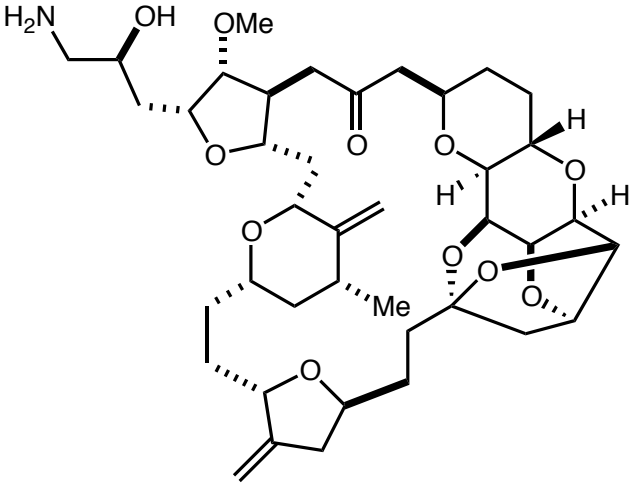
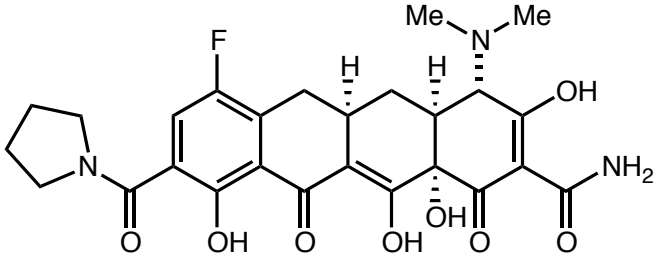
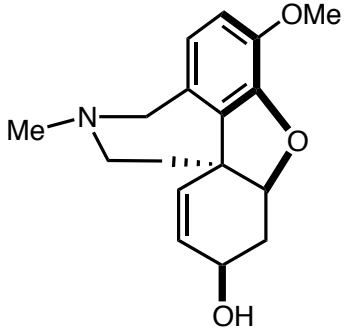
Five Drugs or Clinical Candidates Derived From Natural Products

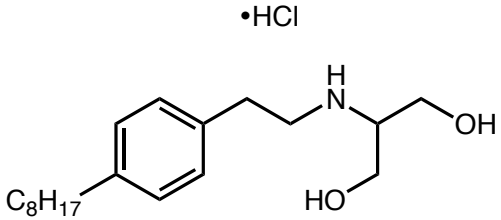
That Are Produced on Scale by Total Synthesis

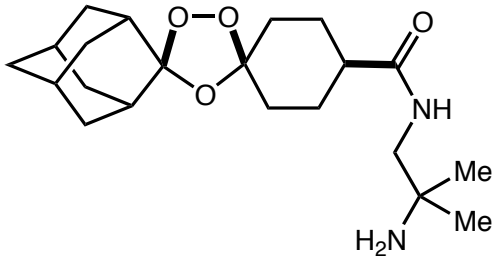
Jeff Garber
MacMillan Group Meeting
April 27, 2012











Why Pursue Total Synthesis of Natural Products?

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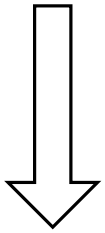


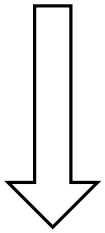
Academic and Pegagogical

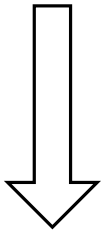
Test New Methodology

Develop New Methodology

Train Organic Chemists

Why Pursue Total Synthesis of Natural Products?





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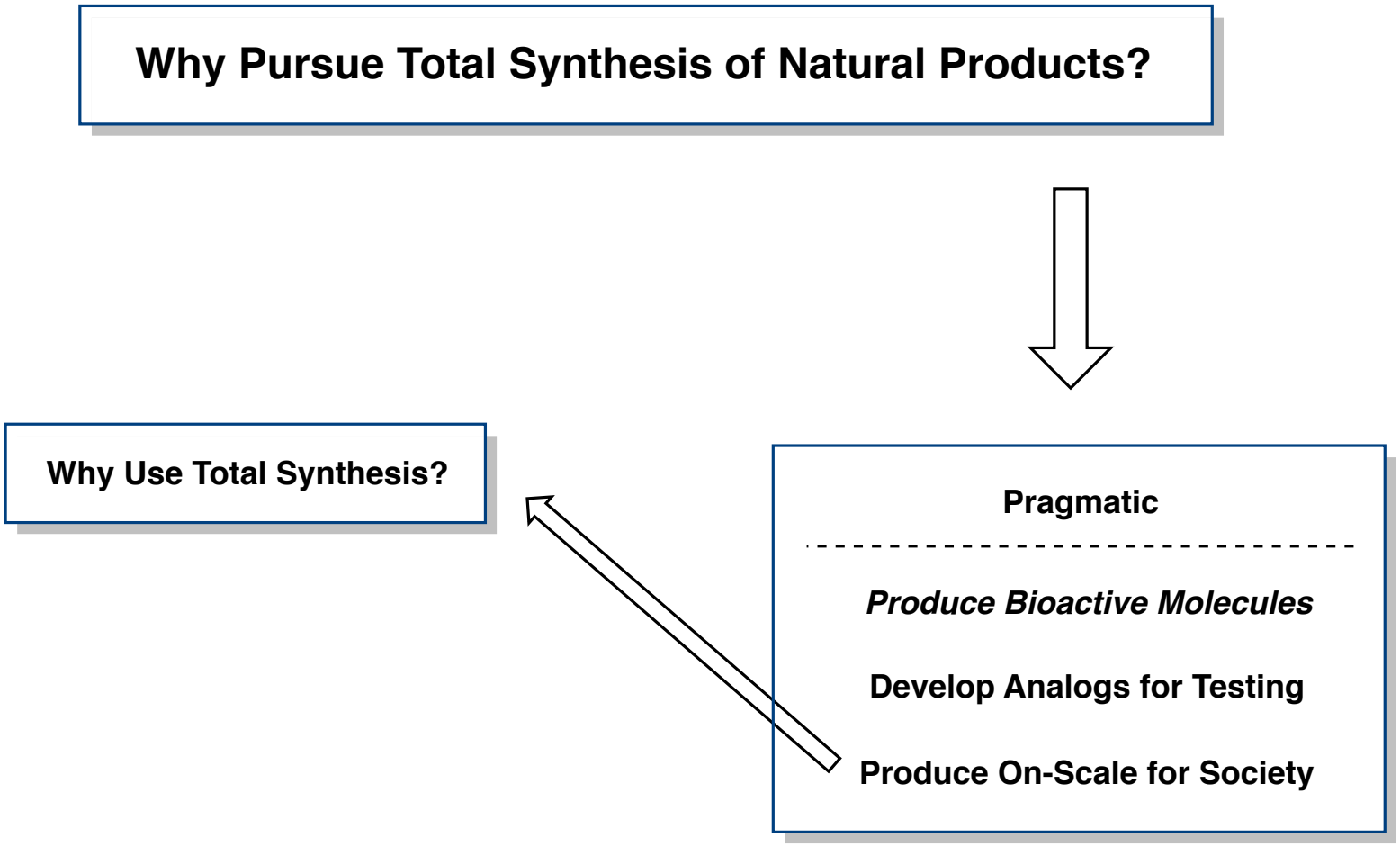
Pragmatic

Produce Bioactive Molecules

Develop Analogs for Testing

Produce On-Scale for Society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Why Use Total Synthesis?
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Produce Bioactive Molecules
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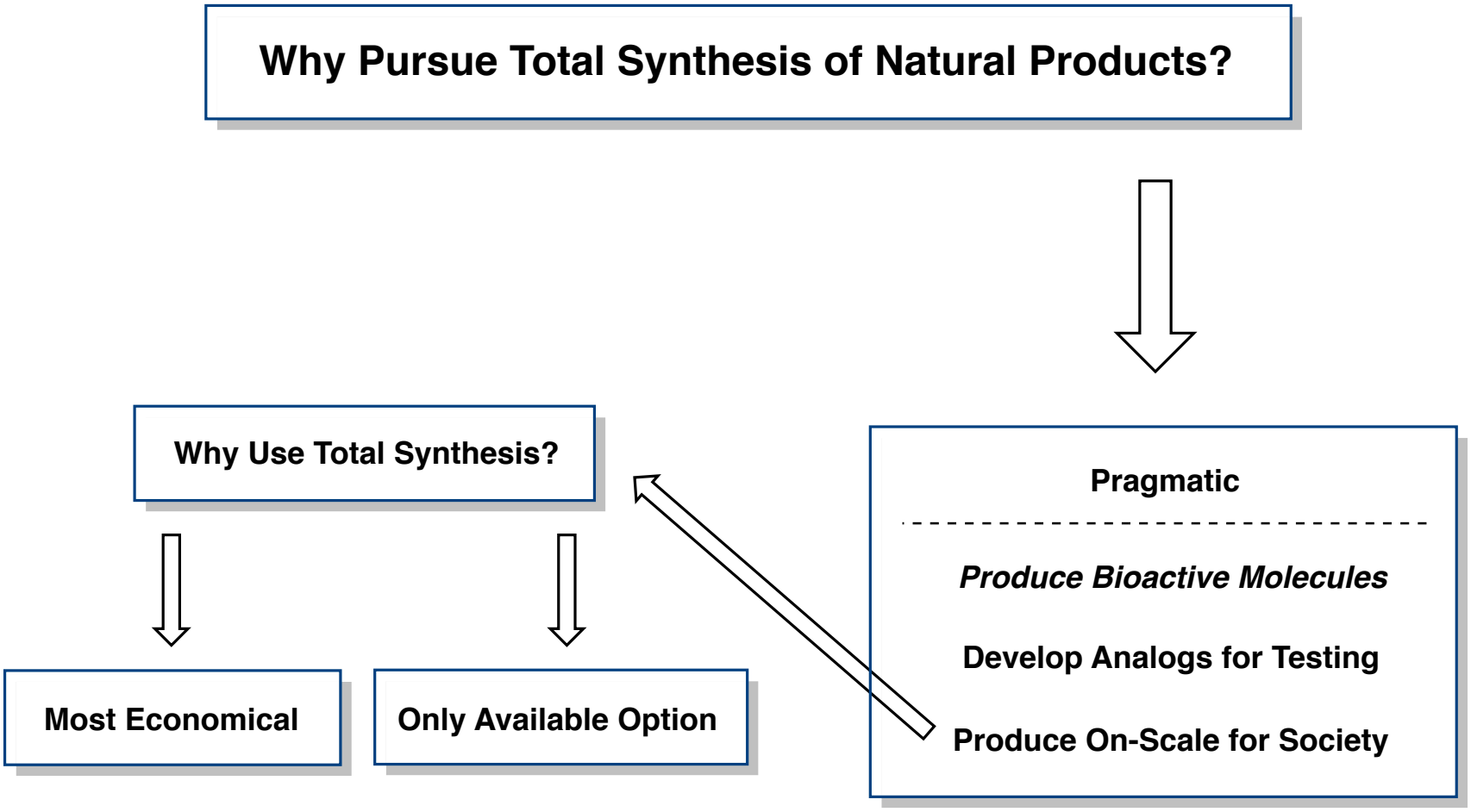
Why Pursue Total Synthesis of Natural Products?
Why Use Total Synthesis?
Most Economical
Only Available Option
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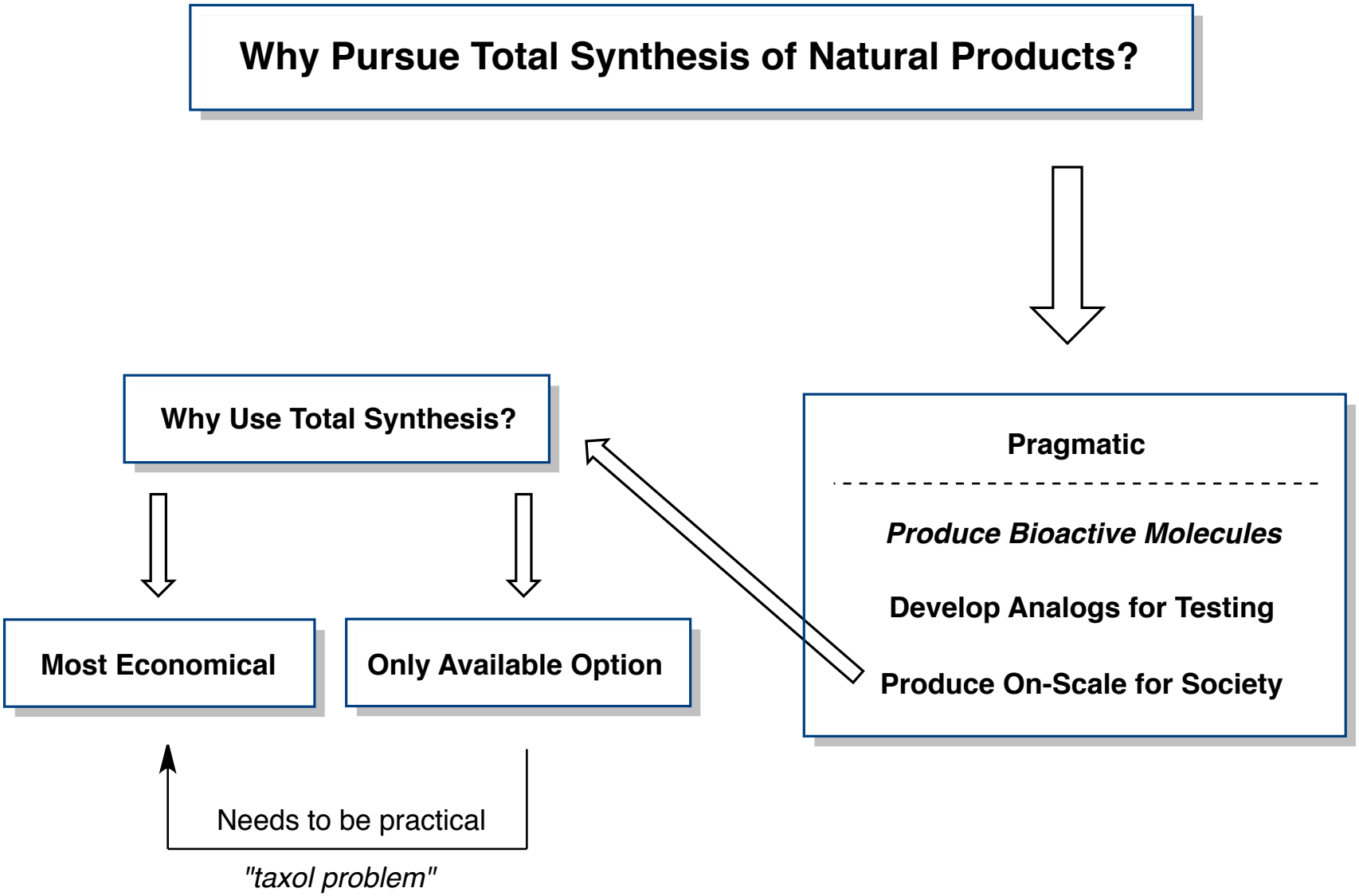
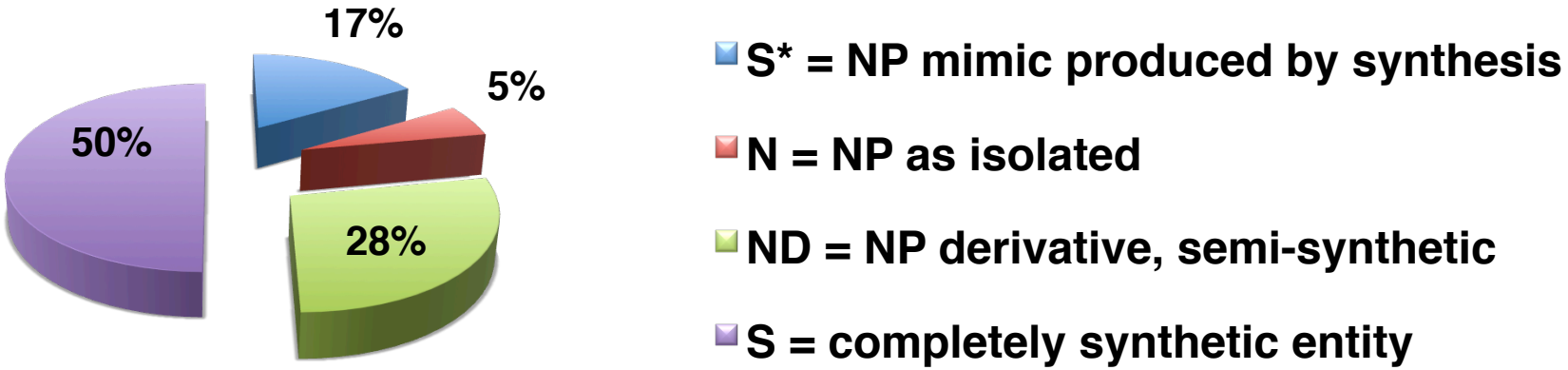
Produce Bioactive Molecules
Develop Analogs for Testing
Produce On-Scale for Society


Why Pursue Total Synthesis of Natural Products?
Why Use Total Synthesis?
Most Economical
Only Available Option
Needs to be practical
"taxol problem"
Pragmatic
Produce Bioactive Molecules
Develop Analogs for Testing
Produce On-Scale for Society

Natural products are clearly a useful source of new drugs

All 1135 new drugs approved from 1981-2010



Adapted from Newman and Clark, *J. Nat. Prod.* **2012** 311.

What Makes a Total Synthesis Interesting or Valuable?

Academic Synthesis

Elegant

concise route **atom efficiency**

Creative

disconnections **methodology**

Novel Architecture

complex structure **first synthesis**

Bioactive

produce for testing **analog synthesis**

What Makes a Total Synthesis Interesting or Valuable?

Commercial Synthesis

Proven Bioactivity

producing for testing or sale

Practicality of Length

yield vs. steps **reactor time**

Reagent Selection

safety **availability** **cost**

Purification Methods

limit chrom. **rextl. improv. ee**

What Makes a Total Synthesis Interesting or Valuable?

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disconnections methodology	yield vs. steps reactor time
Novel Architecture	***Reagent Selection***
complex structure first synthesis	safety availability cost
Bioactive	***Purification Methods***
produce for testing analog synthesis	limit chrom. rextl. improv. ee

Among many other factors

Production Considerations: Analogues and Natural Products

Recrystallization, Resolution

Utilize Very Robust Chemistry

Production Considerations: Analogues and Natural Products

Recrystallization, Resolution

Utilize Very Robust Chemistry

Target Considerations: Development of Analogues and Derviatives

Retain Only Necessary Parts

Production Considerations: Analogues and Natural Products

Recrystallization, Resolution

Utilize Very Robust Chemistry

Target Considerations: Development of Analogues and Derviatives

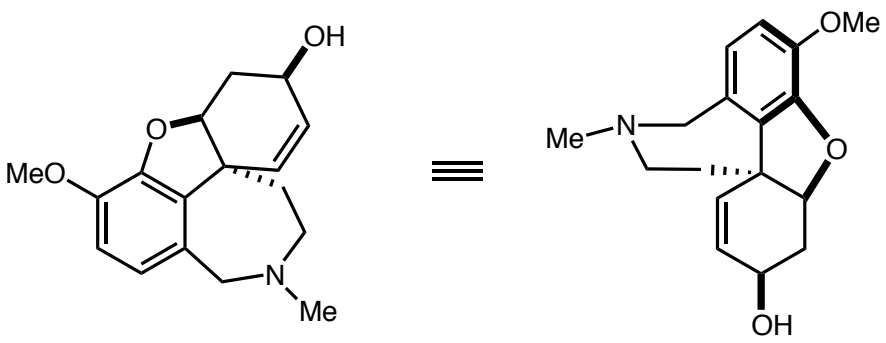
Retain Only Necessary Parts

Improve Activity or Properties

Shorten Production Route

(–)-galanthamine: Overview

(–)-galanthamine



- First studied in USSR in 1950's
- Inhibits acetylcholine esterase
- USSR used for varous CNS disorders

(–)-galanthamine: Overview

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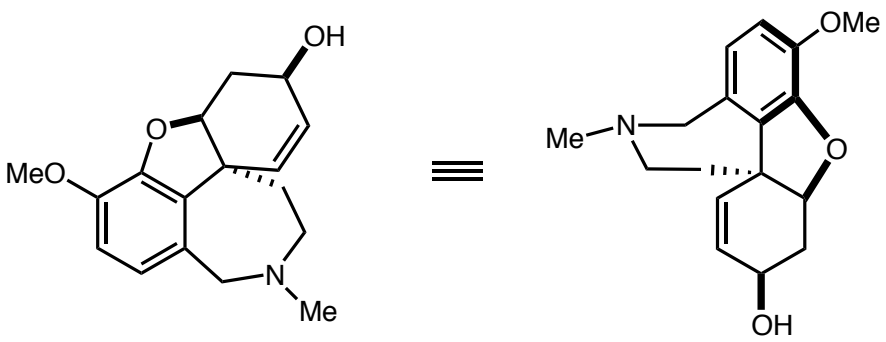

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- Used to treat mild to moderate cases

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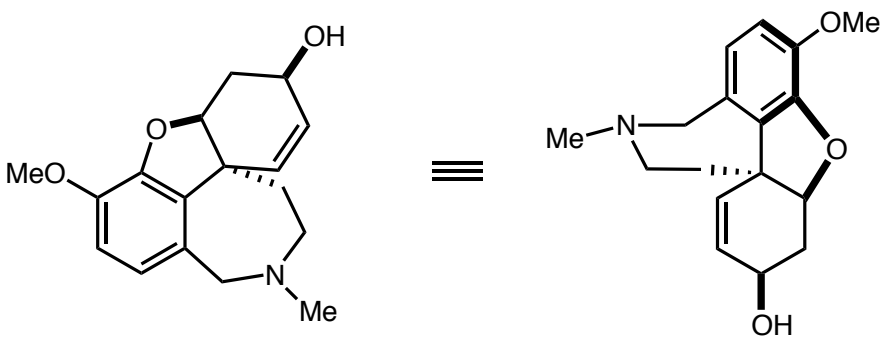
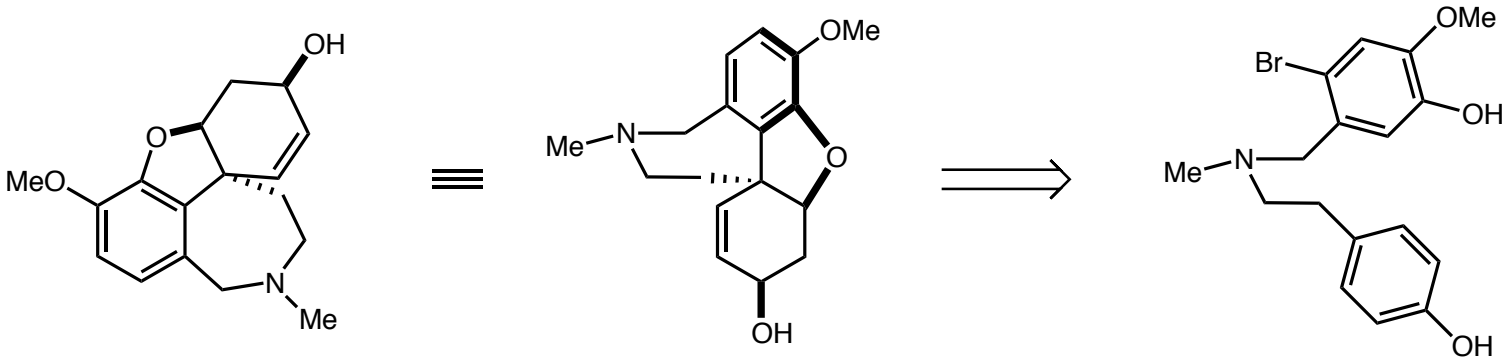


- First studied in USSR in 1950's
- Inhibits acetylcholine esterase
- USSR used for varous CNS disorders

- FDA approved in 2001 for treatment of Alzheimer's
- Used to treat mild to moderate cases
- Natural source (daffodils) not considered economical on scale
- Sanochemia patented (1996) and later improved synthetic route (2008)

(–)-galanthamine: Retrosynthetic Analysis

(–)-galanthamine



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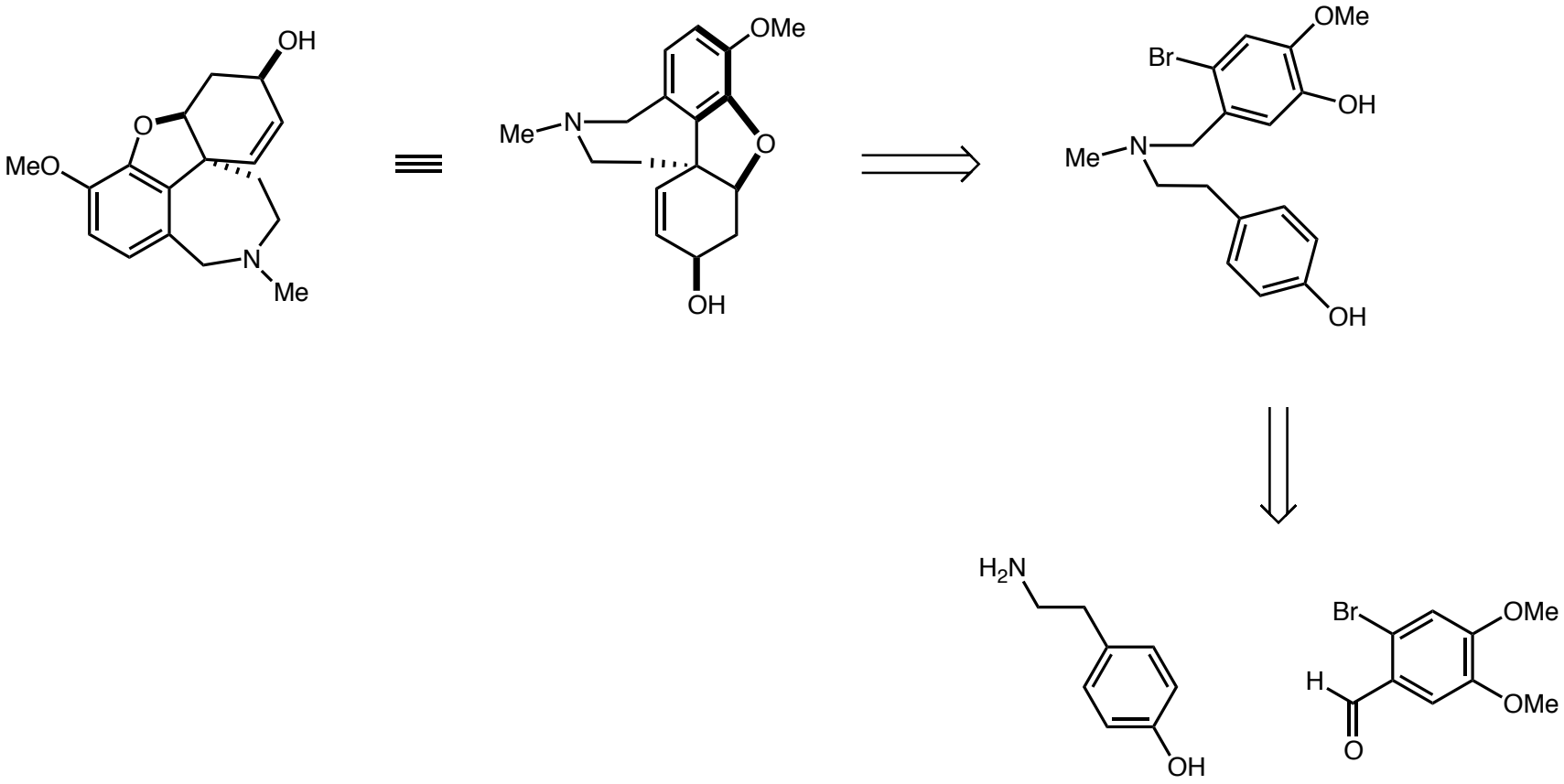

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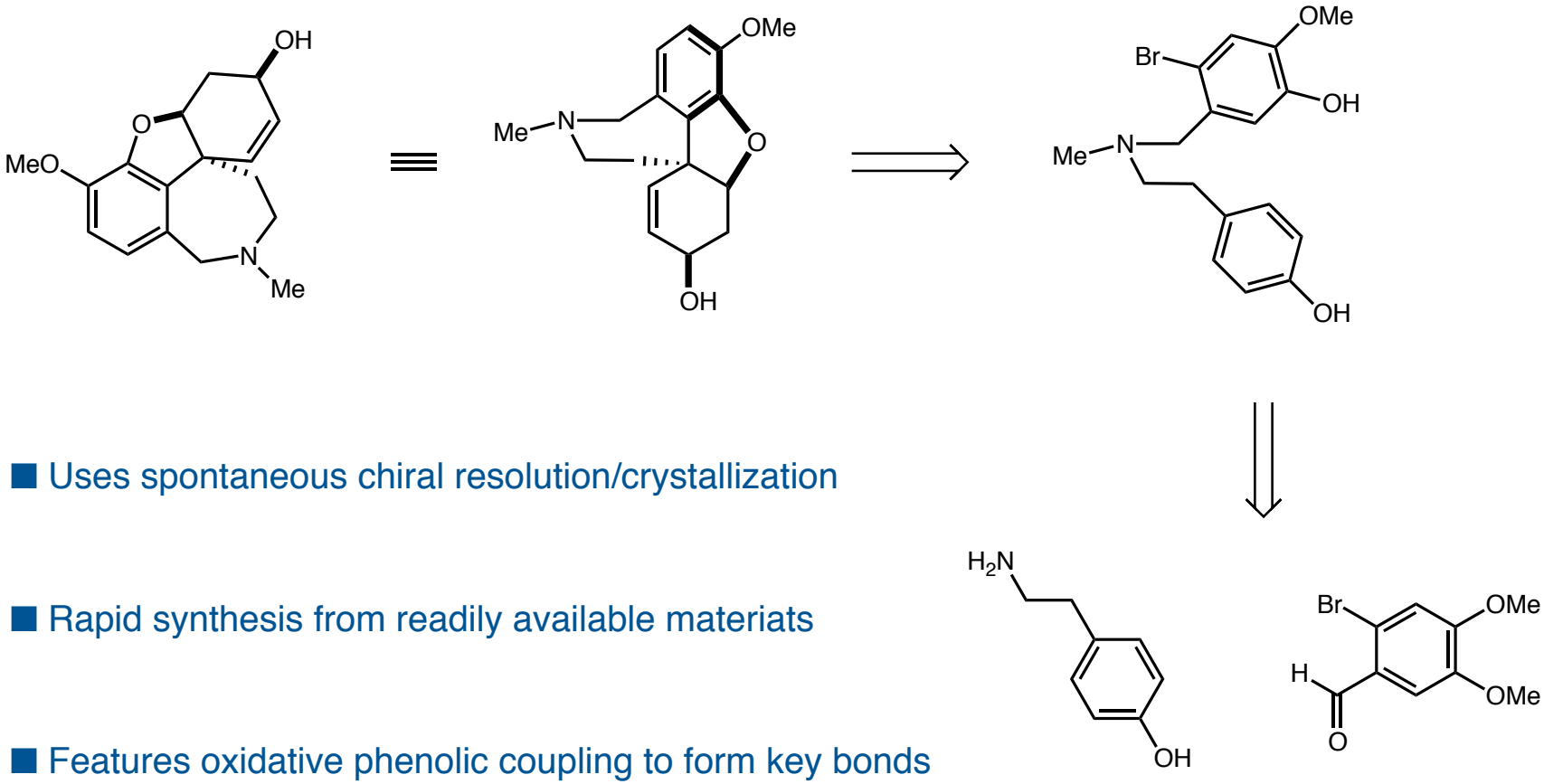
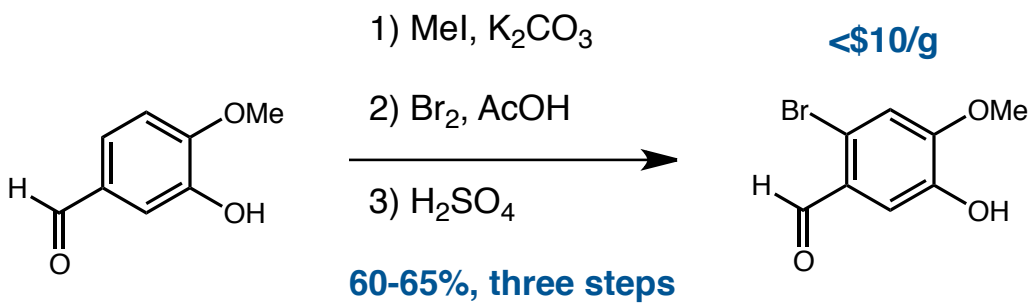


- Uses spontaneous chiral resolution/crystallization
- Rapid synthesis from readily available materiats
- Features oxidative phenolic coupling to form key bonds

(–)-galanthamine: Dynamic Resolution



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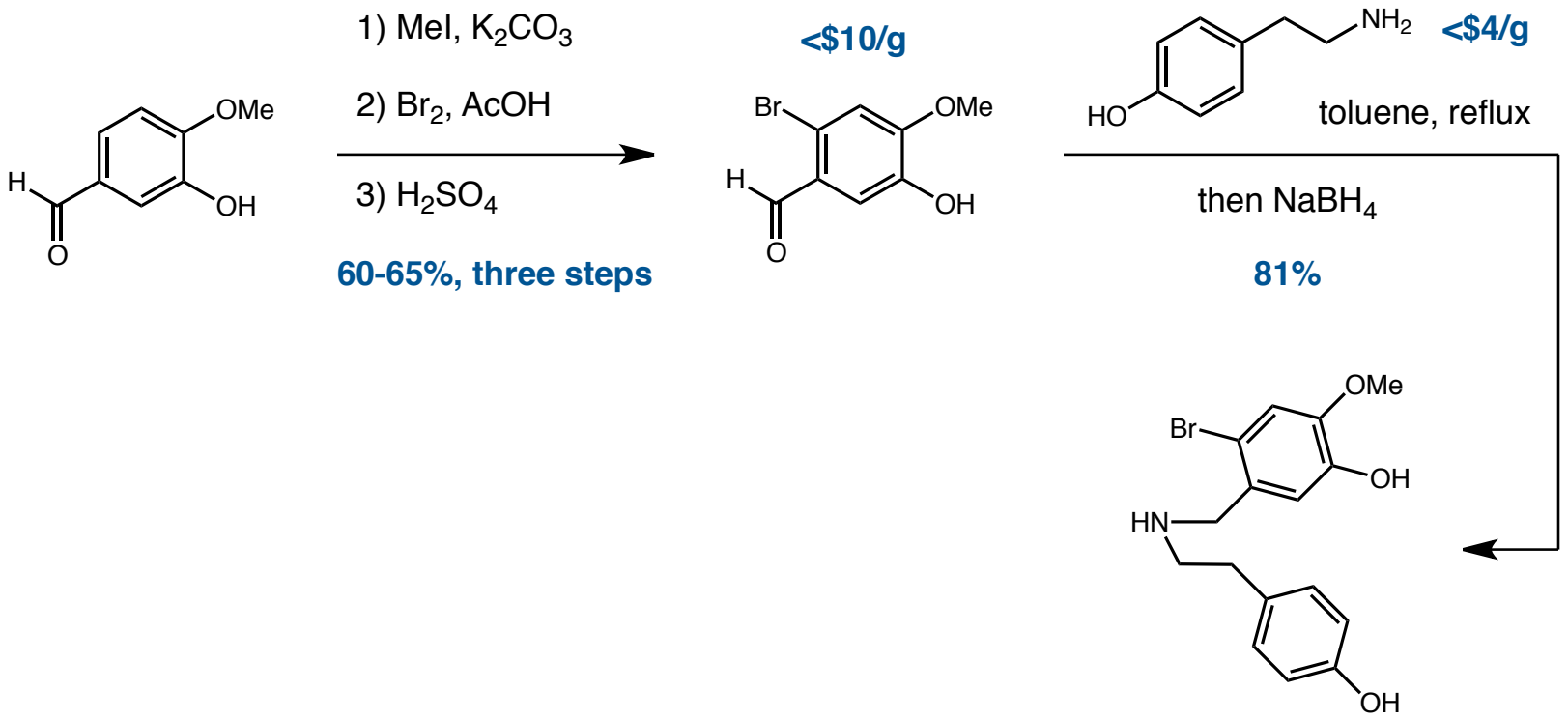

