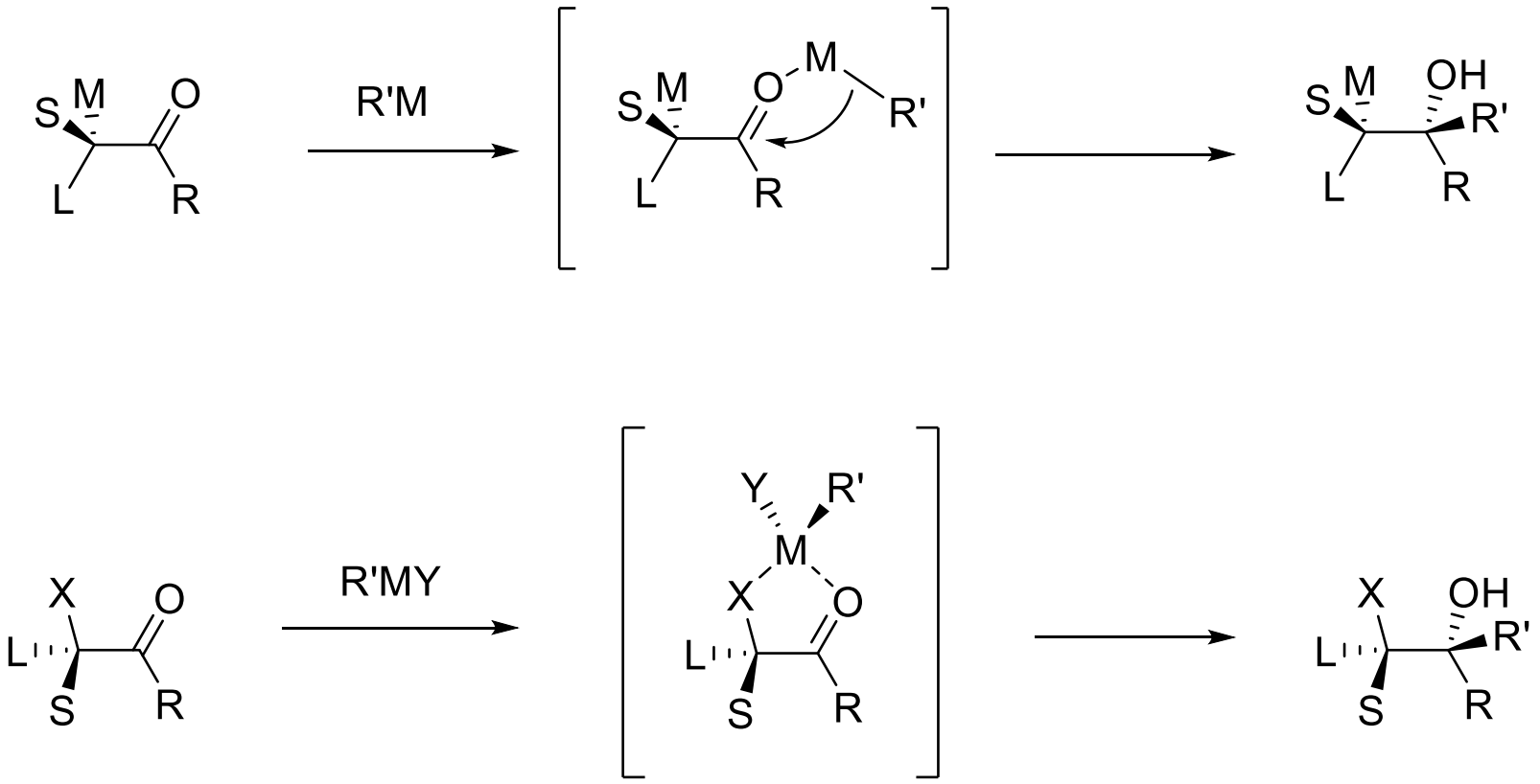
Monensin
W. C. Still, 1980

Katarina Keel

Monensin: Background

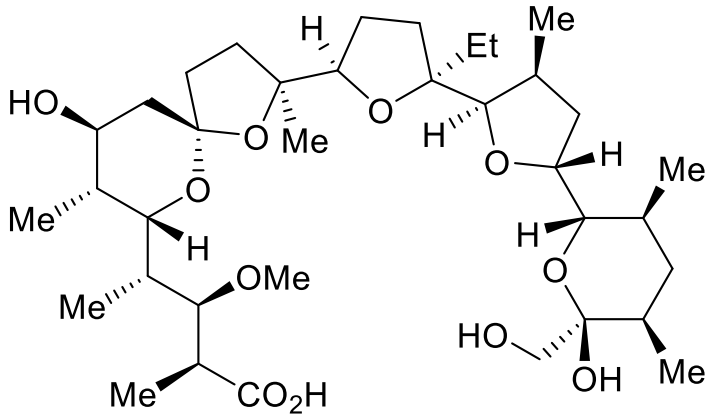
- First isolated in 1967 by Agtarap *et al.* from *Streptomyces cinnamonensis*
- Used as an antibiotic in animal feeds to prevent Coccidiosis, an intestinal tract parasitic disease
- First synthesized by Kishi et al. in 1979
- Constructed of 17 asymmetric centers, 5 rings and has the ability to complex with metals

Chelation-Controlled Addition

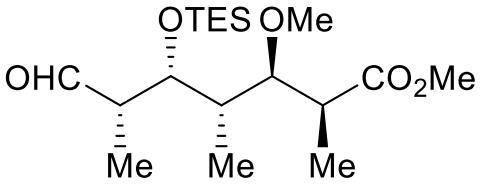


Nicolaou, K. C., & Sorensen, E. J. (1996). Monensin W. C. Still (1980). In *Classics in Total Synthesis*(pp. 227-248). Wiley.

