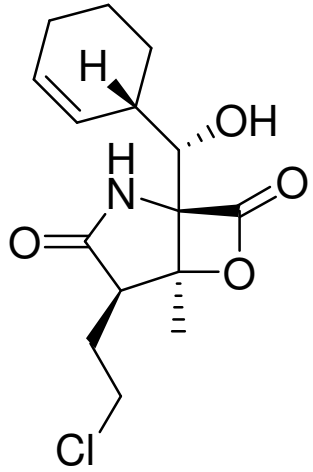
Enantioselective Total Synthesis of (-)-Salinosporamide A (NPI-0052)



Organic Letters, **2007**, *9*, 2289

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Current Lit. 6/16/07

Erikah Englund

Outline

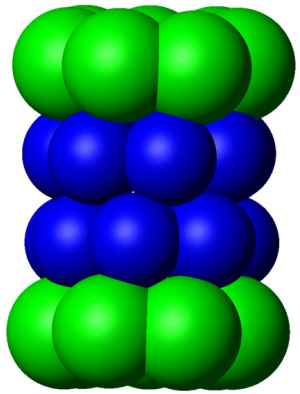
- Salinosporamide Background
- 20S Proteasome
- Previous Salnosporamide Syntheses
- Title Paper Synthesis
- Conclusion

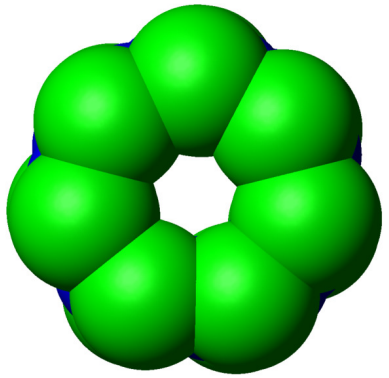
Salinosporamide A

- Salinosporamide A
  - Secondary metabolite of marine actinomycete *salinispora tropica* found in ocean sediment (*Angew.Chem.Int.Ed,* **2003**, *42*, 355)
    - Actinomycete
      - Bacteria in phylum Actinobacteria
      - Soil derived actinomycete produce important antibiotics such as streptomycin (dictionary.com)
      - Marine Actinomycetes largely overlooked
  - In vitro activity of 10 uM or less against tumors
  - Salinosporamide is a potent inhibitor of 20S proteasome (*Cancer Cell*, **2005**, *8*, 407 and *J. Med. Chem*, **2005**, *48*, 3684)

20S Proteasome

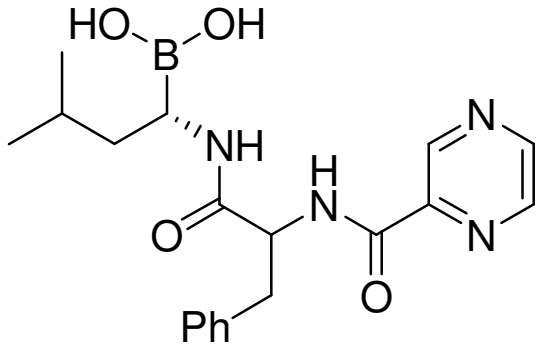
- Proteasomes are large protein complexes found in the nucleus and cytoplasm that degrade ubiquitin marked proteins
- Early proteasome work done in 1970's and 80's resulted in 2004 Nobel Prize in Chemistry for Hershko, Rose and Ciechanover
- Most common proteasome is 26S which contains two 19S caps and one 20S core
- 20S core contains 4 stacked heptameric subunits. Inner subunits contain protease active sites





20S Inhibition

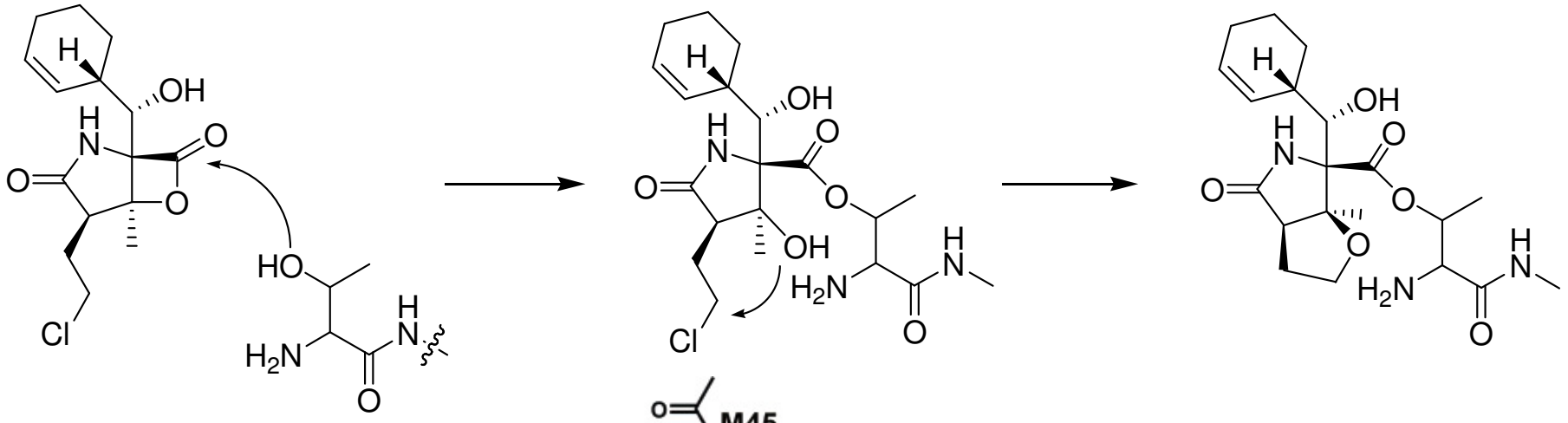
- Bortezomib first proteosome inhibitor to reach market
  - Marketed as Velcade

