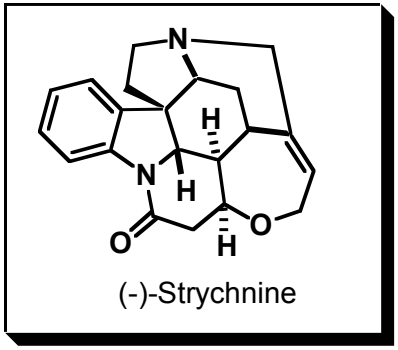
Total Synthesis of (±)-Strychnine via a [4+2]-Cycloaddition/Rearrangement Cascade

Hongjun Zhang, Jutatip Boonsombat, and Albert Padwa*

Org. Lett., **2007,** *9, 279-282.*

William Paquette
5-12-07 Literature Presentation
Wipf Group

Strychnine - A Highly Toxic Alkaloid



(-)-Strychnine

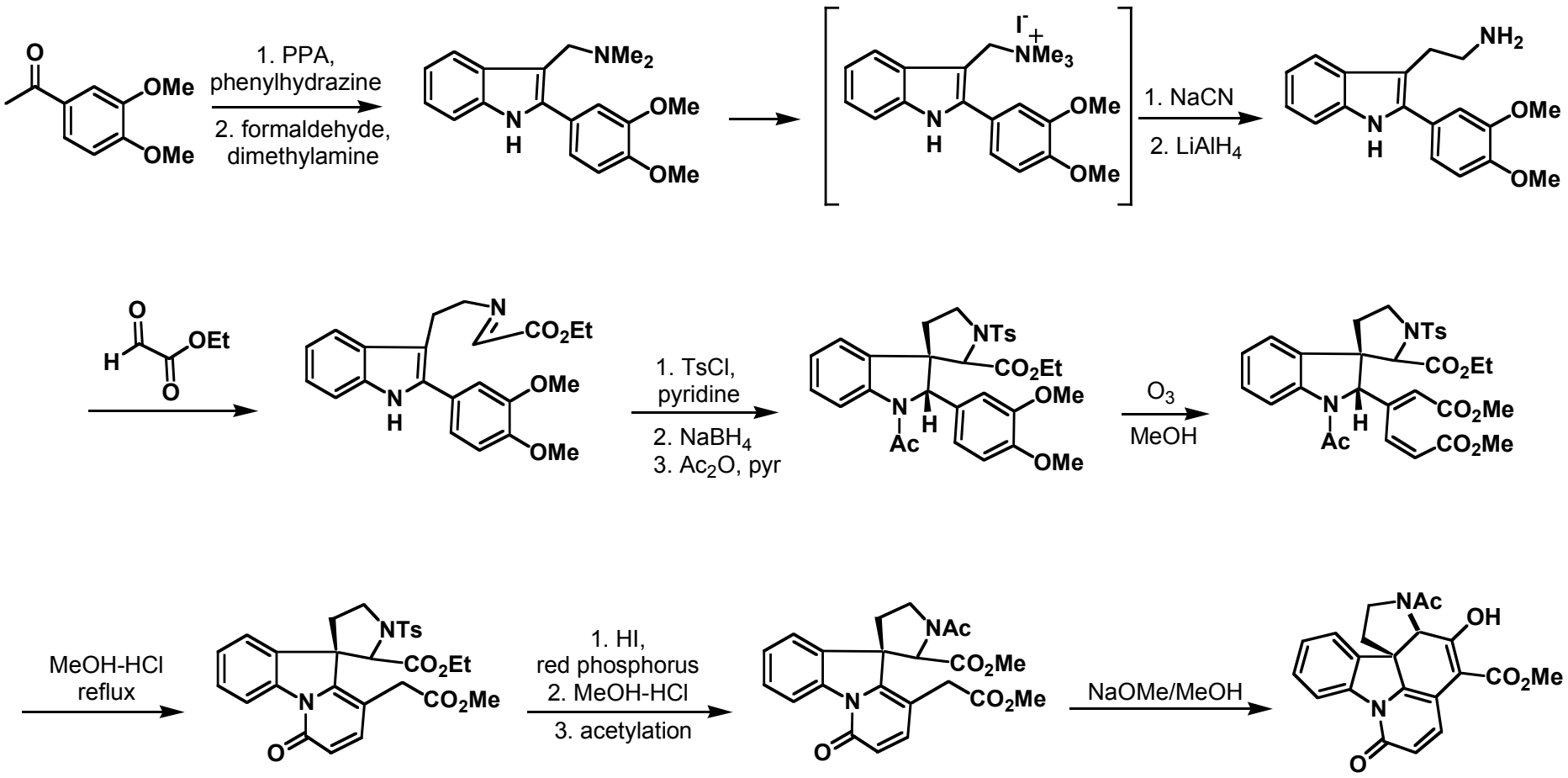
Strychnos nux vomica
(found in southern Asia and Australia)

- Isolated in 1818 from an Indian poison nut
- Its structure was determined in 1947 by Robert Robinson
- Highly toxic to humans and animals
- Commonly used as a pesticide

- From a synthetic perspective, its structure has fascinated organic chemists for decades
- Consists of a heptacyclic core with 6 contiguous stereocenters
- Numerous synthetic efforts have been conducted

