Asymmetric Total Synthesis of (−)-Lycospidine A

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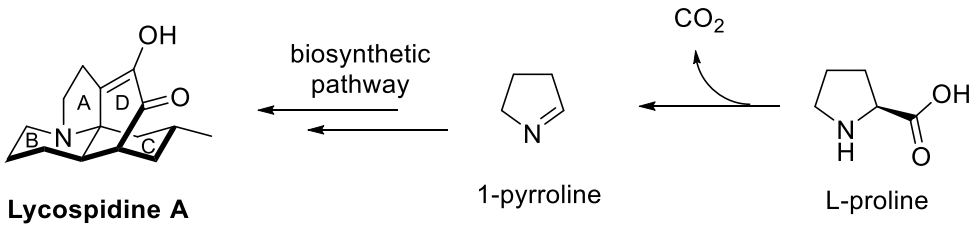
I. Introduction

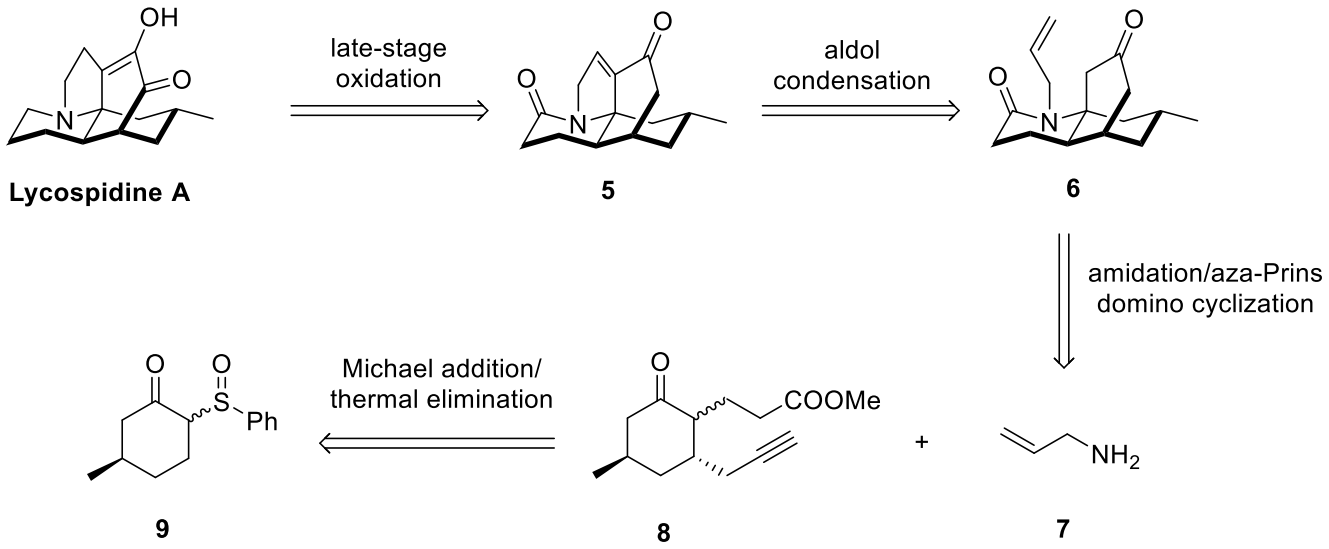
- Lycopodium alkaloids: antipyretic and anticholinesterase activity.
- Lycospidine A: isolated from *Lycopodium complanatum* by Zhao and co-workers in 2013[1)].
- Exhibits an extraordinary [5,6,6,6] fused tetracyclic ring system with a unique aza five-membered A-ring and diosphenol D-ring, with four stereocenters.



- Biosynthetically derived from L-proline.
- The first asymmetric total synthesis in 10 steps with 21.6% overall yield.

