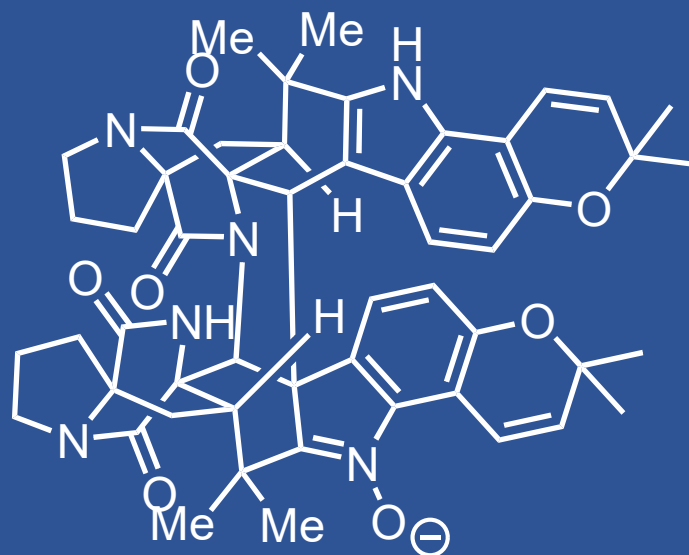


# Recent Highlights in Total Syntheses of Prenylated Indole Alkaloids

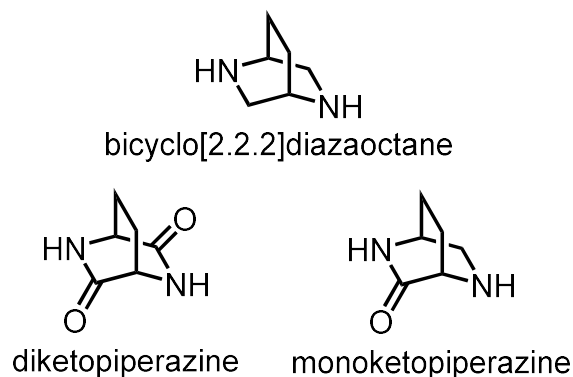
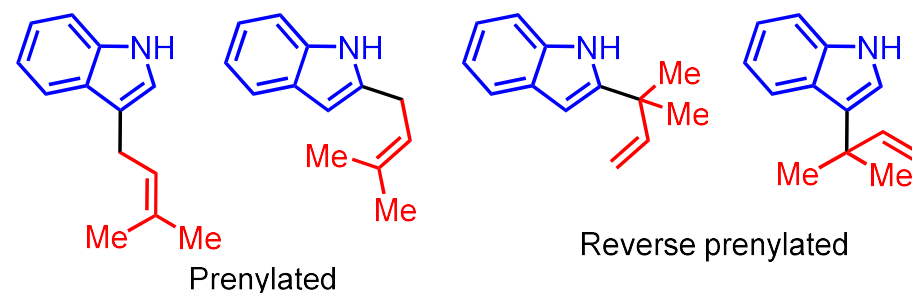
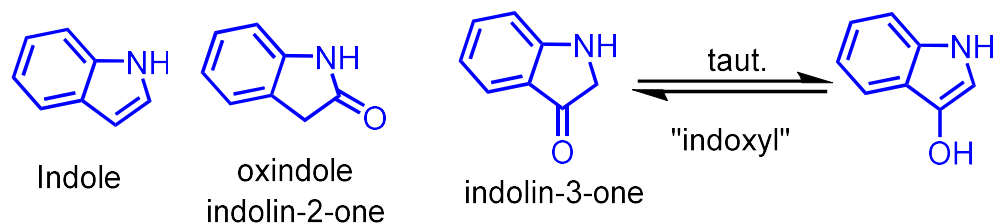
Emily Mumford

May 18, 2021

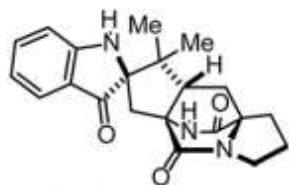


# Features of Prenylated Indole Alkaloids

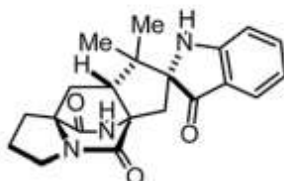
- Indole or derivative
- (vestiges of) prenyl group
- Diverse structures, diverse bioactivities
- Marine and terrestrial fungal secondary metabolites, commonly from genera *Aspergillus*, *Penicillium*, and *Malbranchea*
- Commonly contain a bicyclo[2.2.2]diazaoctene ring, either as a monoketopiperazine or diketopiperazine
- Over 8 families, 70 natural products within those containing a bicyclo[2.2.2]diazaoctane core



# Representative Examples of Prenylated Indole Alkaloids



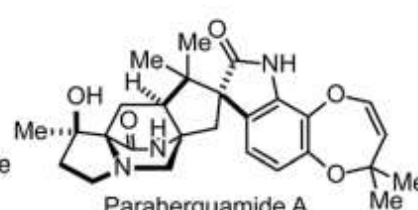
(+)-Brevianamide A  
*Penicillium brevicompactum*



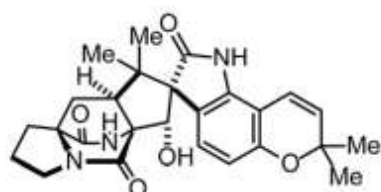
(+)-Brevianamide B  
*Penicillium brevicompactum*



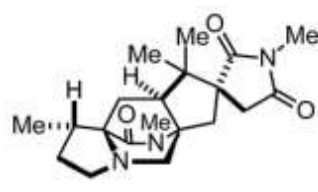
Marcfortine A  
*Penicillium roqueforti*



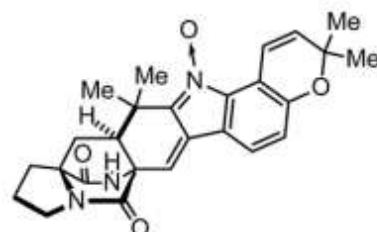
Paraherquamide A  
*Penicillium brasilianum*  
*Penicillium cluniae*



Sclerotiamide  
*Aspergillus sclerotiorum*  
*Aspergillus protuberus*



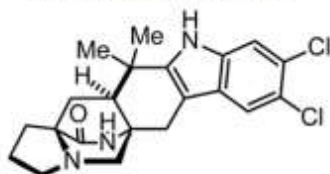
Asperparaline A  
*Aspergillus japonicus*



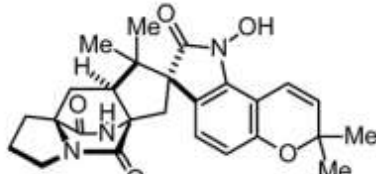
Avrainvillamide  
(CJ-17,665)  
*Aspergillus ochraceus*



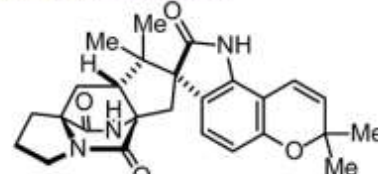
(+)-Stephacidin A  
*Aspergillus ochraceus*  
*Aspergillus protuberus*



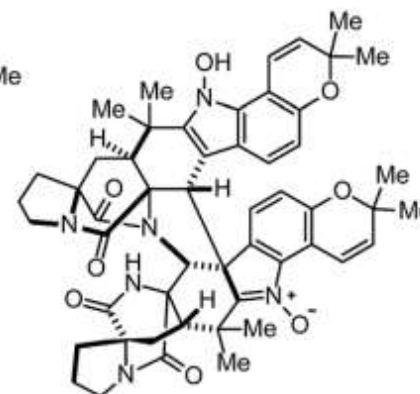
(+)-Malbrancheamide  
*Malbranchea aurantiaca*  
*Malbranchea graminicola*



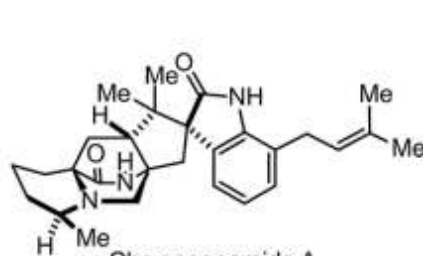
(-)-Notoamide A  
*Aspergillus protuberus*



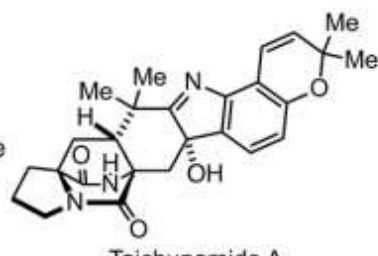
(+)-Versicolamide B  
*Aspergillus amoenus*  
*Aspergillus protuberus*  
*Aspergillus taichungensis*



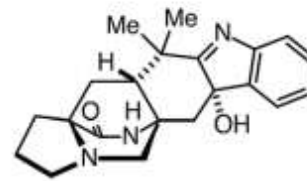
(-)-Stephacidin B  
*Aspergillus ochraceus*



Chrysogenamide A  
*Penicillium chrysogenum*

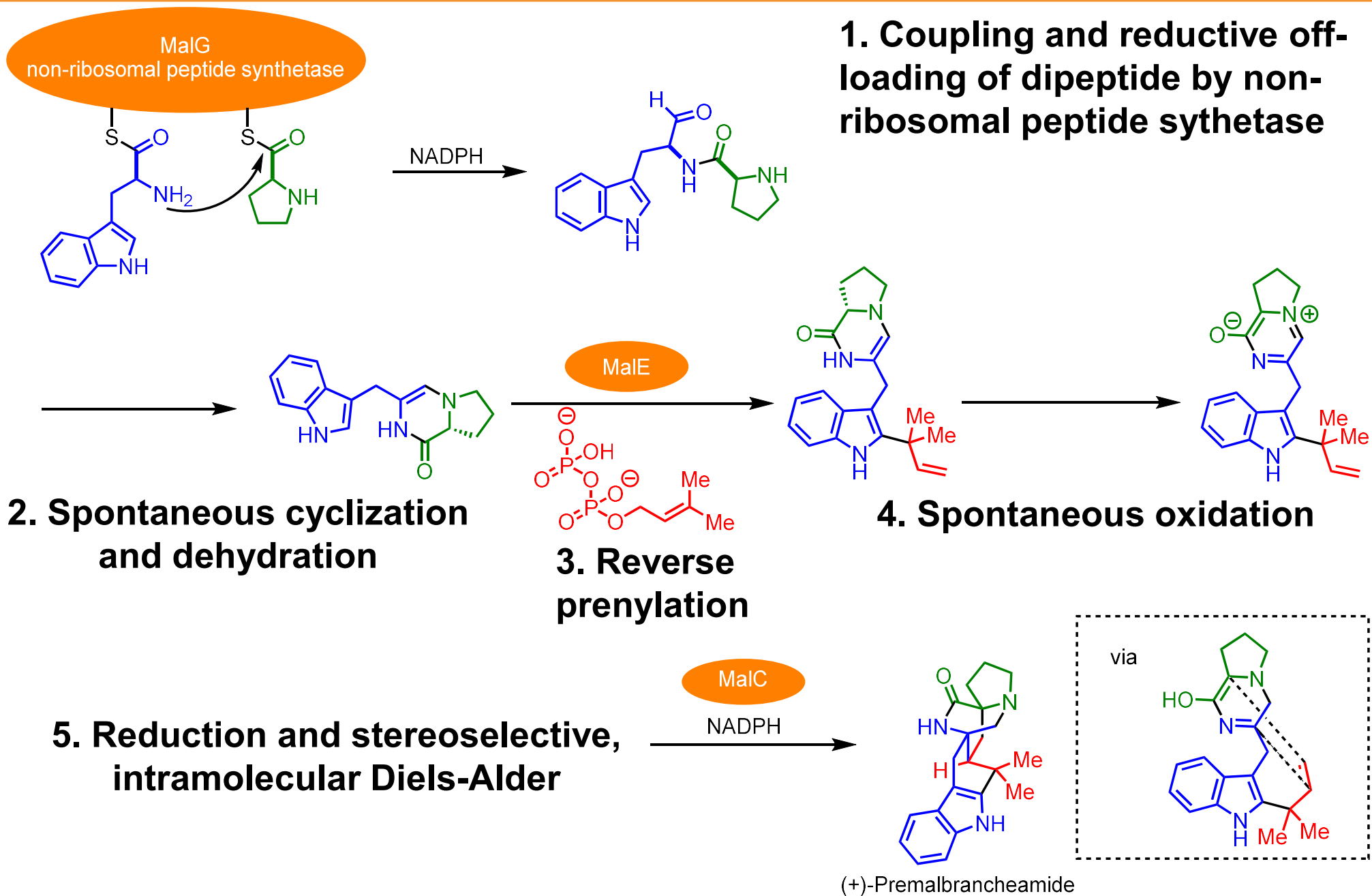


Taichunamide A  
*Aspergillus taichungensis*

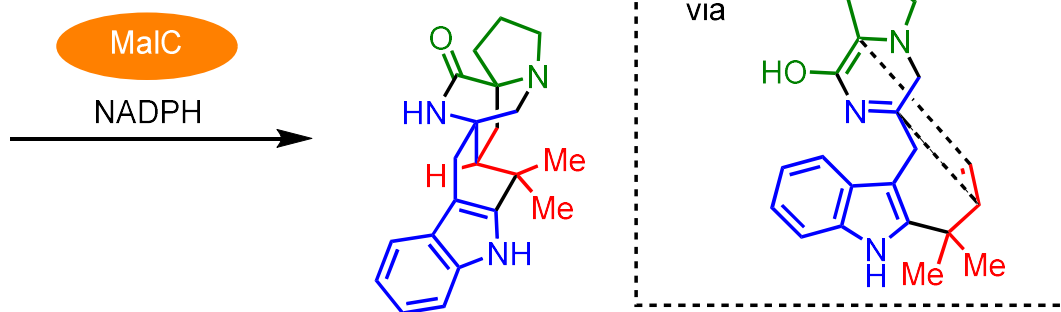
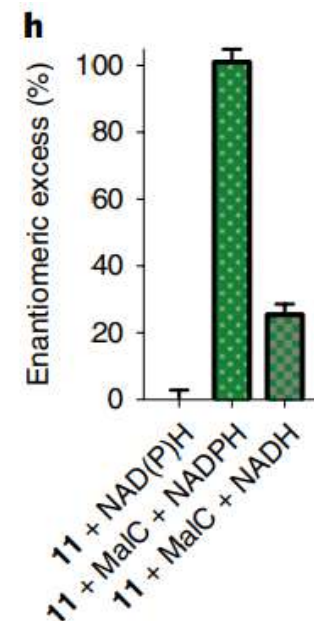
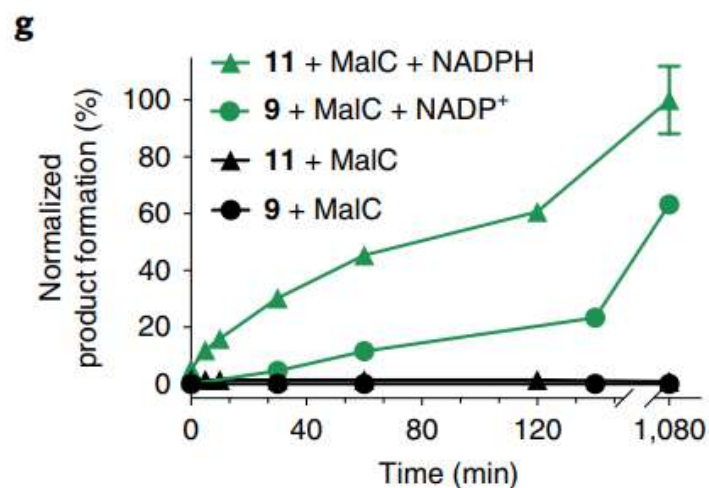
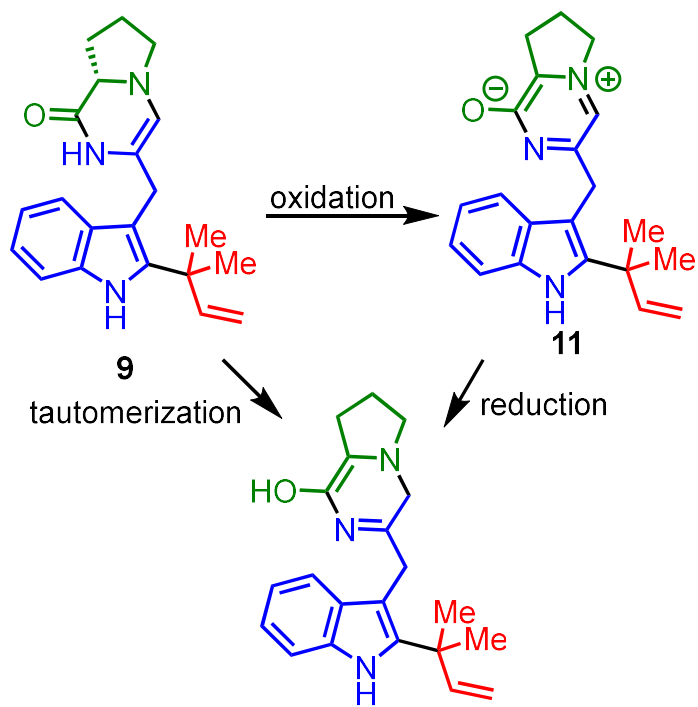


