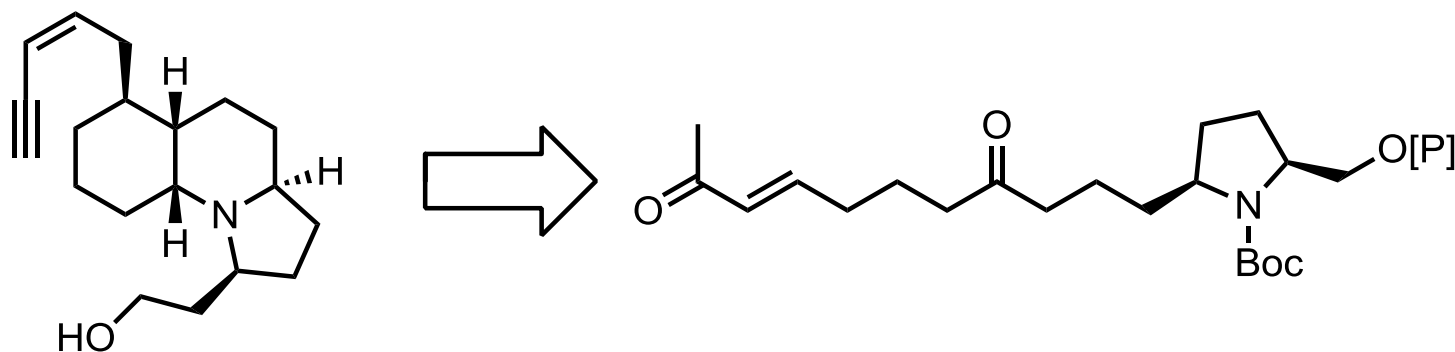


A Cascade Strategy Enables a Total Synthesis of (-)-Gephyrotoxin

Shuyu Chu, Stephen Wallace, and Martin D. Smith
Angew. Chem. Int. Ed. **2014**, 53, 1-5

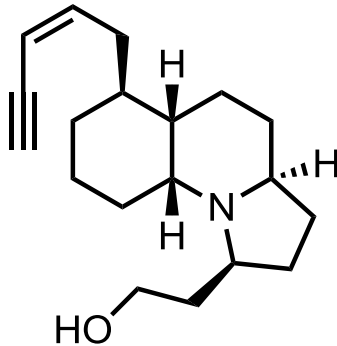


Nicholas Reed

Wipf Group Current Literature

November 8, 2014

(-)-Gephyrotoxin



- Isolated from *dendrobates histrionicus* (15 mg from 3200 frogs)

- Structure determined by 1-D and 2-D NMR, mass spectrometry, and X-ray diffraction

- Perhydropyrroloquinoline core with 5 stereocenters

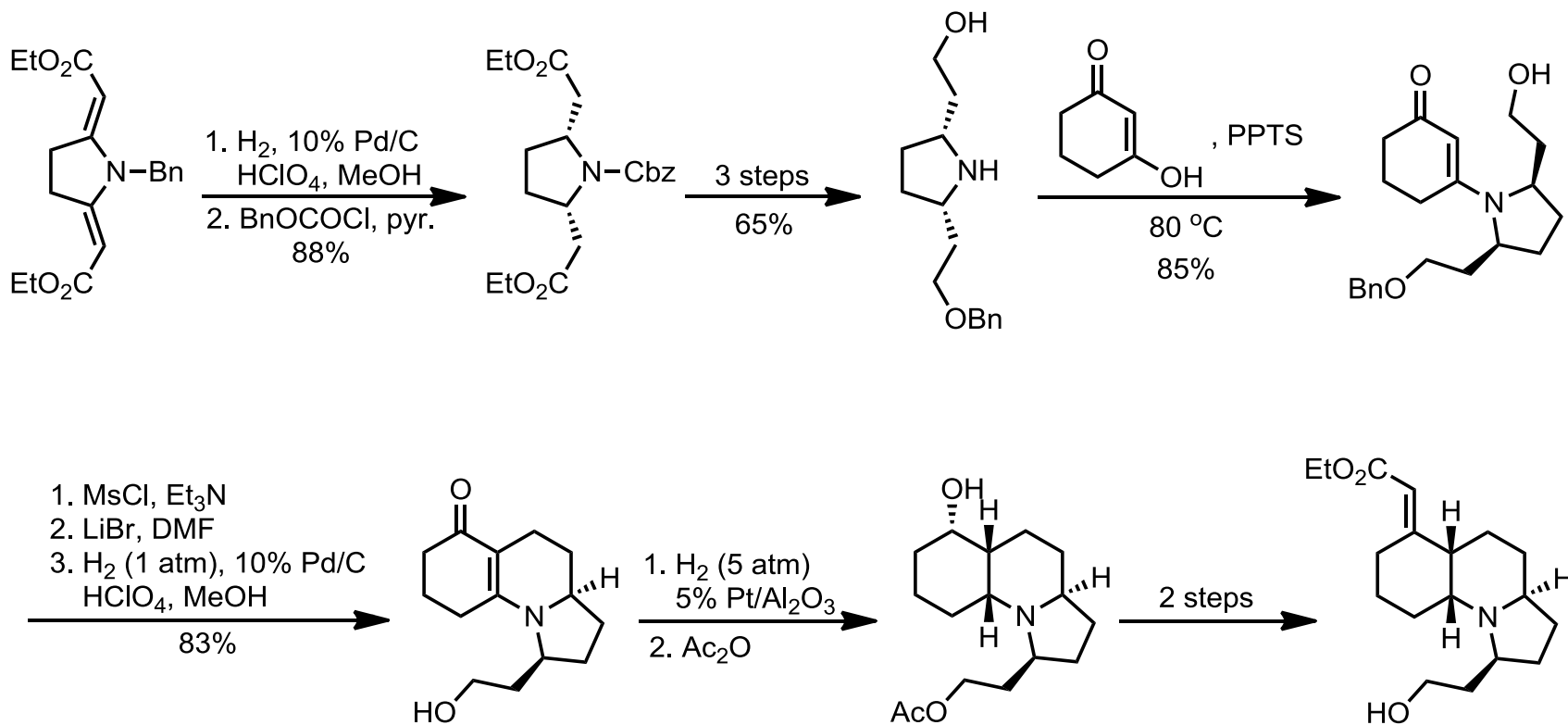
- Absolute stereochemistry established via X-ray diffraction of the HBr salt

