

If *Haplophytine* were our Molecule
of the Month, I'd Cry

Tim Martin
Literature Group Meeting
7/22/2009



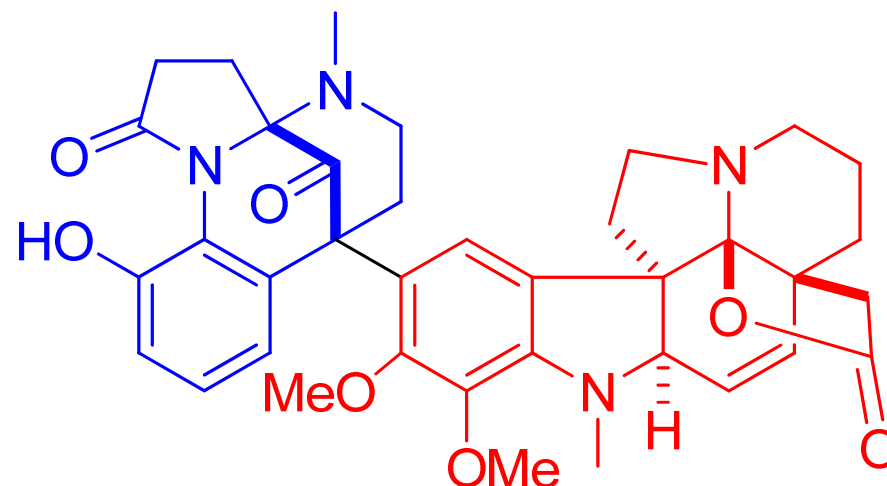
Background

- Indole alkaloid isolated from dried leaves of *Haplophyton cimicidum*
- Isolated in 1952
- “La hierba de la cucaracha”
- Used since the Aztecs were around



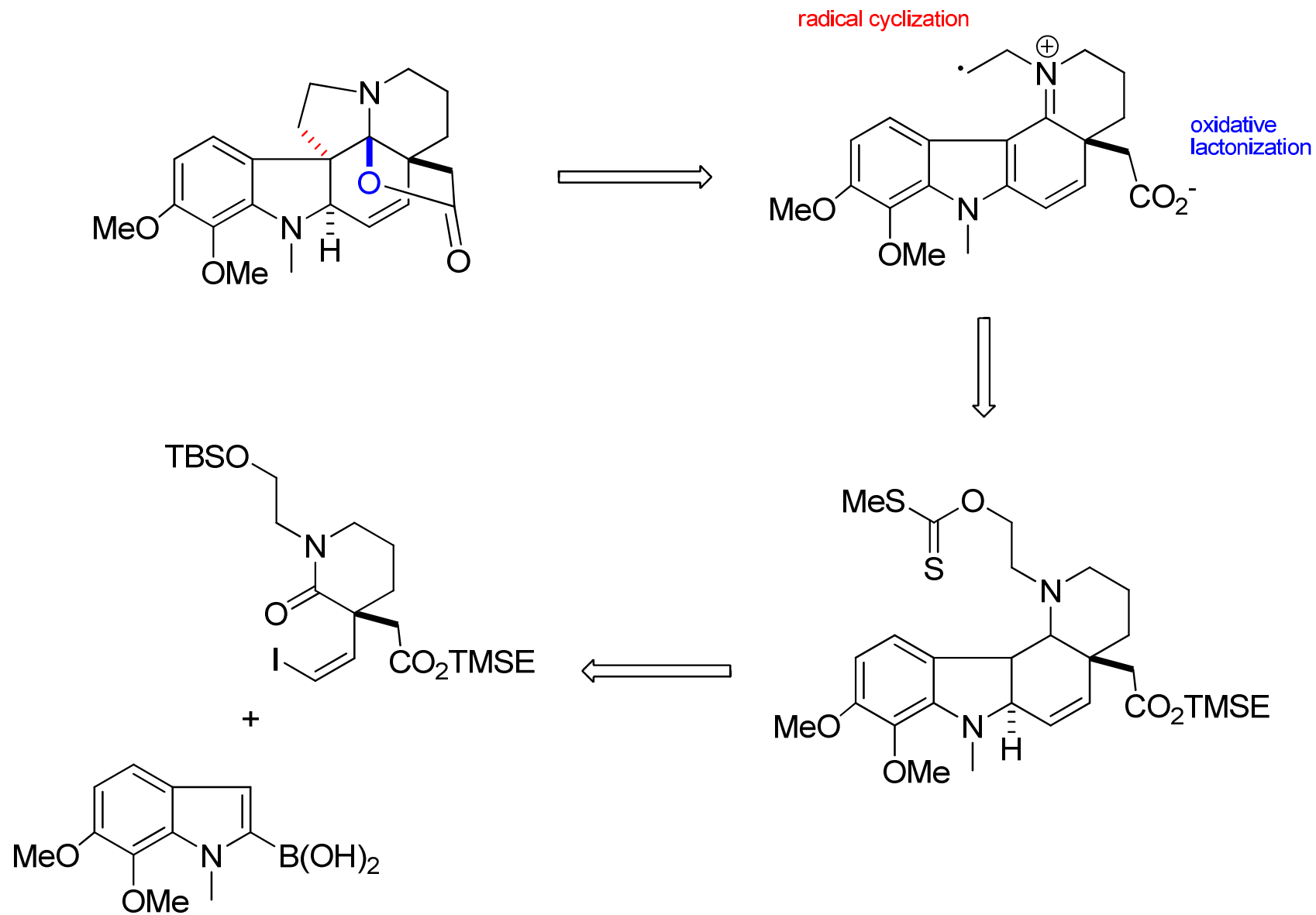
Structure

- $C_{37}H_{40}N_4O_7$
- Molecular Weight: 652.74
- 5 quaternary centers
- 6 stereocenters
- Comprised of two segments
- **Left hand segment:** unique [3.3.1] skeleton with bridged ketone and aminal functionalities
- **Right hand segment:** hexacyclic alkaloid, aspidophytine

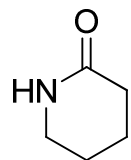


(+)-haplophytine

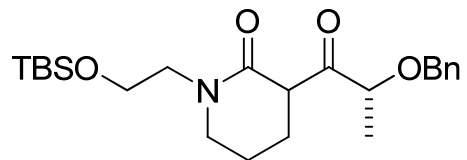
Nicolaou's Aspidophytine Synthesis



Vinyl Iodide Synthesis

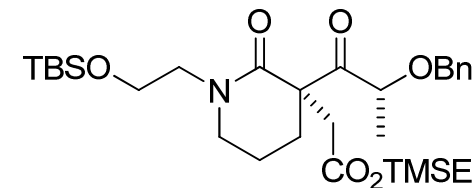


i) NaH, **8**, 68%
ii) LDA, **9**, 89%

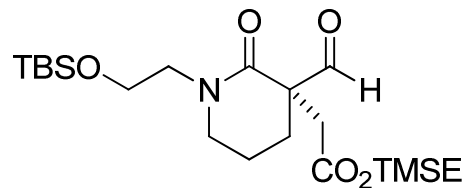


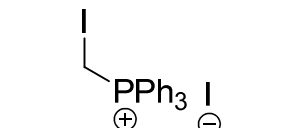
KHMDS, **11**

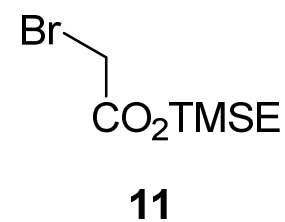
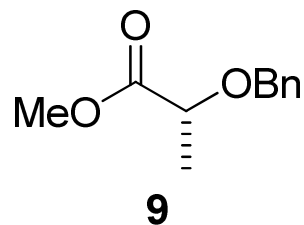
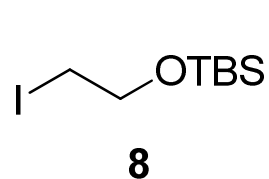
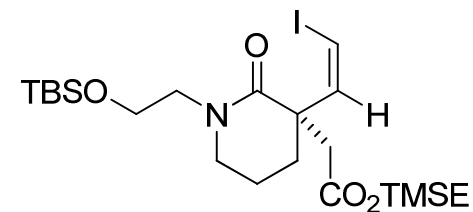
66%



