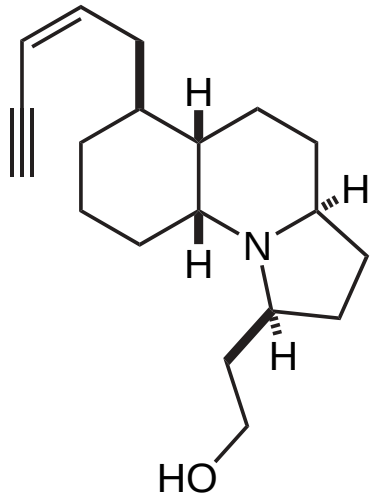
Synthesis of Gephyrotoxin

A Friday Evening Seminar

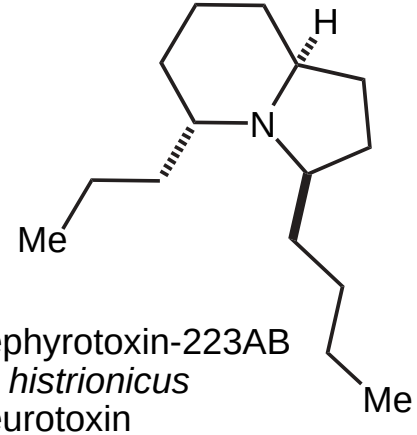


Jonathan R. Scheerer

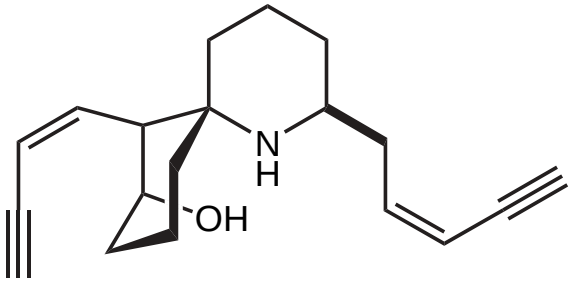
8 November 2002

Keywords: gephyrotoxin, alkaloid, total synthesis

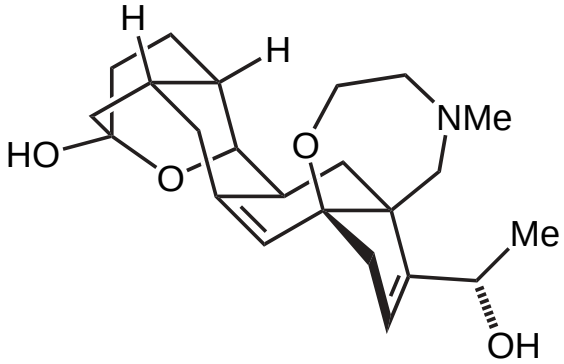
Alkaloids from Dendrobatidae Frogs



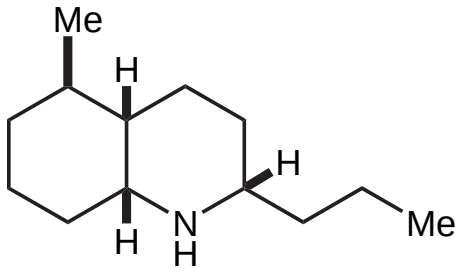
gephyrotoxin-223AB
D. histrionicus
neurotoxin



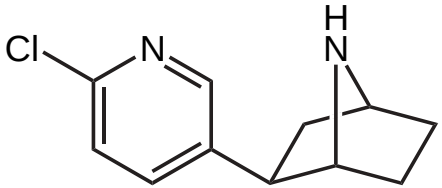
histrionicotoxin
D. histrionicus
neurotoxin



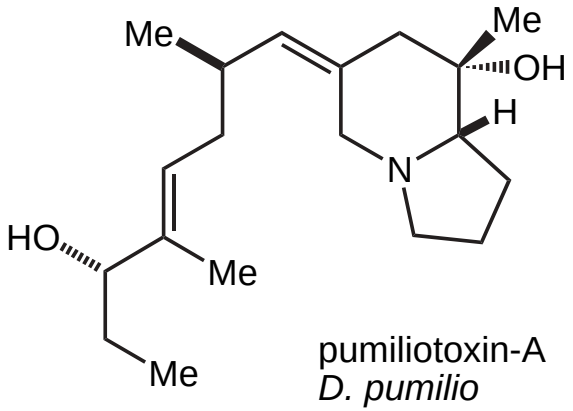
batrachotoxin
D. phyllobates
toxic!



pumiliotoxin-C
D. pumilio

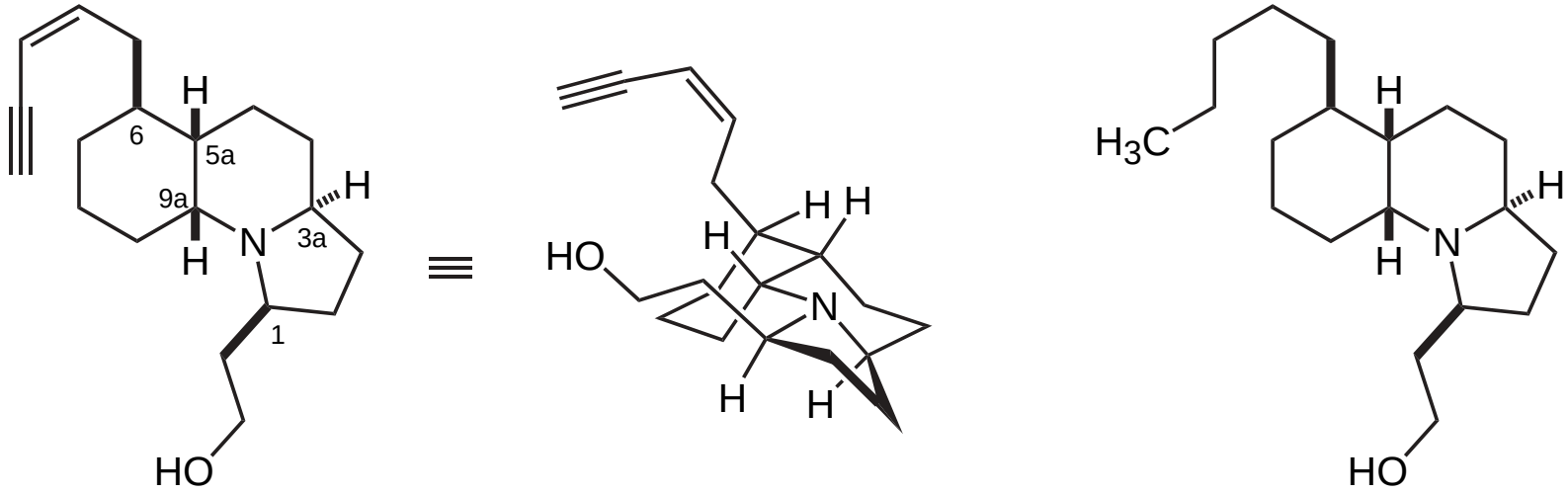


epibatidine
D. epipedobates
analgesic



pumiliotoxin-A
D. pumilio
cardiotonic

(+)-Gephyrotoxin



perhydrogephyrotoxin

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.

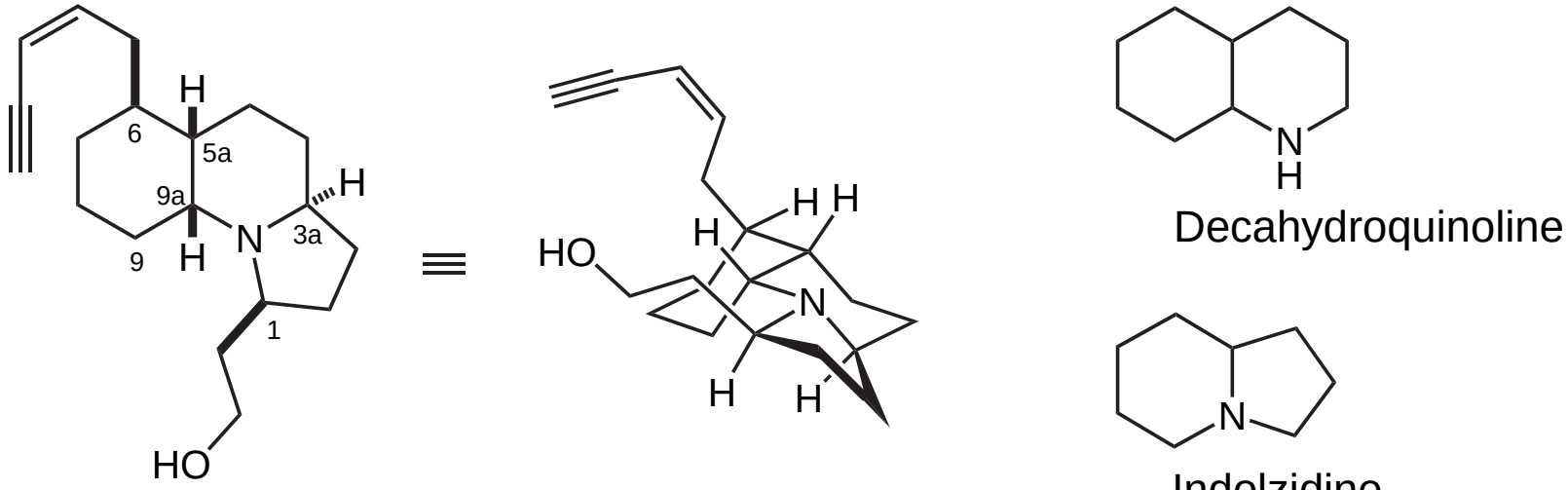
Perhydrogephyrotoxin Syntheses:
Overman, L. *J. Am. Chem. Soc.* **1980**, *102*, 1454.
Hart, D. *J. Org. Chem.* **1981**, *46*, 3576.
Ibuka, T. *Chem. Pharm. Bull.* **1986**, *34*, 2380.

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

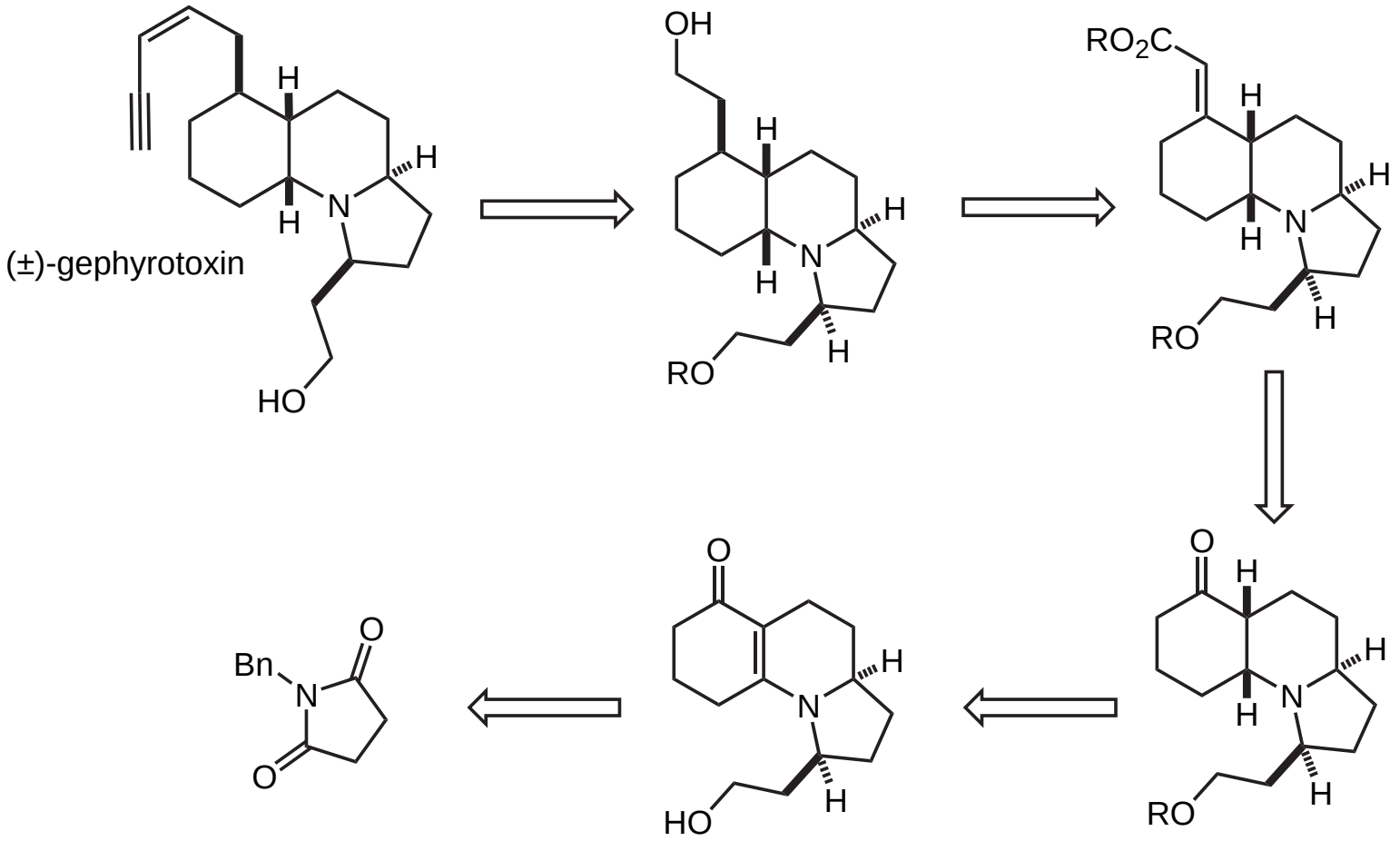


Name: *Gephyra* (Greek: meaning bridge)