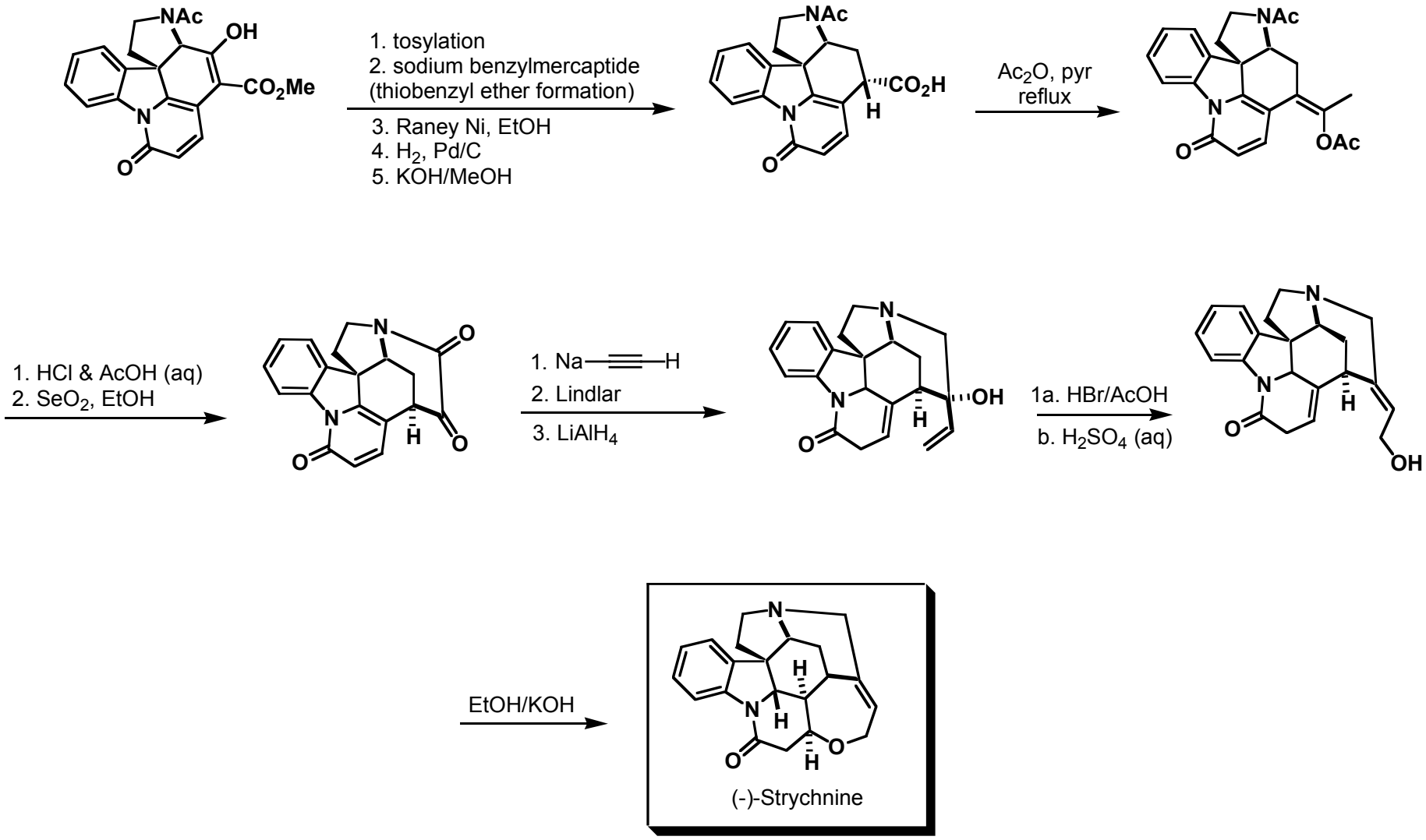
"For its molecular size it is the most complex substance known" (R.B. Woodward, ca. 1963)

