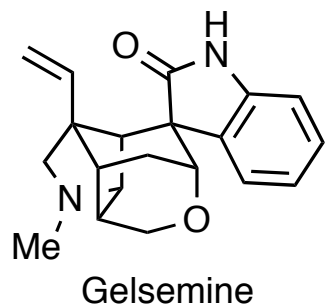
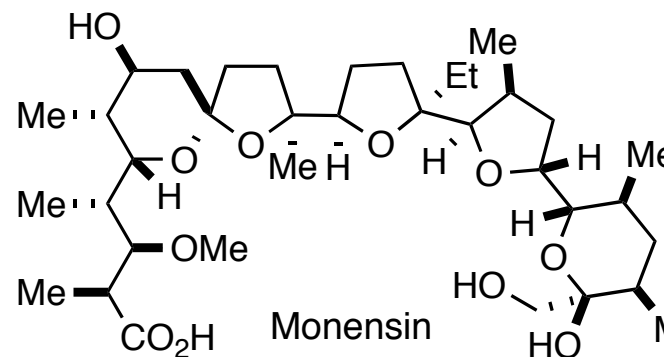
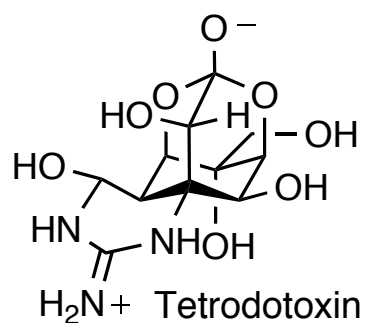
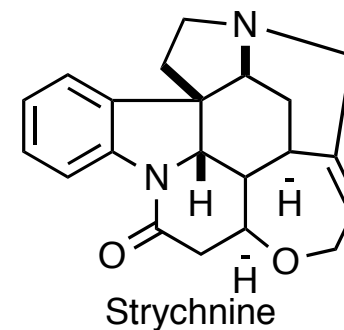


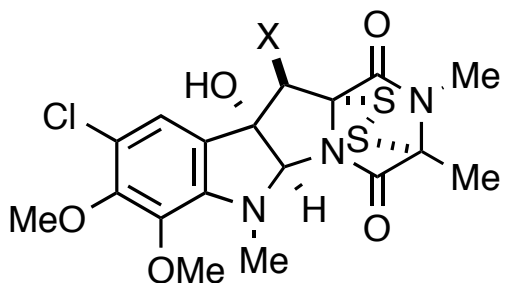
Tohru Fukuyama: *Inspiring Nature Through Total Synthesis*



Chris Regens
SED Group Meeting
Sept. 11, 2007



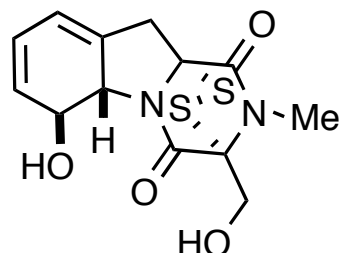
Fukuyama's Graduate and Post Doc. Work With Kishi



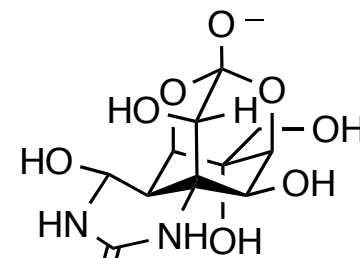
Sporidesmin A: X = OH *J. A.C.S.* **1973**, *95*, 6490; 6492; 6493.

Sporidesmin B: X = H *J. A.C.S.* **1976**, *98*, 6723.

Tetrahedron Lett. **1974**, 1549; **1971**, 4657; **1976**, 3393.



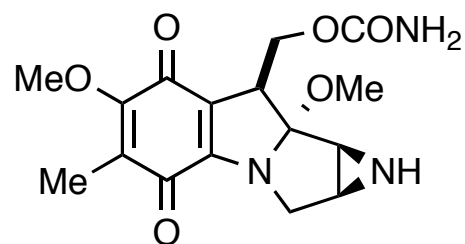
Gliotoxin



H₂N⁺ Tetrodotoxin

J. A.C.S. **1972**, *94*, 9217; 9219.

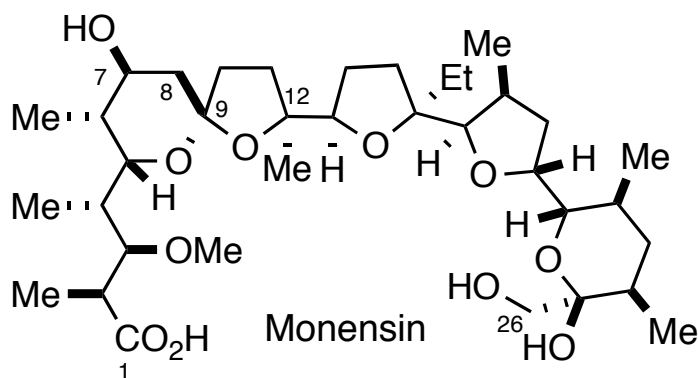
Tetrahedron Lett. **1970**, *59*, 5127; 5129



Mitomycin A

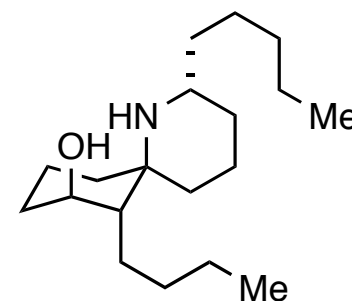
J. A.C.S. **1977**, *99*, 8115.

Tetrahedron Lett. **1977**, 4295.

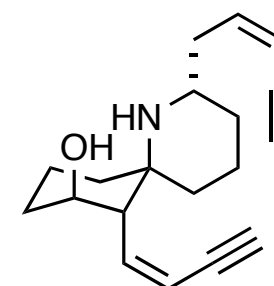


Monensin

J. A.C.S. **1979**, *101*, 259; 260; 262.

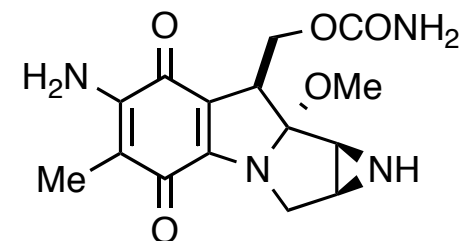


Perhydrohistrionicotoxin



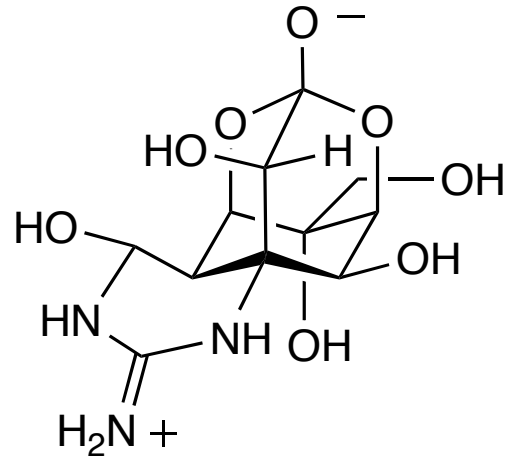
Histrionicotoxin

J. Org. Chem. **1975**, *40*, 2009; 2011.



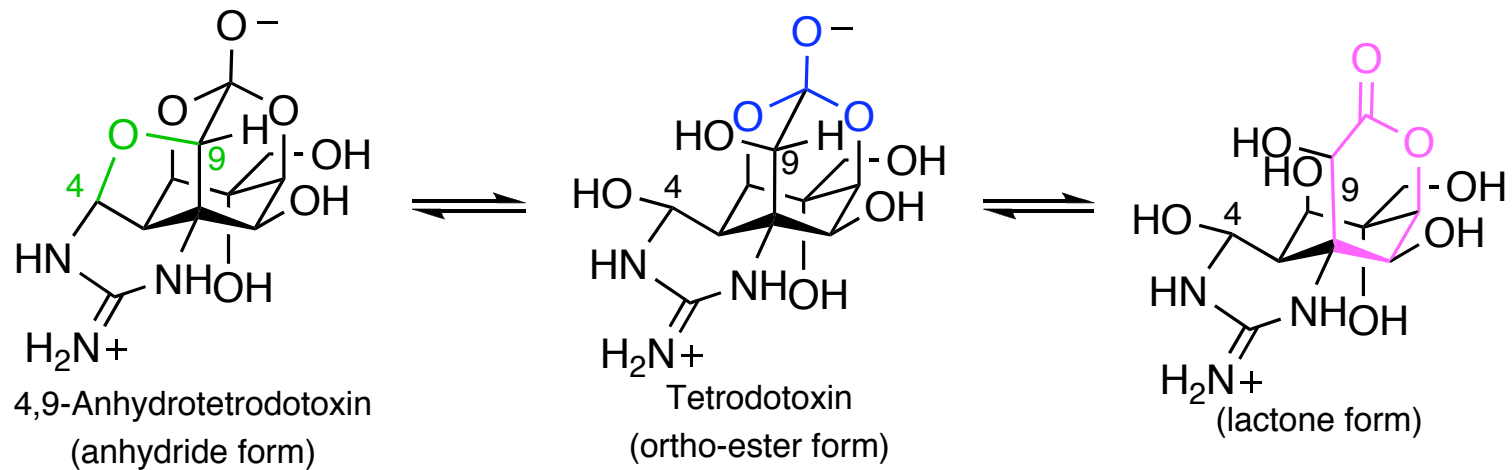
Porfiromycin

Three Different Forms of Tetrodotoxin



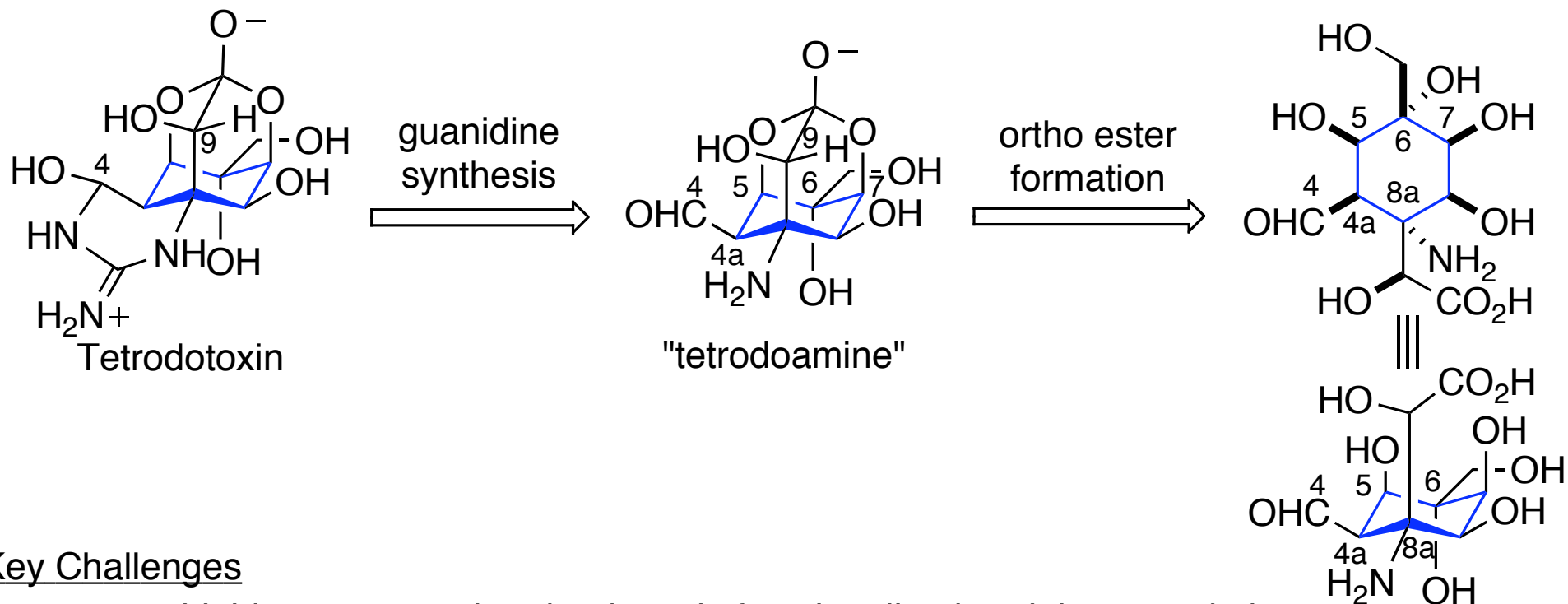
Structural Features:

- Contains a unique dioxadamantane skeleton with hydroxyl functionality
- Ortho-ester functional group
- Cyclic guanidine with a hemiaminal group



(±)-Tetrodotoxin: Densely Functionalized 6-Membered Ring

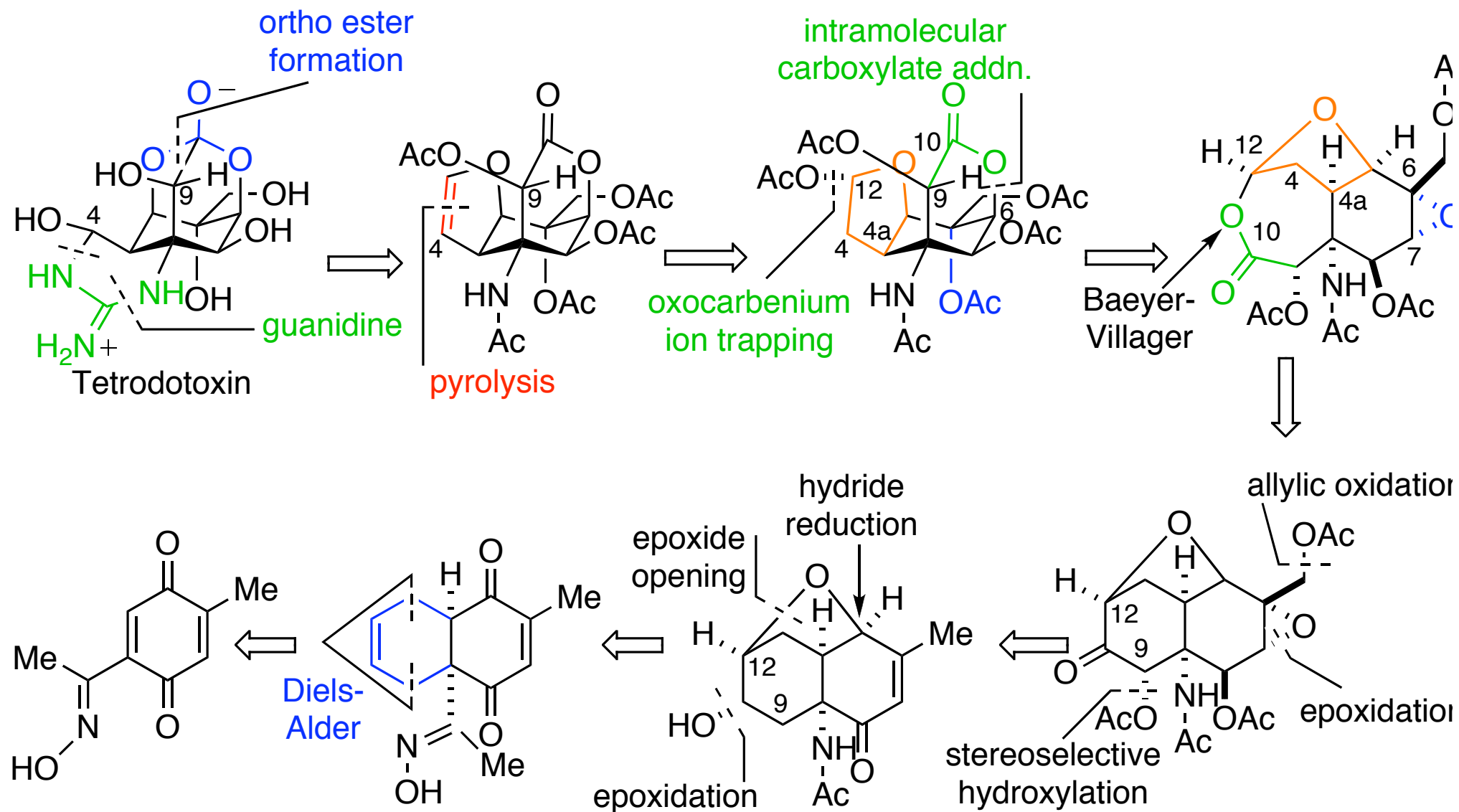
-General Retrosynthetic Analysis



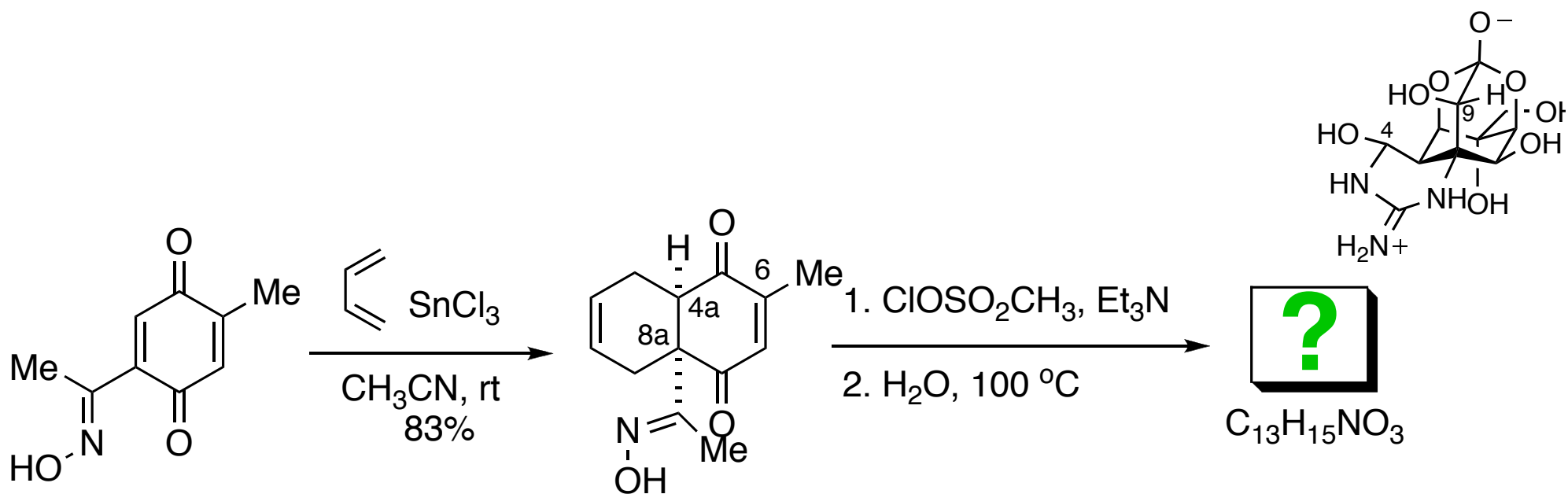
- Key Challenges

- Construct a highly oxygenated and a densely functionalized cyclohexane skeleton
- Construction of tetrasubstituted stereocenters C(6) and C(8a)
- Introduction of the C(8a) amine
- Prevent epimerization at C(9) and β -elimination of the hydroxyl group at C(5)
- This is 1972 so, stereochemistry was determined through coupling constants and chemical derivatization

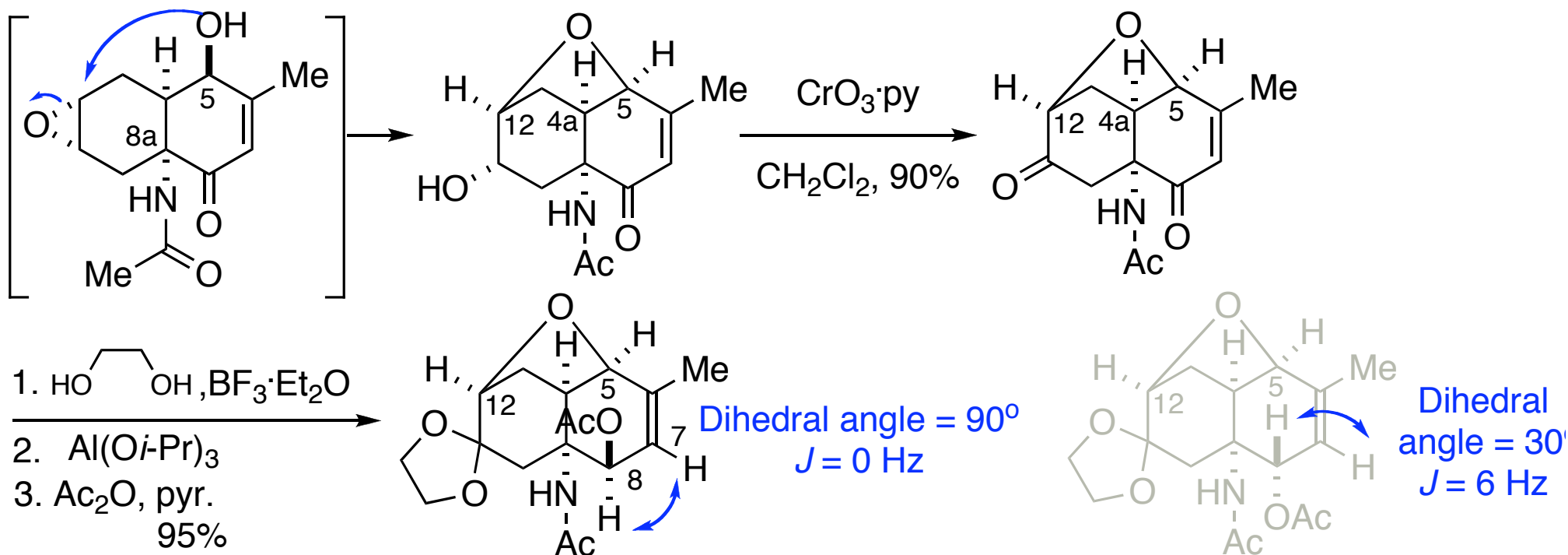
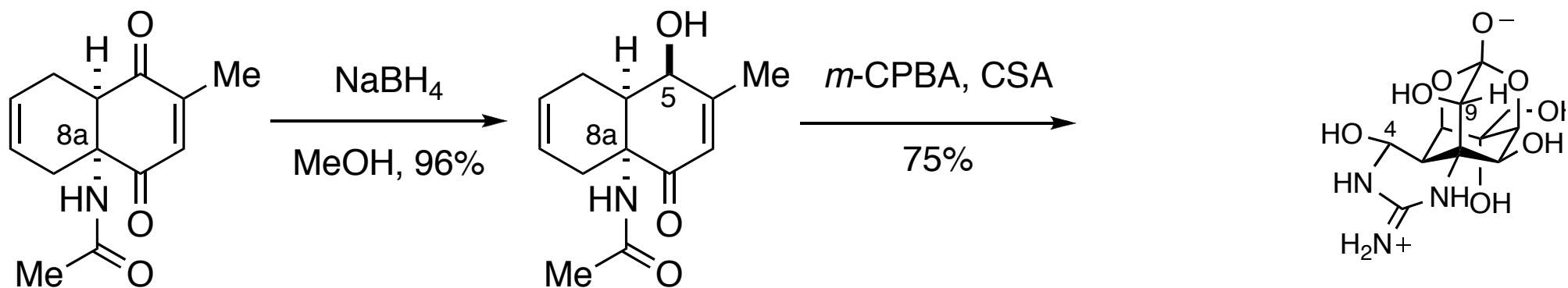
(±)-Tetrodotoxin: Beginning Diels Alder