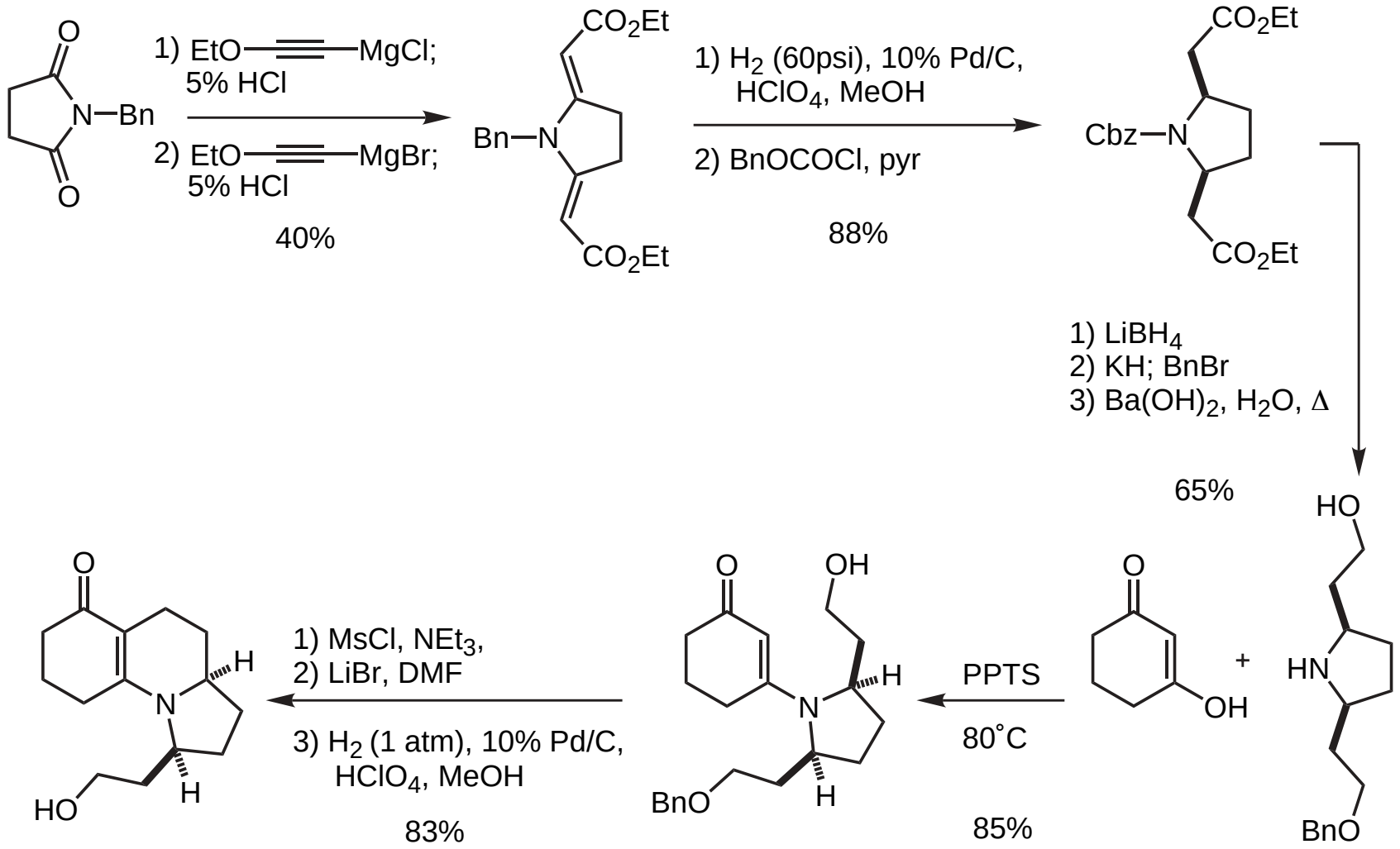
Isolation (1974): 15 mg from 3200 frogs (*D. histrionicus)*

Pharmacology:
mild K^+ conductance disruptance (anticholinergic properties)
potent muscarinic antagonist
neurological disfunction

Kishi: Retrosynthesis

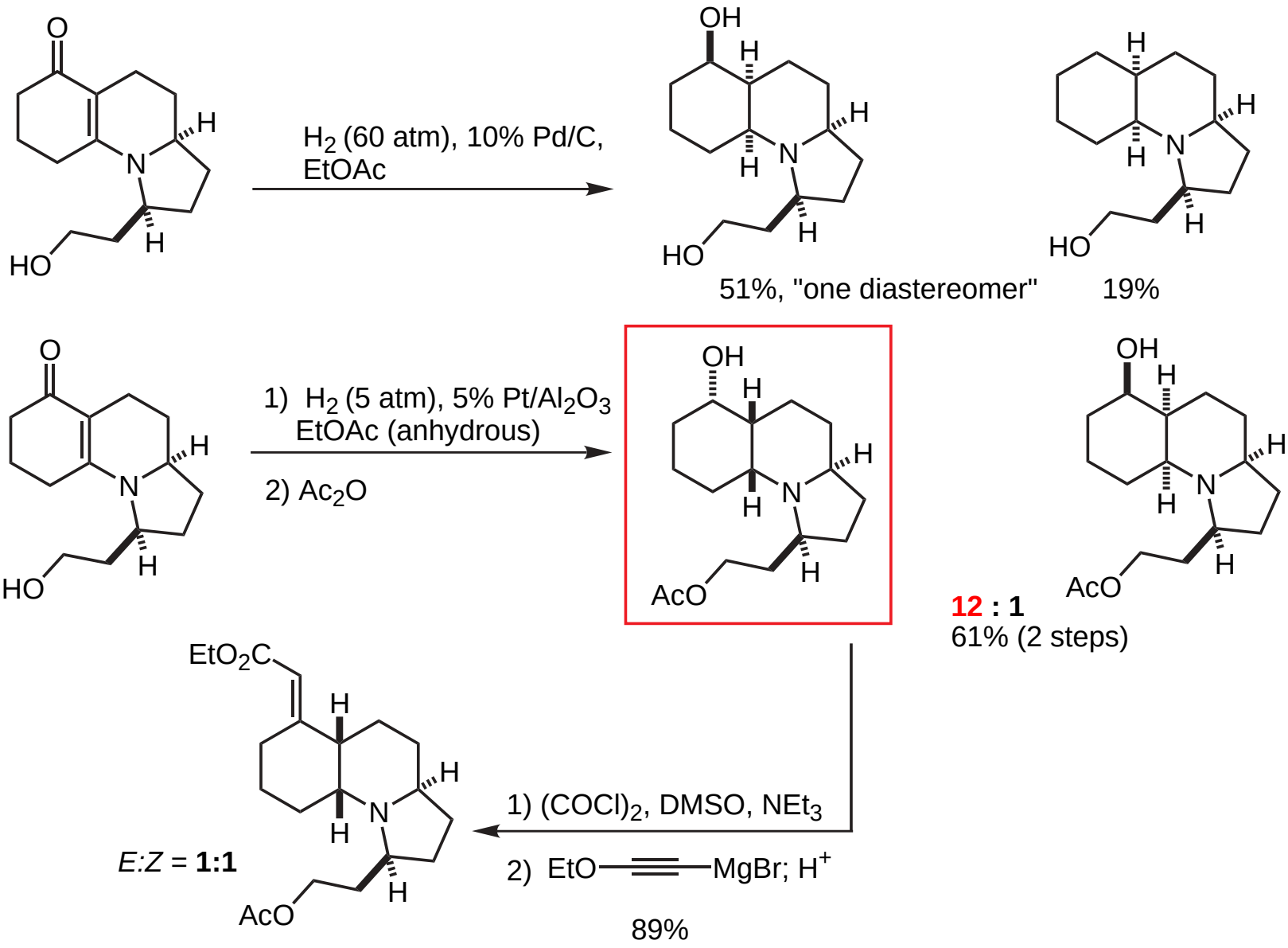


Kishi: Construction of Tricycle



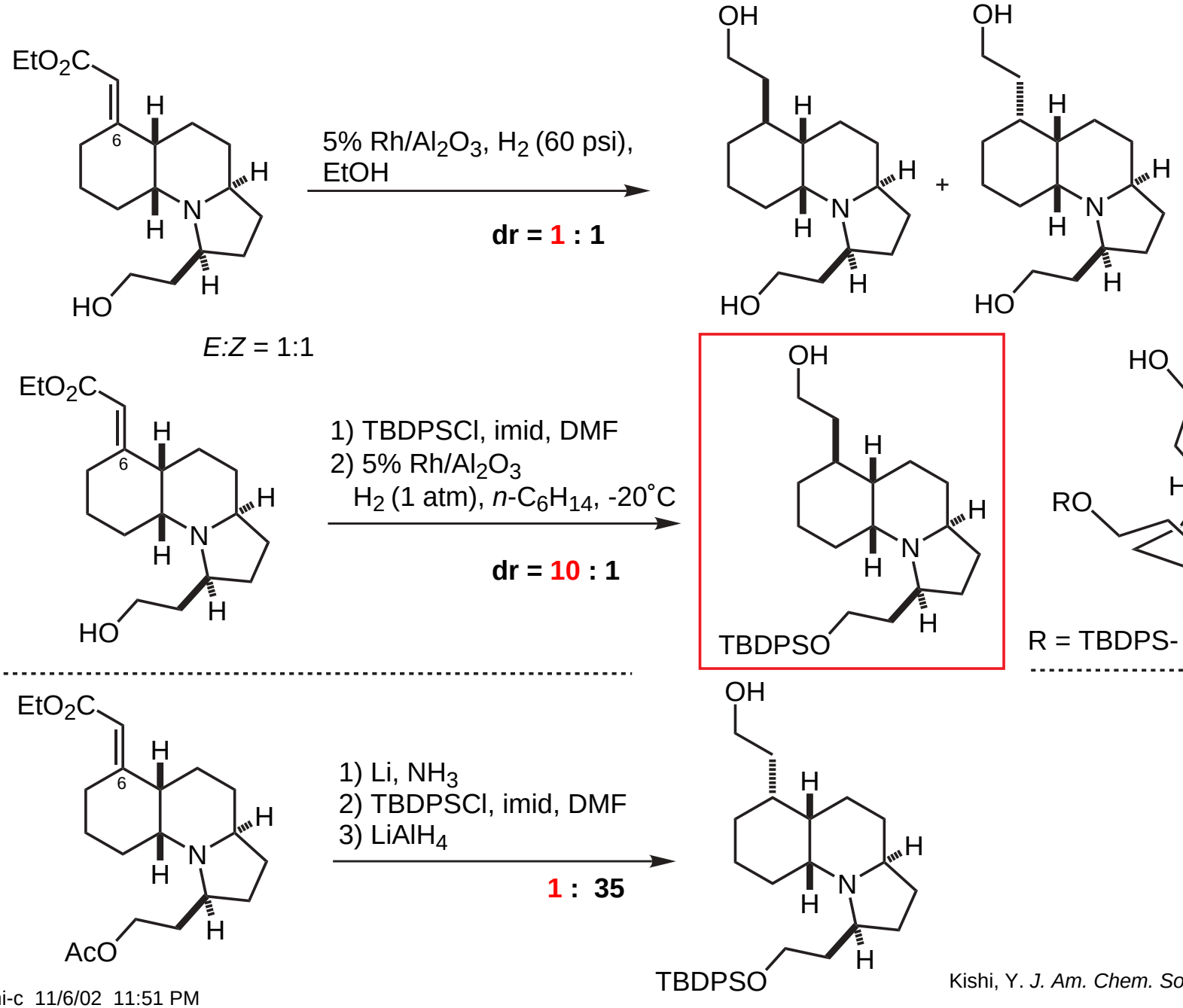
Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7154.

Kishi: Cis-fused Hydroquinoline



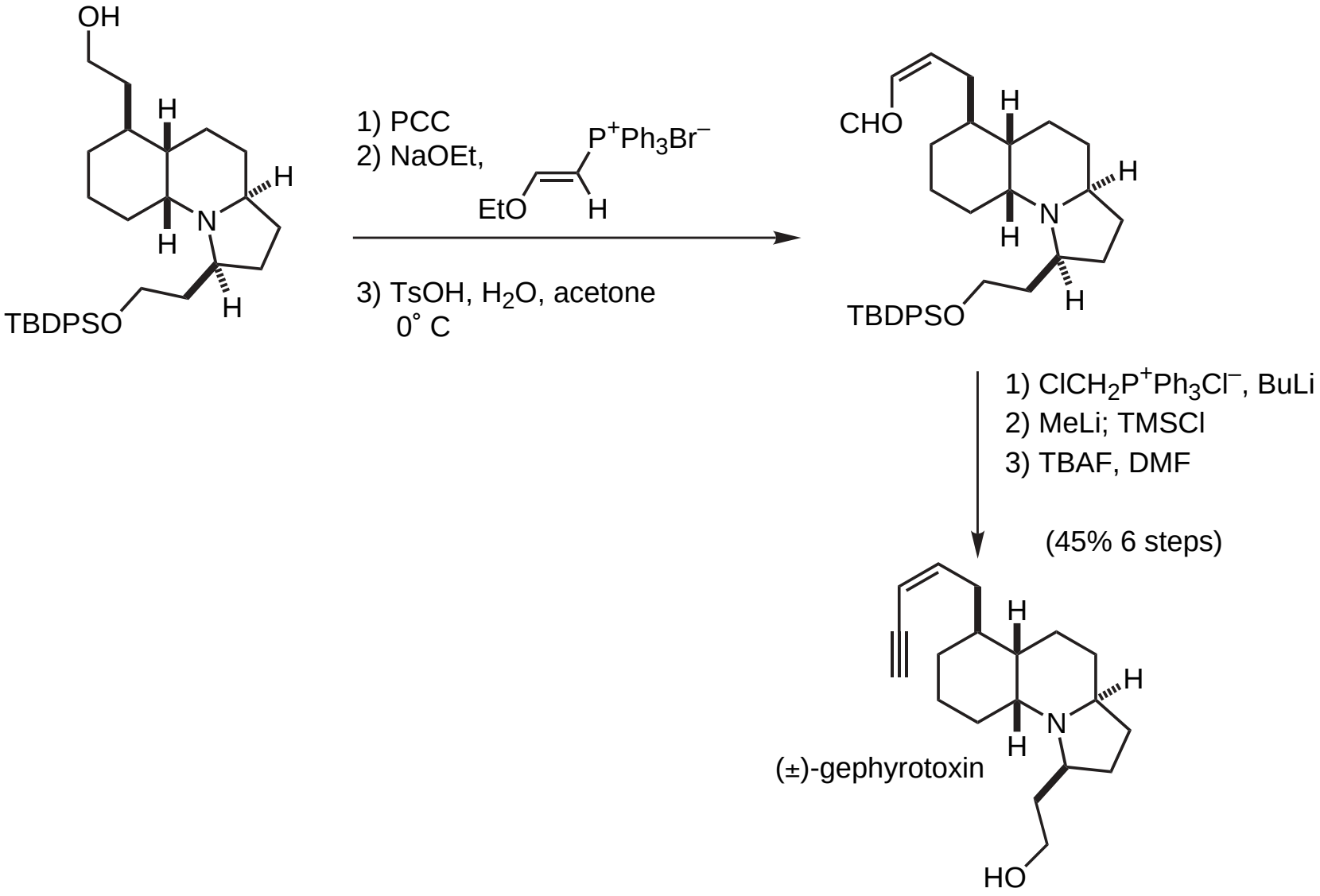
Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7154.

