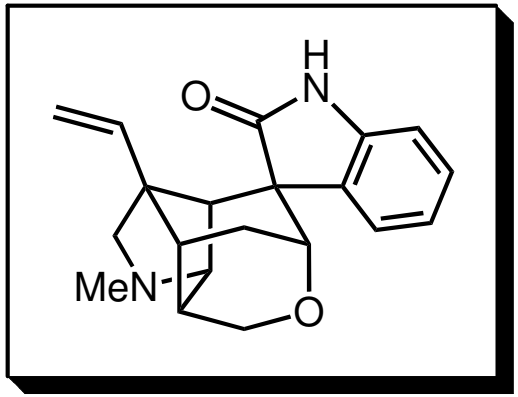


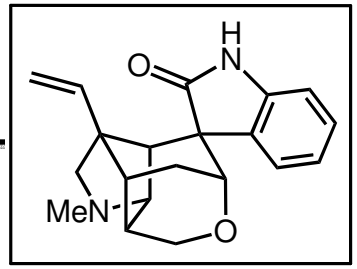
Gelsemine

Molecule in Review

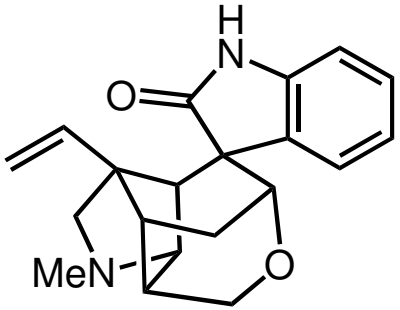
Julia Allen (Lambert Group)
Synthesis Literacy Group
9/25/09
Columbia Chemistry

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

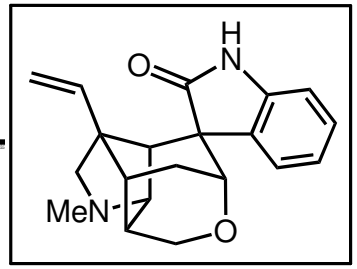
Gelsemine: Historical perspective



- Discovery
  - Major alkaloid component of *Gelsemium sempervirens* (Carolina Jasmine) - isolated in 1883 by Gerrard
  - Gelsemine held the status of “orphan alkaloid” until 1959, when the groups of Conroy and Wilson finally elucidated its structure by NMR and X-ray crystallography



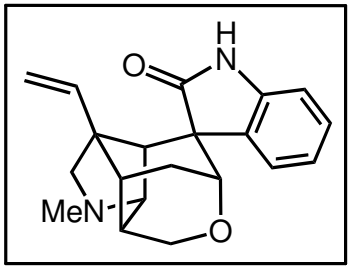
Gelsemine: Synthetic Interest



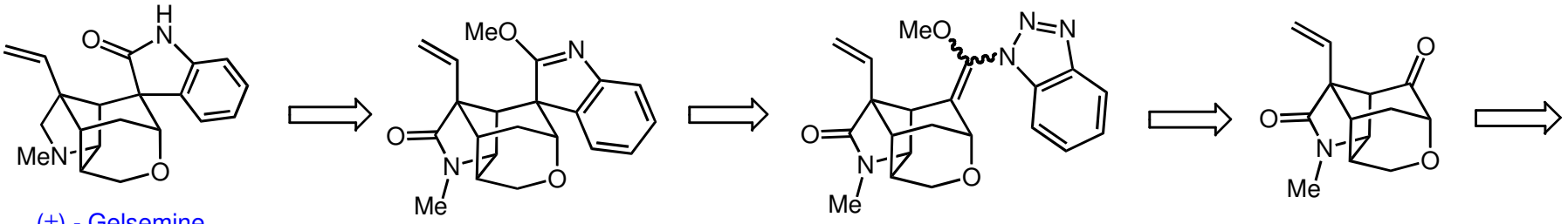
- Biological activity:
  - No concrete evidence
  - Undocumented accounts of Strychnine-like activity as a CNS stimulant

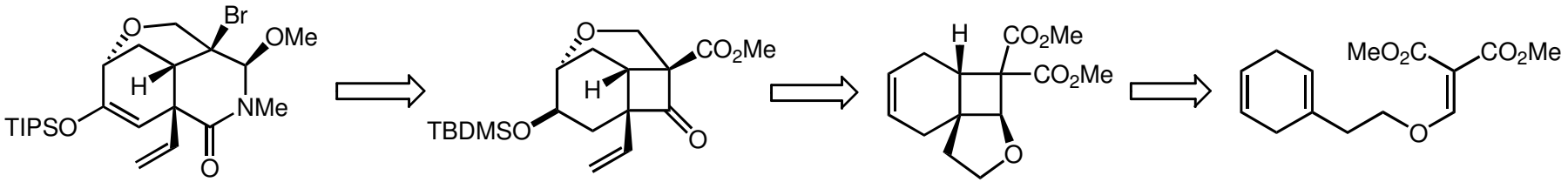
- Synthetic Interest:
  - Synthetically intriguing because of its unique hexacyclic cage structure
  - Partial syntheses:
    - Stork, G. (1987); Fleming, I. (1988); Cha, J. K. (1999); Penkett, C. S. (1999)
  - Racemic total syntheses:
    - Speckamp, W. N. (1994); **Johnson, A. P. (1994)**; Hart, D. J. (1994); Fukuyama, T. (1996); Overman (1999); **Danishefsky (2002)**
  - Enantioselective total synthesis:
    - **Fukuyama (1997)**

Johnson's Approach: Retrosynthesis



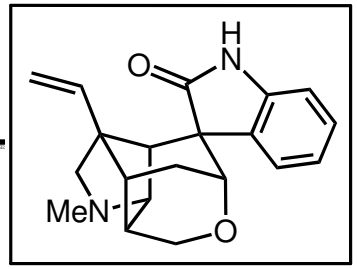
- Key steps:
  - Photoinduced intramolecular cycloaddition
  - Intramolecular Mannich reaction
  - Novel oxindole synthesis