Penicimutamide D  
*Penicillium purpurogenum* G59

# A Case Study in Biosynthesis: Premalbrancheamide



# MaIC: A Bifunctional, Stereoselective Diels-Alderase

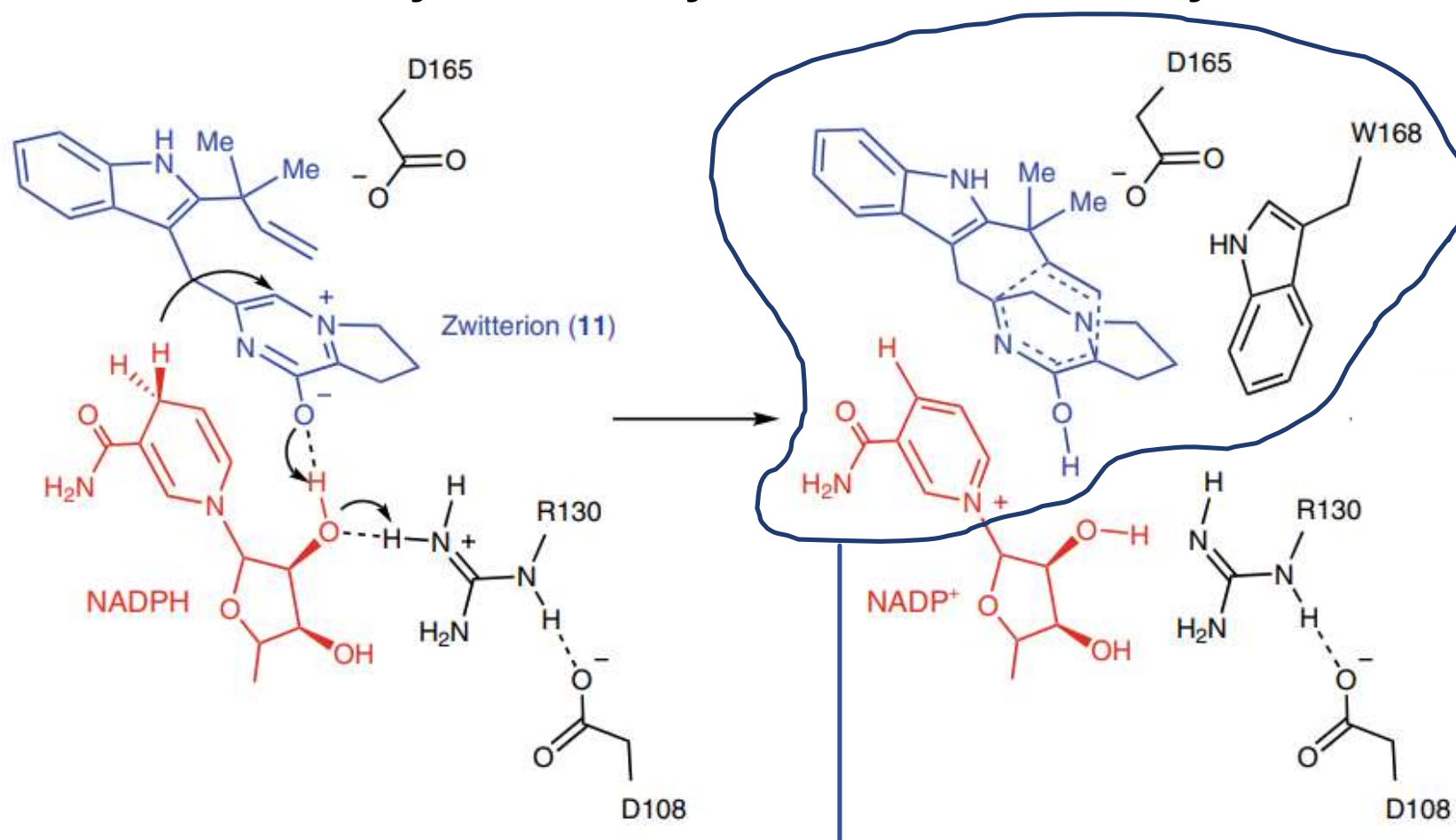


**Zwitterionic intermediate is the optimal substrate for MaIC (g) and enantioselectivity is reductant-dependent (h)**

**Reduction and cycloaddition both occur in the same active site**

# MalC: A Bifunctional, Stereoselective Diels-Alderase

Site-directed mutagenesis revealed which residues were key to reactivity and enantioselectivity



Close packing restricts azadiene conformation

# Key Contributors and Syntheses Covered



**Robert M. Williams (1953-2020)**  
Colorado State University  
*Bioinspired syntheses*

*Radiolabeled feeding experiments  
probing biosynthetic origins*



**Richmond Sarpong**  
University of California, Berkeley  
*Diversity-oriented syntheses*

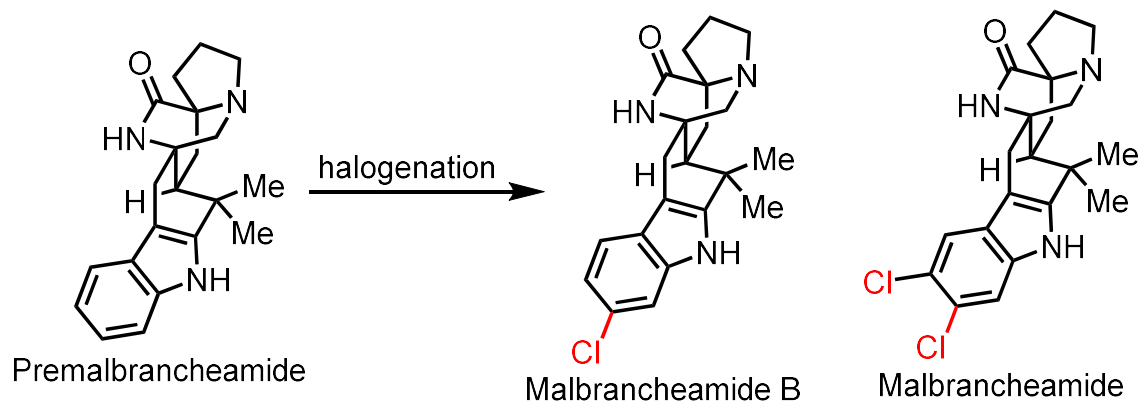
Also highlighted in this presentation:

- **Andrew Lawrence**  
(brevianamide A)
- **Andrew Myers**  
(stephacidin B and avrainvillamide)
- **Deqian Sun and Chaozhong Li**  
(Notoamides and Sclerotiamide)
- **Phil Baran**  
(Avrainvillamide)
- **Nigel Simpkins**  
(malbrancheamide B)



# SYNTHESIS BY DIELS-ALDER CYCLIZATION

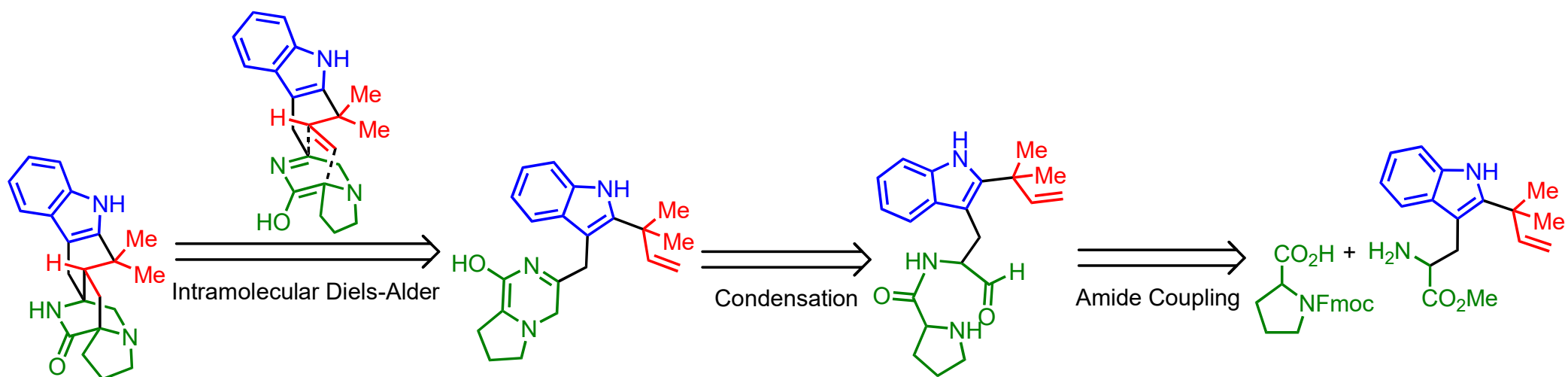
# Premalbranchamide



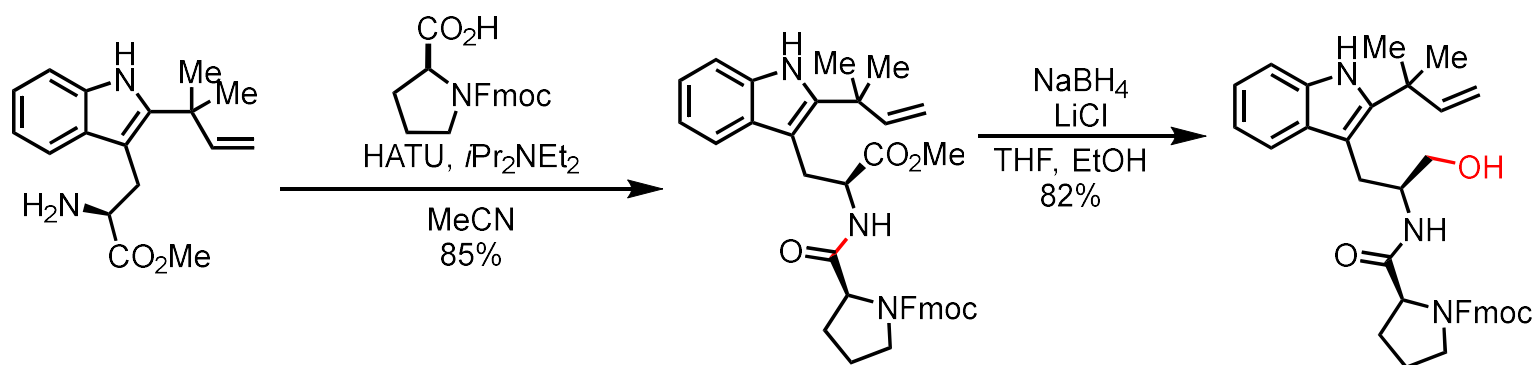
- Biosynthetic precursor to halogenated malbranchamide and malbranchamide B (determined by synthesis of isotopically labeled compound and feeding studies)
- Metabolites from *Malbranchea aurantiaca*, a fungus isolated from bat detritus from a cave in Mexico
- Synthesis by Williams supports biosynthetic hypothesis of a “protected” oxidized resting state that after reduction undergoes [4+2] cyclization

# Synthesis by Diels-Alder: Premalbrancheamide

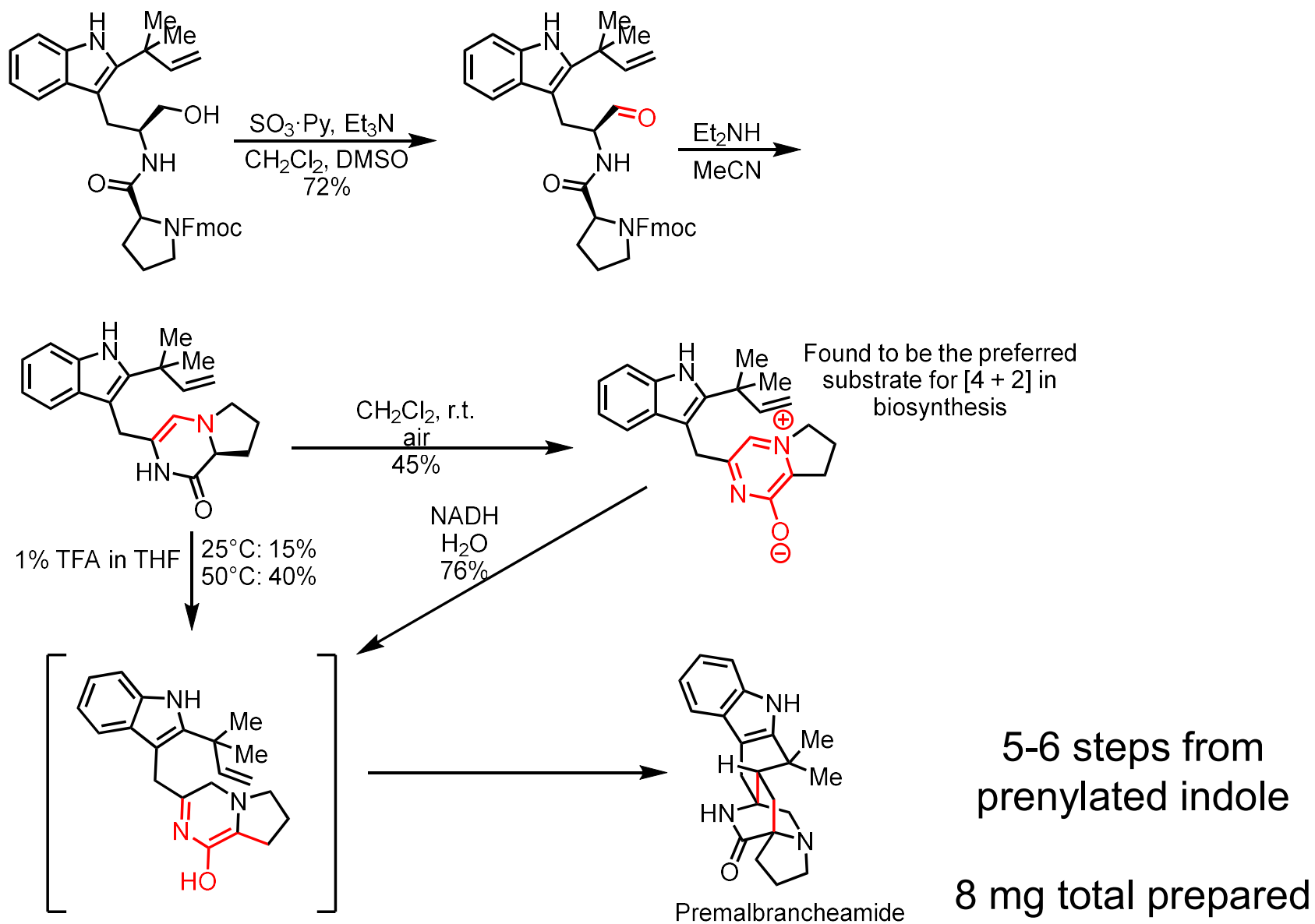
## Retrosynthesis of premalbrancheamide to key intermediate for intramolecular Diels-Alder



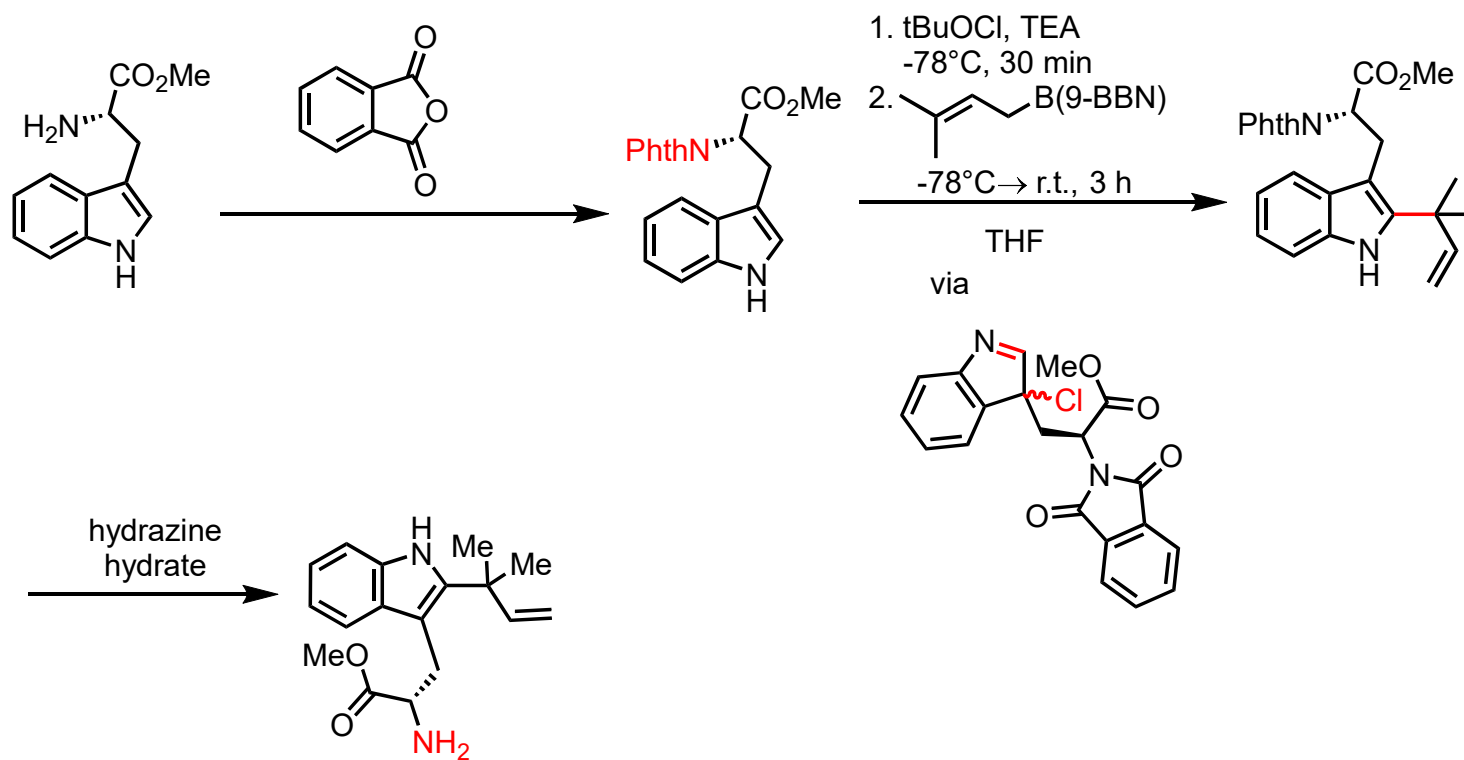
## Full Synthesis



# Synthesis by Diels-Alder: Premalbrancheamide

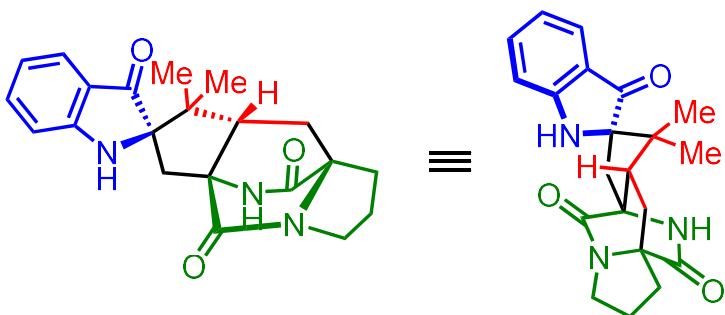


# Chemical Synthesis of Reverse Prenylated Indoles



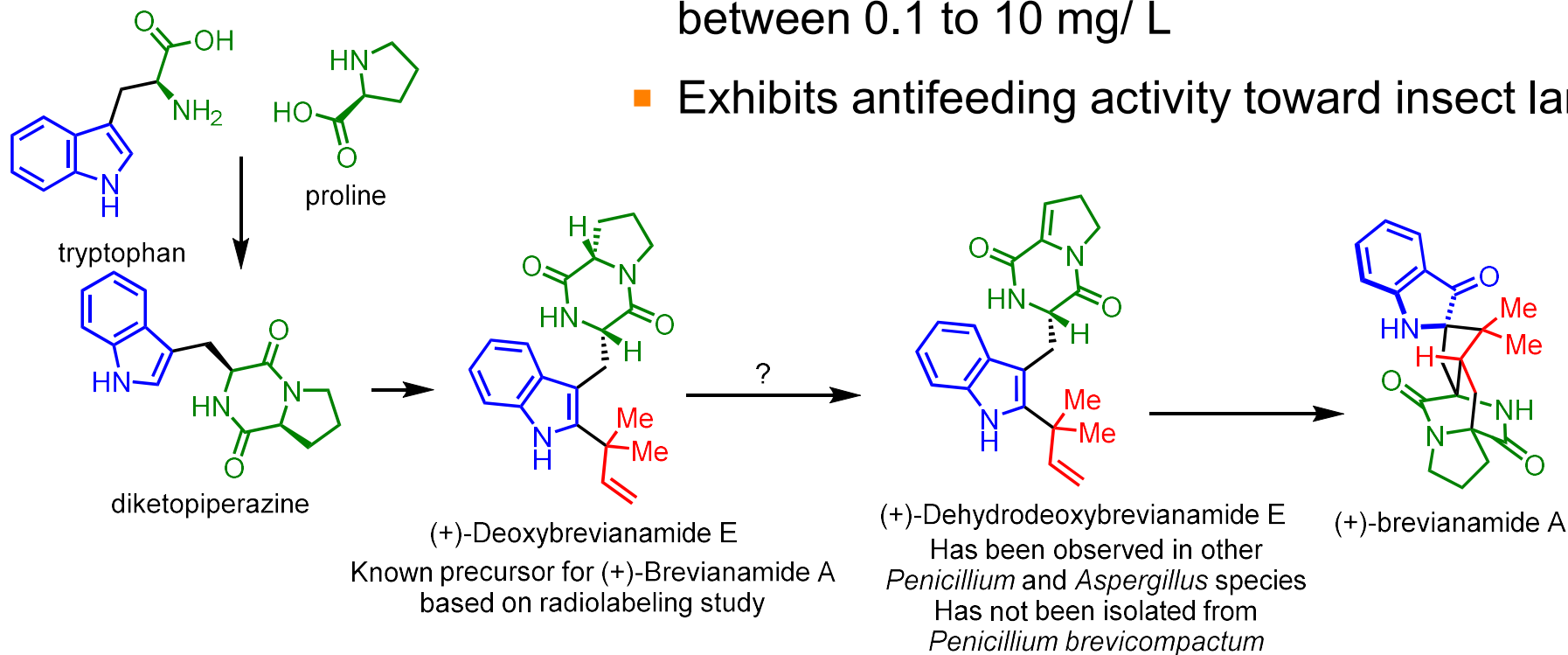
Synthesis of prenylated indole adds ~4 steps

