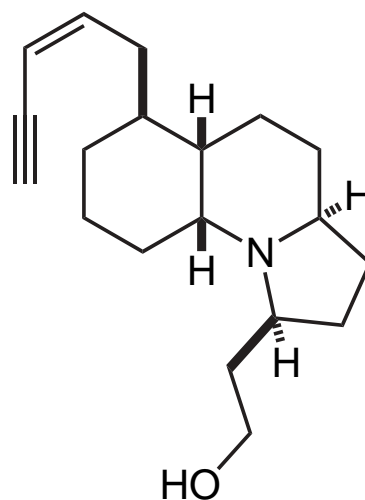


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# Synthesis of Gephyrotoxin

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A Friday Evening Seminar



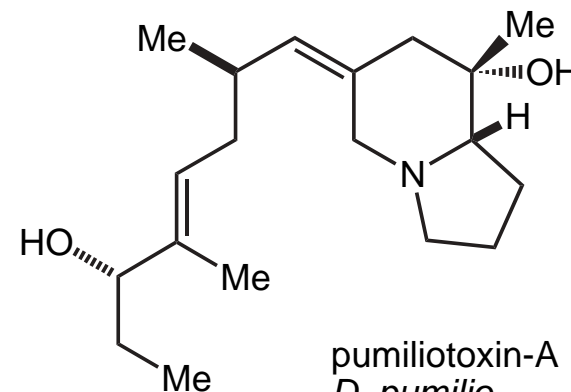
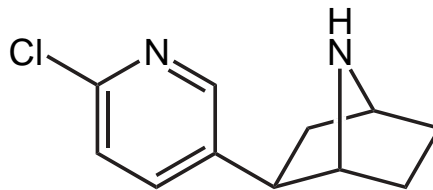
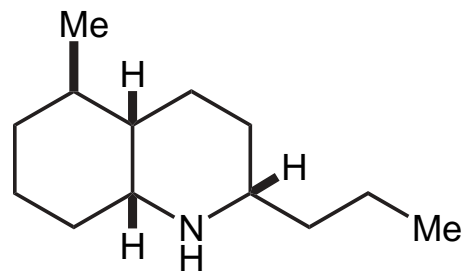
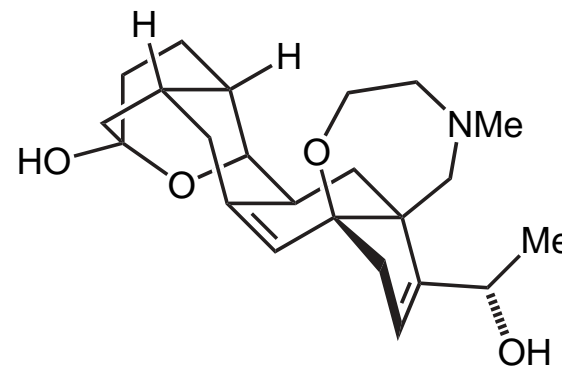
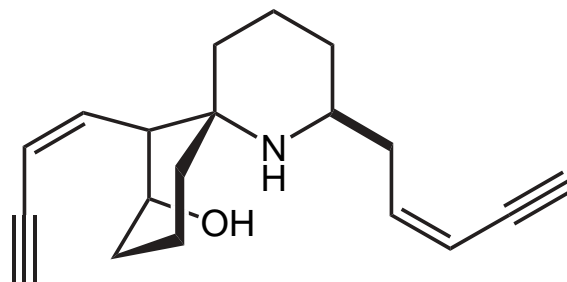
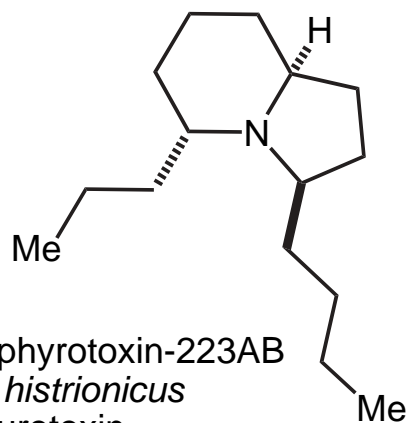
Jonathan R. Scheerer

8 November 2002

Keywords: gephyrotoxin, alkaloid, total synthesis

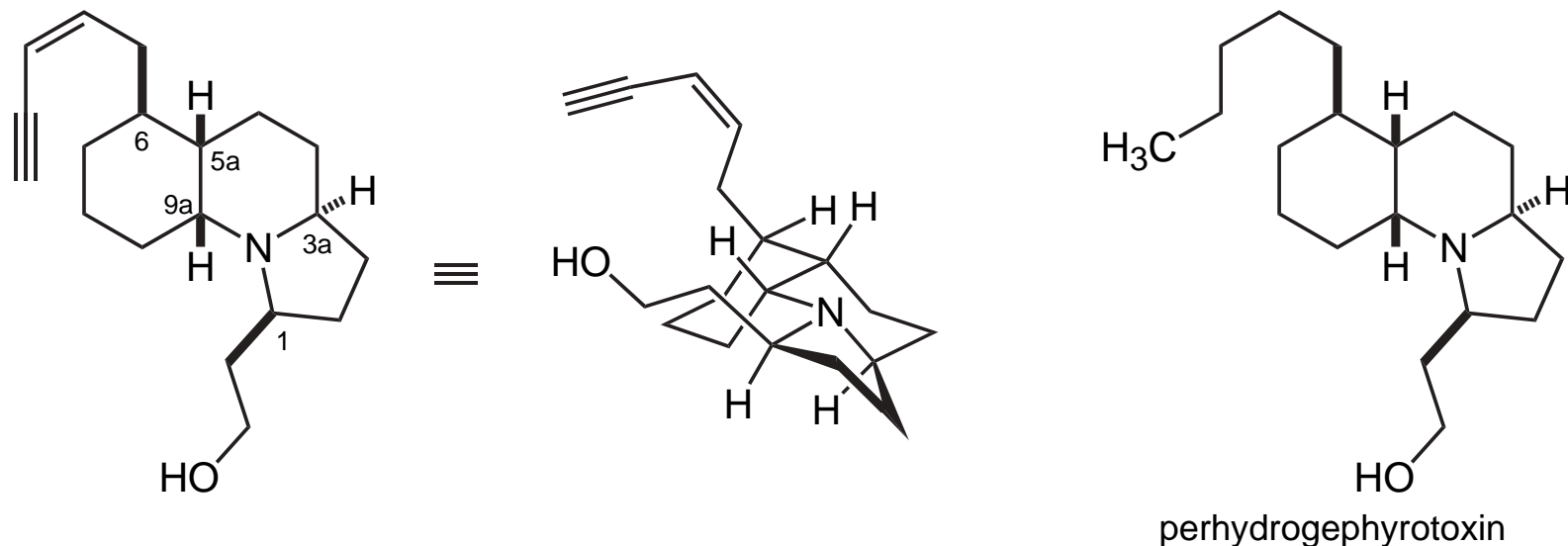
# Alkaloids from Dendrobatidae Frogs

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## (+)-Gephyrotoxin

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Isolation/elucidation: (X-ray):  
Daly, J.W. *Helv. Chim. Acta.* **1977**, *60*, 1128.

Total Syntheses:  
Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7154.  
Kishi, Y. *Tet. Lett.* **1981**, *42*, 4197.\*  
Overman, L. *J. Am. Chem. Soc.* **1983**, *105*, 5373.  
Hart, D. *J. Am. Chem. Soc.* **1983**, *105*, 1255.

Perhydrogephyrotoxin Syntheses:  
Overman, L. *J. Am. Chem. Soc.* **1980**, *102*, 1454.  
Hart, D. *J. Org. Chem.* **1981**, *46*, 3576.  
Ibuka, T. *Chem. Pharm. Bull.* **1986**, *34*, 2380.

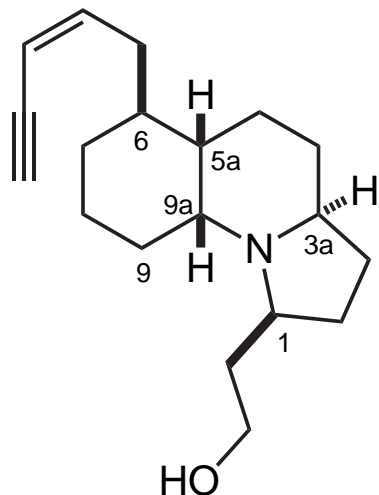
Dendrobatidae alkaloids:  
Daly, J.W. *Fortschr. Chem. Org. Naturst.* **1982**,  
*41*, 205-340.  
Daly, J.W. *J. Nat. Prod.* **1998**, *61*, 162.

Formal Syntheses:  
Ito, Y. and T. Saegusa. *Tet. Lett.* **1983**, *24*, 2881.  
Pearson, W.H. *J. Org. Chem.* **2000**, *65*, 7158.  
Hsung, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 1516.\*

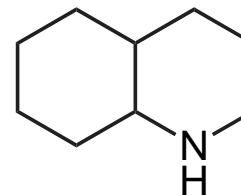
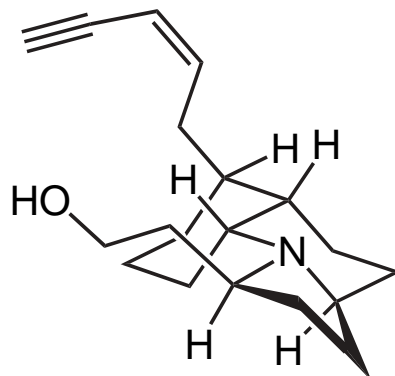
\* = asymmetric

## **(+)-Gephyrotoxin**

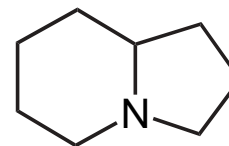
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≡



Decahydroquinoline



Indolizidine

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Name: *Gephyra* (Greek: meaning bridge)

Isolation (1974): 15 mg from 3200 frogs (*D. histrionicus*)

Pharmacology:

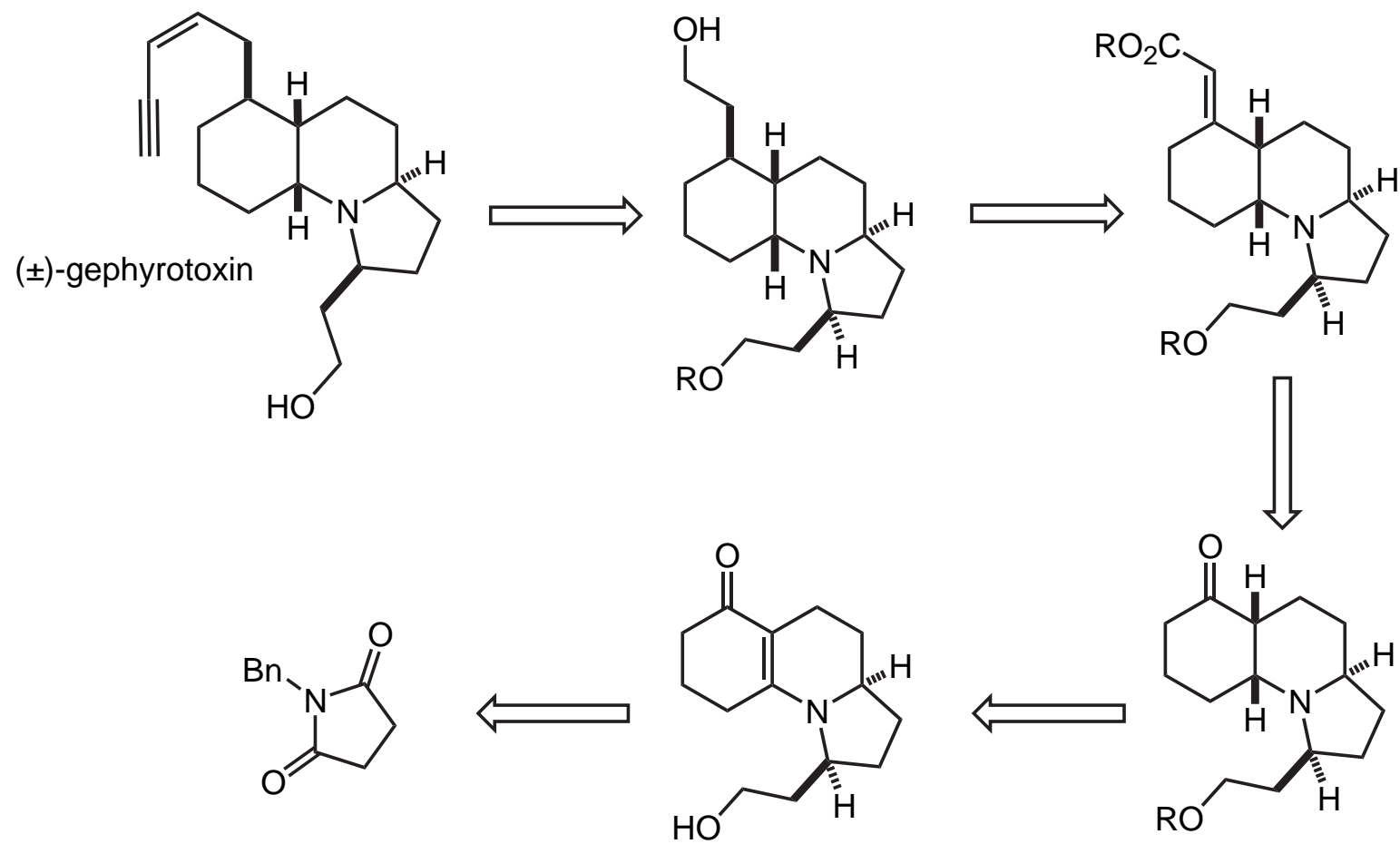
mild  $K^+$  conductance disruptance (anticholinergic properties)