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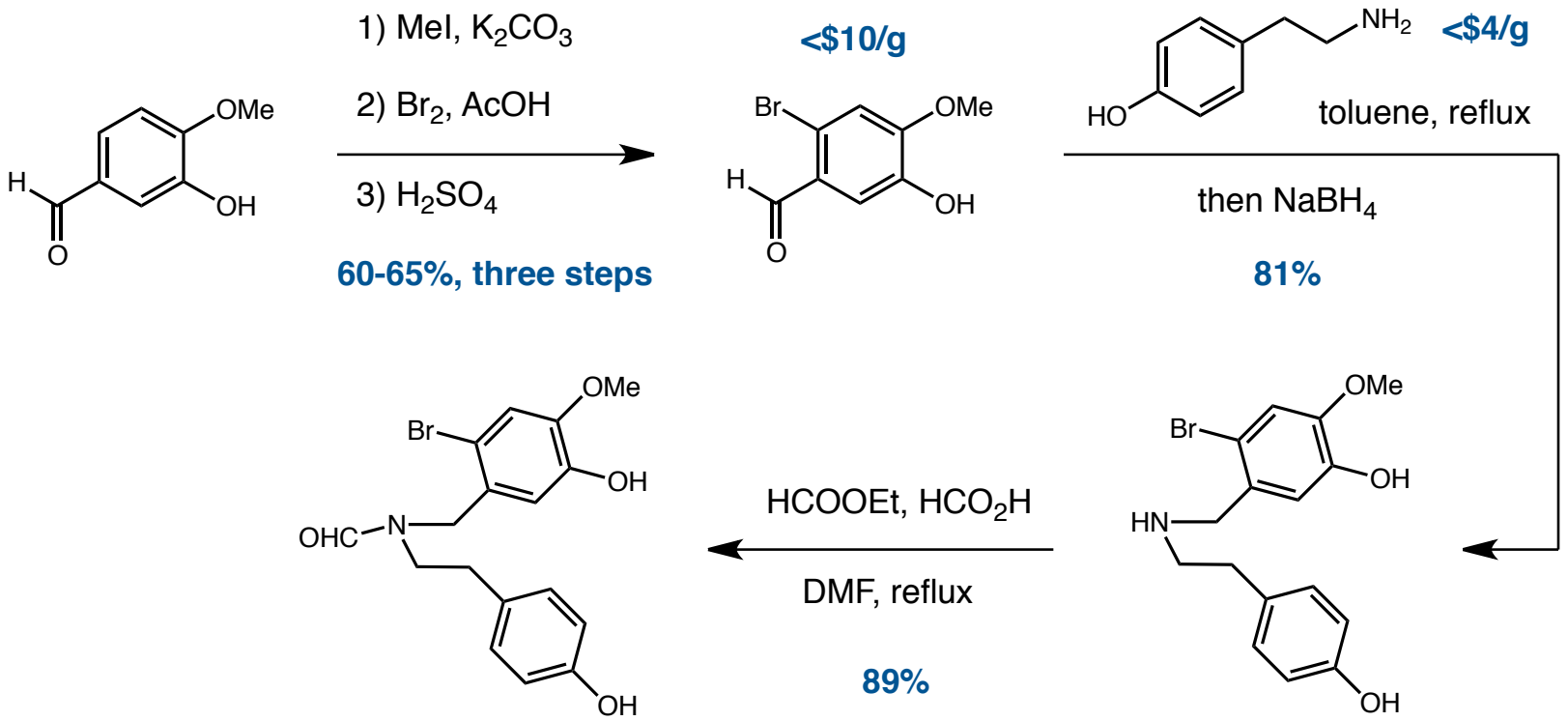

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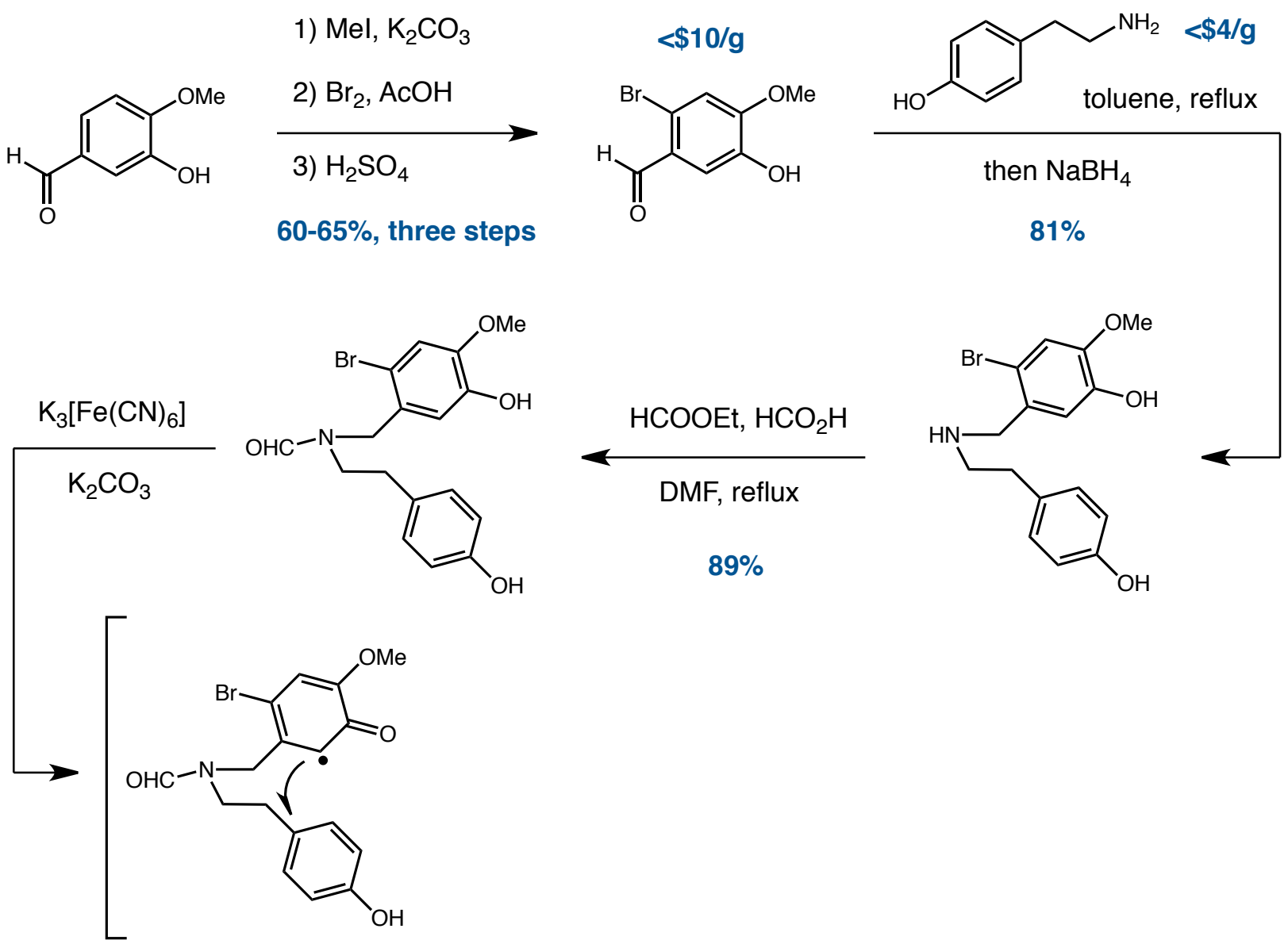

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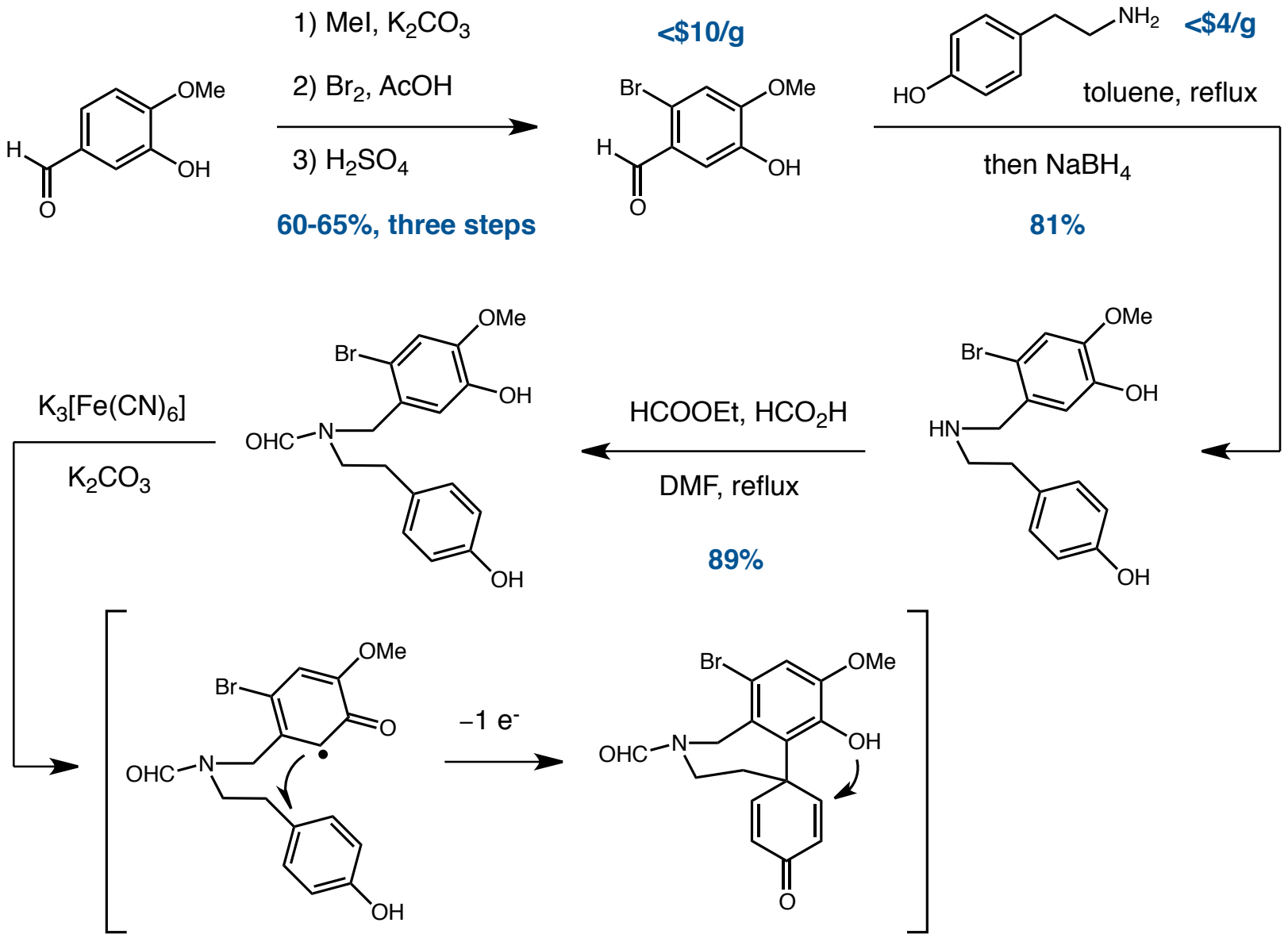

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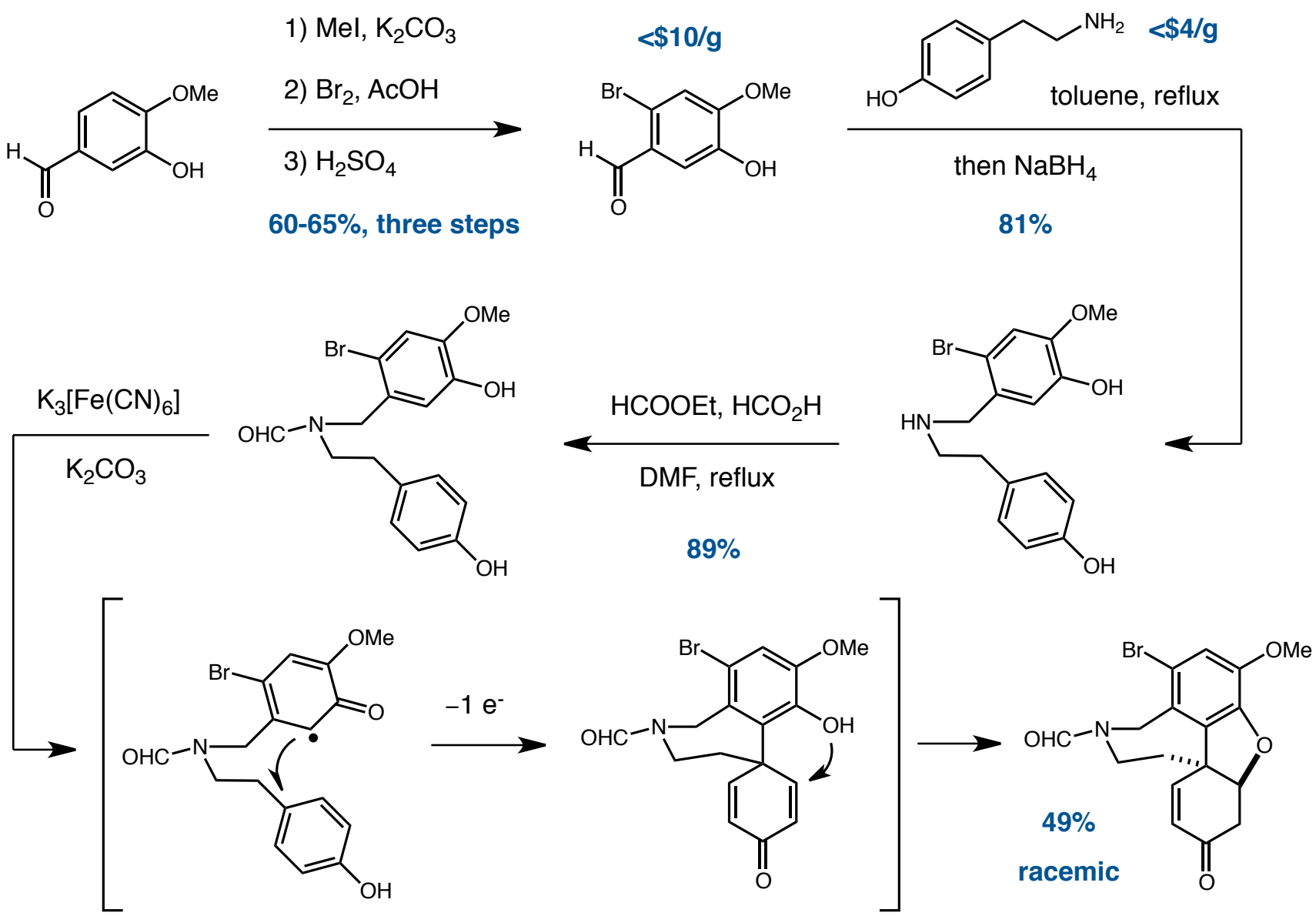

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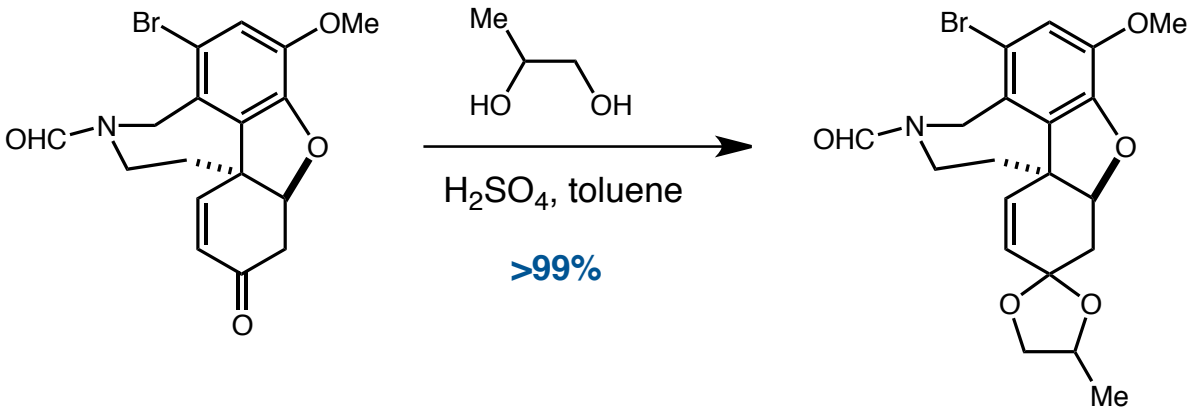

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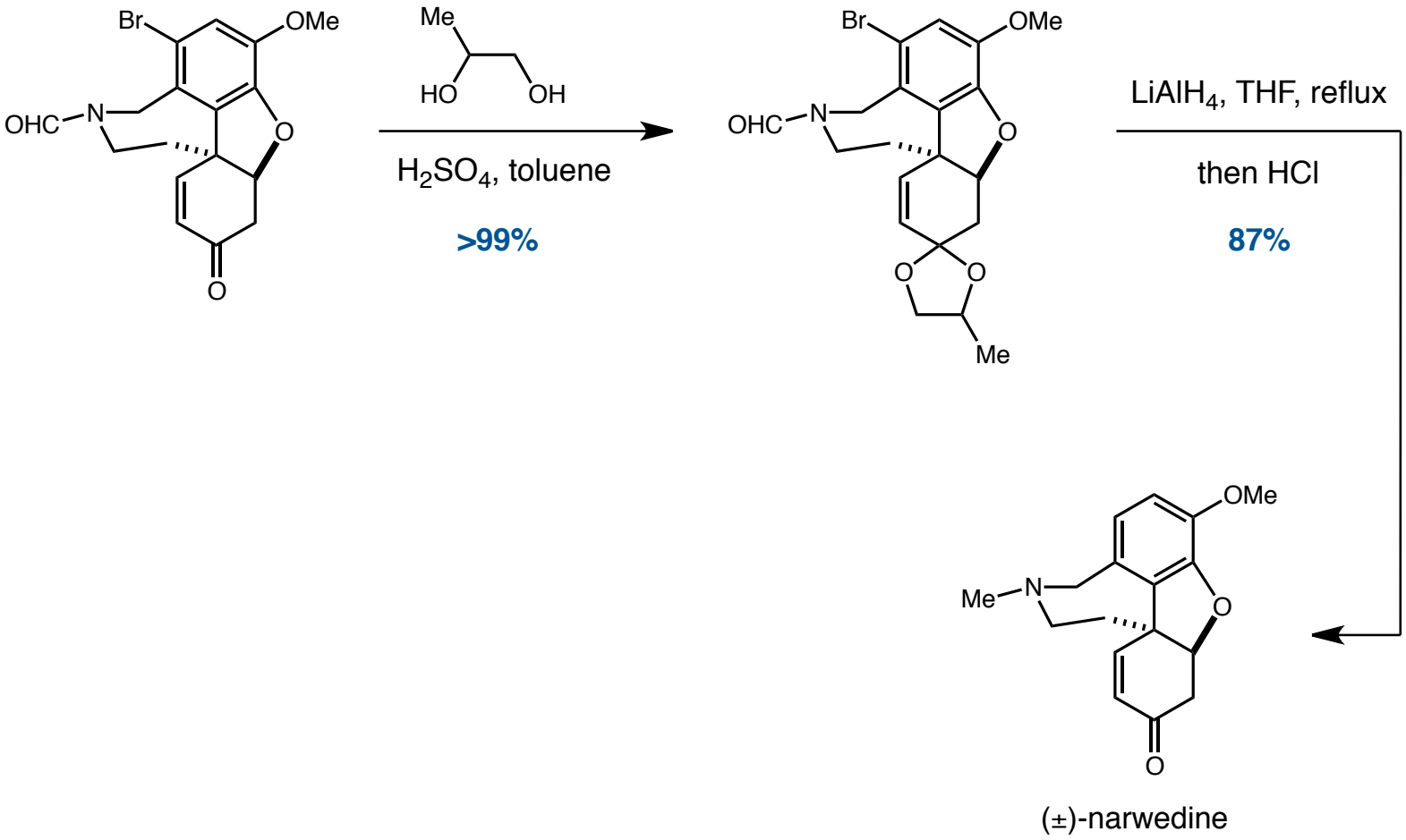

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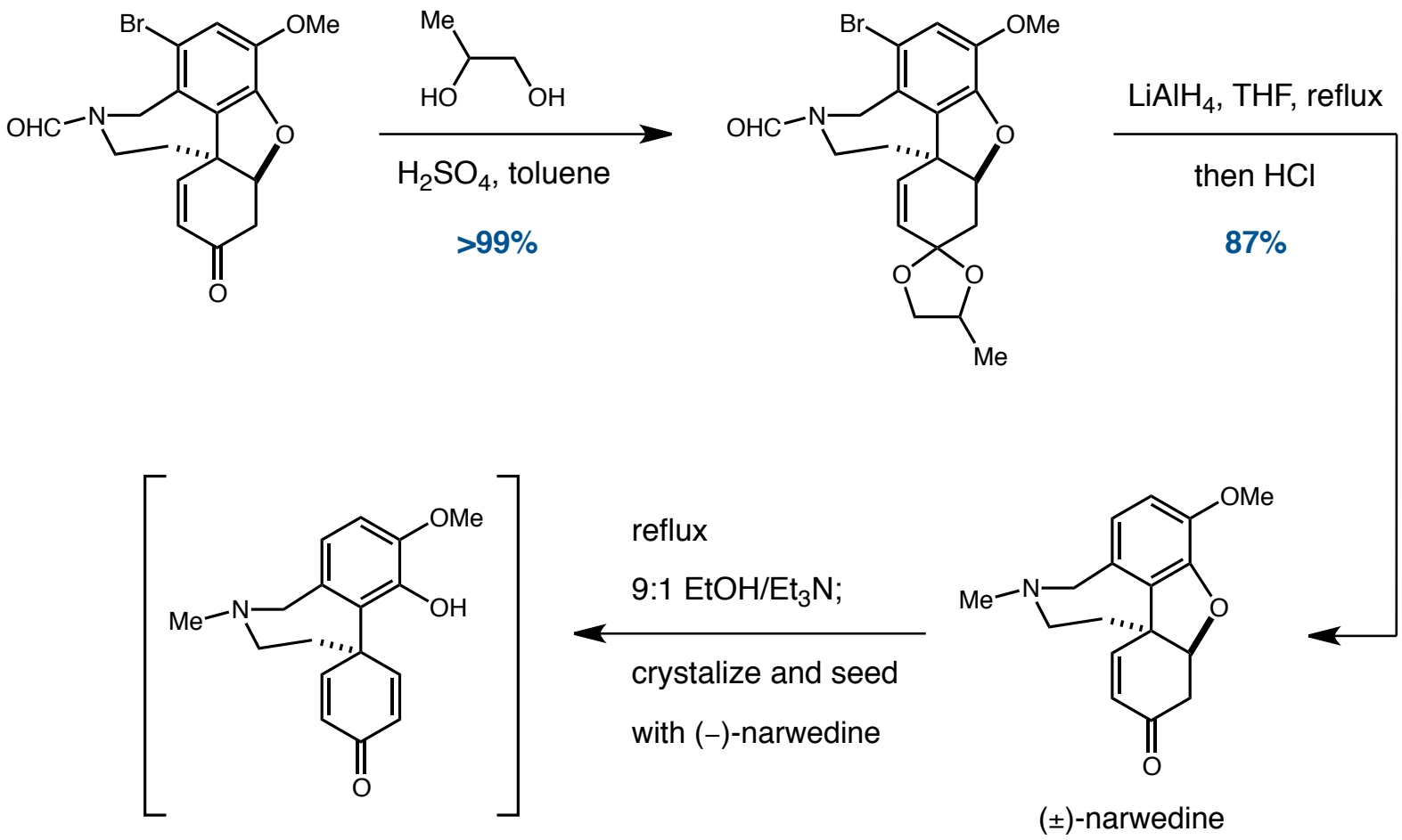

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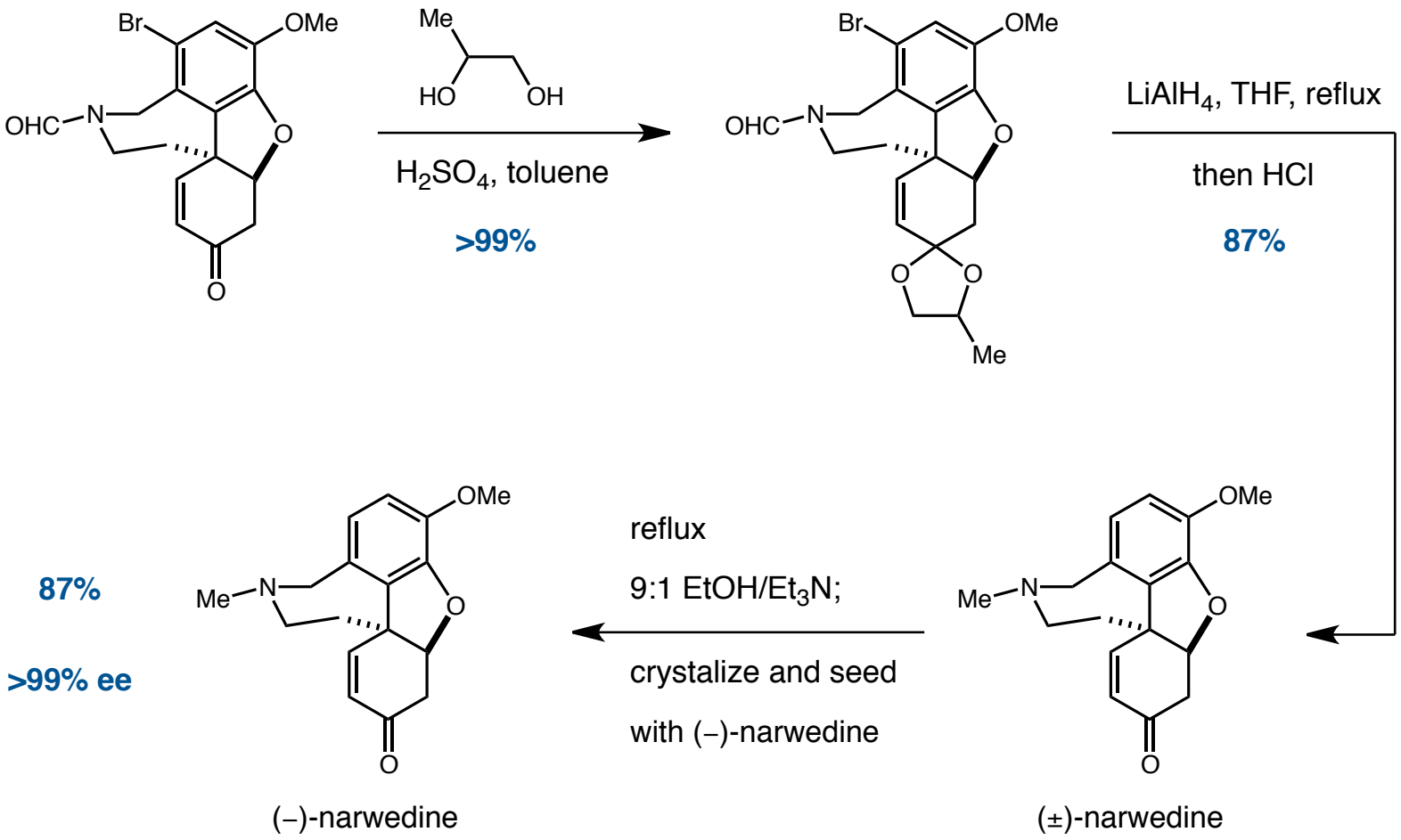
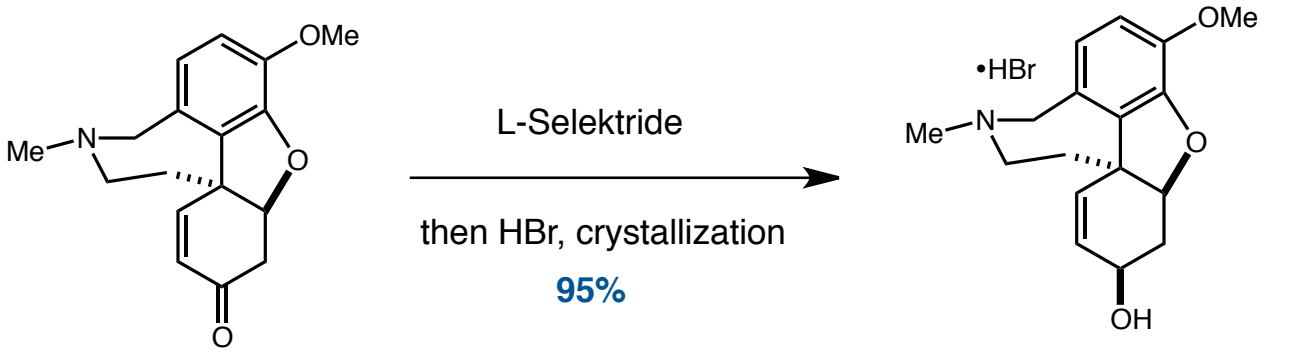


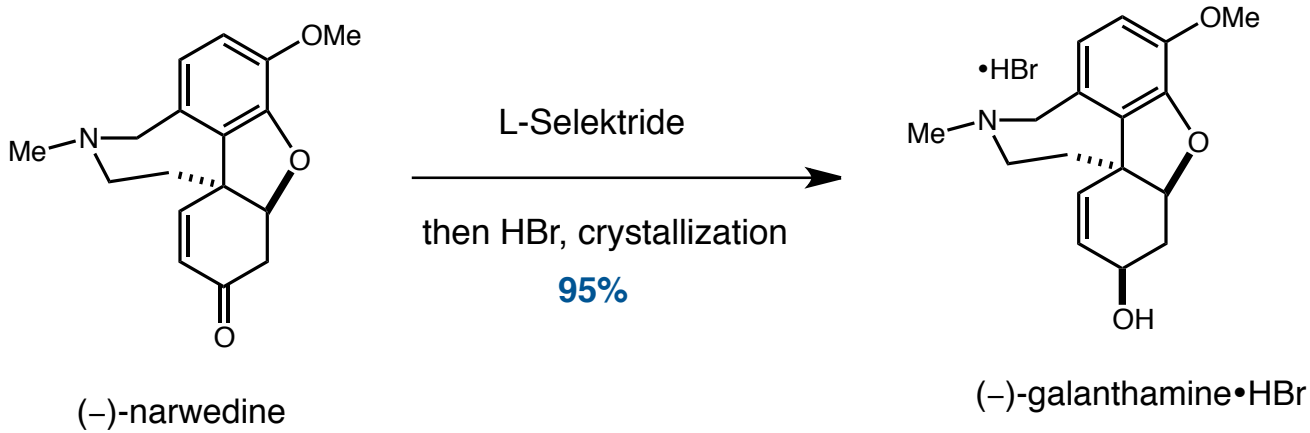
(–)-galanthamine: Completion of Synthesis



(–)-narwedine

(–)-galanthamine•HBr

(–)-galanthamine: Completion of Synthesis



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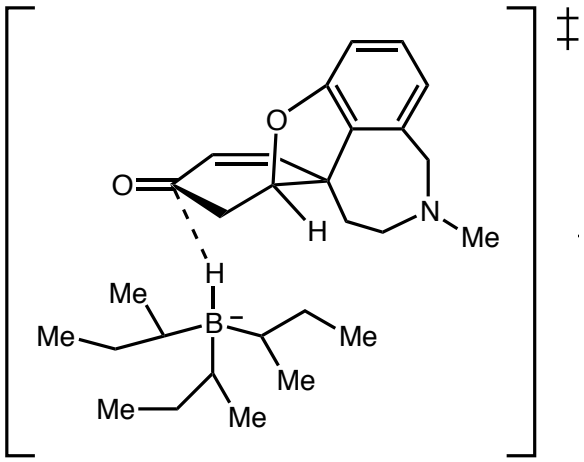

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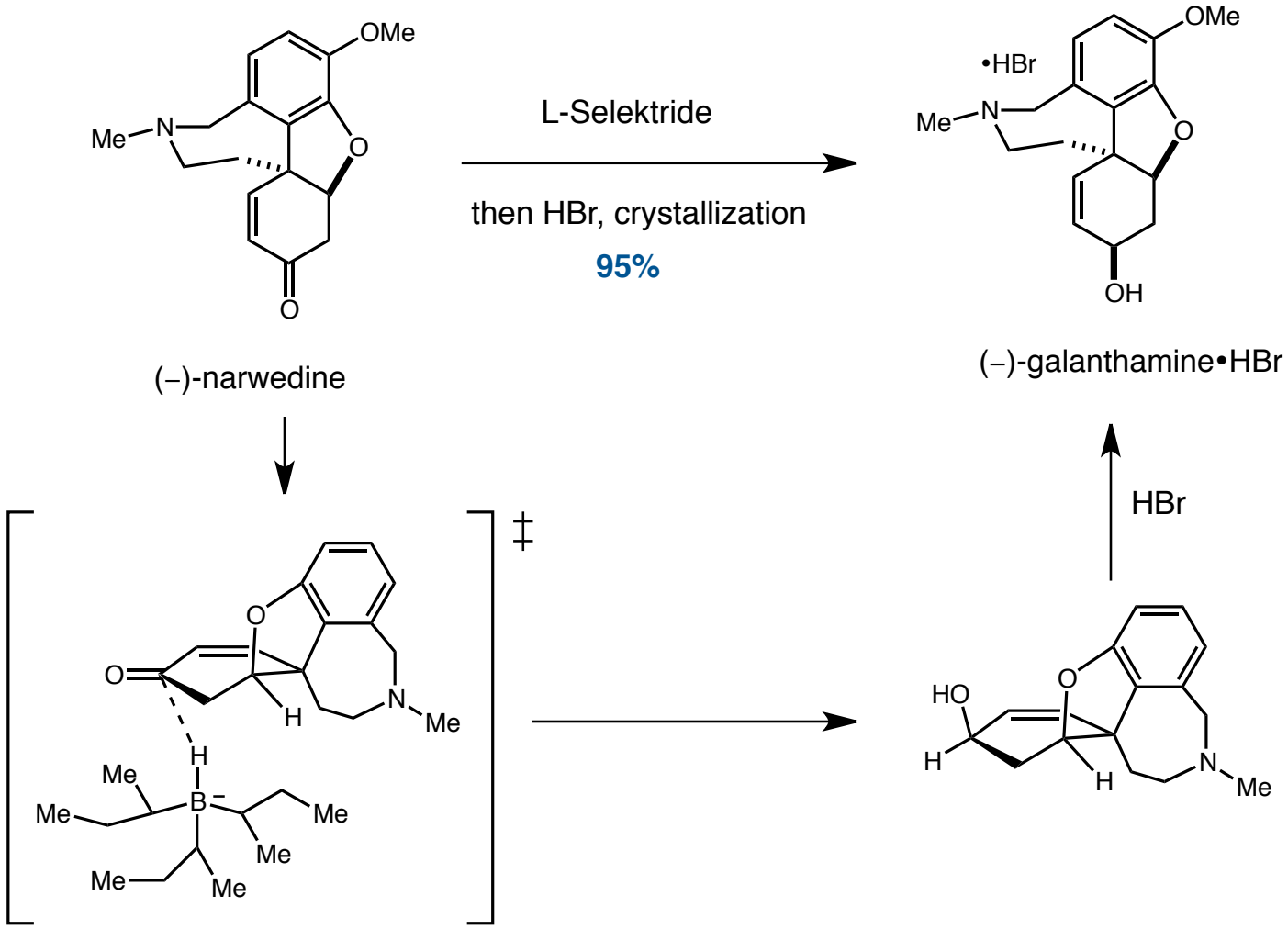

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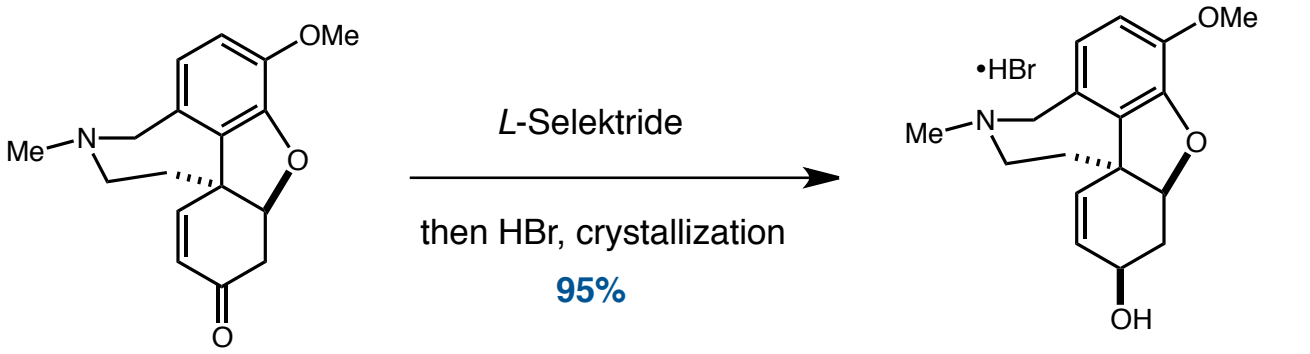


(–)-narwedine

(–)-galanthamine•HBr

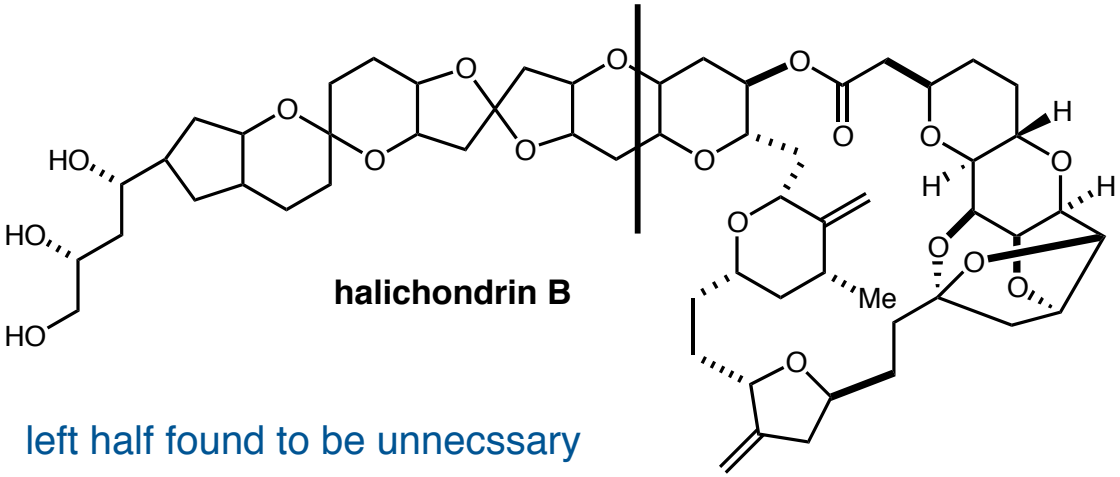
- From isovanillin: 16% overall yield, 9 steps (10 including dynamic resolution)
- From commercial bromide: 27% overall yield, 6 or 7 steps
- Resolution establishes stereochemistry, no enantioselective reactions

