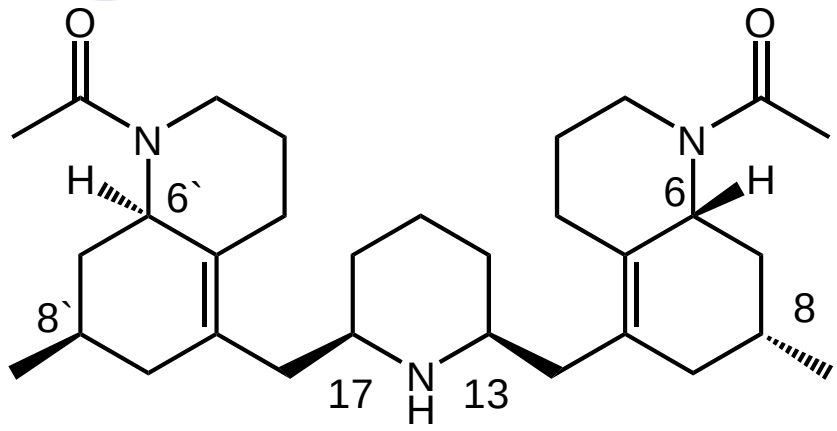
Literature Report
Total Synthesis of (-)-Lycoperine A

Checker: O.-A. Chen

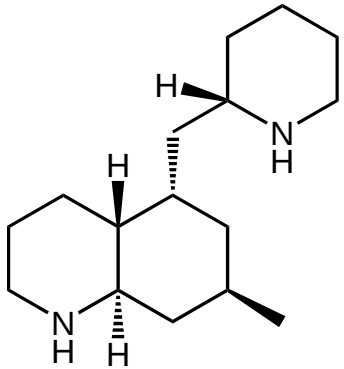
J. Tang

2009-12-29

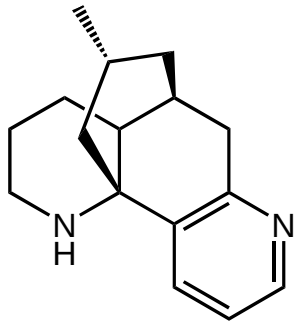
Rychnovsky, S. D. *et al*. *Org. Lett.* **2009**, ASAP