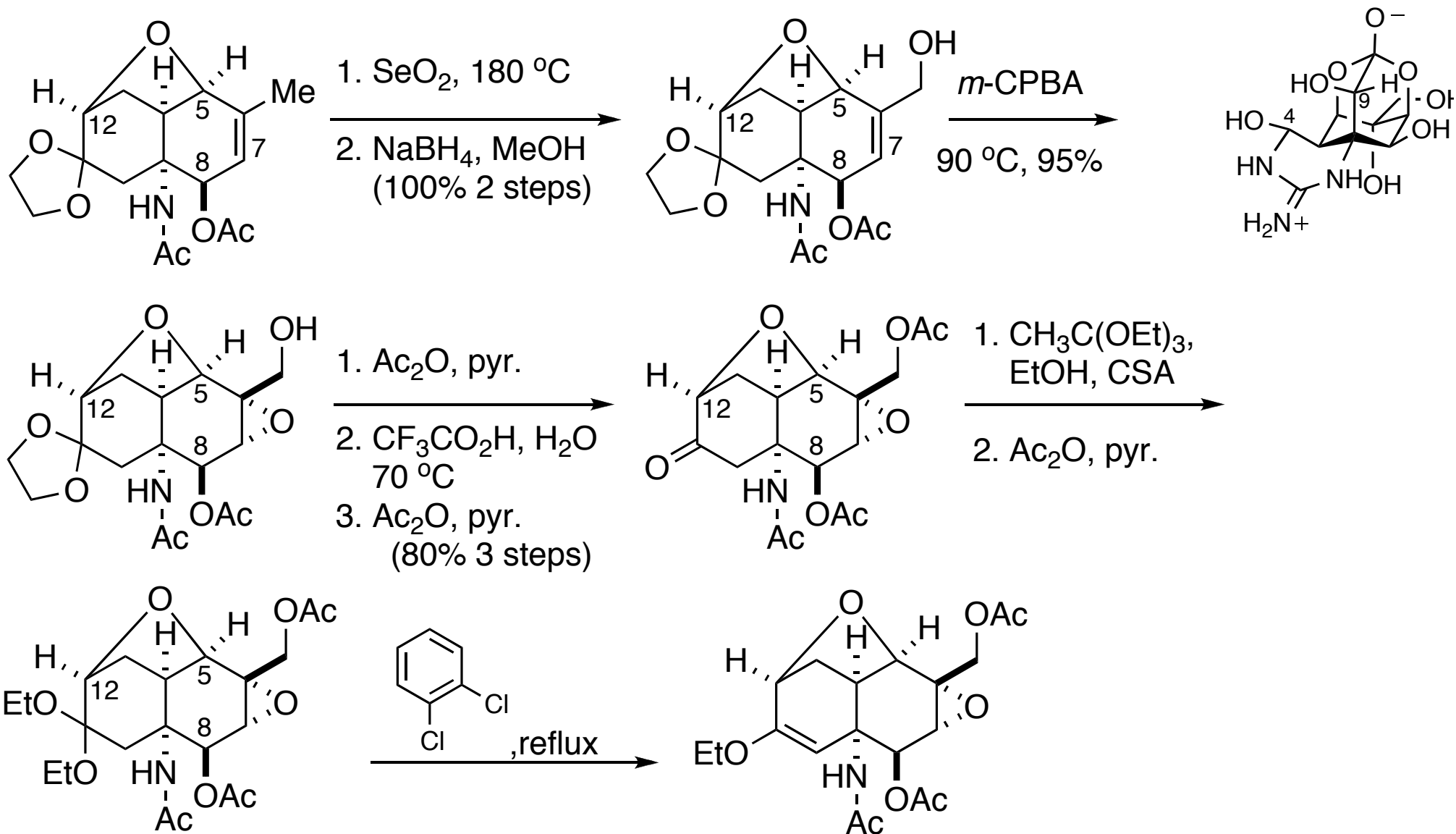
(±)-Tetrodotoxin: How Does One Install the C(8a) Nitrogen?



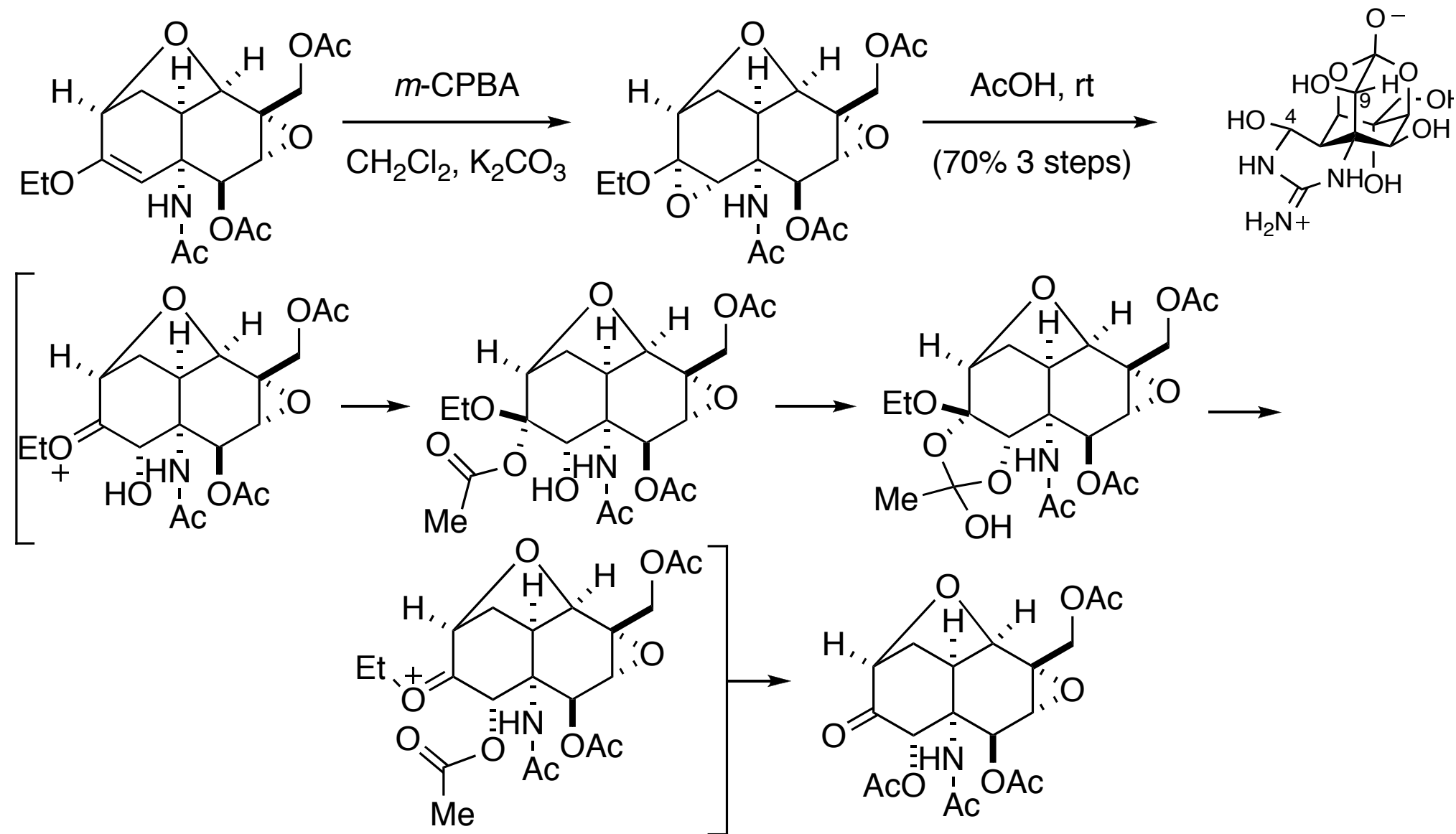
(±)-Tetrodotoxin: Building the Tricycle



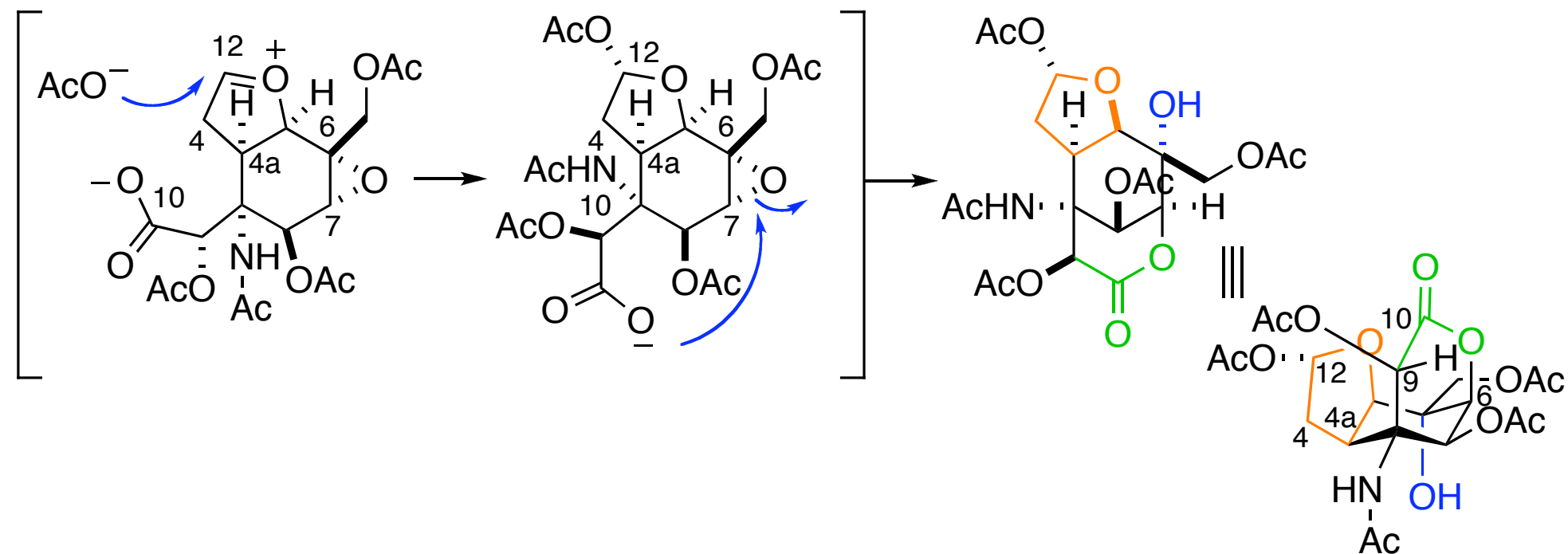
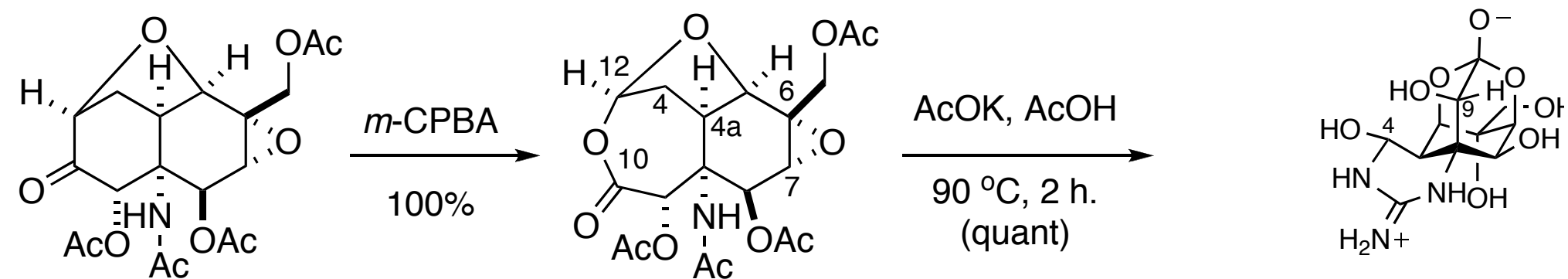
(±)-Tetrodotoxin: Finishing the 6-Membered Ring



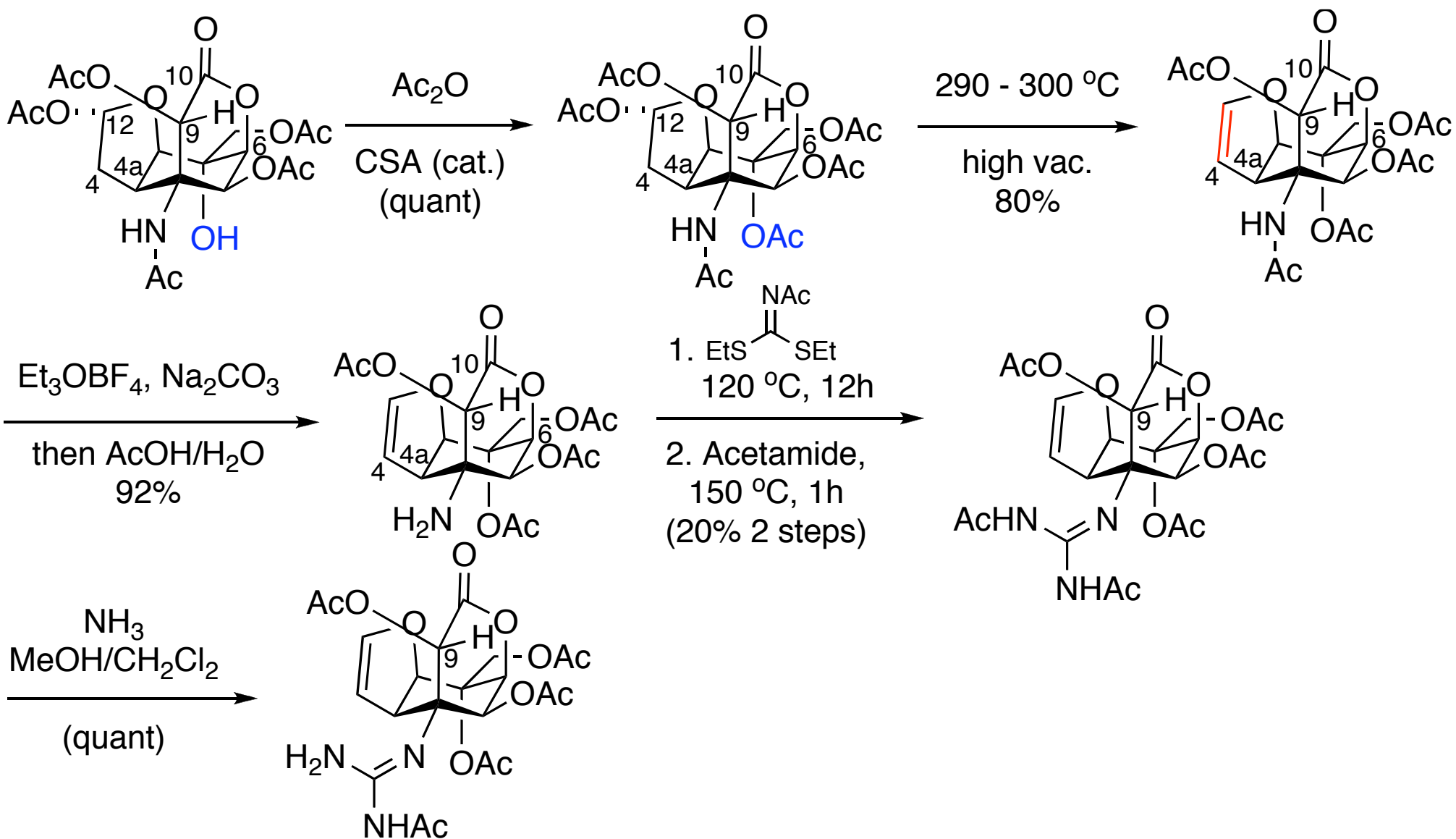
(±)-Tetrodotoxin: Installing the C(9) Hydroxyl Group



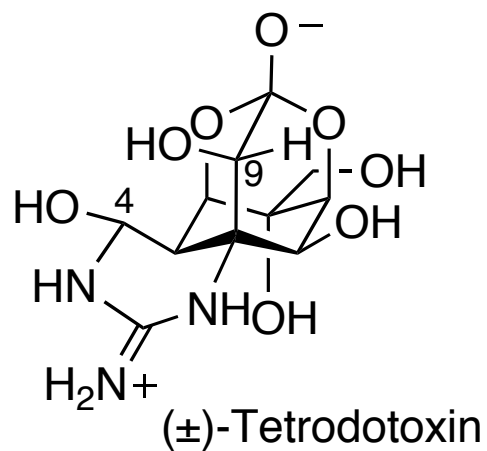
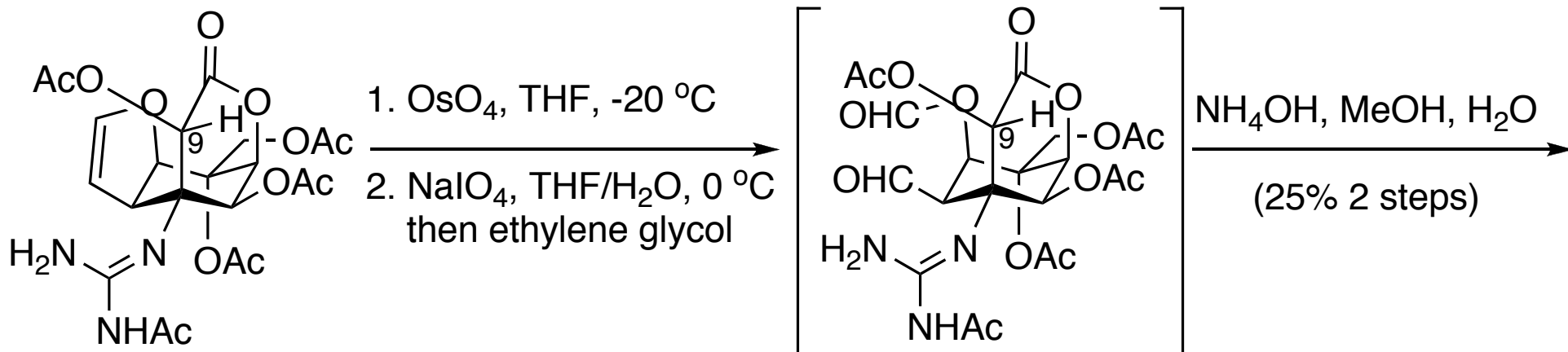
(±)-Tetrodotoxin: Key Step



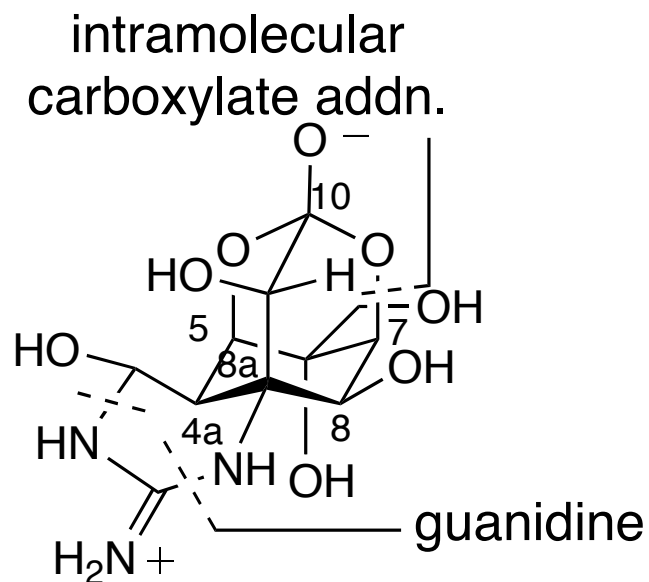
(±)-Tetrodotoxin: Assembling the Cyclic Guanidine



(±)-Tetrodotoxin: Done!



