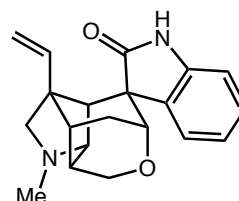


Comparative syntheses of Gelsemine

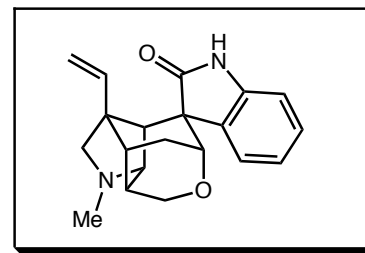
- ◆ Historical context
- ◆ Approaches to Racemic Gelsemine
- ◆ Asymmetric Synthesis of Gelsemine

Joel Austin
MacMillan Group Meeting
January 9, 2002



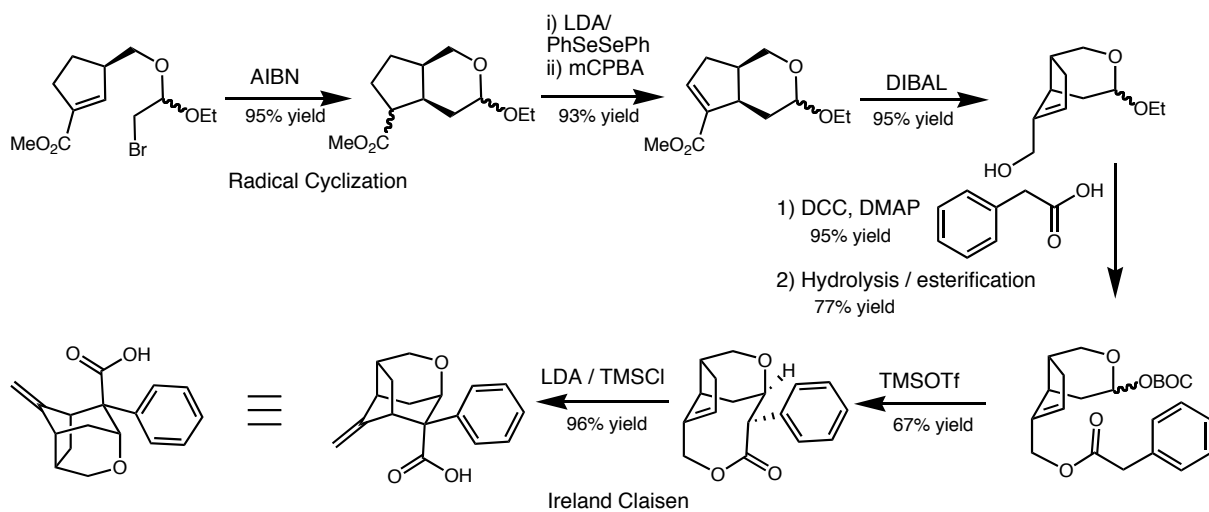
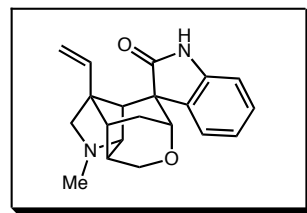
Historical Background of Gelsemine

- ◆ Isolated as an amorphous base from the roots of the *Gelsemium Sempervirens* (Carolina or Yellow Jasmine) in 1870 by Wormley.
- ◆ Obtained in crystalline form by Gerrard in 1883.
- ◆ Molecular formula elucidated in 1910 by Moore.
- ◆ 80 years of largely inconclusive degradative studies still had not produced a structure.
- ◆ Structure determined independently by the groups of Conroy and Wilson in 1959 via NMR and X-ray crystallography.
- ◆ Unique hexacyclic cage structure.
- ◆ Strychnine like activity, strong CNS stimulant as well as antihypertensive activity.



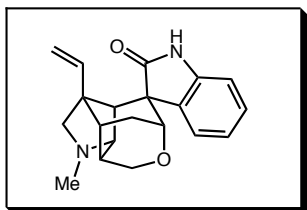
Stork's approach to Gelsemine Core

- ◆ Key steps include mixed acetal radical cyclization and a sequential transannular alkylation - Claisen rearrangement sequence.
- ◆ No further work on gelsemine is reported from the Stork lab beyond synthesis of model core.

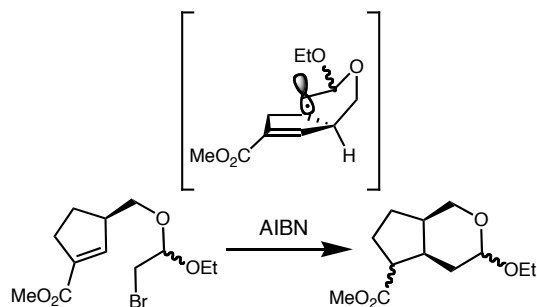


Stork, G.; Krafft, M.E.; Biller, S.A.; *Tet. Lett.* **1987**, 28, 10, 1035-1038

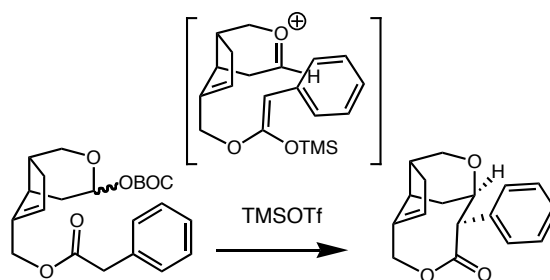
Stork's approach to Gelsemine Core Stereochemical Rationale



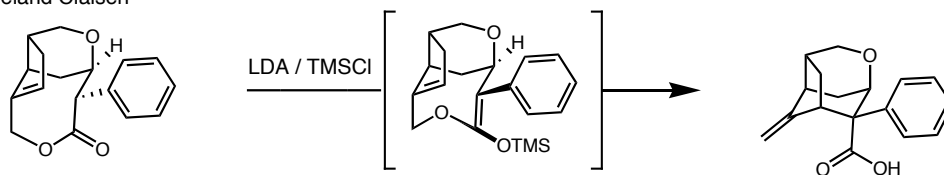
- ◆ Mixed acetal radical cyclization



- ◆ Transannular Alkylation



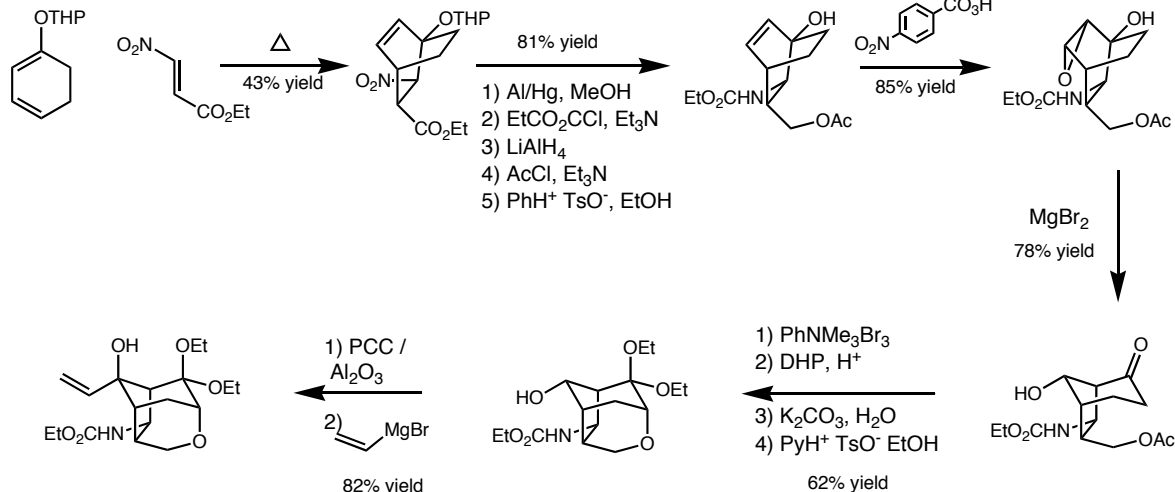
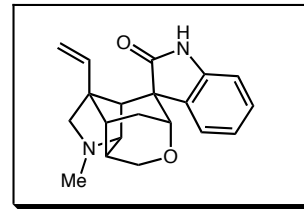
- ◆ Ireland Claisen



Stork, G.; Krafft, M.E.; Biller, S.A.; *Tet. Lett.* **1987**, 28, 10, 1035-1038

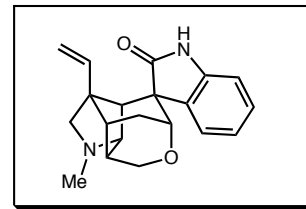
Fleming's approach to Gelsemine Core

- ◆ Key steps are the use of a Diels-Alder to make bicycle core, bicycle rearrangement, addition of an allylsilane to an acyliminium ion.
- ◆ No further work on gelsemine is reported from the Fleming lab after considerable work to install the oxindole. Twenty steps.

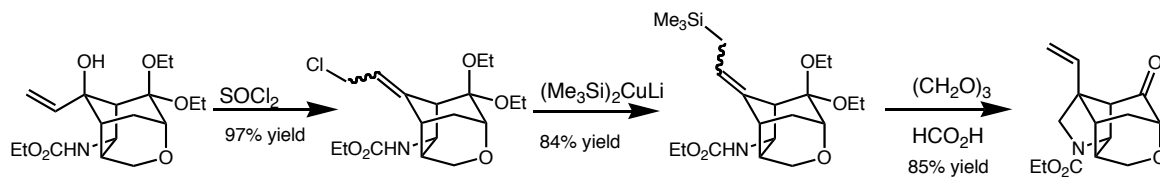


Clarke, C; Fleming, I; Fortunak, J.M.D; Gallagher, P.T. *Tetrahedron* **1988**, 44, 13, 3931-3944

Fleming's approach to Gelsemine Core and approach to introduction of oxindole

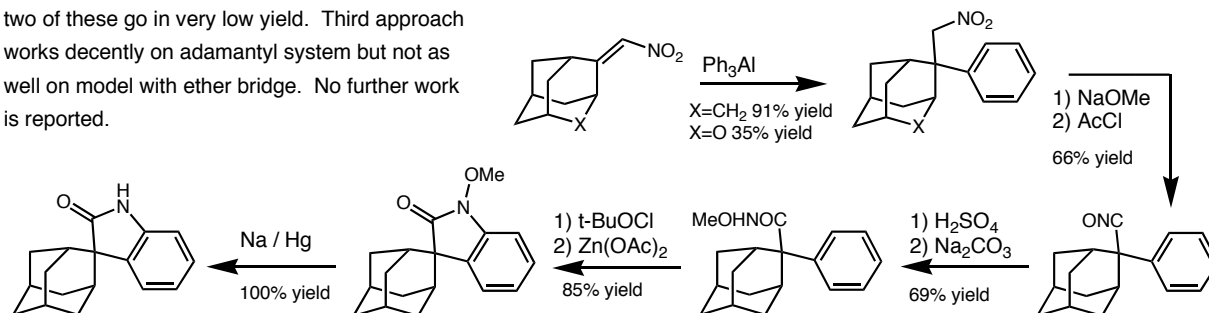


- ◆ Key allylsilane construction of quaternary carbon.