Retrosynthetic Analysis



1: Monensin



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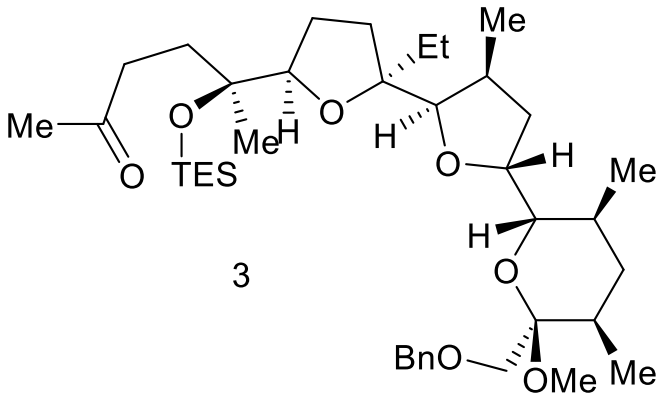

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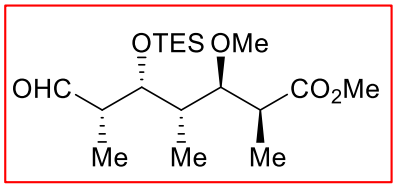
Retrosynthesis Analysis



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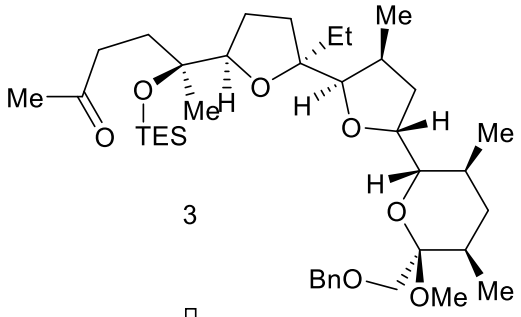

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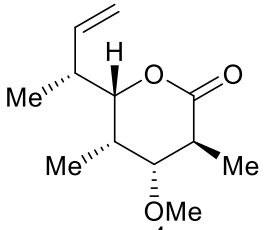

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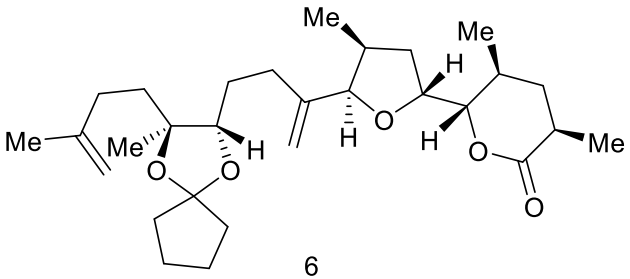

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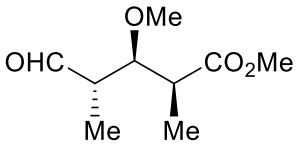

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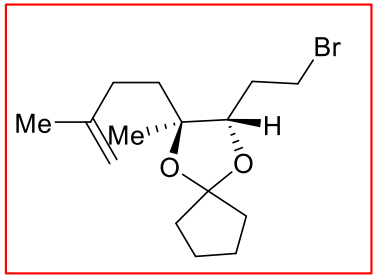