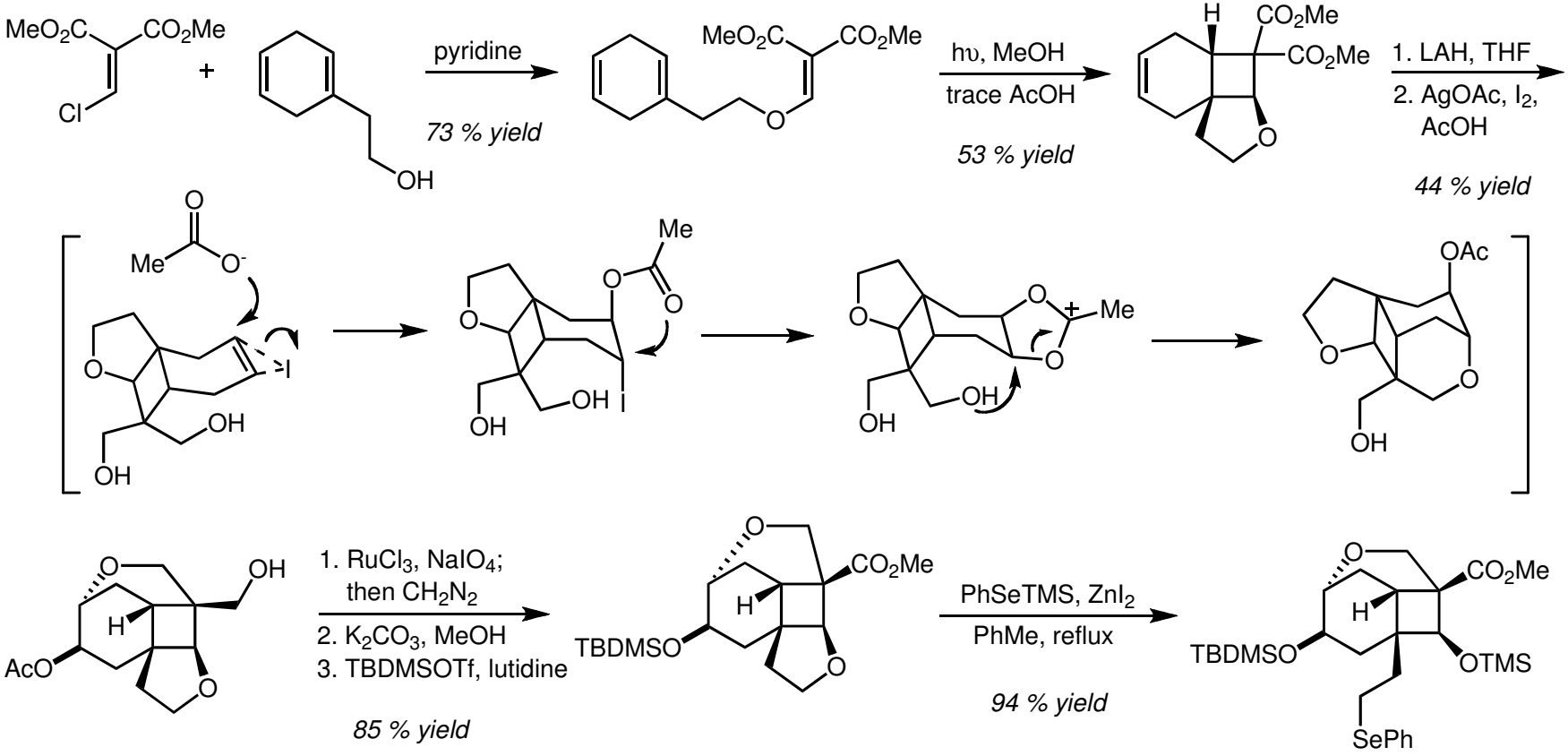




COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

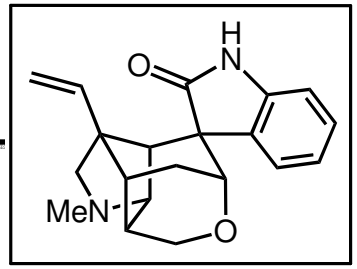
Johnson's Synthesis

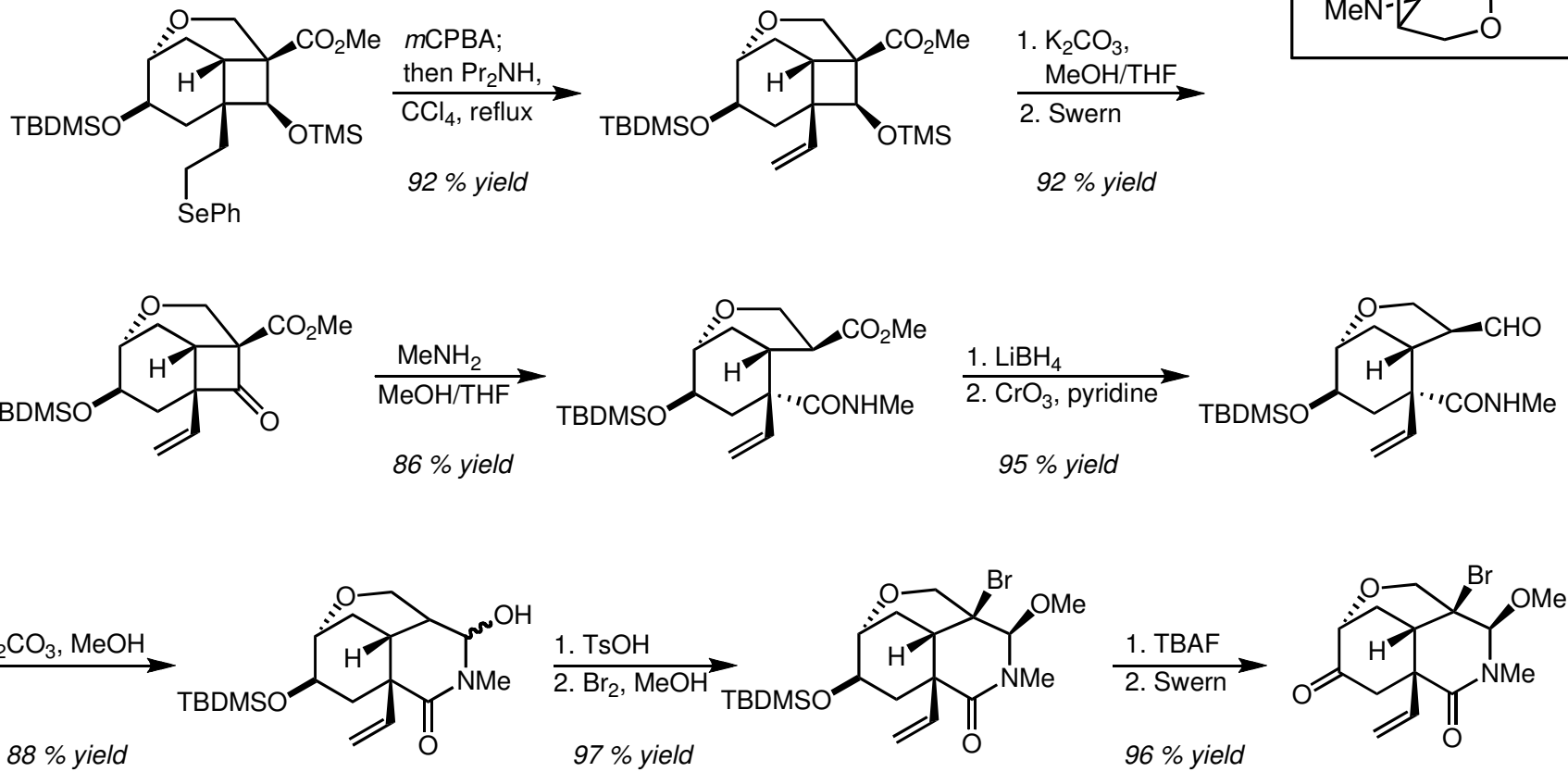




Sheikh, Z.; Steel, R.; Tasker, A. S.; Johnson, A. P. *J. Chem. Soc., Chem. Comm.* **1994**, 763.