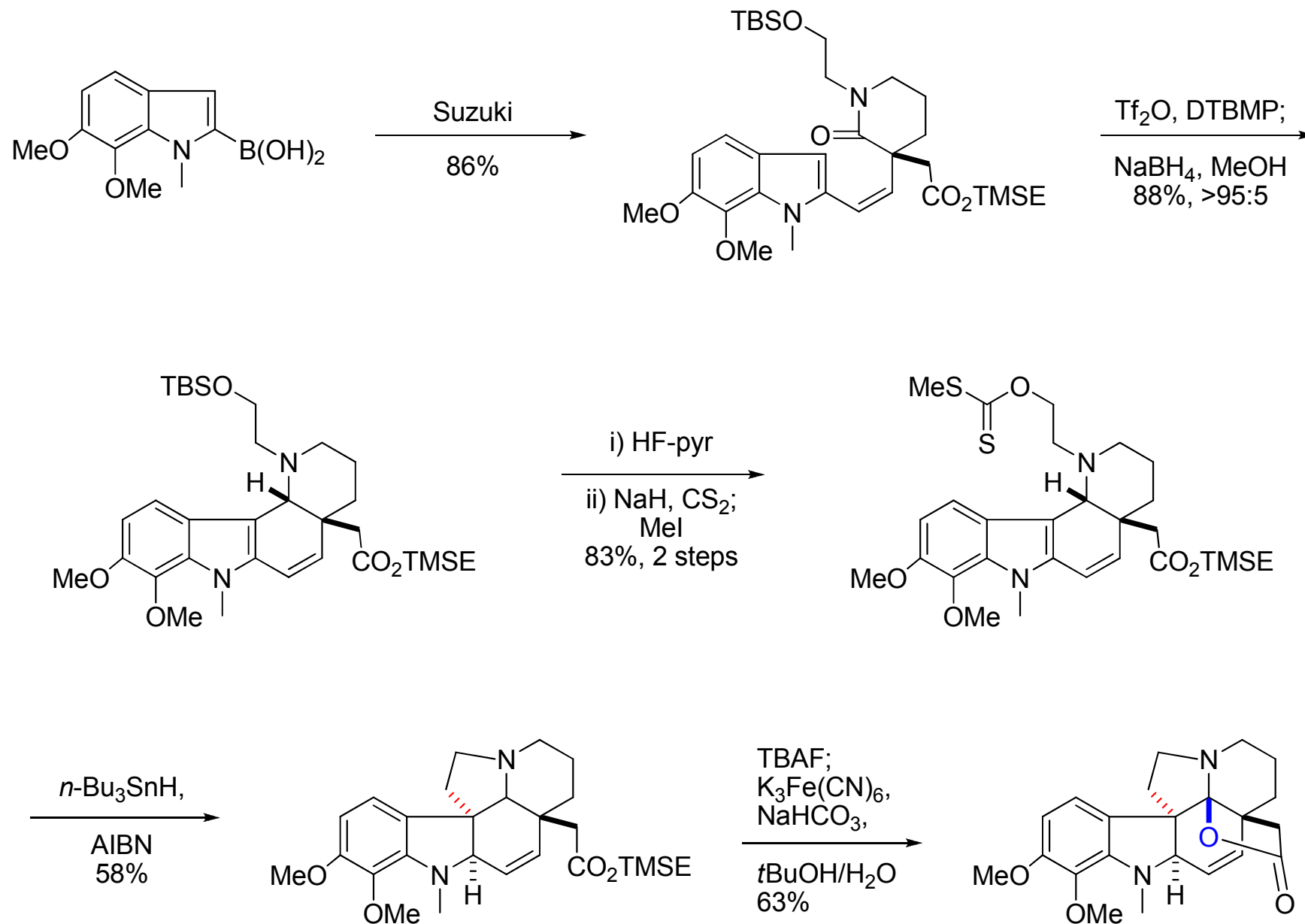
i) H₂, Pd(OH)₂, 82%
ii) NaBH₄, NaIO₄, 79%



