

Synthesis towards *Aconitum* Alkaloids

Yang Jiao

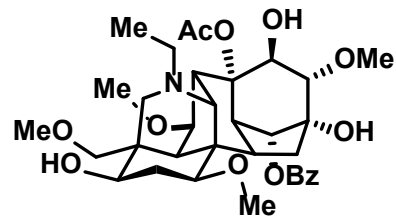
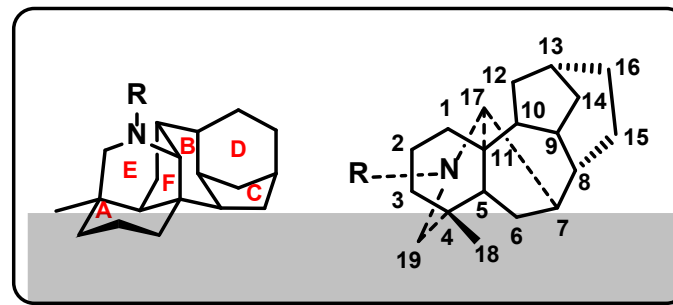
College of Chemistry and Molecular Engineering

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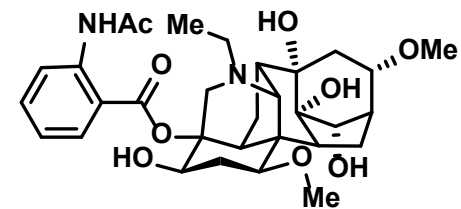
Outline

- **Introduction**
- **[2.2.2] to [3.2.1] as Core Strategy**
Wiesner, Fukuyama, Inoue and Sarpong
- **Construct [3.2.1]-Ring System Early & Directly**
Gin, Reisman and Qin
- **Summary**

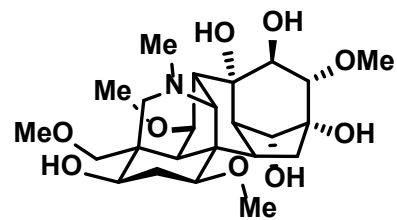
Aconitum Alkaloids



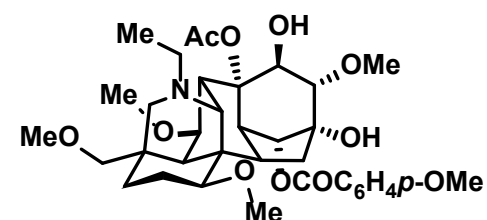
aconitine
highly toxic



lappaconitine
non-narcotic analgesic
anti-arrhythmia drug

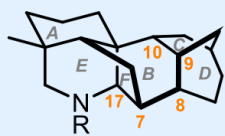


mesaconitine
cardiotonic

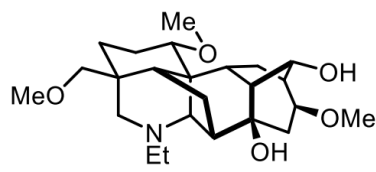


bulleyaconitine A
non-narcotic analgesic

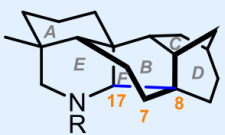
Aconitum Alkaloids



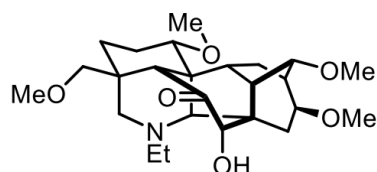
aconitine-type
C₁₉-DTAs



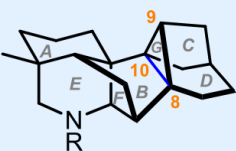
talatisamine & congeners



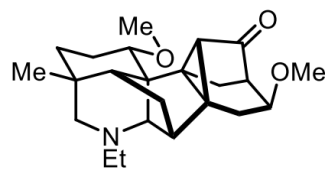
rearranged-type I
C₁₉-DTAs



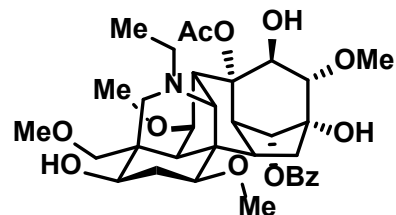
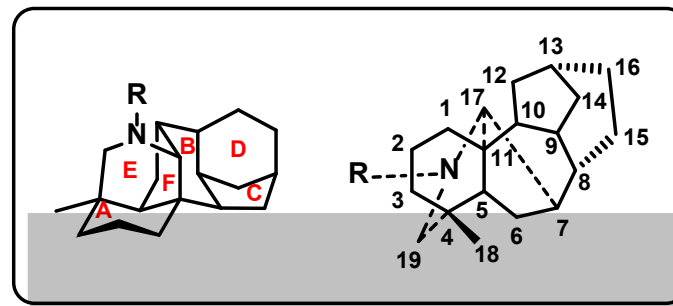
puberuline C



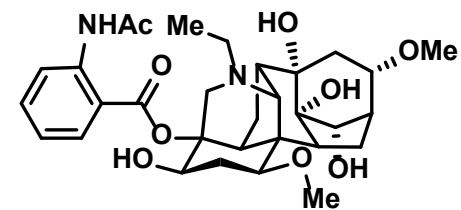
rearranged-type II
C₁₉-DTAs



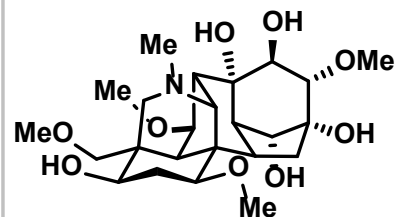
vilmoraconitine



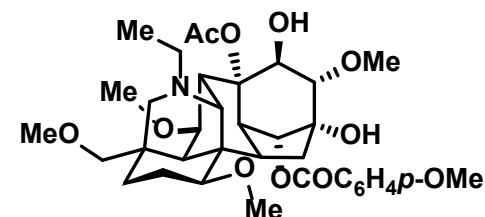
aconitine
highly toxic



lappaconitine
non-narcotic analgesic
anti-arrhythmia drug

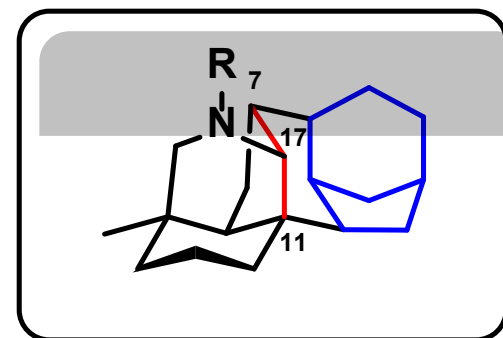
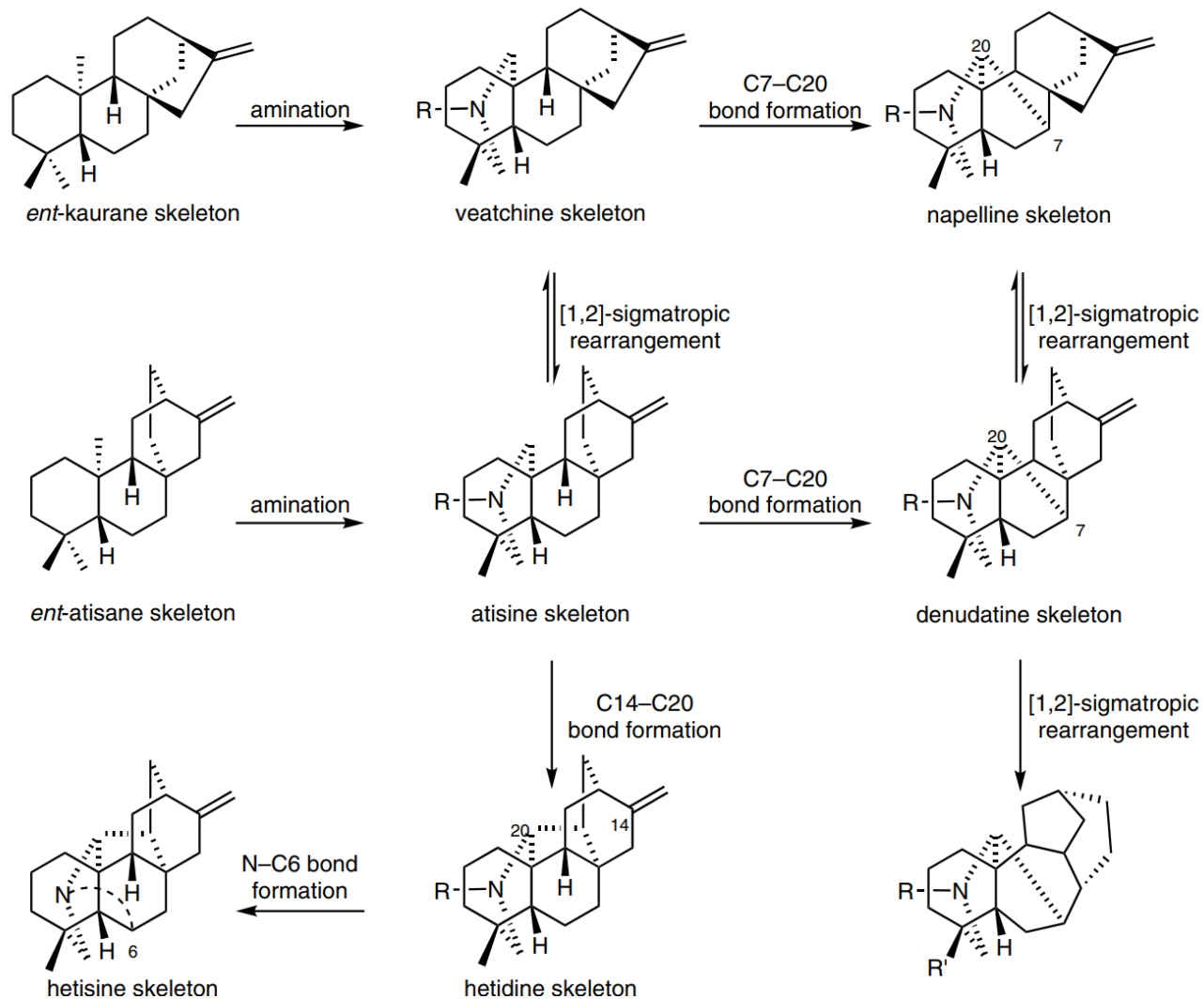


