Massachusetts Institute of Technology
Organic Chemistry 5.512

March 1st, 2005
Wesley Austin

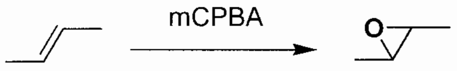
Problem Set 1 Solutions
Review of Stereochemical Principles

1. Define "stereogenic center". What is the difference between a chiral center and a stereogenic center?

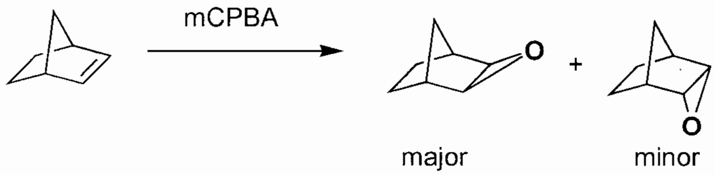
A stereogenic center is an element where the interchange of two substituents will lead to a stereoisomer. A chiral center is a specific type of stereogenic center where reflection of the molecule results in a non-superimposable mirror image of that center.

2. Define the terms "stereoselective reaction" and "sterospecific reaction" and give an example of each.

A "stereoselective reaction" results in the preferential formation of one stereoisomer over the other possible stereoisomers. A reaction is stereospecific if the starting materials are converted specifically to distinct stereoisomers depending on the starting configuration.



Stereospecific reaction--
only trans product observed



Stereoselective reaction--
the exo epoxide is prefered

3. Define the terms "diastereotopic face" and "enantiotopic face" and give an example of each.

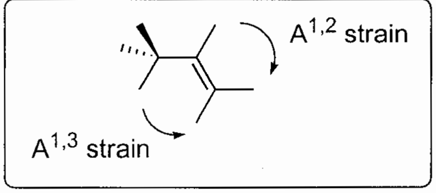
If addition of a ligand to either face of a double bond will result in a pair of diastereomers, the faces are diastereotopic. If addition of a ligand to either face of a double bond will result in a pair of enantiomers, the faces are enantieotopic.

4. Why is the following title nonsensical? "A Chiral Total Synthesis of Strychnine"

Chiral is an adjective meaning "not superimposable with its mirror image"; as such it can only be applied to physical objects.

5. Define "allylic strain". Give an example of a molecule with $A^{1,2}$ strain and one with $A^{1,3}$ strain.

Allylic strain is the comparatively increased repulsive non-bonded interactions between medium or large groups held near to each other by the presence of sp^2 hybridized atoms.



6. Why will we discuss the products of reactions in terms of "enantiomeric purity" rather than "optical purity" in 5.512?

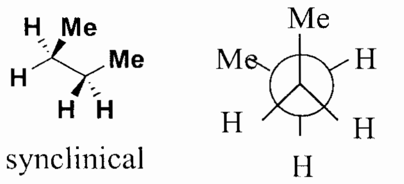
Enantiomeric purity is a measure of the ratio of the enantiomers present in a sample. Optical purity instead refers to the ratio of the optical rotation of a sample containing enantiomers to the optical rotation of a pure sample of a single enantiomer. Optical purity does not always correlate directly to the ratio of the enantiomers present in a sample. In addition, optical rotation can be difficult to measure accurately due to the presence of trace impurities with large rotations, and the optical rotation of enantiomerically pure compound is not always known precisely.

7. Define "kinetic resolution".

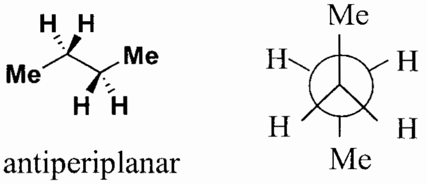
Kinetic resolution is the separation of a single enantiomer from a racemic mixture by reaction of the mixture with a sub-stoichiometric amount of chiral reagent that reacts faster with and consumes the undesired enantiomer.

8. Define "antiperiplanar"and "synclinical" and illustrate each using both Newman projections and sawhorse representations for *n*-butane.

Two groups are synclinical if they are attached to adjacent, bound atoms and the angle formed formed by the groups when viewed along the axis of the bound atoms is approximately 60 degrees. Two groups are antiperiplanar if they are attached to adjacent, bound atoms and the angle formed is approximately 180 degrees.



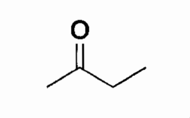
synclinical



antiperiplanar

9. Define "prochiral faces" and illustrate with an example.

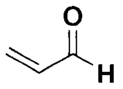
If the addition of a group to a face of a double bond in an achiral molecule would lead to a product that is chiral, that face is prochiral.



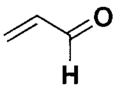
10. What is the barrier to rotation (in kcal/mol) about the carbon-carbon bond in ethane?

2.9 kcal/mol

11. Draw the *s-cis* and *s-trans* conformations of acrolein. Which is lower in energy?



s-cis



s-trans

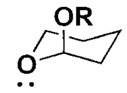
s-trans is more stable by 1.7 kcal/mol

12. Rank the following substituents in term of conformation free energies on cyclohexane rings: CH_3, OH, CN, OMe, ethynyl, *i*-Pr, CHO, Br, CO_2Et, H.

H < CN < ethynyl < OH ~ OMe ~ CHO ~ Br < CO_2Et < Me < *i*-Pr

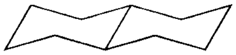
13. Define the "anomeric effect" and provide an example.

The anomeric effect is the preference for synclinical isomers in fragments of type Y-C-X-C where Y and X are heteroatoms with at least one being O, N, or F possessing a lone pair of electrons. It is generally attributed to stabilization resulting from donation of an electron density from an adjacent antiperiplanar lone pair into the σ^* orbital of a carbon-heteroatom bond.

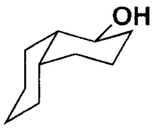


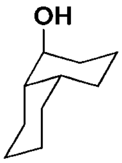
the axial position is prefered

14. Draw an artistic and accurate representation of *trans*-decalin and the two alternative conformers of *cis*-1-hydroxydecalin.

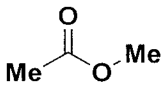


trans-decalin

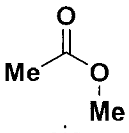




15. Draw the cis and trans conformational isomers of methyl acetate. Which is lower in energy? By how much?



trans



cis

The trans isomer is lower by 8.5 kcal/mol

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March 15, 2005
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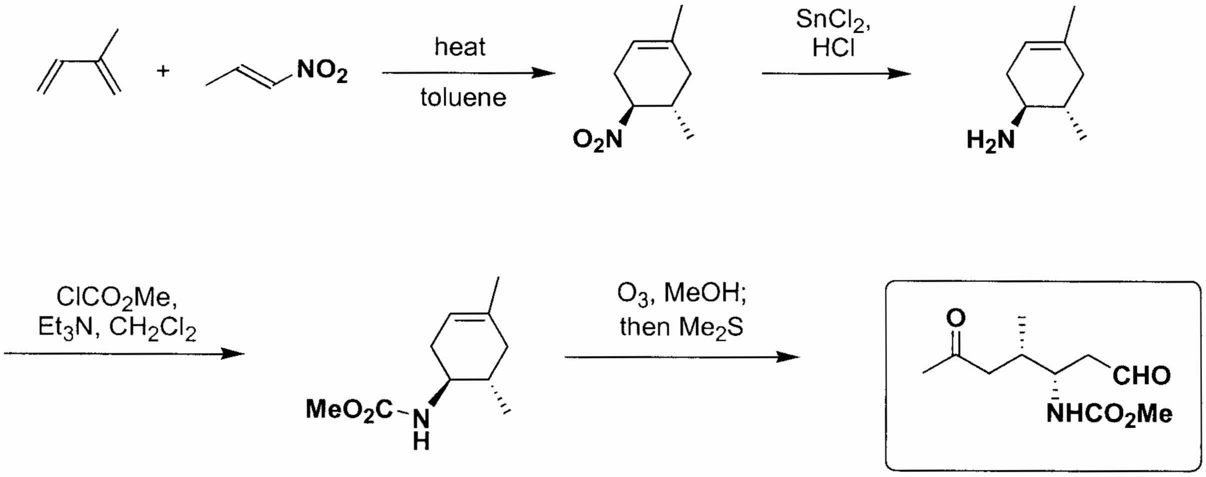
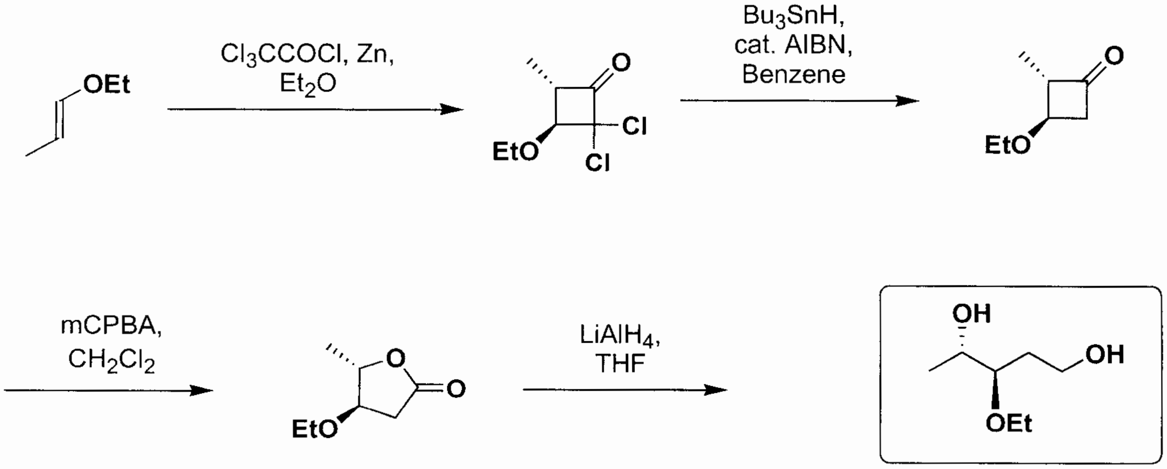
Problem Set 2 Solutions
Strategies for Synthesis of Acyclic Molecules Based on Desymmetrization, Chirality Transfer, the "Chiron Approach", and Ring Template Strategies

1.



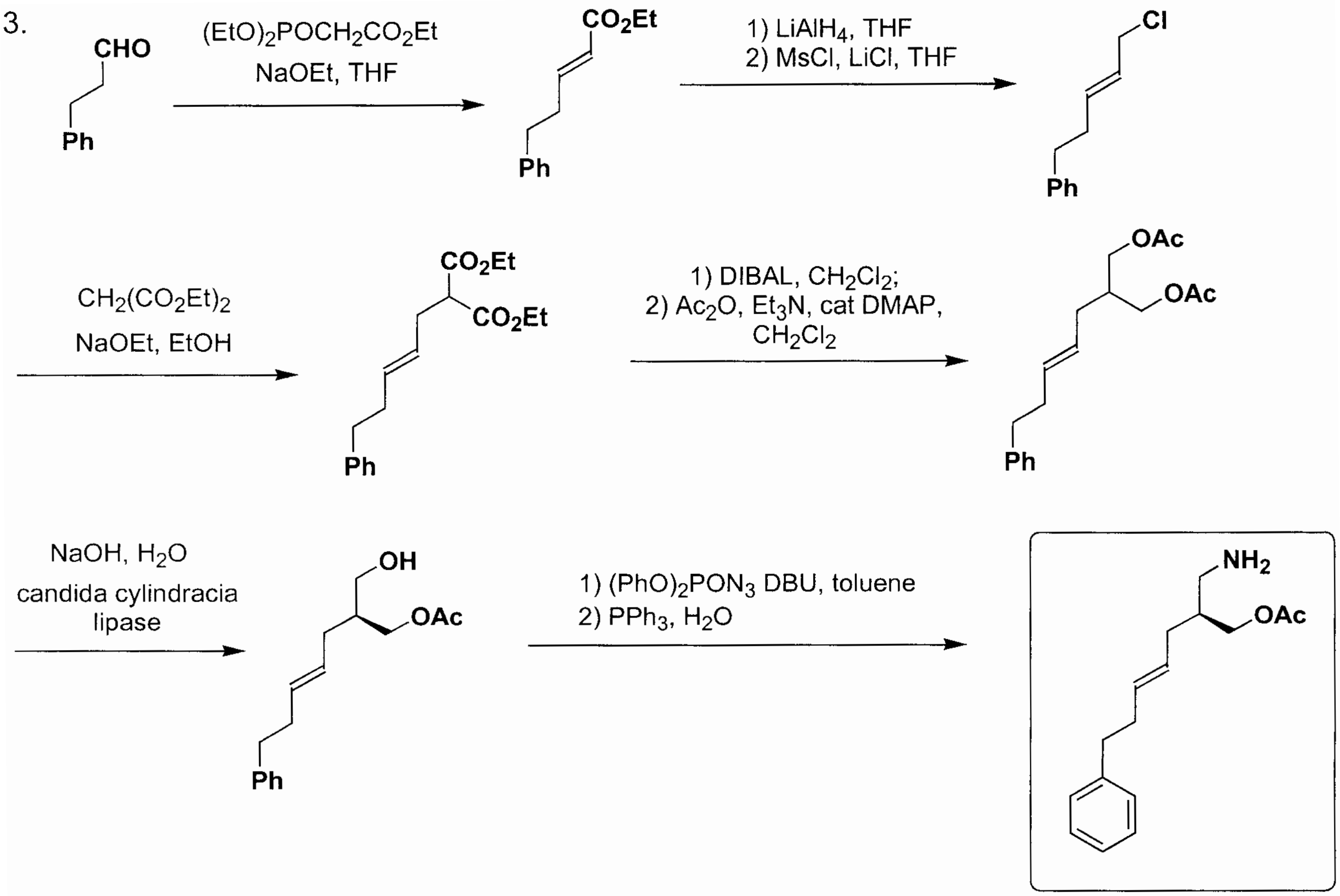
+
NO2
heat
toluene
O2N
SnCl2,
HCl
H2N
ClCO2Me,
Et3N, CH2Cl2
MeO2C
N
H
O3, MeOH;
then Me2S
O
CHO
NHCO2Me

2.

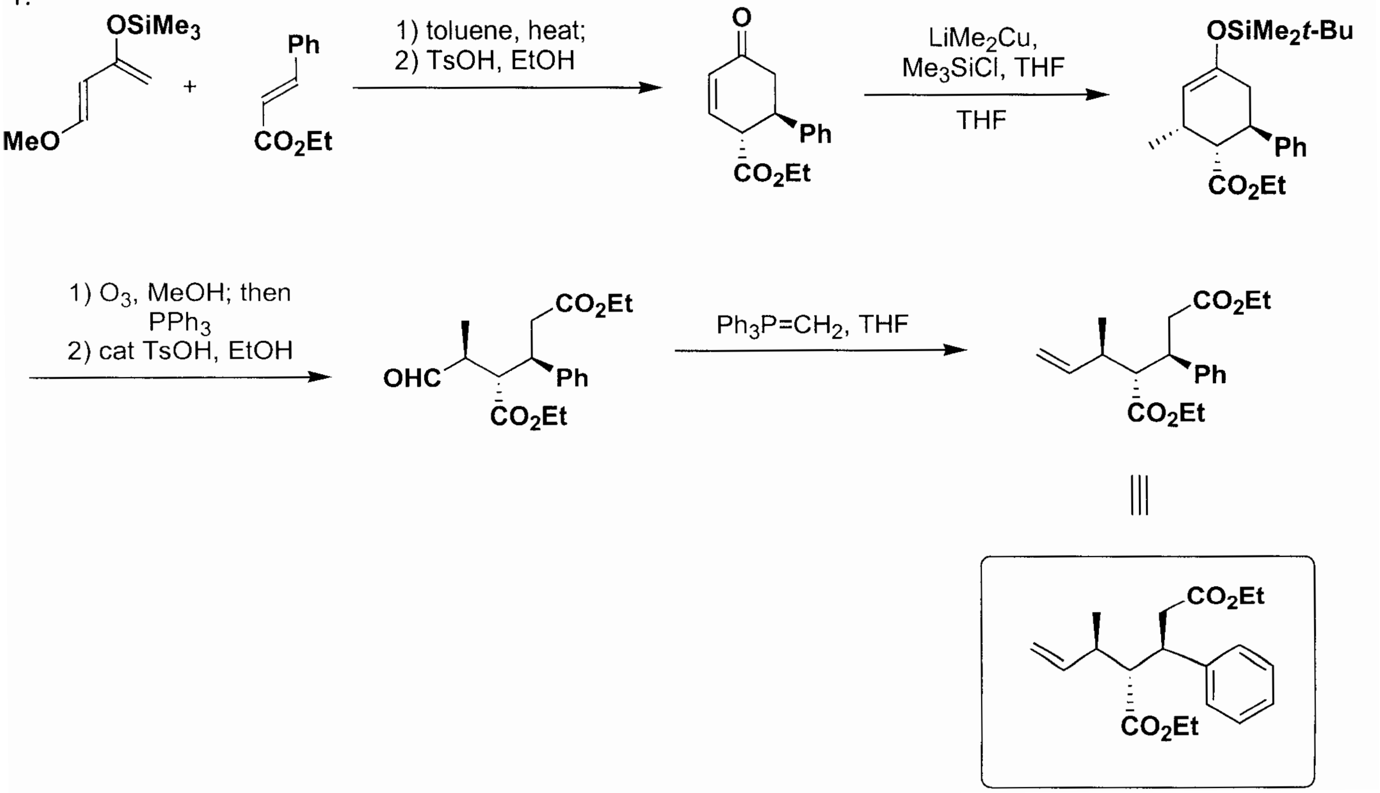


OEt
Cl3CCOCl, Zn,
Et2O
O
Cl
EtO
Cl
Bu3SnH,
cat. AIBN,
Benzene
O
EtO
mCPBA,
CH2Cl2
O
O
EtO
LiAlH4,
THF
OH
OH
OEt

3.


CHO
Ph
(EtO)2POCH2CO2Et
NaOEt, THF
CO2Et
Ph
1) LiAlH4, THF
2) MsCl, LiCl, THF
Cl
Ph
CH2(CO2Et)2
NaOEt, EtOH
CO2Et
CO2Et
Ph
1) DIBAL, CH2Cl2;
2) Ac2O, Et3N, cat DMAP, CH2Cl2
OAc
OAc
Ph
NaOH, H2O
candida cylindracia lipase
OH
OAc
Ph
1) (PhO)2PON3 DBU, toluene
2) PPh3, H2O
NH2
OAc

4.


OSiMe3
MeO
+
Ph
CO2Et
1) toluene, heat;
2) TsOH, EtOH
O
Ph
CO2Et
LiMe2Cu,
Me3SiCl, THF
THF
OSiMe2t-Bu
Ph
CO2Et
1) O3, MeOH; then PPh3
2) cat TsOH, EtOH
OHC
CO2Et
Ph
CO2Et
Ph3P=CH2, THF
CO2Et
Ph
CO2Et
|||
CO2Et
CO2Et

II. The creation of a mixture of products favoring one enantiomer over another from a racemic mixture in the absence of chiral reactants is impossible. In the case of the "asymmetric synthesis" of santonin from 2-methyl-2-formylcyclohexanone, the optical rotation is likely due to the presence of impurities in the sample.

Cornforth J. W., R. H. Cornforth, and M. J. S. Dewar. "Reported Asymmetric Synthesis of Antonin." *Nature* 153(1944): 317.

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March 30, 2005
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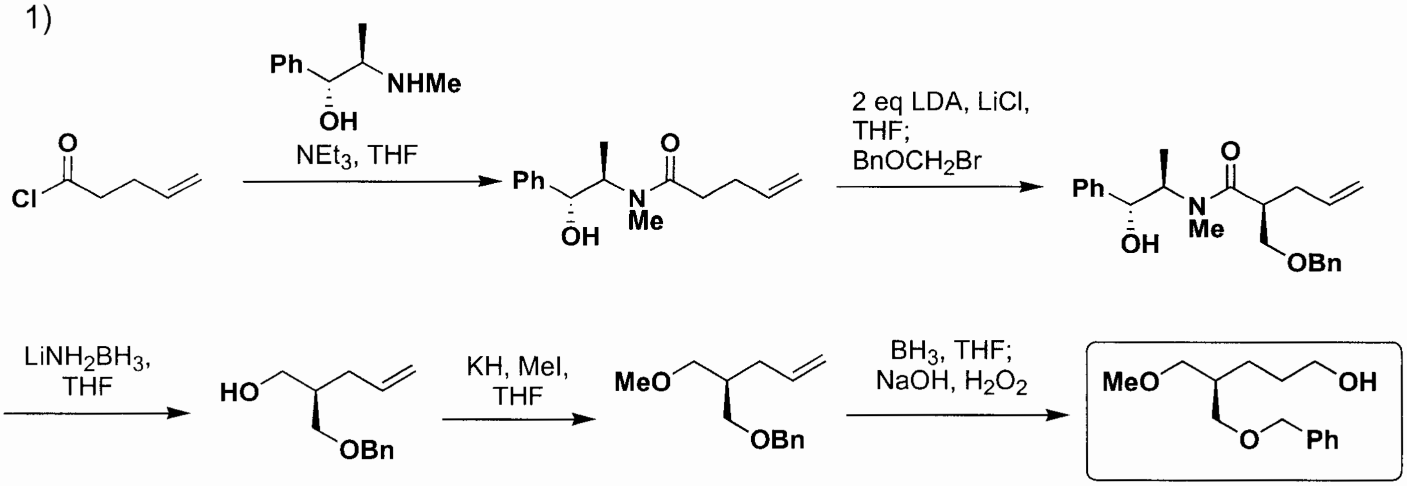
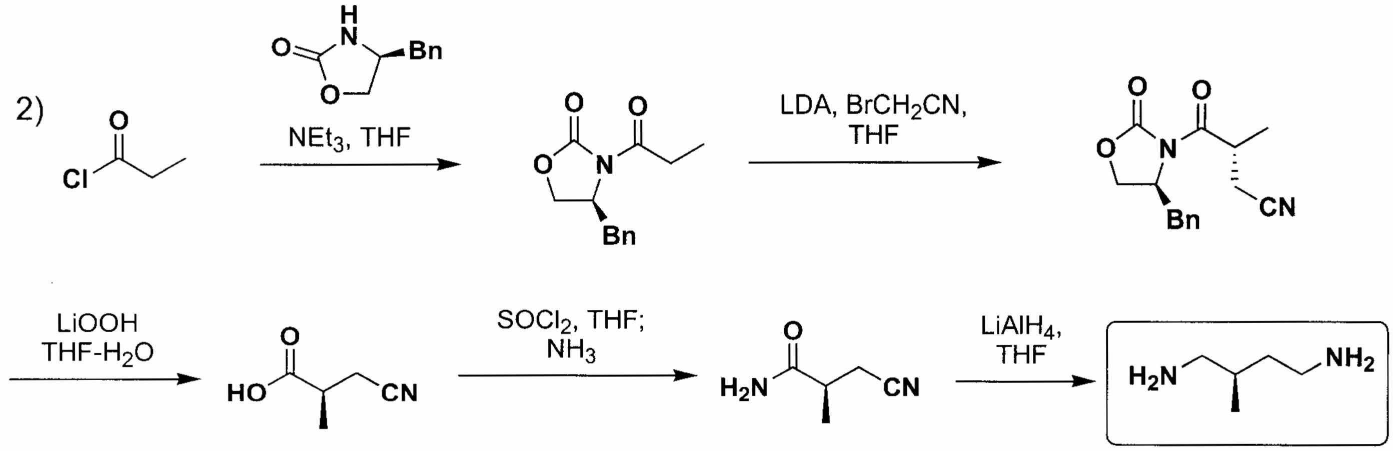
Problem Set 3 Solutions
Stereocontrolled Alkylation and Related Strategies

1)



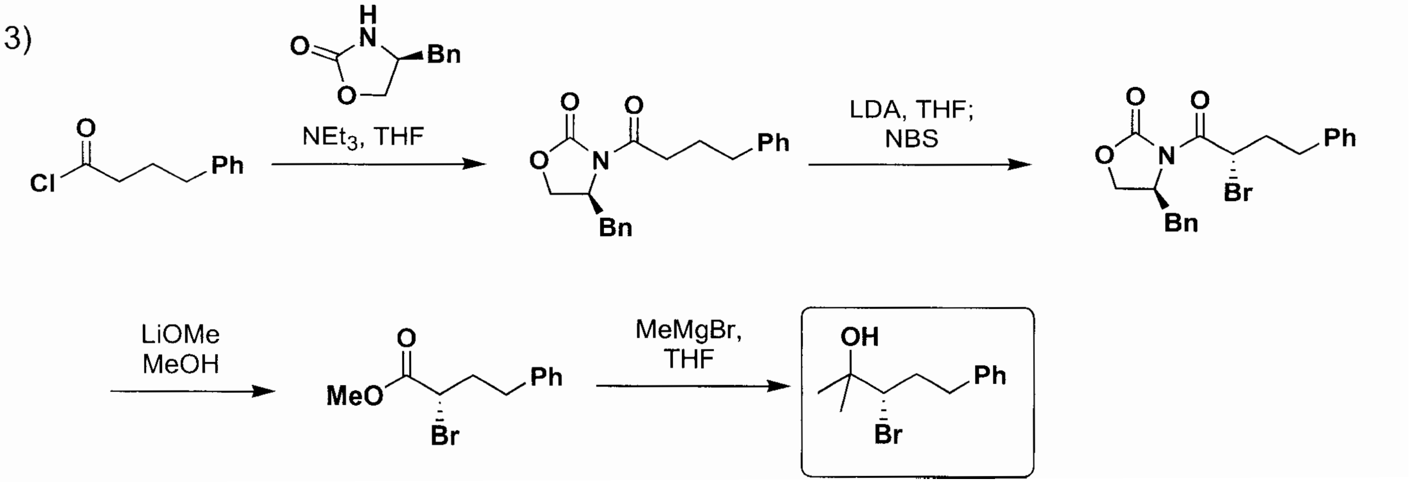
Cl
O
Ph
NHMe
OH
NEt₃, THF
N
Me
2 eq LDA, LiCl,
THF;
BnOCH₂Br
OBn
LiNH₂BH₃,
THF
HO
KH, MeI,
THF
MeO
BH₃, THF;
NaOH, H₂O₂
OH

2)



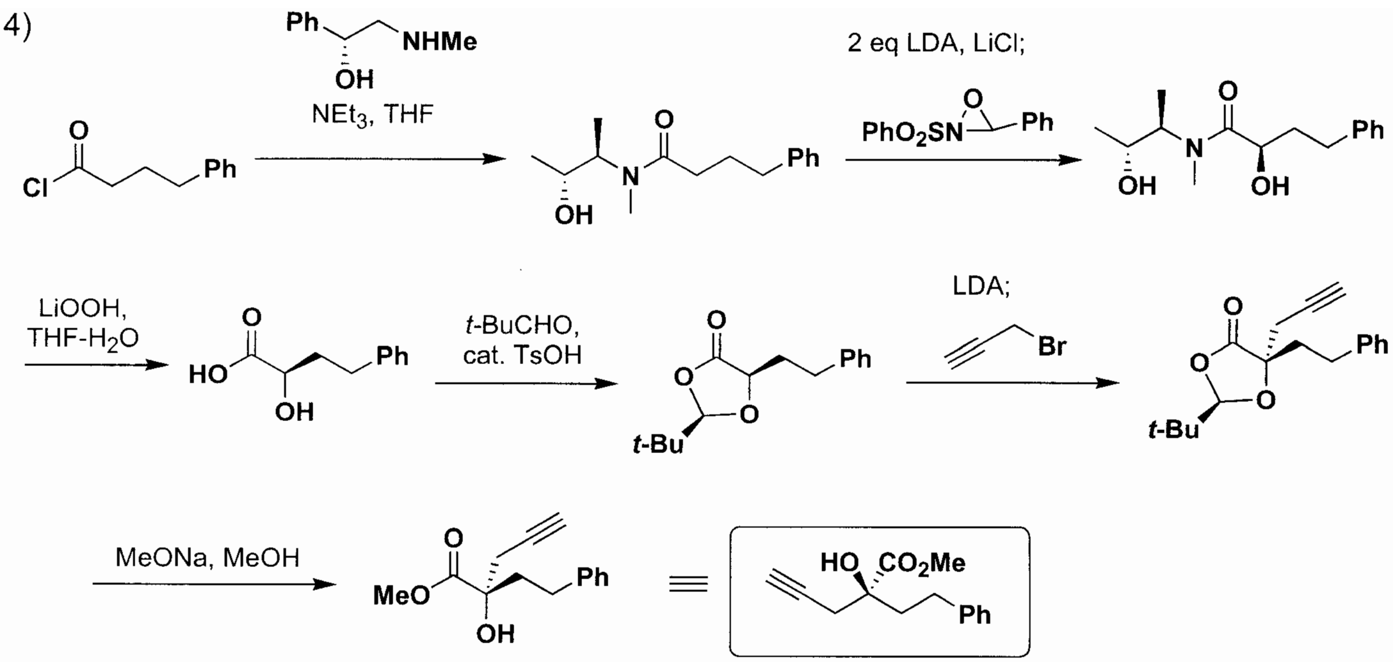
H
N
O
Bn
Cl
NEt₃, THF
LDA, BrCH₂CN,
THF
CN
LiOOH
THF-H₂O
HO
SOCl₂, THF;
NH₃
H₂N
LiAlH₄,
THF
NH₂

3)

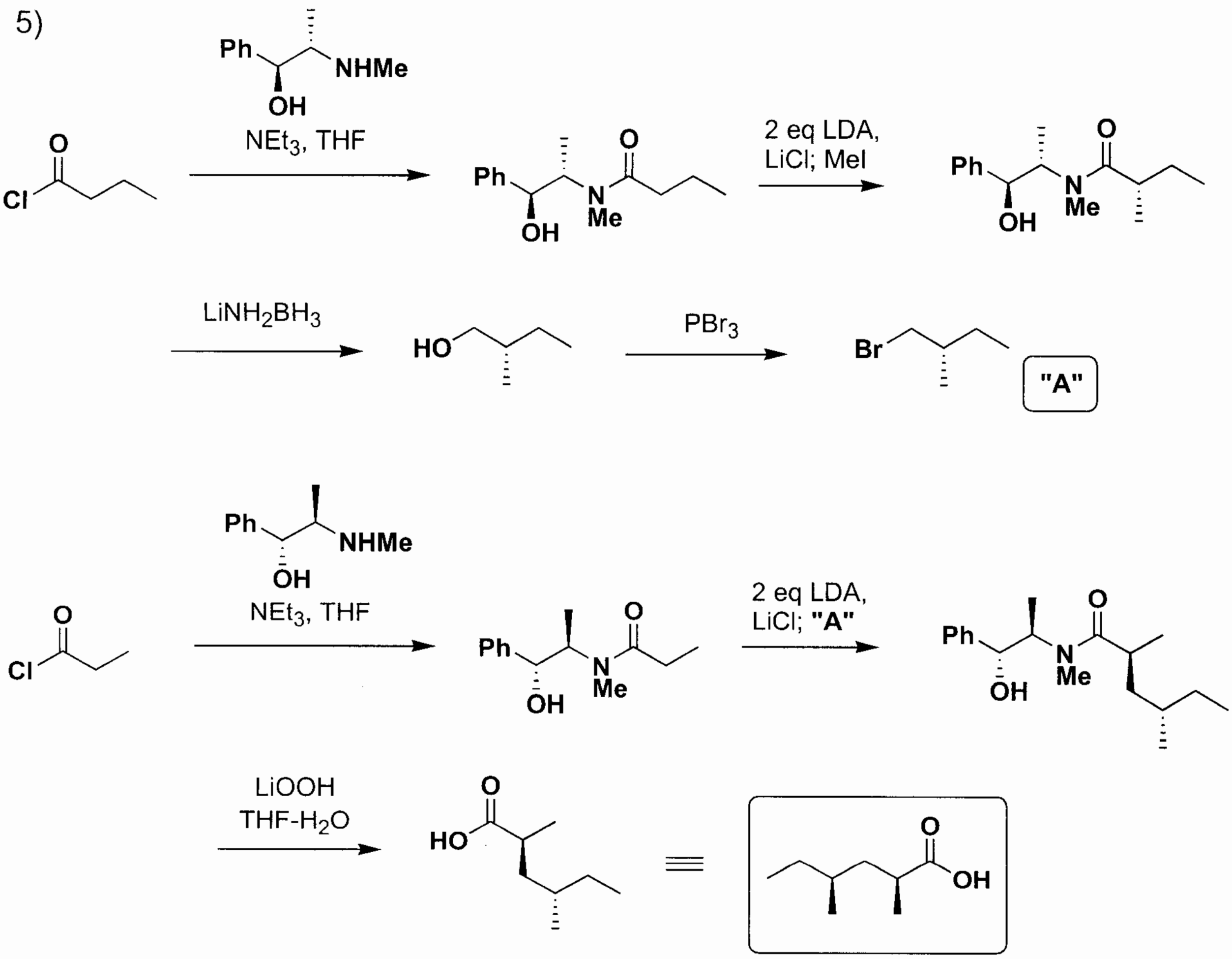


H
N
O
Bn
Cl
Ph
NEt₃, THF
LDA, THF;
NBS
Br
LiOMe
MeOH
MeO
MeMgBr,
THF
OH

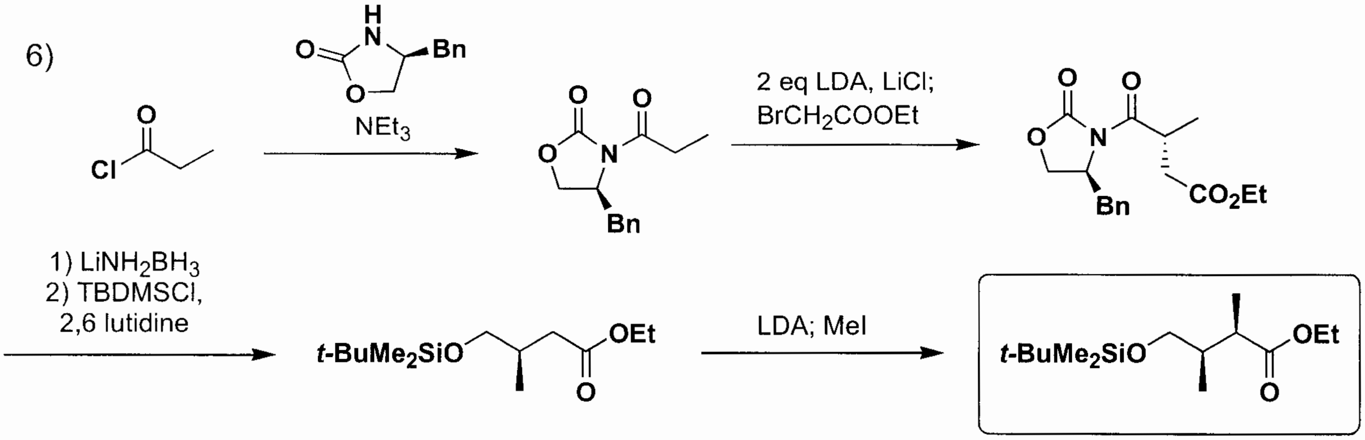
4)


Ph
NHMe
OH
NEt3, THF
Cl
O
Ph
N
2 eq LDA, LiCl;
PhO2SN
Ph
LiOOH,
THF-H2O
HO
OH
t-BuCHO,
cat. TsOH
t-Bu
LDA;
Br
MeONa, MeOH
MeO
HO
CO2Me