- Affects K⁺ conductance at neuromuscular junction and has antimuscarinic properties

- Does not interact with acetylcholine binding site

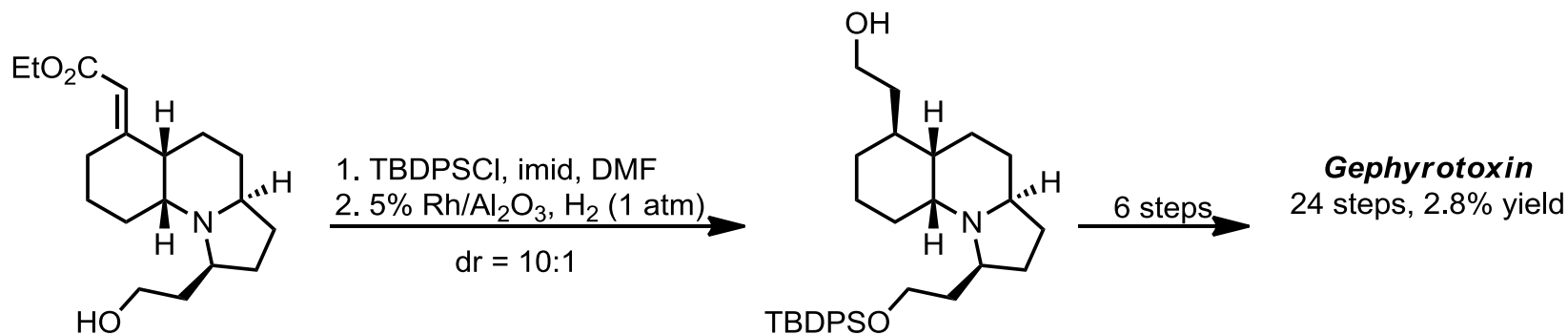
Helv. Chim. Acta. **1977**, *60*, 1128.