Kishi: C(6) Stereochemistry



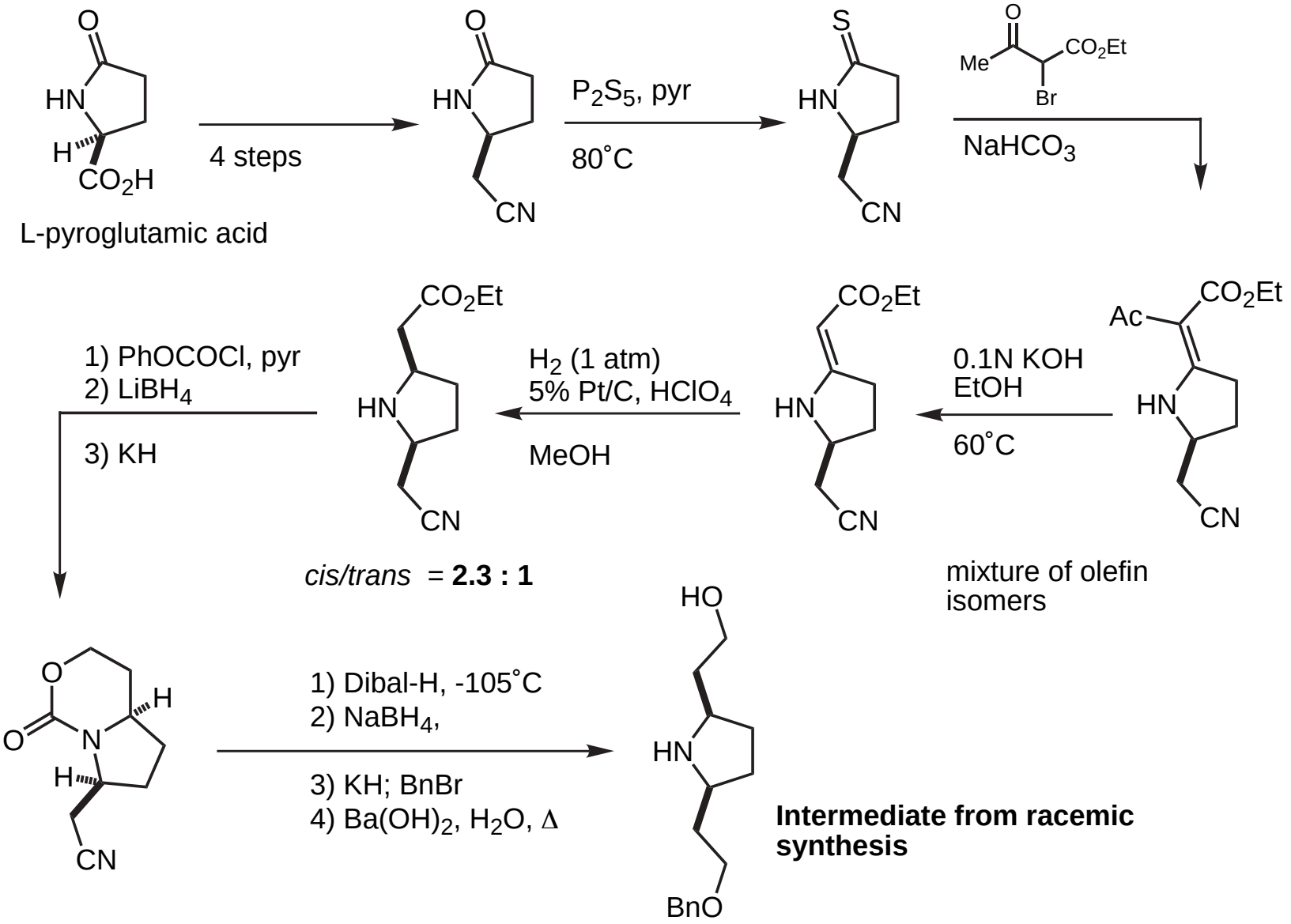
Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7154.

Kishi: Completion of Gephyrotoxin (enyne installation)



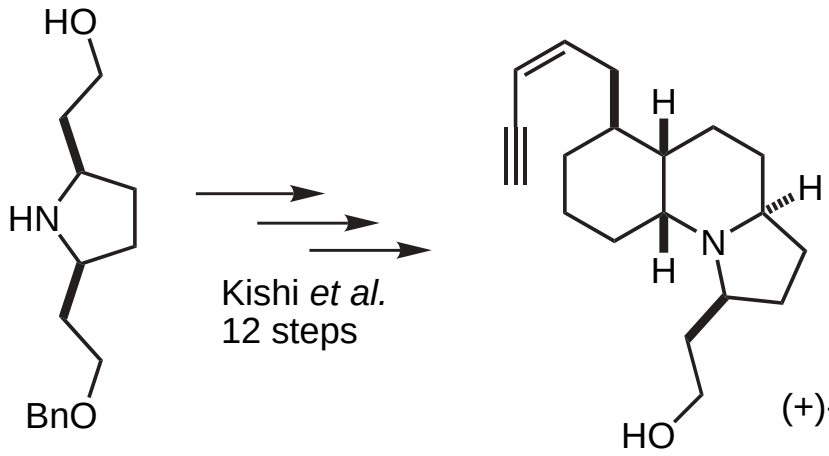
Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7154.

Kishi: Toward Asymmetric Gephyrotoxin



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

Kishi: Absolute Configuration Questioned

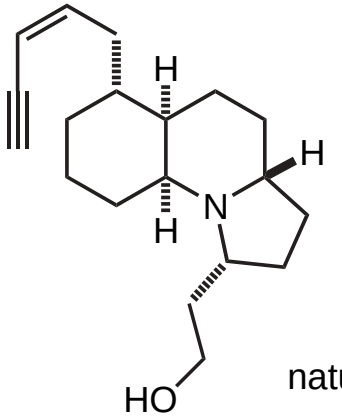


(+)-gephyrotoxin

Original stereoconfiguration assigned by X-ray from HBr salt of gephyrotoxin (anomalous scattering of Br^-)

Synthetic
(c =1.0, EtOH)

$[\alpha]_D$ = +50.0°



Natural
(c =1.0, EtOH)

$[\alpha]_D$ = –51.5°

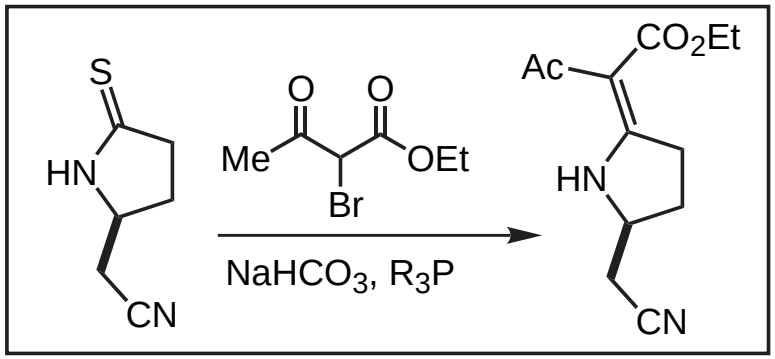
Kishi suggests structural reassignment based on optical rotation.

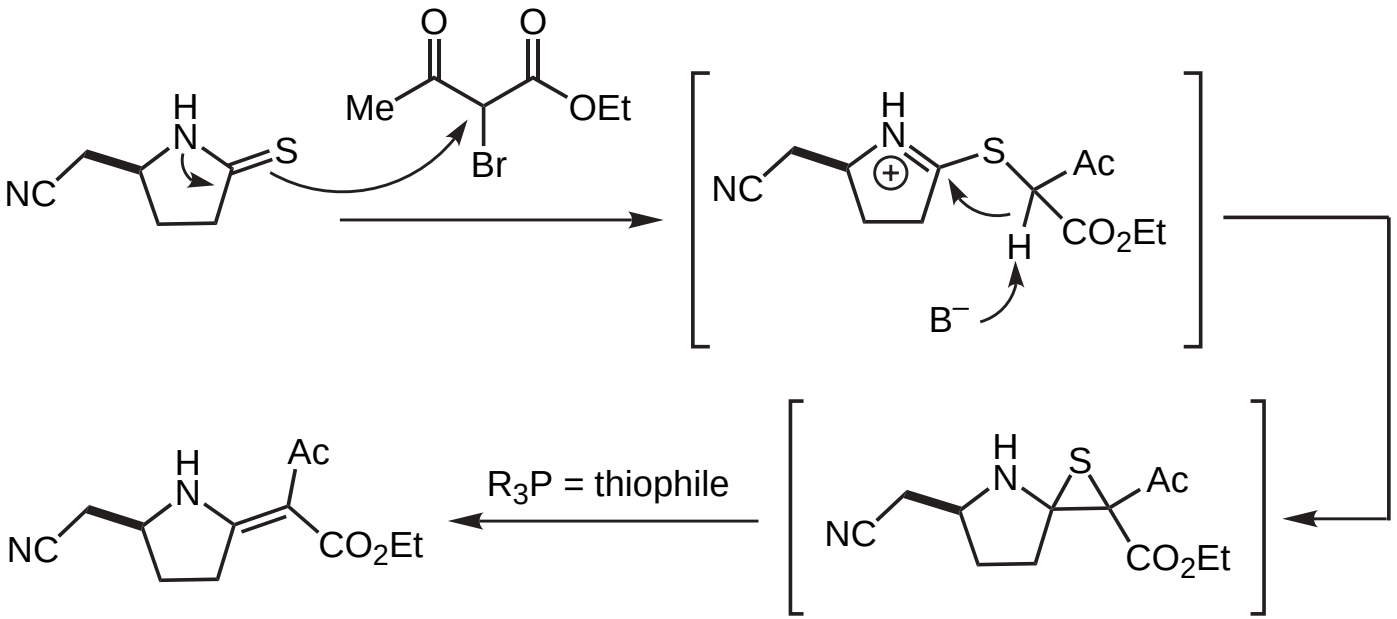
natural (–)-gephyrotoxin (?)

Insufficient natural supply to confirm reassignment

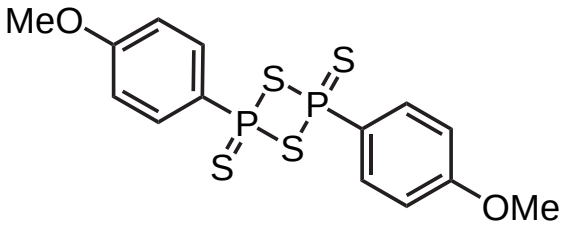
Tet. Lett. **1981**, *42*, 4197.

Eschenmoser Contraction:
Formation of Vinylogous Amides and Urethanes



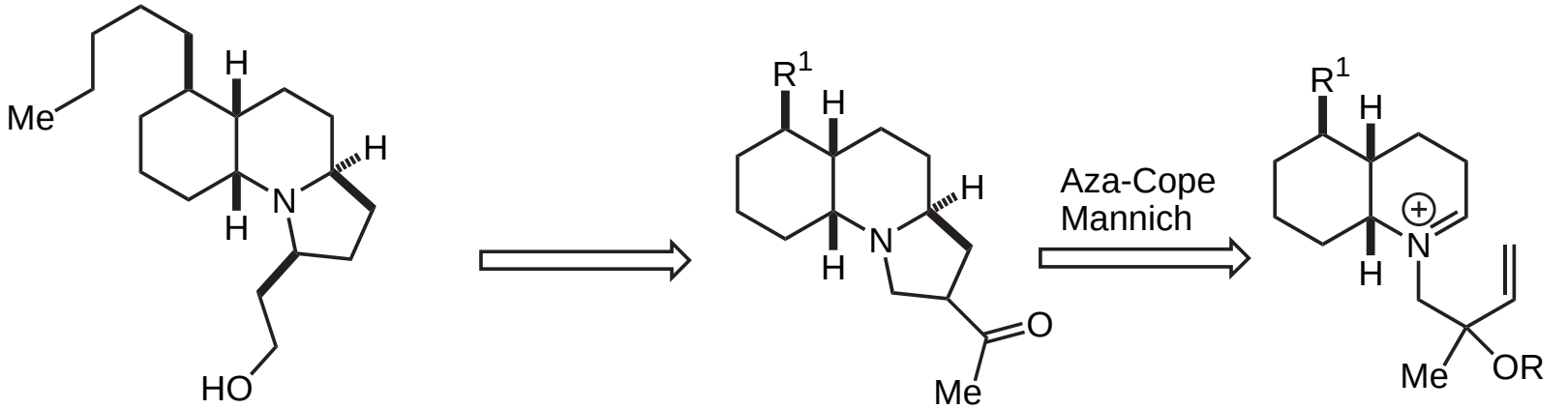


• Thioamides usually prepared with Lawesson's reagent:

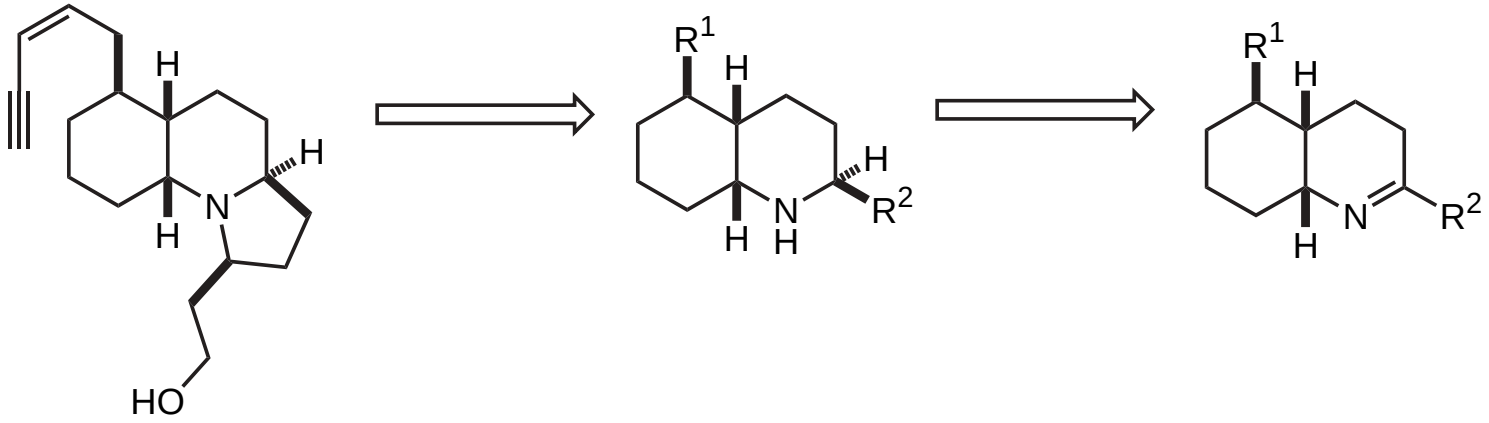


Eschenmoser, *Helv. Chim. Acta*. **1971**, *54*, 710.
Tet. Lett. **1981**, *42*, 4197.