potent muscarinic antagonist

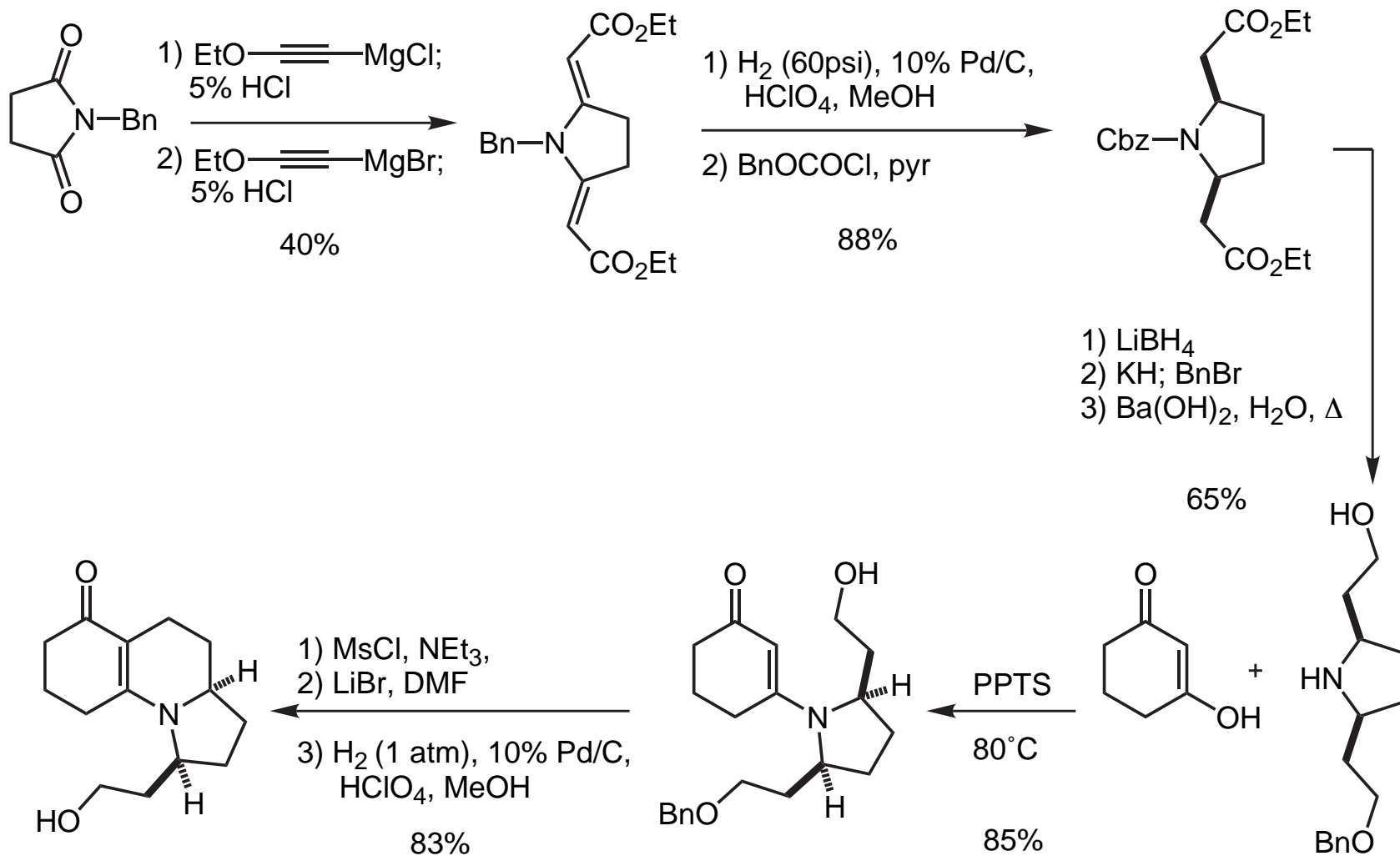
neurological disfunction

## Kishi: Retrosynthesis

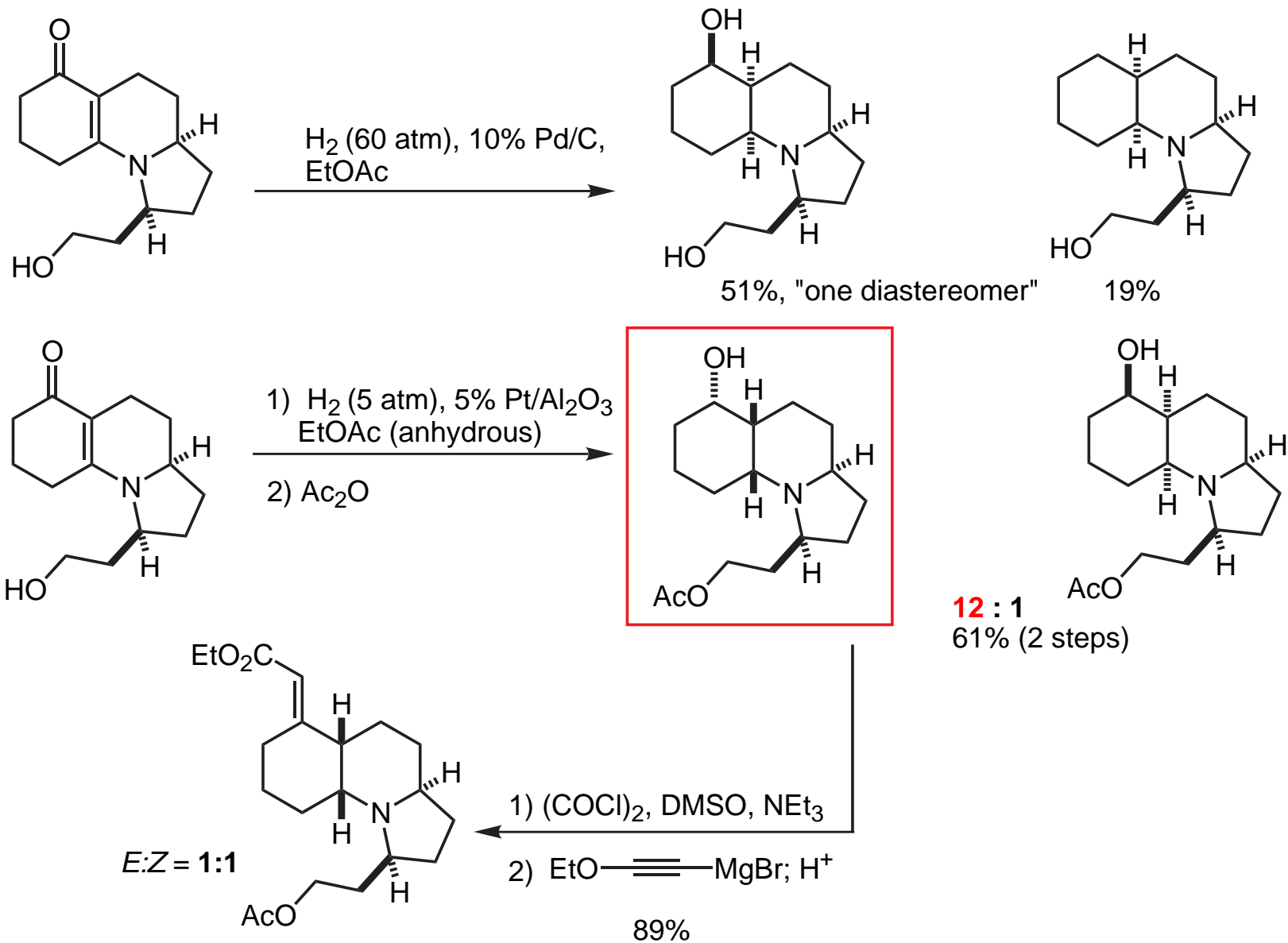
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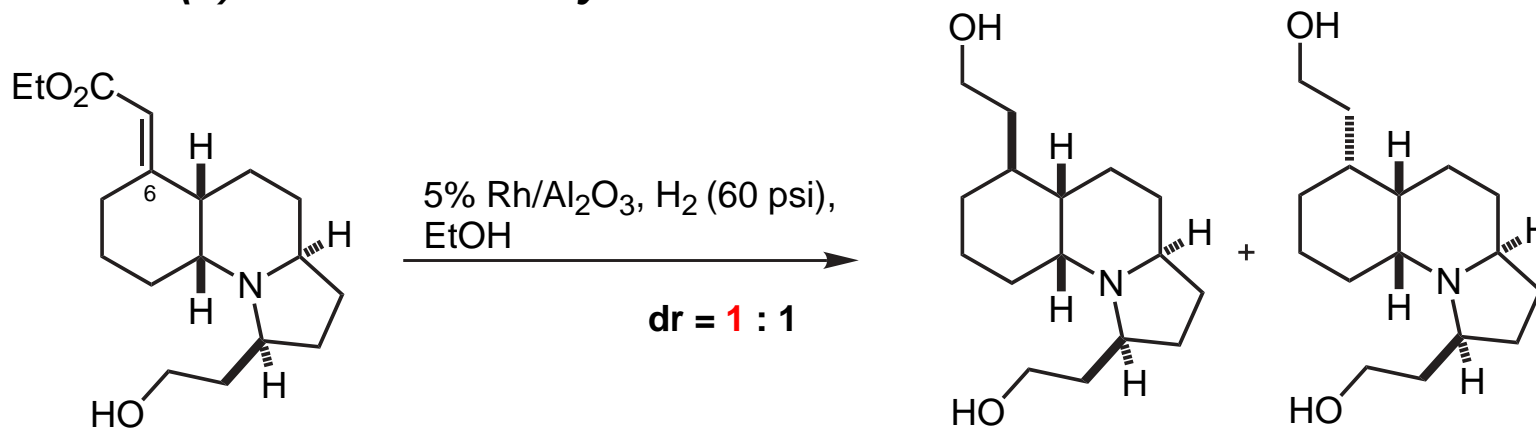
## Kishi: Construction of Tricycle



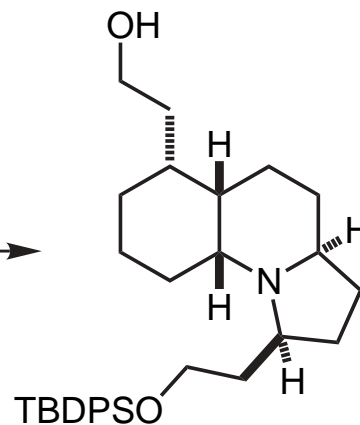
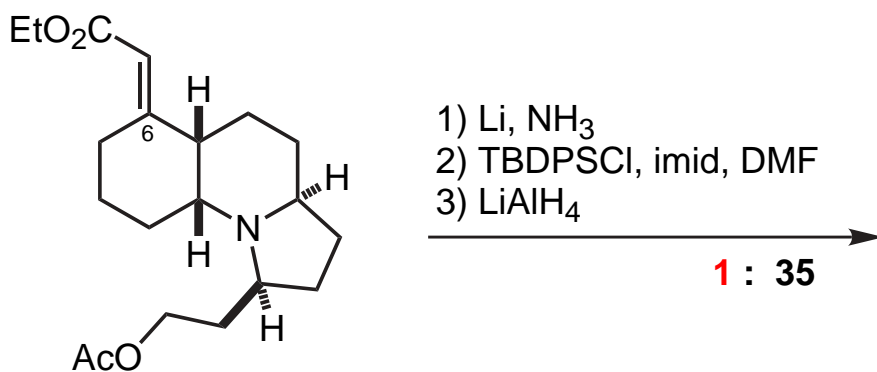
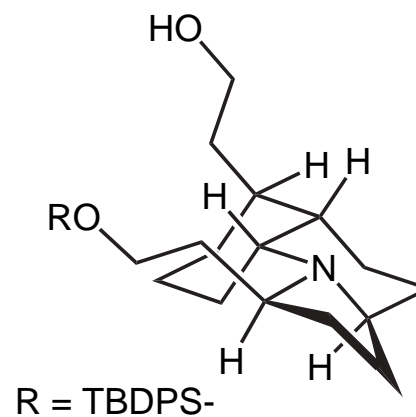
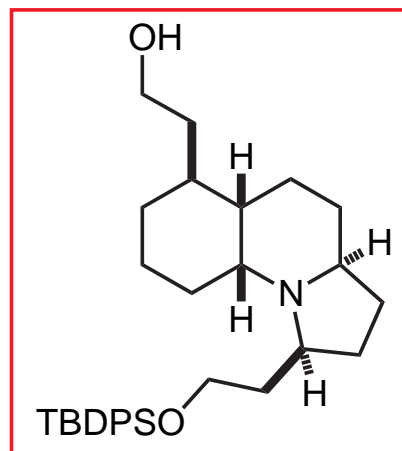
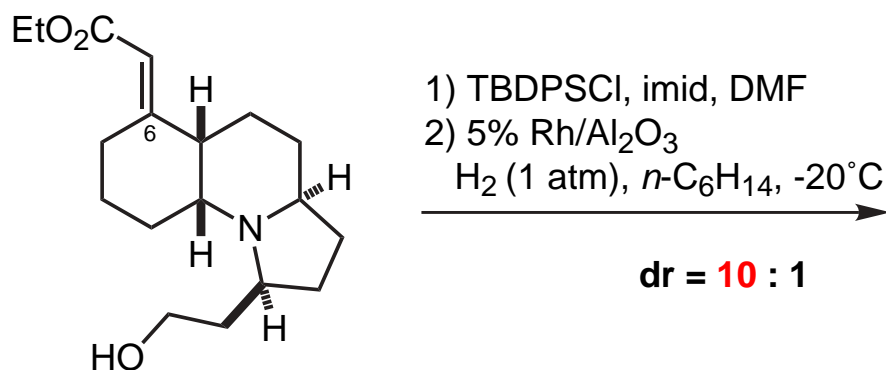
## Kishi: *Cis*-fused Hydroquinoline