A Historical Perspective:
The First Total Synthesis of Strychnine

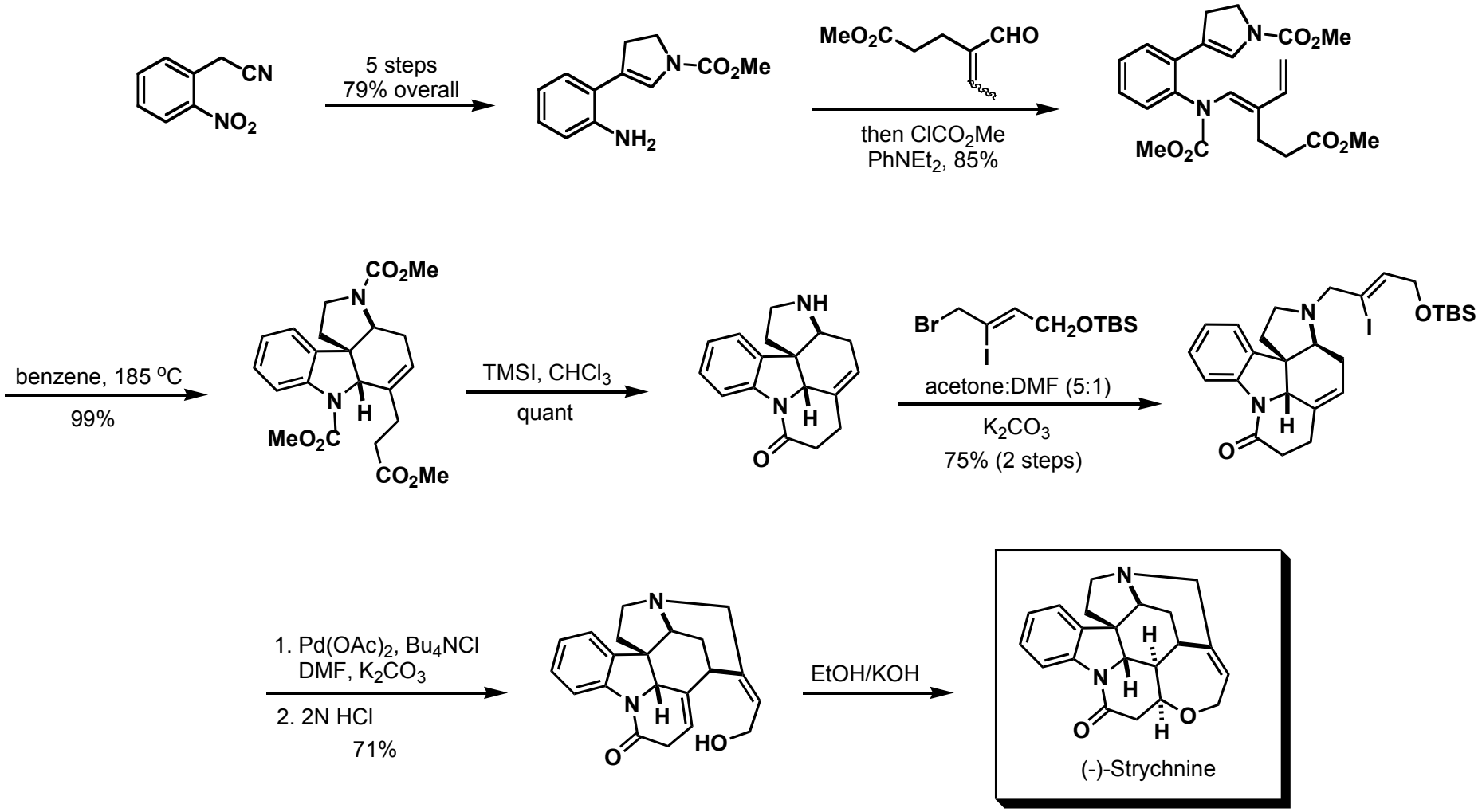


Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954,** *76,* 4749.
Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963,** *19,* 247.

