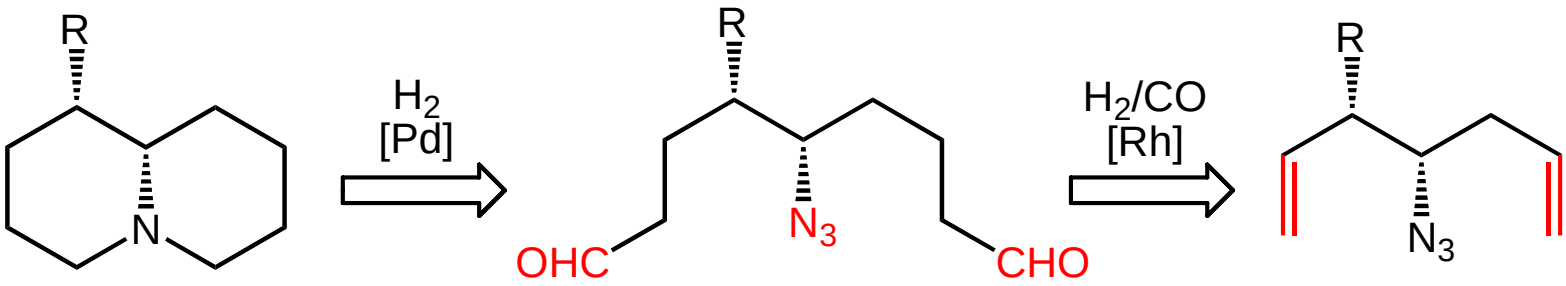
Short Access to (+)-Lupinine and (+)-Epiquinamide via Double Hydroformylation

Kai Gao Checker: Changbin Yu

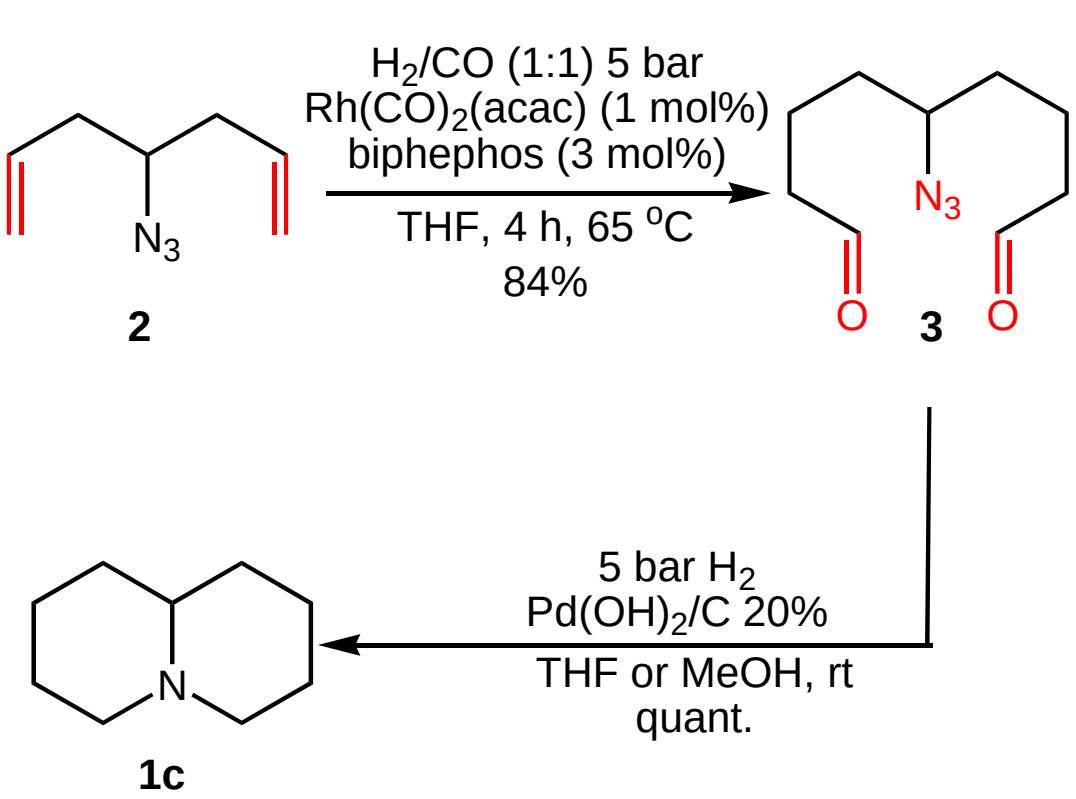
Mann, A.* *et al Org. Lett.* **2009**, *ASAP*

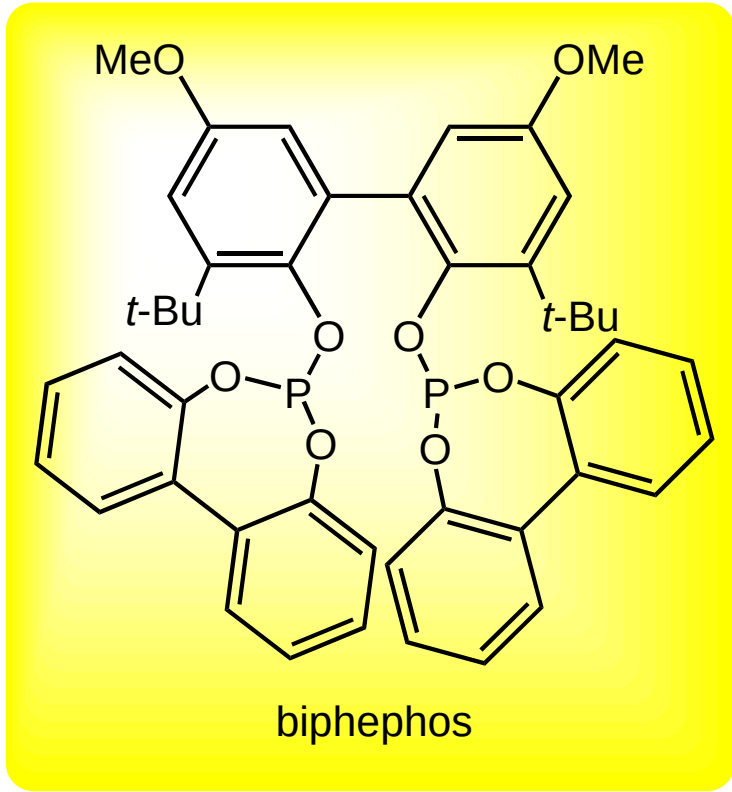
Strategy for the formation of quinolizidine alkaloids



