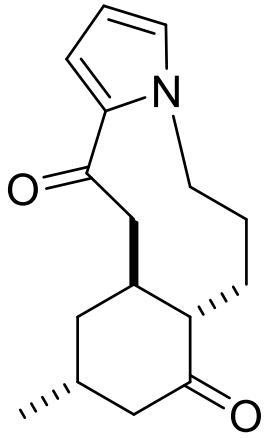
Asymmetric Total Synthesis and Structure Elucidation of Huperzine H

Shinya Shiomi, Kaewsri Wilailak, Wataru Soutome, Hiromitsu Takayama, Mariko Kitajima, and Hayato Ishikawa*



Huperzine H (**1**)

- Huperzine H is a *lycopodium* alkaloid that was isolated from the plant *Huperzia serrata* in 1999 by Zhu and co-workers
- Acts as a cholinesterase inhibitor to improve levels of neurotransmitters in the brain
- Tricyclic skeleton with a 9-membered ring and a pyrrole moiety with three stereogenic centers
- This work: synthesis has two pathways with two key steps
  - Key steps: Mukaiyama-Michael addition and intramolecular S_N2

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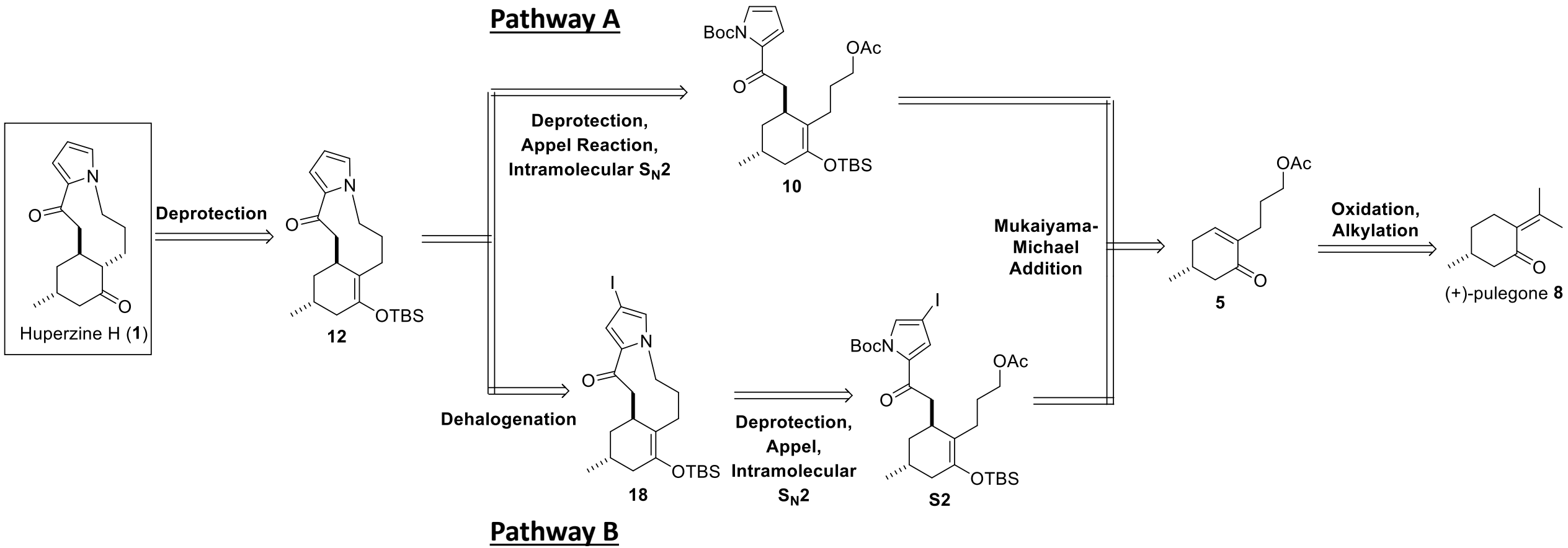
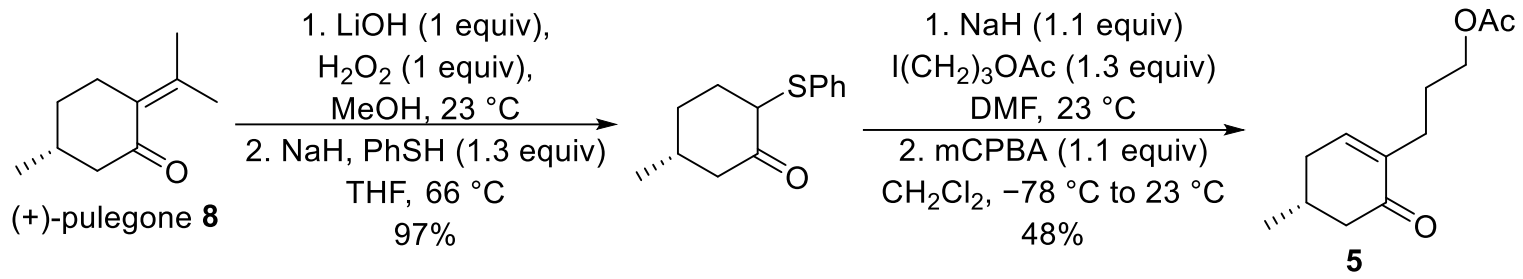
Jennifer LaPoff
Liu Group
April 29th, 2022