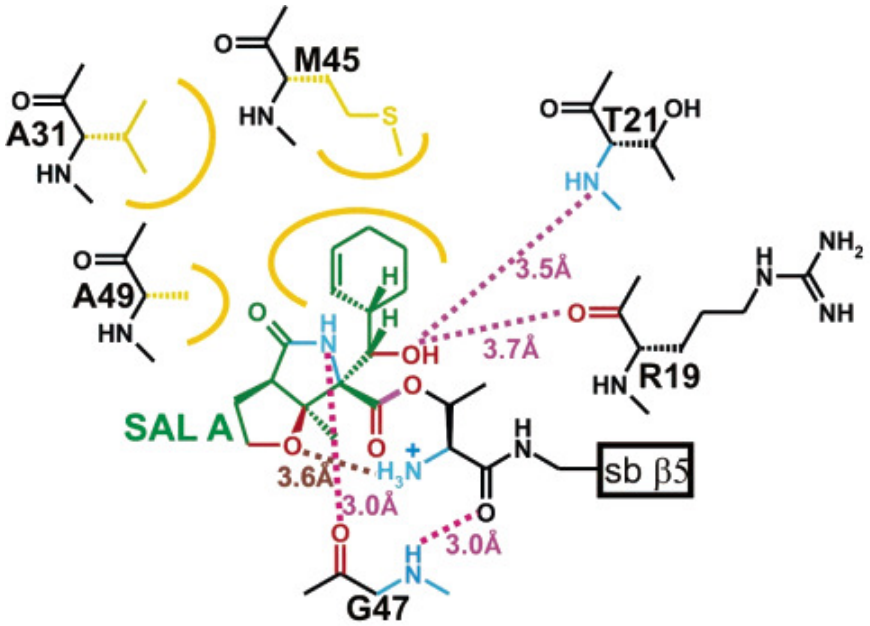


- Anti-tumor activity is attributed to inhibition of pro-growth proteins and disruption of protein balance in cell (*Cancer Res*. **1999**, 59 (11), 2615)