# Brevianamide A



Brevianamide A

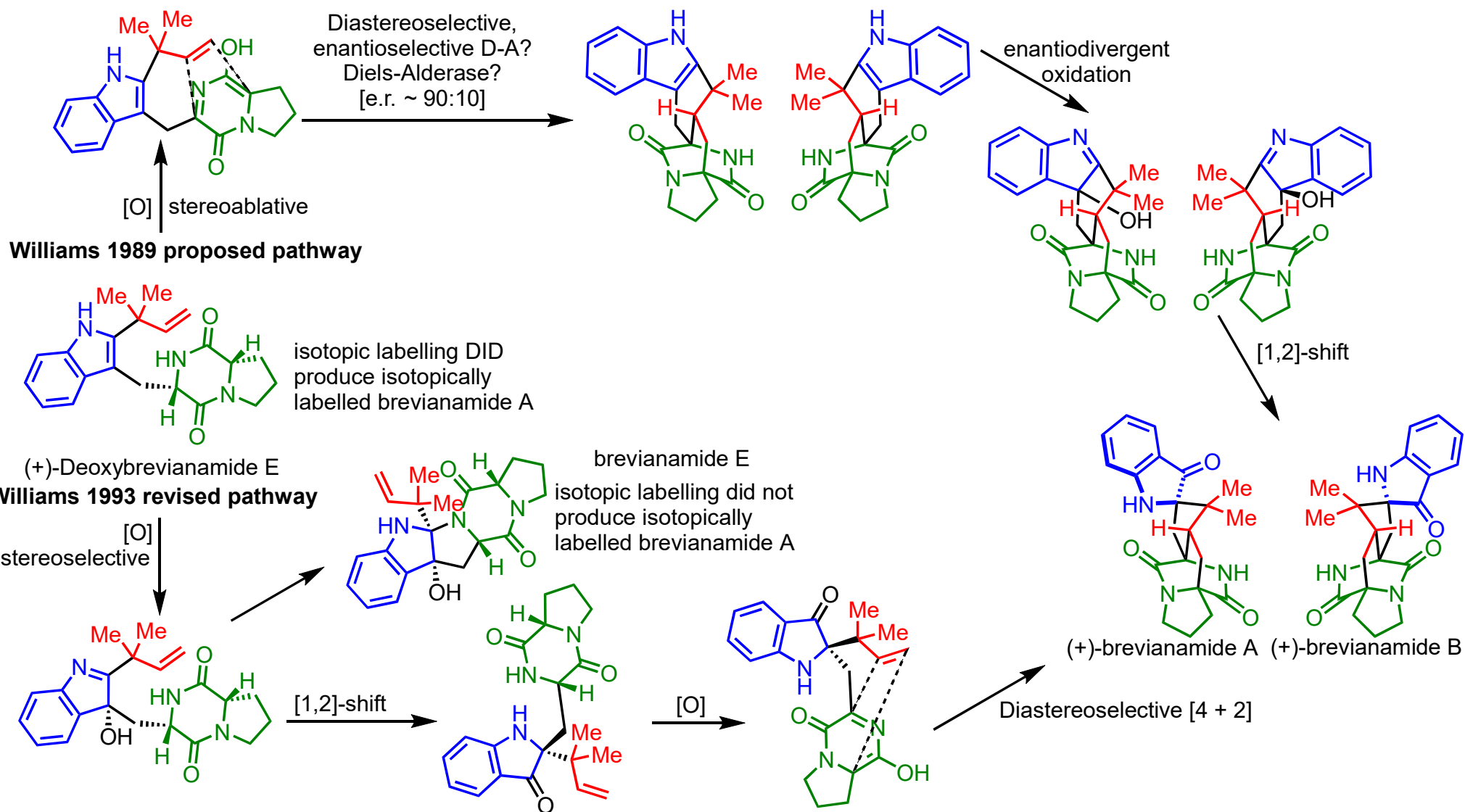
**Biosynthetic pathway has not been fully elucidated**



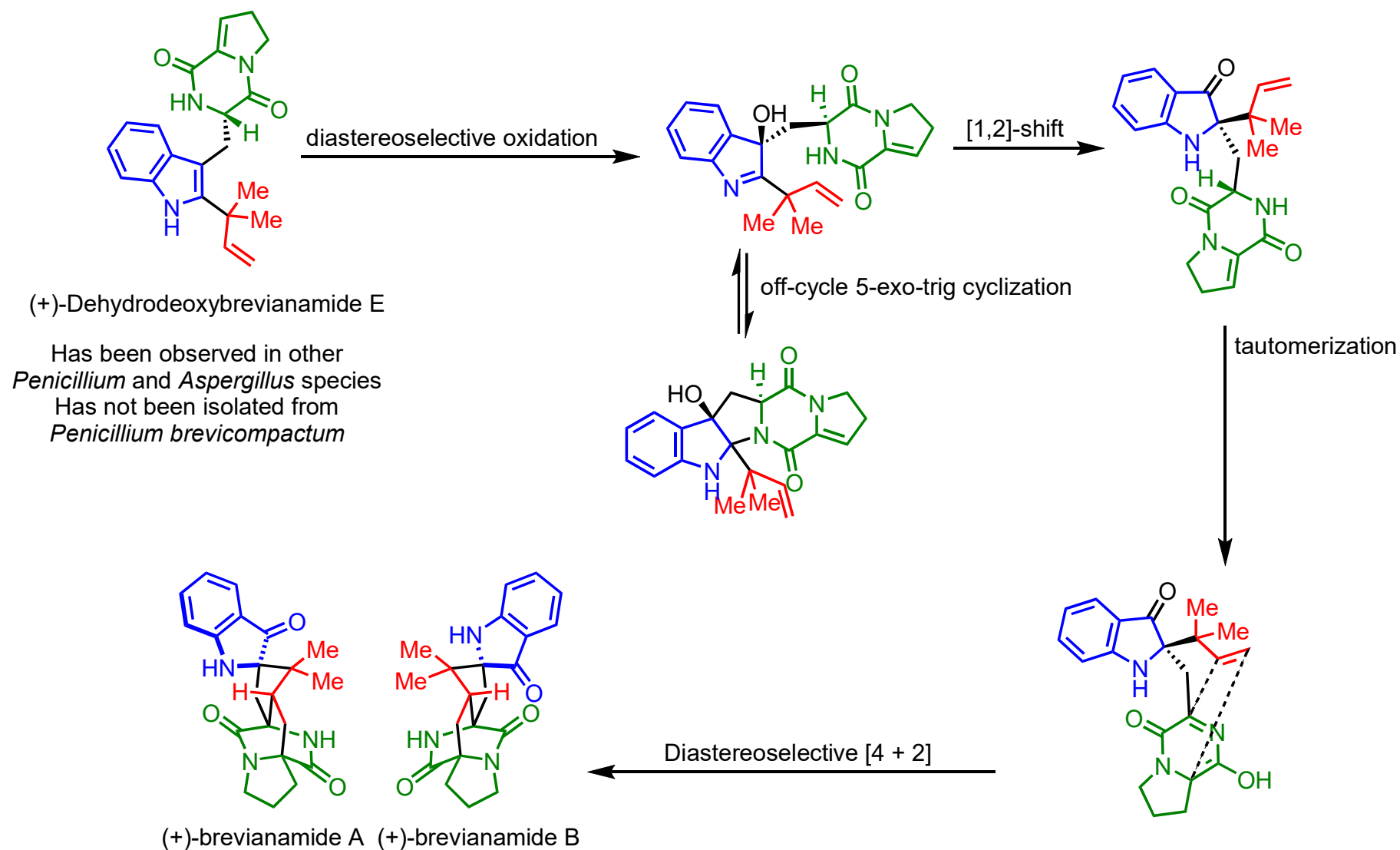
- First isolated by Wright and Birch in 1969 from the culture medium of *Penicillium brevicompactum*
- Brevianamide A more abundant than the fungi's other prenylated alkaloids (9 times more abundant than brevianamide B)
- Yield of brevianamides from culture fluid between 0.1 to 10 mg/ L
- Exhibits antifeeding activity toward insect larvae

# Brevianamide A: Biosynthetic Hypotheses

How to rationalize selectivity for brevianamide A, but presence of both brevianamide A and B?



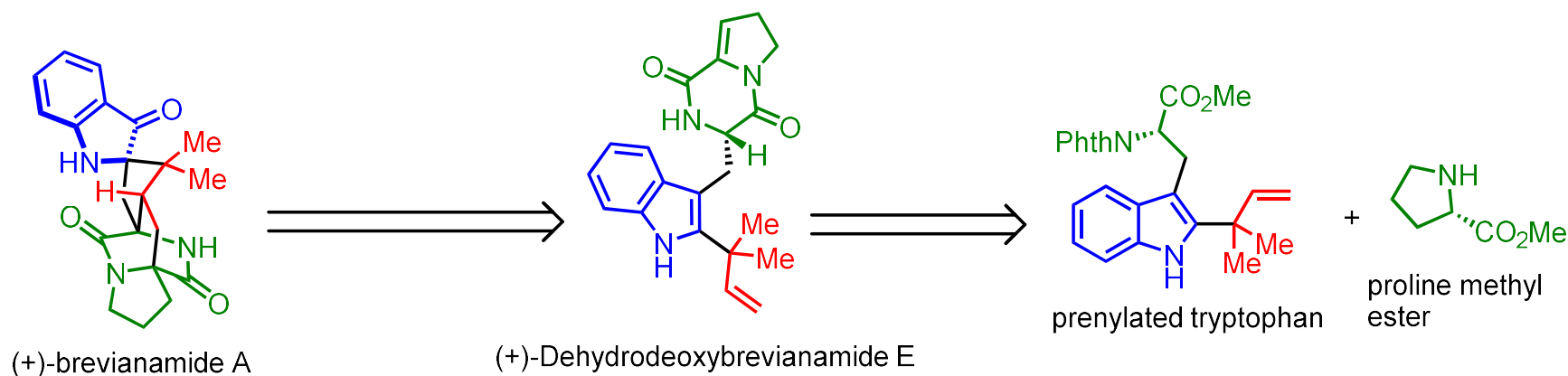
# Brevianamide A: Lawrence *et al.* Biosynthetic Hypothesis



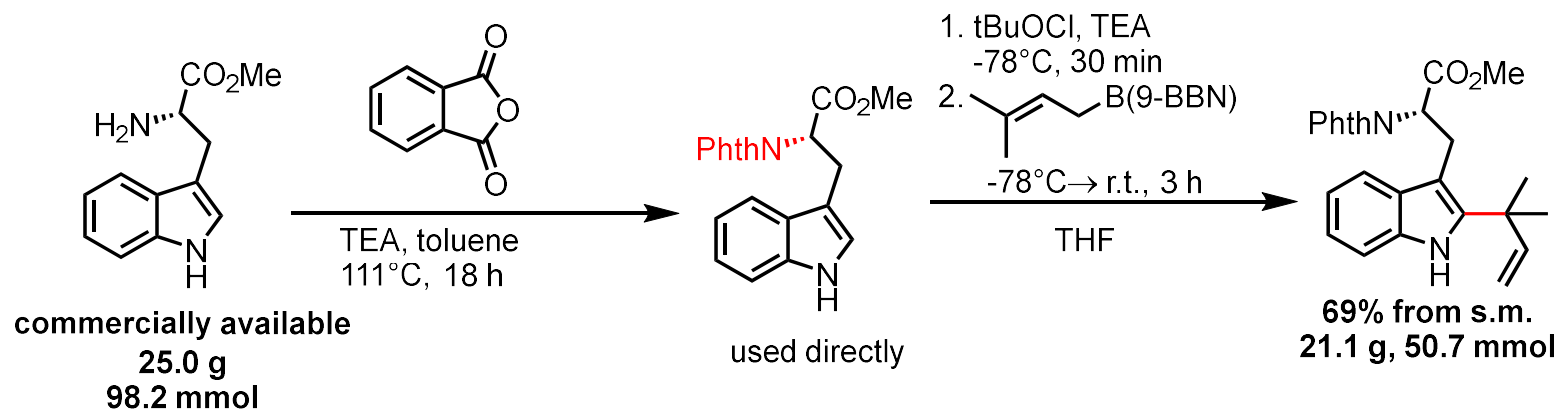
**This biosynthetic hypothesis informed their synthetic approach**