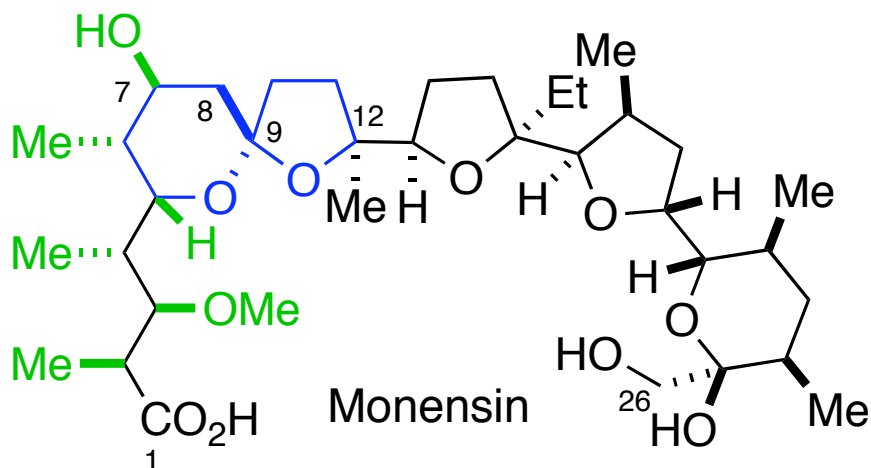
(±)-Tetrodotoxin: Conclusion



- 32 Steps
- C(8a) and C(4a): diastereoselective Diels-Alder Reaction
- C(8) and C(5) stereospecific, substrate controlled hydride reductions
- C(7) carboxylate attack onto epoxide

- Development of a novel way to synthesize a cyclic guanidine

(+)-Monensin: Historically Significant



Properties:

- Ionophore: ability to complex inorganic cations for translocation through a lipophilic interface.
- Polyether antibiotic (terminates with a carboxylate and contains numerous cyclic ethers).
- Isolated from *Streptomyces cinamonensis*
- Displays anticoccidial activity, used to combat such infections in cattle and poultry.

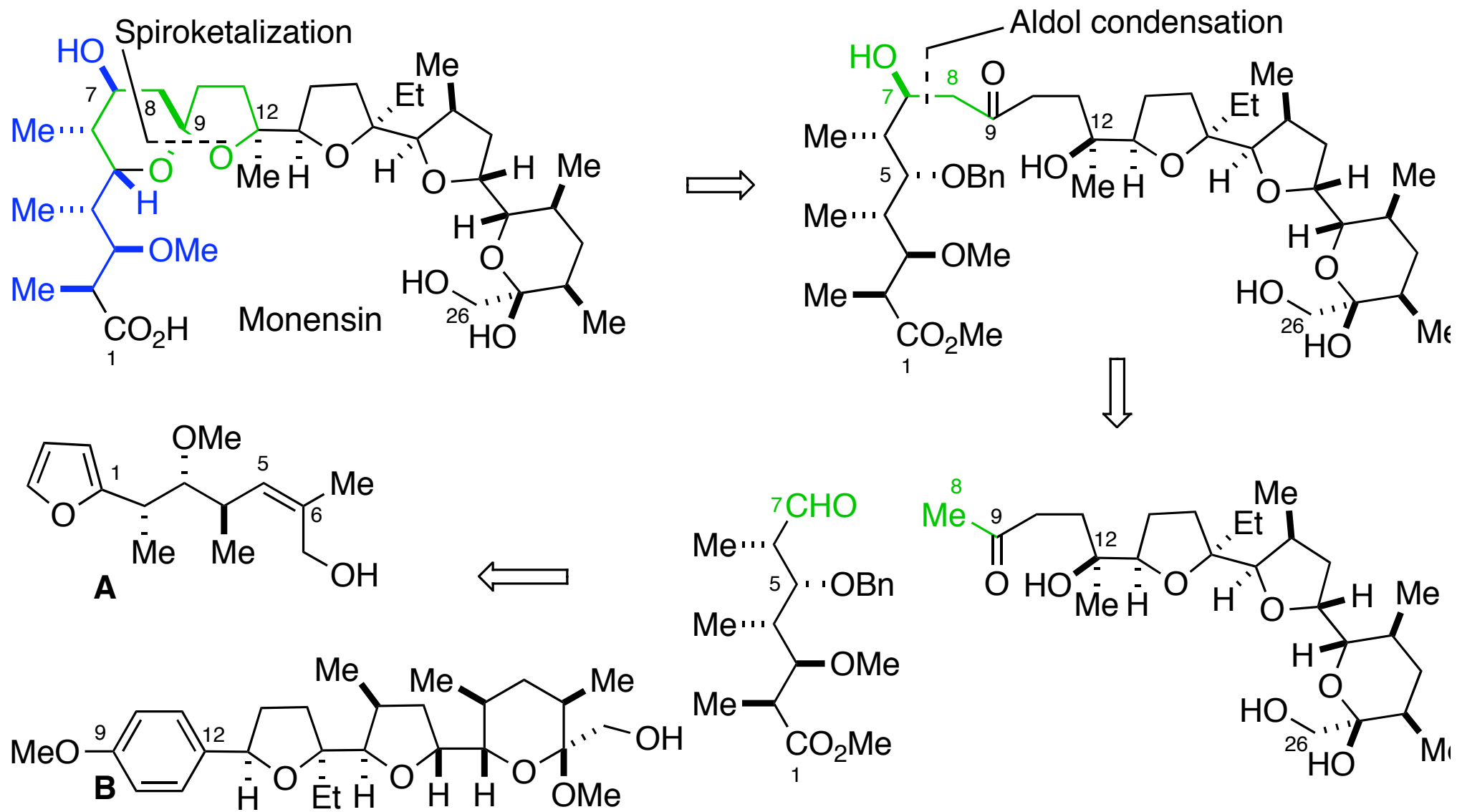
Structure:

- 17 stereocenters, 6 contiguous of the 26 carbons
- Contains only 3 elements O, H, C.
- Monensin maintains a cyclic structure through H-bonding at C(1) and HO at C(26)
- 2 THF rings 1 THP ring and a unique 1,6-dioxaspiro[4.5]decane

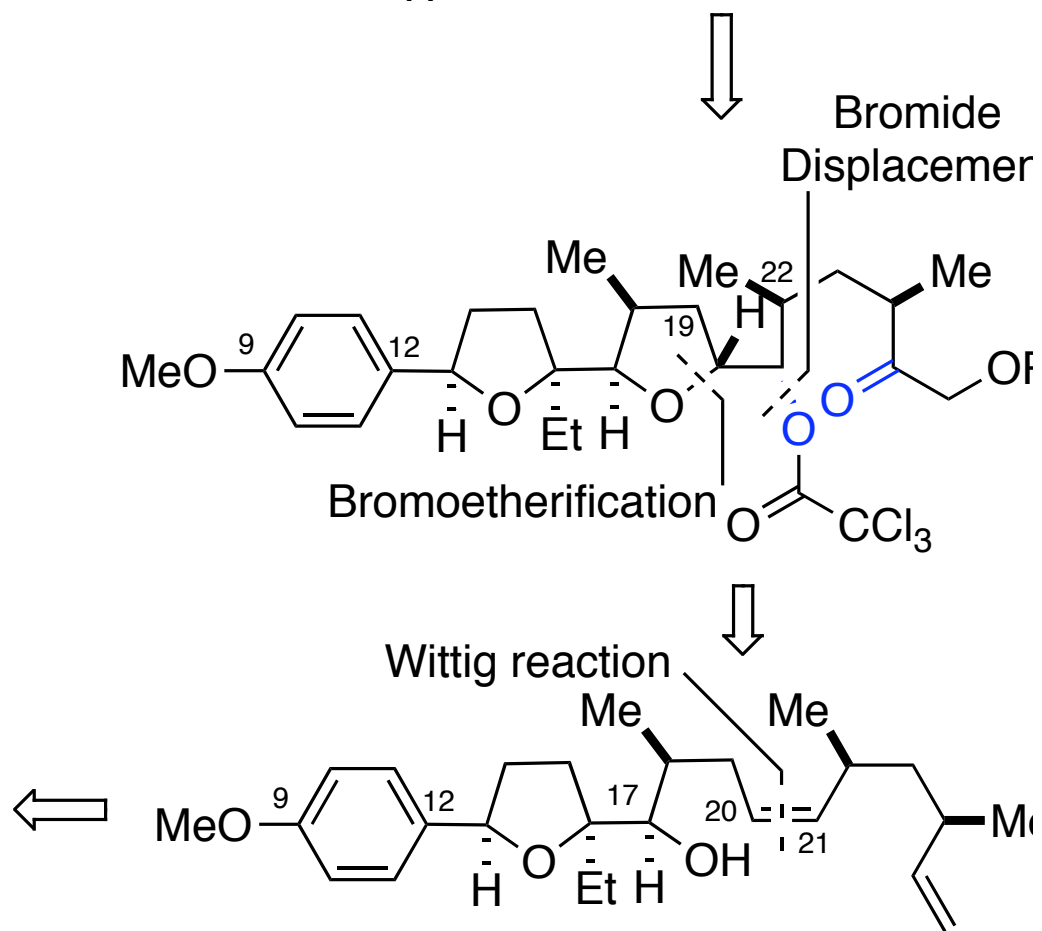
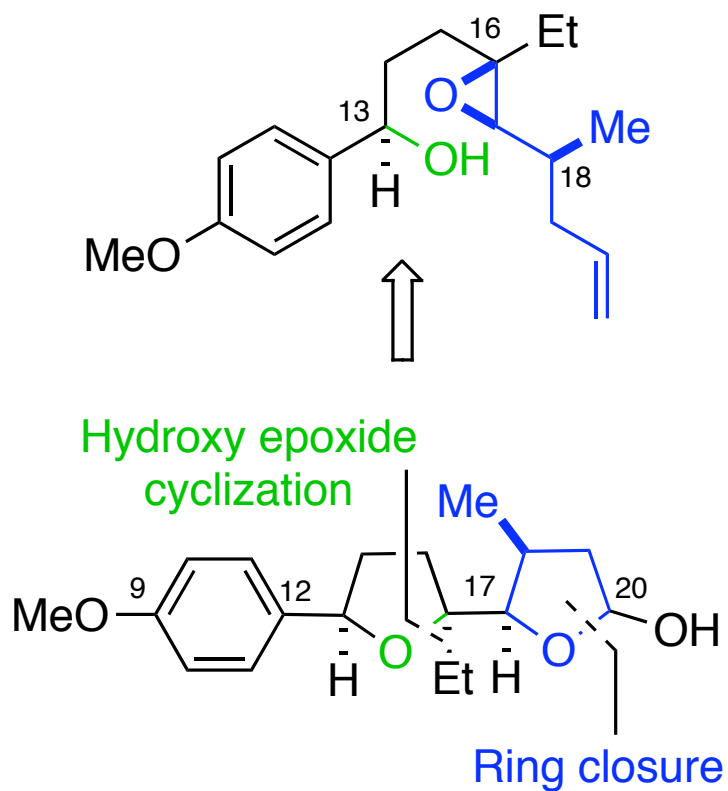
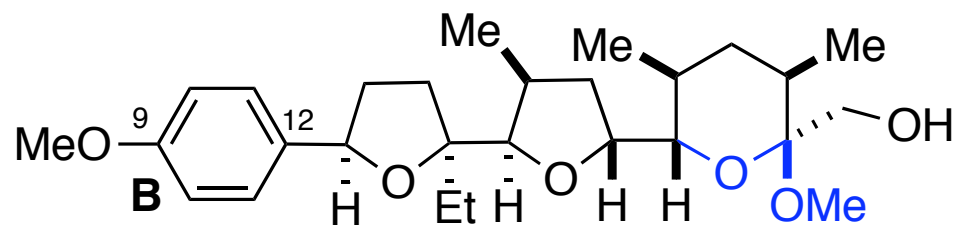
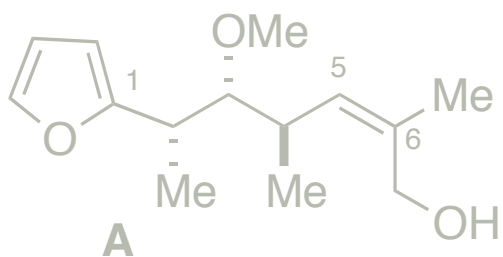
History:

- 5th polyether isolated, 1st characterized
- Kishi reported the first synthesis (1979)
- The synthesis is noted for:
 - Convergency
 - The way it exploits acyclic conformational control elements allylic 1,3-strain, to achieve stereochemical control in acyclic systems

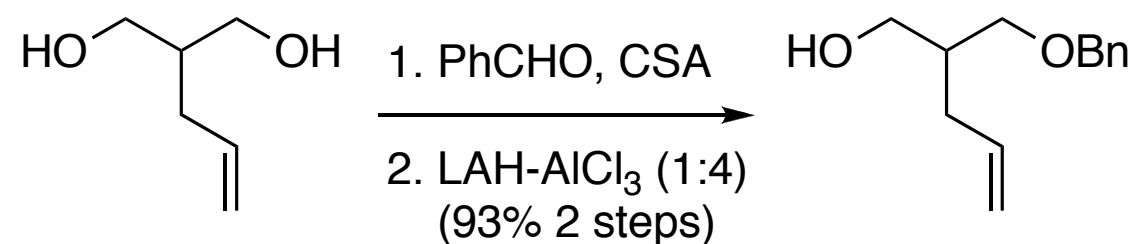
(+)-Monensin: Retrosynthesis



(+)-Monensin: Retrosynthesis of Fragment B

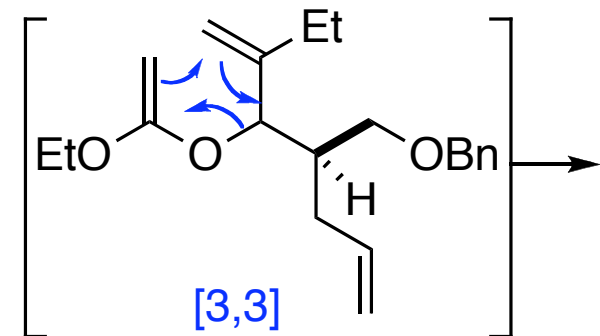
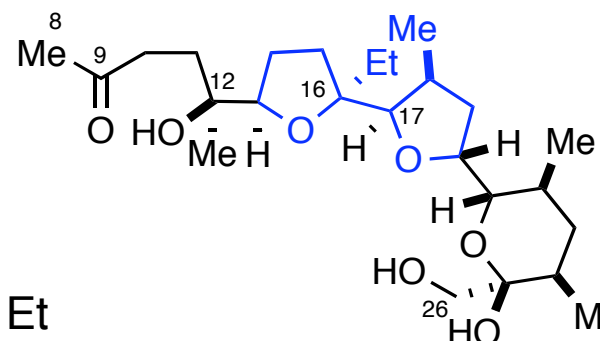
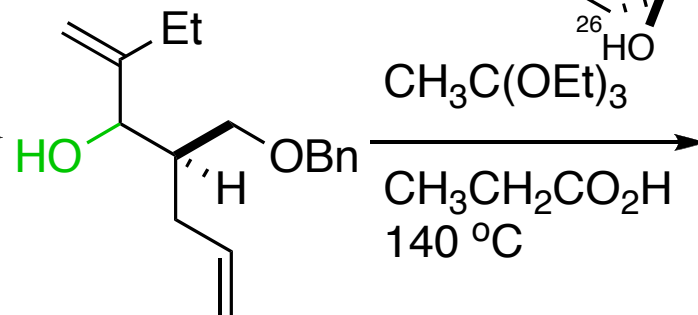
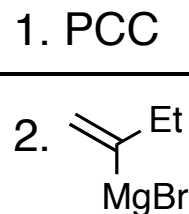
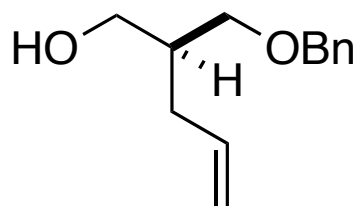
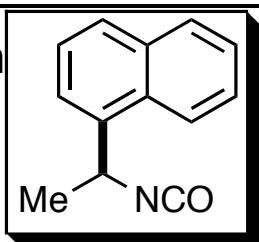


(+)-Monensin: Nice Johnson Ortho Claisen

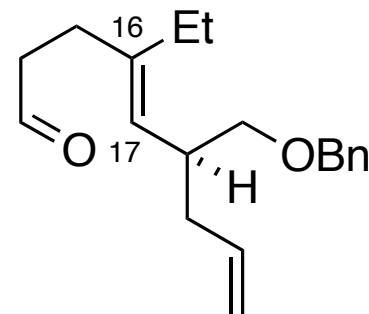
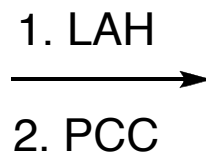
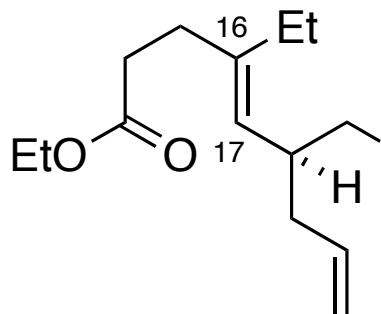


1. (S)-(+)-1-(1-naphthyl)
ethyl isocyanate, Et₃N

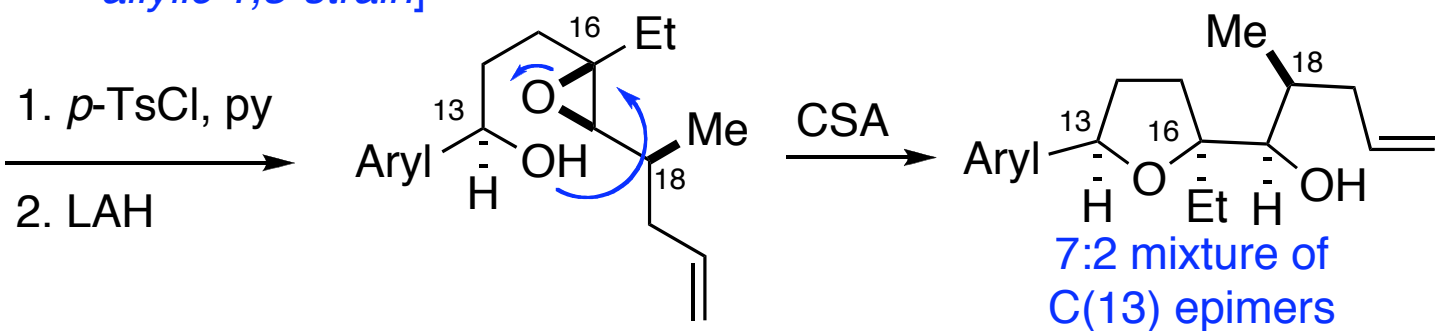
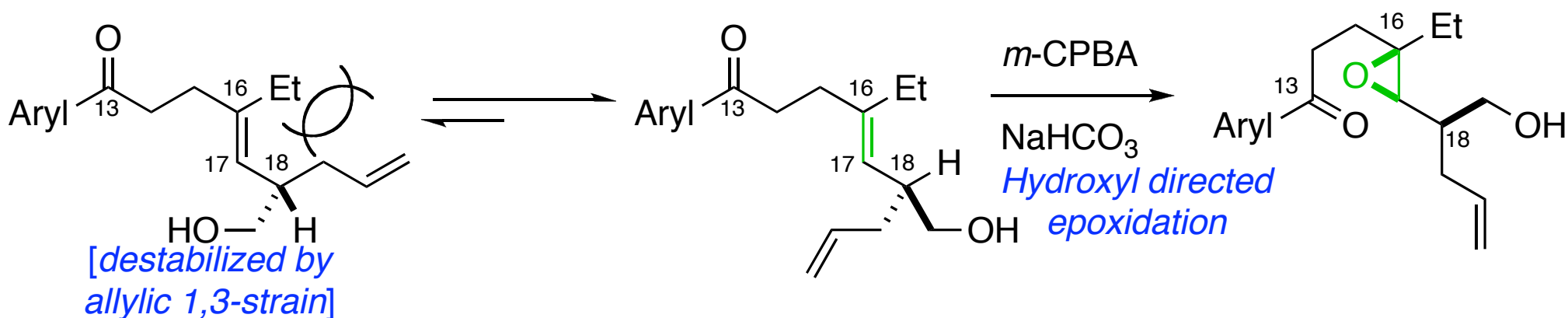
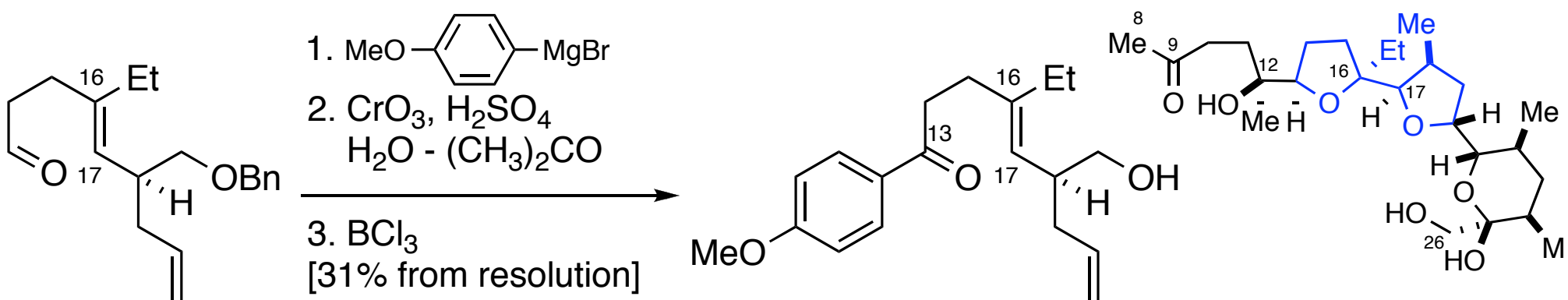
2. resolution
3. LAH