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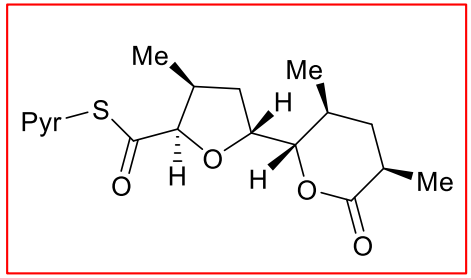
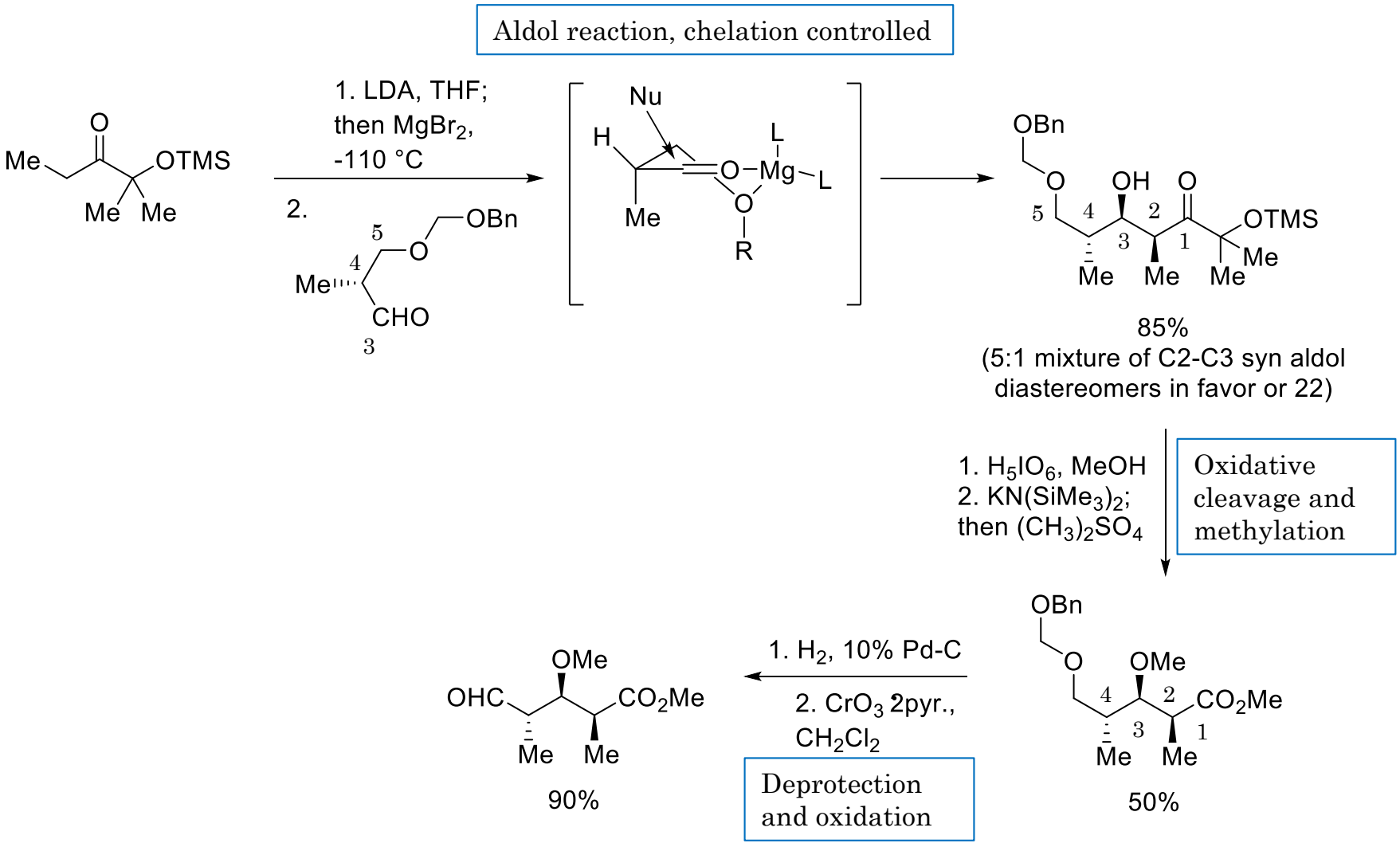
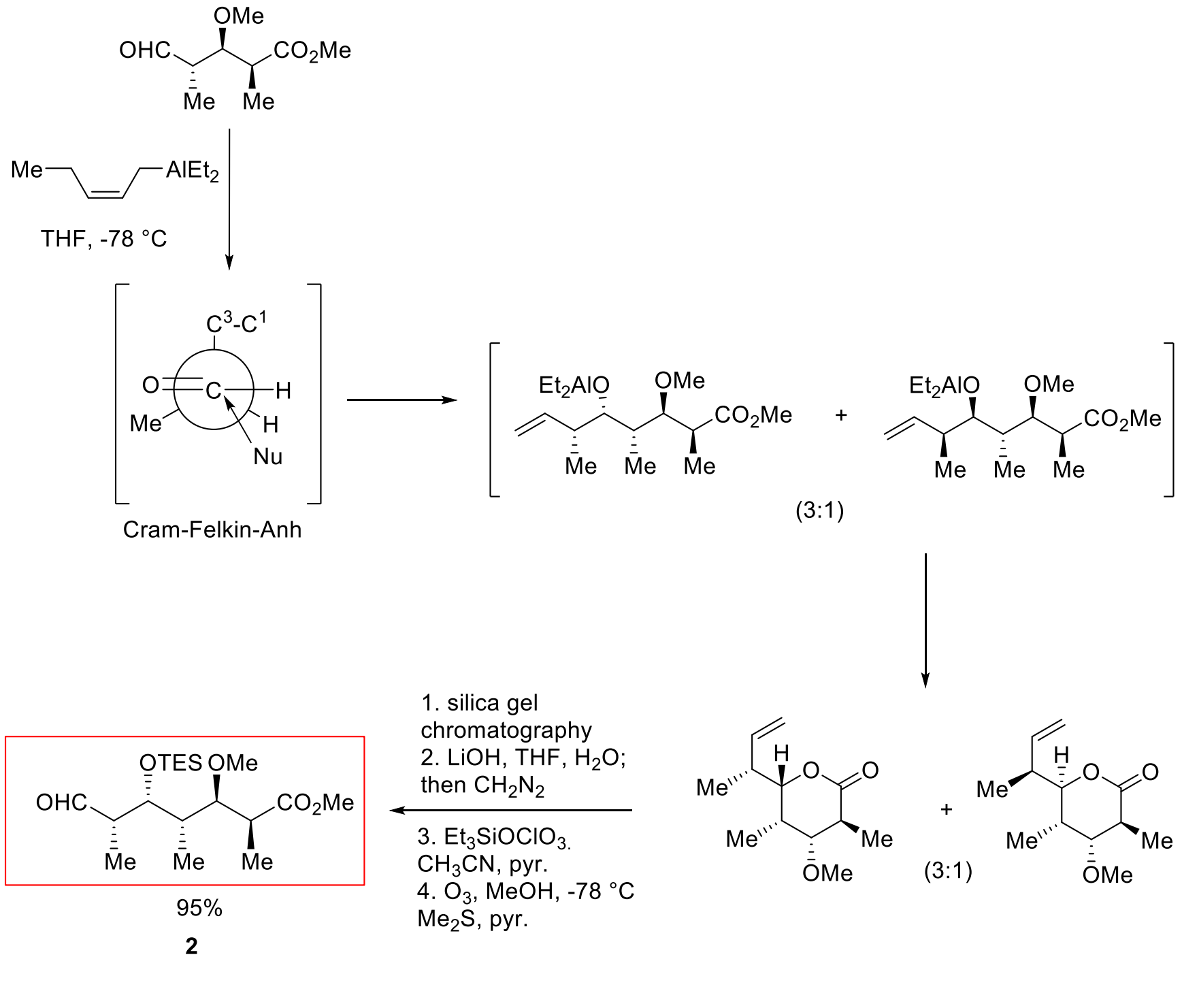
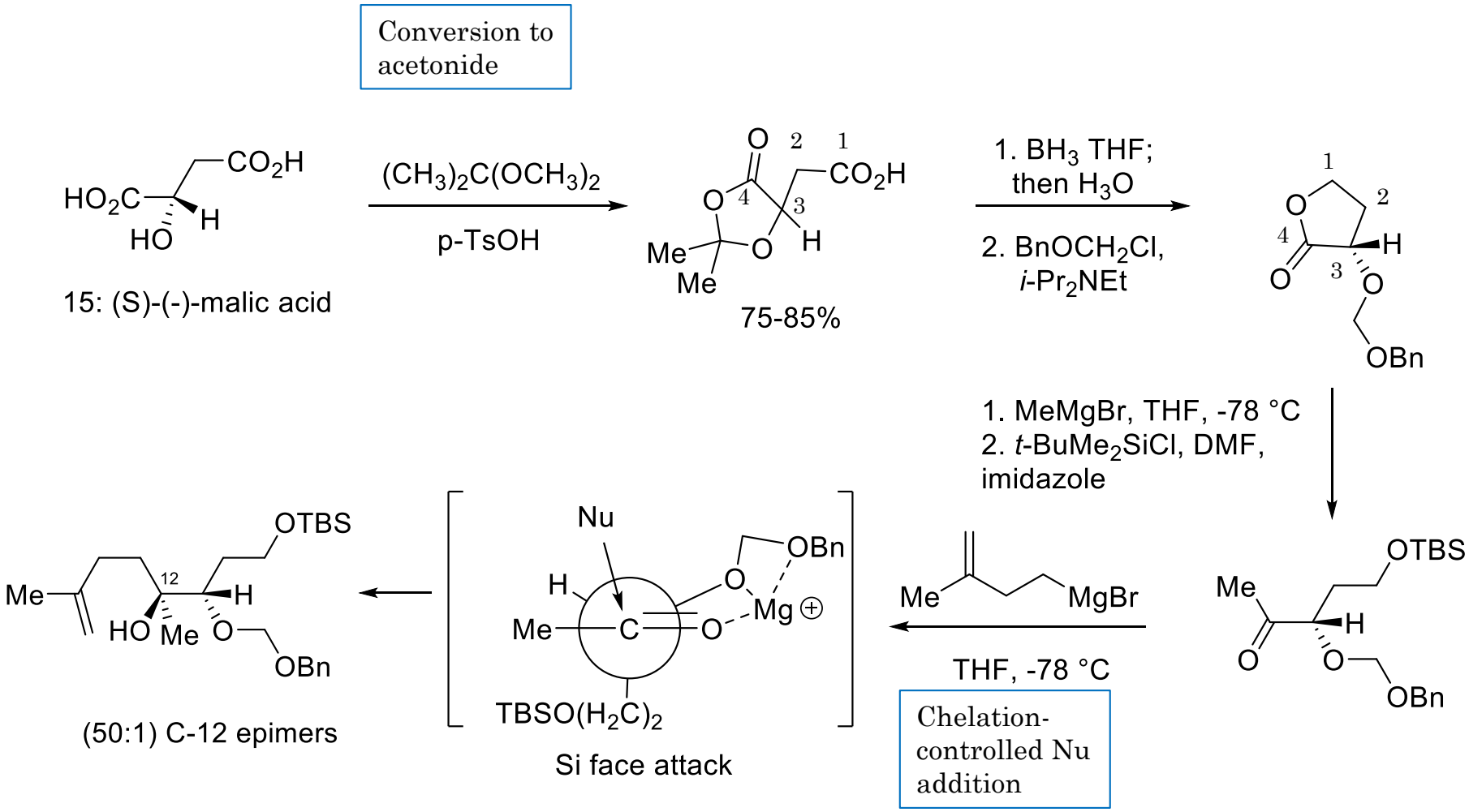