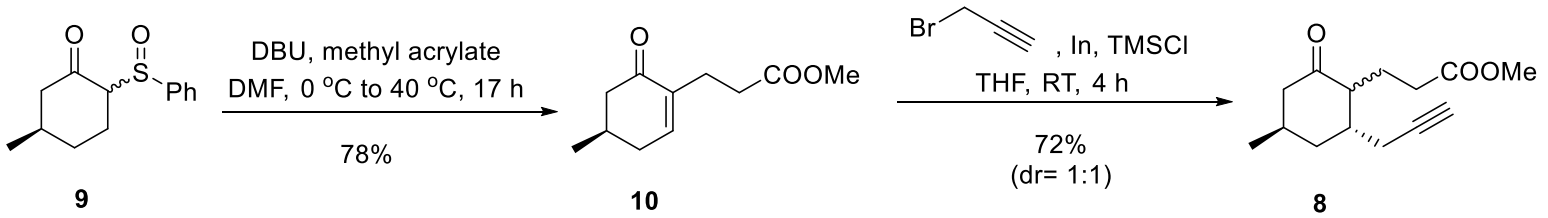
1) Cheng, J.-T.; Liu, F.; Li, X.-N.; Wu, X.-D.; Dong, L.-B.; Peng, L.-Y.; Huang, S.-X.; He, J.; Zhao, Q.-S. *Org. Lett*. **2013**, *15*, 2438−2441.

II. Retrosynthesis

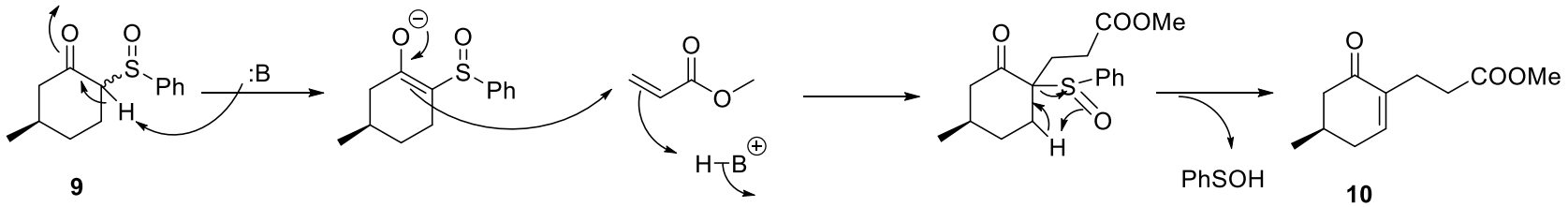


- Key step: amidation/ aza-Prins domino cyclization.
- Late-stage oxidation inspired by biosynthesis pathway.
- Intramolecular aldol condensation to synthesize the unique five-membered ring.