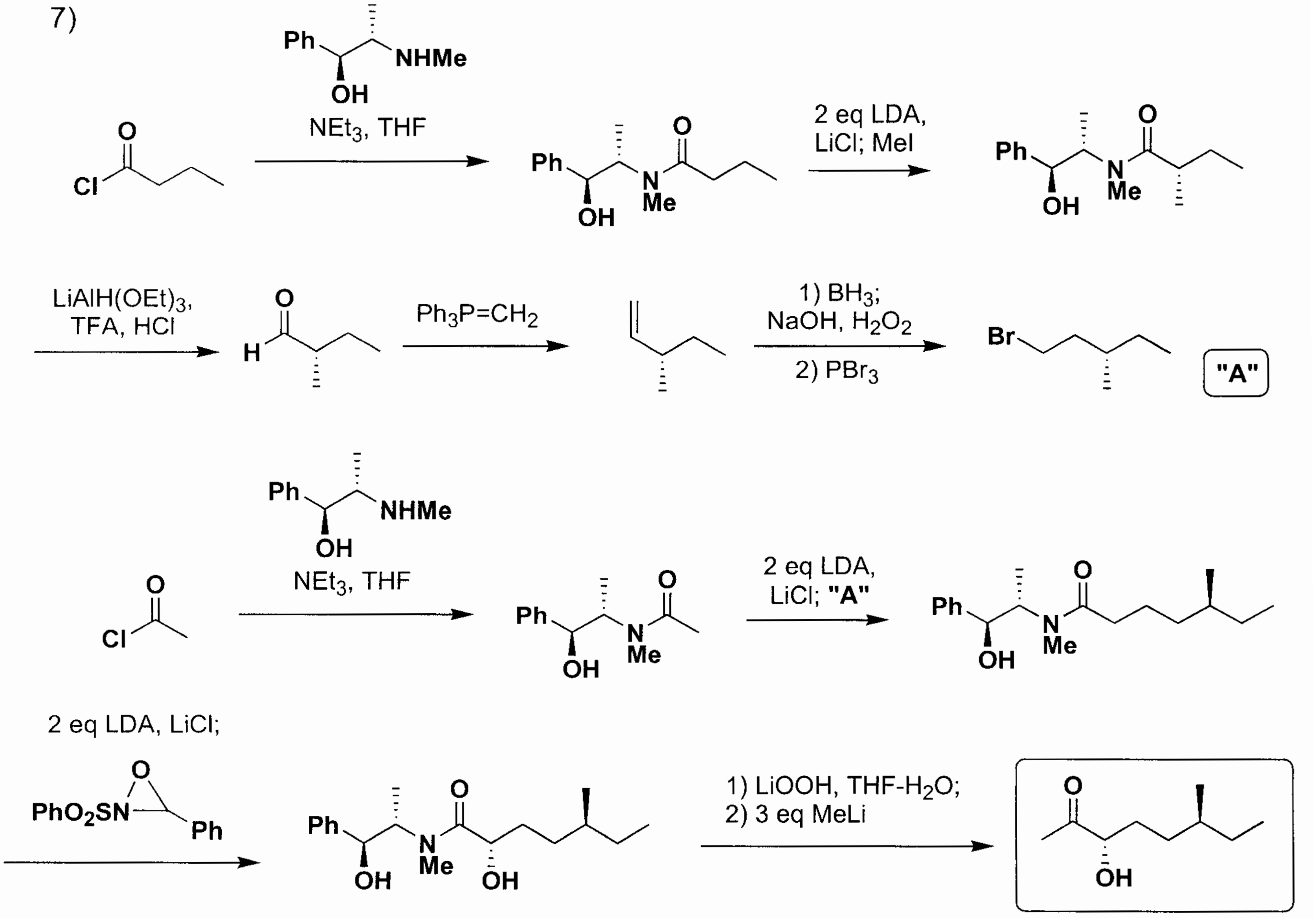
5)


Ph
NHMe
OH
NEt3, THF
Cl
O
N
Me
2 eq LDA,
LiCl; MeI
LiNH2BH3
HO
PBr3
Br
"A"
2 eq LDA,
LiCl; "A"
LiOOH
THF-H2O
OH

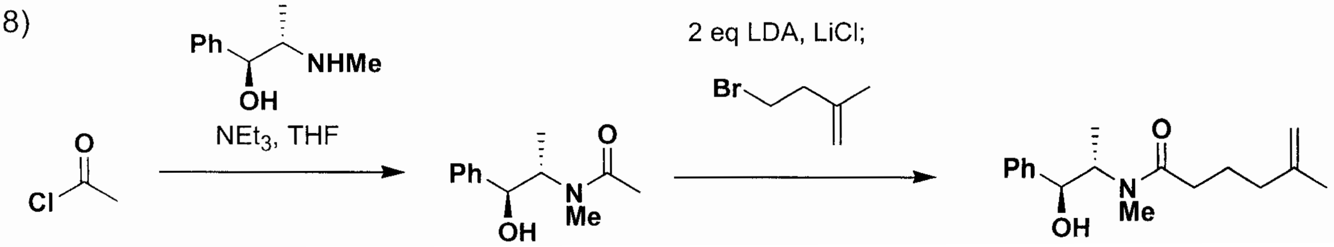
6)

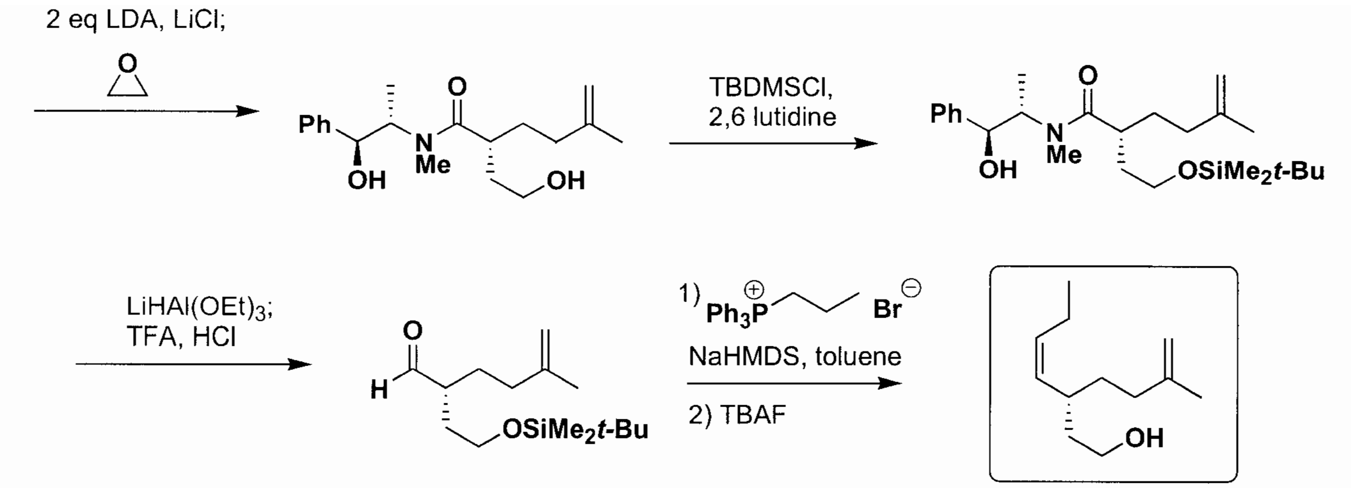

Cl
NEt3
Bn
2 eq LDA, LiCl;
BrCH2COOEt
CO2Et
1) LiNH2BH3
2) TBDMSCl,
2,6 lutidine
t-BuMe2SiO
OEt
LDA; MeI
t-BuMe2SiO
OEt

7)

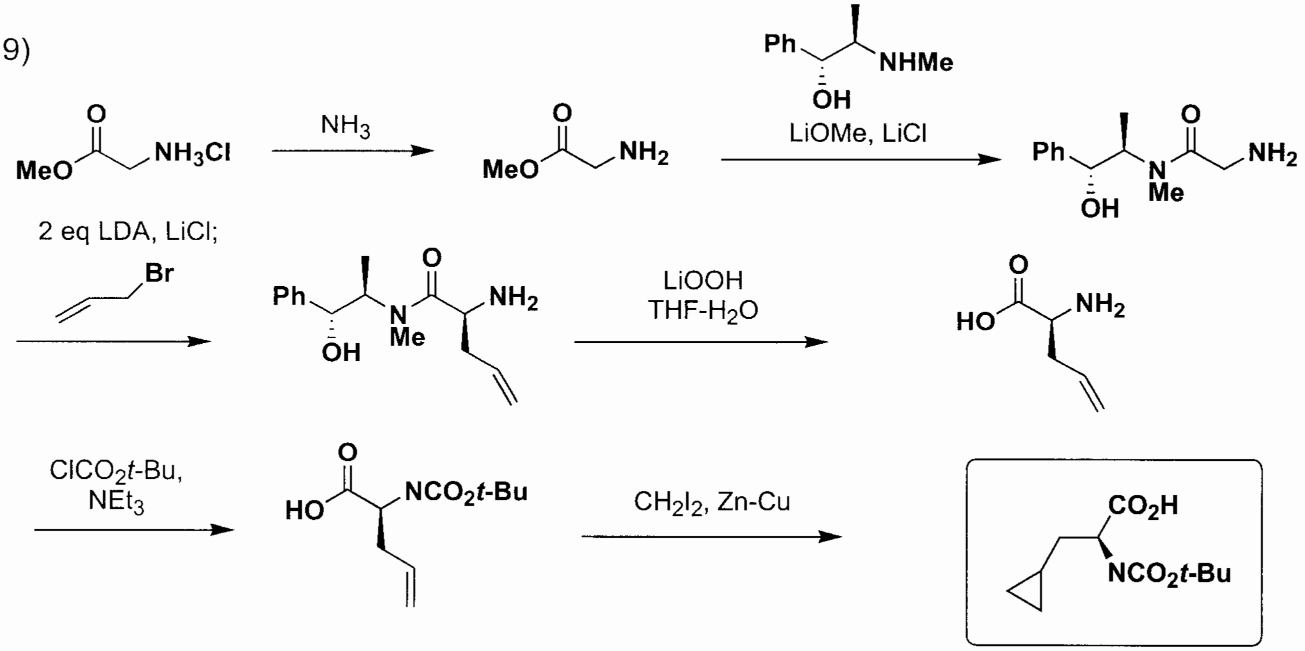

Ph
NHMe
OH
NEt3, THF
Cl
N
Me
2 eq LDA,
LiCl; MeI
LiAlH(OEt)3,
TFA, HCl
H
Ph3P=CH2
1) BH3;
NaOH, H2O2
2) PBr3
Br
"A"
2 eq LDA,
LiCl; "A"
2 eq LDA, LiCl;
PhO2SN
Ph
1) LiOOH, THF-H2O;
2) 3 eq MeLi

8)

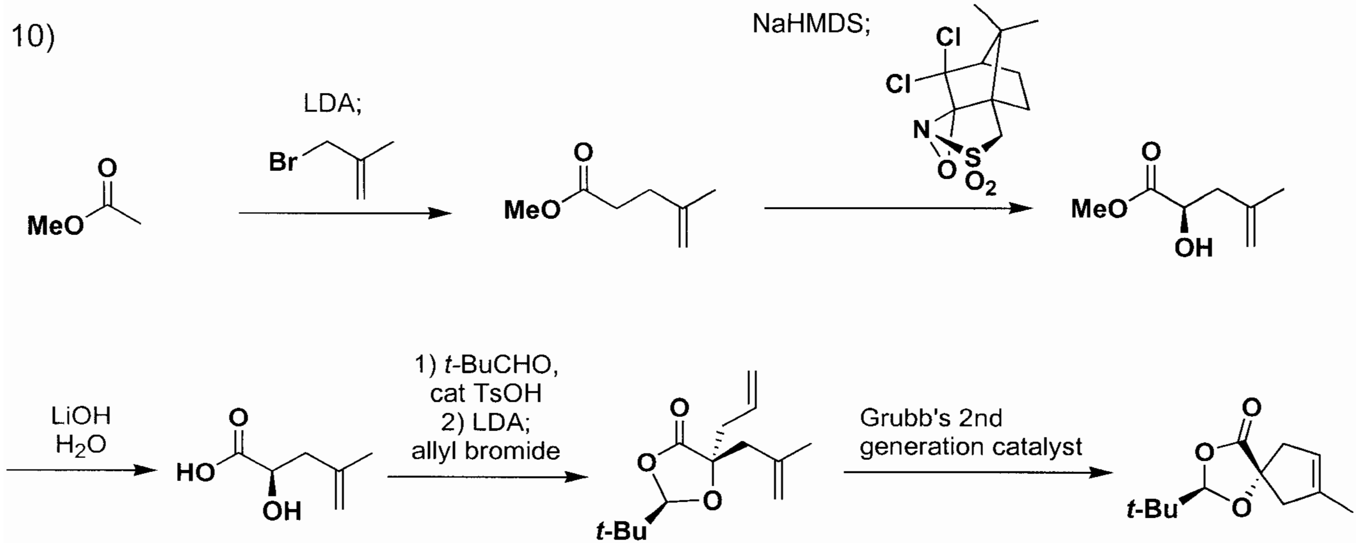

Ph
NHMe
OH
NEt3, THF
Cl
2 eq LDA, LiCl;
Br
N
Me

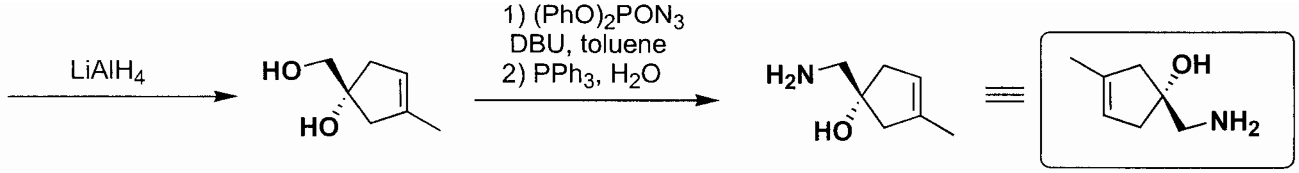

2 eq LDA, LiCl;
Ph
OH
N
Me
O
OH
TBDMSCl,
2,6 lutidine
Ph
OH
N
Me
O
OSiMe2t-Bu
LiHAl(OEt)3;
TFA, HCl
O
H
OSiMe2t-Bu
1) Ph3P⊕ Br⊖
NaHMDS, toluene
2) TBAF
OH

9)

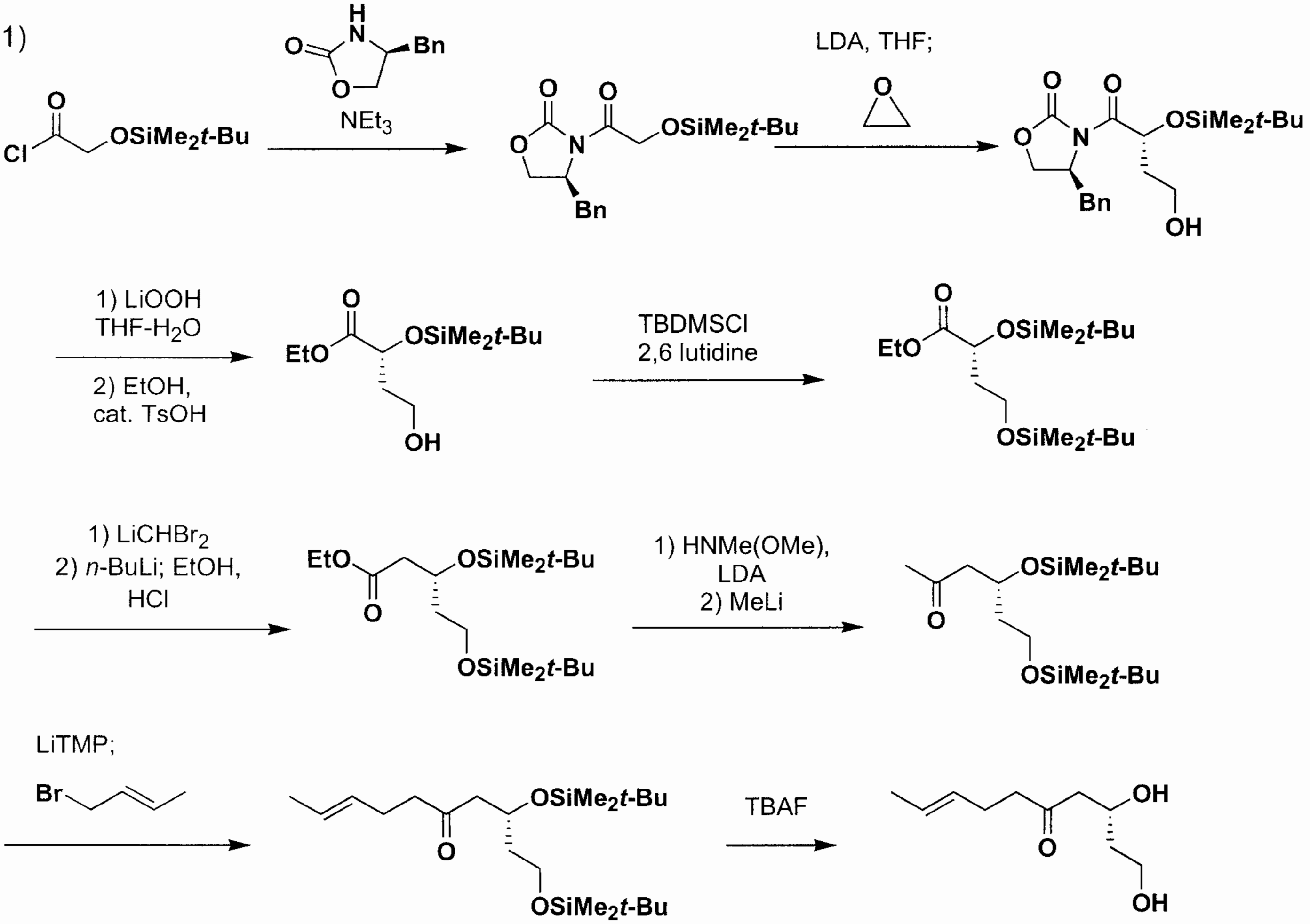

MeO
O
NH3Cl
NH3
MeO
O
NH2
Ph
OH
NHMe
LiOMe, LiCl
Ph
OH
N
Me
O
NH2
2 eq LDA, LiCl;
Br
Ph
OH
N
Me
O
NH2
LiOOH
THF-H2O
HO
O
NH2
ClCO2t-Bu,
NEt3
HO
O
NCO2t-Bu
CH2I2, Zn-Cu
CO2H
NCO2t-Bu

10)


MeO
O
LDA;
Br
MeO
O
NaHMDS;
Cl
Cl
N
O
S
O2
MeO
O
OH
LiOH
H2O
HO
O
OH
1) t-BuCHO,
cat TsOH
2) LDA;
allyl bromide
O
O
O
t-Bu
Grubb's 2nd
generation catalyst
O
O
O
t-Bu

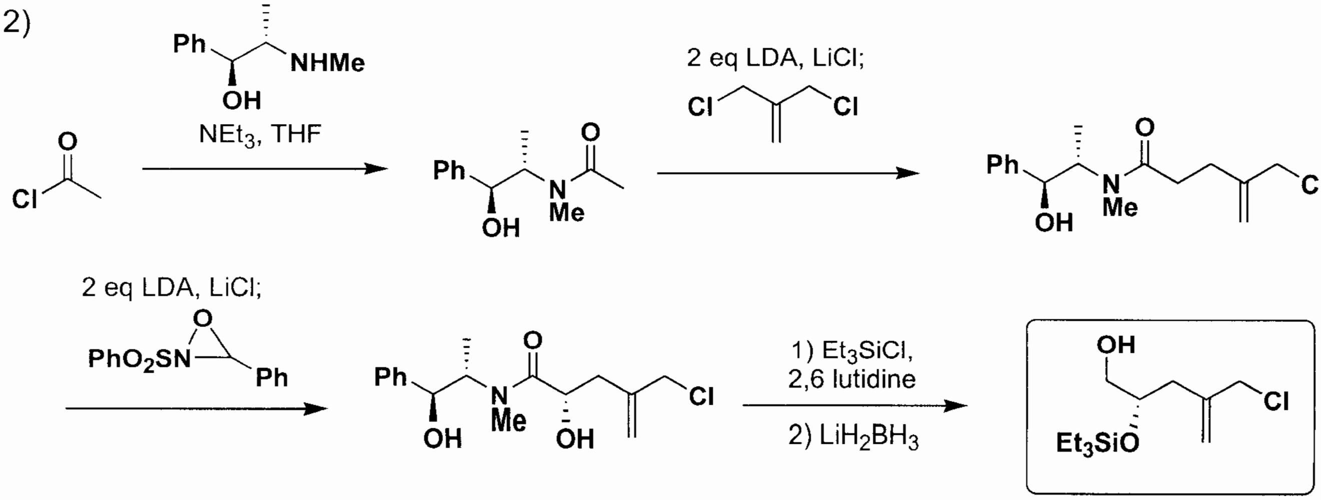

LiAlH4
HO
HO
1) (PhO)2PON3
DBU, toluene
2) PPh3, H2O
H2N
HO
OH
NH2

11)


Cl
O
OSiMe2t-Bu
H
N
O
O
Bn
NEt3
O
O
N
O
OSiMe2t-Bu
Bn
LDA, THF;
O
O
O
N
O
OSiMe2t-Bu
Bn
OH
1) LiOOH
THF-H2O
2) EtOH,
cat. TsOH
O
EtO
OSiMe2t-Bu
OH
TBDMSCl
2,6 lutidine
O
EtO
OSiMe2t-Bu
OSiMe2t-Bu
1) LiCHBr2
2) n-BuLi; EtOH,
HCl
EtO
O
OSiMe2t-Bu
OSiMe2t-Bu
1) HNMe(OMe),
LDA
2) MeLi
O
OSiMe2t-Bu
OSiMe2t-Bu
LiTMP;
Br
O
OSiMe2t-Bu
OSiMe2t-Bu
TBAF
O
OH
OH

For an alternate route using SAMP-hydrazone, see Enders *European J. Org. Chem.* **1999**, 751.

12)


Cl
O
Ph
NHMe
OH
NEt3, THF
Ph
O
N
Me
OH
2 eq LDA, LiCl;
Cl
Cl
Ph
O
N
Me
OH
Cl
2 eq LDA, LiCl;
O
PhO2SN
Ph
Ph
O
N
Me
OH
OH
Cl
1) Et3SiCl,
2,6 lutidine
2) LiH2BH3
OH
Et3SiO
Cl

See also Crimmins *Org. Lett.* **2001**, *3*, 949.

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April 6, 2005
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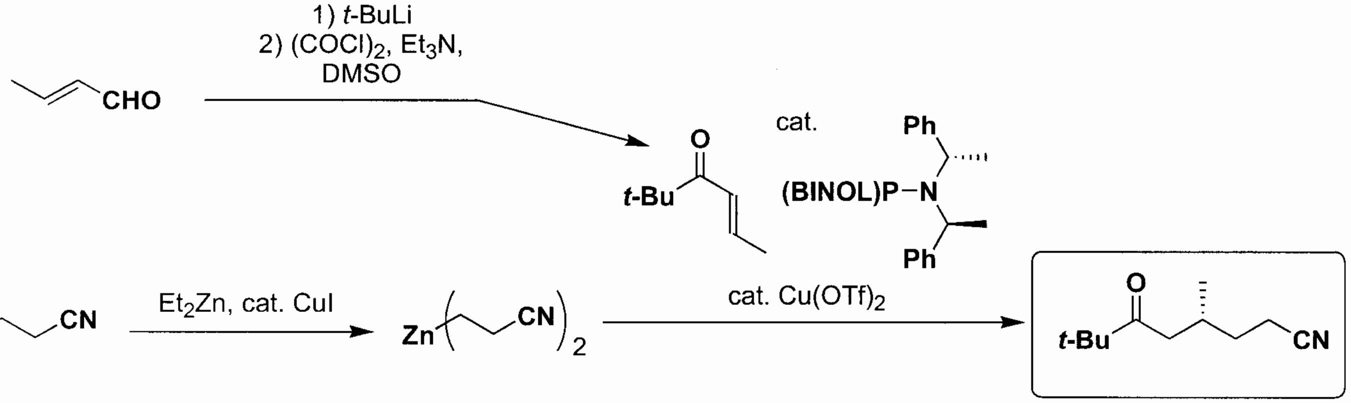
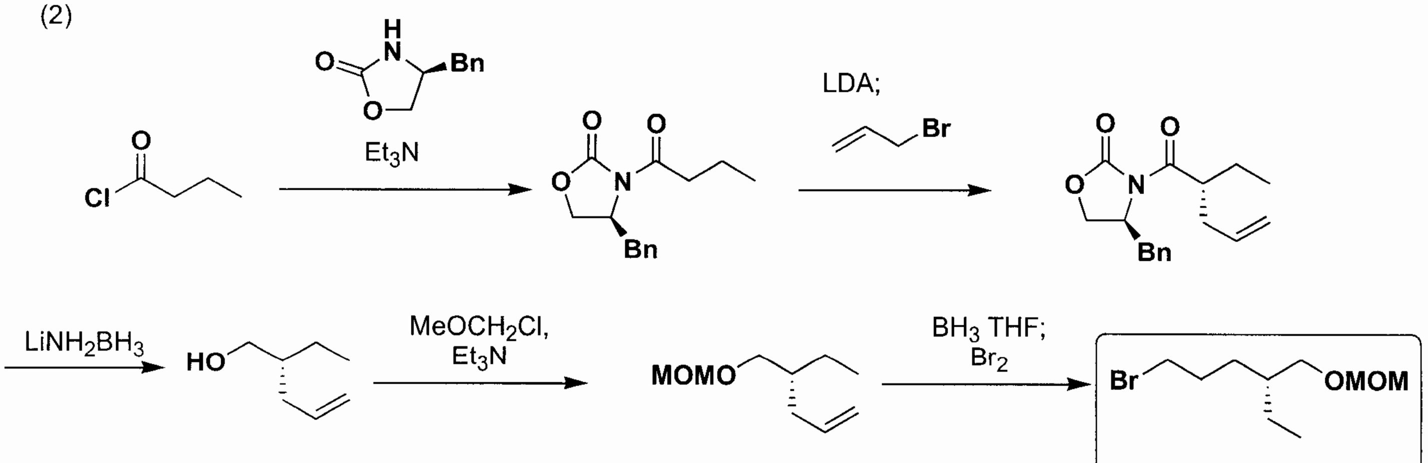
Problem Set 4 Solutions
Practice Problems for First Exam

(1)



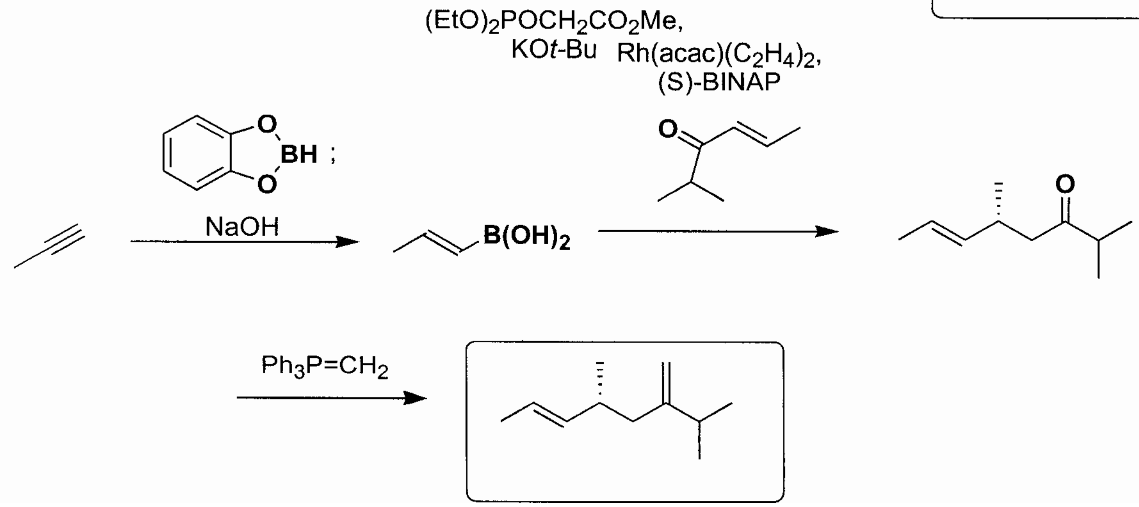
CHO
1) t-BuLi
2) (COCl)$_2$, Et$_3$N, DMSO
O
t-Bu
cat.
Ph
(BINOL)P–N
Ph
I
CN
Et$_2$Zn, cat. CuI
Zn
CN
2
cat. Cu(OTf)$_2$
O
t-Bu
CN

(2)



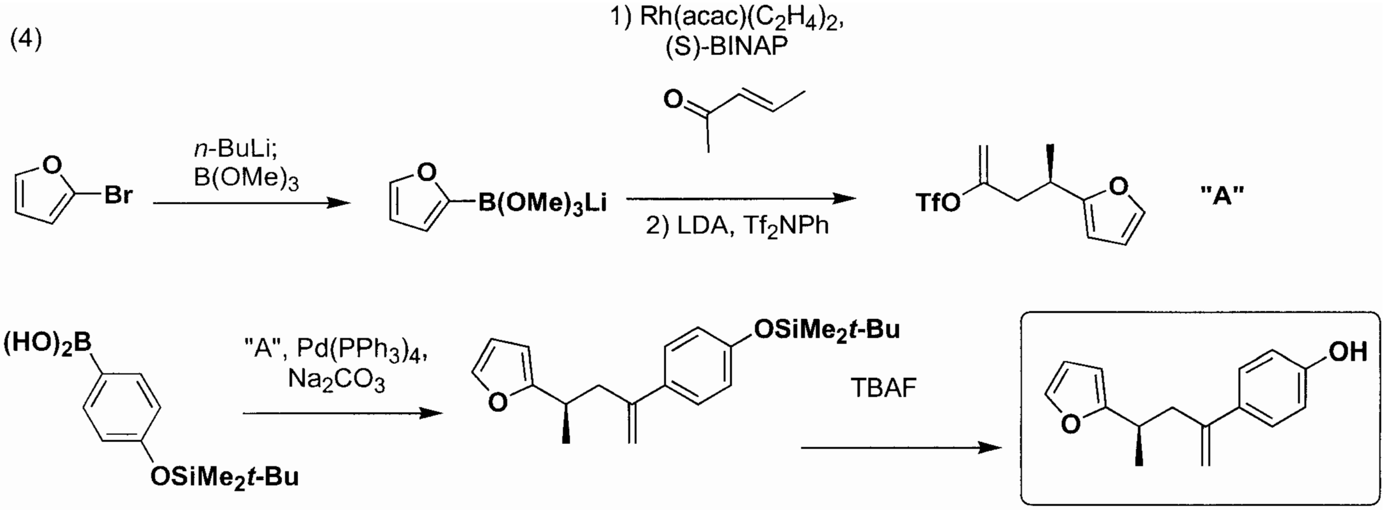
H
N
O
O
Bn
Et$_3$N
O
Cl
O
O
O
N
Bn
LDA;
Br
O
O
O
N
Bn
LiNH$_2$BH$_3$
HO
MeOCH$_2$Cl, Et$_3$N
MOMO
BH$_3$ THF; Br$_2$
Br
OMOM

(3)

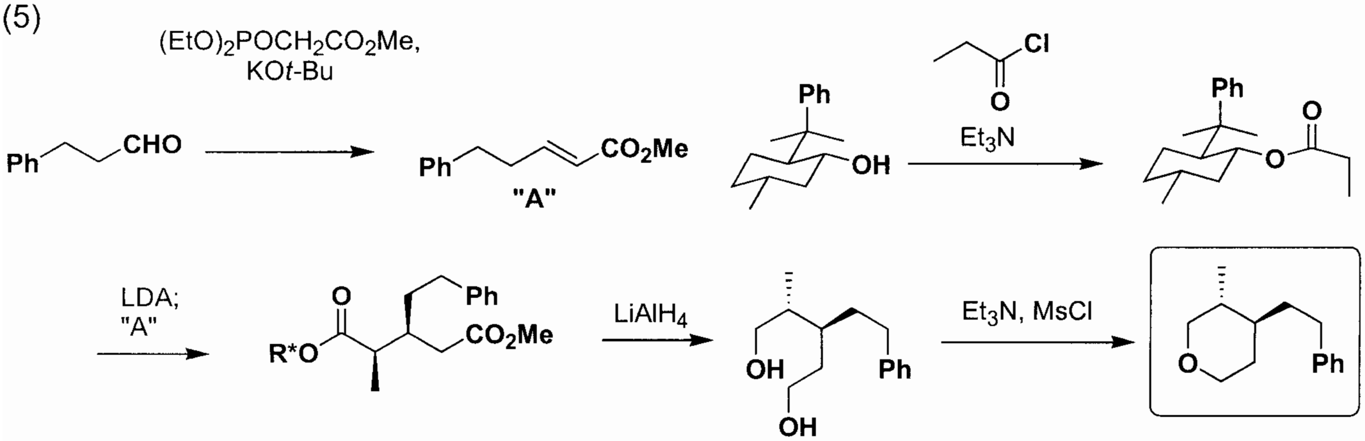


(EtO)$_2$POCH$_2$CO$_2$Me, KOt-Bu
Rh(acac)(C$_2$H$_4$)$_2$, (S)-BINAP
O
BH ;
O
NaOH
B(OH)$_2$
O
O
Ph$_3$P=CH$_2$

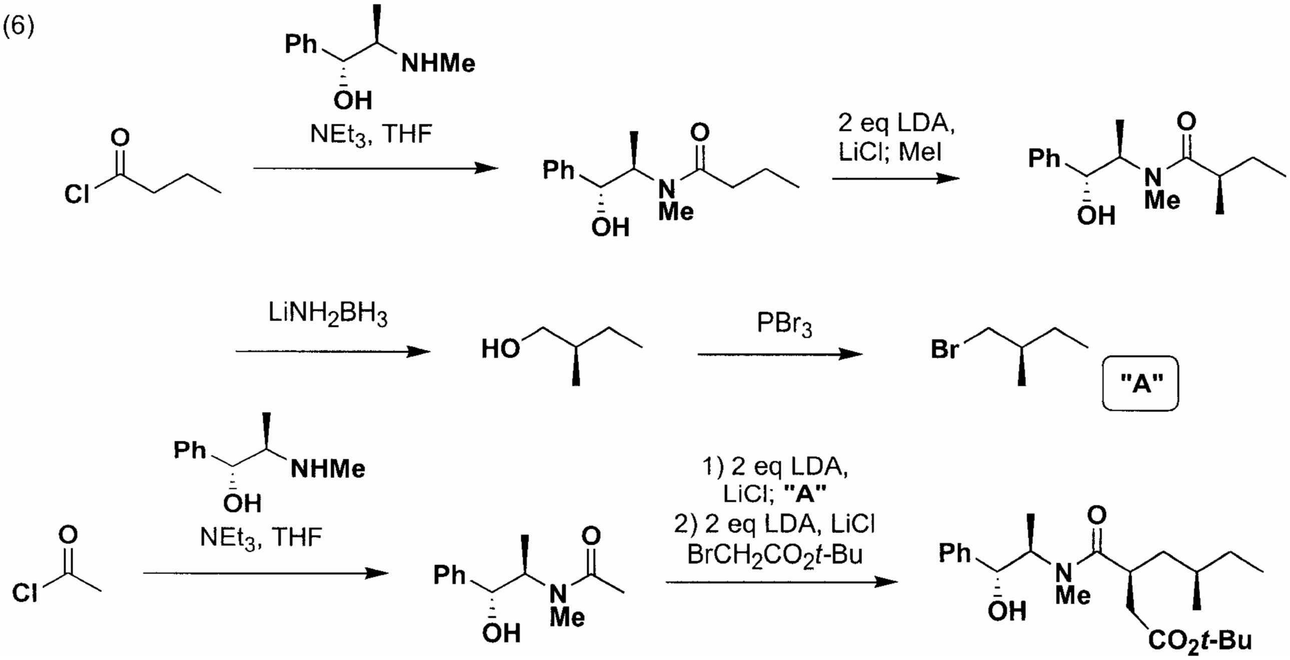
(4)