The Woodward Synthesis:
Final Approach

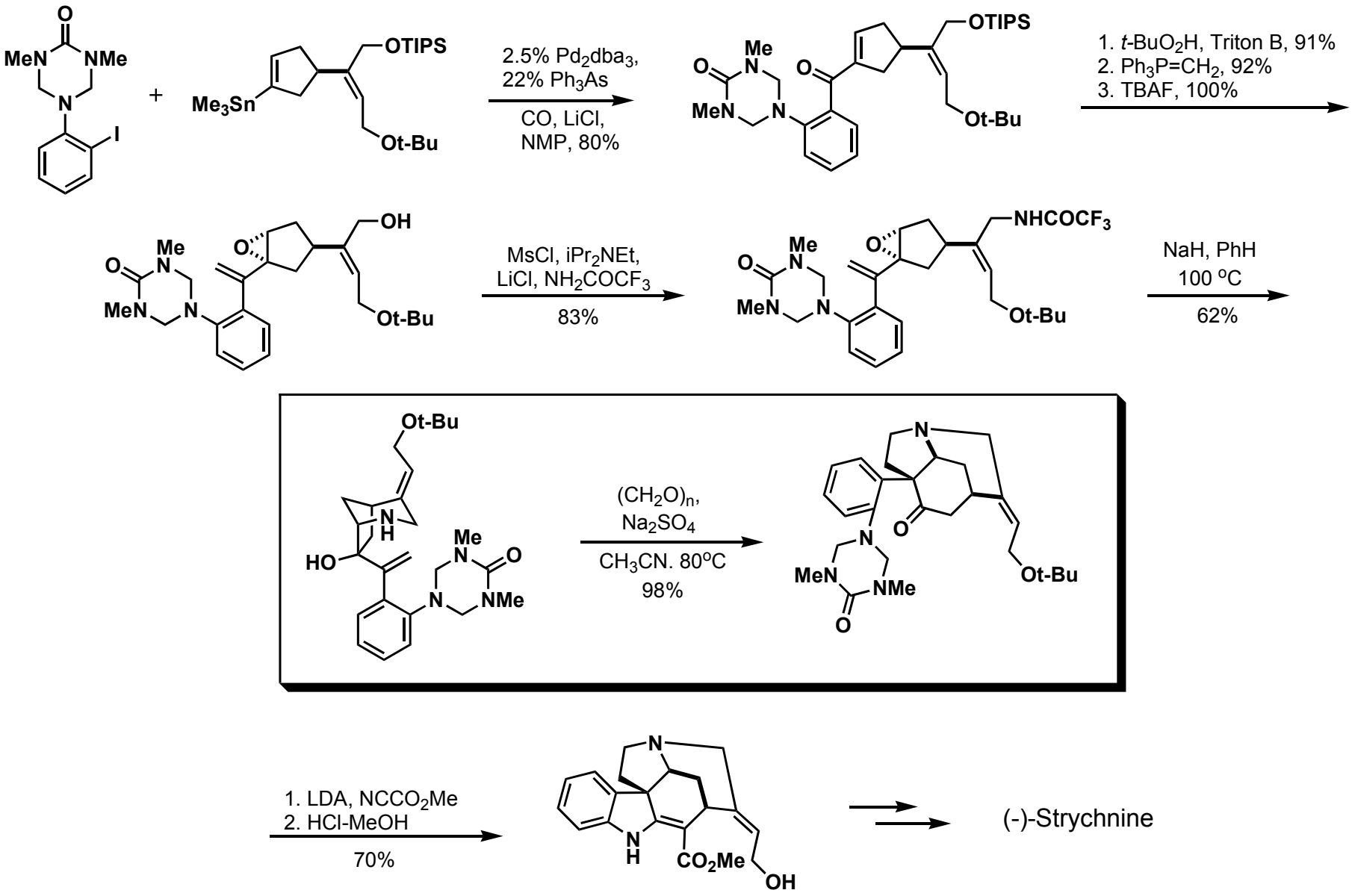


Diastereoselective Synthesis of Strychnine
Rapid Access to the Heptacyclic Natural Product



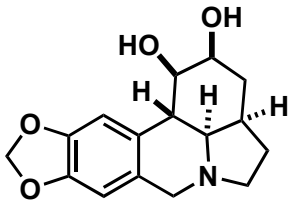
Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994,** *59,* 2685.

Strychnine Synthesis via an aza-Cope-Mannich Reaction

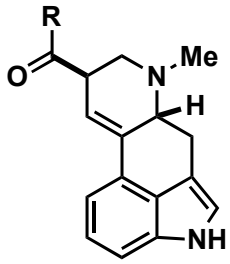


Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993,** *115,* 9293.

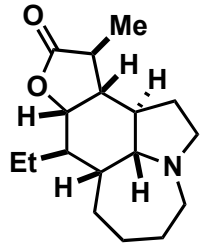
Padwa's Approach Toward the Synthesis of Complex Alkaloids