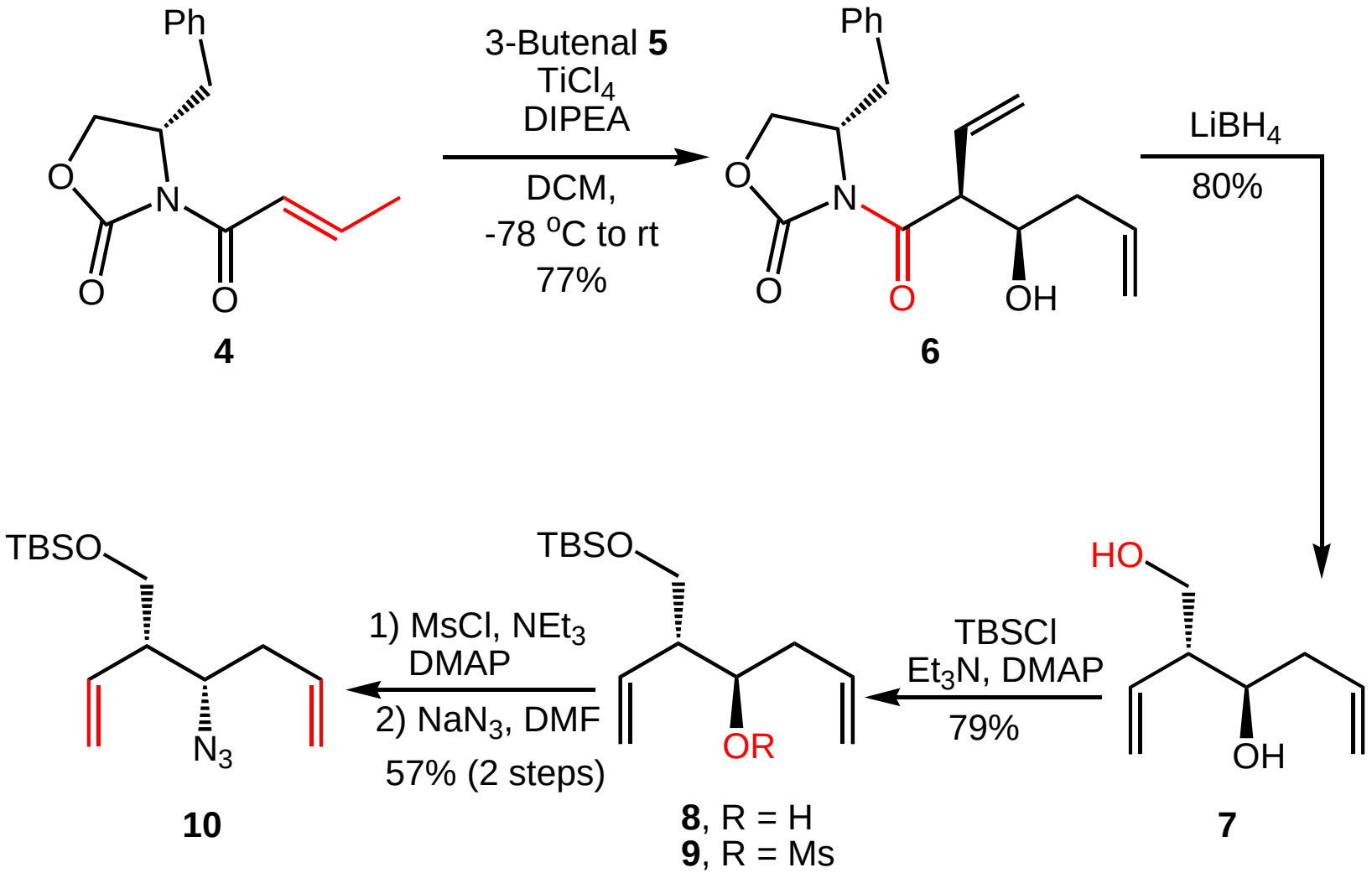
R = CH_2OH, **(+)-lupinine, 1a**
R = NHAc, **(+)-epiquinamide, 1b**
R = H, quinolizidine, 1c