Salinosporamide 20S Inhibition

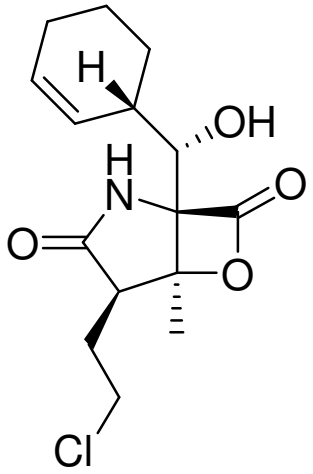
- *JACS*, **2006**, *128*, 5136



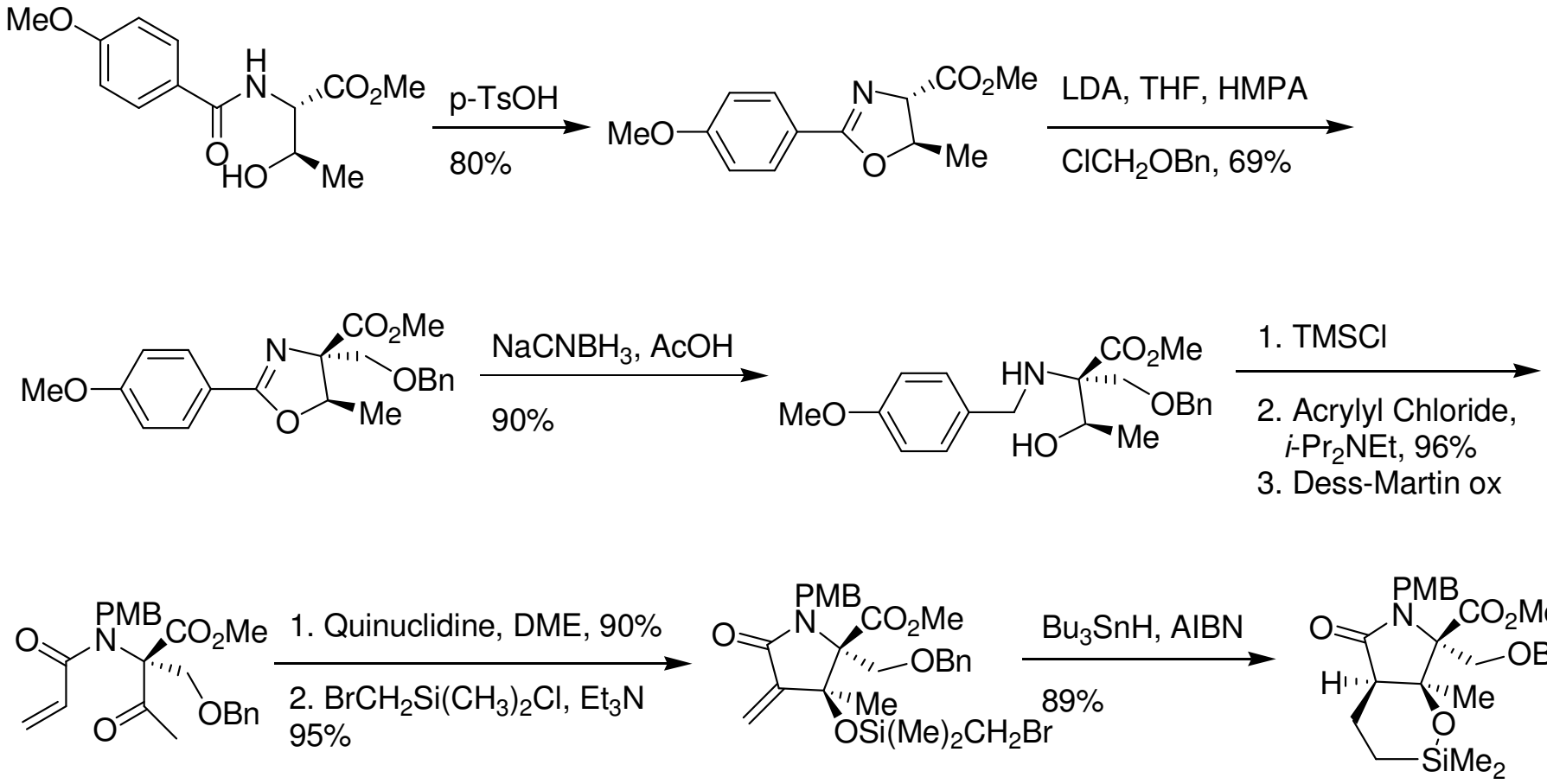


Other Salinosporamide Syntheses

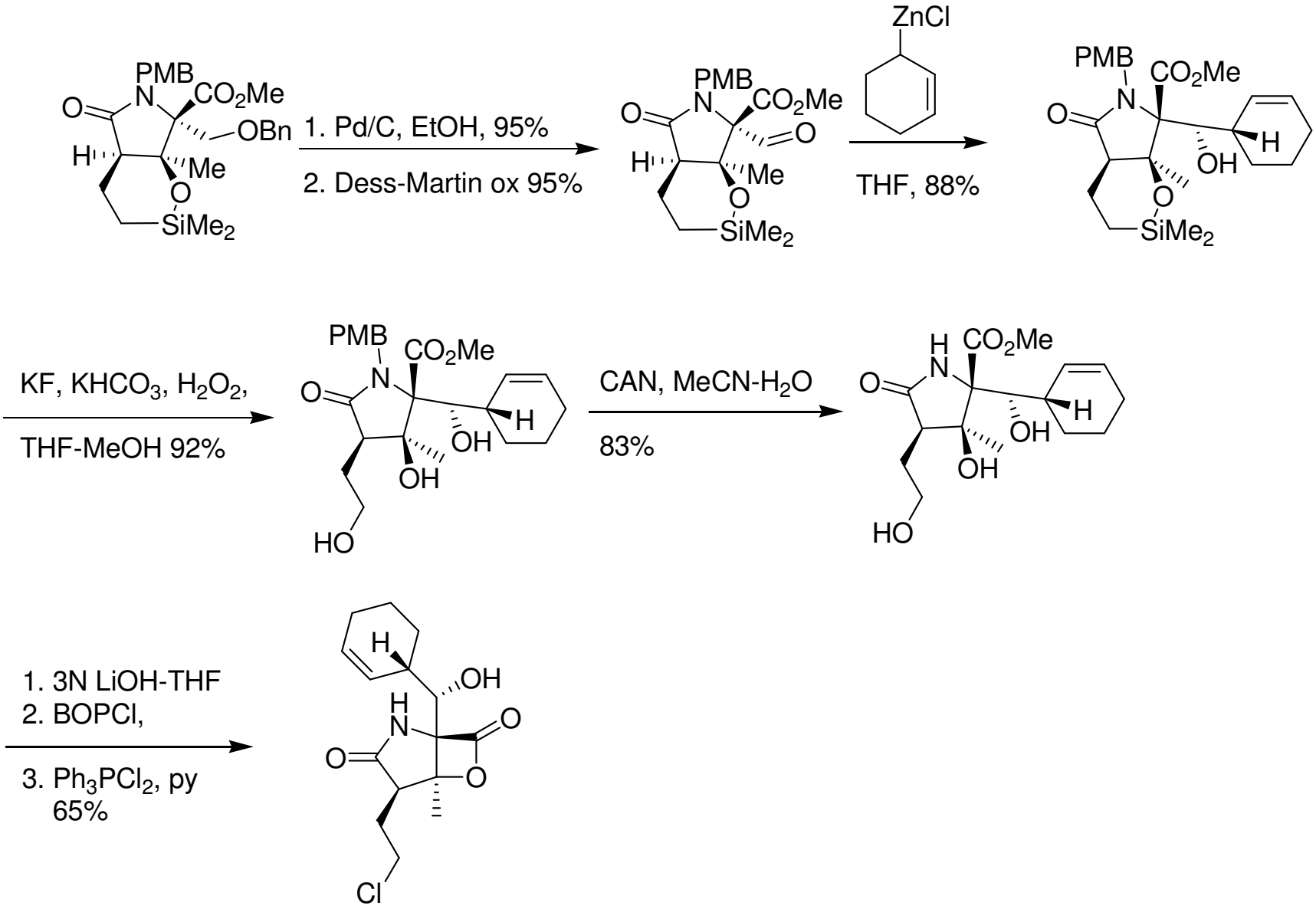
- Other Synthesis
  - Corey, *JACS*, **2004**, *126*, 6230 (enantioselective, 17 steps, 13.7%)
  - Corey, *Org. Lett*, **2005**, *7*, 2699 (enantioselective analogue, 14 steps, 30.5%)
  - Danishefsky, *JACS*, **2005**, *127*, 8298 (28 steps, 2.2%)
  - Langlois, *Tett. Lett*, **2007**, *48*, 381 (enantioselective formal synthesis)
  - Pattendon, *OBC*, **2006**, *4*, 2845 (rac. 14 steps, 11.5%)
- Title Paper
  - 20 steps and 0.4%
- Approaches
  - Functionalization of gamma γ-lactam followed by late stage incorporation of cyclohexene and final introduction of lactone



