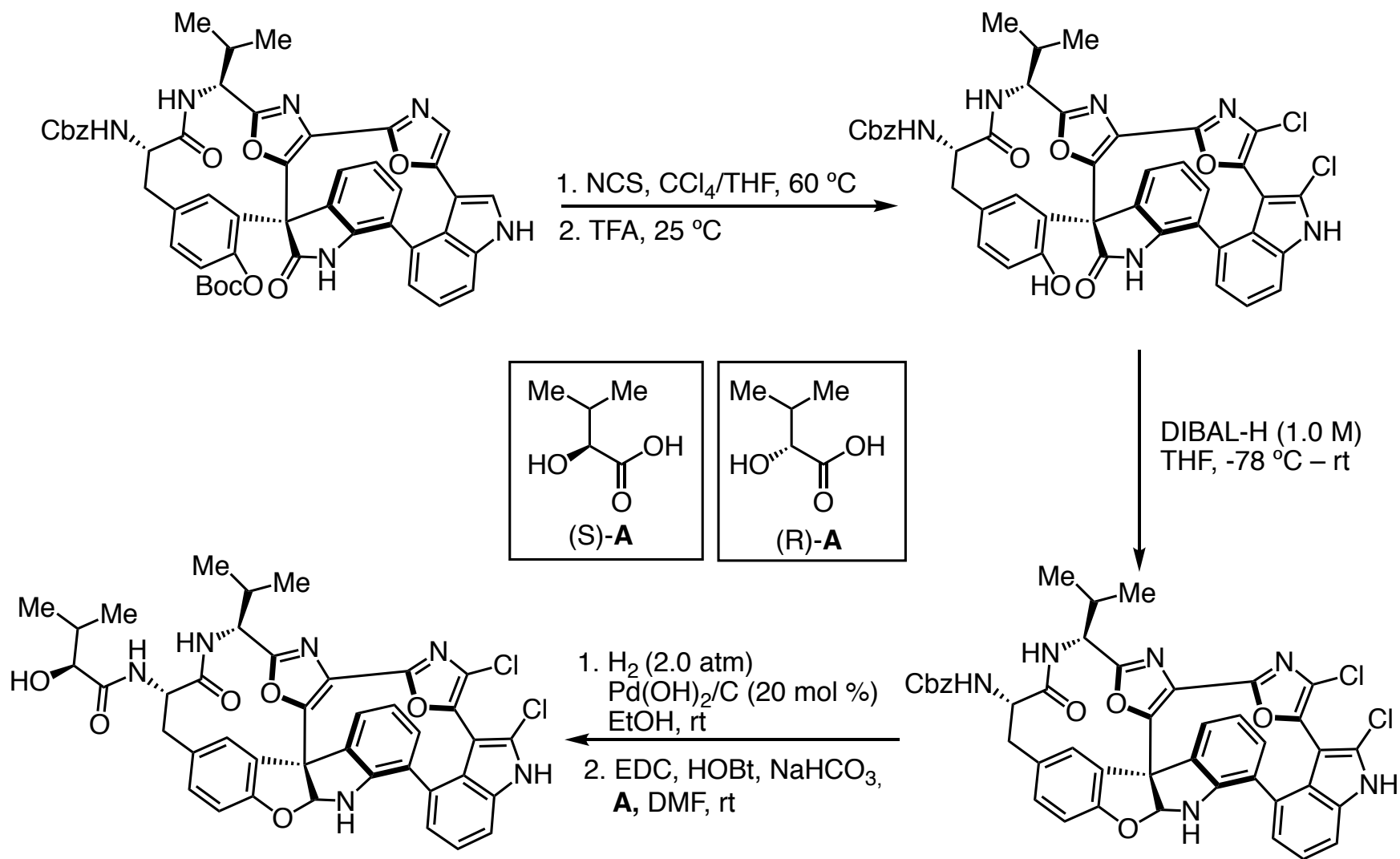
Witkop Photocyclization – Harran Precedent



Harran and coworkers *Angew. Chem. Int. Ed.* **2001**, *40*, 4765.