Production Considerations: Analogues and Natural Products

Recrystallization, Resolution

Utilize Very Robust Chemistry

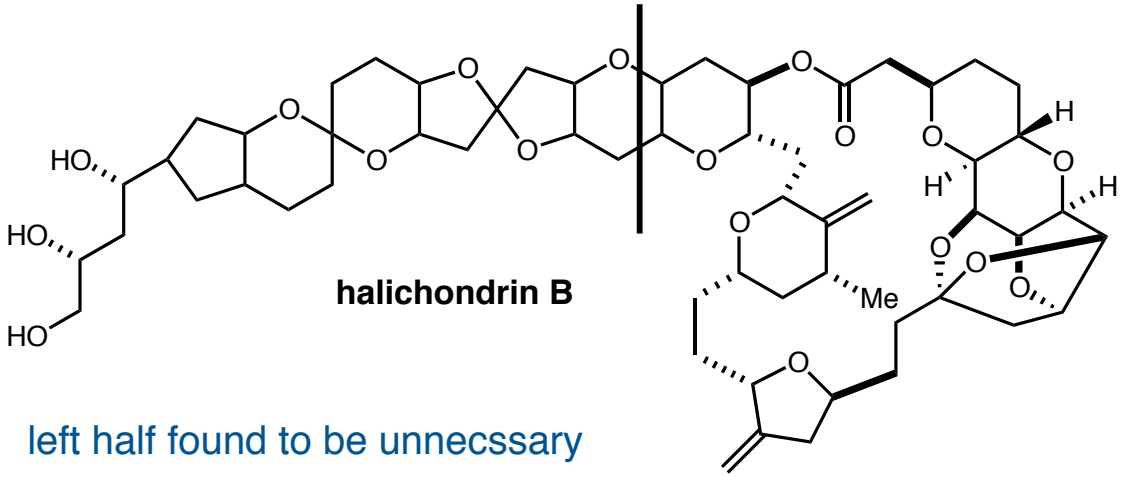
Eribuline: Overview



halichondrin B

left half found to be unnecssary

Eribuline: Overview



halichondrin B

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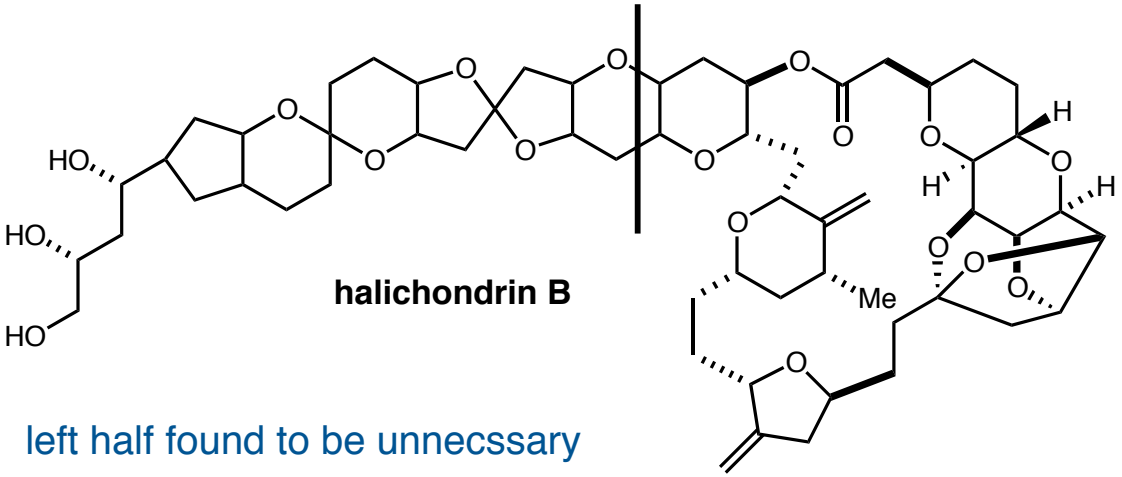
Halichondrin B

- Halichondrin B isolated from sponges in 1986
- Activity further demonstrated by Nat. Cancer Inst.
- Total synthesis complete by Kishi in 1992

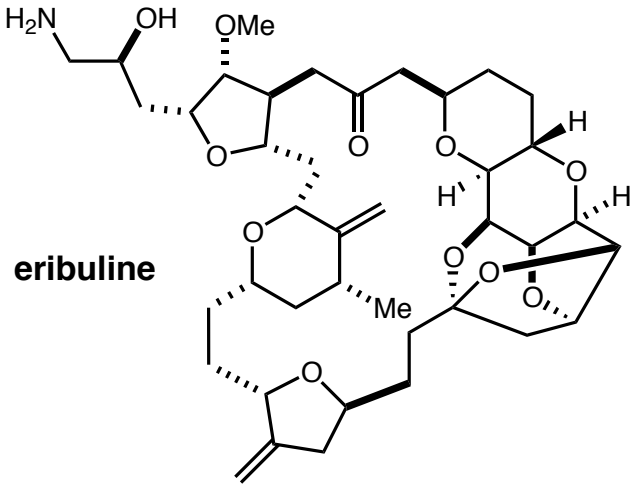
Eribuline: Overview



halichondrin B

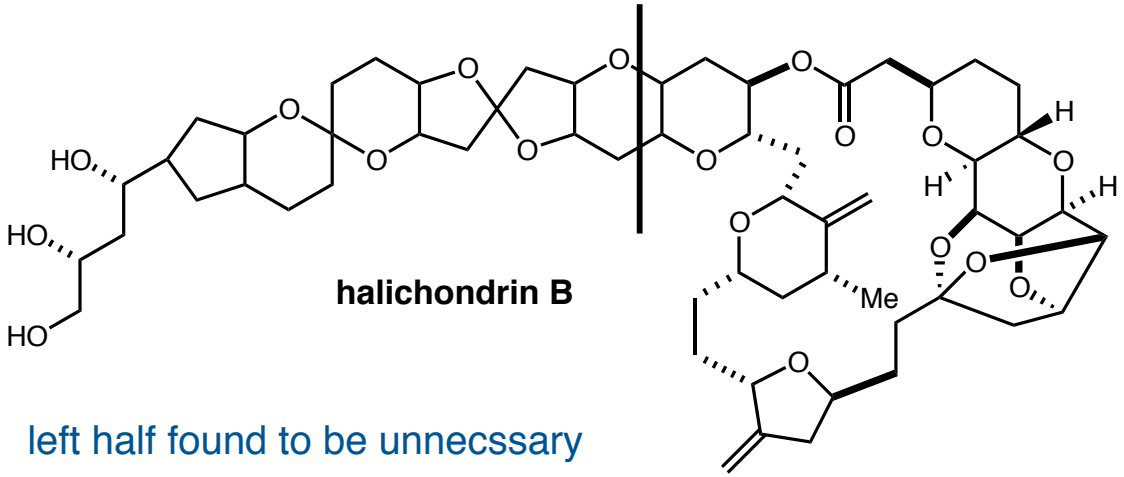
left half found to be unnecssary

highly conserved right hand portion



eribuline

Eribuline: Overview



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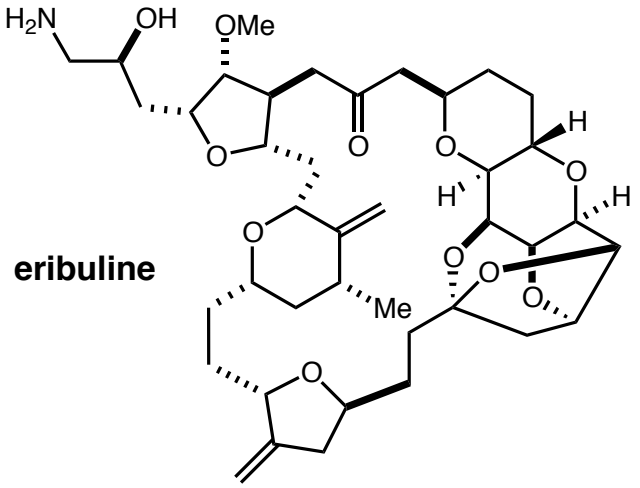
Eribuline

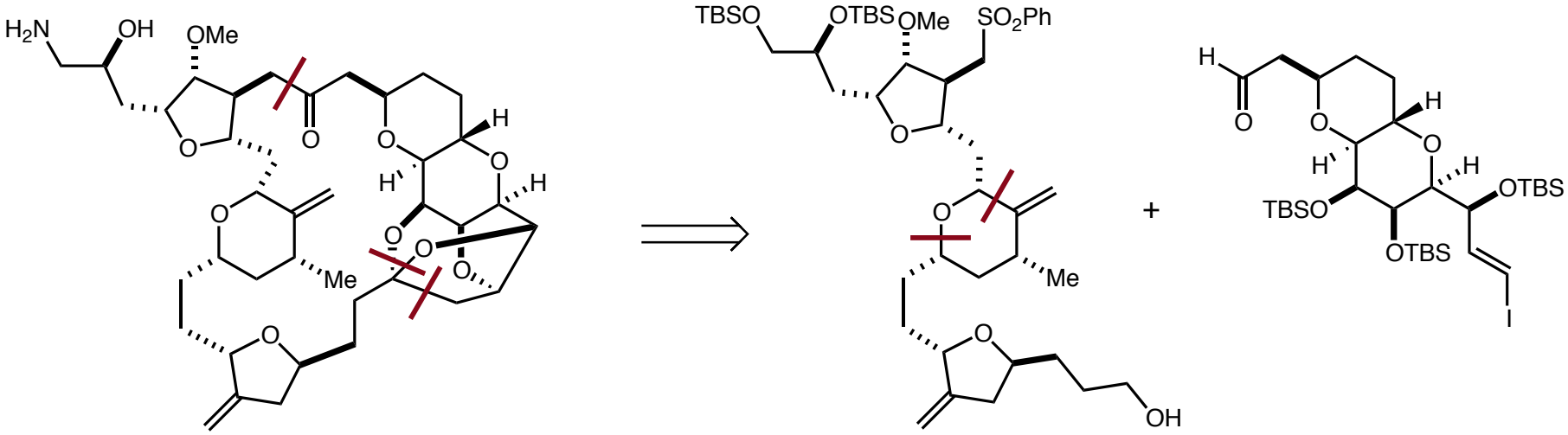
highly conserved right hand portion



eribuline

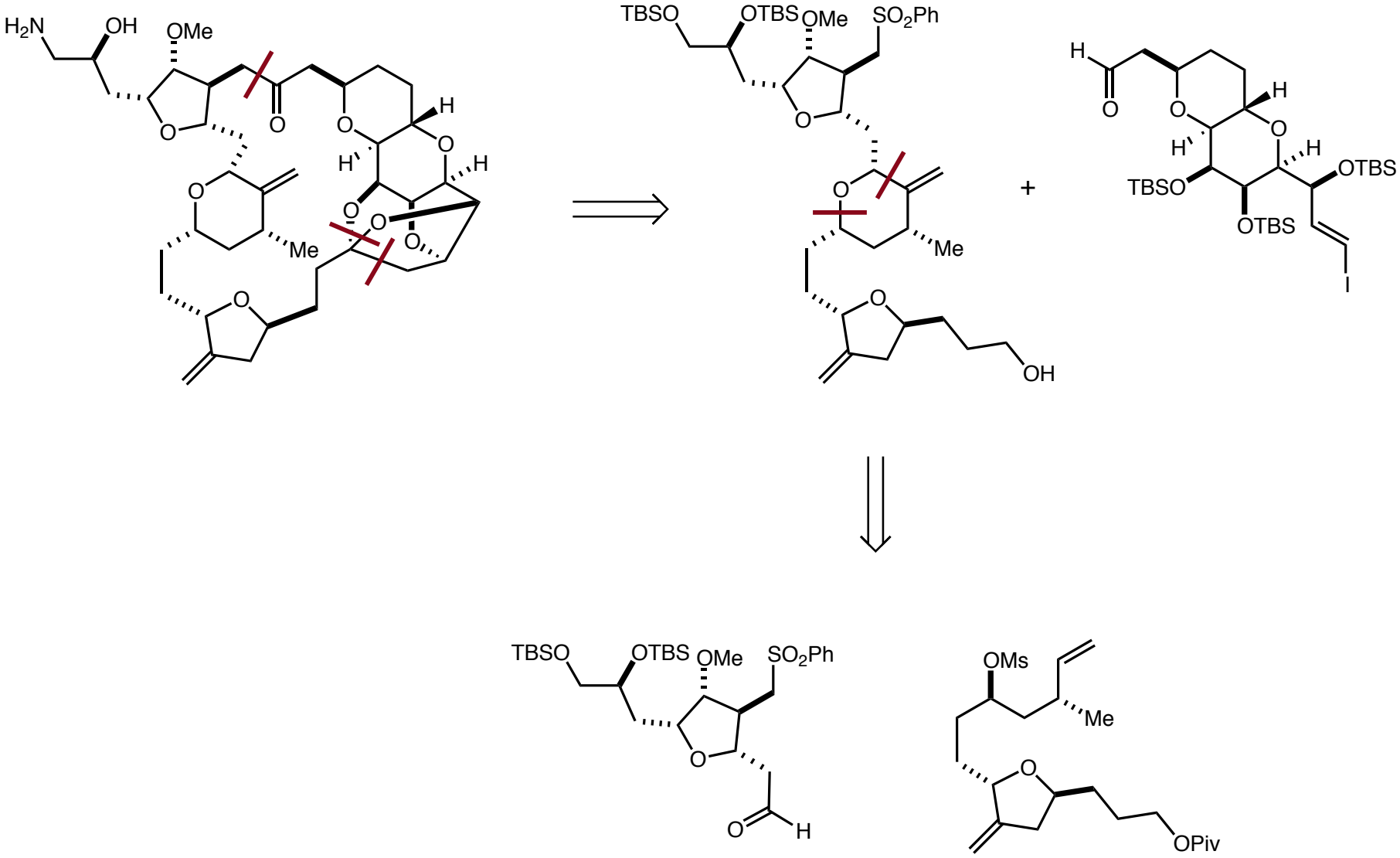
- Approved to treat metastatic breast cancer in 2010
- Class has mechanistically unique inhibition pathway
- Marketed by Eisai with global partnerships

Eribuline: Retrosynthetic Analysis



Bioorg. Med. Chem. **2012** 1155

Eribuline: Retrosynthetic Analysis



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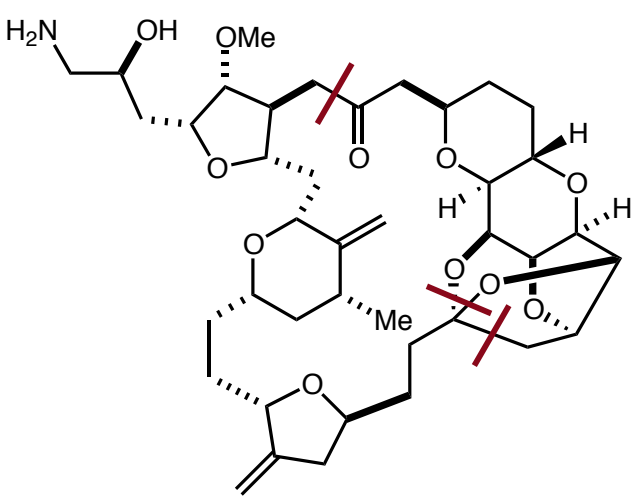

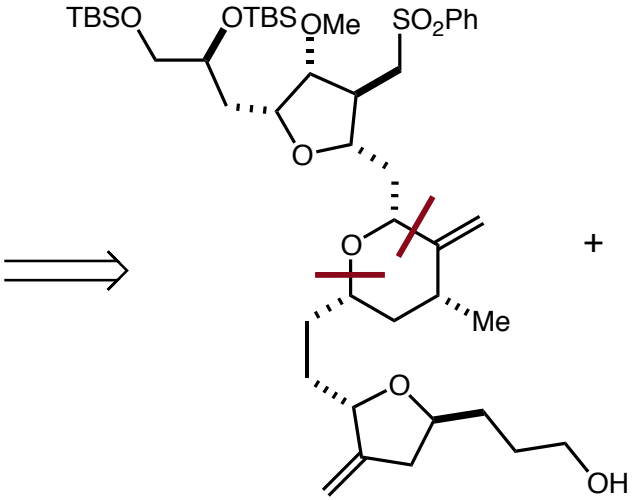

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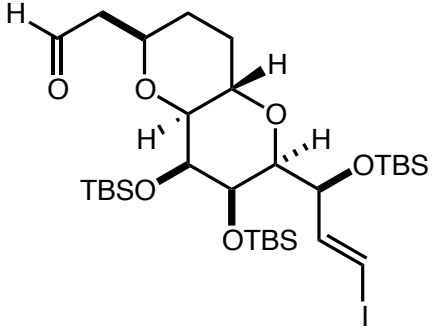
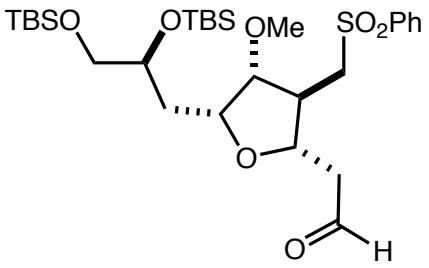
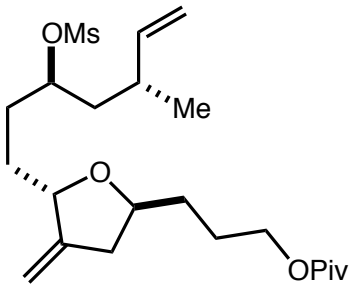


- Highly convergent
- Late stage coupling
- Utilizes chiral pool





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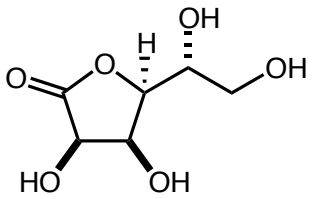
Eribuline: Eastern Fragment



L-mannonic acid γ-lactone

$50/g (Aldrich)

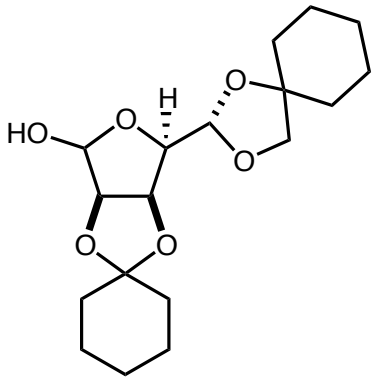
1) *c*-hexanone, *p*TSA

$PhCH_3$, reflux

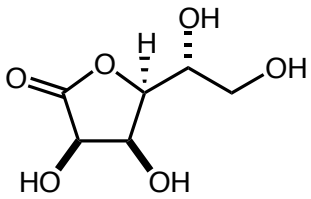
2) DIBAL-H, -15 °C

$PhCH_3$, THF

84%, two steps



Eribuline: Eastern Fragment



L-mannonic acid γ-lactone

$50/g (Aldrich)

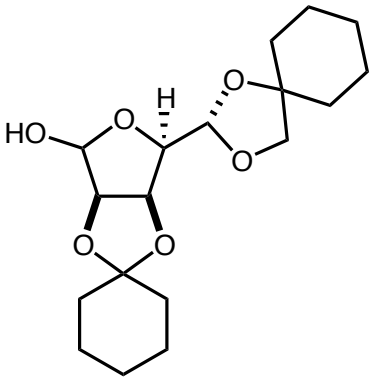
1) *c*-hexanone, *p*TSA

$PhCH_3$, reflux

2) DIBAL-H, -15 °C

$PhCH_3$, THF

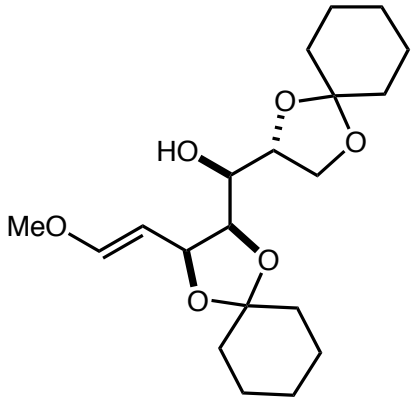
84%, two steps



$ClPh_3PCH_2OMe$

KOtBu, THF

81%



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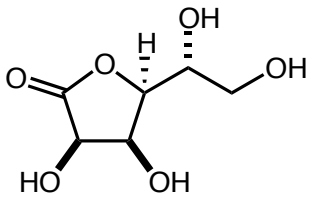

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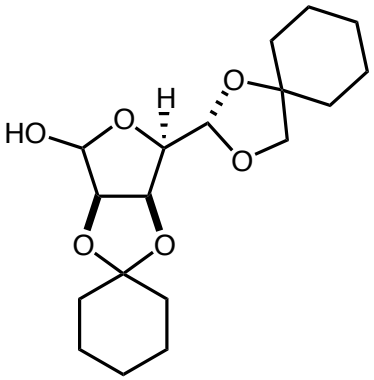

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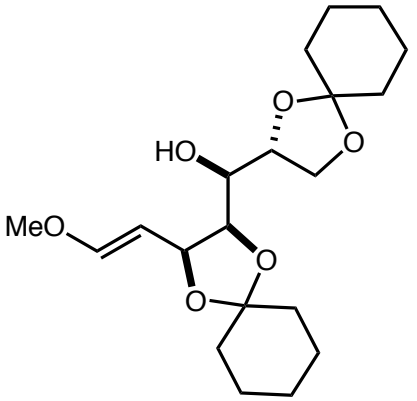
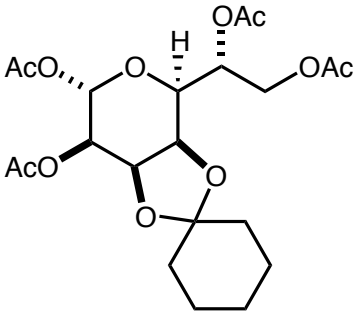


1) OsO_4, NMO
acetone, H_2O

2) Ac_2O, AcOH
$ZnCl_2$, 40 °C

44%, two steps



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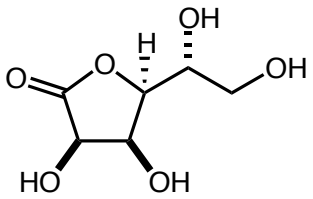

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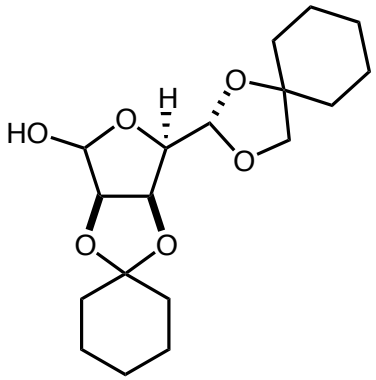

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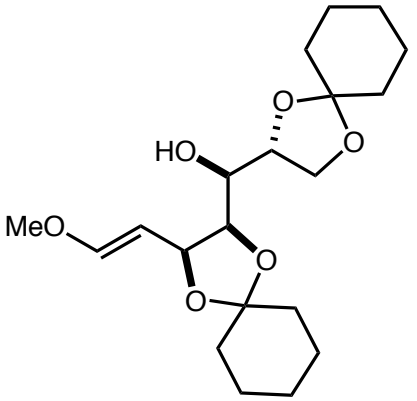

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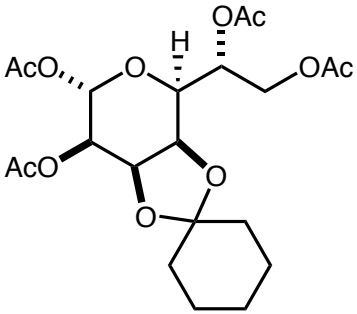
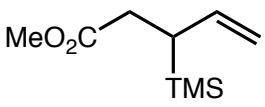
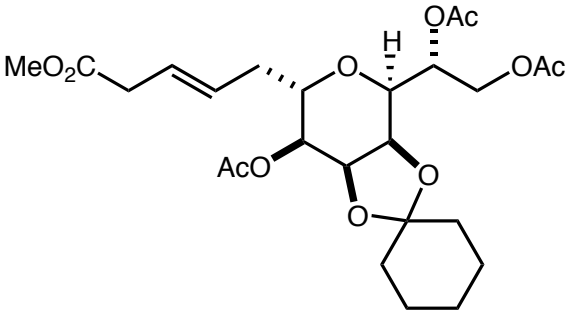
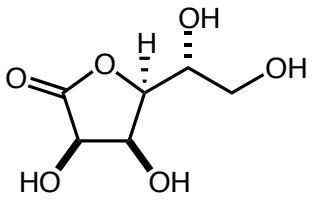




BF_3•OEt, MeCN



Eribuline: Eastern Fragment



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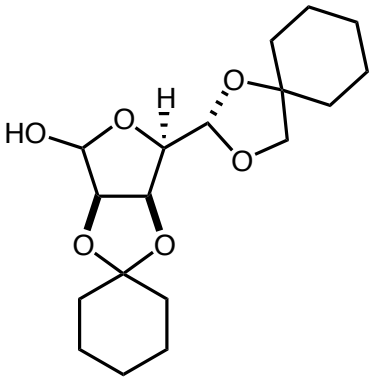
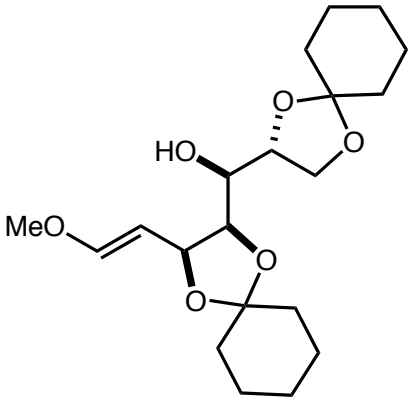
84%, two steps



$ClPh_3PCH_2OMe$

KOtBu, THF

81%



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$ZnCl_2$, 40 °C

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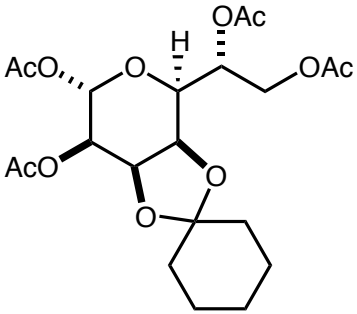
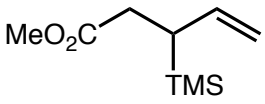
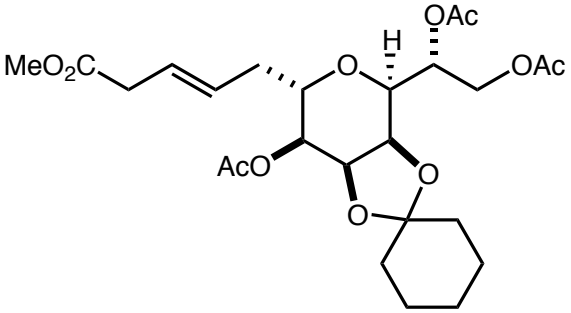




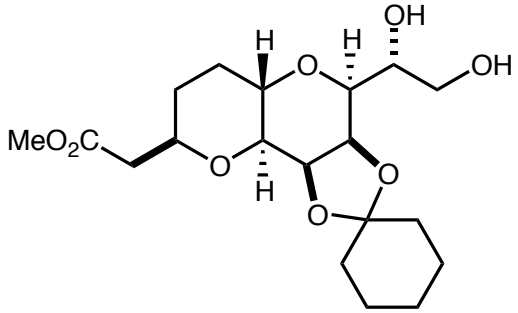
BF_3•OEt, MeCN



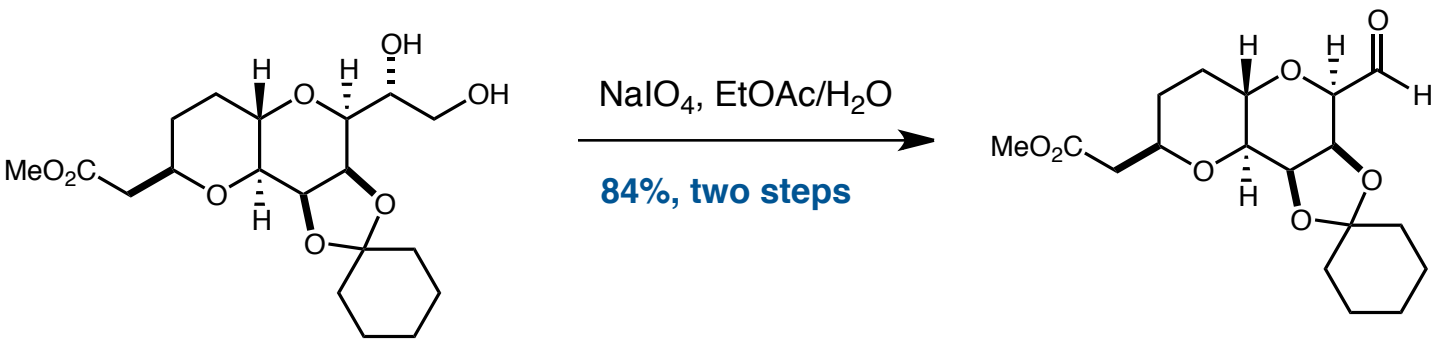
Triton B(OH)

THF, MeOAc

38%, two steps



Eribuline: Completion of Eastern Fragment



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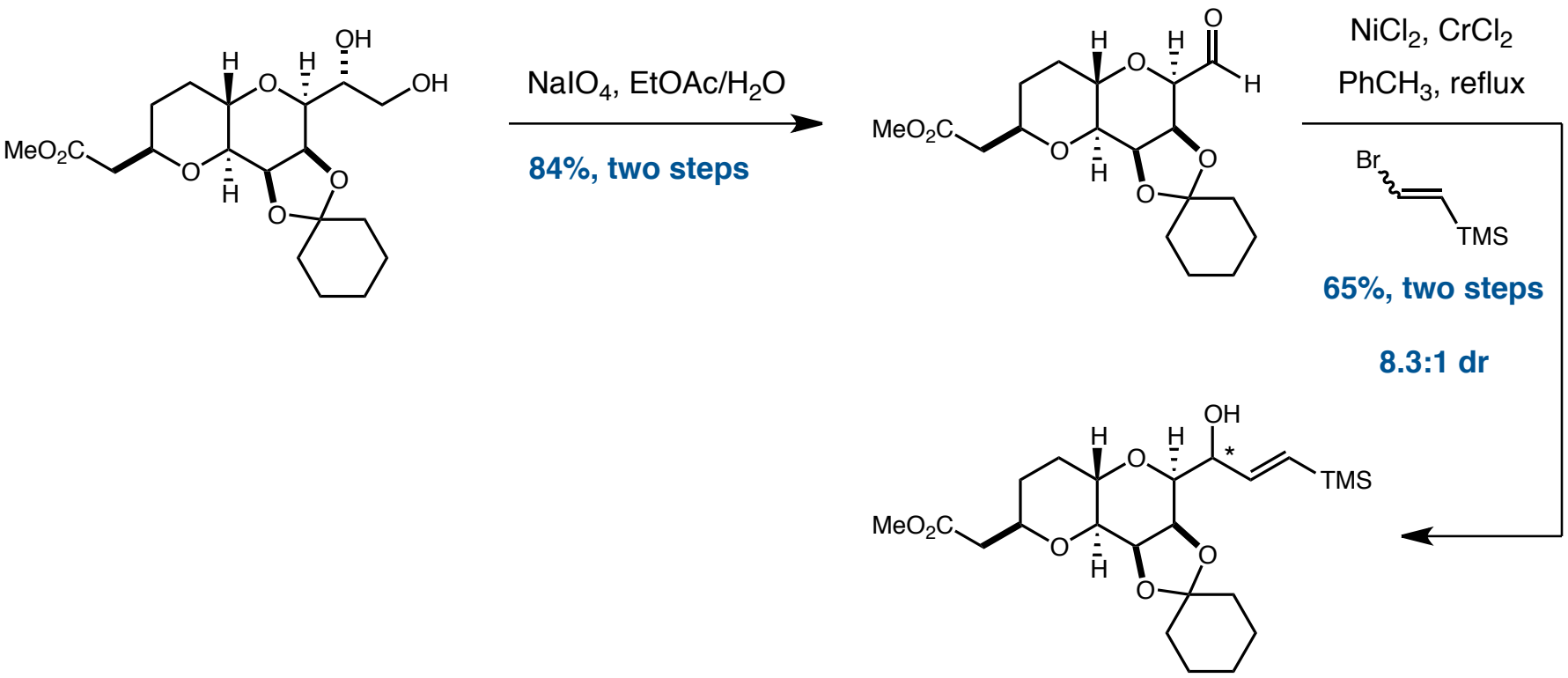

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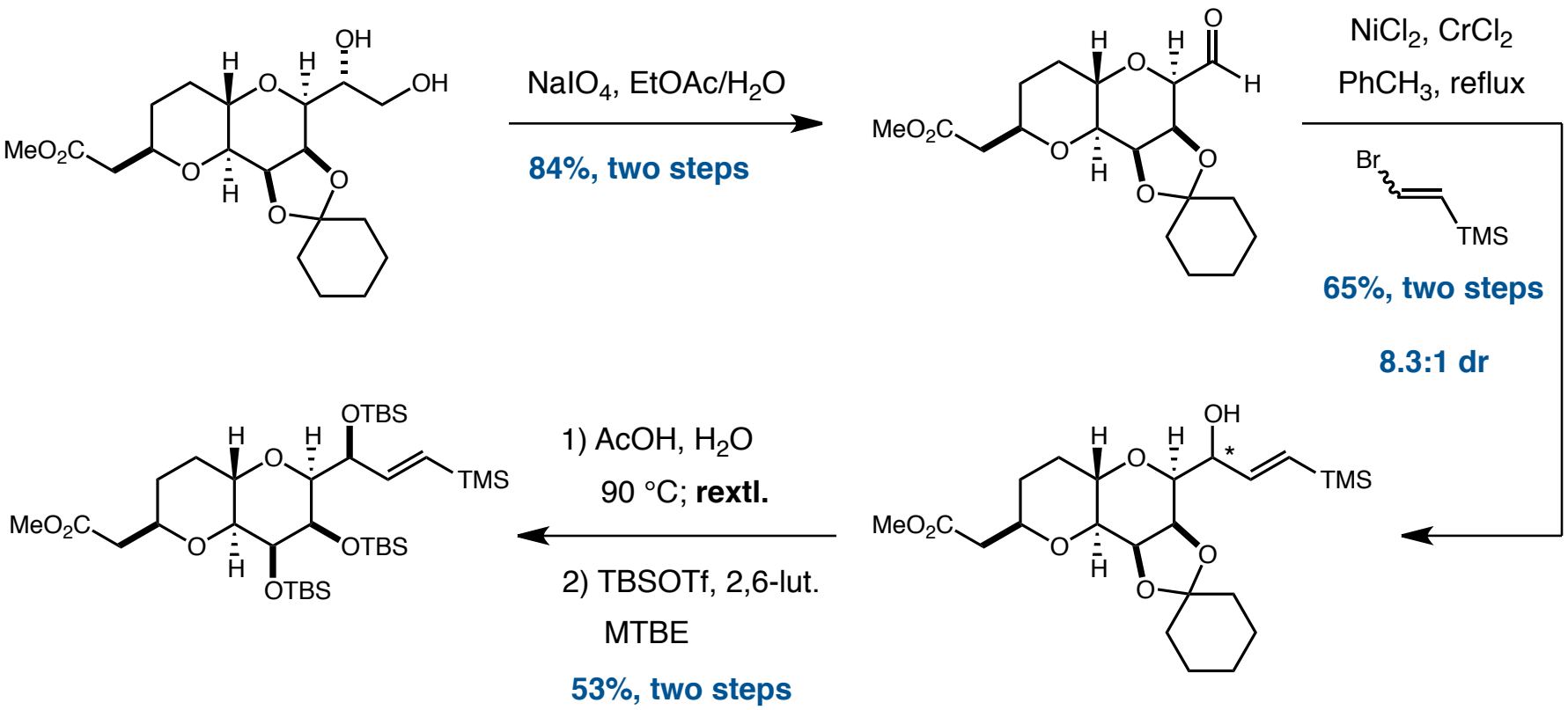

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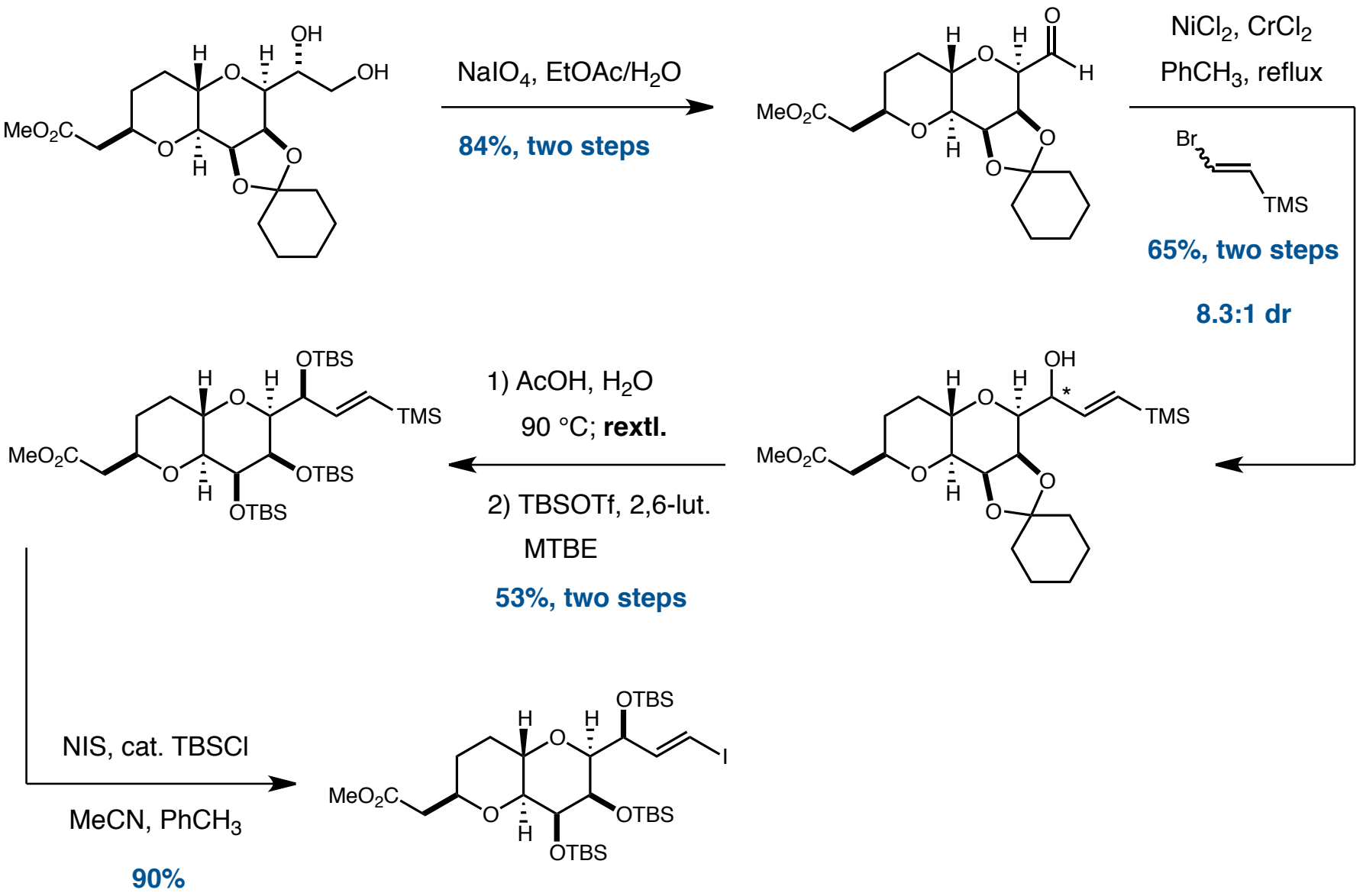

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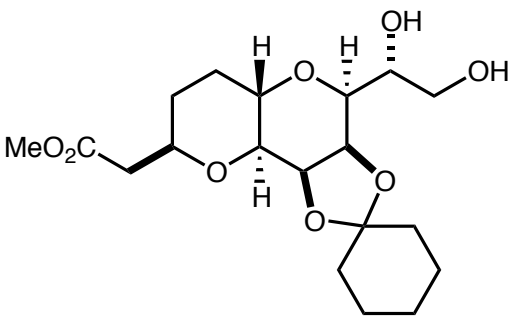
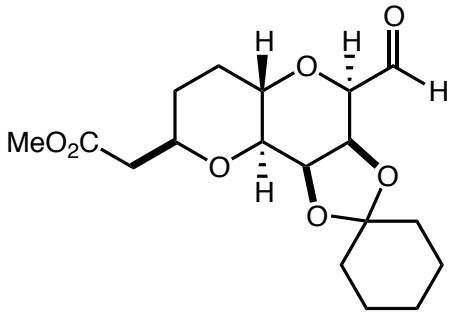


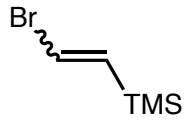
$NaIO_4$, EtOAc/H_2O

84%, two steps



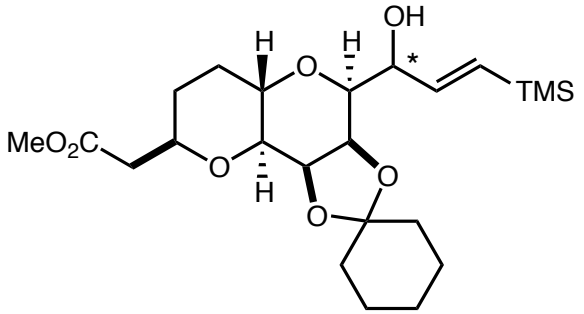
$NiCl_2$, $CrCl_2$

$PhCH_3$, reflux



65%, two steps

8.3:1 dr



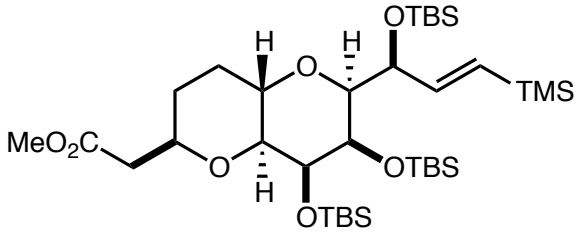
1) AcOH, H_2O

90 °C; **rextl.**

2) TBSOTf, 2,6-lut.