Kishi's Synthesis - Racemic



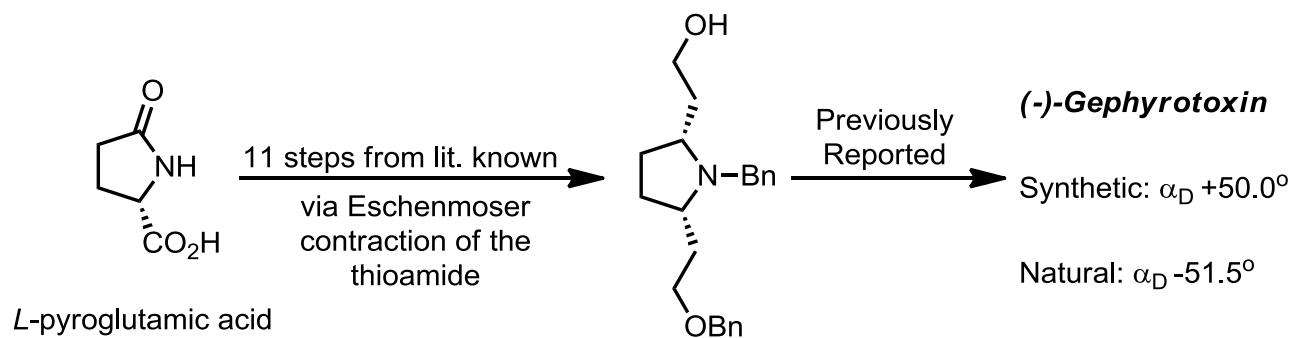
J. Am. Chem. Soc. **1980**, *102*, 7154

Kishi's Synthesis – Completion and Enantioselective Synthesis



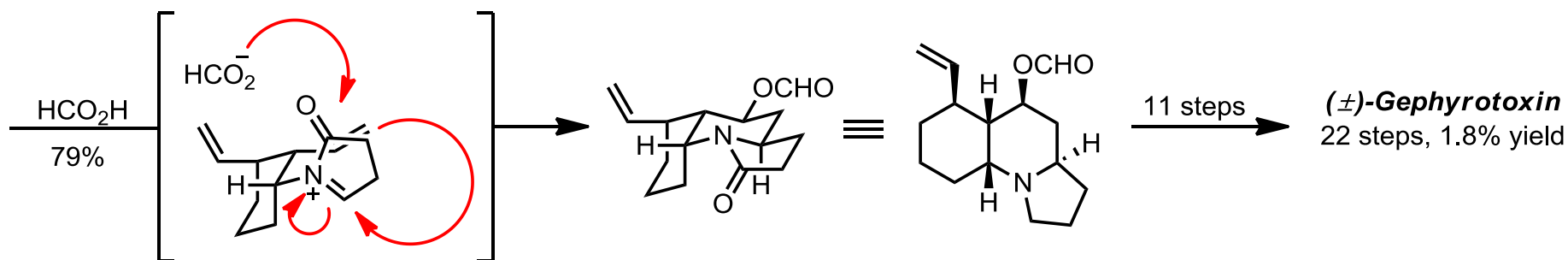
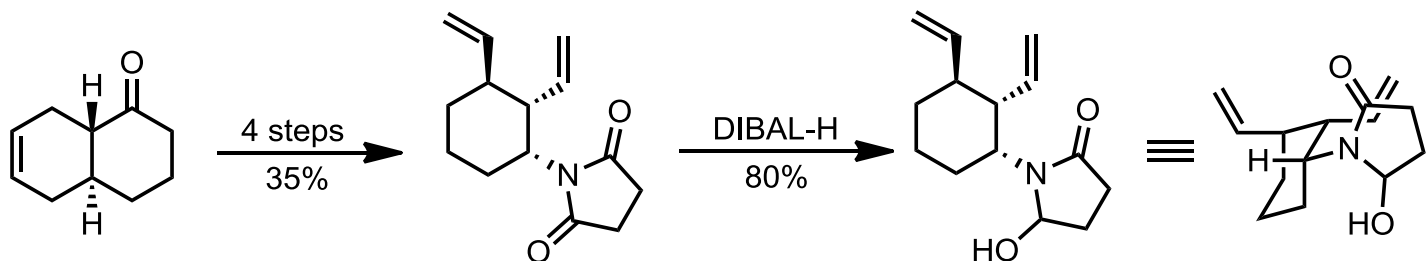
J. Am. Chem. Soc. **1980**, *102*, 7154

Enantioselective Synthesis (Unanswered Stereochemical Questions)