Retrosynthetic Analysis

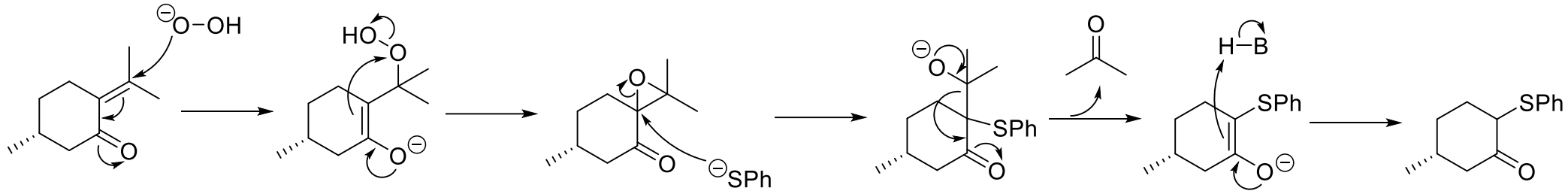




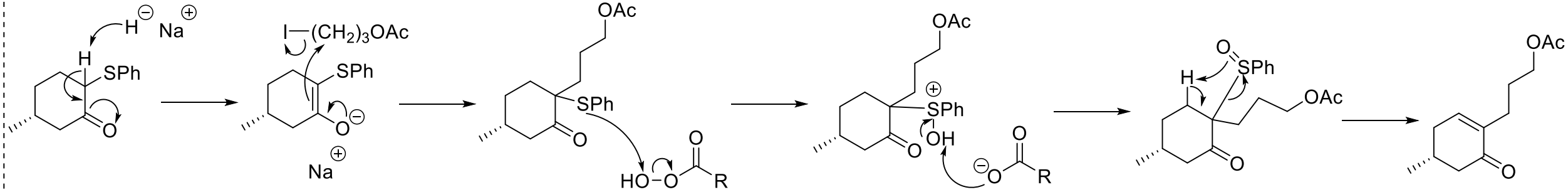
(+)-pulegone **8**

5