## Kishi: C(6) Stereochemistry



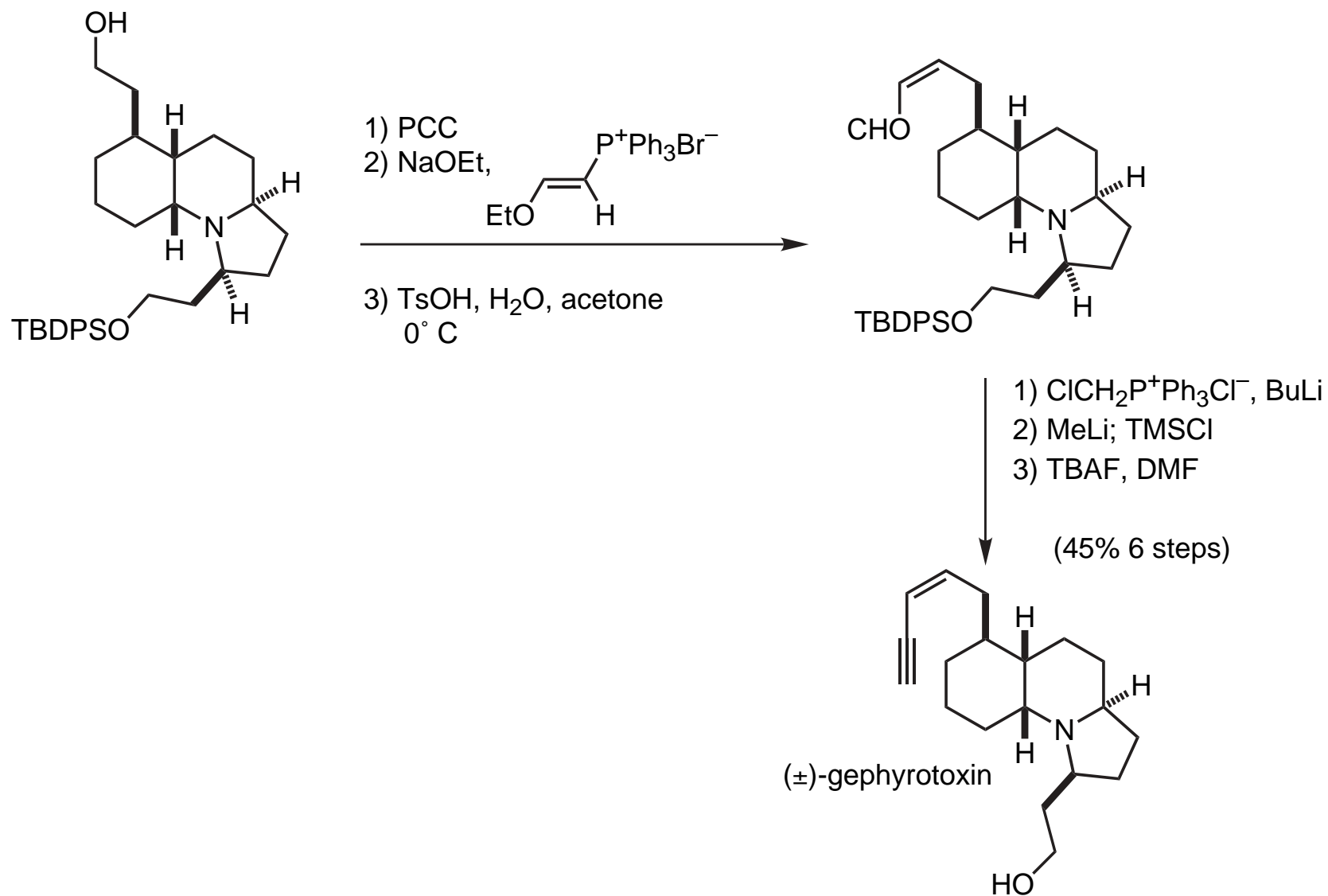
*E*:*Z* = 1:1



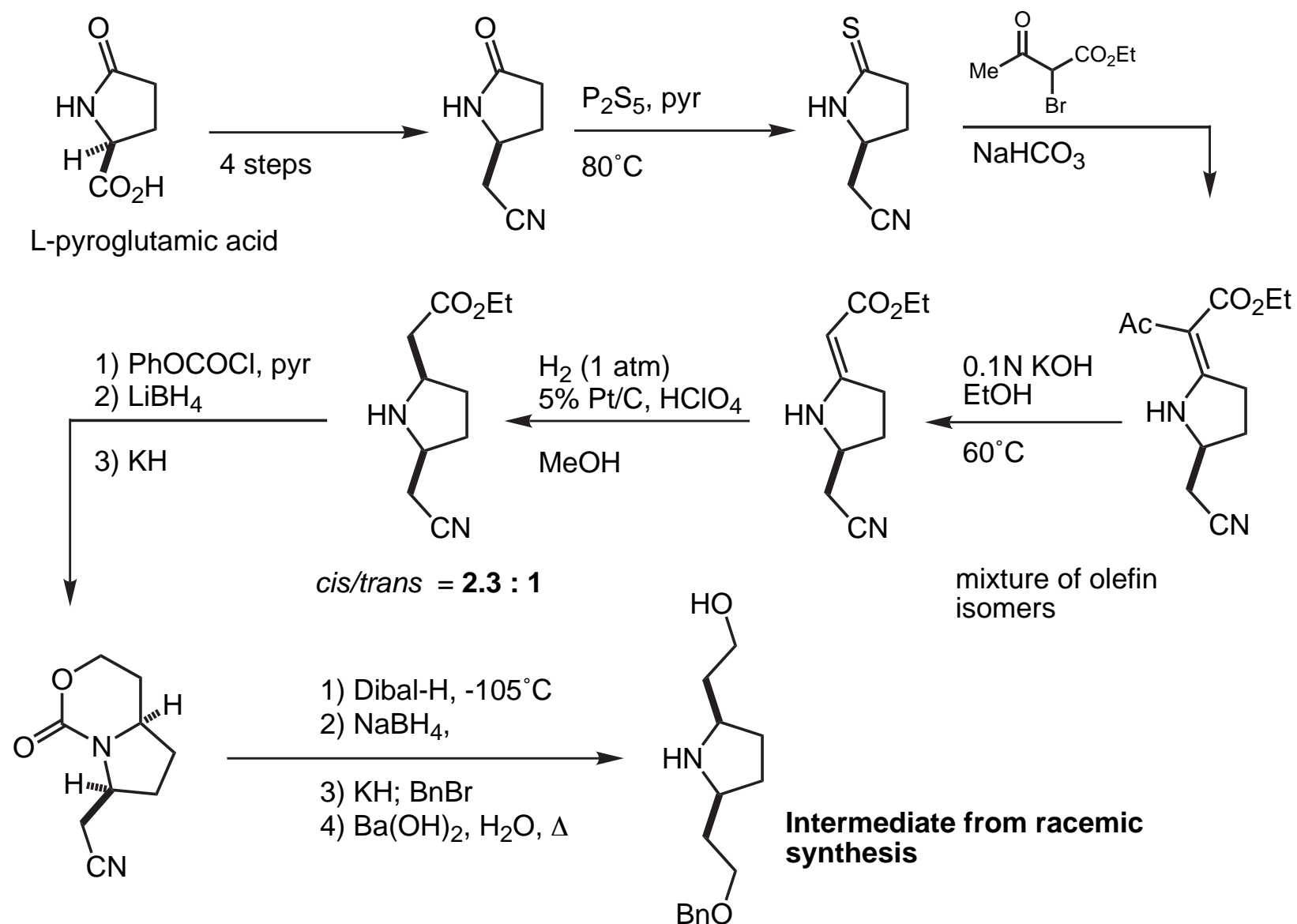
Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7154.



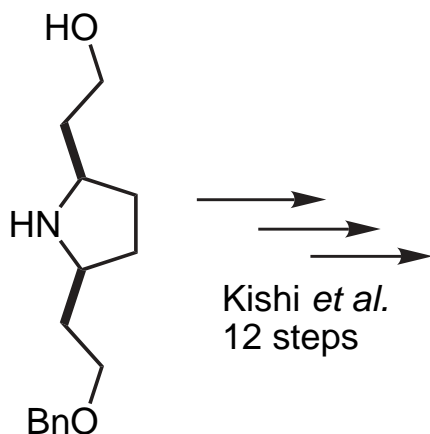
## Kishi: Completion of Gephyrotoxin (enyne installation)



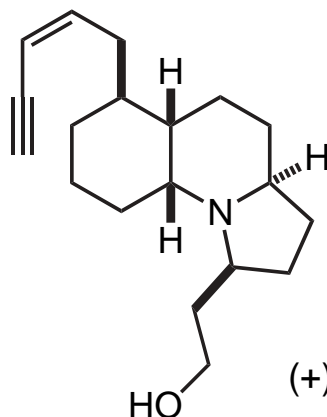
## Kishi: Toward Asymmetric Gephyrotoxin



## Kishi: Absolute Configuration Questioned



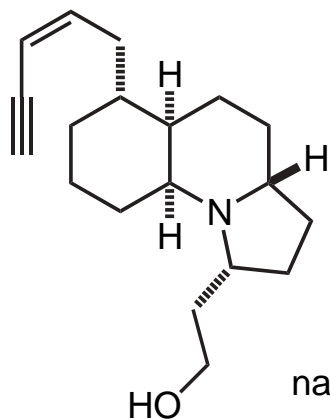
→  
→  
→  
Kishi *et al.*  
12 steps



Original stereoconfiguration assigned  
by X-ray from HBr salt of gephyrotoxin  
(anomalous scattering of Br<sup>-</sup>)

Synthetic  
(c = 1.0, EtOH)

$[\alpha]_D = +50.0^\circ$



Natural  
(c = 1.0, EtOH)

$[\alpha]_D = -51.5^\circ$

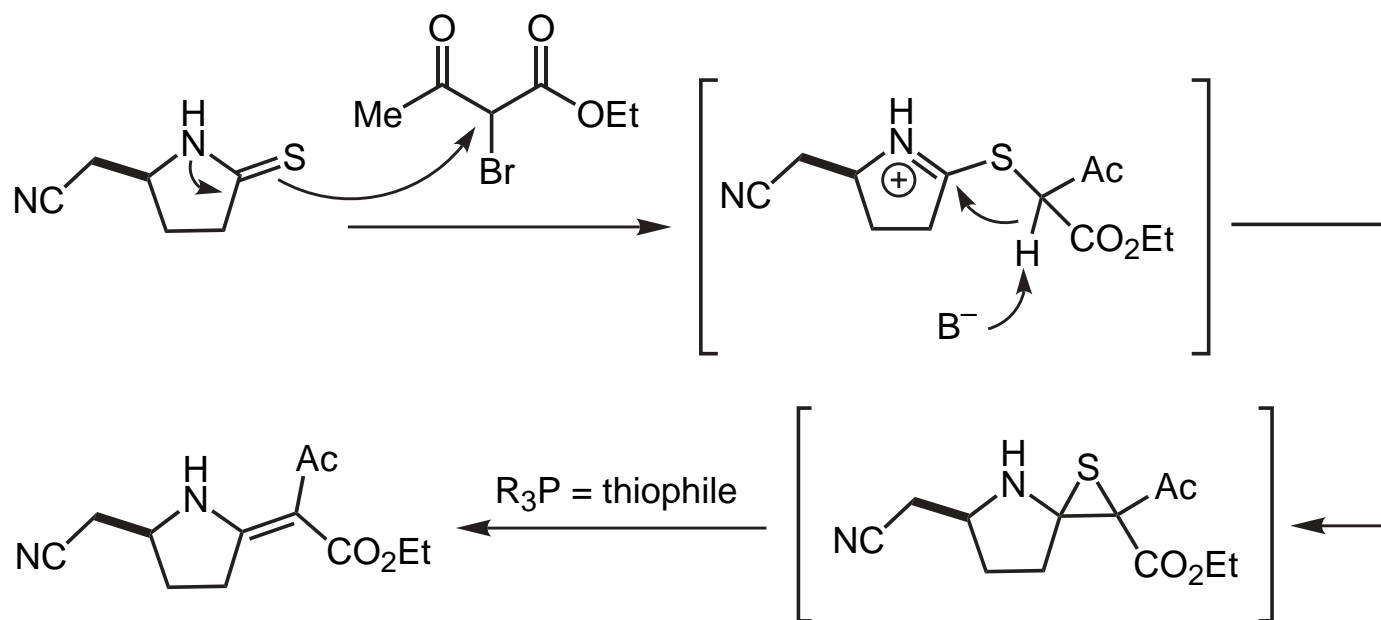
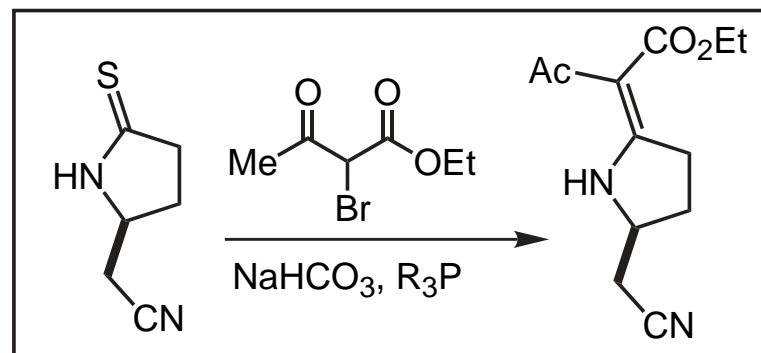
Kishi suggests structural reassignment based on  
optical rotation.

natural (-)-gephyrotoxin (?)

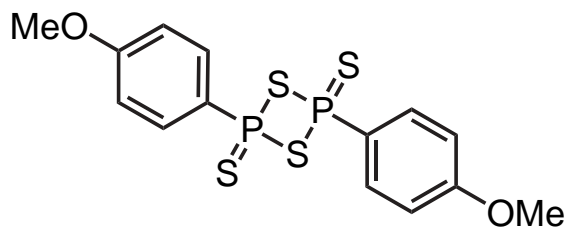
Insufficient natural supply to confirm  
reassignment

*Tet. Lett.* **1981**, *42*, 4197.

**Eschenmoser Contraction:**  
Formation of Vinylogous Amides  
and Urethanes

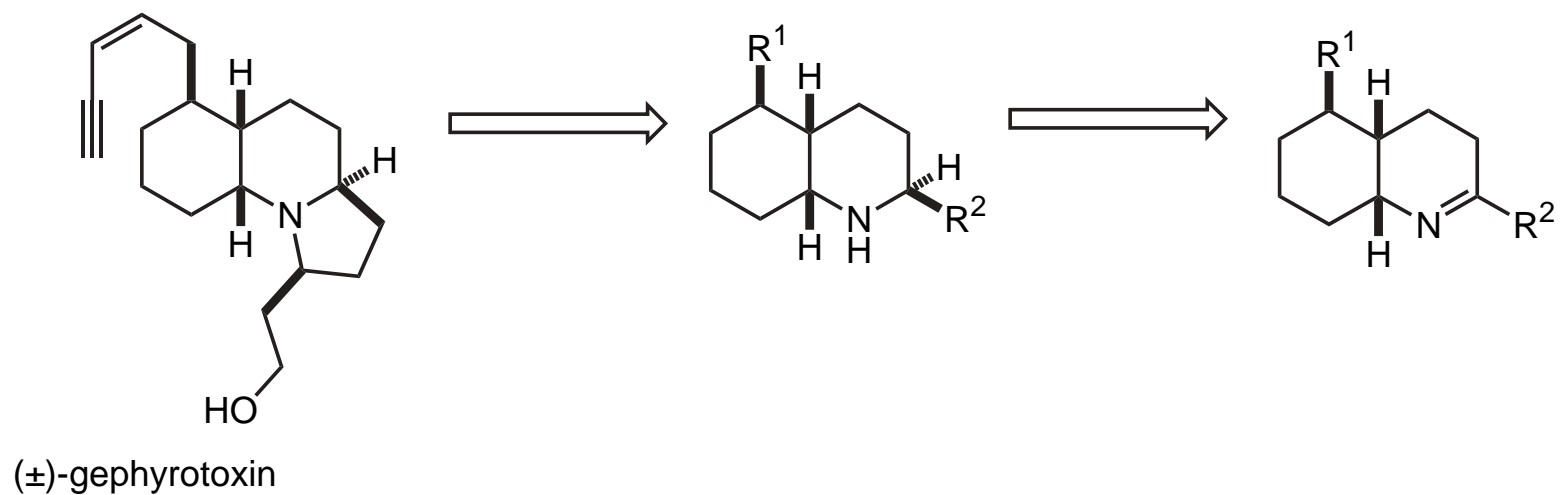
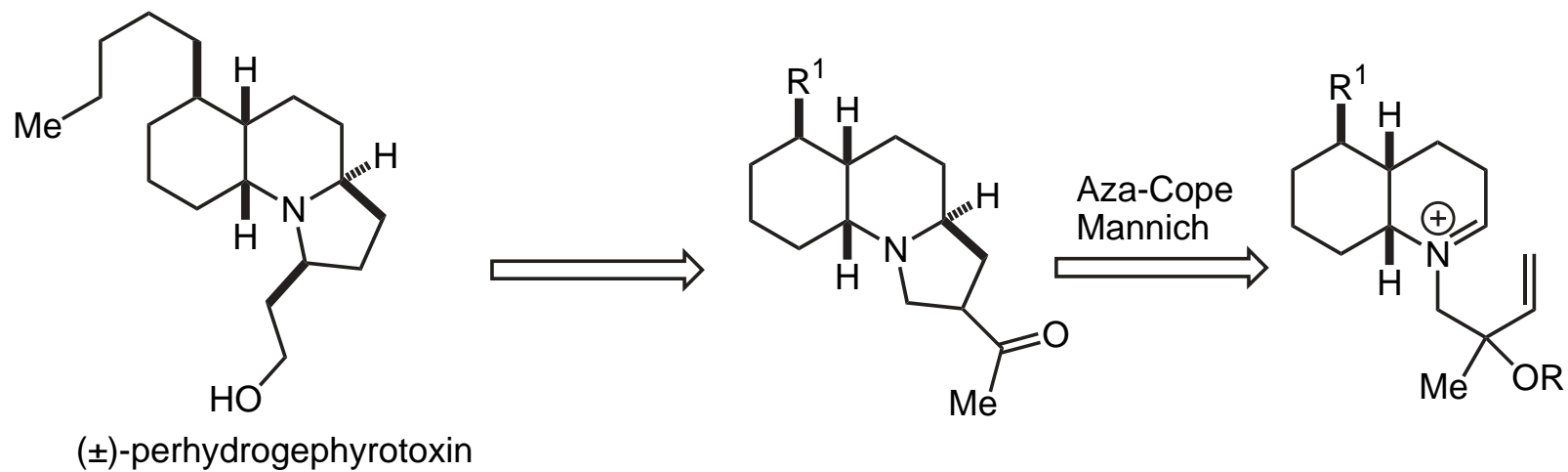