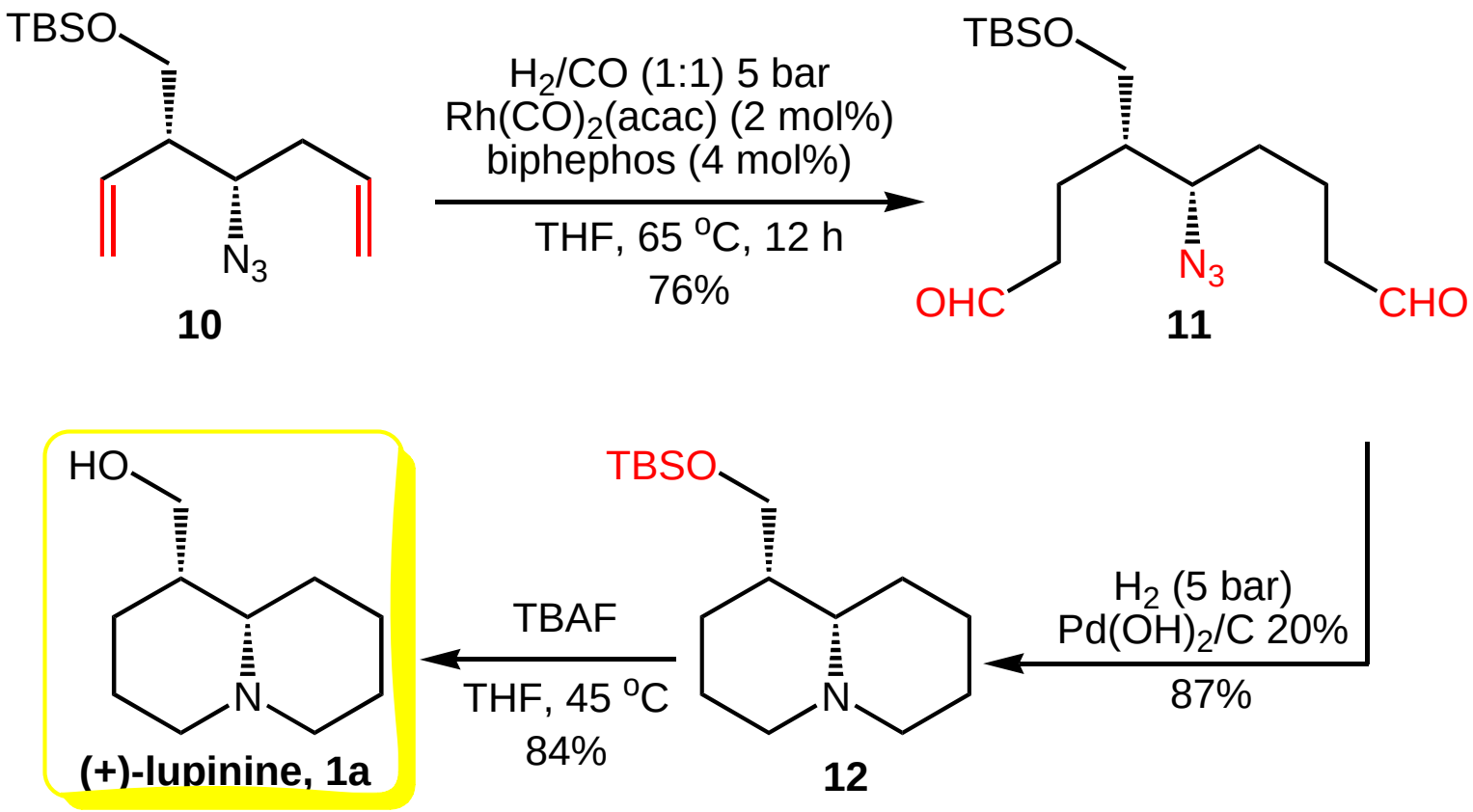
Model Reaction



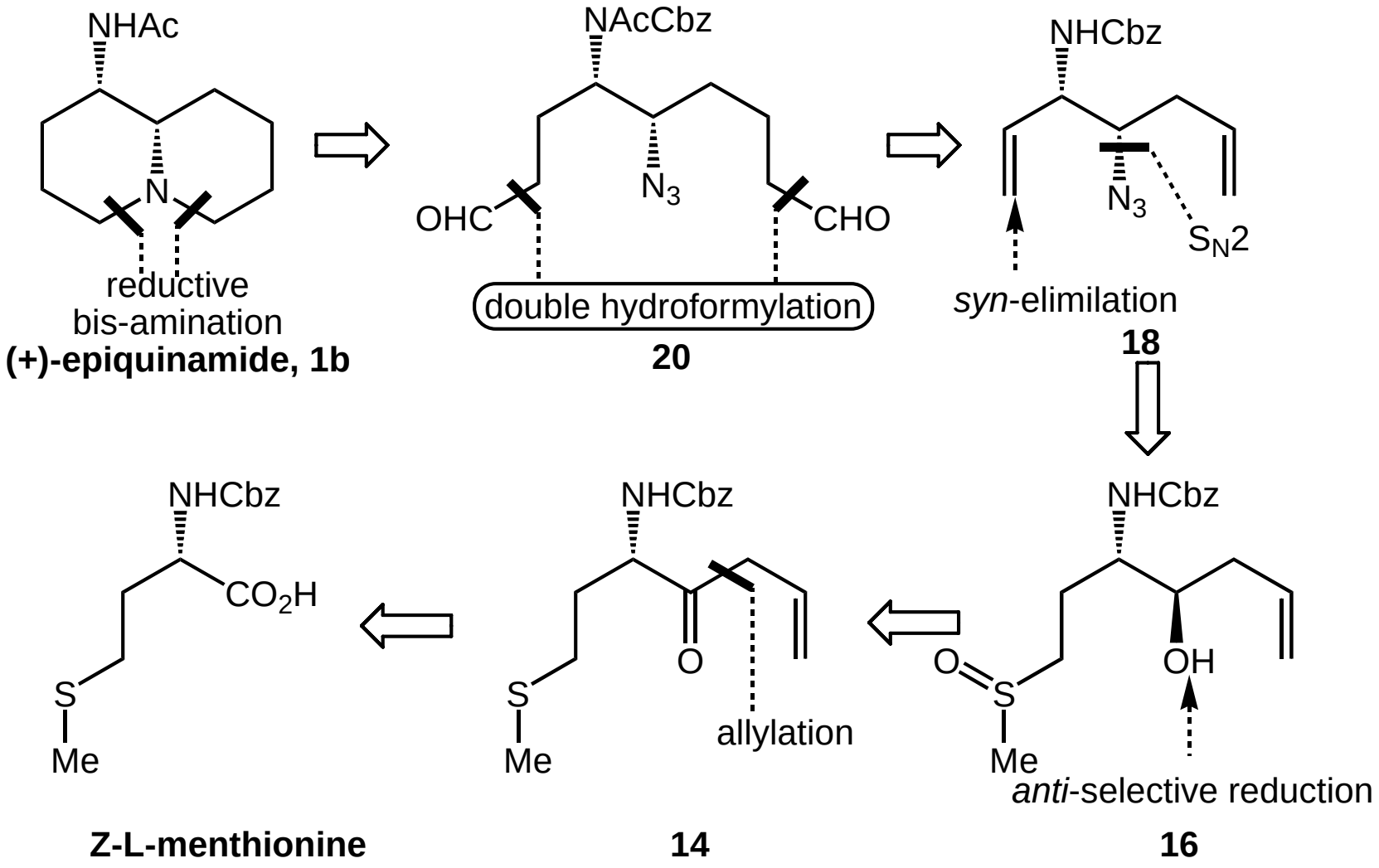


Sythesis of (+)-Lupinine, **1a**

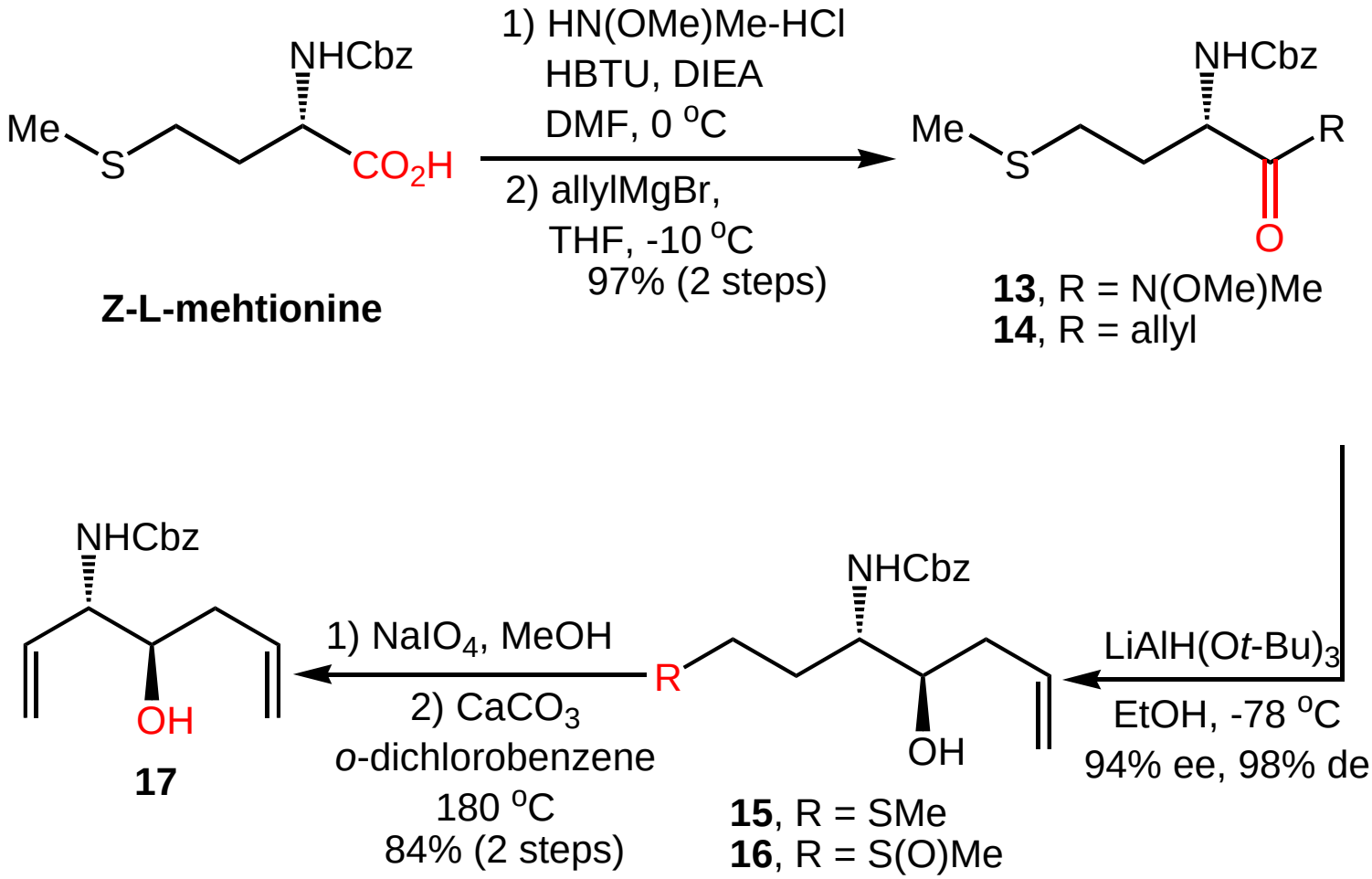


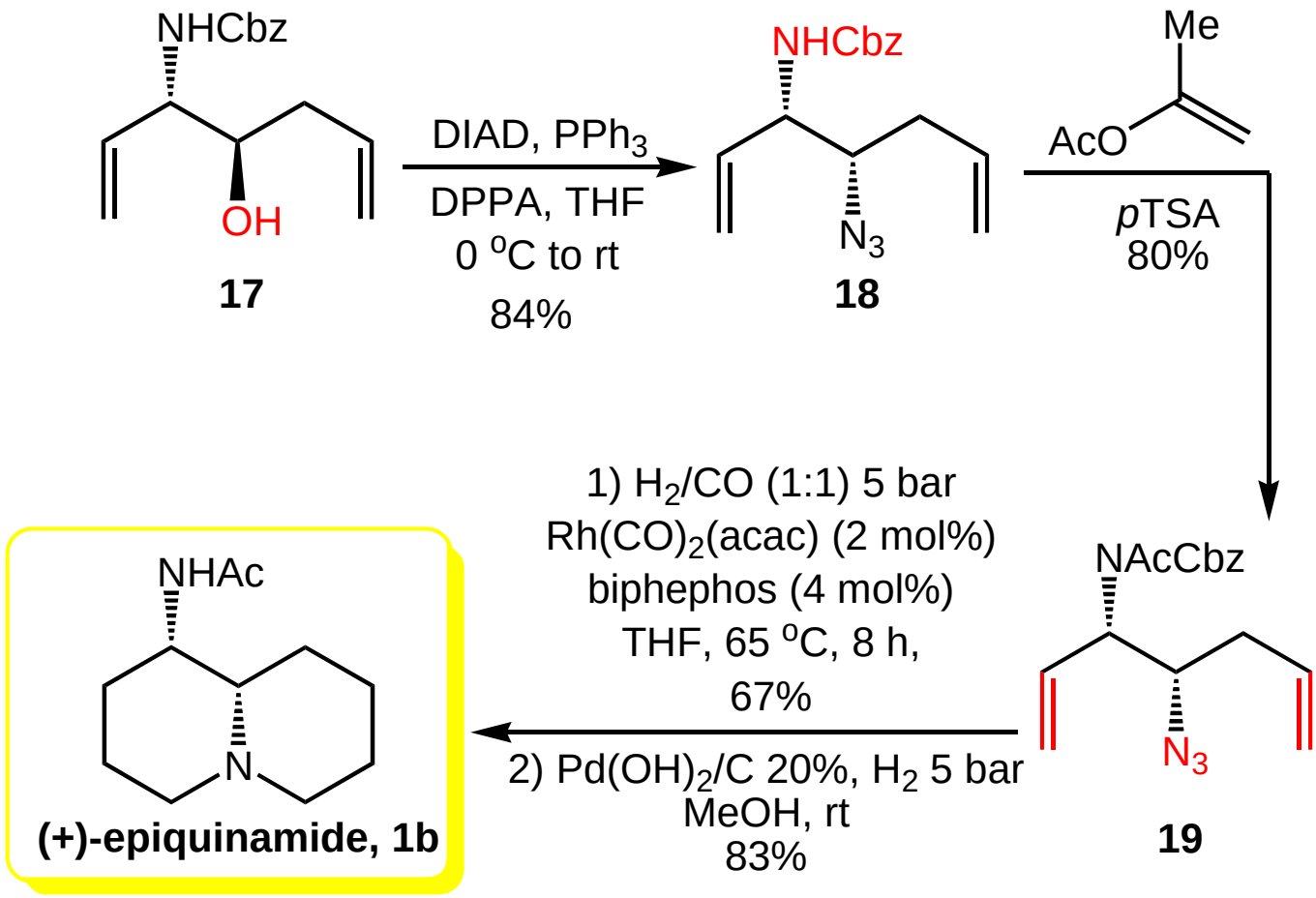

TBSO
N3
10
H2/CO (1:1) 5 bar
Rh(CO)2(acac) (2 mol%)