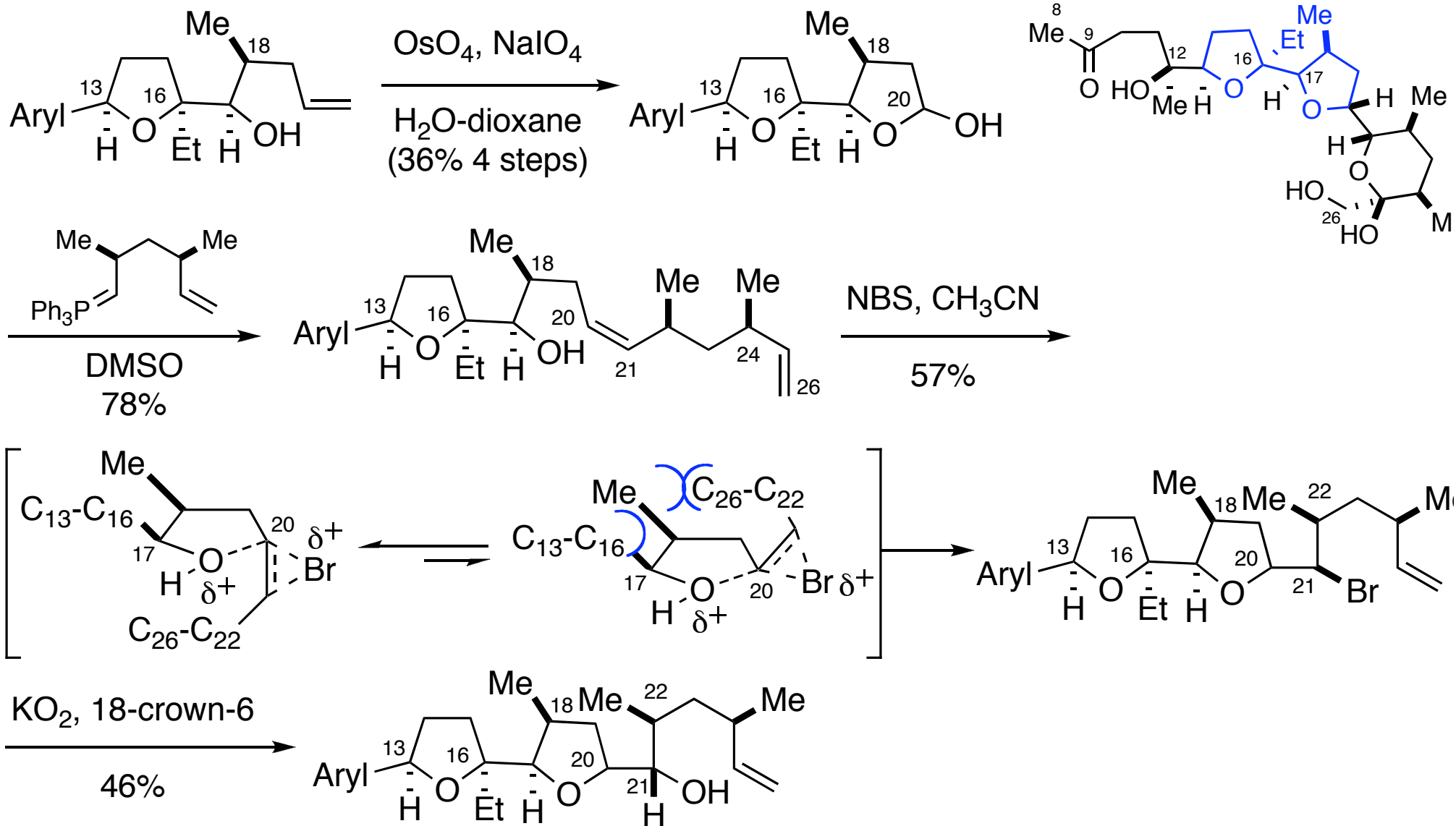
[3,3]
Johnson ortho ester
Claisen



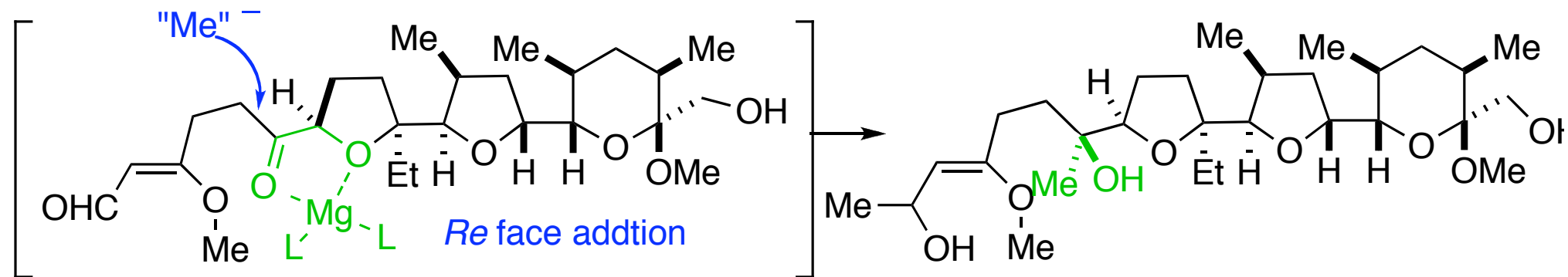
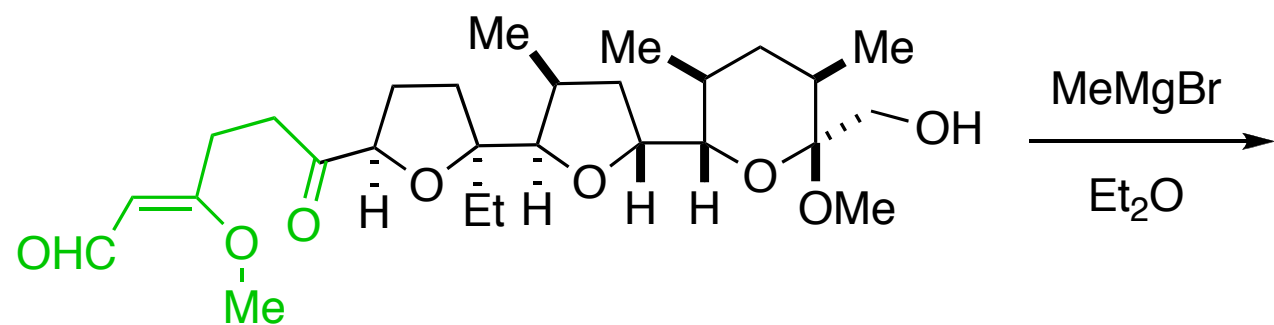
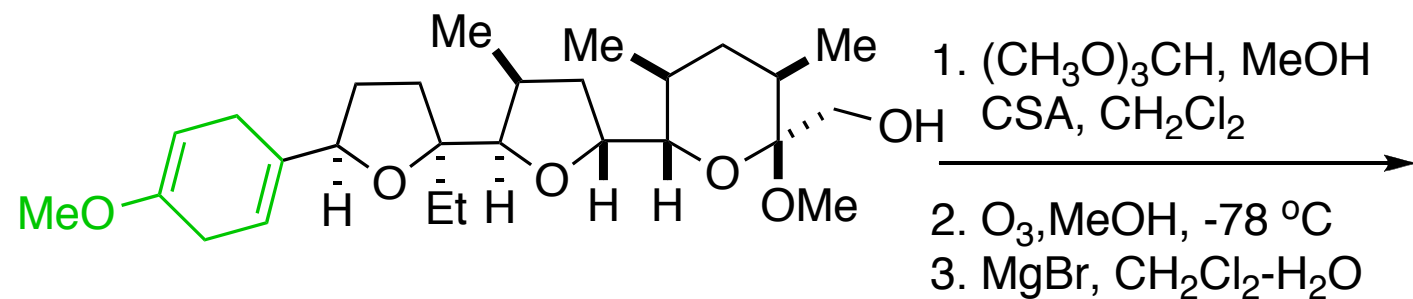
(+)-Monensin: Epoxide Opening



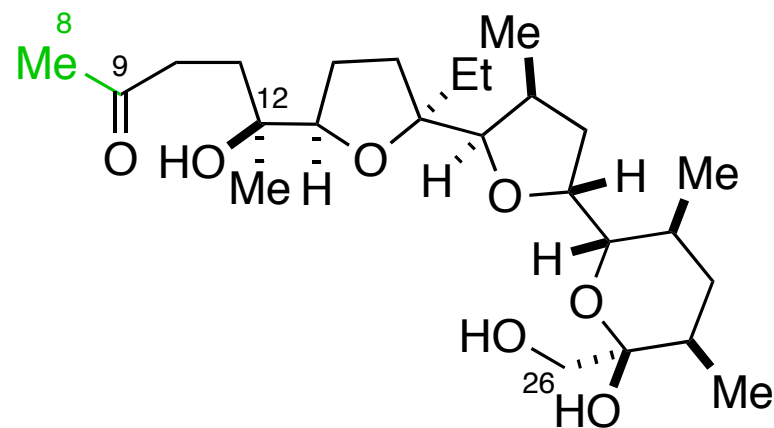
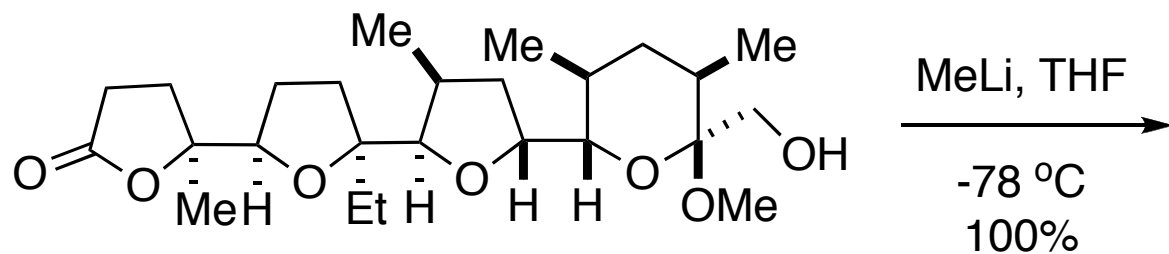
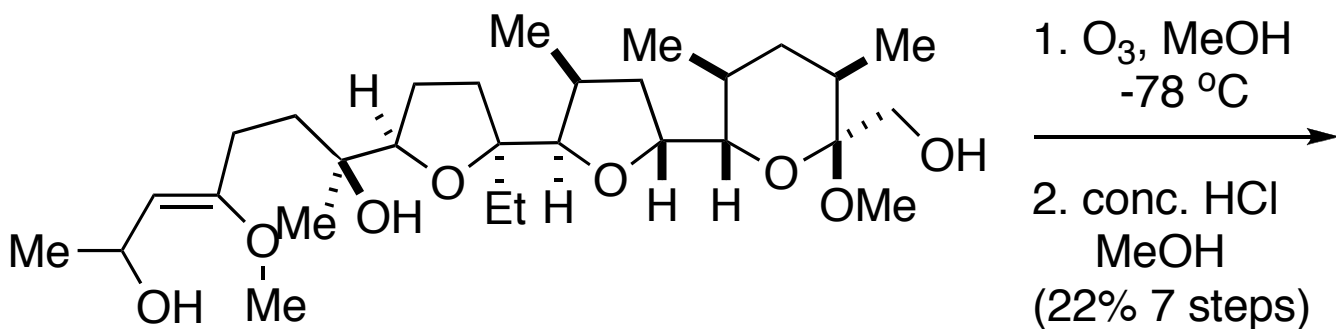
(+)-Monensin: S_N^2 Displacement with KO_2



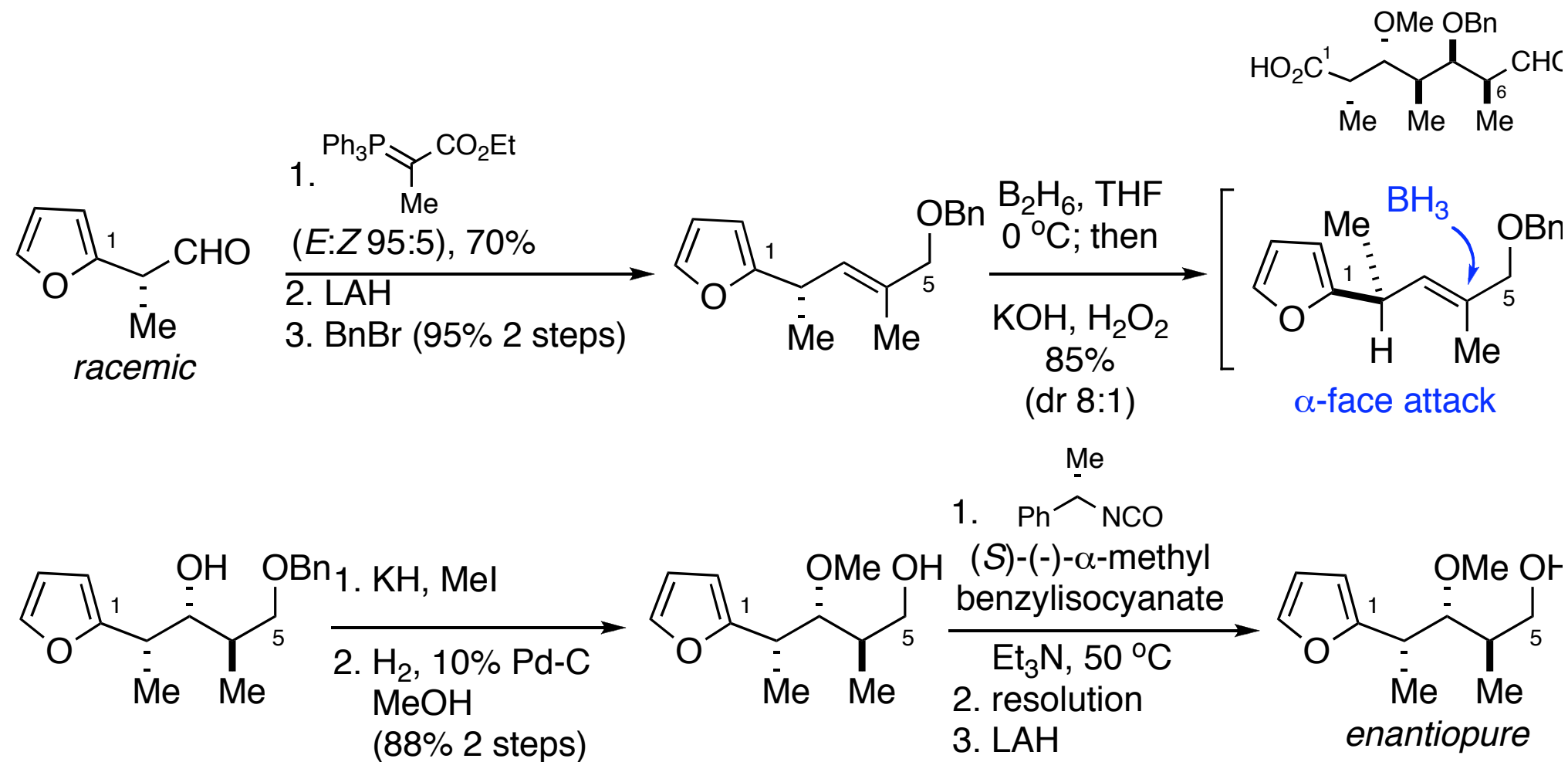
(+)-Monensin: One Last THF Ring To Go



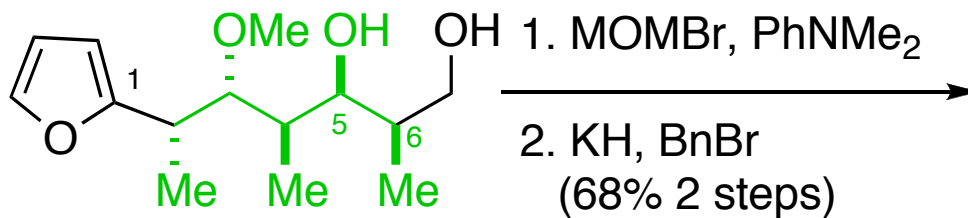
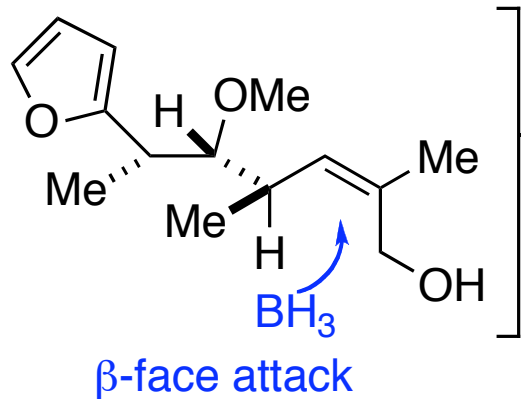
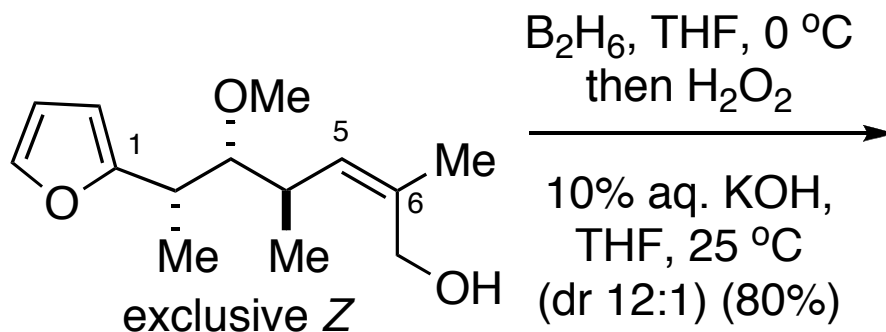
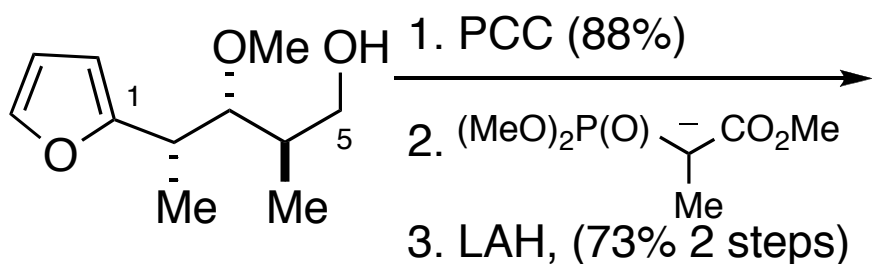
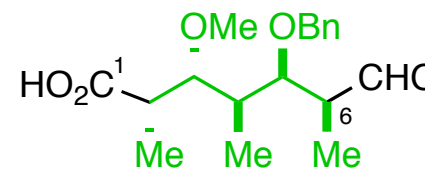
(+)-Monensin: Completing the Right Hand Portion