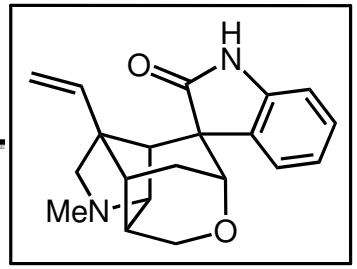
Johnson's Synthesis

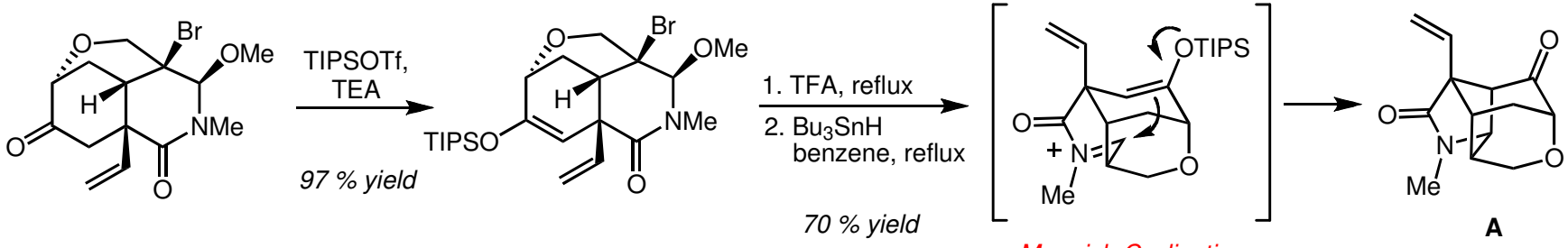


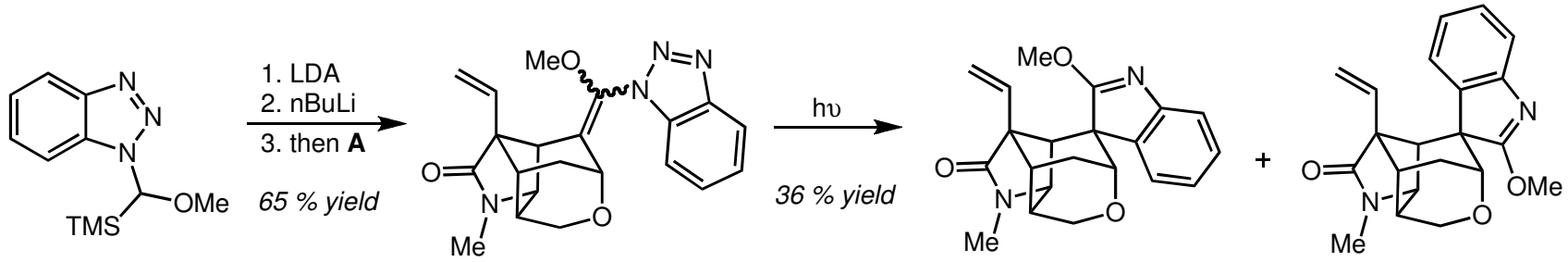


Sheikh, Z.; Steel, R.; Tasker, A. S.; Johnson, A. P. *J. Chem. Soc., Chem. Comm.* **1994**, 763.

Johnson's Synthesis

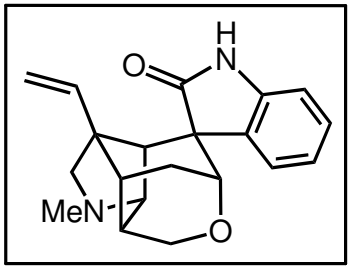




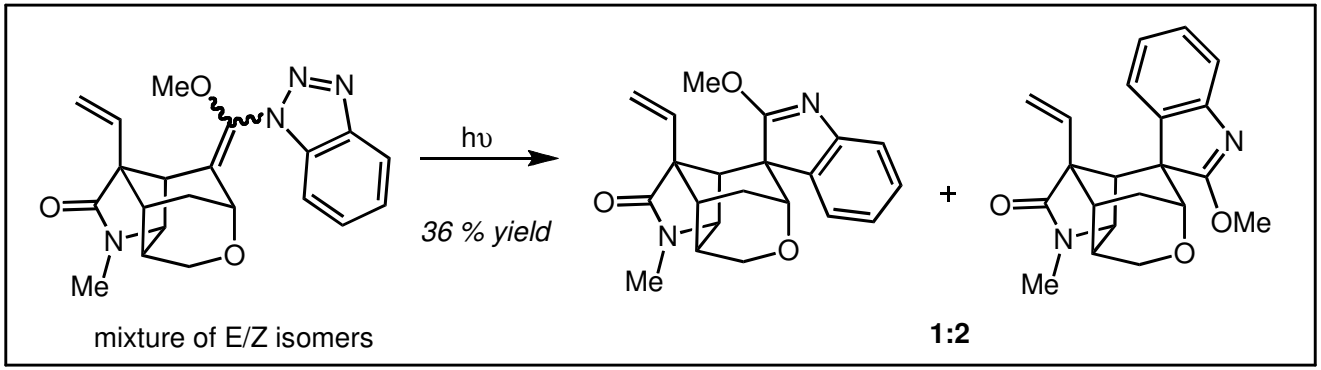


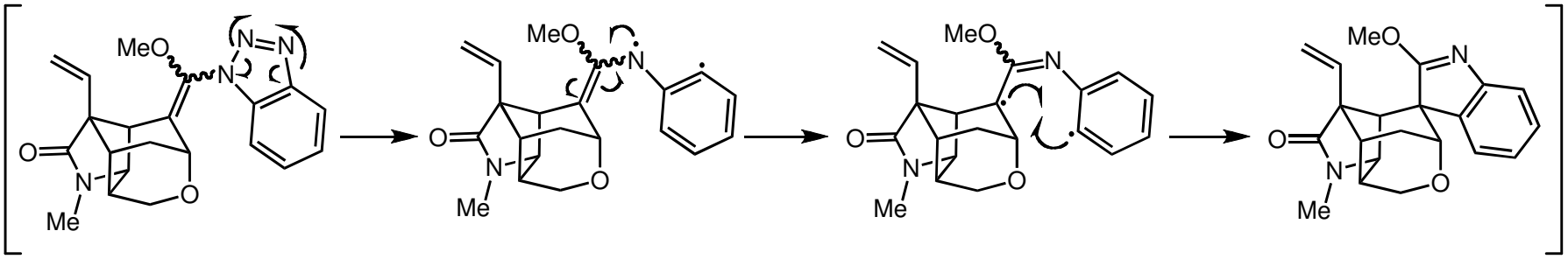
Sheikh, Z.; Steel, R.; Tasker, A. S.; Johnson, A. P. *J. Chem. Soc., Chem. Comm.* **1994**, 763.
Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Comm.* **1994**, 765.

Johnson's Synthesis



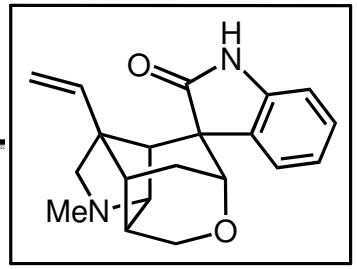
- Oxindole ring formation:

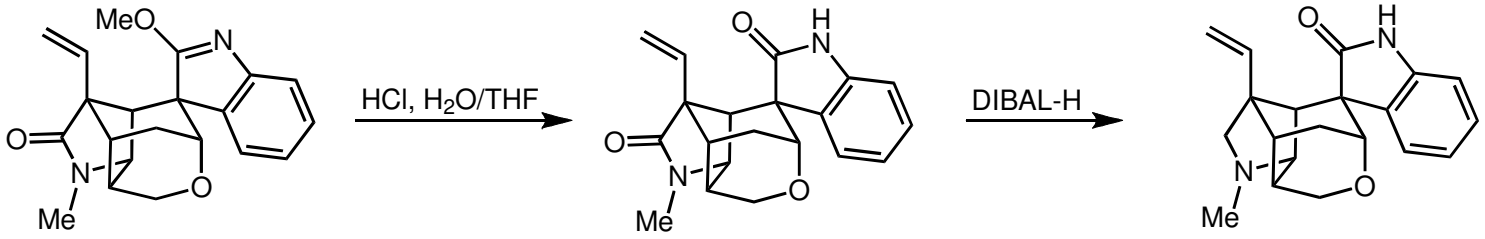




Sheikh, Z.; Steel, R.; Tasker, A. S.; Johnson, A. P. *J. Chem. Soc., Chem. Comm.* **1994**, 763.
Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Comm.* **1994**, 765.