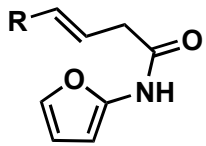
epi-zephyranthine



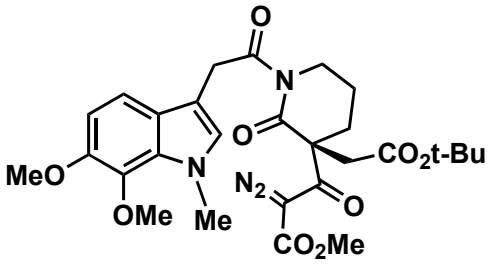
Ergot alkaloid

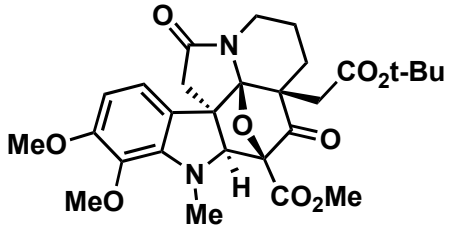


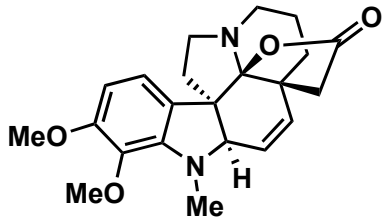
(±)-stenine



Structural Motif



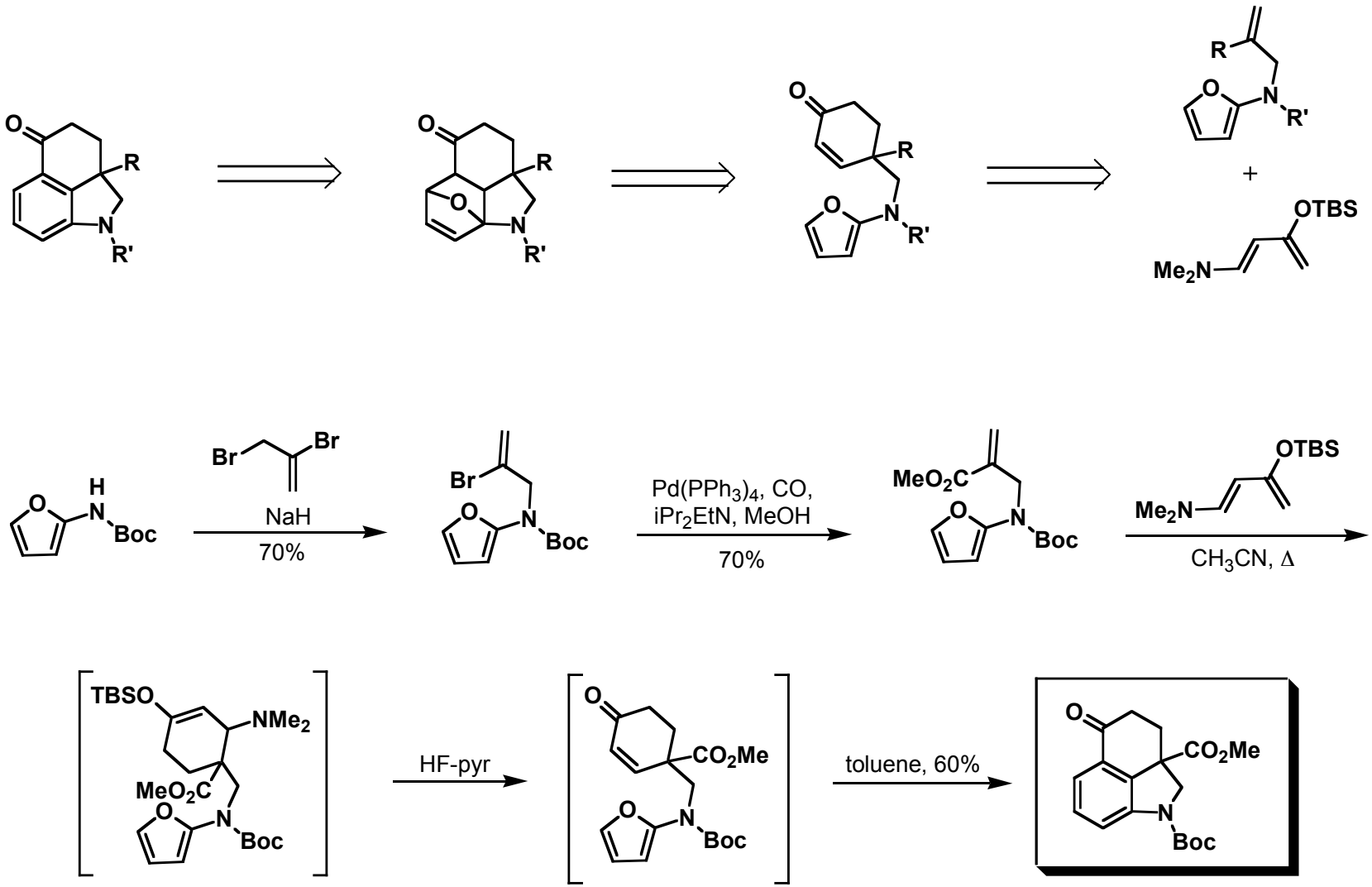




(±)-aspidophytine

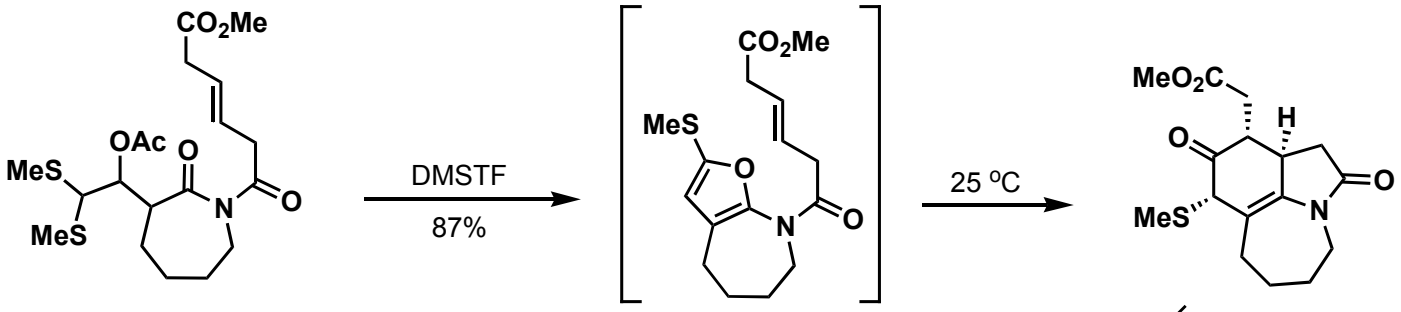
Org. Lett. **2006,** *8,* 3275

Construction of the Ergot Alkaloid Skeleton



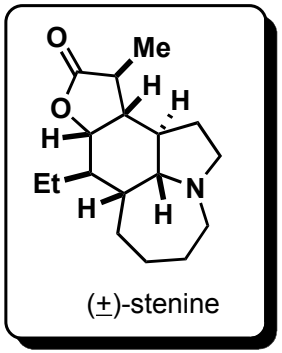
Padwa, A.; Bur, S. K.; Zhang, H. *J. Org. Chem.* **2005,** *70,* 6833.

Diverse Approaches Toward the Synthesis of Stenine

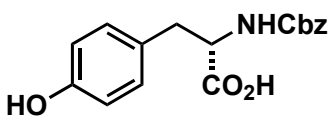


DMSTF - dimethyl(methylthio)sulfonium tetrafluoroborate

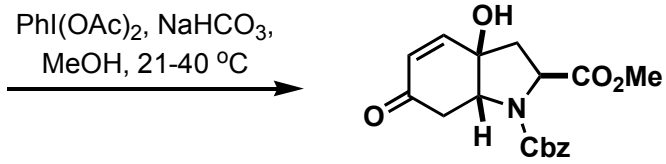
Padwa, A.; Ginn, J. D. *J. Org. Chem.* **2005,** *70,* 5197.