Epoxidation-Thiolation

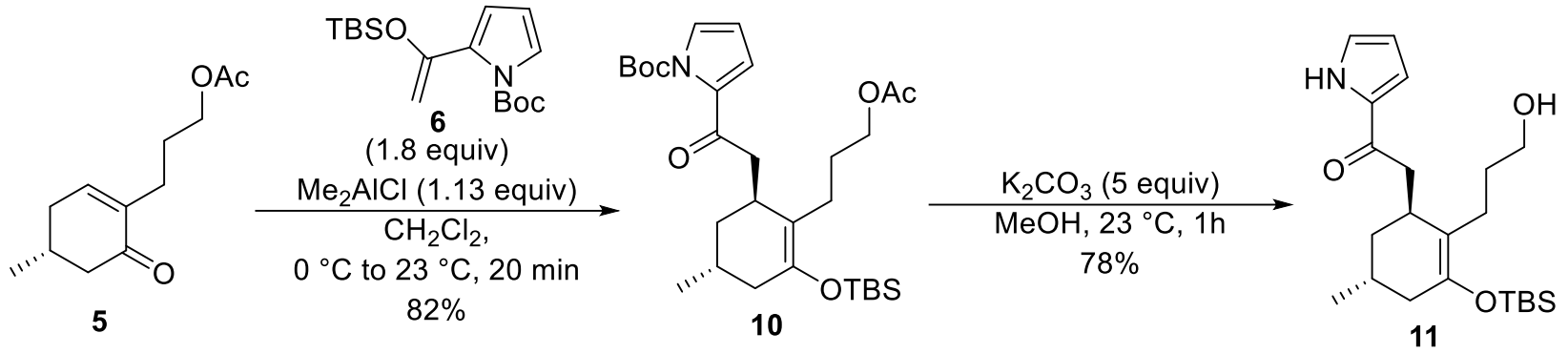


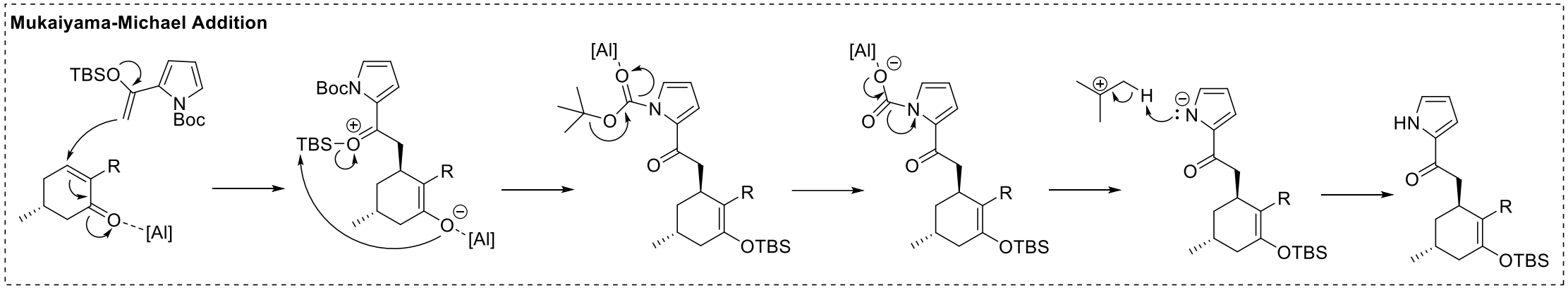
Alkylation then Oxidation

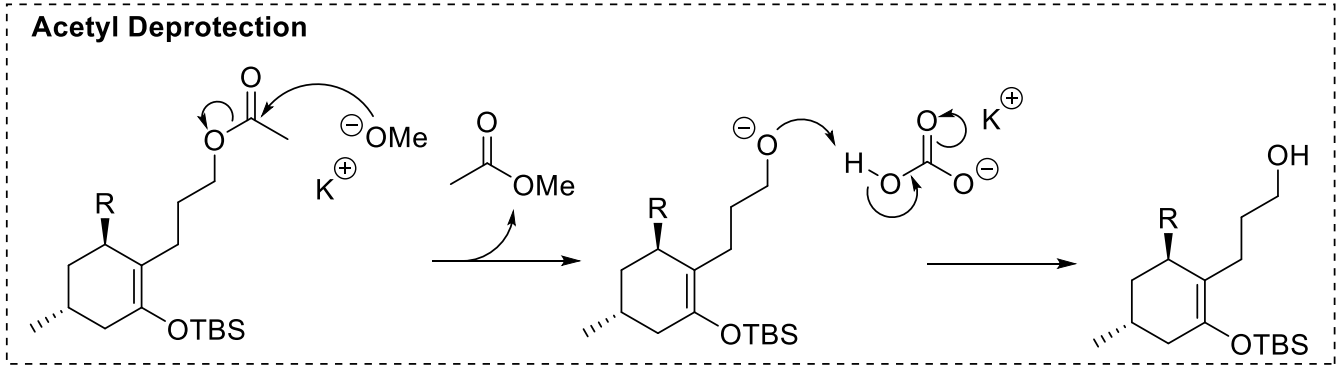