- Thioamides usually prepared with Lawesson's reagent:

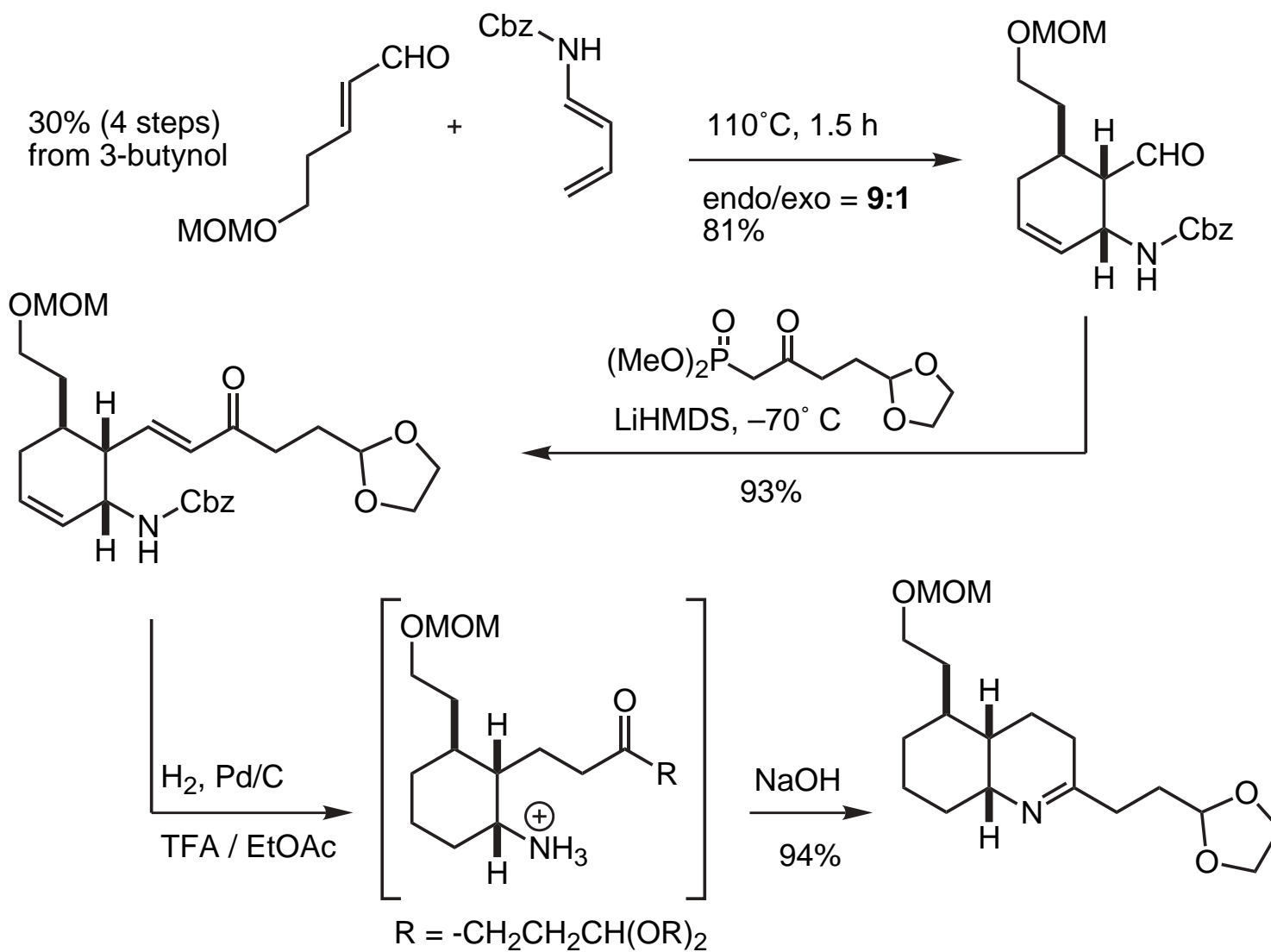


Eschenmoser, *Helv. Chim. Acta.* **1971**, *54*, 710.  
*Tet. Lett.* **1981**, *42*, 4197.

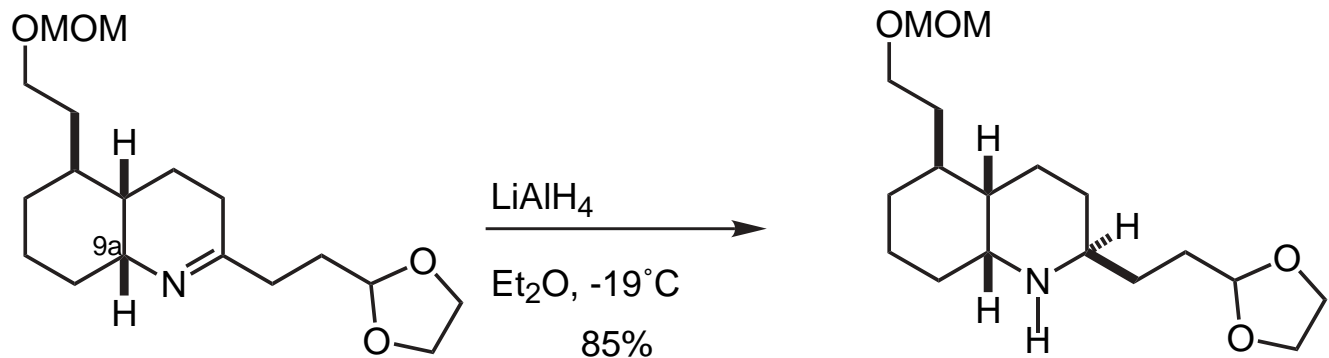
## Overman: Retrosynthesis



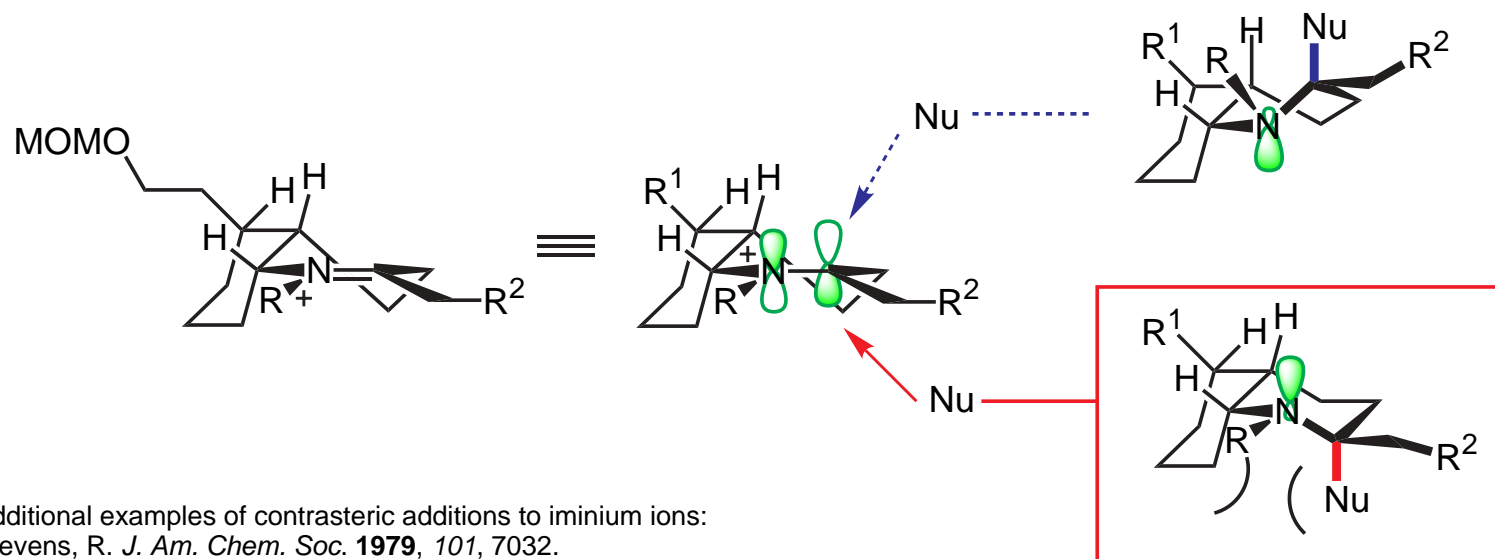
# Overman: ( $\pm$ )-Gephyrotoxin, Hydroquinoline Formation