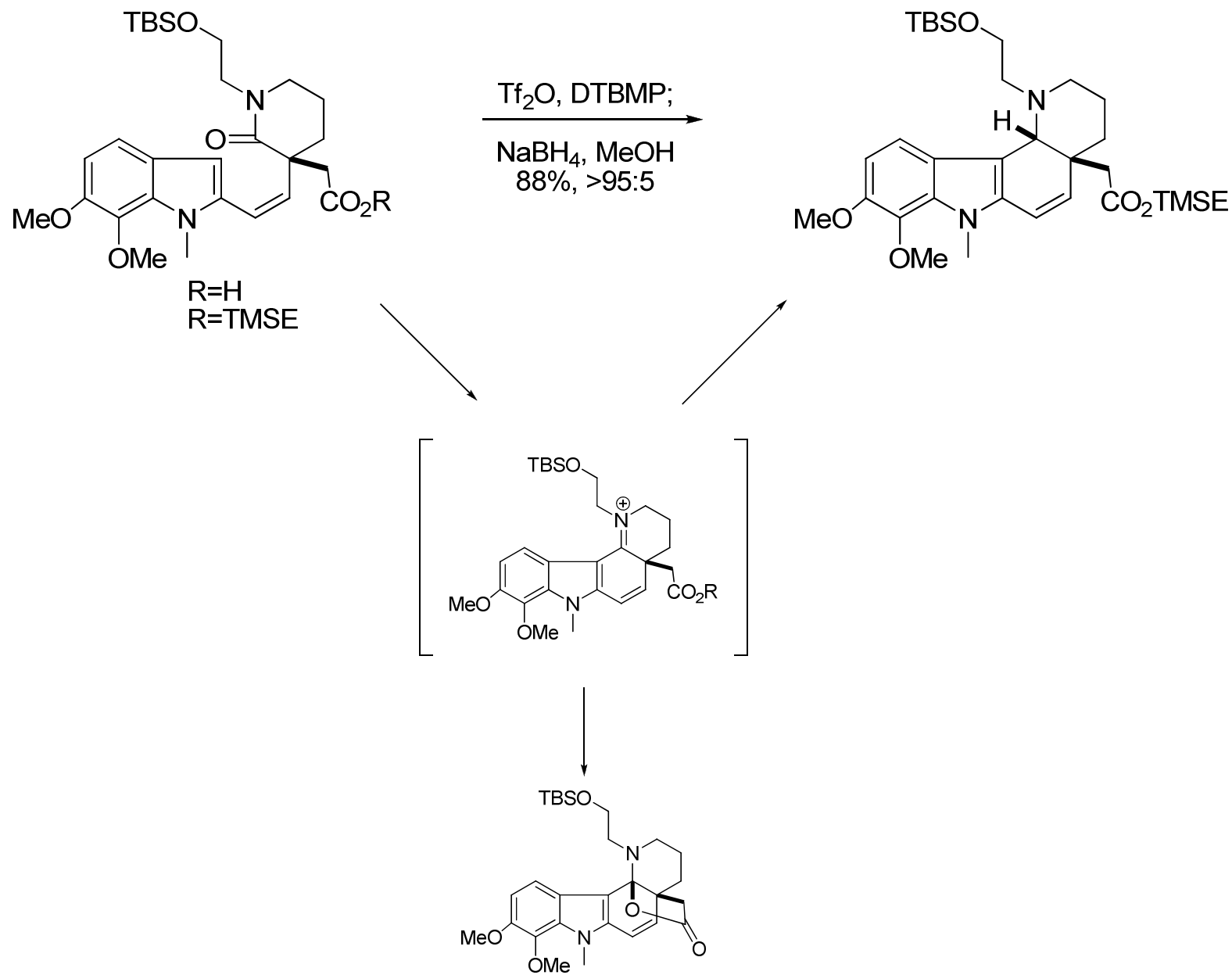

NaHMDS, 88%



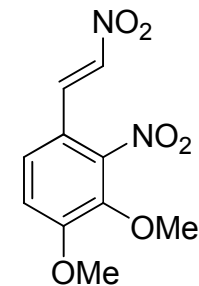
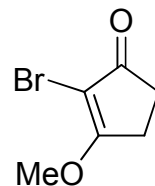
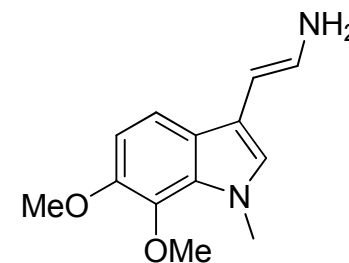
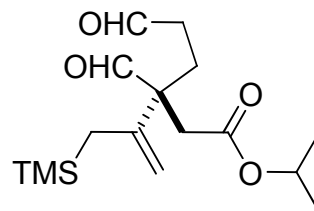
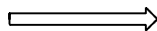
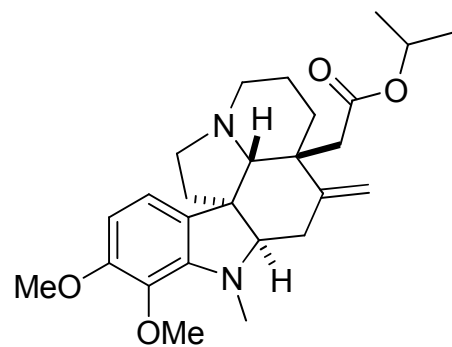
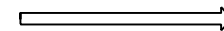
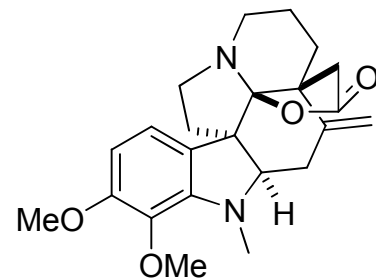
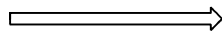
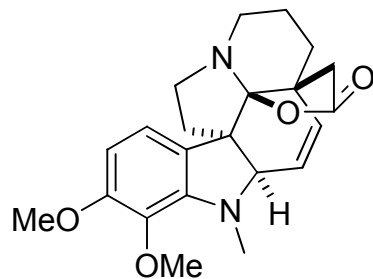
Coupling and Elaboration