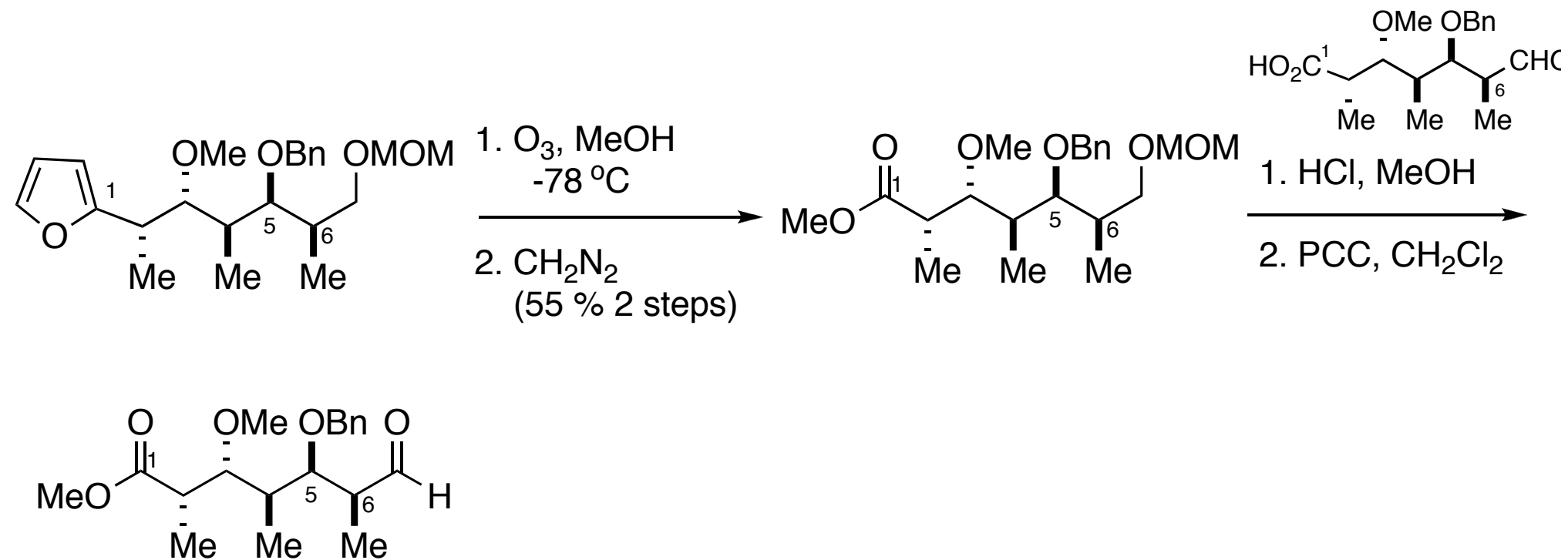
(+)-Monensin: Resolution



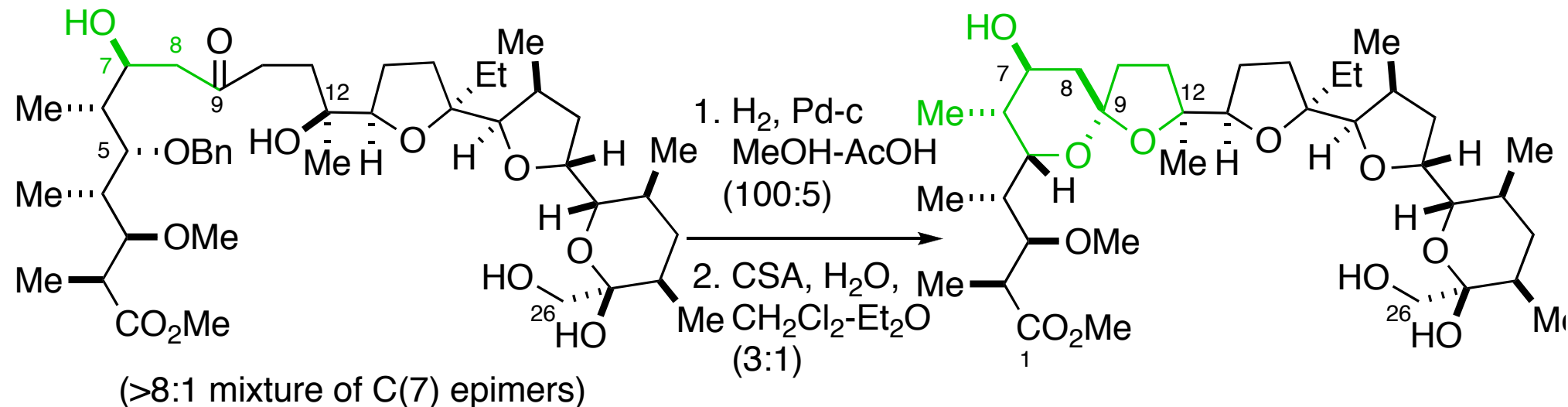
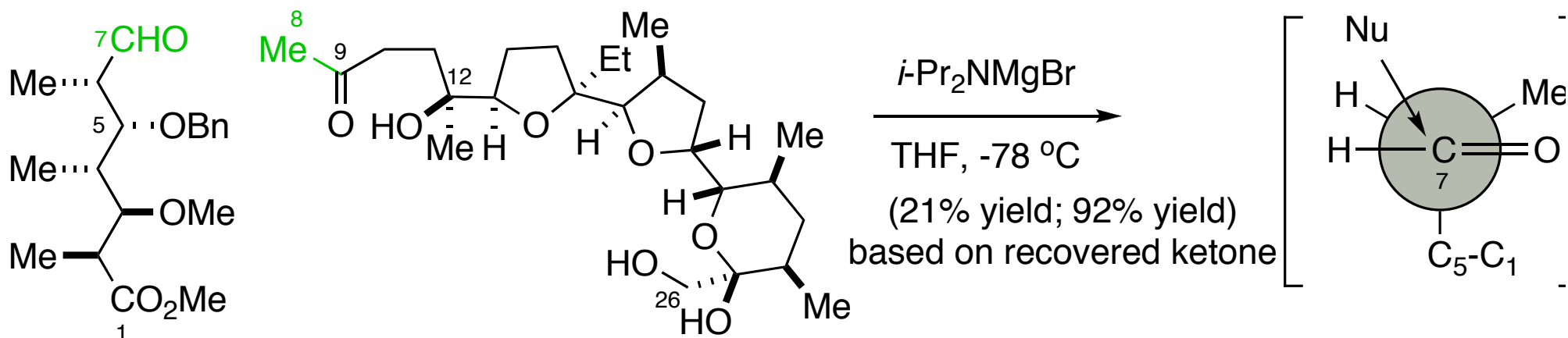
(+)-Monensin: Hydroboration to Set C(5)-C(6) Stereocenters



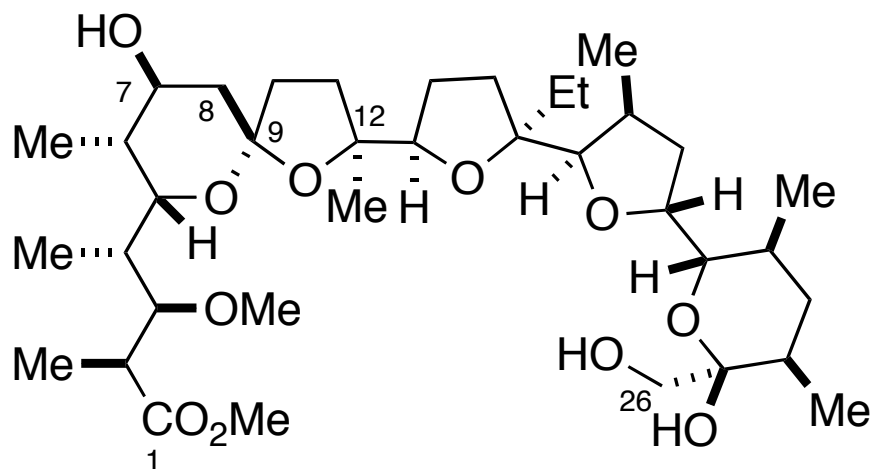
(+)-Monensin: Completing the Left Hand Portion



(+)-Monensin: Building the Spiroketal

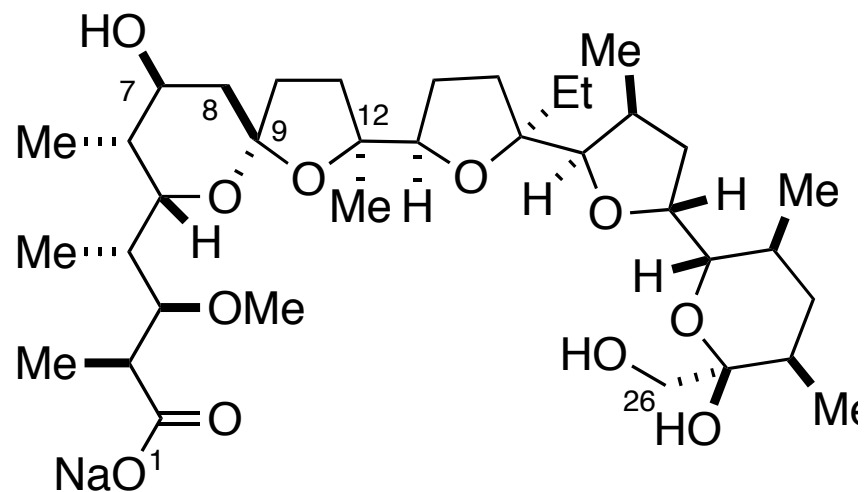


(+)-Monensin: Completing the Synthesis



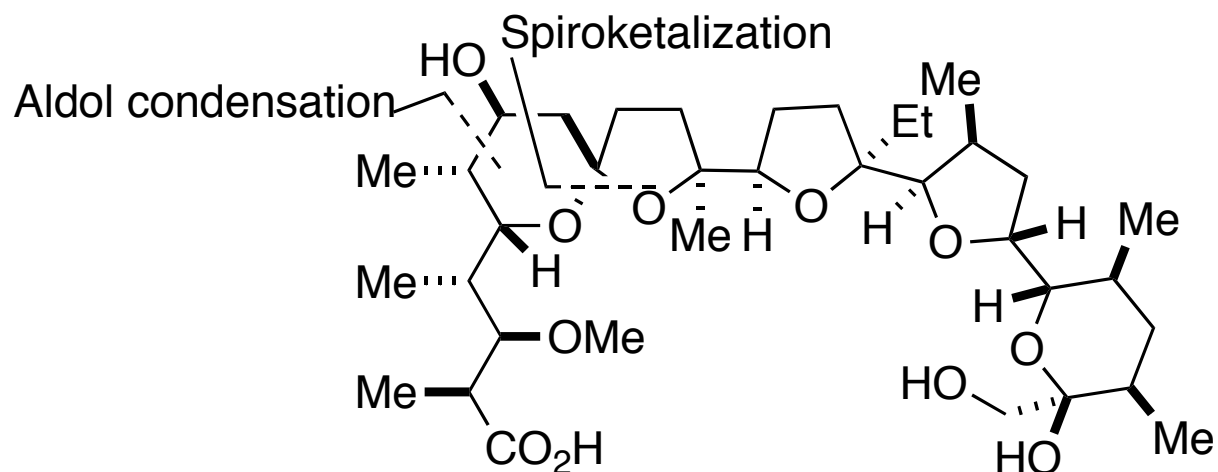
1N NaOH-MeOH (1:5)

60 °C
(quant)



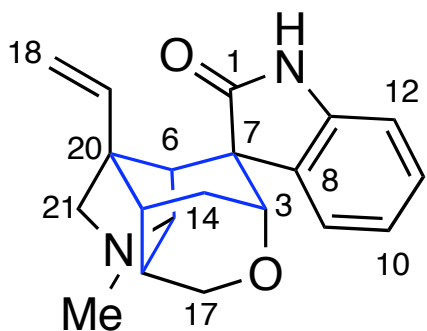
(+)-monensin sodium salt

(+)-Monensin: Conclusion

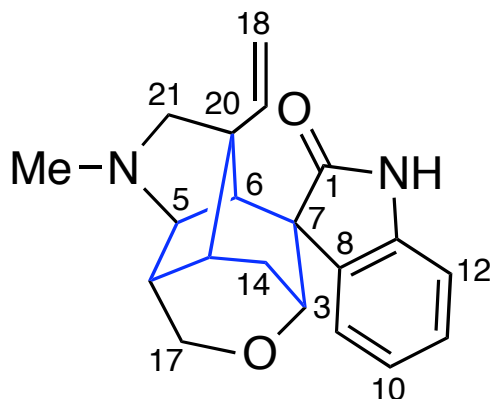


- First Total Synthesis of (+)-Monensin in 1979
- Cross-Aldol to bring together both left and right fragments
- Beautiful illustration of "*stereospecific synthesis by induction or stereochemical communication*" by influence of preexisting stereocenters
- Hydroboration to establish 4 of the 5 stereocenters
- Demonstrated the importance of using allylic 1,3-strain as a controlling element

(+)-Gelsemine: Biological Activity?



(+)-Gelsemine



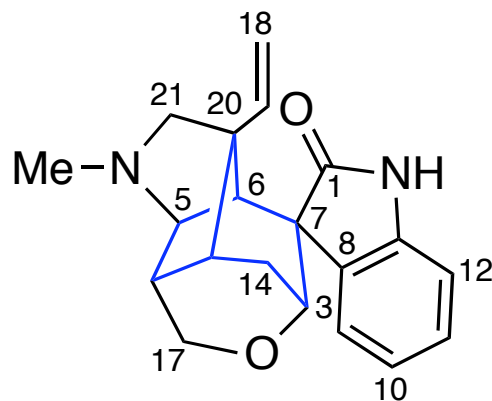
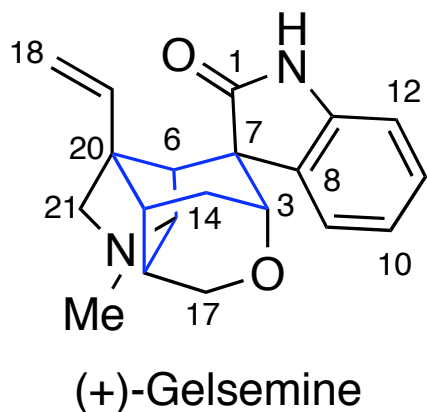
- contains a [3.2.1] octane skeleton
- unique hexacyclic cage structure
- The C(20) and C(7) stereogenic centers are anchoring the spirooxindole the pyrrolidine moiety, and the very hindered tetrahydropyranyl ring on the concave face of the molecule

- isolated from *gelsemium sempervirens*
- it has been known since 1870
- Biological activity?

" The degree of attention which has been lavished by many laboratories on the total synthesis of gelsemine surely did not arise from any documented information suggesting that this alkaloid might have valuable properties. Actually, reports concerning any biological activity associated with gelsemine are at best sketchy and often anecdotal in style. Rather, the attraction to gelsemine as a target in total synthesis has been driven by its fascinating three-dimensional architecture."

-Danishefsky

(+)-Gelsemine: Key Challenges in the Synthesis

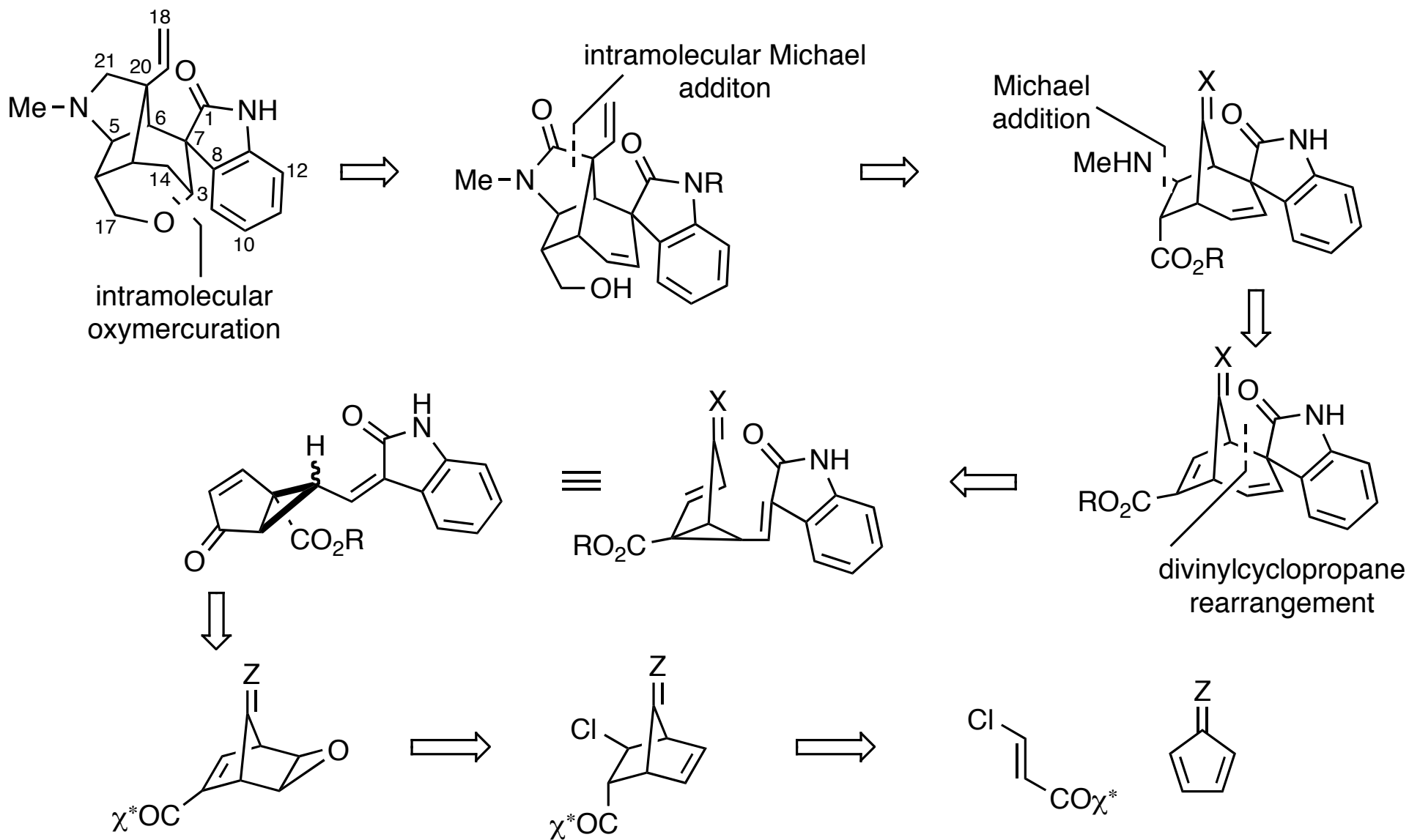


- contains a [3.2.1] octane skeleton
- unique hexacyclic cage structure
- The C(20) and C(7) stereogenic centers are anchoring the spirooxindole the pyrrolidine moiety, and the very hindered tetrahydropyranyl ring on the concave face of the molecule

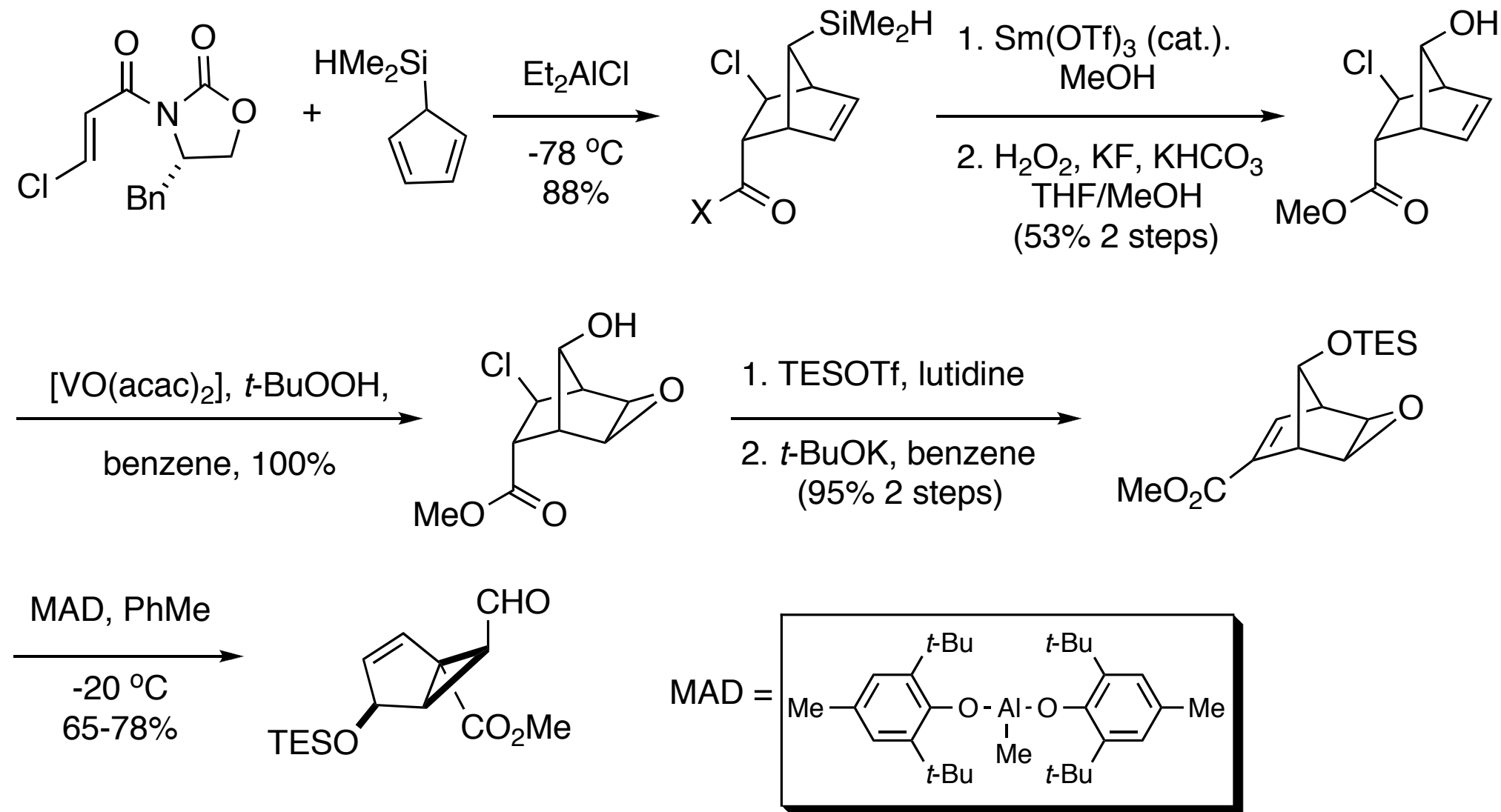
Challenges:

- Controlling the stereochemistry of the spiroindolinone system
- Formation of the C(5) and C(6) bond

