Total Syntheses of (+)-Lyconadin A and (-)-Lyconadin B

Douglas C. Beshore and Amos B. Smith, III
University of Pennsylvania
JACS ASAP

Julia Vargas

April 7th, 2007

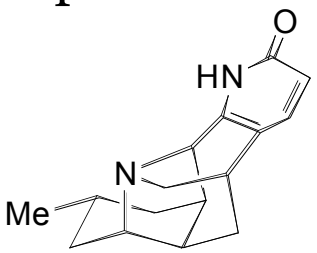
Outline

- Elucidation and Activity of Lyconadin A and B
- Overview of Lycopodium Alkaloids
- Retrosynthesis
- Synthesis of Lyconadin A and B
- Summary/Conclusions

Lyconadin A and B

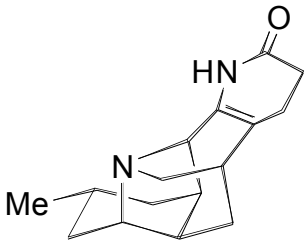
http://www.borealforest.org/ferns/fern10.htm

- isolated from club moss, *Lycopodium complanatum - 2001 and 2006*
- α-pyridinone ring fused tetracyclic core
- Structural elucidation determined by HRMS, 1D and 2D NMR, IR, optical rotation, etc.



(+)-Lyconadin A

murine lymphoma L1210 cells
IC_{50} 0.46 μg/mL
human epidermoid carcinoma KB cells
IC_{50} 1.7 μg/mL



(-)-Lyconadin B

not cytotoxic against either cell lines (IC_{50} >10 μg/mL)

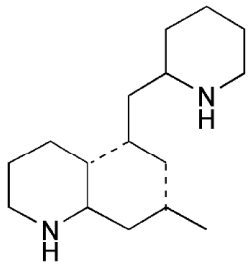
Kobayashi, J. et al *J. Org. Chem.* **2001**, 66, 5901; Kobayashi, J. et al *J. Bioorg. Med. Chem.* **2006**, 14, 5995

Lycopodium Alkaloids

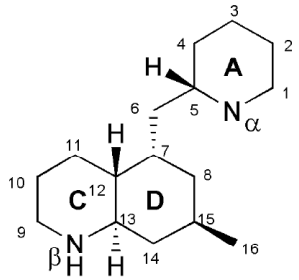
- First investigations traced back to 1881, Today 201 alkaloids identified from 54 species

- Quinolizine, or pyridine and α-pyridinone type structures
  - $C_{16}N$, $C_{16}N_2$, $C_{27}N_3$

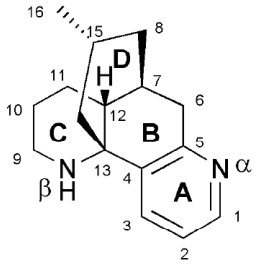
- Four Major Classes of Lycopodium Alkaloids:



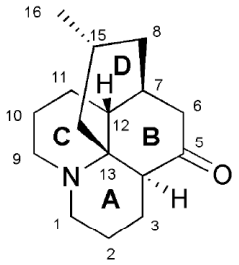
1



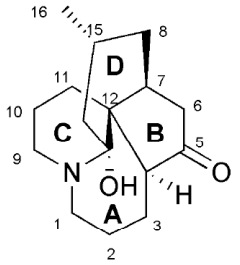
2 phlegmarine



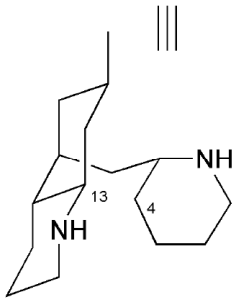
3 lycodine

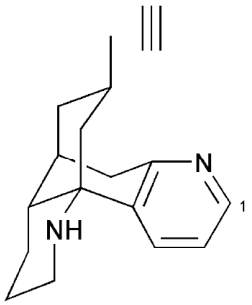


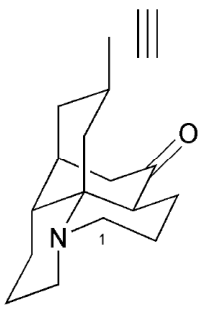
4 lycopodine

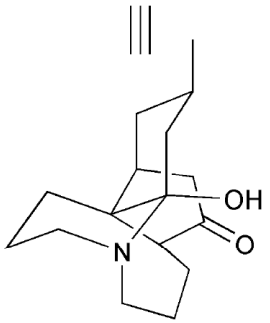


5 fawcettimine



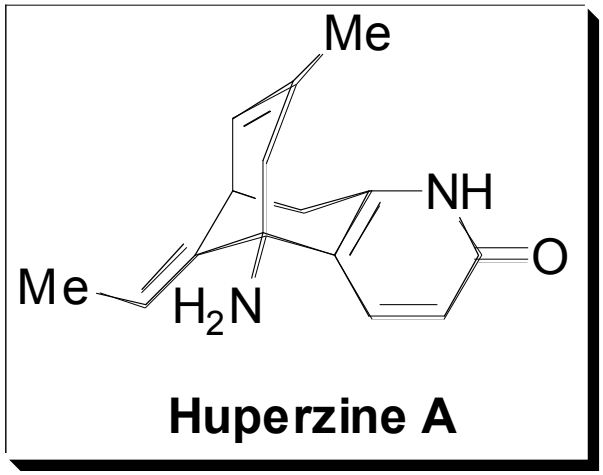






Gang, D. R., *Nat. Prod. Rep.* **2004**, 21, 752

Lycopodium Alkaloids



Huperzine A

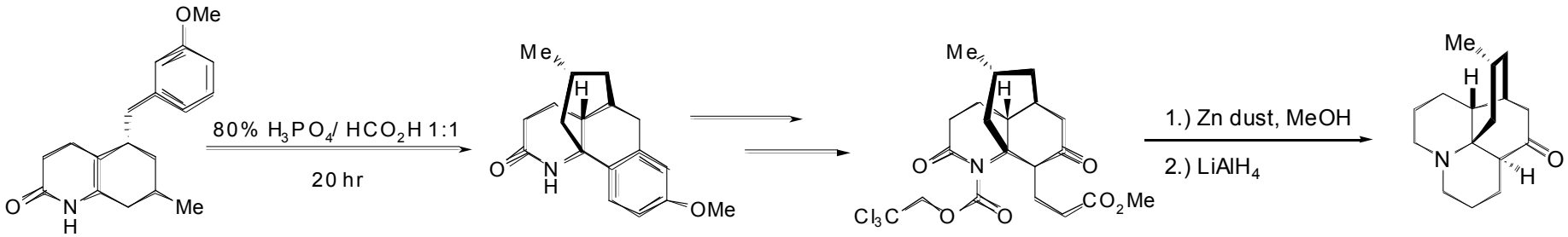
shiretoko.muratasystem.or.jp/.../060504af.html

- 1980's Potent inhibitors of acetylcholinesterase
- Huperzine A (HupA) most potent
- Isolated by Liu and co-workers from club moss *Huperzia serrata*
- Found to increase efficiency for learning and memory in animals
- Potential treatment for Alzheimer's Disease

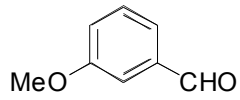
Gang, D. R., *Nat. Prod. Rep.* **2004**, 21, 752
Liu, J. S., *Acta Chim, Sin. (Engl. Ed.), 1986, **44**, 1035*
Liu, J. S., *Can J. Chem., 1986, **64**, 837*
Zhang, R.W. *Acta Pharmacol. Sin.1991, **12**, 250*
Y.S. Cheng, *New Drugs Clin. Remedies, 1986, **5**, 197*