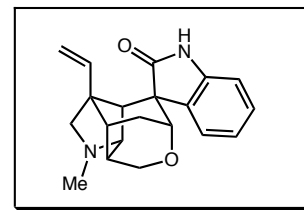
- ◆ Developed three new methods for introduction of oxindole moiety.

two of these go in very low yield. Third approach works decently on adamantyl system but not as well on model with ether bridge. No further work is reported.

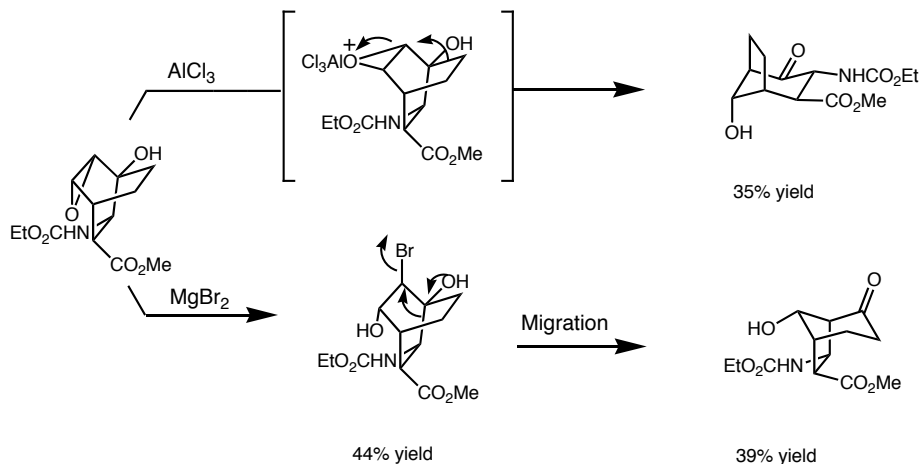
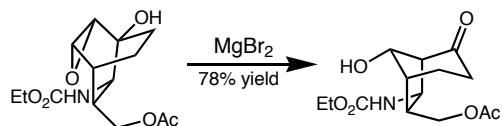


Clarke, C; Fleming, I; Fortunak, J.M.D; Gallagher, P.T. *Tetrahedron* **1988**, 44, 13, 3931-3944
Fleming, I; Moses, R.C.; Tercel, M.; Ziv, J. *J. Chem. Soc. Perkin Trans 1* **1991** 617-626

Fleming's approach to Gelsemine Core Stereochemical Rationale

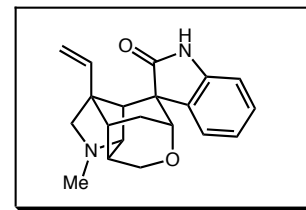


- ◆ Bicyclic rearrangement.

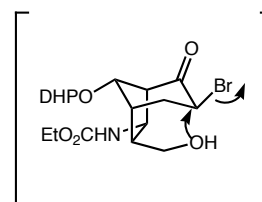
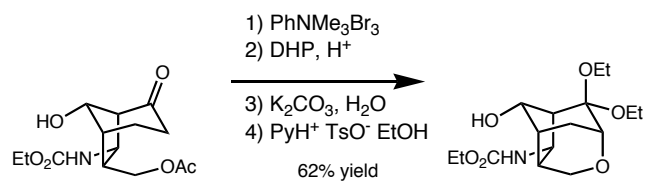


Clarke, C; Fleming, I; Fortunak, J.M.D; Gallagher, P.T. *Tetrahedron* **1988**, 44, 13, 3931-3944

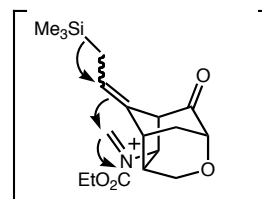
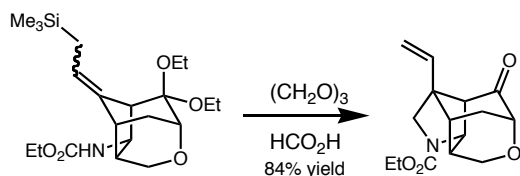
Fleming's approach to Gelsemine Core Stereochemical Rationale



- ◆ Pyran formation via intramolecular S_N2



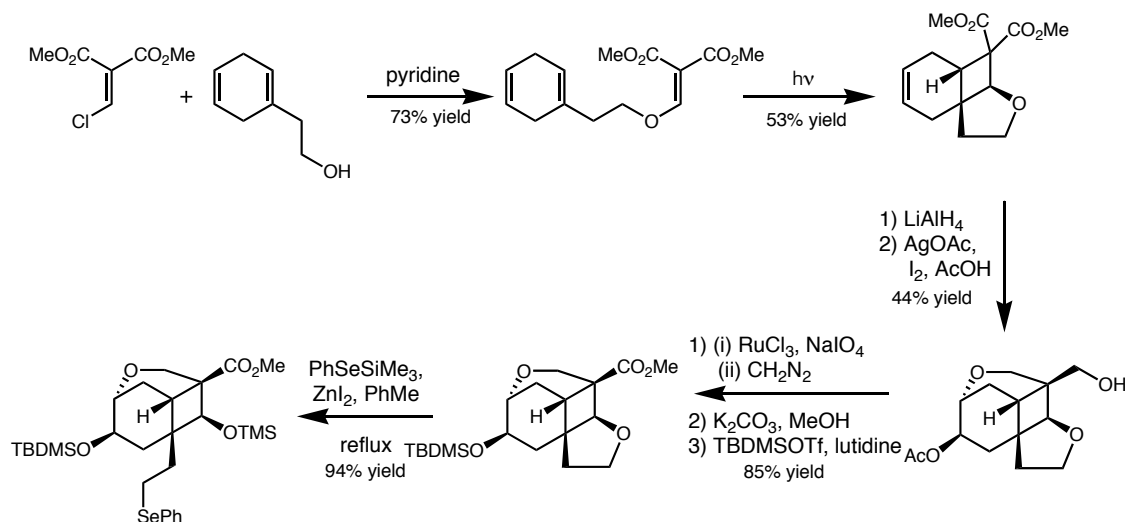
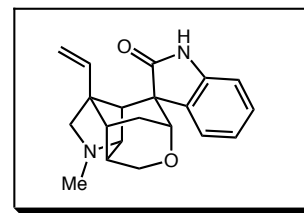
- ◆ Allylsilane addition to acyliminium ion



Clarke, C; Fleming, I; Fortunak, J.M.D; Gallagher, P.T. *Tetrahedron* **1988**, 44, 13, 3931-3944

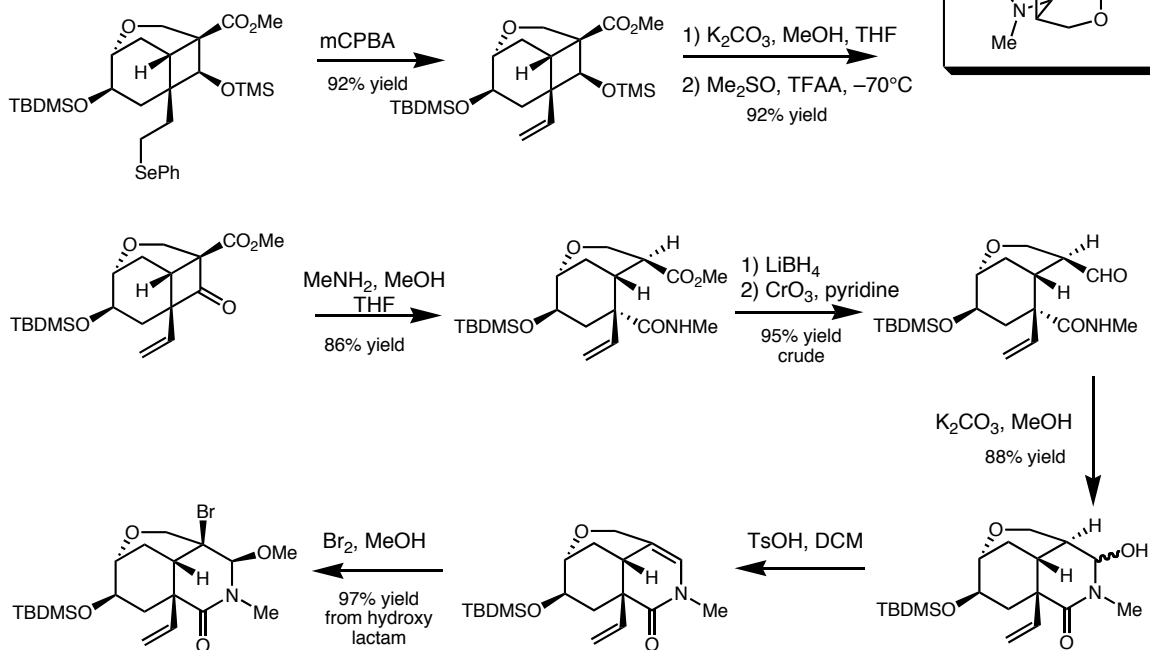
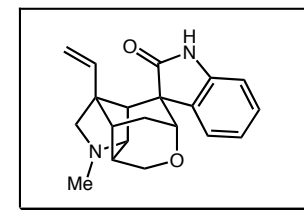
Johnson's synthesis of Gelsemine

- ◆ Key steps are the use of a photoinduced intramolecular cycloaddition, retro-Claisen condensation, intramolecular Mannich, novel oxindole synthesis.
- ◆ Stops synthesis at racemic imino-ether of 21-oxogelsemine; this natural product has previously been shown to be readily converted to gelsemine. 28 steps.