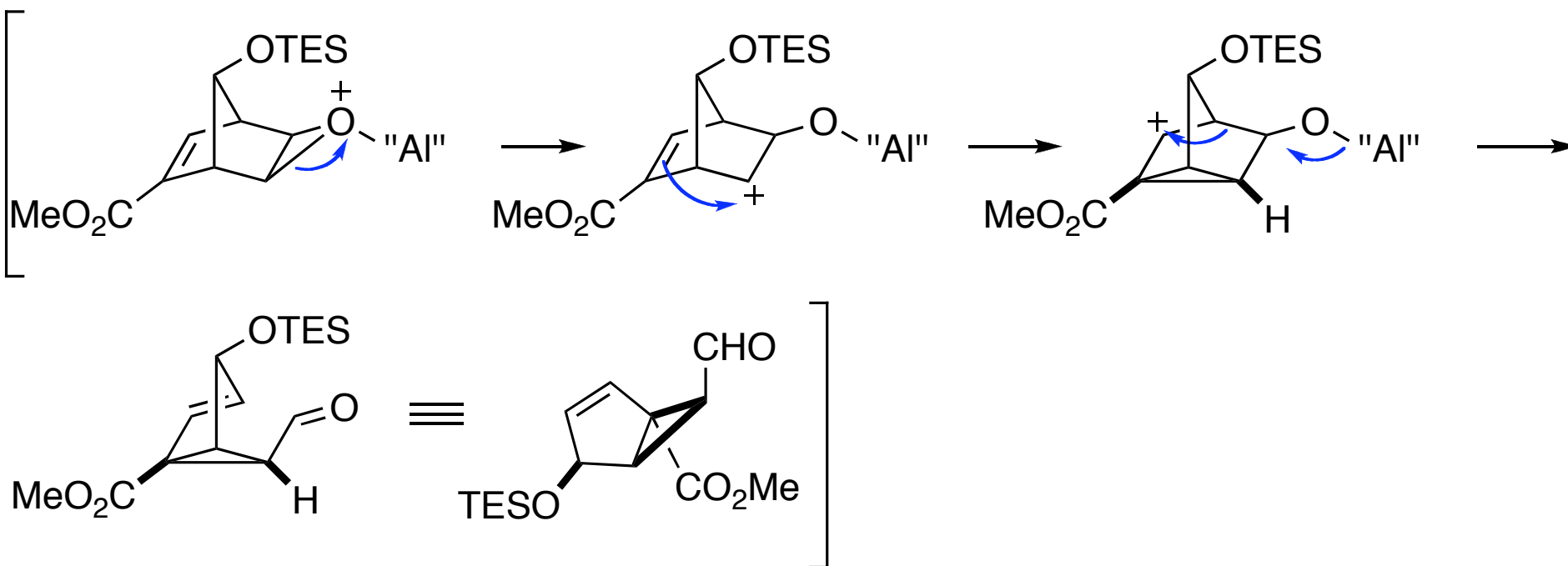
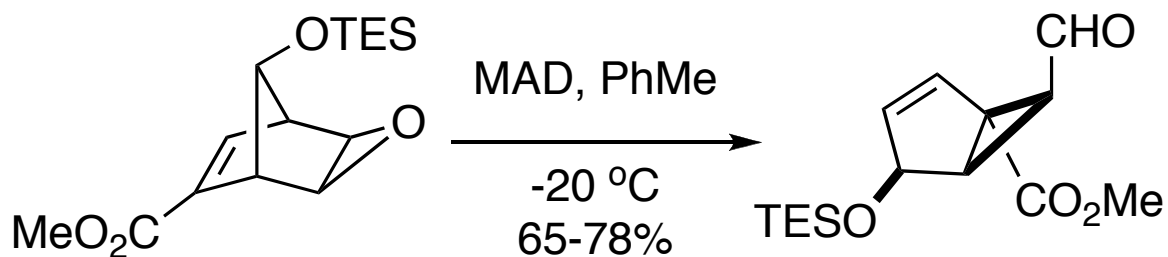
(+)-Gelsemine: Retrosynthesis



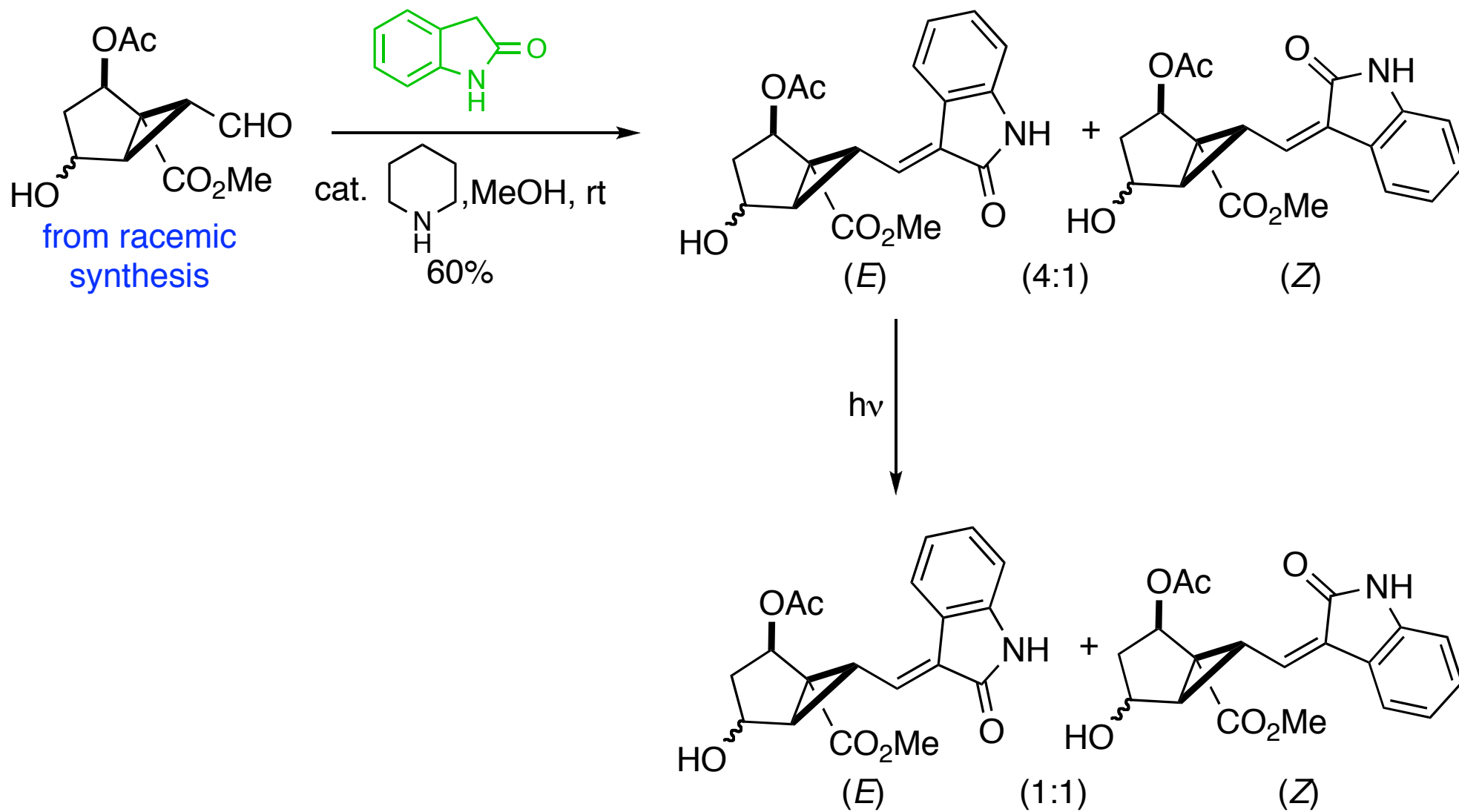
(+)-Gelsemine: Rearrangement of *exo* Epoxide to Cyclopropane



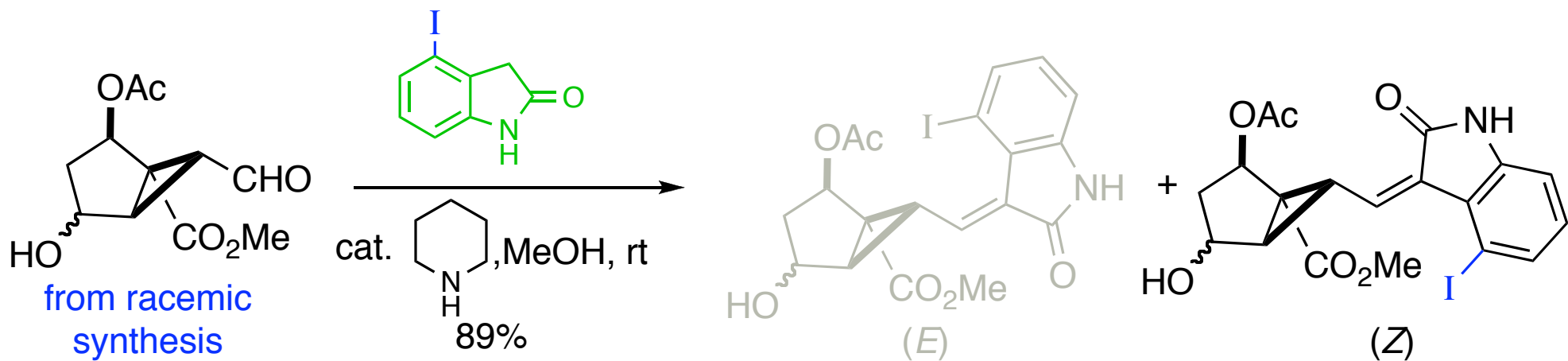
(+)-Gelsemine: Rearrangement of *exo* Epoxide to Cyclopropane



(+)-Gelsemine: Installing the Oxindole

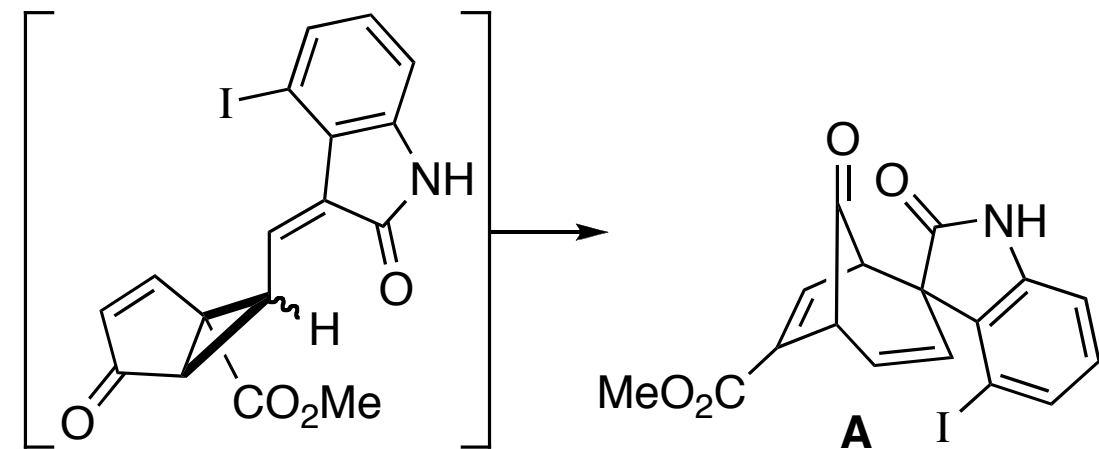
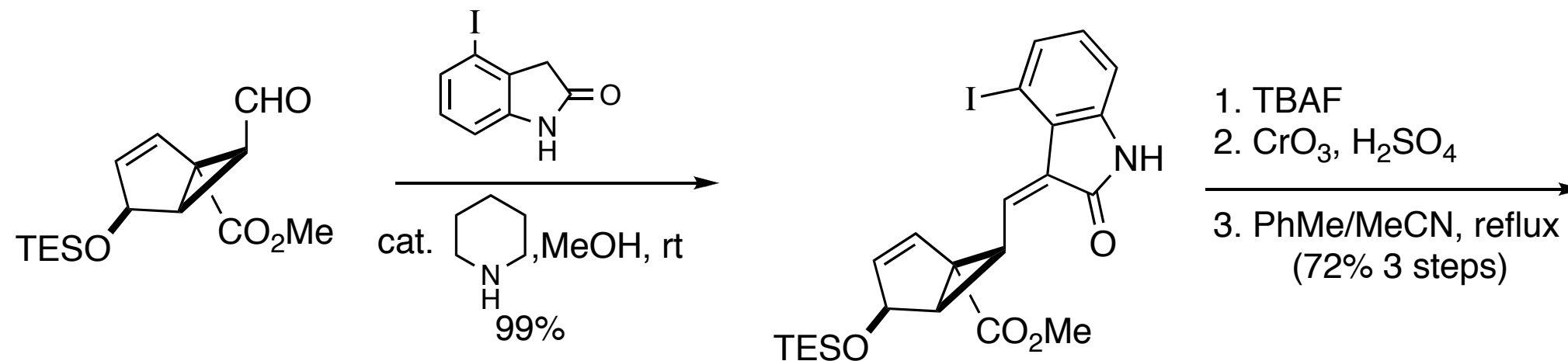


(+)-Gelsemine: 4-Iodoindole Saves the Day

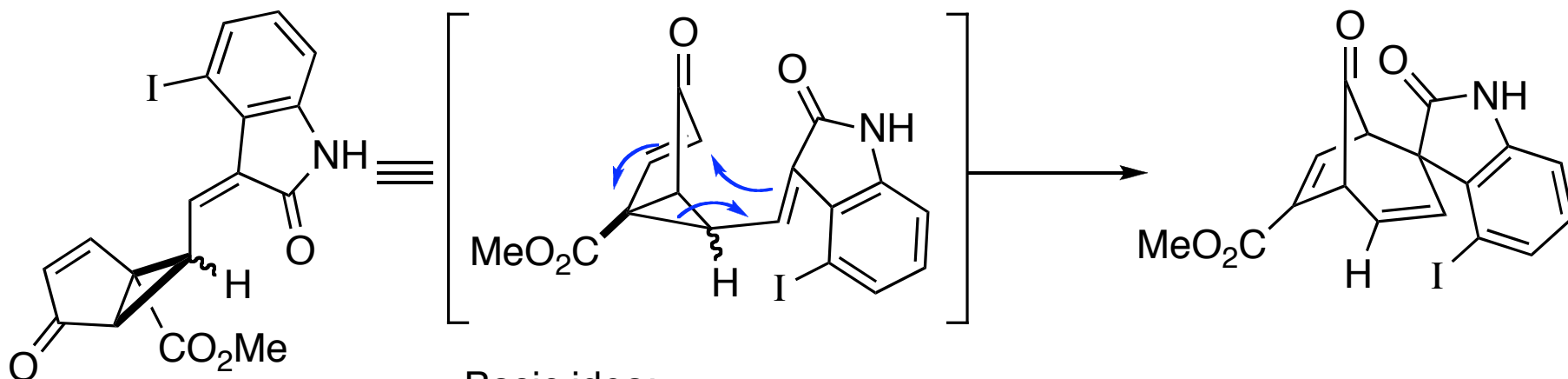


PM3 calculations suggest that the Z-isomer is more stable by 9.4 kcal/mol

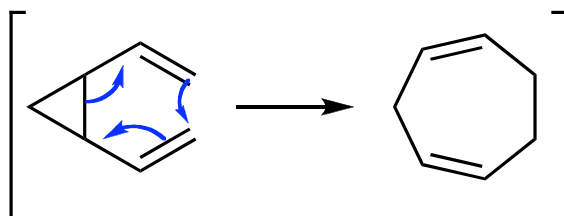
(+)-Gelsemine: Divinylcyclopropane Rearrangement



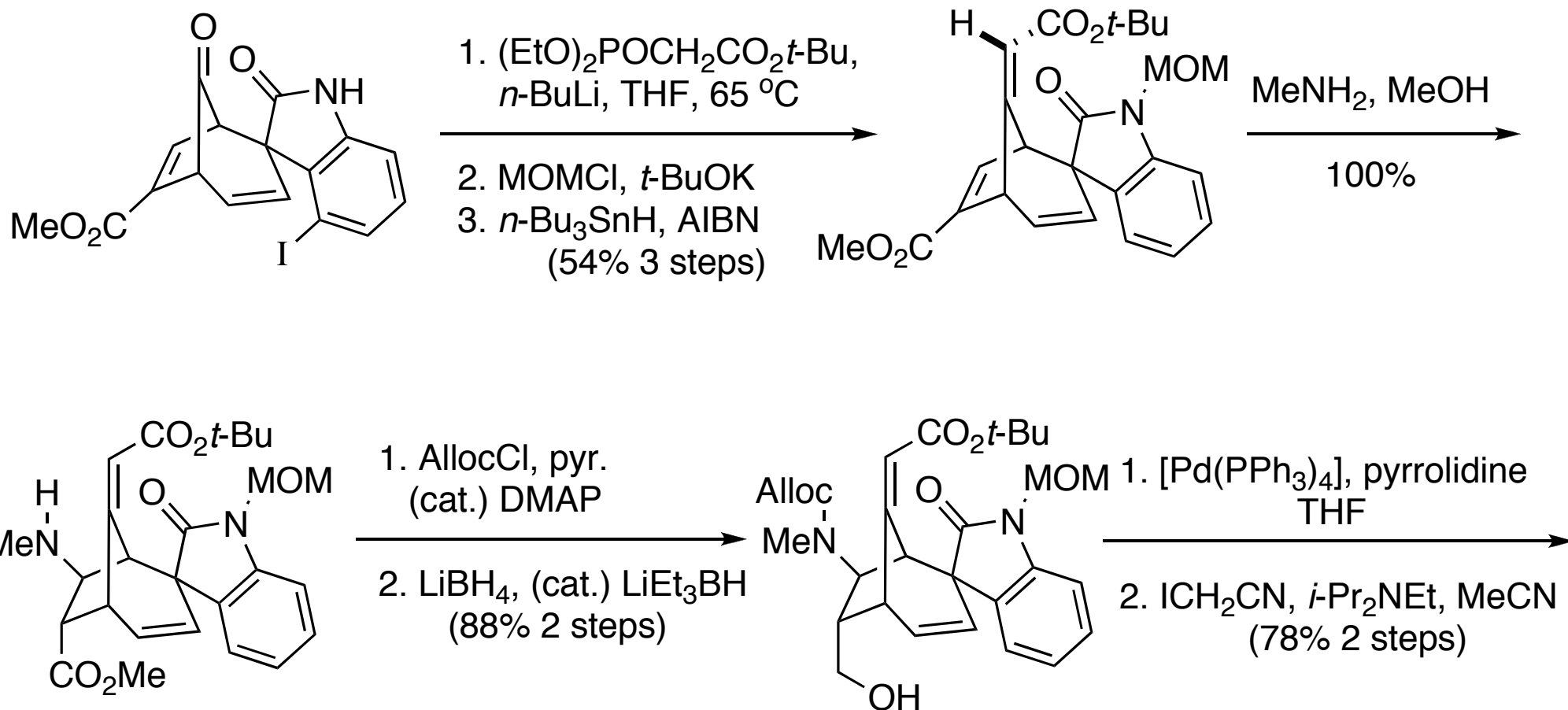
(+)-Gelsemine: How It Works.