Johnson's Synthesis



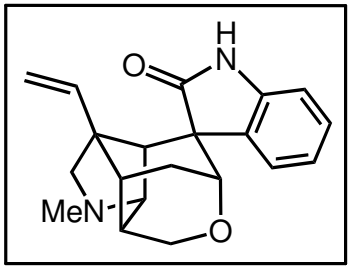


oxo-gelsemine

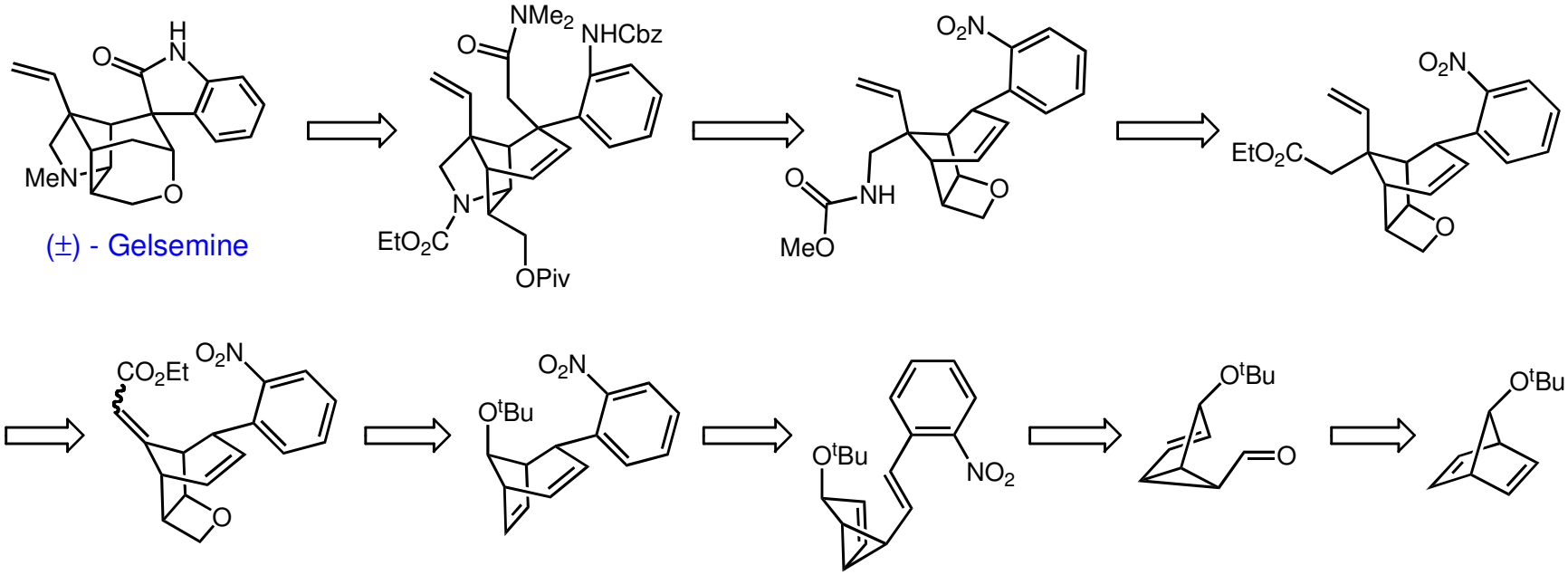
(±) - gelsemine

Sheikh, Z.; Steel, R.; Tasker, A. S.; Johnson, A. P. *J. Chem. Soc., Chem. Comm.* **1994**, 763.
Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Comm.* **1994**, 765.

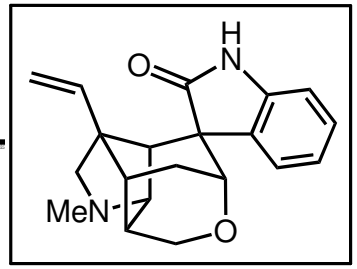
Danishefsky's Approach: Retrosynthesis

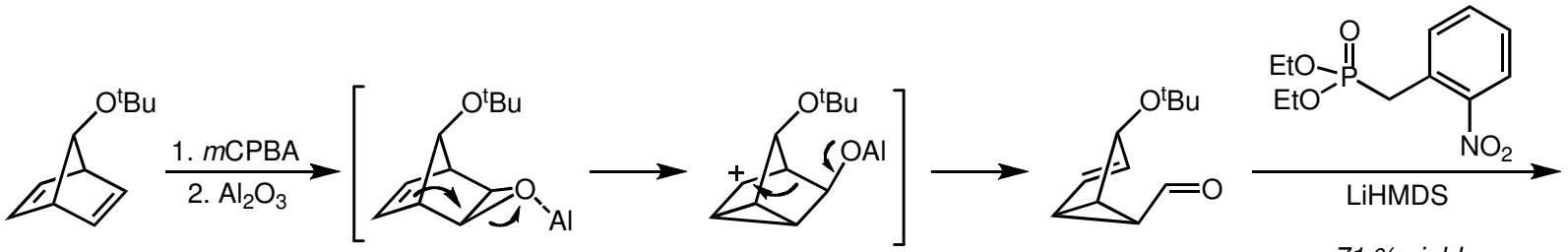


- Key Steps:
  - Norbene epoxide rearrangement
  - Cope rearrangement
  - Eschenmoser Claisen rearrangement