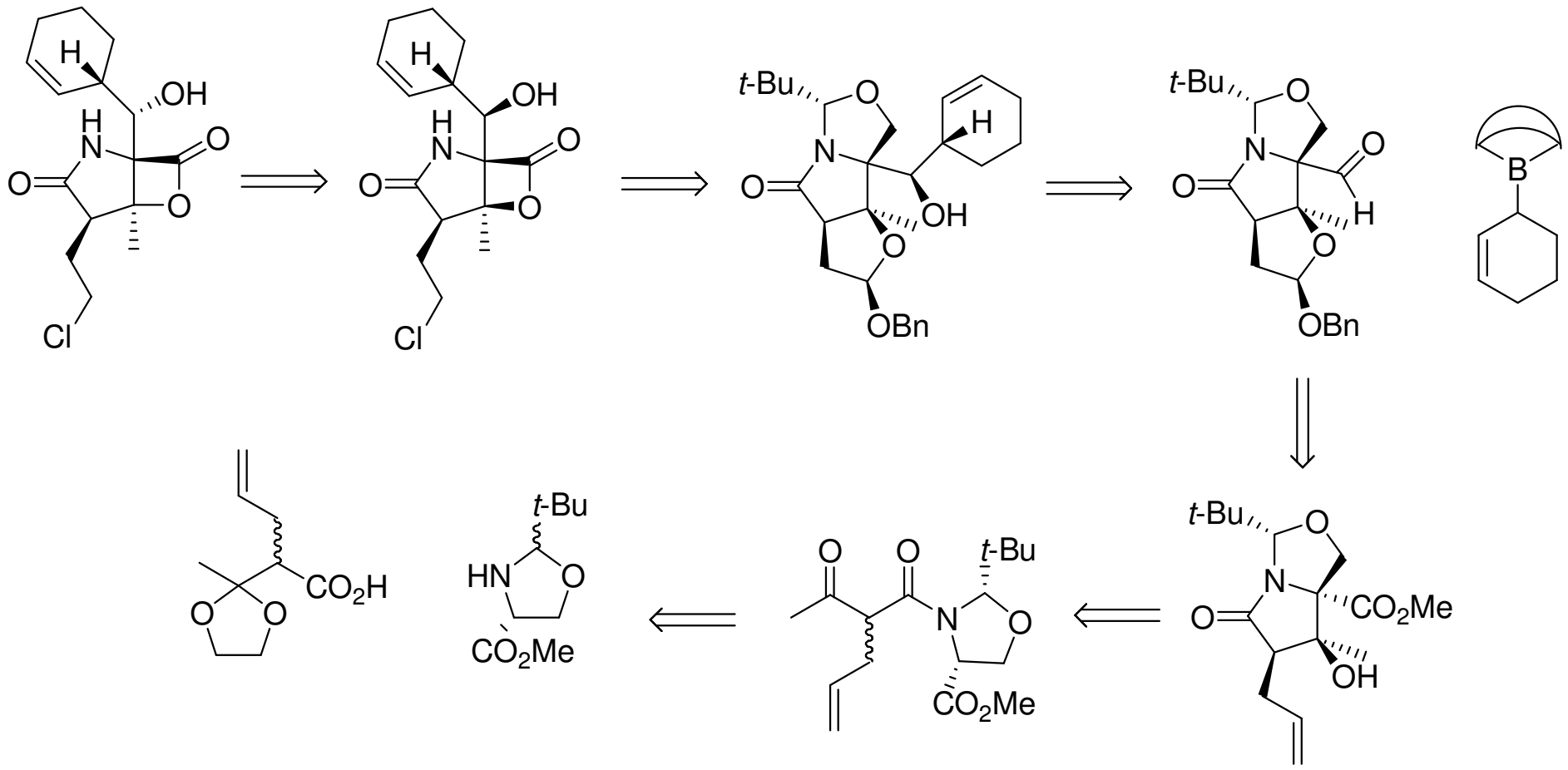
Corey's Synthesis



Corey's Synthesis (cont.)