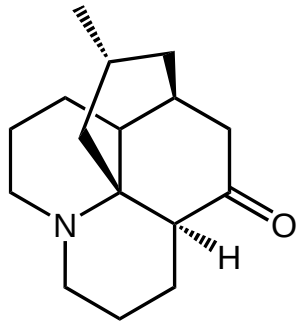
Lycoperine A



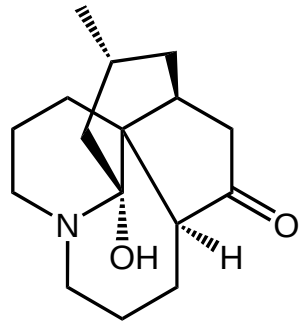
Phlegmarine



Lycodine

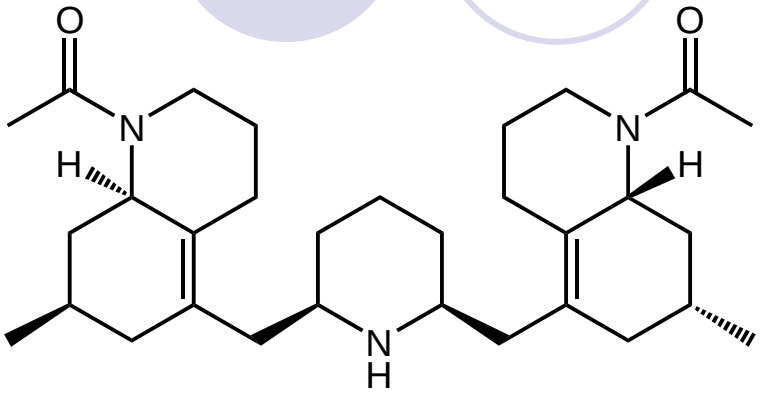


Lycopodine

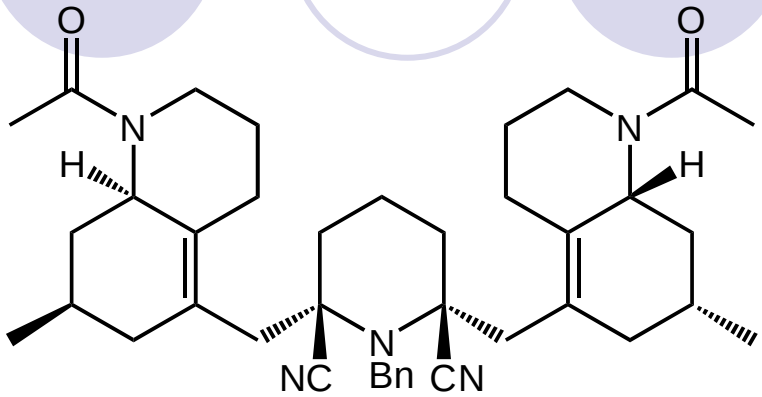


Fawcettimine

Retrosynthetic Analysis for Lycoperine A

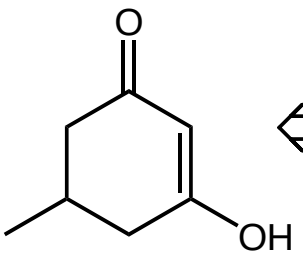


1



2

Alkylation



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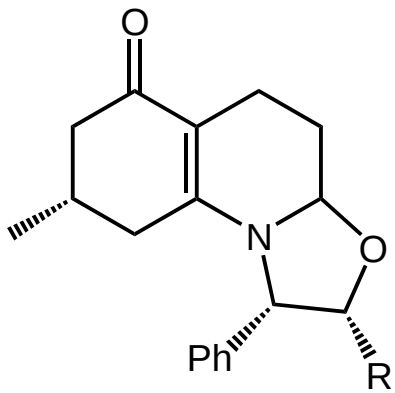

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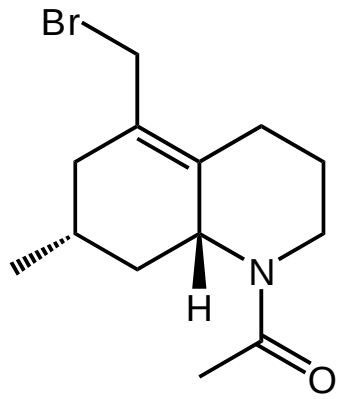

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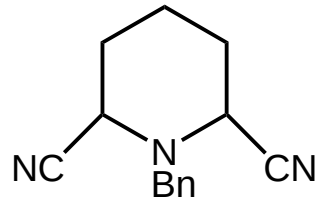
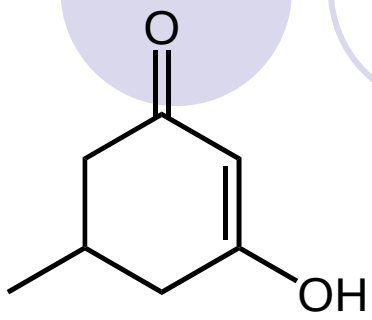


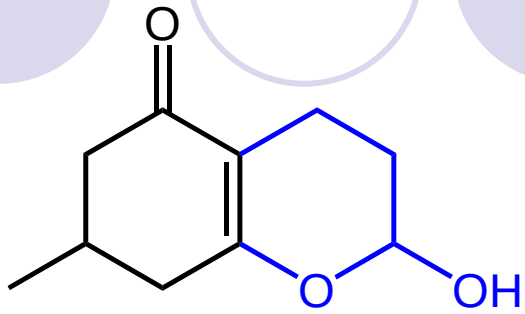
3

Synthesis of Allyl Bromide **4** for Double Alkylation



6

acrolein, THF,
Al_2O_3, 62%



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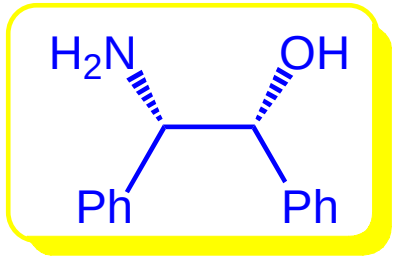
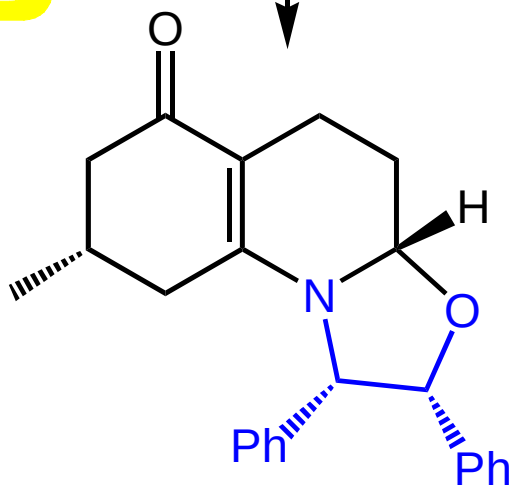