First Syntheses of Lycopodine

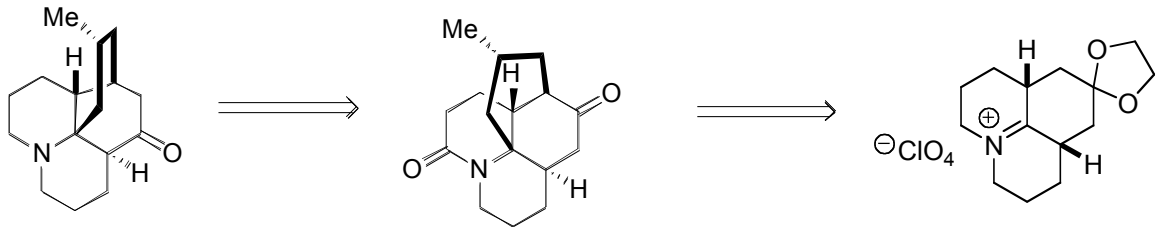
Stork, G. JACS,**1968,** *90, 1647*



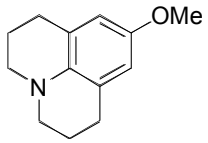
• 17 steps, (1.1%) from



Ayer, W. A. JACS,**1968,** *90, 1648*

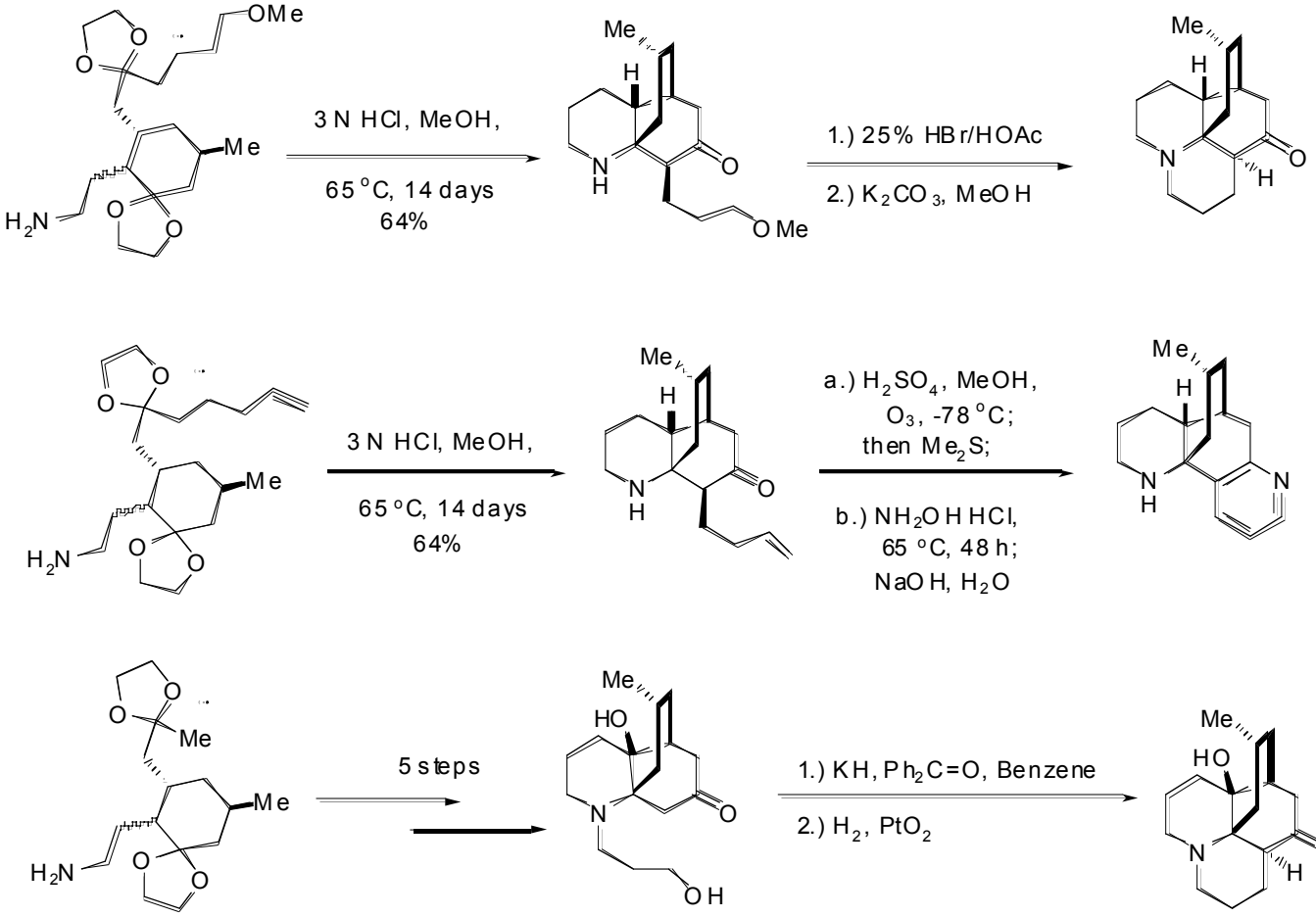


• 17 steps, (0.06%) from



Heathcock's Approach...

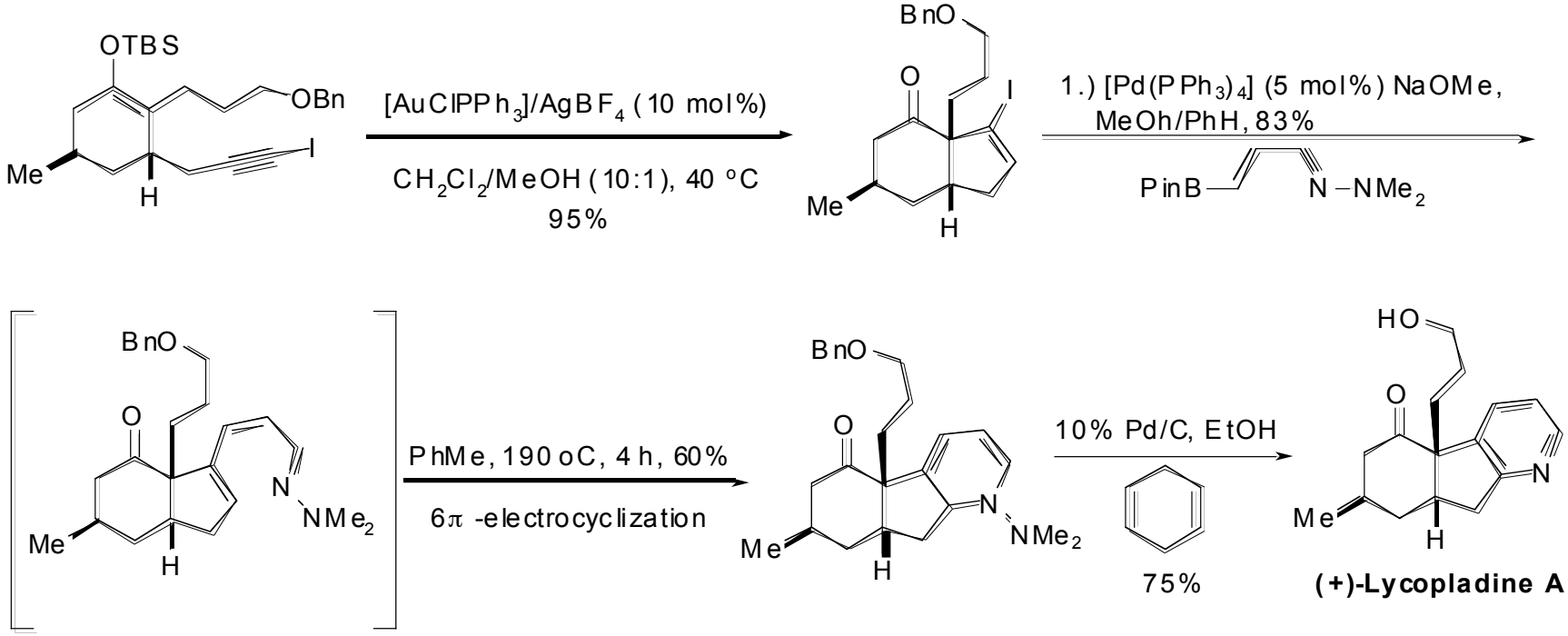
Early 1980s...