MTBE

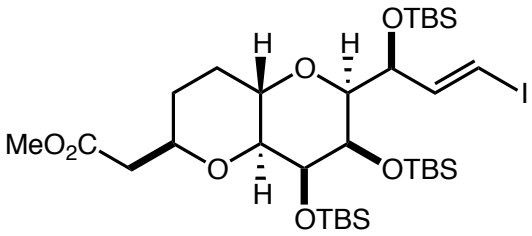
53%, two steps



NIS, cat. TBSCl

$MeCN$, $PhCH_3$

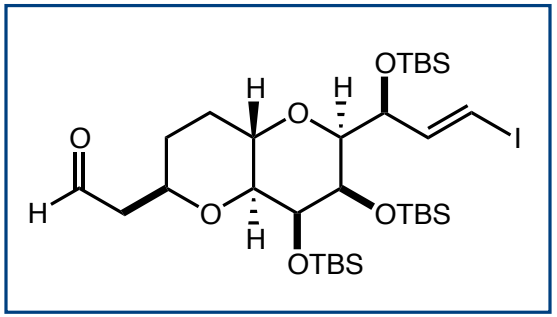
90%



DIBALH

-75 °C

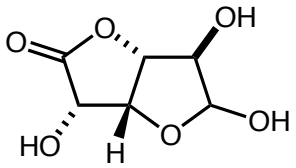
93%



2.8%, 15 steps

Eribuline: Northern Fragment Synthesis

<$1/g (TCI)



D-glucorono-

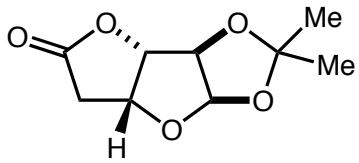
6,3 lactone

1) acetone, H_2SO_4

2) SO_2Cl_2, pyr., MeCN

3) H_2, Pd/C, THF

59%, three steps



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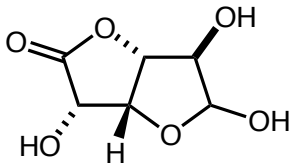

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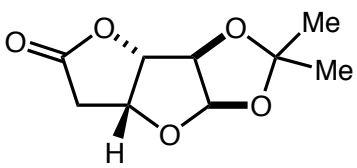
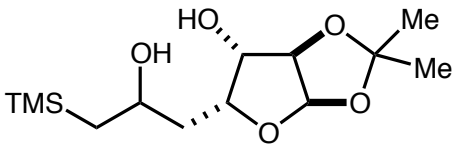


1) DIBALH, $PhCH_3$, -40 °C

2) $TMSCH_2MgCl$, THF

72%, two steps



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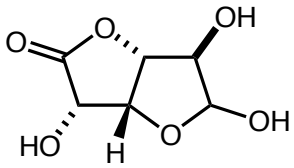

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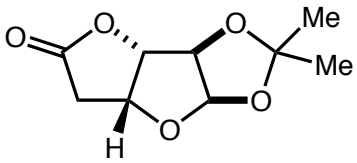

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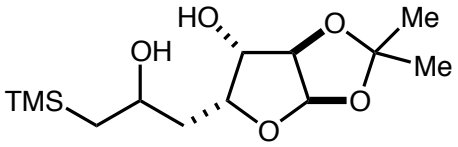
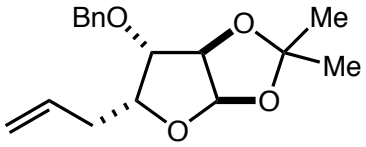


1) KHMDS, THF

2) BnBr, KO*t*Bu

89%, two steps



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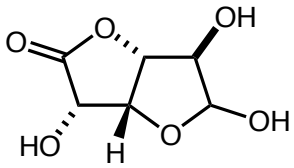

D-glucorono-
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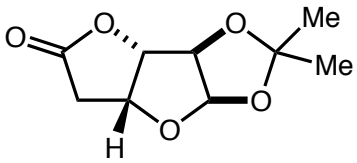
2) SO_2Cl_2, pyr., MeCN
3) H_2, Pd/C, THF

59%, three steps



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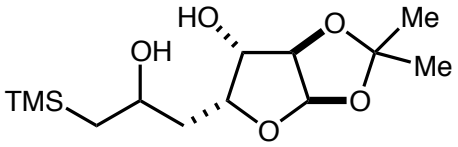

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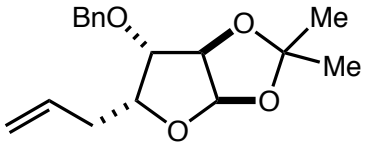
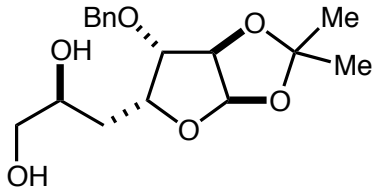


$(DHQ)_2AQN$
K_2OsO_4, $K_3Fe(CN)_6$

*t*BuOH, H_2O

95%, 3:1 dr



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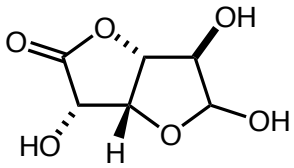

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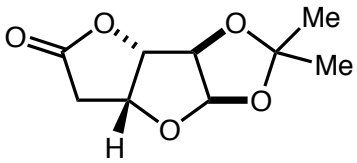

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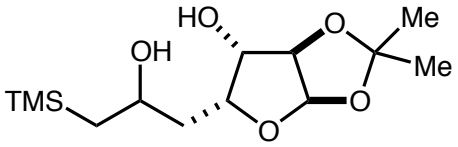
72%, two steps



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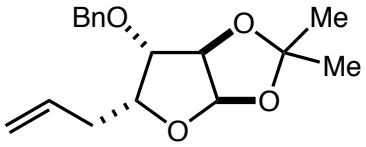
89%, two steps



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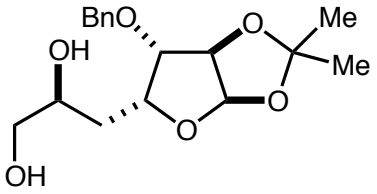
K_2OsO_4, $K_3Fe(CN)_6$

*t*BuOH, H_2O

95%, 3:1 dr

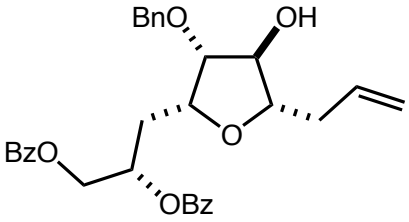


1) BzCl, NMM, DMAP

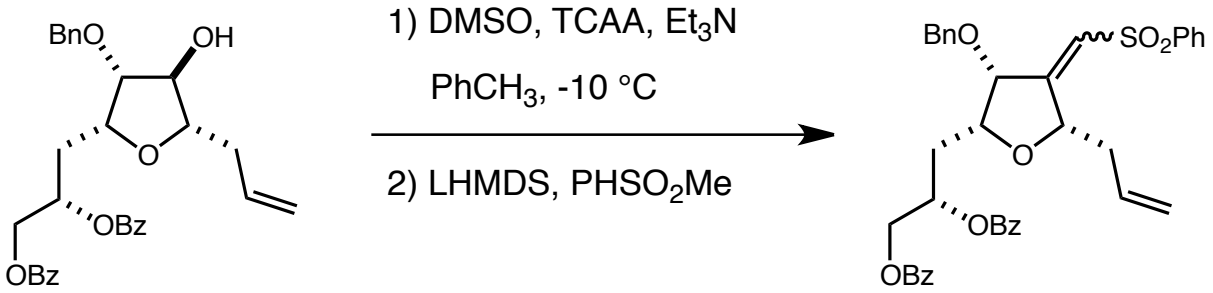
2) AllylTMS, $TiCl_3O$*i*Pr

recrystalize

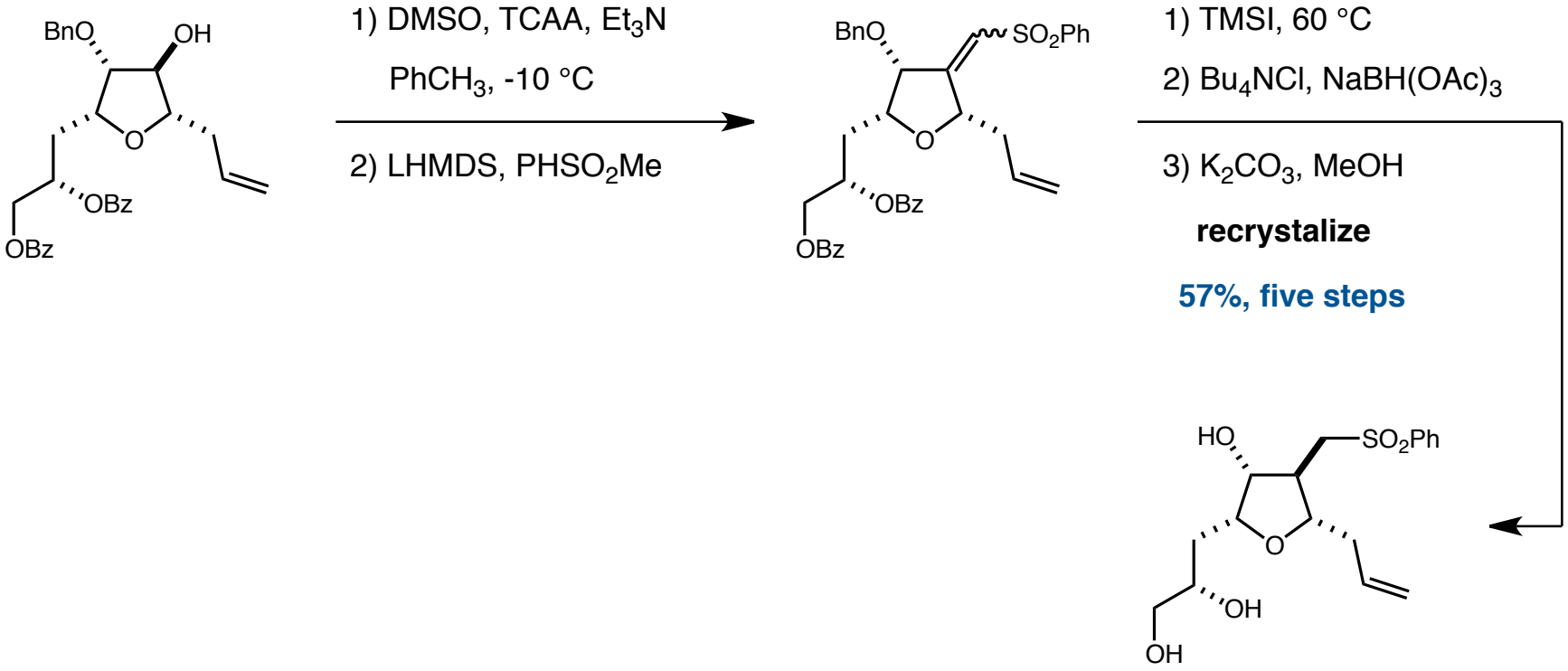
56%, >99.5% de



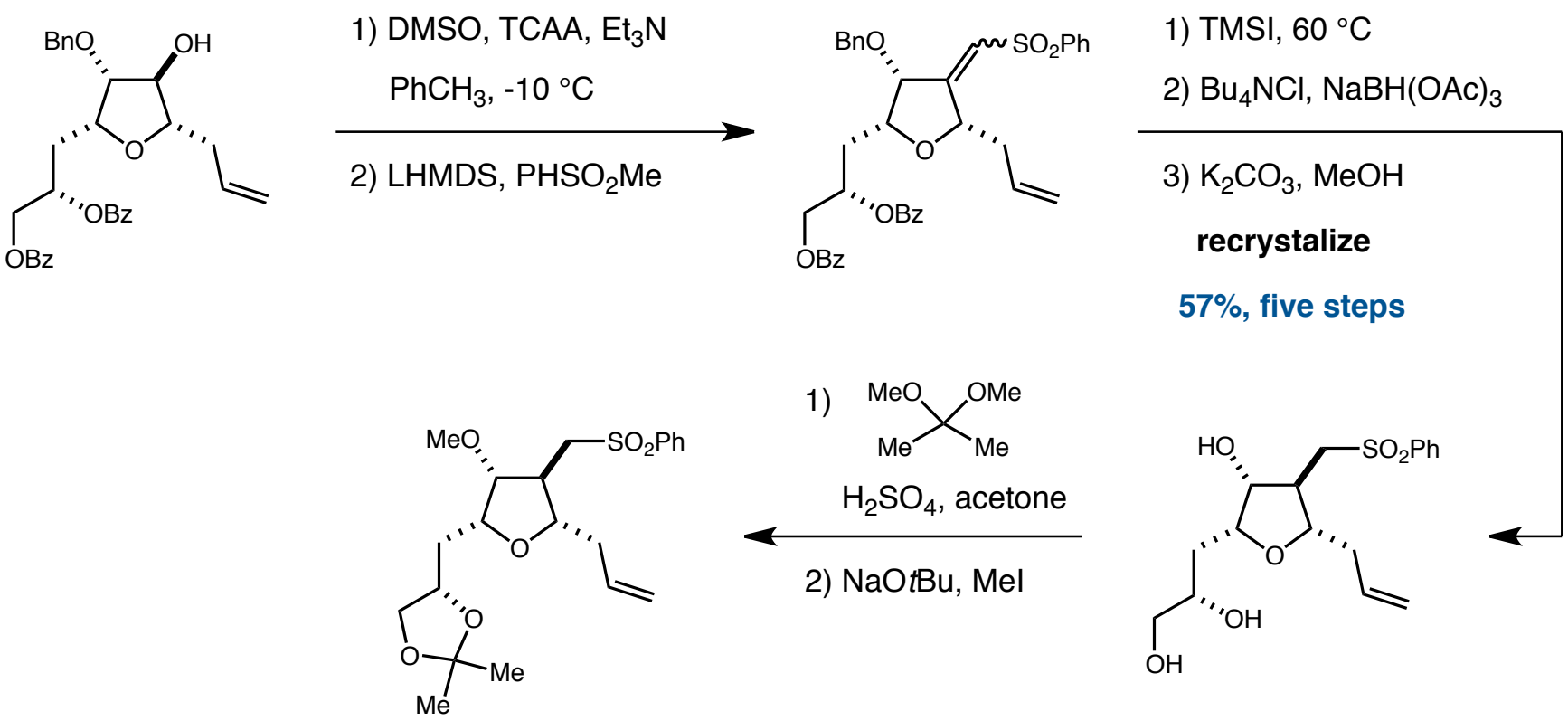
Eribuline: Northern Fragment Synthesis



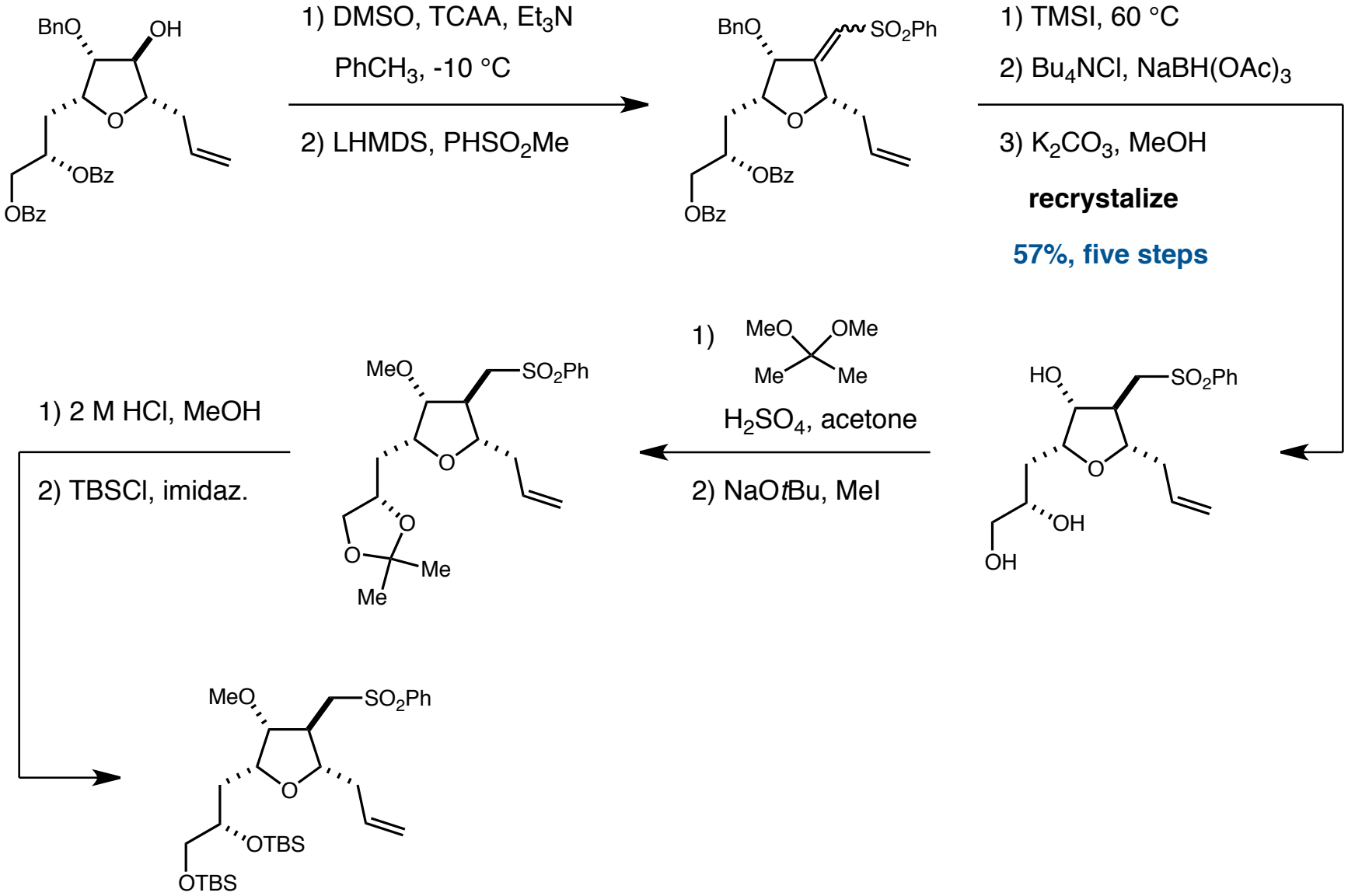
Eribuline: Northern Fragment Synthesis



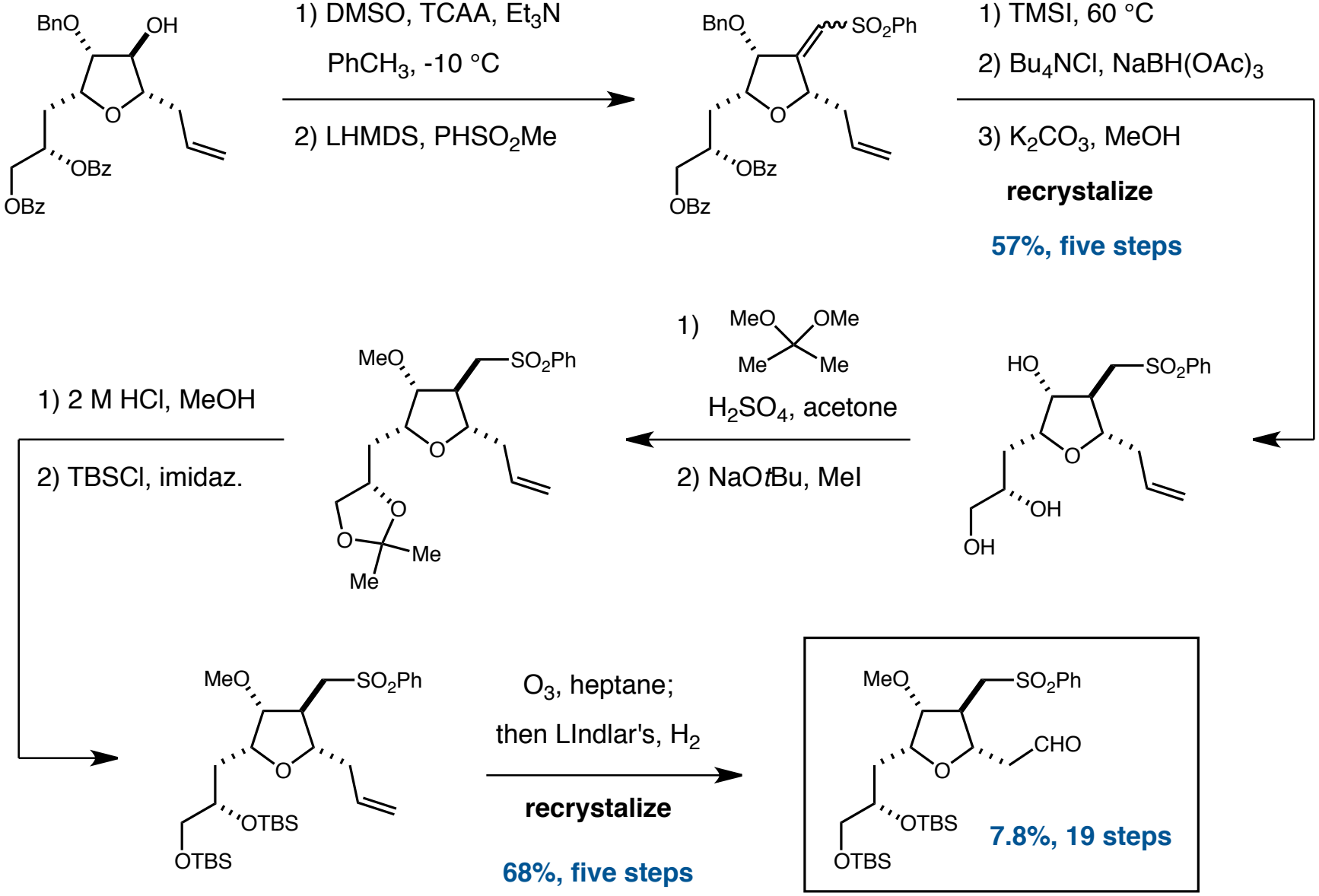
Eribuline: Northern Fragment Synthesis



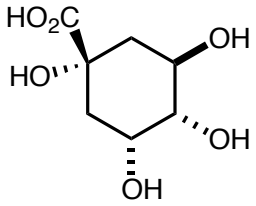
Eribuline: Northern Fragment Synthesis



Eribuline: Northern Fragment Synthesis



Eribuline: Southern Fragment Synthesis



D-quinic acid

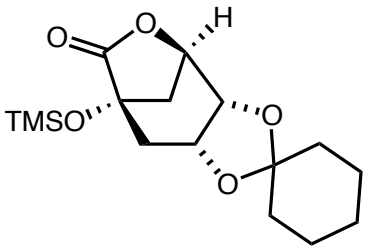
$2/g (Aldrich)

1) *c*-hexanone

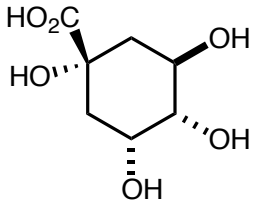
H_2SO_4, 160 °C

2) TMSCl, imidaz.

73%, two steps



Eribuline: Southern Fragment Synthesis



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$2/g (Aldrich)

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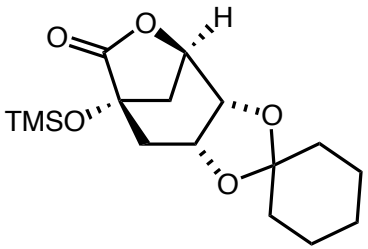
H_2SO_4, 160 °C

2) TMSCl, imidaz.

73%, two steps



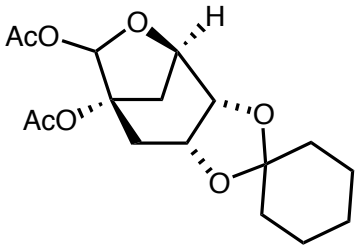
1) DIBALH, -78 °C

2) AcOH, H_2O

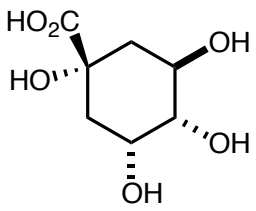
3) Et_3N, DMAP, Ac_2O

recrystalize

65%, three steps



Eribuline: Southern Fragment Synthesis



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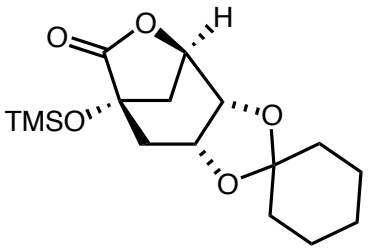
$2/g (Aldrich)

1) *c*-hexanone

H_2SO_4, 160 °C

2) TMSCl, imidaz.

73%, two steps



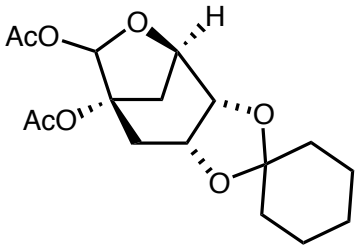
1) DIBALH, -78 °C

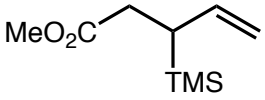
2) AcOH, H_2O

3) Et_3N, DMAP, Ac_2O

recrystalize

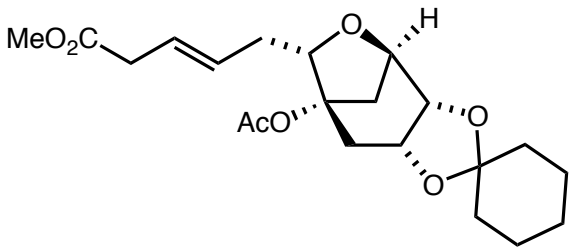
65%, three steps



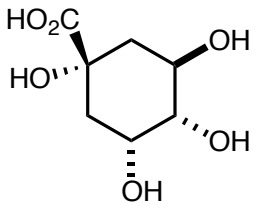


BF_3•OEt, MeCN, TCAA

62%



Eribuline: Southern Fragment Synthesis



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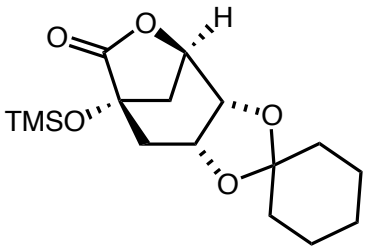
$2/g (Aldrich)

1) *c*-hexanone

H_2SO_4, 160 °C

2) TMSCl, imidaz.

73%, two steps



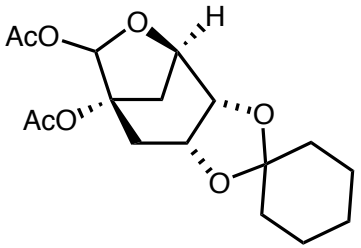
1) DIBALH, -78 °C

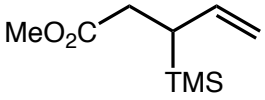
2) AcOH, H_2O

3) Et_3N, DMAP, Ac_2O

recrystalize

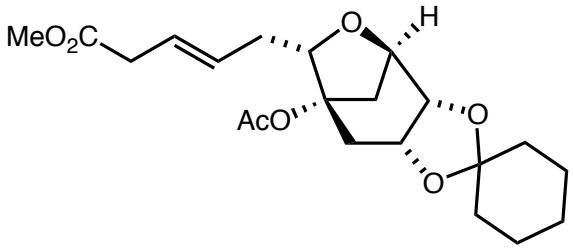
65%, three steps





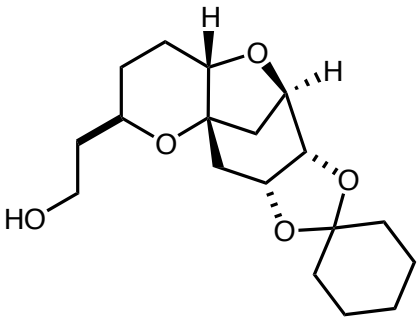
BF_3•OEt, MeCN, TCAA

62%

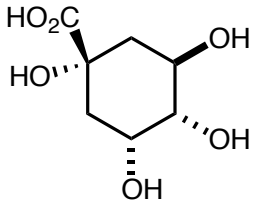


1) NaOMe, MeOH

2) $LiAlH_4$, THF



Eribuline: Southern Fragment Synthesis



D-quinic acid

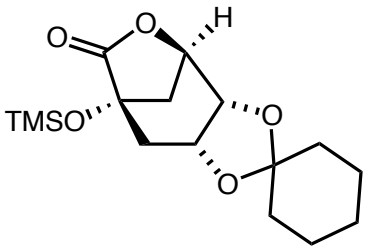
$2/g (Aldrich)

1) *c*-hexanone

H_2SO_4, 160 °C

2) TMSCl, imidaz.