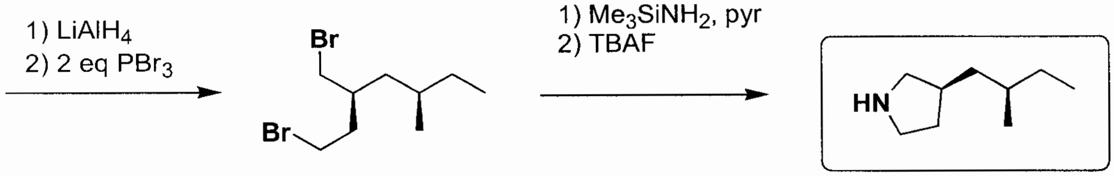

Br
n-BuLi;
B(OMe)3
B(OMe)3Li
1) Rh(acac)(C2H4)2,
(S)-BINAP
2) LDA, Tf2NPh
TfO
"A"
(HO)2B
OSiMe2t-Bu
"A", Pd(PPh3)4,
Na2CO3
OSiMe2t-Bu
TBAF
OH

(5)

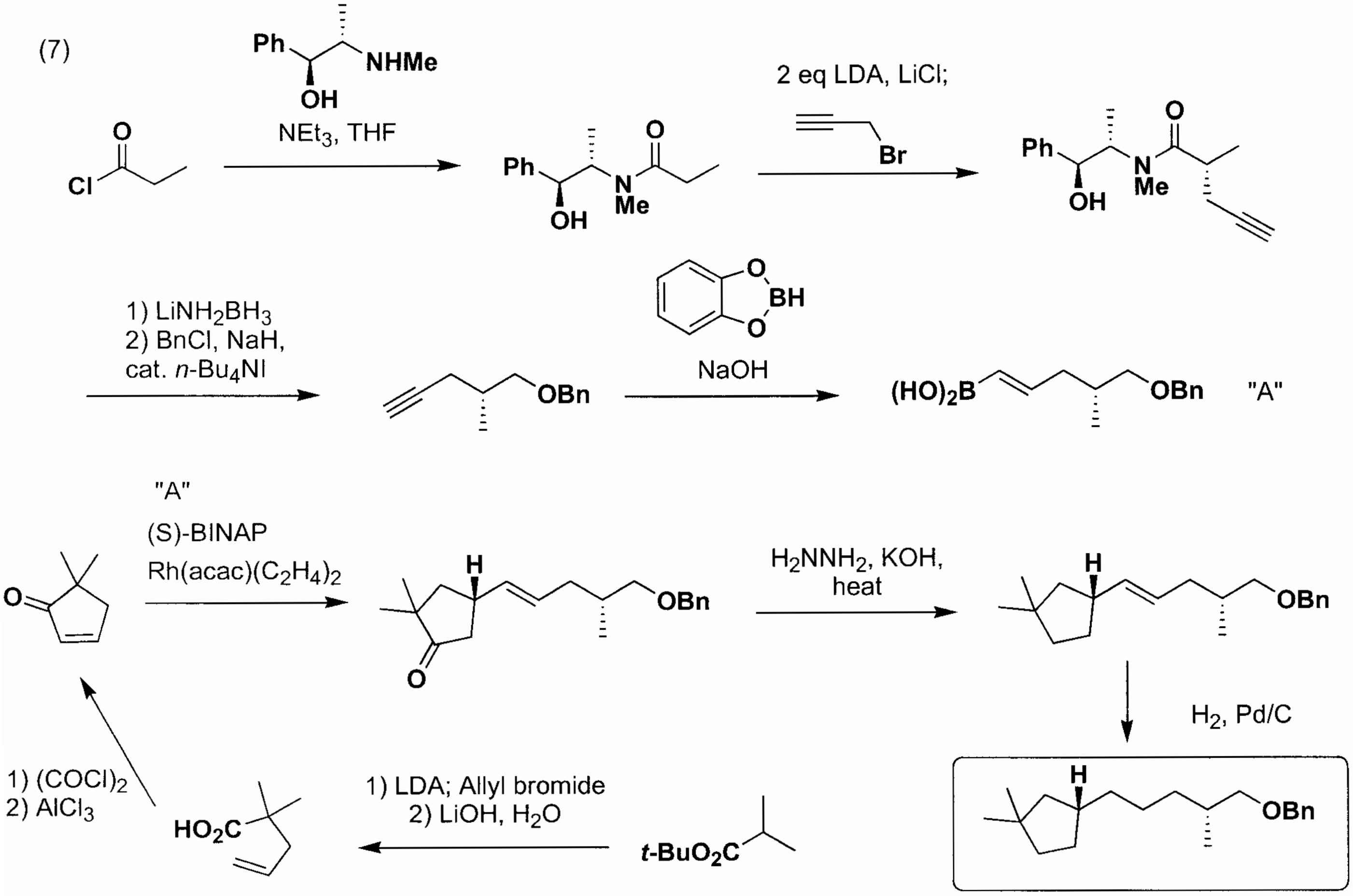

(EtO)2POCH2CO2Me,
KOt-Bu
Ph
CHO
Ph
CO2Me
"A"
Ph
OH
Cl
O
Et3N
Ph
O
O
LDA;
"A"
O
Ph
R*O
CO2Me
LiAlH4
OH
Ph
OH
Et3N, MsCl
O
Ph

(6)

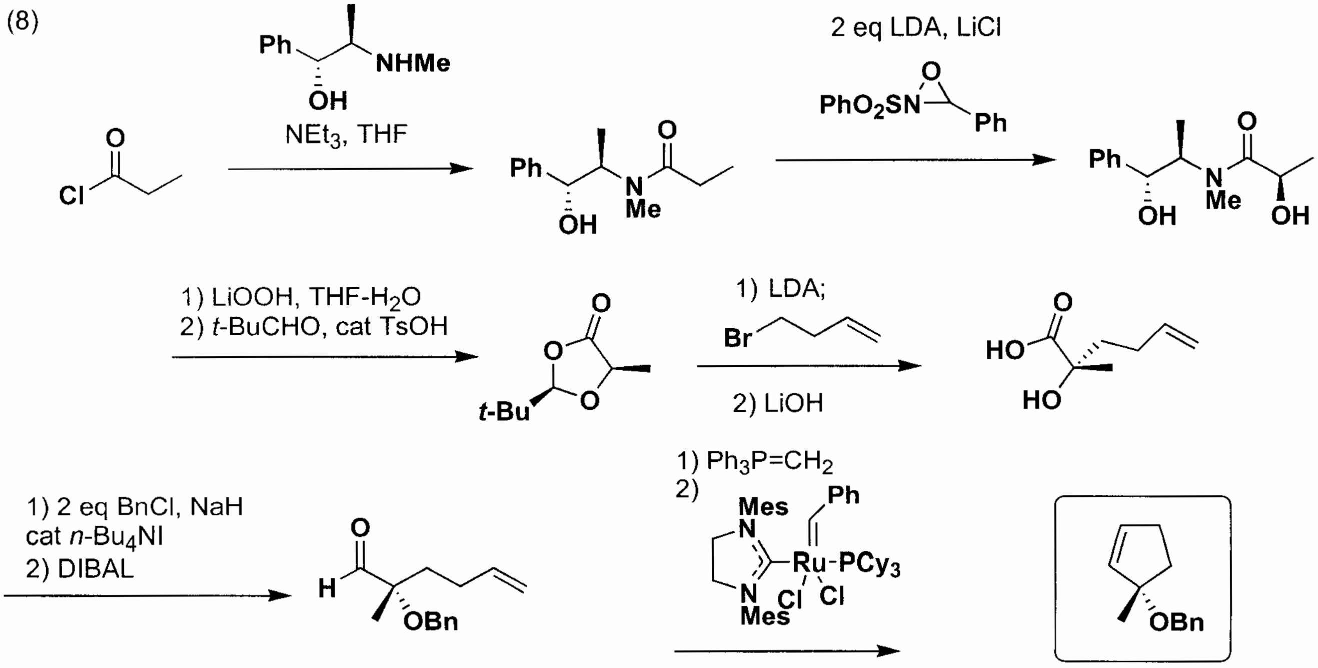

Ph
NHMe
OH
NEt3, THF
O
Cl
Ph
O
N
Me
OH
2 eq LDA,
LiCl; MeI
Ph
O
N
Me
OH
LiNH2BH3
HO
PBr3
Br
"A"
Ph
NHMe
OH
NEt3, THF
O
Cl
Ph
O
N
Me
OH
1) 2 eq LDA,
LiCl; "A"
2) 2 eq LDA, LiCl
BrCH2CO2t-Bu
Ph
O
N
Me
OH
CO2t-Bu


1) LiAlH$_4$
2) 2 eq PBr$_3$
Br
Br
1) Me$_3$SiNH$_2$, pyr
2) TBAF
HN

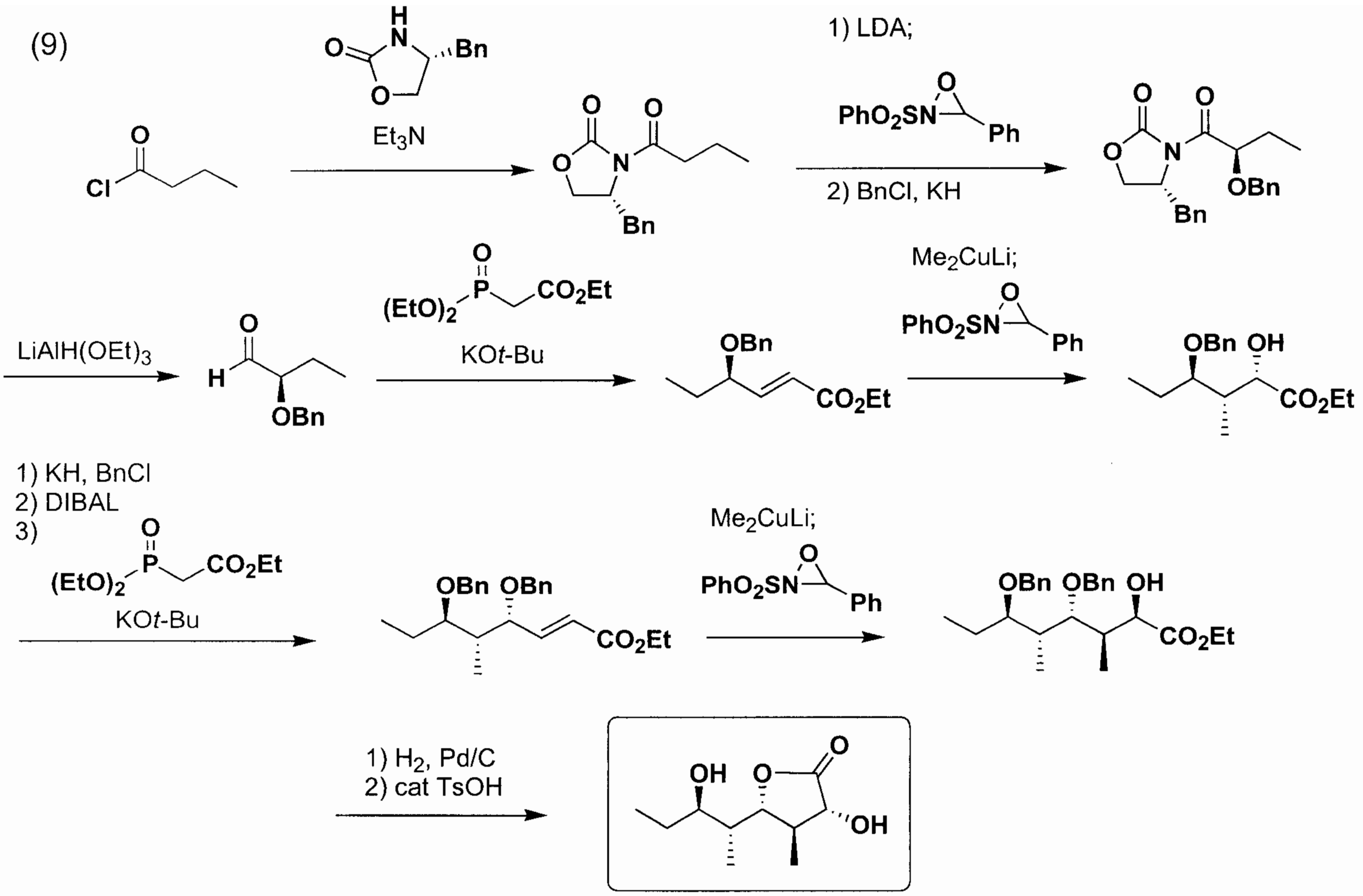
(7)


Ph
NHMe
OH
NEt$_3$, THF
Cl
O
Ph
N
Me
OH
O
2 eq LDA, LiCl;
Br
Ph
OH
N
Me
O
1) LiNH$_2$BH$_3$
2) BnCl, NaH, cat. *n*-Bu$_4$NI
OBn
BH
NaOH
(HO)$_2$B
OBn
"A"
"A"
(S)-BINAP
Rh(acac)(C$_2$H$_4$)$_2$
O
H
OBn
O
H$_2$NNH$_2$, KOH, heat
H
OBn
H$_2$, Pd/C
H
OBn
1) (COCl)$_2$
2) AlCl$_3$
HO$_2$C
1) LDA; Allyl bromide
2) LiOH, H$_2$O
t-BuO$_2$C

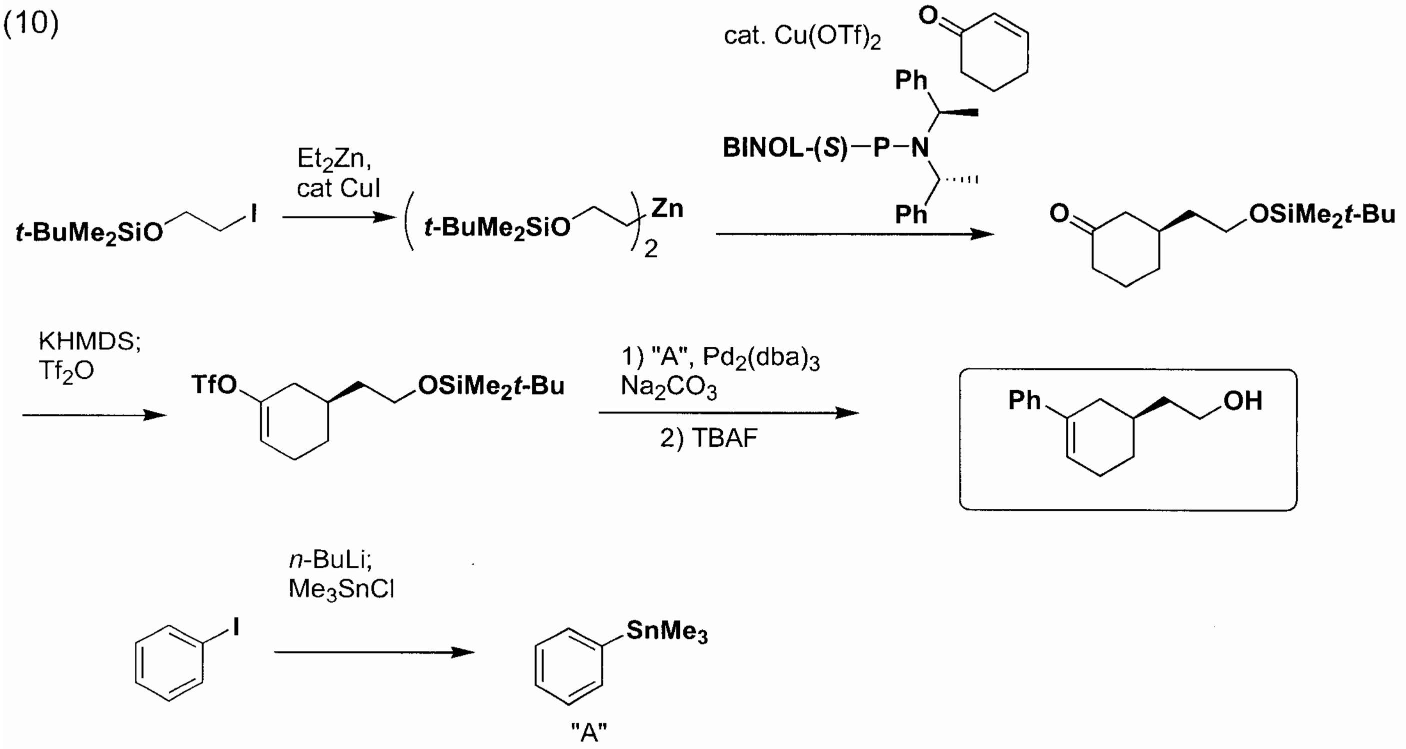
(8)


Ph
NHMe
OH
NEt$_3$, THF
Cl
O
Ph
N
Me
OH
O
2 eq LDA, LiCl
PhO$_2$SN
O
Ph
Ph
N
Me
OH
OH
O
1) LiOOH, THF-H$_2$O
2) *t*-BuCHO, cat TsOH
O
O
O
t-Bu
1) LDA;
Br
2) LiOH
HO
O
HO
1) 2 eq BnCl, NaH cat *n*-Bu$_4$NI
2) DIBAL
O
H
OBn
1) Ph$_3$P=CH$_2$
2)
Mes
N
N
Mes
Ph
Ru-PCy$_3$
Cl
Cl
OBn

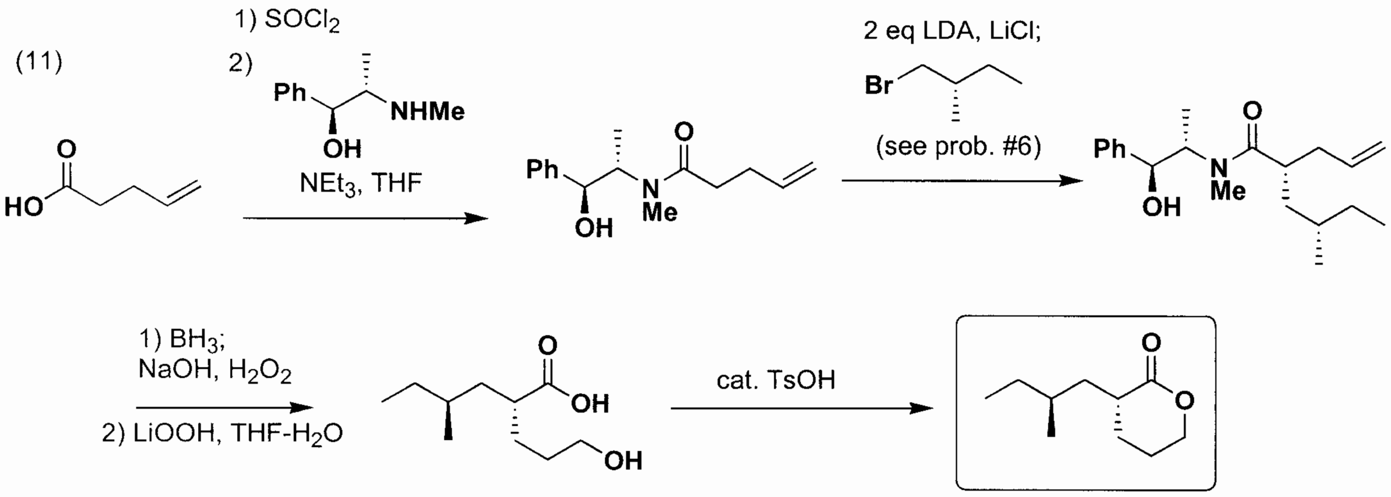
(9)


Et$_3$N
1) LDA;
PhO$_2$SN
Ph
2) BnCl, KH
Bn
OBn
LiAlH(OEt)$_3$
(EtO)$_2$P CO$_2$Et
KO*t*-Bu
CO$_2$Et
Me$_2$CuLi;
OH
1) KH, BnCl
2) DIBAL
3)
1) H$_2$, Pd/C
2) cat TsOH

(10)

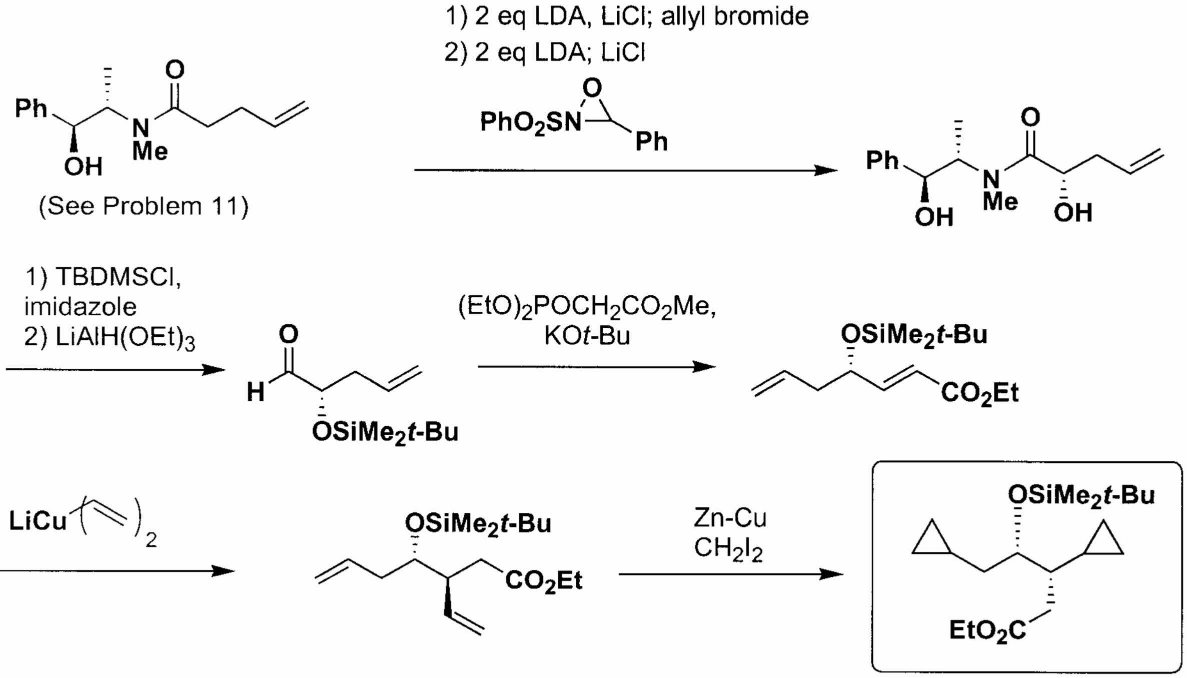

t-BuMe$_2$SiO
Et$_2$Zn,
cat CuI
Zn
2
cat. Cu(OTf)$_2$
BINOL-(*S*)—P—N
Ph
OSiMe$_2$*t*-Bu
KHMDS;
Tf$_2$O
TfO
1) "A", Pd$_2$(dba)$_3$
Na$_2$CO$_3$
2) TBAF
OH
n-BuLi;
Me$_3$SnCl
SnMe$_3$
"A"

(11)



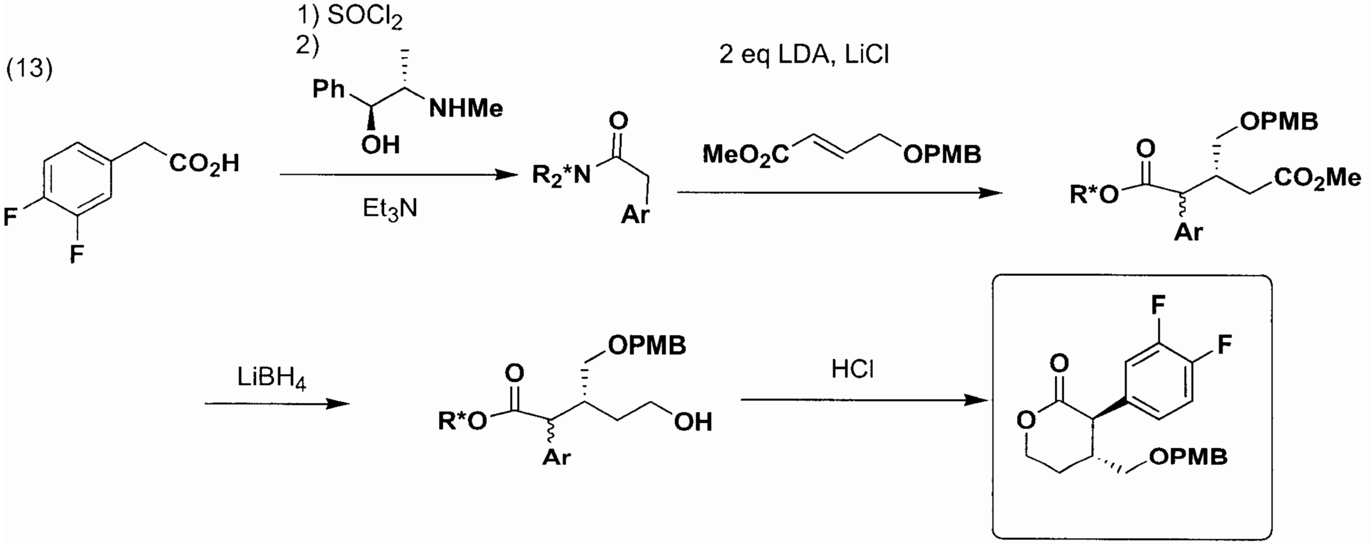
1) SOCl2
2)
Ph
NHMe
OH
NEt3, THF
HO
O
Ph
OH
N
Me
O
2 eq LDA, LiCl;
Br
(see prob. #6)
Ph
OH
N
Me
O
1) BH3;
NaOH, H2O2
2) LiOOH, THF-H2O
O
OH
OH
cat. TsOH
O
O

(12)



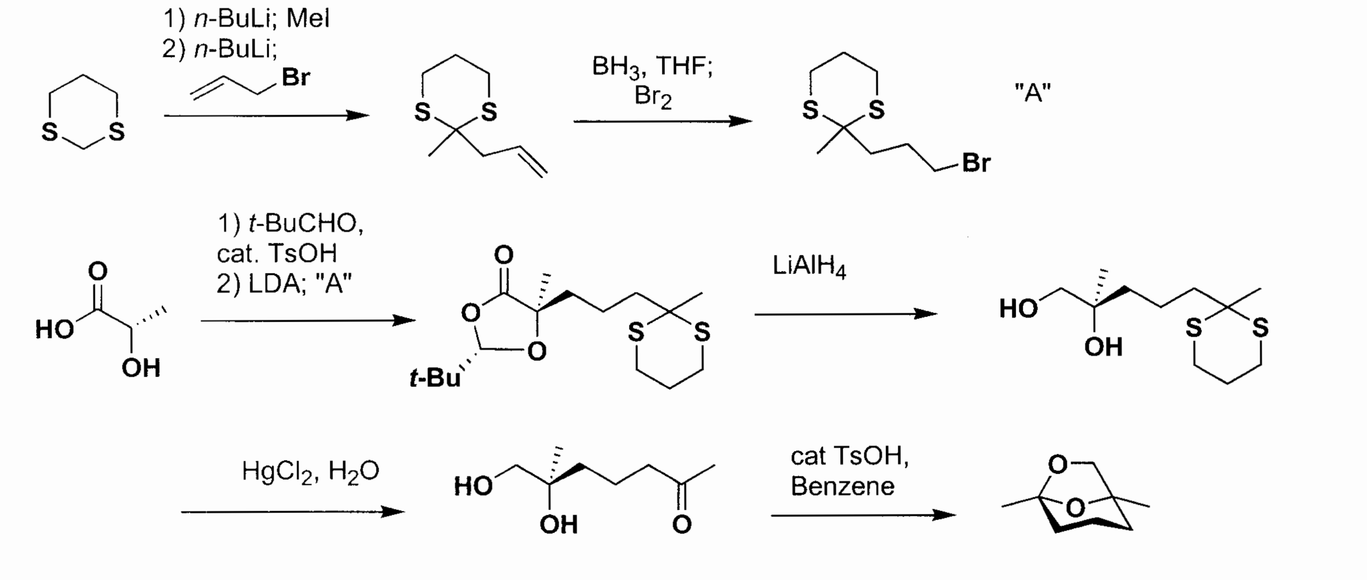
Ph
OH
N
Me
O
(See Problem 11)
1) 2 eq LDA, LiCl; allyl bromide
2) 2 eq LDA; LiCl
PhO2SN
O
Ph
Ph
OH
N
Me
O
OH
1) TBDMSCl,
imidazole
2) LiAlH(OEt)3
O
H
OSiMe2t-Bu
(EtO)2POCH2CO2Me,
KOt-Bu
OSiMe2t-Bu
CO2Et
LiCu
2
OSiMe2t-Bu
CO2Et
Zn-Cu
CH2I2
OSiMe2t-Bu
EtO2C

(13)

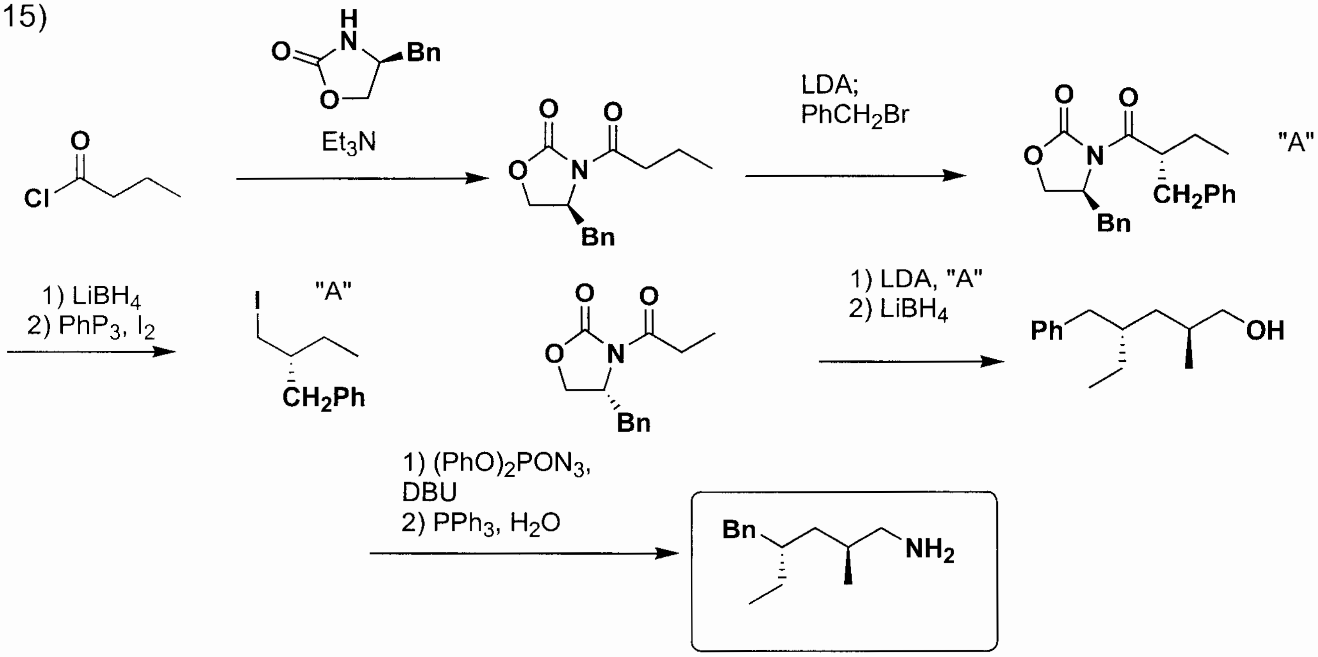


F
F
CO2H
1) SOCl2
2)
Ph
NHMe
OH
Et3N
R2*N
O
Ar
2 eq LDA, LiCl
MeO2C
OPMB
R*O
O
Ar
OPMB
CO2Me
LiBH4
R*O
O
Ar
OPMB
OH
HCl
F
F
O
O
OPMB

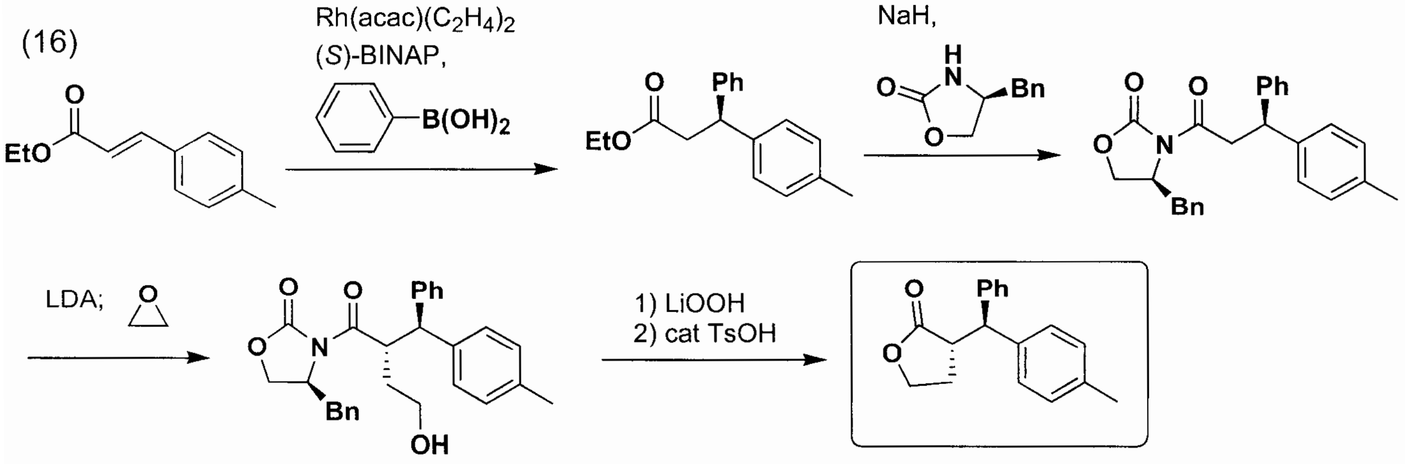
14) (-)-Frontalin. See also Seebach, *Liebigs Ann. Chem.* **1983,** 1930.