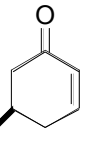


Heathcock, C. H., *J. Am. Chem. Soc.* **1982**, 104, 105

Synthesis of (+)-Lycopladine A

Toste's Approach...

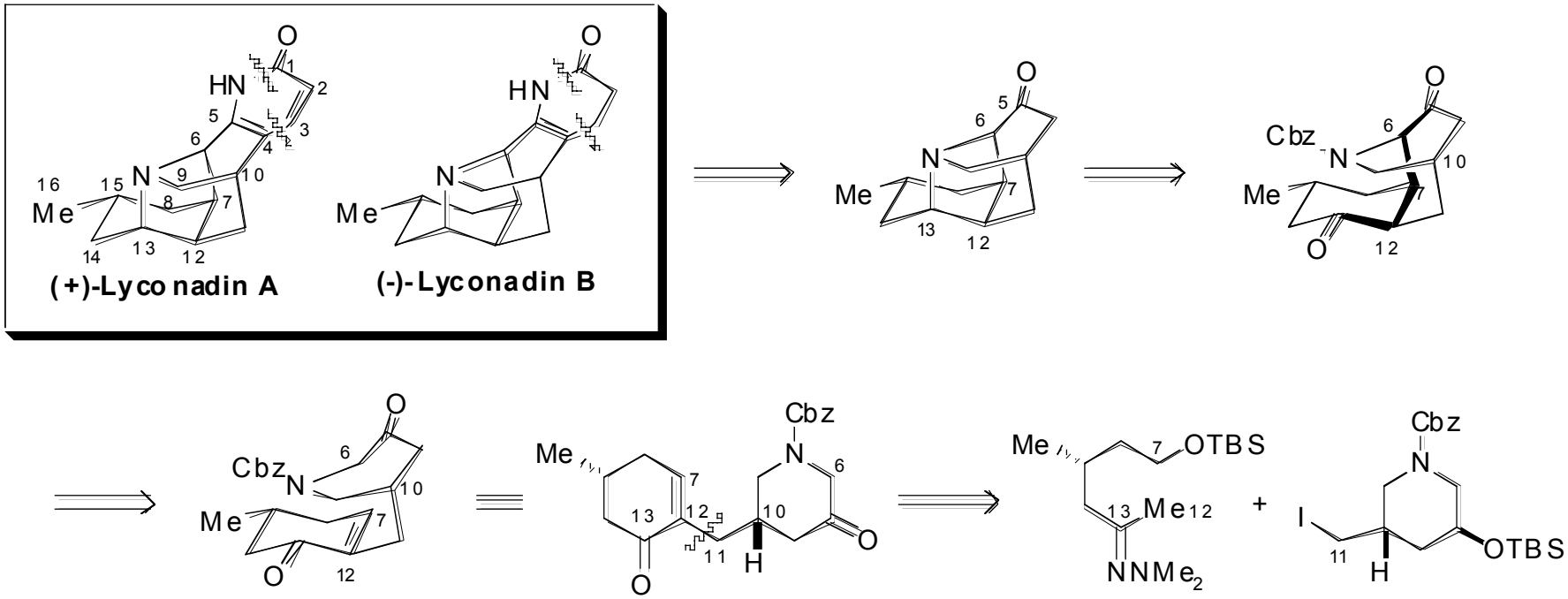


• 8 steps from 

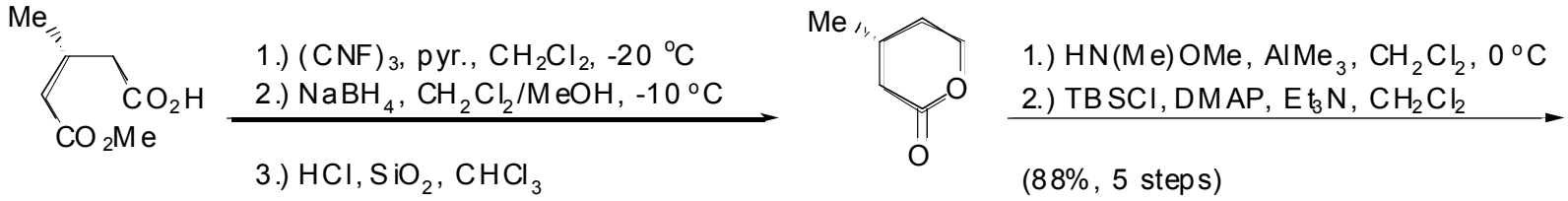
17% overall yield

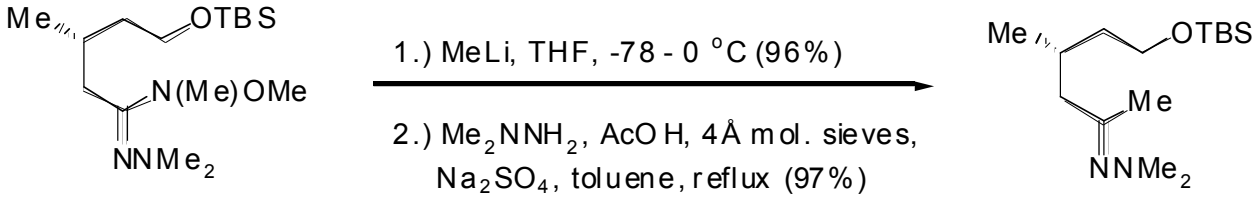
Toste, D. F., *Angew. Chem. Int. Ed.* **2006**, 45, 5991

