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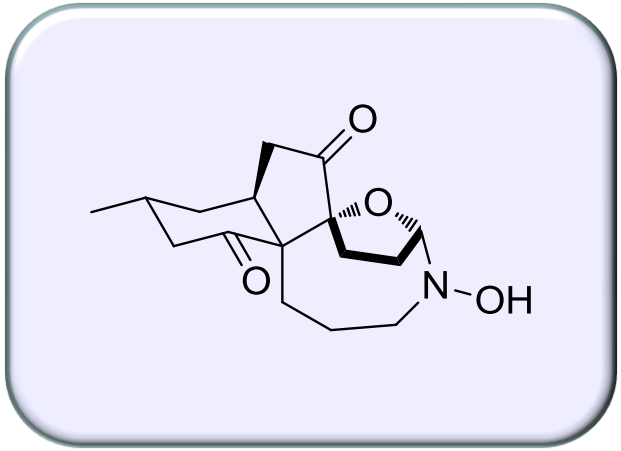
# Total Synthesis of Sieboldine A



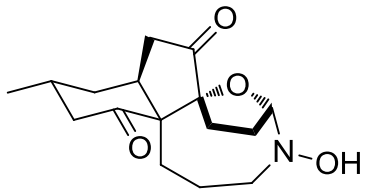

Denksport, 16.06.2011

# Sieboldine A

## Introduction:

- *Lycopodium* alkaloid
- isolated from the club moss *Lycopodium sieboldii*
- native in Japan
- structure elucidation in 2003 by Kobayashi *et al.*
- up to now 2 total synthesis published

  (Overman *et al.*, Tu *et al.*)




*Sieboldine A*

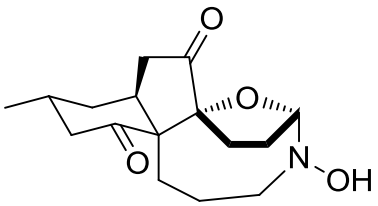
# Sieboldine A

## Biological activity:

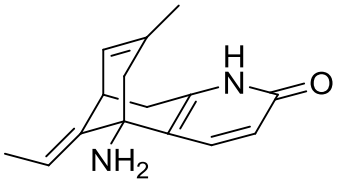
- cytotoxicity against murine lymphoma L1210 cells ($IC_{50}$ 5.1 µg/mL)
- acetylcholinesterase inhibitor ($IC_{50}$ 2.0 µg/mL)

  comparable to huperzine A ($IC_{50}$ 1.6 µg/mL)

  (huperzine A: clinical evaluation for treatment of Alzheimer's disease and schizophrenia (NCT00083590))