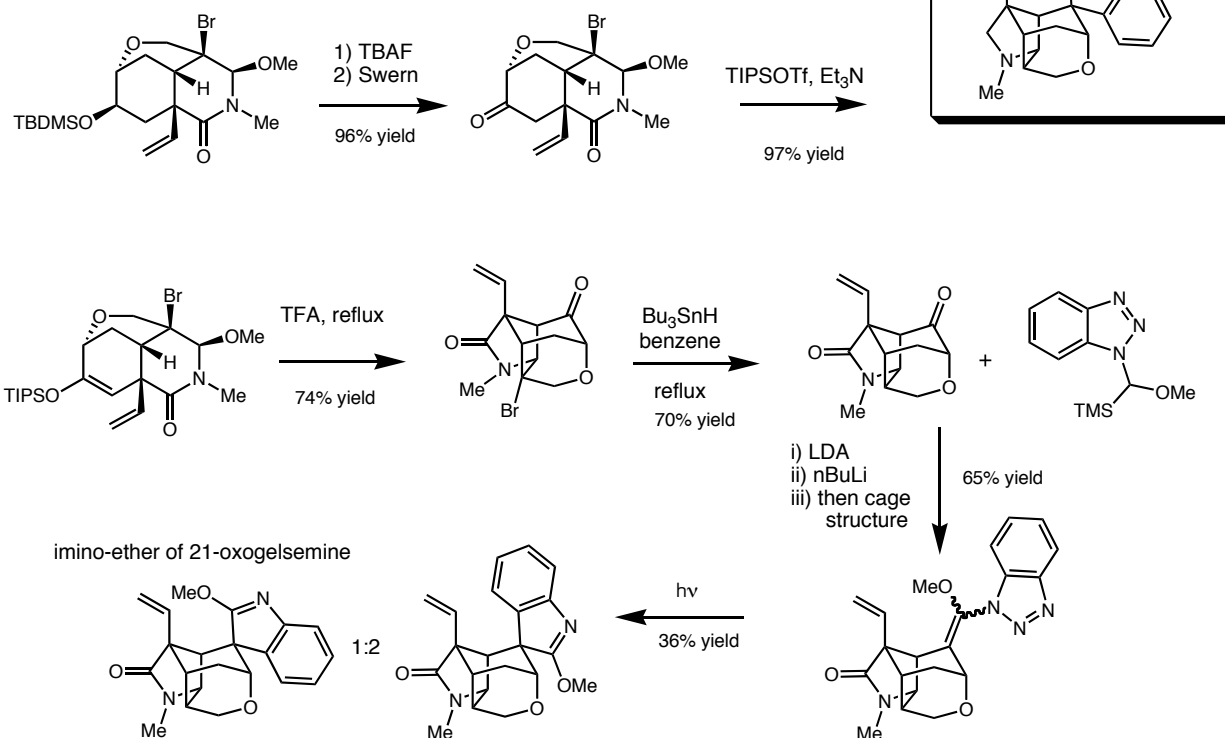
Sheikh, Z; Steel, R; Tasker, A.S.; Johnson, A.P. *J. Chem. Soc., Chem. Commun.* **1994**, 763-764

Johnson's synthesis of Gelsemine



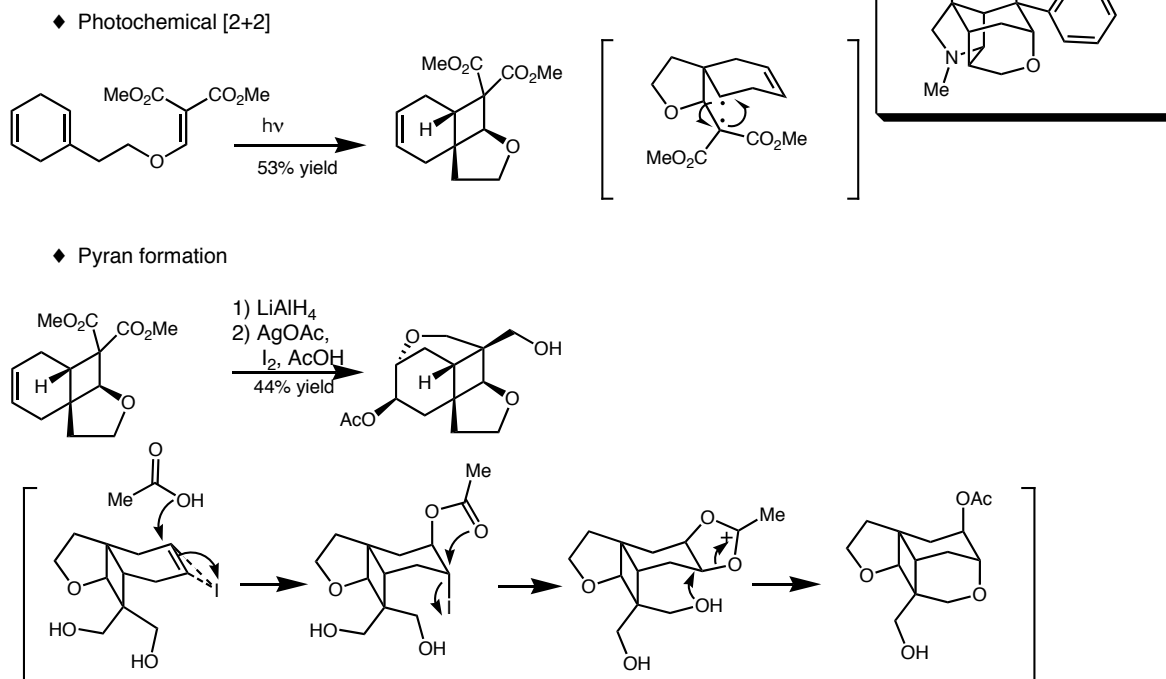
Sheikh, Z; Steel, R; Tasker, A.S.; Johnson, A.P. *J. Chem. Soc., Chem. Commun.* **1994**, 763-764

Johnson's synthesis of Gelsemine



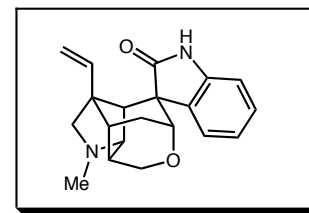
Sheikh, Z.; Steel, R.; Tasker, A.S.; Johnson, A.P. *J. Chem. Soc., Chem. Commun.* **1994**, 763-764
 Dutton, J.K.; Steel, R.W.; Tasker, A.S.; Popsavin, V.; Johnson, A.P. *J. Chem. Soc., Chem. Commun.* **1994**, 765-766

Johnson's Synthesis of Gelsemine Stereochemical Rationale

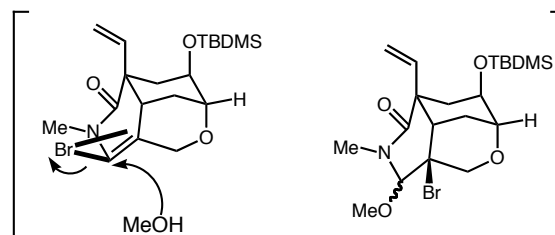
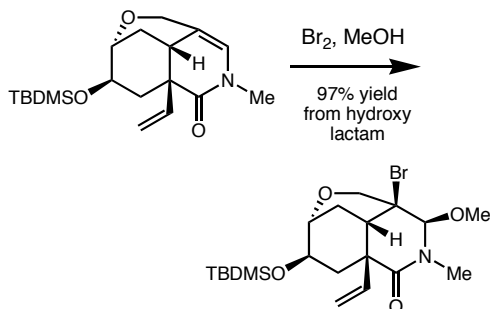


Sheikh, Z.; Steel, R.; Tasker, A.S.; Johnson, A.P. *J. Chem. Soc., Chem. Commun.* **1994**, 763-764

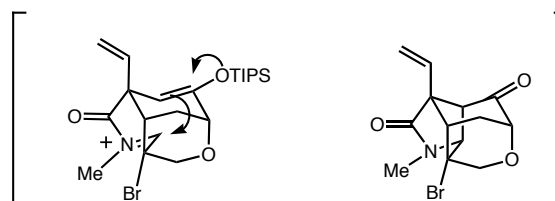
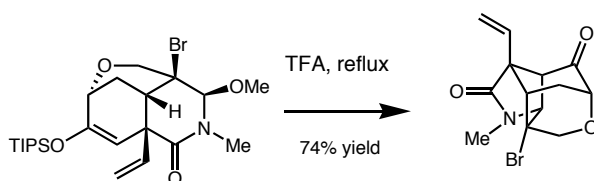
Johnson's Synthesis of Gelsemine Stereochemical Rationale



◆ Methoxy bromination

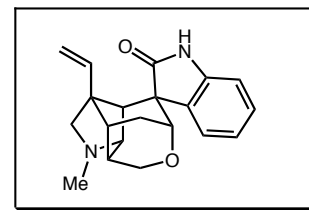


◆ Intramolecular Mannich cyclization

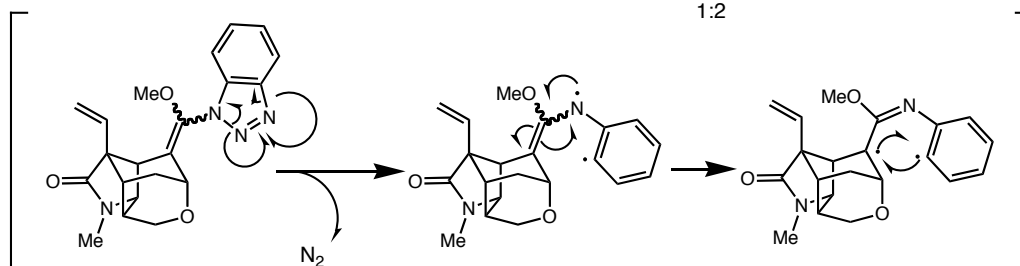
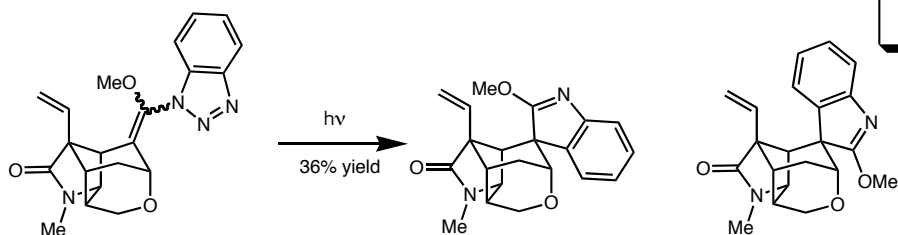