mesaconitine
cardiotonic



bulleyaconitine A
non-narcotic analgesic

Biosynthetic Relationships

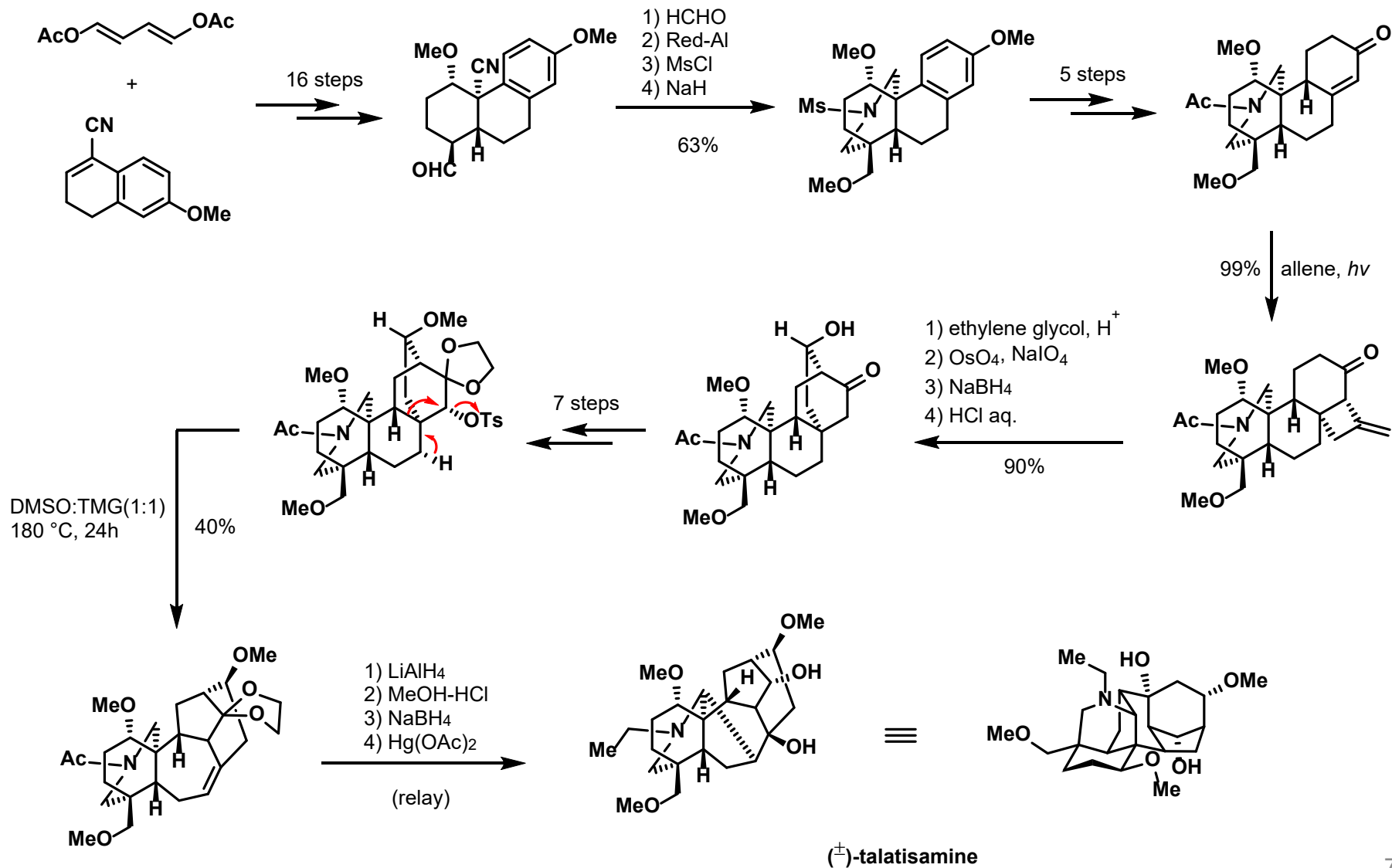


High-strained bonds
Highly continuous
[3.2.1]-ring system
Oxidation degree

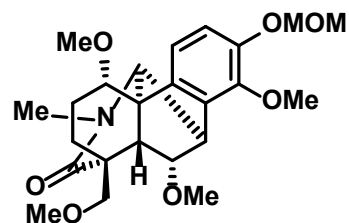
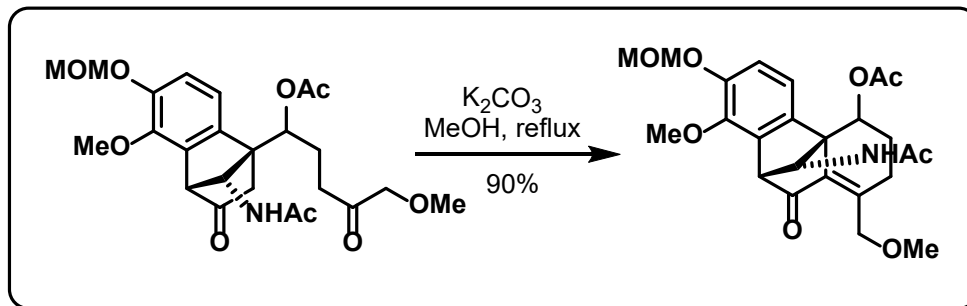
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- **Introduction**
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Wiesner, Fukuyama, Inoue and Sarpong
- **Construct [3.2.1]-Ring System Early & Directly**
Gin, Reisman and Qin
- **Summary**