Tetrahedron Lett. **1981**, *42*, 4197

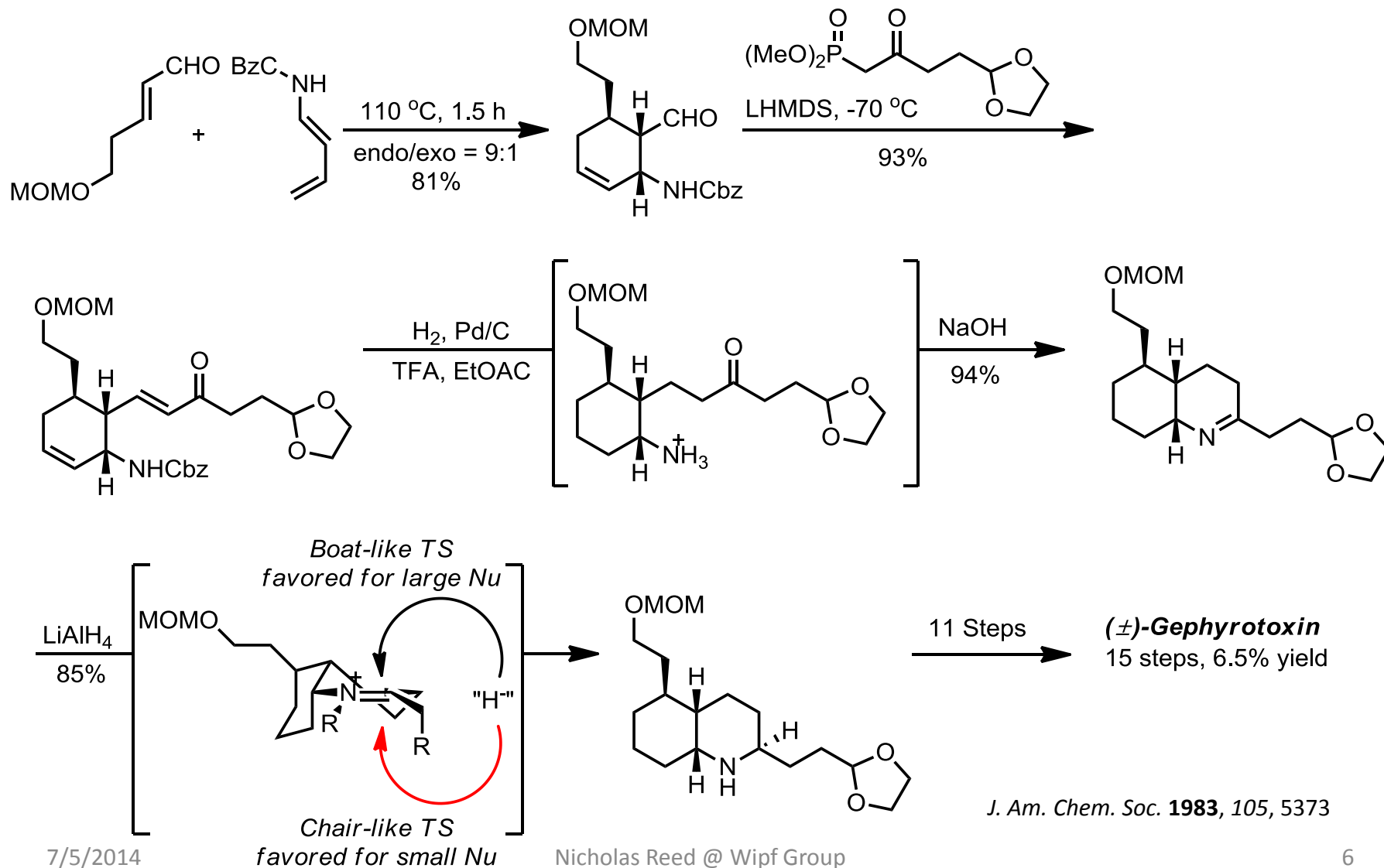
Hart's Synthesis - Racemic



N-Acyliminium Ion Cyclization

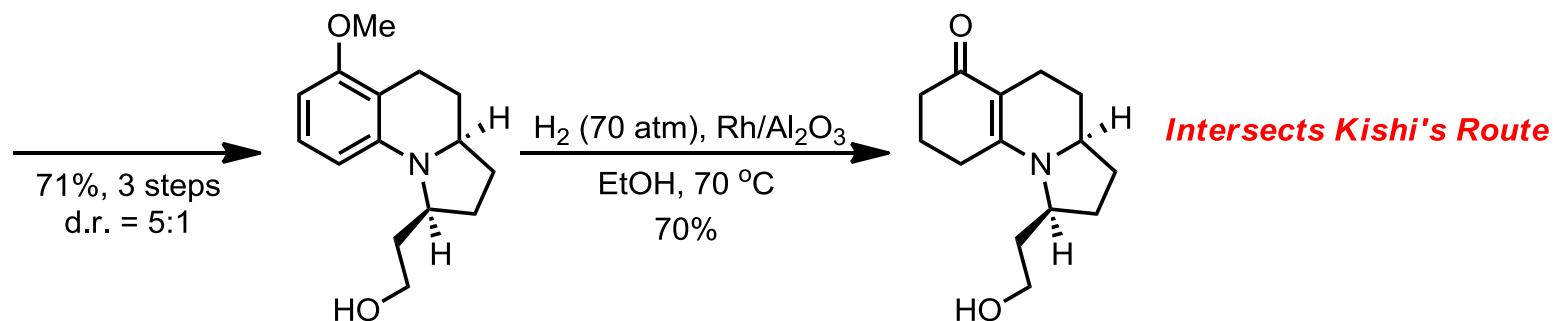
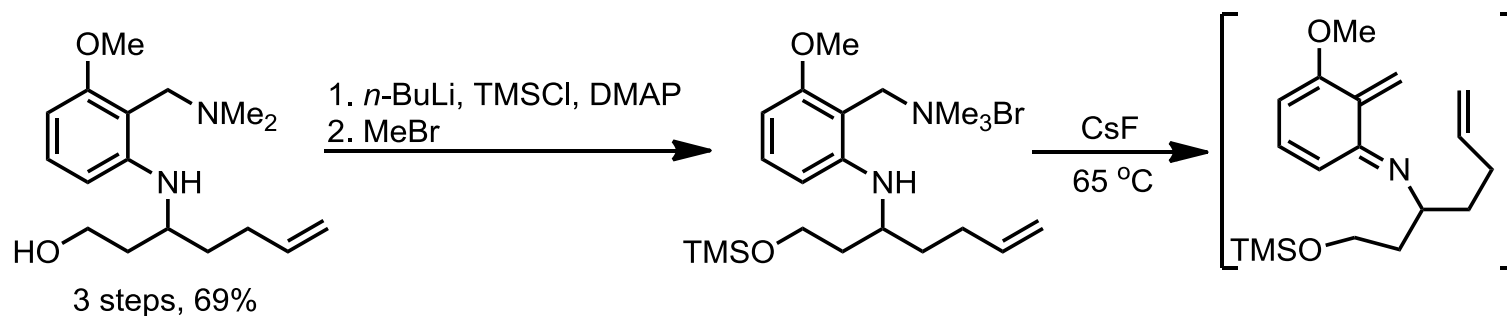
Starting Material: *Synth. Comm.* **1979**, 9, 391
J. Am. Chem. Soc. **1983**, 105, 1255