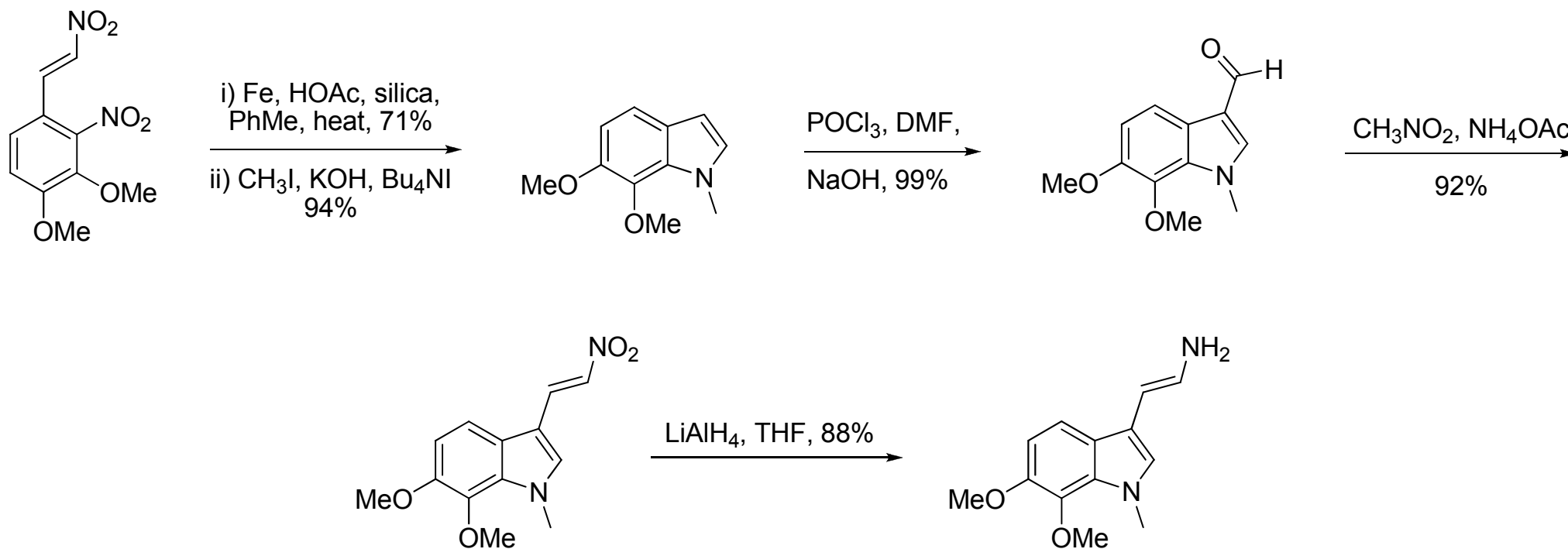
C-ring Formation



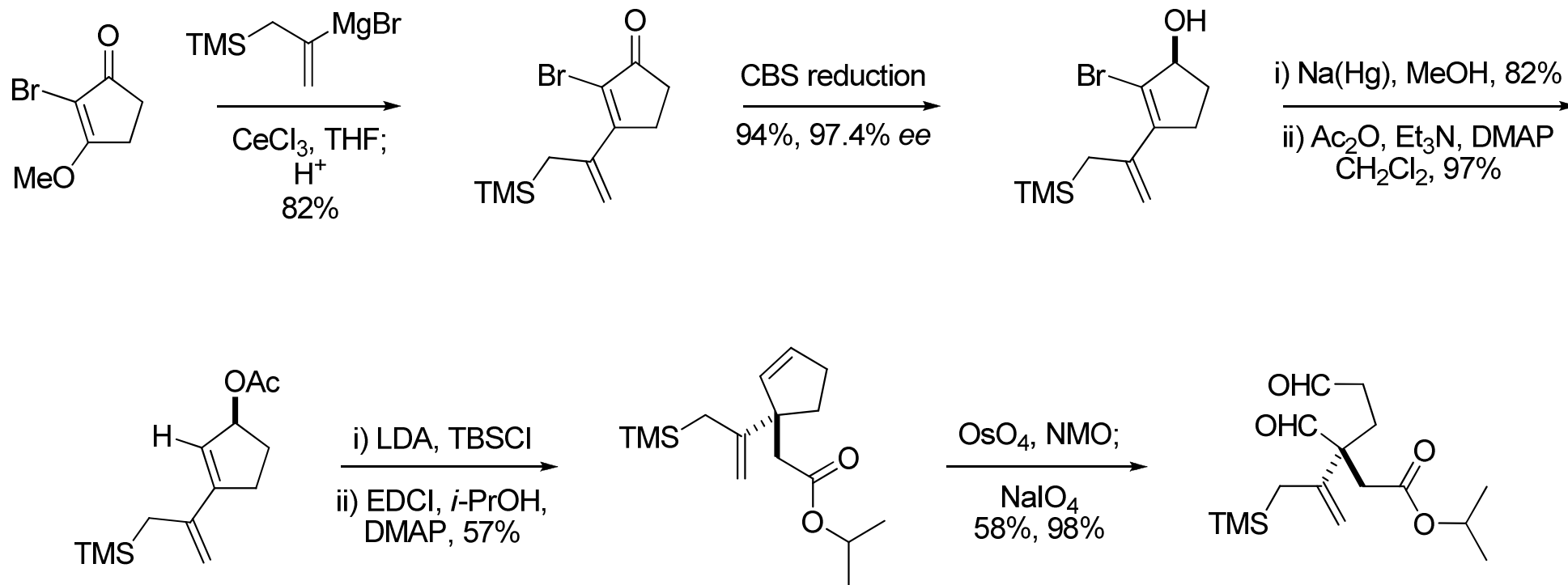
Corey's Aspidophytine Synthesis



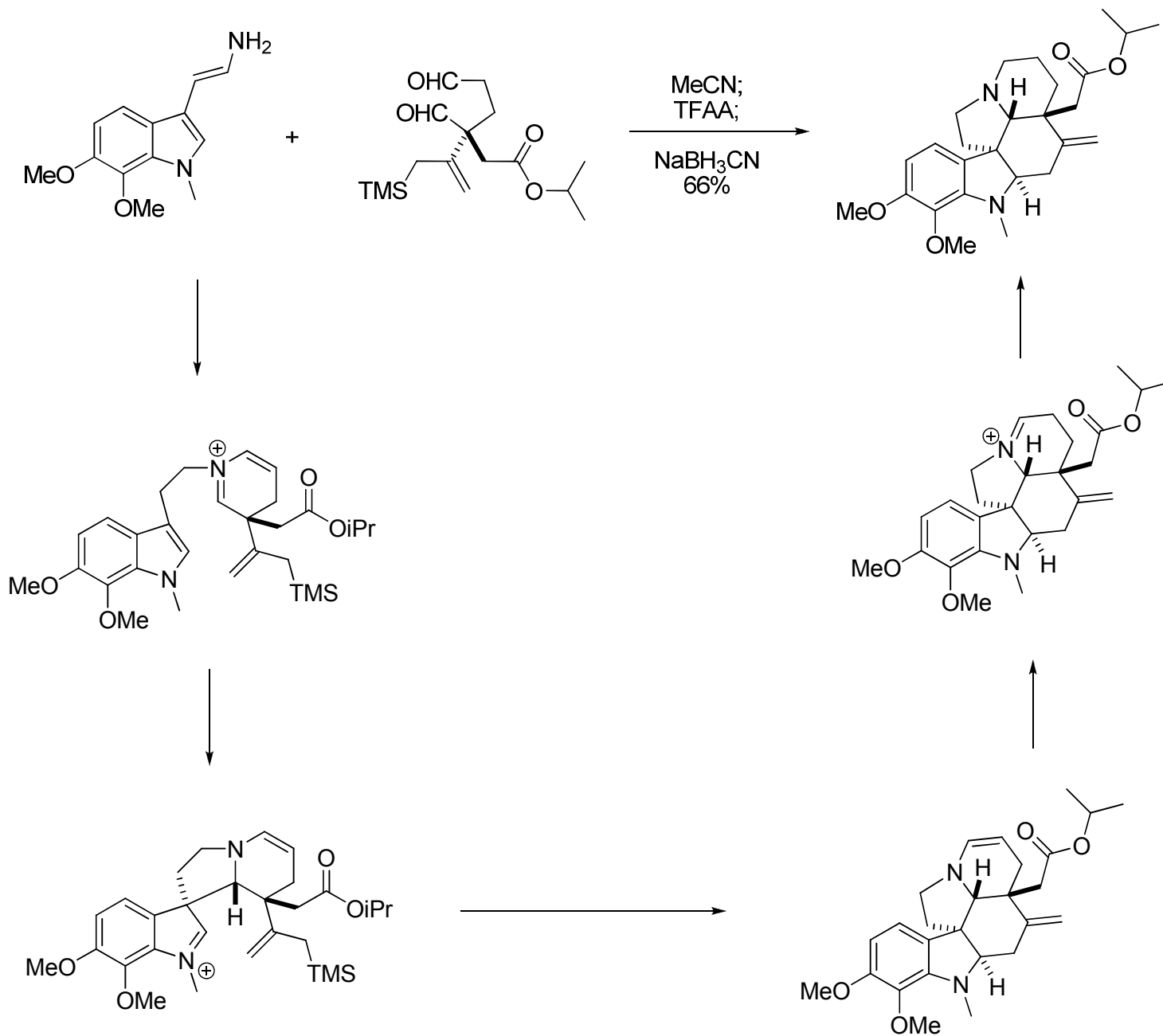
Synthesis of the Tryptamine Coupling Partner