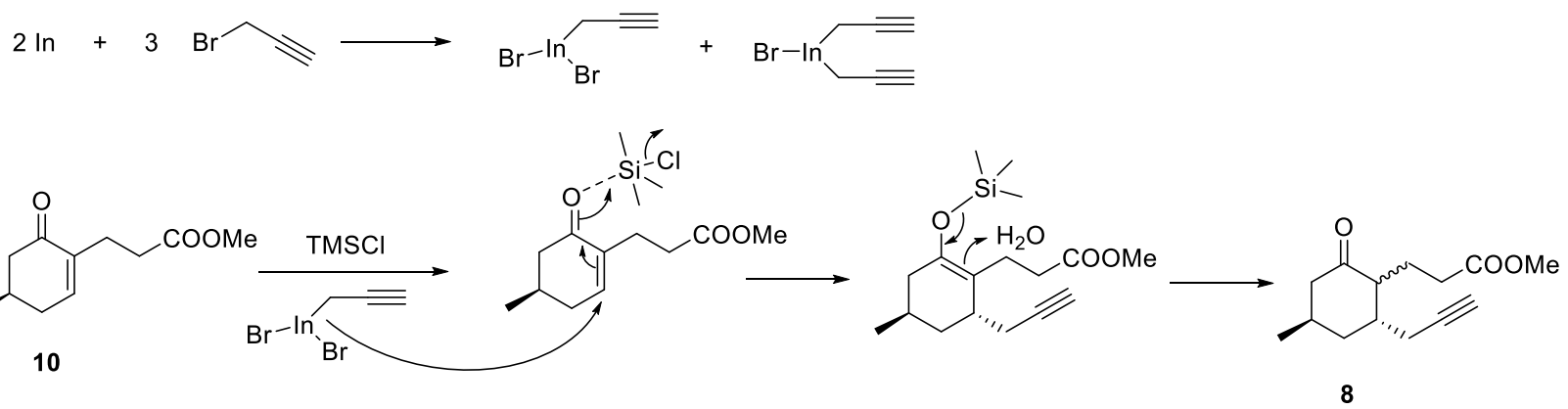
III. Forward synthesis



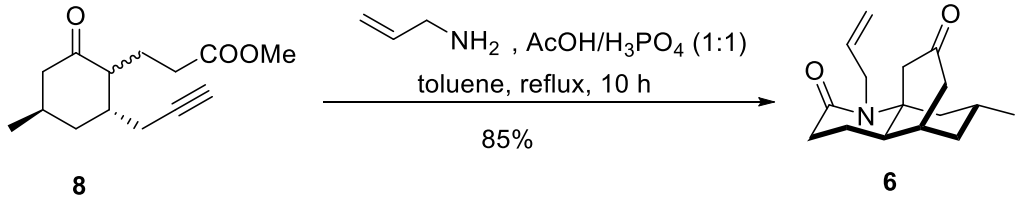
Michael addition/ thermal elimination



Michael-type addition with propargylindium reagent