Overman's Synthesis - Racemic



Selected Formal Syntheses

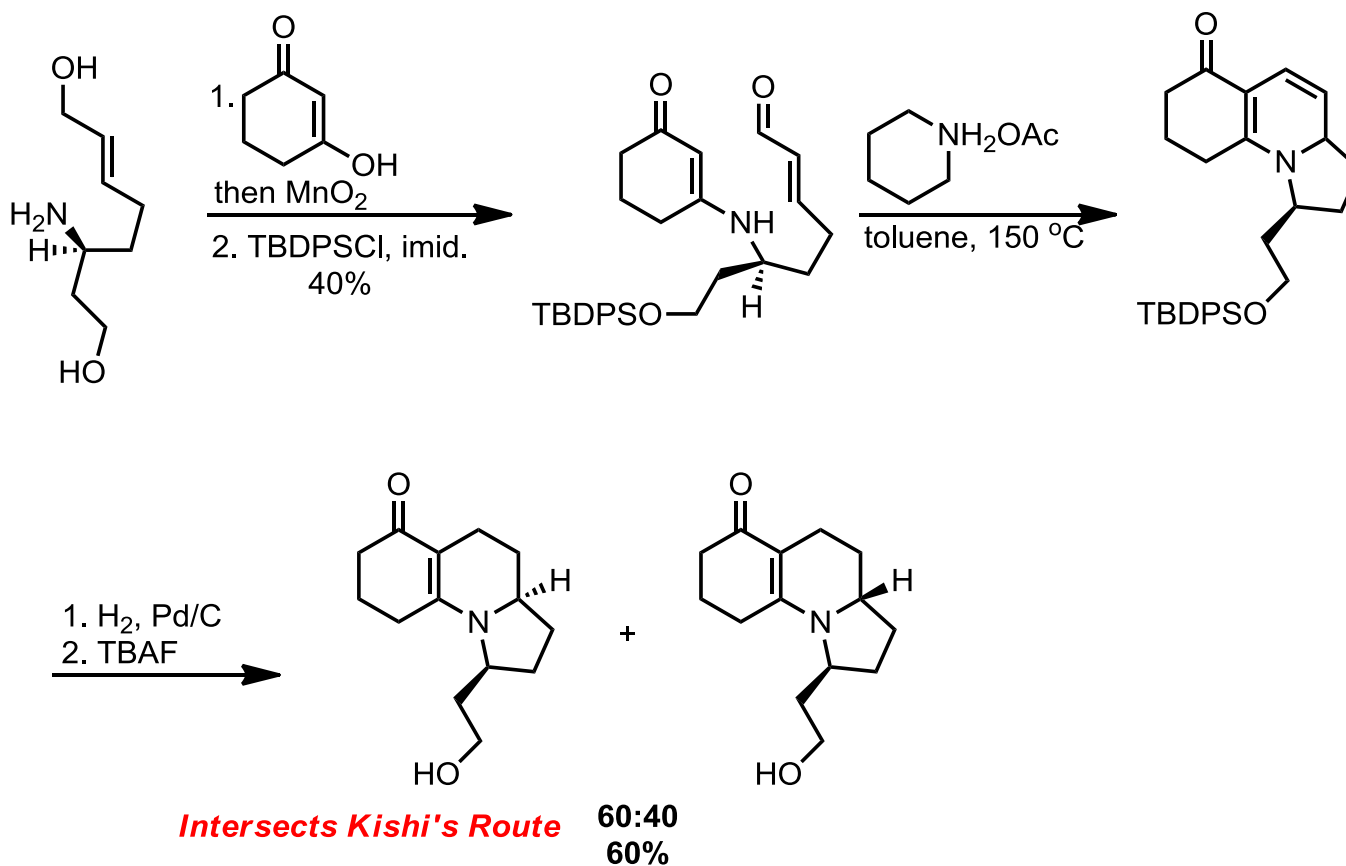
Ito and Saegusa:



Tetrahedron Lett. **1983**, 24, 2881

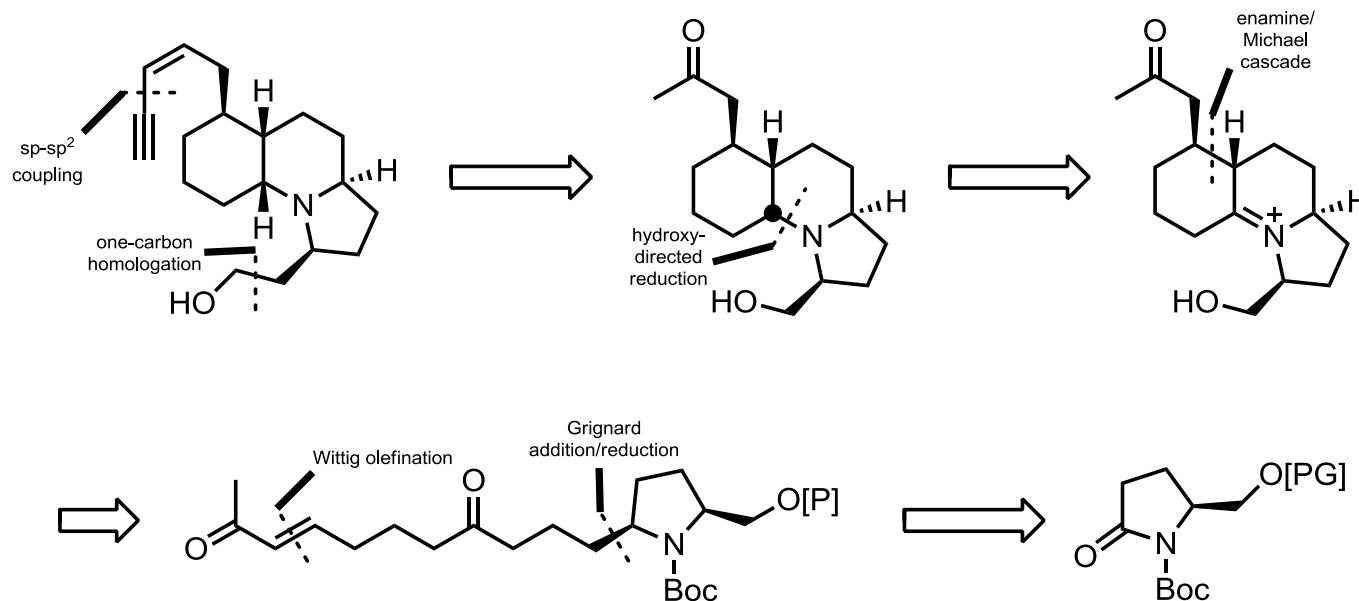
Selected Formal Syntheses

Hsung:



Angew. Chem. Int. Ed. **2001**, 41, 1516

Smith's Retrosynthesis

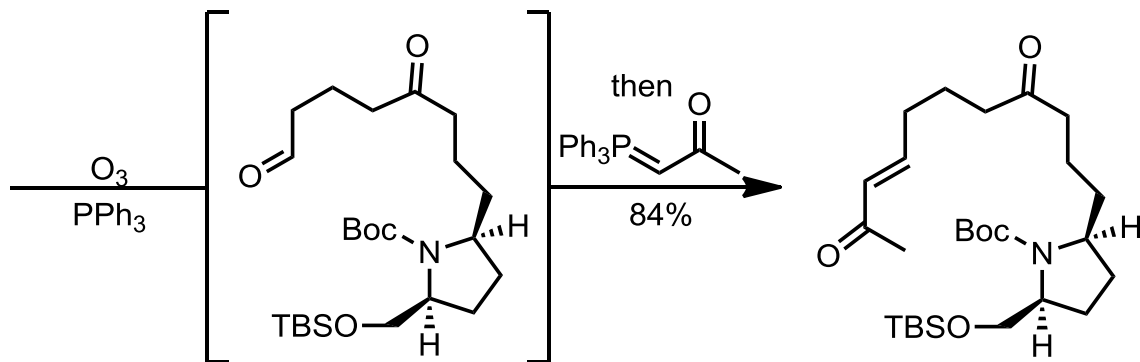
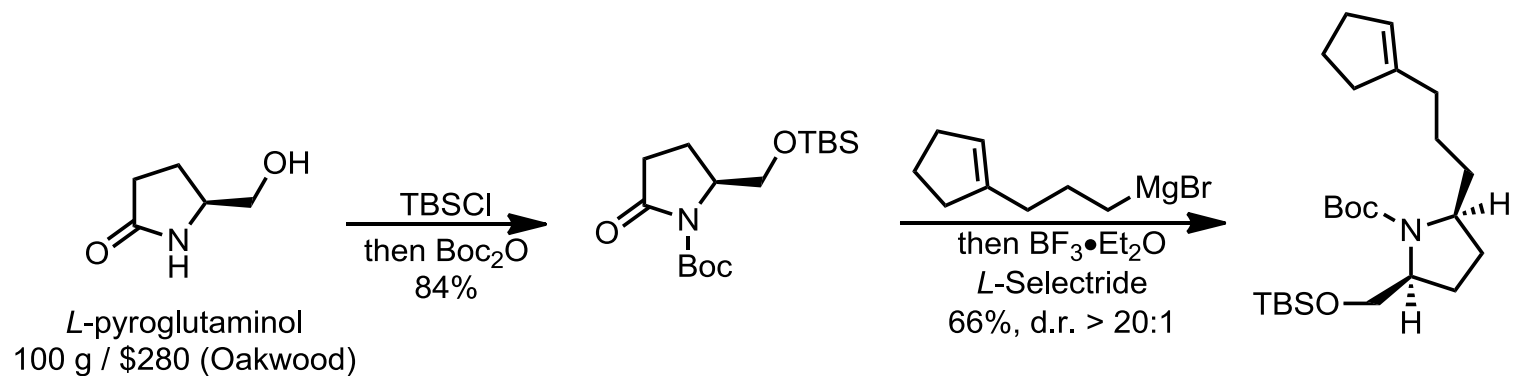