Overman: Retrosynthesis

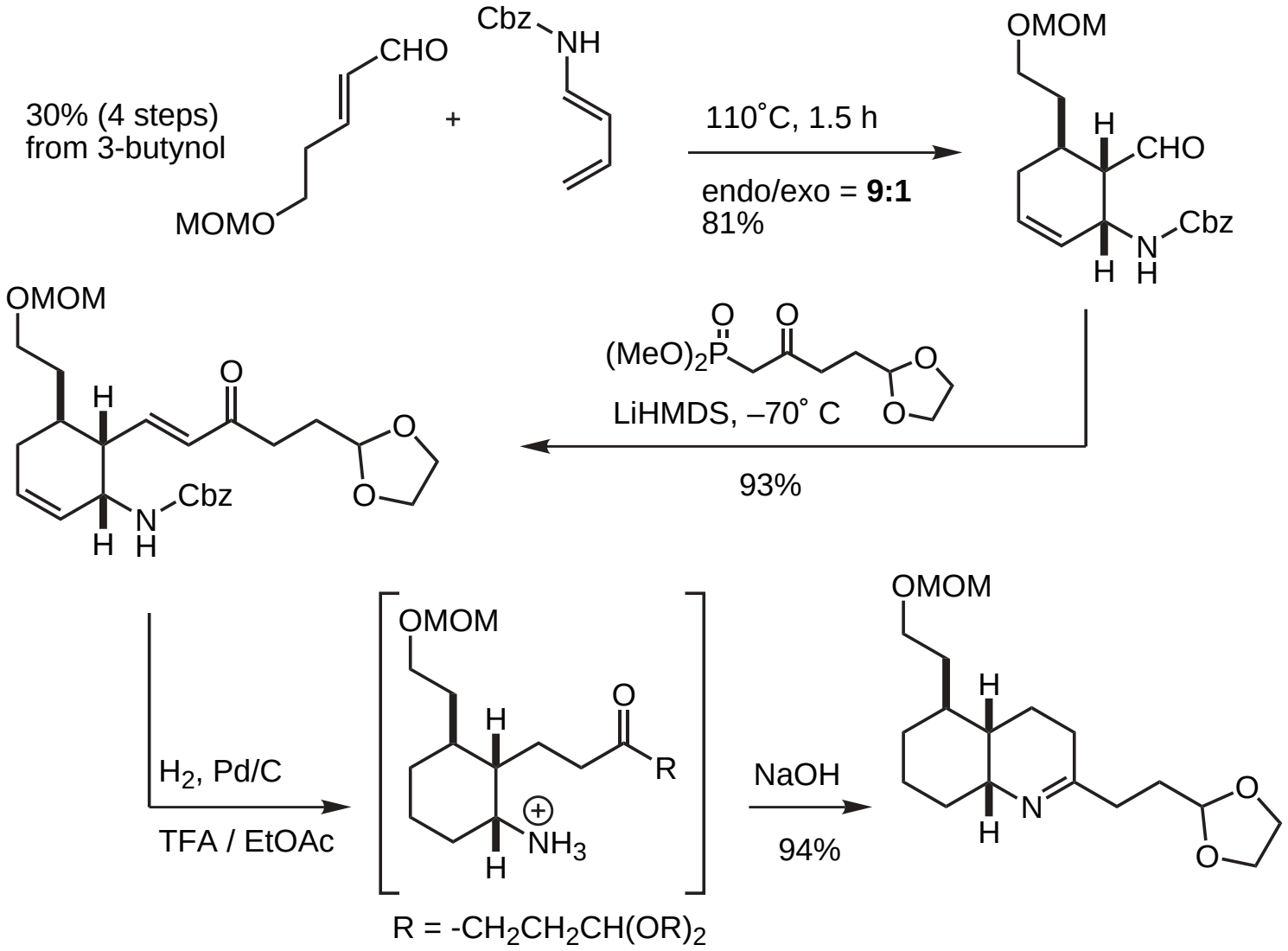


(±)-perhydrogephyrotoxin



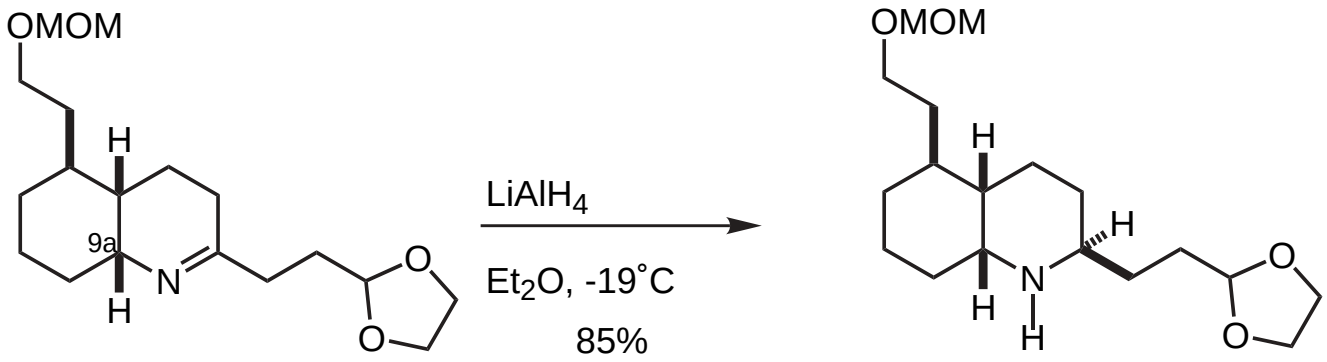
(±)-gephyrotoxin

Overman: (±)-Gephyrotoxin, Hydroquinoline Formation

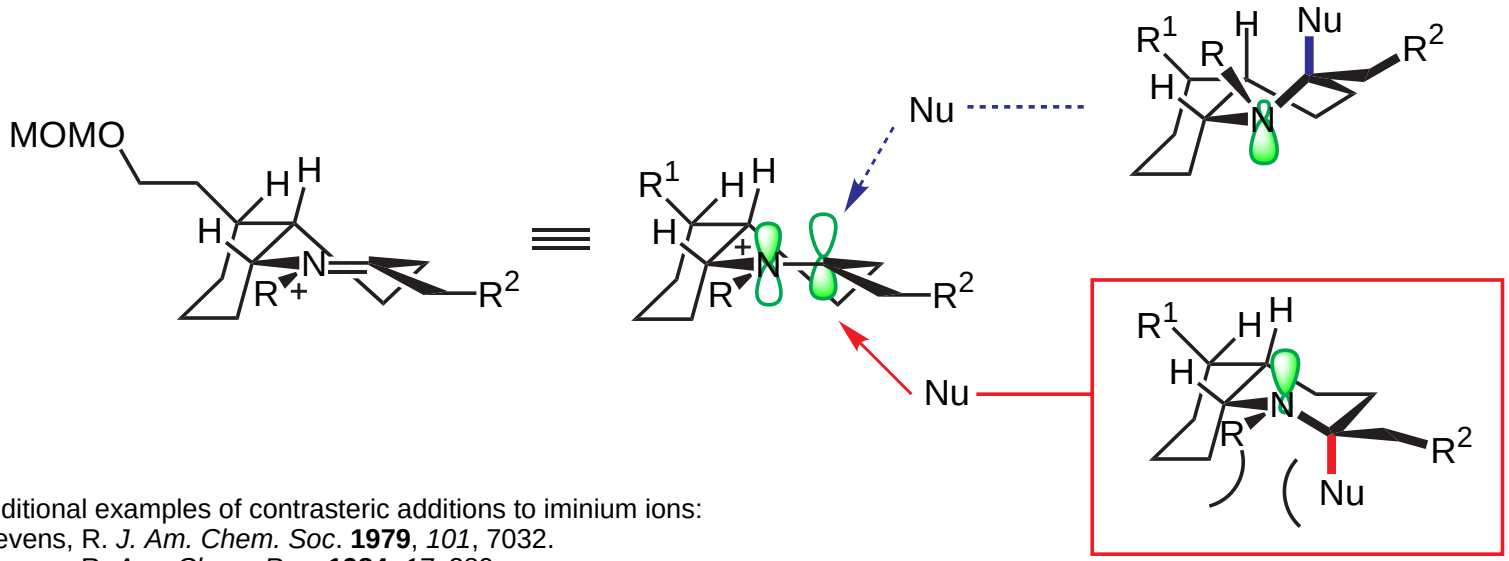


J. Am. Chem. Soc. **1983**, *105*, 5373-5379.

Overman: Contrasteric Iminium Reduction



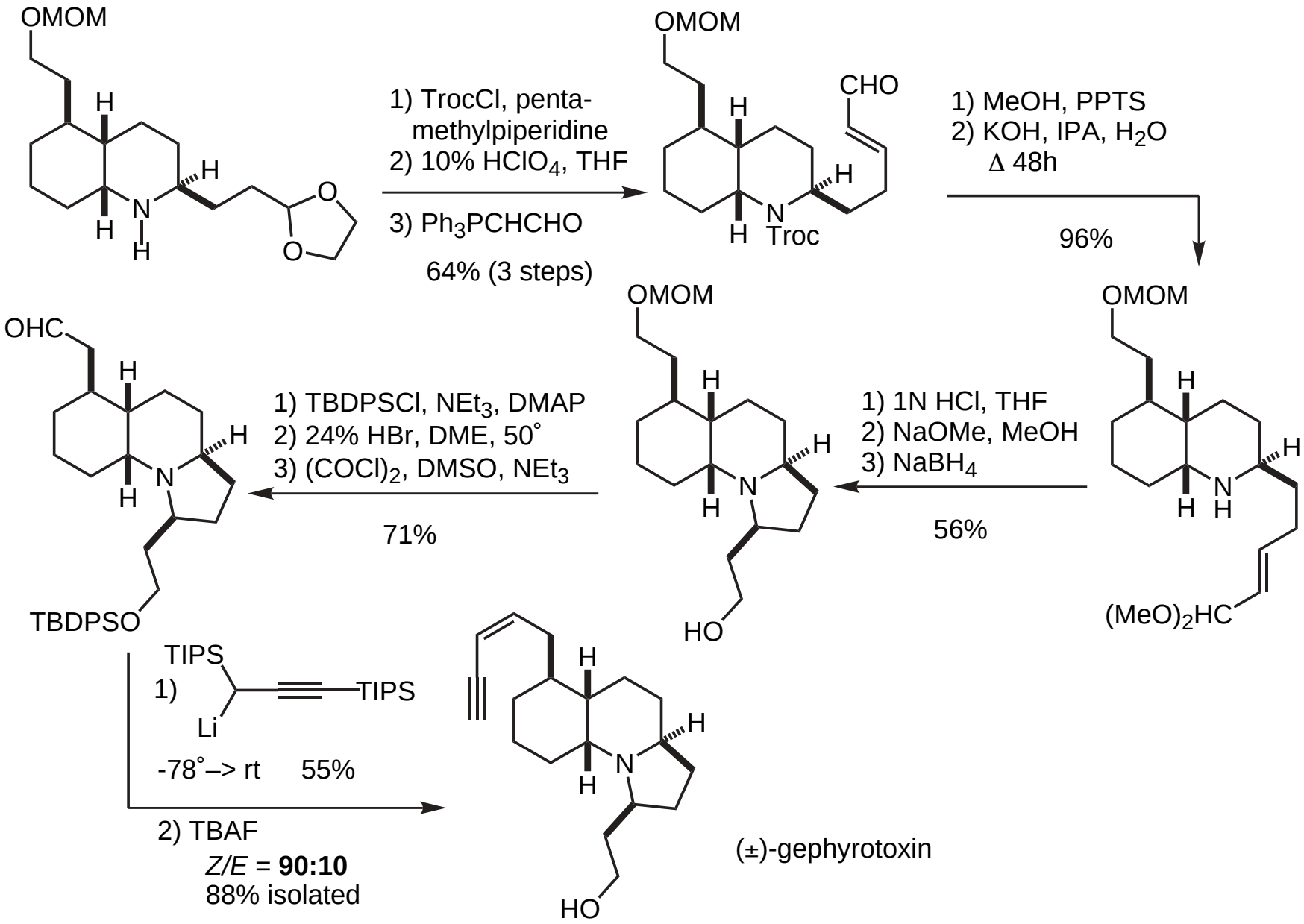
dr = 9:1 to 16:1



Additional examples of contrasteric 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.