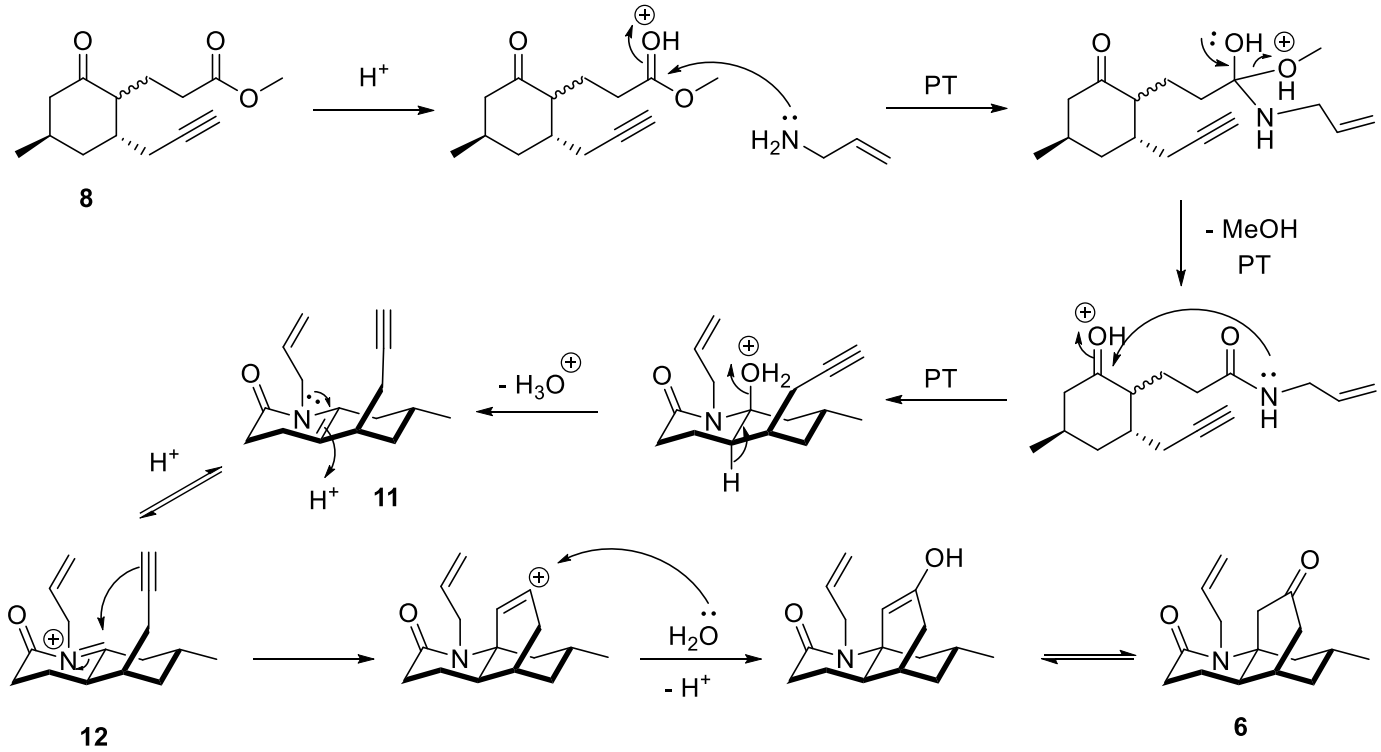


2) Lee, P. H.; Kim, H.; Lee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Lee, M.; Shim, E.; Lee, S.; Kim, M.; Han, M.; Noh, K.; Sridhar, M. Bull. Korean Chem. Soc. 2004, 25, 1687−1691.