*Sieboldine A*

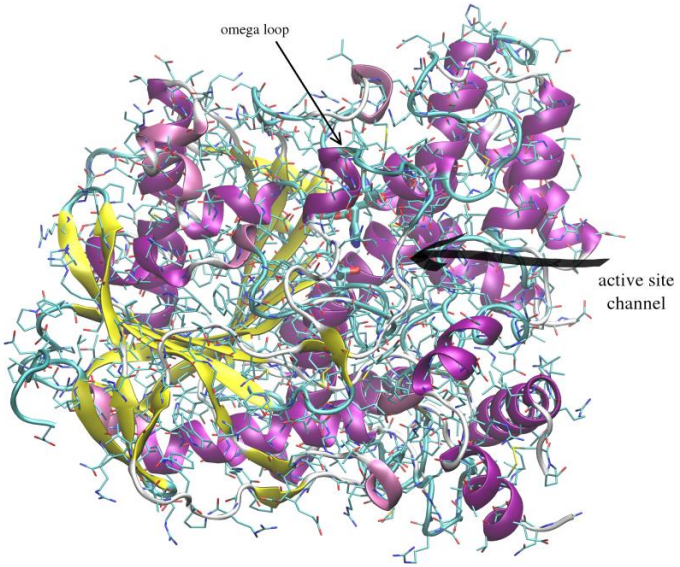


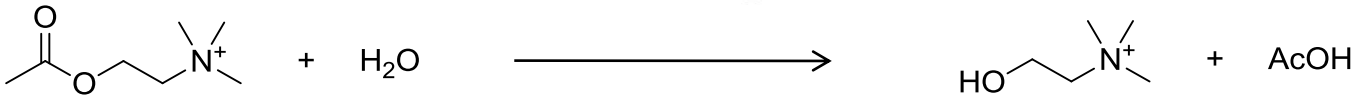

*Huperzine A*

# Sieboldine A

## Acetylcholinesterase:

... family of enzymes that catalyze the hydrolysis of acetylcholin




acetylcholin acts as neurotransmitter for the: PNS (peripheral nervous system)

CNS (central nervous system)

# Acetylcholinesterase

**Mode of action:**

- PNS (peripheral nervous system)

acetylcholin binds to acetylcholine receptors on skeletal muscle fibers

↓

ligand-gated sodium channels is opened

↓

muscle contraction

↓

acetylcholinesterase hydrolizes acetylcholin

↓

muscle relaxation

# Acetylcholinesterase

**Mode of action:**

- PNS (peripheral nervous system)

acetylcholin binds to acetylcholine receptors on skeletal muscle fibers

↓

ligand-gated sodium channels is opened

↓

muscle contraction

⇊ ***Inhibition*** → ***muscle spasm, ultimately death***

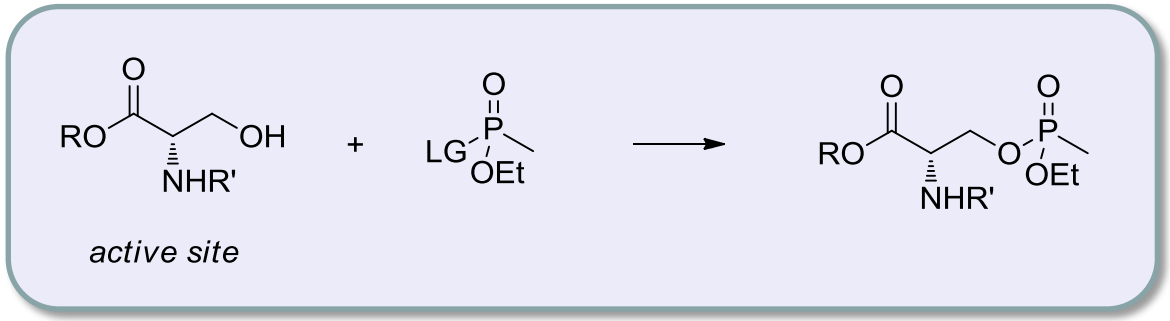
acetylcholinesterase hydrolizes acetylcholin

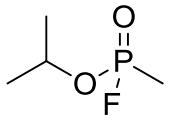
↓

muscle relaxation

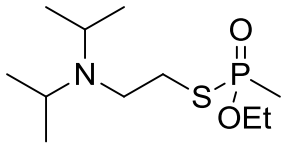
# Acetylcholinesterase

## Acetylcholinesterase Inhibition:



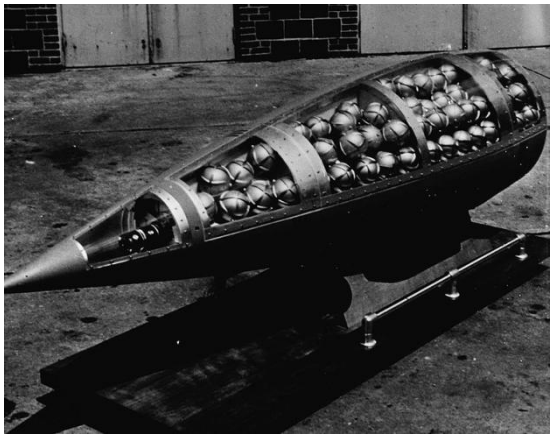

*Sarin*




*VX*

- developed in the late 1930s
- originally used as pesticides
- extremly high toxicity
- penetrates skin