73%, two steps



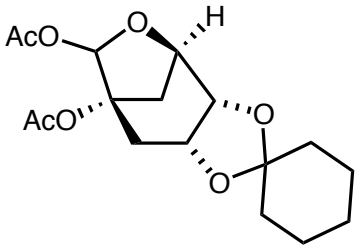
1) DIBALH, -78 °C

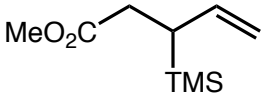
2) AcOH, H_2O

3) Et_3N, DMAP, Ac_2O

recrystalize

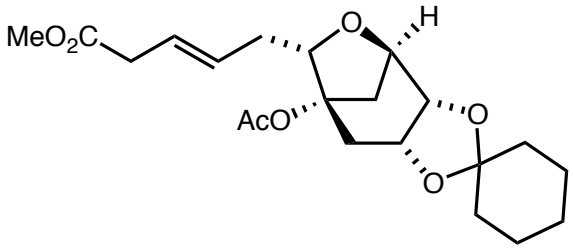
65%, three steps





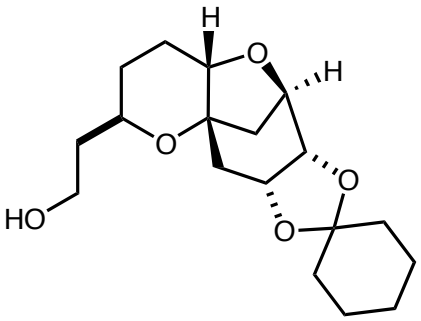
BF_3•OEt, MeCN, TCAA

62%



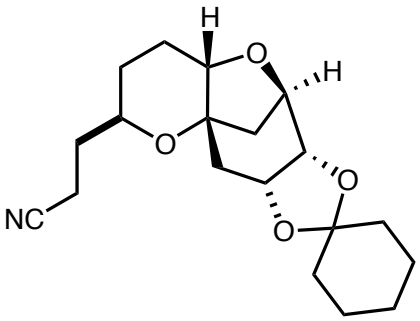
1) NaOMe, MeOH

2) $LiAlH_4$, THF

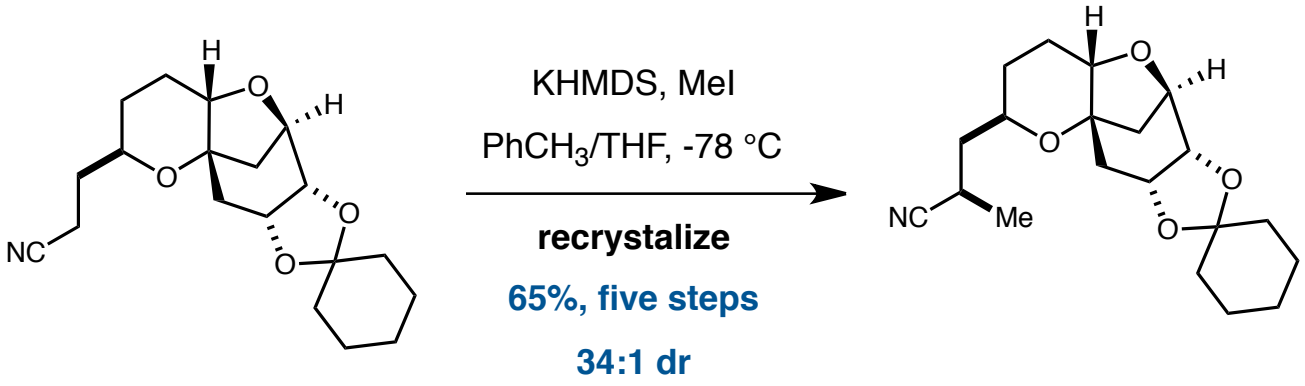


1) MsCl, Et_3N

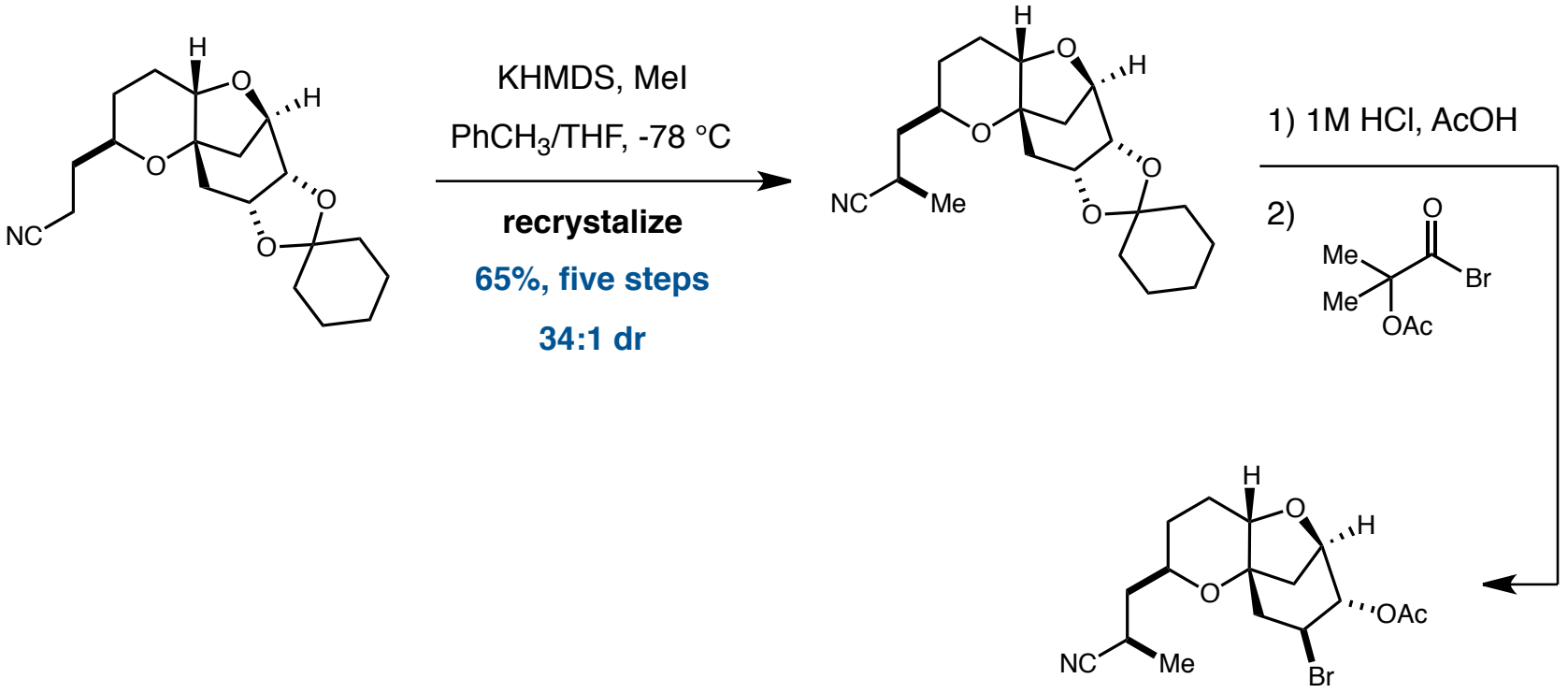
2) KCN, EtOH/H_2O



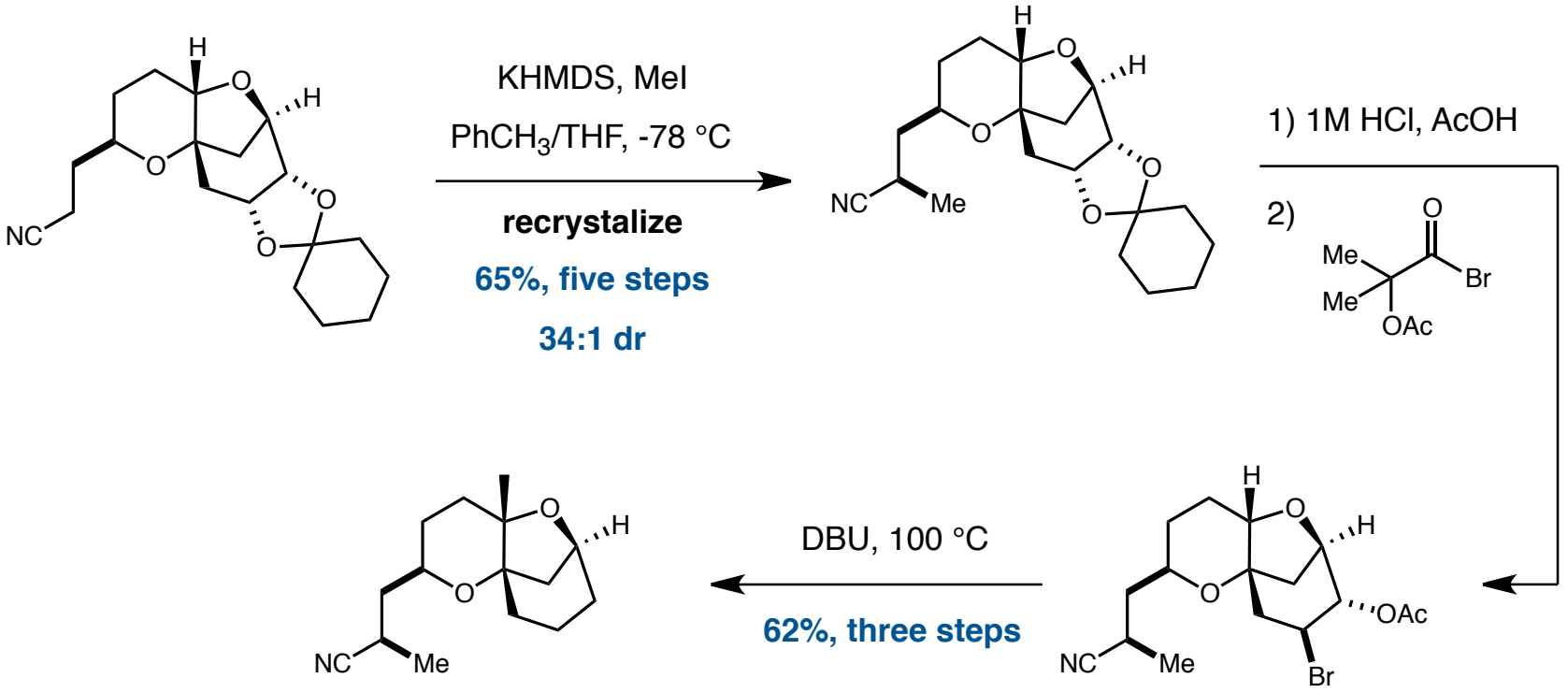
Eribuline: Southern Fragment Synthesis



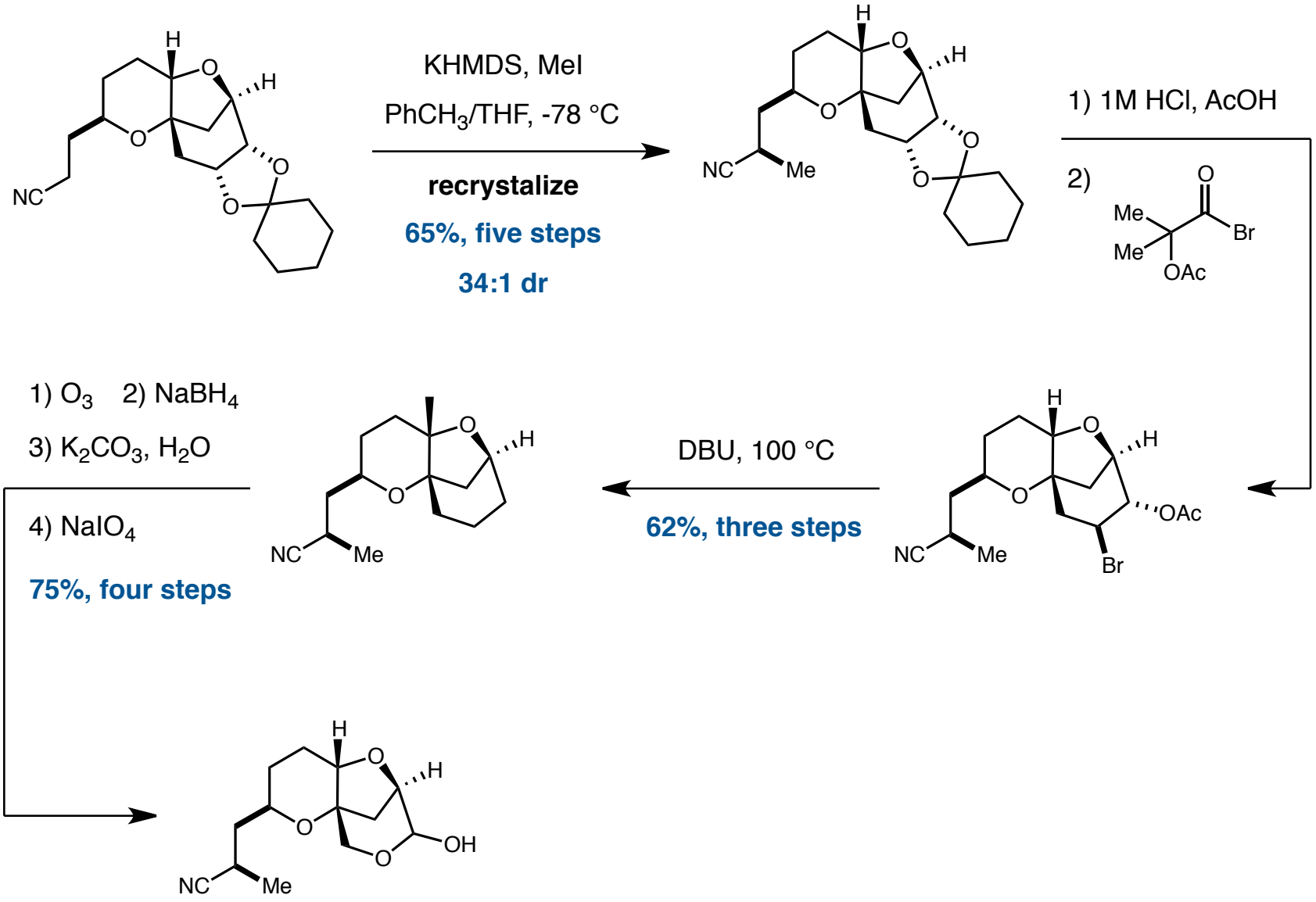
Eribuline: Southern Fragment Synthesis



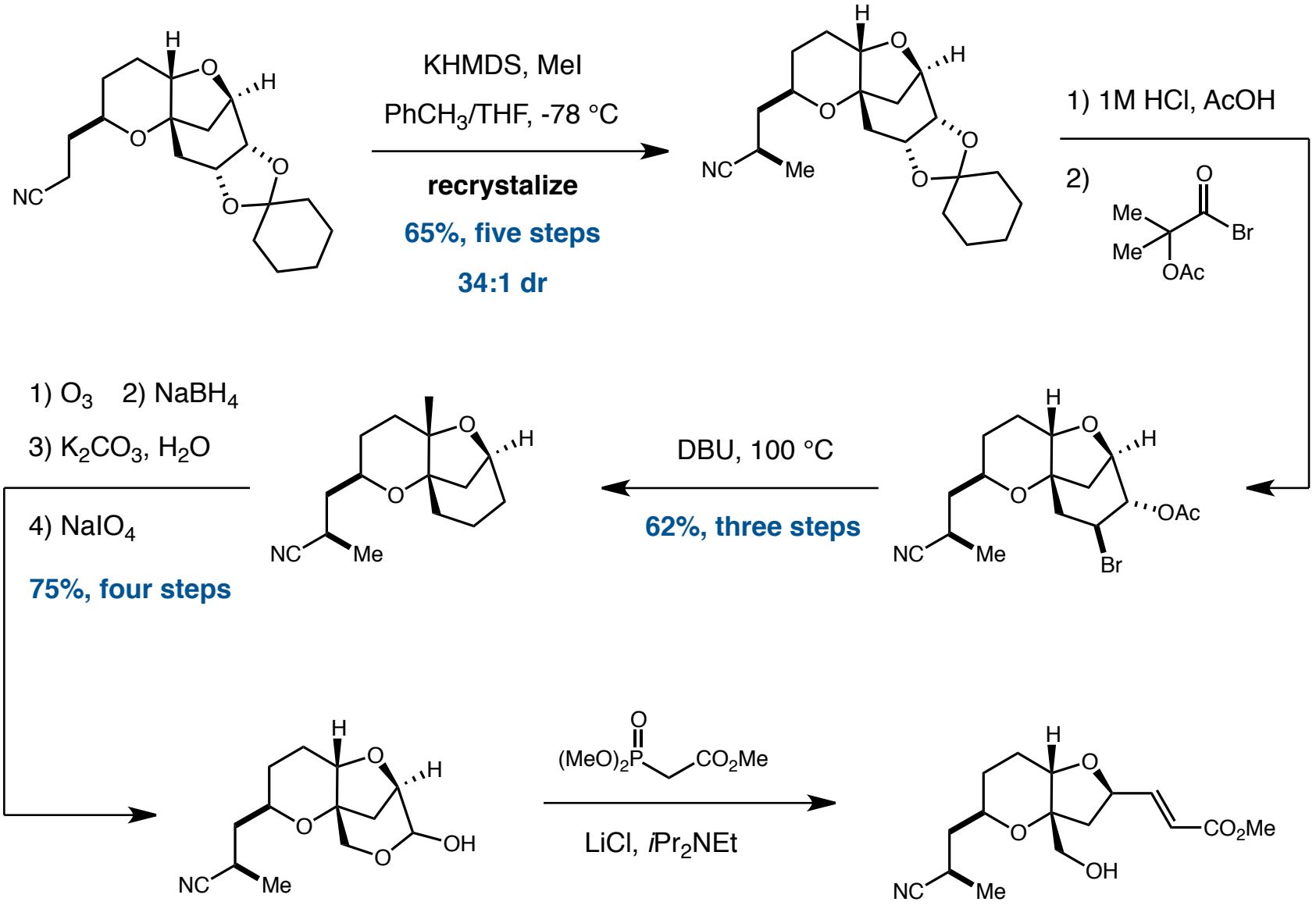
Eribuline: Southern Fragment Synthesis



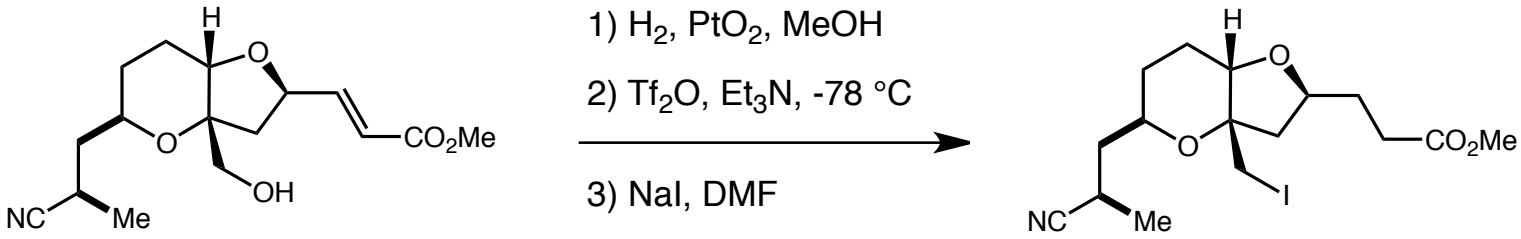
Eribuline: Southern Fragment Synthesis



Eribuline: Southern Fragment Synthesis

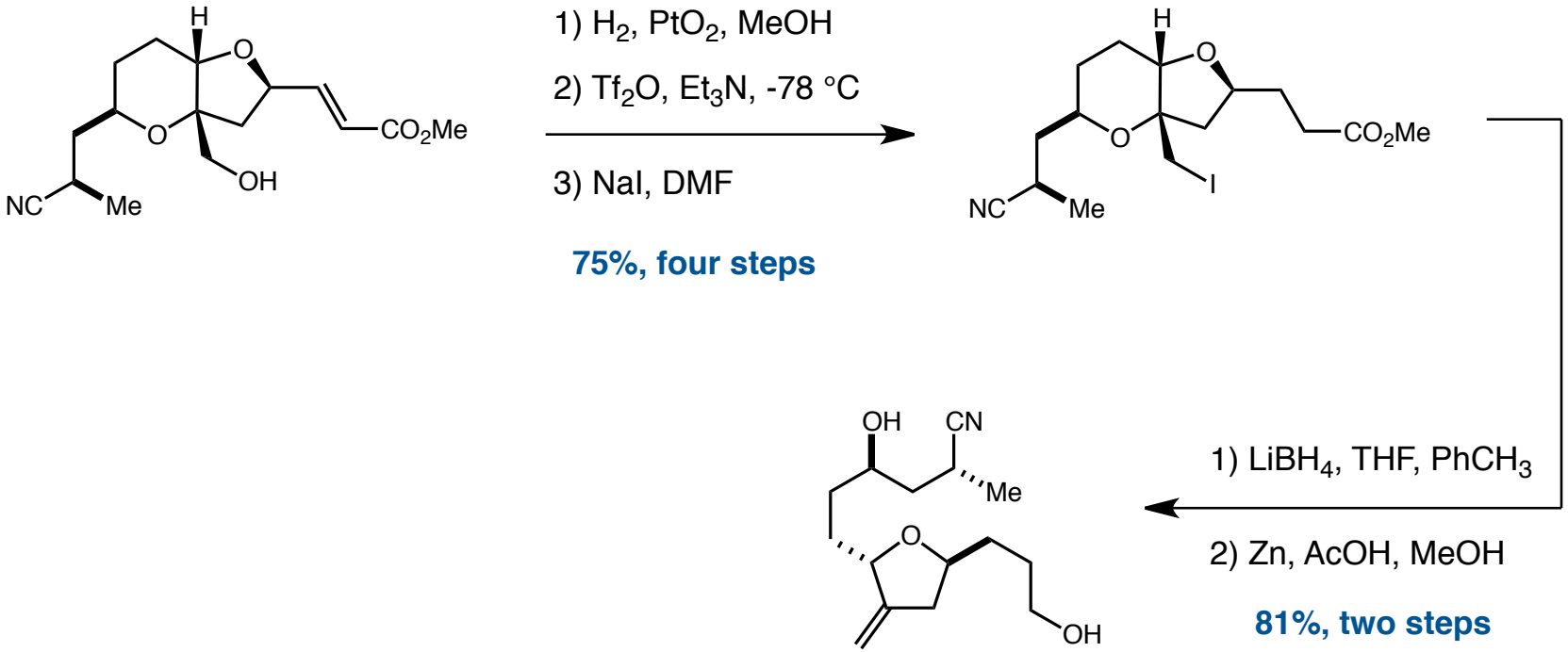


Eribuline: Southern Fragment Synthesis

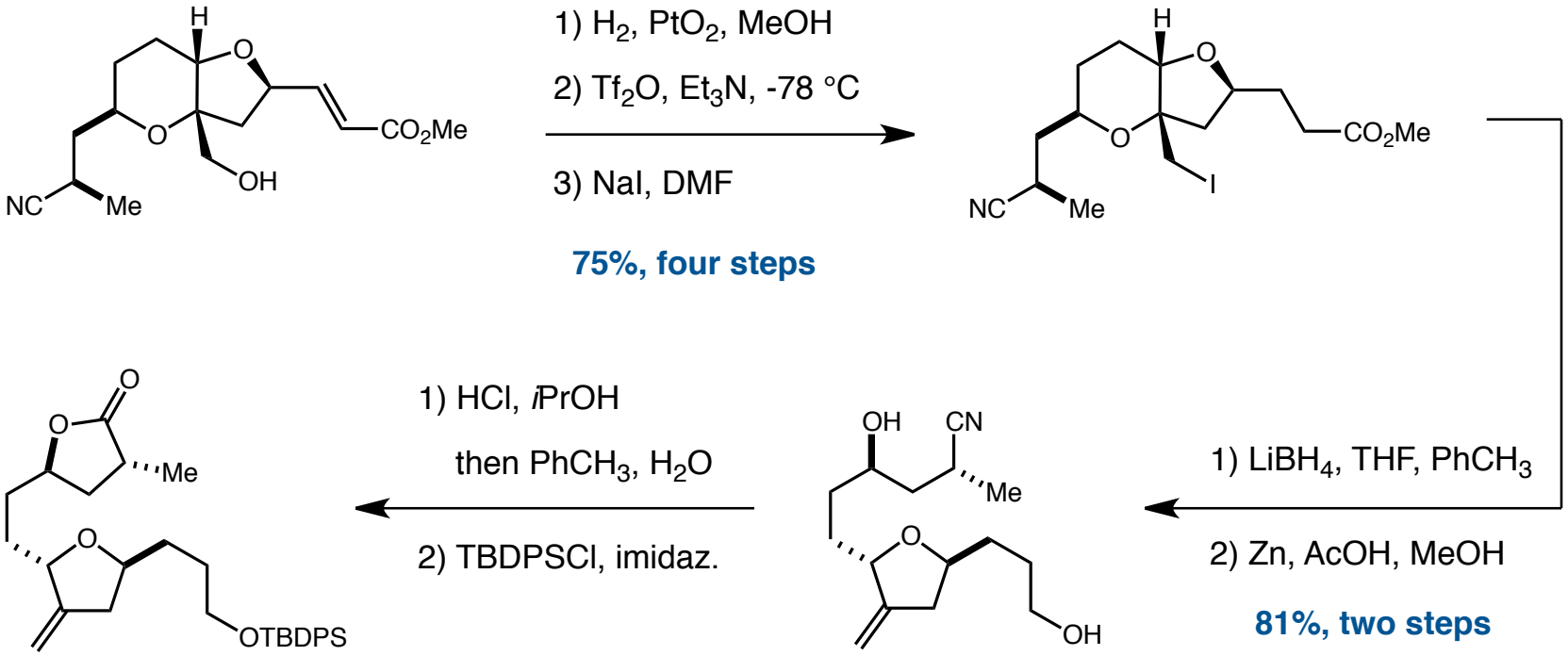


75%, four steps

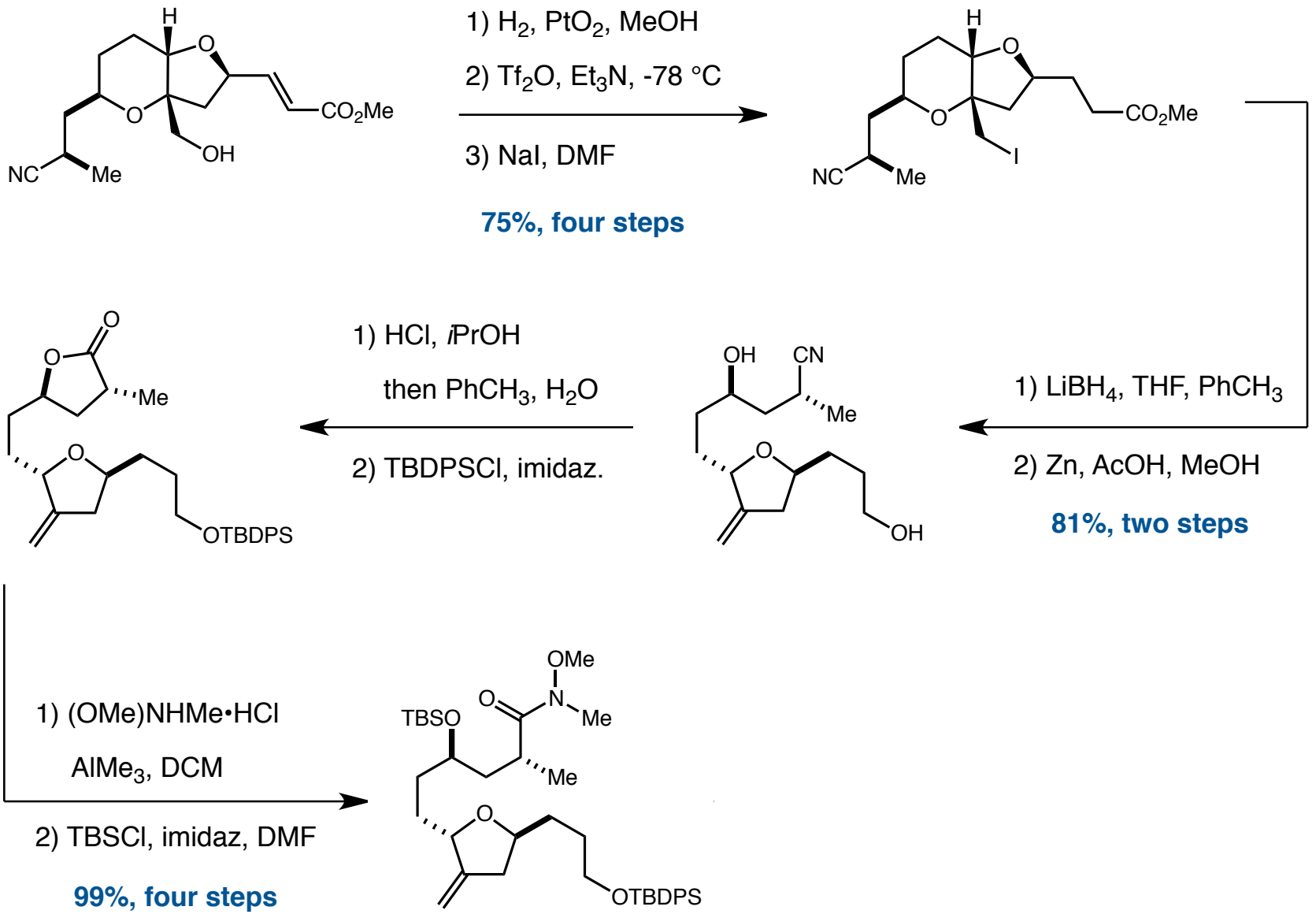
Eribuline: Southern Fragment Synthesis



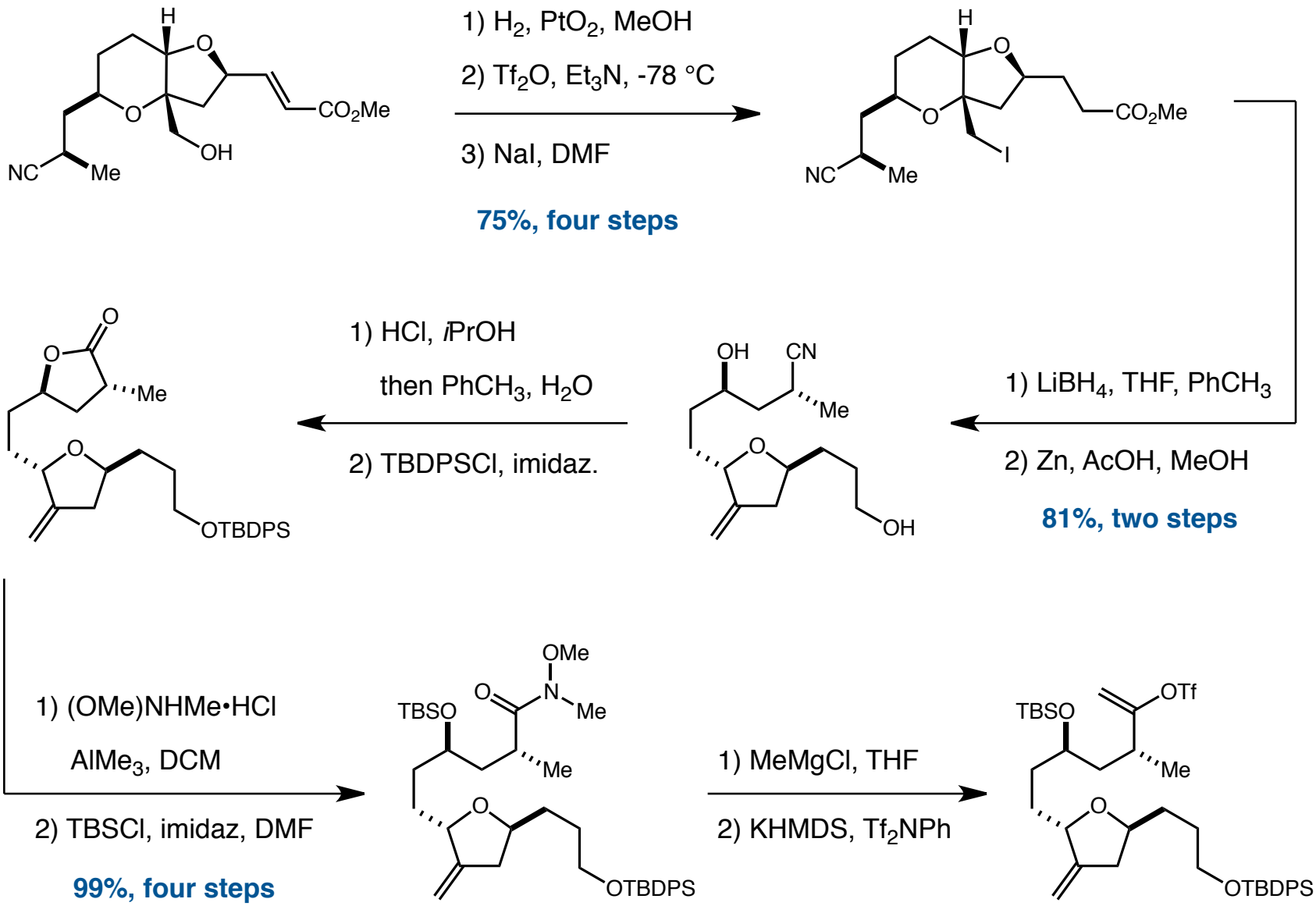
Eribuline: Southern Fragment Synthesis



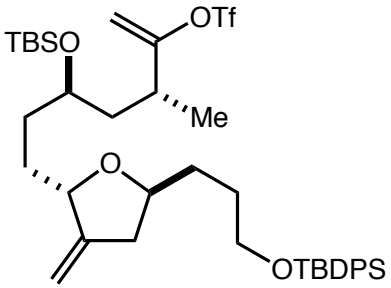
Eribuline: Southern Fragment Synthesis



Eribuline: Southern Fragment Synthesis



Eribuline: Southern Fragment and Ligand Synthesis

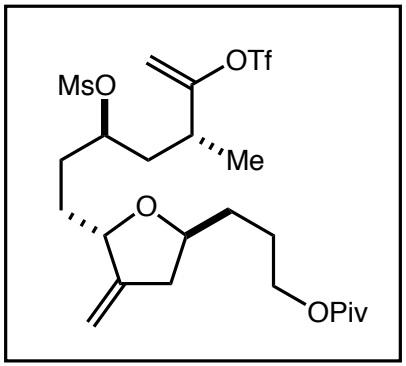


1) HCl, *i*PrOH, MeOH

2) PivCl, collidine, DMAP

3) MsCl, Et_3N, THF

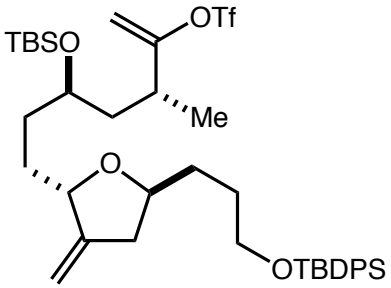
62%, five steps



3.3% overall

33 steps

Eribuline: Southern Fragment and Ligand Synthesis

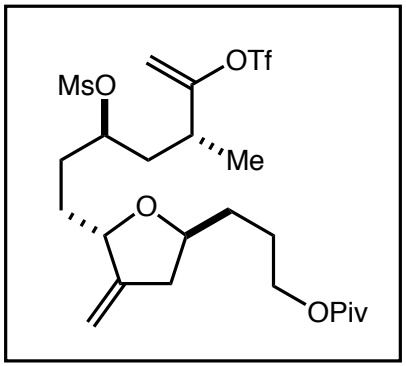


1) HCl, *i*PrOH, MeOH

2) PivCl, collidine, DMAP

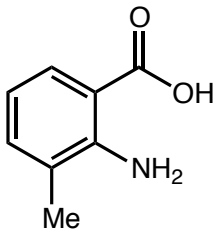
3) MsCl, Et_3N, THF

62%, five steps



3.3% overall

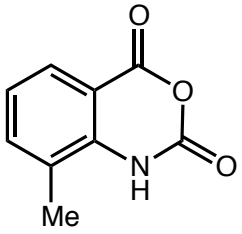
33 steps



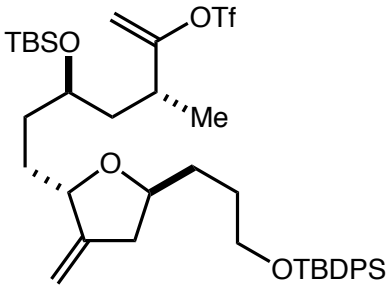
$(Cl_3CO)_2CO$

THF

97%



Eribuline: Southern Fragment and Ligand Synthesis

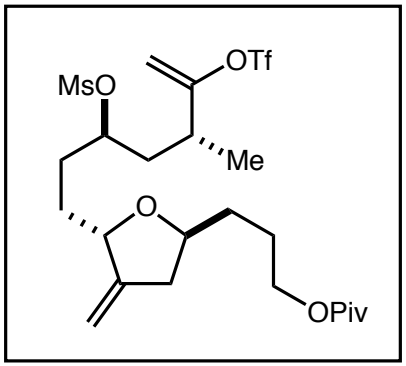


1) HCl, *i*PrOH, MeOH

2) PivCl, collidine, DMAP

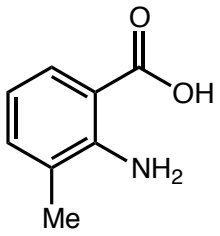
3) MsCl, Et_3N, THF

62%, five steps



3.3% overall

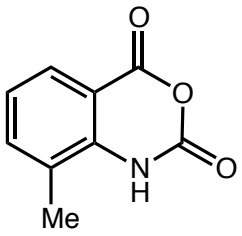
33 steps



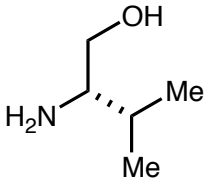
$(Cl_3CO)_2CO$

THF

97%

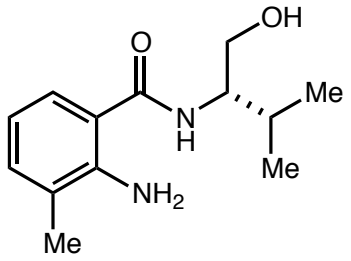


1)

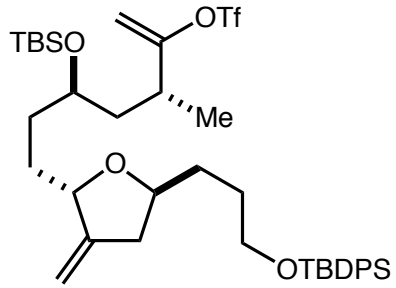


2) LiOH, H_2O, 60 °C

65%, two steps



Eribuline: Southern Fragment and Ligand Synthesis

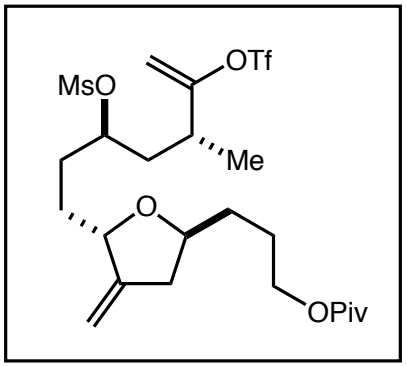


1) HCl, *i*PrOH, MeOH

2) PivCl, collidine, DMAP

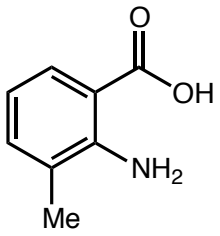
3) MsCl, Et_3N, THF

62%, five steps



3.3% overall

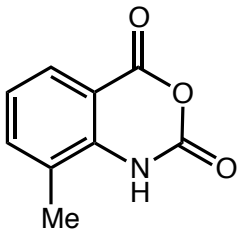
33 steps



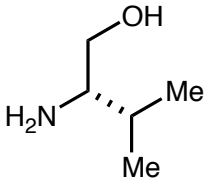
$(Cl_3CO)_2CO$

THF

97%

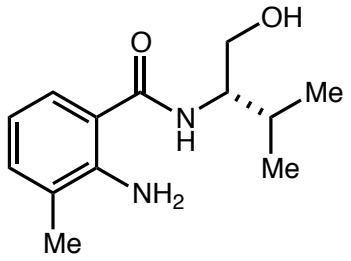


1)



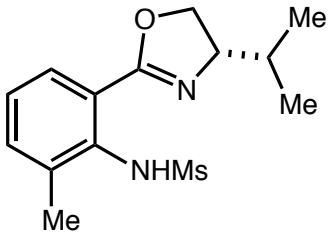
2) LiOH, H_2O, 60 °C

65%, two steps

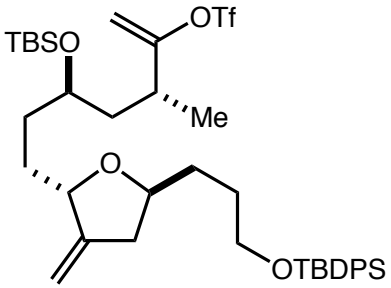


MsCl, pyr., DMAP

85%



Eribuline: Southern Fragment and Ligand Synthesis

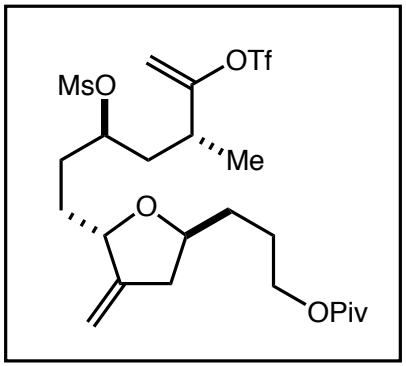


1) HCl, *i*PrOH, MeOH

2) PivCl, collidine, DMAP

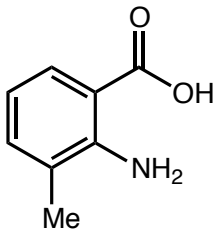
3) MsCl, Et_3N, THF

62%, five steps



3.3% overall

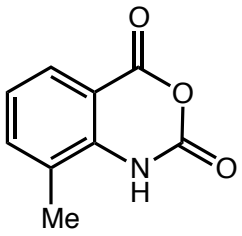
33 steps



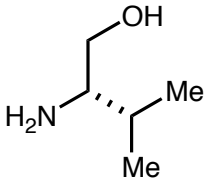
$(Cl_3CO)_2CO$

THF

97%

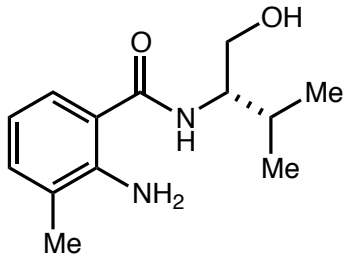


1)