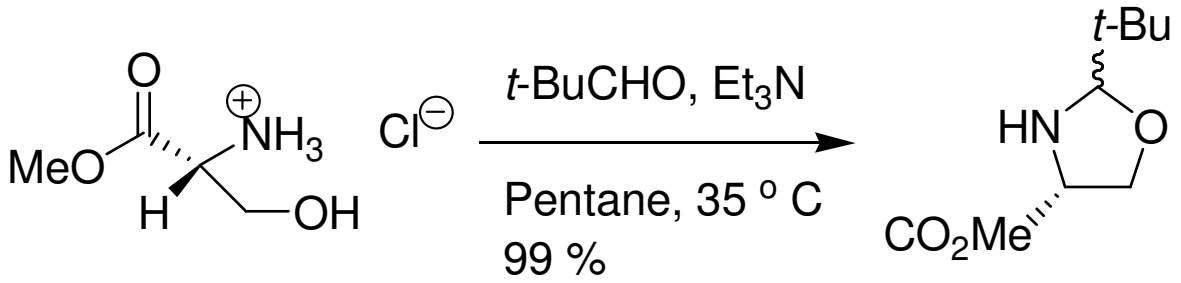
Retrosynthesis



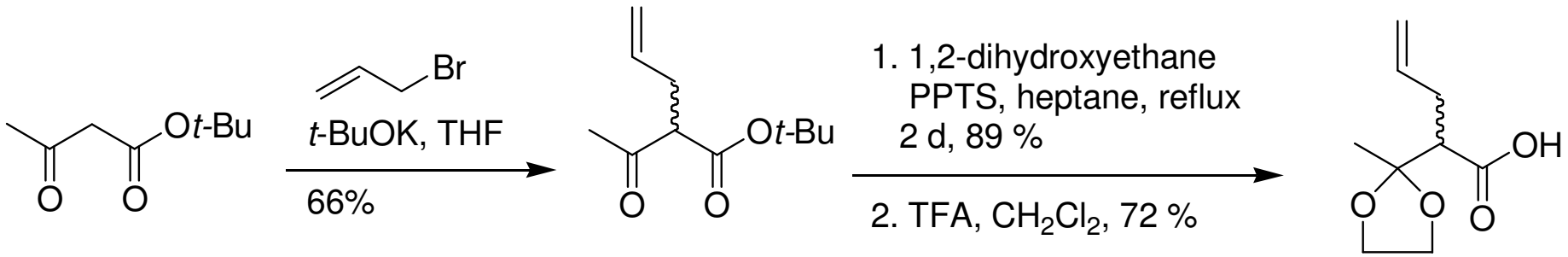
Starting Material Synthesis

- Oxazolidine synthesized from D-serine

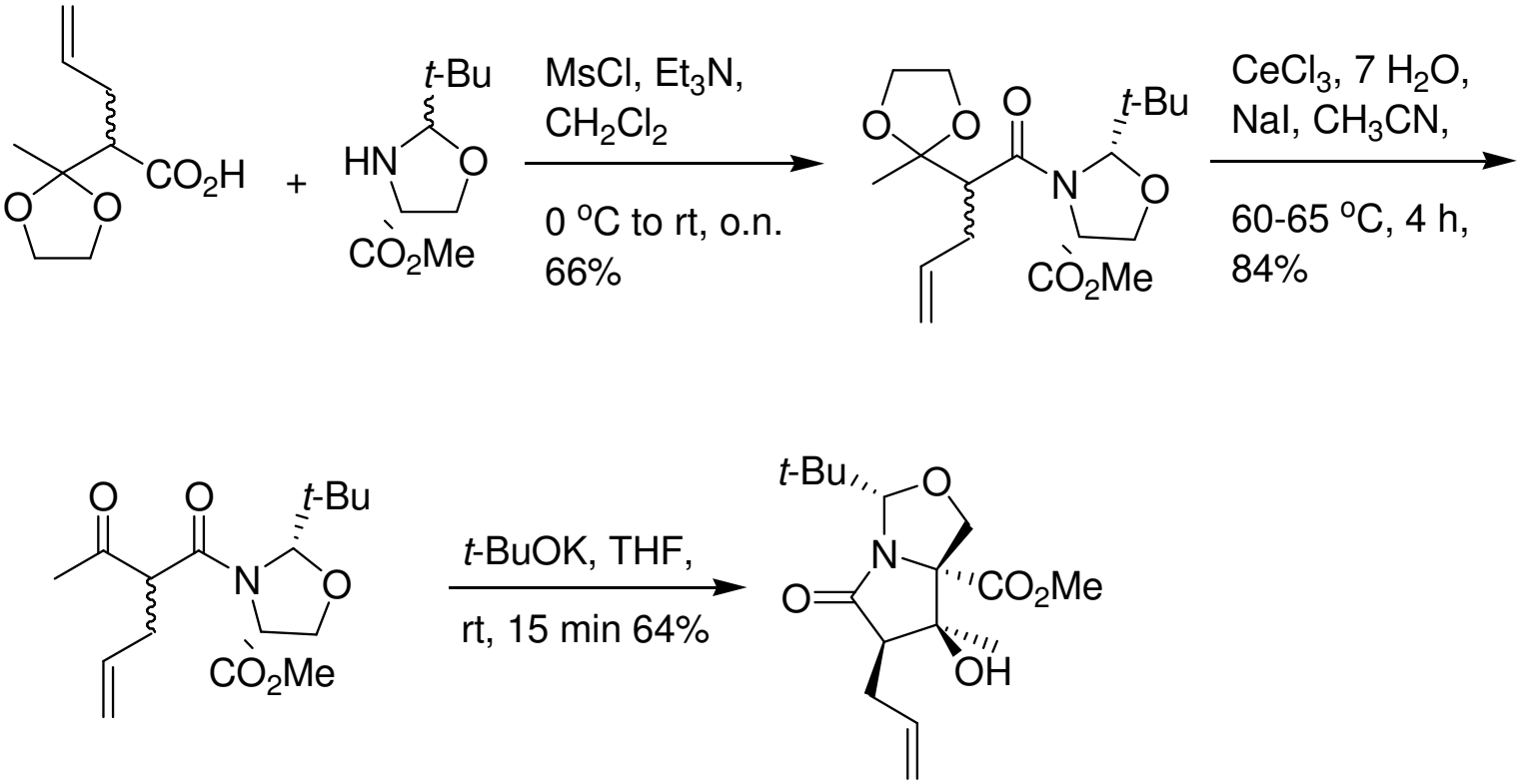
  (Seebach, *Tet.Lett*, **1984**, *25*, 2545)