1) n-BuLi; MeI
2) n-BuLi;
Br
S
S
BH3, THF;
Br2
"A"
1) t-BuCHO,
cat. TsOH
2) LDA; "A"
HO
OH
O
t-Bu
LiAlH4
HgCl2, H2O
cat TsOH,
Benzene

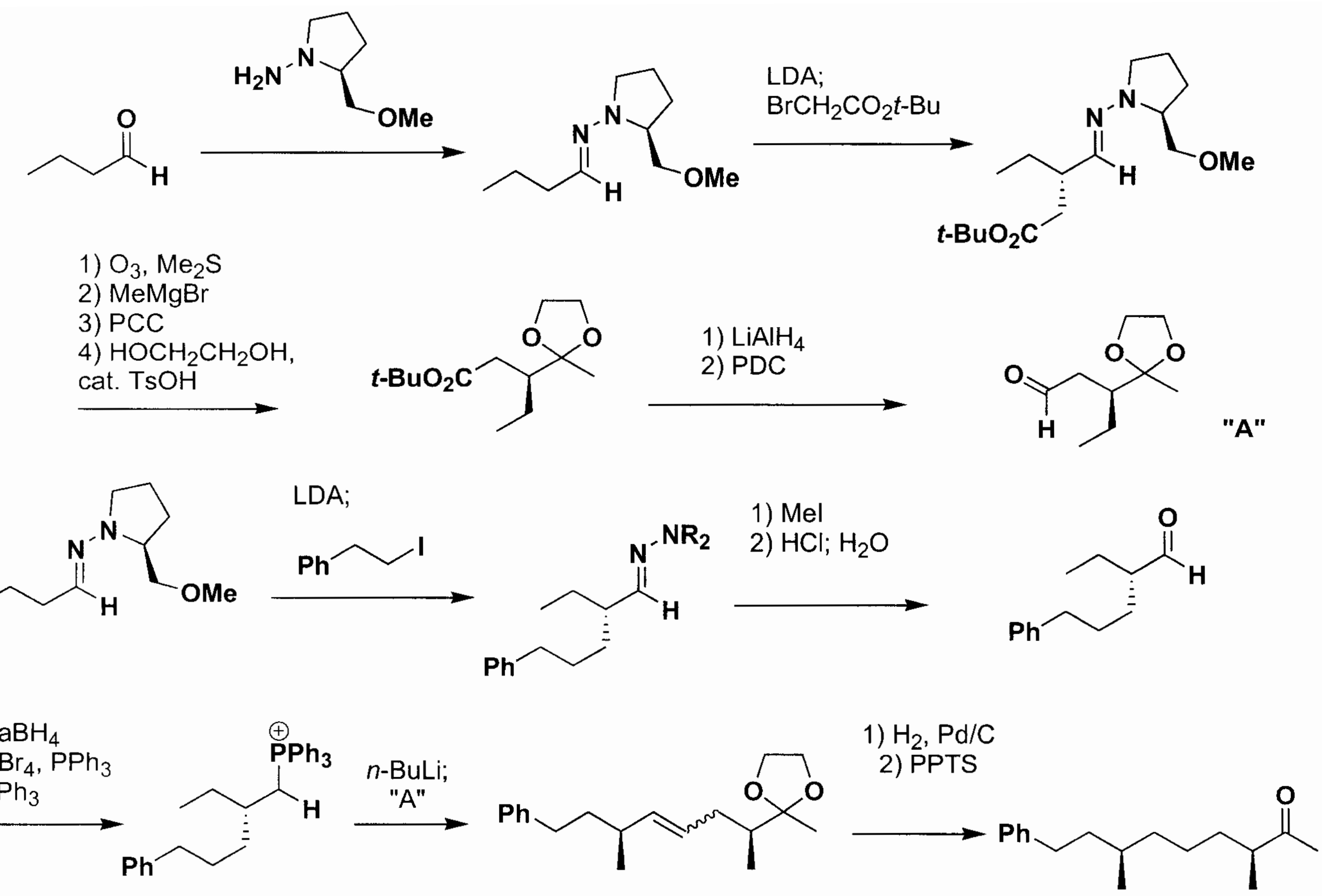
(15)


H
N
O
Bn
Et3N
Cl
LDA;
PhCH2Br
"A"
CH2Ph
1) LiBH4
2) PhP3, I2
I
"A"
1) LDA, "A"
2) LiBH4
Ph
OH
1) (PhO)2PON3,
DBU
2) PPh3, H2O
Bn
NH2

(16)

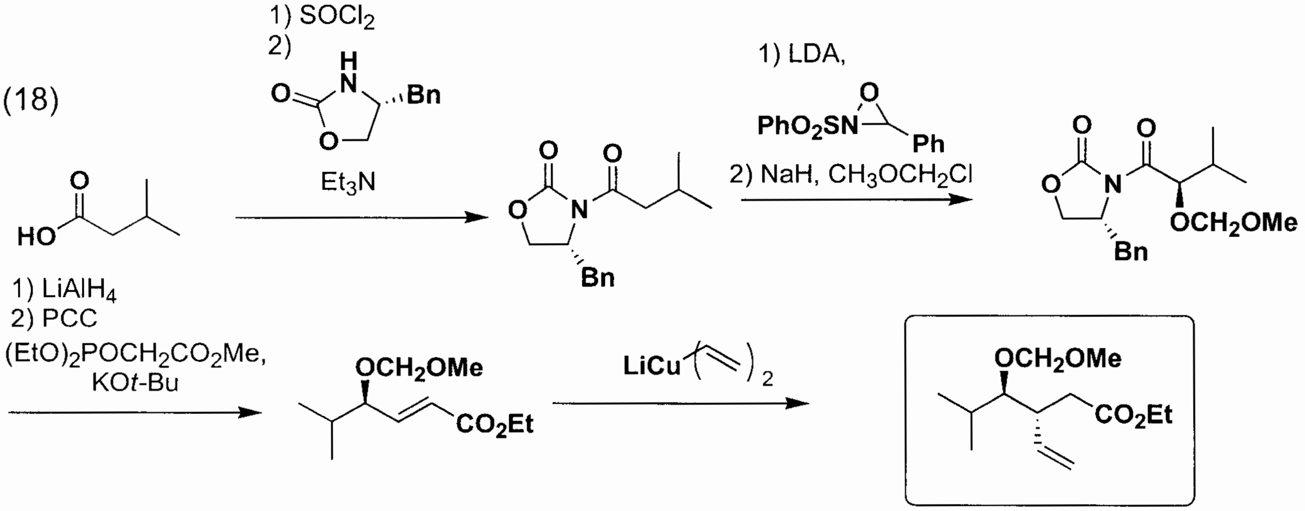

Rh(acac)(C2H4)2
(S)-BINAP,
B(OH)2
EtO
Ph
NaH,
H
N
O
Bn
LDA;
N
OH
1) LiOOH
2) cat TsOH

(17)



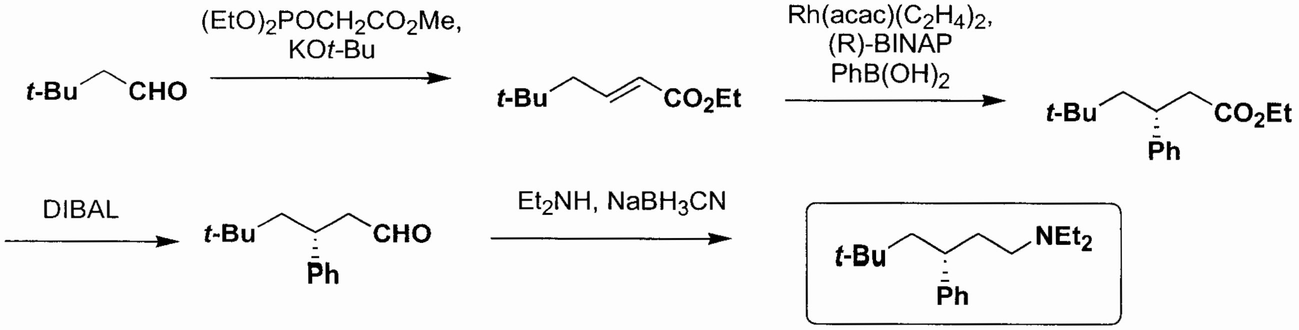
H2N
OMe
LDA;
BrCH2CO2t-Bu
t-BuO2C
1) O3, Me2S
2) MeMgBr
3) PCC
4) HOCH2CH2OH, cat. TsOH
1) LiAlH4
2) PDC
"A"
LDA;
Ph
1) MeI
2) HCl; H2O
NR2
1) NaBH4
2) CBr4, PPh3
3) PPh3
PPh3
n-BuLi;
"A"
1) H2, Pd/C
2) PPTS
Ph

(18)



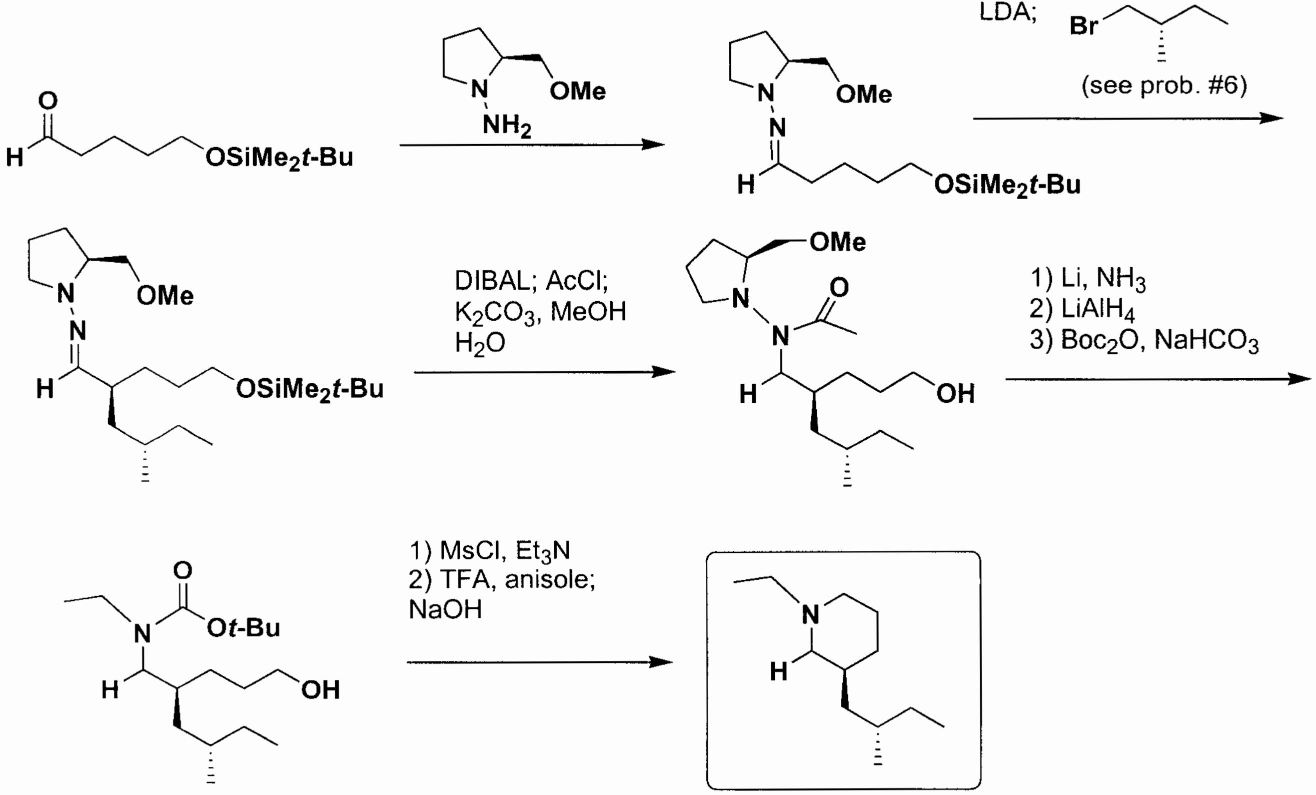
1) SOCl2
2)
Bn
Et3N
HO
1) LDA,
PhO2SN
Ph
2) NaH, CH3OCH2Cl
OCH2OMe
Bn
1) LiAlH4
2) PCC
(EtO)2POCH2CO2Me,
KOt-Bu
CO2Et
LiCu
2

(19)



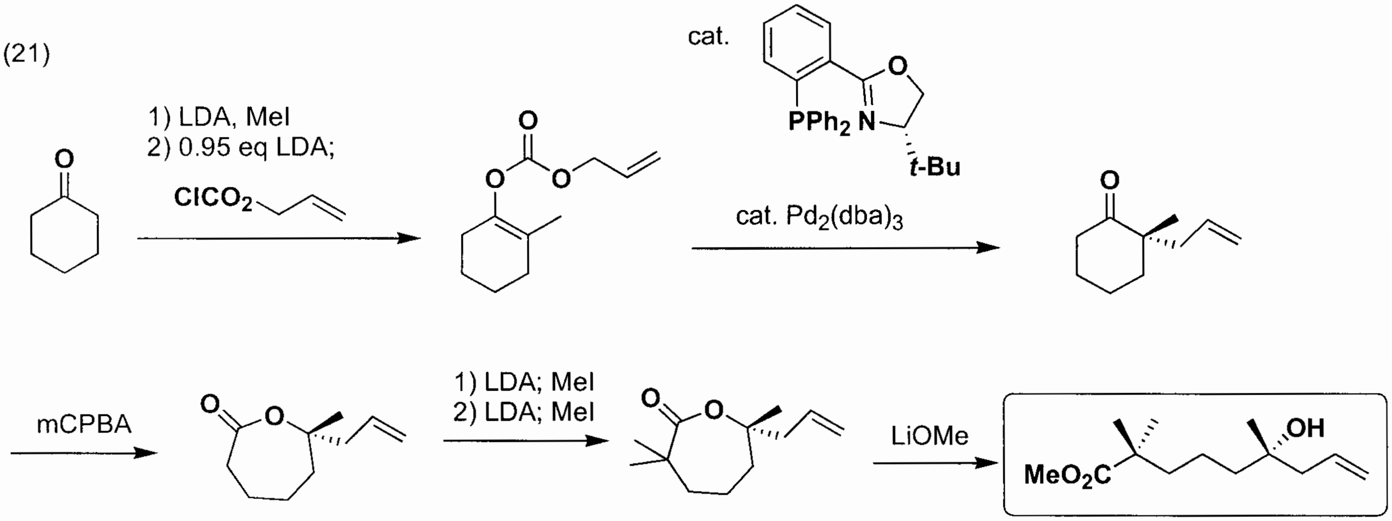
t-Bu
CHO
(EtO)2POCH2CO2Me,
KOt-Bu
CO2Et
Rh(acac)(C2H4)2,
(R)-BINAP
PhB(OH)2
Ph
DIBAL
Et2NH, NaBH3CN
NEt2

(20) (*S*,*S*)-Stenusine. See Enders, *J. Org. Chem.* **1993**, *58*, 4881.



OSiMe2t-Bu
OMe
NH2
LDA;
Br
(see prob. #6)
DIBAL; AcCl;
K2CO3, MeOH
H2O
1) Li, NH3
2) LiAlH4
3) Boc2O, NaHCO3
OH
Ot-Bu
1) MsCl, Et3N
2) TFA, anisole;
NaOH

(21)



1) LDA, MeI
2) 0.95 eq LDA;
ClCO2
cat.
PPh2
t-Bu
cat. Pd2(dba)3
mCPBA
1) LDA; MeI
2) LDA; MeI
LiOMe
MeO2C
OH

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April 22, 2005
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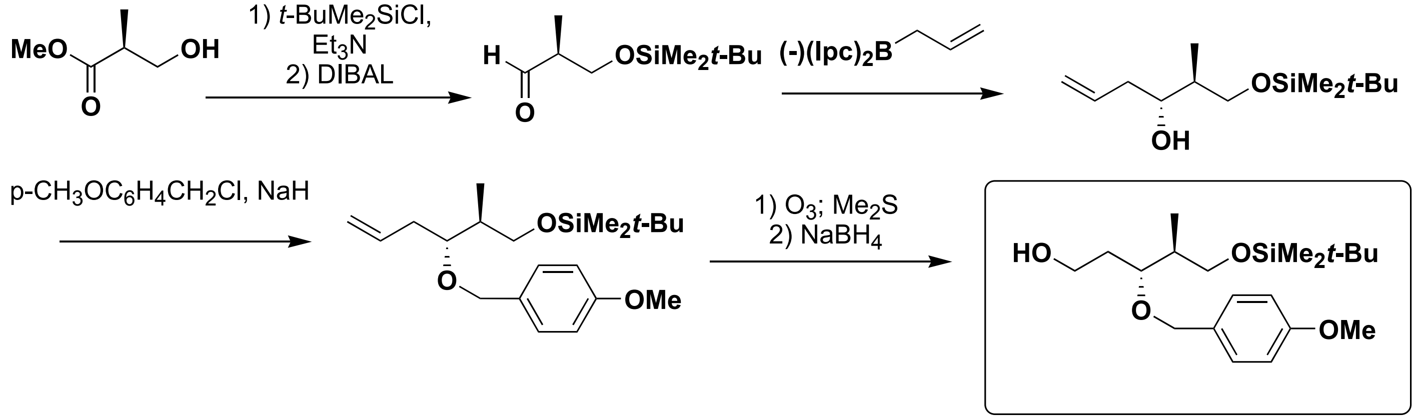
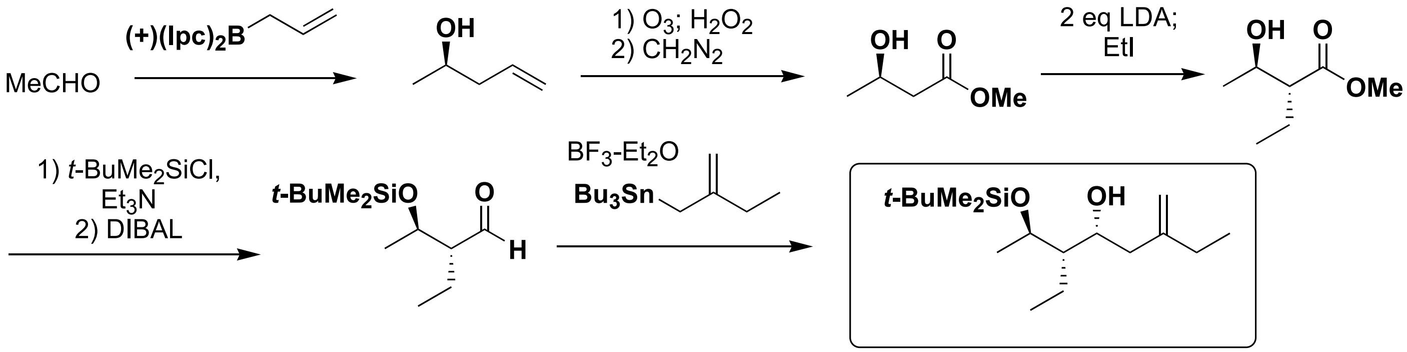
Problem Set 5 Solutions
Stereocontrolled Addition to Carbonyl Compounds

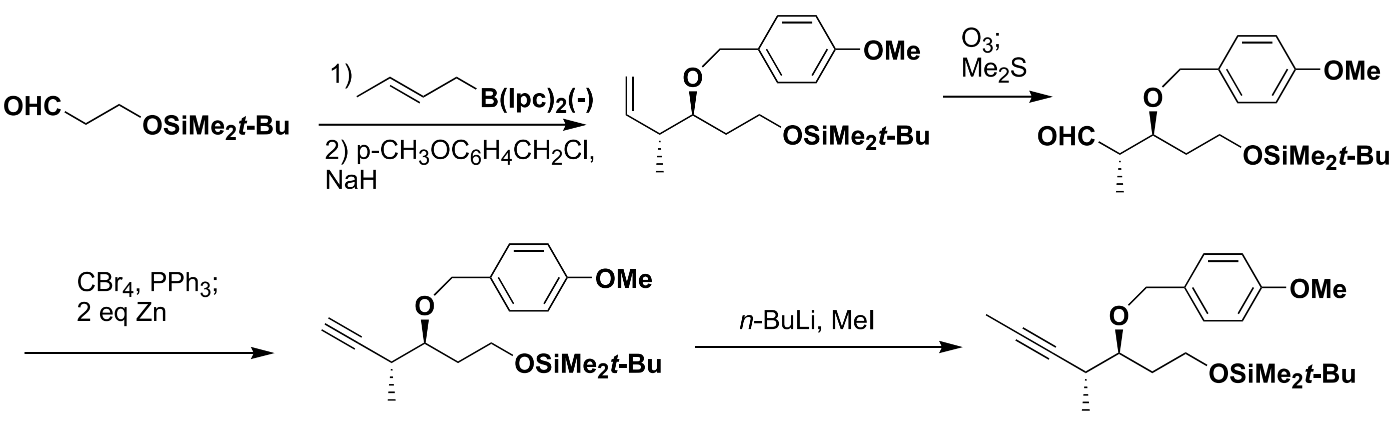
(1) See also K. Buzek. *J. Am. Chem. Soc.* **1994**, *116*, 5511.


MeO
OH
O
1) t-BuMe2SiCl, Et3N
2) DIBAL
H
OSiMe2t-Bu
(-)(Ipc)2B
OH
p-CH3OC6H4CH2Cl, NaH
O
OMe
1) O3; Me2S
2) NaBH4
HO

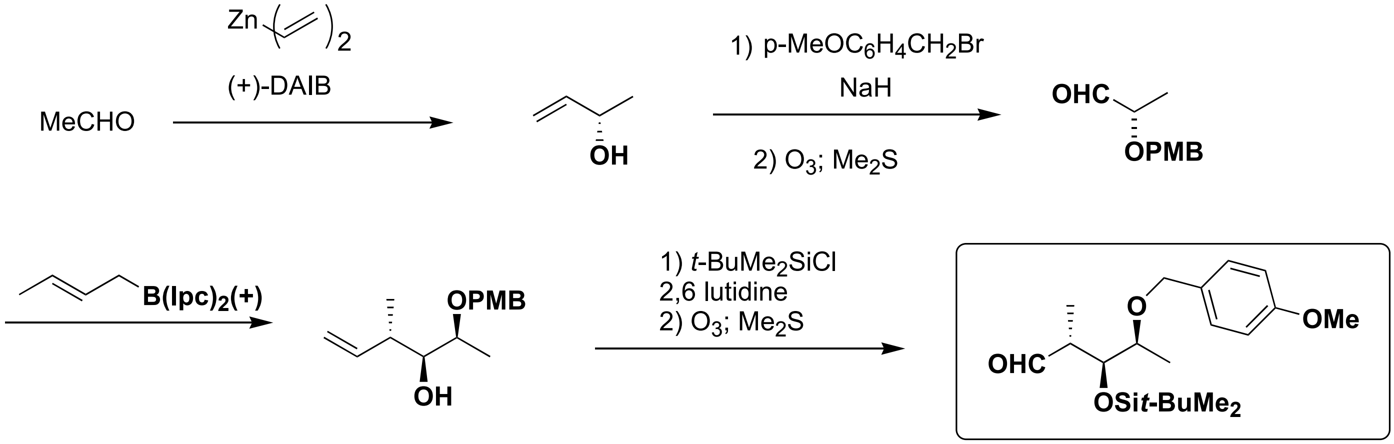
(2) See also D. A. Evans. *J. Org. Chem.* **1997**, *62*, 454.


MeCHO
(+)(Ipc)2B
OH
1) O3; H2O2
2) CH2N2
O
OMe
2 eq LDA; EtI
1) t-BuMe2SiCl, Et3N
2) DIBAL
t-BuMe2SiO
H
BF3-Et2O
Bu3Sn

(3) See also K. C. Nicolaou. *J. Am. Chem. Soc.* **1993**, *115*, 4419.

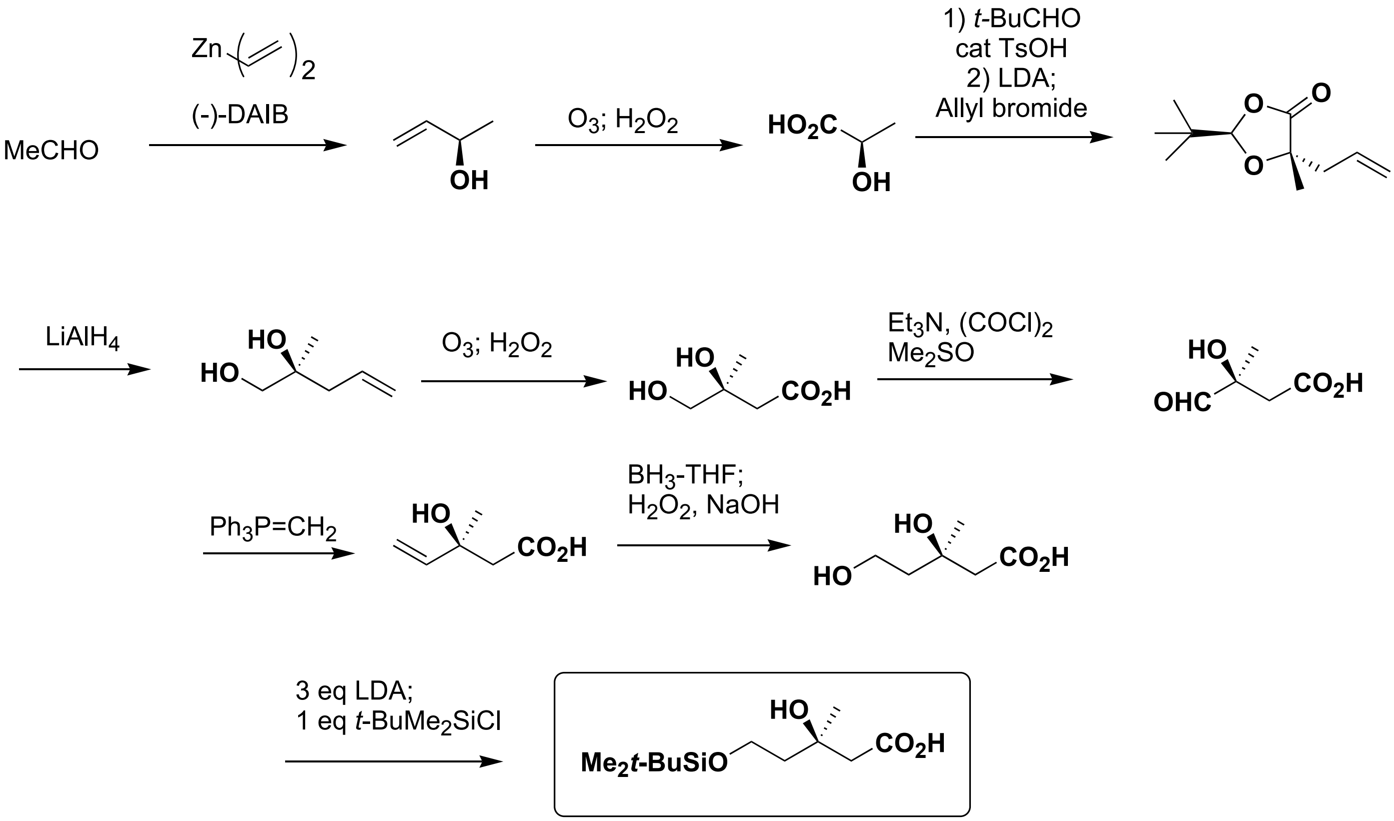

OHC
OSiMe2t-Bu
1) B(Ipc)2(-)
2) p-CH3OC6H4CH2Cl, NaH
O
OMe
O3; Me2S
CBr4, PPh3; 2 eq Zn
n-BuLi, MeI

(4) See also Z. Jin. *Org. Lett.* **2001**, *3*, 1447.



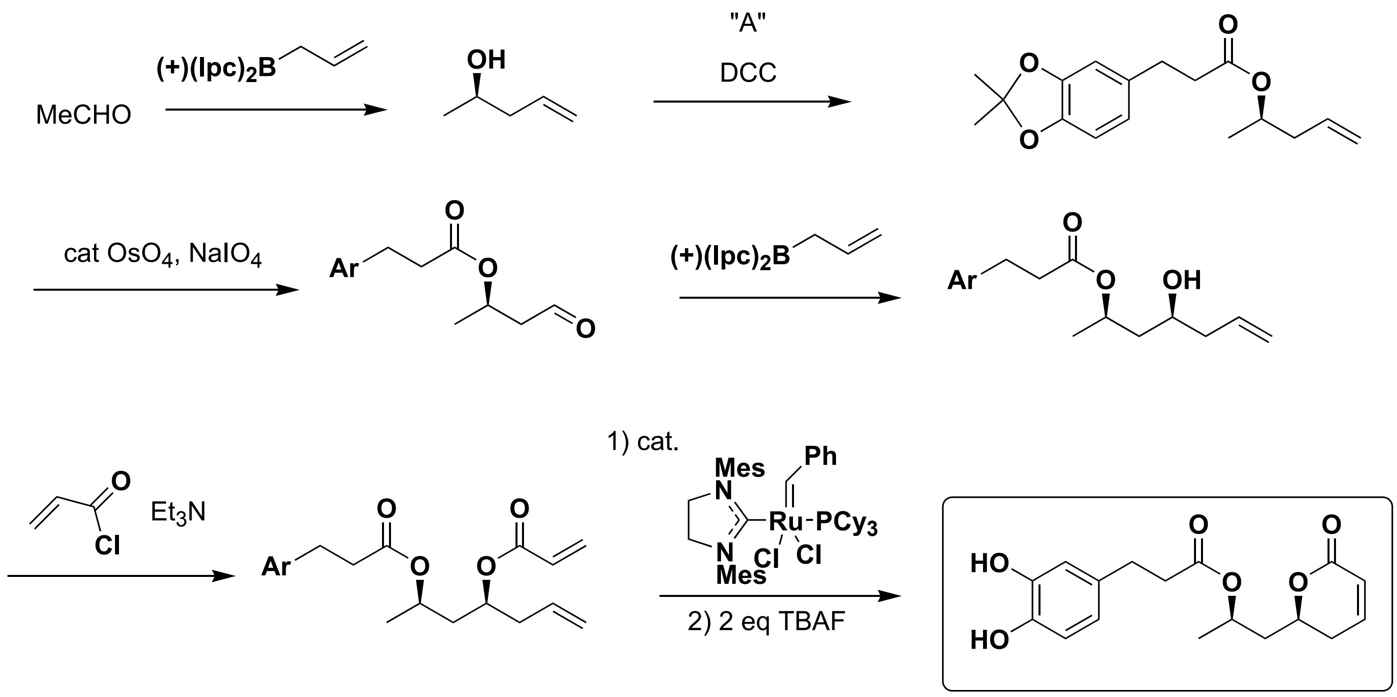
Zn( )2
(+)-DAIB
MeCHO
OH
1) p-MeOC6H4CH2Br
NaH
2) O3; Me2S
OHC
OPMB
B(Ipc)2(+)
OPMB
OH
1) t-BuMe2SiCl
2,6 lutidine
2) O3; Me2S
O
OMe
OHC
OSit-BuMe2

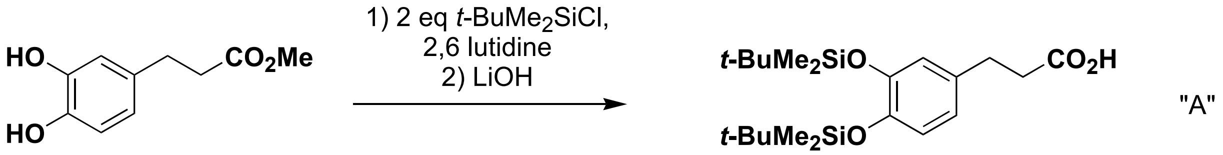
(5) See also K. Krohn. *Liebigs Ann. Chem.* **1994**, 167.



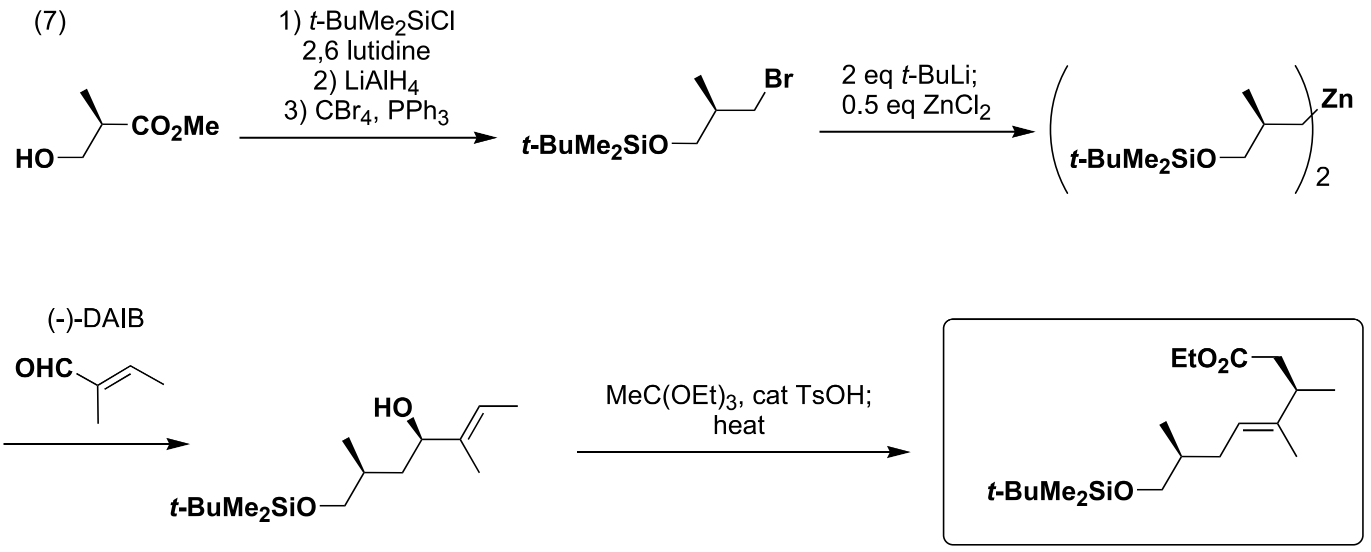
Zn( )2
(-)-DAIB
MeCHO
OH
O3; H2O2
HO2C
OH
1) t-BuCHO
cat TsOH
2) LDA;
Allyl bromide
O
O
O
LiAlH4
HO
HO
O3; H2O2
HO
HO
CO2H
Et3N, (COCl)2
Me2SO
HO
OHC
CO2H
Ph3P=CH2
HO
CO2H
BH3-THF;
H2O2, NaOH
HO
HO
CO2H
3 eq LDA;
1 eq t-BuMe2SiCl
HO
Me2t-BuSiO
CO2H

(6) See also P. V. Ramachandran *J. Org. Chem.* **2001**, *66*, 2512.