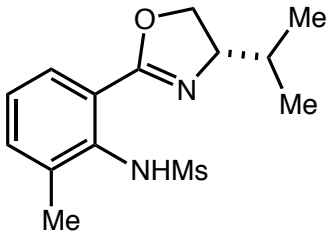
2) LiOH, H_2O, 60 °C

65%, two steps



MsCl, pyr., DMAP

85%

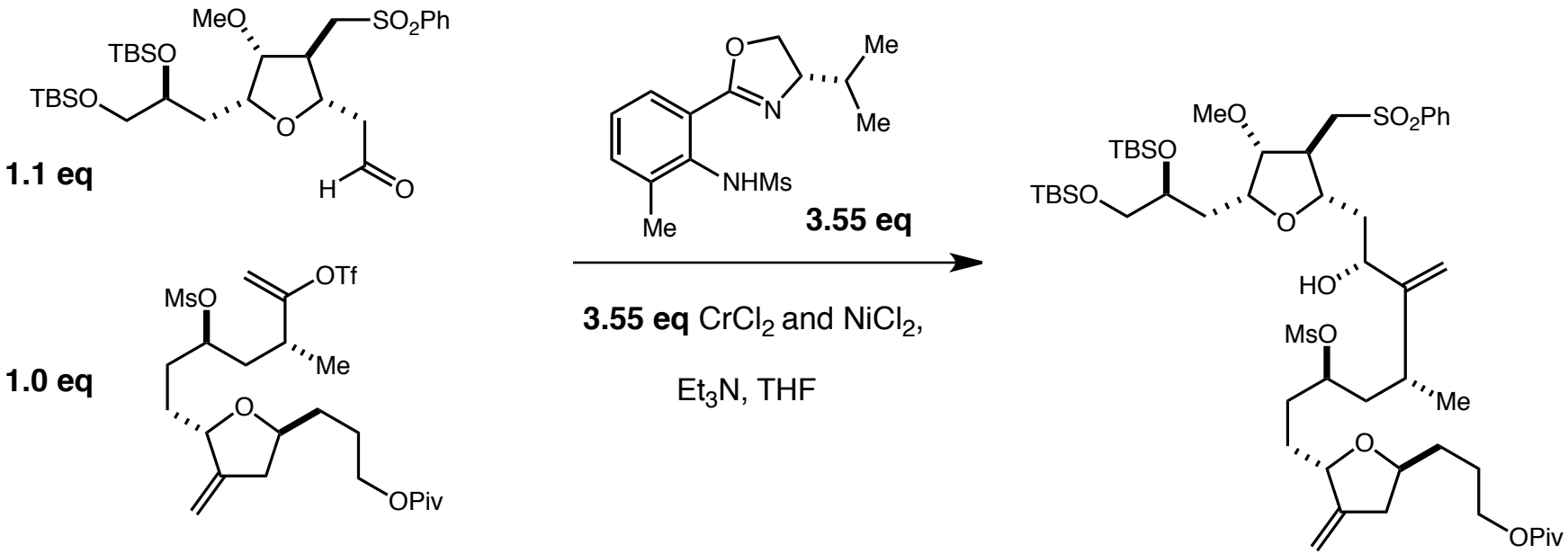


Ligand for N-H-K

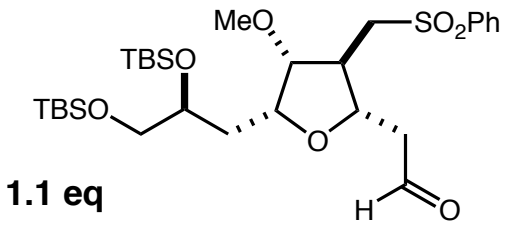
54% overall

four steps

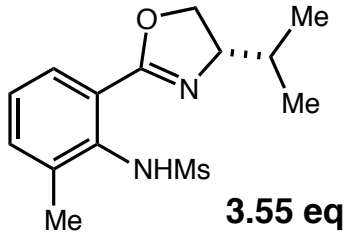
Eribuline: Coupling Western Fragments



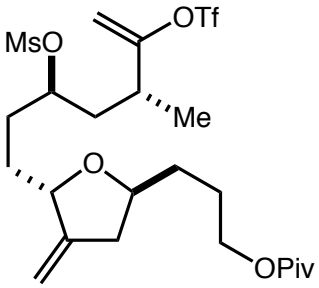
Eribuline: Coupling Western Fragments



1.1 eq



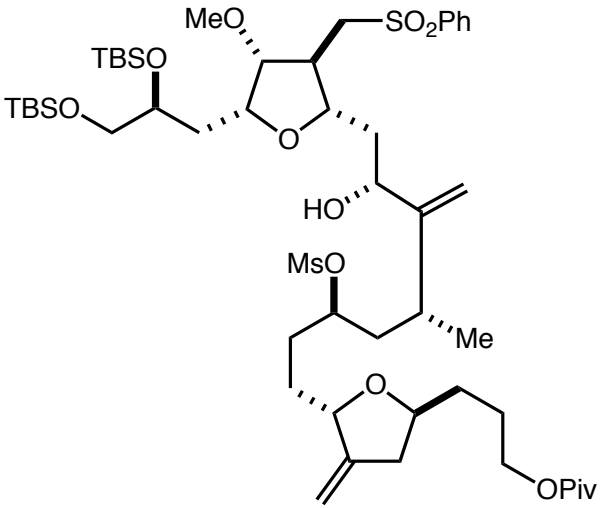
3.55 eq



1.0 eq

3.55 eq $CrCl_2$ and $NiCl_2$,

Et_3N, THF



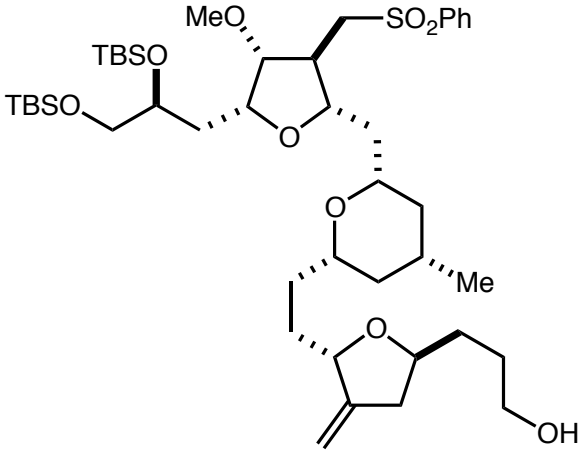
1) KHMDS, THF -14 °C

chromatography

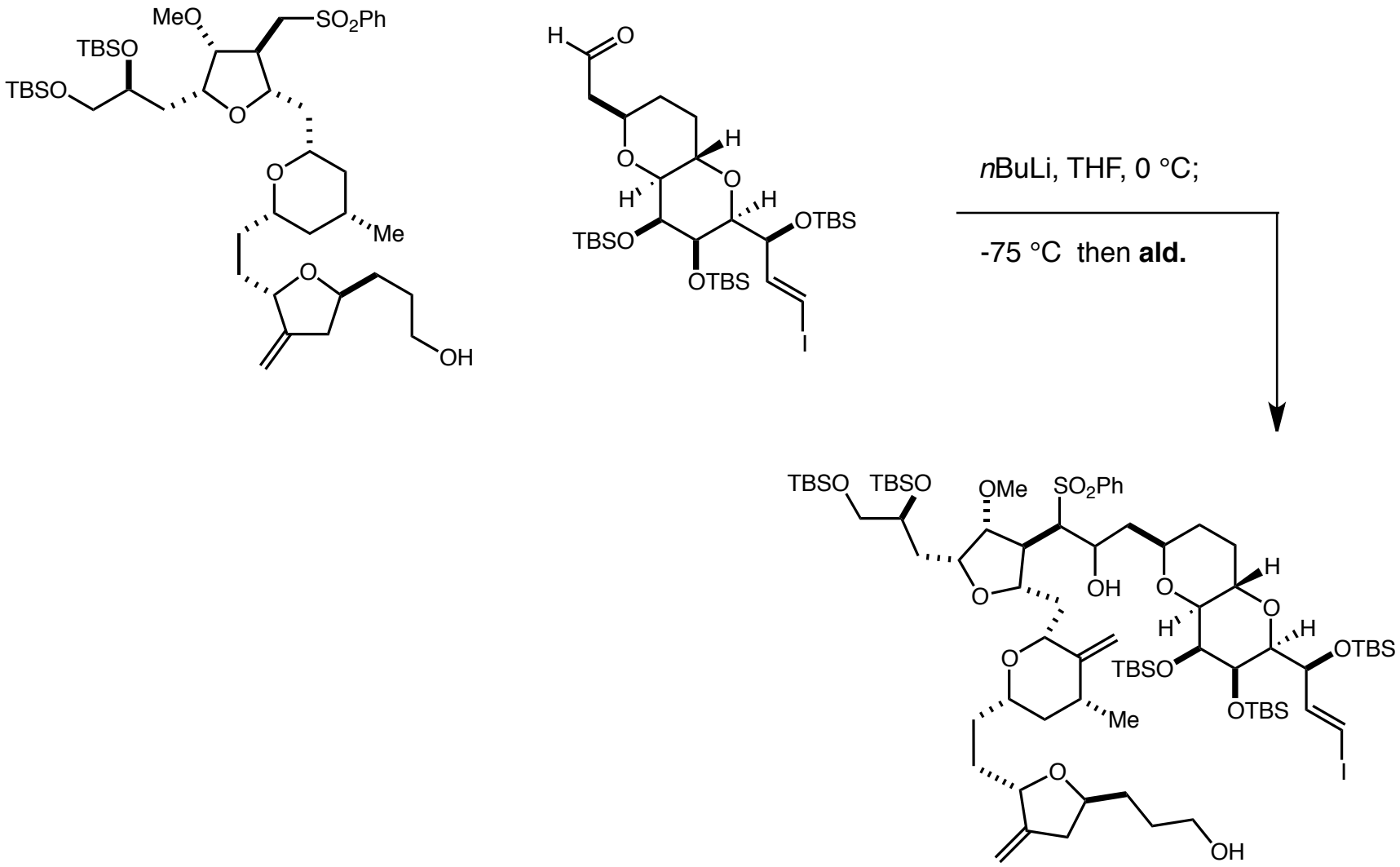
2) DIBALH, DCM

68%, three steps

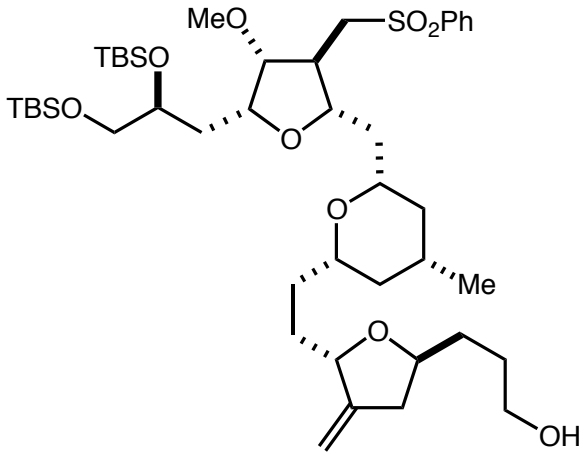
(20:1 dr before chrom.)

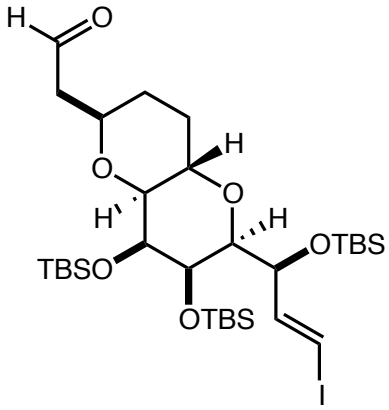


Eribuline: Completion of Synthesis



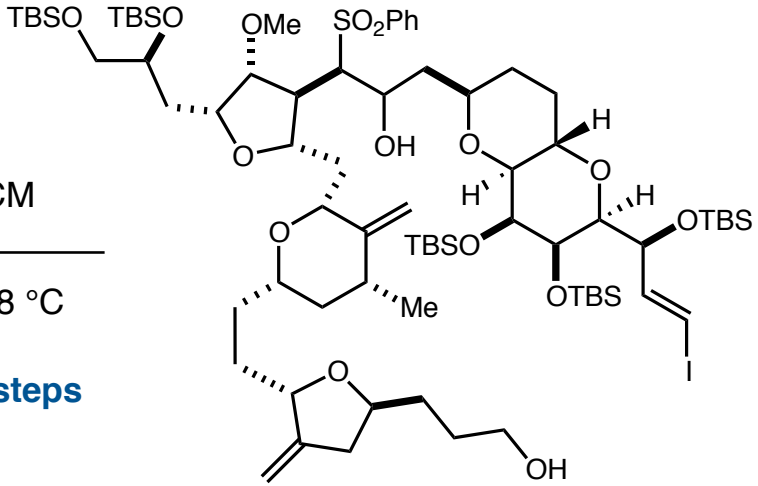
Eribuline: Completion of Synthesis





*n*BuLi, THF, 0 °C;

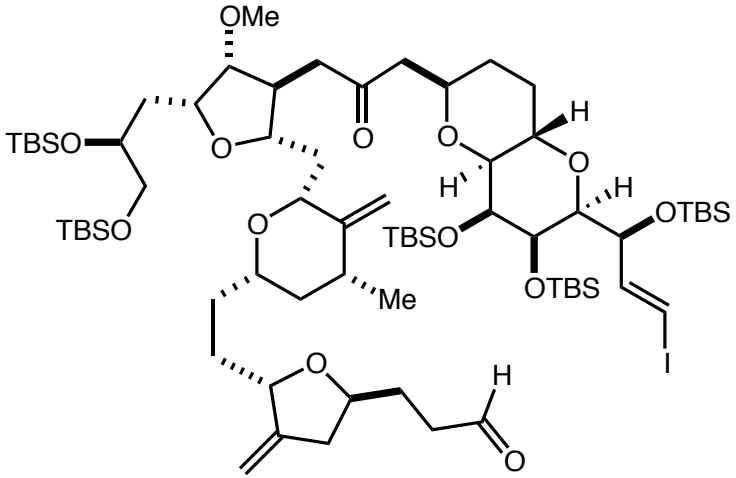
-75 °C then **ald.**



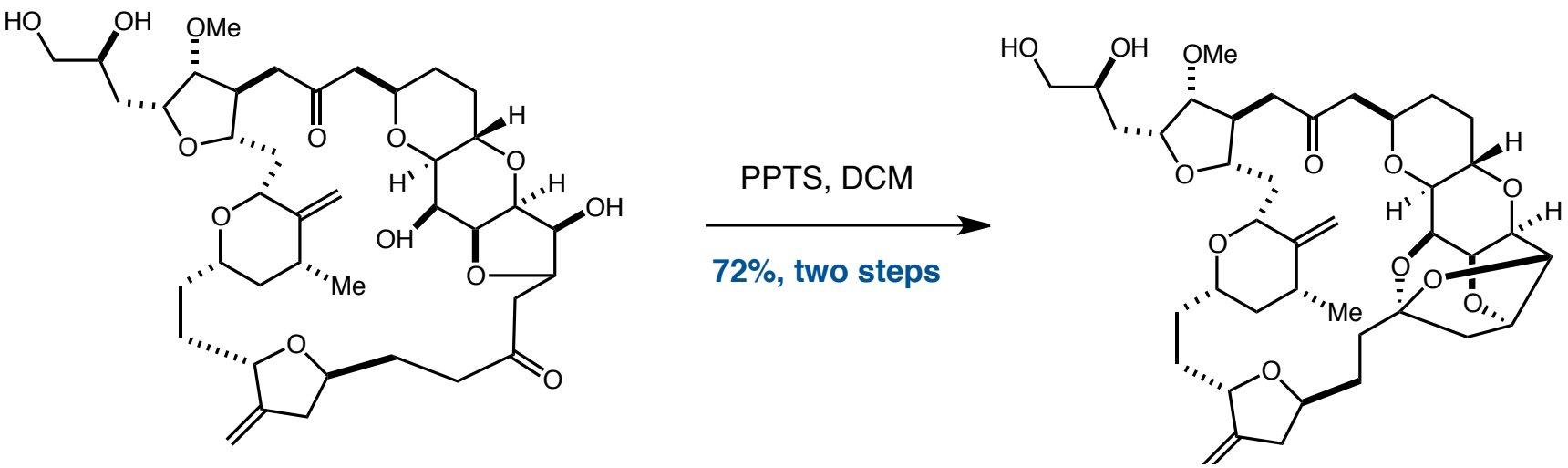
1) DMP, DCM

2) SmI_2, -78 °C

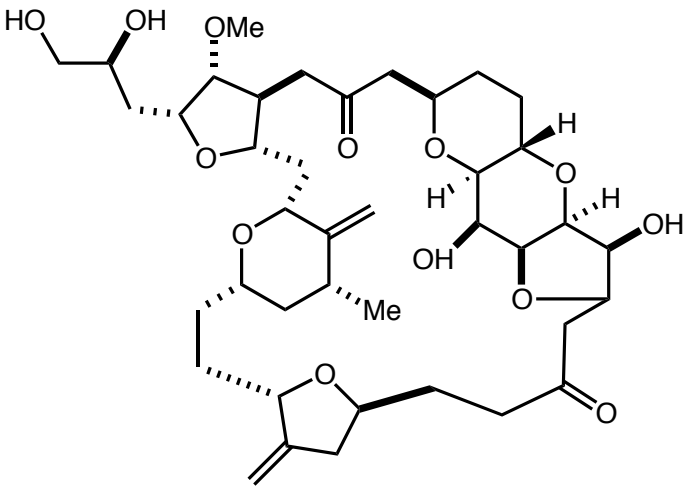
64%, three steps



Eribuline: Completion of Synthesis

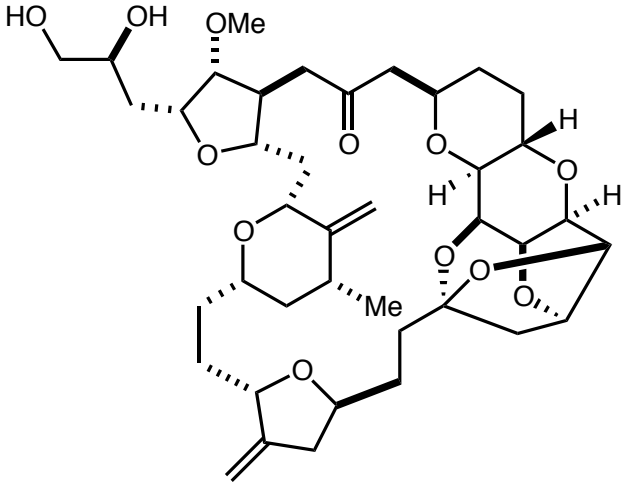


Eribuline: Completion of Synthesis



PPTS, DCM

72%, two steps

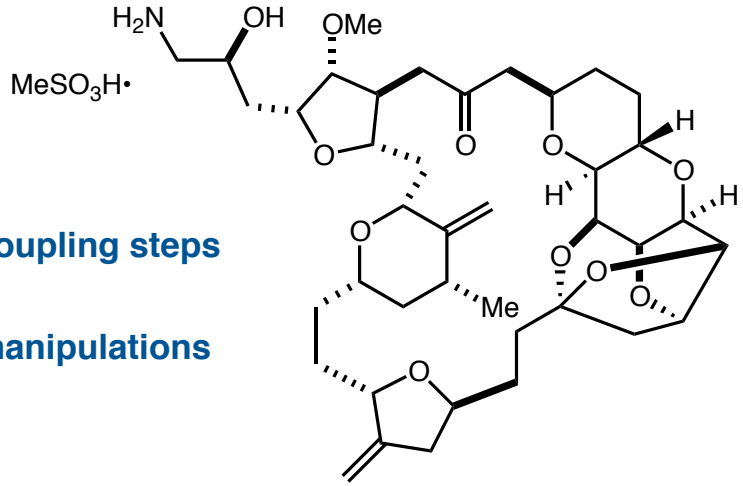


1) Ts_2O, collidine, pyrid. (cat.)

2) NH4OH, *i*PrOH

3) $MeSO_3H$, NH_4OH, H_2O

84%, three steps



26% for coupling steps

11 final manipulations

Production Considerations: Analogues and Natural Products

Recrystallization, Resolution

Utilize Very Robust Chemistry

Target Considerations: Development of Analogues and Derviatives

Retain Only Necessary Parts

Production Considerations: Analogues and Natural Products

Recrystallization, Resolution

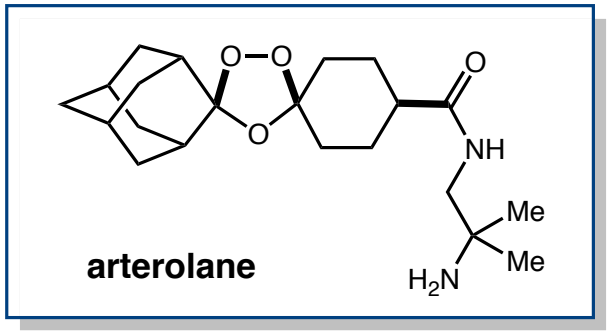
Utilize Very Robust Chemistry

Target Considerations: Development of Analogues and Derviatives

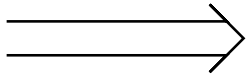
Retain Only Necessary Parts

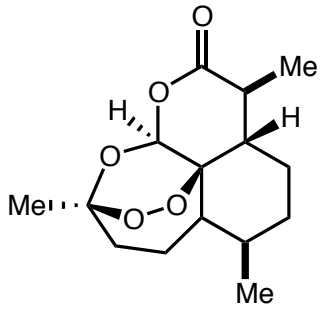
Shorten Production Route

Arterolane: Complete synthesis



arterolane

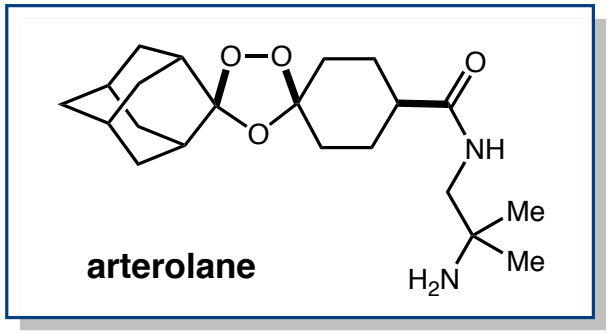




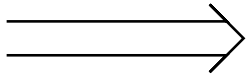
artemesinin

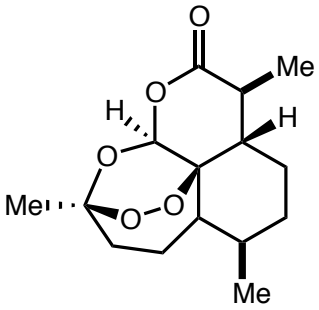
Vennerstrom et al. *Nature* **2004** 900

Arterolane: Complete synthesis



arterolane





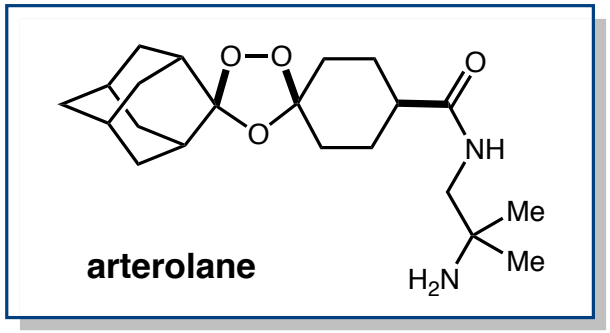
artemesinin

Artemesinin

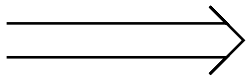
- First discovered by Chinese army project, *Project 523*, in 1960's
- Use of source plant, *Artemsia annua*, dates back 2,000 years in China
- Isolated material approved for worldwide treatment of malaria

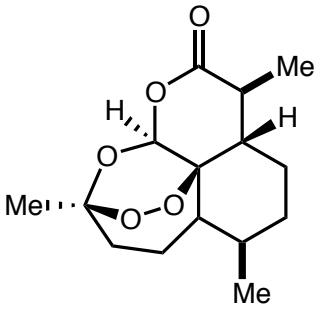
Vennerstrom et al. *Nature* **2004** 900

Arterolane: Complete synthesis



arterolane





artemesinin

Artemesinin

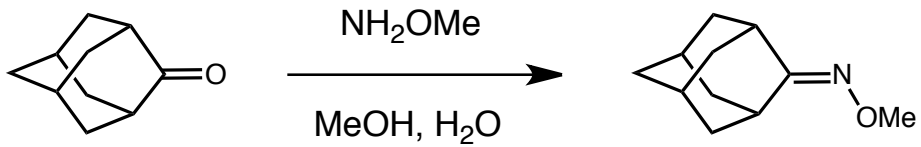
- First discovered by Chinese army project, *Project 523*, in 1960's
- Use of source plant, *Artemsia annua*, dates back 2,000 years in China
- Isolated material approved for worldwide treatment of malaria

Arterolane

- First synthesized and identified by broad collaboration of chemists in 2001
- Phase III trials began in India in 2009 by Indian company Ranbaxy
- Ozonide bridge retains the active radical reactivity found in artemesin, improved PK

Vennerstrom et al. *Nature* **2004** 900

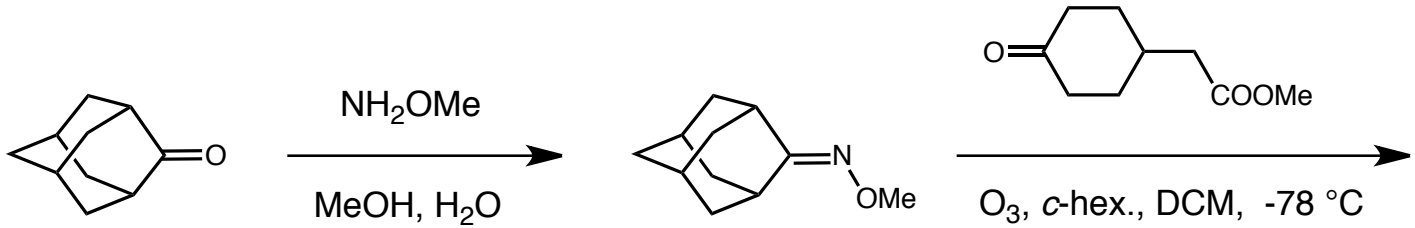
Arterolane: Complete synthesis



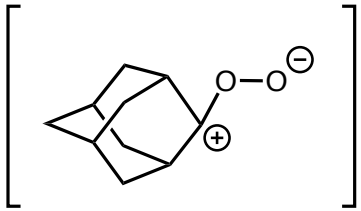
<$1/g **98%**

Ranbaxy Labs 2011 patent

Arterolane: Complete synthesis

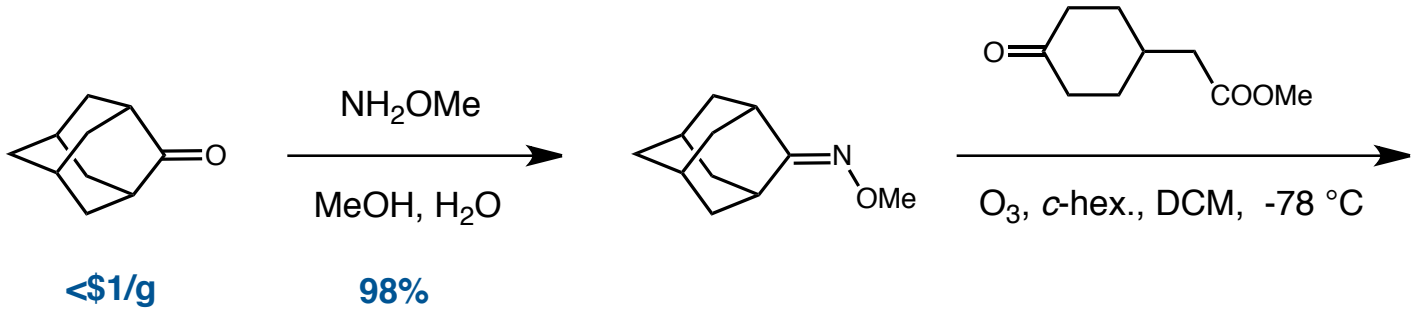


<$1/g **98%**



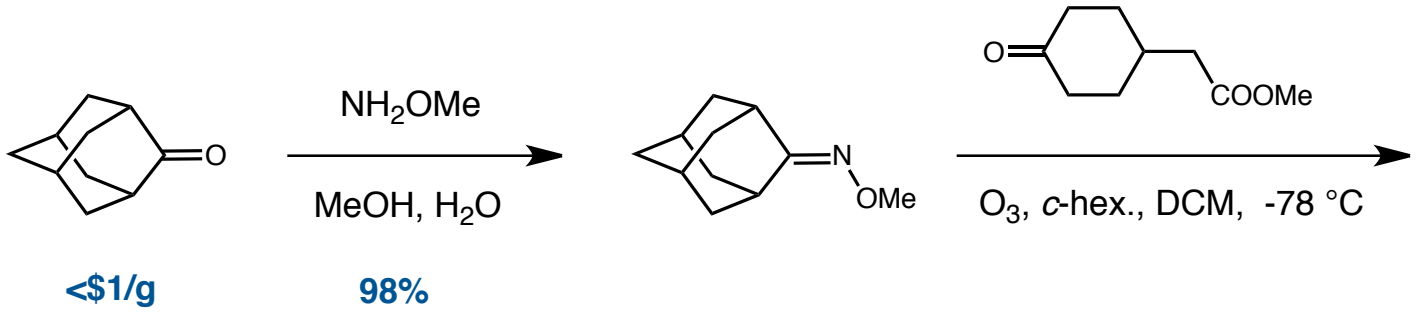
Ranbaxy Labs 2011 patent

Arterolane: Complete synthesis

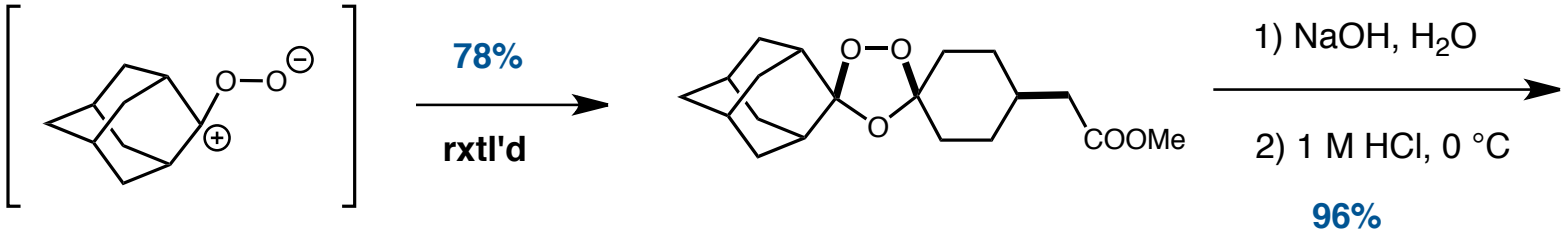


Ranbaxy Labs 2011 patent

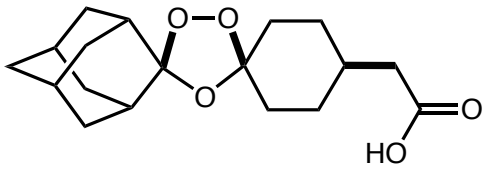
Arterolane: Complete synthesis



<$1/g **98%**

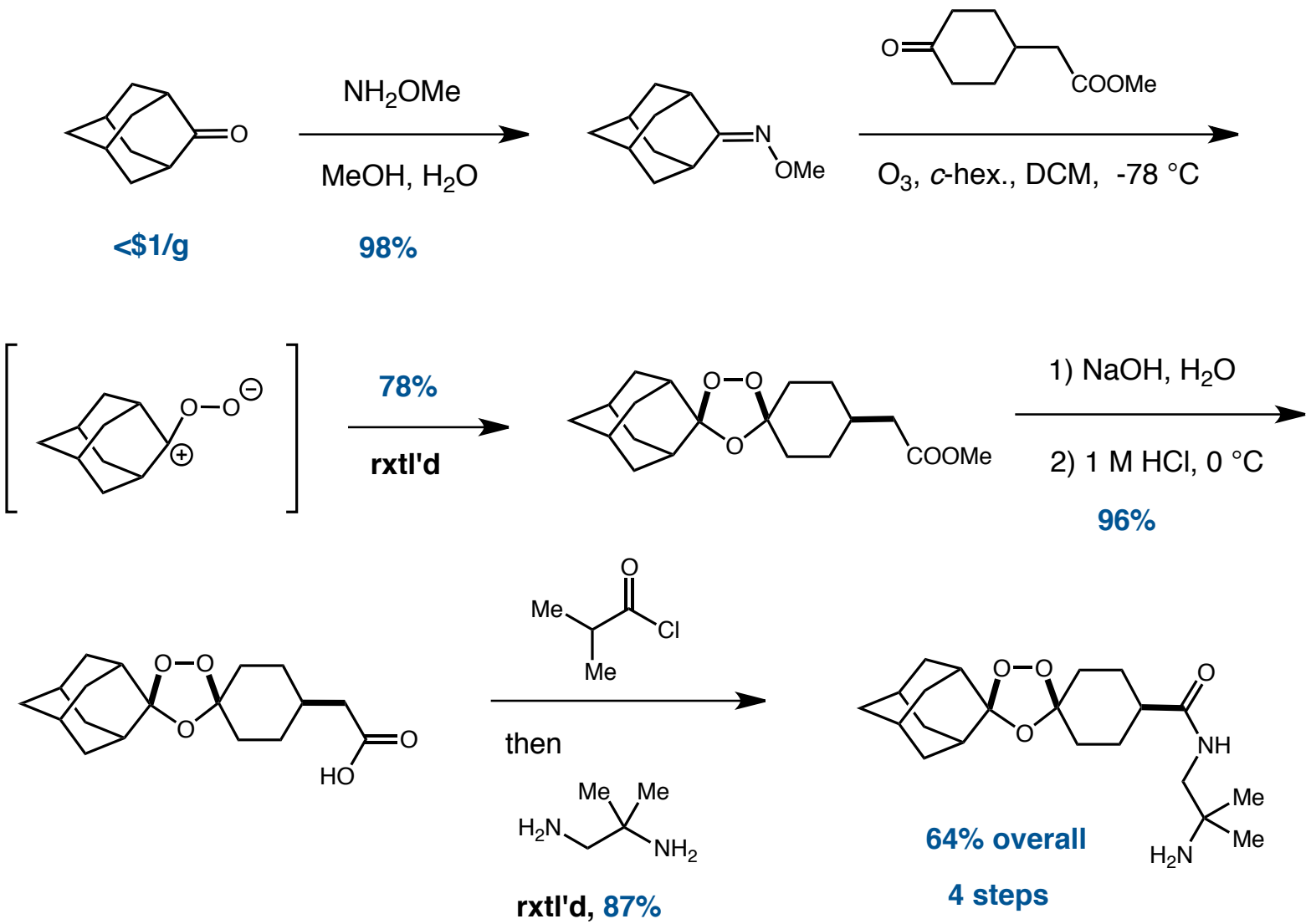


96%



Ranbaxy Labs 2011 patent

Arterolane: Complete synthesis



Ranbaxy Labs 2011 patent

Production Considerations: Analogues and Natural Products

Recrystallization, Resolution

Target Considerations: Development of Analogues and Derviatives

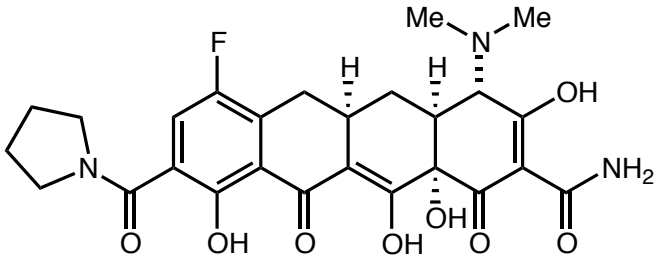
Retain Only Necessary Parts

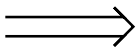
Improve Activity or Properties

Shorten Production Route

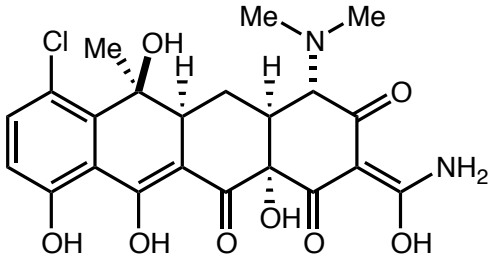
TP-434 Synthesis: Overview

TP-434



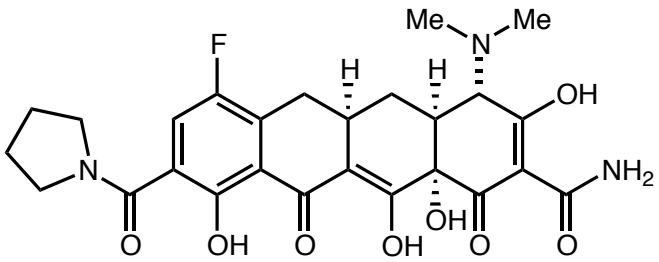


chlorotetracycline

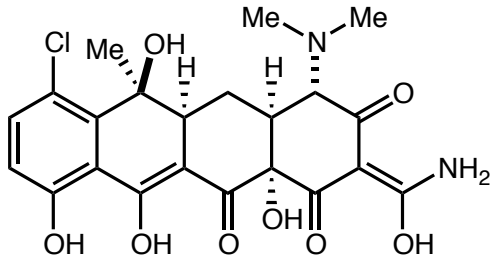


TP-434 Synthesis: Overview

TP-434



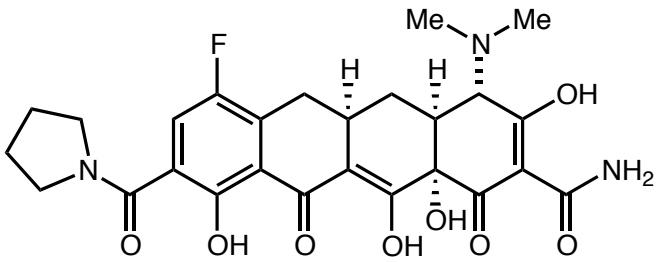
chlorotetracycline



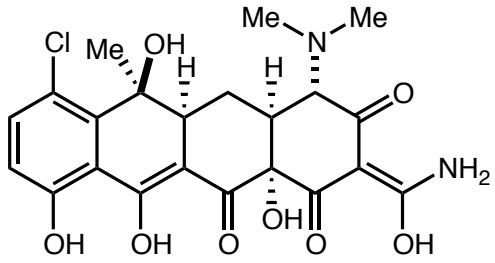
- Produced by Meyers Lab and Tetraphase
- First identified 1945 from soil bacteria
- Broad spectrum antiobiotics, though resistance is increasing