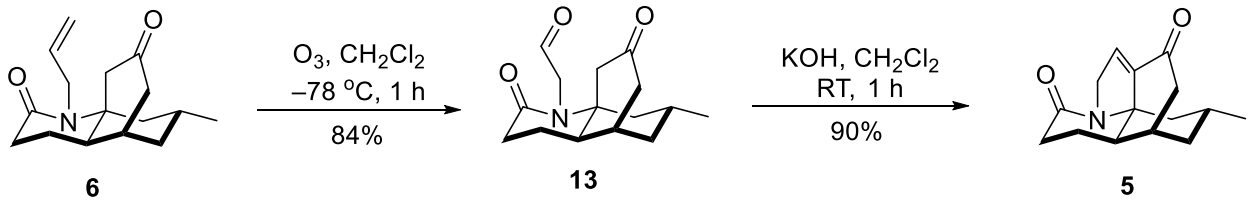


8 6

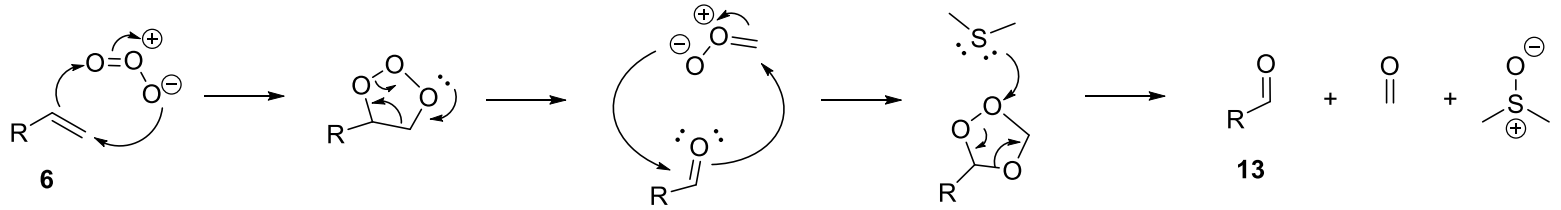
Amidation/ aza-Prins domino cyclization



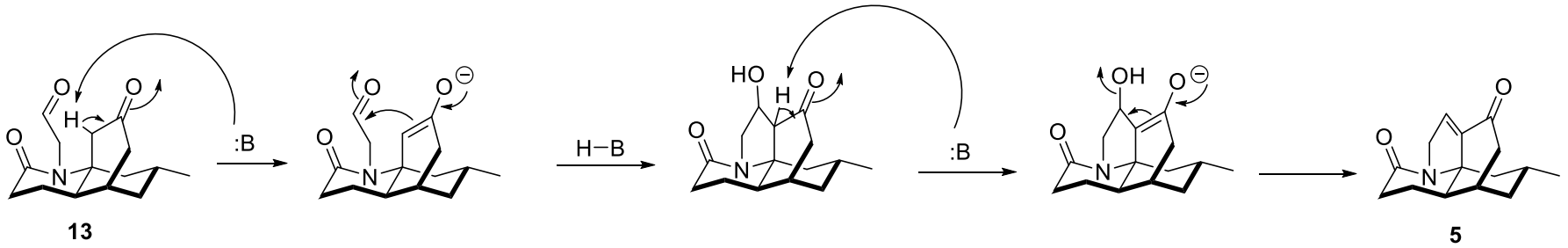
8 12 6

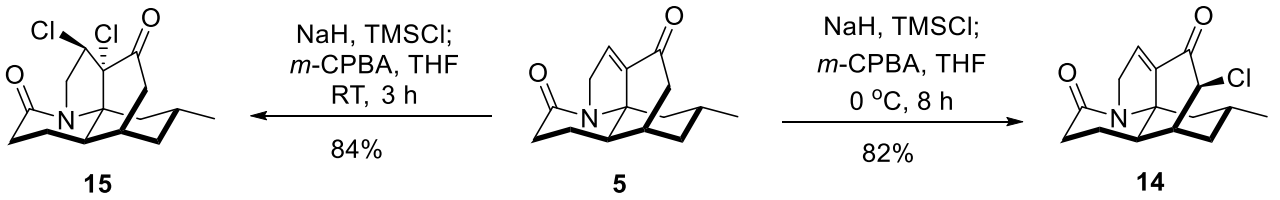


Ozonolysis