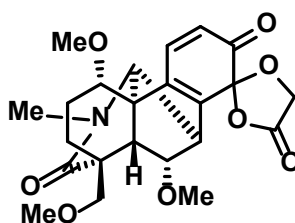
Wiesner (1974): [2.2.2]-Intermediate



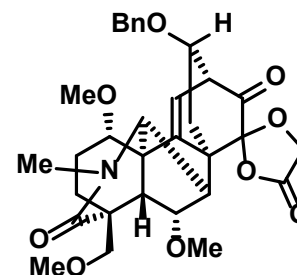
High Oxidation Degree: Restriction



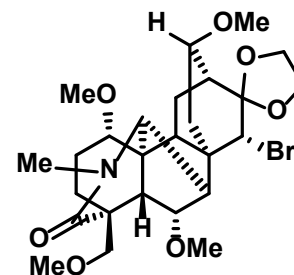
4 steps



46%



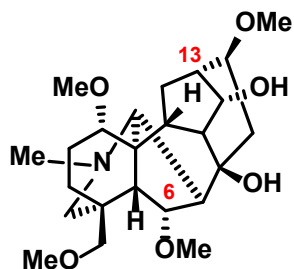
11 steps



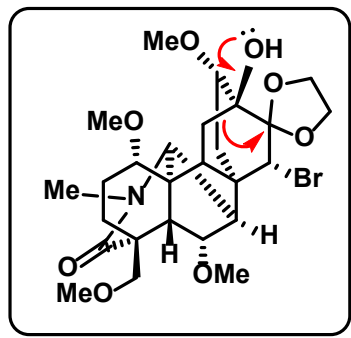
180 °C, DMSO
o-xylene

89%

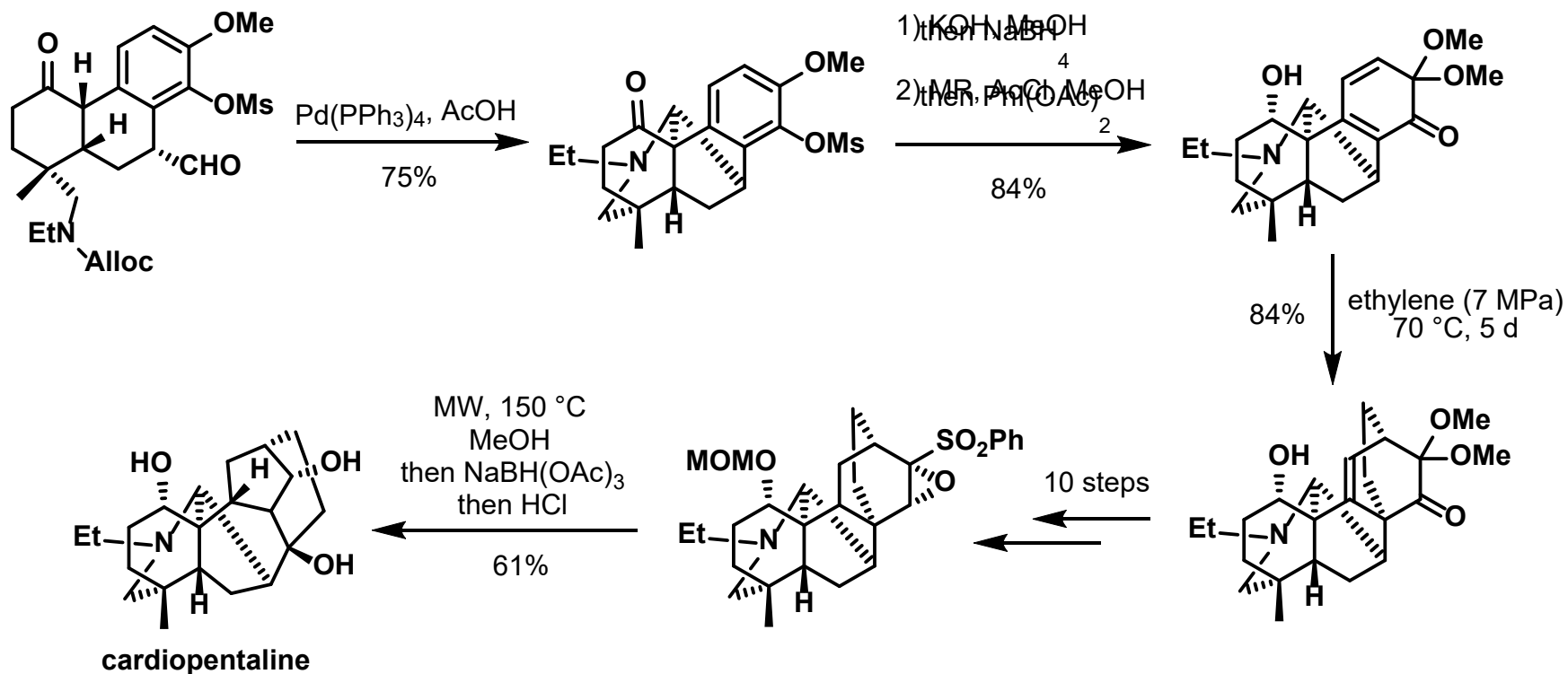
7 steps



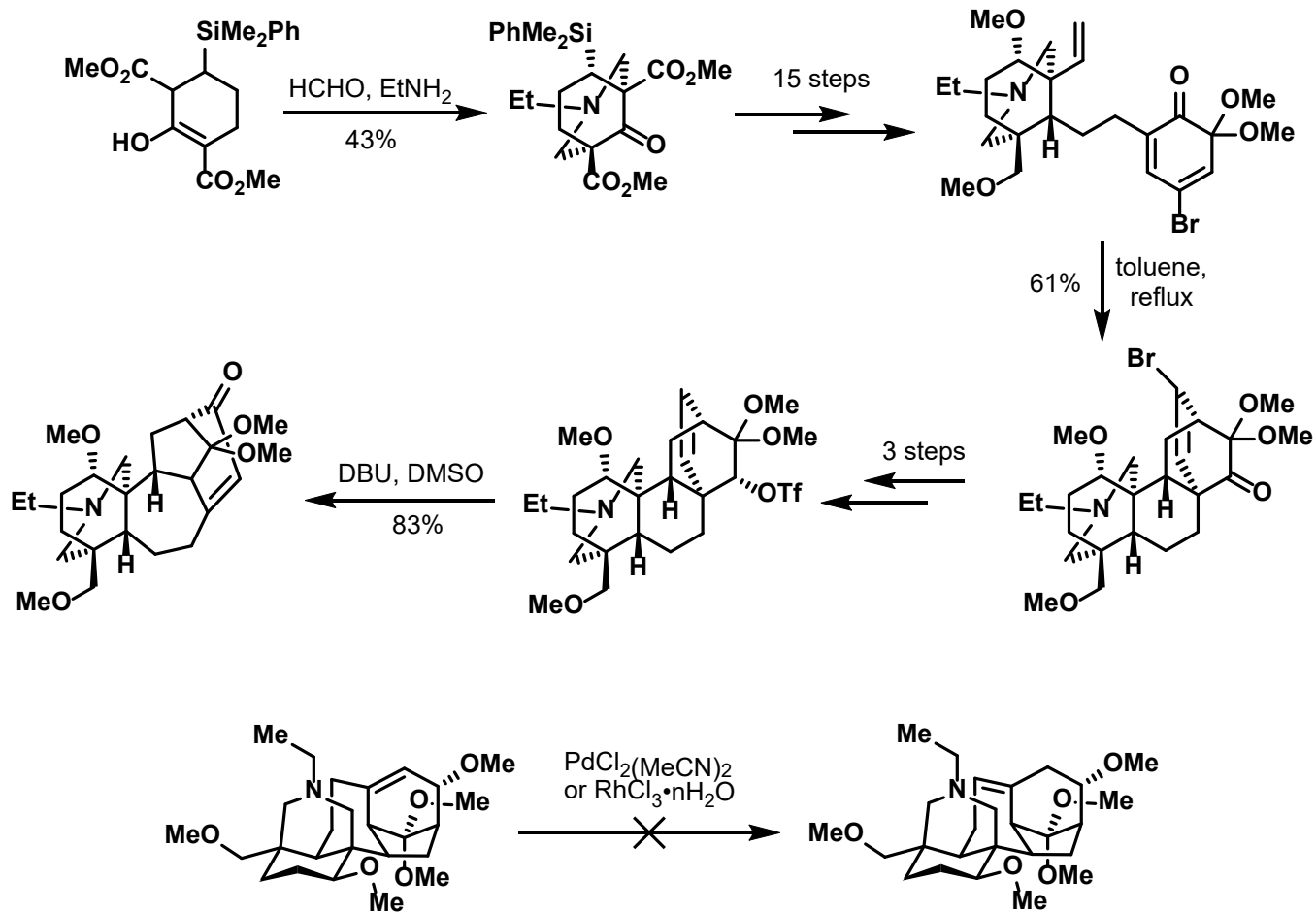
(±)-13 desoxydelphonine



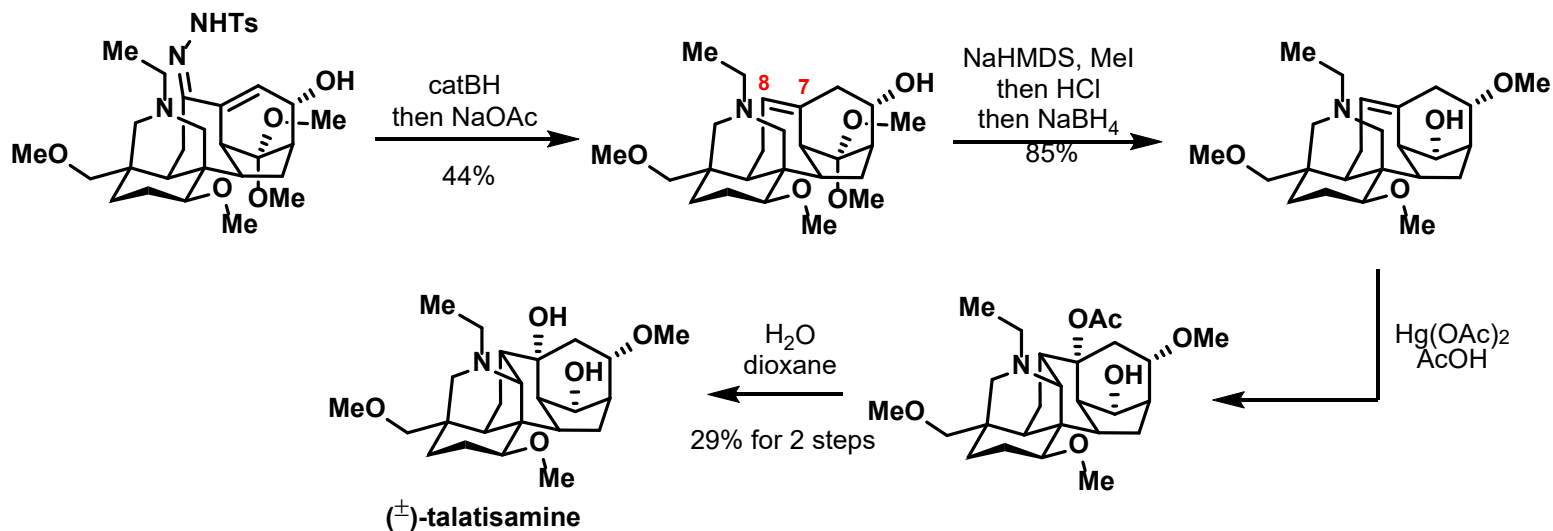
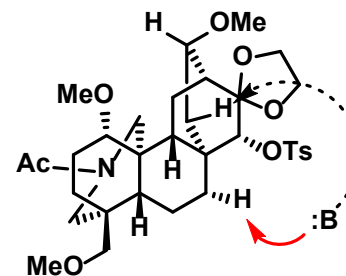
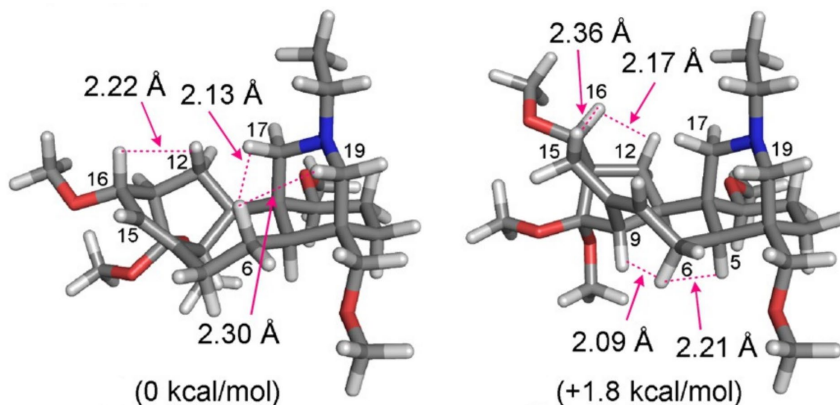
Fukuyama (2016): Diels-Alder