TP-434 Synthesis: Overview

TP-434



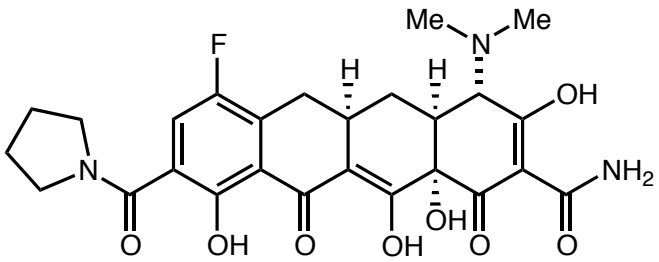
chlorotetracycline



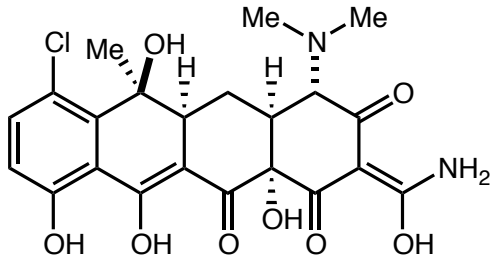
- Produced by Meyers Lab and Tetraphase
- First identified 1945 from soil bacteria
- Broad spectrum antiobiotics, though resistance is increasing
- TP-434 currently in Phase II trials for treatment of resistant infections
- Most recent tetracycline derivative (tigecycline) approved in 2005, 1st in 20 years

TP-434 Synthesis: Overview

TP-434



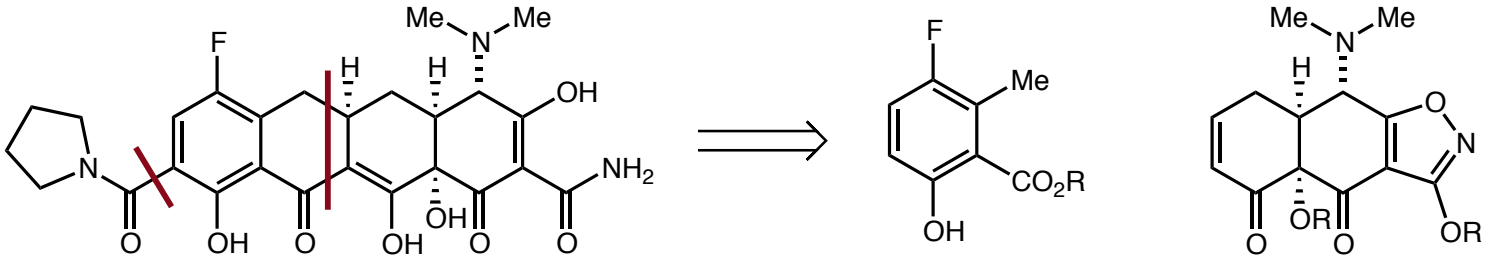
chlorotetracycline



- Produced by Meyers Lab and Tetraphase
- First identified 1945 from soil bacteria
- Broad spectrum antiobiotics, though resistance is increasing
- TP-434 currently in Phase II trials for treatment of resistant infections
- Most recent tetracycline derivative (tigecycline) approved in 2005, 1st in 20 years
- All but those produced by Tetraphase are semi-synthetic variants

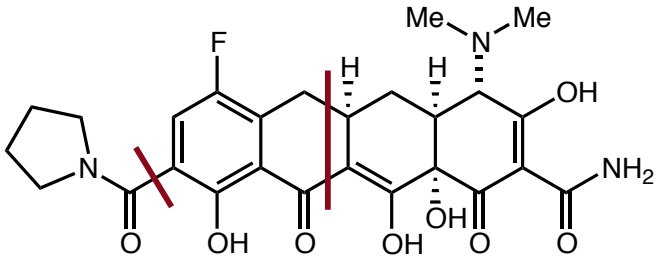
TP-434 Synthesis: Retrosynthetic Analysis

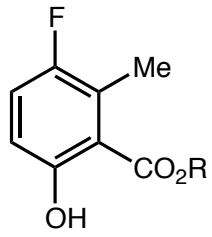
TP-434

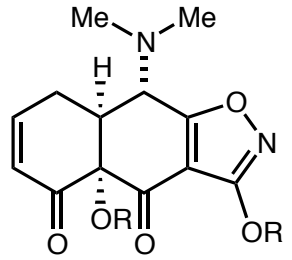


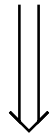
TP-434 Synthesis: Retrosynthetic Analysis

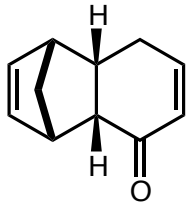
TP-434

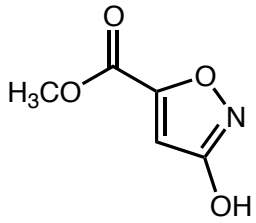






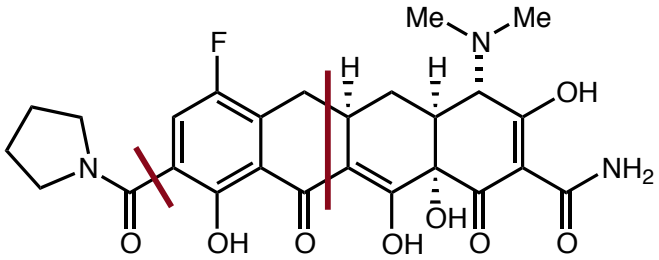


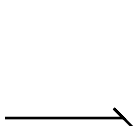


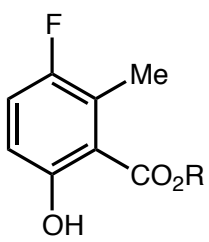


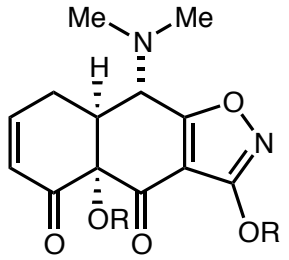
TP-434 Synthesis: Retrosynthetic Analysis

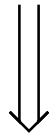
TP-434



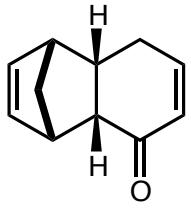


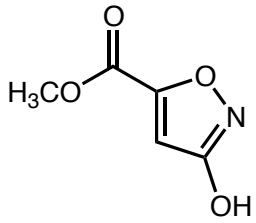




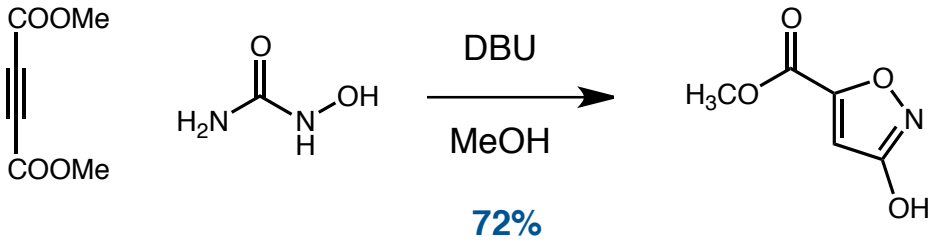


- Multiple generations of dienone synthesis
- Highly convergent, easily modified
- Similar route used to produce mulitple analogs

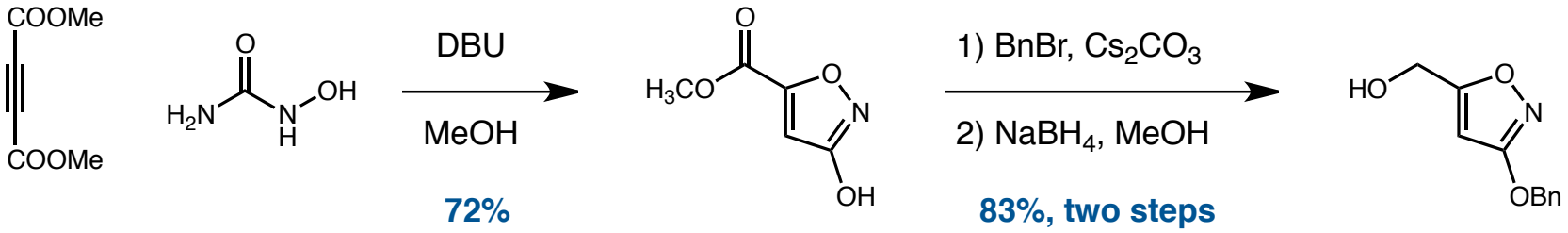




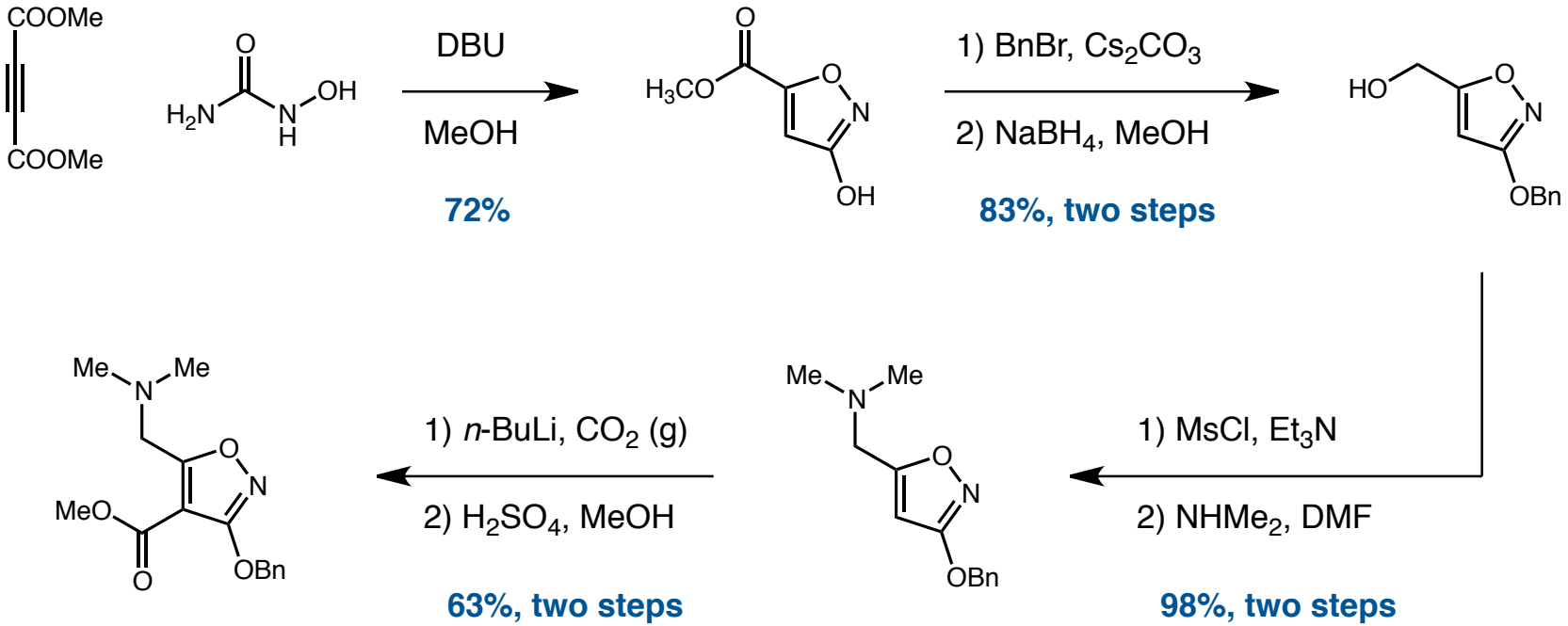
TP-434 Synthesis: C/D Ring Precursor Synthesis



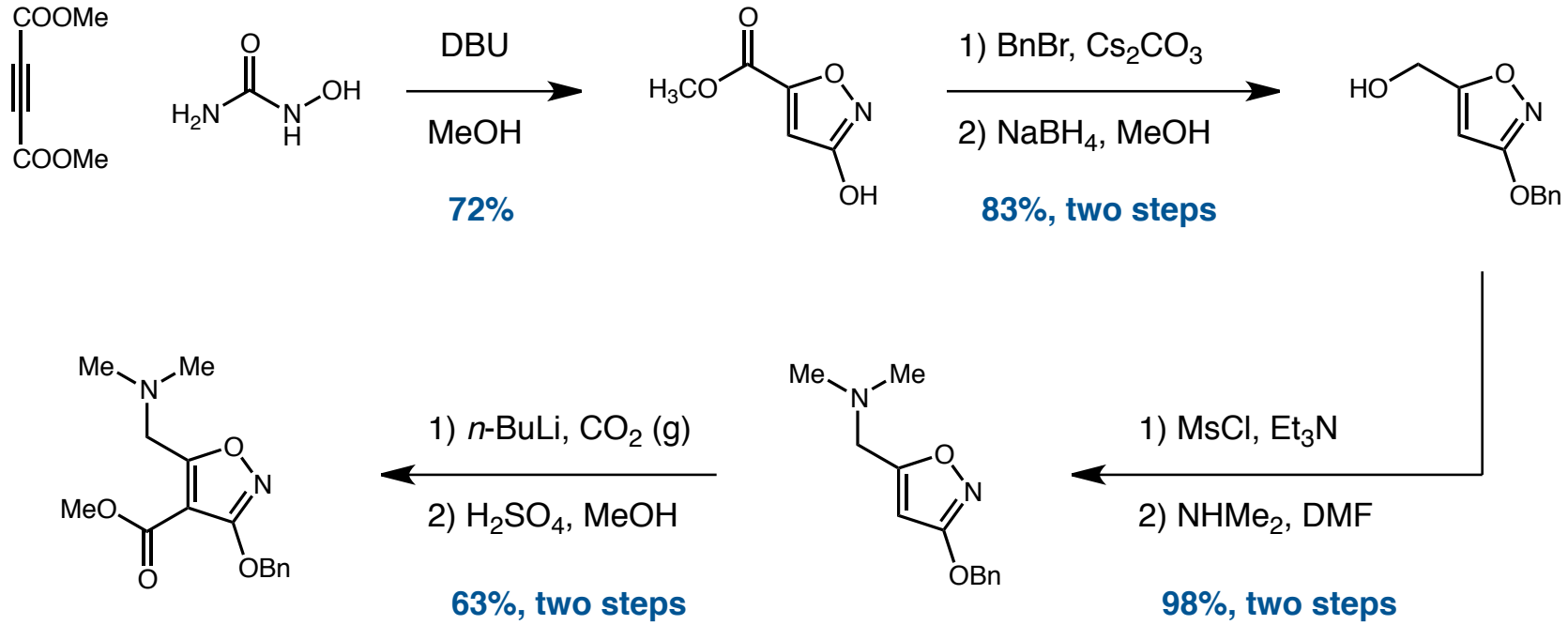
TP-434 Synthesis: C/D Ring Precursor Synthesis

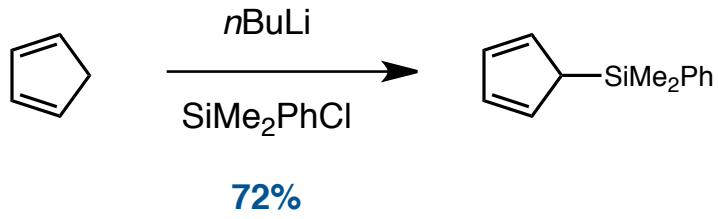


TP-434 Synthesis: C/D Ring Precursor Synthesis

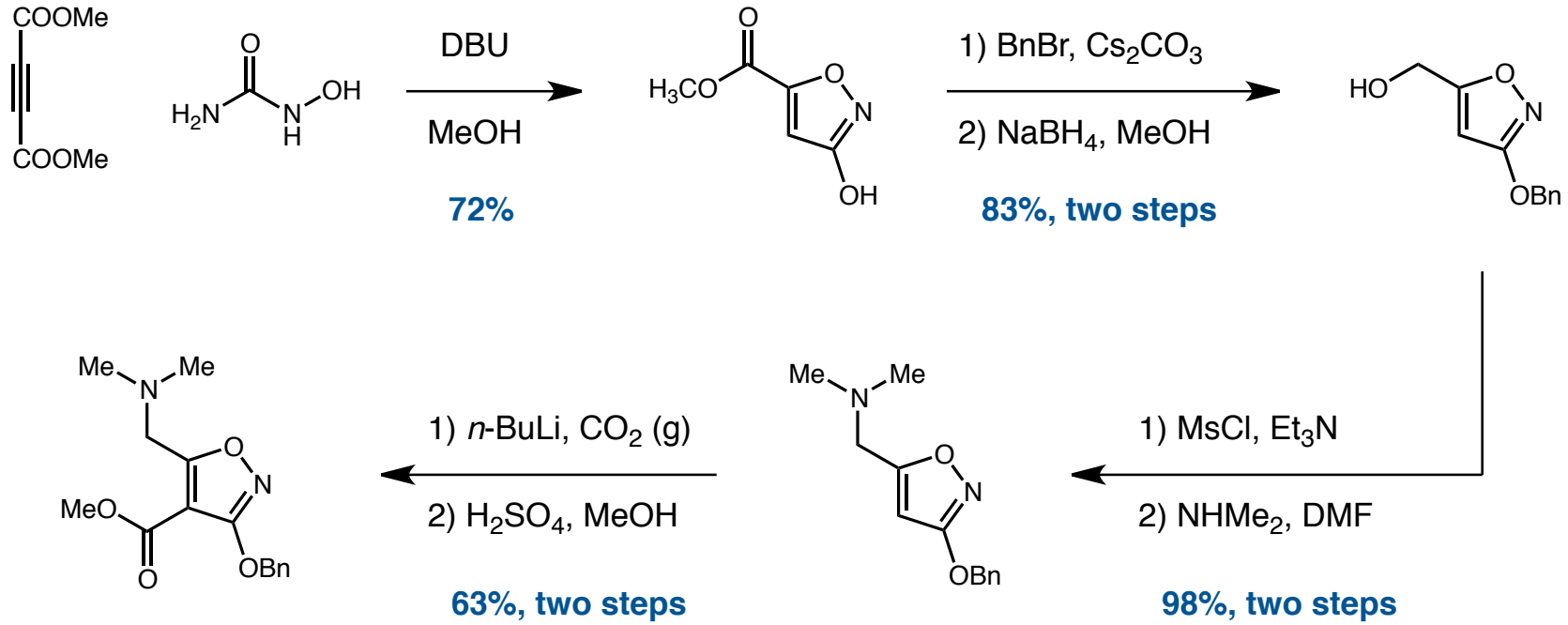


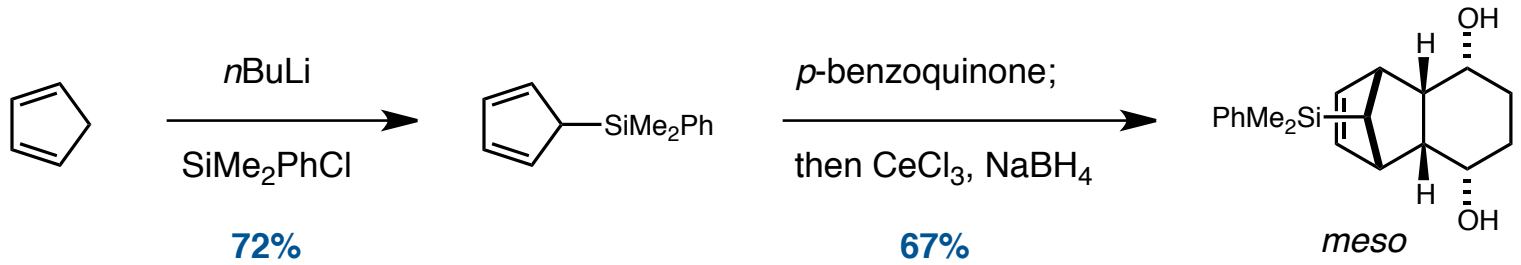
TP-434 Synthesis: C/D Ring Precursor Synthesis



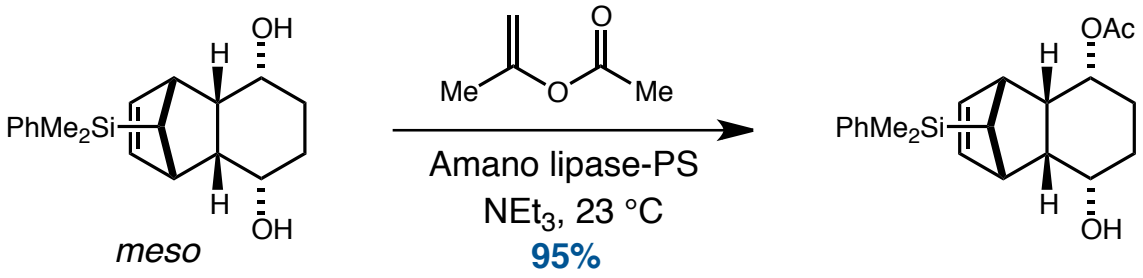


TP-434 Synthesis: C/D Ring Precursor Synthesis

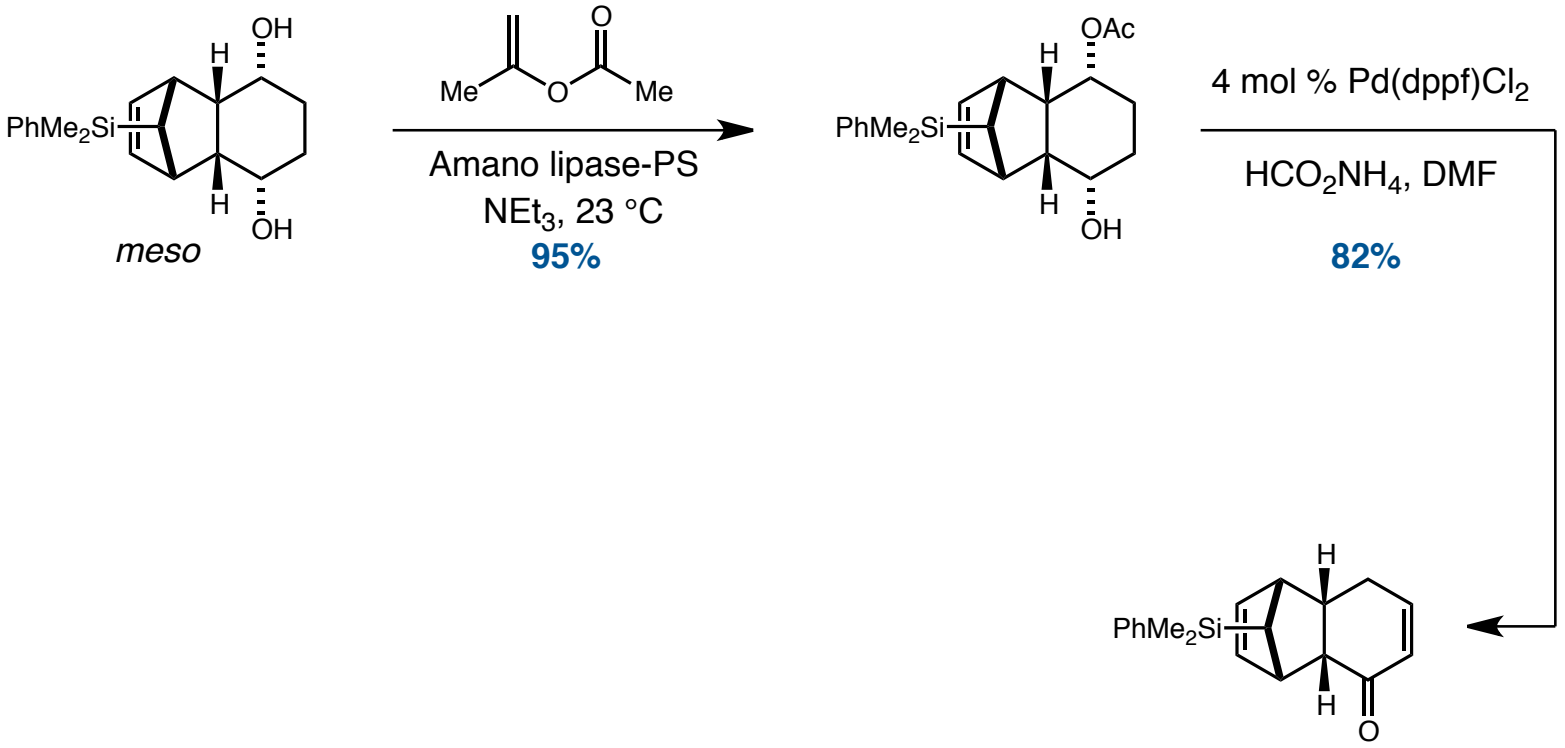




TP-434 Synthesis: C/D Ring Precursor Synthesis



TP-434 Synthesis: C/D Ring Precursor Synthesis



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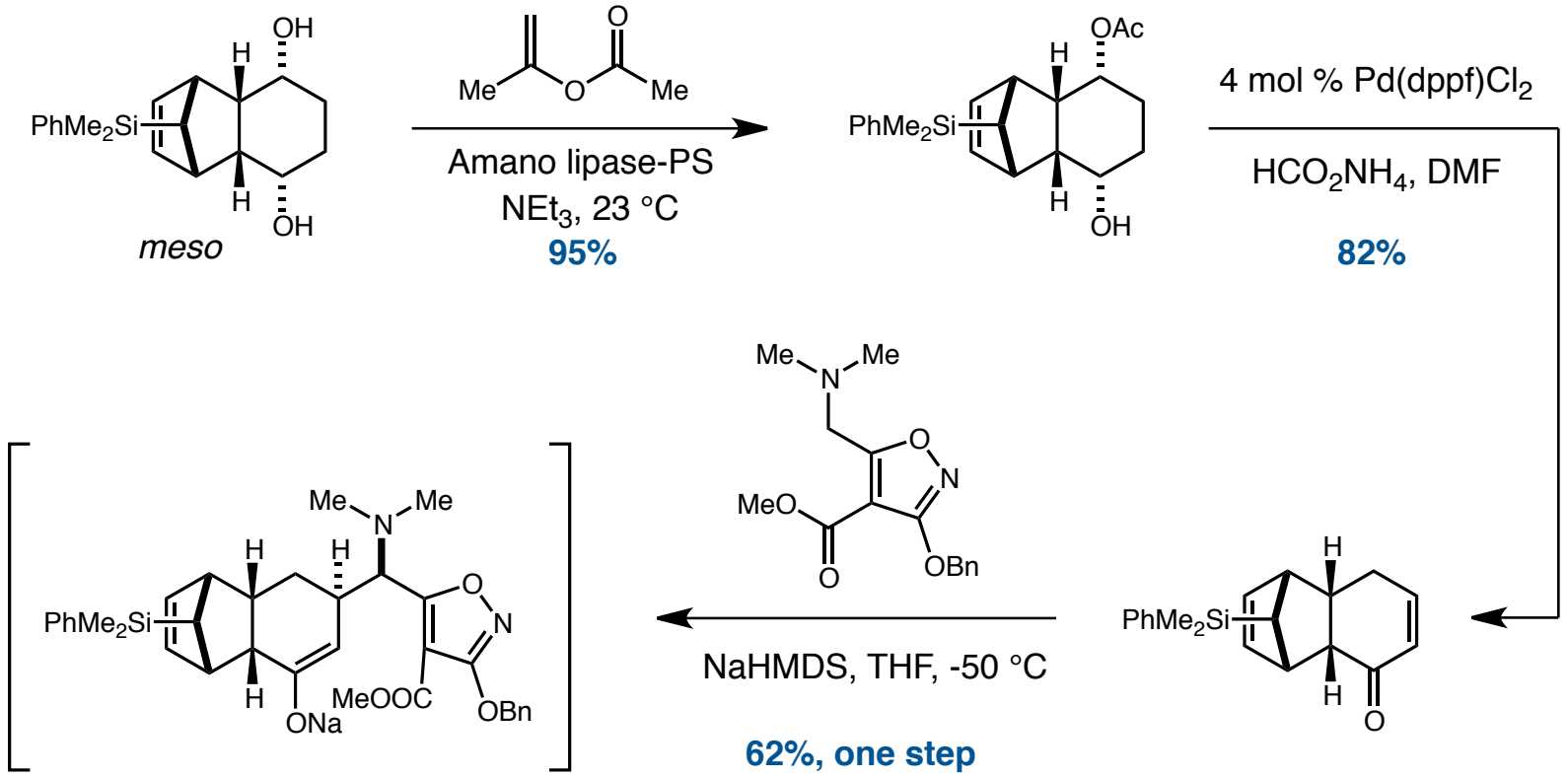
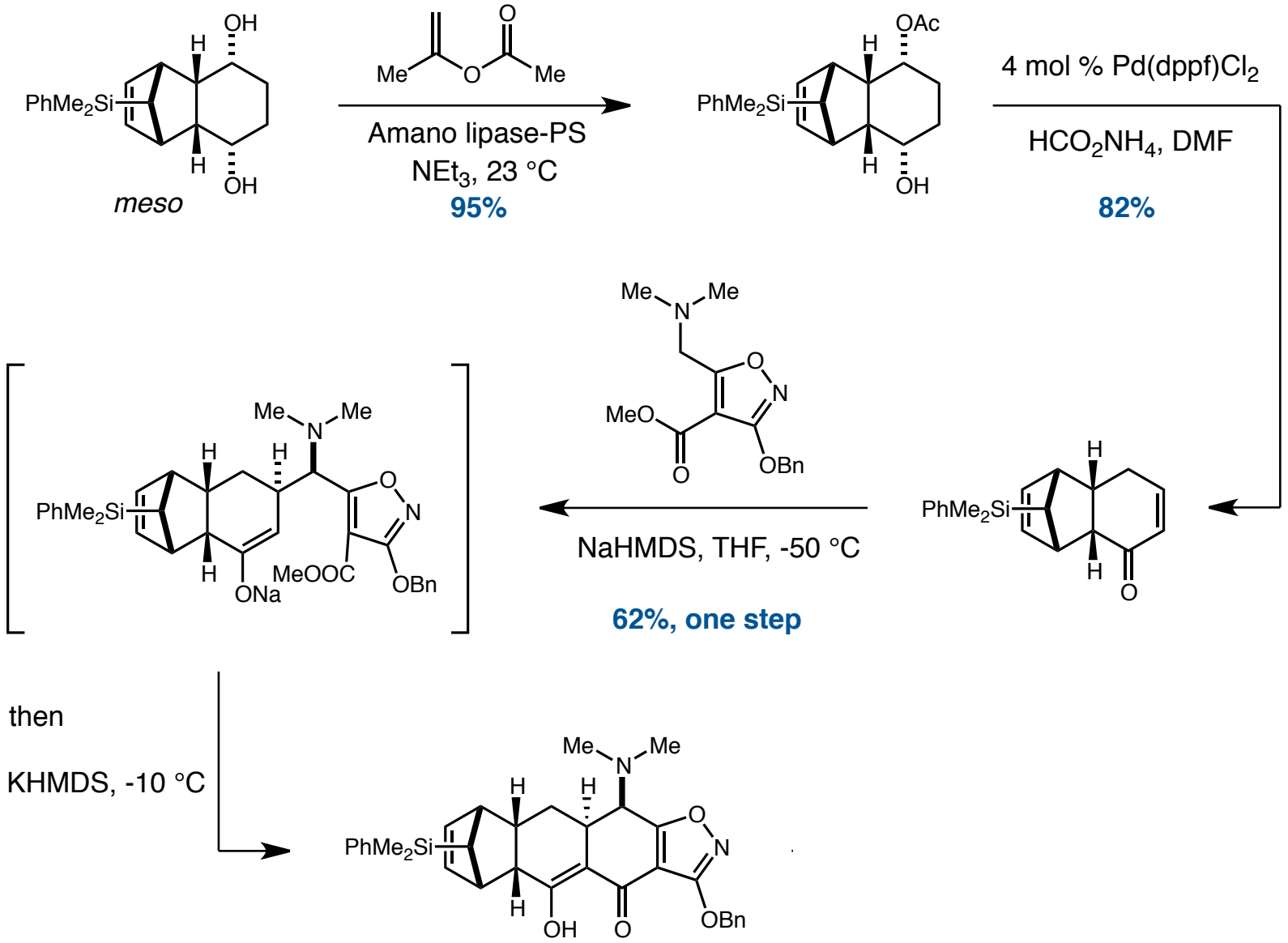
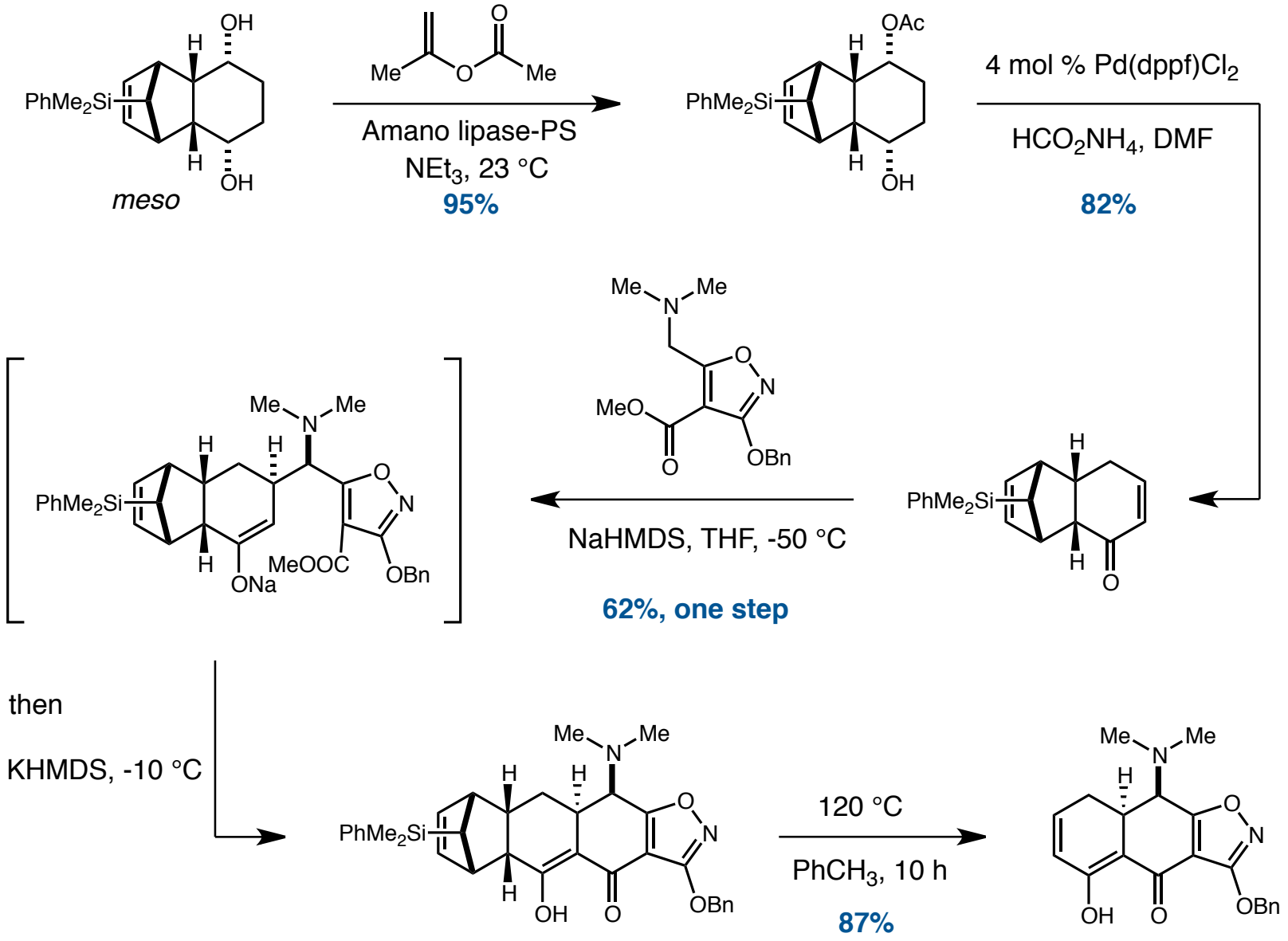


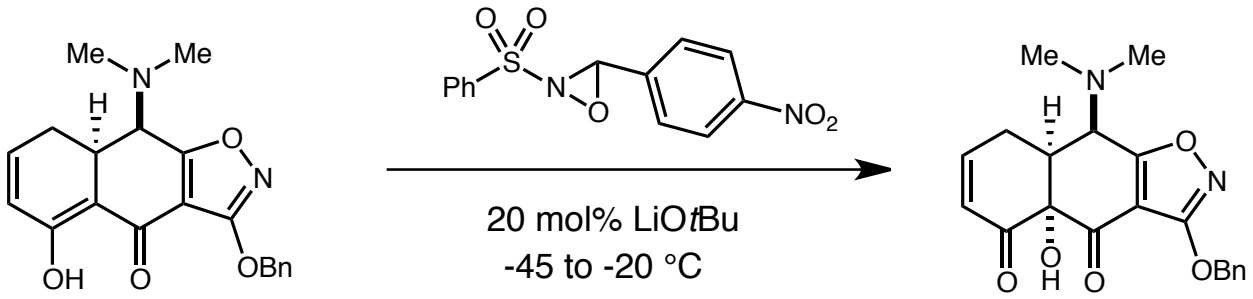
TP-434 Synthesis: C/D Ring Precursor Synthesis