# Synthesis by Diels-Alder: Brevianamide A

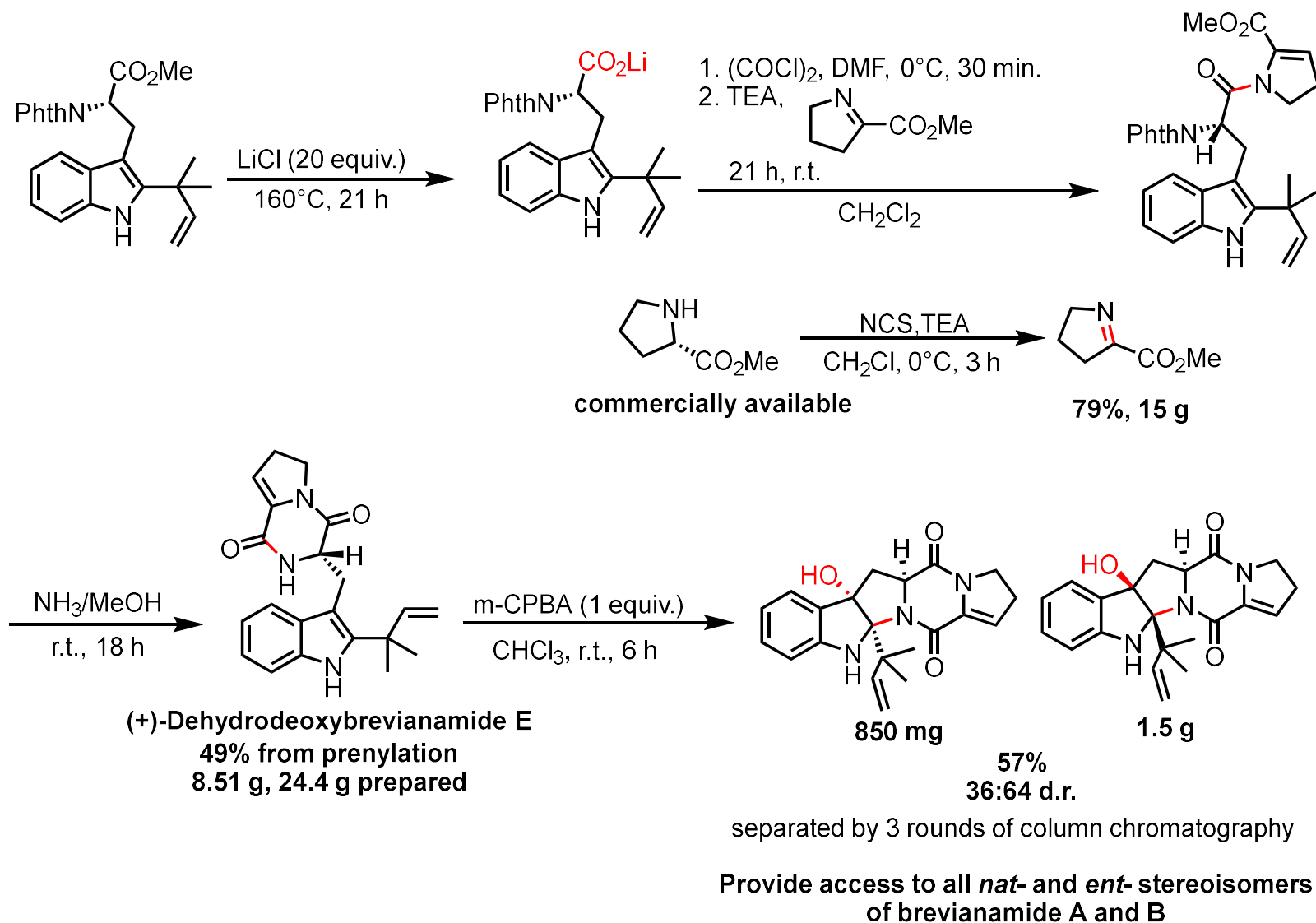
## Retrosynthesis



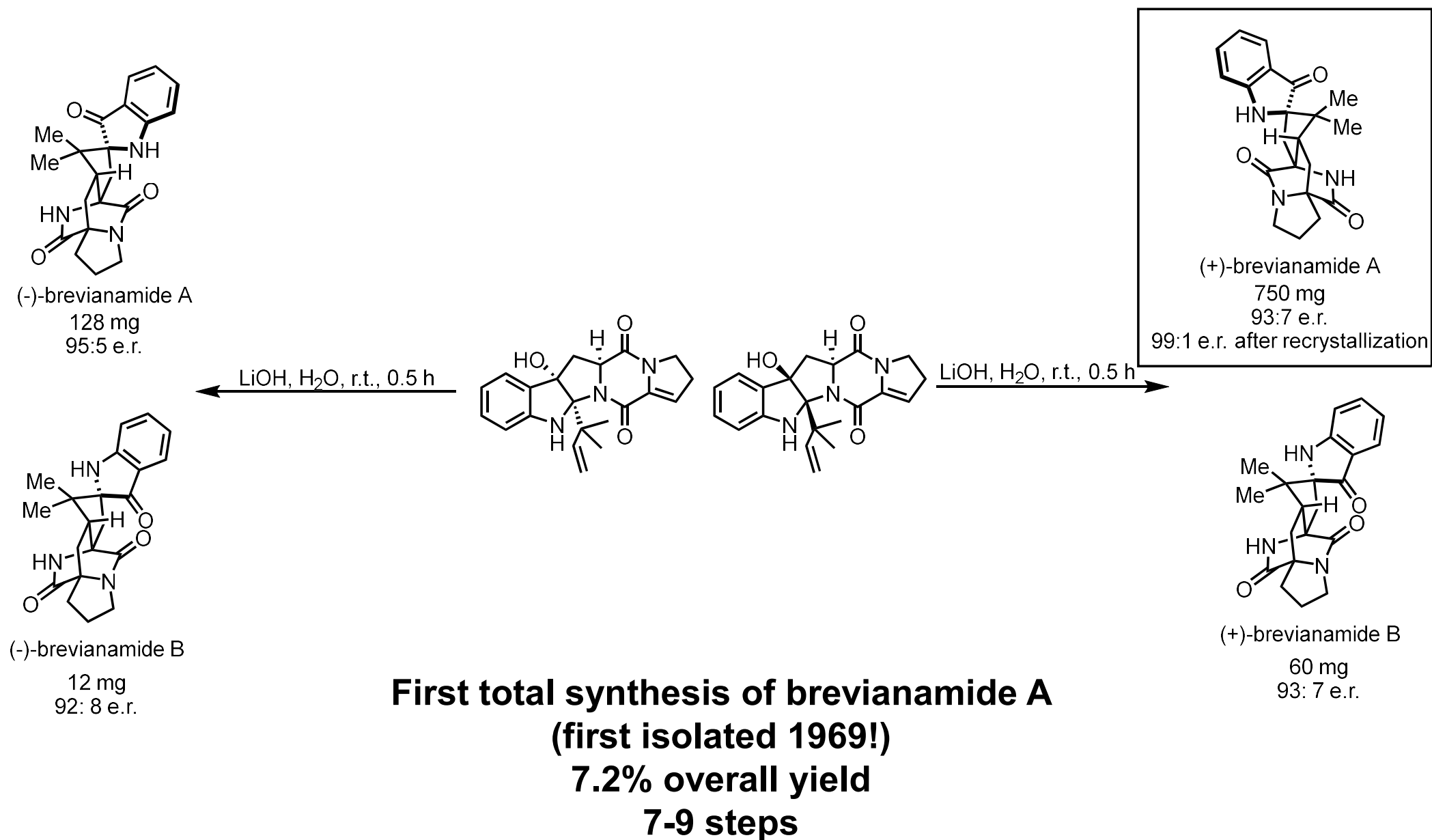
## Forward Synthesis



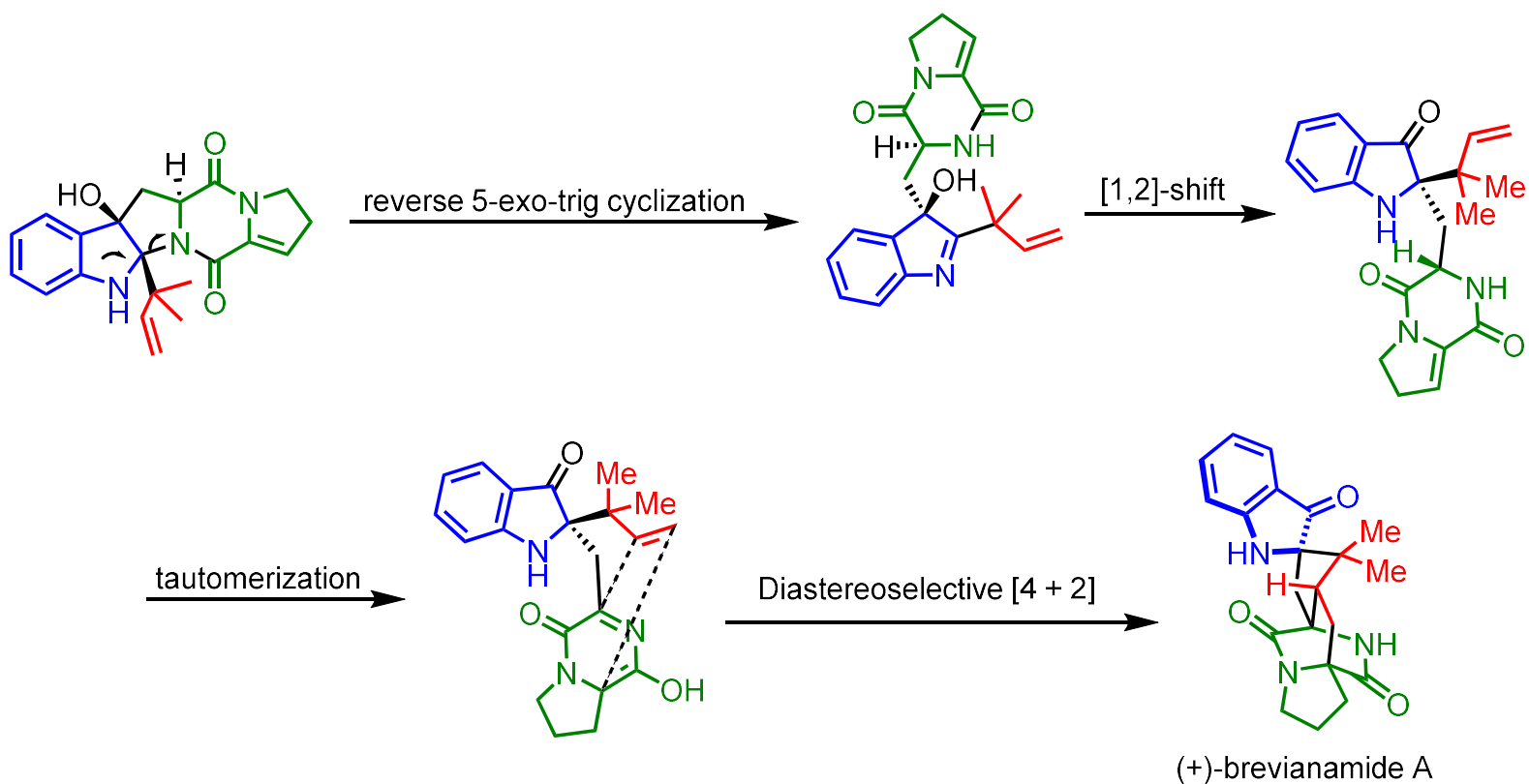
# Synthesis by Diels-Alder: Brevianamide A



# Synthesis by Diels-Alder: Brevianamide A

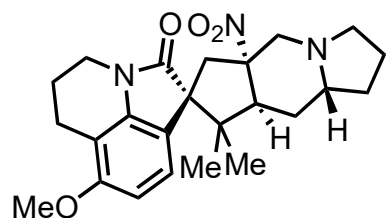


# Synthesis by Diels-Alder: Brevianamide A



**Proposed mechanism follows their biosynthetic hypothesis**

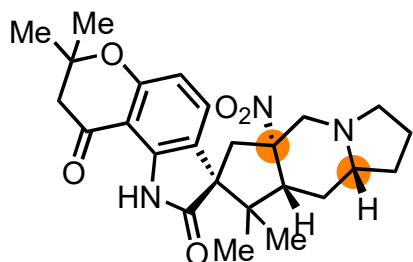
# Citrinalin B and Cyclopiamine B



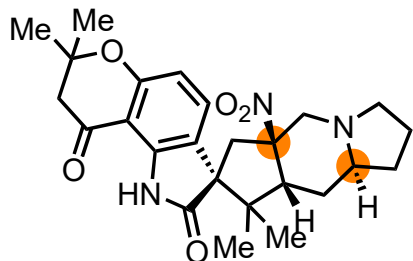
**Cyclopiamine B**

discovered in 1979 from *Penicillium cyclopium*

**Lack the bicyclo[2.2.2]diazaoctane core  
Possess alkyl nitro group, extremely rare in  
natural products  
Exact biosynthetic origin unknown**



**Citrinalin B (originally proposed)**

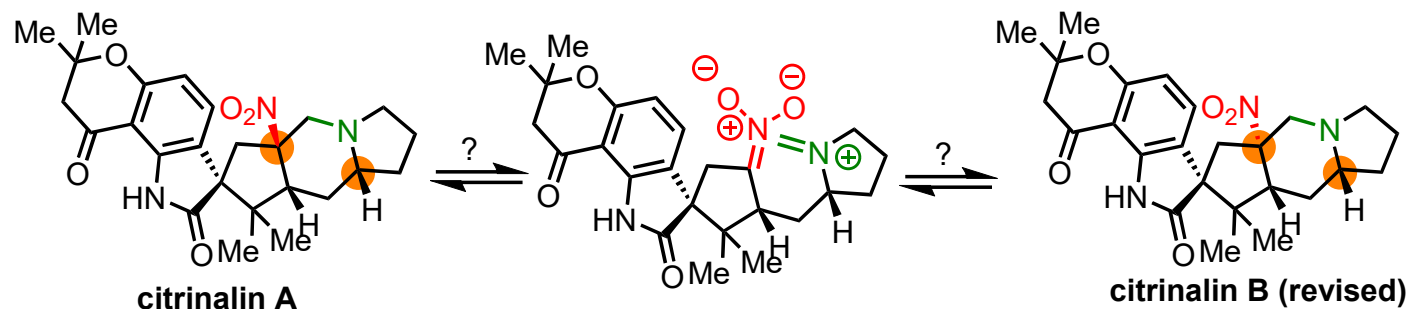
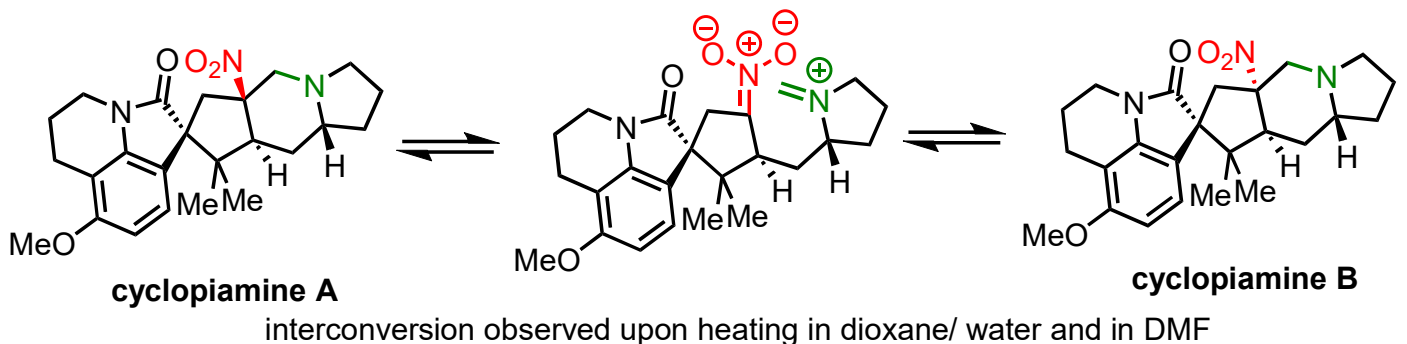


**Citrinalin B (revised)**

discovered in 2010 from *Penicillium citrinum*

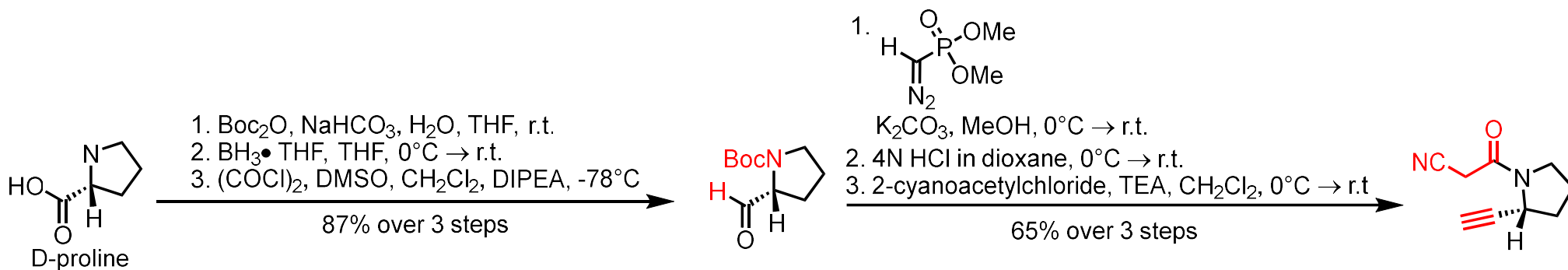
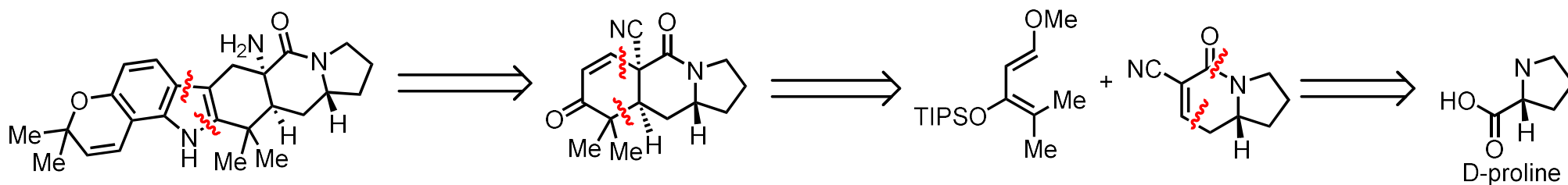
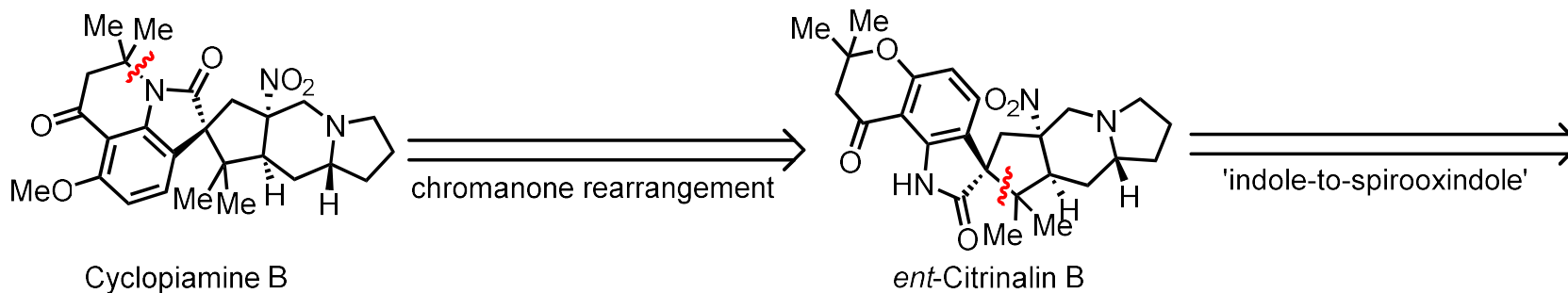
## Basis for structural revision of Citrinalin B:

Analogy of citrinalin A and B to cyclopiamine A and B

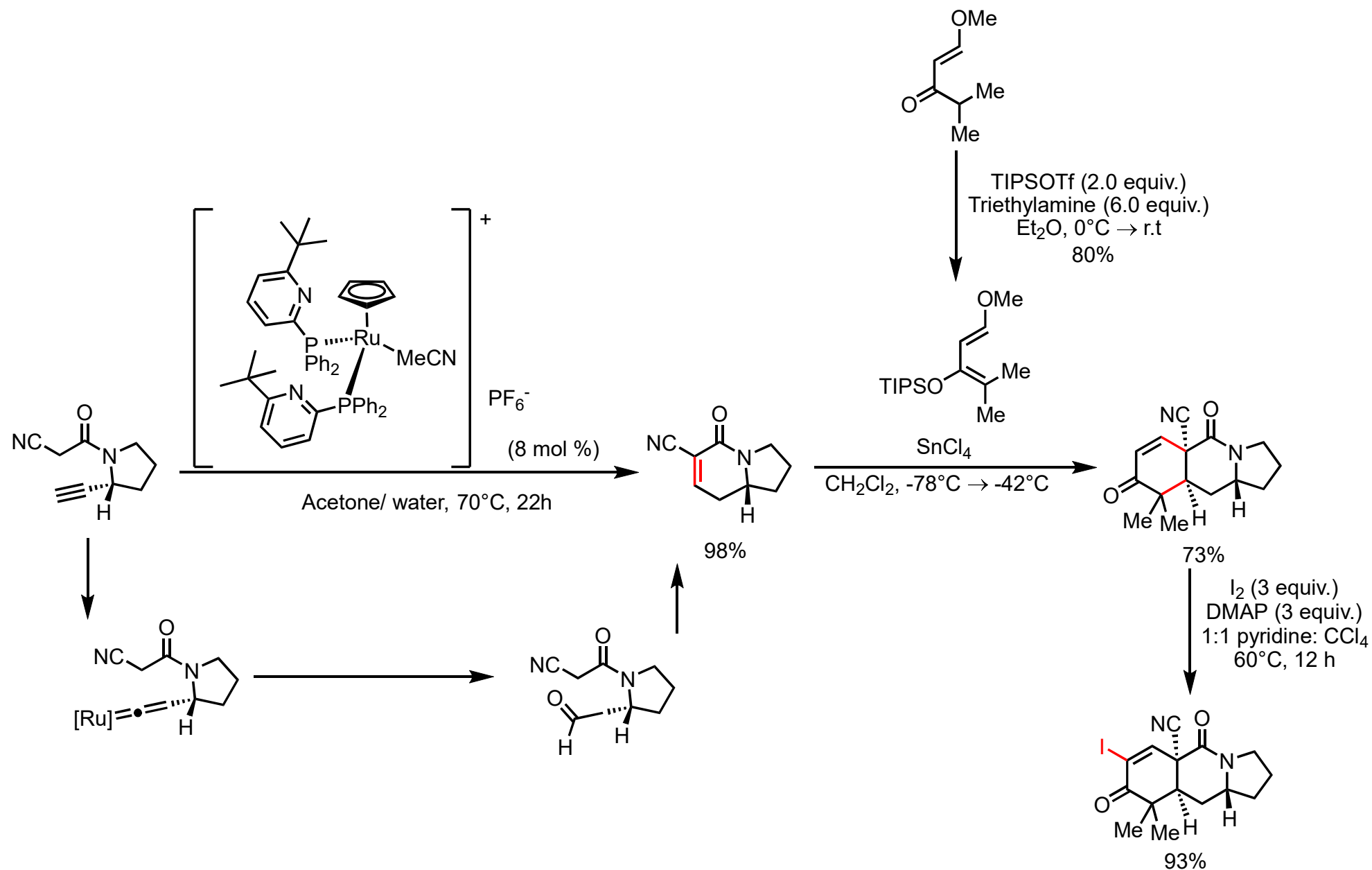


Calculations also suggested that **citrinalin A** structure was correct but that the revised structure was a better fit for **citrinalin B** based on  $^1\text{H}$ ,  $^{13}\text{C}$  NMR data