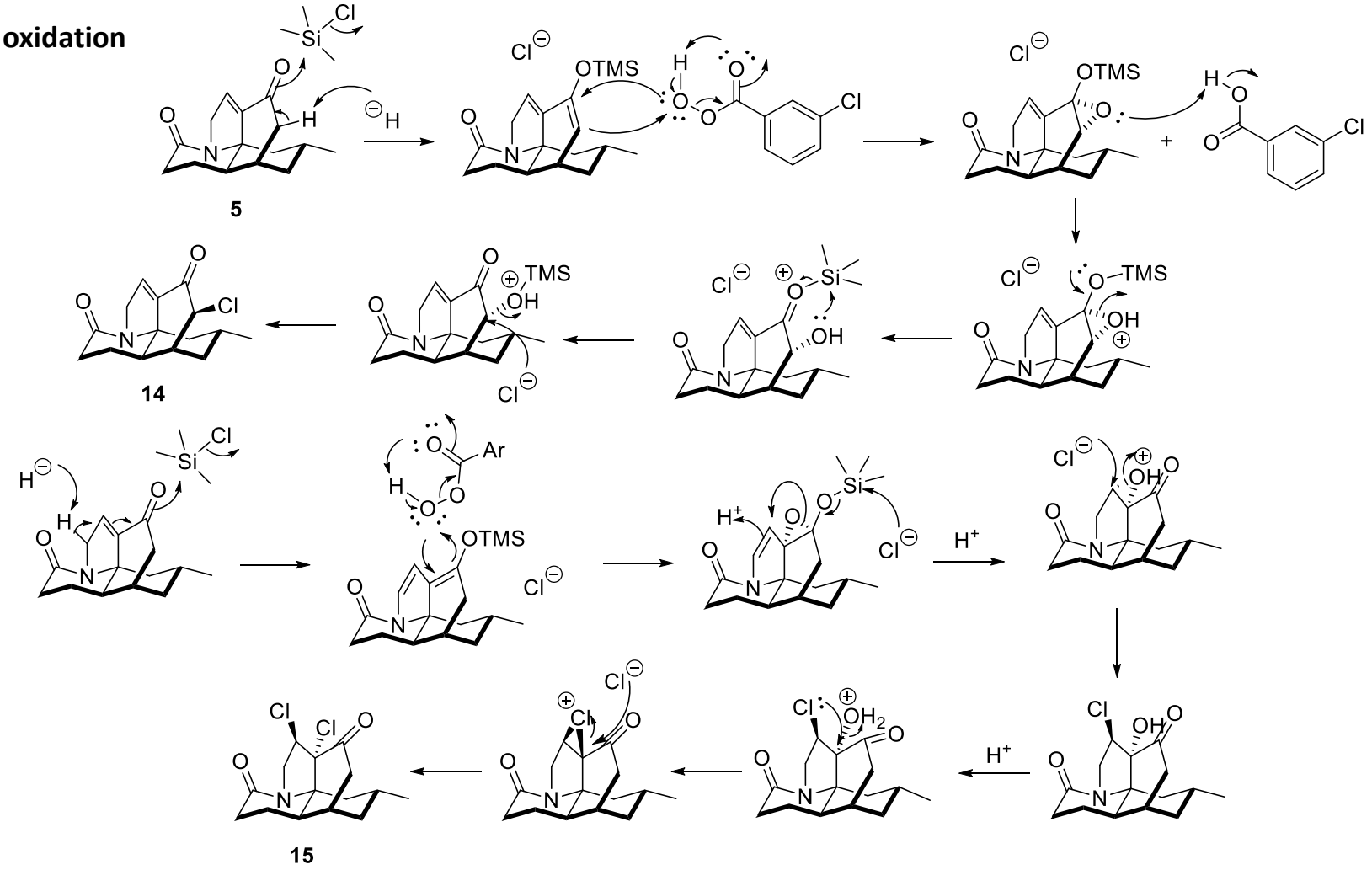


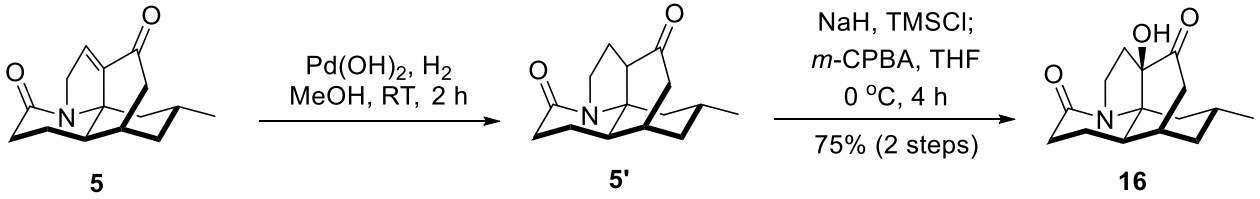
Aldol condensation

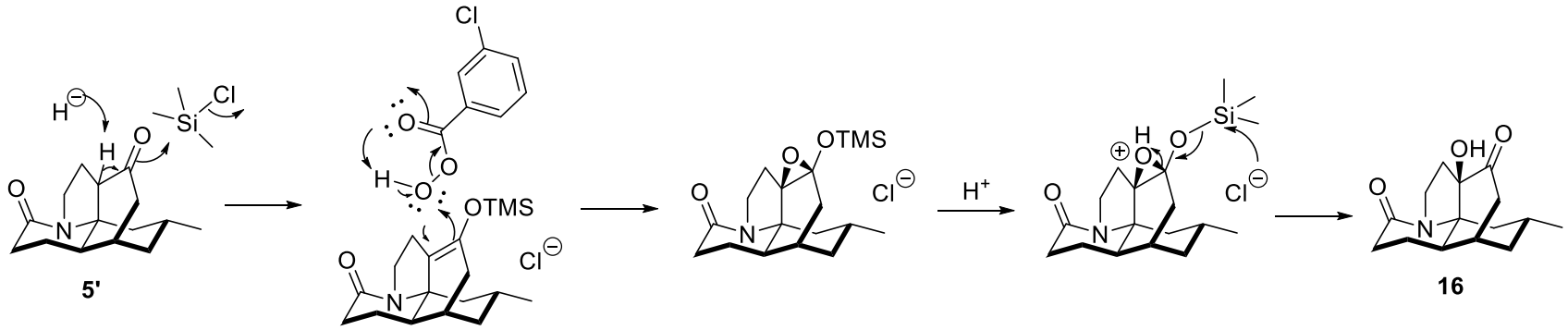


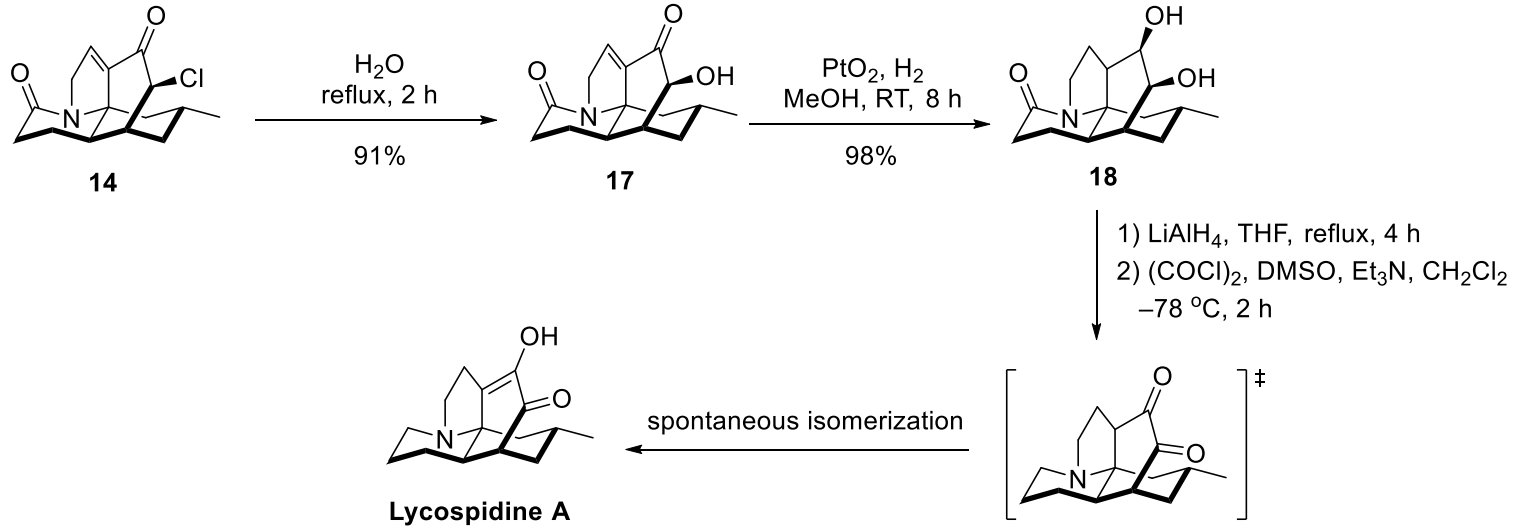


Late-stage oxidation




Pd(OH)2, H2
MeOH, RT, 2 h
NaH, TMSCl;
m-CPBA, THF
0 °C, 4 h
75% (2 steps)
OH
5
5'
16


Cl
H
Si
Cl
OTMS
Cl
H+
5'
16


Cl
H2O
reflux, 2 h
91%
OH
PtO2, H2
MeOH, RT, 8 h
98%
OH
14
17
18
1) LiAlH4, THF, reflux, 4 h
2) (COCl)2, DMSO, Et3N, CH2Cl2
–78 °C, 2 h
spontaneous isomerization
OH
Lycospidine A