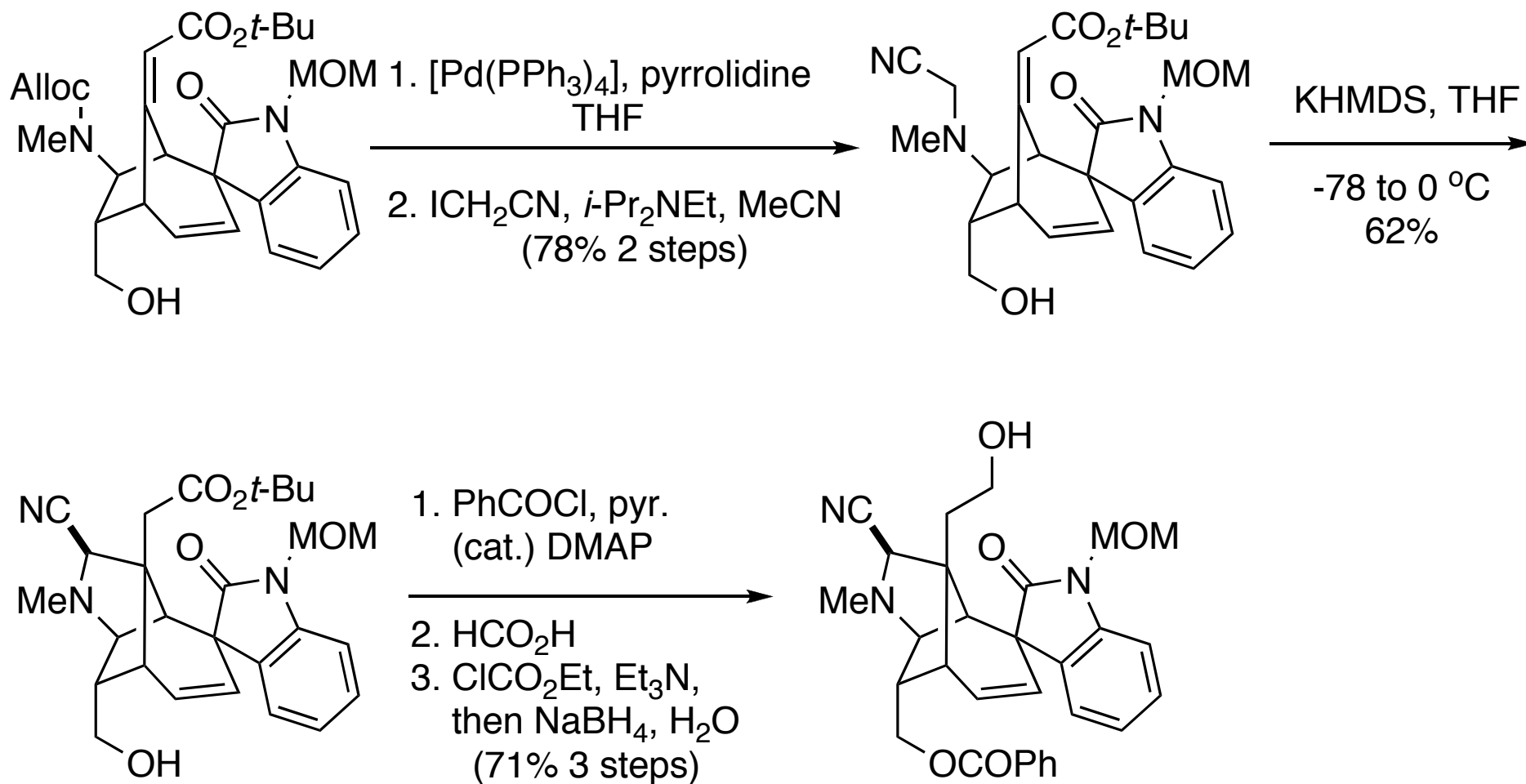
Basic idea:



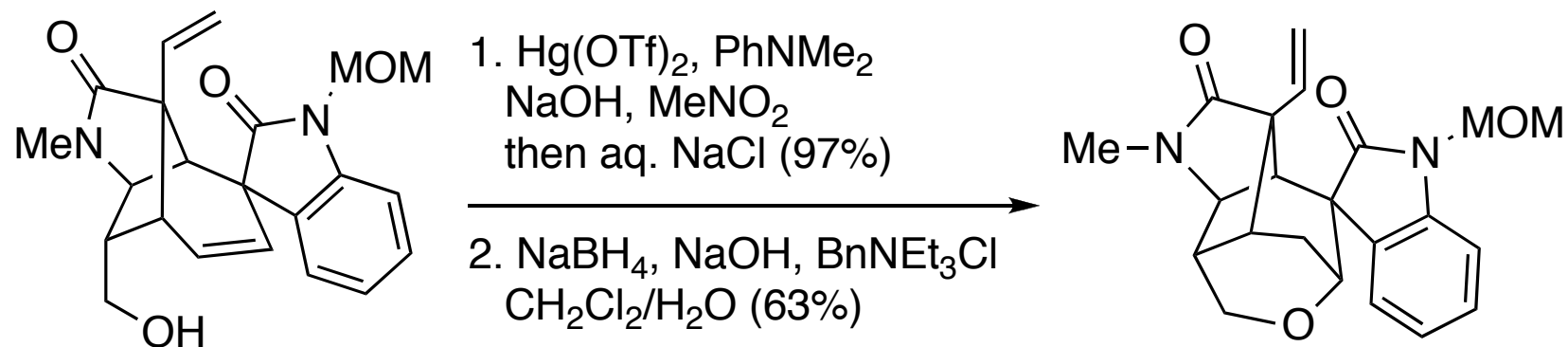
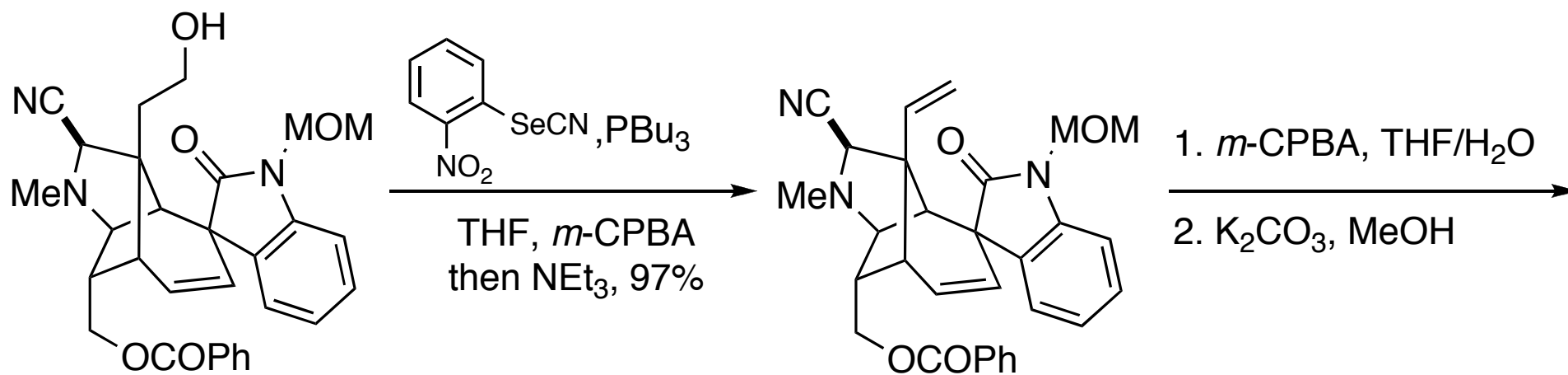
Two Michael Additions: Building the Pyrrolidine Ring



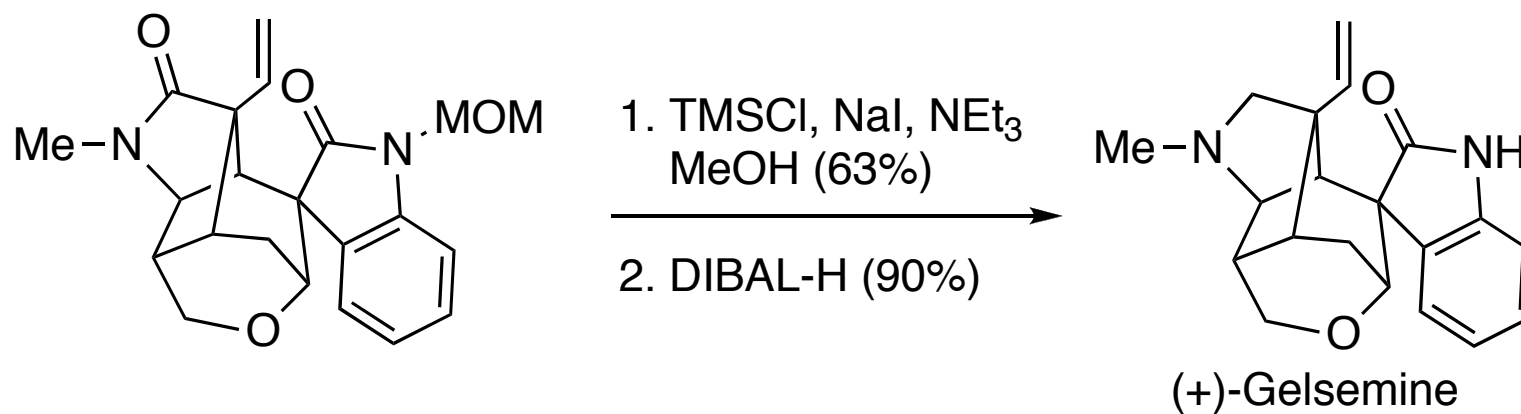
(+)-Gelsemine: Reduction and Protection



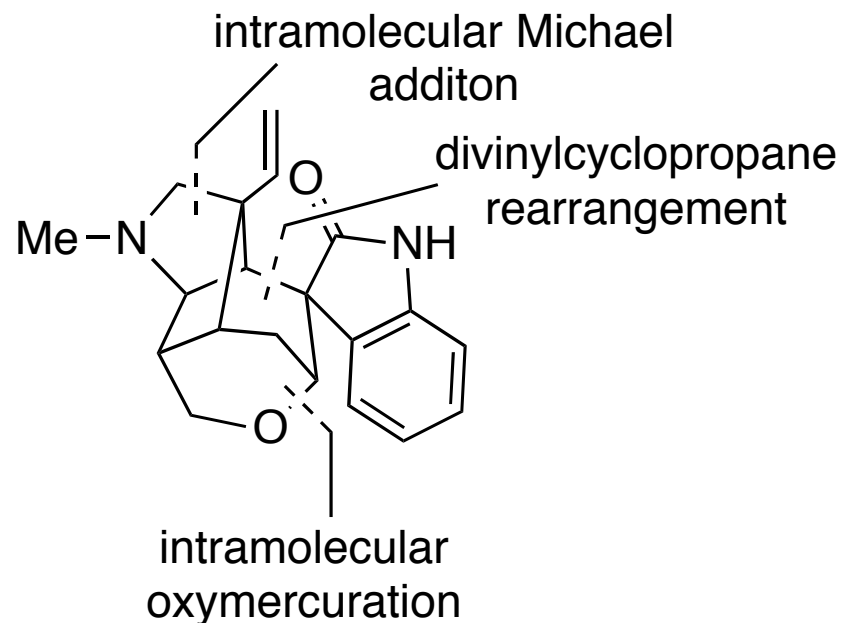
(+)-Gelsemine: Oxidation of Cyanopyrrolidine and Oxymercuration



(+)-Gelsemine: Completing the Synthesis

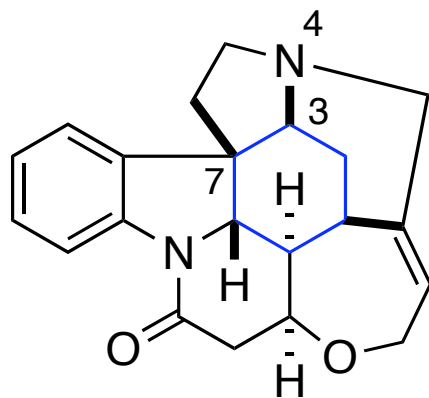


(+)-Gelsemine: Conclusion



- 21 Steps, enantioselective synthesis
- Recognized that the spiro-indoline was the most challenging and was able to control the stereochemistry by simple condensation of 4-iodooxindole
- The bicyclic [3.2.1] core was assembled through a divinylcyclopropane rearrangement

(-)-Strychnine: Structure and Properties



(-)-Strychnine

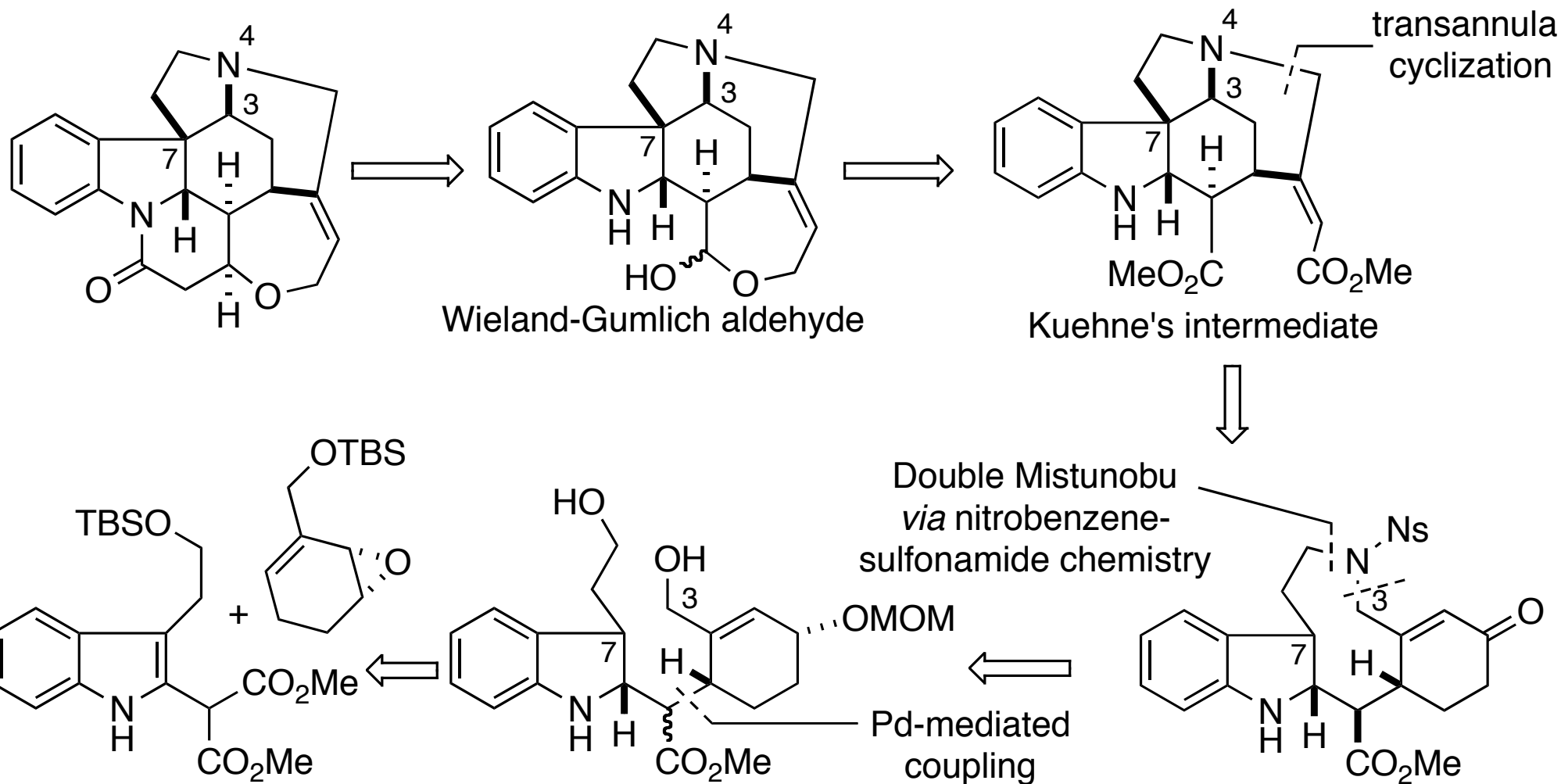
Biological Properties:

- LD₅₀ 10 mg, used as a pesticide for killing small vertebrates
- Causes muscular convulsions and eventually death through asphyxia
- Most bitter substances known. Its taste is detectable in concentrations as low as 1 ppm.

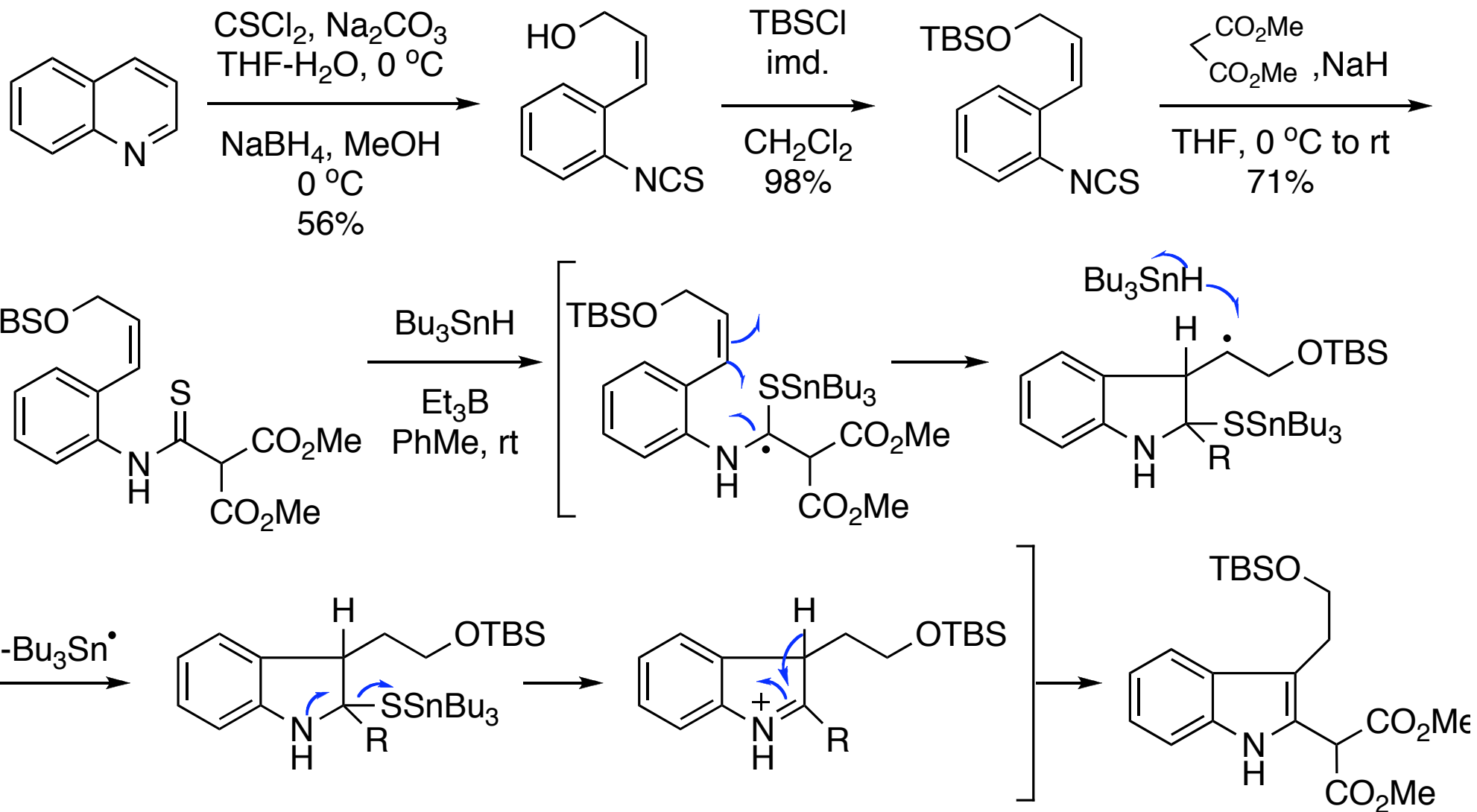
Structure:

- Most celebrated member of the *Strychnos* alkaloids
- Isolated from the seeds of the *Strychnos nux vomica* tree
- Possess a complex polycyclic structure, assembled from 24 atoms
- Unique heptacyclic framework as well as 6 contiguous chiral centers with 5 of them in one unsaturated 6-membered ring

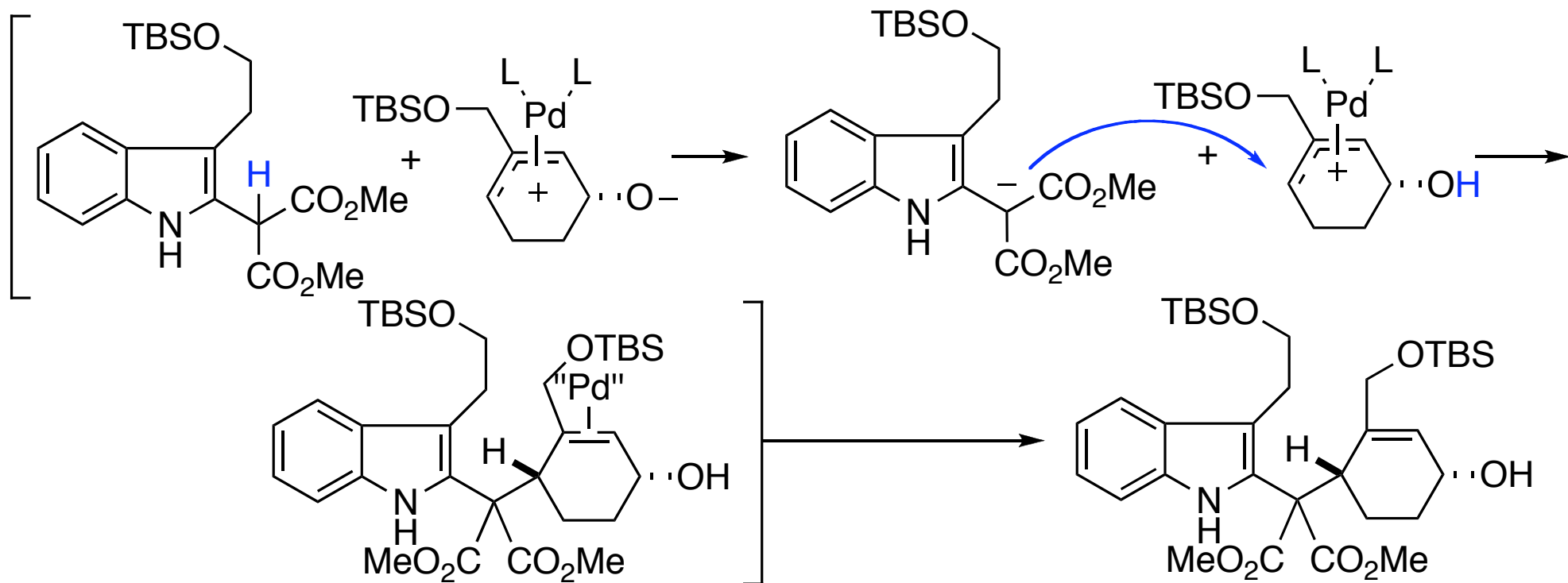
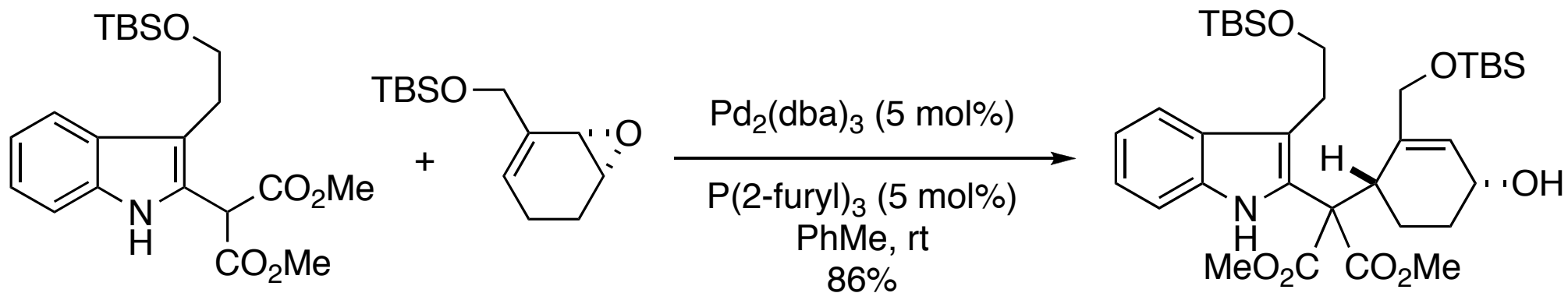
(-)-Strychnine: Key Step Using Nitrobenzenesulfonamide Chemistry