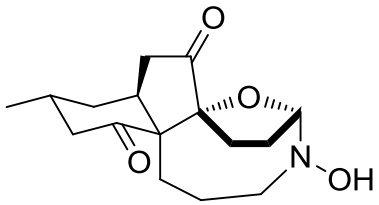
weapon of mass destruction:



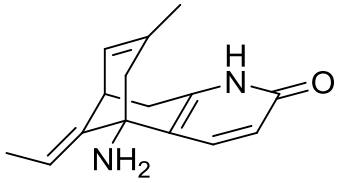
# Acetylcholinesterase

**Mode of action:** • CNS (central nervous system)

- inhibition of AChE reduces memory deficits, if the cholinergic (acetylcholine -producing) system is damaged → application against Alzheimer disease
- important role in the enhancement of sensory perceptions



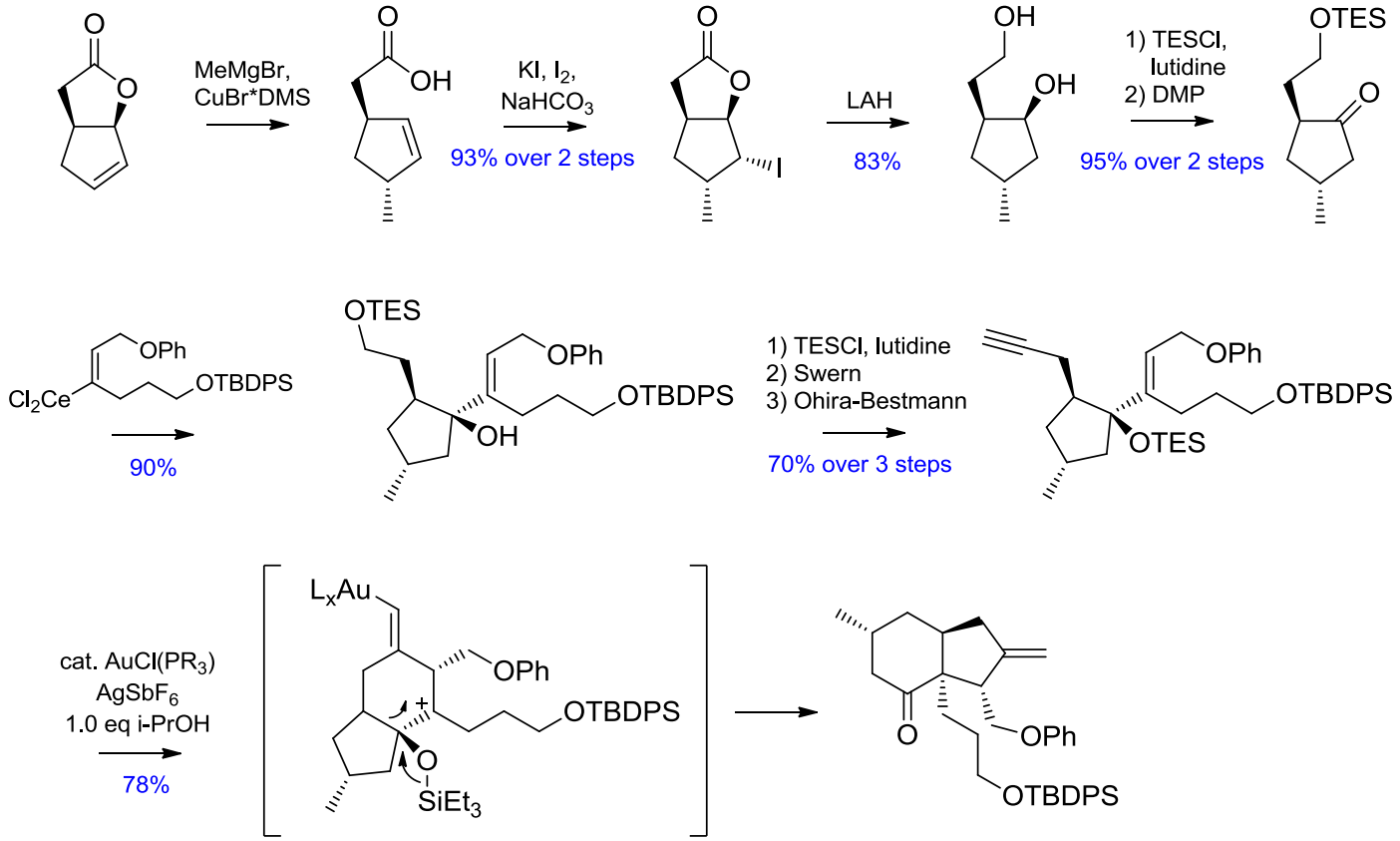

*Sieboldine A*




*Huperzine A*

# Sieboldine A

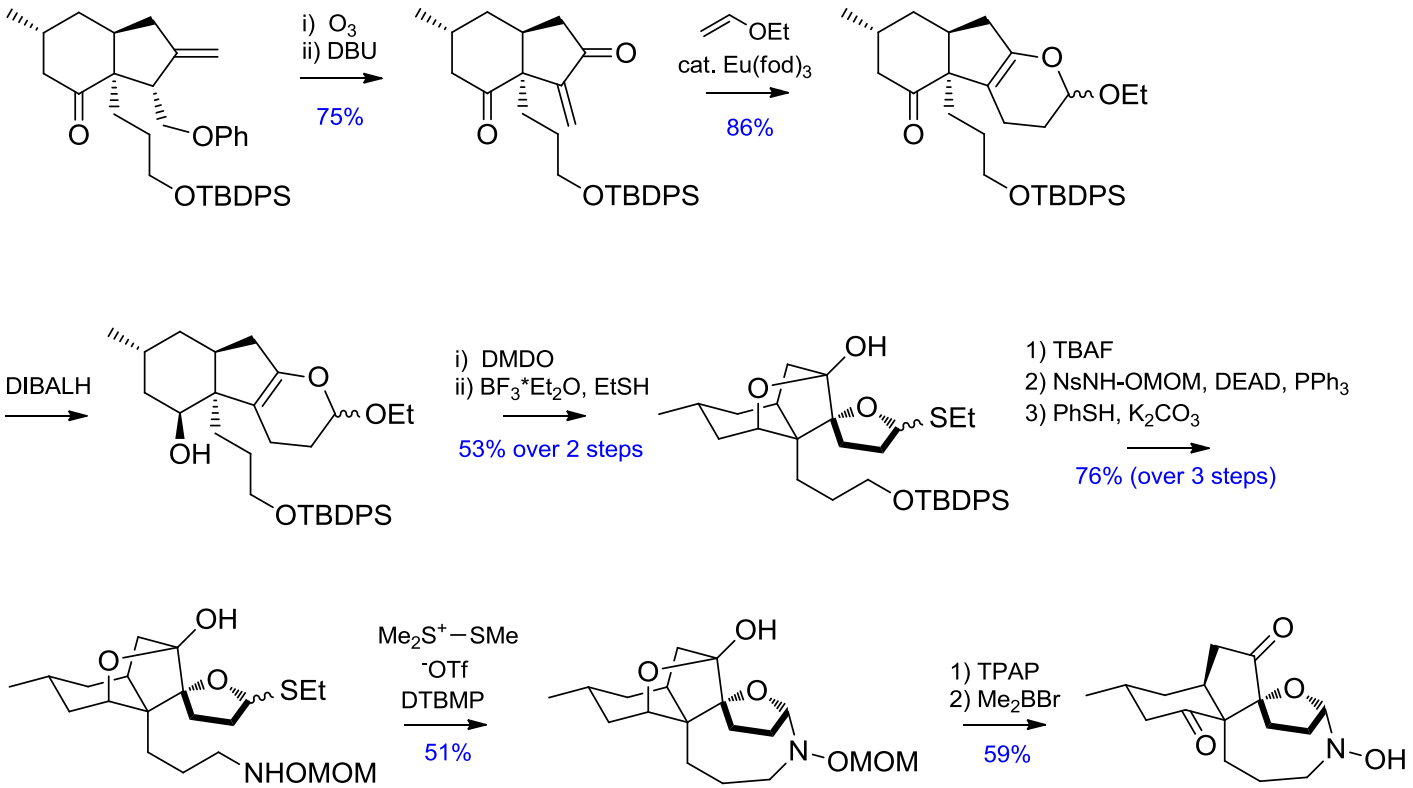
## 1st Total Synthesis by Overman *et al.*:




Overman, L. E. *et al. JACS*, **2010**, *132*, 7876

# Sieboldine A

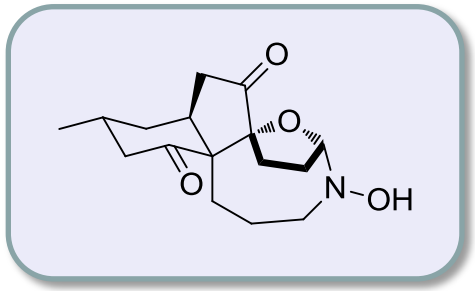
## 1st Total Synthesis by Overman *et al.*:




Overman, L. E. *et al. JACS*, **2010**, *132*, 7876

# Sieboldine A

## Summary:

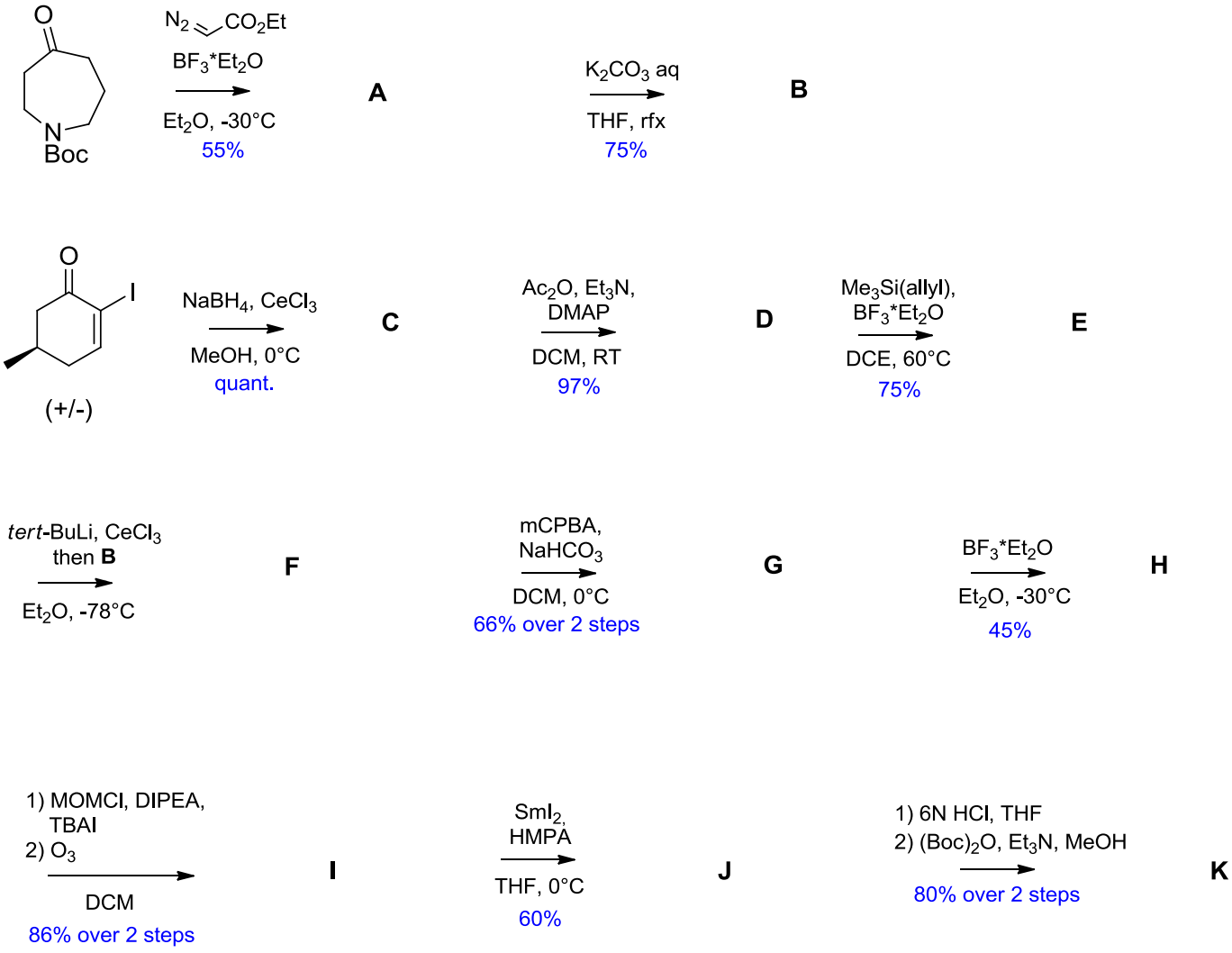



- 20 steps
- 3% overal yield

## 2nd Total Synthesis by Tu *et al.*:

???

# Sieboldine A



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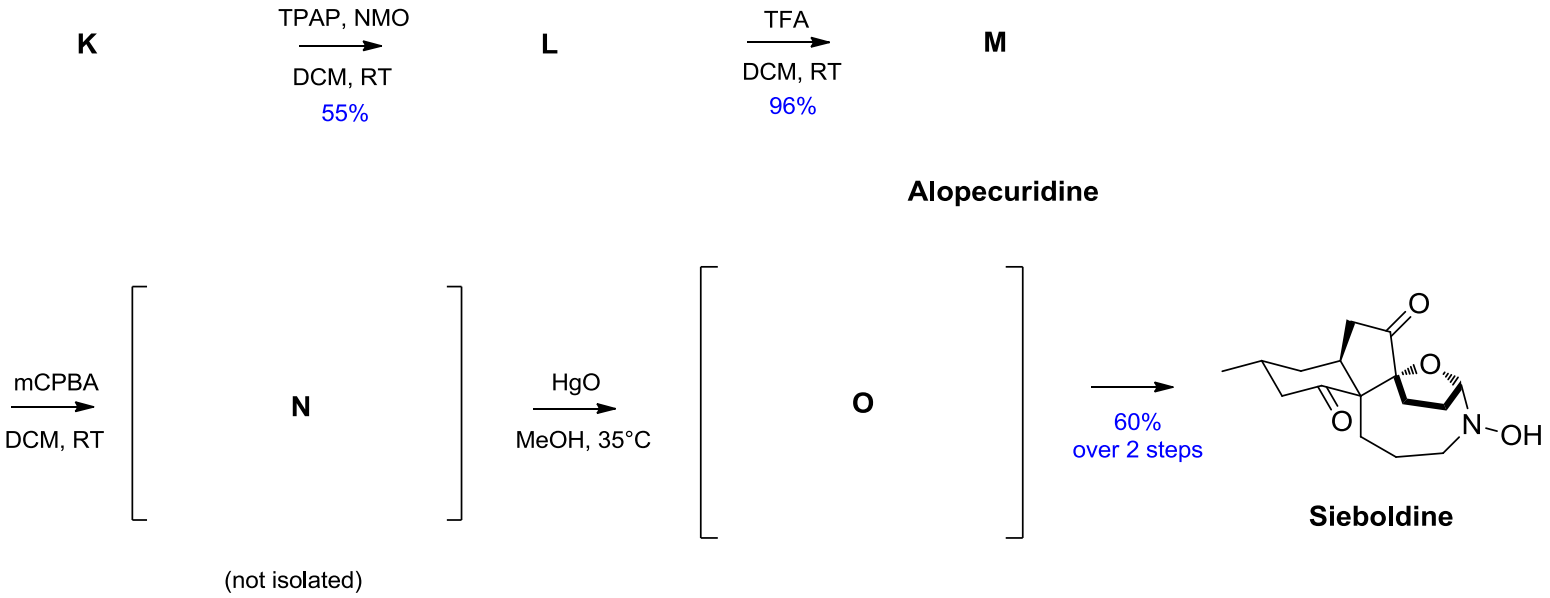