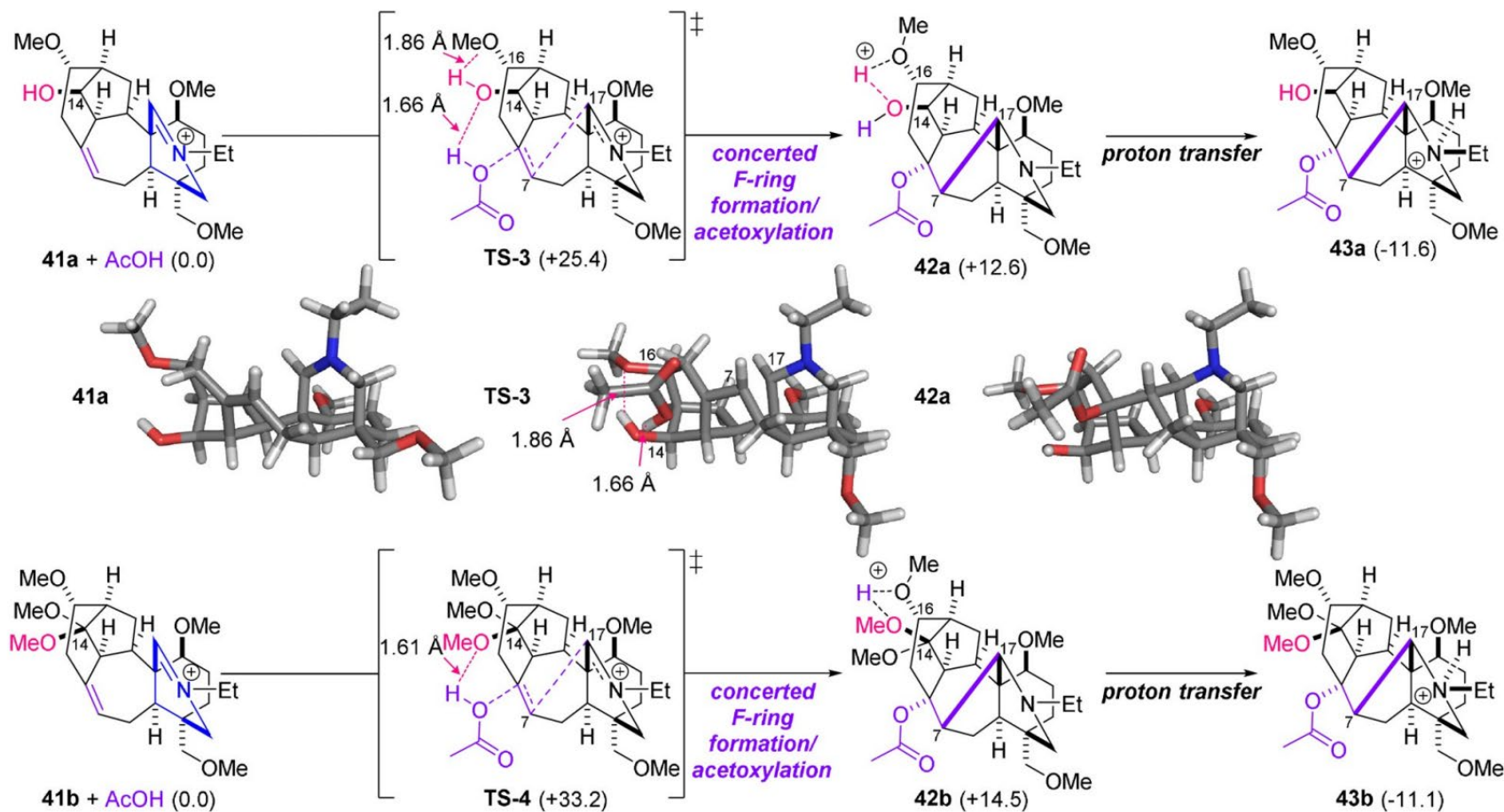
Inoue (2020): Type-II Diels-Alder



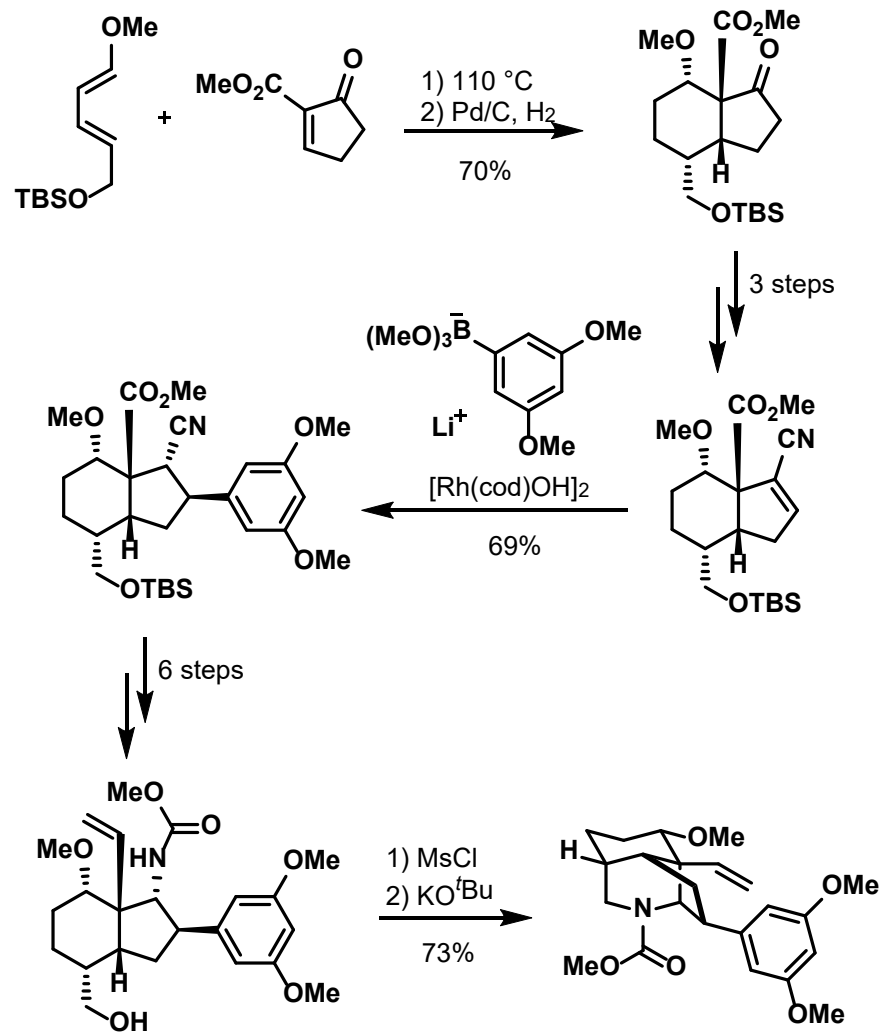
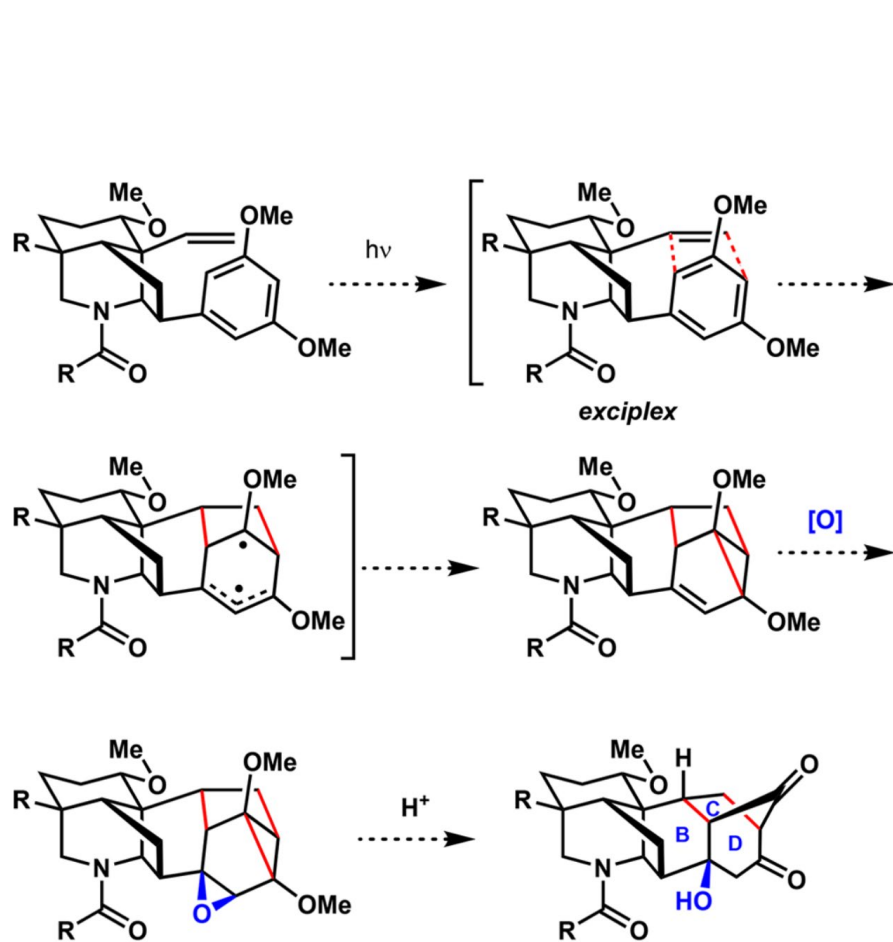
High-Strained C₇-C₈ Double Bond