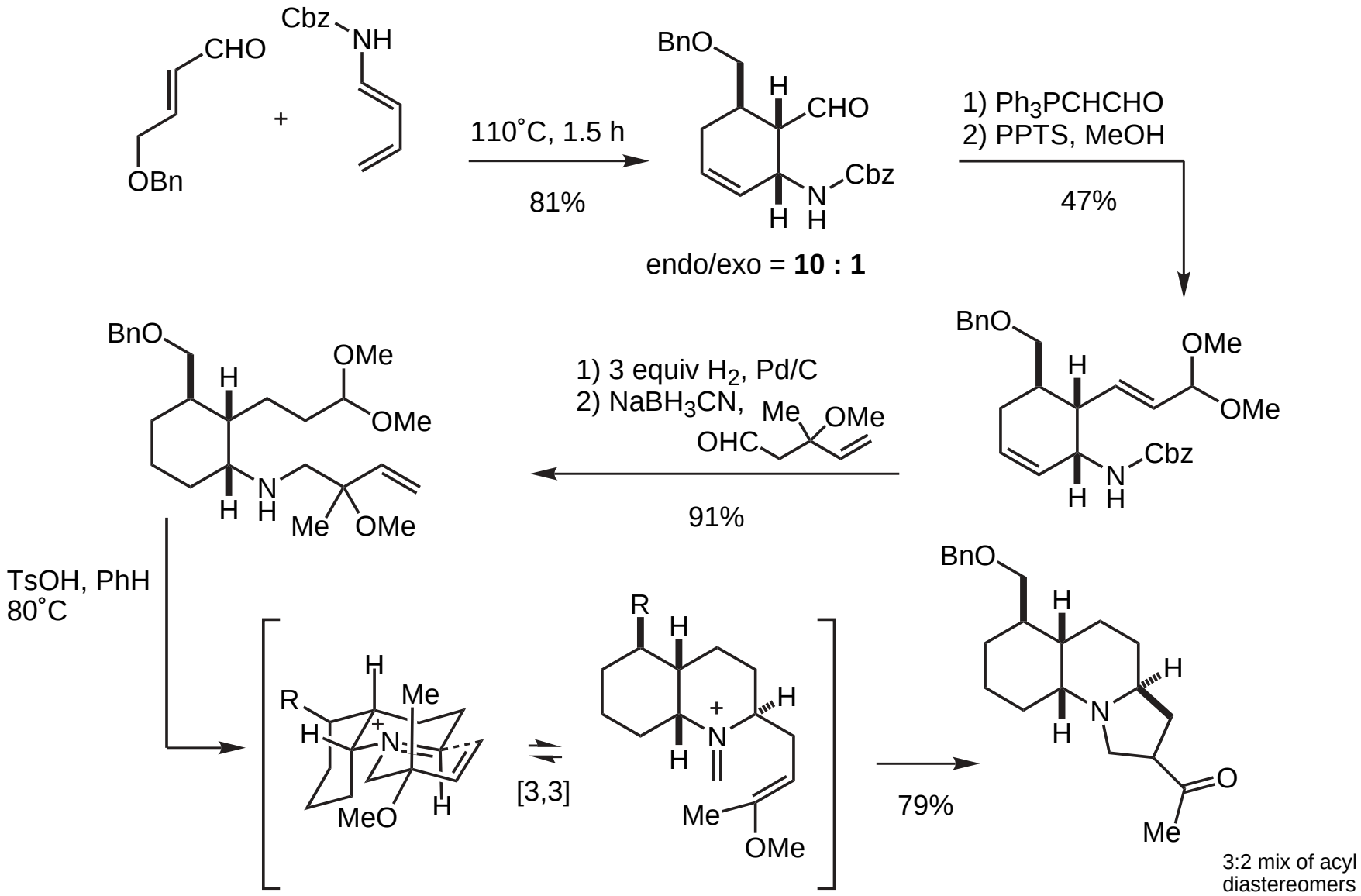
J. Am. Chem. Soc. **1983**, *105*, 5373-5379.

Overman: C-ring and Endgame



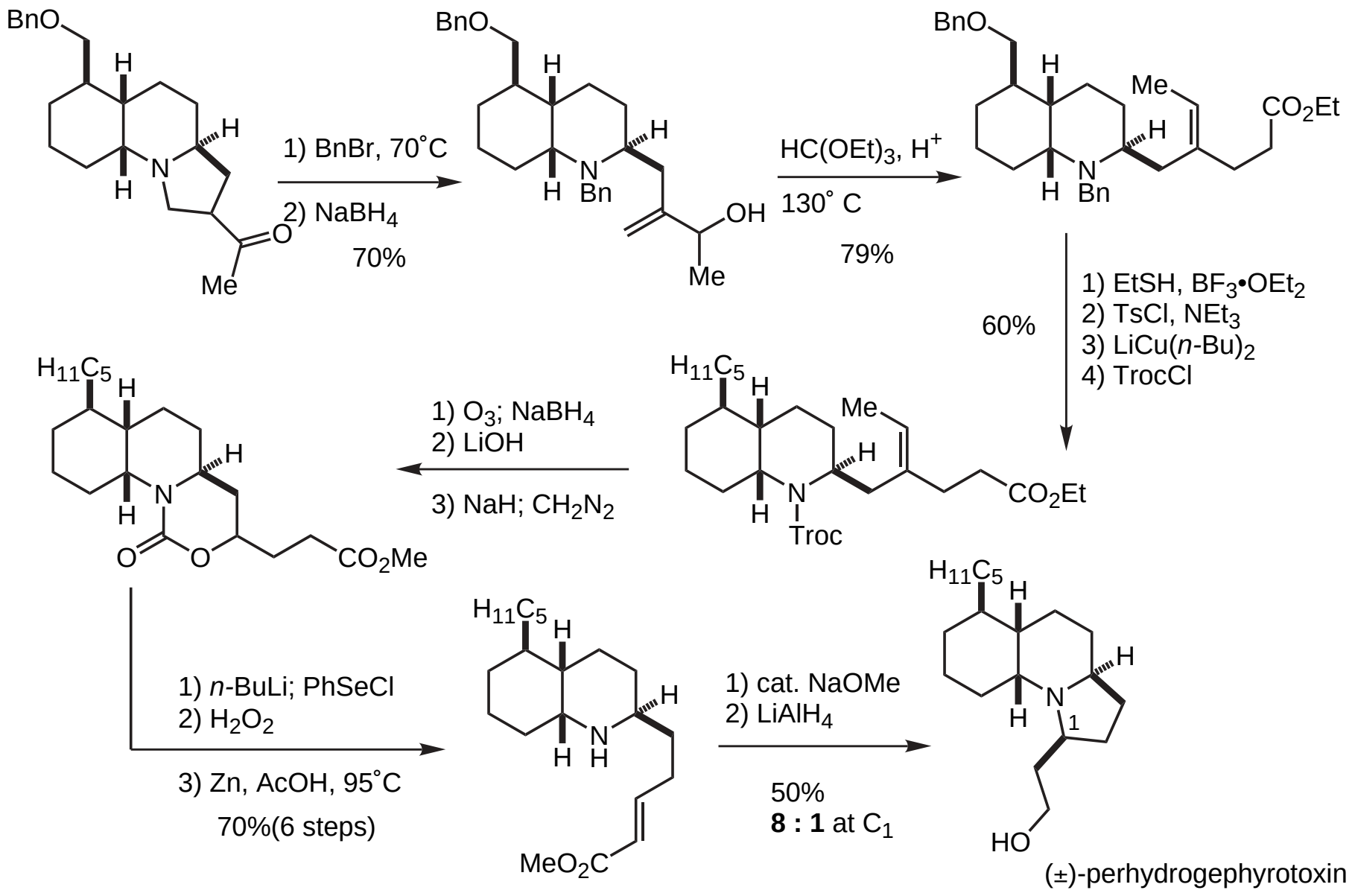
J. Am. Chem. Soc. **1983**, *105*, 5373-5379.

Overman: (±)-Perhydrogephyrotoxin, Hydroquinoline Formation



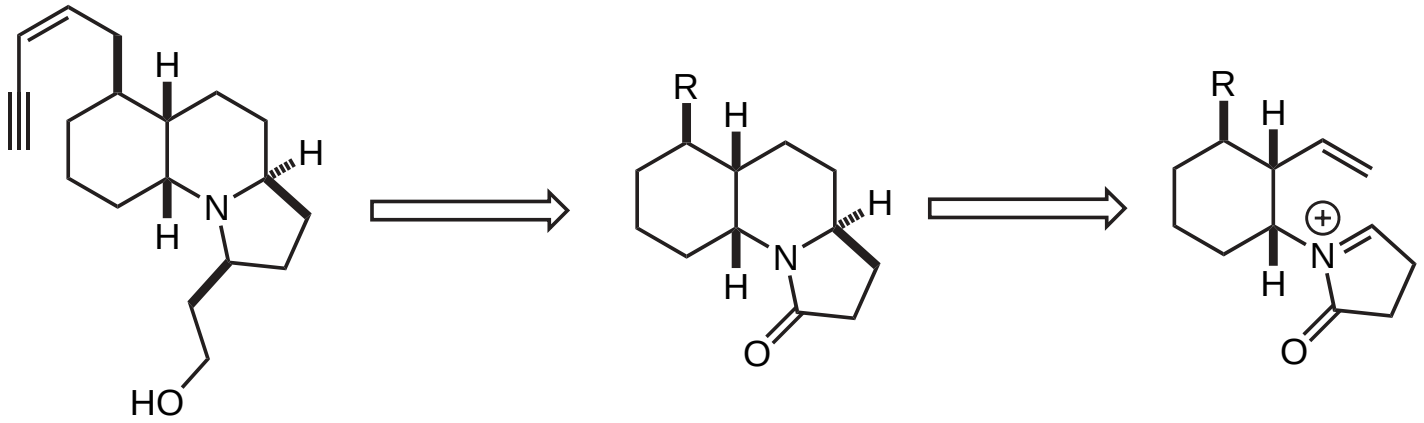
J. Am. Chem. Soc. **1980**, *102*, 1453.