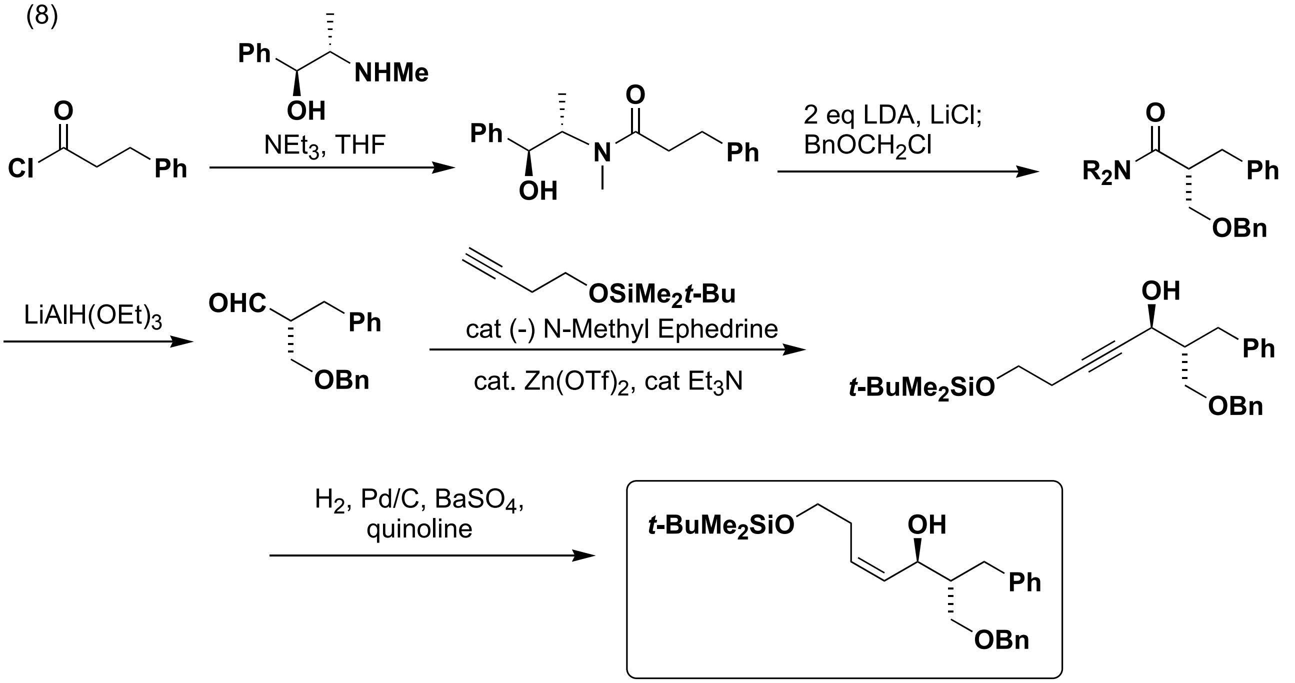

MeCHO
(+)(Ipc)$_2$B
OH
"A"
DCC
O
O
O
O
cat OsO$_4$, NaIO$_4$
Ar
O
O
O
(+)(Ipc)$_2$B
Ar
O
O
OH
O
Cl
Et$_3$N
Ar
O
O
O
O
1) cat.
Mes
N
N
Mes
Ph
Ru-PCy$_3$
Cl
Cl
2) 2 eq TBAF
HO
HO
O
O
O
O


HO
HO
CO$_2$Me
1) 2 eq *t*-BuMe$_2$SiCl,
2,6 lutidine
2) LiOH
t-BuMe$_2$SiO
t-BuMe$_2$SiO
CO$_2$H
"A"

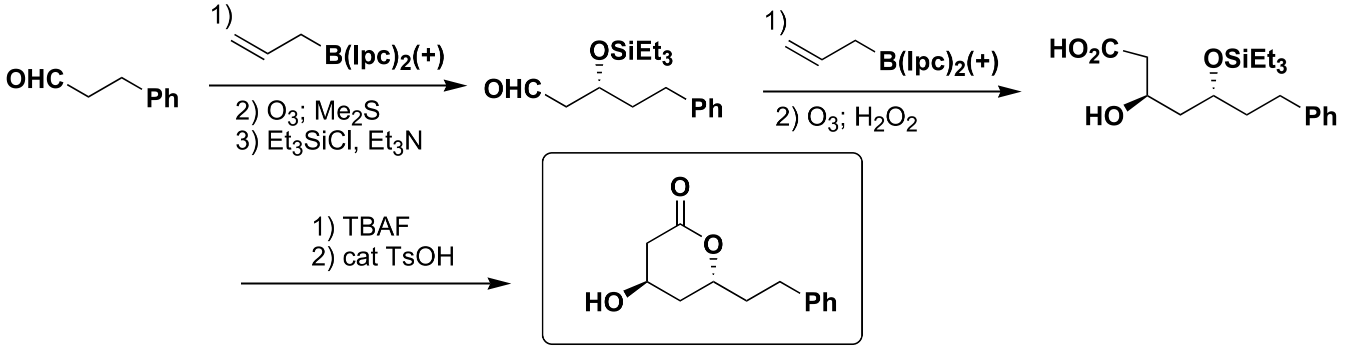
(7)


HO
CO$_2$Me
1) *t*-BuMe$_2$SiCl
2,6 lutidine
2) LiAlH$_4$
3) CBr$_4$, PPh$_3$
t-BuMe$_2$SiO
Br
2 eq *t*-BuLi;
0.5 eq ZnCl$_2$
t-BuMe$_2$SiO
Zn
2
(-)-DAIB
OHC
HO
t-BuMe$_2$SiO
MeC(OEt)$_3$, cat TsOH;
heat
EtO$_2$C
t-BuMe$_2$SiO

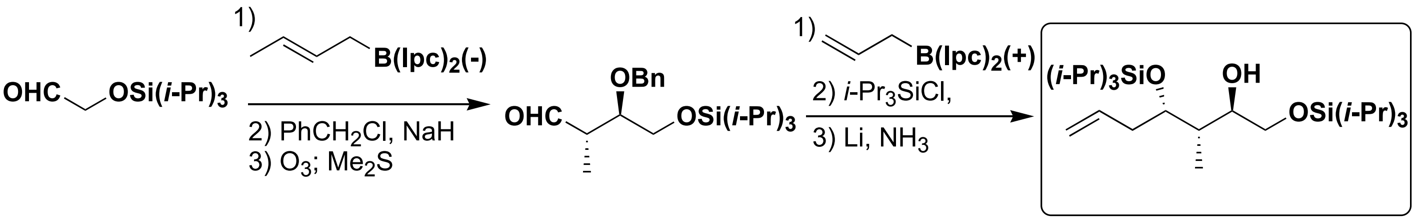
(8)


O
Cl
Ph
Ph
NHMe
OH
NEt$_3$, THF
Ph
OH
N
O
Ph
2 eq LDA, LiCl;
BnOCH$_2$Cl
O
R$_2$N
Ph
OBn
LiAlH(OEt)$_3$
OHC
Ph
OBn
OSiMe$_2$t-Bu
cat (-) N-Methyl Ephedrine
cat. Zn(OTf)$_2$, cat Et$_3$N
OH
Ph
t-BuMe$_2$SiO
OBn
H$_2$, Pd/C, BaSO$_4$,
quinoline
t-BuMe$_2$SiO
OH
Ph
OBn

(9) See also J. Cossy. *Tetrahedron Lett.* **2000**, *41*, 3363.


OHC
Ph
1)
B(Ipc)$_2$(+)
2) O$_3$; Me$_2$S
3) Et$_3$SiCl, Et$_3$N
OSiEt$_3$
OHC
Ph
1)
B(Ipc)$_2$(+)
2) O$_3$; H$_2$O$_2$
HO$_2$C
OSiEt$_3$
HO
Ph
1) TBAF
2) cat TsOH
O
O
HO
Ph

(10) See also Y. Kishi. *Angew. Chem. Int. Ed.* **1998**, *37*, 190.


OHC
OSi(i-Pr)$_3$
1)
B(Ipc)$_2$(-)
2) PhCH$_2$Cl, NaH
3) O$_3$; Me$_2$S
OBn
OHC
OSi(i-Pr)$_3$
1)
B(Ipc)$_2$(+)
2) i-Pr$_3$SiCl,
3) Li, NH$_3$
(i-Pr)$_3$SiO
OH
OSi(i-Pr)$_3$

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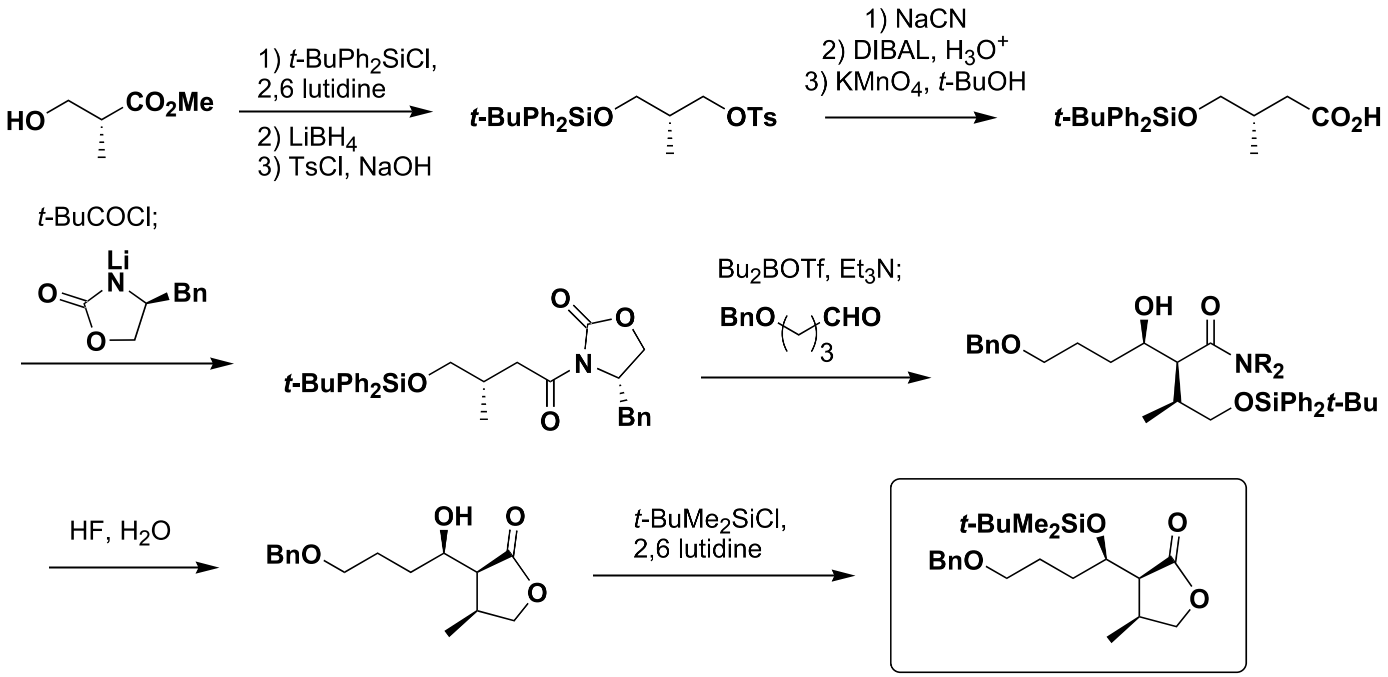
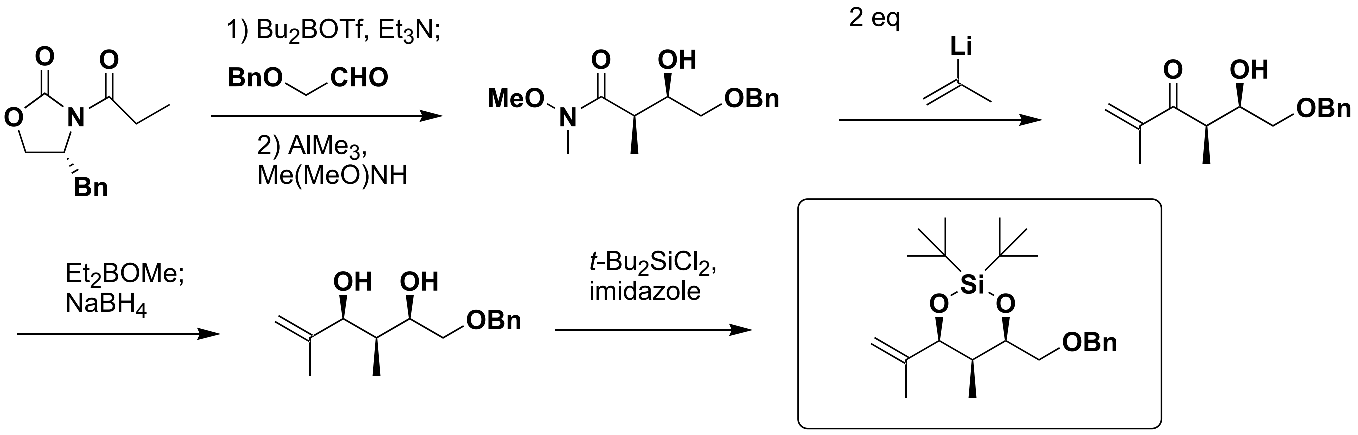
Problem Set 6 Solutions
Stereocontrolled Carbonyl Reduction and Aldol Reactions

(1)



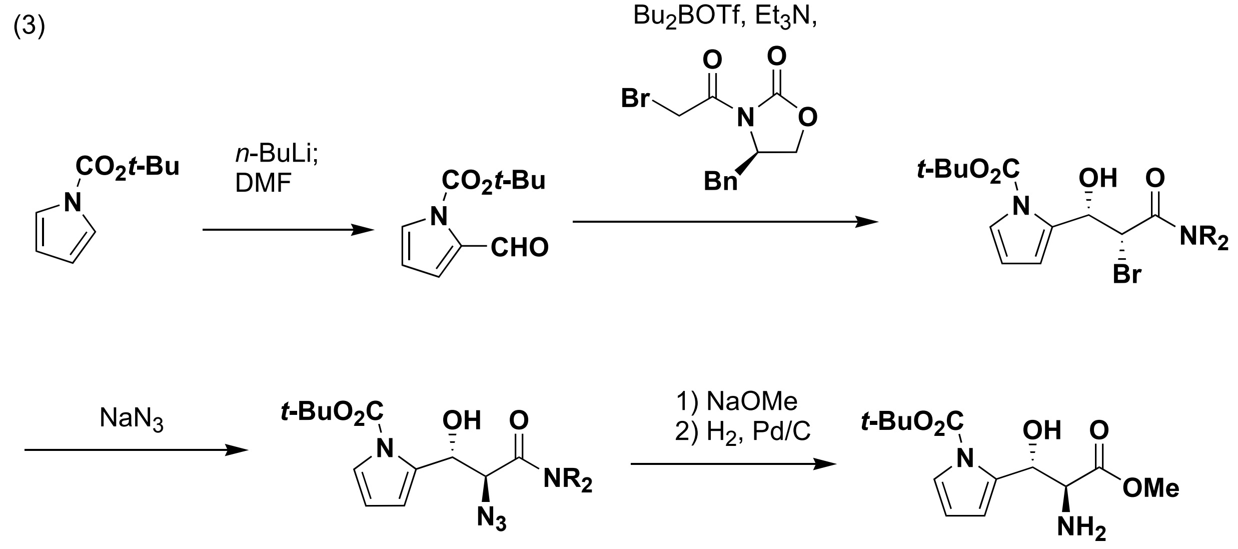
HO
CO$_2$Me
1) t-BuPh$_2$SiCl, 2,6 lutidine
2) LiBH$_4$
3) TsCl, NaOH
t-BuPh$_2$SiO
OTs
1) NaCN
2) DIBAL, H$_3$O$^+$
3) KMnO$_4$, t-BuOH
t-BuPh$_2$SiO
CO$_2$H
t-BuCOCl;
Li
N
Bn
O
O
t-BuPh$_2$SiO
N
O
Bn
Bu$_2$BOTf, Et$_3$N;
BnO
CHO
3
OH
O
BnO
NR$_2$
OSiPh$_2$$t$-Bu
HF, H$_2$O
BnO
OH
O
O
t-BuMe$_2$SiCl, 2,6 lutidine
t-BuMe$_2$SiO
BnO
O
O

(2)



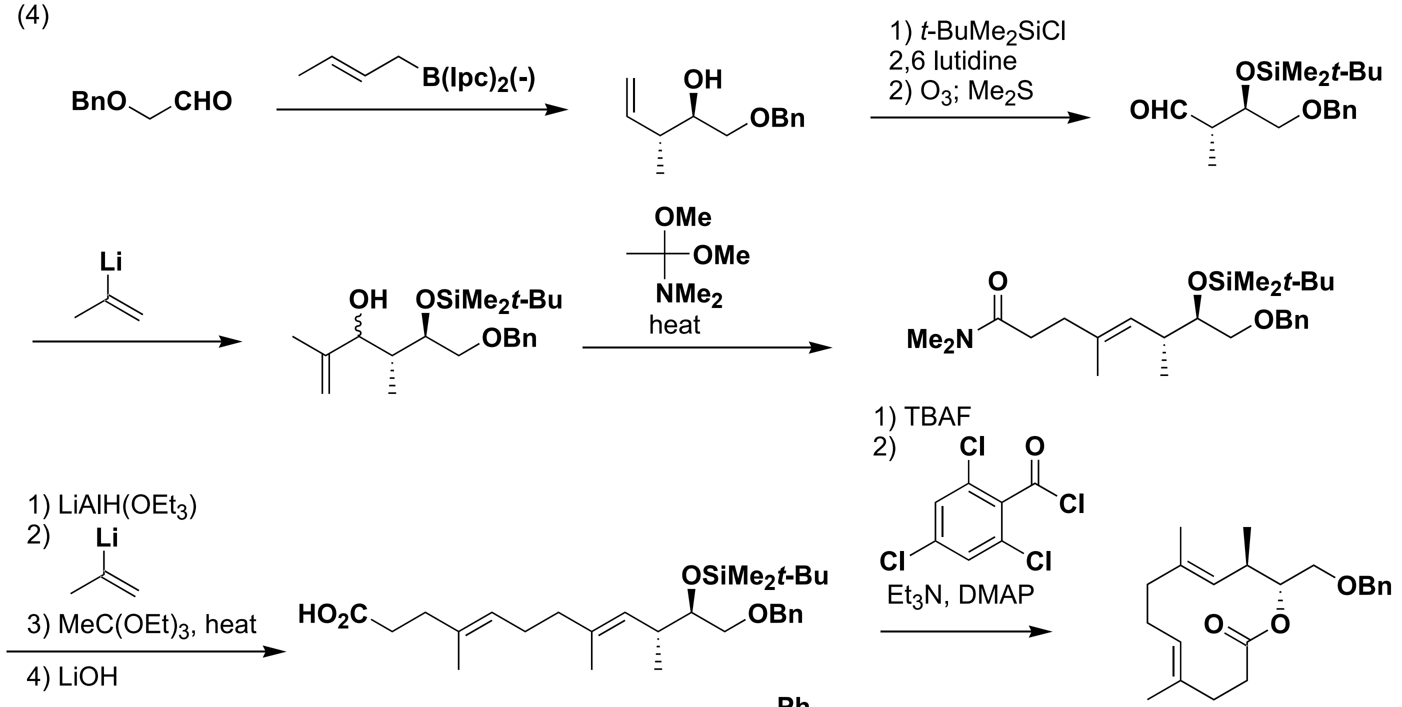
O
O
O
N
Bn
1) Bu$_2$BOTf, Et$_3$N;
BnO
CHO
2) AlMe$_3$, Me(MeO)NH
MeO
N
O
OH
OBn
2 eq
Li
O
OH
OBn
Et$_2$BOMe; NaBH$_4$
OH
OH
OBn
t-Bu$_2$SiCl$_2$, imidazole
Si
O
O
OBn

(3)



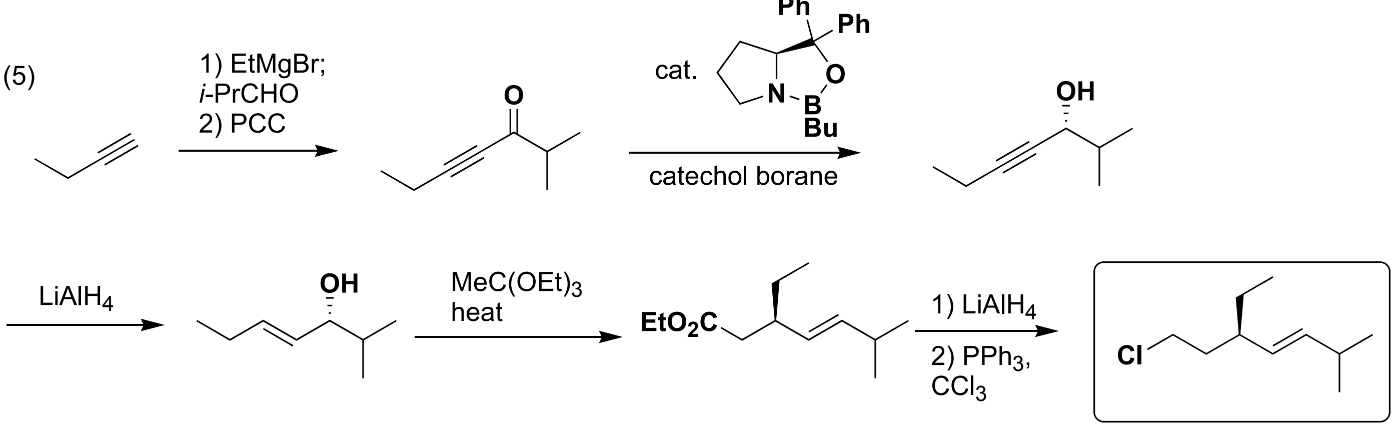
CO2t-Bu
N
n-BuLi;
DMF
CHO
Bu2BOTf, Et3N,
Br
O
N
O
Bn
t-BuO2C
OH
NR2
Br
NaN3
N3
1) NaOMe
2) H2, Pd/C
OMe
NH2

(4)



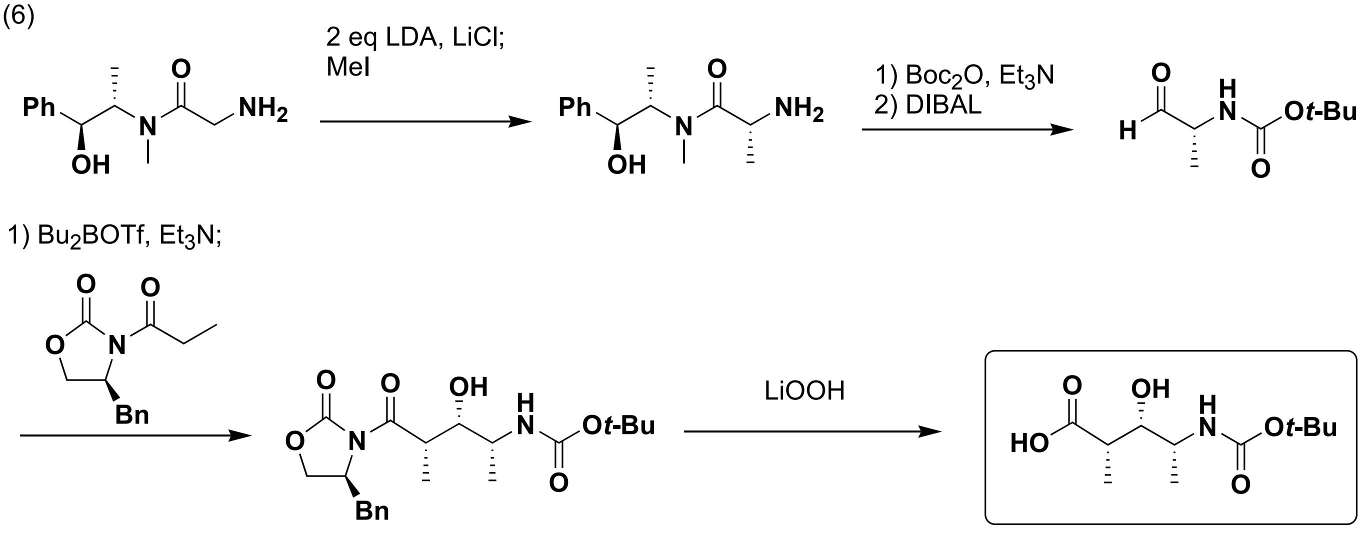
BnO
CHO
B(Ipc)2(-)
OH
OBn
1) t-BuMe2SiCl
2,6 lutidine
2) O3; Me2S
OHC
OSiMe2t-Bu
Li
OMe
OMe
NMe2
heat
Me2N
1) LiAlH(OEt3)
2)
3) MeC(OEt)3, heat
4) LiOH
HO2C
1) TBAF
2)
Cl
Et3N, DMAP

(5)

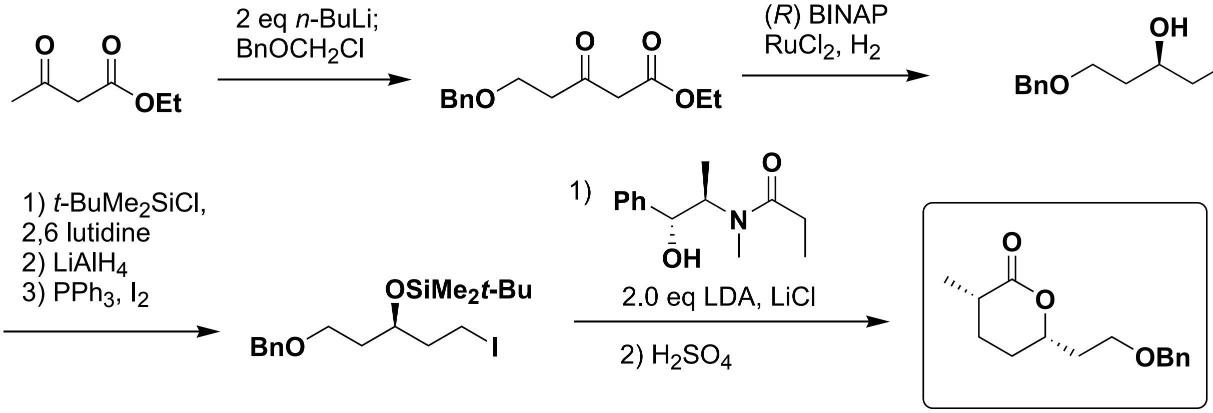


1) EtMgBr;
i-PrCHO
2) PCC
O
cat.
Ph
Ph
N
B
O
Bu
catechol borane
OH
LiAlH4
MeC(OEt)3
heat
EtO2C
1) LiAlH4
2) PPh3,
CCl3
Cl

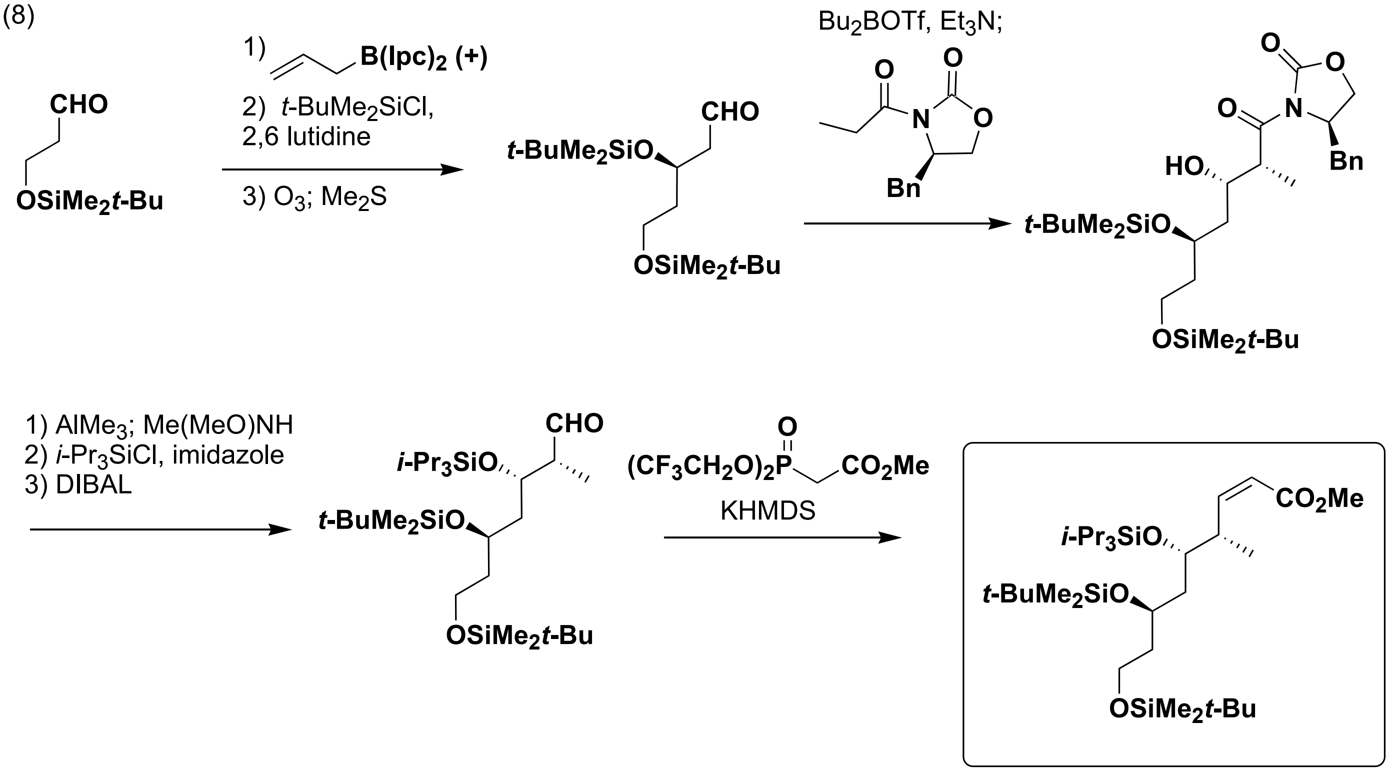
(6)


2 eq LDA, LiCl;
MeI
1) Boc$_2$O, Et$_3$N
2) DIBAL
1) Bu$_2$BOTf, Et$_3$N;
LiOOH
Ph
OH
N
NH$_2$
O
H
Ot-Bu
Bn

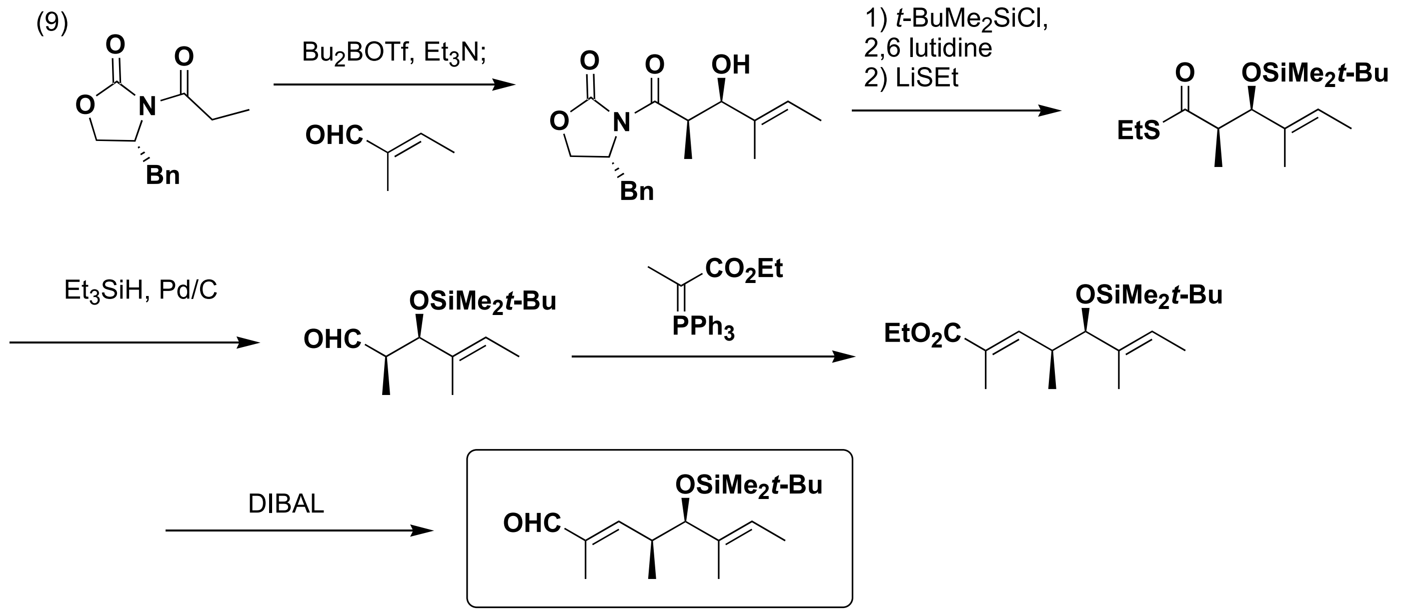
(7)


2 eq n-BuLi;
BnOCH$_2$Cl
(R) BINAP
RuCl$_2$, H$_2$
1) t-BuMe$_2$SiCl,
2,6 lutidine
2) LiAlH$_4$
3) PPh$_3$, I$_2$
1)
2.0 eq LDA, LiCl
2) H$_2$SO$_4$
OEt
BnO
OH
OSiMe$_2$t-Bu
I
Ph
N
OBn

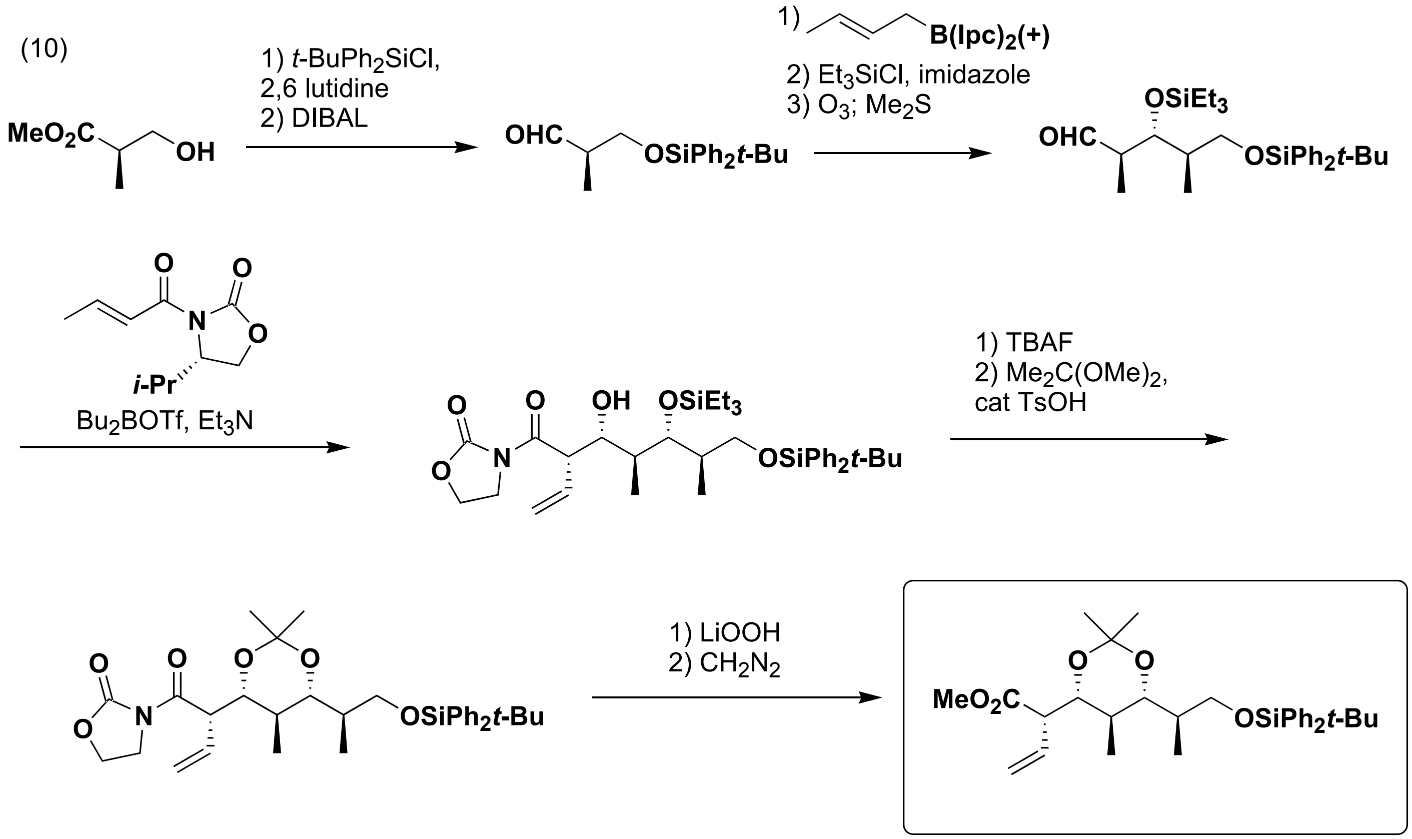
(8)