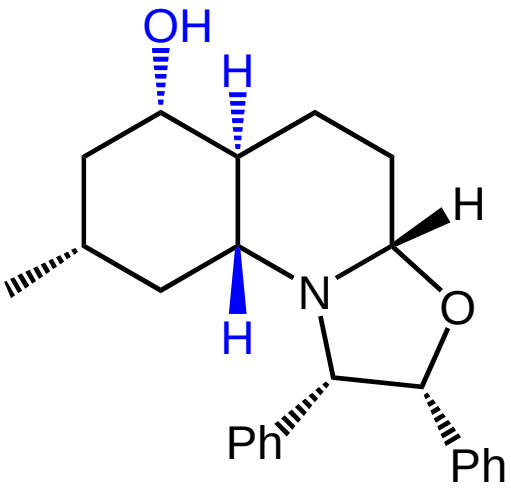
$Cu(OTf)_2$, $MgSO_4$,
CH_2Cl_2, 96%



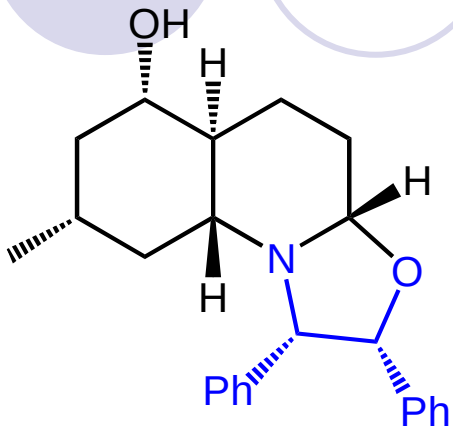
11

Na

THF/IPA
67%



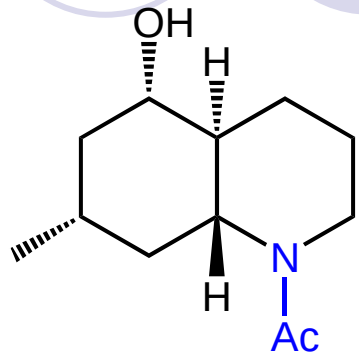
12



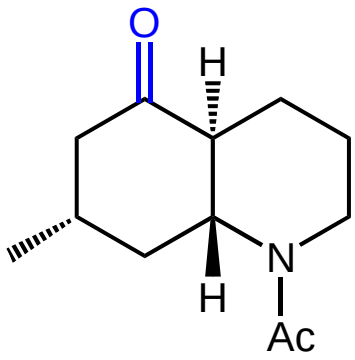
12

1) H_2 (500 psi), HCl
$Pd(OH)_2/C$

2) Ac_2O, Et_3N, MeOH,
70% over 2 steps