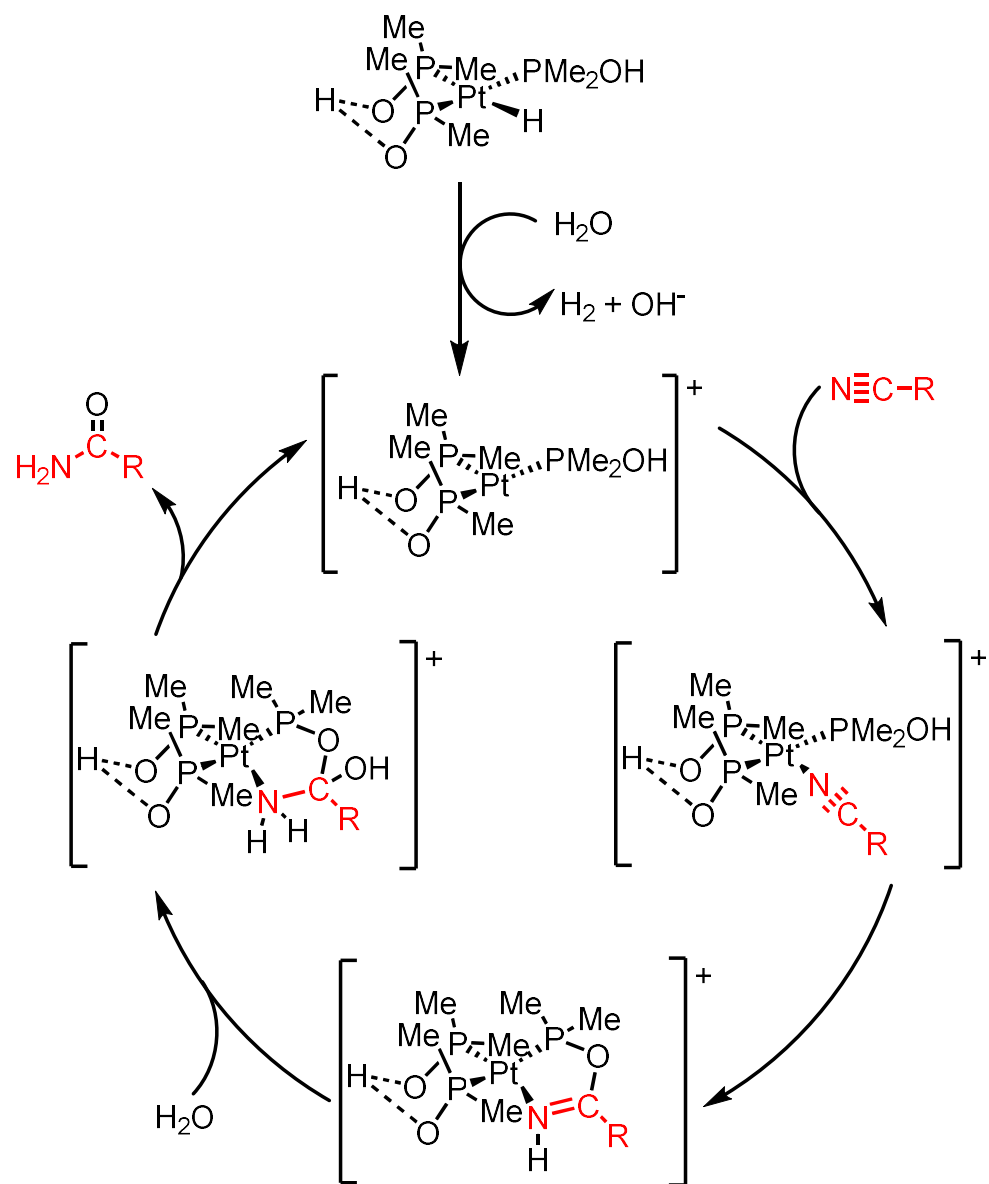
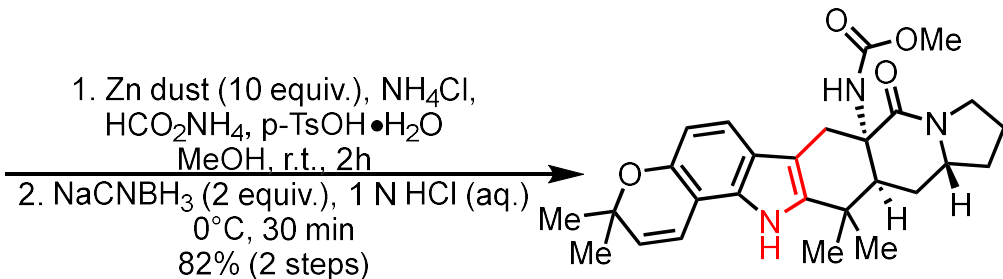
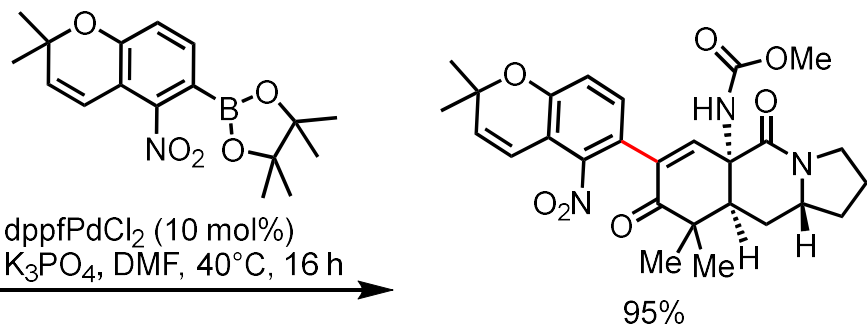
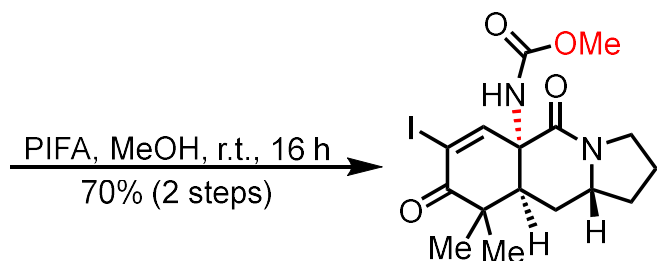
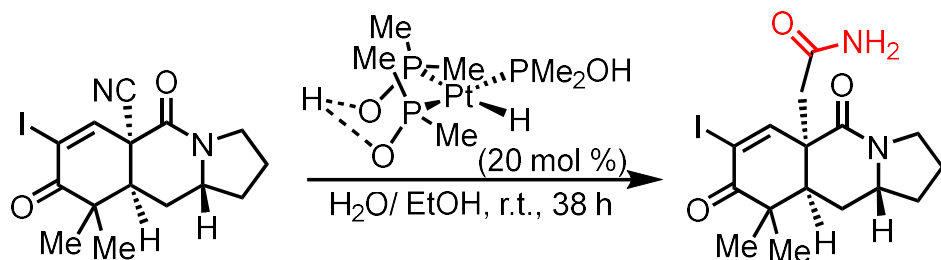
# Synthesis by Diels-Alder: *ent*-Citranalin B and Cyclopiamine B



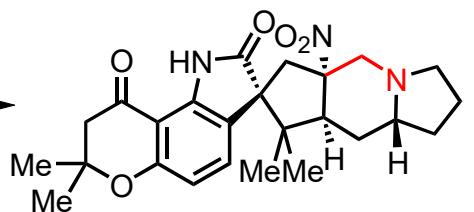
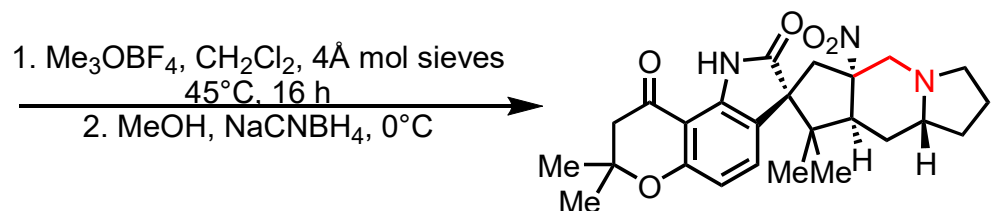
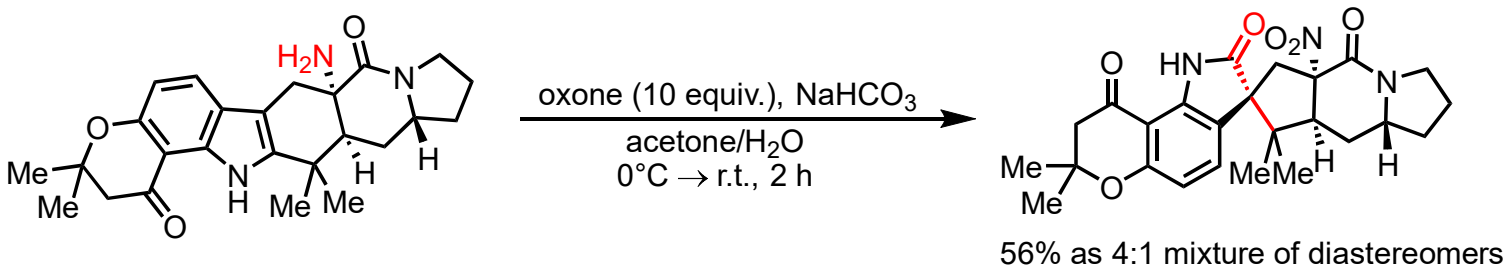
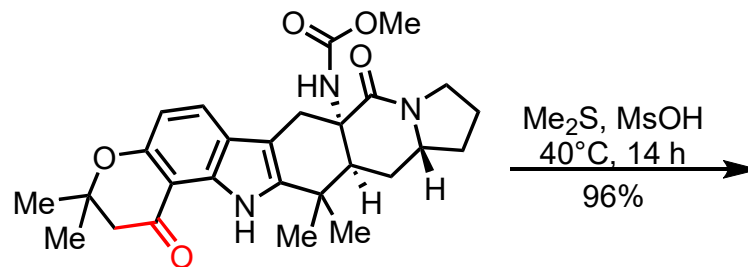
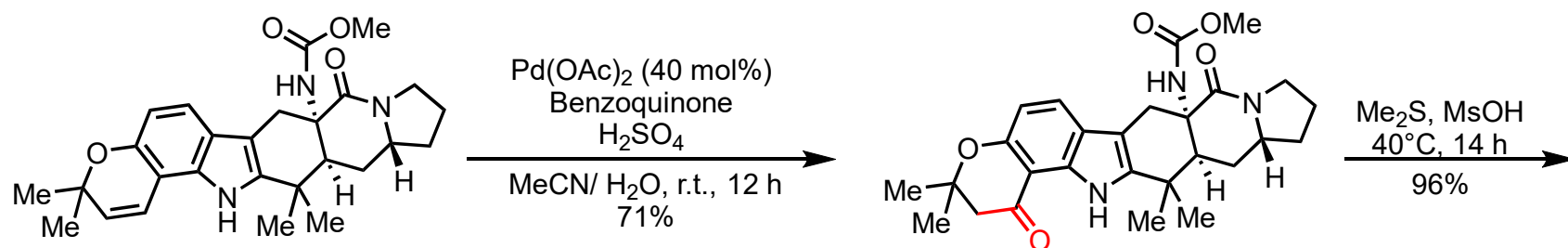
# Synthesis by Diels-Alder: *ent*-Citranalin B and Cyclopiamine B



# Synthesis by Diels-Alder: *ent*-Citranalin B and Cyclopiamine B



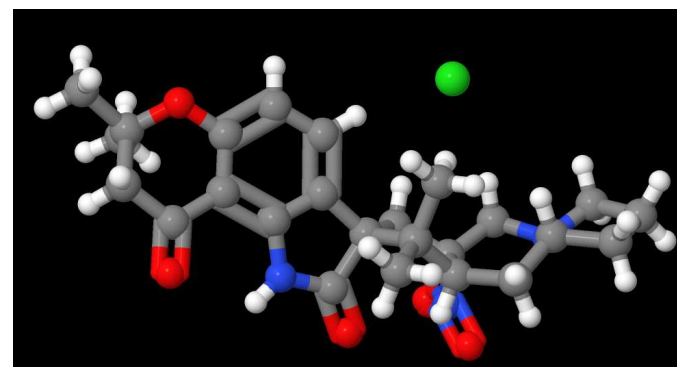
# Synthesis by Diels-Alder: *ent*-Citranalin B and Cyclopiamine B



*ent*-citranalin B

consistent with spectroscopic data of isolated citranalin B; opposite sign of optical rotation

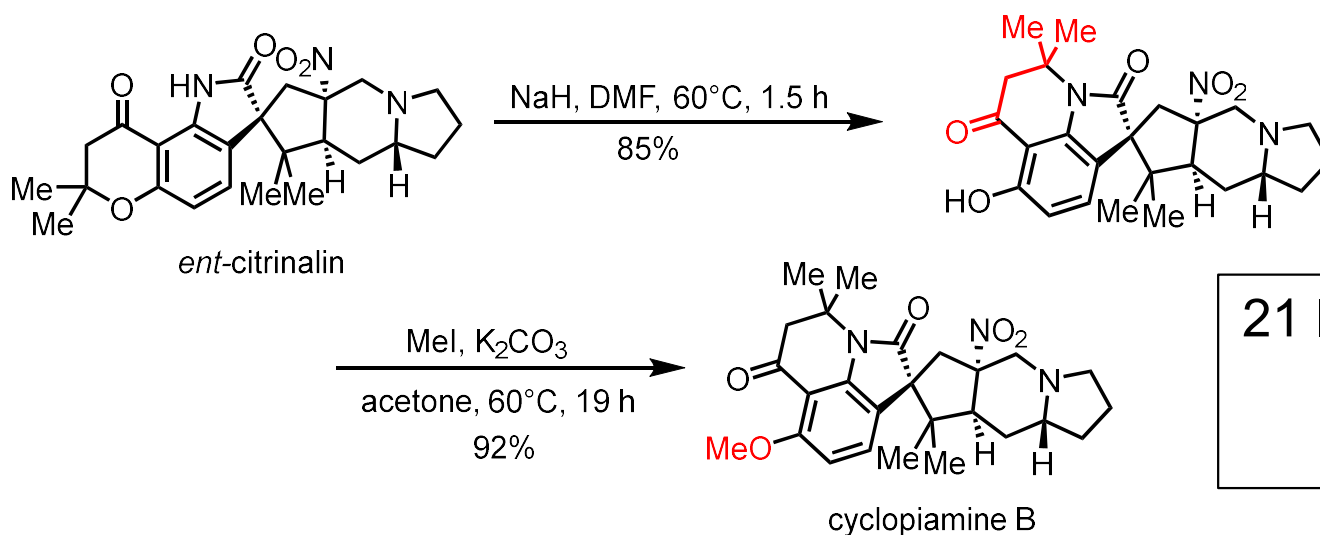
19 linear steps from proline  
6.4 mg prepared  
5.5% overall yield



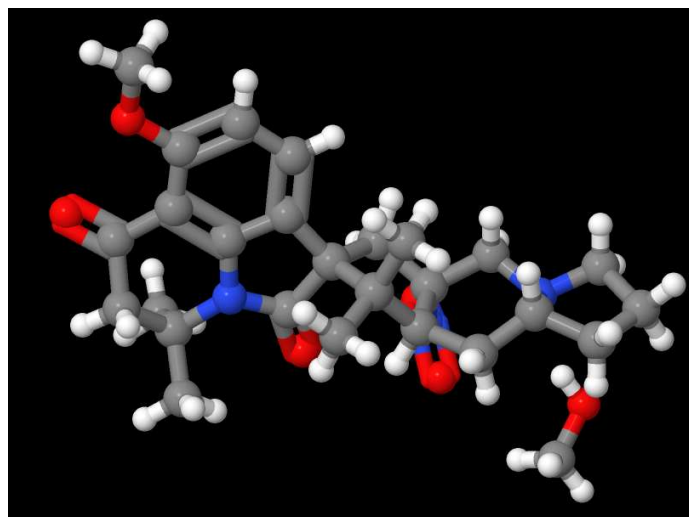
Structure confirmed  
crystallographically (HCl salt)

# Synthesis by Diels-Alder: *ent*-Citranalin B and Cyclopiamine B

## Conversion of *ent*-citranalin B to cyclopiamine B



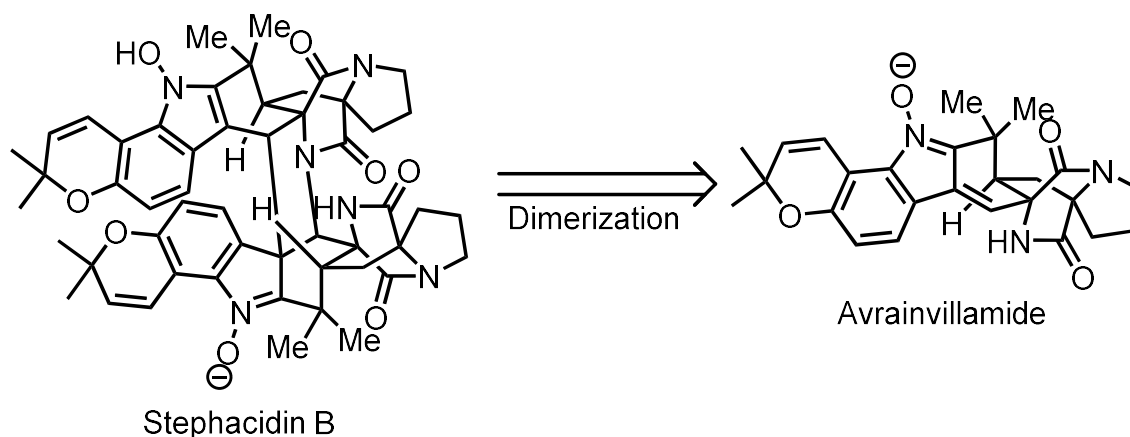
21 linear steps from proline  
4.0 mg prepared  
4.3% overall yield