J. Org. Chem. **2013**, 78, 5647-5668.

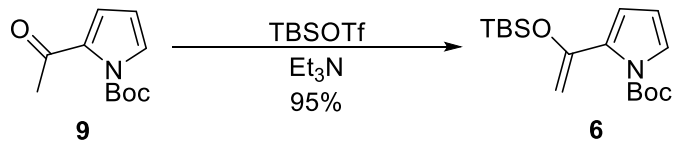
Pathway A

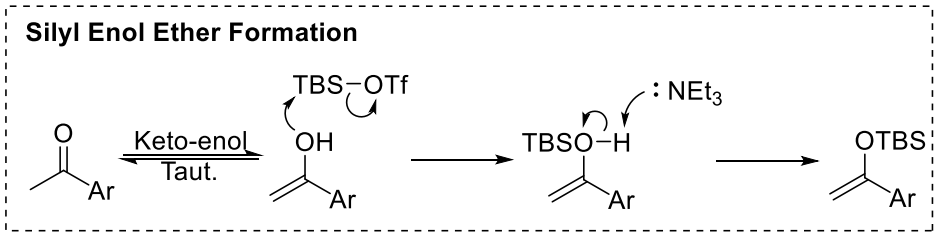


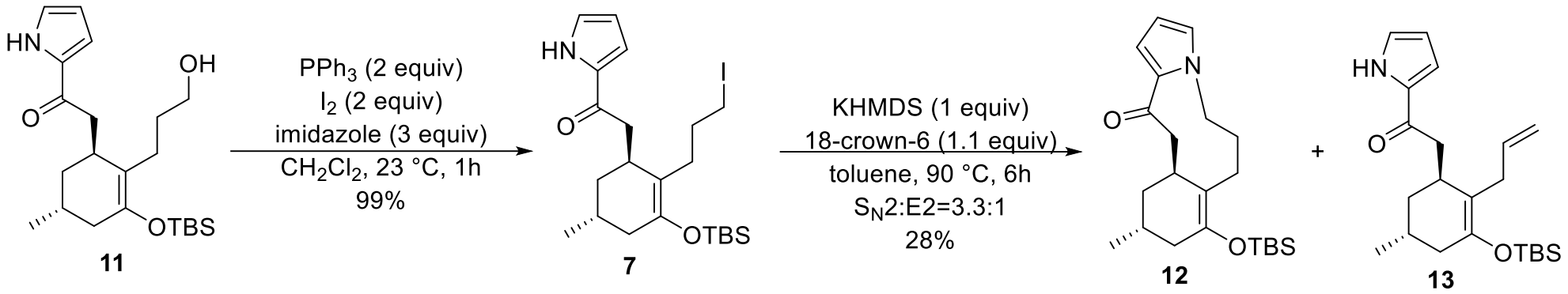


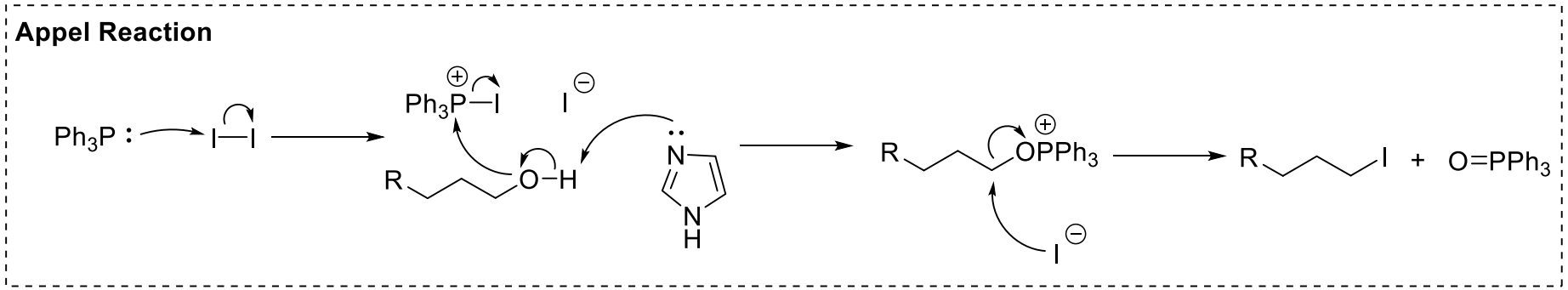


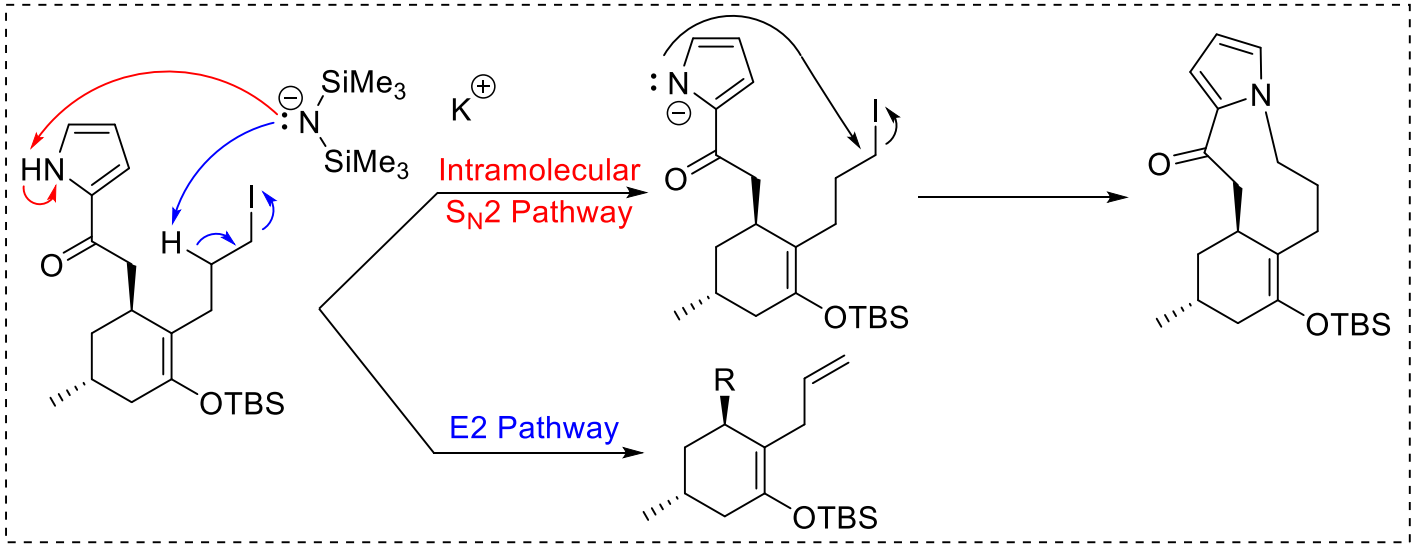
Aside:



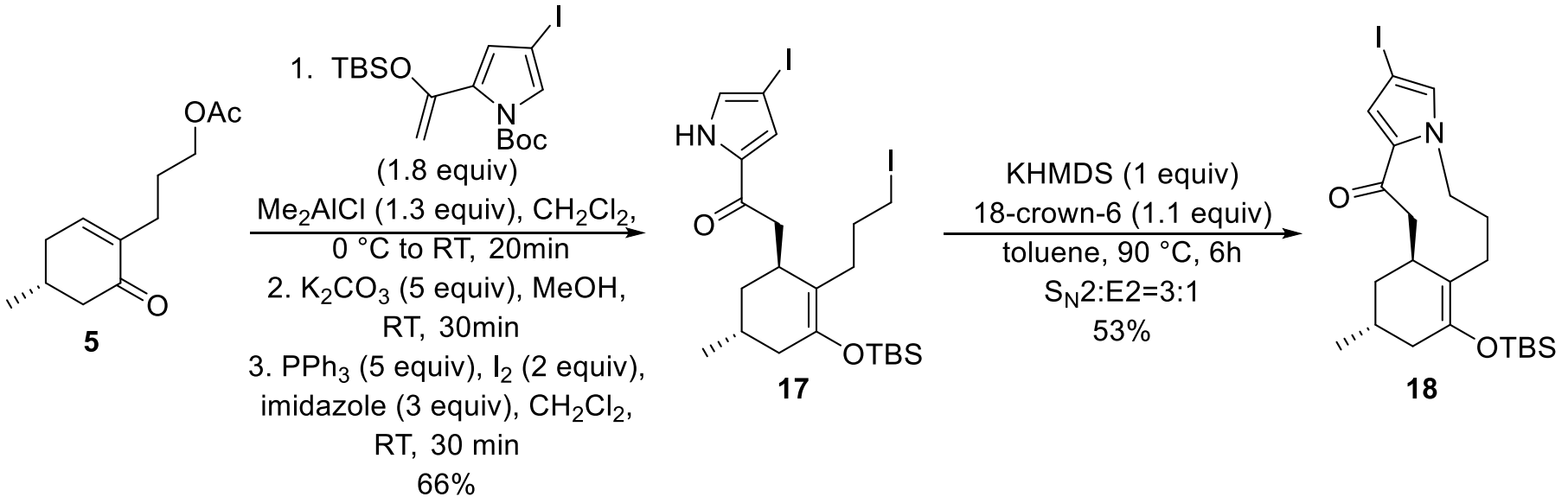


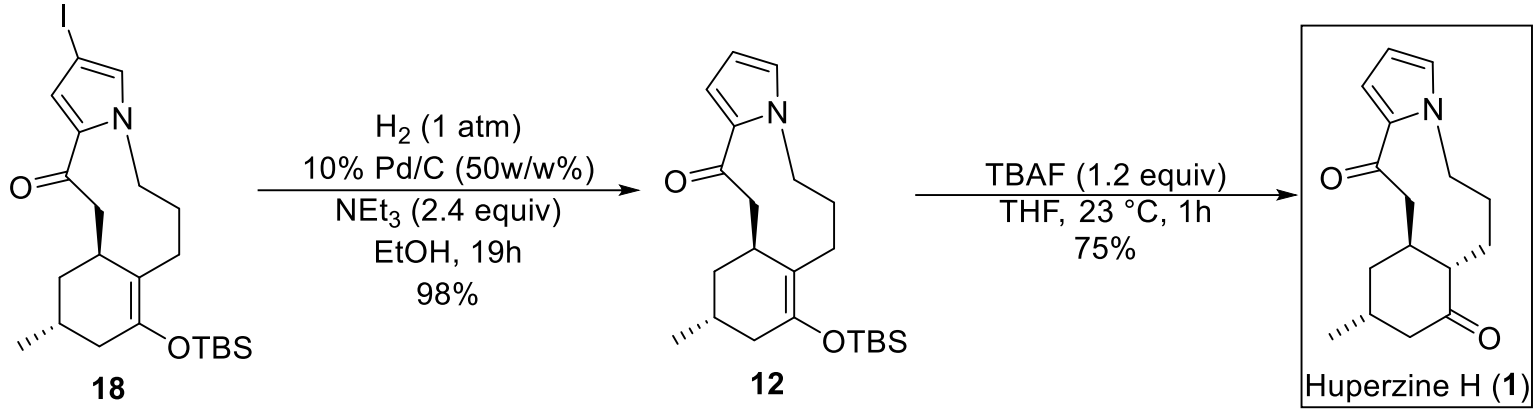

HN
OH
O
OTBS
11
PPh3 (2 equiv)
I2 (2 equiv)
imidazole (3 equiv)
CH2Cl2, 23 °C, 1h
99%
HN
I
O
OTBS
7
KHMDS (1 equiv)
18-crown-6 (1.1 equiv)
toluene, 90 °C, 6h
SN2:E2=3.3:1
28%
N
O
OTBS
12
+
HN
O
OTBS
13


Appel Reaction
Ph3P :
I—I
Ph3P—I
I
R
O—H
N
N
H
R
OPPh3
I
R
I
+
O=PPh3


SiMe3
N
SiMe3
K
HN
O
H
I
OTBS
Intramolecular
SN2 Pathway
E2 Pathway
N
I
O
OTBS
R
OTBS
N
O
OTBS

- **Pathway B** using iodinated pyrrole
- Same mechanisms from compound **5** to compound **12**





Pathway A: 6.2% overall yield

Pathway B: 12.1% overall yield