1)
B(Ipc)$_2$ (+)
2) t-BuMe$_2$SiCl,
2,6 lutidine
3) O$_3$; Me$_2$S
Bu$_2$BOTf, Et$_3$N;
1) AlMe$_3$; Me(MeO)NH
2) i-Pr$_3$SiCl, imidazole
3) DIBAL
(CF$_3$CH$_2$O)$_2$P
CO$_2$Me
KHMDS
CHO
OSiMe$_2$t-Bu
t-BuMe$_2$SiO
HO
Bn
i-Pr$_3$SiO

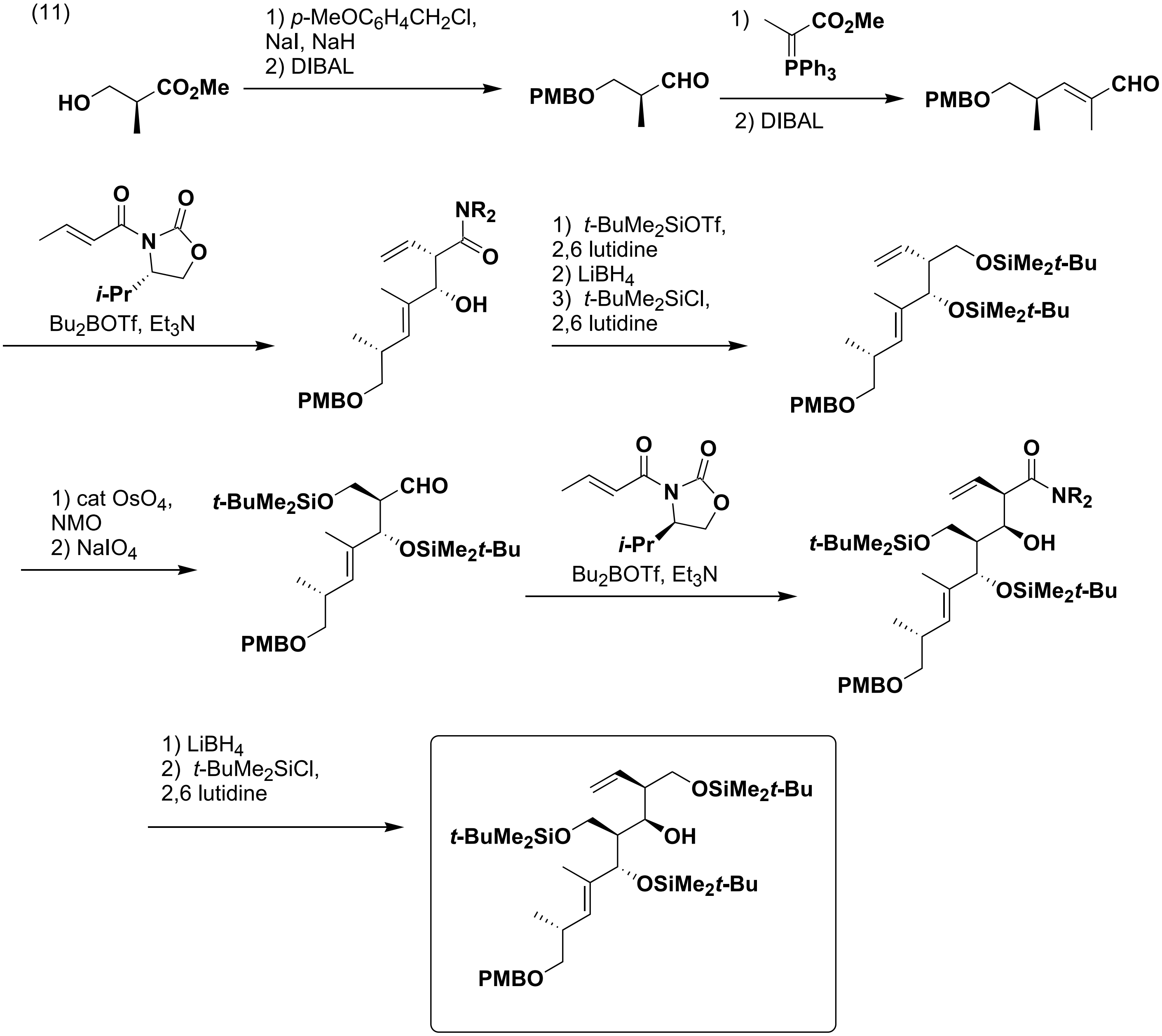
(9)


Bu2BOTf, Et3N;
OHC
1) t-BuMe2SiCl,
2,6 lutidine
2) LiSEt
OSiMe2t-Bu
EtS
Bn
OH
Et3SiH, Pd/C
OHC
CO2Et
PPh3
EtO2C
DIBAL

(10)


MeO2C
OH
1) t-BuPh2SiCl,
2,6 lutidine
2) DIBAL
OHC
OSiPh2t-Bu
1) B(Ipc)2(+)
2) Et3SiCl, imidazole
3) O3; Me2S
OSiEt3
i-Pr
Bu2BOTf, Et3N
1) TBAF
2) Me2C(OMe)2,
cat TsOH
1) LiOOH
2) CH2N2
MeO2C

(11)

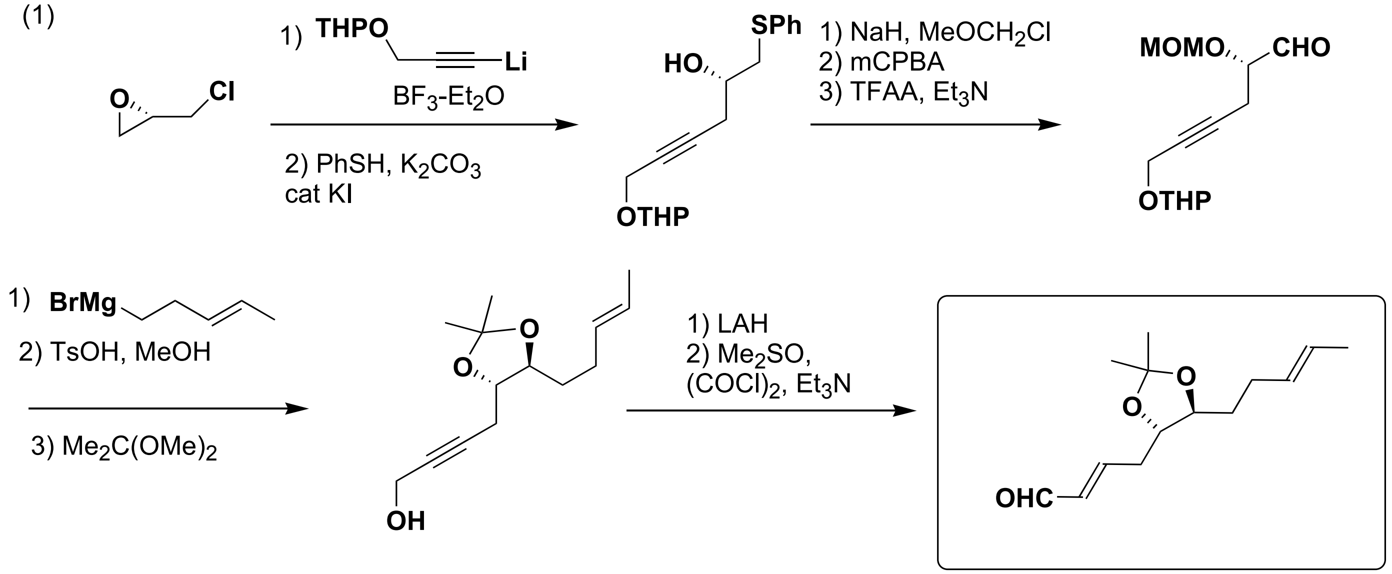

HO
CO2Me
1) p-MeOC6H4CH2Cl,
NaI, NaH
2) DIBAL
PMBO
CHO
1) CO2Me
PPh3
2) DIBAL
PMBO
CHO
O
O
N
O
i-Pr
Bu2BOTf, Et3N
NR2
O
OH
PMBO
1) t-BuMe2SiOTf,
2,6 lutidine
2) LiBH4
3) t-BuMe2SiCl,
2,6 lutidine
OSiMe2t-Bu
OSiMe2t-Bu
PMBO
1) cat OsO4,
NMO
2) NaIO4
t-BuMe2SiO
CHO
OSiMe2t-Bu
PMBO
O
O
N
O
i-Pr
Bu2BOTf, Et3N
O
NR2
t-BuMe2SiO
OH
OSiMe2t-Bu
PMBO
1) LiBH4
2) t-BuMe2SiCl,
2,6 lutidine
OSiMe2t-Bu
t-BuMe2SiO
OH
OSiMe2t-Bu
PMBO

Massachusetts Institute of Technology
Organic Chemistry 5.512

May 4, 2005
Wesley Austin

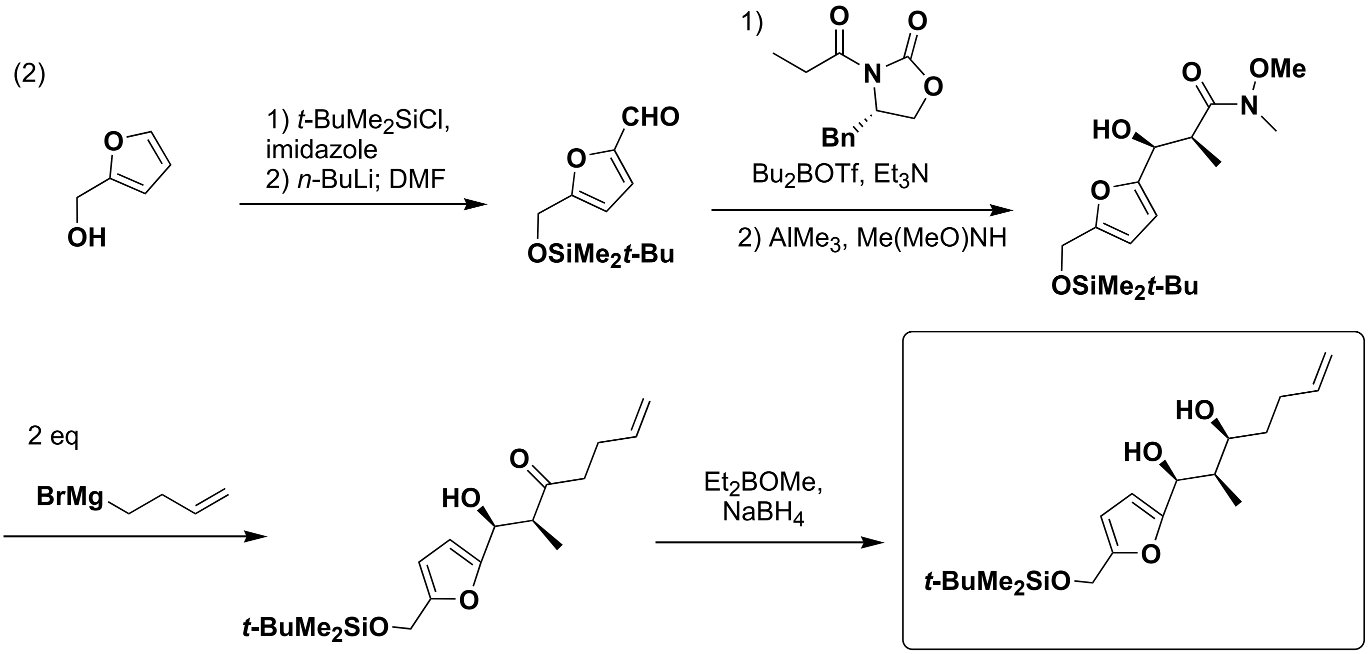
Problem Set 7 Solutions
Practice Problems for Second Exam

(1)



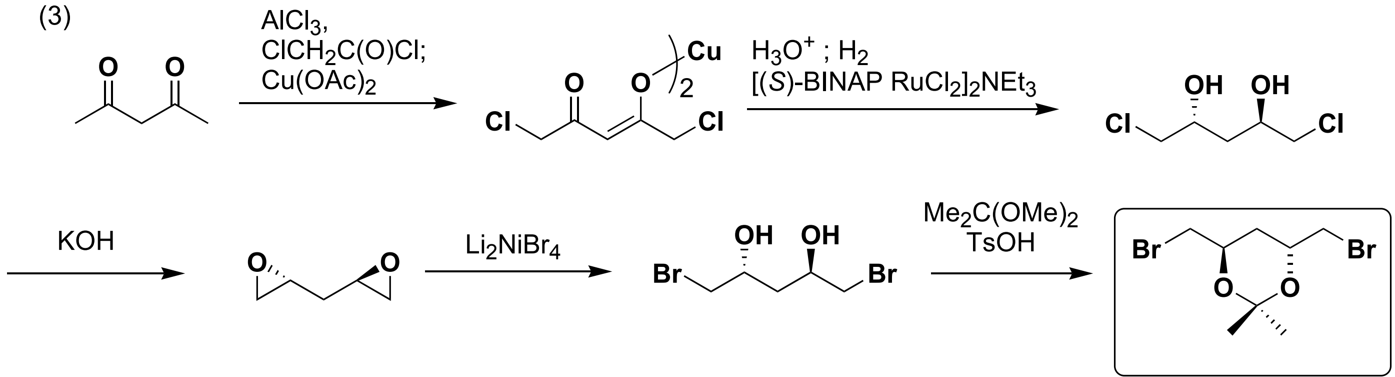
1) THPO—≡—Li
BF3-Et2O
2) PhSH, K2CO3
cat KI
Cl
O
HO
SPh
OTHP
1) NaH, MeOCH2Cl
2) mCPBA
3) TFAA, Et3N
MOMO
CHO
OTHP
1) BrMg
2) TsOH, MeOH
3) Me2C(OMe)2
O
O
OH
1) LAH
2) Me2SO,
(COCl)2, Et3N
O
O
OHC

(2)

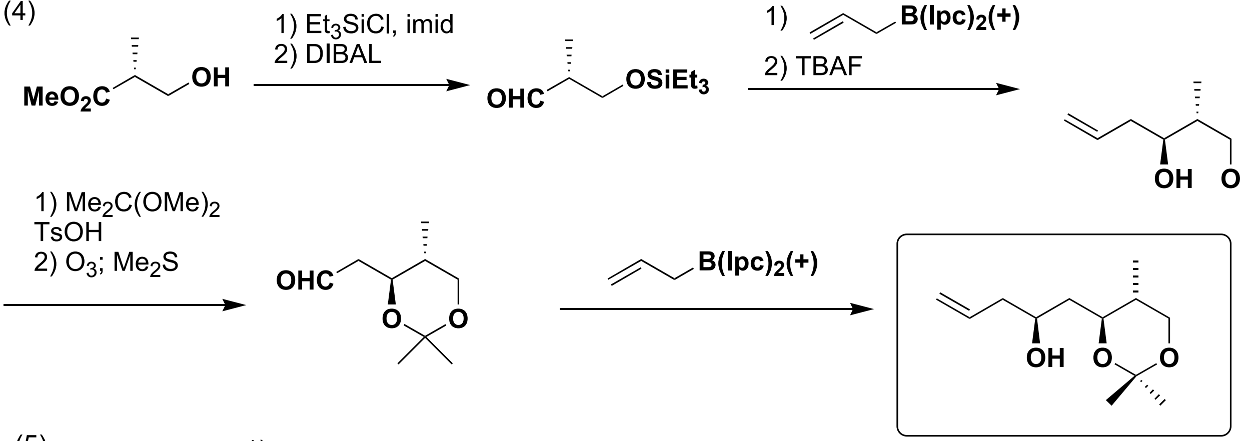


O
OH
1) t-BuMe2SiCl,
imidazole
2) n-BuLi; DMF
CHO
O
OSiMe2t-Bu
1)
O
O
N
O
Bn
Bu2BOTf, Et3N
2) AlMe3, Me(MeO)NH
O
OMe
N
HO
O
OSiMe2t-Bu
2 eq
BrMg
O
HO
O
t-BuMe2SiO
Et2BOMe,
NaBH4
HO
HO
O
t-BuMe2SiO

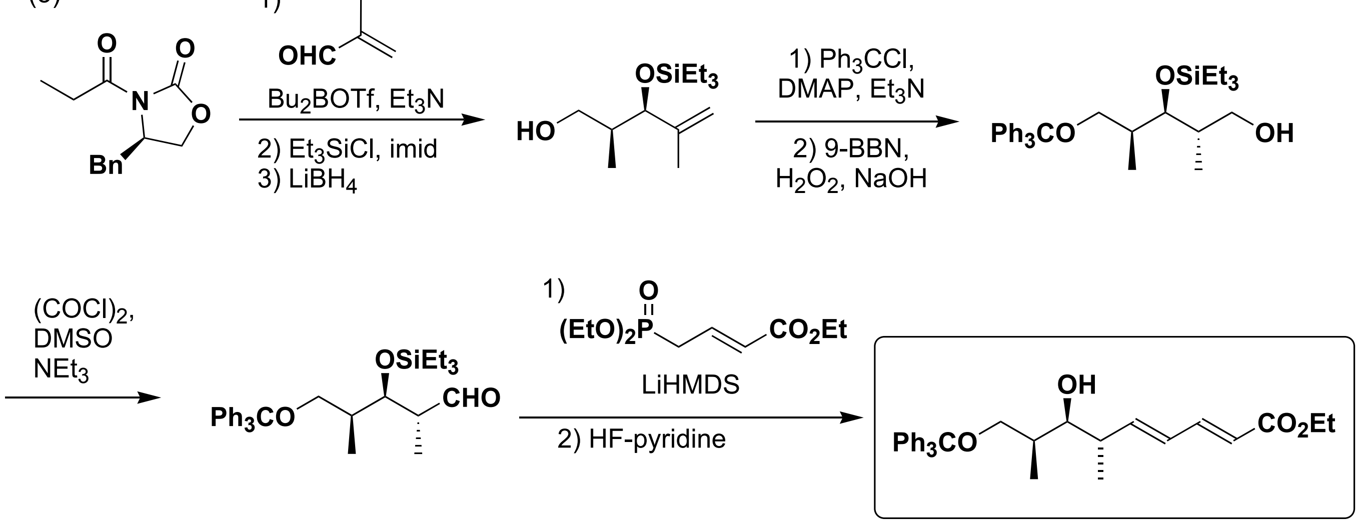
(3)


AlCl3,
ClCH2C(O)Cl;
Cu(OAc)2
Cu
O
O
2
Cl
Cl
H3O+ ; H2
[(S)-BINAP RuCl2]2NEt3
OH OH
Cl
Cl
KOH
O
O
Li2NiBr4
OH OH
Br
Br
Me2C(OMe)2
TsOH
Br
Br
O
O

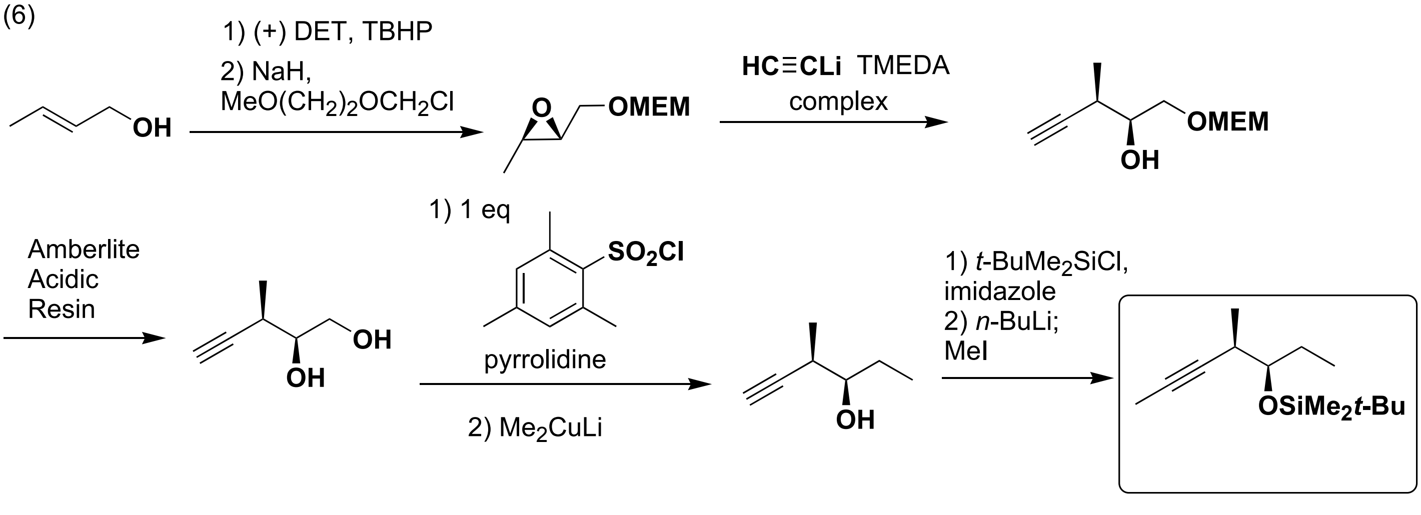
(4)


MeO2C
OH
1) Et3SiCl, imid
2) DIBAL
OHC
OSiEt3
1) B(Ipc)2(+)
2) TBAF
OH OH
1) Me2C(OMe)2
TsOH
2) O3; Me2S
OHC
O
O
B(Ipc)2(+)
OH
O
O

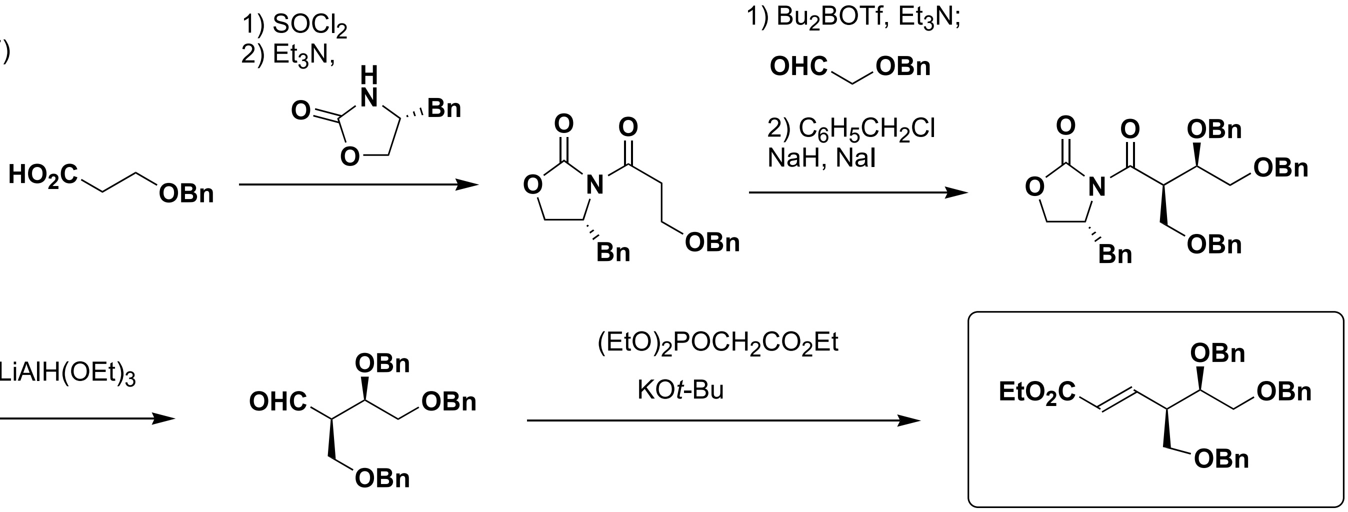
(5)


O
O
N
O
Bn
1) OHC
Bu2BOTf, Et3N
2) Et3SiCl, imid
3) LiBH4
OSiEt3
HO
1) Ph3CCl,
DMAP, Et3N
2) 9-BBN,
H2O2, NaOH
OSiEt3
Ph3CO
OH
(COCl)2,
DMSO
NEt3
OSiEt3
Ph3CO
CHO
1) (EtO)2P(O) CO2Et
LiHMDS
2) HF-pyridine
OH
Ph3CO
CO2Et

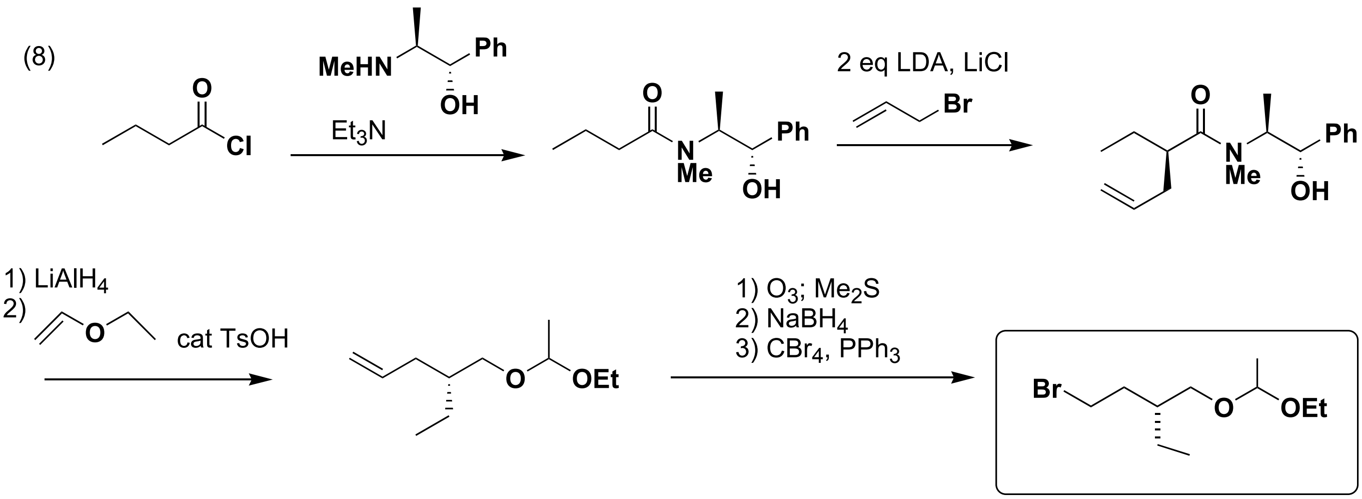
(6)


OH
1) (+) DET, TBHP
2) NaH,
MeO(CH2)2OCH2Cl
O
OMEM
HC≡CLi TMEDA
complex
OMEM
OH
Amberlite
Acidic
Resin
OH
OH
1) 1 eq
SO2Cl
pyrrolidine
2) Me2CuLi
OH
1) t-BuMe2SiCl,
imidazole
2) n-BuLi;
MeI
OSiMe2t-Bu

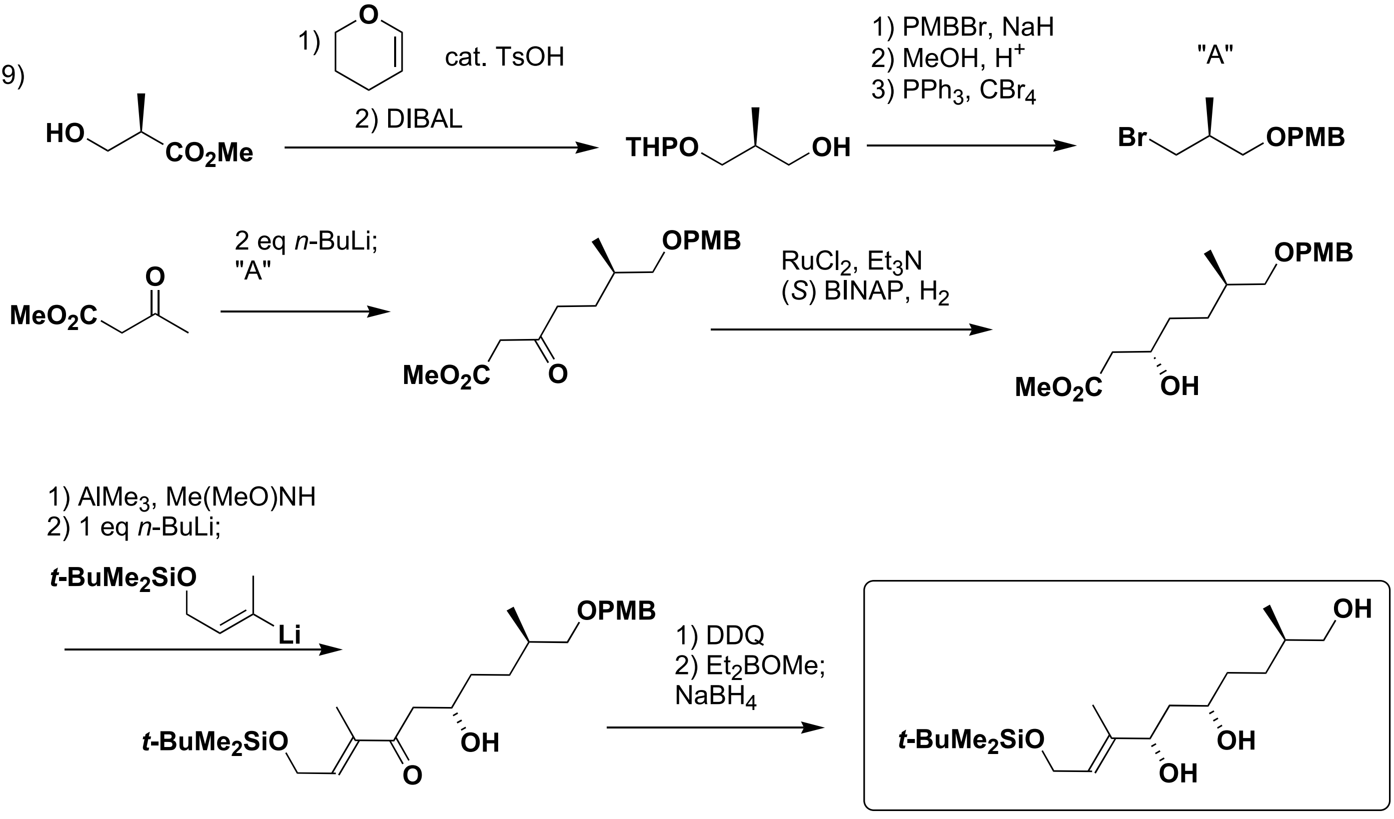
(7)


1) $SOCl_2$
2) Et_3N,
Bn
1) Bu_2BOTf, Et_3N;
OHC OBn
2) $C_6H_5CH_2Cl$
NaH, NaI
HO_2C
OBn
LiAlH(OEt)$_3$
OHC
(EtO)$_2$POCH$_2$CO$_2$Et
KO*t*-Bu
EtO_2C

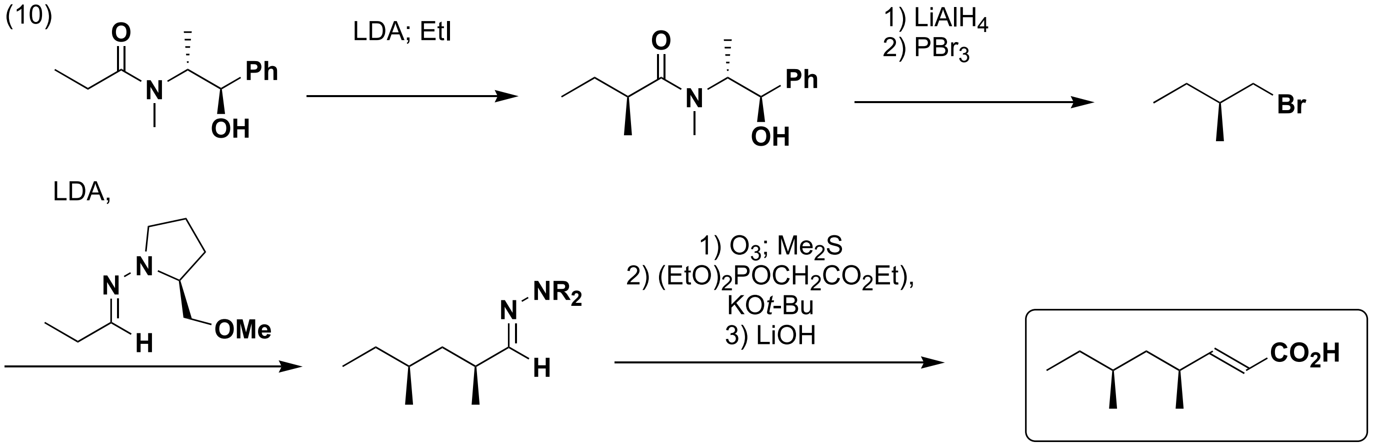
(8)


MeHN
Ph
OH
Cl
Et_3N
2 eq LDA, LiCl
Br
N
Me
1) $LiAlH_4$
2)
cat TsOH
OEt
1) O_3; Me_2S
2) $NaBH_4$
3) CBr_4, PPh_3
Br

(9)

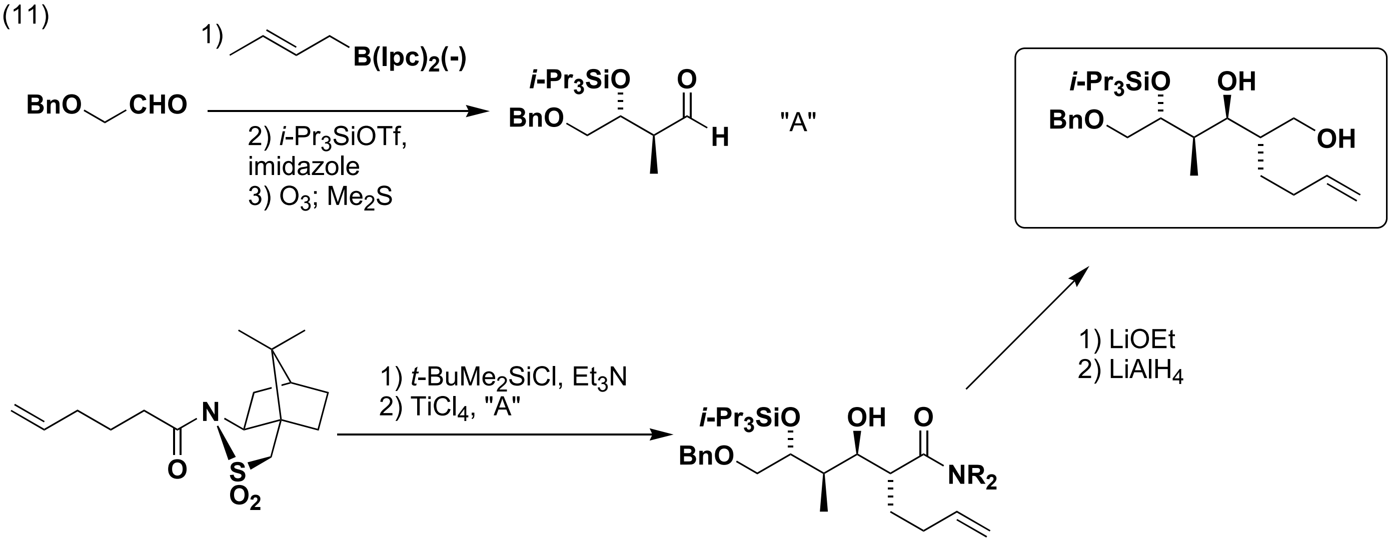

1)
cat. TsOH
2) DIBAL
HO
CO_2Me
THPO
OH
1) PMBBr, NaH
2) MeOH, H^+
3) PPh_3, CBr_4
"A"
Br
OPMB
MeO_2C
2 eq *n*-BuLi;
"A"
$RuCl_2$, Et_3N
(*S*) BINAP, H_2
1) $AlMe_3$, Me(MeO)NH
2) 1 eq *n*-BuLi;
t-$BuMe_2SiO$
Li
1) DDQ
2) Et_2BOMe;
$NaBH_4$