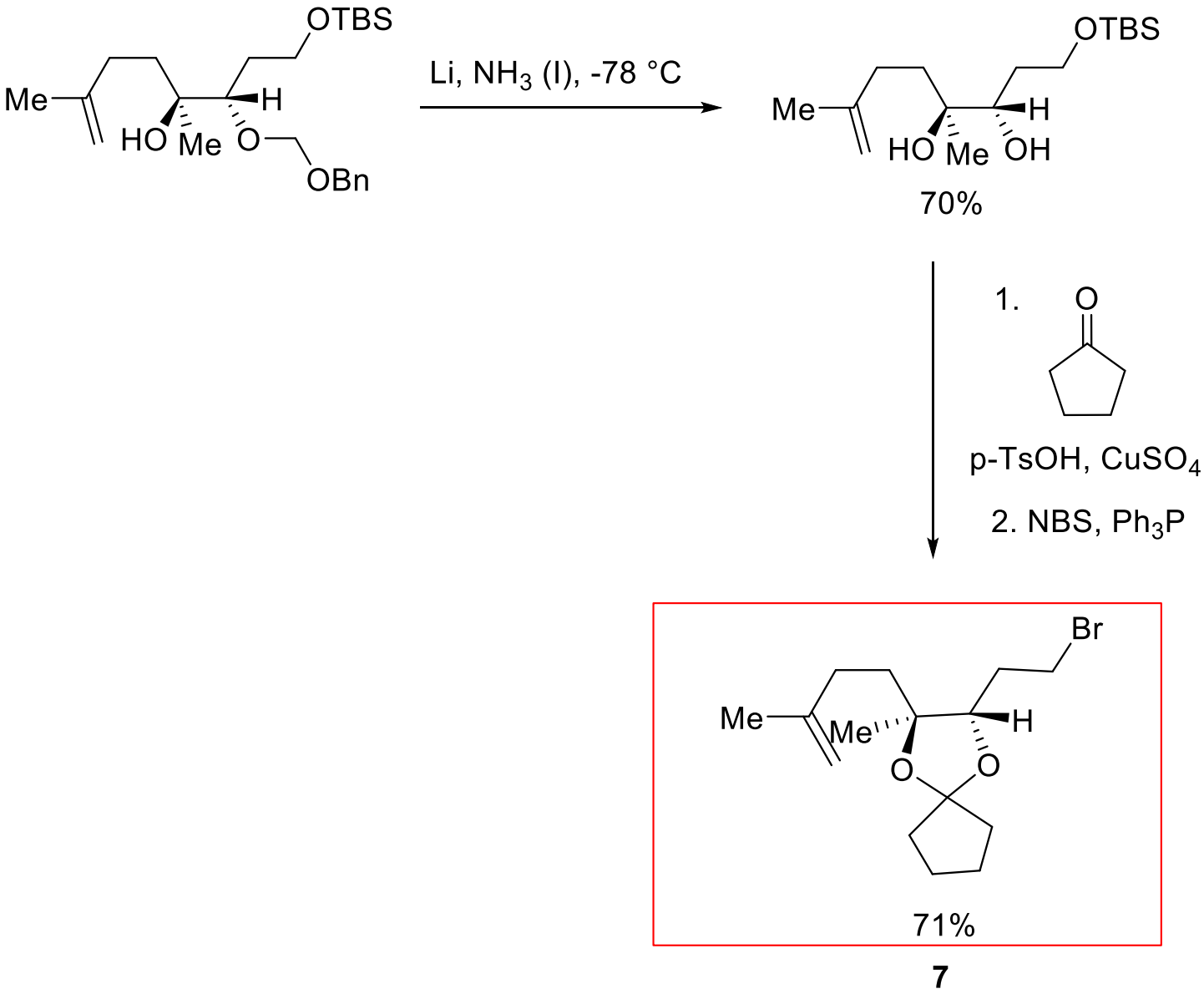
8

Forward Synthesis

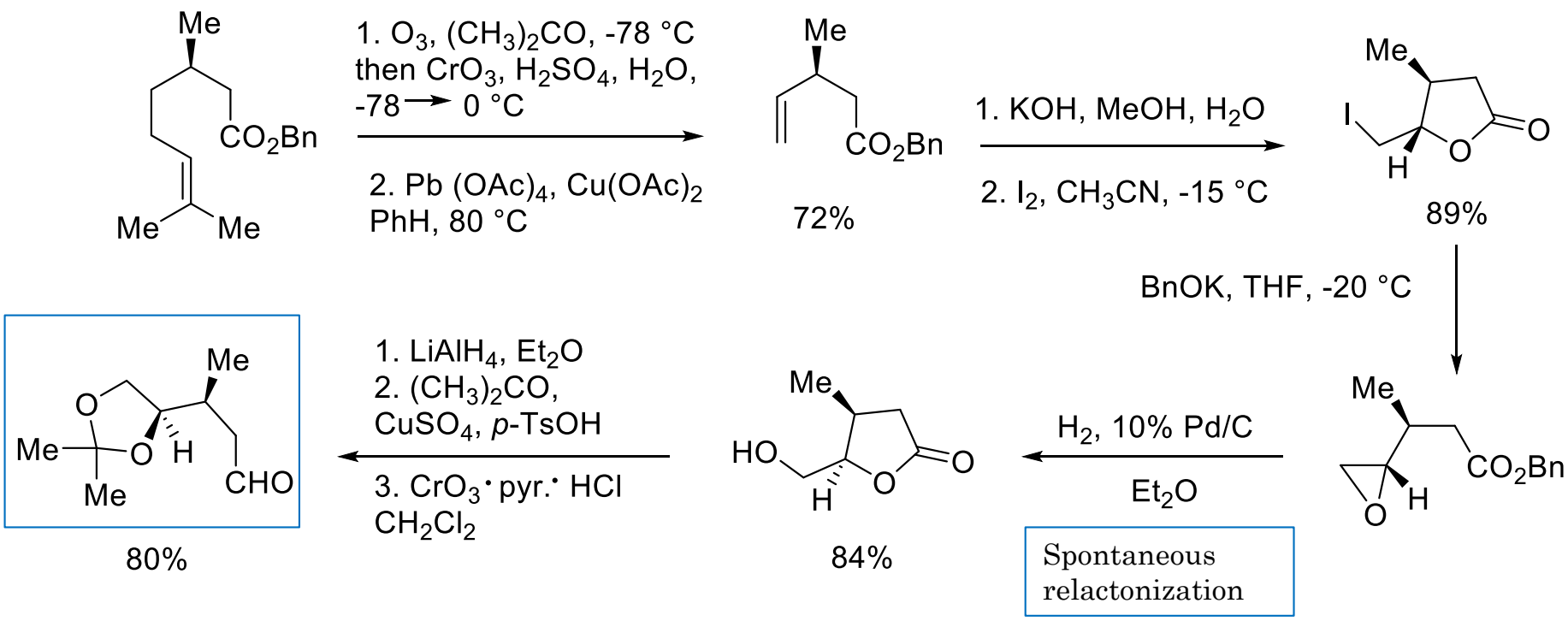


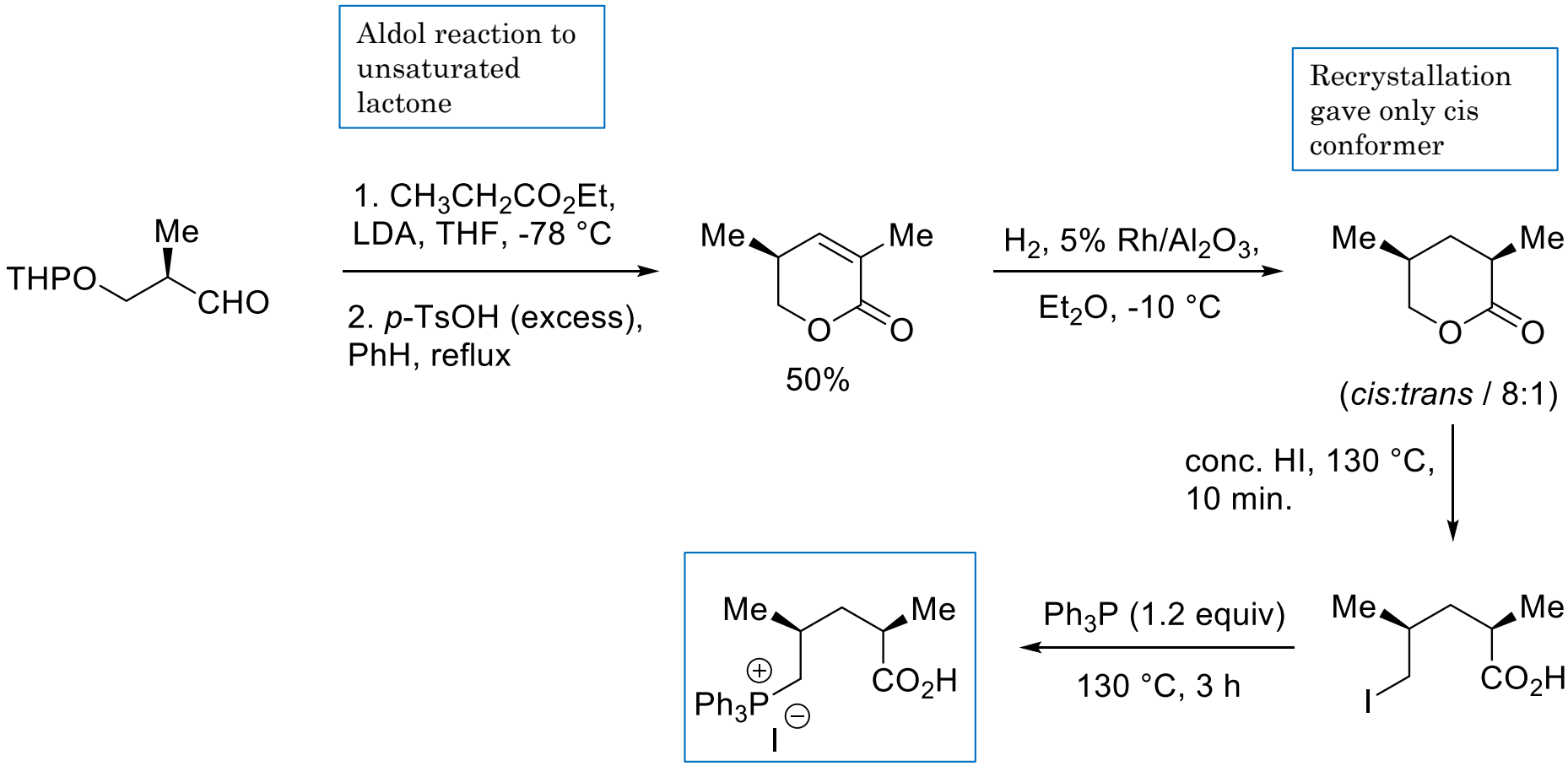

OMe
OHC
CO2Me
Me
Me
Me
AlEt2
THF, -78 °C
C3-C1
O
C
H
Me
H
Nu
Cram-Felkin-Anh
Et2AlO
OMe
CO2Me
Me
Me
Me
+
Et2AlO
OMe
CO2Me
Me
Me
Me
(3:1)
H
O
O
Me
Me
Me
OMe
+
(3:1)
H
O
O
Me
Me
Me
OMe
1. silica gel chromatography
2. LiOH, THF, H2O; then CH2N2
3. Et3SiOClO3. CH3CN, pyr.
4. O3, MeOH, -78 °C
Me2S, pyr.
OTES OMe
OHC
CO2Me
Me
Me
Me
95%
2