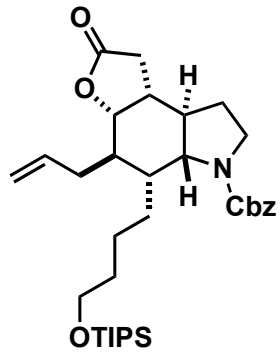


(±)-stenine



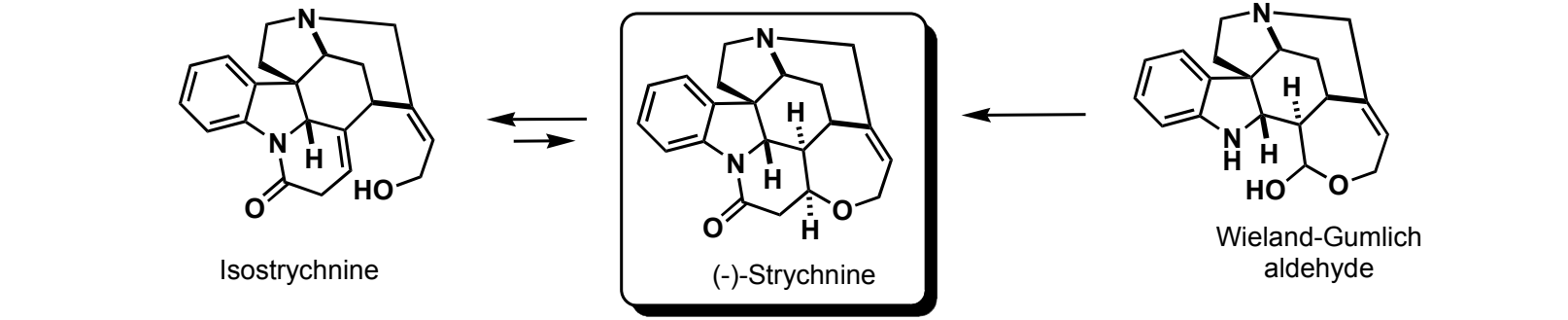
L-Tyrosine

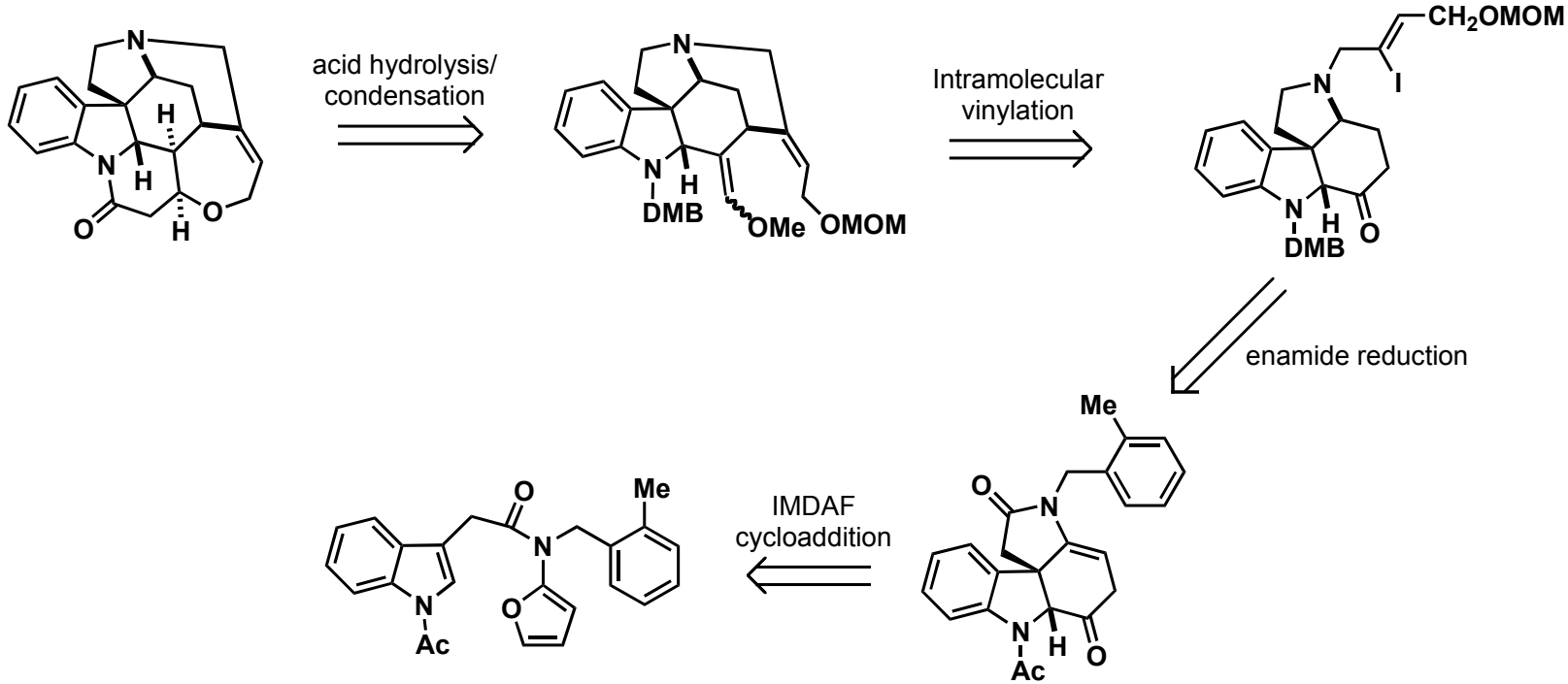




Wipf, P; Kim, Y.; Goldstein, D. M. *J. Am Chem. Soc.* **1995,** *117,* 11106.