(10)



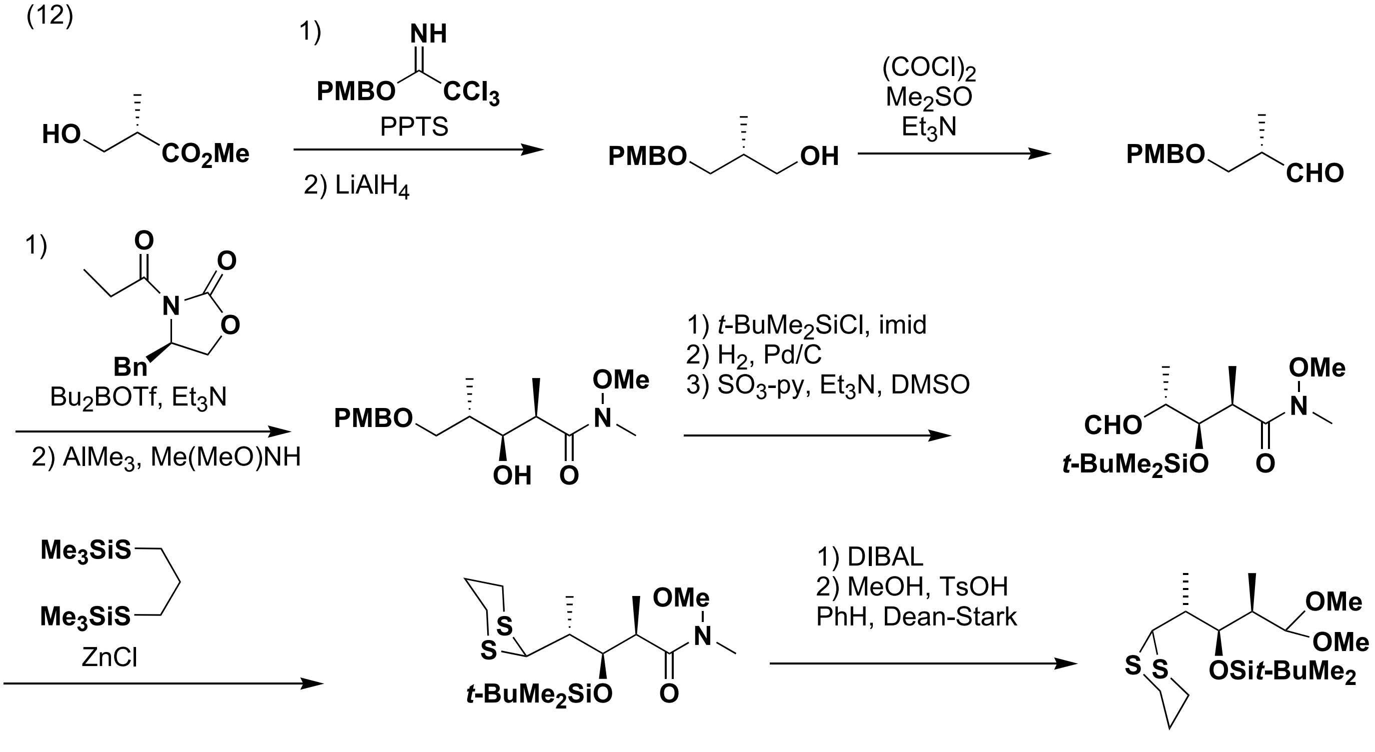
O
N
Ph
OH
LDA; EtI
O
N
Ph
OH
1) LiAlH$_4$
2) PBr$_3$
Br
LDA,
N
N
H
OMe
N
NR$_2$
H
1) O$_3$; Me$_2$S
2) (EtO)$_2$POCH$_2$CO$_2$Et),
KO*t*-Bu
3) LiOH
CO$_2$H

(11)

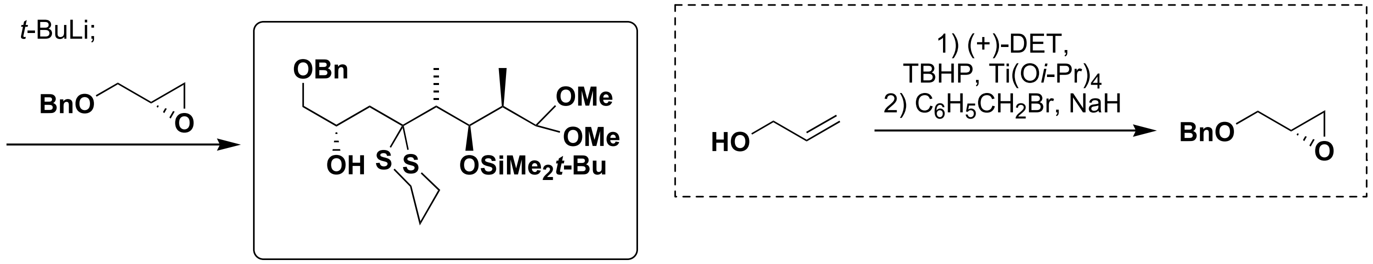


1)
B(Ipc)$_2$(-)
BnO
CHO
2) *i*-Pr$_3$SiOTf,
imidazole
3) O$_3$; Me$_2$S
i-Pr$_3$SiO
O
BnO
H
"A"
i-Pr$_3$SiO
OH
BnO
OH
N
O
S
O$_2$
1) *t*-BuMe$_2$SiCl, Et$_3$N
2) TiCl$_4$, "A"
i-Pr$_3$SiO
OH
O
BnO
NR$_2$
1) LiOEt
2) LiAlH$_4$

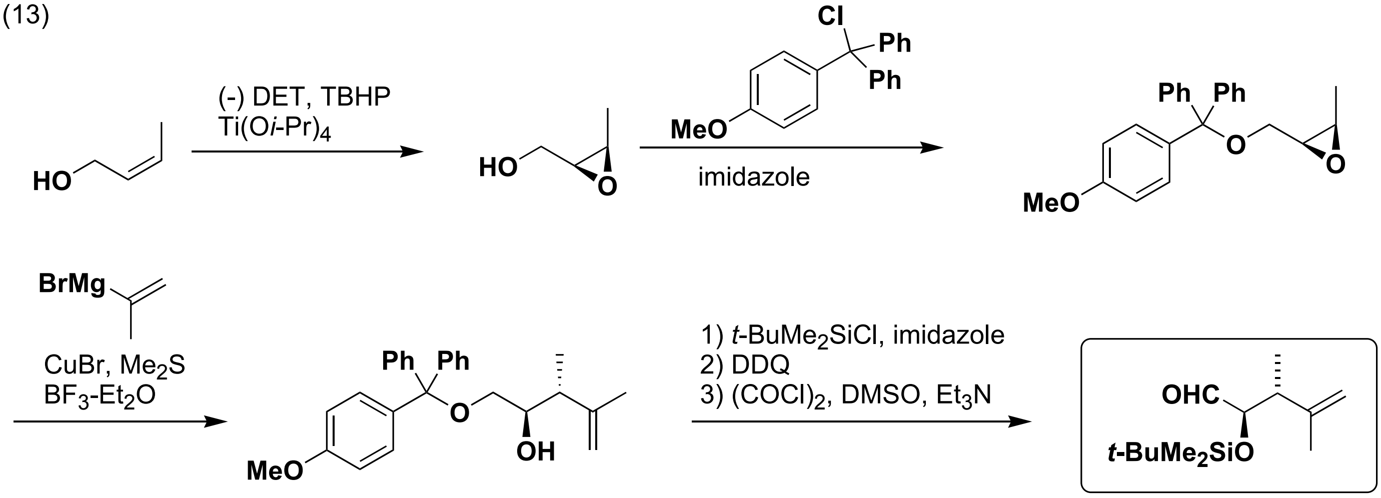
(12)



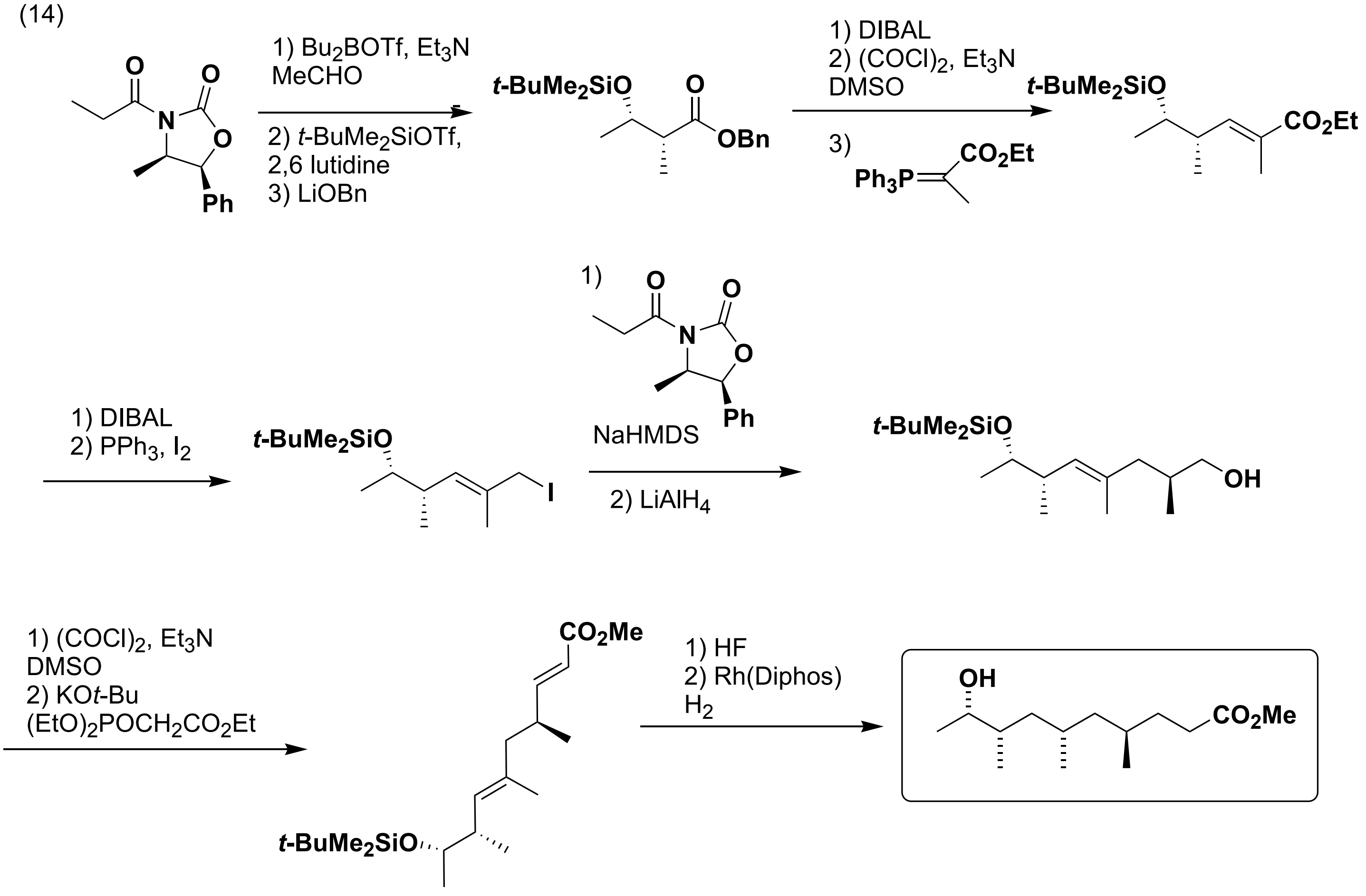
1)
NH
PMBO
CCl$_3$
PPTS
HO
CO$_2$Me
2) LiAlH$_4$
PMBO
OH
(COCl)$_2$
Me$_2$SO
Et$_3$N
PMBO
CHO
1)
O
O
N
O
Bn
Bu$_2$BOTf, Et$_3$N
2) AlMe$_3$, Me(MeO)NH
PMBO
OMe
N
OH
O
1) *t*-BuMe$_2$SiCl, imid
2) H$_2$, Pd/C
3) SO$_3$-py, Et$_3$N, DMSO
OMe
N
CHO
t-BuMe$_2$SiO
O
Me$_3$SiS
Me$_3$SiS
ZnCl
S
S
OMe
N
t-BuMe$_2$SiO
O
1) DIBAL
2) MeOH, TsOH
PhH, Dean-Stark
OMe
OMe
S
S
OSi*t*-BuMe$_2$


t-BuLi;
BnO
O
OBn
OMe
OMe
OH
S
S
OSiMe2t-Bu
1) (+)-DET,
TBHP, Ti(Oi-Pr)4
2) C6H5CH2Br, NaH
HO
BnO
O

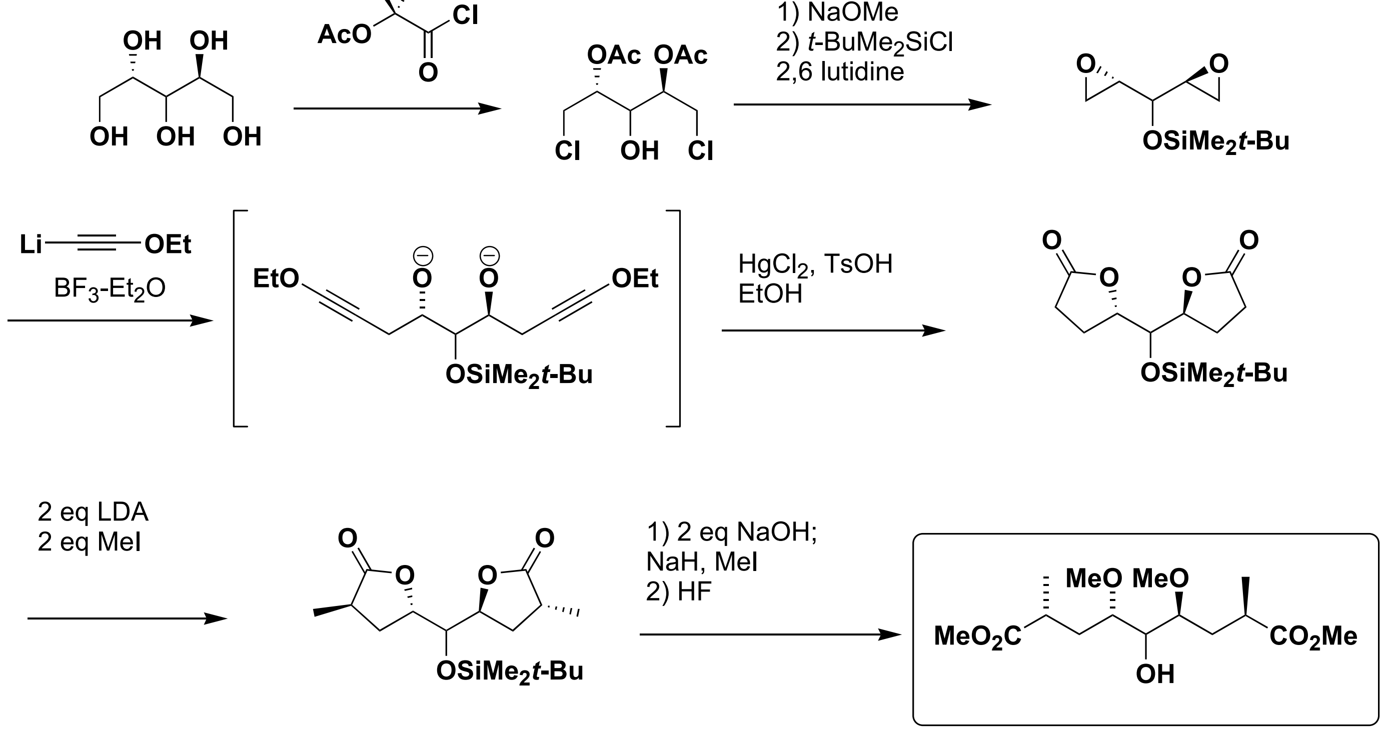
(13)


HO
(-) DET, TBHP
Ti(Oi-Pr)4
HO
O
Cl
Ph
Ph
MeO
imidazole
Ph
Ph
O
O
MeO
BrMg
CuBr, Me2S
BF3-Et2O
Ph
Ph
O
OH
MeO
1) t-BuMe2SiCl, imidazole
2) DDQ
3) (COCl)2, DMSO, Et3N
OHC
t-BuMe2SiO

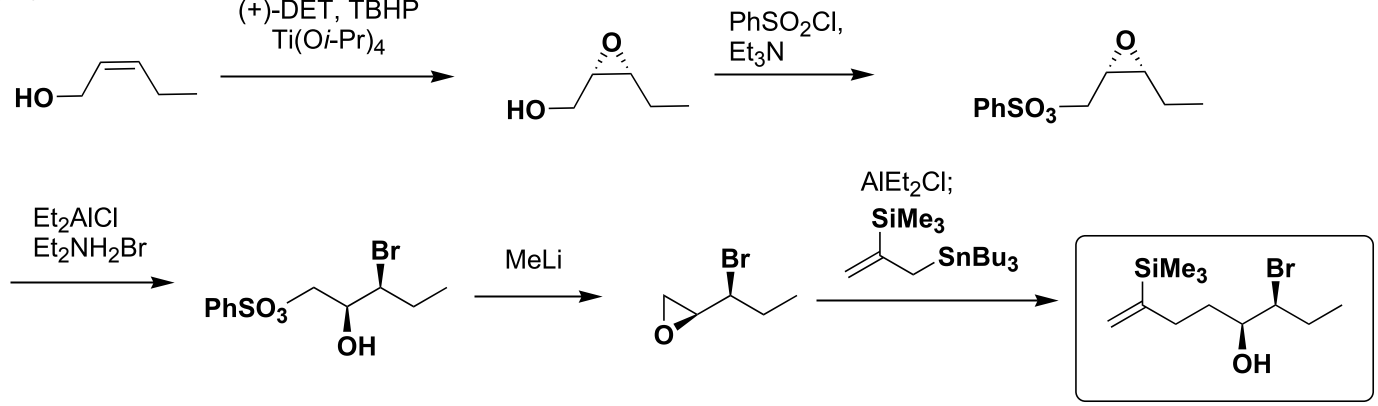
(14)


O
O
N
O
Ph
1) Bu2BOTf, Et3N
MeCHO
2) t-BuMe2SiOTf,
2,6 lutidine
3) LiOBn
t-BuMe2SiO
O
OBn
1) DIBAL
2) (COCl)2, Et3N
DMSO
3)
CO2Et
Ph3P
t-BuMe2SiO
CO2Et
1) DIBAL
2) PPh3, I2
t-BuMe2SiO
I
1)
O
O
N
O
Ph
NaHMDS
2) LiAlH4
t-BuMe2SiO
OH
1) (COCl)2, Et3N
DMSO
2) KOt-Bu
(EtO)2POCH2CO2Et
CO2Me
t-BuMe2SiO
1) HF
2) Rh(Diphos)
H2
OH
CO2Me

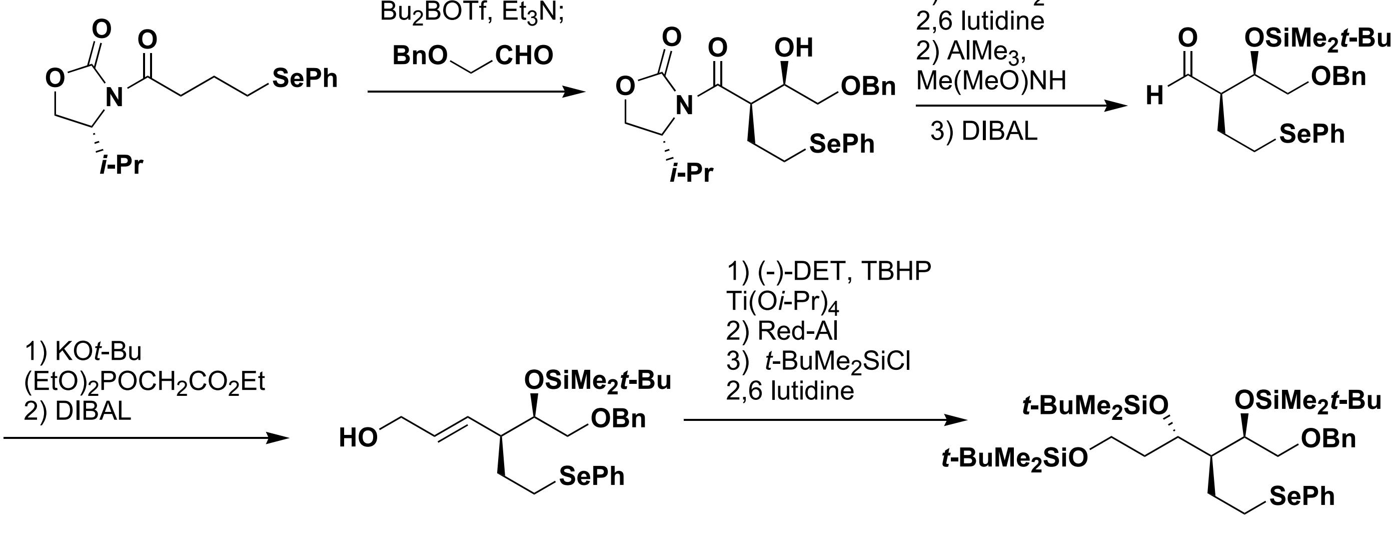
(15)

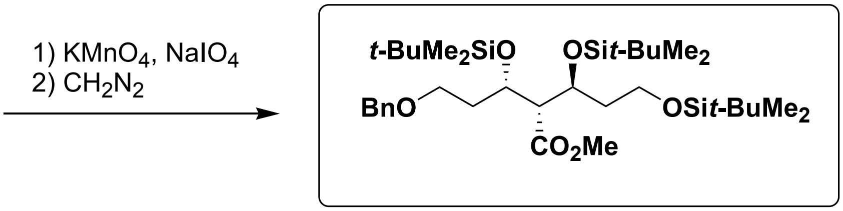

OH OH
OH OH OH
AcO
Cl
O
OAc OAc
Cl OH Cl
1) NaOMe
2) t-BuMe2SiCl
2,6 lutidine
O O
OSiMe2t-Bu
Li—≡—OEt
BF3-Et2O
EtO
OEt
OSiMe2t-Bu
HgCl2, TsOH
EtOH
OSiMe2t-Bu
2 eq LDA
2 eq MeI
OSiMe2t-Bu
1) 2 eq NaOH;
NaH, MeI
2) HF
MeO MeO
MeO2C
CO2Me
OH

(16)

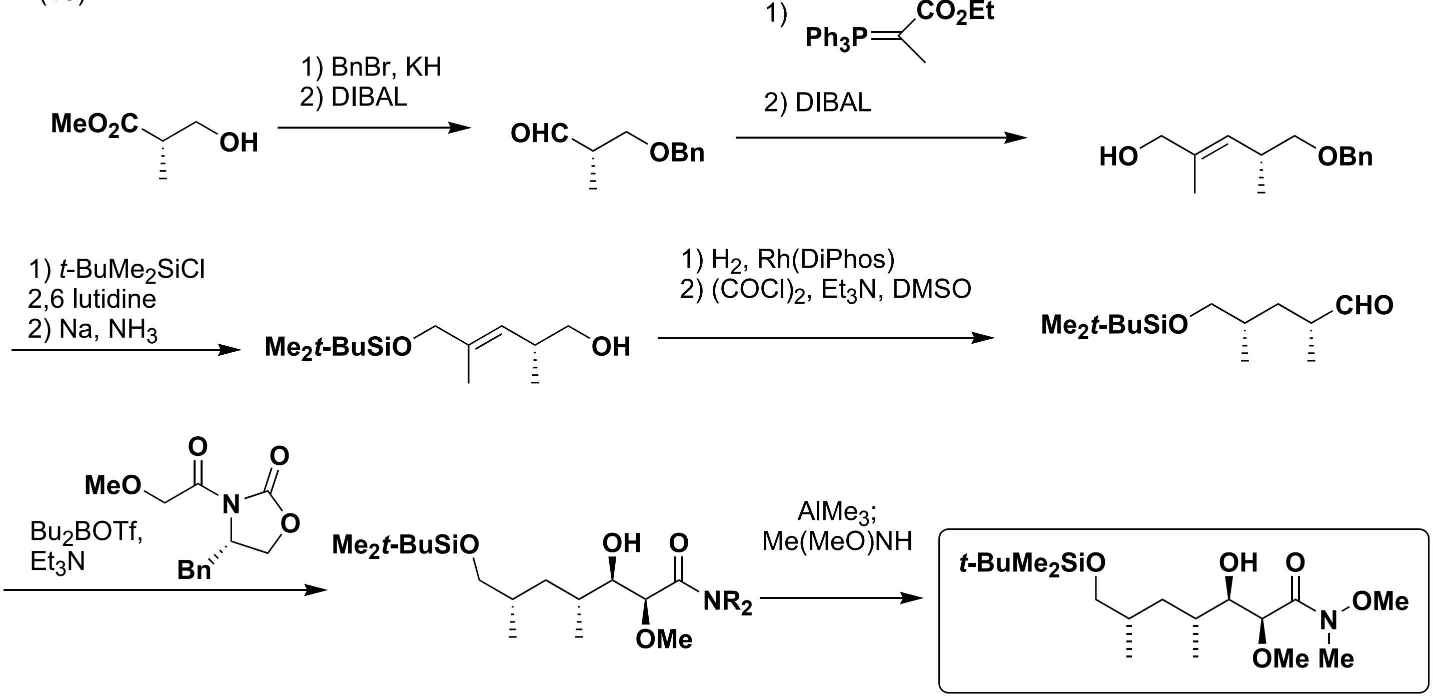

HO
(+)-DET, TBHP
Ti(Oi-Pr)4
HO
PhSO2Cl,
Et3N
PhSO3
Et2AlCl
Et2NH2Br
Br
PhSO3
OH
MeLi
Br
O
AlEt2Cl;
SiMe3
SnBu3
SiMe3
Br
OH

(17)

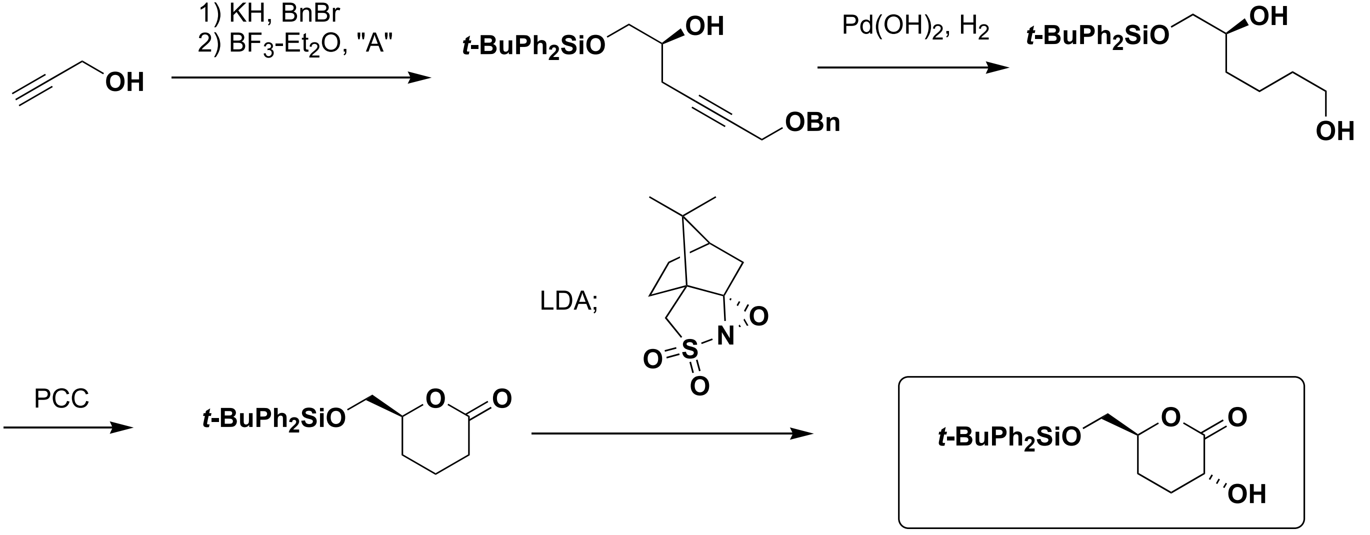

O
O
O
N
SePh
i-Pr
Bu2BOTf, Et3N;
BnO CHO
OH
OBn
SePh
i-Pr
1) t-BuMe2SiCl
2,6 lutidine
2) AlMe3,
Me(MeO)NH
3) DIBAL
H
OSiMe2t-Bu
OBn
SePh
1) KOt-Bu
(EtO)2POCH2CO2Et
2) DIBAL
HO
OSiMe2t-Bu
OBn
SePh
1) (-)-DET, TBHP
Ti(Oi-Pr)4
2) Red-Al
3) t-BuMe2SiCl
2,6 lutidine
t-BuMe2SiO
t-BuMe2SiO
OSiMe2t-Bu
OBn
SePh


1) KMnO$_4$, NaIO$_4$
2) CH$_2$N$_2$
t-BuMe$_2$SiO
OSit-BuMe$_2$
BnO
OSit-BuMe$_2$
CO$_2$Me

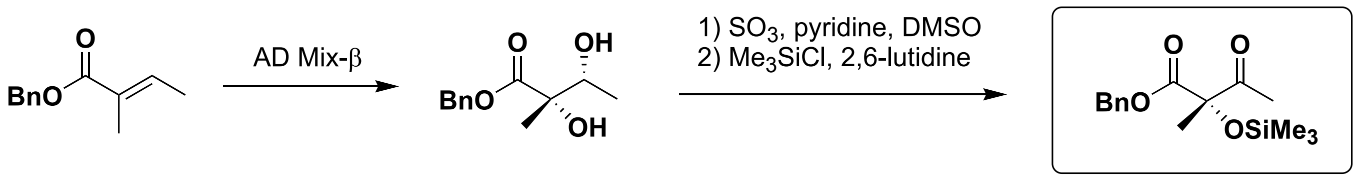
(18)


MeO$_2$C
OH
1) BnBr, KH
2) DIBAL
OHC
OBn
1) Ph$_3$P=C(CH$_3$)CO$_2$Et
2) DIBAL
HO
OBn
1) t-BuMe$_2$SiCl
2,6 lutidine
2) Na, NH$_3$
Me$_2$t-BuSiO
OH
1) H$_2$, Rh(DiPhos)
2) (COCl)$_2$, Et$_3$N, DMSO
Me$_2$t-BuSiO
CHO
MeO
O
O
N
O
Bn
Bu$_2$BOTf,
Et$_3$N
Me$_2$t-BuSiO
OH
O
NR$_2$
OMe
AlMe$_3$;
Me(MeO)NH
t-BuMe$_2$SiO
OH
O
N
OMe
OMe
Me

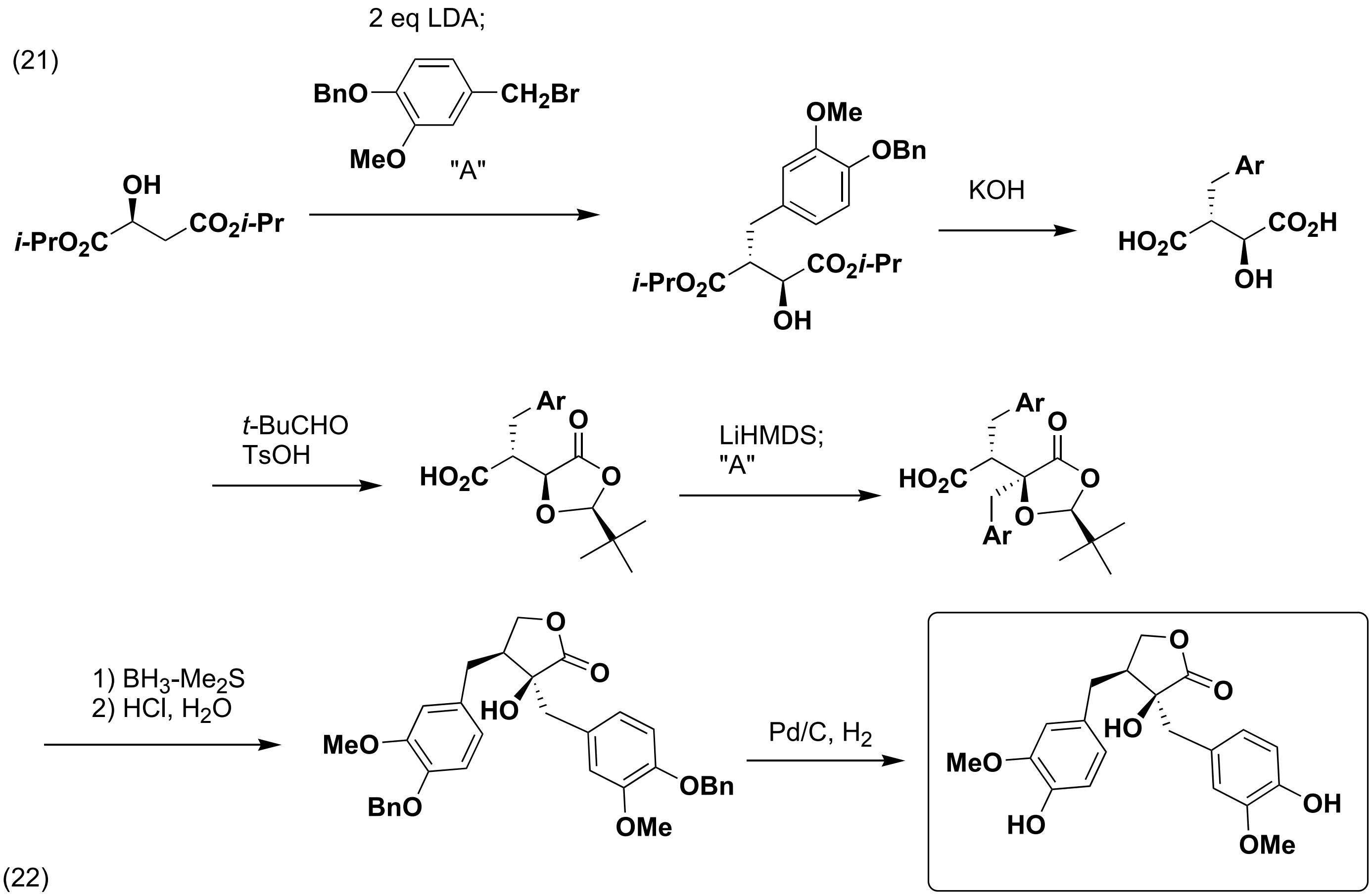
(19)