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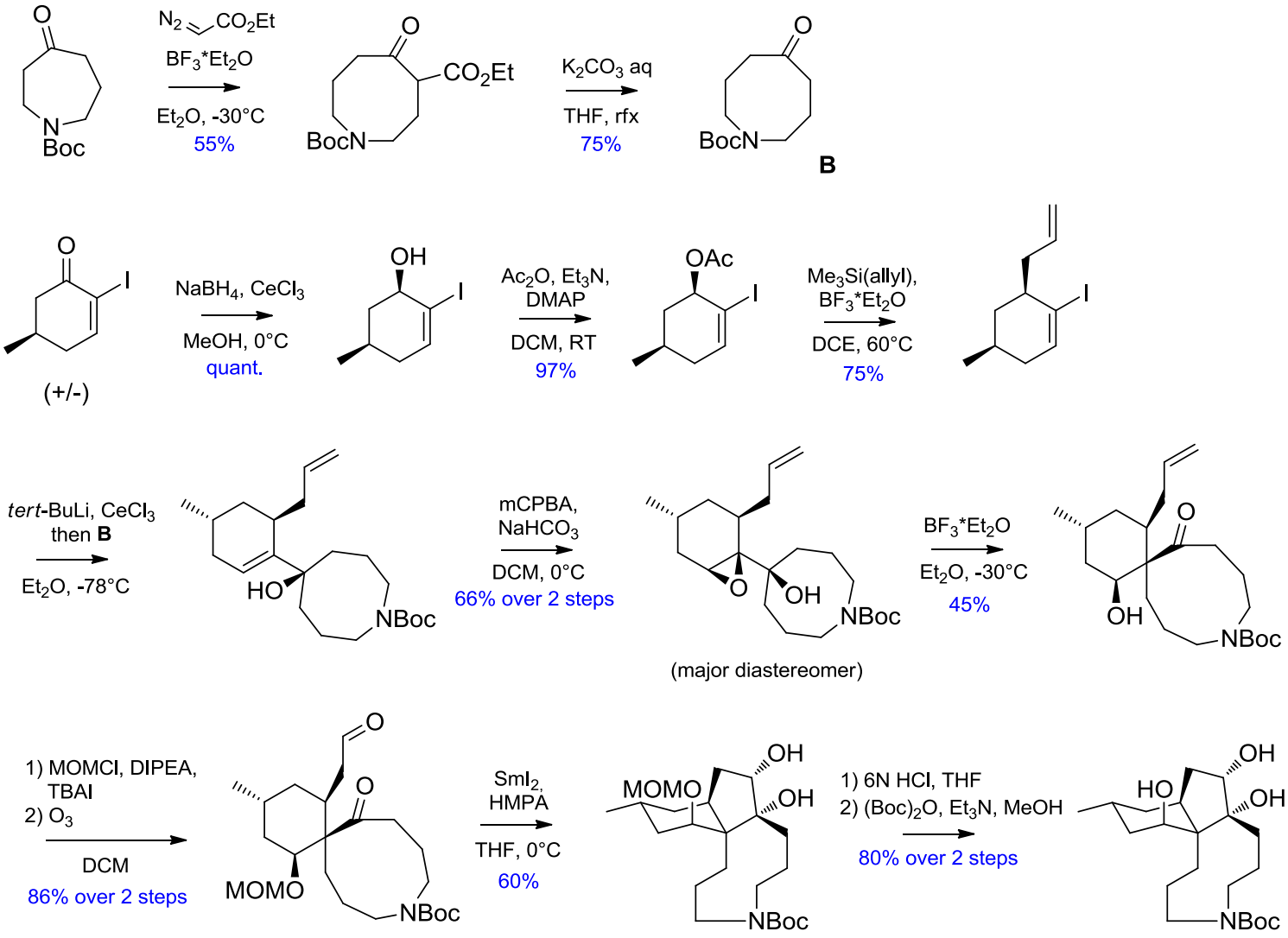