## Overman: Contrasteric Iminium Reduction

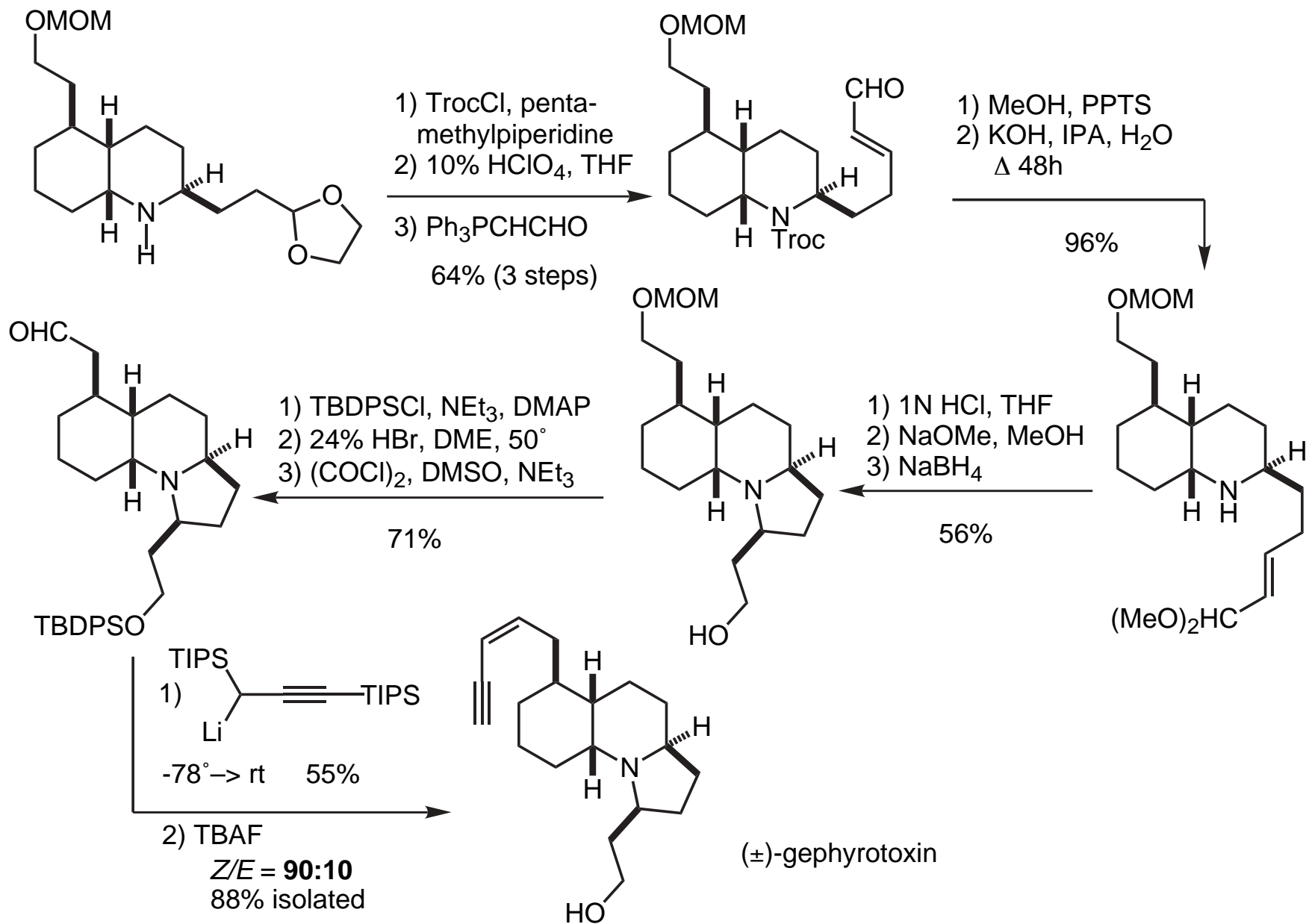


**dr = 9:1 to 16:1**



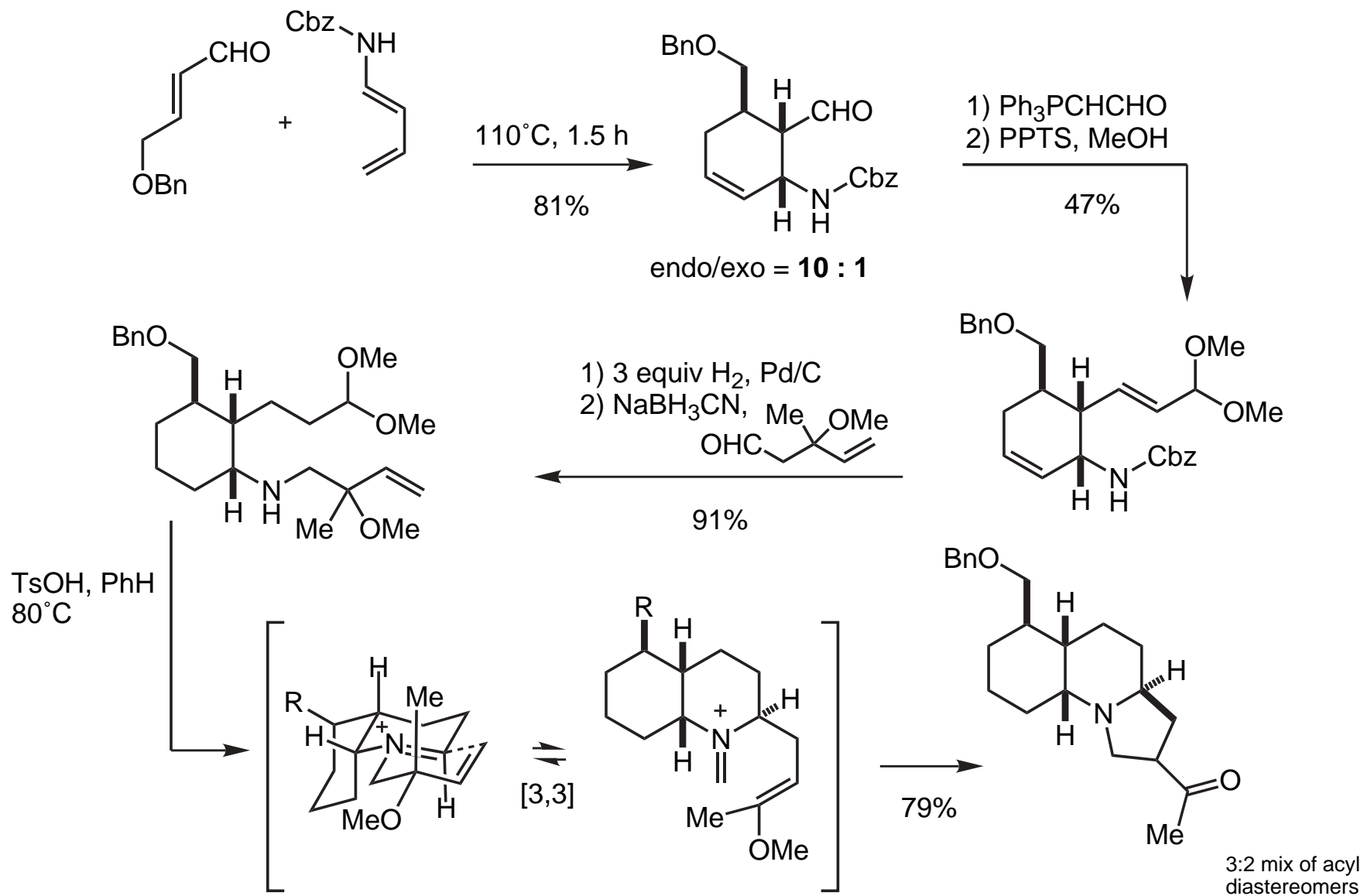
Additional examples of contrastric additions to iminium ions:  
 Stevens, R. *J. Am. Chem. Soc.* **1979**, *101*, 7032.  
 Stevens, R. *Acc. Chem. Res.* **1984**, *17*, 289.  
 Hart, D. *Tet.* **1995**, *51*, 5757.

## Overman: C-ring and Endgame

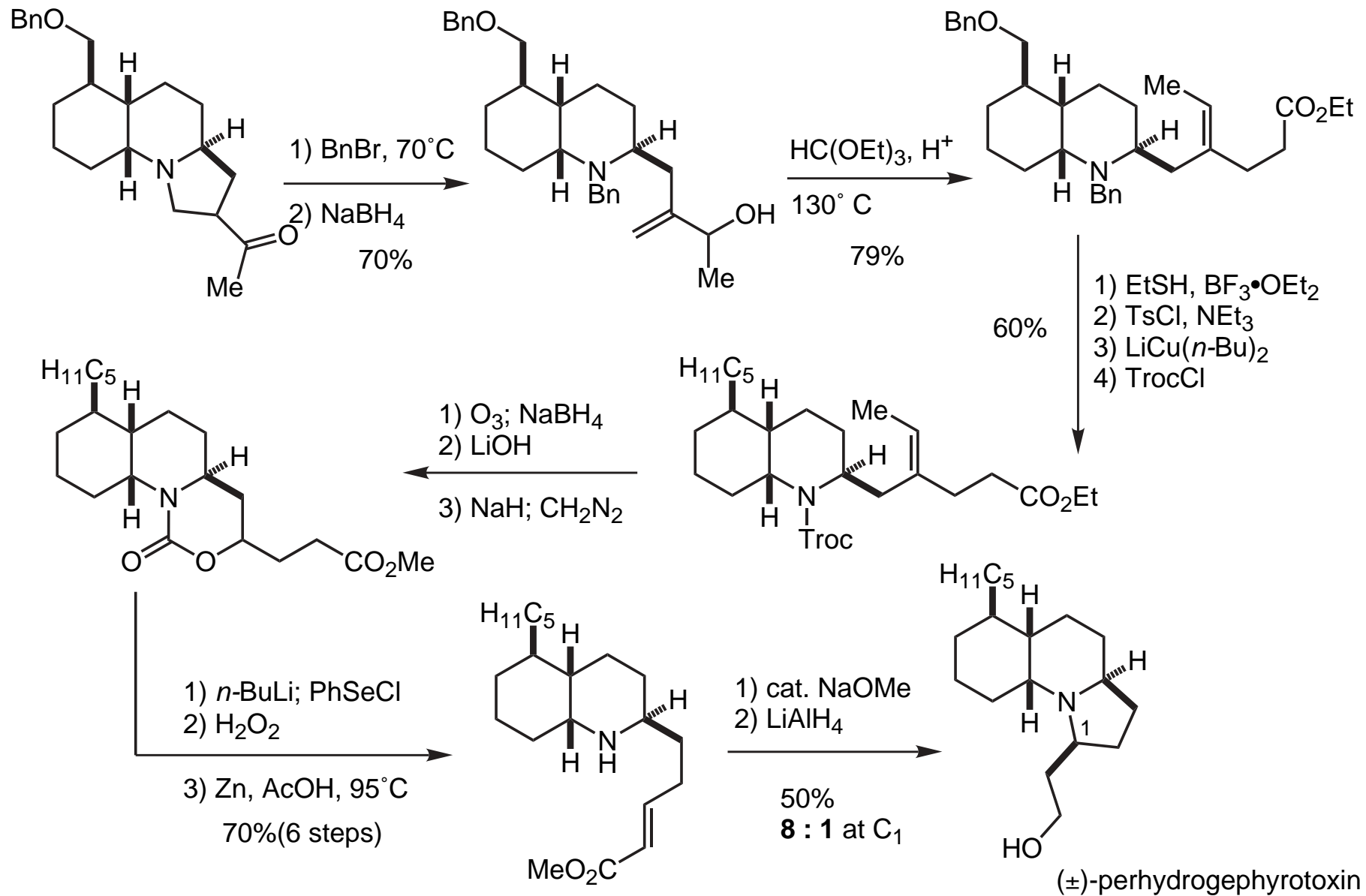




# Overman: ( $\pm$ )-Perhydrogephyrotoxin, Hydroquinoline Formation

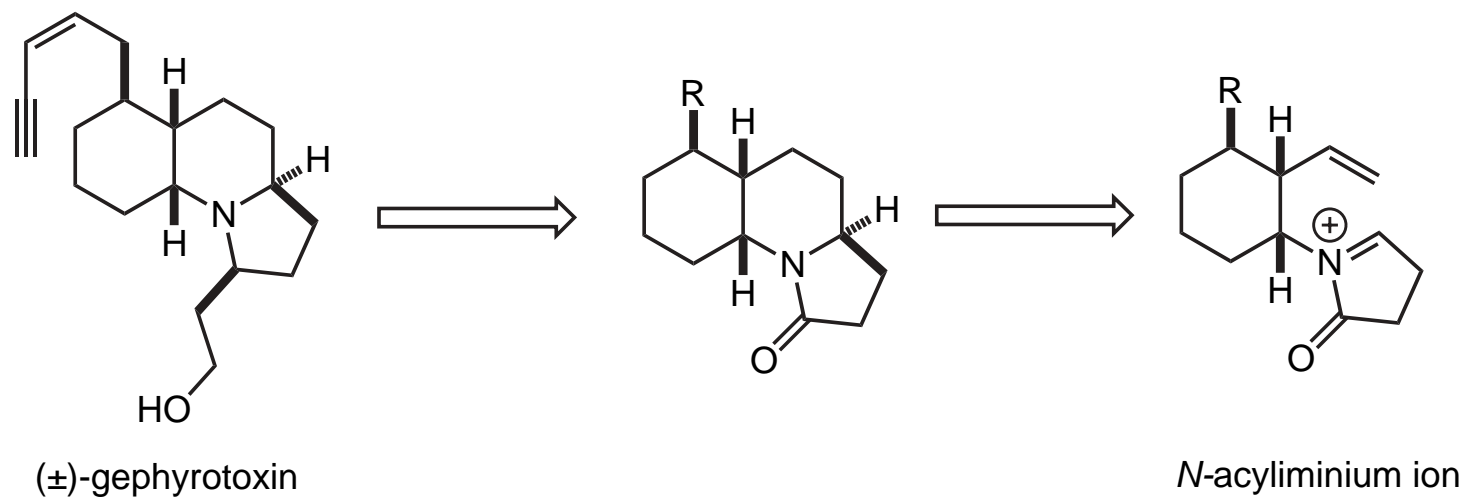


## Overman: Perhydrogephyrotoxin, C-Ring

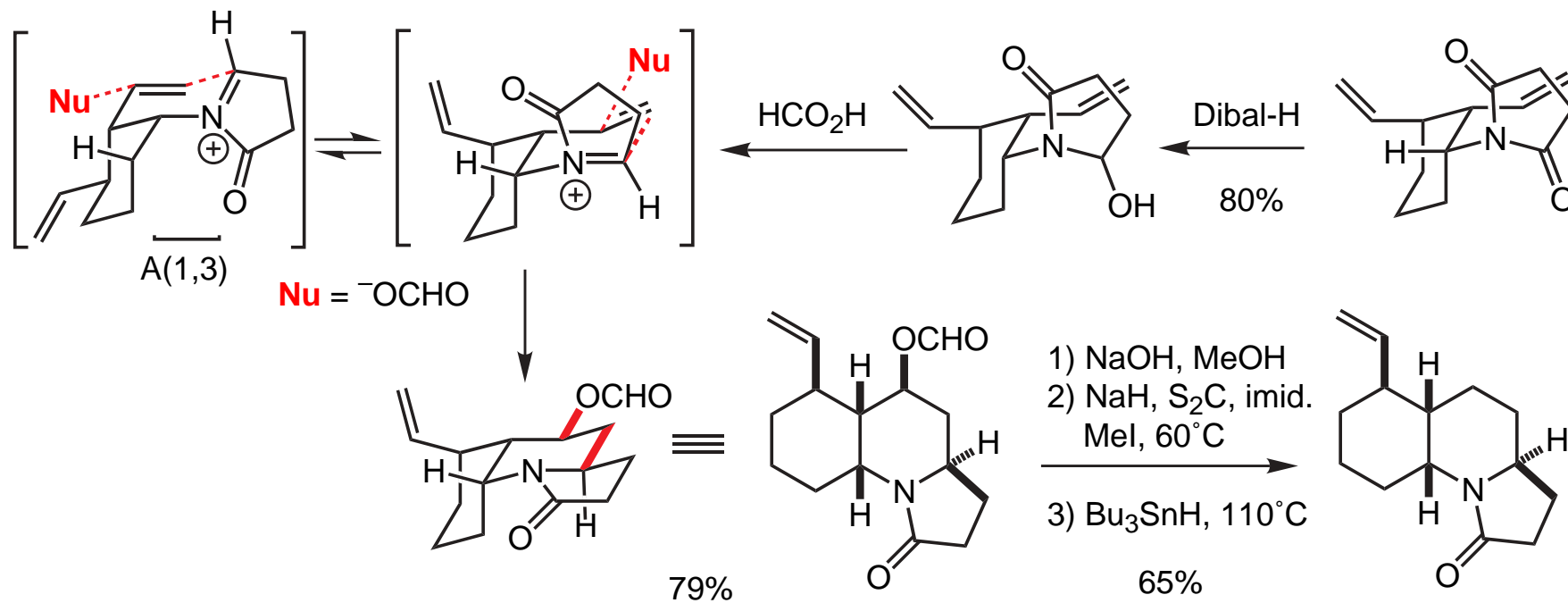
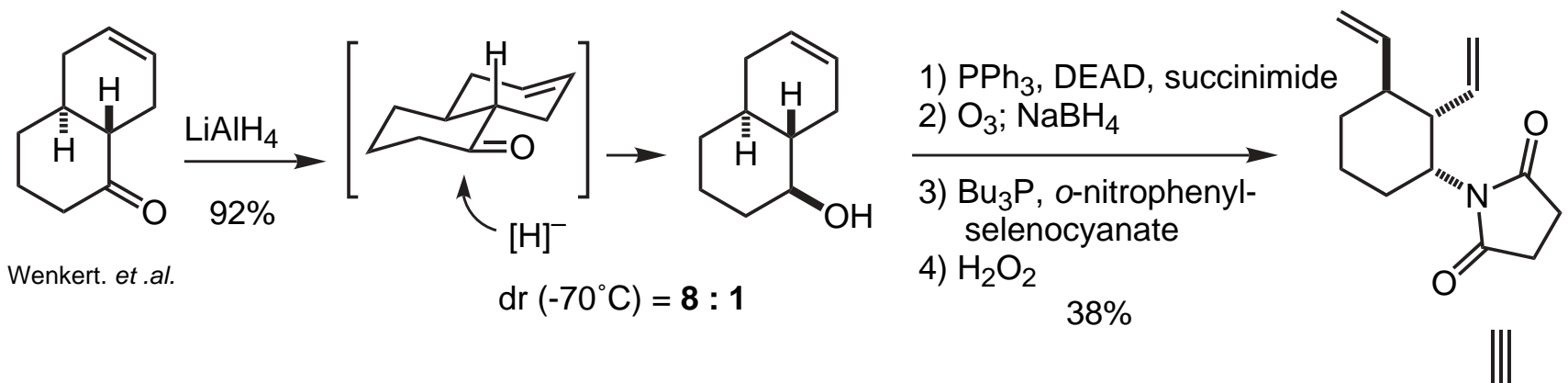


## Hart: Retrosynthesis

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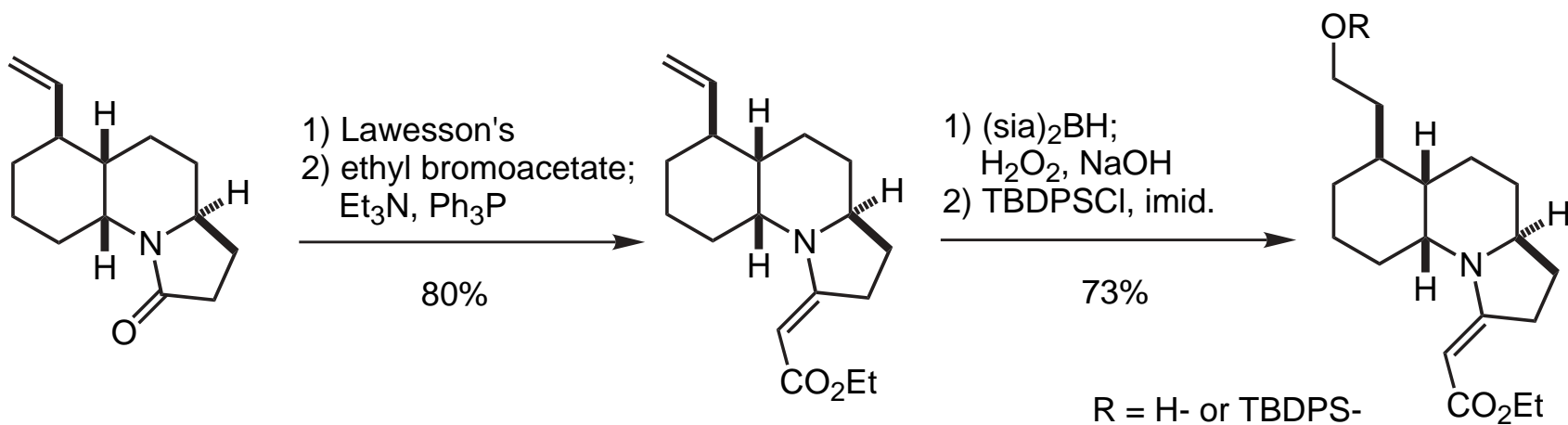


## Hart: N-Acyliminium Ion Cyclization

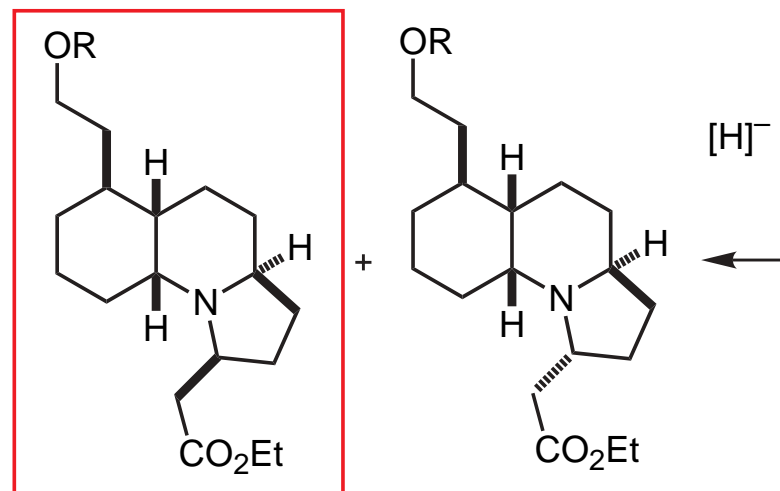


Wenkert. *Synth. Commun.* **1979**, 9, 391.  
*J. Am. Chem. Soc.* **1983**, 105, 1255.