Key steps

Grignard Addition/Reduction
Enamine/Michael Cascade
sp-sp² coupling

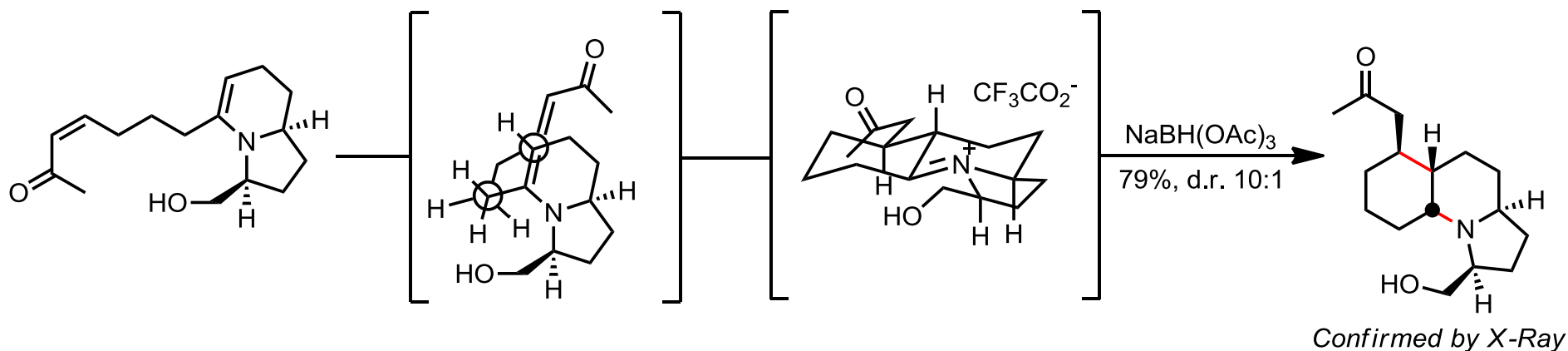
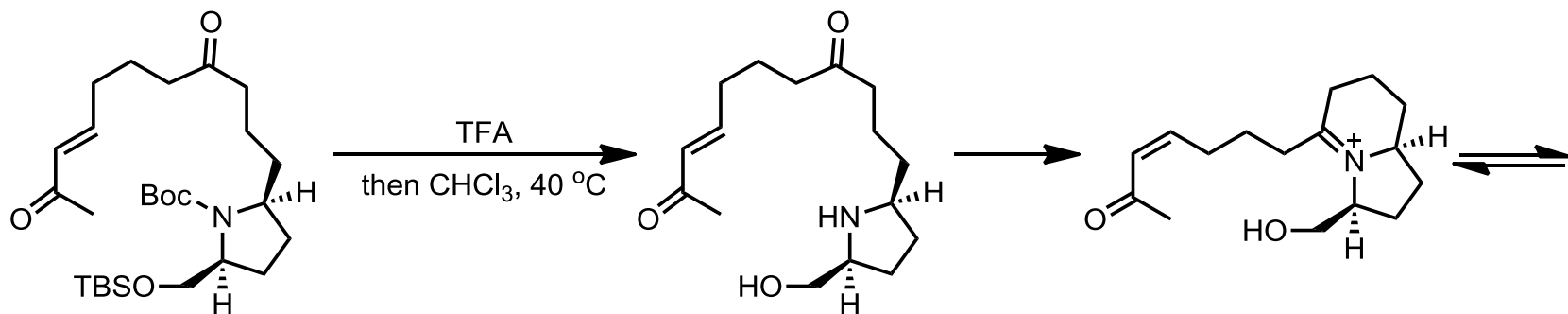
Angew. Chem. Int. Ed. **2014**, *53*, 1