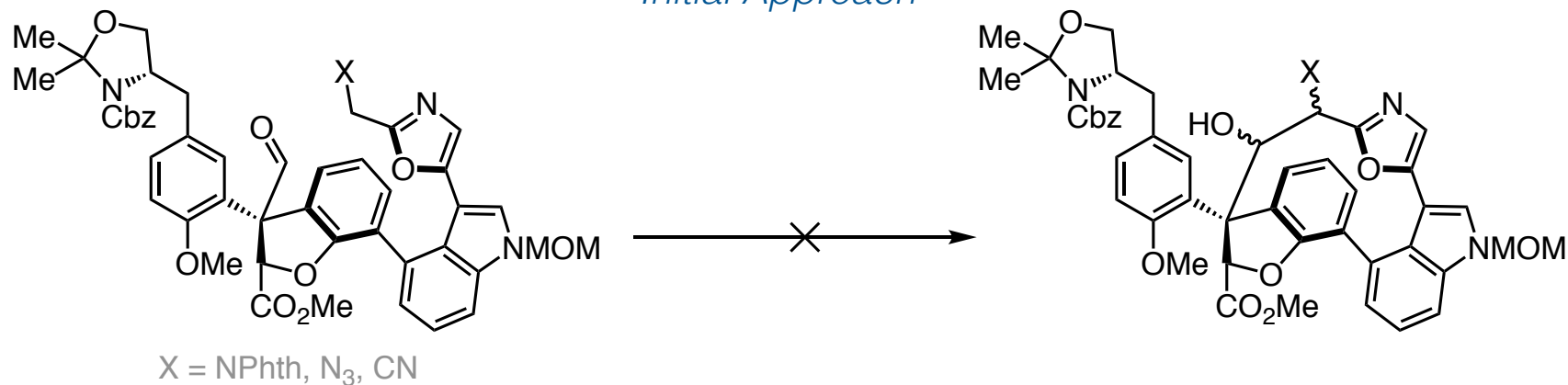
Nicolau and coworkers *J. Am. Chem. Soc.* **2004**, *126*, 12888.