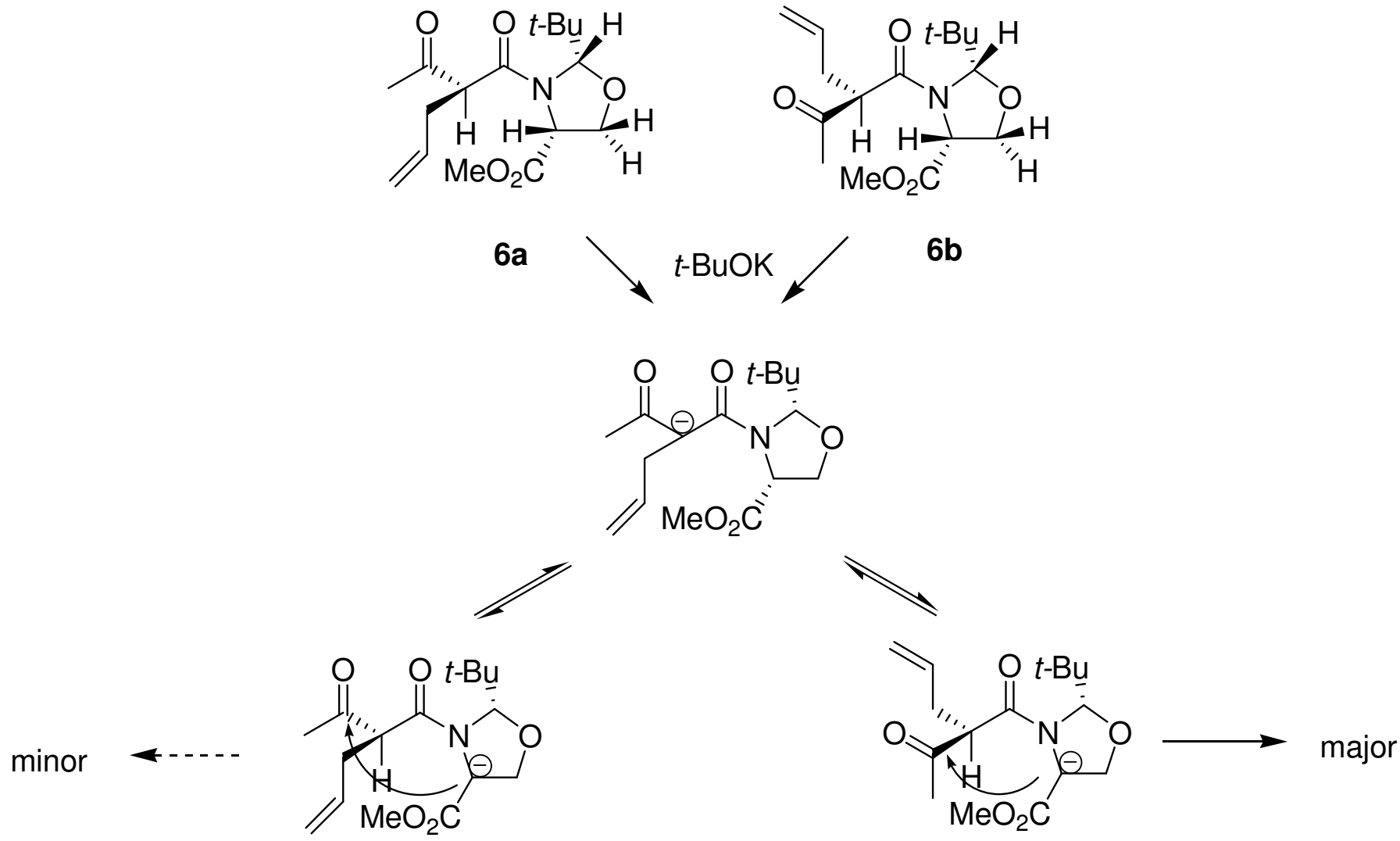
- Acid synthesis



Synthesis

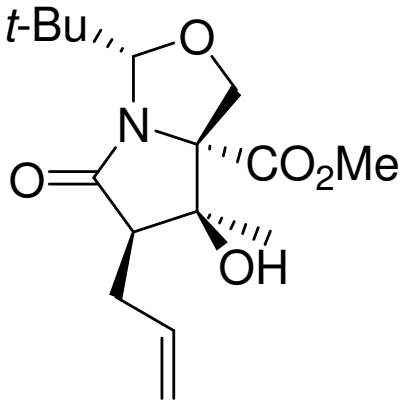

CO2H
+
t-Bu
HN
O
CO2Me
MsCl, Et3N,
CH2Cl2
0 °C to rt, o.n.
66%
O
O
O
t-Bu
N
O
CO2Me
CeCl3, 7 H2O,
NaI, CH3CN,
60-65 °C, 4 h,
84%
O
O
t-Bu
N
O
CO2Me
t-BuOK, THF,
rt, 15 min 64%
t-Bu
O
N
O
CO2Me
OH