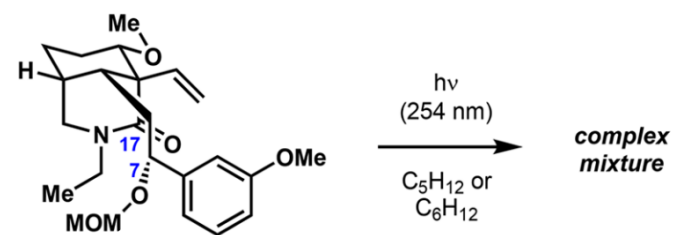
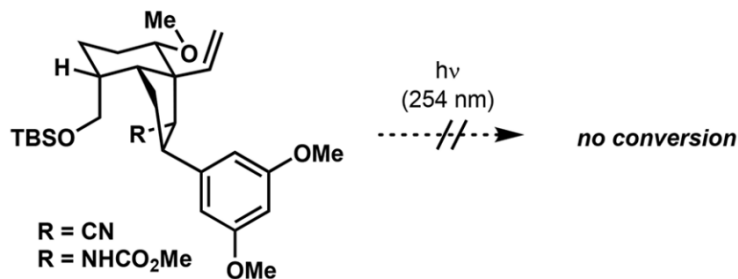
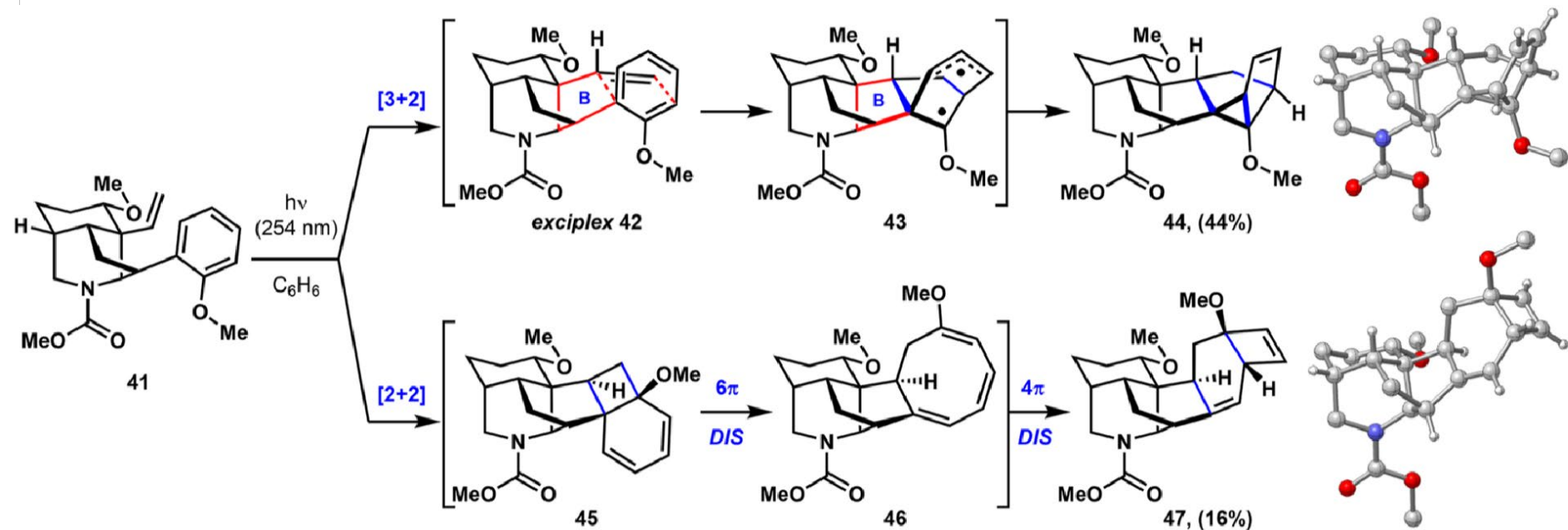
Hydrogen Bond Acceptor is Important