Conversion to acetonide
CO_2H
HO_2C
H
HO
15: (S)-(-)-malic acid
$(CH_3)_2C(OCH_3)_2$
p-TsOH
O 2 1
O 4 3
CO_2H
Me
Me
O
H
75-85%
1. BH_3 THF; then H_3O
2. $BnOCH_2Cl$, *i*-Pr_2NEt
1
O 2
4
H
O 3
O
OBn
1. MeMgBr, THF, -78 °C
2. *t*-$BuMe_2SiCl$, DMF, imidazole
OTBS
Me
H
O
O
OBn
Me
MgBr
THF, -78 °C
Chelation-controlled Nu addition
Nu
OBn
H
O
Me
C
O
Mg ⊕
$TBSO(H_2C)_2$
Si face attack
OTBS
Me
12
H
HO
Me
O
OBn
(50:1) C-12 epimers

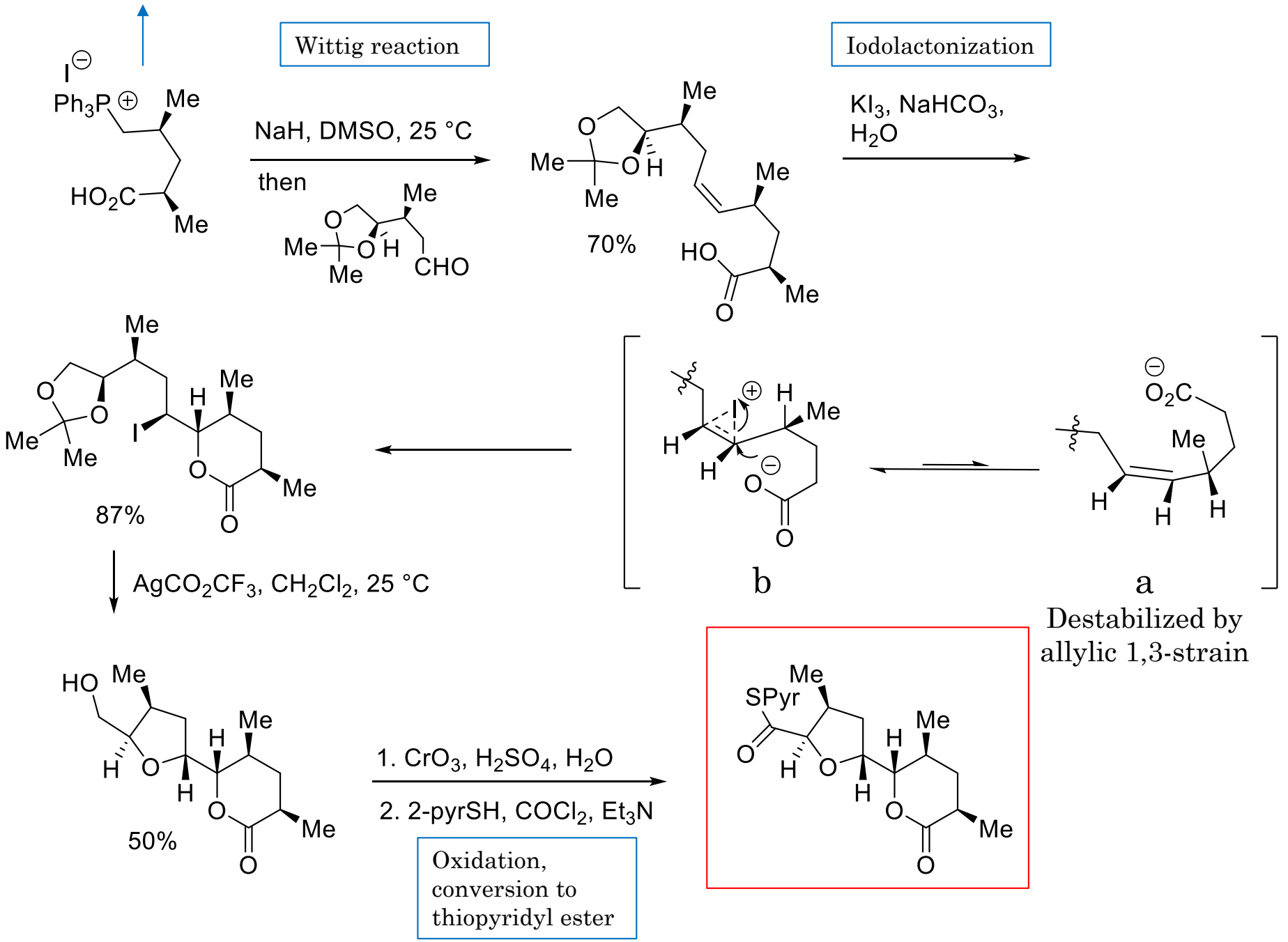

OTBS
Me
H
HO
Me
O
OBn
Li, NH3 (l), -78 °C
OTBS
Me
H
HO
Me
OH
70%
1.
O
p-TsOH, CuSO4
2. NBS, Ph3P
Br
Me
Me
H
O
O
71%