Sheikh, Z.; Steel, R.; Tasker, A.S.; Johnson, A.P. *J. Chem. Soc., Chem. Commun.* **1994**, 763-764

Johnson's Synthesis of Gelsemine Stereochemical Rationale



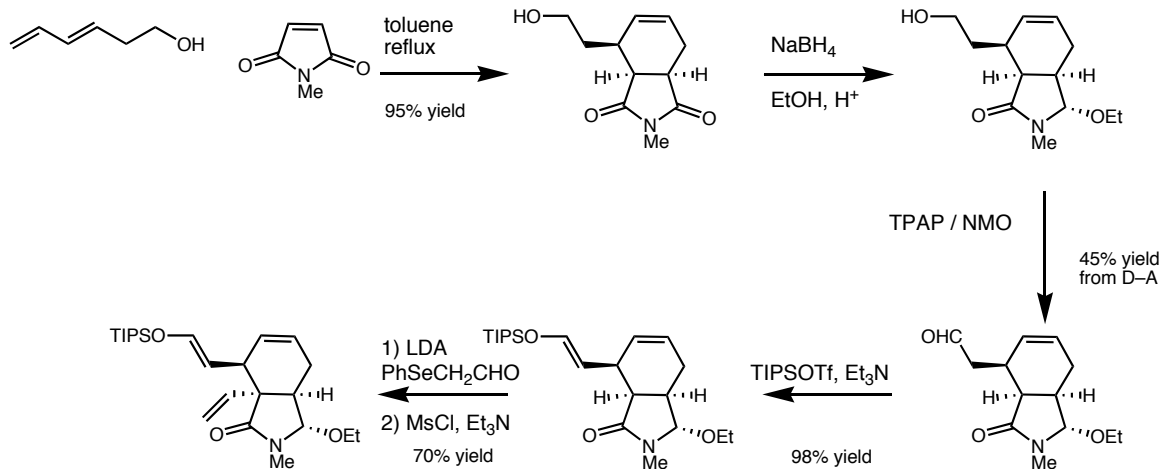
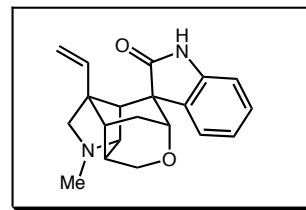
◆ Oxindole synthesis



Sheikh, Z.; Steel, R.; Tasker, A.S.; Johnson, A.P. *J. Chem. Soc., Chem. Commun.* **1994**, 763-764

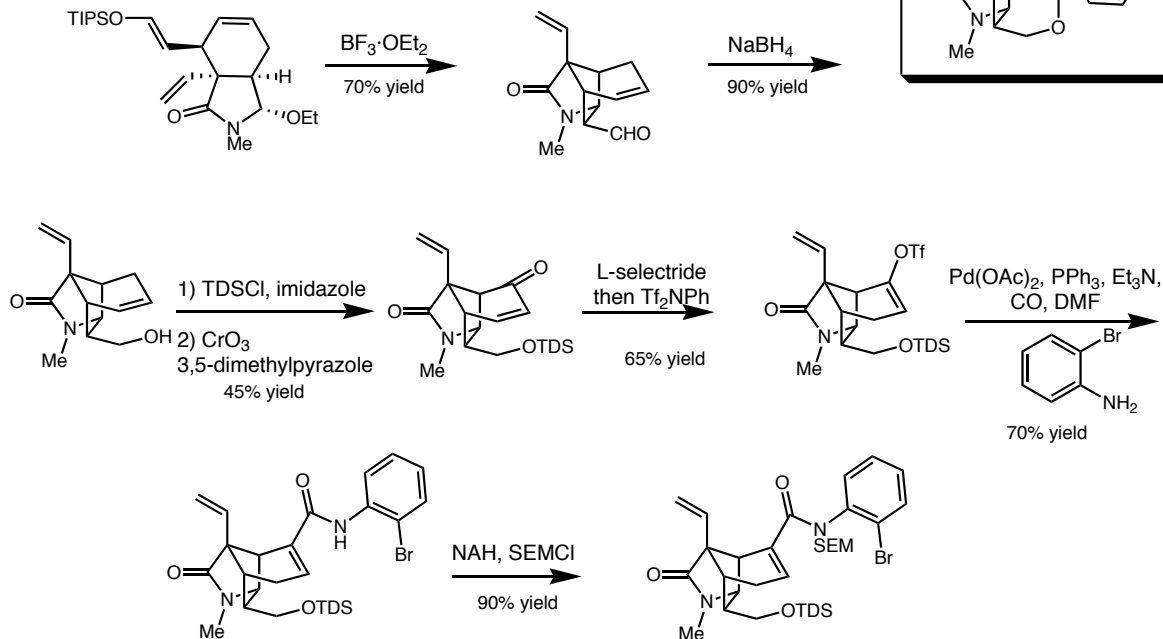
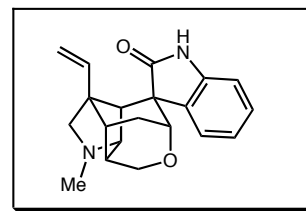
Speckamp and Hiemstra's synthesis of Gelsemine

- ◆ Key steps are the use of a Diels-Alder, intramolecular Mannich, Overman oxindole synthesis.
- ◆ Completes gelsemine in racemic form, enzymatic route to enantiopure starting material is known. 19 steps.



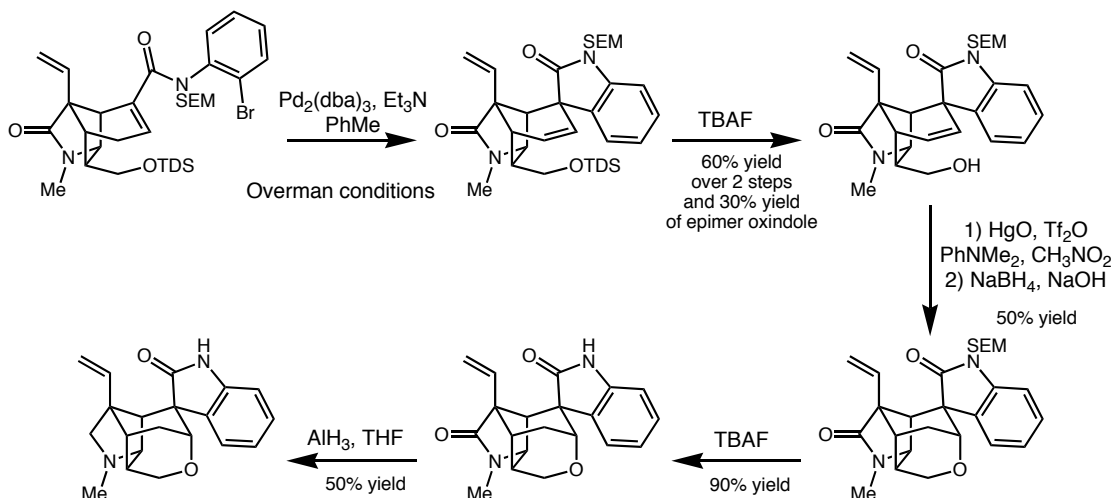
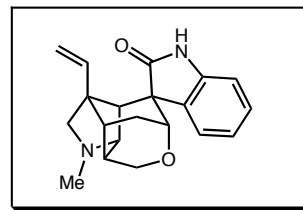
Newcombe, N.J.; Ya, F.; Vijn, R.J.; Hiemstra, H.; Speckamp, W.N. *J. Chem. Soc., Chem. Commun.* **1994**, 767-768
 Speckamp, W.N.; Newcombe, N.W.; Hiemstra, H.; Ya, F.; Vijn, R.J.; Koot, W.J. *Pure & Appl. Chem.* **1994**, 66, 10, 2163-2166
 (+) enantiomer of intermediate Koot, W.J.; Hiemstra, H.; Speckamp, W.N. *J. Org. Chem.* **1992**, 57, 1059-1061
 (-) enantiomer of intermediate Dijink, J.; Cintrat, J.C.; Speckamp, W.N.; Hiemstra, H. *Tet. Lett.* **1999**, 40, 5919-5922

Speckamp and Hiemstra's synthesis of Gelsemine



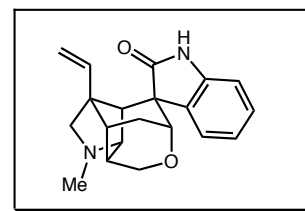
Newcombe, N.J.; Ya, F.; Vijn, R.J.; Hiemstra, H.; Speckamp, W.N. *J. Chem. Soc., Chem. Commun.* **1994**, 767-768
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 (R) enantiomer of intermediate Koot, W.J.; Hiemstra, H.; Speckamp, W.N. *J. Org. Chem.* **1992**, 57, 1059-1061
 (S) enantiomer of intermediate Dijink, J.; Cintrat, J.C.; Speckamp, W.N.; Hiemstra, H. *Tet. Lett.* **1999**, 40, 5919-5922