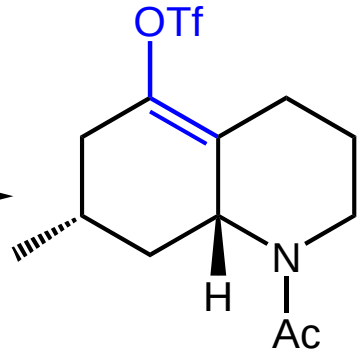
DMP, DCM, 99%



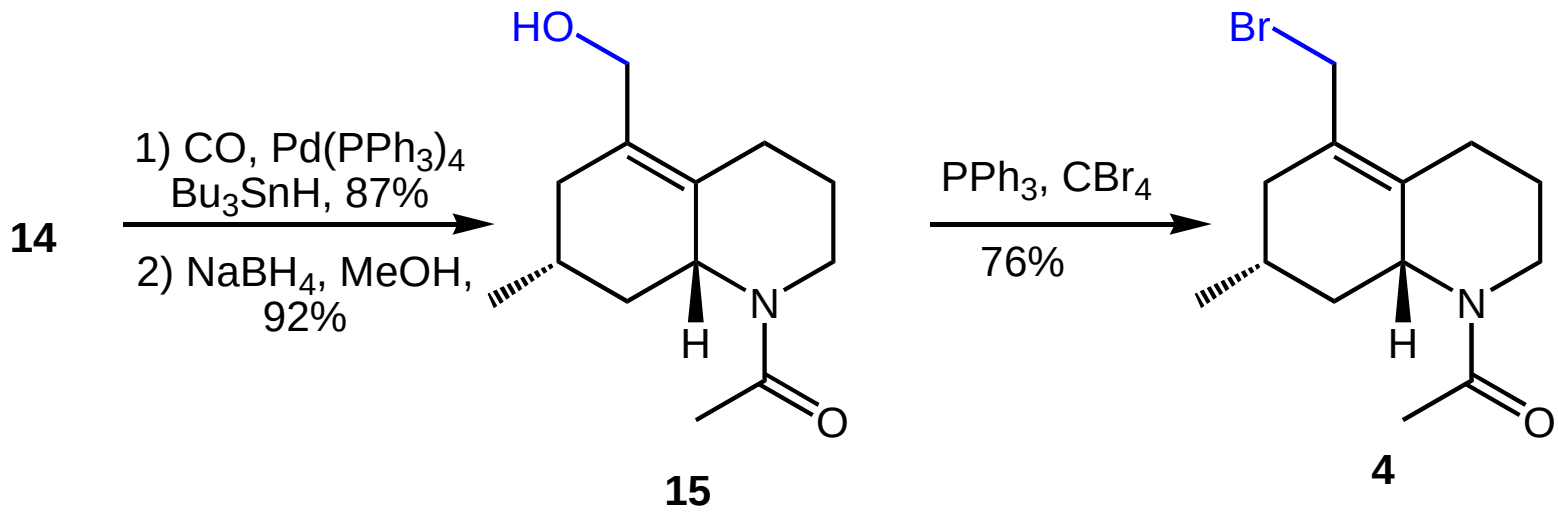
13

t-BuOK, $PhNTf_2$

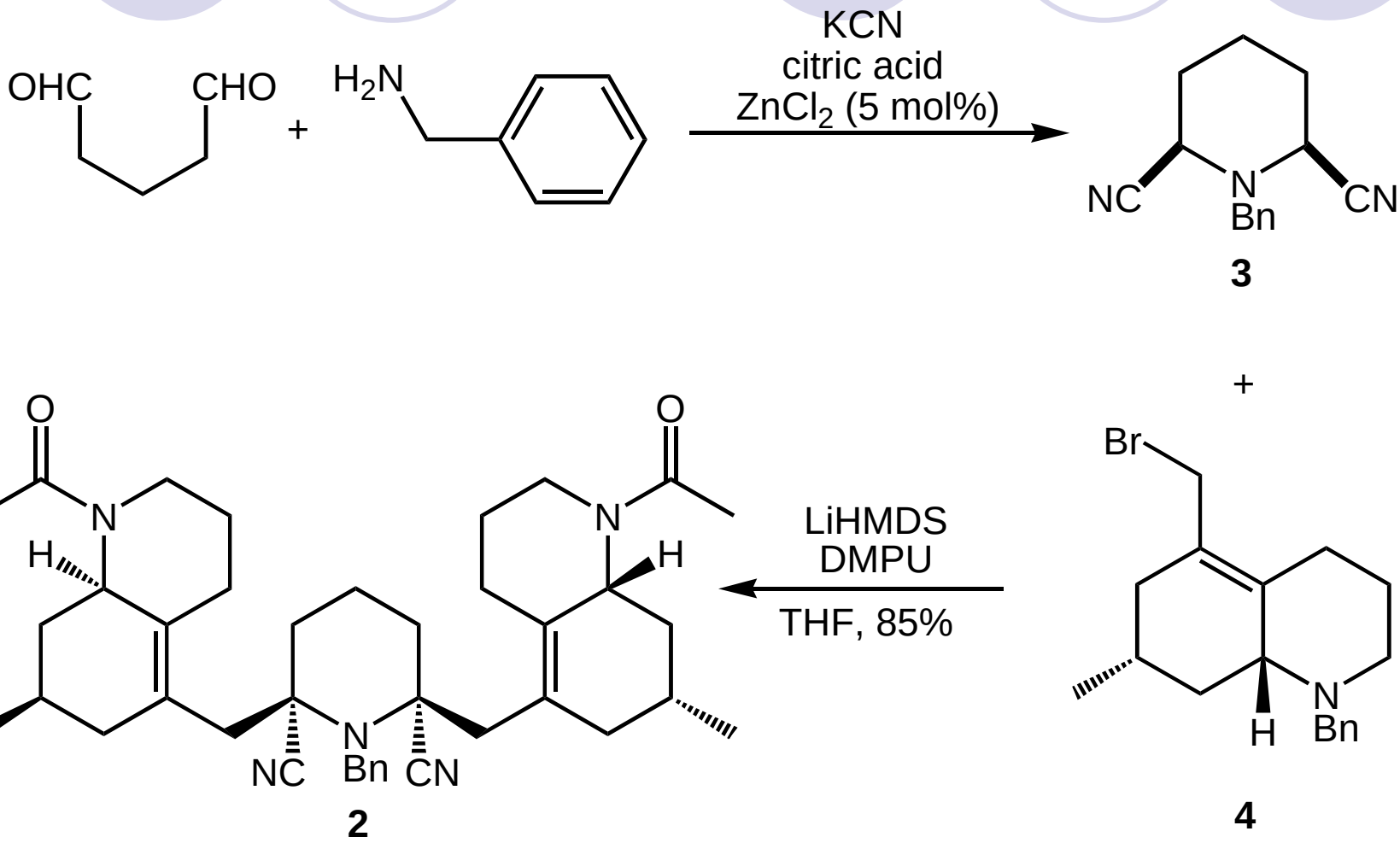
DMF/THF
-78 ^{o}C, 79%



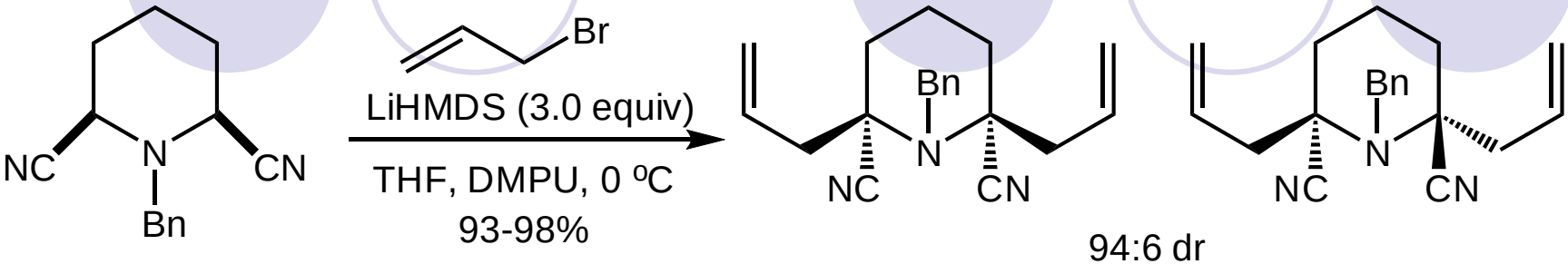
14


14
1) CO, Pd(PPh3)4
Bu3SnH, 87%
2) NaBH4, MeOH,
92%
HO
N
H
O
15
PPh3, CBr4
76%
Br
N
H
O
4