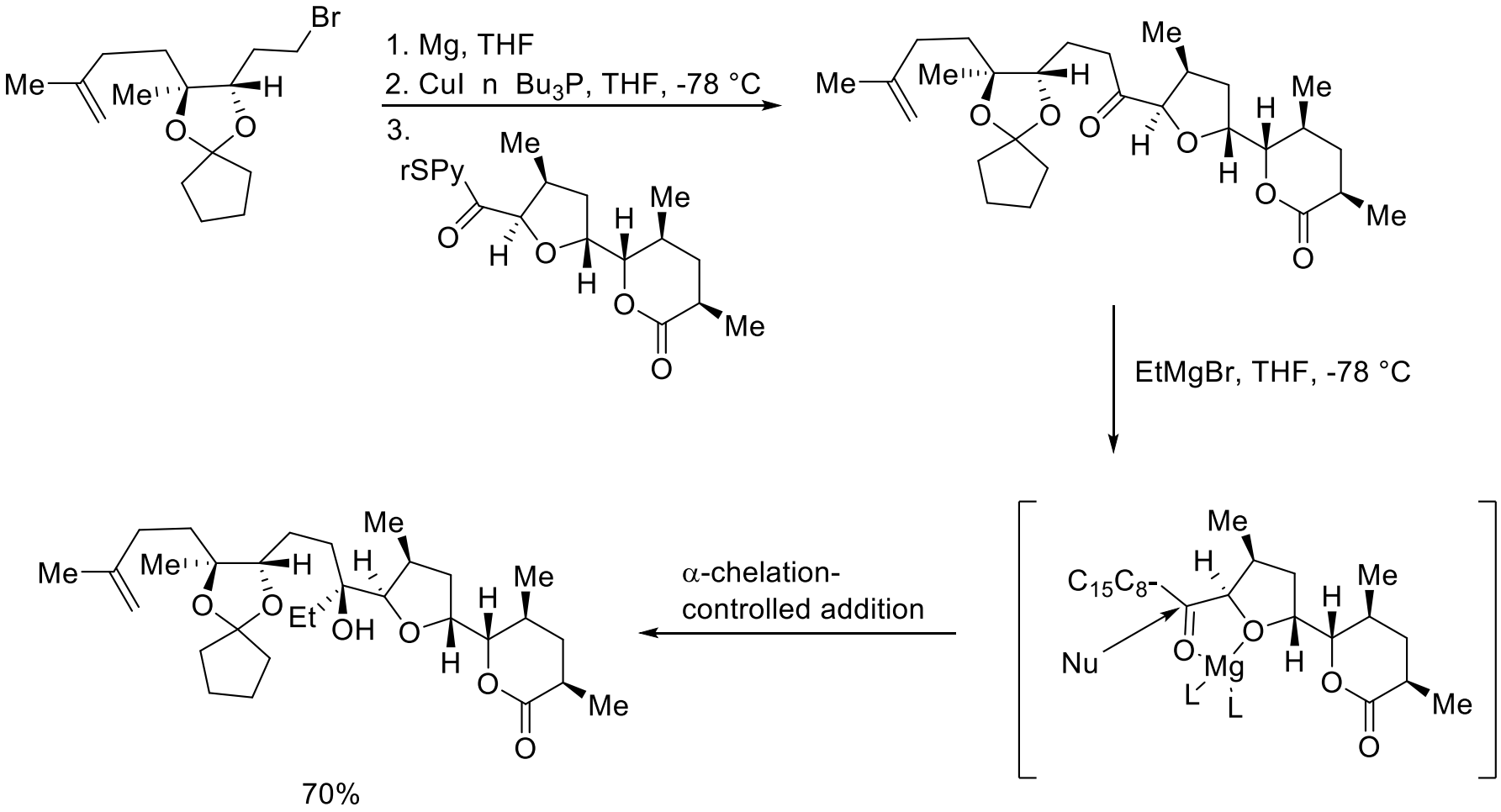
7

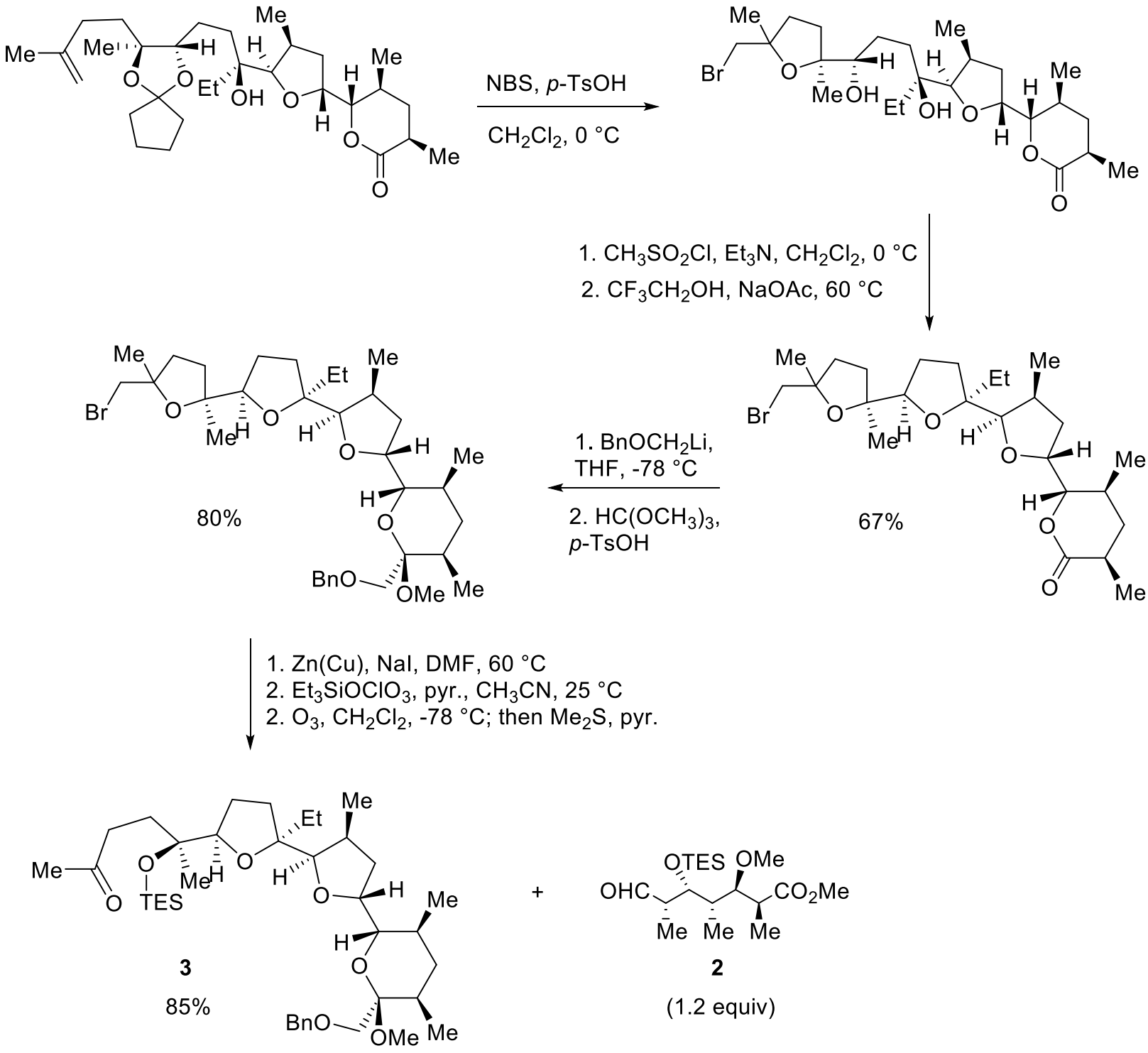

Me
CO2Bn
Me
Me
1. O3, (CH3)2CO, -78 °C
then CrO3, H2SO4, H2O,
-78 → 0 °C
2. Pb (OAc)4, Cu(OAc)2
PhH, 80 °C
Me
CO2Bn
72%
Saponification
and
lactonization
1. KOH, MeOH, H2O
2. I2, CH3CN, -15 °C
Me
I
O
H
O
89%
BnOK, THF, -20 °C
Me
CO2Bn
O
H
H2, 10% Pd/C
Et2O
Spontaneous
relactonization
Me
HO
O
H
O
84%
1. LiAlH4, Et2O
2. (CH3)2CO,
CuSO4, p-TsOH
3. CrO3 • pyr. • HCl
CH2Cl2
Me
O
Me
O
H
Me
CHO
80%