# SYNTHESIS BY RADICAL CYCLIZATION

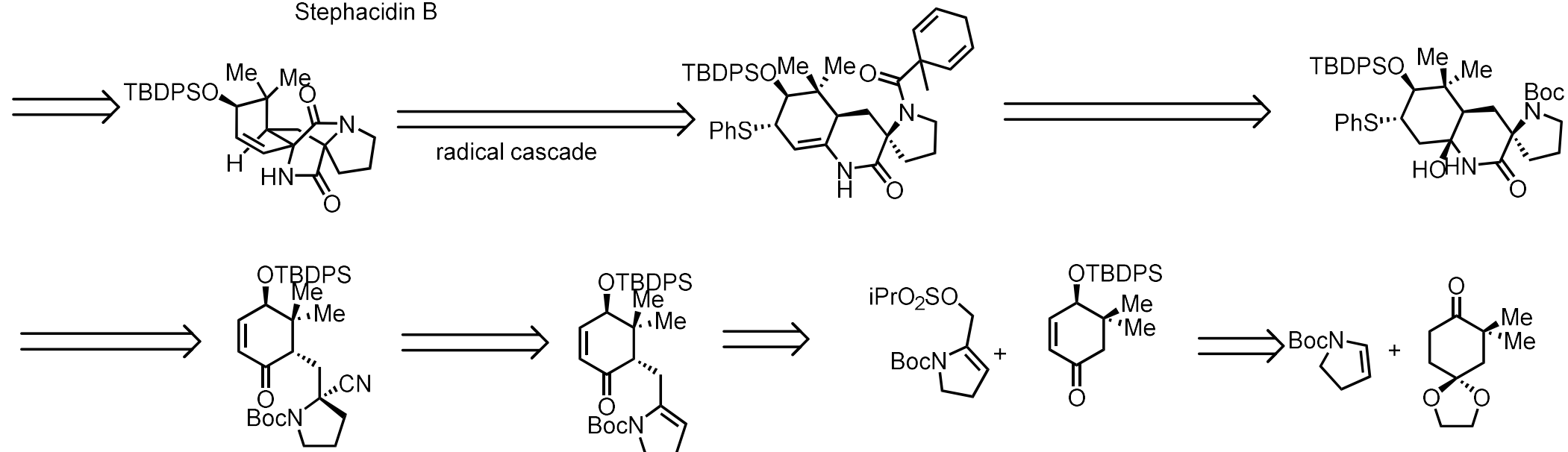
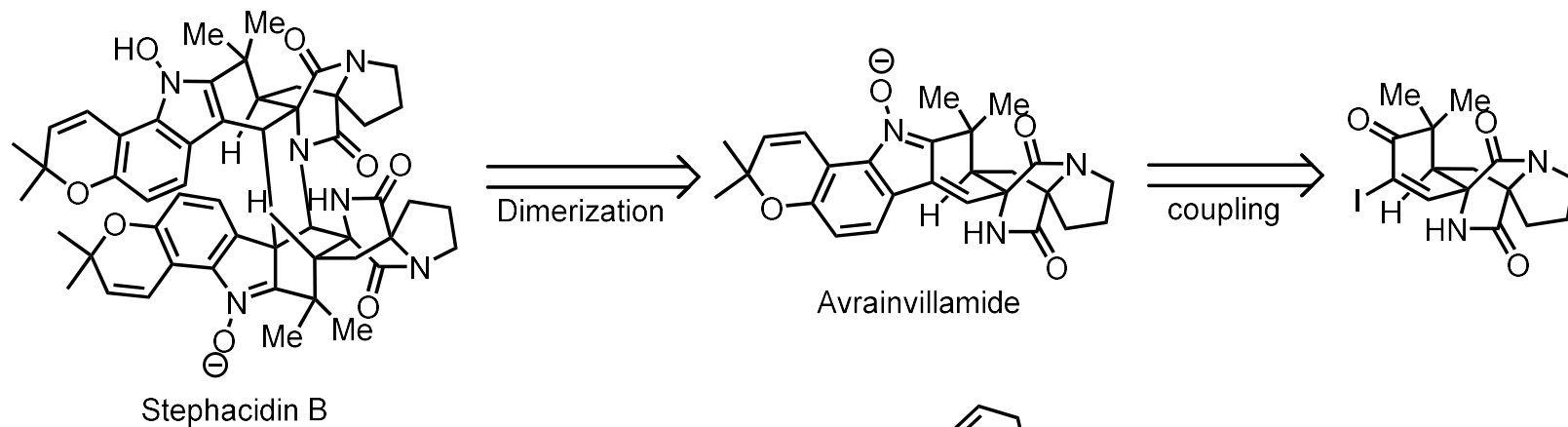
# Stephacidin B and Avrainvillamide



- Stephacidin B was isolated from *Aspergillus ochraceus* WC76566 (fungus from Indian clay) in 2002 by researchers at Bristol-Myers Squibb and found to exhibit antiproliferative effects on cancer cell lines
- Avrainvillamide was independently described by Fenical *et al.* in 2000 and Sugie *et al.* in 2001 in which cytotoxic and antibiotic effects were described

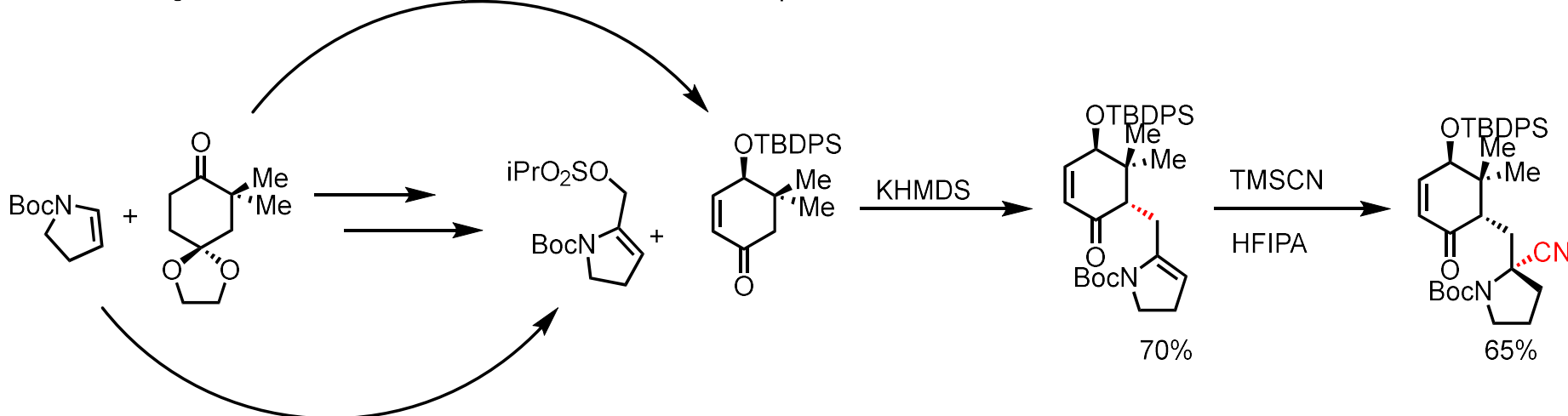
# Myers Retrosynthesis

Retrosynthesis

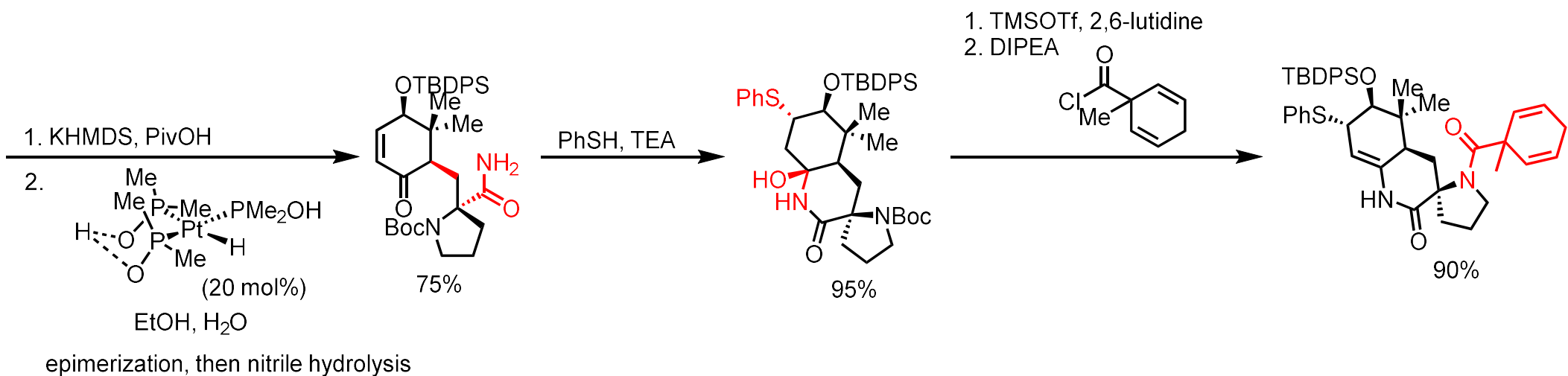


# Stephacidin B and Avrainvillamide

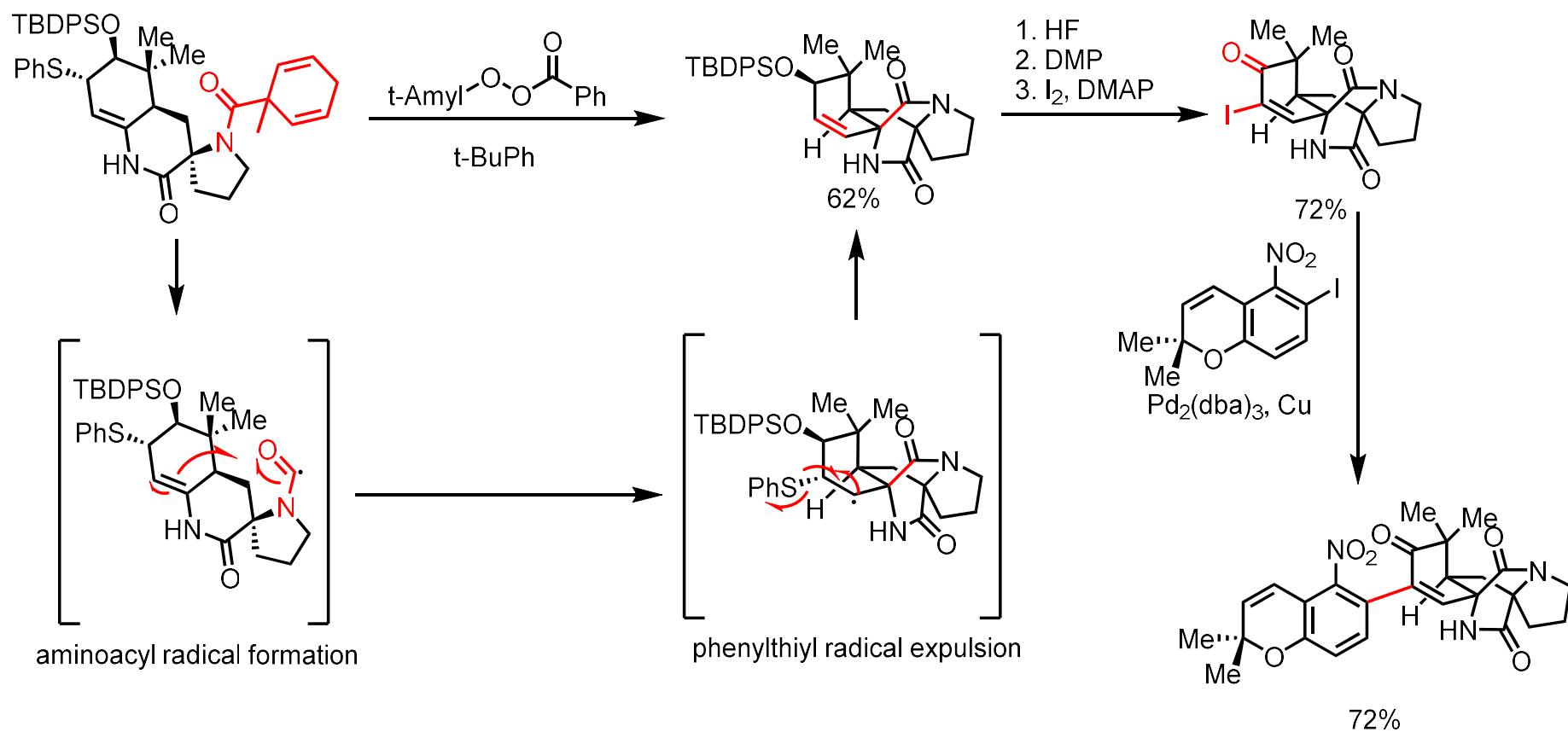
IBX or Saegusa-Ito oxidation, Corey-Itsuno reduction, TBDPS protection



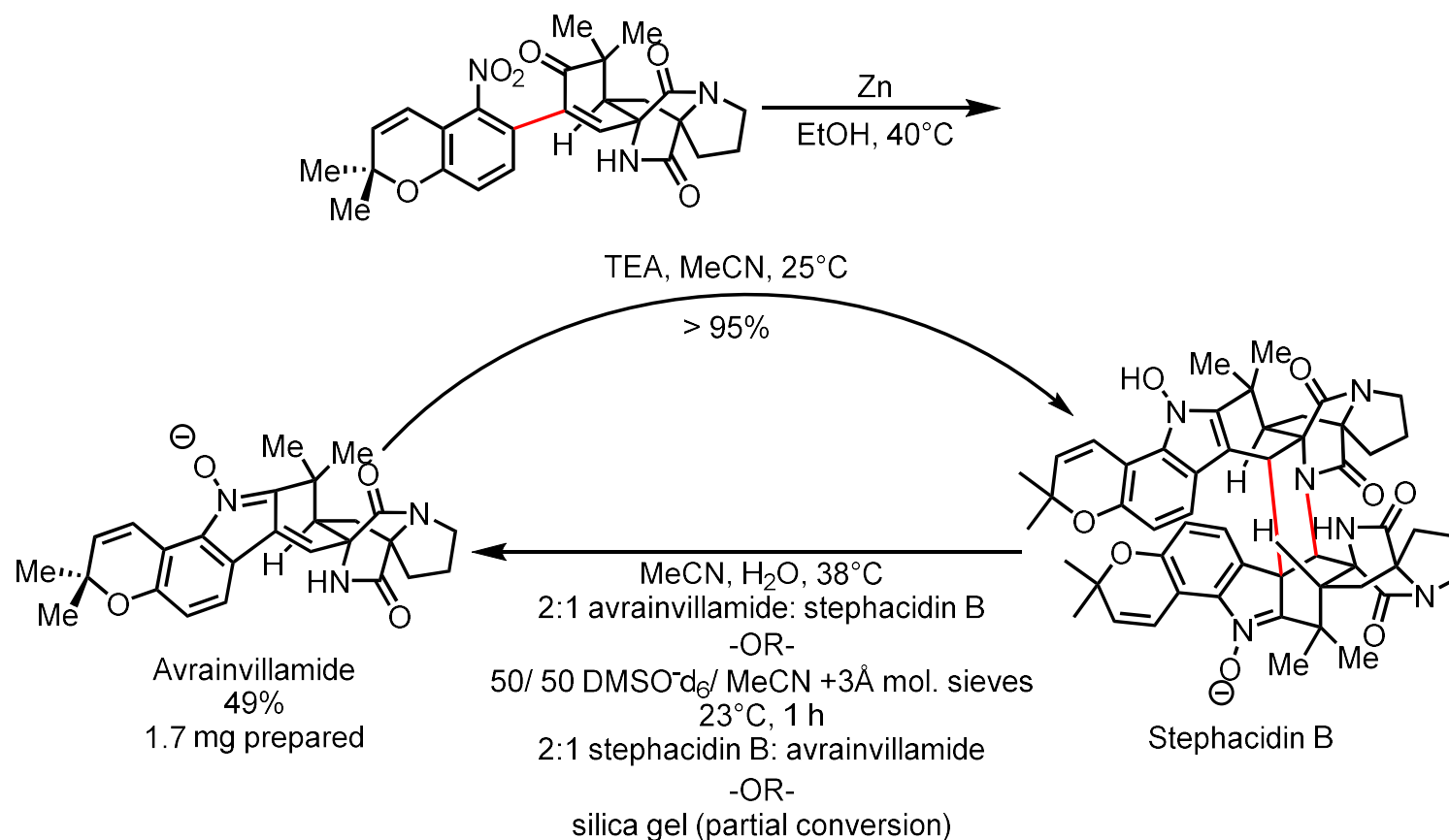
Lithiation, formylation, reduction,  $i\text{PrSO}_2\text{Cl}$