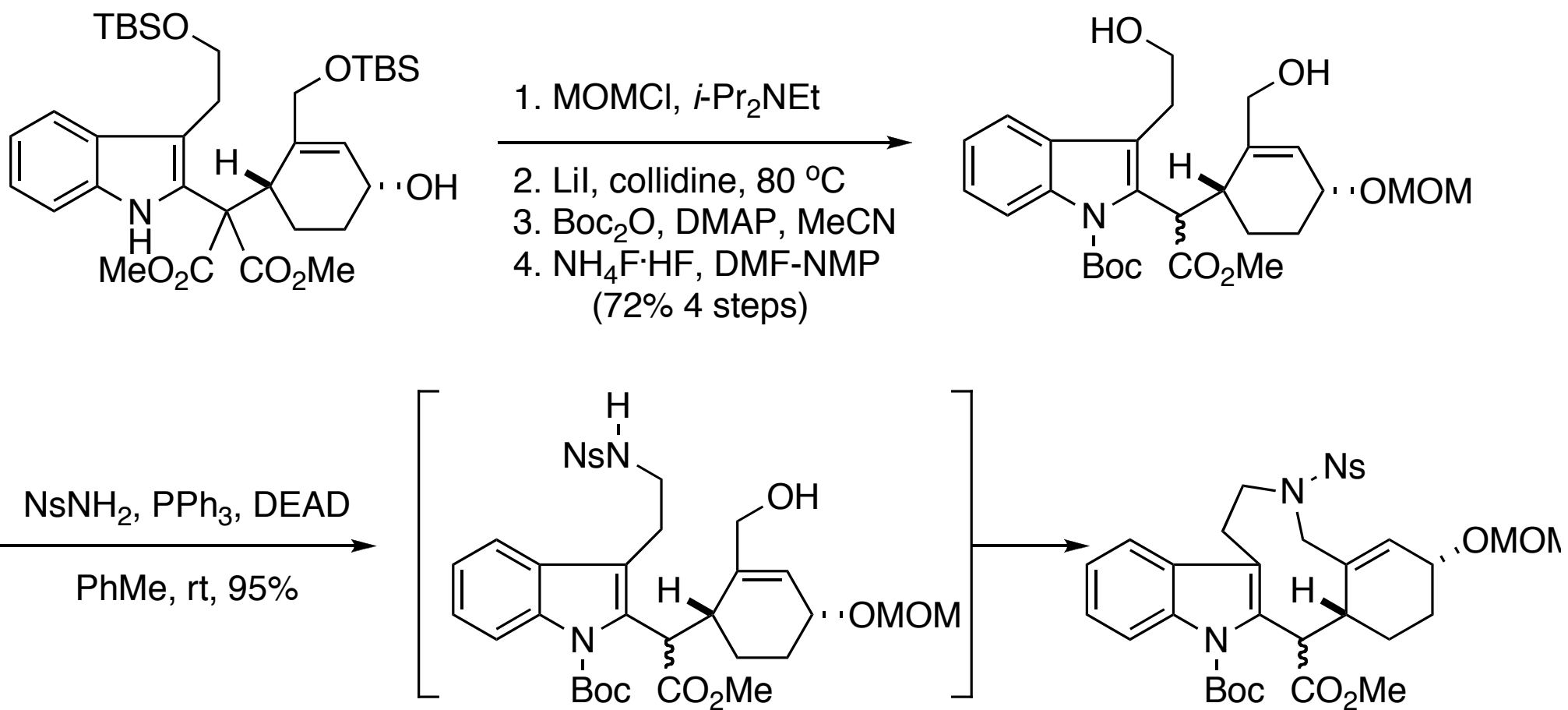
(-)-Strychnine: Radical Cyclization of 2-Alkenylthioanilides



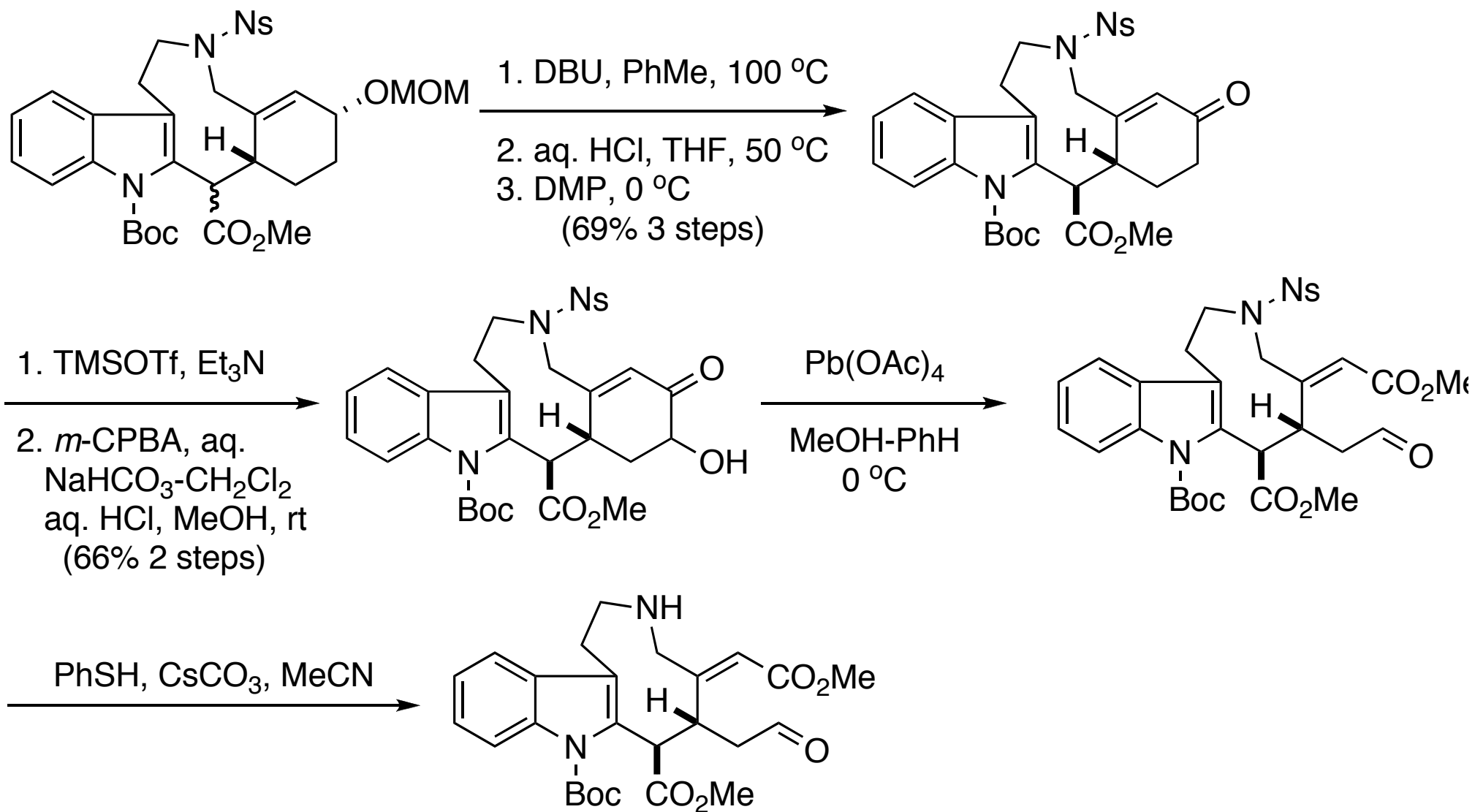
(-)-Strychnine: Palladium-Mediated Coupling



(-)-Strychnine: Building the 9-Membered Ring



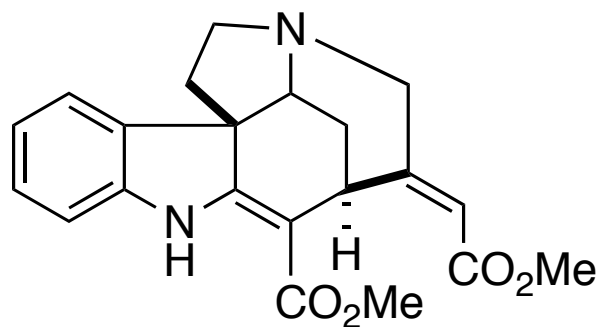
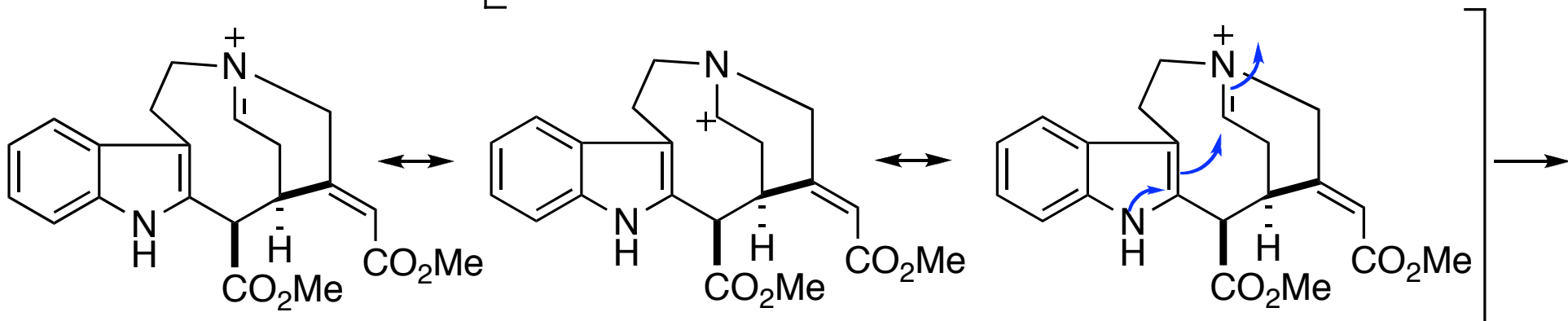
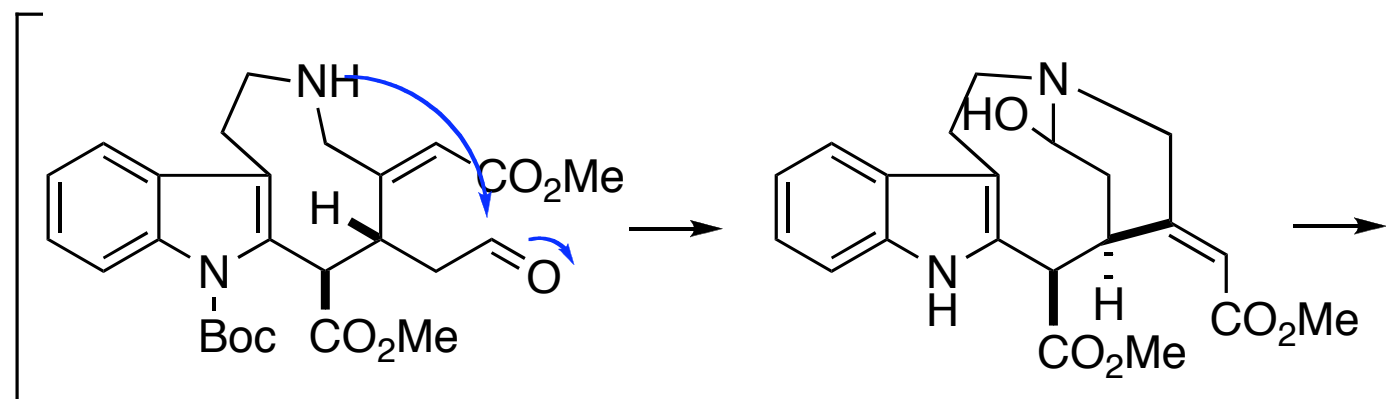
(-)-Strychnine: Setting the Stage for Cross-Transannulation



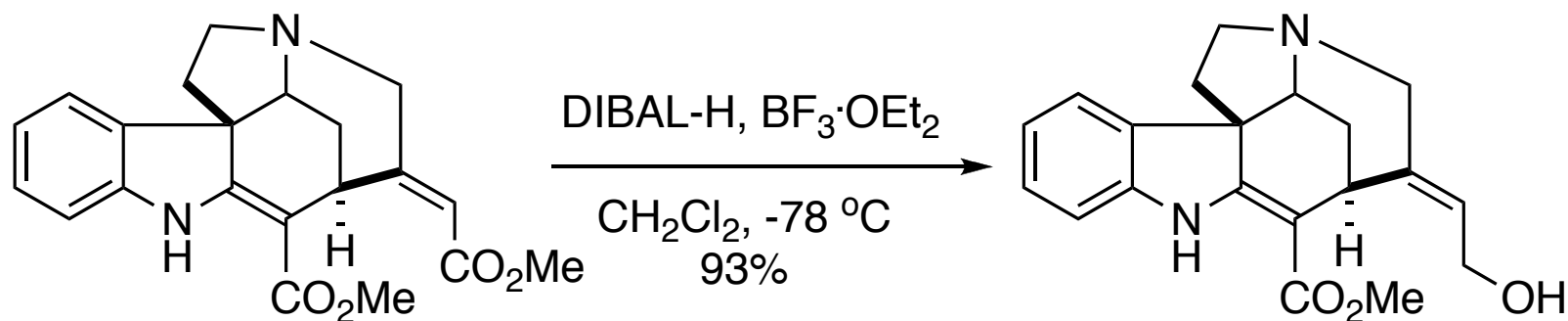
(-)-Strychnine: Transannulation-How Does it Work?

PhSH, CsCO₃, MeCN

then TFA, Me₂S, CH₂Cl₂
50 °C (84% 2 steps)

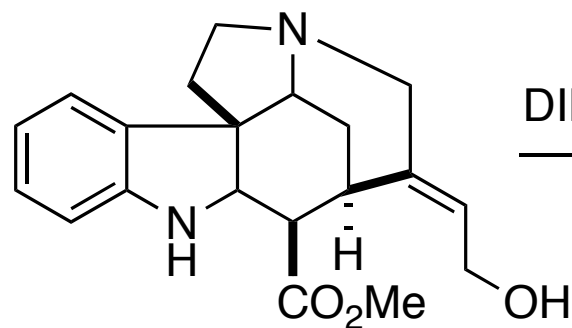


(-)-Strychnine: Completing the Synthesis



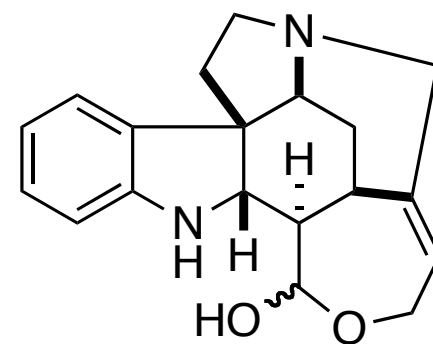
1. NaBH_3CN , AcOH , 10°C

2. NaOMe , MeOH-THF , rt



DIBAL-H , -98°C

CH_2Cl_2

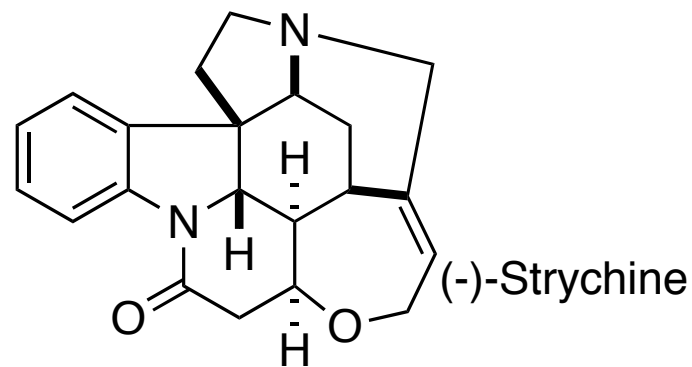


Wieland-Gumlich
aldehyde

$\text{CH}_2(\text{CO}_2\text{H})_2$, NaOAc

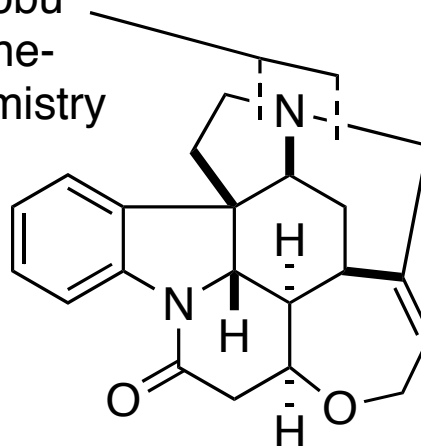
Ac_2O , AcOH , 110°C

(42 %, 4 steps)



(-)-Strychnine: Conclusion

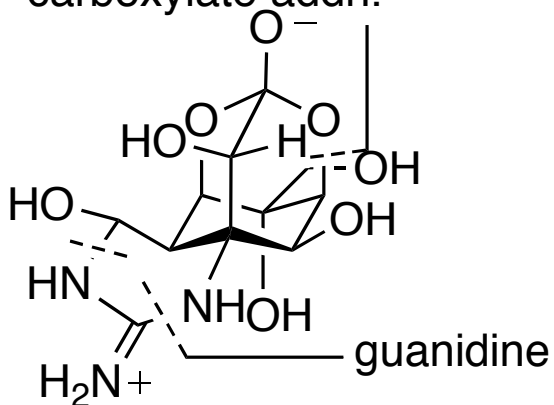
Double Mitsunobu
via nitrobenzene-
sulfonamide chemistry



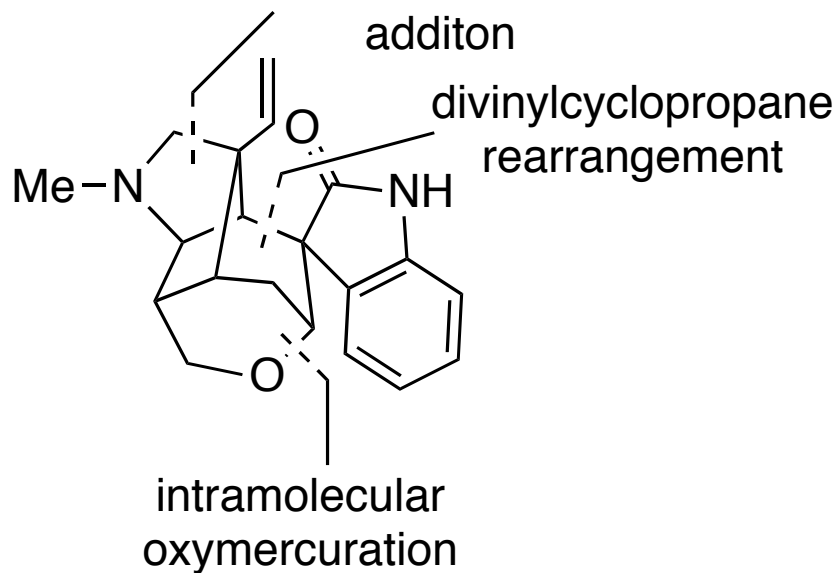
- Utilized their own chemistry nitrobenzenesulfonamide Mitsunobu reaction
- radical cyclizations of 2-alkenylthioanilides
- Double Mitsunobu nice way to build the 9-membered ring
- Cross-Transannulation beautiful cascade to pentacyclic core

Conclusion

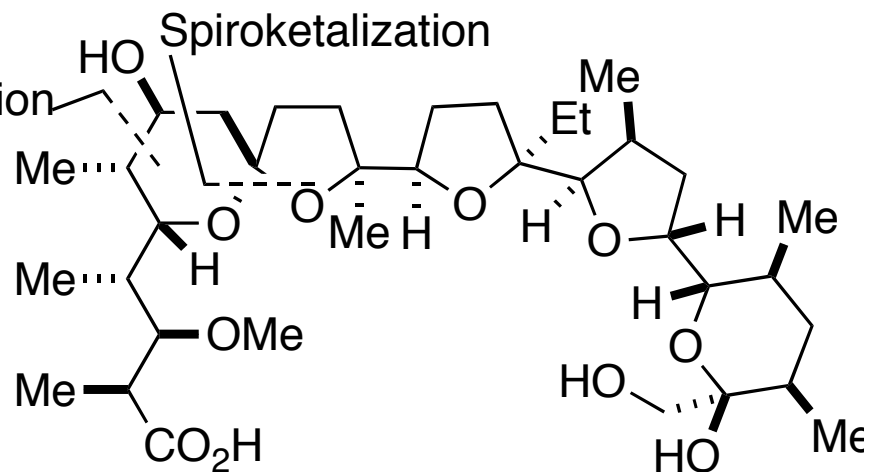
intramolecular
carboxylate addn.



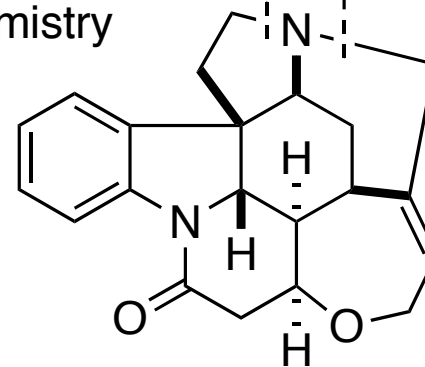
intramolecular Michael
addition



Aldol condensation
Spiroketalization



Double Mistunobu
via nitrobenzene-
sulfonamide chemistry



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