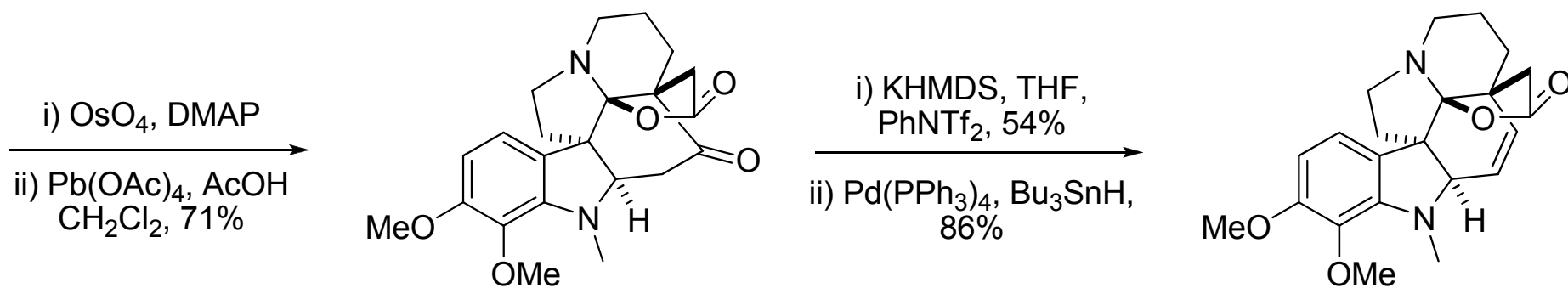
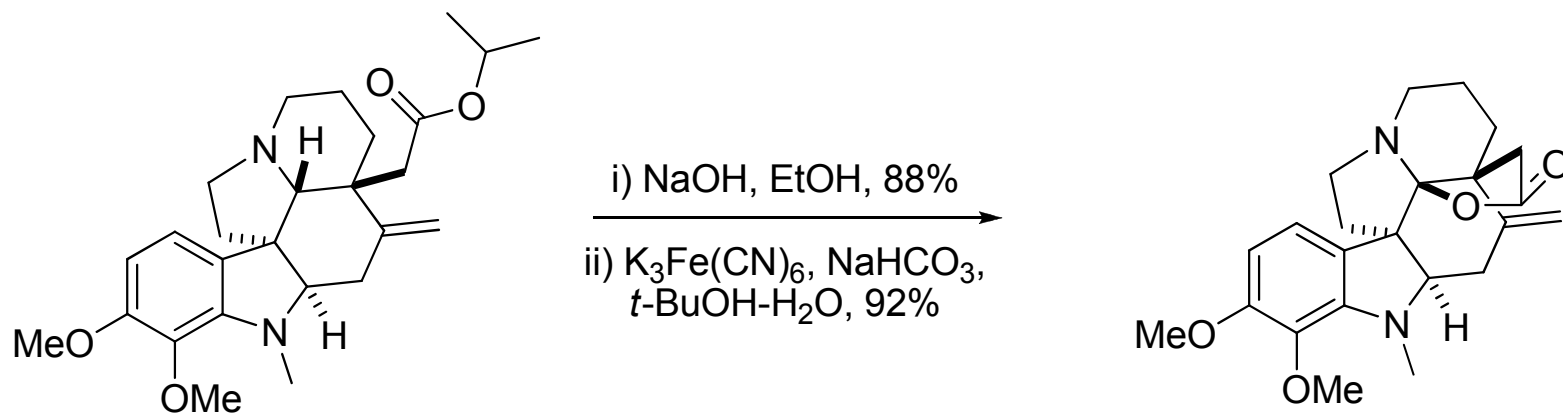
Synthesis of the Dialdehyde



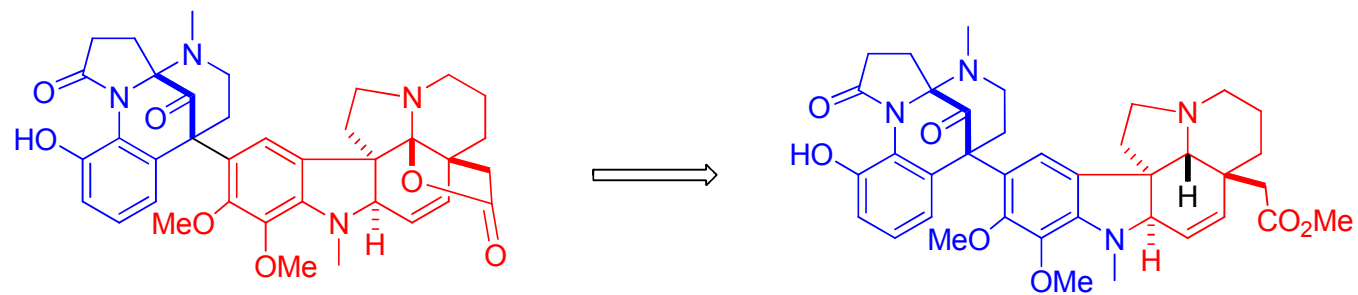
Fragment Coupling



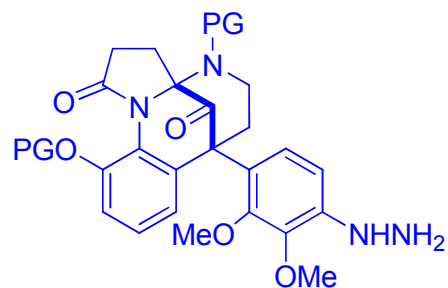
Elaboration to Aspidophytine



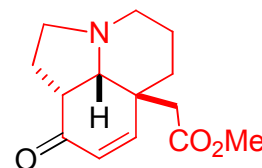
The First Total Synthesis of Haplophytine