Double Alkylation and Preparation of Lycoperine A

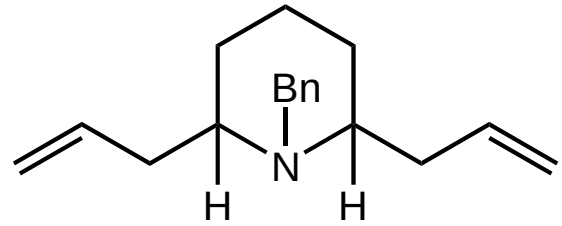


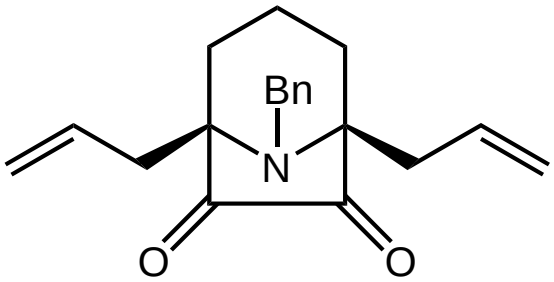
Alkylation and Decyanation of Dinitrile **3**



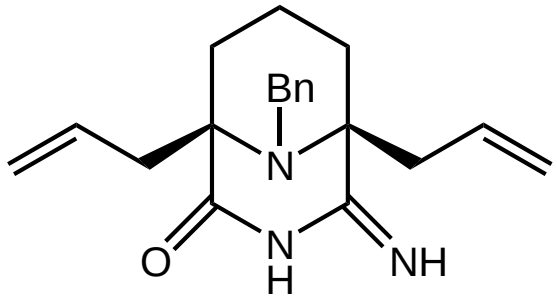
3 ***cis*-16** ***trans*-16**

***cis*-16** → (Li, (*ca.* 12 equiv), liq. NH_3/THF, -78 °C, 5 min, 0.02 M) → (2 M HCl aq., THF, RT, 15 min) → **17**: 4%, 1:1 dr