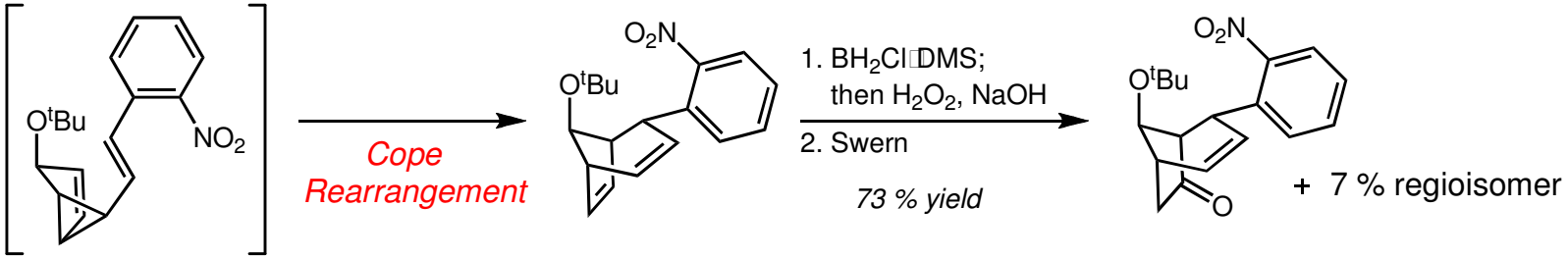
Danishefsky's Synthesis





71 % yield

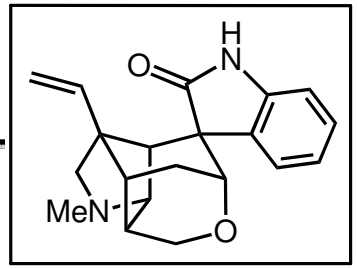
HWE Olefination

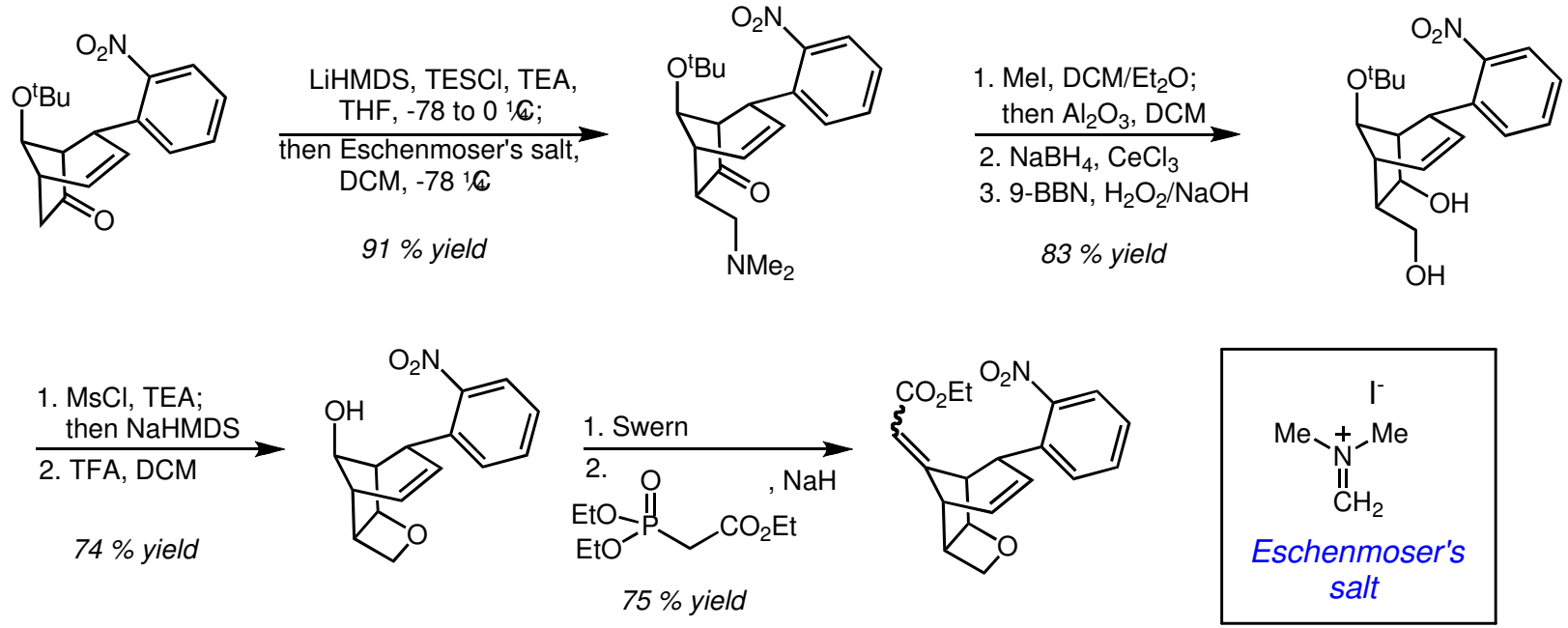


Ng, F. W.; Lin, H.; Danishefsky, S. J. *JACS* **2002**, *124*, 9812.
Lin, H.; Ng, F. W.; Danishefsky, S. J. *Tet. Lett.* **2002,** *43*, 549.
Ng, F. W.; Lin, H.; Tan, Q.; Danishefsky, S. J. *Tet. Lett.* **2002**, *43*, 545.

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

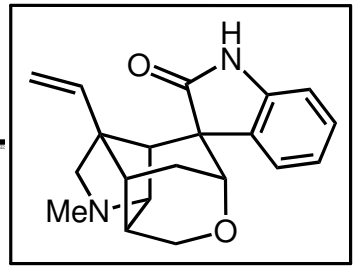
Danishefsky's Synthesis

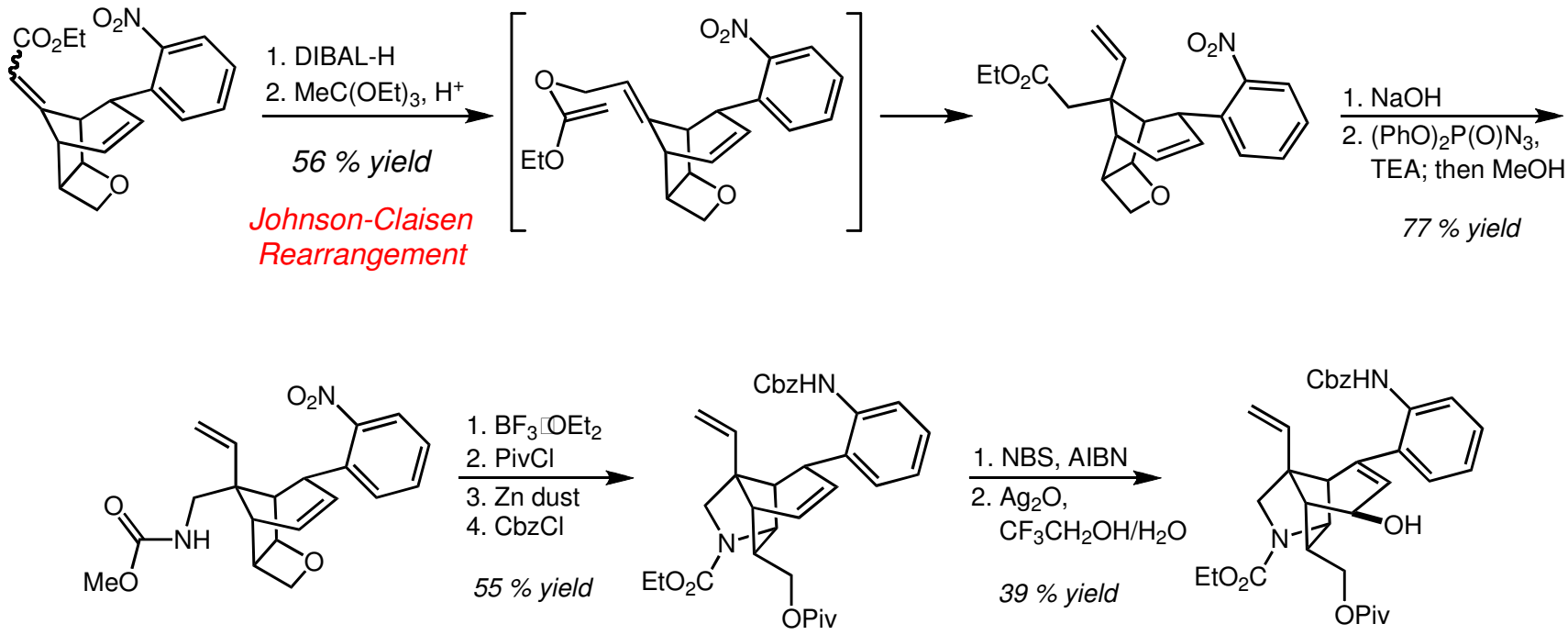




Ng, F. W.; Lin, H.; Danishefsky, S. J. *JACS* **2002**, *124*, 9812.
Lin, H.; Ng, F. W.; Danishefsky, S. J. *Tet. Lett.* **2002,** *43*, 549.
Ng, F. W.; Lin, H.; Tan, Q.; Danishefsky, S. J. *Tet. Lett.* **2002**, *43*, 545.