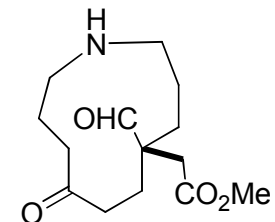
Fischer Indole Synthesis



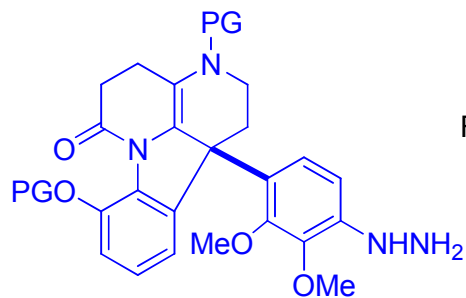
+



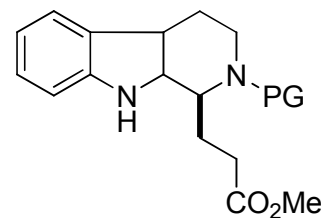
Intramolecular Mannich Reaction



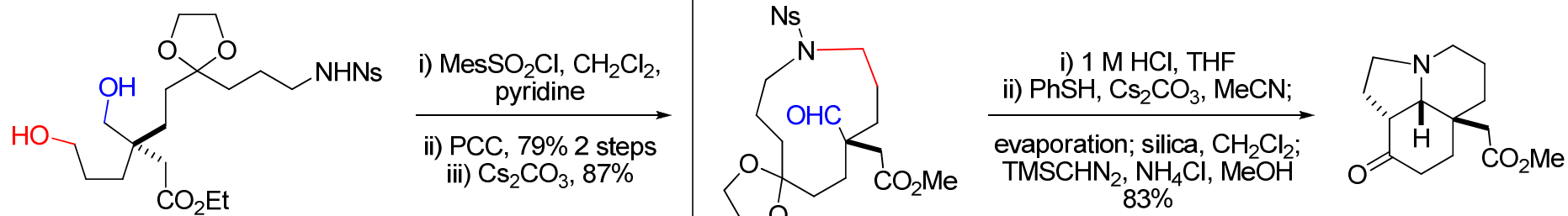
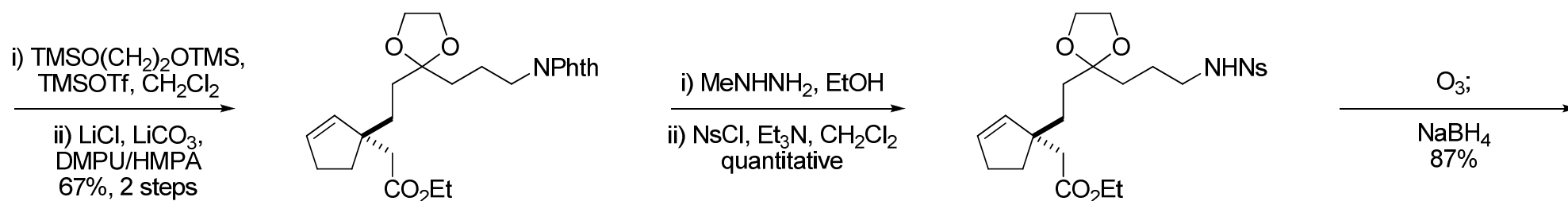
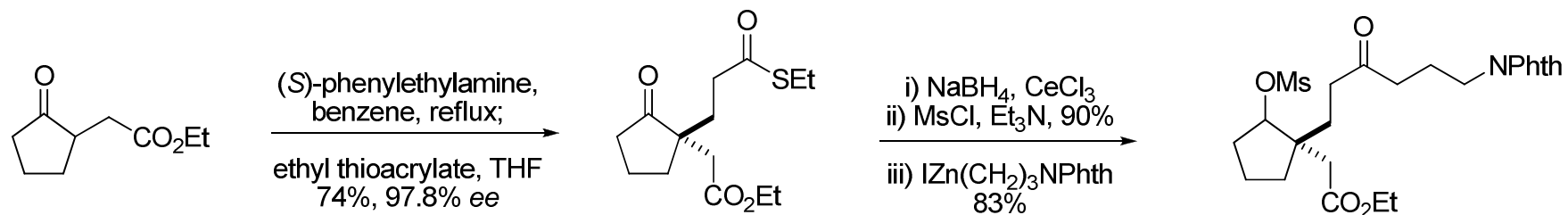
Oxidative Skeletal Rearrangement



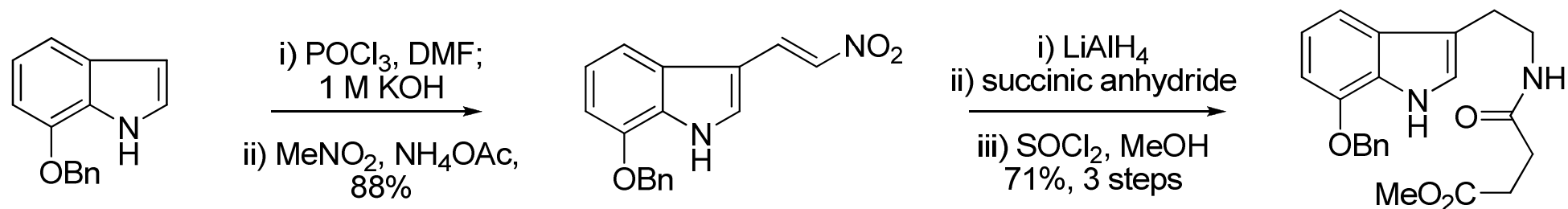
Friedel-Crafts



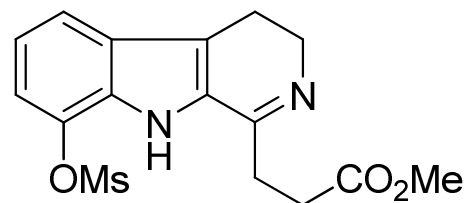
Synthesis of Ketone Fragment



Synthesis of Hydrazine Fragment

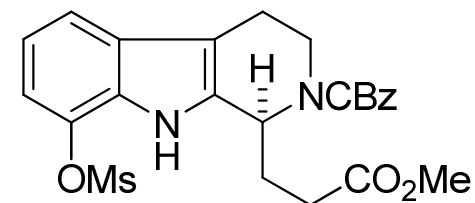


i) H_2 , Pd/C
ii) MsCl, Et_3N , 86%
iii) POCl_3 , CH_2Cl_2

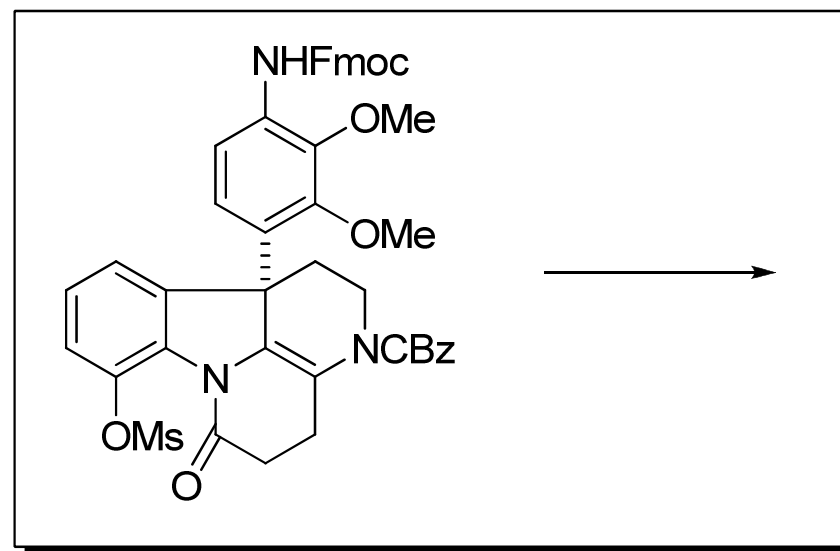
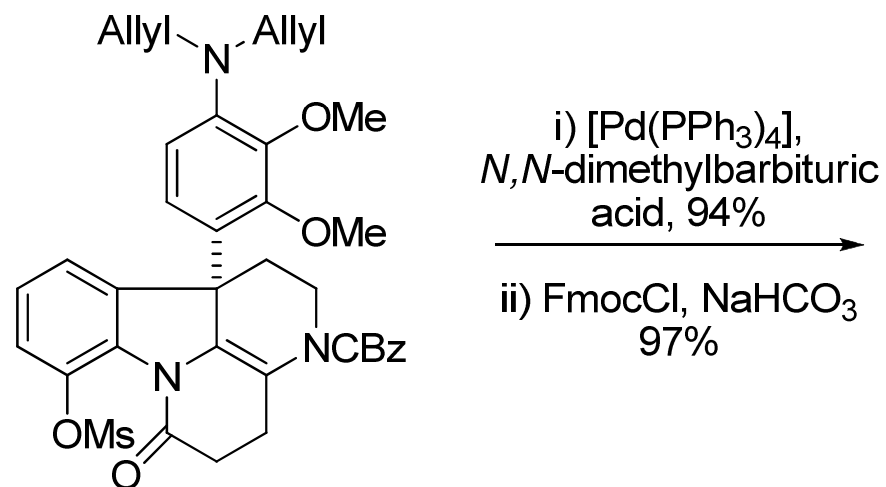
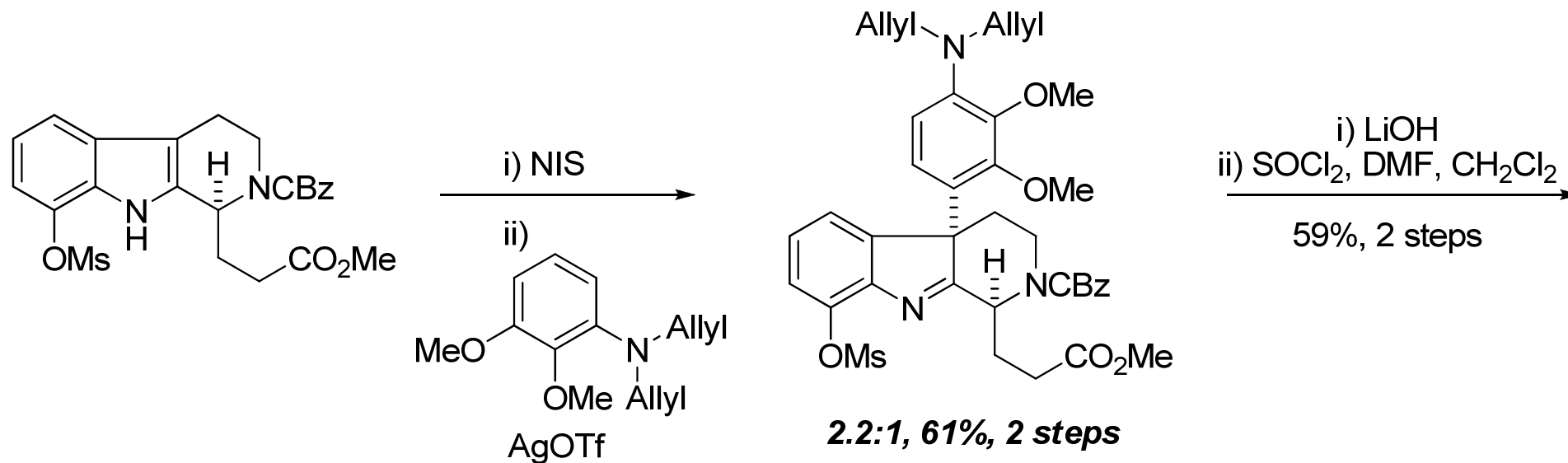