Speckamp and Hiemstra's synthesis of Gelsemine

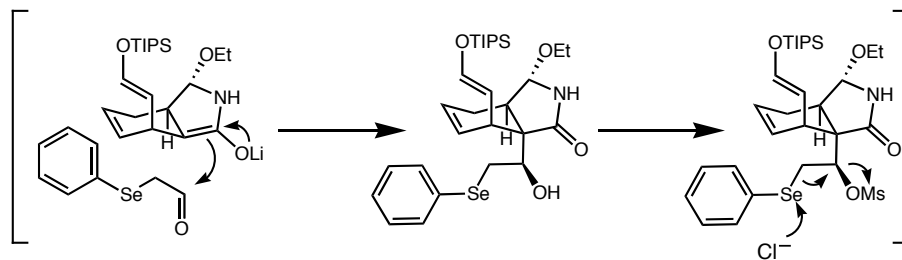
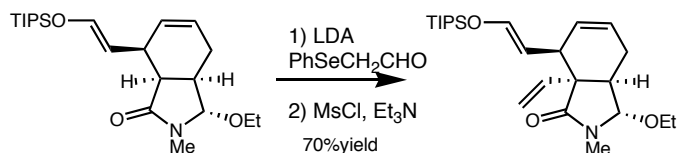


Newcombe, N.J.; Ya, F.; Vijn, R.J.; Hiemstra, H.; Speckamp, W.N. *J. Chem. Soc., Chem. Commun.* **1994**, 767-768
 Speckamp, W.N.; Newcombe, N.W.; Hiemstra, H.; Ya, F.; Vijn, R.J.; Koot, W.J. *Pure & Appl. Chem.* **1994**, 66, 10, 2163-2166
 (R) enantiomer of intermediate Koot, W.J.; Hiemstra, H.; Speckamp, W.N. *J. Org. Chem.* **1992**, 57, 1059-1061
 (S) enantiomer of intermediate Dijink, J.; Cintrat, J.C.; Speckamp, W.N.; Hiemstra, H. *Tet. Lett.* **1999**, 40, 5919-5922

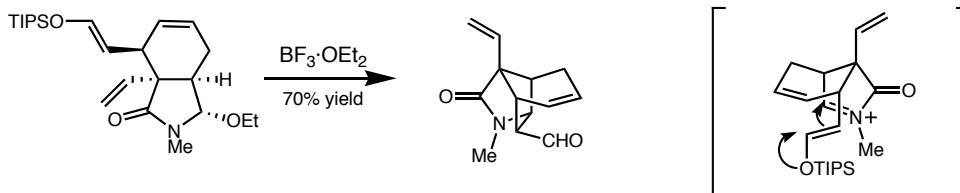
Speckamp and Hiemstra's synthesis of Gelsemine, Stereochemical Rationale



◆ Appendage of vinyl group



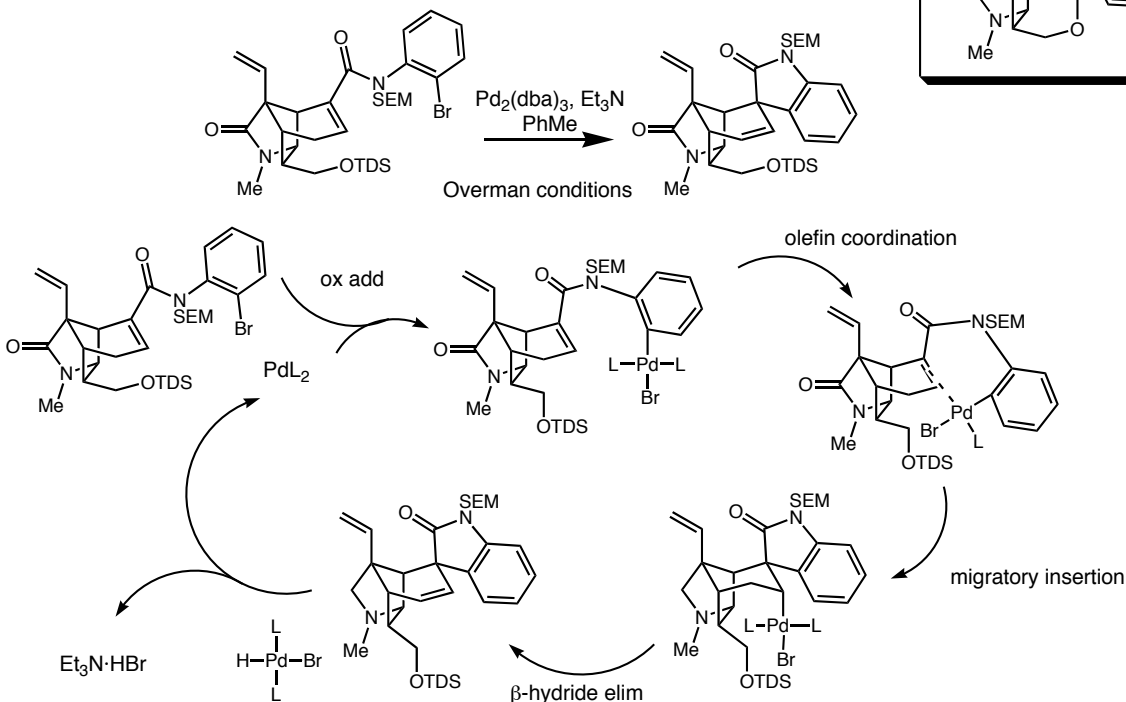
◆ Intramolecular Mannich cyclization



Newcombe, N.J.; Ya, F.; Vijn, R.J.; Hiemstra, H.; Speckamp, W.N. *J. Chem. Soc., Chem. Commun.* **1994**, 767-768
 Speckamp, W.N.; Newcombe, N.W.; Hiemstra, H.; Ya, F.; Vijn, R.J.; Koot, W.J. *Pure & Appl. Chem.* **1994**, 66, 10, 2163-2166

Speckamp and Hiemstra's synthesis of Gelsemine, Stereochemical Rationale

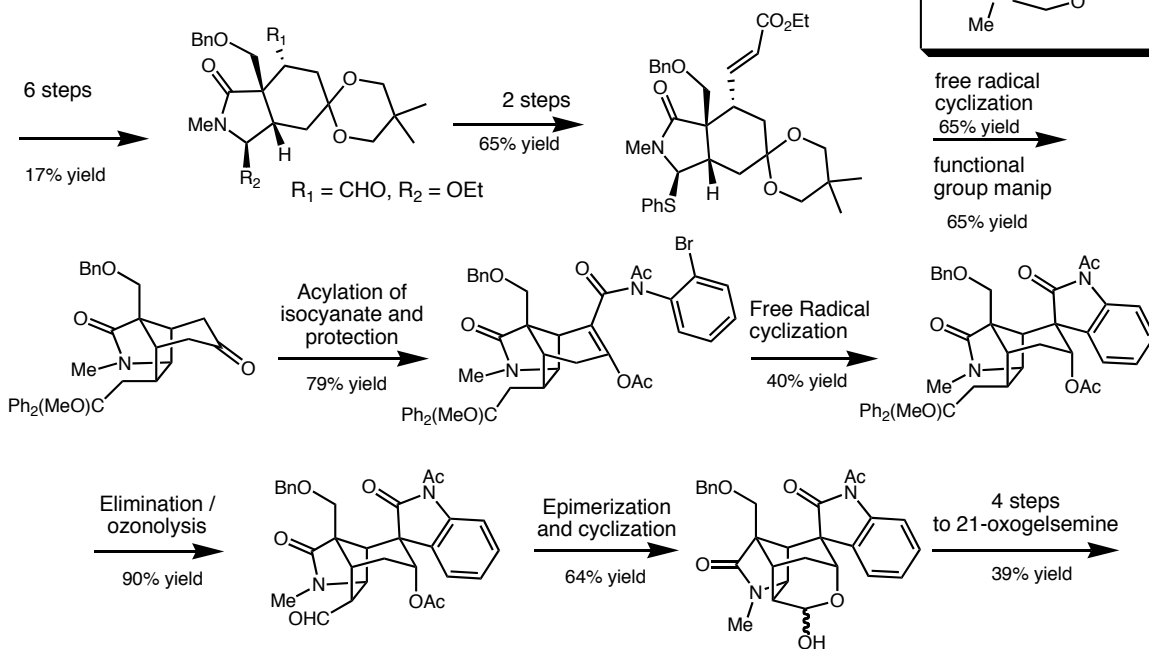
- ◆ Overman Intramolecular Heck for Oxindole synthesis



Newcombe, N.J.; Ya, F.; Vijn, R.J.; Hiemstra, H.; Speckamp, W.N. *J. Chem. Soc., Chem. Commun.* **1994**, 767-768
 Speckamp, W.N.; Newcombe, N.W.; Hiemstra, H.; Ya, F.; Vijn, R.J.; Koot, W.J. *Pure & Appl. Chem.* **1994**, 66, 10, 2163-2166

Hart's synthesis of Gelsemine

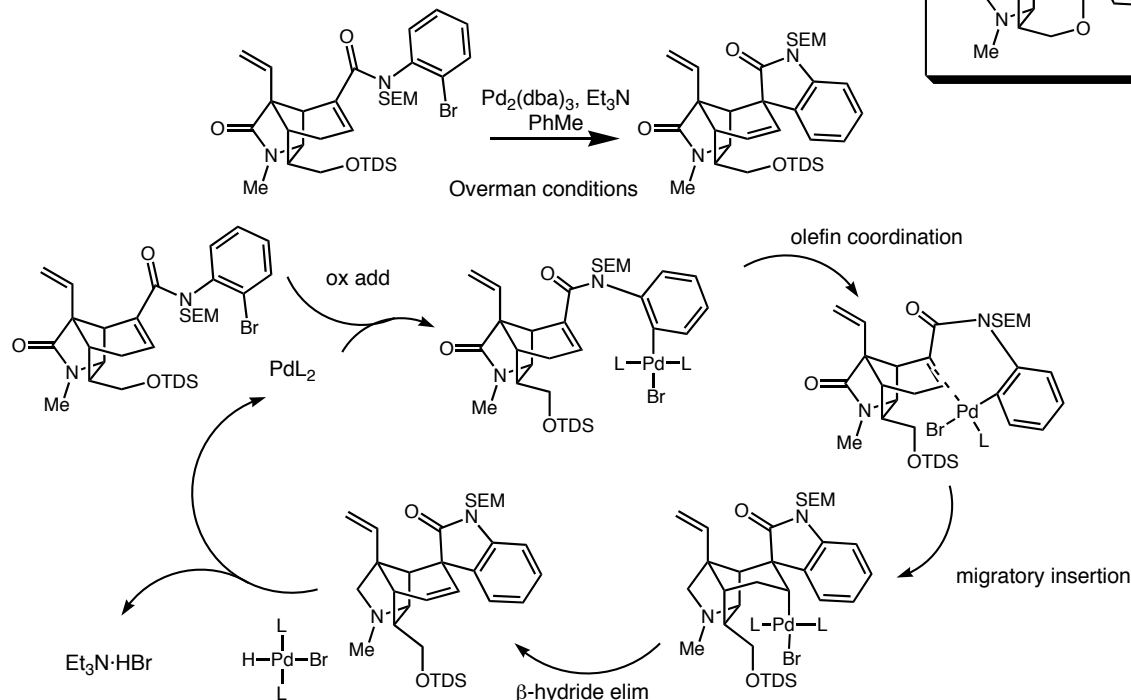
- ◆ Key steps are two free radical cyclization and an isomerization / cyclization.
- ◆ Completes 21-oxogelsemine in racemic form. 23 steps.