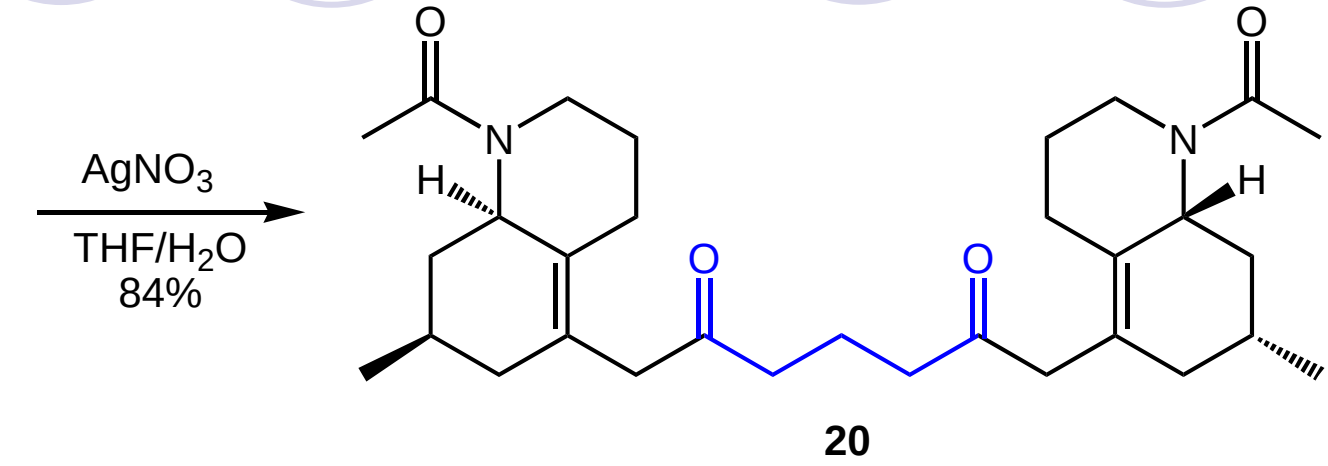




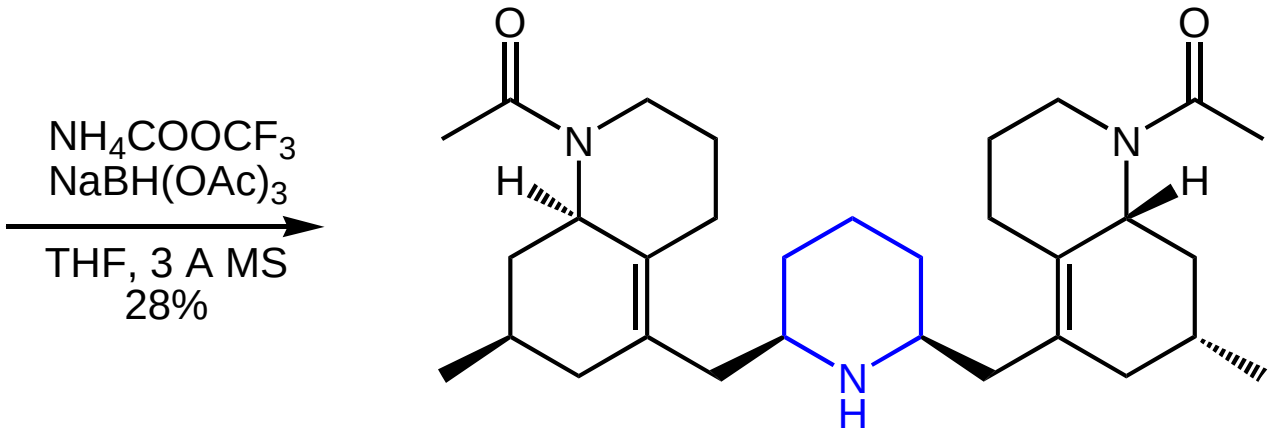
+



18: 13% **19**: 10%

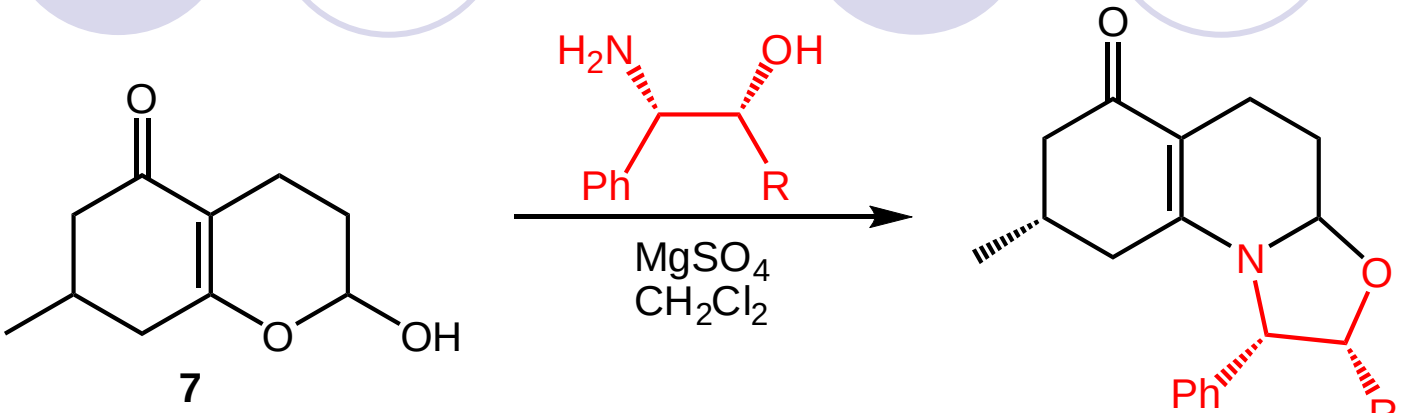

AgNO3
THF/H2O
84%
O
N
H
O
O
O
N
H

20


NH4COOCF3
NaBH(OAc)3
THF, 3 A MS
28%
O
N
H
N
H
O
N
H

1

Desymmetrization of Hemiacetal **7** with Amino Alcohols



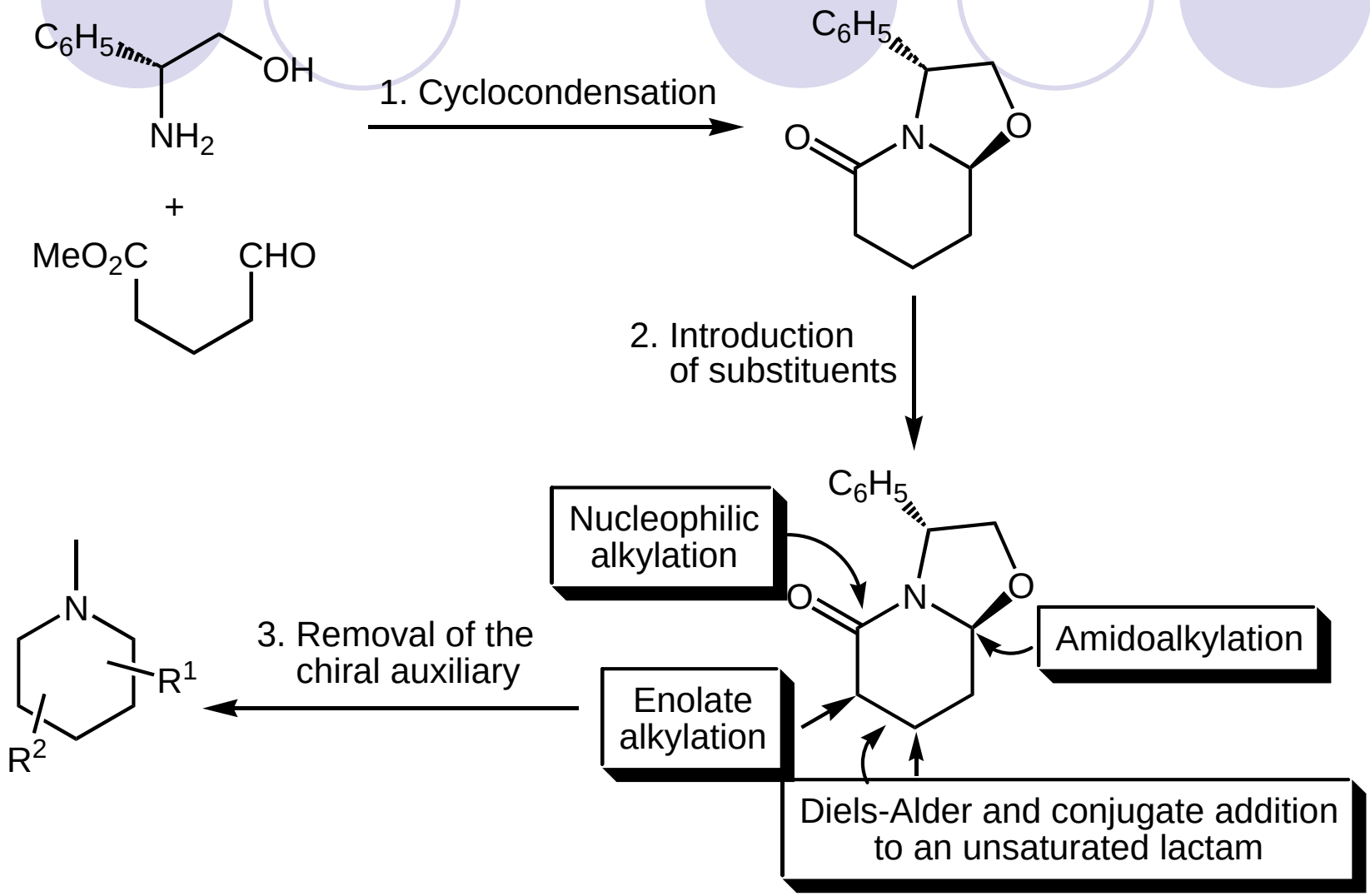
7

8 (R = H)
9 (R = Ph)

10 (R = H)
11 (R = Ph)