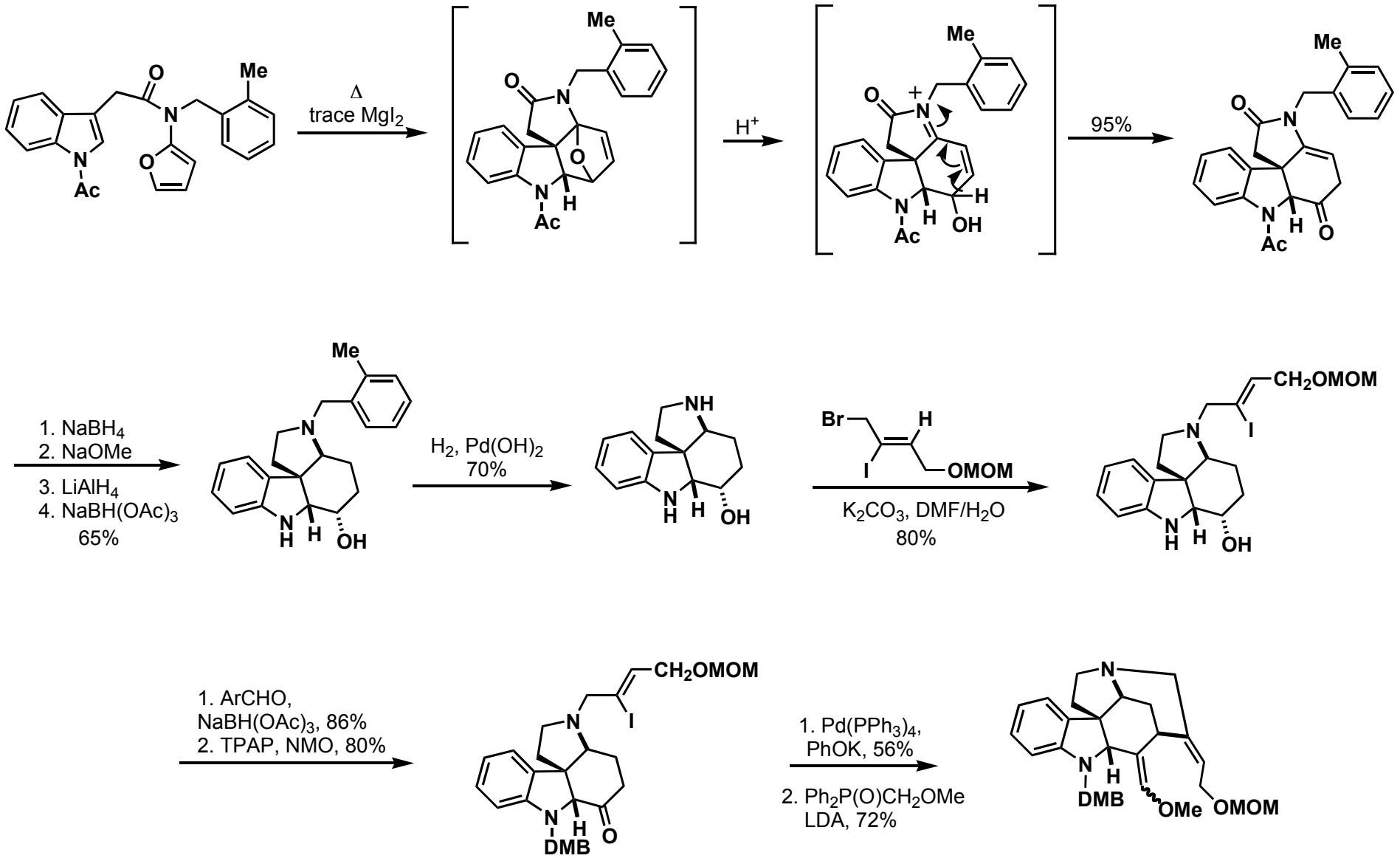
Total Synthesis of (±)-Strychnine via a Cycloaddition/Rearrangement Pathway