Kuzmich, D.; Wu, S.C.; Ha, D.C.; Lee, C.S.; Ramesh, S.; Atarahi, S.; Choi, J.K.; Hart, D.J. *JACS* **1994**, 116, 6943-6944
 Atarahi, S.; Choi, J.K.; Ha, D.C.; Hart, D.J.; Kuzmich, D.; Lee, C.S.; Ramesh, S.; Wu, S.C. *JACS* **1997**, 119, 6226-6241

Speckamp and Hiemstra's synthesis of Gelsemine, Stereochemical Rationale

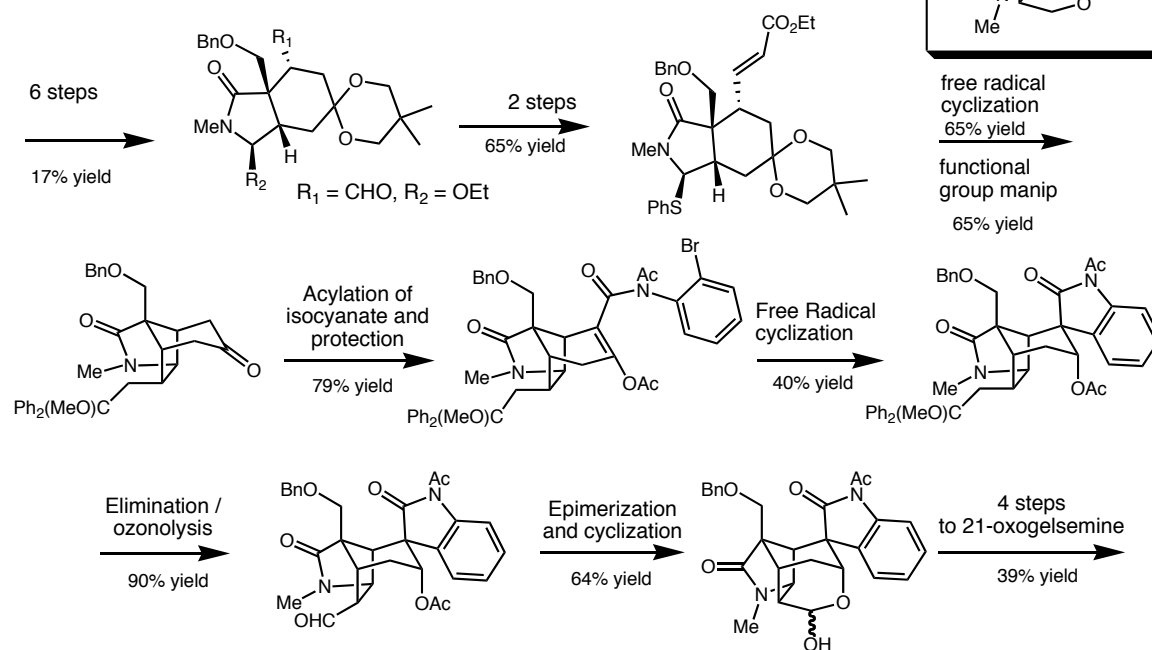
- ◆ Overman Intramolecular Heck for Oxindole synthesis



Newcombe, N.J.; Ya, F.; Vijn, R.J.; Hiemstra, H.; Speckamp, W.N. *J. Chem. Soc., Chem. Commun.* **1994**, 767-768
 Speckamp, W.N.; Newcombe, N.W.; Hiemstra, H.; Ya, F.; Vijn, R.J.; Koot, W.J. *Pure & Appl. Chem.* **1994**, 66, 10, 2163-2166

Hart's synthesis of Gelsemine

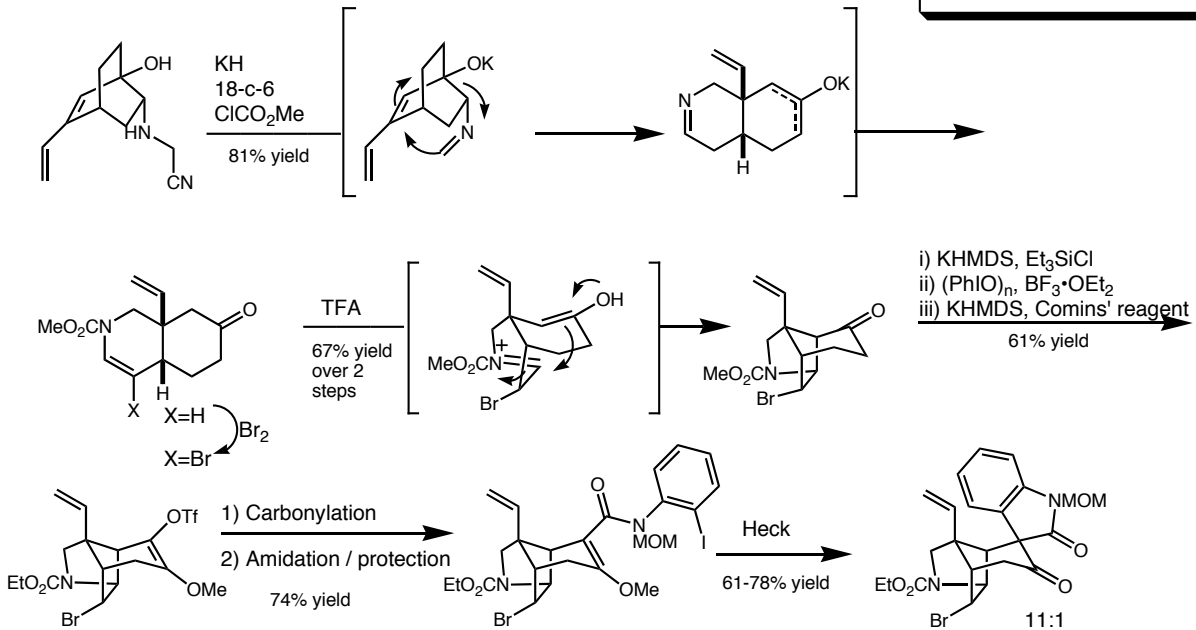
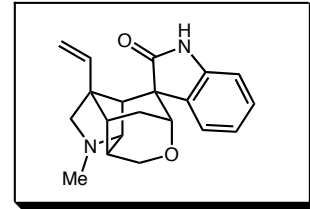
- ◆ Key steps are two free radical cyclization and an isomerization / cyclization.
- ◆ Completes 21-oxogelsemine in racemic form. 23 steps.



Kuzmich, D.; Wu, S.C.; Ha, D.C.; Lee, C.S.; Ramesh, S.; Atarahi, S.; Choi, J.K.; Hart, D.J. *JACS* **1994**, 116, 6943-6944
 Atarahi, S.; Choi, J.K.; Ha, D.C.; Hart, D.J.; Kuzmich, D.; Lee, C.S.; Ramesh, S.; Wu, S.C. *JACS* **1997**, 119, 6226-6241

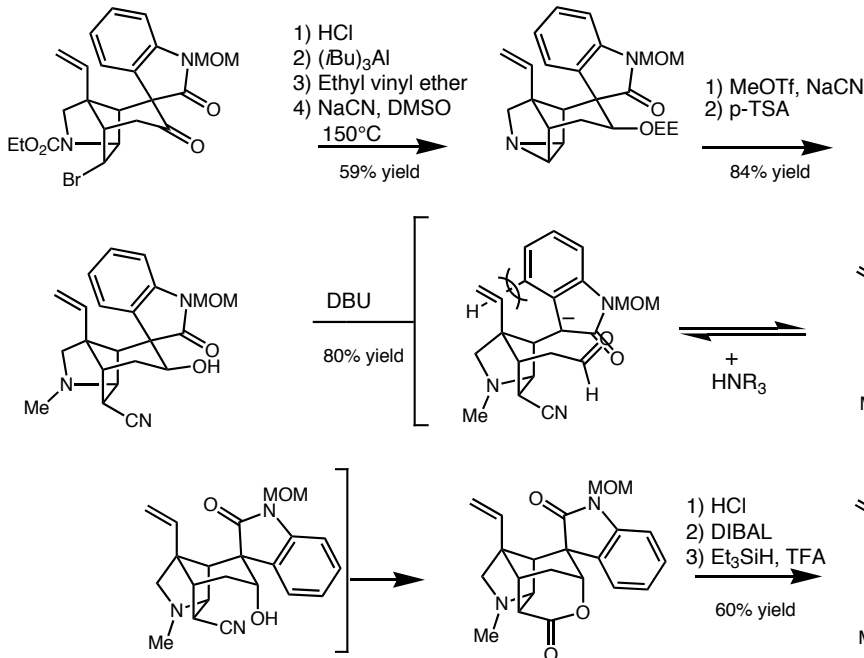
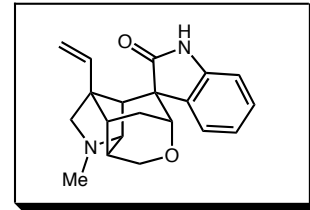
Overman's synthesis of Gelsemine

- ◆ Key steps are Aza-Cope rearrangement, Mannich cyclization, intramolecular Heck, base promoted reorganization of oxindole. This synthesis is of note in that the mannich cyclization was demonstrated well in advance of the other syntheses.
- ◆ Completes gelsemine in racemic form. 26 isolated intermediates.