biphephos (4 mol%)
THF, 65 °C, 12 h
76%
TBSO
OHC
N3
CHO
11
H2 (5 bar)
Pd(OH)2/C 20%
87%
TBSO
N
12
TBAF
THF, 45 °C
84%
HO
N
(+)-lupinine, 1a

Retrosynthetic Analysis for (+)-Epiquinamide



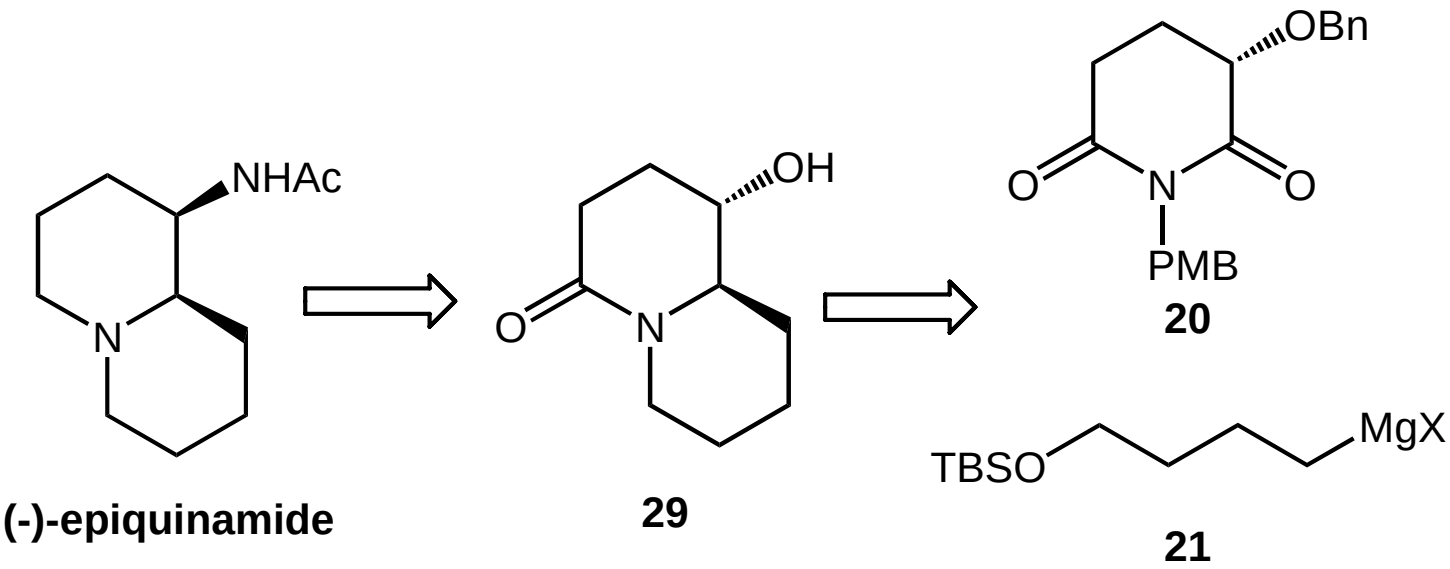
Synthesis of (+)-Epiquinamide, **1b**




NHCbz
OH
17
DIAD, PPh3
DPPA, THF
0 oC to rt
84%
NHCbz
N3
18
Me
AcO
pTSA
80%
NAcCbz
N3
19
1) H2/CO (1:1) 5 bar
Rh(CO)2(acac) (2 mol%)
biphephos (4 mol%)
THF, 65 oC, 8 h,
67%
2) Pd(OH)2/C 20%, H2 5 bar
MeOH, rt
83%
NHAc
N
(+)-epiquinamide, 1b