Retrosynthesis



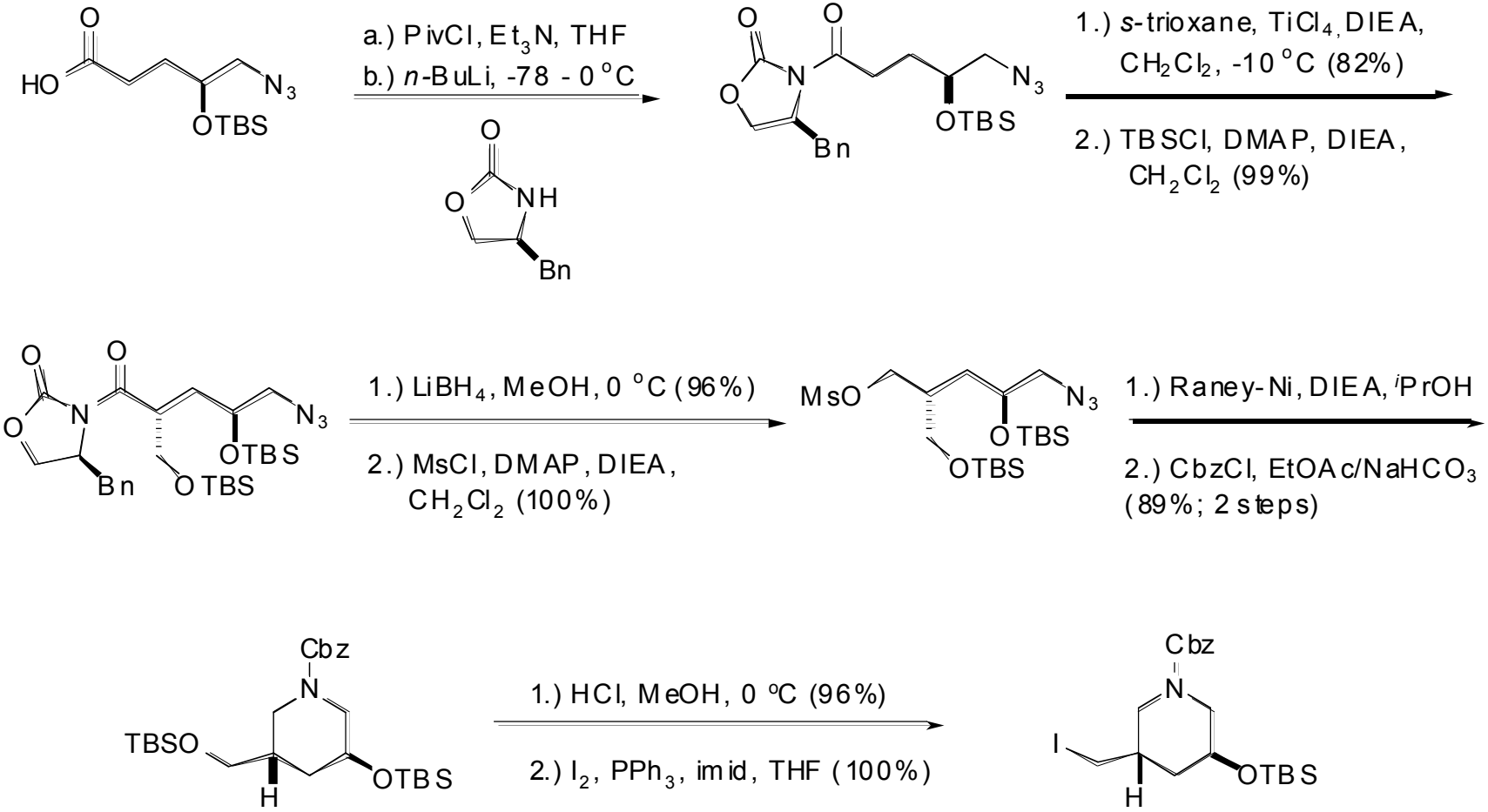
Synthesis of hydrazone fragment





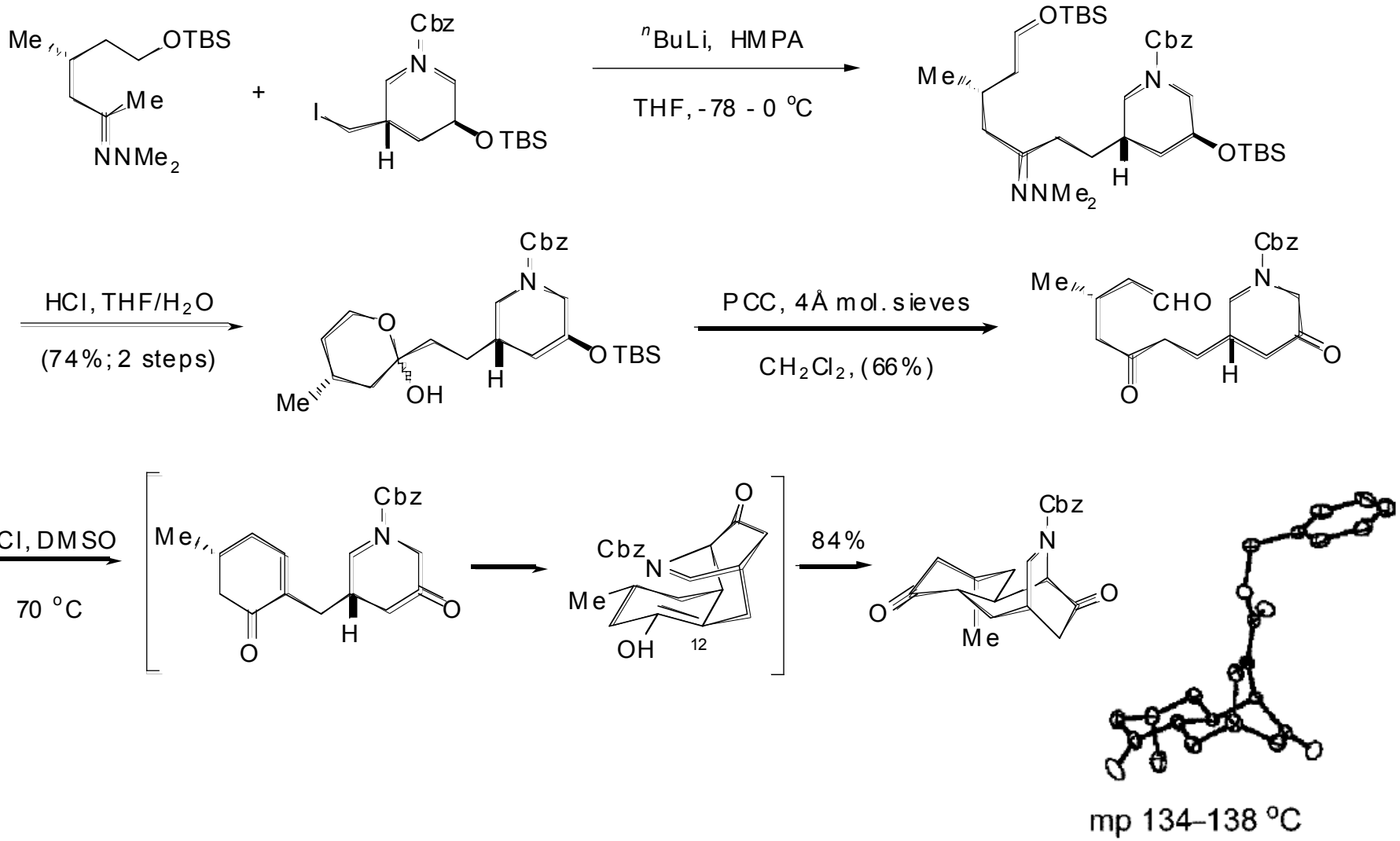
- 7 step sequence, overall yield 82%

Synthesis of iodide fragment



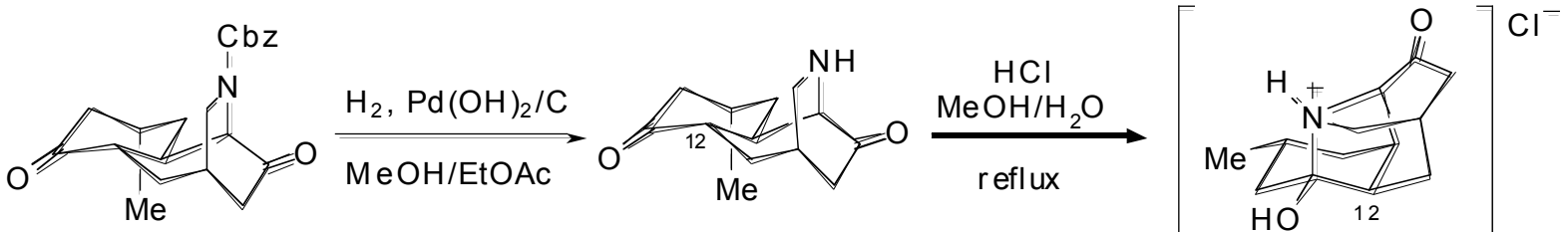
- 9 step sequence, overall yield 61%