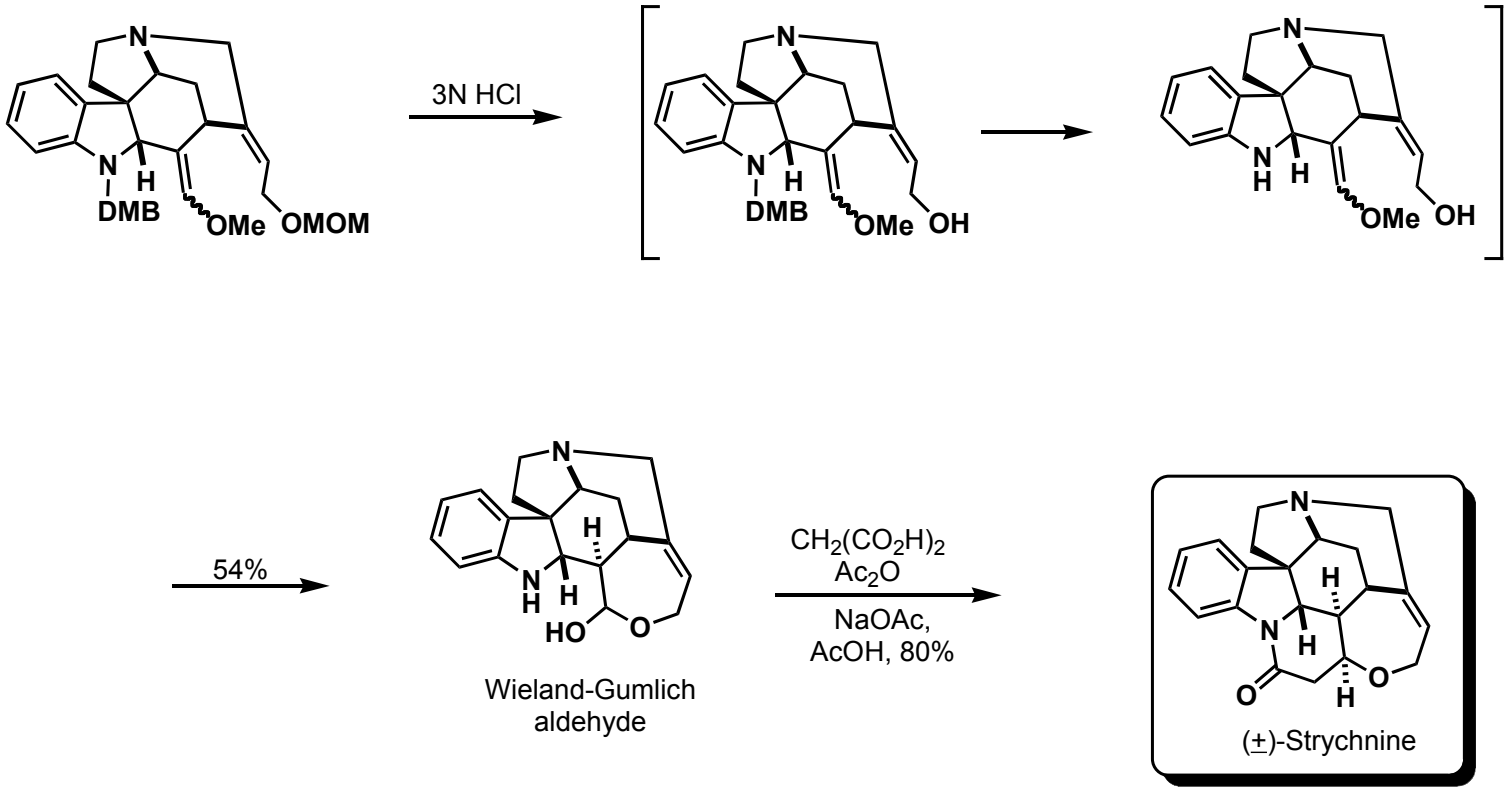


Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007,** *9,* 279.

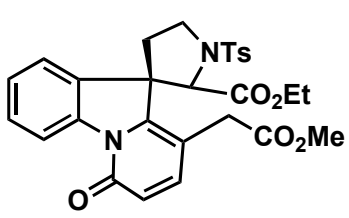
Diastereoselective Construction of the Strychnine Core



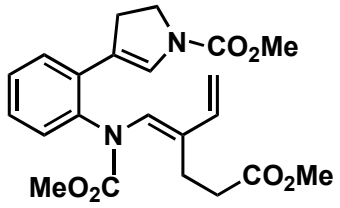
Completion of the Total Synthesis



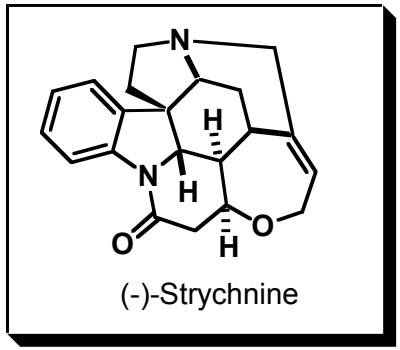
Summary



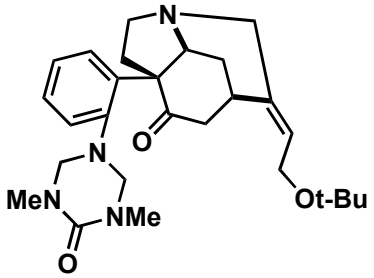
Woodward
The First Total Synthesis



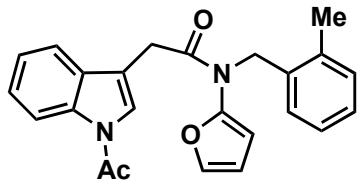
Rawal
A Concise Approach



(-)-Strychnine



Overman
Utilization of an aza-Cope-Mannich Reaction



Padwa
Cycloaddition/Rearrangement Strategy

•Strychnine's complex structure provides a great opportunity to showcase unique and powerful methodologies *en route* to its synthesis