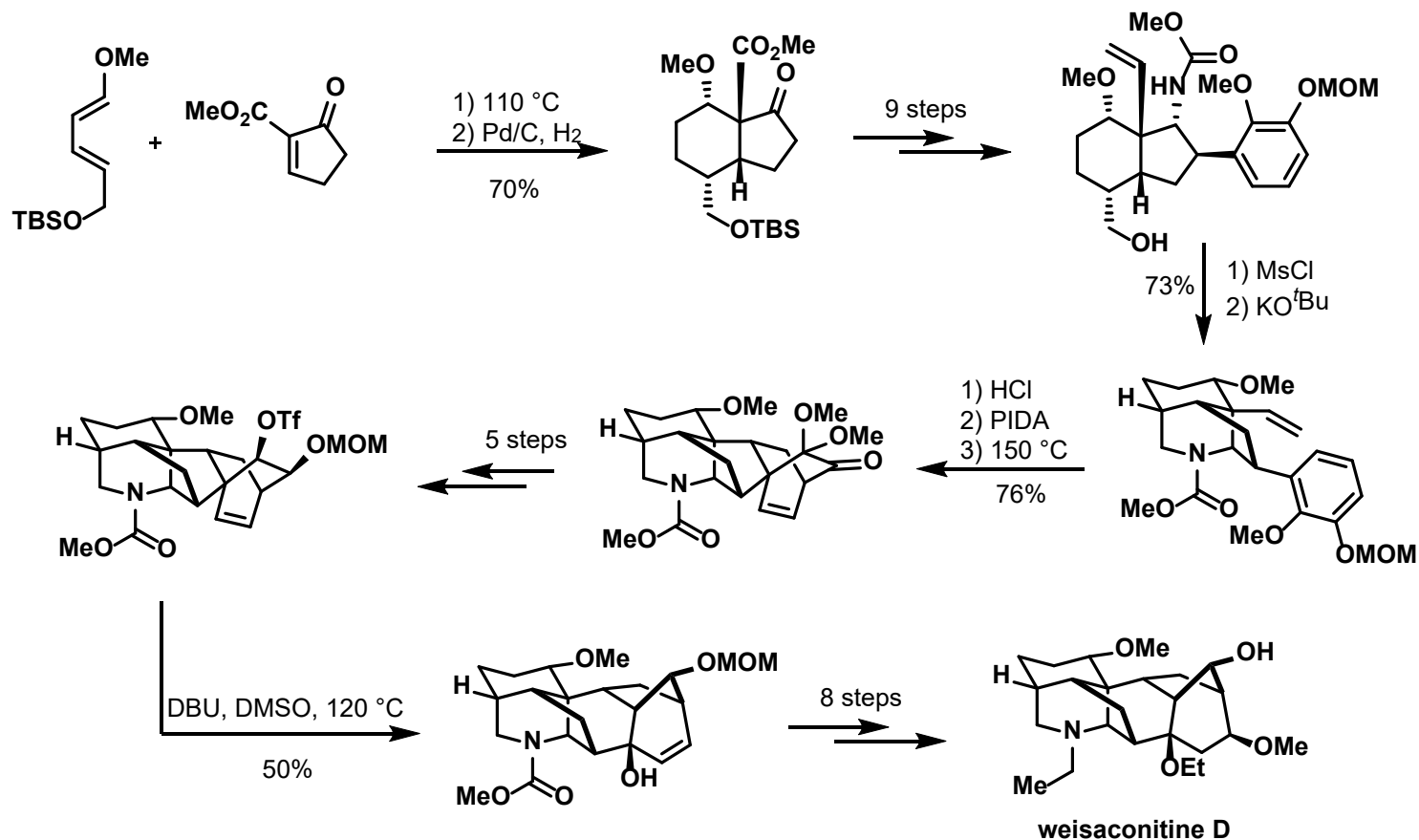
Sarpong (2015): Arene-[3+2] Attempt



Bridgehead Double Bond in TS



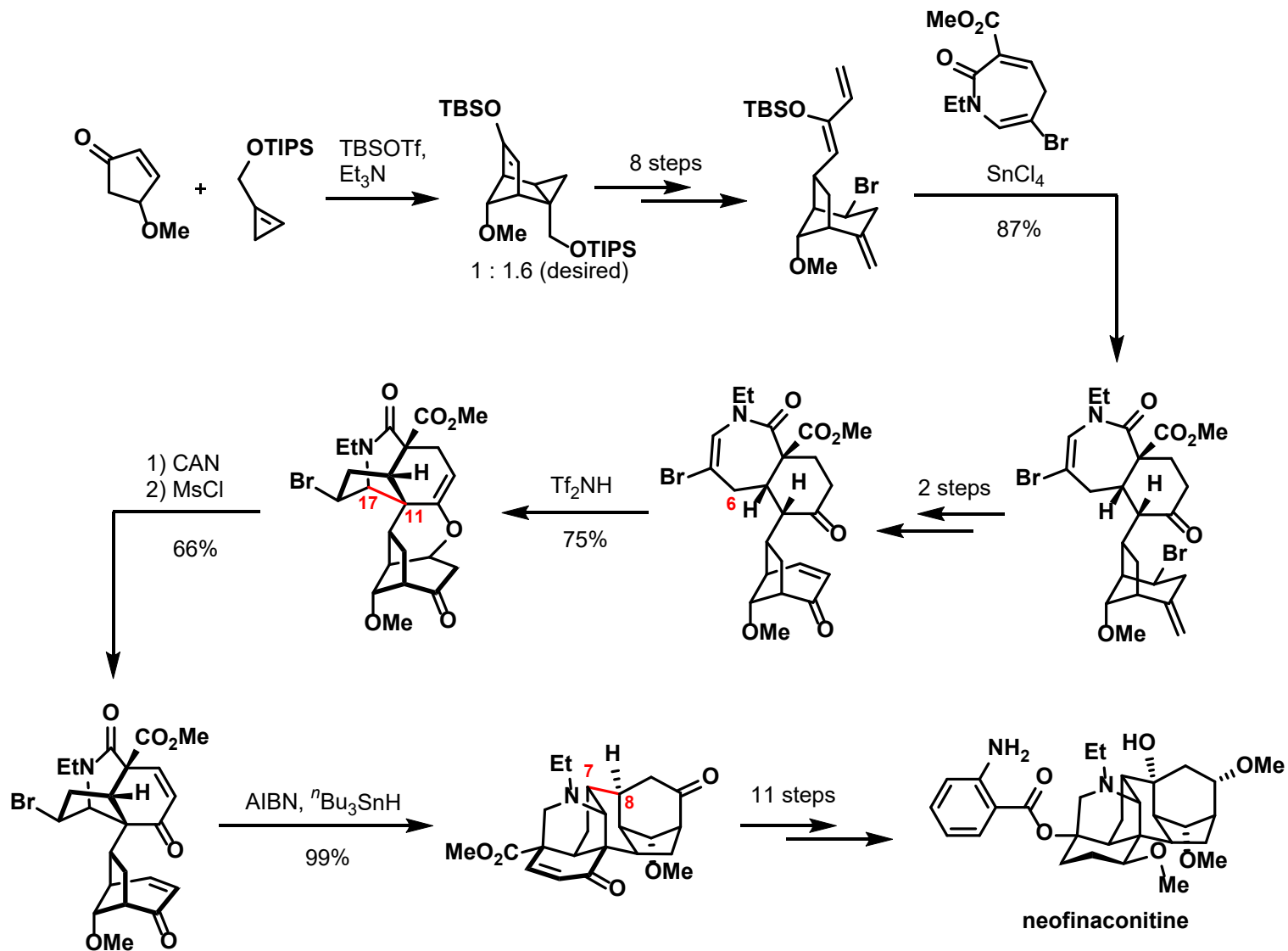
Back to [2.2.2]→[3.2.1] Rearrangement



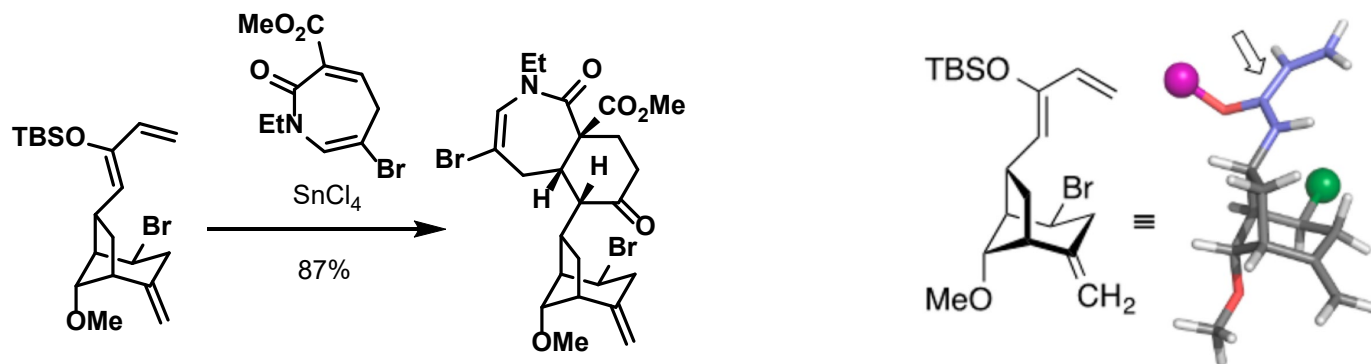
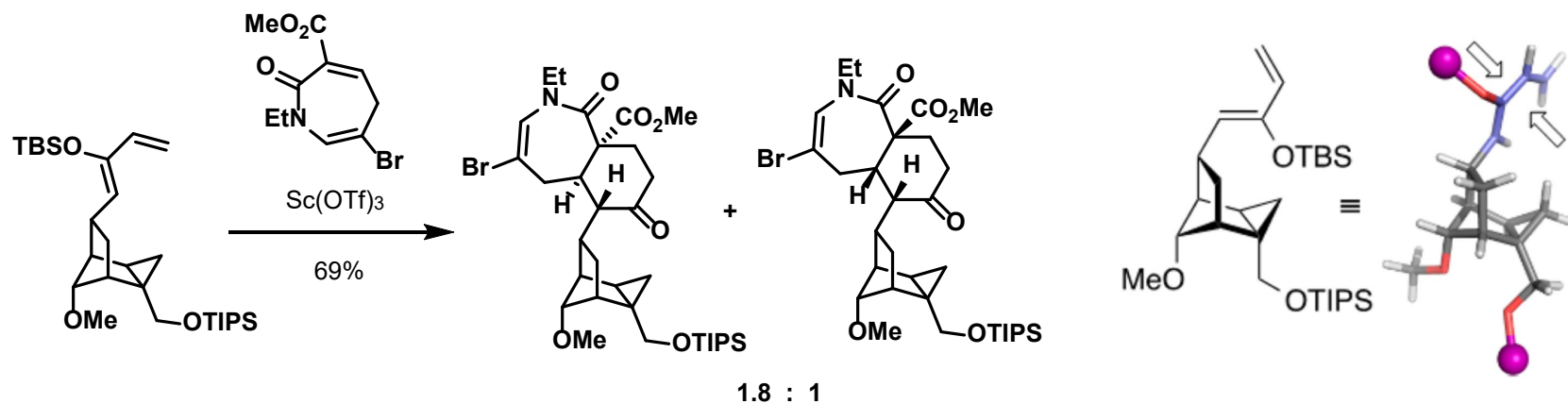