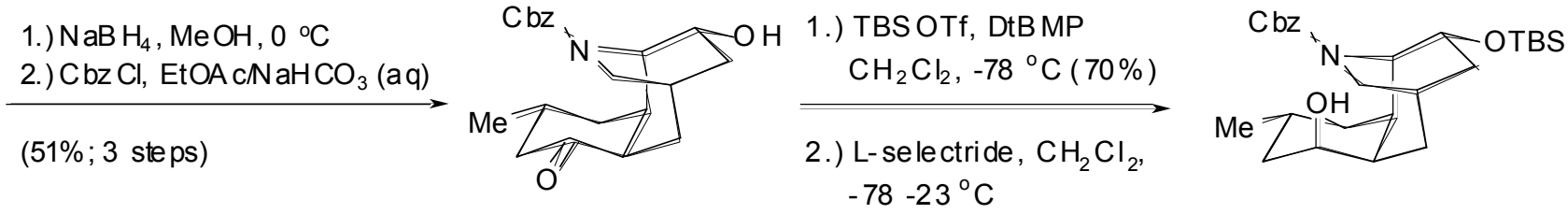
Synthesis of Lyconadin Core



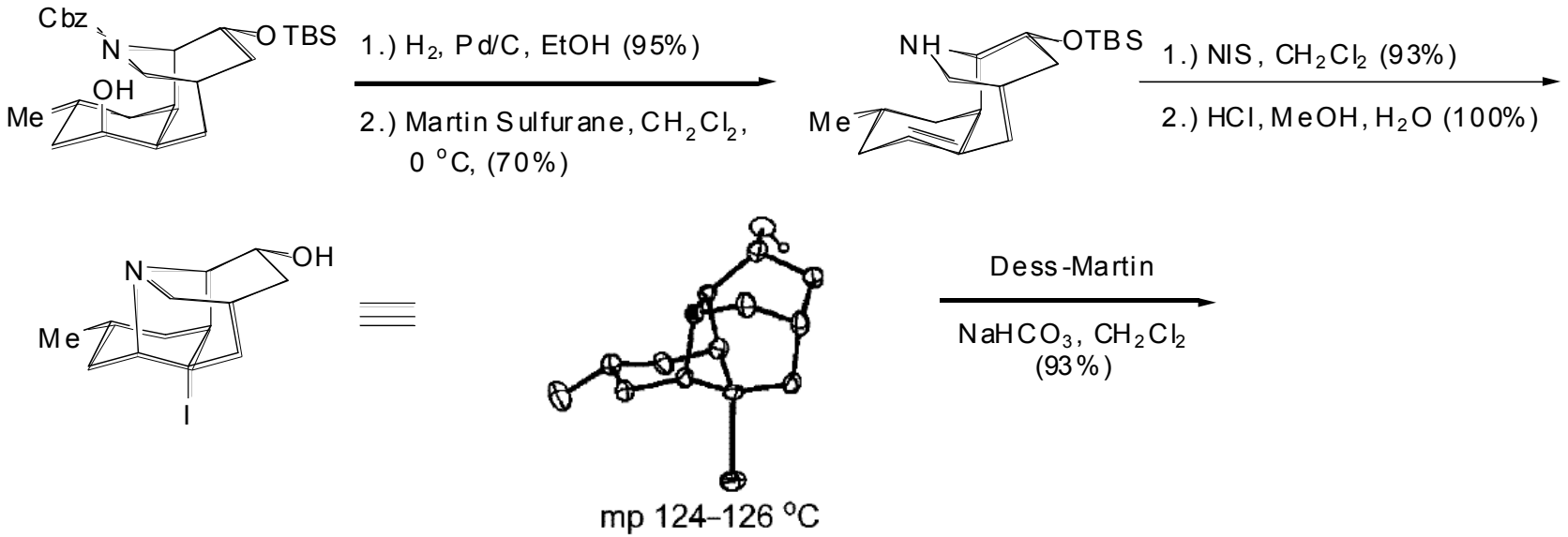
mp 134–138 °C

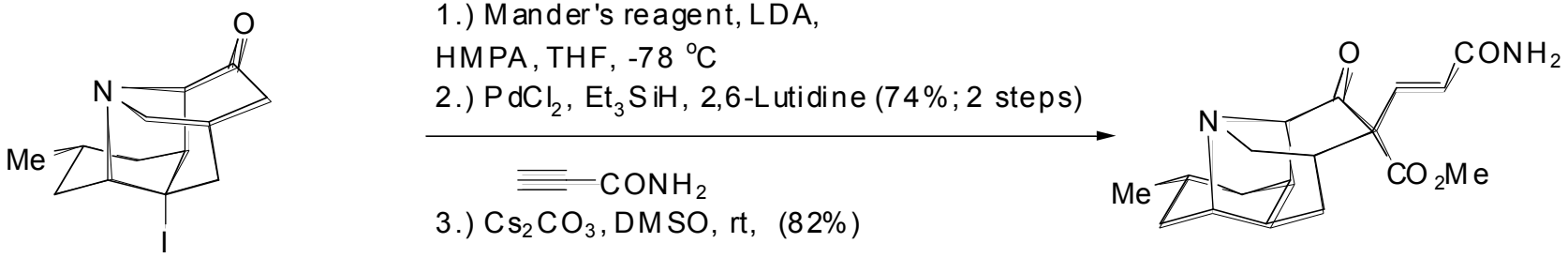
Synthesis of Lyconadin Core



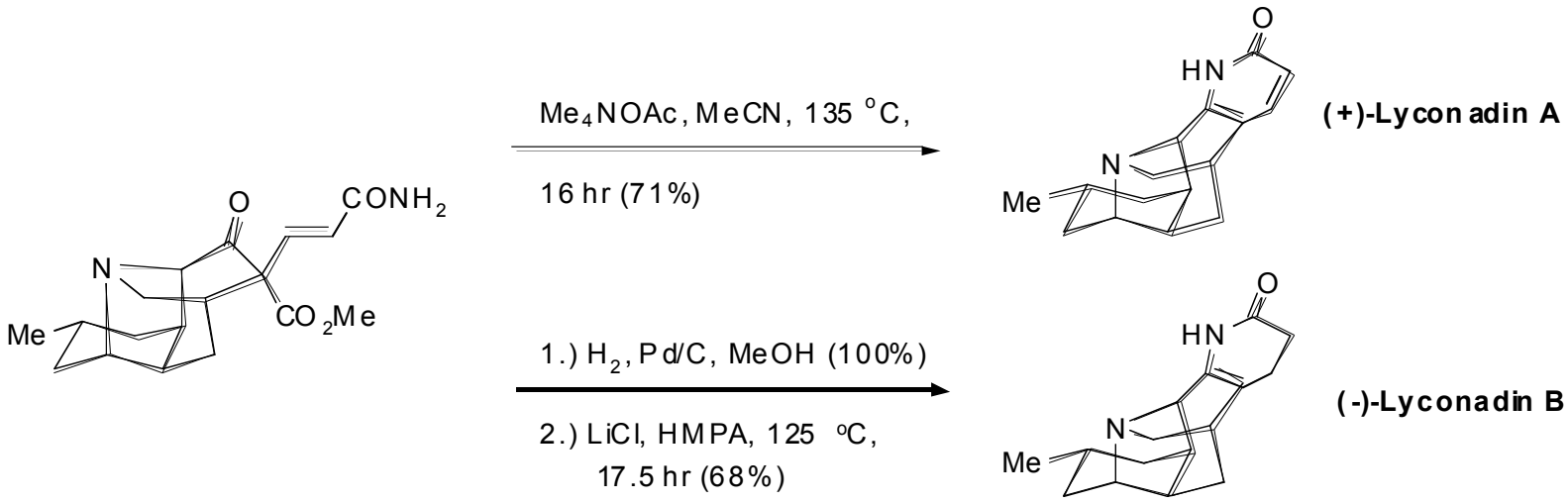


Synthesis of Lyconadin Core