i) Noyori reduction
ii) CbzCl, $i\text{-Pr}_2\text{NEt}$

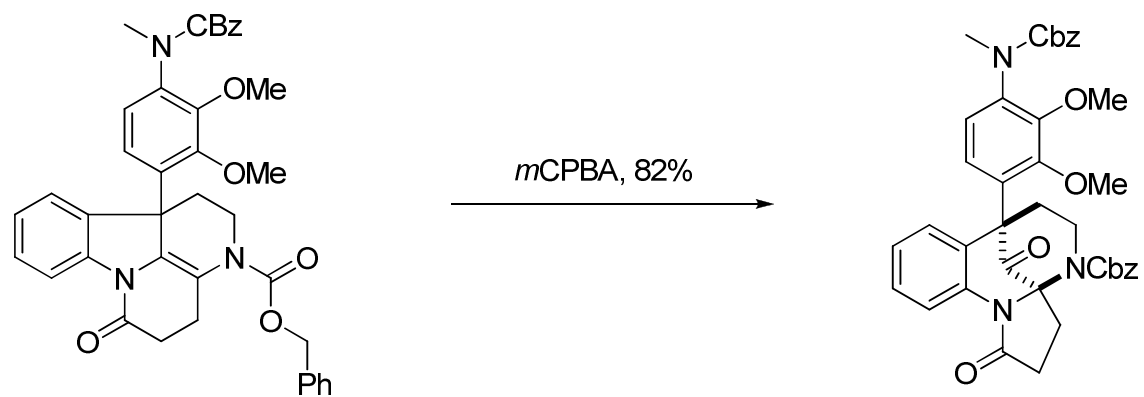
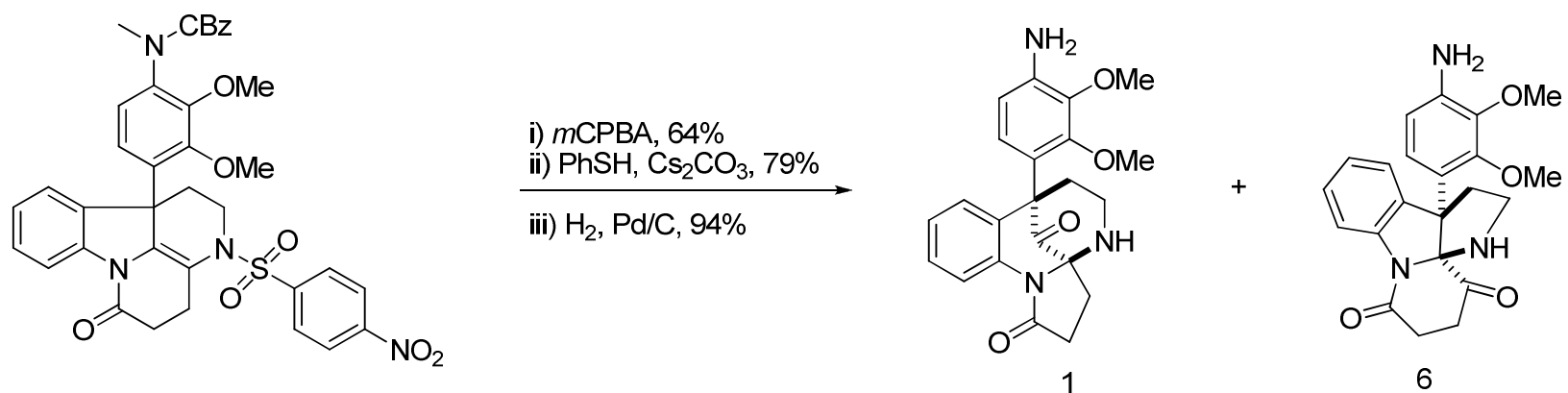
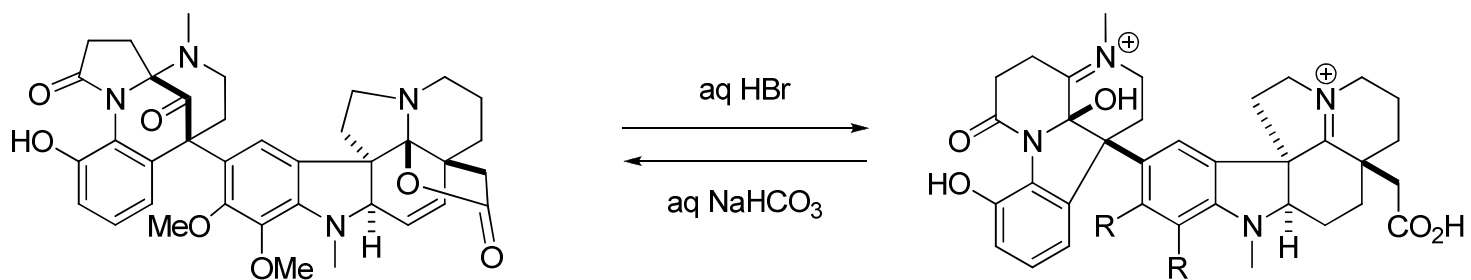
67%, 96.6% ee