Nicolau's First Synthesis of Diazonamide A

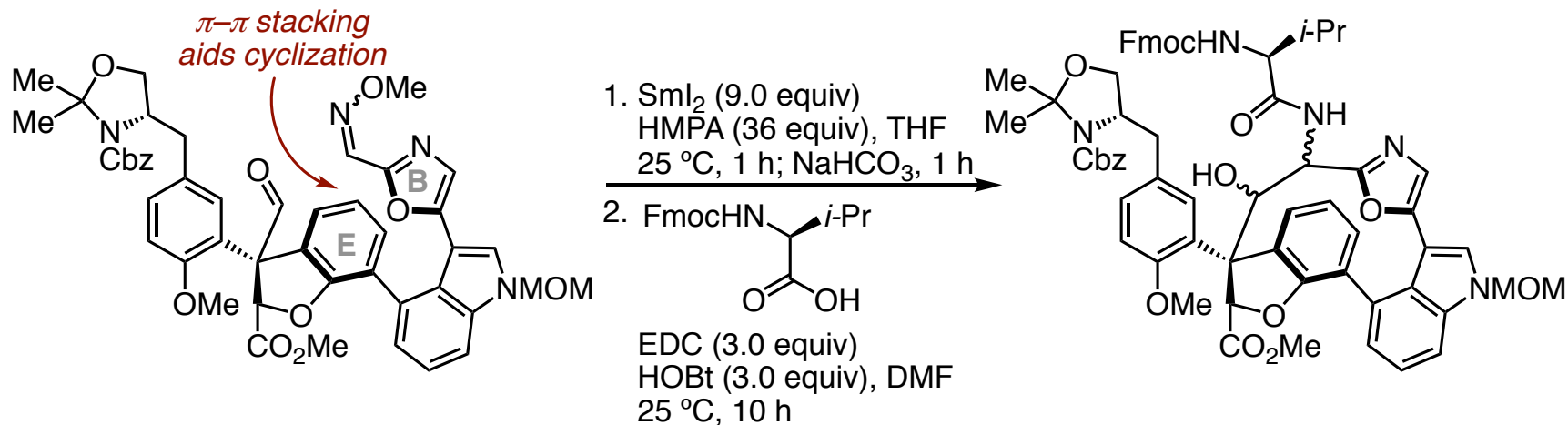


Methodology Developments - Macrocyclization

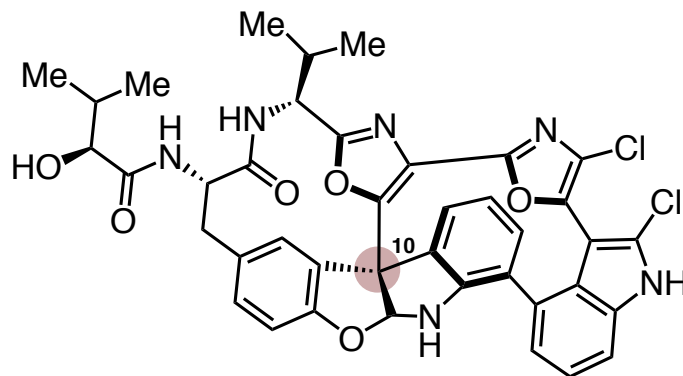
Initial Approach



Hetero-Pinacol Macrocyclization Cascade

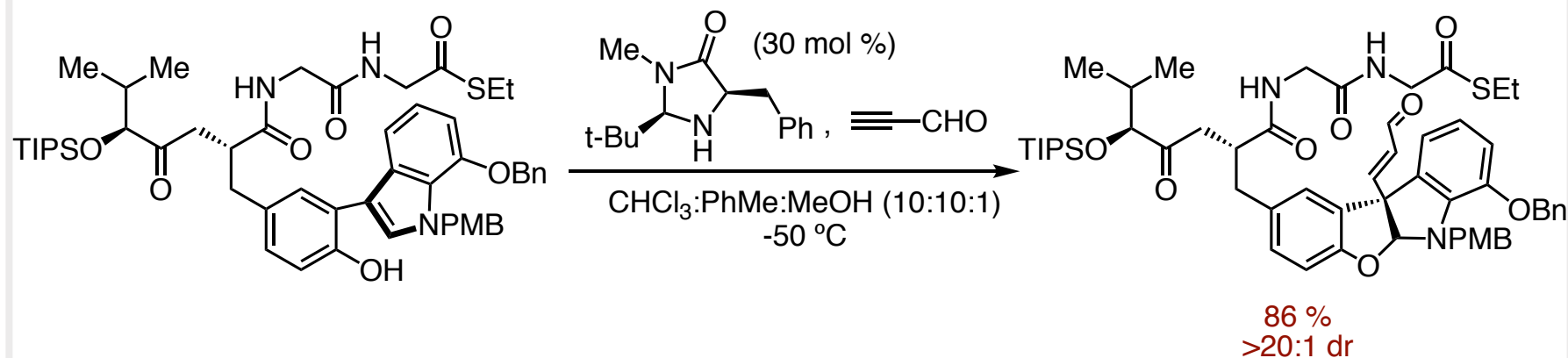


Methodology Application - C10 Quaternary Stereocenter



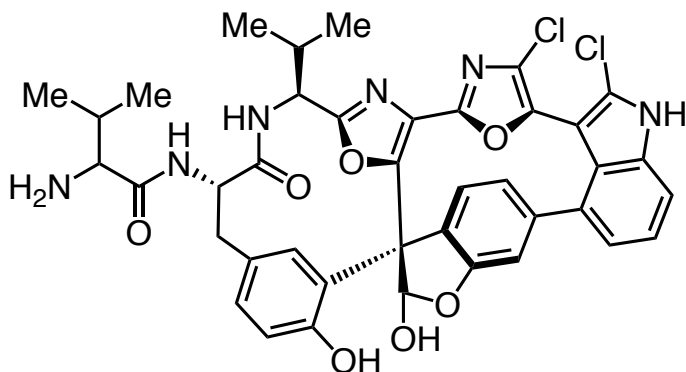
- C10 quaternary stereocenter = significant challenge
- Previous approaches had poor stereocontrol

Asymmetric Iminium Organocatalysis

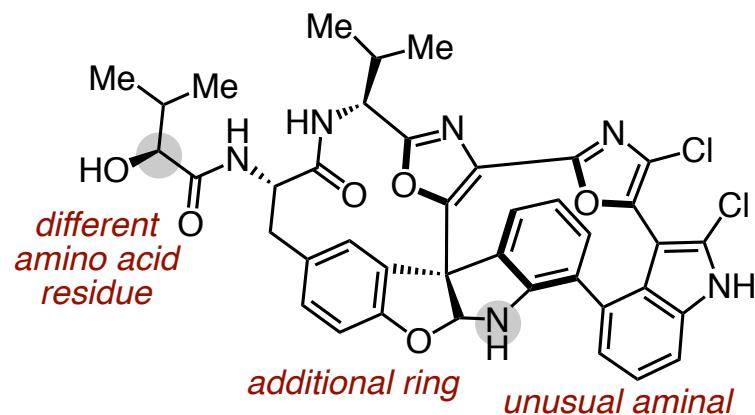


Conclusion

Original structure



Revised structure



- Total synthesis (Harran and coworkers) revealed an incorrect natural product assignment
- Atropaxes in natural products can complicate the synthesis/generate unusual synthetic targets
- New methodology developed to address synthetic challenges posed by diazonamide A