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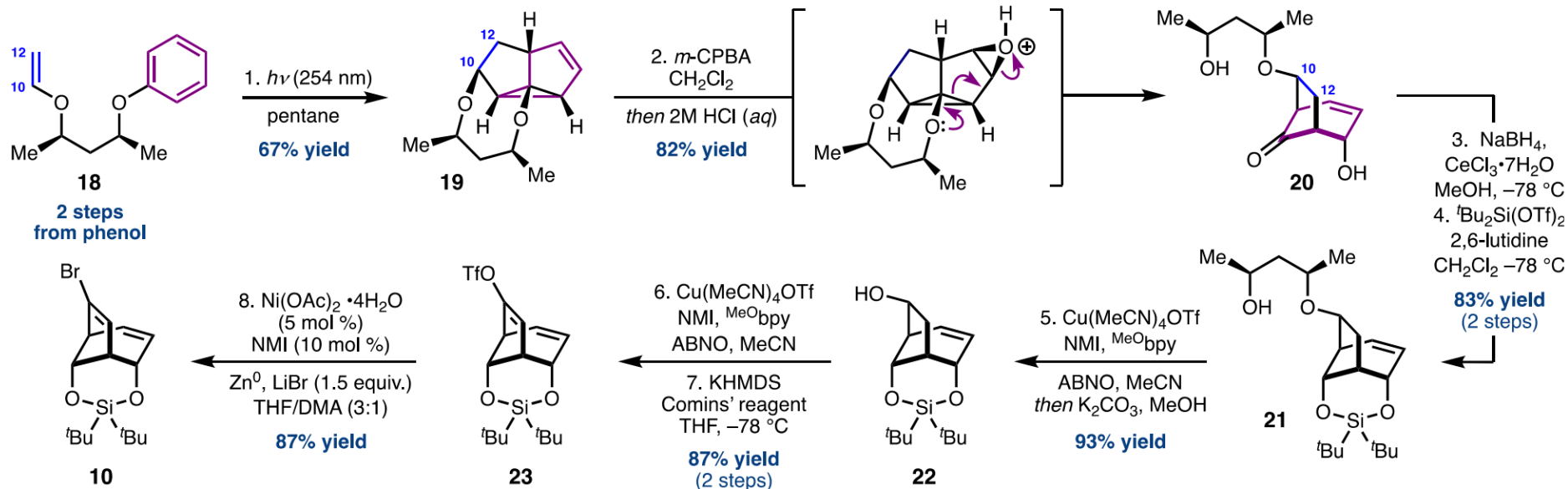
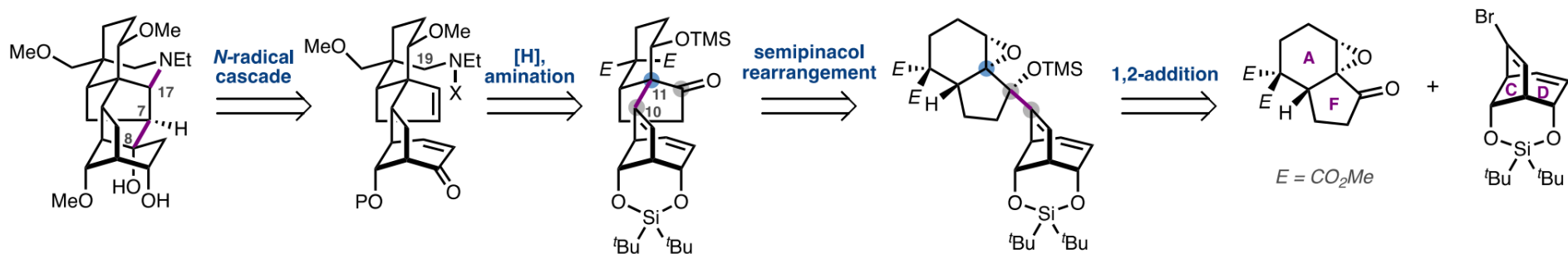
Gin (2013): Direct [3.2.1] Construction



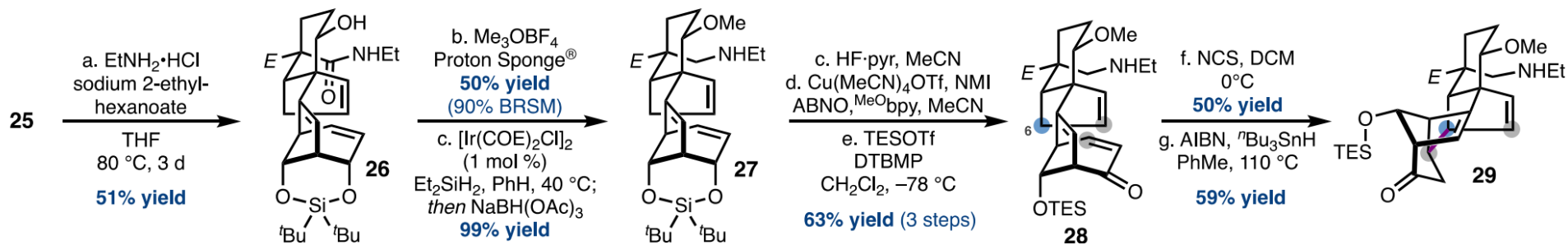
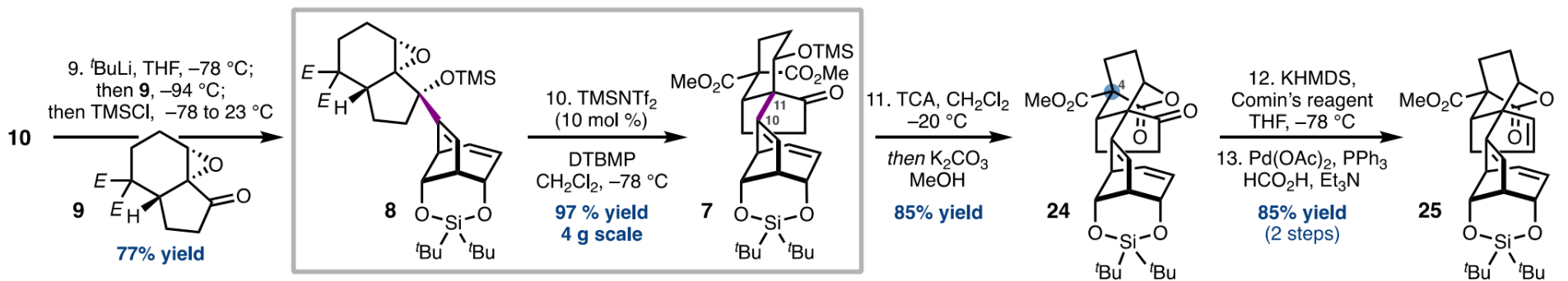
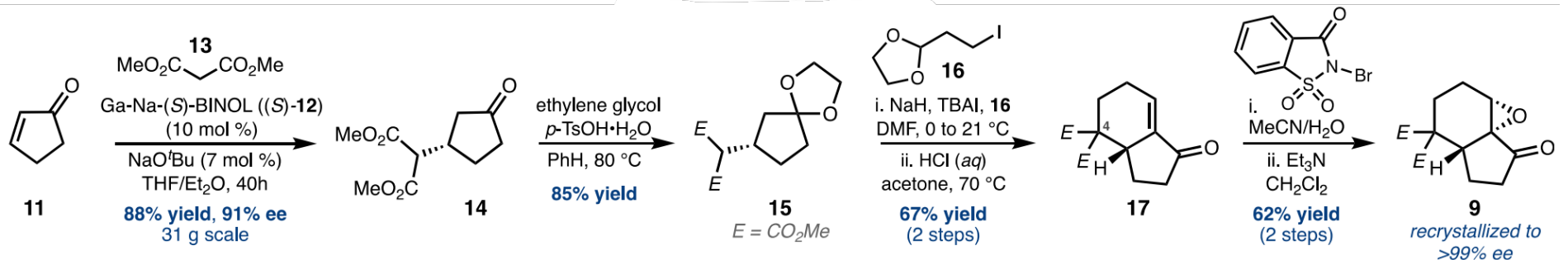
Stereoselectivity of D-A Reaction