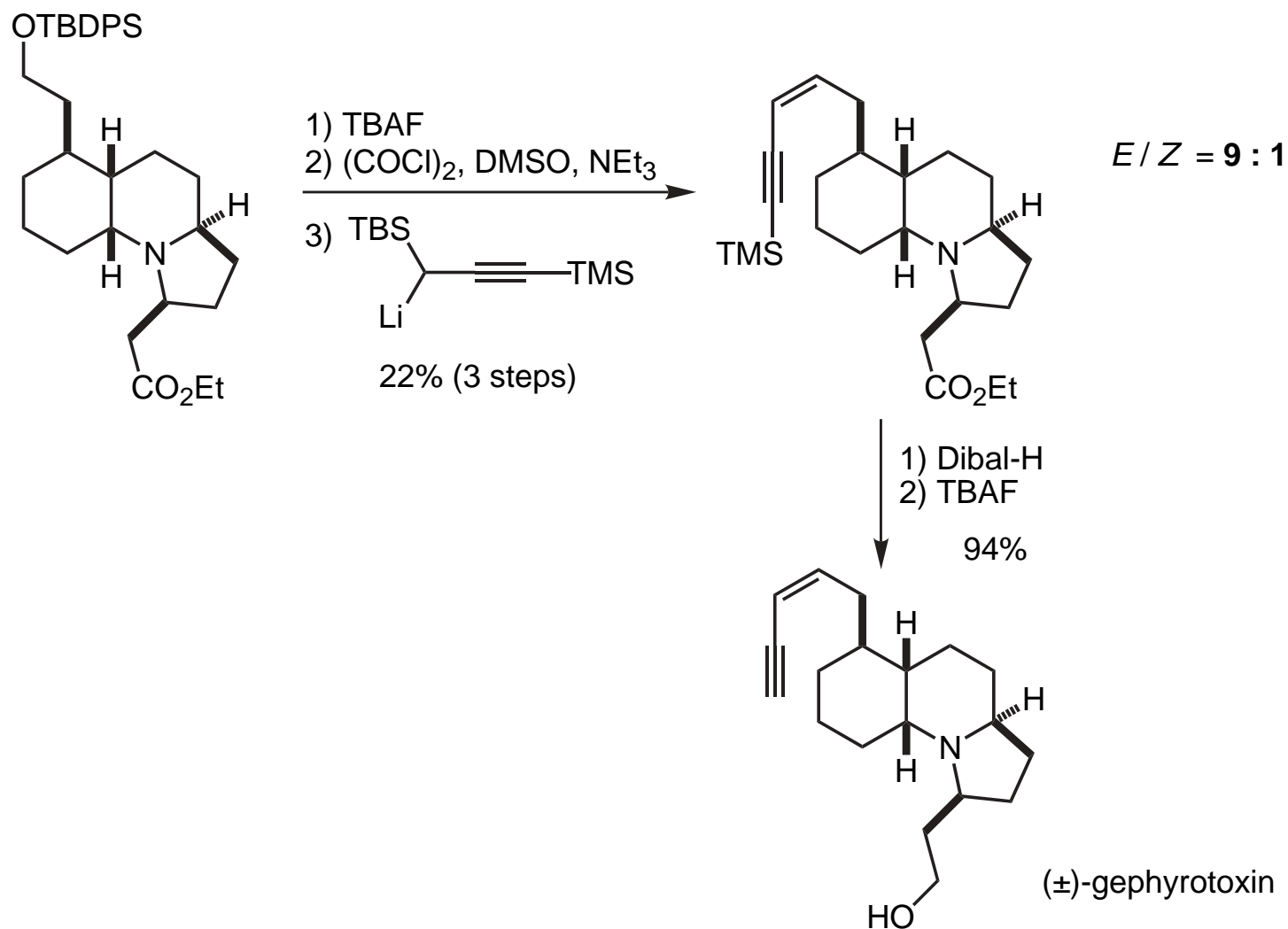
## Hart: C(1) Reduction



R =	conditions	yield	dr
TBDPS	50 psi, Pt/Al <sub>2</sub> O <sub>3</sub>	96	<b>96</b> : 4
H	"	84	32 : 68
TBDPS	NaCNBH <sub>3</sub> , pH 4	92	65 : 35
H	"	90	67 : 33