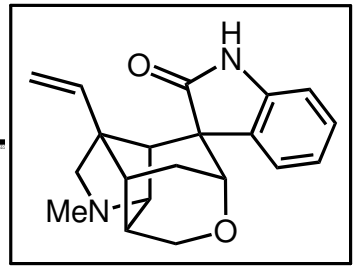
Danishefsky's Synthesis

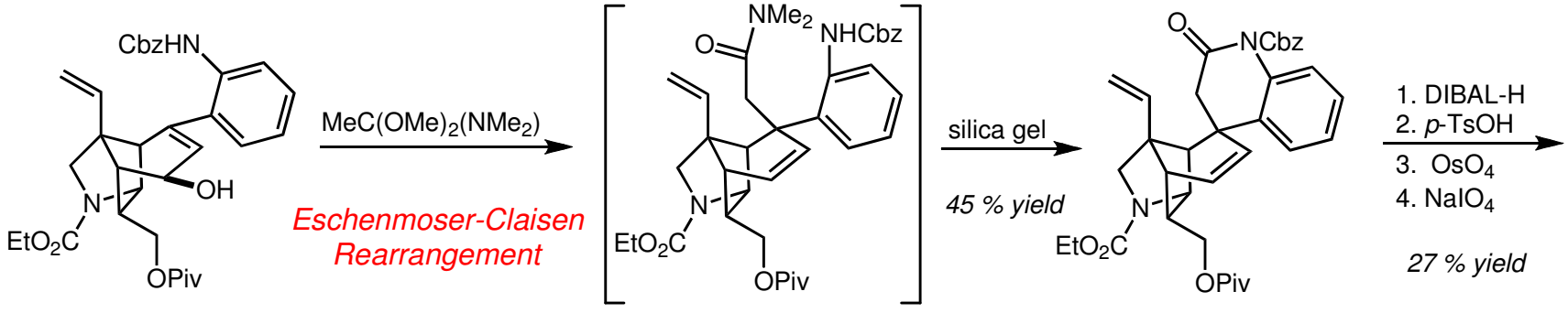


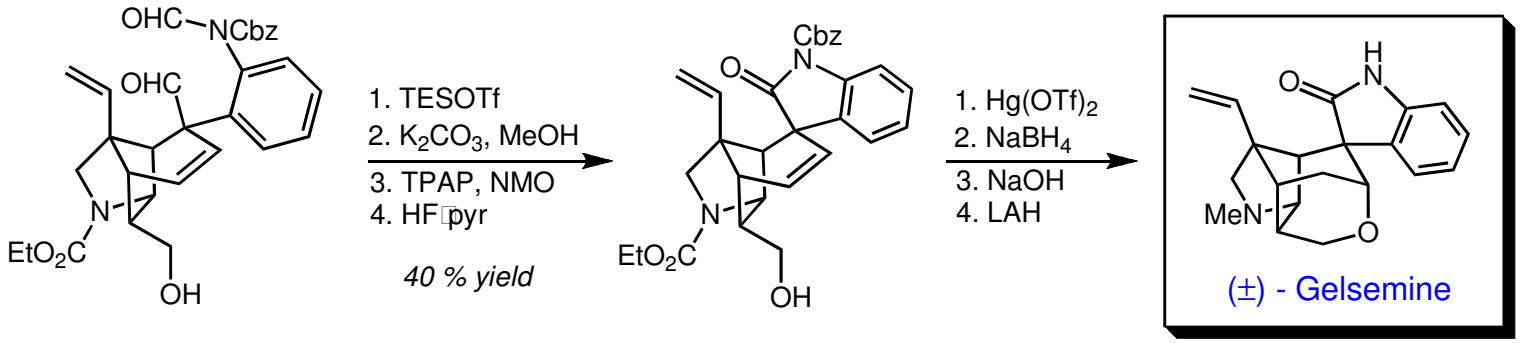


Ng, F. W.; Lin, H.; Danishefsky, S. J. *JACS* **2002**, *124*, 9812.
Lin, H.; Ng, F. W.; Danishefsky, S. J. *Tet. Lett.* **2002,** *43*, 549.
Ng, F. W.; Lin, H.; Tan, Q.; Danishefsky, S. J. *Tet. Lett.* **2002**, *43*, 545.

Danishefsky's Synthesis

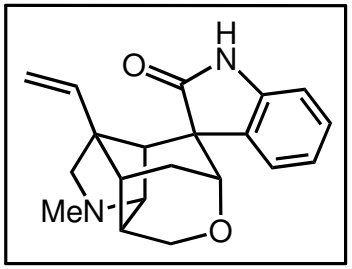




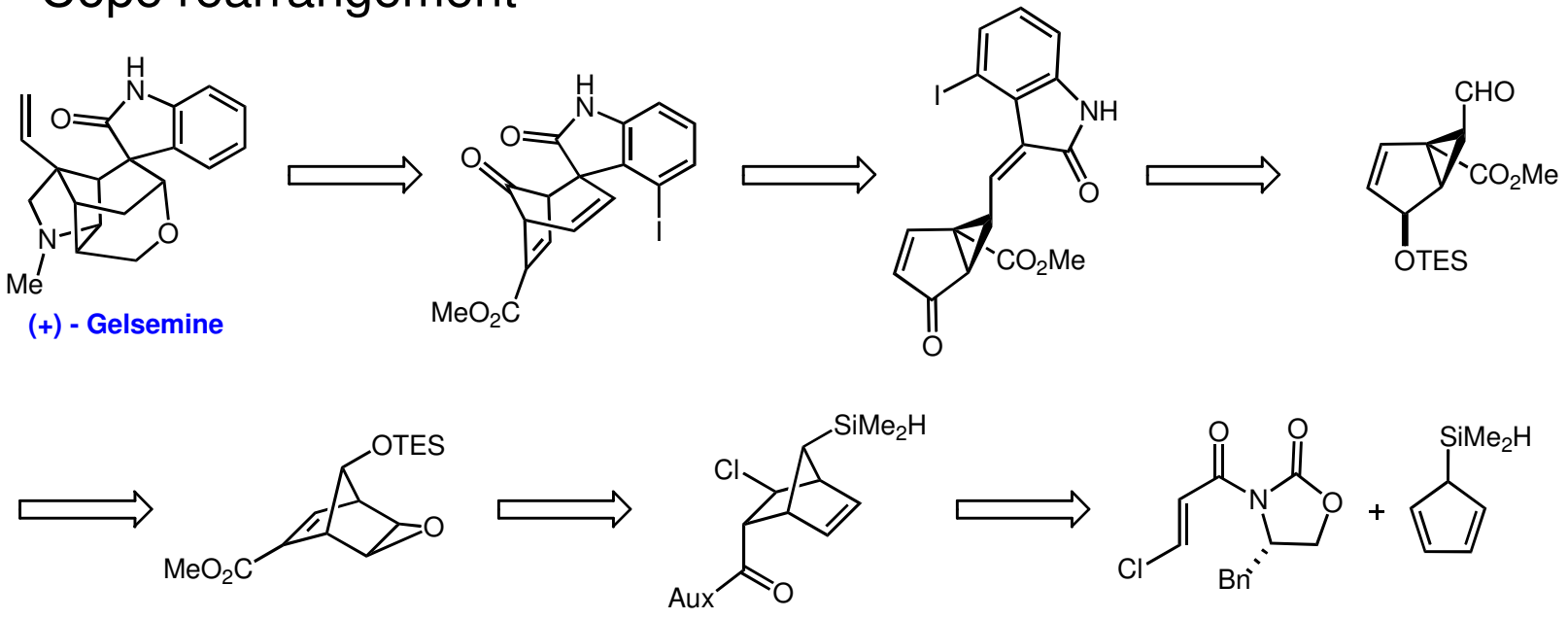


Ng, F. W.; Lin, H.; Danishefsky, S. J. *JACS* **2002**, *124*, 9812.
Lin, H.; Ng, F. W.; Danishefsky, S. J. *Tet. Lett.* **2002,** *43*, 549.
Ng, F. W.; Lin, H.; Tan, Q.; Danishefsky, S. J. *Tet. Lett.* **2002**, *43*, 545.