Overman: Perhydrogephyrotoxin, C-Ring



J. Am. Chem. Soc. **1980**, *102*, 1453.

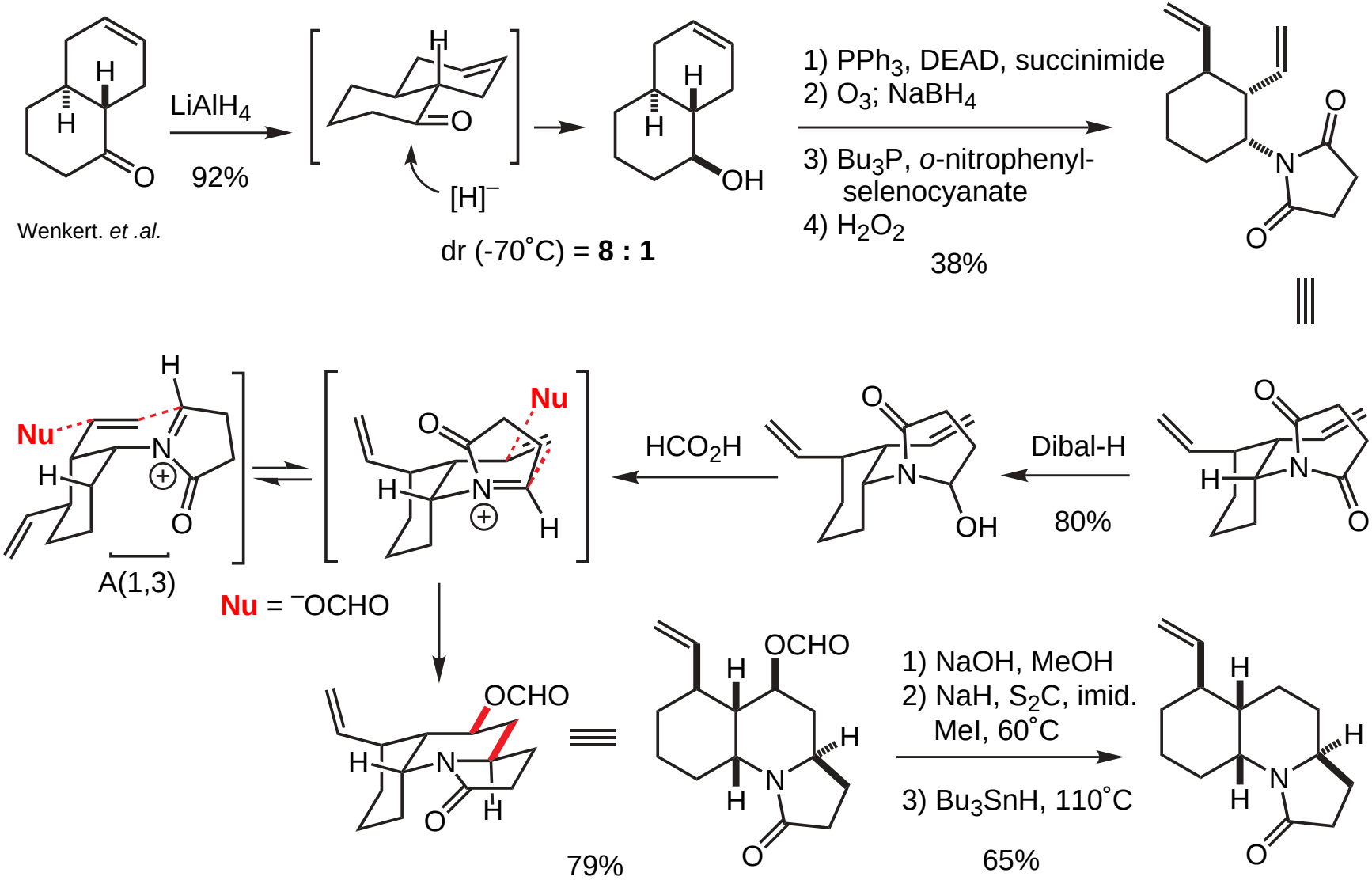
Hart: Retrosynthesis



(±)-gephyrotoxin

N-acyliminium ion

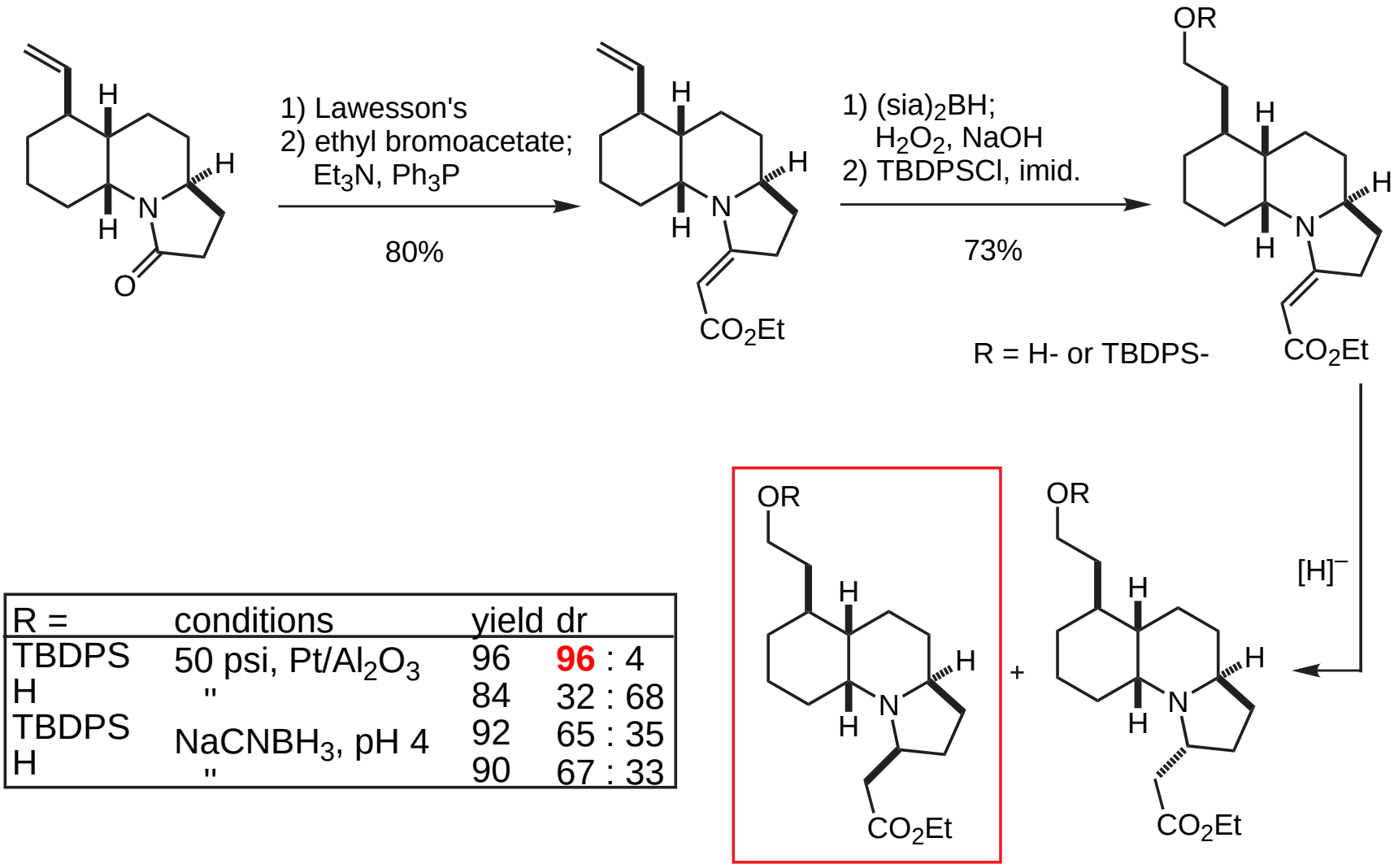
Hart: N-Acyliminium Ion Cyclization



Wenkert. *et .al.*

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

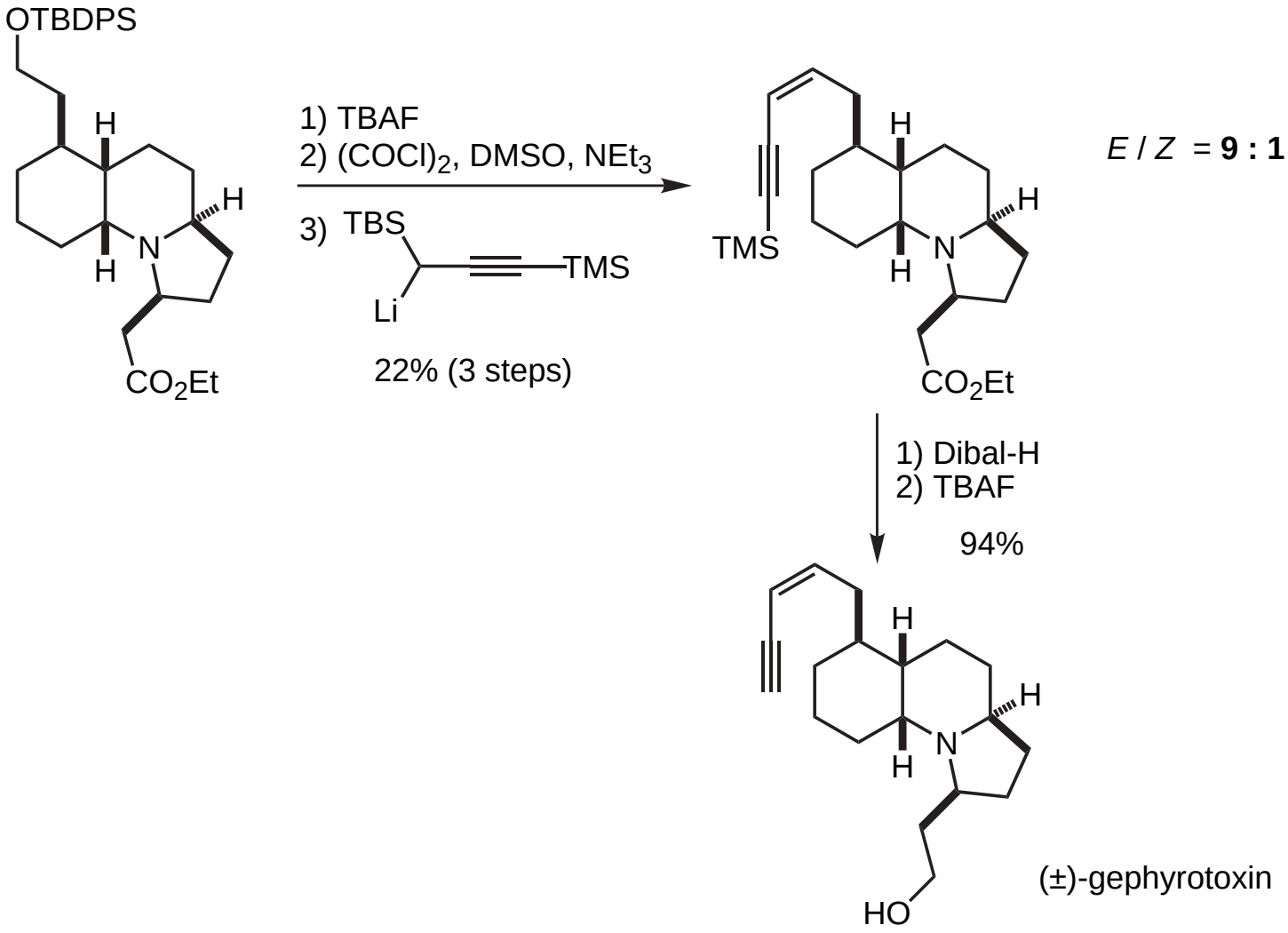
Hart: C(1) Reduction



R =	conditions	yield	dr
TBDPS	50 psi, Pt/Al_2O_3	96	**96** : 4
H	"	84	32 : 68
TBDPS	$NaCNBH_3$, pH 4	92	65 : 35
H	"	90	67 : 33

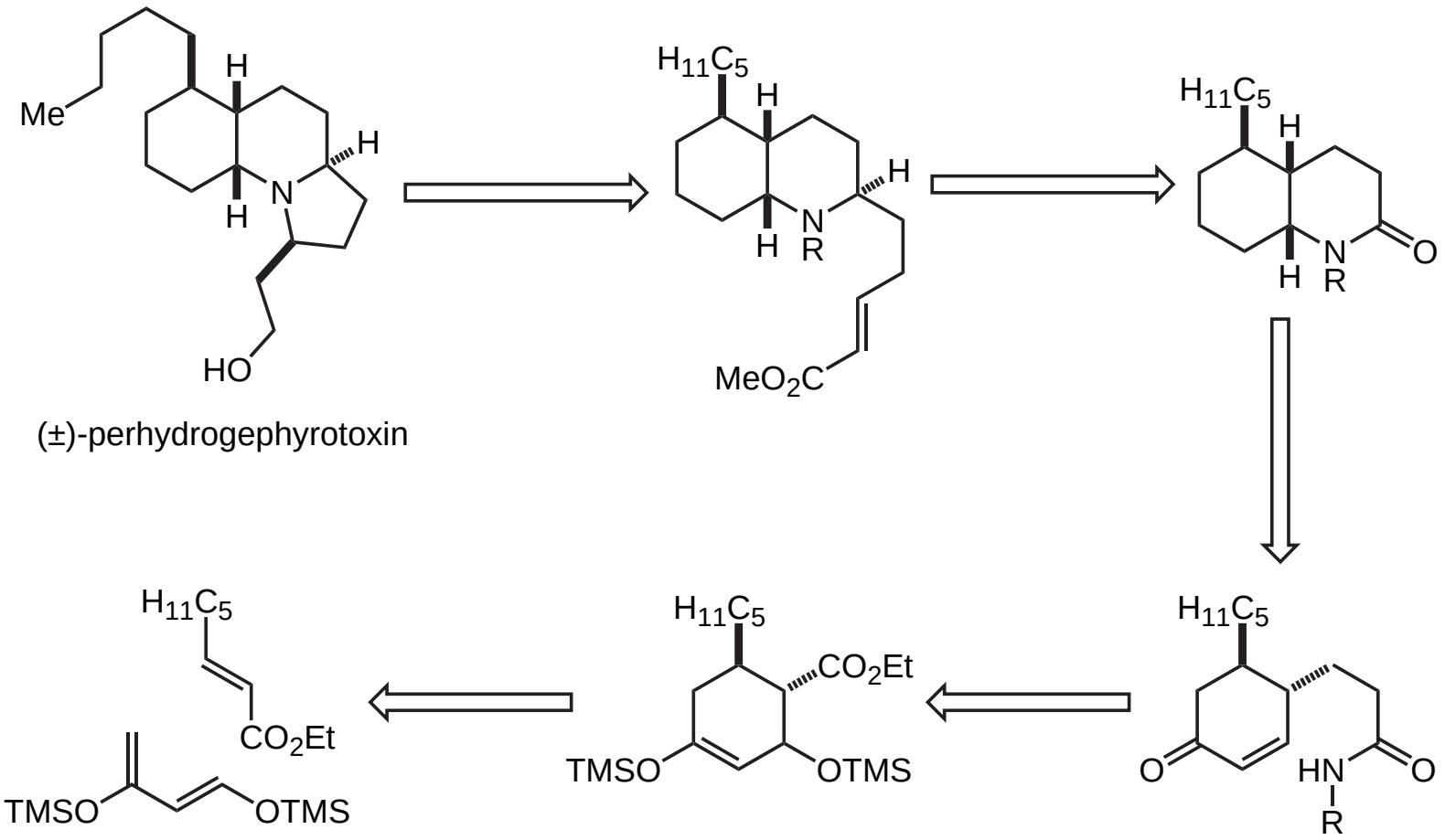
J. Am. Chem. Soc. **1983**, *105*, 1255.