Synthesis of the Cascade Precursor



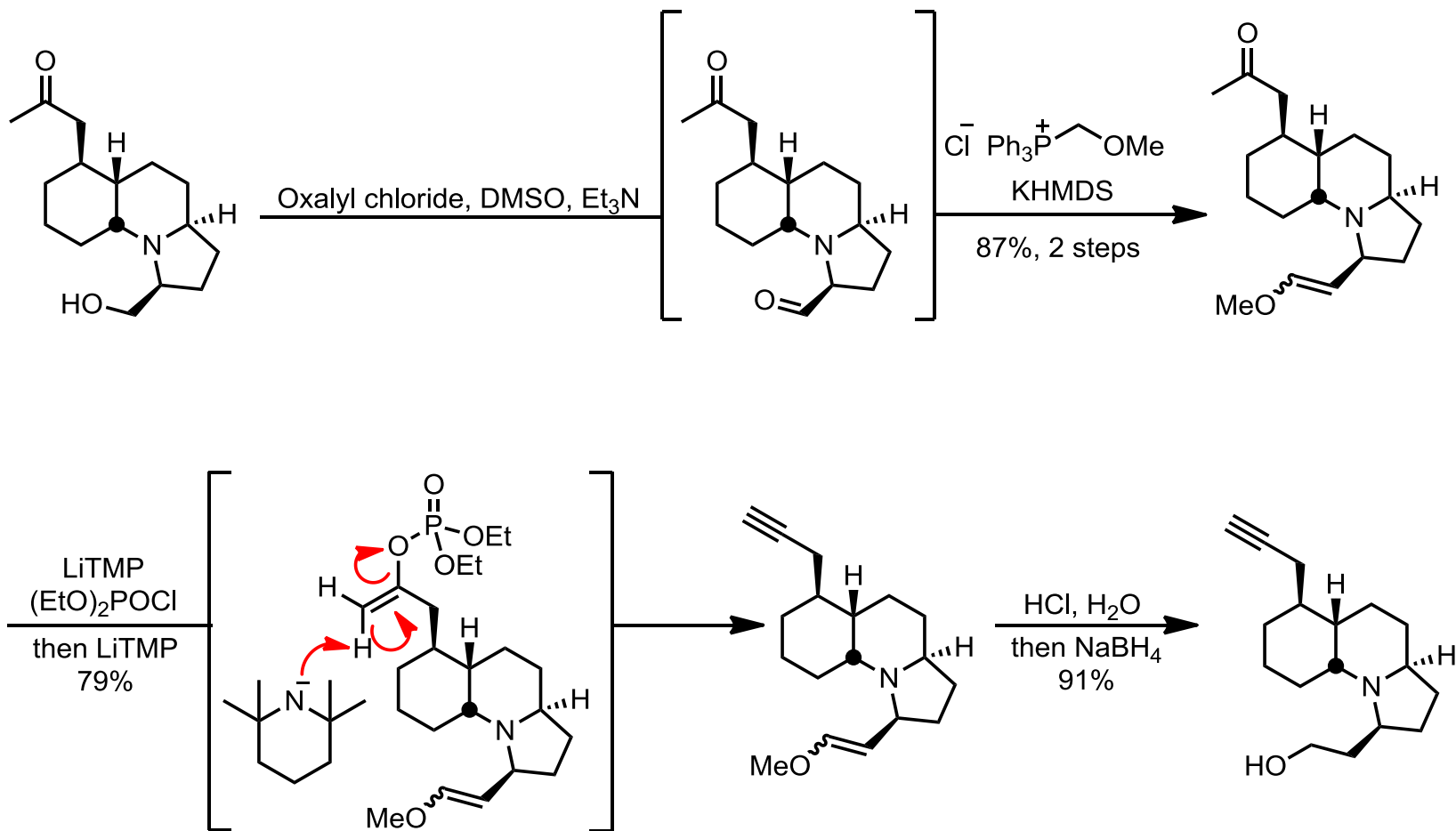
Angew. Chem. Int. Ed. **2014**, *53*, 1

Cascade Cyclization



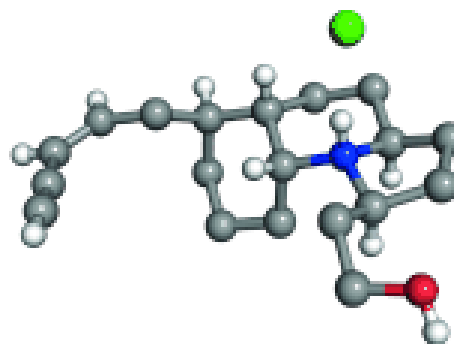
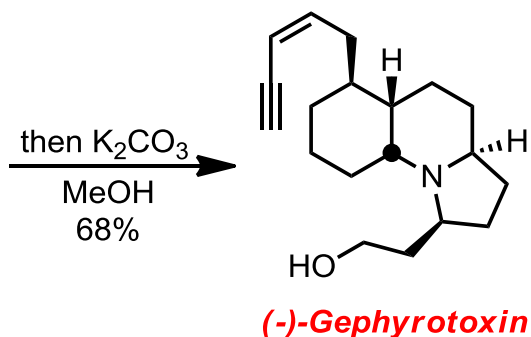
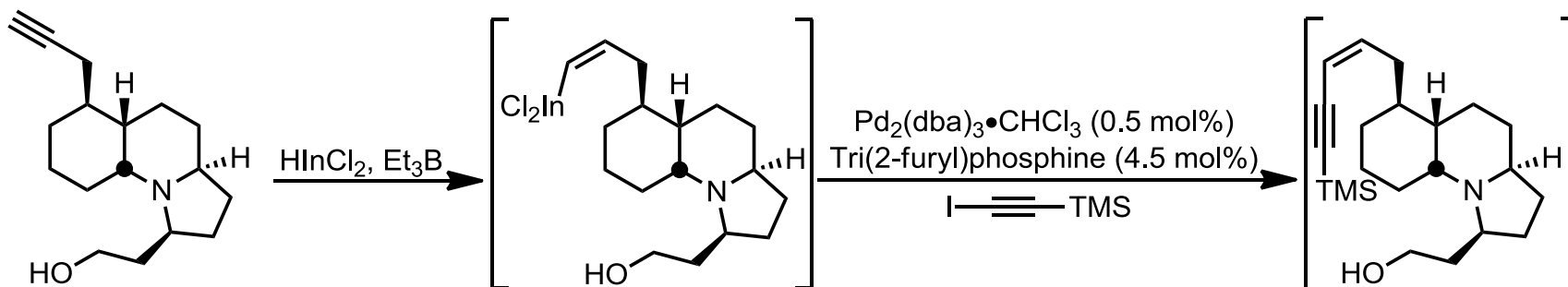
Angew. Chem. Int. Ed. **2014**, *53*, 1

Synthesis of the Penultimate Compound



Angew. Chem. Int. Ed. **2014**, *53*, 1

Hydrometalation/Cross-Coupling to (-)-Gephyrotoxin

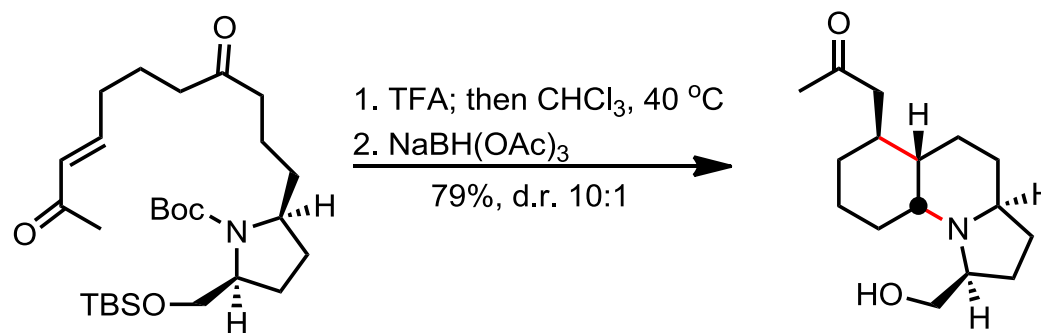


- X-Ray confirmation of HCl salt
- Preparation of Both Mosher Esters Confirms Enantiomeric Purity
- Optical Rotation: -52.3 ($c = 1.0$, EtOH)
- Kishi Reports $+50.0$ ($c=1.0$, EtOH) for same absolute configuration!
- Not Enough Natural Product to Confirm Structural Assignment

Angew. Chem. Int. Ed. **2014**, *53*, 1
Org. Lett. **2002**, *4*, 2993

Conclusions

- Total synthesis of (-)-gephyrotoxin (9 steps LLS, 14% overall from *L*-pyroglutaminol)
- Intramolecular enamine/Michael cascade



- Poor step/redox economy (alcohol homologation)
- Possible revision of absolute configuration for natural product