Entry	Auxiliary	Lewis acid	Conditions	Yield (%)	dr
1	**8** (2 equiv)	$Zn(ClO_4)_2 \cdot 6H_2O$	RT, 15 h	100	2.7:1
2	**8** (2 equiv)	$Sc(OTf)_3$	0 °C, 2 d	96	2.7:1
3	**8** (2 equiv)	$Cu(OTf)_2$	0 °C, 2 d	92	4:1
4	**9** (2 equiv)	$Cu(OTf)_2$	0 - 10 °C, 16 h	95	20:1
5	**9** (1.1 equiv)	$Cu(OTf)_2$	0 °C, 22 h	96	20:1

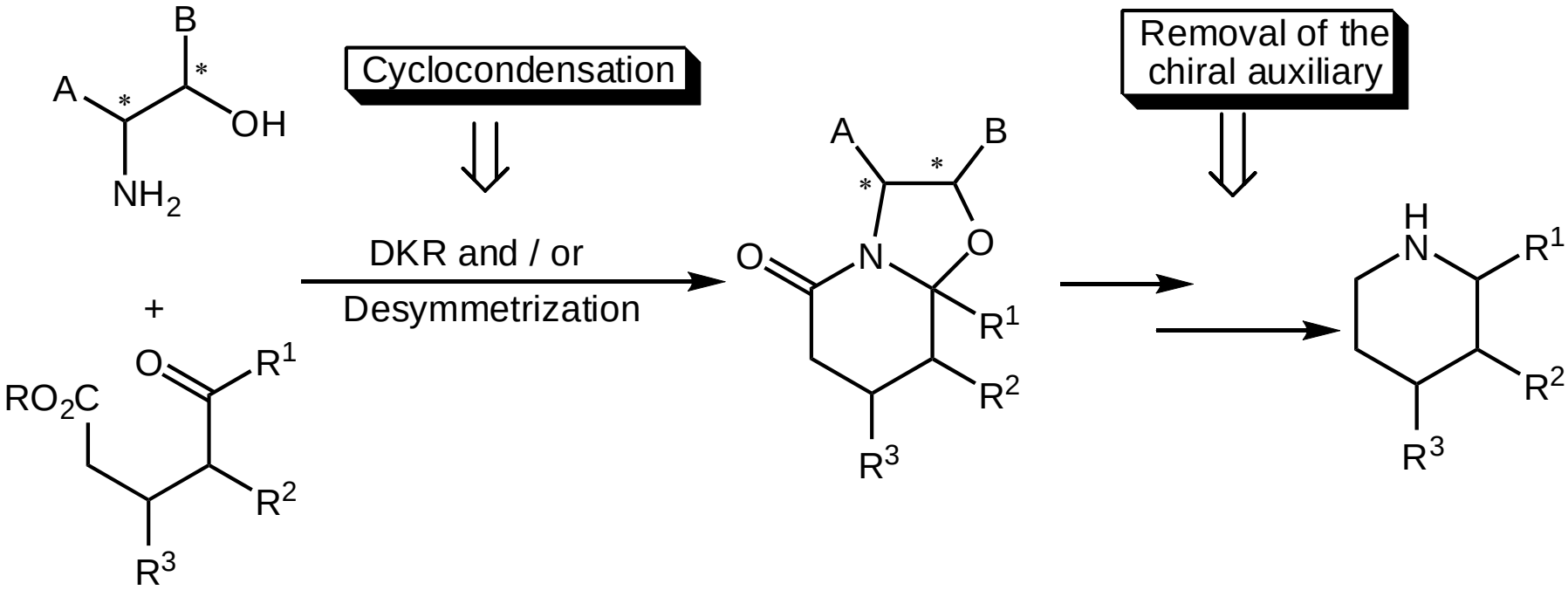
Synthetic strategy: First generation oxazolopiperidone lactams.