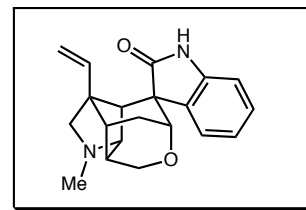
Earley, W.G.; Jacobsen, E.J.; Meier, P.; Oh, T.; Overman, L.E. *Tet. Lett.* **1988**, 29, 31, 3781-3784
Madin, A.; Overman, L.E. *Tet. Lett.* **1992**, 33, 34, 4859-4862
Madin, A.; O'Donnell, C.J.; Oh, T.; Old, D.W.; Overman, L.E.; Sharp, M.J. *Angew. Chem. Int. Ed.* **1999**, 38, 19, 2934-2936

Overman's synthesis of Gelsemine

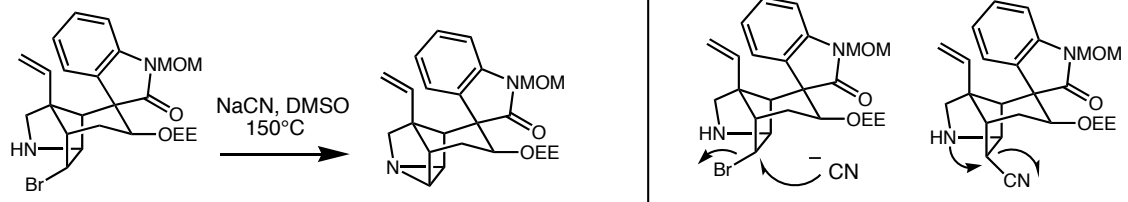


Earley, W.G.; Jacobsen, E.J.; Meier, P.; Oh, T.; Overman, L.E. *Tet. Lett.* **1988**, 29, 31, 3781-3784
Madin, A.; Overman, L.E. *Tet. Lett.* **1992**, 33, 34, 4859-4862
Madin, A.; O'Donnell, C.J.; Oh, T.; Old, D.W.; Overman, L.E.; Sharp, M.J. *Angew. Chem. Int. Ed.* **1999**, 38, 19, 2934-2936

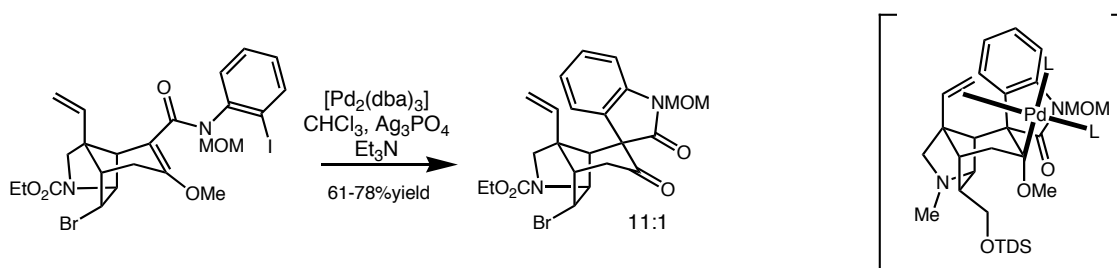
Overman's synthesis of Gelsemine



◆ Aziridine formation

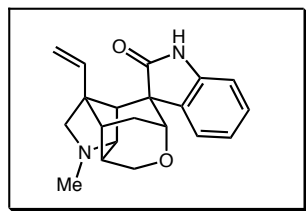


◆ New Heck conditions

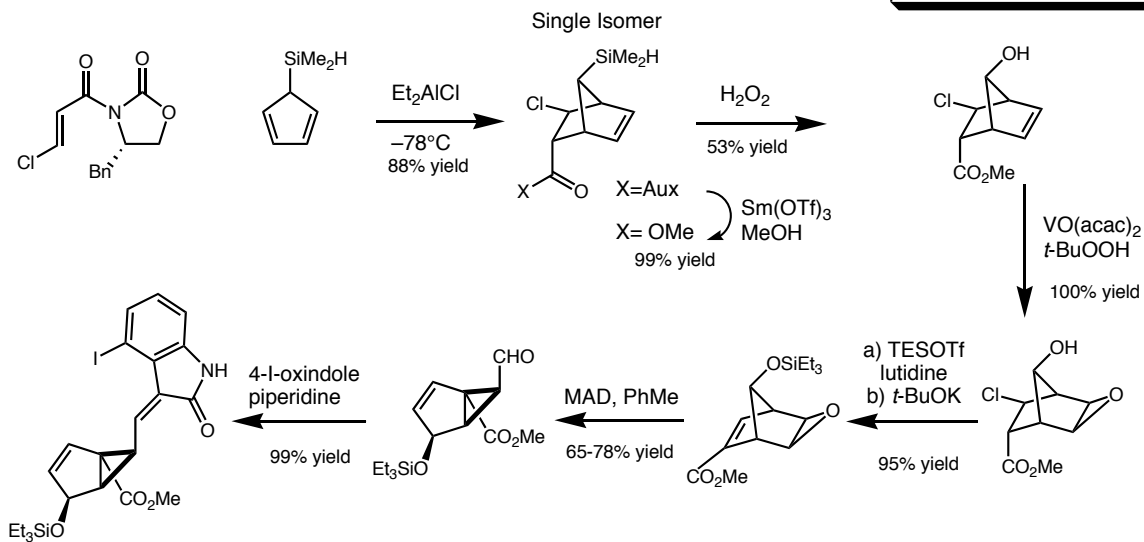


Earley, W.G.; Jacobsen, E.J.; Meier, P.; Oh, T.; Overman, L.E. *Tet. Lett.* **1988**, 29, 31, 3781-3784
 Madin, A.; Overman, L.E. *Tet. Lett.* **1992**, 33, 34, 4859-4862
 Madin, A.; O'Donnell, C.J.; Oh, T.; Old, D.W.; Overman, L.E.; Sharp, M.J. *Angew. Chem. Int. Ed.* **1999**, 38, 19, 2934-2936

Fukuyama's synthesis of (+)-Gelsemine

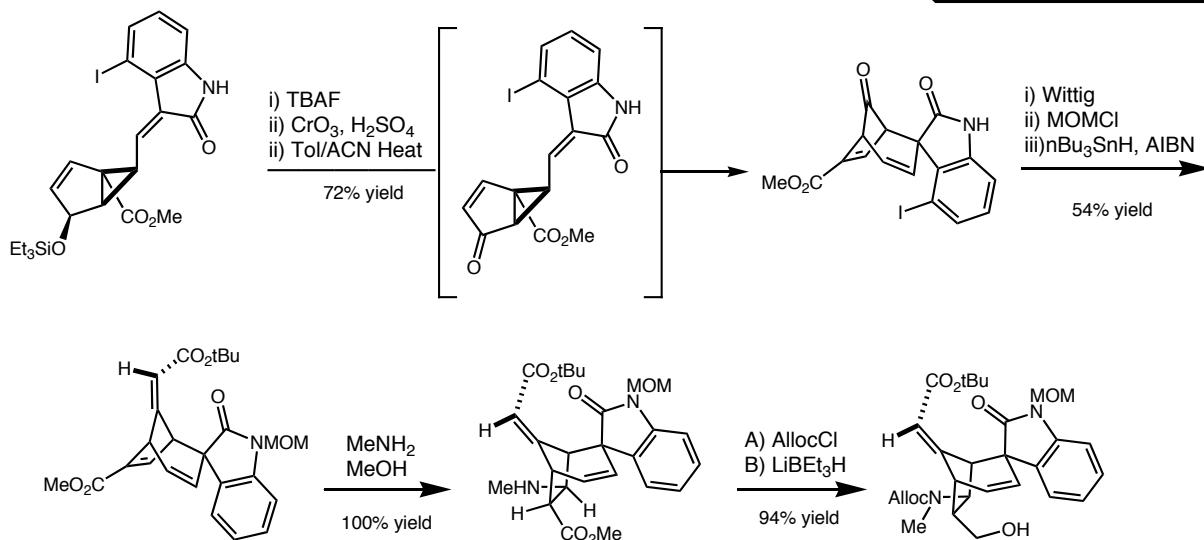
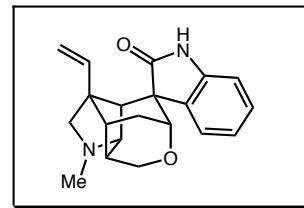


- ◆ Key steps are an epoxide rearrangement and a divinylcyclopropane rearrangement.
- ◆ Completes gelsemine enantioselectively. Shorter endgame than racemic synthesis. 21 steps.



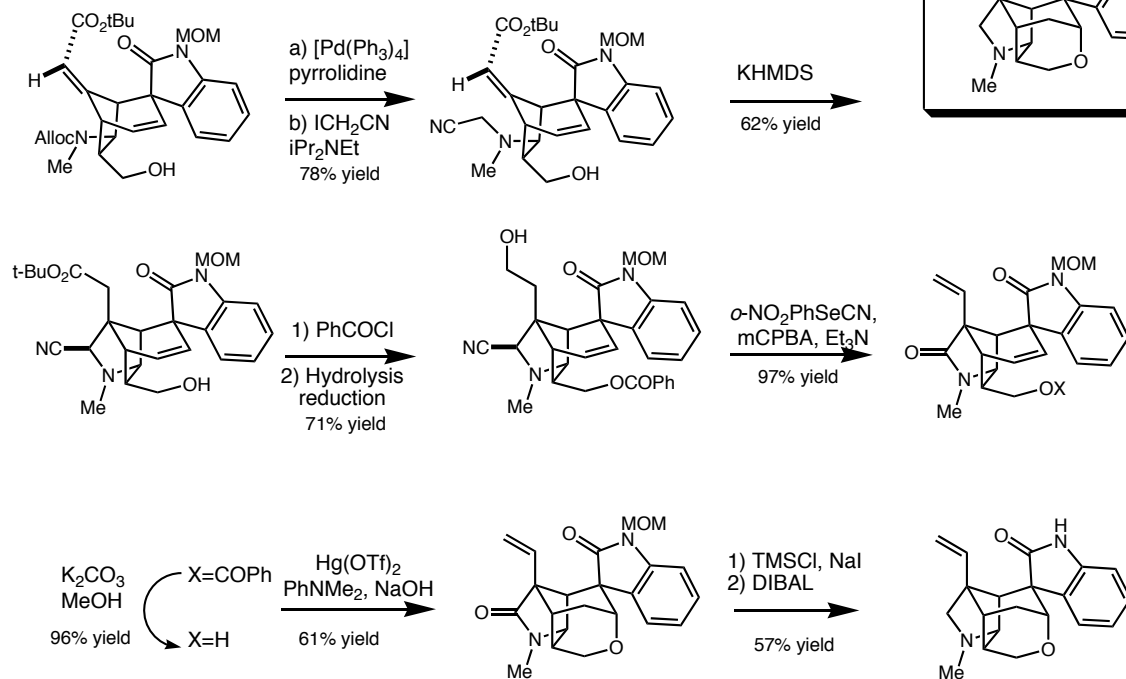
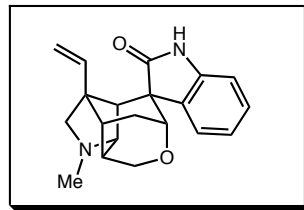
Fukuyama, T.; Liu, G. *JACS* **1996**, 118, 7426-7427
 Fukuyama, T.; Liu, G. *Pure & Appl. Chem.* **1997**, 69, 3, 501-505
 Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2000**, 39, 22, 4073-4075