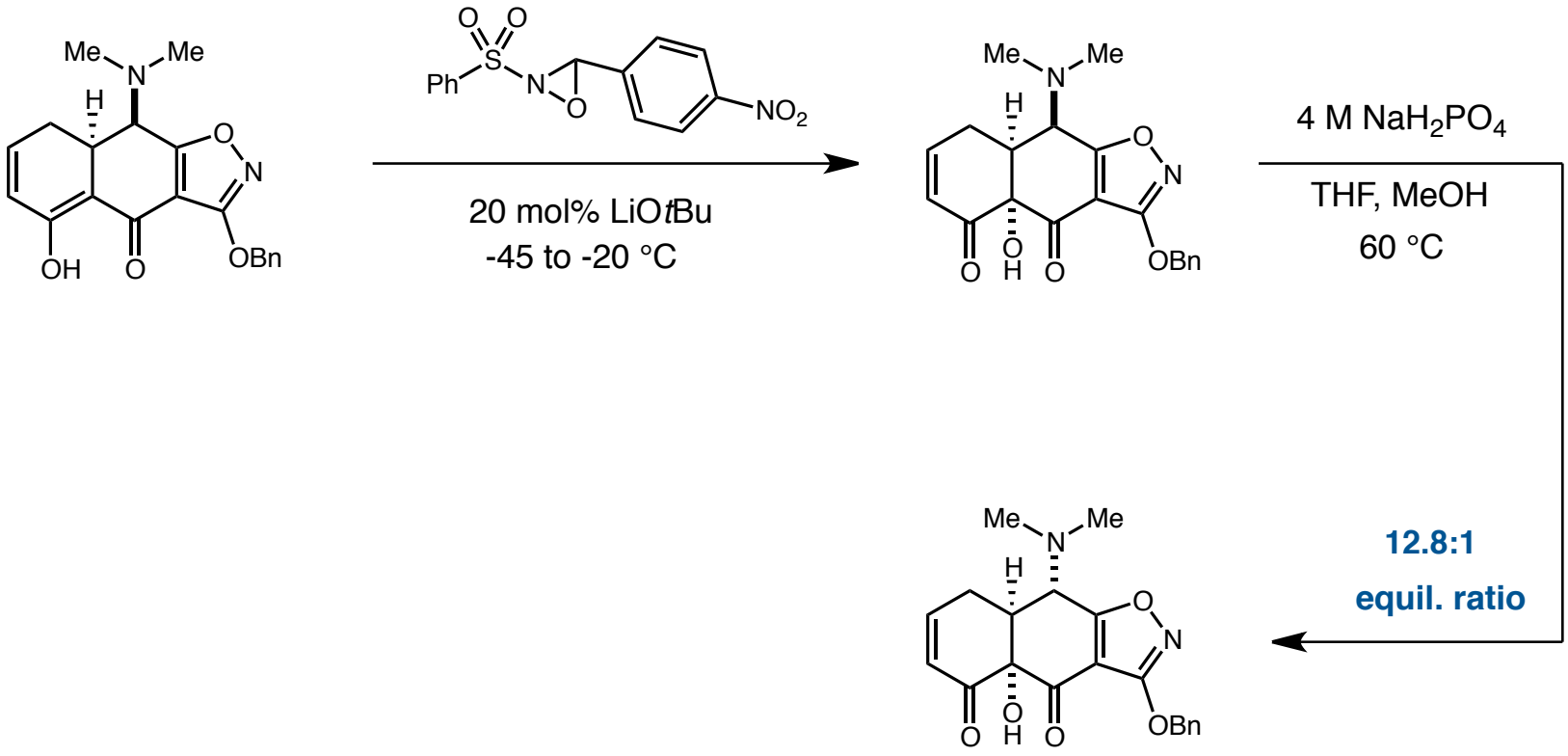
TP-434 Synthesis: C/D Ring Precursor Synthesis



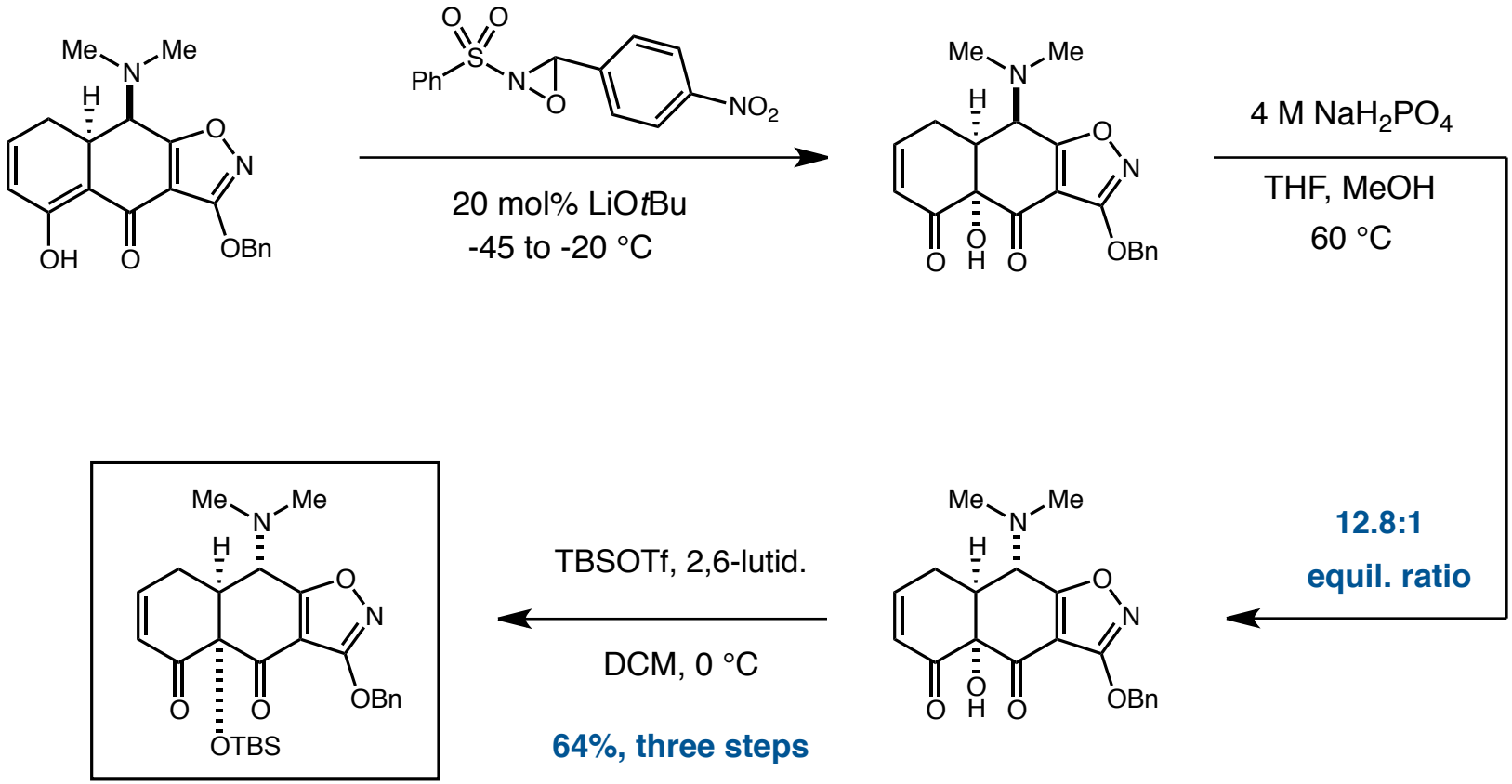
TP-434 Synthesis: A/B Ring Precursor Synthesis



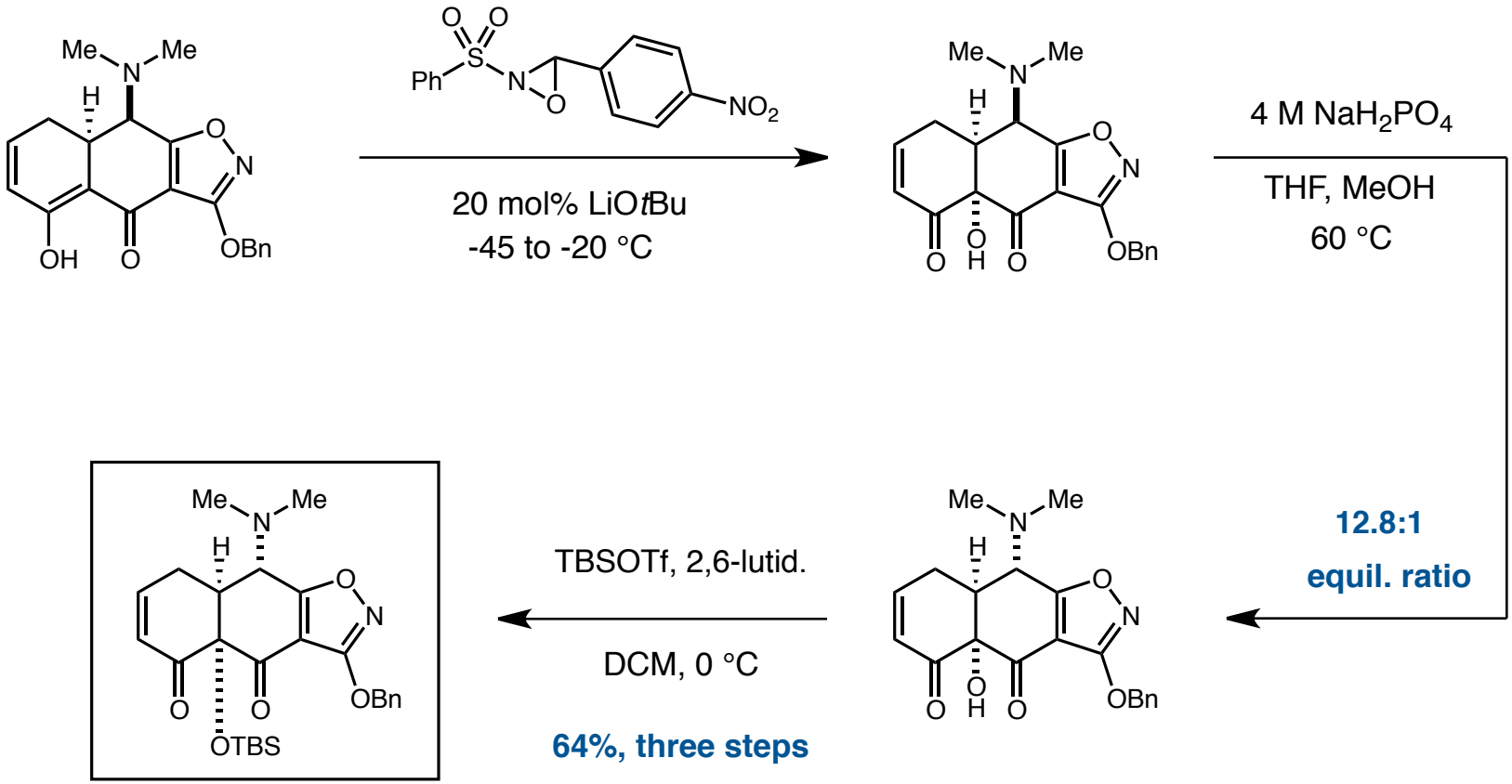
TP-434 Synthesis: A/B Ring Precursor Synthesis



TP-434 Synthesis: A/B Ring Precursor Synthesis

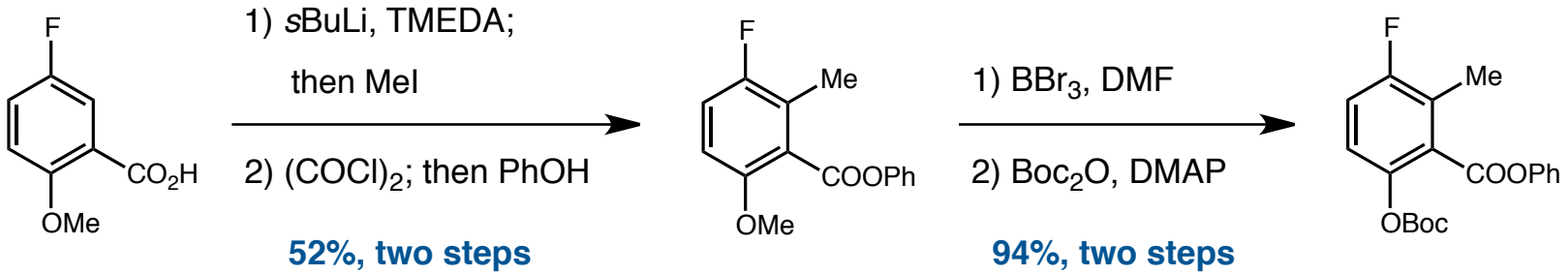


TP-434 Synthesis: A/B Ring Precursor Synthesis

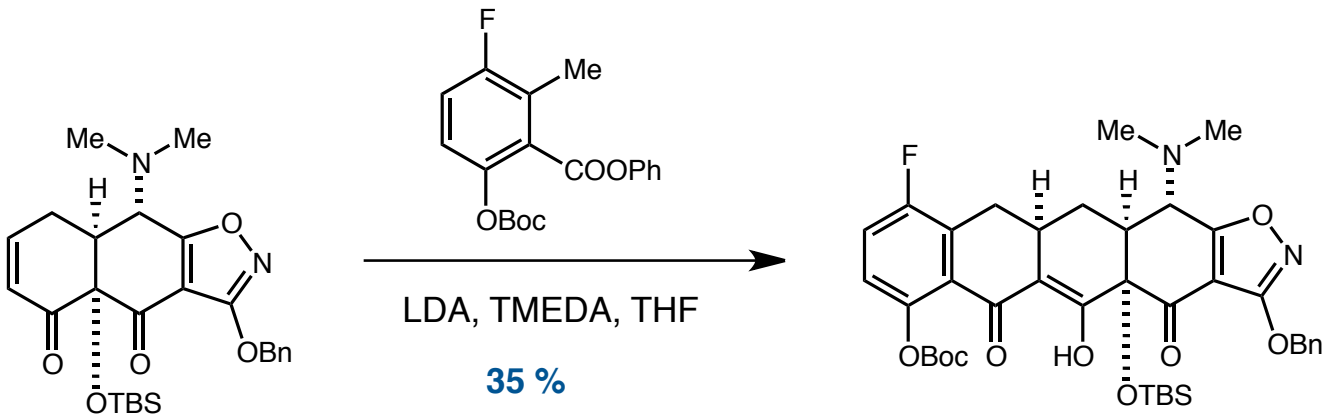


- From Michael-Claisen: 5 steps, 35 %, no chromatographic purificiation
- Overall: 13% yield from alkyne, 14 steps including all starting materials

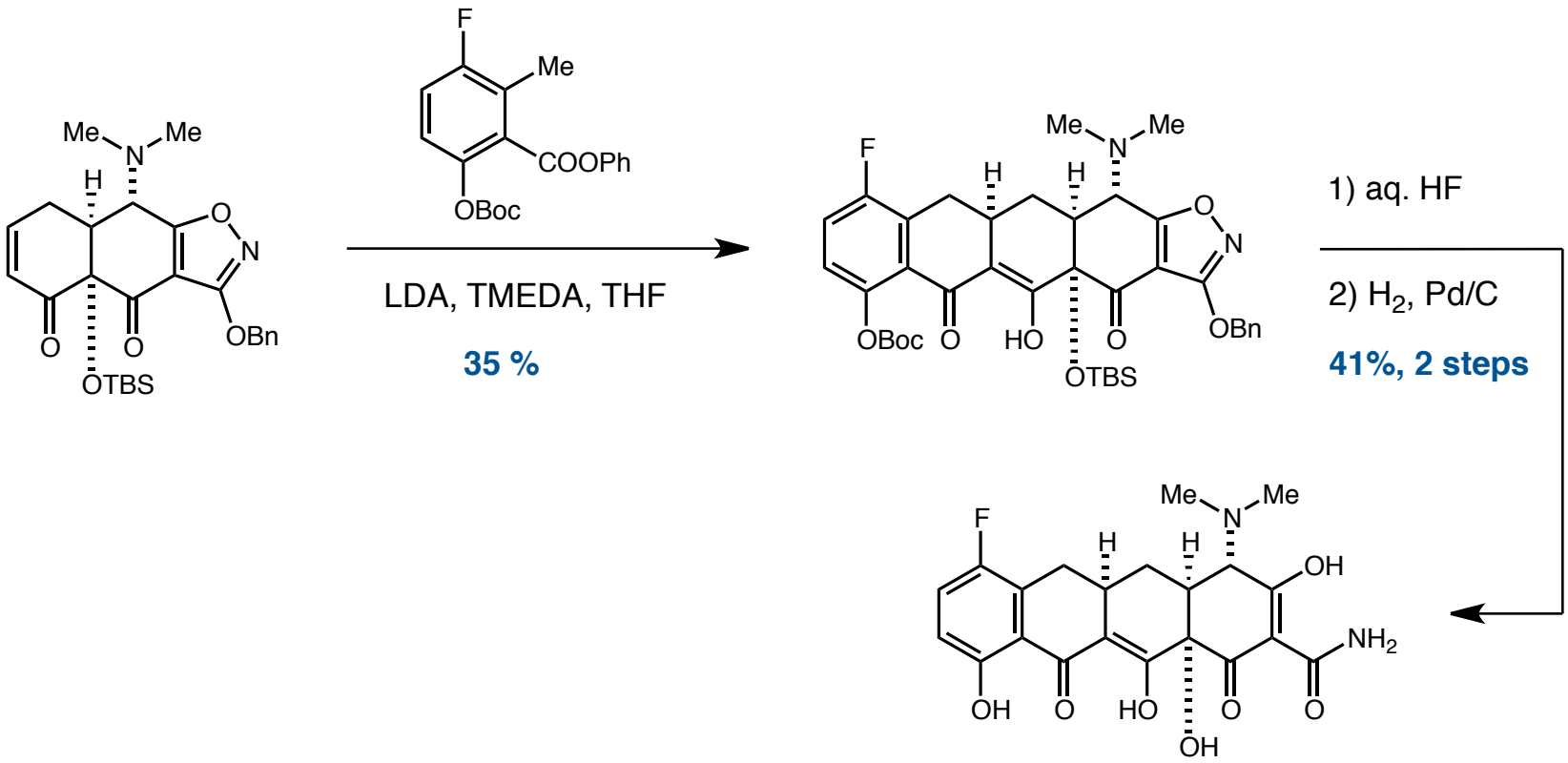
TP-434 Synthesis: C/D Ring Precursor Synthesis



TP-434 Synthesis: Cyclization and Final Steps



TP-434 Synthesis: Cyclization and Final Steps



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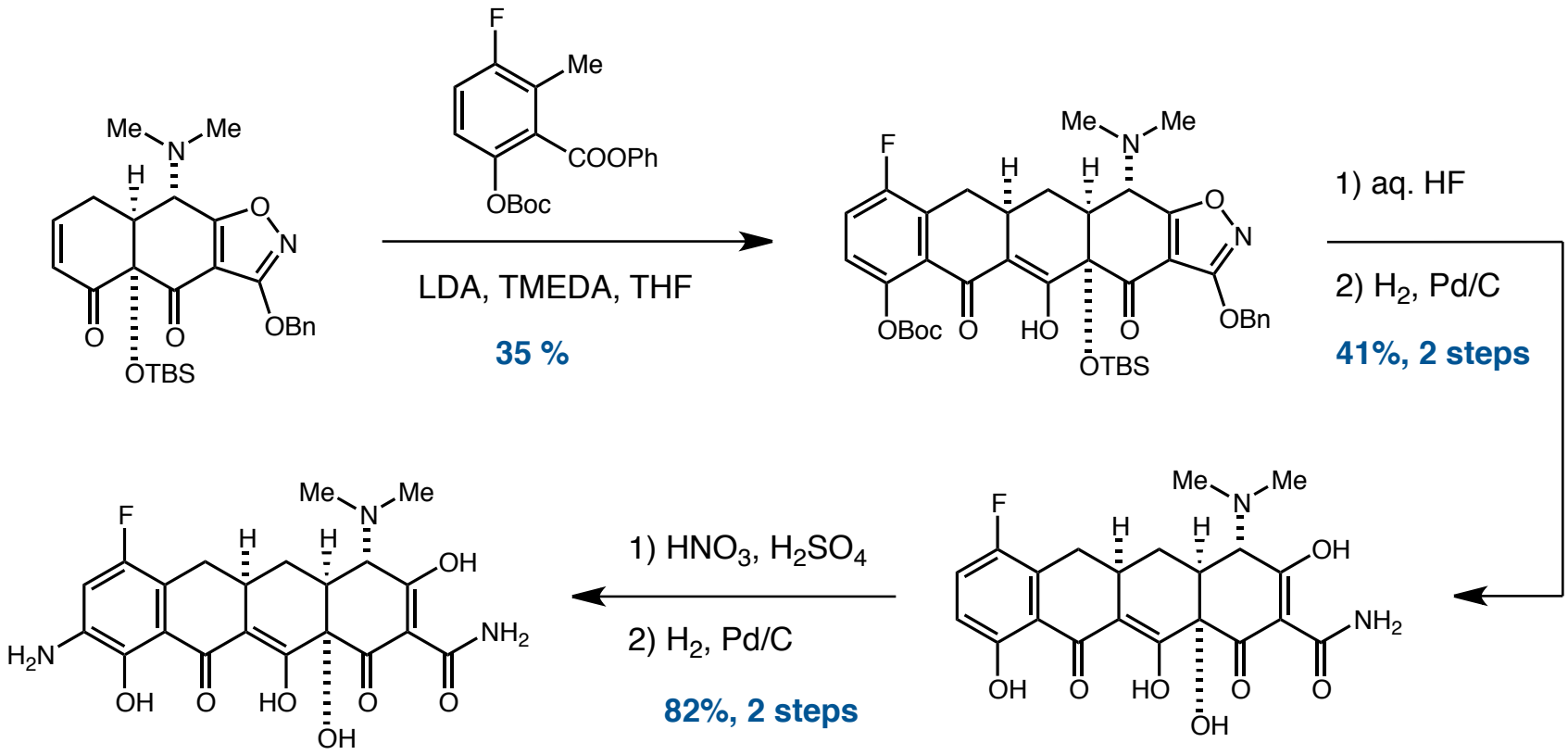

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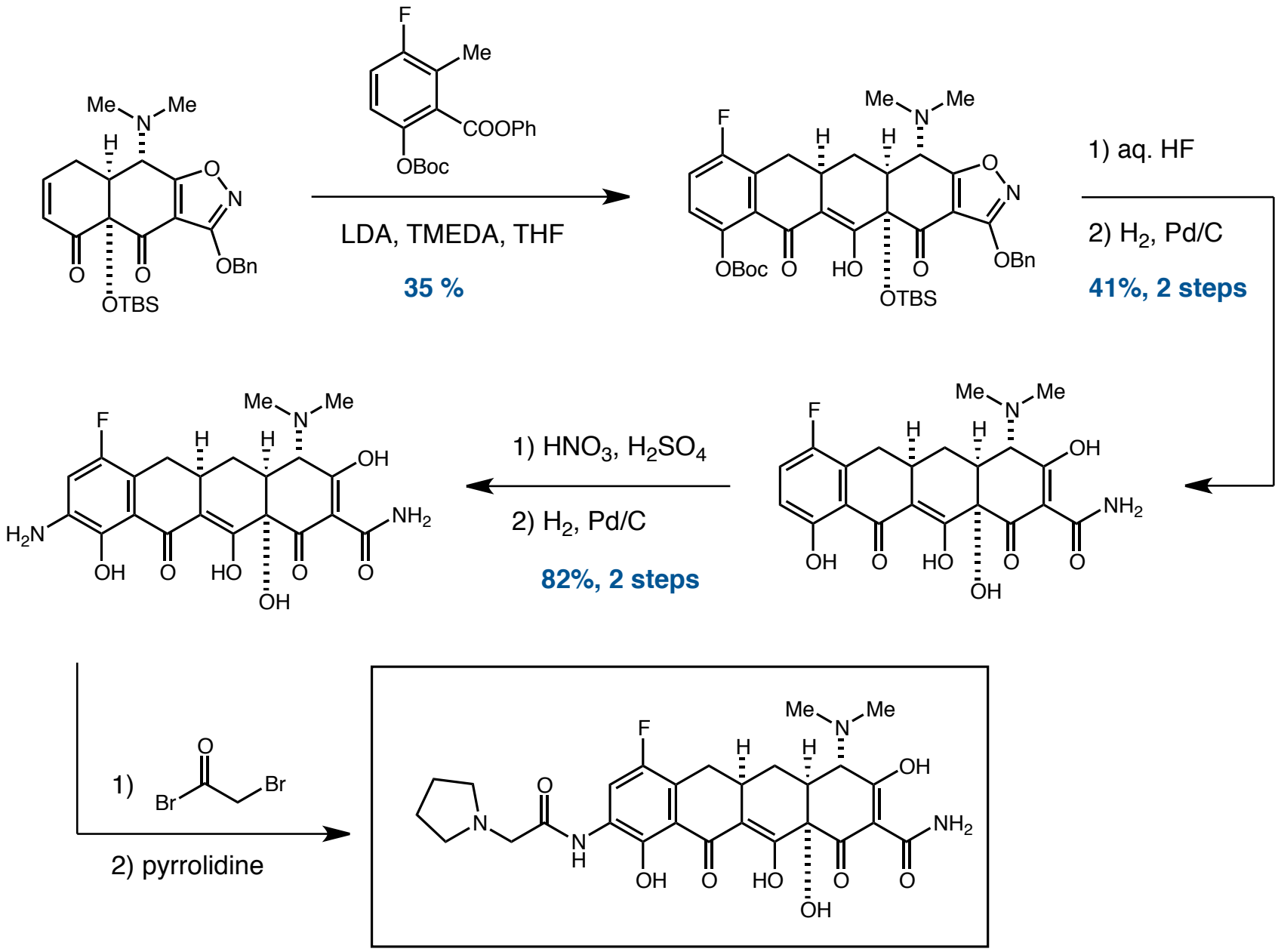
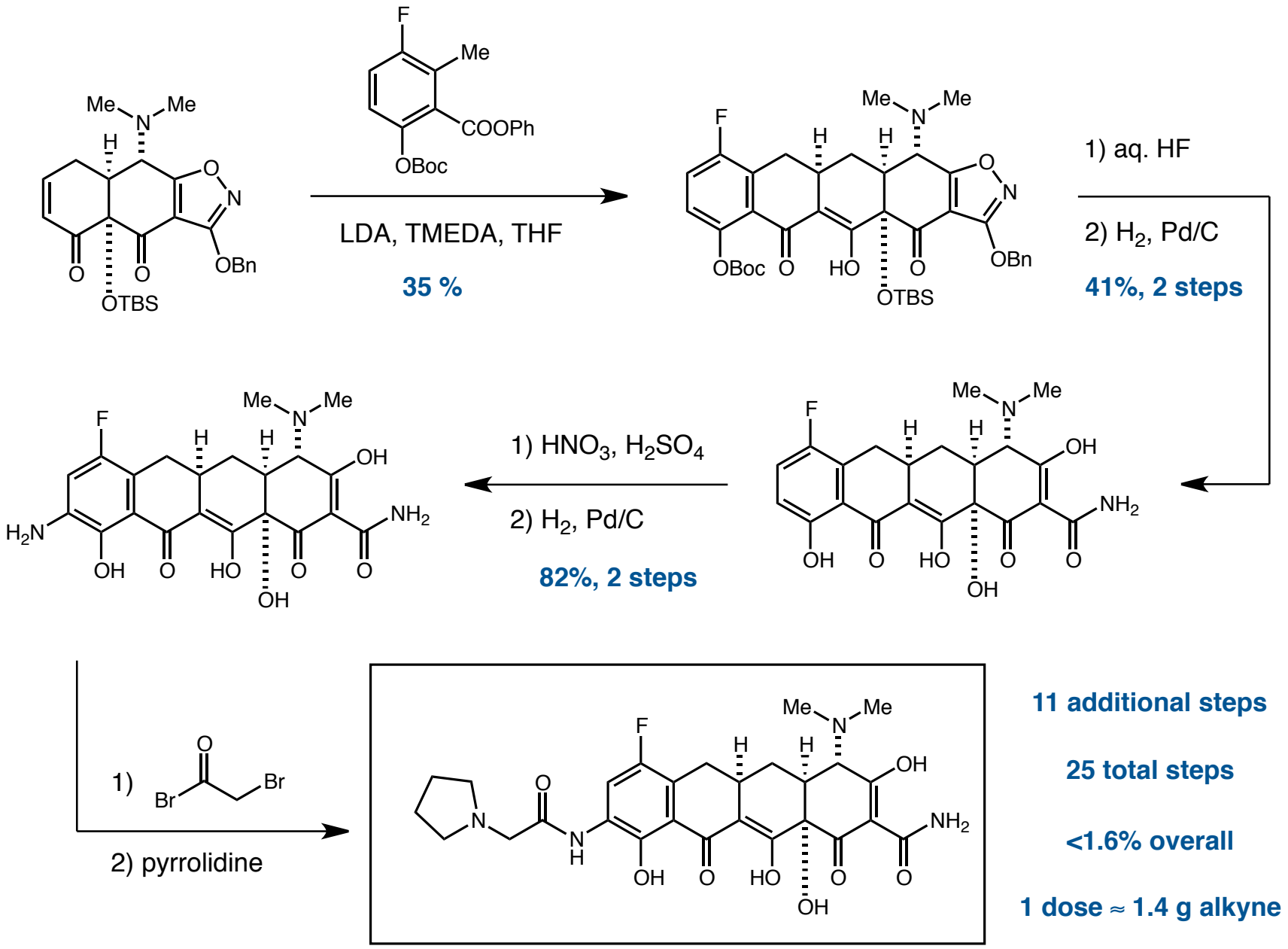


TP-434 Synthesis: Cyclization and Final Steps



11 additional steps

25 total steps

<1.6% overall

1 dose ≈ 1.4 g alkyne

Production Considerations: Analogues and Natural Products

Recrystallization, Resolution

Utilize Very Robust Chemistry

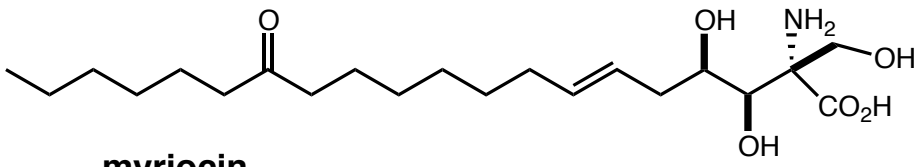
Target Considerations: Development of Analogues and Derviatives

Retain Only Necessary Parts

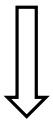
Improve Activity or Properties

Shorten Production Route

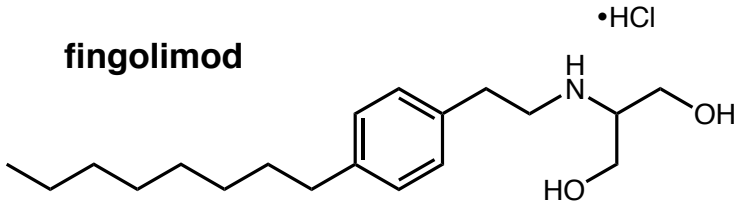
Fingolimod: Introduction



myriocin

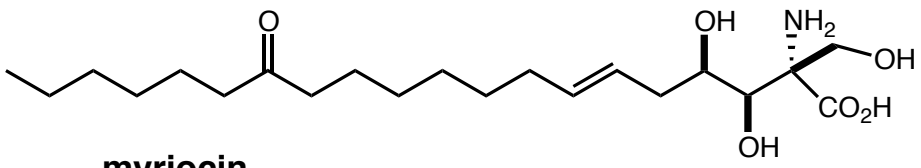


fingolimod



Persp. Med. Chem. **2007**, 11.

Fingolimod: Introduction



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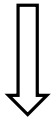

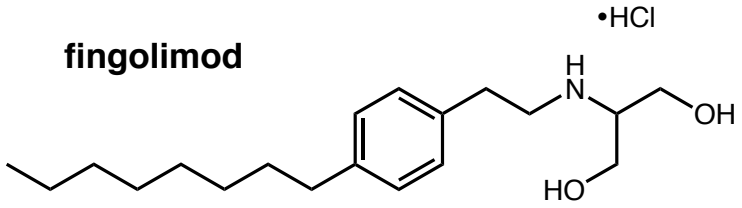

fingolimod

- From thermophilic fungii species
- Isolated in 1994, studied for bioactivity

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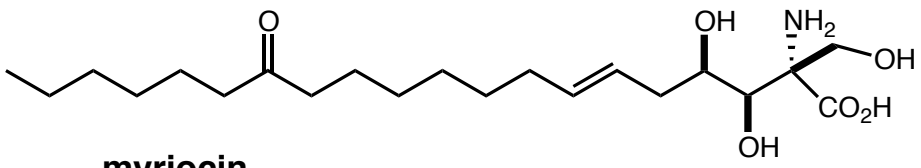
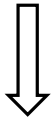
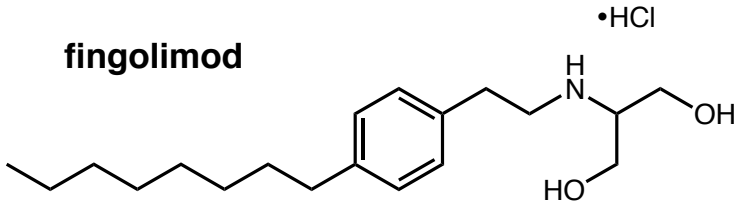


myriocin





fingolimod

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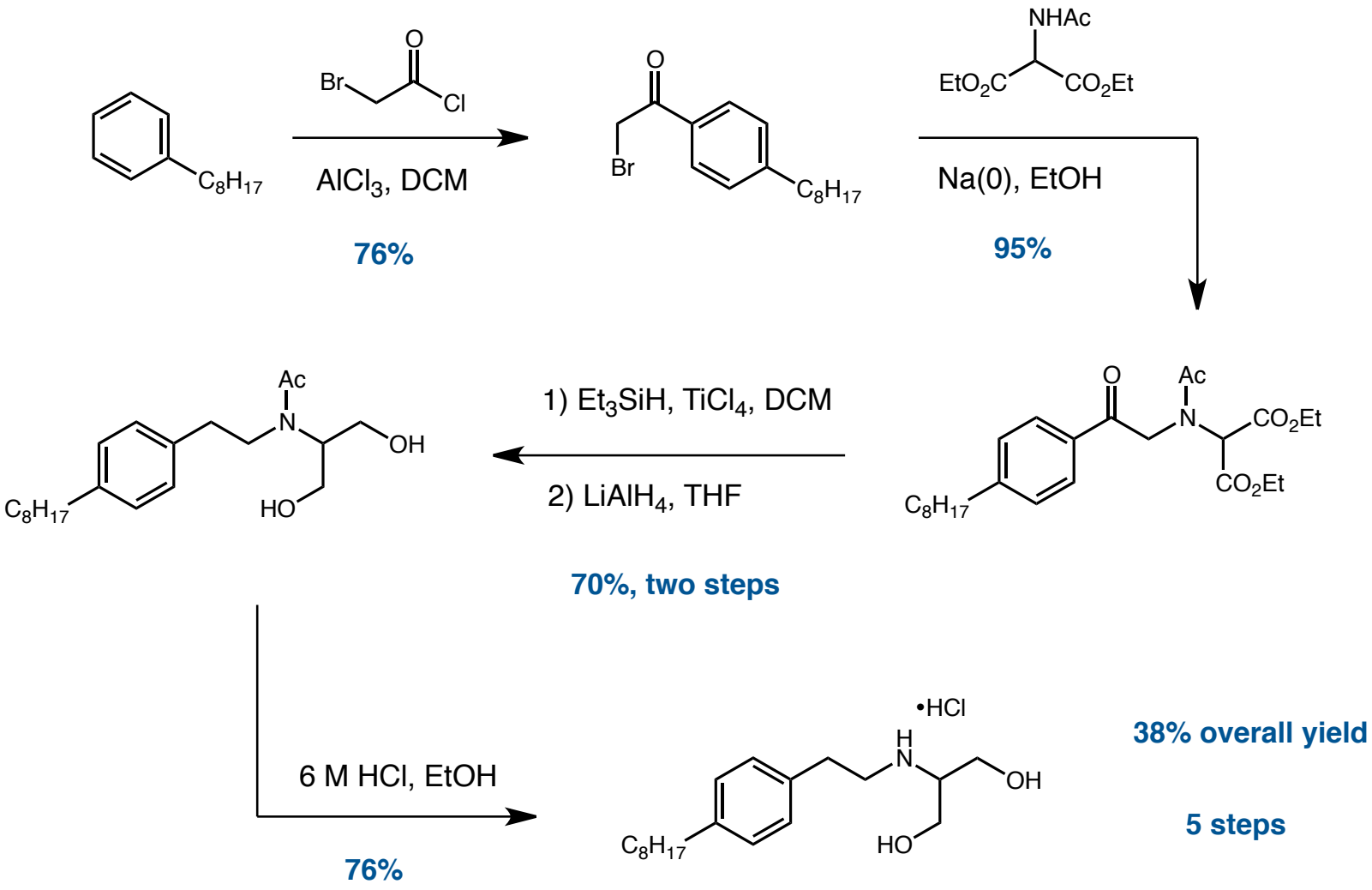
Fingolimod: Complete synthesis



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