Fukuyama's Approach: Retrosynthesis

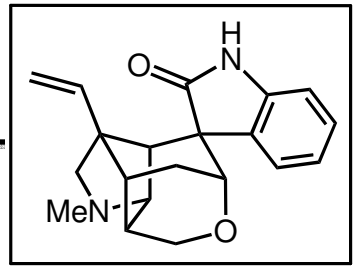


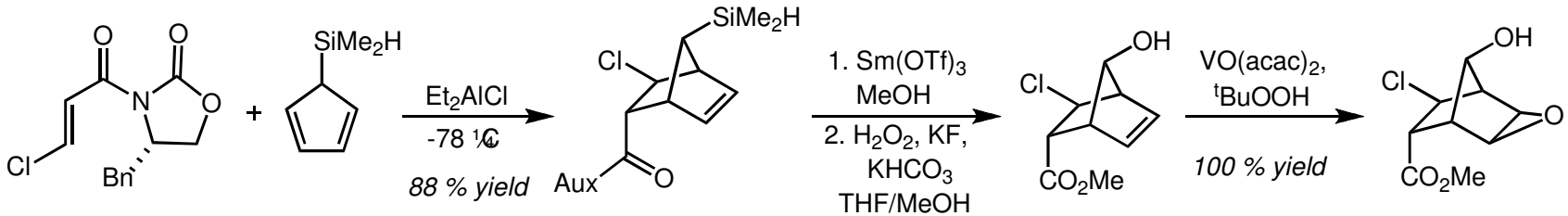
- First enantioselective synthesis of (+) Gelsemine!
- **Key steps include:**
  - chiral-auxilliary controlled enantioselective Diels-Alder reaction
  - norbornene epoxide rearrangement
  - Cope rearrangement

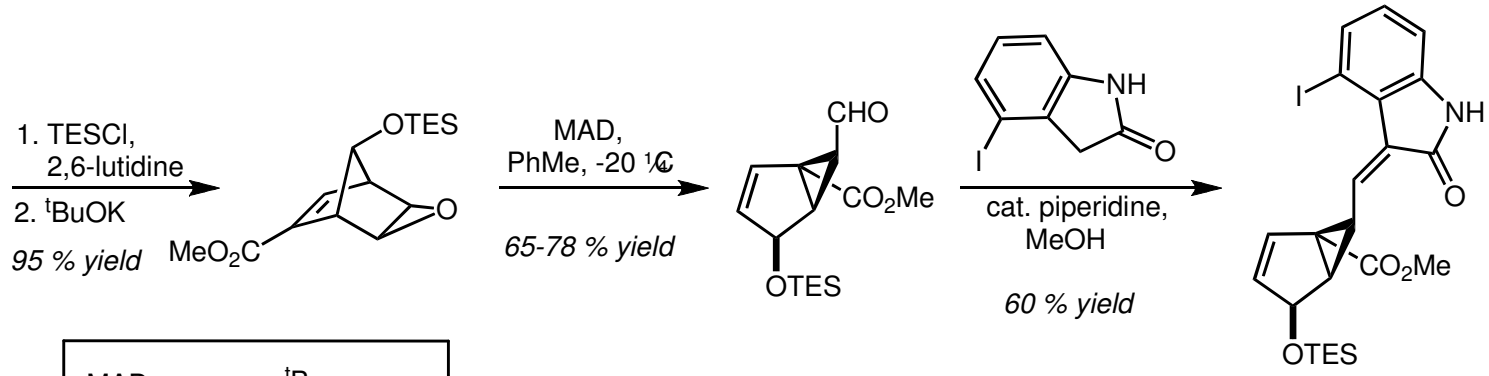


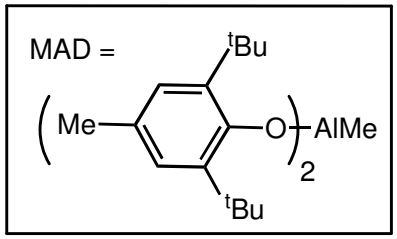
COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

Fukuyama's Asymmetric Synthesis



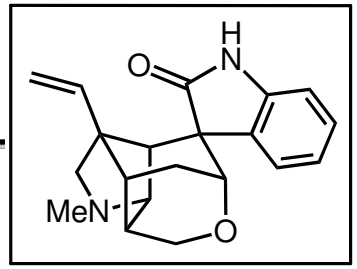


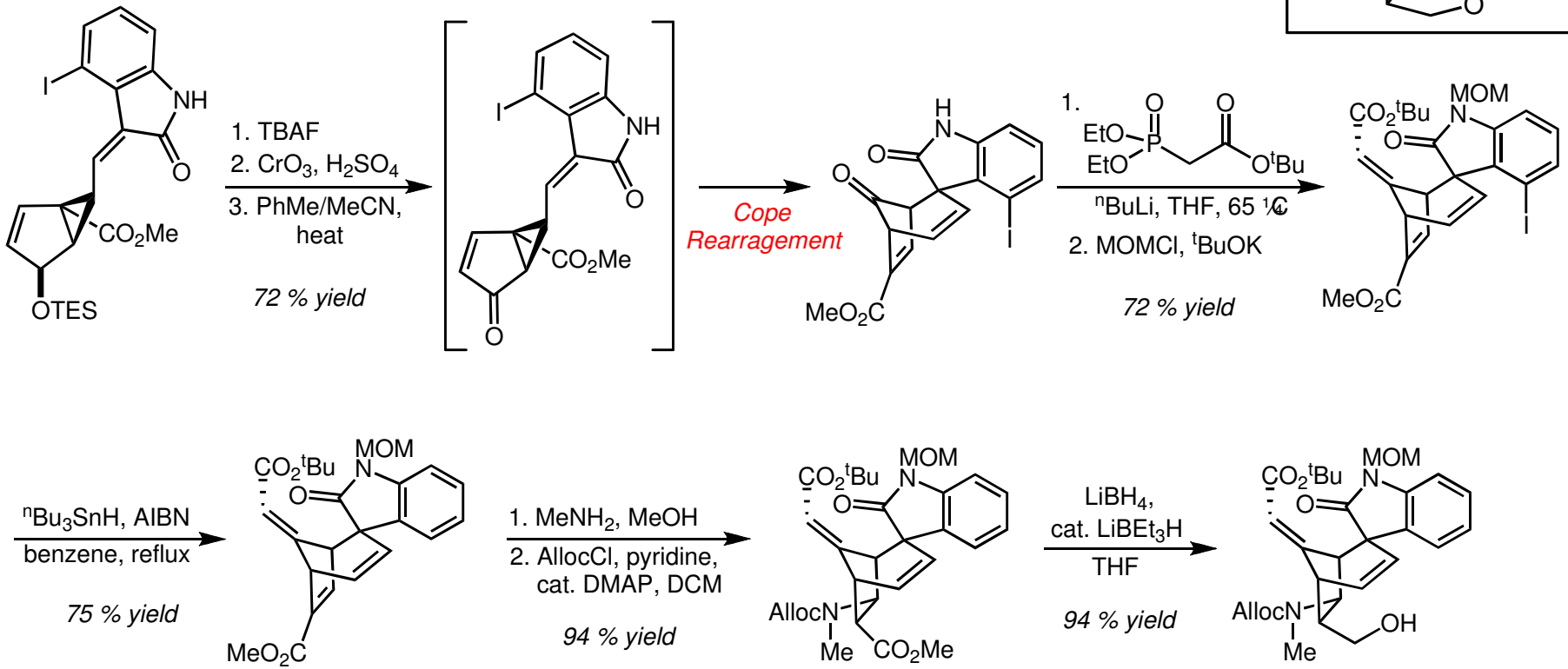




Fukuyama, T.; Liu, G. *JACS* **1996**, *118*, 7426.
Fukuyama, T.; Lui, G. *Pure & Appl. Chem.* **1997**, *69*, 3, 501.
Yokoshima, S.; Tokuyama, H.; Fukuyama, T. Angew. Chem. Int. Ed. **2000**, *39*, 4073.