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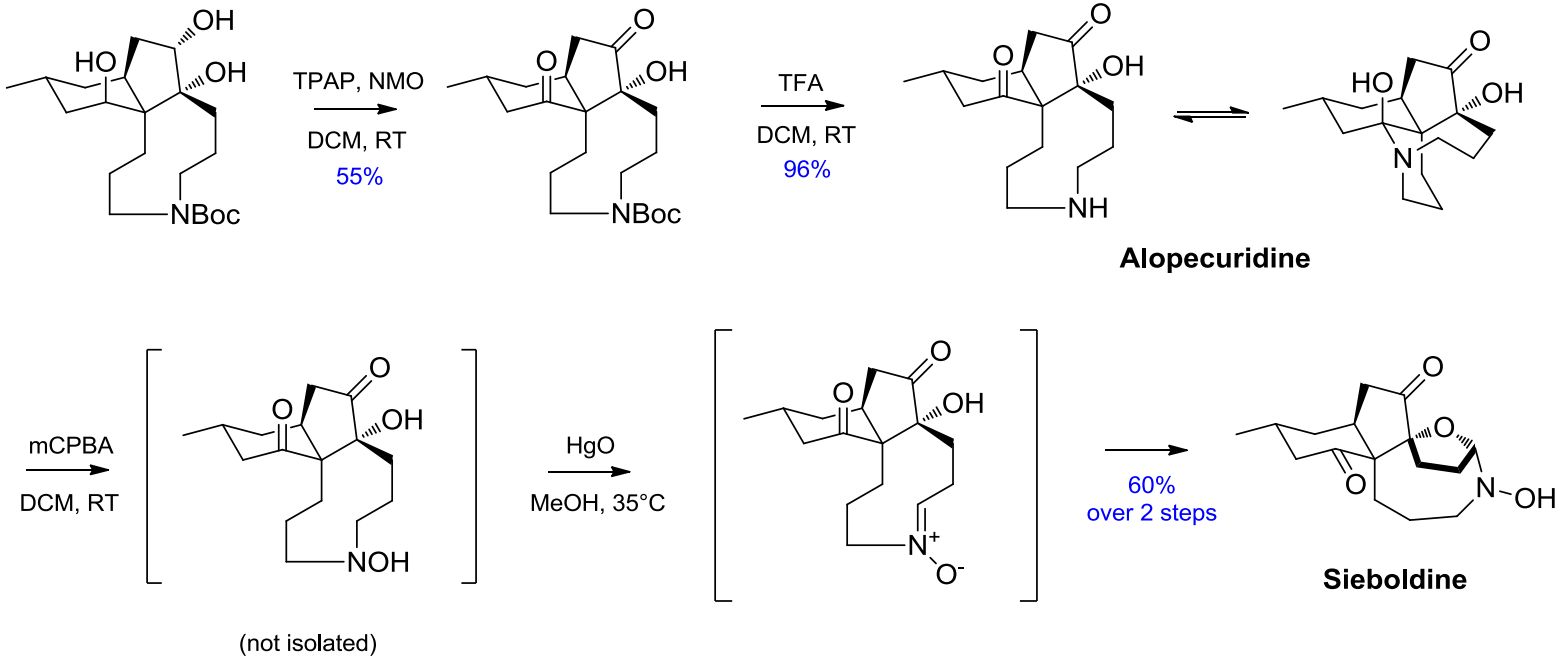

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