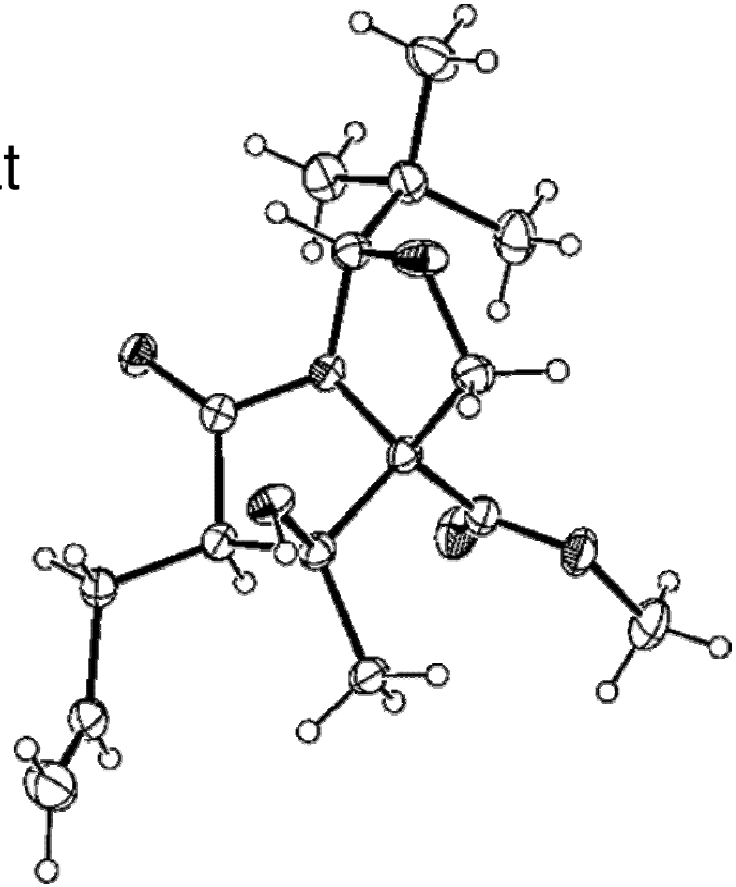
Aldol Cyclization Mechanism



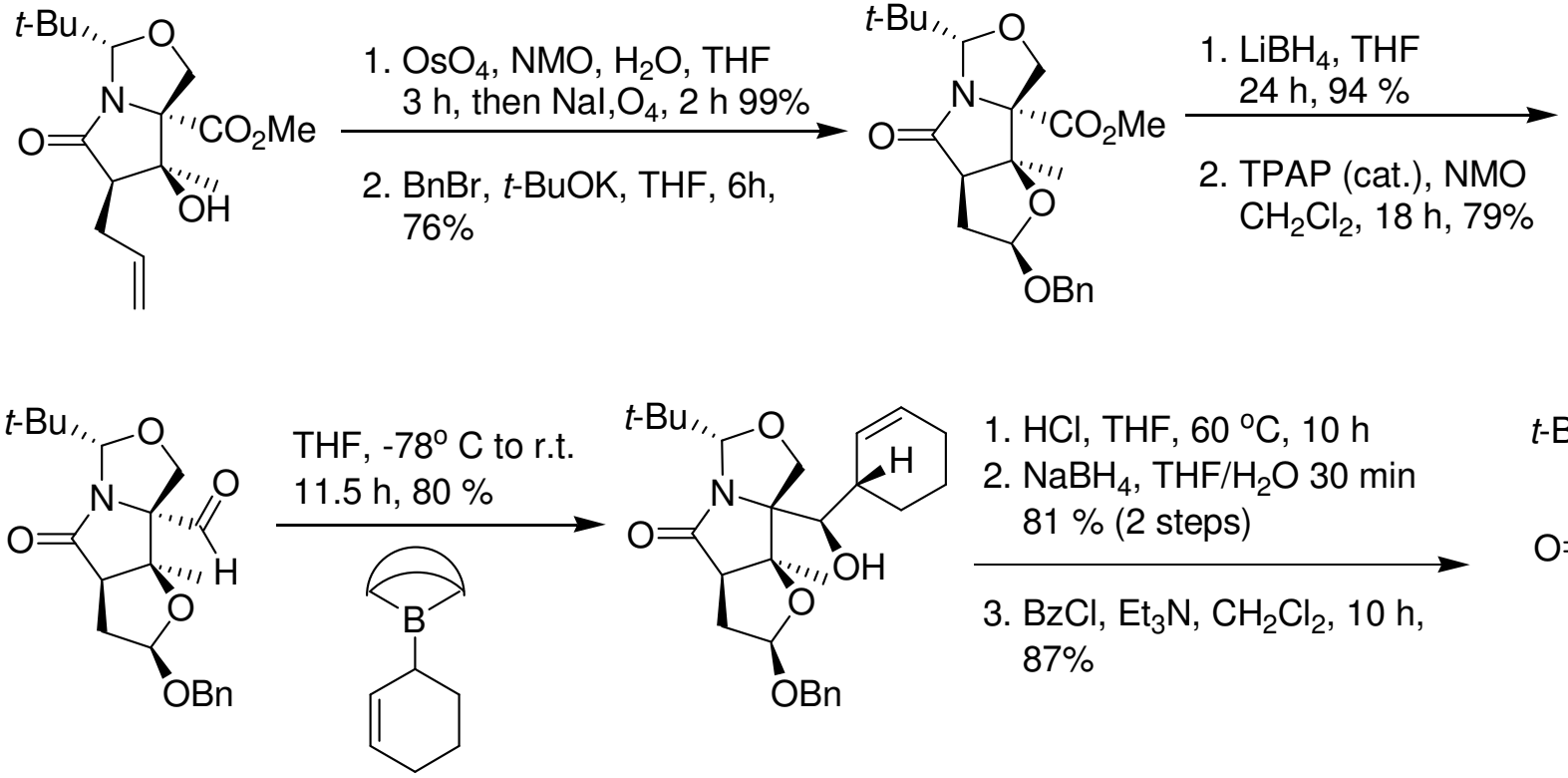
X-Ray

- X-ray of **5**
- Up to 100 g of **5** can be synthesized using this scheme
- **5** was produced with 70% de
- Purification of **6** was only step that required column chromatography