Fukuyama's Asymmetric Synthesis



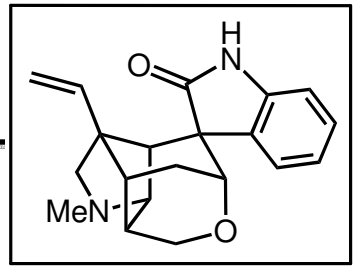


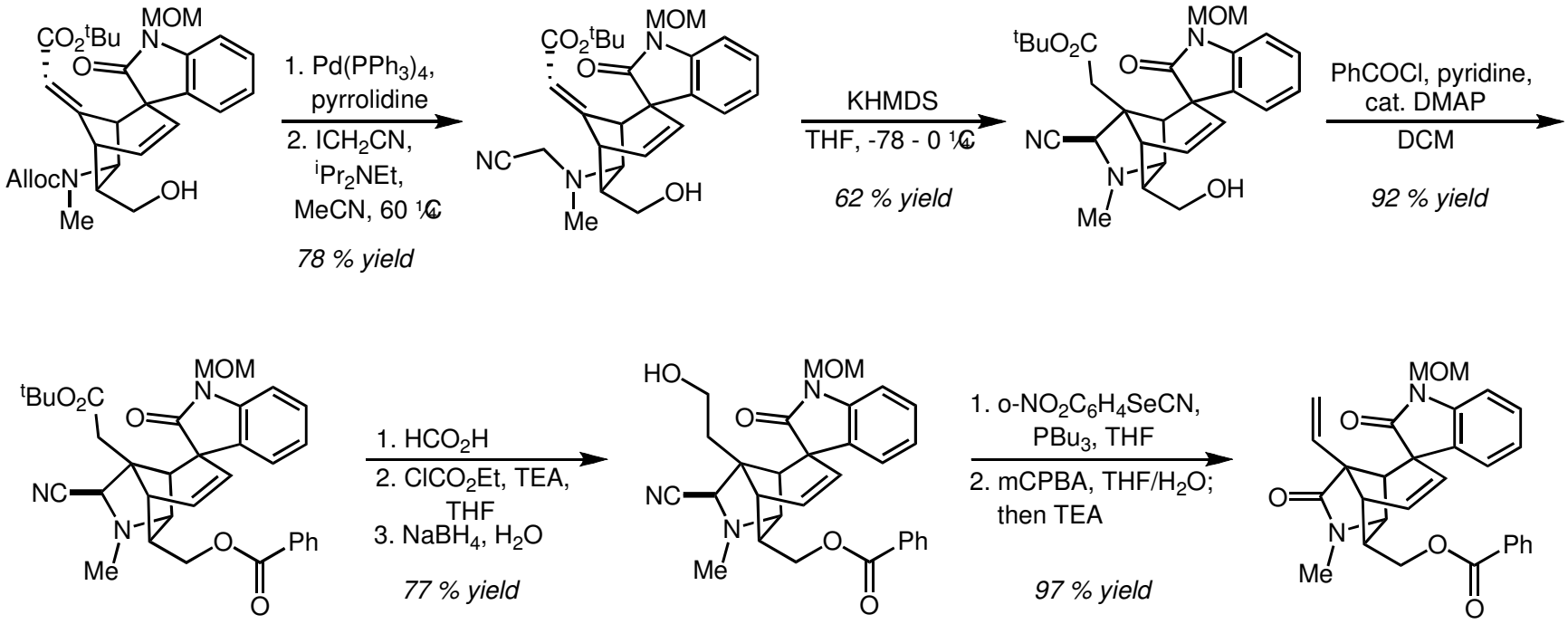
Fukuyama, T.; Liu, G. *JACS* **1996**, *118*, 7426.
Fukuyama, T.; Lui, G. *Pure & Appl. Chem.* **1997**, *69*, 3, 501.
Yokoshima, S.; Tokuyama, H.; Fukuyama, T. Angew. Chem. Int. Ed. **2000**, *39*, 4073.

Allen 17 - CU Synthesis Lit Group - Gelsemine

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

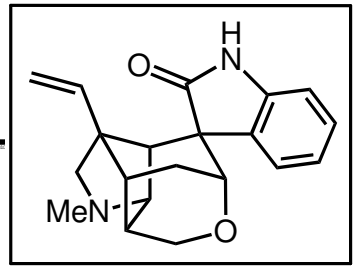
Fukuyama's Asymmetric Synthesis

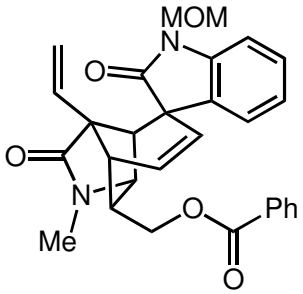




Fukuyama, T.; Liu, G. *JACS* **1996**, *118*, 7426.
Fukuyama, T.; Lui, G. *Pure & Appl. Chem.* **1997**, *69*, 3, 501.
Yokoshima, S.; Tokuyama, H.; Fukuyama, T. Angew. Chem. Int. Ed. **2000**, *39*, 4073.

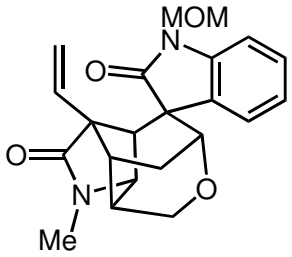
Fukuyama's Asymmetric Synthesis





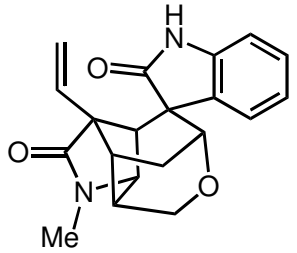
1. K_2CO_3, MeOH
2. $Hg(OTf)_2$ PhNMe$_2$
   $MeNO_2$
3. $NaBH_4$, NaOH
   $BnNEt_3Cl$, DCM/H_2O

59 % yield



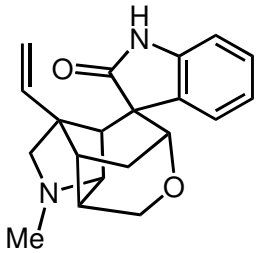
TMSCl, NaI, MeCN;
then TEA, MeOH

63 % yield



DIBAL-H
PhMe

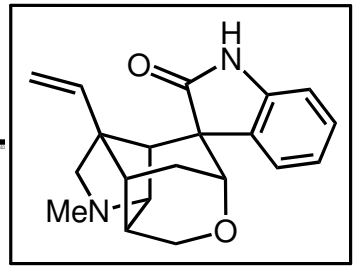
90 % yield



(+) - Gelsemine

Fukuyama, T.; Liu, G. *JACS* **1996**, *118*, 7426.
Fukuyama, T.; Lui, G. *Pure & Appl. Chem.* **1997**, *69*, 3, 501.
Yokoshima, S.; Tokuyama, H.; Fukuyama, T. Angew. Chem. Int. Ed. **2000**, *39*, 4073.

Summary



- Many synthetic groups have devoted a large amount of time investigating routes towards the total synthesis of gelsemine due to the intriguing, caged architecture

- **A. Johnson and W. Speckamp** - independantly completely the first total syntheses of gelsemine in 1994

- Many racemic total syntheses reported

- **T. Fukuyama** - completed the first and only enantioselective total synthesis to date in 1997