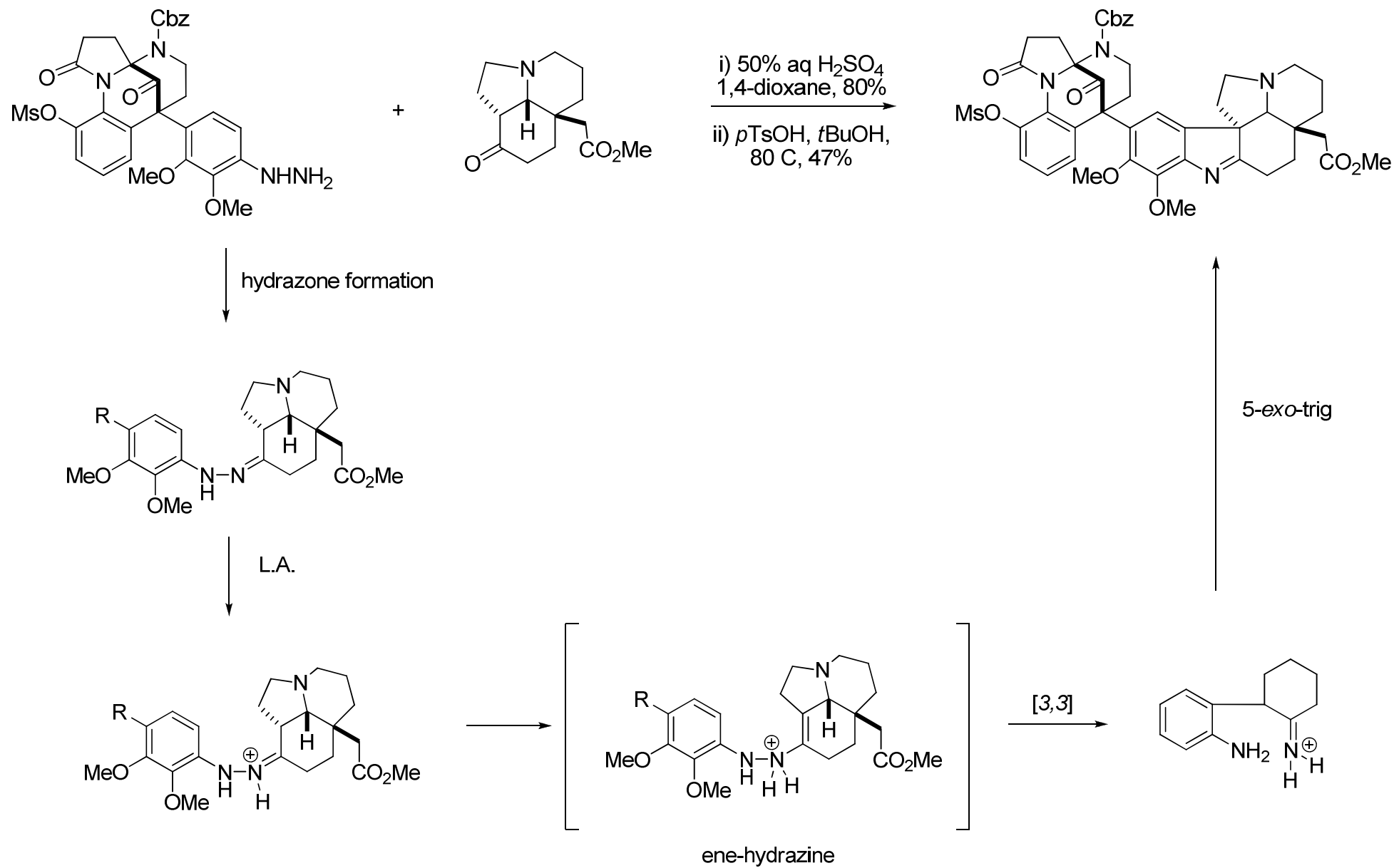
Hydrazine Fragment



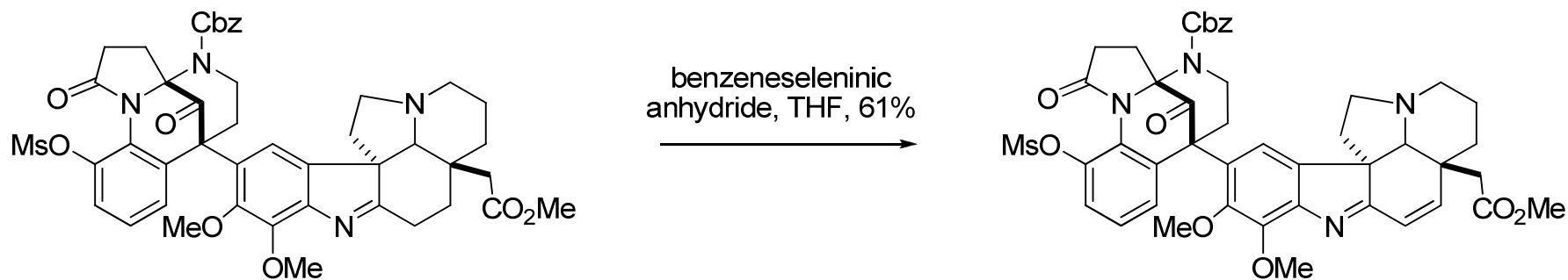
Rearrangement Studies



Indole Formation

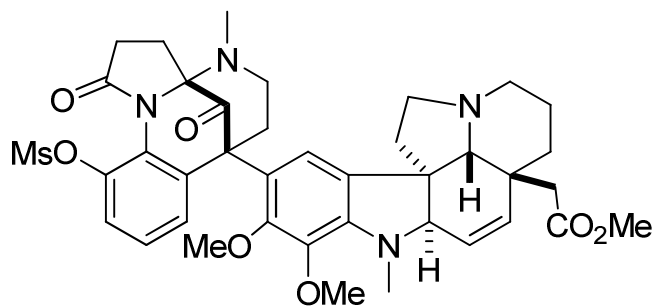


End Game



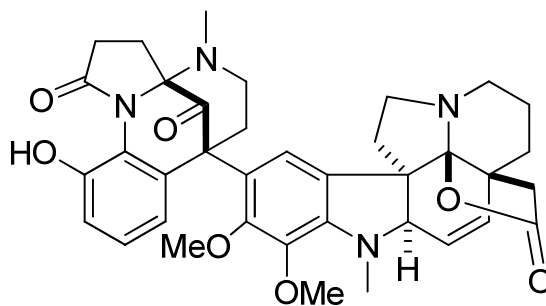
i) BBr_3 , pentamethylbenzene,
 CH_2Cl_2 , 67%

ii) NaBH_3CN , AcOH,
 $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 55%



i) 1 M NaOH, MeOH

ii) $\text{K}_3[\text{Fe}(\text{CN})_6]$, NaHCO_3 ,
 $t\text{BuOH}$, 70%



Victory!

Conclusions

- Now, haplophytine wouldn't be such a bad MotM
- First total synthesis utilizing an intramolecular Mannich reaction and Friedel Crafts alkylation to introduce key stereocenters
- Interesting oxidative skeletal rearrangement
- Fischer Indole Synthesis to couple the two fragments
- Quaternary center synthesis: Ireland-Claisen (Corey), auxiliary directed alkylation (Nicalaou) and an asymmetric Michael addition (Tokuyama)



References

- *ACIE*, **48**, ASAP
- *Synlett*, **20**, 3137-3140
- *JACS*, **121**, 6771-6772
- *OL*, **8**, 3117-3120
- *JACS*, **130**, 14942-14943