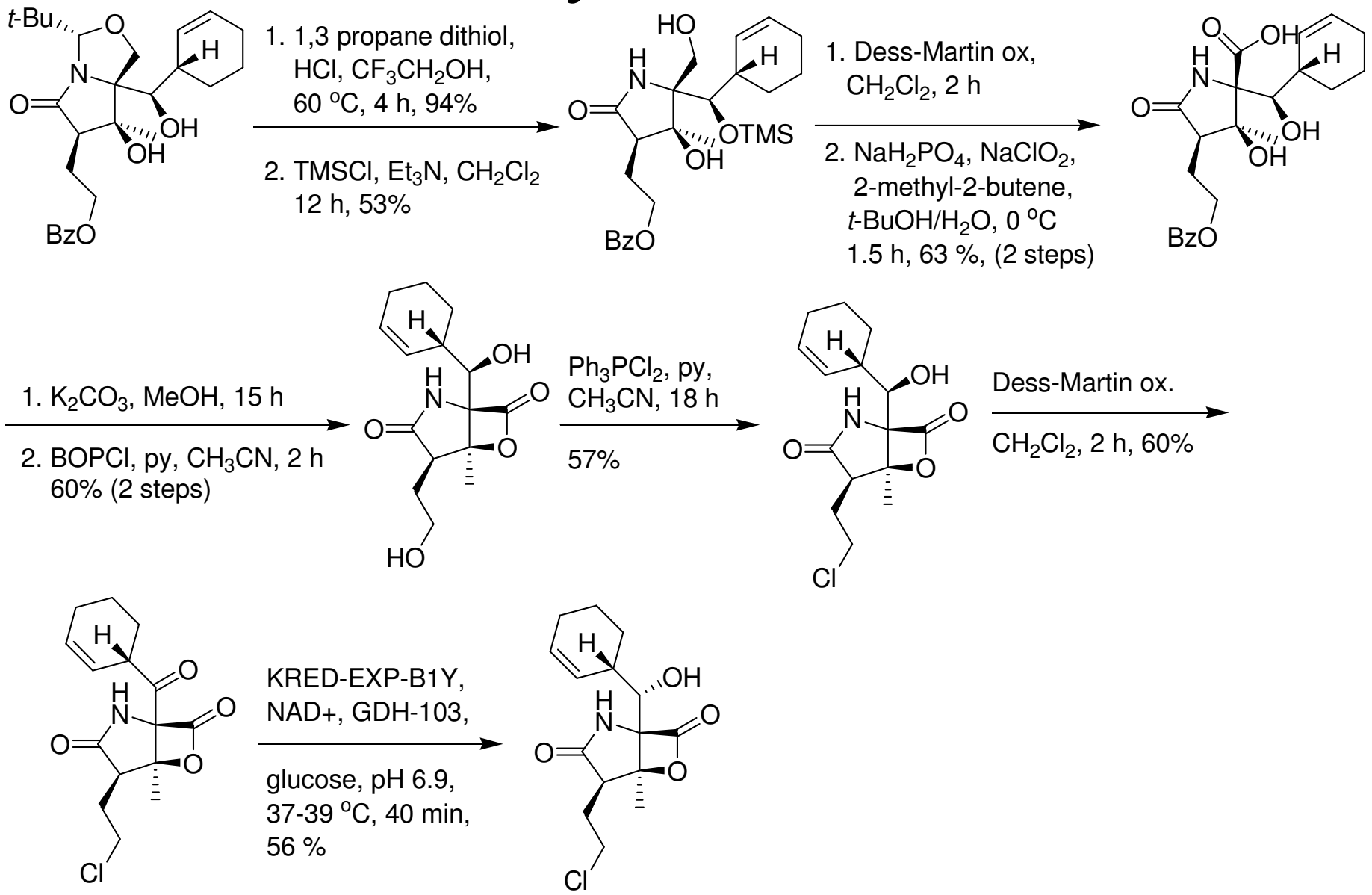




Synthesis


t-Bu
O
N
O
CO2Me
OH
1. OsO4, NMO, H2O, THF
3 h, then NaI,O4, 2 h 99%
2. BnBr, t-BuOK, THF, 6h,
76%
OBn
1. LiBH4, THF
24 h, 94 %
2. TPAP (cat.), NMO
CH2Cl2, 18 h, 79%
H
THF, -78° C to r.t.
11.5 h, 80 %
B
1. HCl, THF, 60 °C, 10 h
2. NaBH4, THF/H2O 30 min
81 % (2 steps)
3. BzCl, Et3N, CH2Cl2, 10 h,
87%
BzO

Synthesis


t-Bu
O
N
O
H
OH
OH
BzO
1. 1,3 propane dithiol, HCl, CF_3CH_2OH, 60 °C, 4 h, 94%
2. TMSCl, Et_3N, CH_2Cl_2 12 h, 53%
HO
H
N
O
H
OTMS
OH
BzO
1. Dess-Martin ox, CH_2Cl_2, 2 h
2. NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, t-BuOH/H_2O, 0 °C 1.5 h, 63 %, (2 steps)
O
OH
H
N
O
H
OH
OH
BzO
1. K_2CO_3, MeOH, 15 h
2. BOPCl, py, CH_3CN, 2 h 60% (2 steps)
H
OH
H
N
O
O
O
HO
Ph_3PCl_2, py, CH_3CN, 18 h
57%
H
OH
H
N
O
O
O
Cl
Dess-Martin ox.
CH_2Cl_2, 2 h, 60%
H
O
H
N
O
O
O
Cl
KRED-EXP-B1Y, NAD+, GDH-103,
glucose, pH 6.9, 37-39 °C, 40 min, 56 %
H
OH
H
N
O
O
O
Cl

Conclusions

- The total Synthesis of (-)-Salinosporamide A (NPI-0052) has been accomplished in a linear 20 steps and 0.4% overall yield
- Intromolecular aldol proceed through regeneration of stereocenters
- A single chromatography step is needed for purification of aldol precursor
- Amenable to scale-up?
  - Cheap starting materials (pro)
  - Single chromatography (pro)
  - # of linear /yield (con)
  - Dess-Martin Ox (con)
  - Osmium (con)