# Stephacidin B and Avrainvillamide

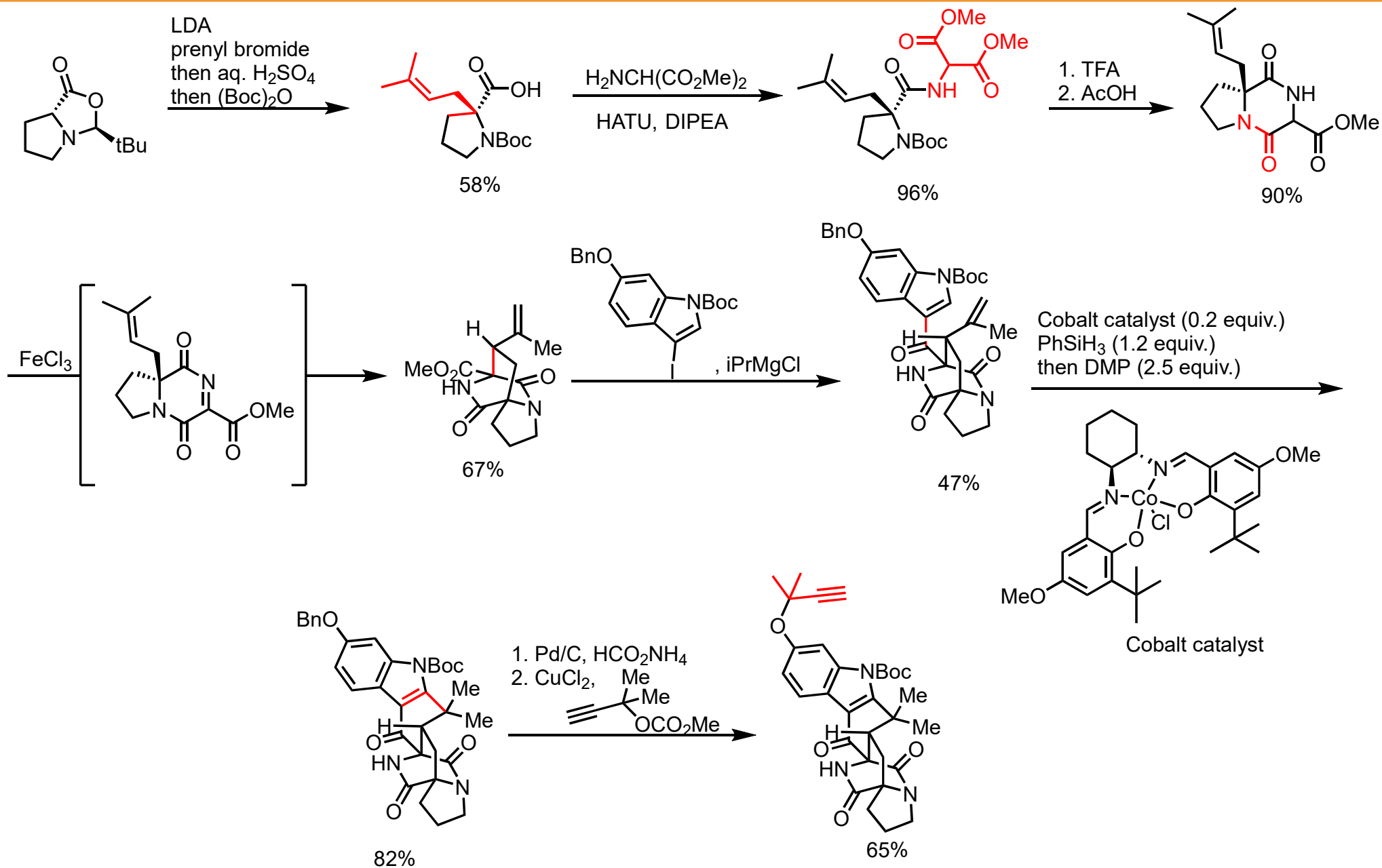


# Stephacidin B and Avrainvillamide

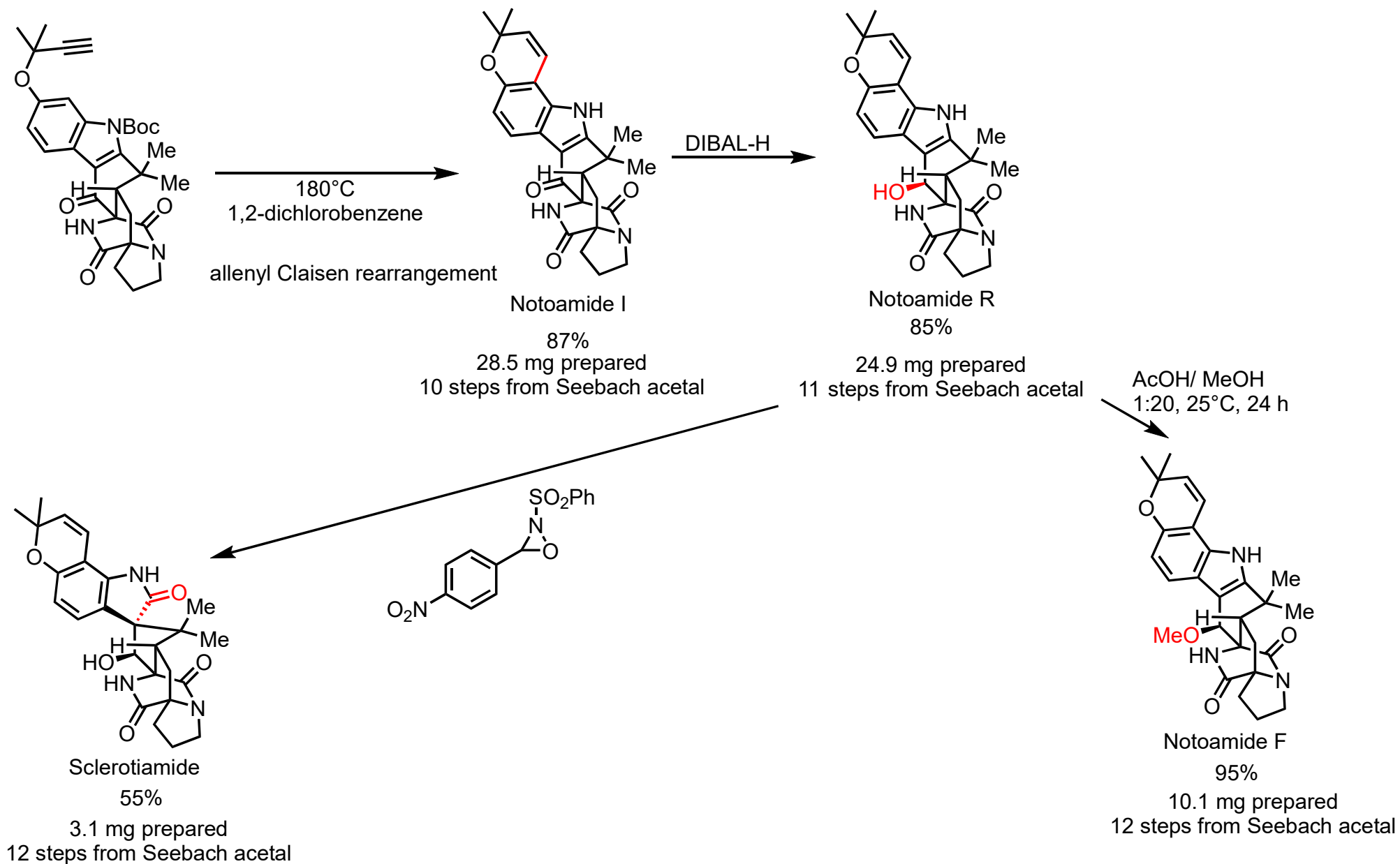


**Is avrainvillamide responsible for stephacidin B's purported activity?  
Later studies by Myers *et al* demonstrated binding of avrainvillamide  
to nucleophosmine, an oncogenic/ cancer-marking protein  
Synthetic avrainvillamide (tethered to biotin) crucial to this discovery**

# Notoamides F, I, R, and Sclerotiamide



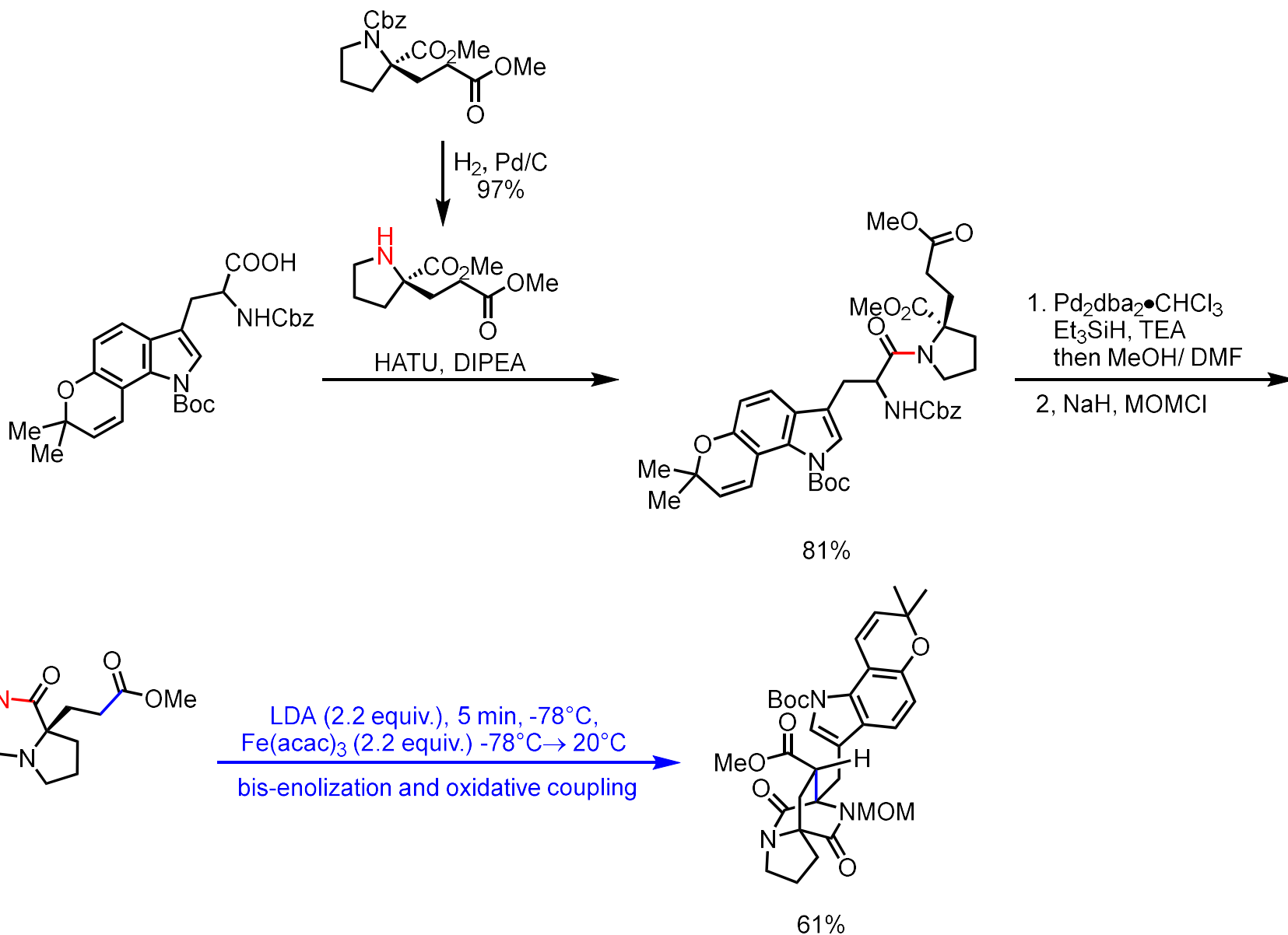
# Notoamides F, I, R, and Sclerotiamide



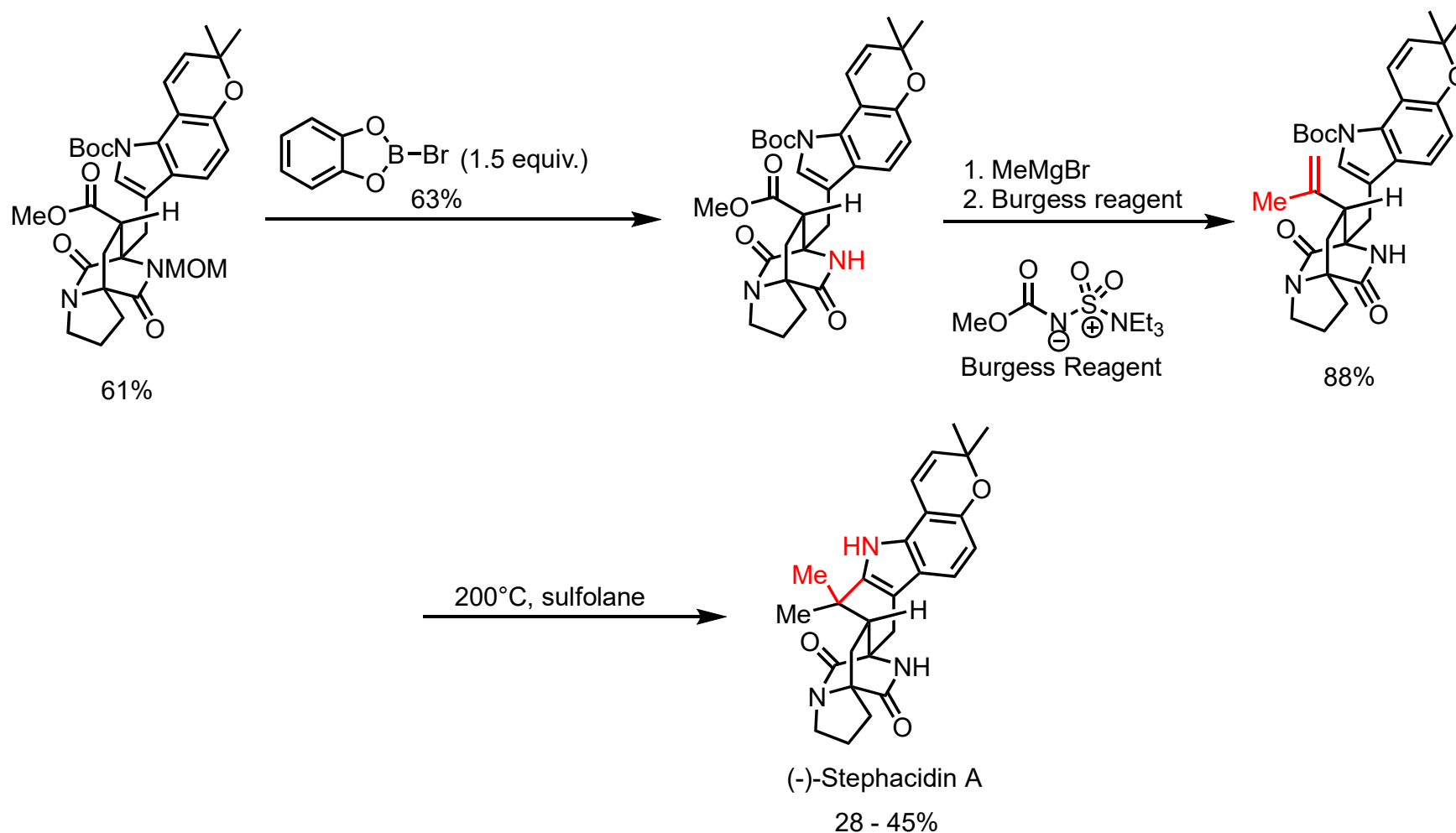


# OXIDATIVE ENOLATE COUPLING

# Baran *et al*'s oxidative enolate coupling



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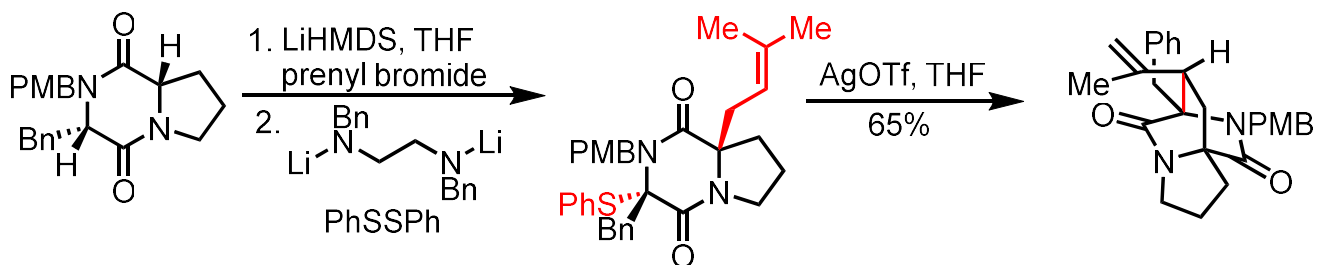
CD revealed opposite enantiomer of isolated *nat*-stephacidin route repeated with D-proline derivative for synthesis of congeners