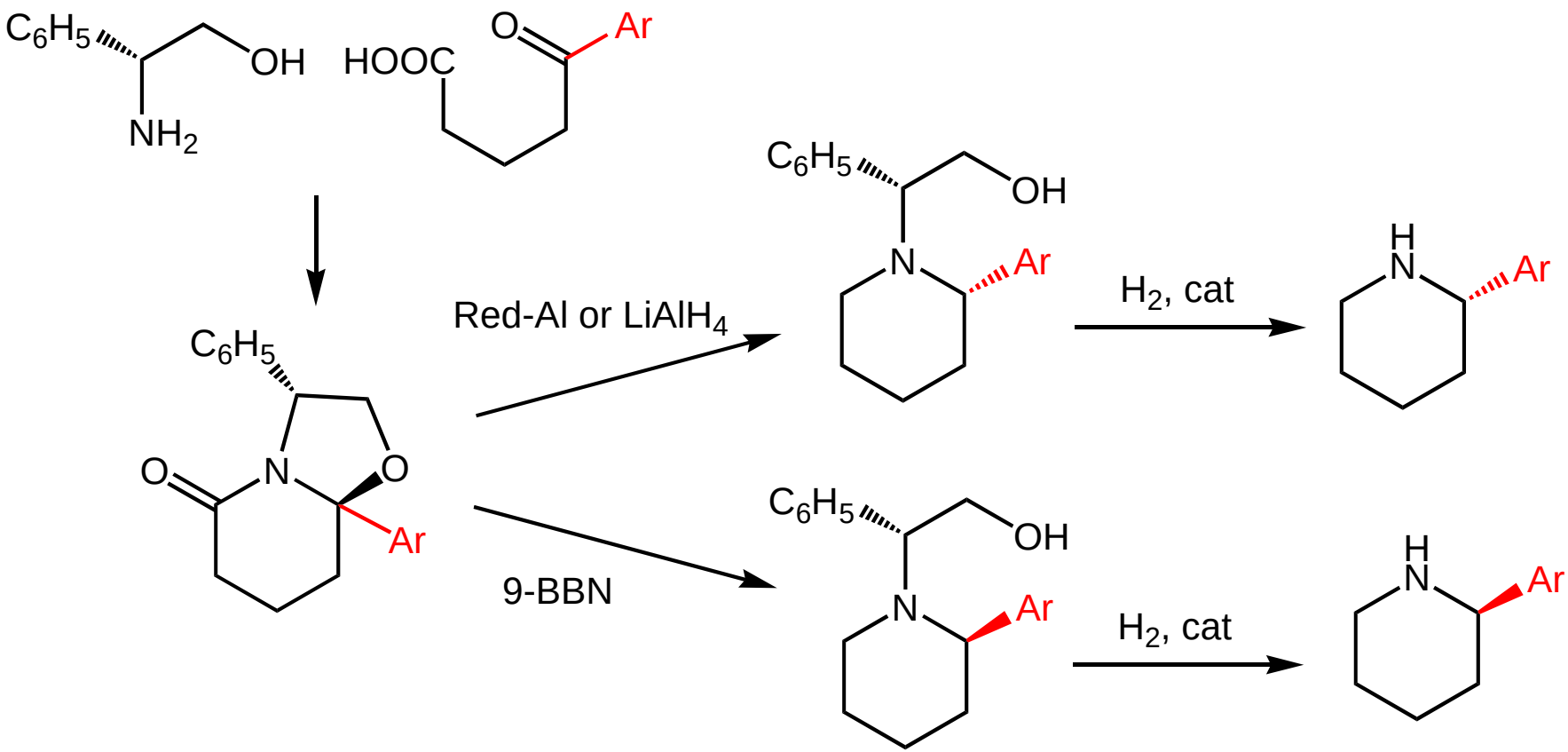
Royer, J. *et al. Chem. Soc. Rev*. **1999**, *28*, 383 –394

Amat, M. *et al. Chem. Eur. J.* **2006**, *12*, 7872-7881

Synthetic strategy: Second generation oxazolopiperidone lactams



Amat, M. *et al. Chem. Eur. J.* **2006**, *12*, 7872-7881



Amat, M. *et al. Chem. Eur. J.* **2006**, *12*, 7872-7881

Lycopodium alkaloids are an important class of natural products due to their diversity and their varied biologicalactivities. Several of these alkaloids inhibit acetylcholinesterase (AChE), which is responsible for the breakdown of the neurotransmitter acetylcholine. After the discovery of this significant biological activity around 1986, there was a surge of interest in Lycopodium alkaloids, and subsequently numerous new alkaloids in this class were discovered and characterized. In the time span from 1993 to 2004, 81 new Lycopodium alkaloids had been reported. Of the Lycopodium alkaloids discovered in the 1980s, huperzine A (HupA) demonstrated the greatest inhibition of acetylcholinesterase, and its synthesis was first reported by Qian and Ji in 1989. Recent studies subjecting rats to HupA have demonstrated increased efficiency in learning and memory and have been considered potential lead compounds for the treatment of Alzheimer's disease.

Synthesis of lycoperine A was accomplished using a desymmetrization reaction that led to an efficient synthesis of the octahydroquinoline **4**. A double alkylation reaction and subsequent piperidine ring formation completed the synthesis and allowed the configuration of the natural product to be assigned as 6*R*, 6`*R*, 8*R*, 8`*R*, 13*S*,17*R*.