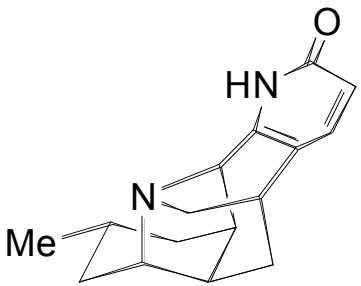




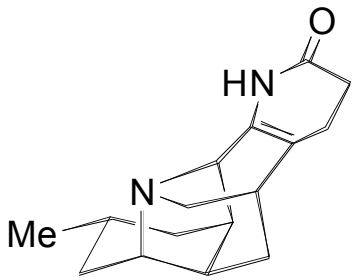
End Game


Me4NOAc, MeCN, 135 °C,
16 hr (71%)
1.) H2, Pd/C, MeOH (100%)
2.) LiCl, HMPA, 125 °C,
17.5 hr (68%)
CONH2
CO2Me
Me
N
O
HN
(+)-Lycon adin A
(-)-Lyconadin B

Summary



(+)-Lyconadin A



(-)-Lyconadin B

- First Total Syntheses of (+)- Lyconadin A (28 steps) and (-)-Lyconadin B (29 steps)
- Syntheses stem from common advanced intermediate
- Intramolecular aldol/conjugate addition cascade
  - 2 new c-c σ-bonds and 3 new stereocenters → tricyclic ring system in one chemical transformation