Hart: Unsaturated Sidechain

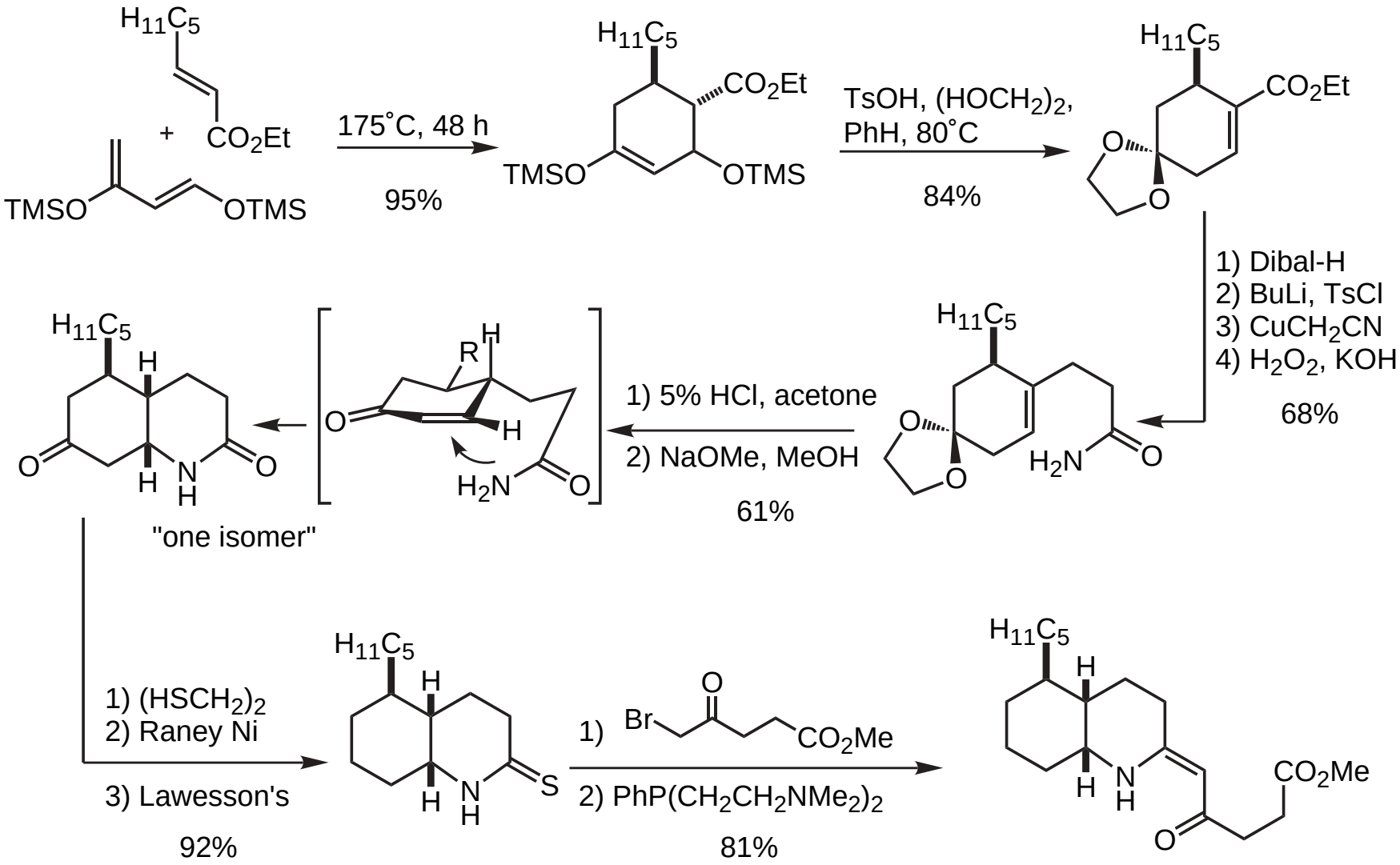


J. Am. Chem. Soc. **1983**, *105*, 1255.

Ibuka: Perhydrogephyrotoxin Retrosynthesis

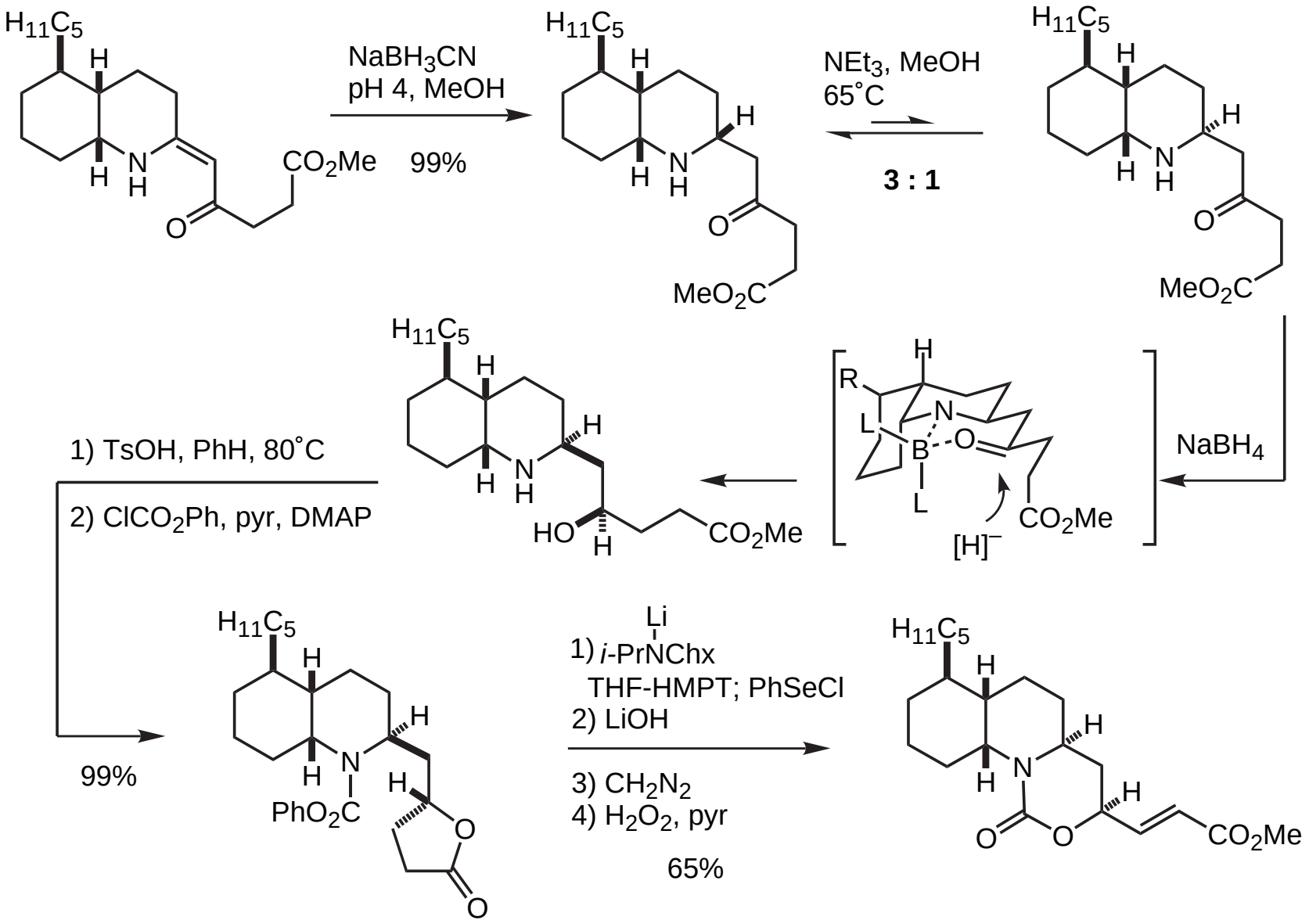


Ibuka: Hydroquinoline Formation



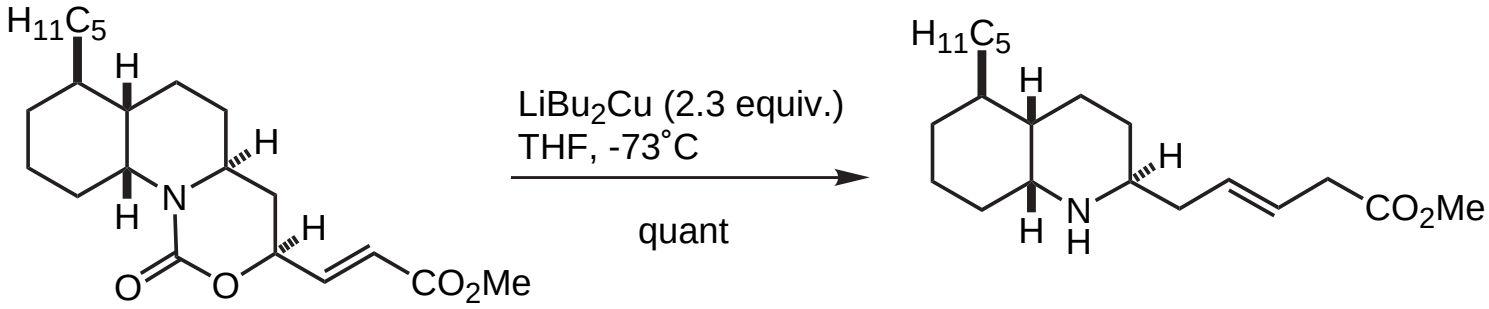
Chem. Comm. **1984**, 597.

Ibuka: C(3a) Stereochemistry

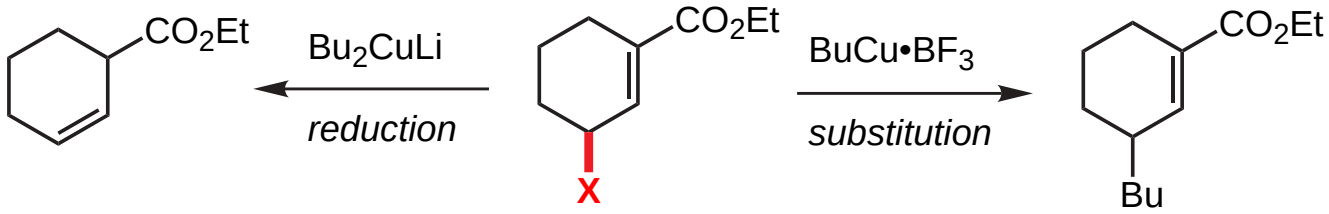


Chem. Comm. **1984**, 597.

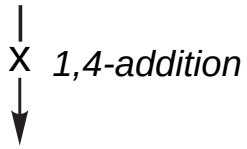
Ibuka: Cuprate Reduction



Later Studies Reveal . . .

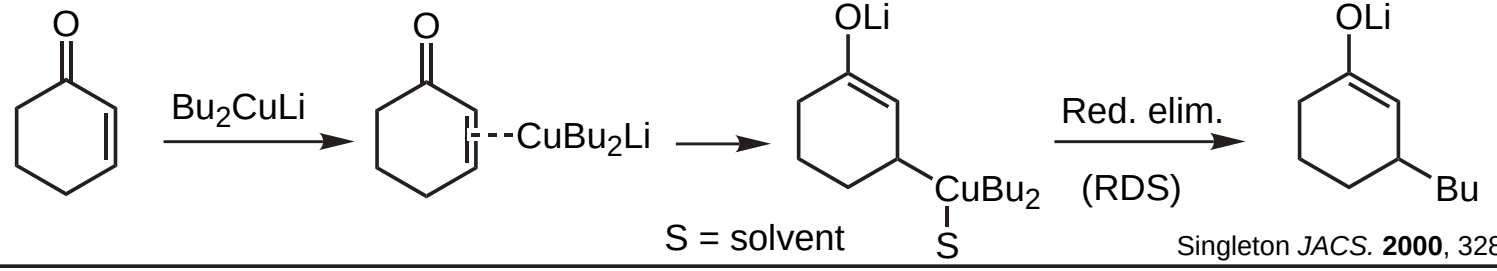


1,4-Addition with cuprates is exceedingly rare with γ–leaving groups **X**: acetoxy, acetonide, carbamoyloxy, ethers, *etc.*



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

Mechanism Involves β-organocuprate:

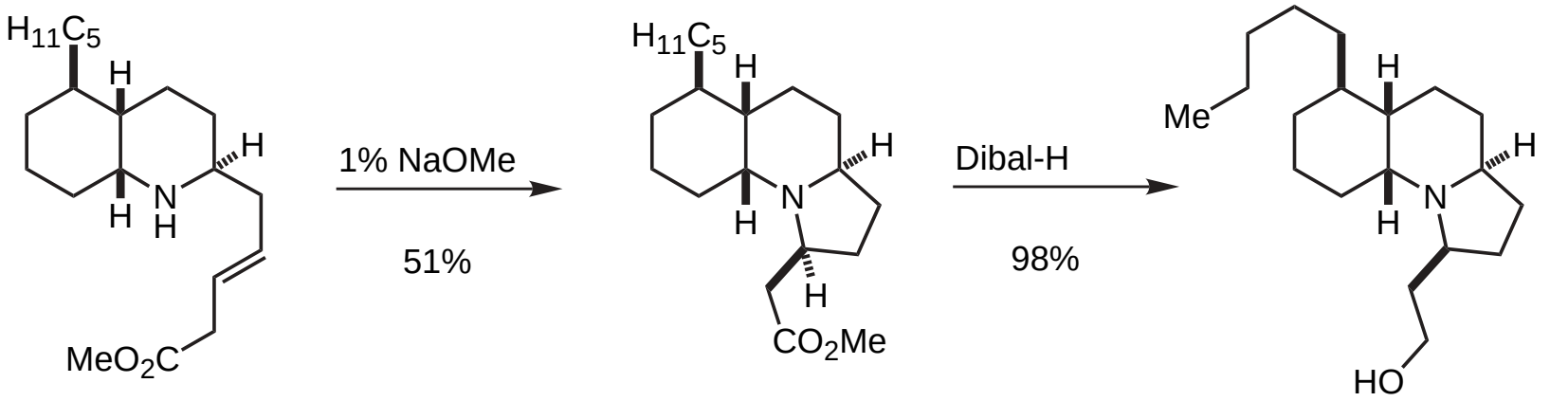


S = solvent

Singleton *JACS.* **2000**, 3289.

Chem. Comm. **1984**, 597.