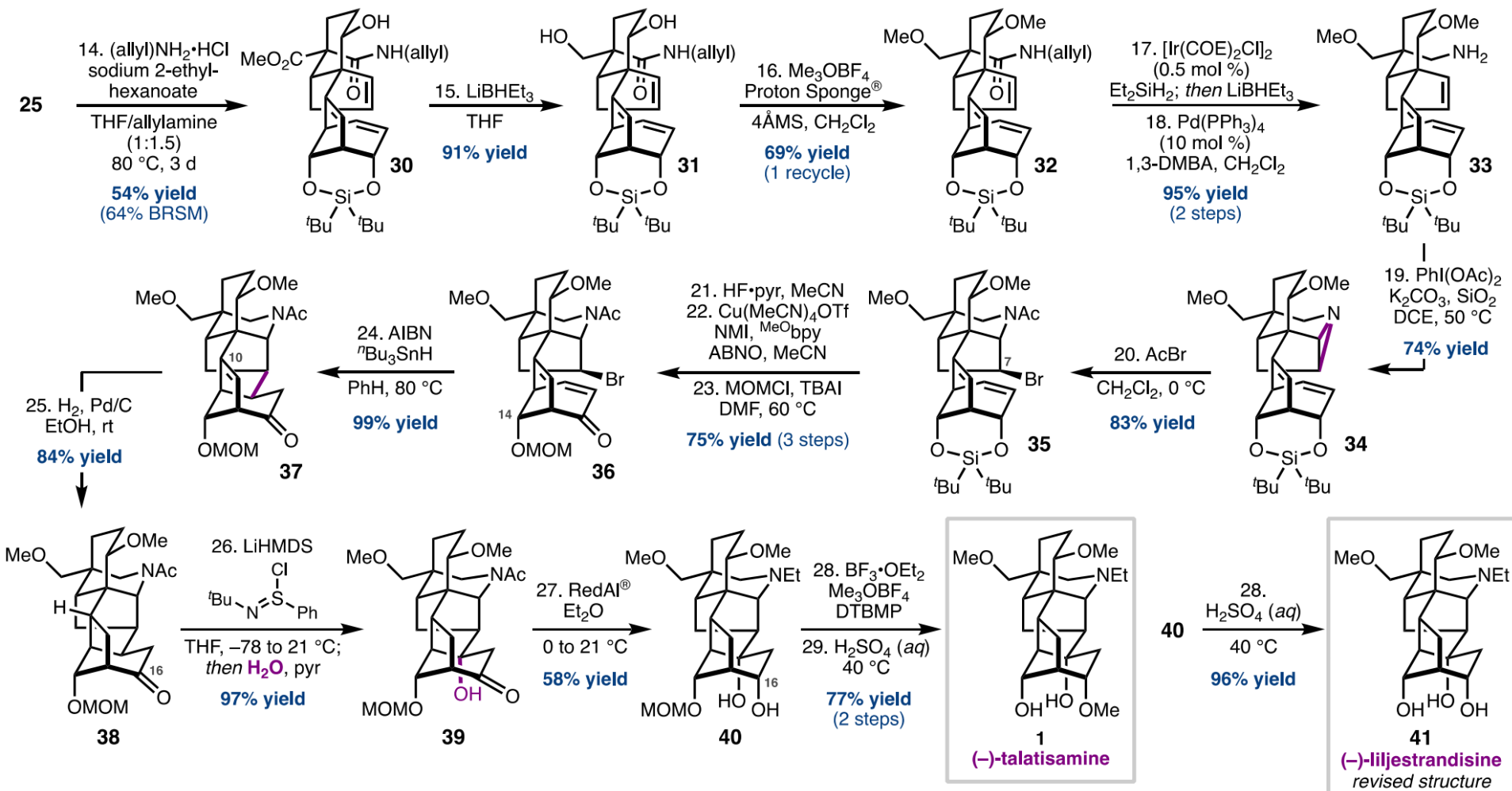
Reisman (2021): Convergent Synthesis



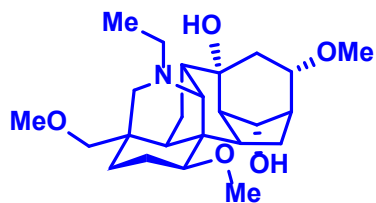
Unsuccessful *N*-Radical Cascade



Step-by-Step N-C₁₇ & C₇-C₈ Construction



Completed Works: Restrictions?

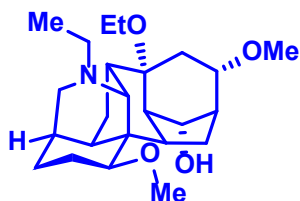


talatisamine

Wiesner (1974)
> 50 steps

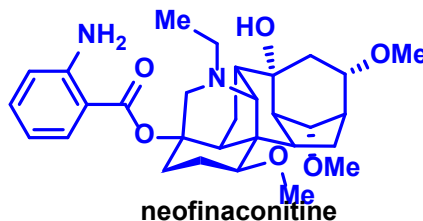
Inoue (2020)
33 steps

Reisman (2021)
29 steps



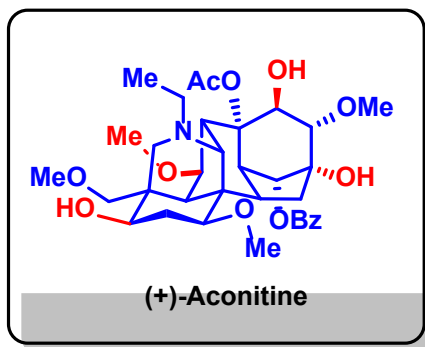
weisaconitine

Sarpong (2015)
30 steps

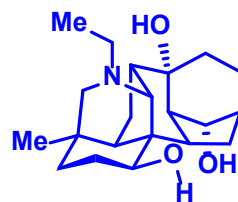


neofinaconitine

Gin (2013)
30 steps



(+)-Aconitine

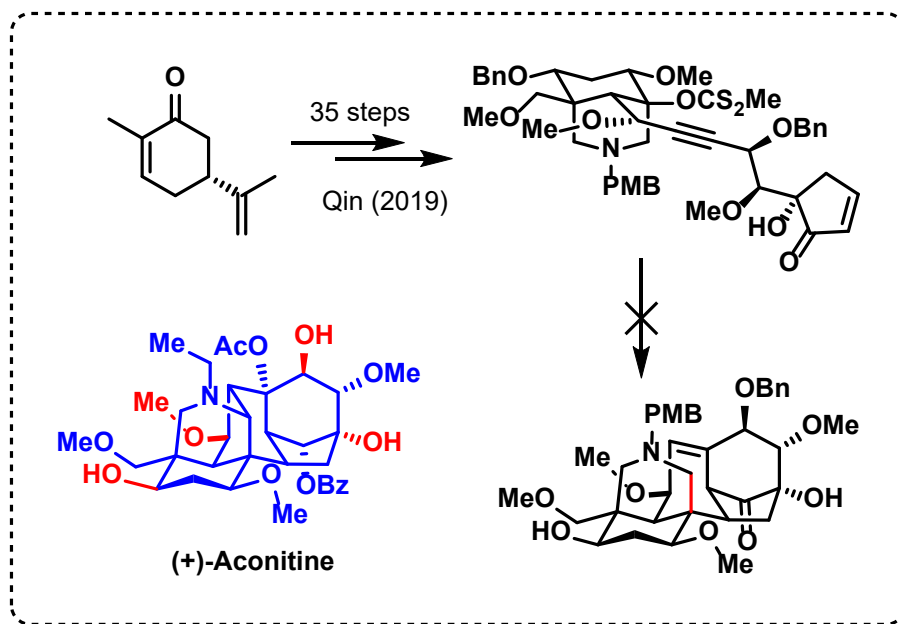


cardiopetaline

Fukuyama (2016)
35 steps

- Long synthetic route
- Low oxidation degree
- Inoue: C₇-C₈ double bond
- Sarpong: bridgehead
- Gin: Mannich & low efficiency convergent
- Reisman: C₁₈&C₁₉ editing
- Working on **Overcoming Strain**
- **High Oxidation Degree**
- **The First Bond** in retrosynthesis?
- **Efficiency Convergent?**

Completed Works: Restrictions?



- Long synthetic route
- Low oxidation degree
- Inoue: C₇-C₈ double bond
- Sarpong: bridgehead
- Gin: Mannich & low efficiency convergent
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- Working on **Overcoming Strain**
- **High Oxidation Degree**
- **The First Bond** in retrosynthesis?
- **Efficiency Convergent?**

Summary

- Long synthetic route restricted by **Linear Synthesis**
- Low oxidation degree restricted by **Strain Increasing**
- C/D ring system: **[2.2.2] to [3.2.1] Rearrangement**
or **Direct Construction**
- Construct [3.2.1]-Ring System **Early & Directly**
- Ready C₁₈&C₁₉ early: avoid the **Lengthy** route
- Strain-increasing conditions: **Functional Tolerance**