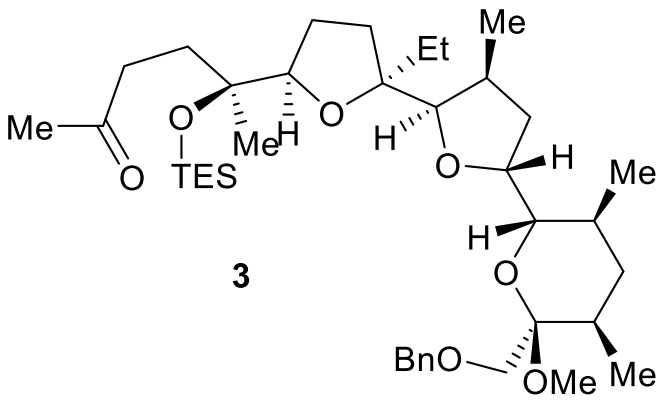

Aldol reaction to unsaturated lactone
1. $CH_3CH_2CO_2Et$, LDA, THF, -78 °C
2. *p*-TsOH (excess), PhH, reflux
50%
H_2, 5% Rh/Al_2O_3,
Et_2O, -10 °C
Recrystallation gave only cis conformer
(*cis:trans* / 8:1)
conc. HI, 130 °C, 10 min.
Ph_3P (1.2 equiv)
130 °C, 3 h

Note: this reaction reported 1.5 equiv of the dianion phosphonium species, which requires more than 1 equiv of NaH. The actual equiv of NaH was not reported.



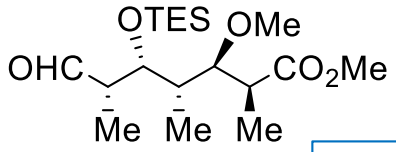

Br
Me
Me
H
O
O
1. Mg, THF
2. CuI n Bu3P, THF, -78 °C
3.
rSPy
Me
Me
H
O
H
O
H
O
Me
O
Me
Me
Me
H
O
O
O
H
O
H
H
O
Me
O
Me
EtMgBr, THF, -78 °C
C15C8-
Me
H
Nu
O
Mg
L
L
O
H
H
O
Me
O
α-chelation-
controlled addition
Me
Me
H
O
O
Et
OH
H
O
H
Me
O
Me
O
70%


NBS, p-TsOH
CH2Cl2, 0 °C
1. CH3SO2Cl, Et3N, CH2Cl2, 0 °C
2. CF3CH2OH, NaOAc, 60 °C
67%
1. BnOCH2Li, THF, -78 °C
2. HC(OCH3)3, p-TsOH
80%
1. Zn(Cu), NaI, DMF, 60 °C
2. Et3SiOClO3, pyr., CH3CN, 25 °C
2. O3, CH2Cl2, -78 °C; then Me2S, pyr.
3
85%
+
2
(1.2 equiv)



3

+

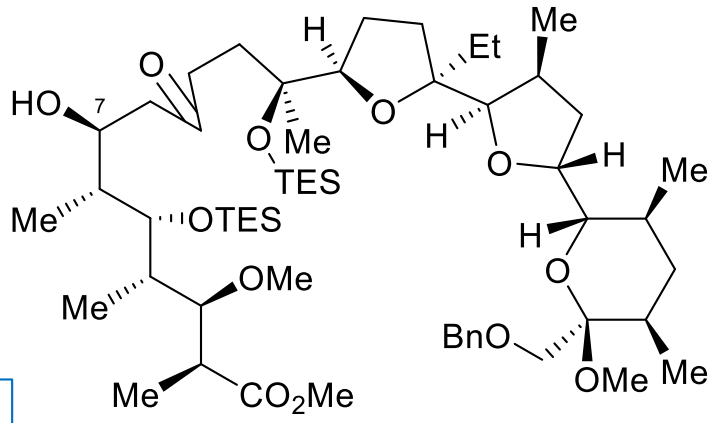


2

(1.2 equiv)

Aldol condensation, Cram product

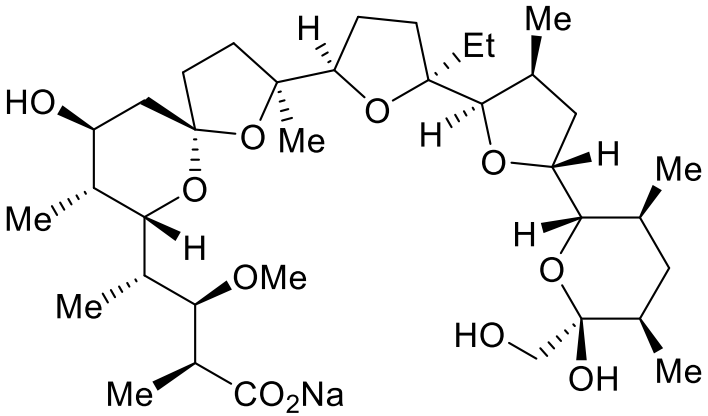
LDA, THF, -78 °C; $MgBr_2$



75%
3:1 mixture of C-7 epimers

1. H_2, 10% Pd/C, Et_2O
2. p-TsOH, CH_2Cl_2, Et_2O, H_2O
3. NaOH, H_2O, MeOH

Hydrogenolysis, spiroketalization, and saponification



Summary

- Highly convergent synthesis
- Linear Steps: 31 steps
- Total Steps: 56 steps
- Overall Yield: 0.26%

Still, W.C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, *21*, 1031.
Still, W.C.; McDonald, J.H.; Schneider, J.A. *ibid.* **1980**, *21*, 1035.
Nicolaou, K. C., & Sorensen, E. J. (1996). Monensin W. C. Still (1980). In *Classics in Total Synthesis*(pp. 227-248). Wiley.