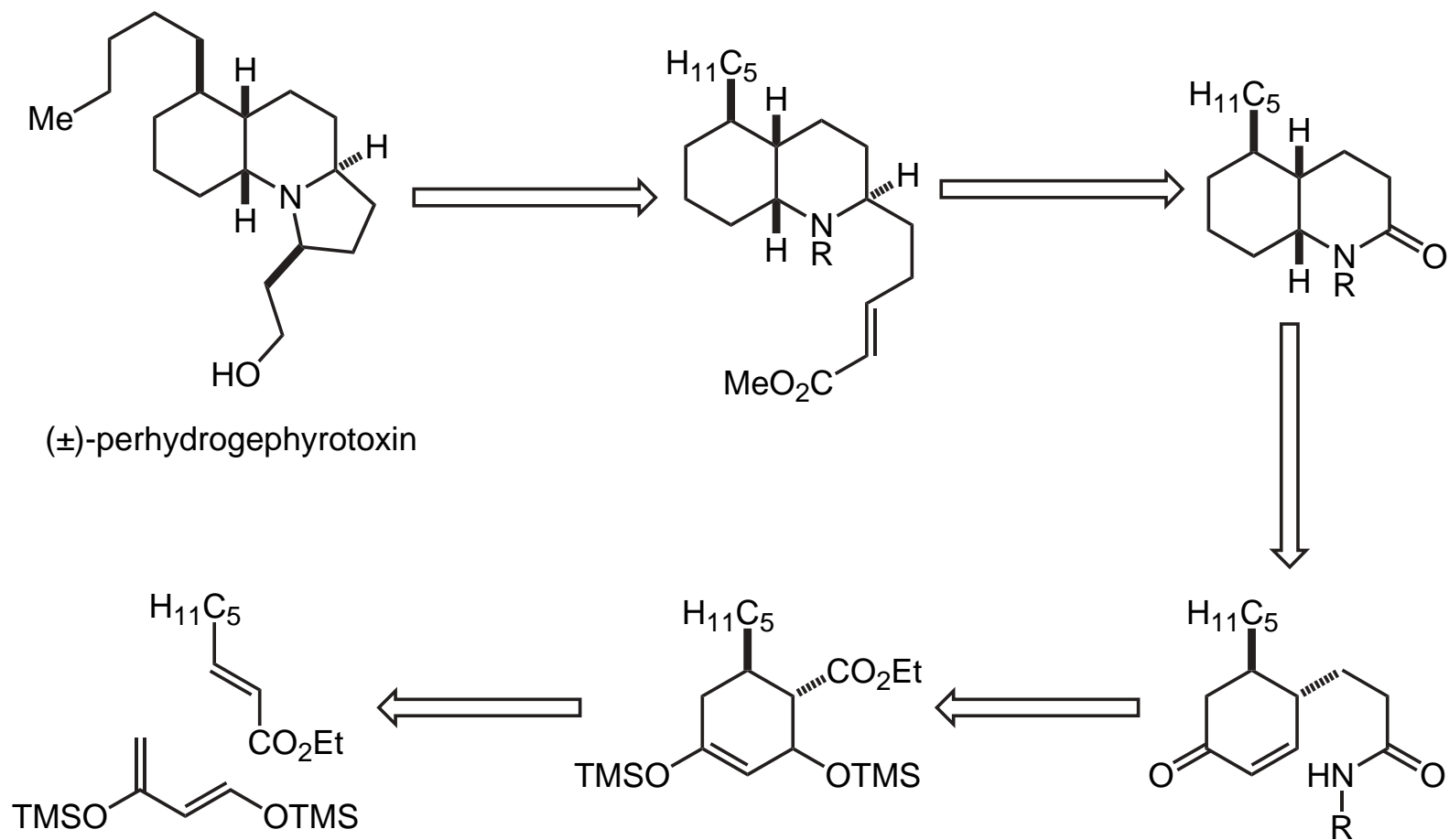


## Hart: Unsaturated Sidechain

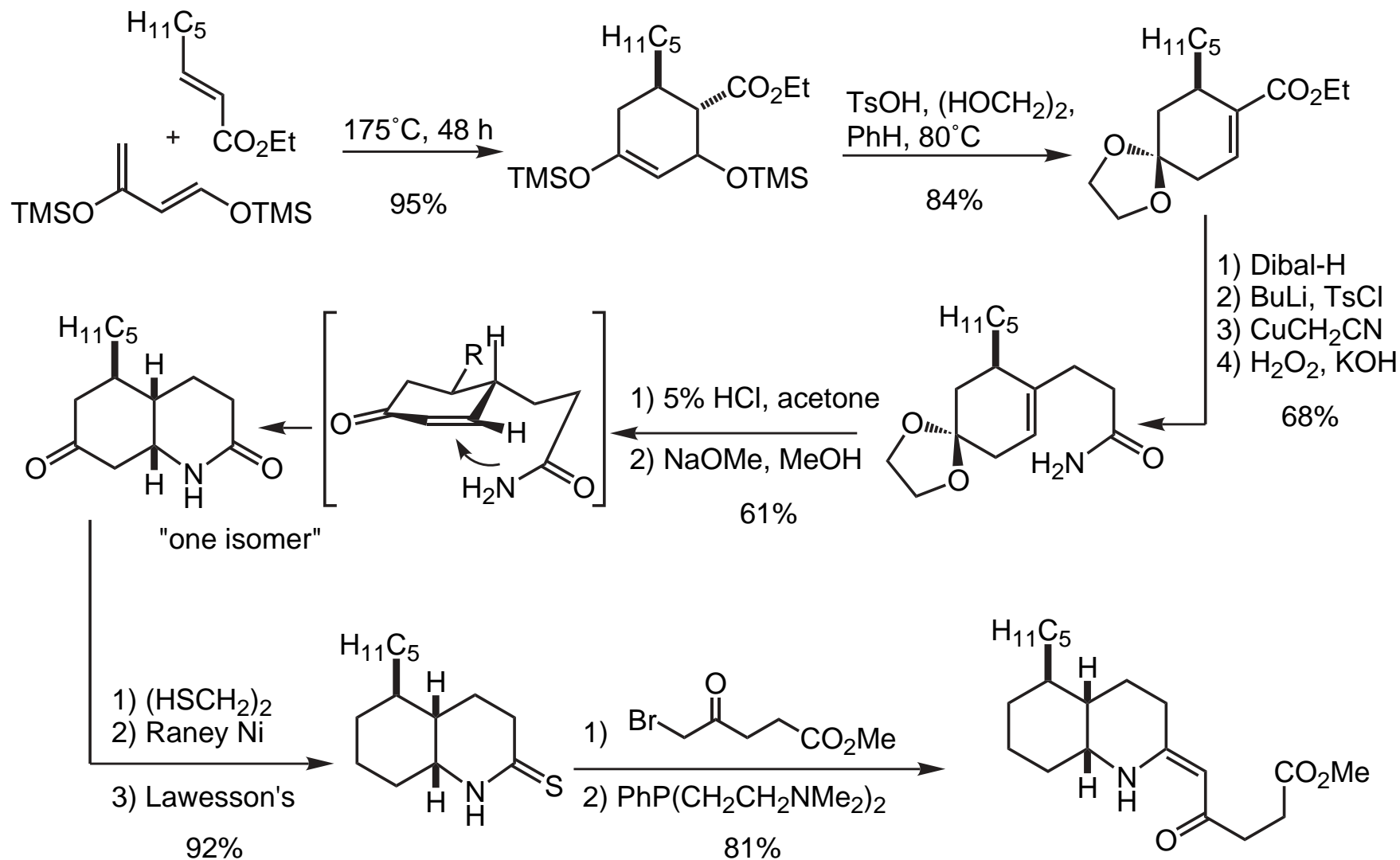


## Ibuka: Perhydrogephyrotoxin Retrosynthesis

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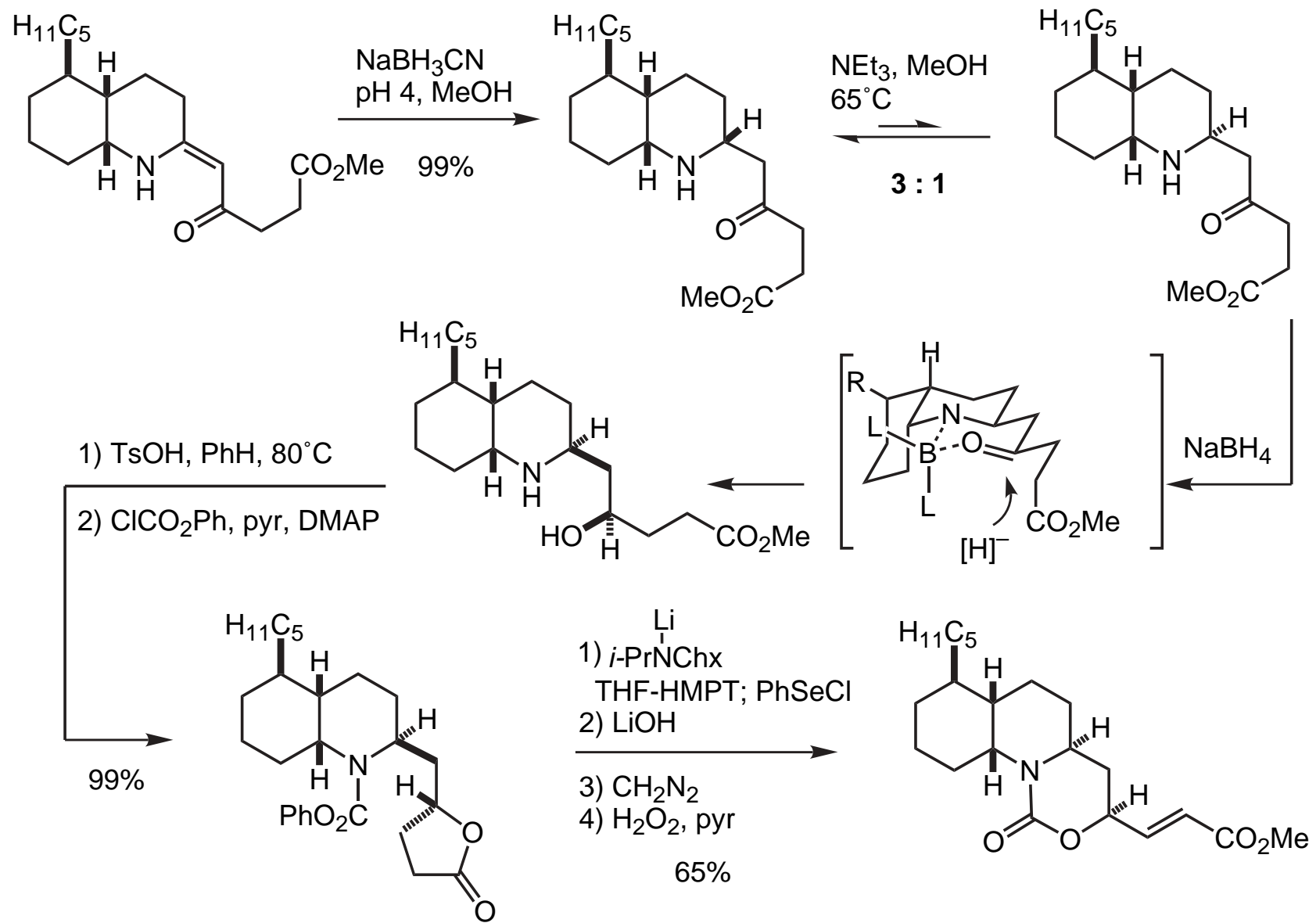


## Ibuka: Hydroquinoline Formation

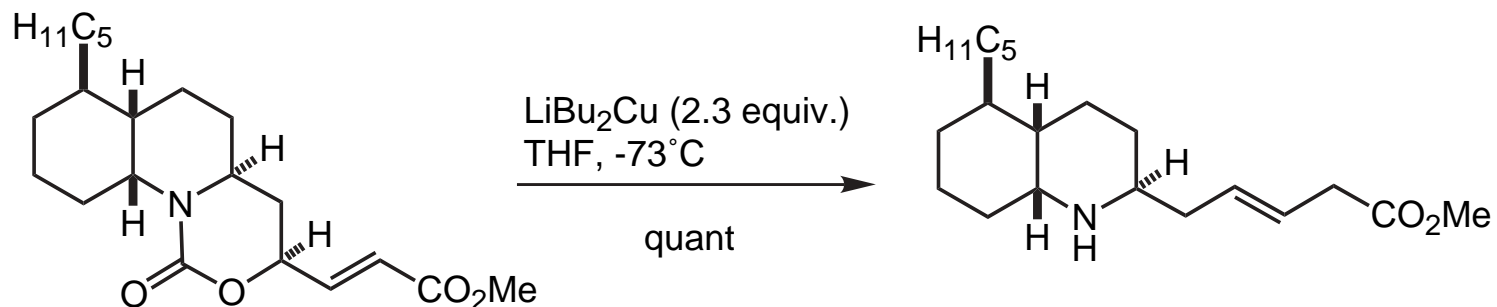




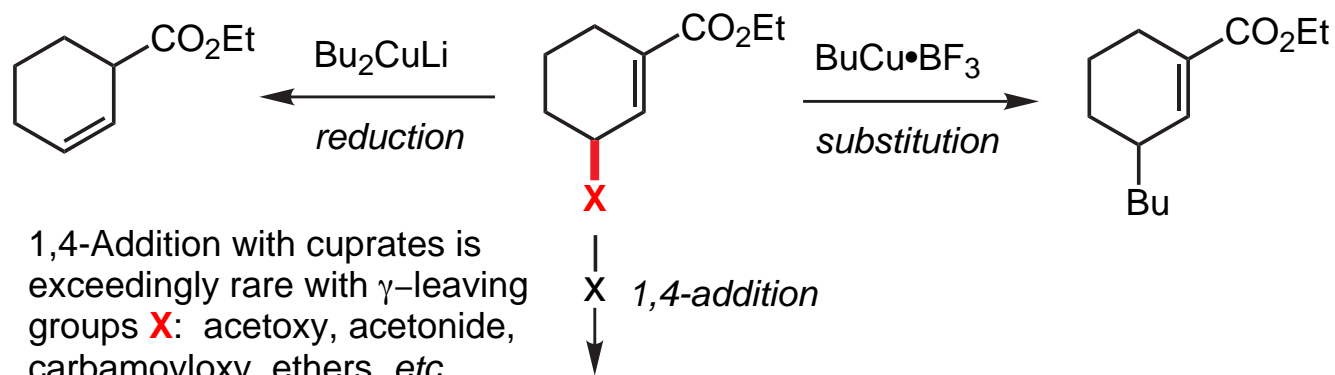
## Ibuka: C(3a) Stereochemistry



## Ibuka: Cuprate Reduction

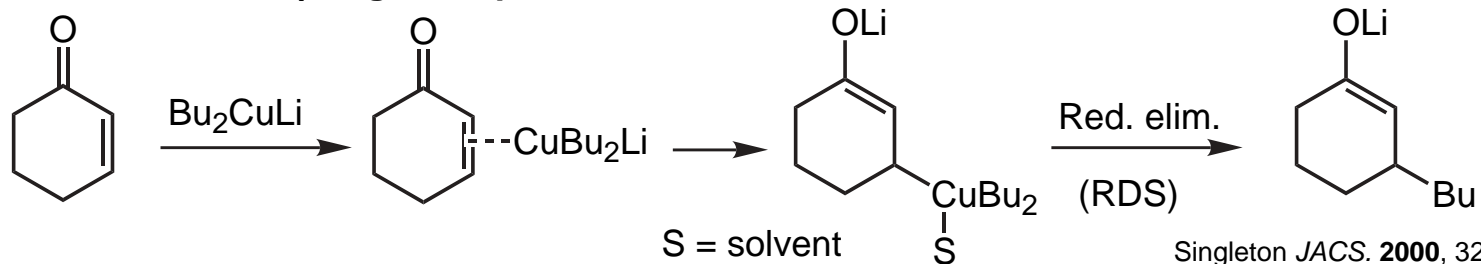


### Later Studies Reveal . . .

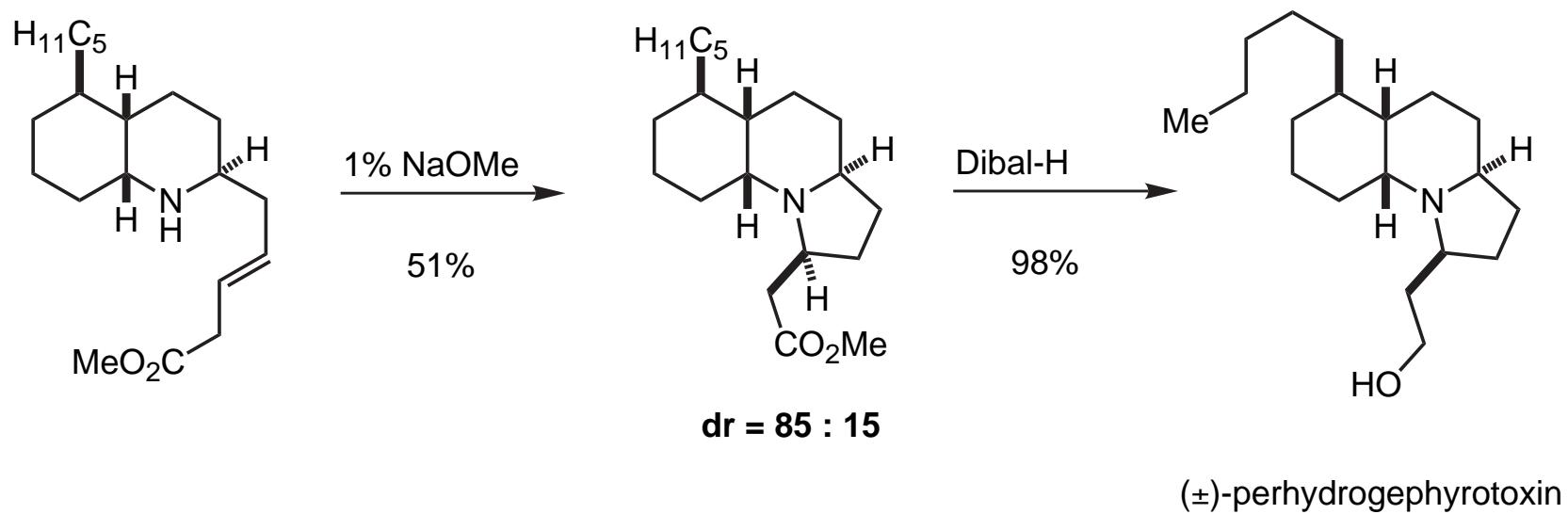


Ibuka et al. *Synlett*. **1992**, 769.

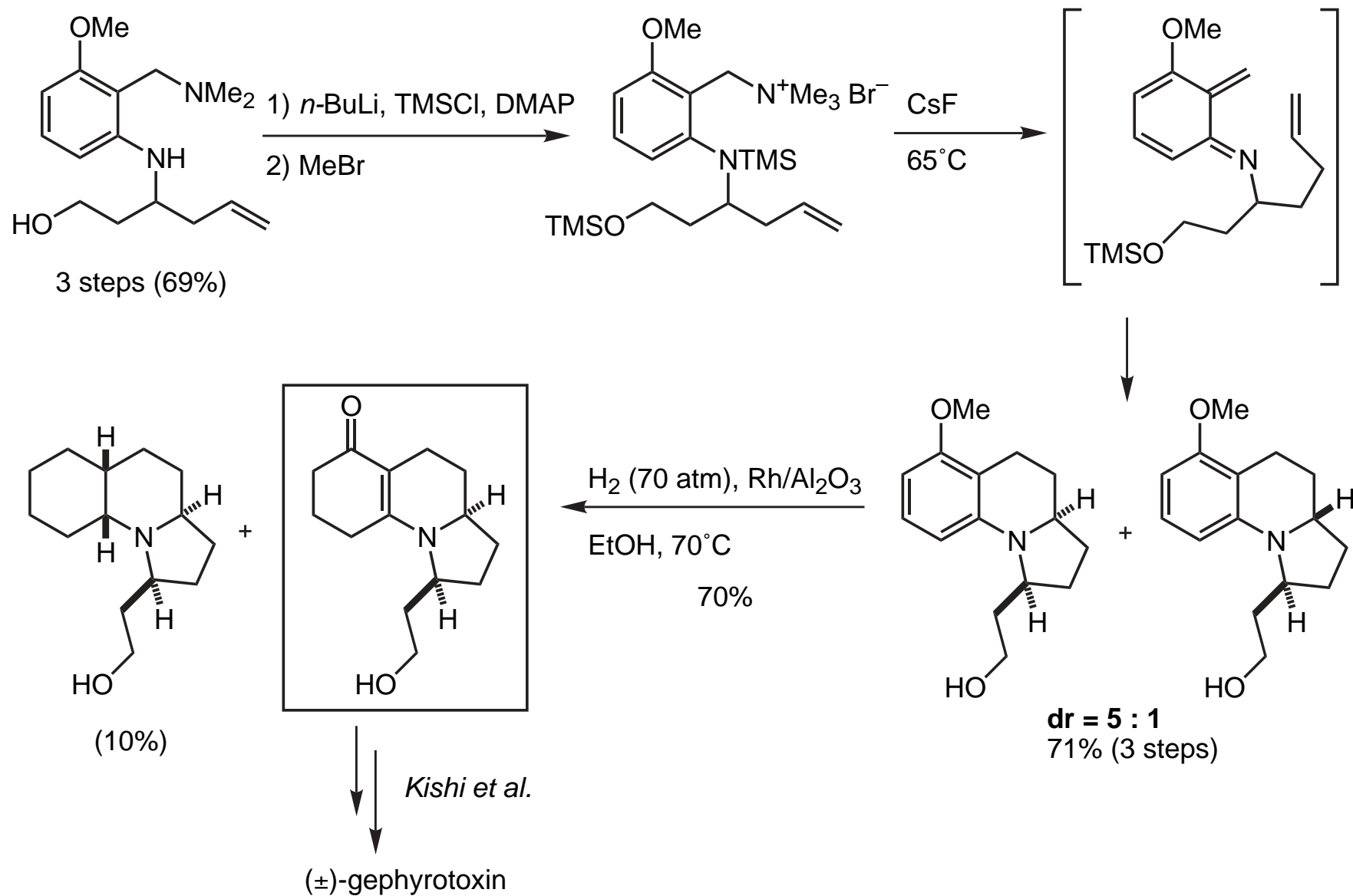
### Mechanism Involves $\beta$ -organocuprate:



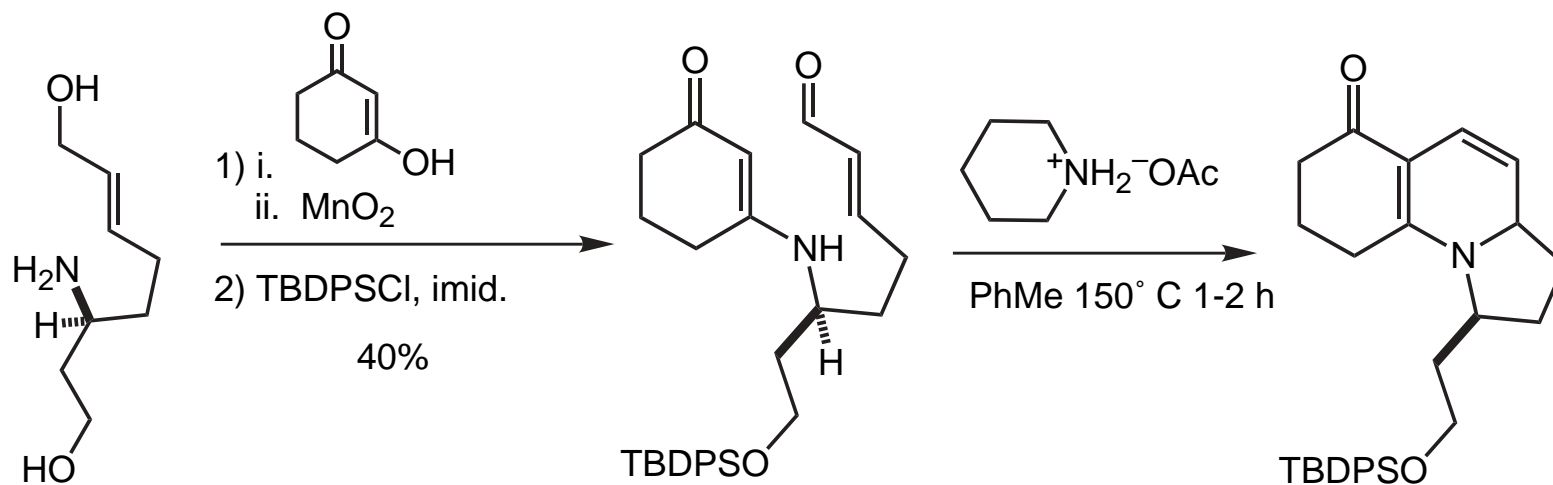
## ***Ibuka: Homestrech***



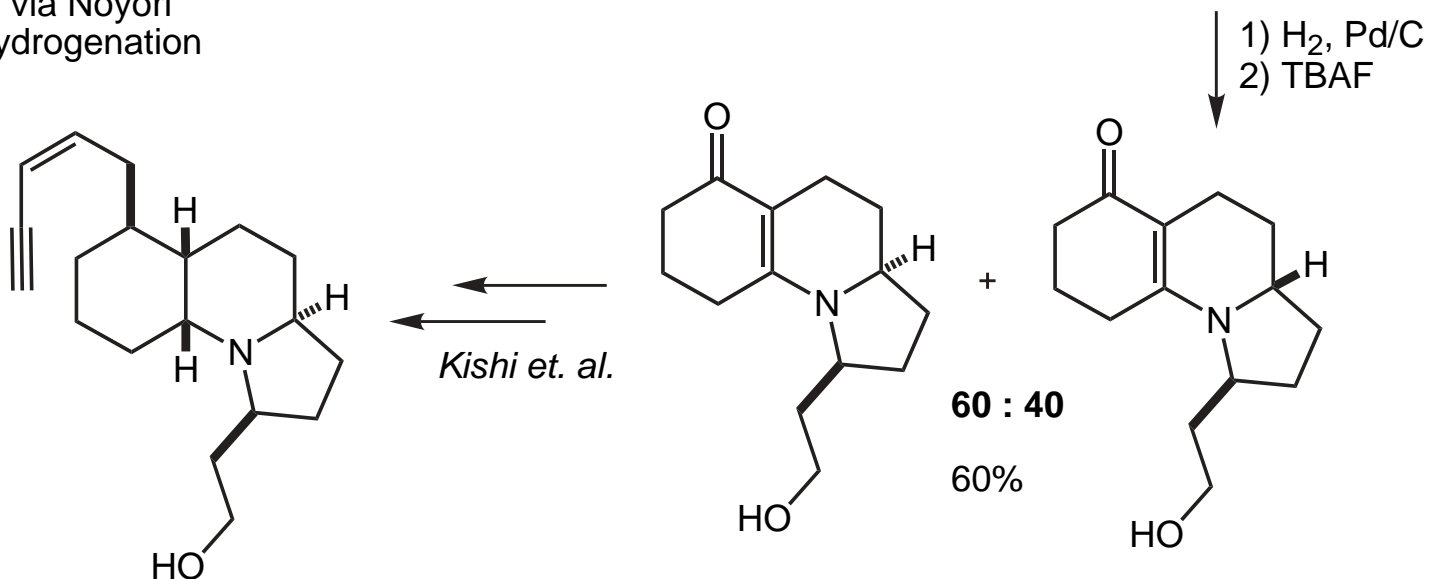
## Ito and Saegusa: Intramolecular Hetero-Diels-Alder



## Hsung: Intramolecular Formal [3+3]



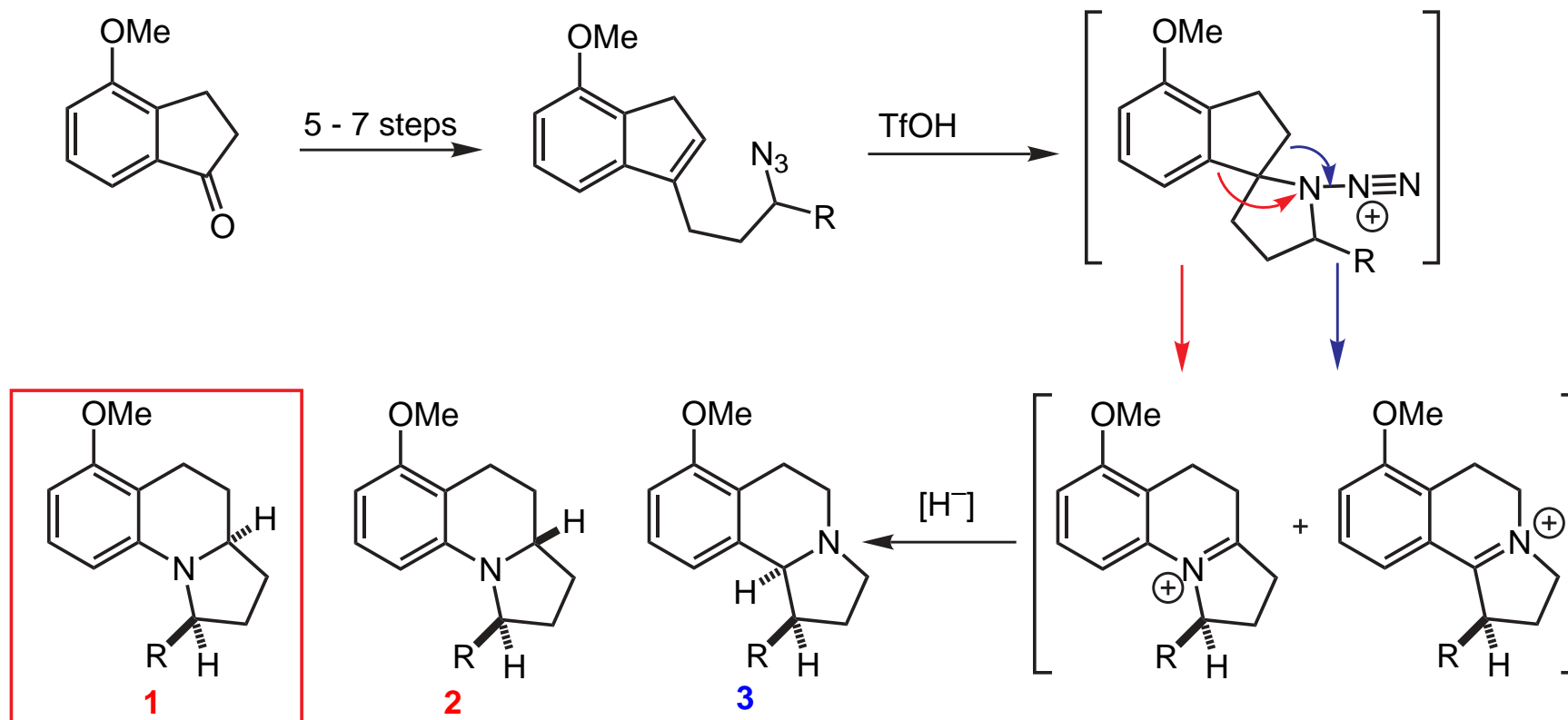
48% (4 steps) via Noyori asymmetric hydrogenation



(+)-gephyrotoxin

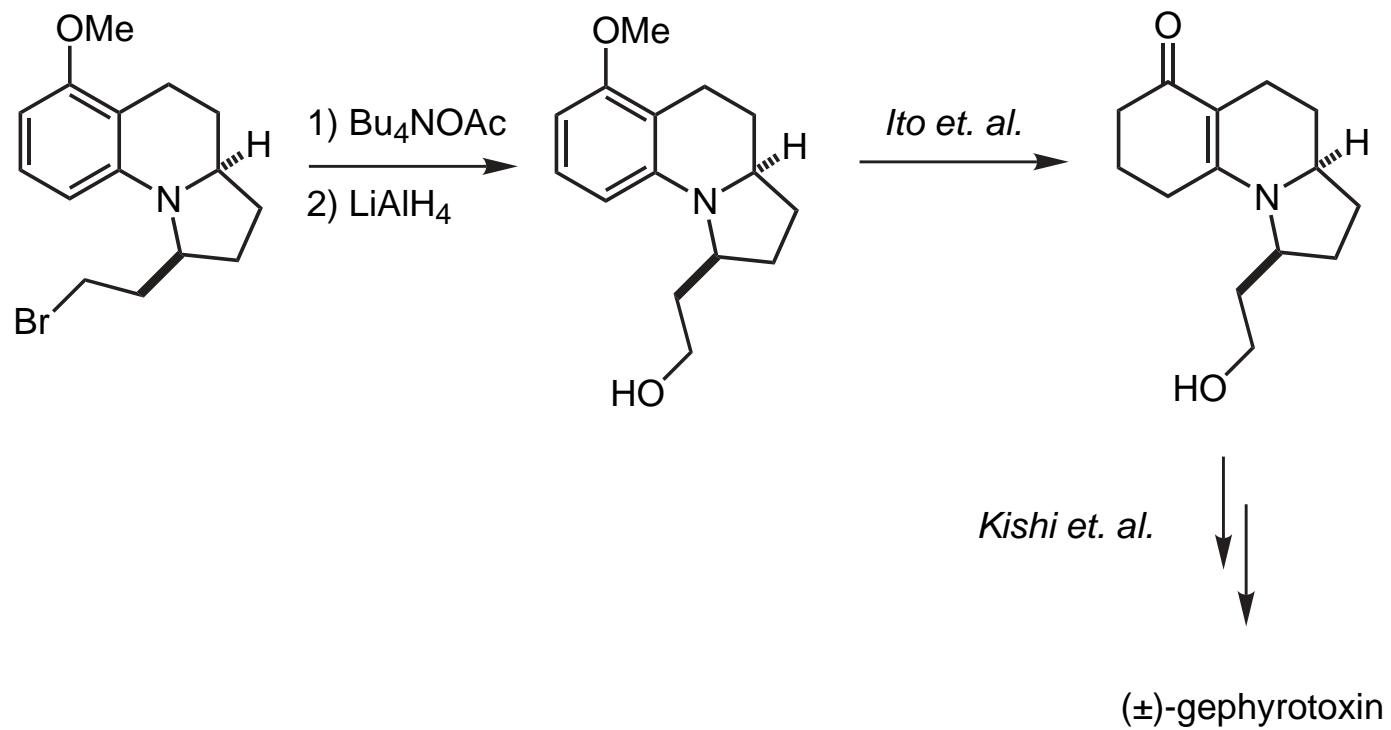
extremely temperature sensitive:  
high selectivity for undesired at 100° C

## Pearson: ( $\pm$ )-Gephyrotoxin via the Schmidt Reaction

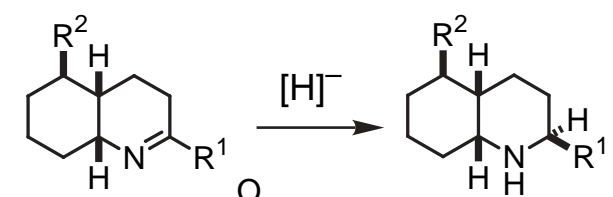
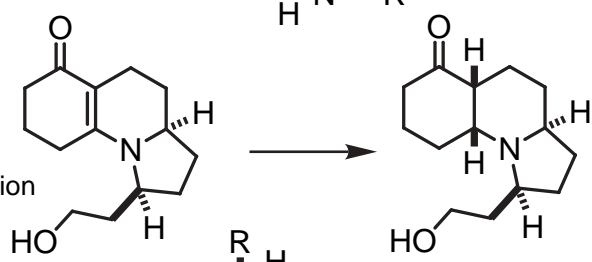
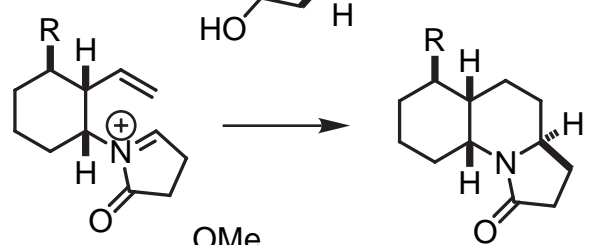
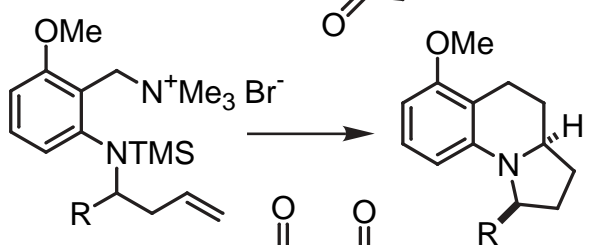
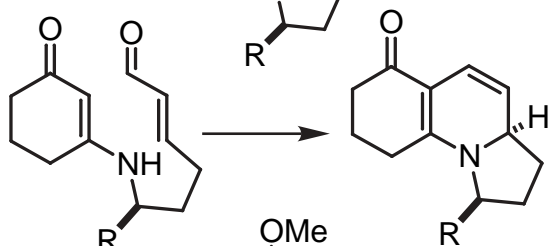
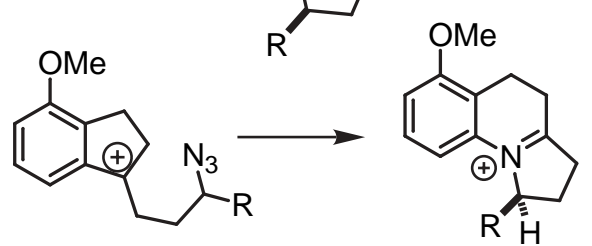


R / hydride reagent	Yield	1 : 2 : 3
CH <sub>2</sub> CH <sub>2</sub> Br / NaBH <sub>4</sub>	72%	39: 39: 22
/ Dibal-H	60%	52: 26: 22
/ L-selectride	55%	82: - : 18
CH <sub>2</sub> CH <sub>2</sub> OMOM	-	-
CH <sub>2</sub> CH=CH <sub>2</sub>	86%	16: 35: 49

## Pearson: Intersection with Ito Intermediate



# Synthesis of ( $\pm$ )-Gephyrotoxin: A Comparison

		Steps:	Total Yield (%):
Overman (1983)	 <p>Reduction to concave face</p>	15	6.5
Kishi (1981)	 <p>Distal directed hydrogenation</p>	24	2.8
Hart (1983)	 <p>N-acyliminium ion cyclization</p>	22	1.8
Ito (1983)	 <p>Intramolecular [4+2]</p>	7 + 12* = 19	7.4
Hsung (2001)	 <p>Formal [3+3]</p>	5 + 12* = 17	1.5
Pearson (2000)	 <p>Schmidt</p>	8 + 12* = 20	3.5

\*from Kishi intermediate