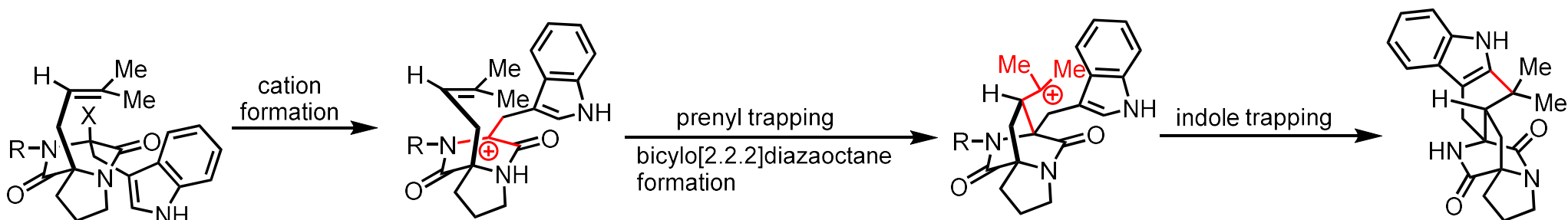
# CATIONIC CASCADE CYCLIZATION

# Synthesis by Cationic Cascade

## Initial studies

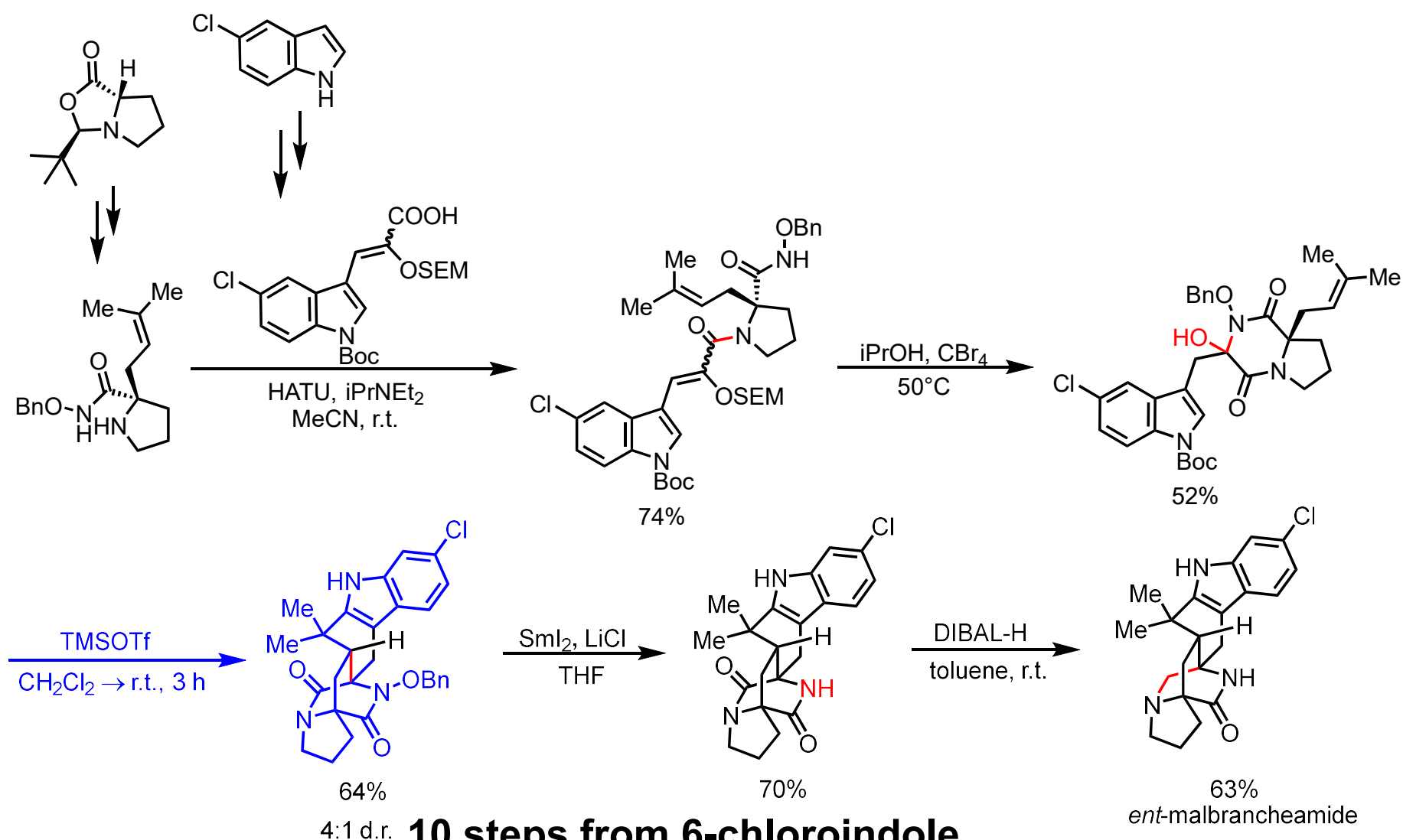


## Envisioned cationic cascade

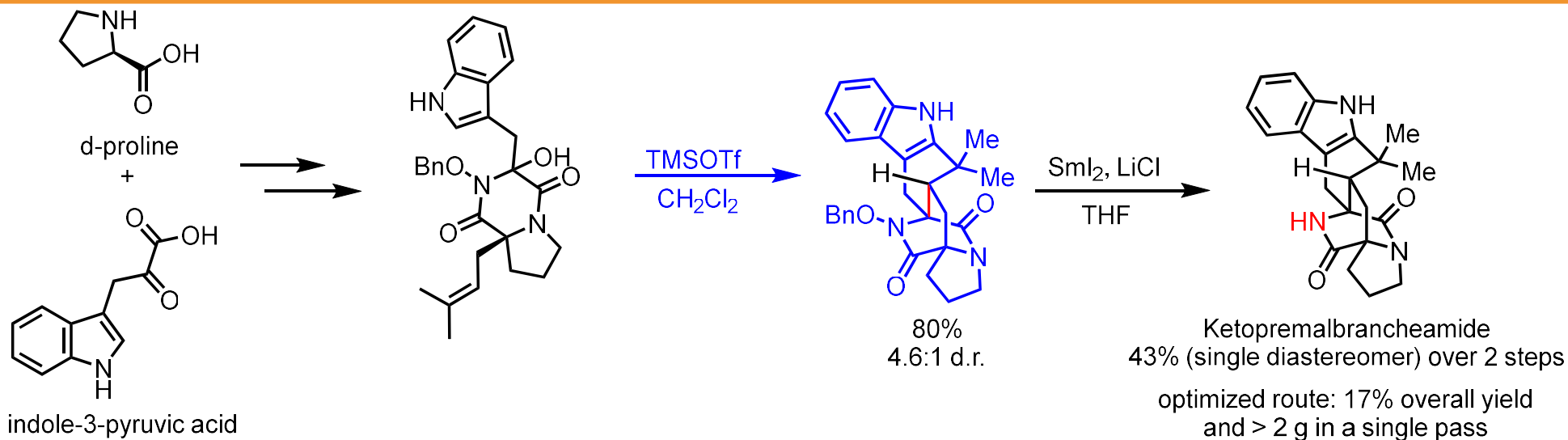


# Synthesis by Cationic Cascade

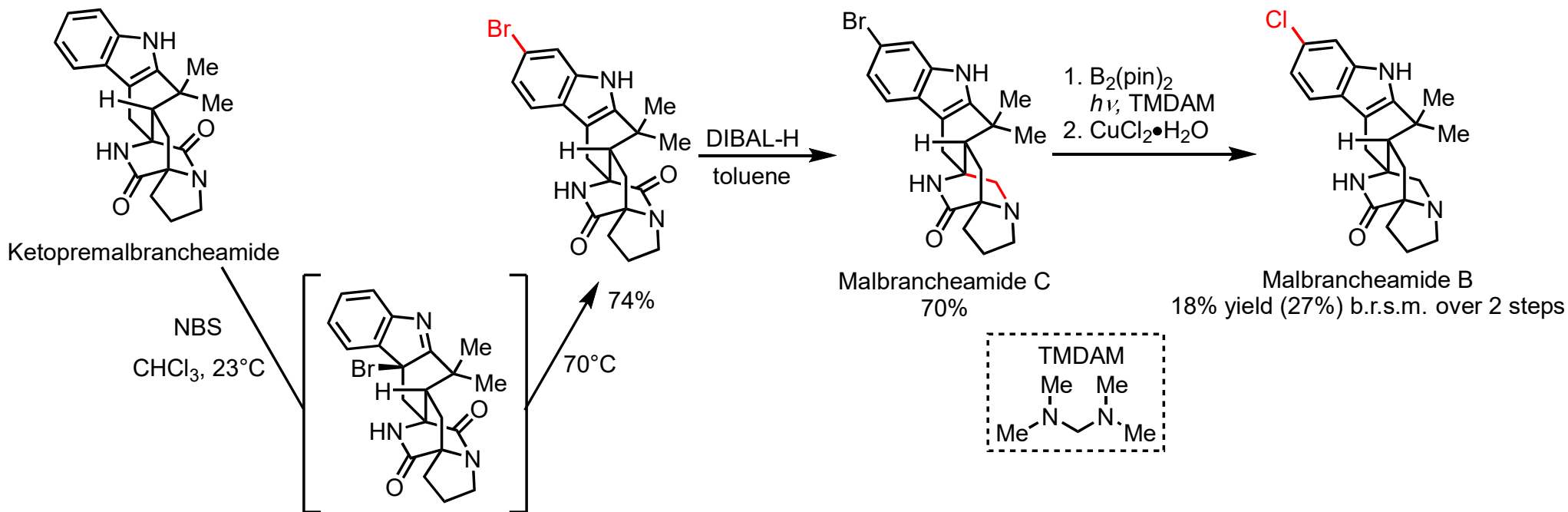
## Application in synthesis of *ent*-malbrancheamide B



# Sarpong *et al.*'s Synthesis of Several Congeners

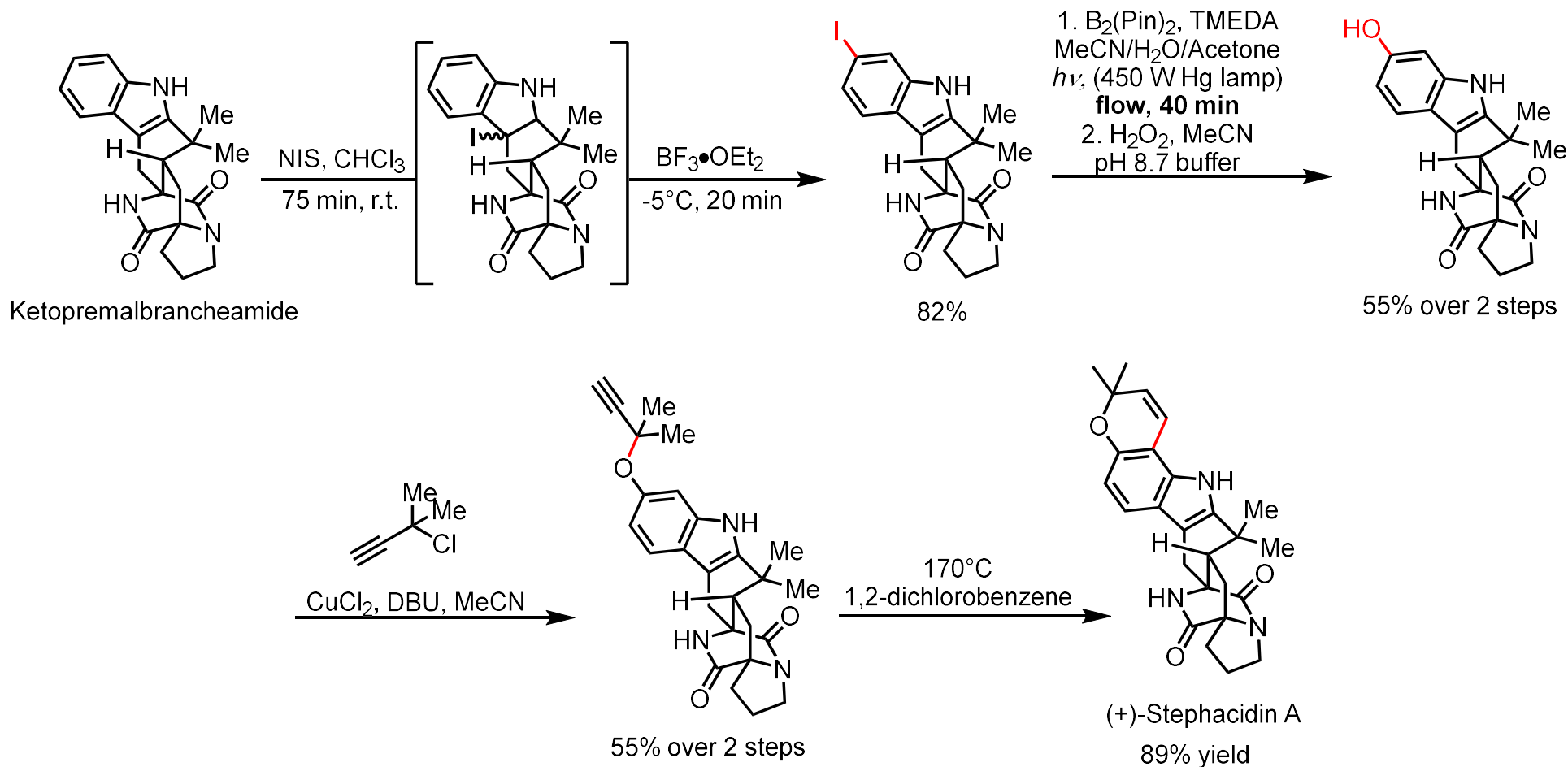


## Route to malbrancheamide C and B



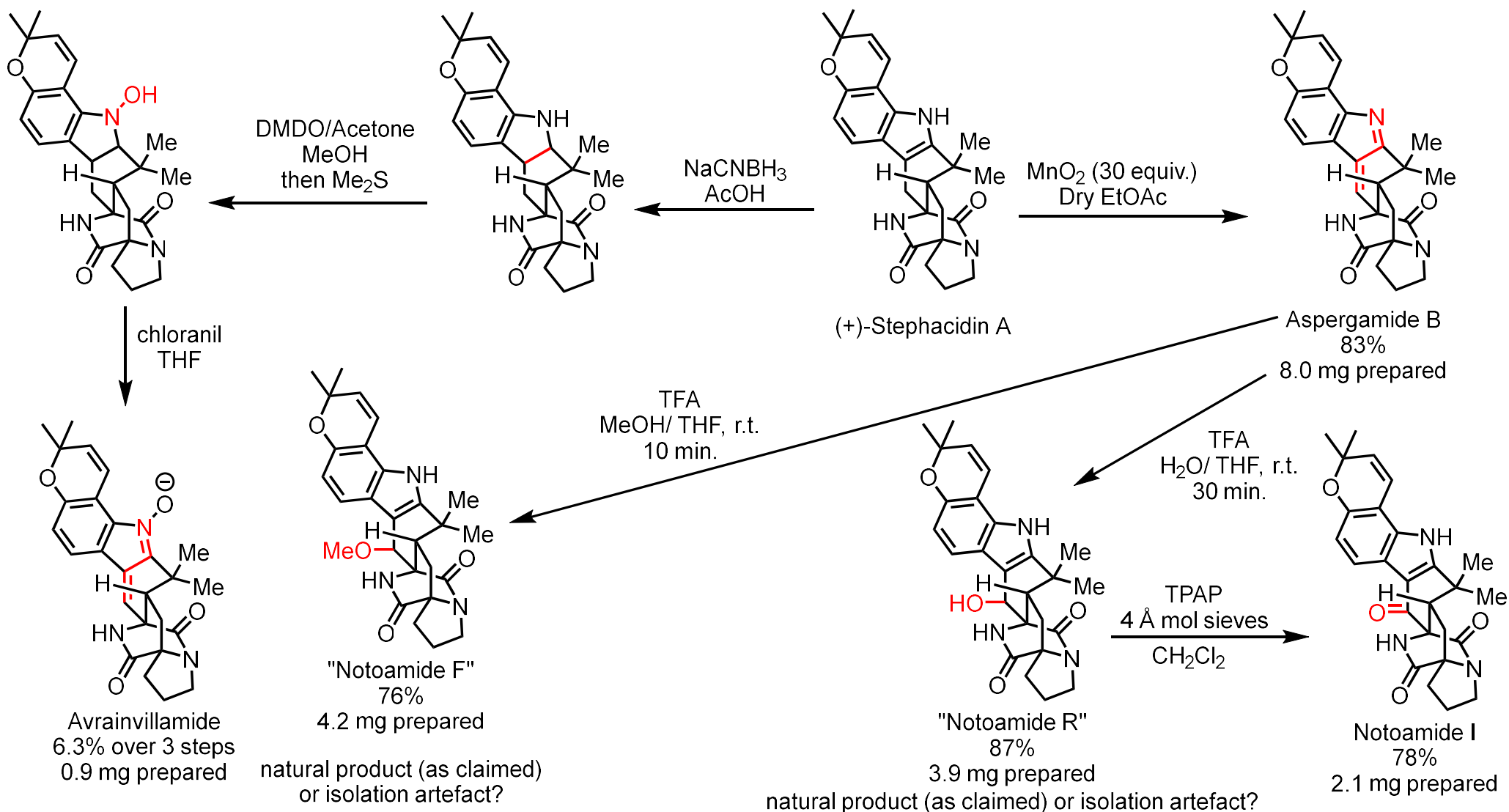
# Sarpong *et al.*'s Synthesis of Several Congeners

## Route to (+)-Stephacidin A



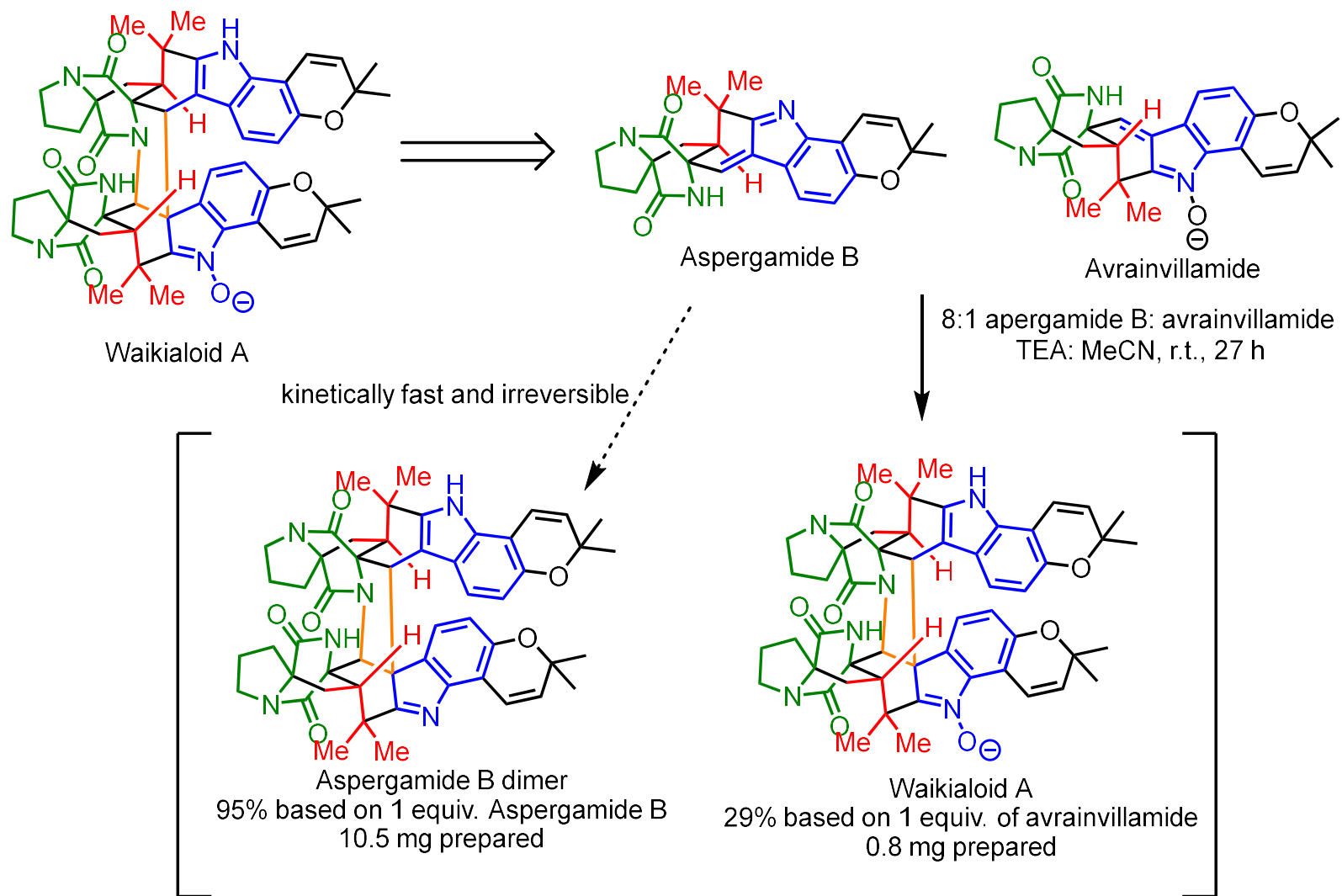
# Sarpong *et al.*'s Synthesis of Several Congeners

## Stephacidin A provides access to other reported natural products



# Sarpong *et al.*'s Synthesis of Several Congeners

## Dimeric products



Aspergamide B dimer has not (yet) been isolated from a natural source; may be a biosynthetic precursor to other congeners

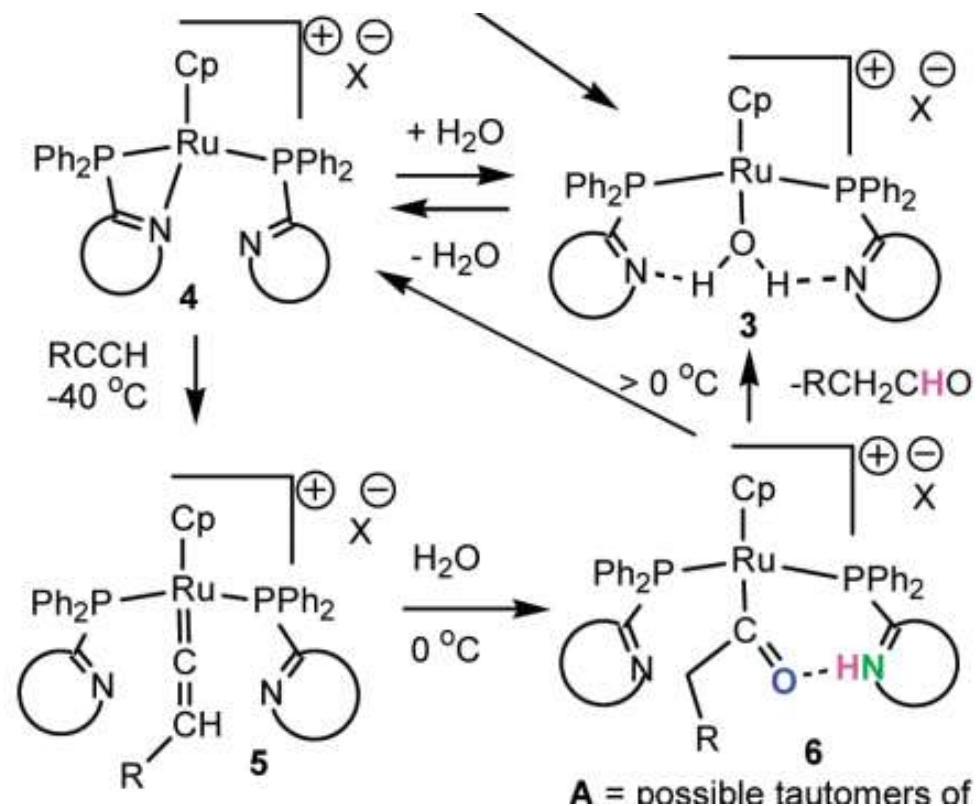
# Conclusions and Future Directions

- Synthetic disconnections: bicyclo[2.2.2]diazaoctane => Diels-Alder, cationic cascade, radical cascade, oxidative enolate coupling; monoketopiperazine and diketopiperazine => tryptophan + proline
- Prenylated indole alkaloids likely to persist as synthetic targets, in part due to a promising future for new discoveries in their isolation and biosynthesis which will provide new targets and bio-inspired routes
- However, diversity-oriented synthesis and late-stage functionalizations can allow access to prenylated indole alkaloids from disparate biosynthetic origins from a common synthetic intermediate
- Reactivity of these natural products through interconversion/ dimerization/ formation of isolation artefacts is appreciable, but extensive studies on this are likely limited by the amount of material available for such studies

# Relevant Reviews

- Williams, R. M. *et. al Chem. Soc. Rev.*, **2009**, 38, 3160-3174
- Sherman, D. H; Tsukamoto, S.; Williams, R. M. *et al. Nat. Prod. Rep.*, **2018**, 35, 532-558

# Grotjahn Anti-Markovnikov Hydration Catalyst



# Synthesis of Coupling Partner