Huang's Work

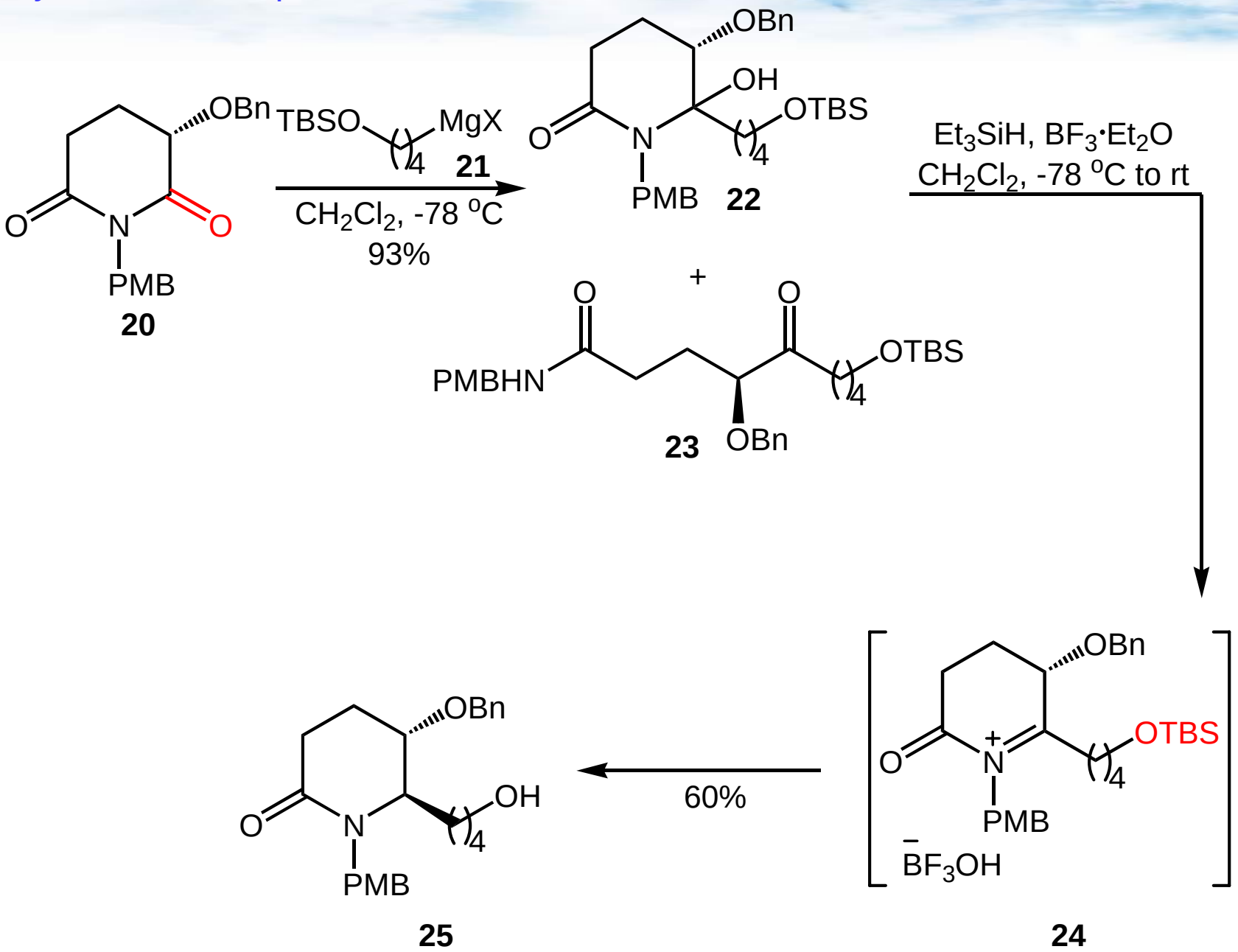
Retrosynthetic Analysis



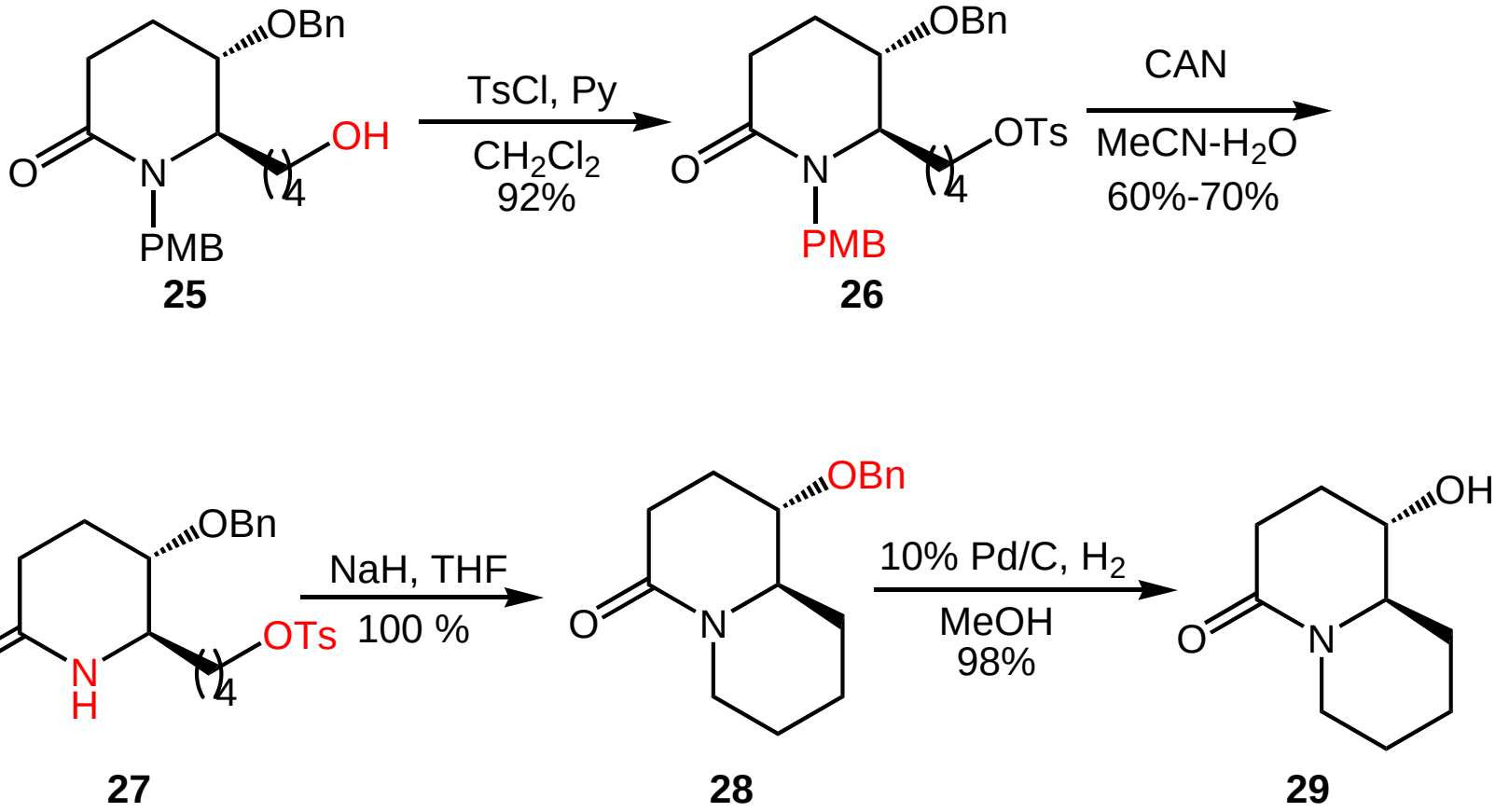
(-)-epiquinamide **29**

Huang, P.-Q. *et al Org. Lett.* **2006**, *8*, 1435-1438

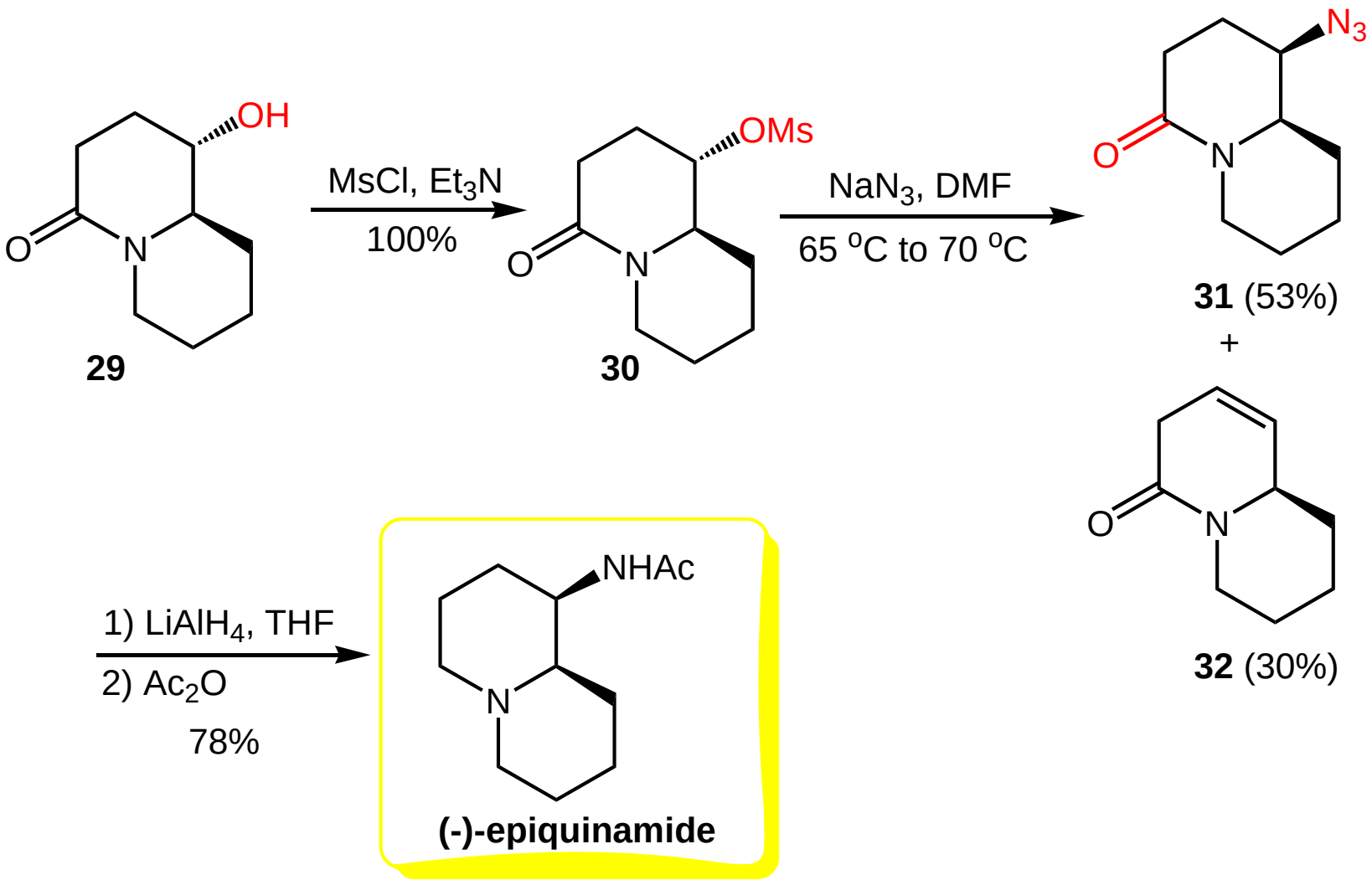
Synthesis of 2-Piperidinone Alcohol **25**



Synthesis of the Common Intermediate **29**

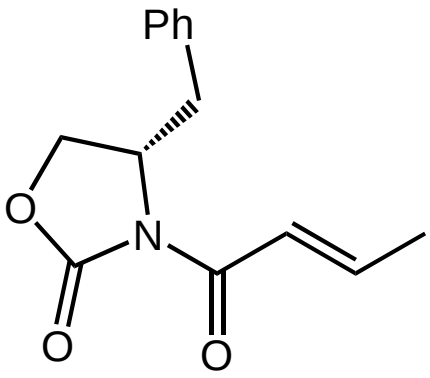


Synthesis of (-)-Epiquinamide



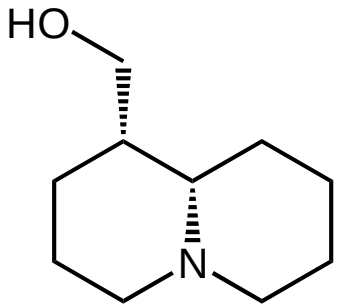
Summary

This Work:

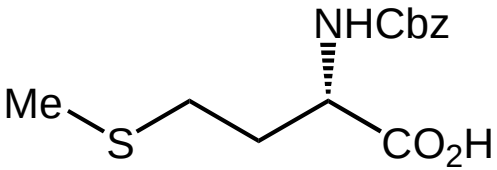


8 steps

overall yield 15%

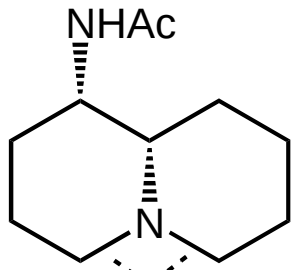


(+)-lupinine, 1a



9 steps

overall yield 29%

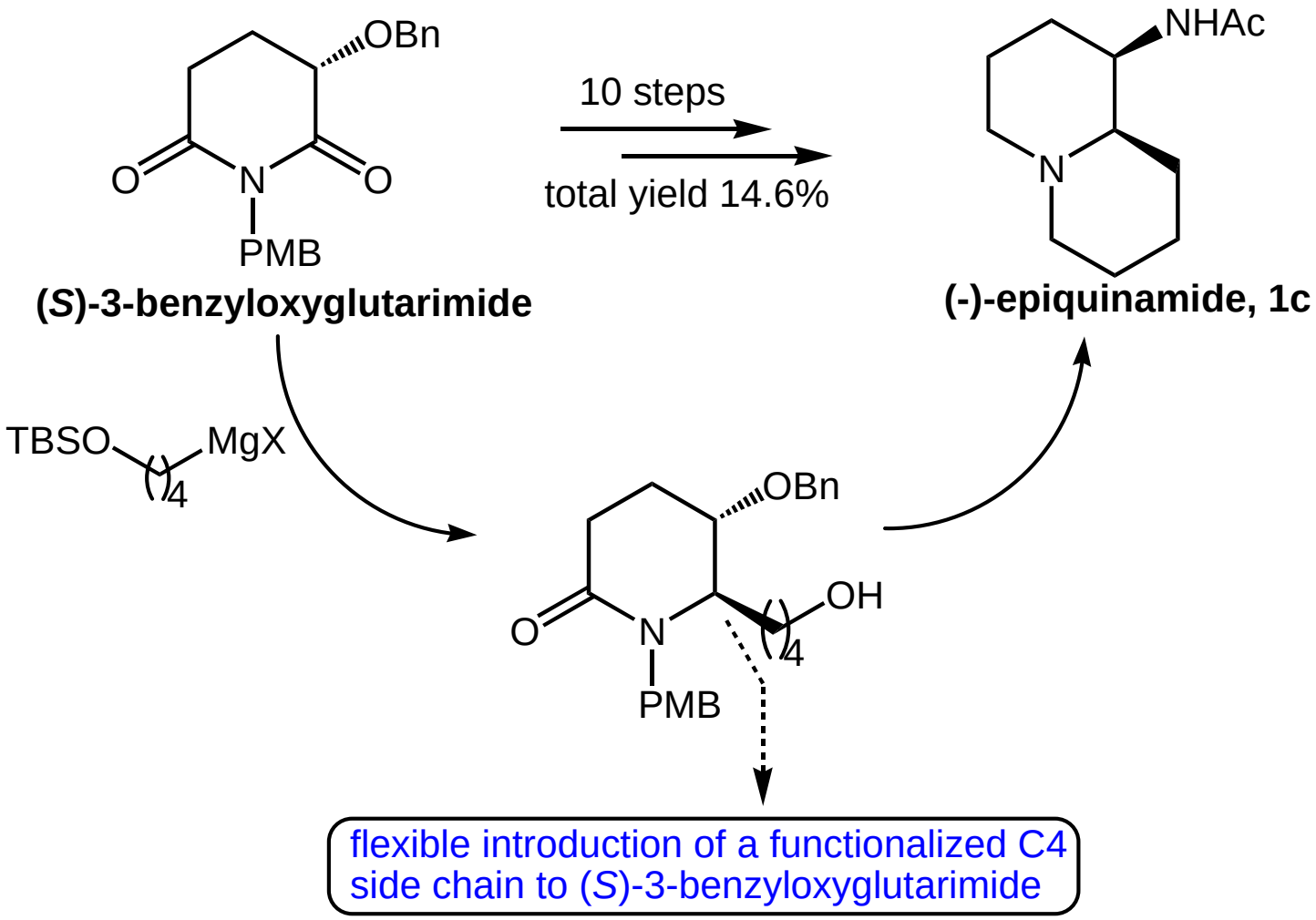


(+)-epiquinamide, 1b

bidirectional regioselective hydroformylation

tandem azide reduction/ reductive bis-amination

Huang's Work


OBn
O
N
O
PMB
(S)-3-benzyloxyglutarimide
10 steps
total yield 14.6%
NHAc
N
(-)-epiquinamide, 1c
TBSO
MgX
4
OBn
OH
O
N
4
PMB
flexible introduction of a functionalized C4 side chain to (S)-3-benzyloxyglutarimide

In recent years, synthetic strategies toward piperidine- and pyrolidine-containing alkaloids have often implemented transition-metal-catalyzed transformations. In this regard, the ring closing metathesis (RCM) has found its way for the construction of many alkaloids, but a prerequisite for performing a RCM is the presence of two olefinic partners in the substrate to be heterocyclized, one of them being generally a homoallylamine. As an alternative, a homoallylamine could also be identified as an ideal substrate for performing a hydroformylation. This atom-economic proprocess consists of a formal addition of H_2/CO across an olefin catalyzed by Rh(I) and has recently emerged as a powerful method in the synthesis of alkaloids. Thus, if the introduction of the aldehyde function occurs regioselectively at the terminal carbon atom of the alkene function, the presence of the nucleophilic nitrogen atom in the allylamine will allow us to form an internal imine directly amenable to a six-membered N-heterocycle.

In conclusion, we successfully realized the total syntheses of two quinolizidine alkaloids, (+)-lupinine **1a** (8 steps, overall yield 15% from **4**) and (+)-epiquinamide **1b** (9 steps, overall yield 29% from Cbz-L-methionine), using a bidirectional regioselective hydroformylation of chiral bis-homoallylic azides as a key step followed by a highly efficient tandem catalytic azide reduction/reductive bis-amination process. Taking advantage of the exceptional stability of azides during the hydroformylation process, the proposed methodology is well suited for the preparation of quinolizidine alkaloids. Moreover, the use of methylsulfide compounds as a hidden terminal alkene function may be an attractive strategy for subsequent hydroformylation. Applying the hydroformylation reaction in the synthesis of other alkaloids is currently underway in our laboratories.