Fukuyama's synthesis of (+) Gelsemine



Fukuyama, T.; Liu, G. *JACS* **1996**, *118*, 7426-7427
 Fukuyama, T.; Liu, G. *Pure & Appl. Chem.* **1997**, *69*, 3, 501-505
 Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 22, 4073-4075

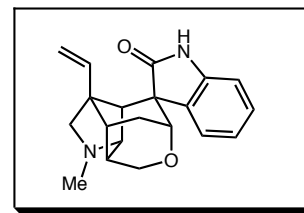
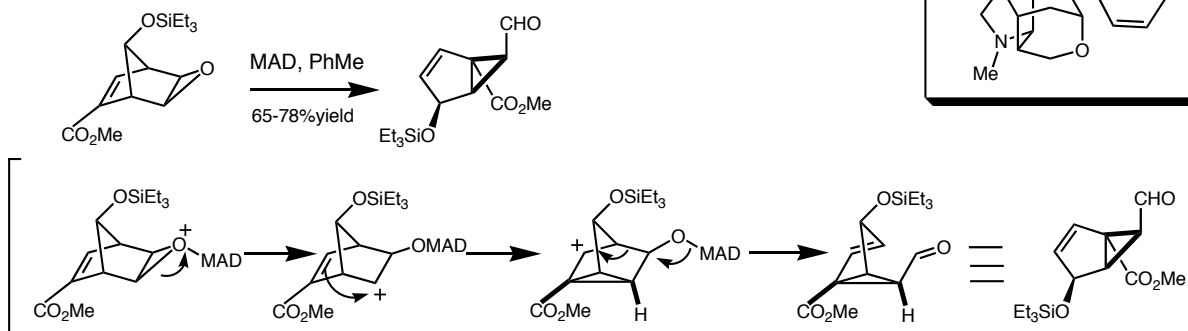
Fukuyama's synthesis of (+)-Gelsemine



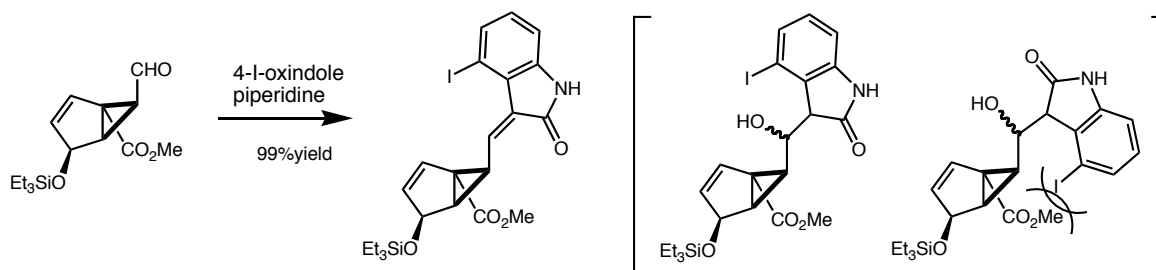
Fukuyama, T.; Liu, G. *JACS* **1996**, *118*, 7426-7427
 Fukuyama, T.; Liu, G. *Pure & Appl. Chem.* **1997**, *69*, 3, 501-505
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Fukuyama's synthesis of (+)-Gelsemine

- ◆ Rearrangement analogous to one previously reported by Meinwald.



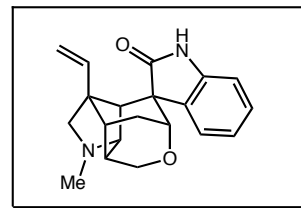
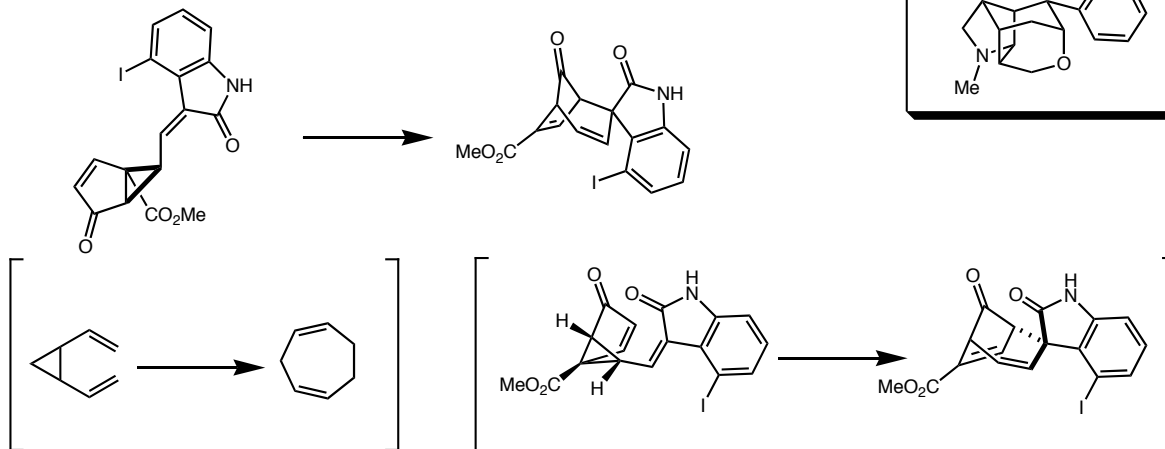
- ◆ Condensation by oxindole, iodine at 4 position helps with olefin geometry.



Meinwald, J.; Labana, S.S.; Chadha, M.S. *JACS*, **1963**, 85, 582
 Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2000**, 39, 22, 4073-4075

Fukuyama's synthesis of (+)-Gelsemine

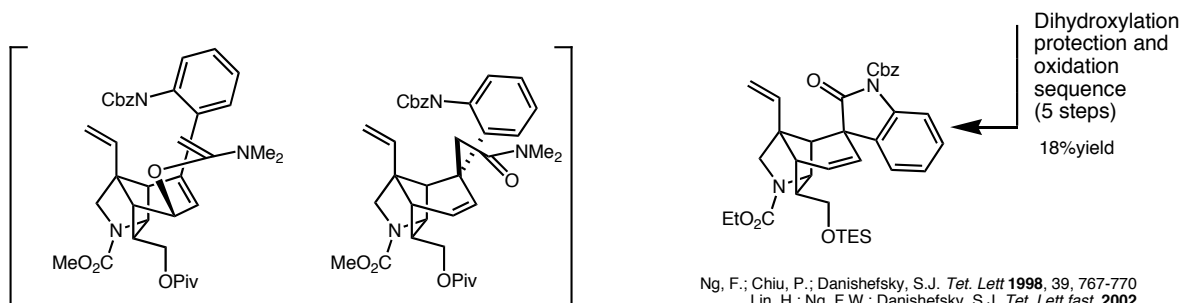
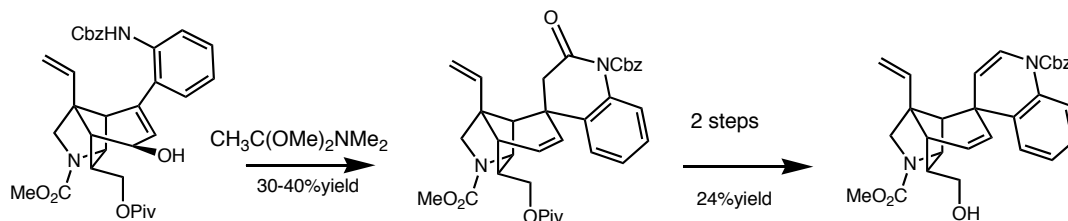
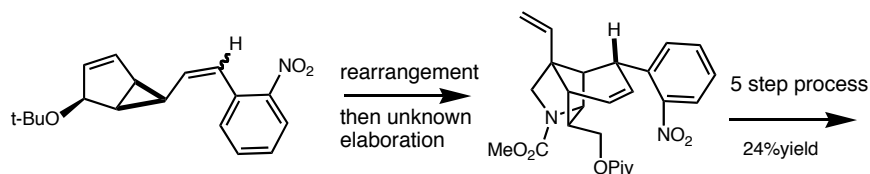
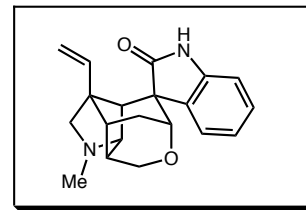
- ◆ Divinyl cyclopropane rearrangement.



Meinwald, J.; Labana, S.S.; Chadha, M.S. *JACS*, **1963**, 85, 582
 Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2000**, 39, 22, 4073-4075

Danishefsky's synthesis of Gelsemine

- ◆ Key step is a divinylcyclopropane rearrangement, new oxindole synthesis from an Eschenmoser Amide acetal Claisen.
- ◆ Completes gelsemine in racemic form. Not completely published. ? steps.



Conclusion

- ◆ Lots of synthetic work on this molecule with two basic premises dominating: cyclisation onto an iminium and rearrangements to build core.
- ◆ Oxindole synthesis at end is problematic but solved.
- ◆ This molecule is SCREAMING for a faster synthesis along a novel strategy.