Ibuka: Homestrech

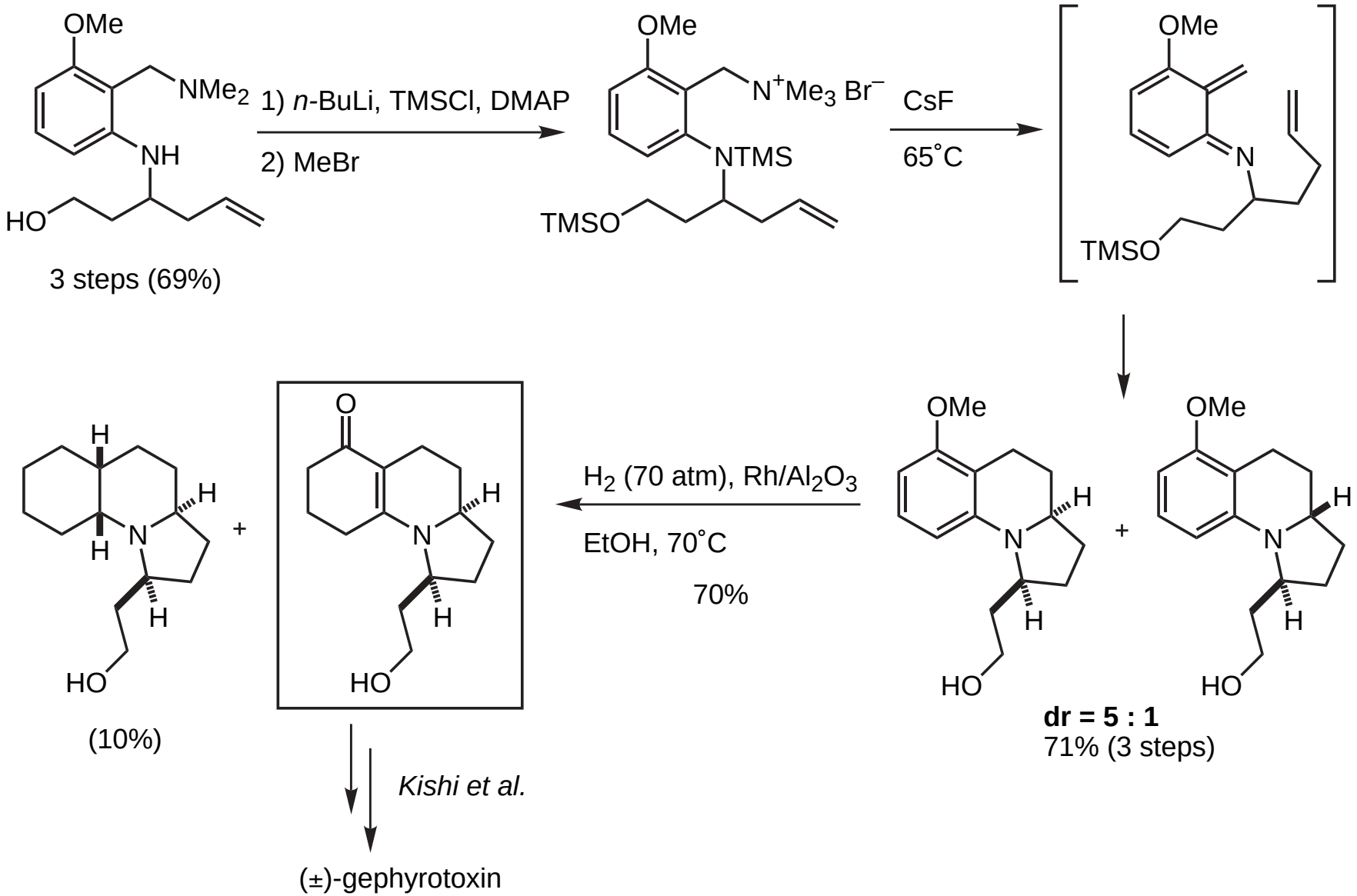


dr = 85 : 15

(±)-perhydrogephyrotoxin

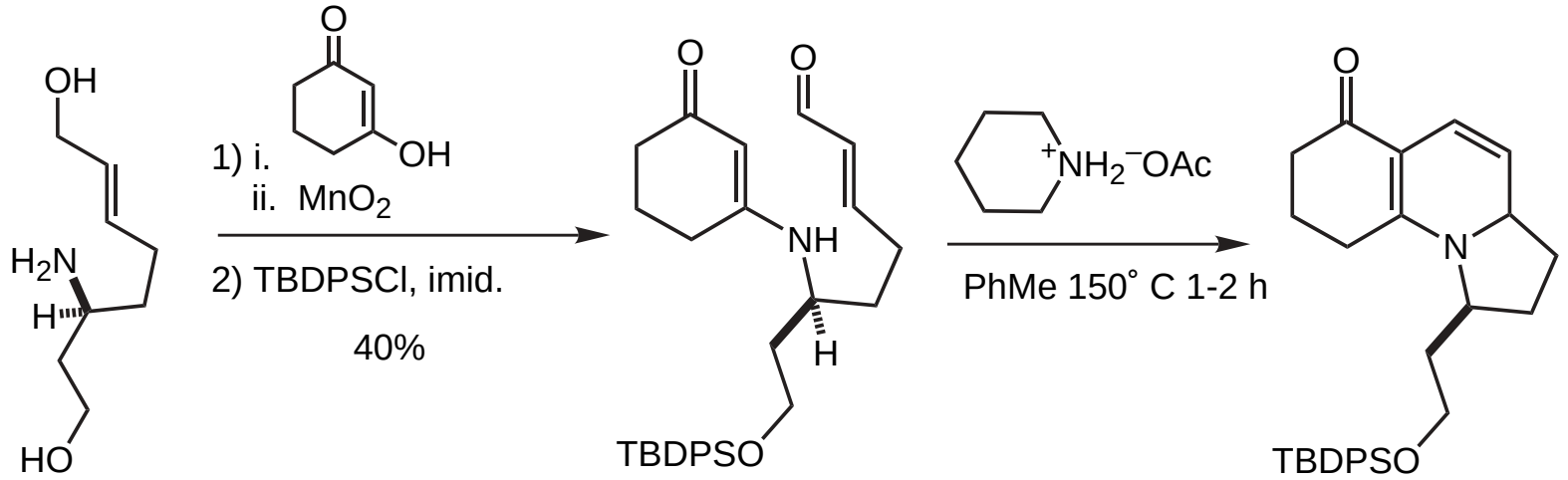
Chem. Comm. **1984**, 597.

Ito and Saegusa: Intramolecular Hetero-Diels-Alder

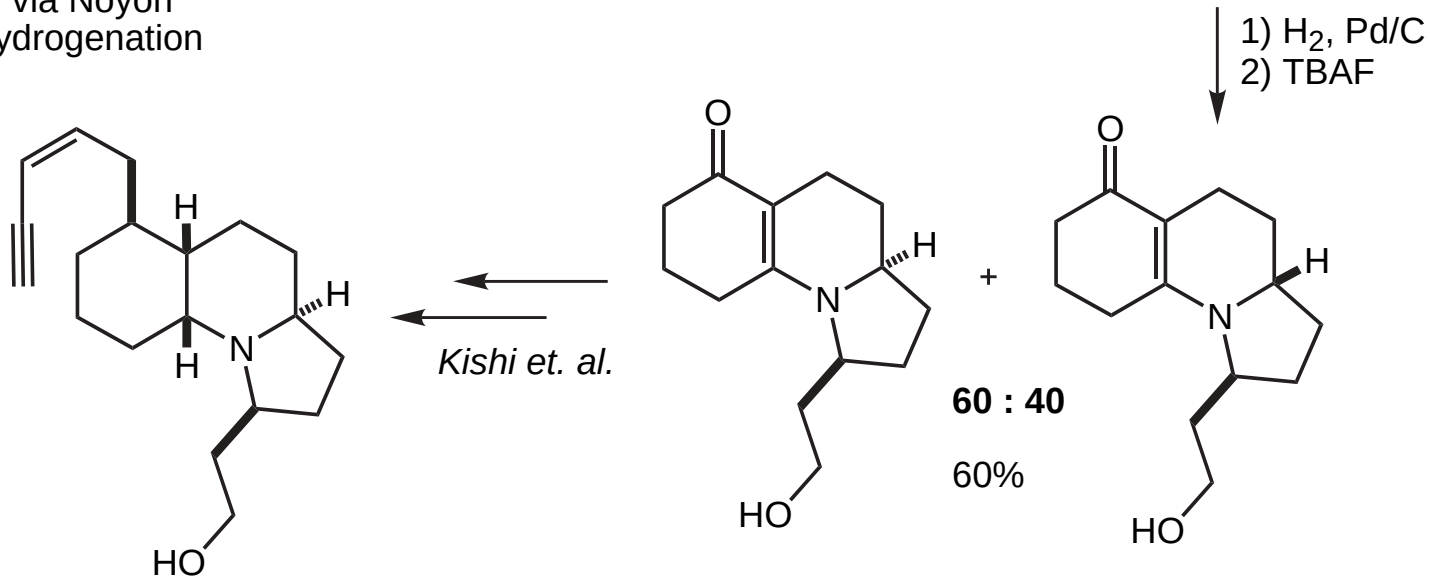


Tet. Lett. **1983**, *24*, 2881.

Hsung: Intramolecular Formal [3+3]



48% (4 steps) via Noyori asymmetric hydrogenation

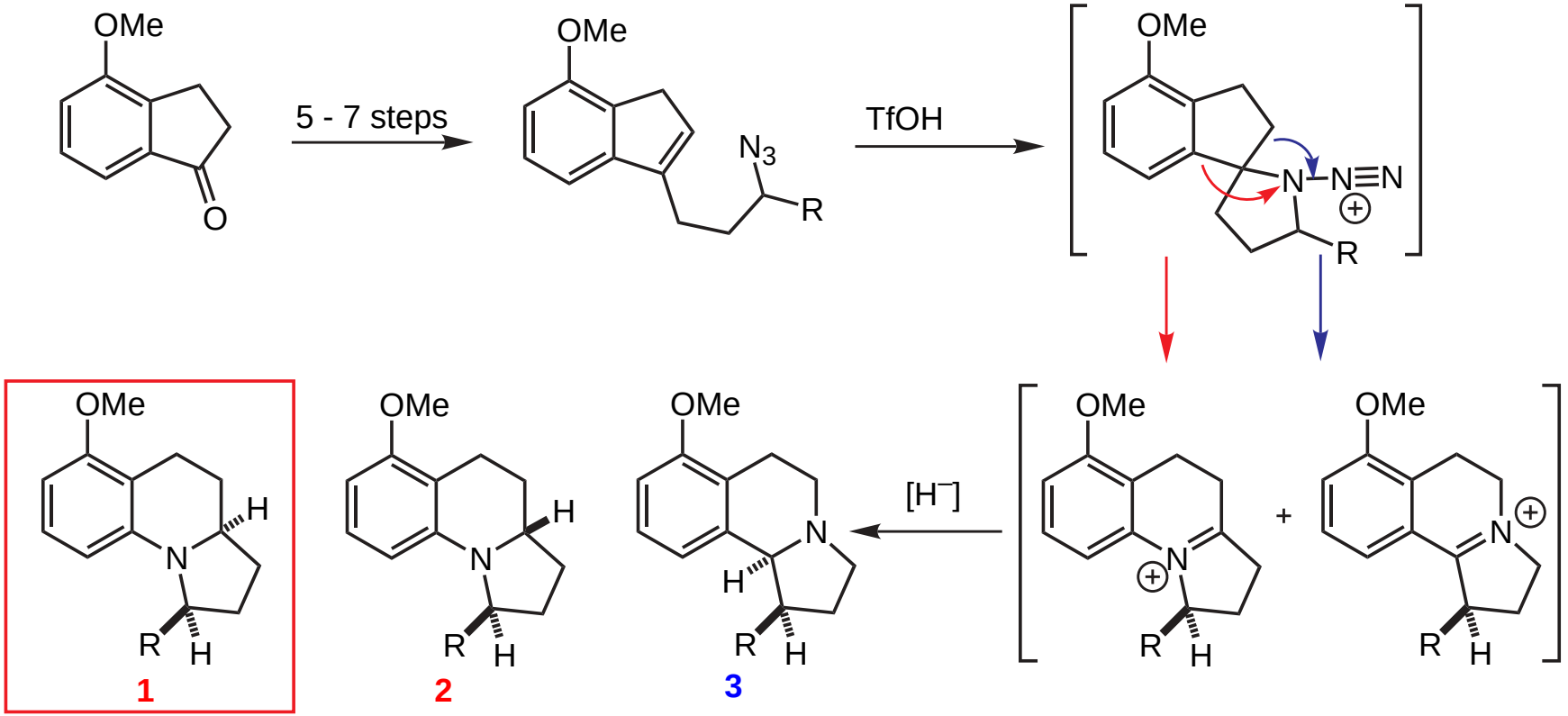


(+)-gephyrotoxin

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

Hsung, R. *Angew. Chem. Int. Ed*. **2001**, *40*, 1516.

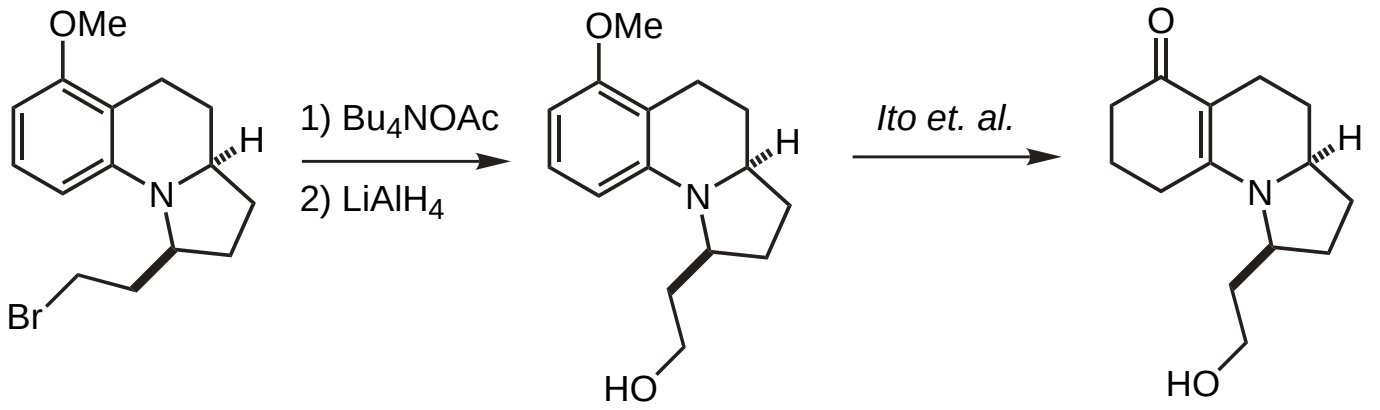
Pearson: (±)-Gephyrotoxin via the Schmidt Reaction



R / hydride reagent	**Yield**	**1 : 2 : 3**
CH_2CH_2Br / $NaBH_4$	72%	39: 39: 22
/ Dibal-H	60%	52: 26: 22
/ L-selectride	55%	82: – : 18
CH_2CH_2OMOM	–	–
$CH_2CH{=}CH_2$	86%	16: 35: 49

J. Org. Chem. **2000**, *65*, 7158.

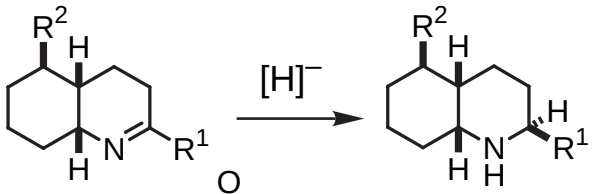
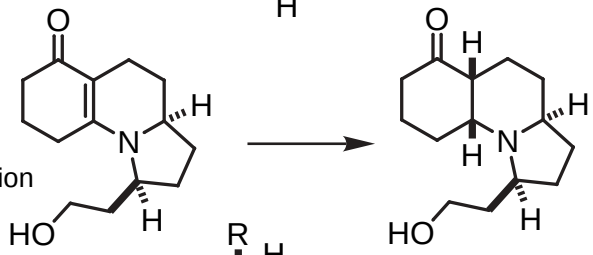
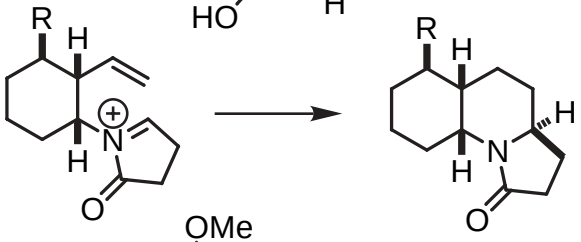
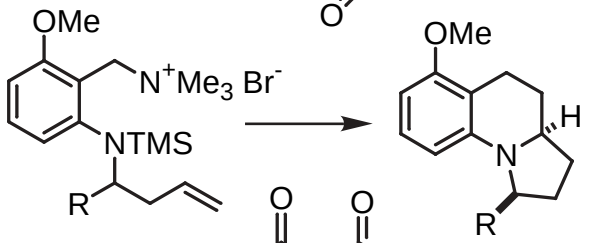
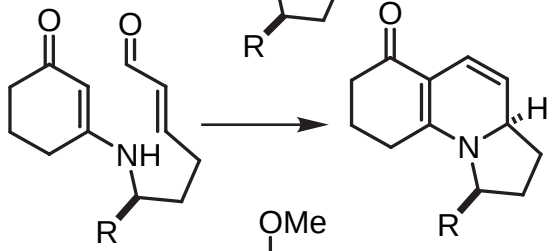
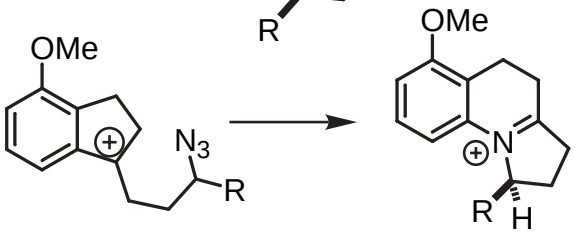
Pearson: Intersection with Ito Intermediate



(±)-gephyrotoxin

J. Org. Chem. **2000**, *65*, 7158.

Synthesis of (±)-Gephyrotoxin: A Comparison

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

*from Kishi intermediate