OH
1) KH, BnBr
2) BF$_3$-Et$_2$O, "A"
t-BuPh$_2$SiO
OH
OBn
Pd(OH)$_2$, H$_2$
t-BuPh$_2$SiO
OH
OH
PCC
t-BuPh$_2$SiO
O
O
LDA;
O
N
S
O
O
t-BuPh$_2$SiO
O
O
OH

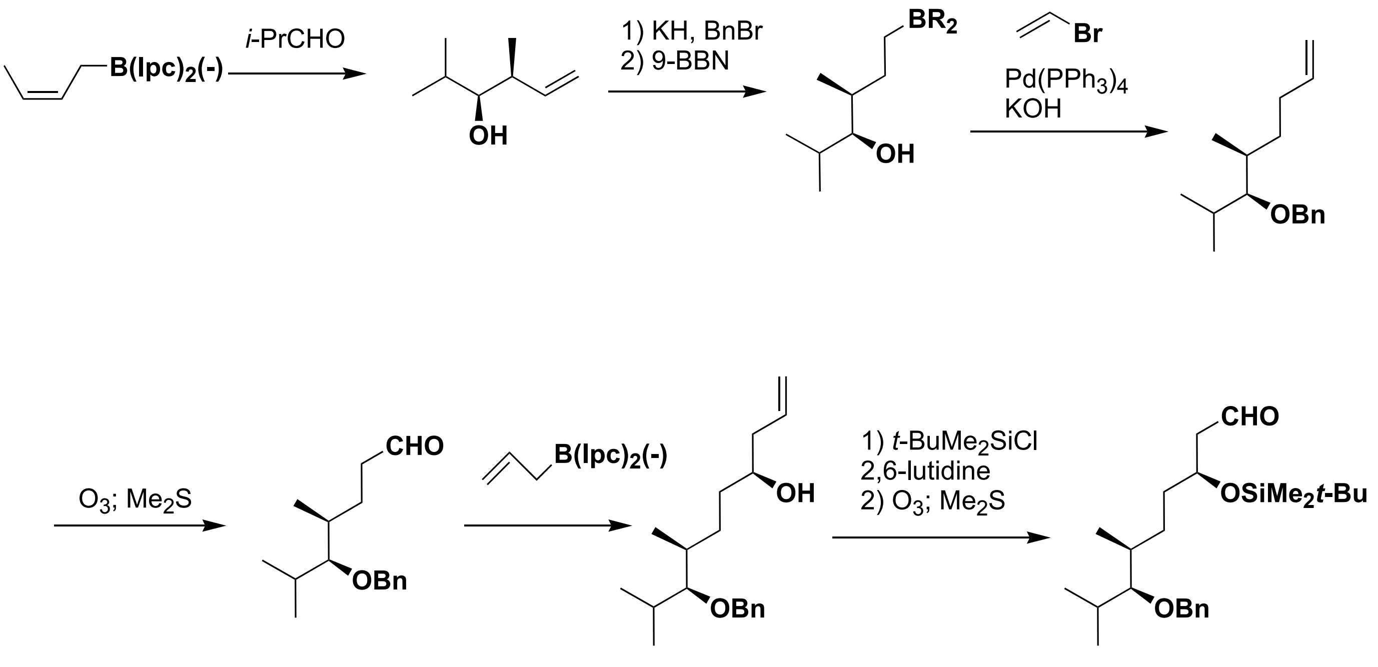
(20)

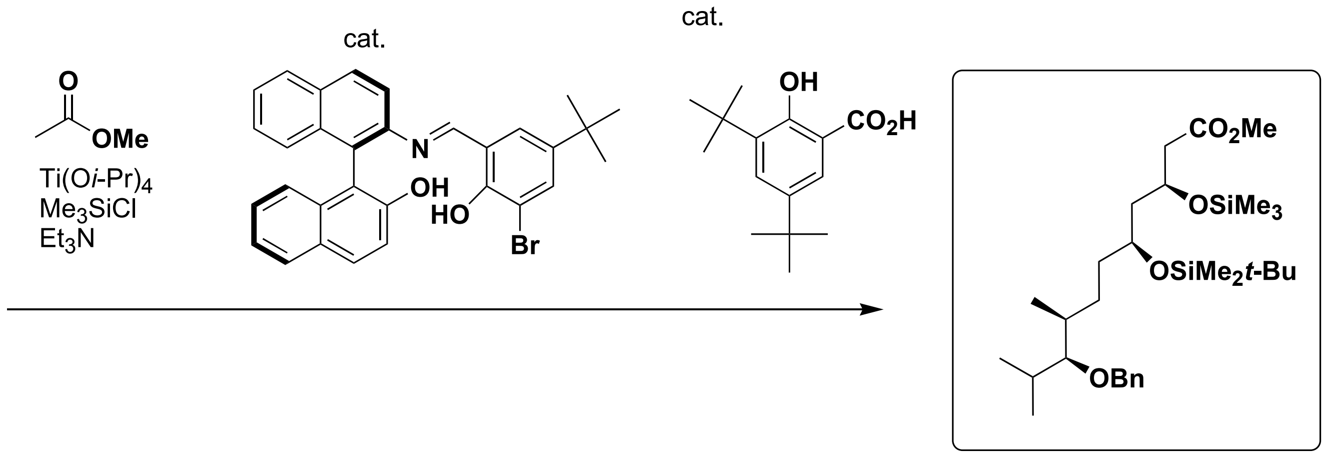

BnO
O
AD Mix-β
BnO
O
OH
OH
1) SO$_3$, pyridine, DMSO
2) Me$_3$SiCl, 2,6-lutidine
BnO
O
O
OSiMe$_3$

(21)

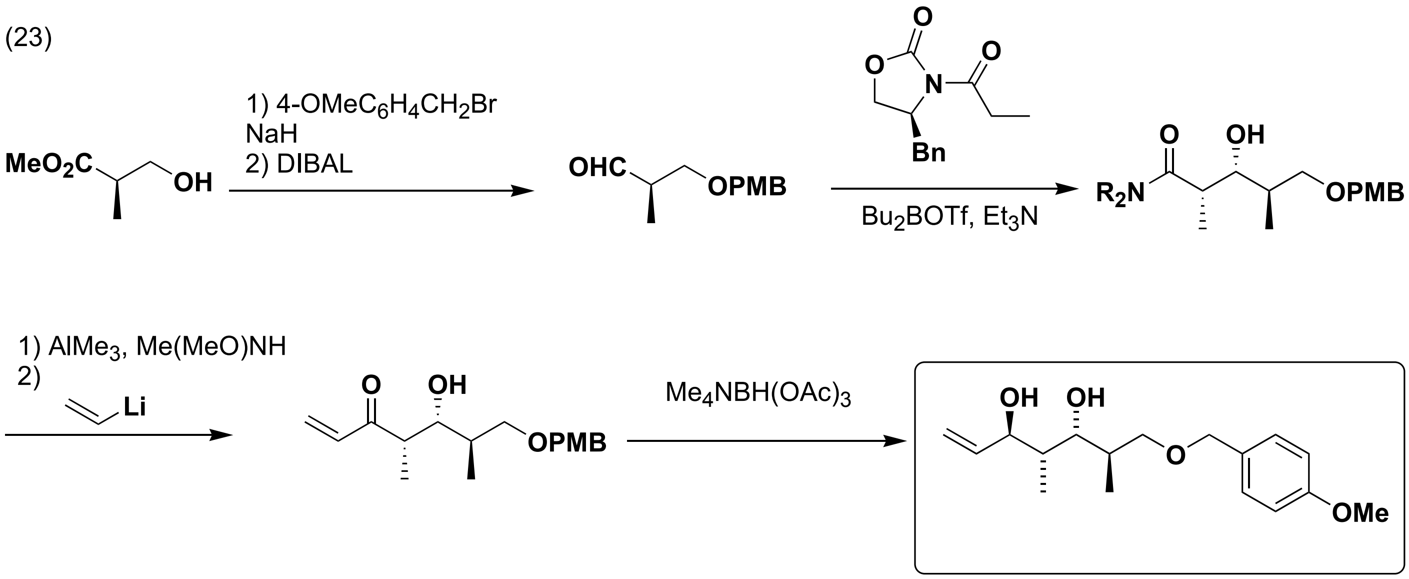

2 eq LDA;
BnO
CH$_2$Br
MeO
"A"
OH
i-PrO$_2$C
CO$_2$i-Pr
OMe
OBn
i-PrO$_2$C
CO$_2$i-Pr
OH
KOH
Ar
HO$_2$C
CO$_2$H
OH
t-BuCHO
TsOH
Ar
O
HO$_2$C
O
O
LiHMDS;
"A"
Ar
O
HO$_2$C
O
O
Ar
1) BH$_3$-Me$_2$S
2) HCl, H$_2$O
O
O
HO
MeO
BnO
OBn
OMe
Pd/C, H$_2$
O
O
HO
MeO
HO
OH
OMe

(22)

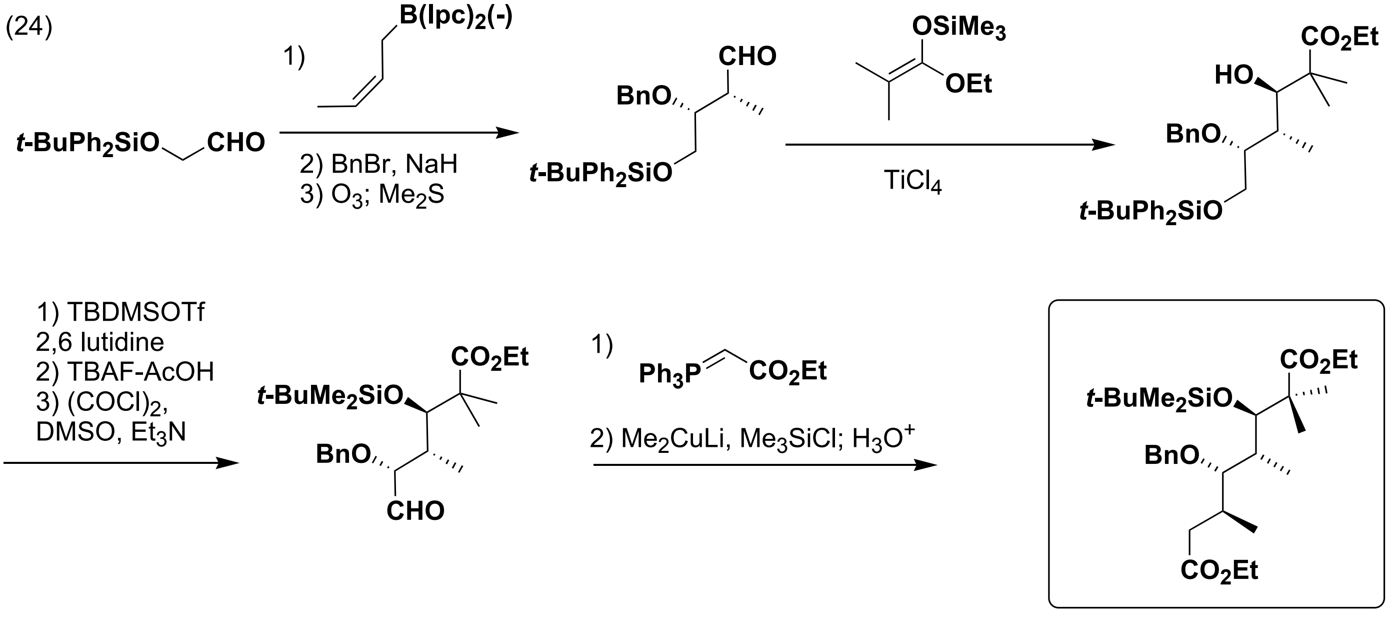

B(Ipc)$_2$(-)
i-PrCHO
OH
1) KH, BnBr
2) 9-BBN
BR$_2$
OH
Br
Pd(PPh$_3$)$_4$
KOH
OBn
O$_3$; Me$_2$S
CHO
OBn
B(Ipc)$_2$(-)
OH
OBn
1) t-BuMe$_2$SiCl
2,6-lutidine
2) O$_3$; Me$_2$S
CHO
OSiMe$_2$t-Bu
OBn


cat.
cat.
O
OMe
$Ti(O\textit{i}-Pr)_4$
Me_3SiCl
Et_3N
N
OH
HO
Br
OH
CO_2H
CO_2Me
$OSiMe_3$
$OSiMe_2\textit{t}-Bu$
OBn

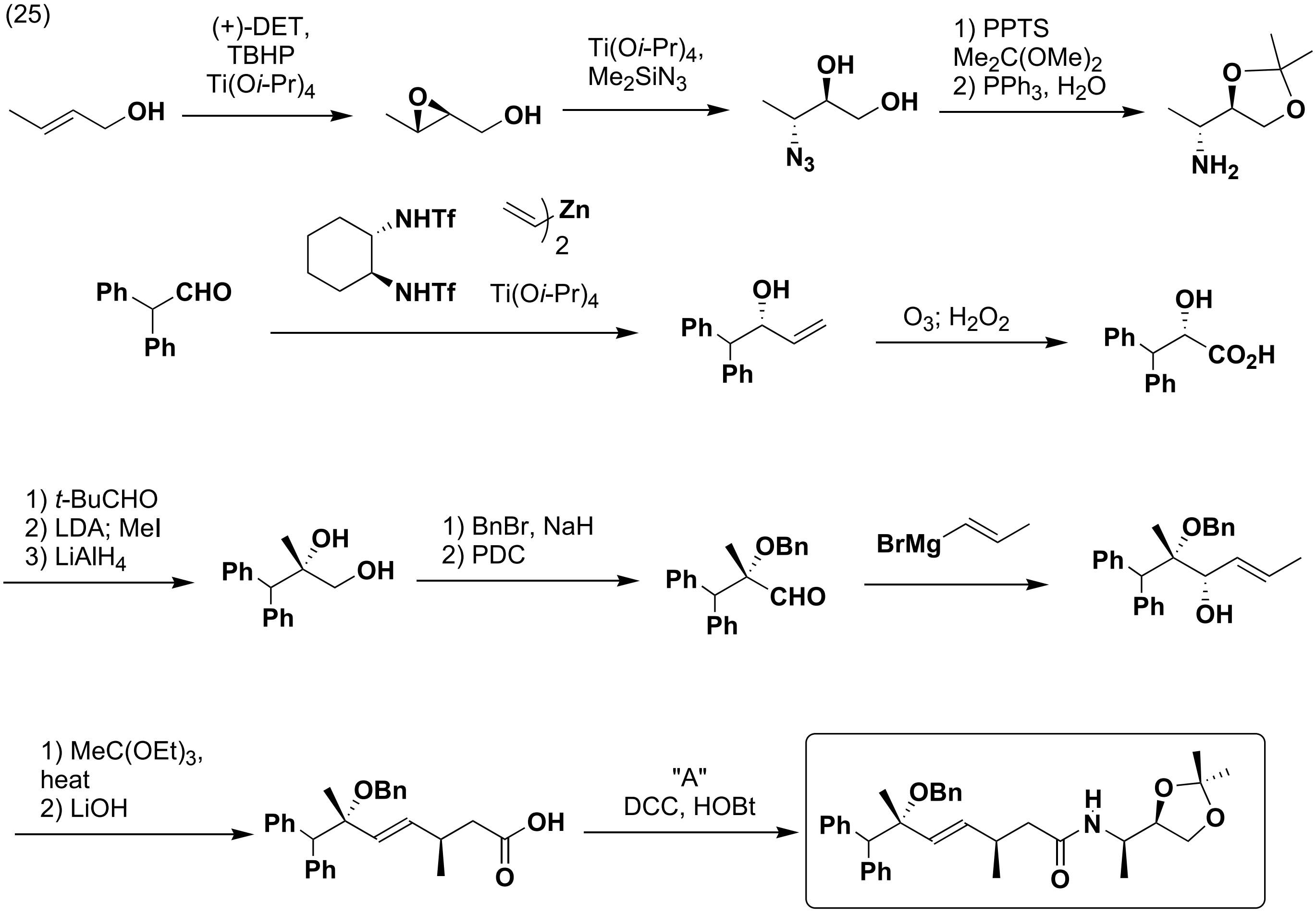
(23)


MeO_2C
OH
1) $4-OMeC_6H_4CH_2Br$
NaH
2) DIBAL
OHC
OPMB
O
O
N
O
Bn
Bu_2BOTf, Et_3N
O
OH
R_2N
OPMB
1) $AlMe_3$, Me(MeO)NH
2)
Li
O
OH
OPMB
$Me_4NBH(OAc)_3$
OH
OH
O
OMe

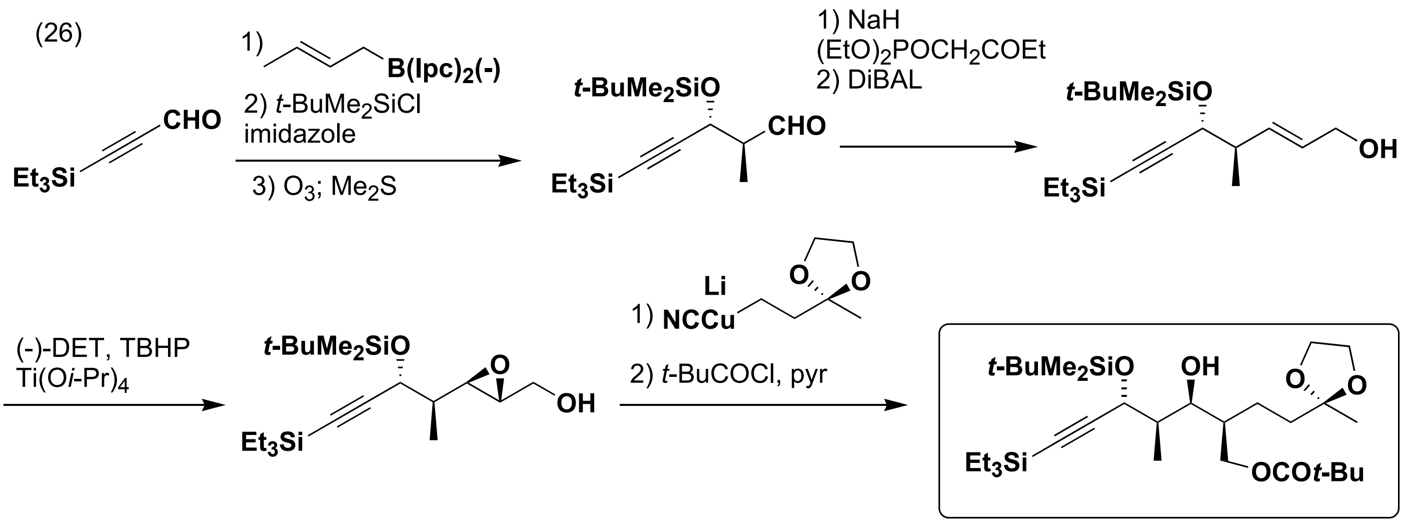
(24)


$B(Ipc)_2(-)$
1)
$\textit{t}-BuPh_2SiO$
CHO
2) BnBr, NaH
3) O_3; Me_2S
CHO
BnO
$\textit{t}-BuPh_2SiO$
$OSiMe_3$
OEt
$TiCl_4$
CO_2Et
HO
BnO
$\textit{t}-BuPh_2SiO$
1) TBDMSOTf
2,6 lutidine
2) TBAF-AcOH
3) $(COCl)_2$,
DMSO, Et_3N
CO_2Et
$\textit{t}-BuMe_2SiO$
BnO
CHO
1)
Ph_3P
CO_2Et
2) Me_2CuLi, Me_3SiCl; H_3O^+
CO_2Et
$\textit{t}-BuMe_2SiO$
BnO
CO_2Et

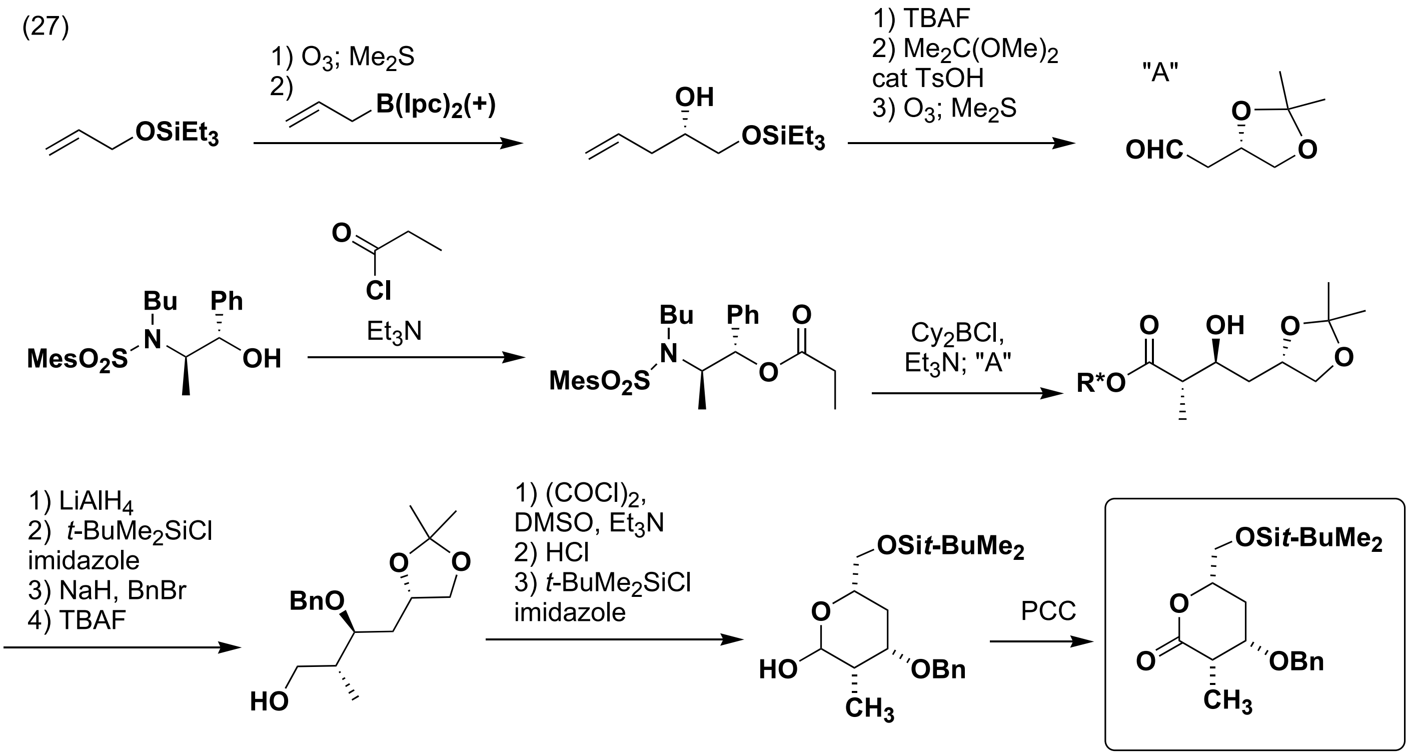
(25)


OH
(+)-DET,
TBHP
Ti(O*i*-Pr)$_4$
O
OH
Ti(O*i*-Pr)$_4$,
Me$_2$SiN$_3$
OH
OH
N$_3$
1) PPTS
Me$_2$C(OMe)$_2$
2) PPh$_3$, H$_2$O
O
O
NH$_2$
Ph
CHO
Ph
NHTf
NHTf
Zn
2
Ti(O*i*-Pr)$_4$
OH
Ph
Ph
O$_3$; H$_2$O$_2$
OH
Ph
CO$_2$H
Ph
1) *t*-BuCHO
2) LDA; MeI
3) LiAlH$_4$
OH
Ph
OH
Ph
1) BnBr, NaH
2) PDC
OBn
Ph
CHO
Ph
BrMg
OBn
Ph
Ph
OH
1) MeC(OEt)$_3$,
heat
2) LiOH
OBn
Ph
OH
Ph
O
"A"
DCC, HOBt
OBn
H
N
O
O
Ph
Ph
O

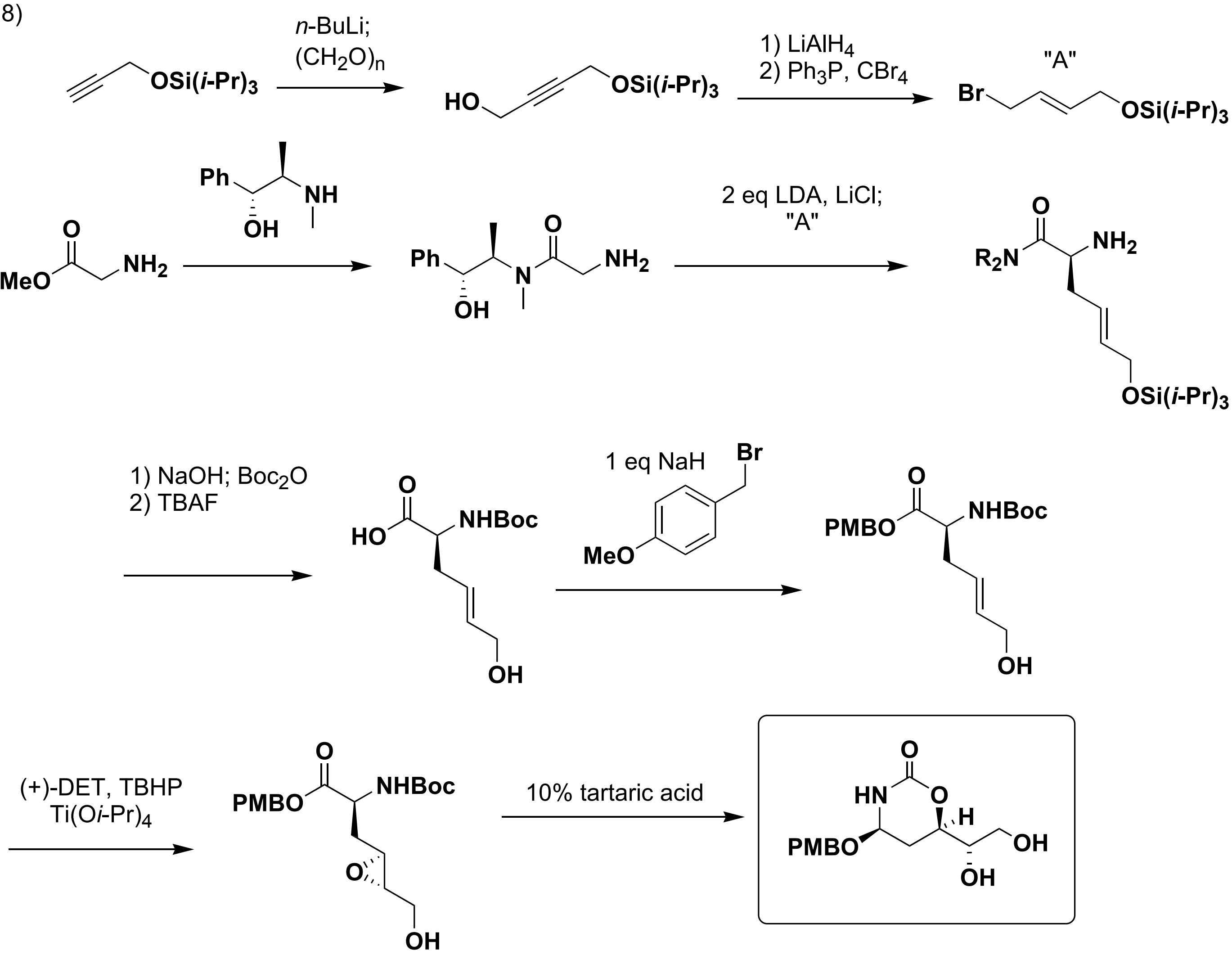
(26)


1)
B(Ipc)$_2$(-)
2) *t*-BuMe$_2$SiCl
imidazole
3) O$_3$; Me$_2$S
CHO
Et$_3$Si
t-BuMe$_2$SiO
CHO
Et$_3$Si
1) NaH
(EtO)$_2$POCH$_2$COEt
2) DiBAL
t-BuMe$_2$SiO
OH
Et$_3$Si
(-)-DET, TBHP
Ti(O*i*-Pr)$_4$
t-BuMe$_2$SiO
O
OH
Et$_3$Si
Li
1) NCCu
O
O
2) *t*-BuCOCl, pyr
t-BuMe$_2$SiO
OH
O
O
Et$_3$Si
OCO*t*-Bu

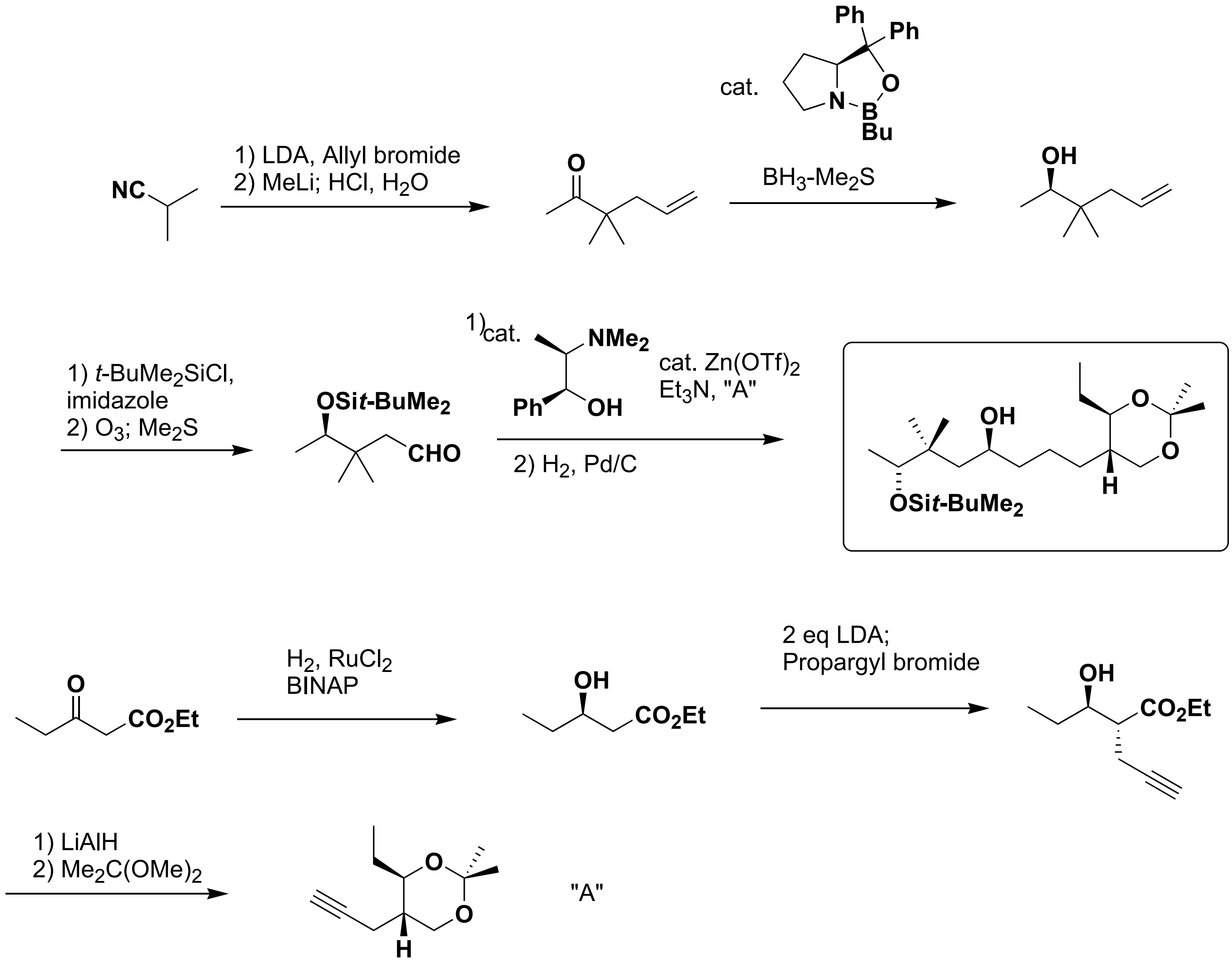
(27)


OSiEt3
1) O3; Me2S
2) B(Ipc)2(+)
OH
OSiEt3
1) TBAF
2) Me2C(OMe)2
cat TsOH
3) O3; Me2S
"A"
OHC
O
O
Bu
Ph
MesO2S
N
OH
O
Cl
Et3N
Cy2BCl,
Et3N; "A"
R*O
1) LiAlH4
2) t-BuMe2SiCl
imidazole
3) NaH, BnBr
4) TBAF
BnO
HO
1) (COCl)2,
DMSO, Et3N
2) HCl
3) t-BuMe2SiCl
imidazole
OSit-BuMe2
HO
OBn
CH3
PCC

(28)

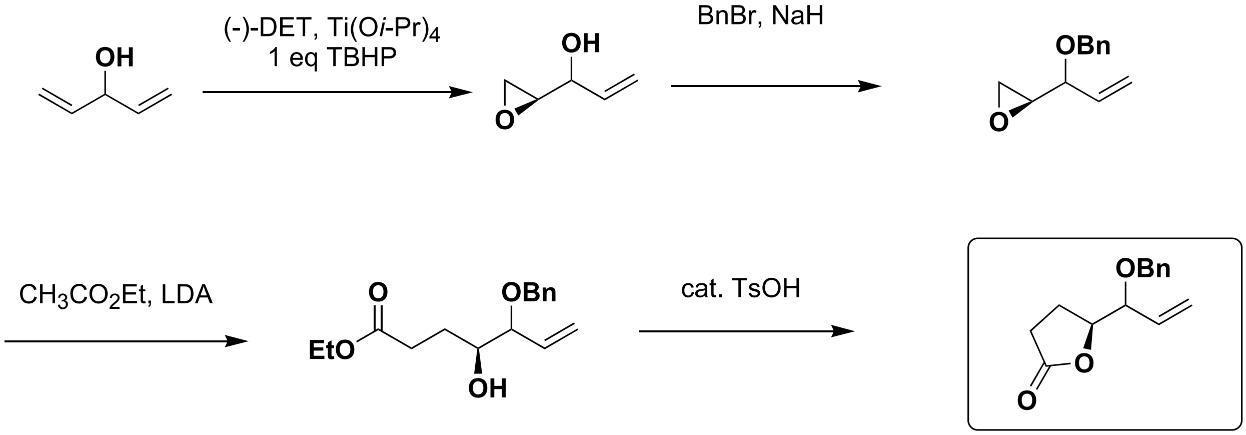

OSi(i-Pr)3
n-BuLi;
(CH2O)n
HO
OSi(i-Pr)3
1) LiAlH4
2) Ph3P, CBr4
"A"
Br
OSi(i-Pr)3
MeO
NH2
Ph
NH
OH
N
2 eq LDA, LiCl;
"A"
R2N
NH2
1) NaOH; Boc2O
2) TBAF
HO
NHBoc
OH
1 eq NaH
Br
MeO
PMBO
NHBoc
(+)-DET, TBHP
Ti(Oi-Pr)4
10% tartaric acid
HN
O
H
PMBO
OH

(29)



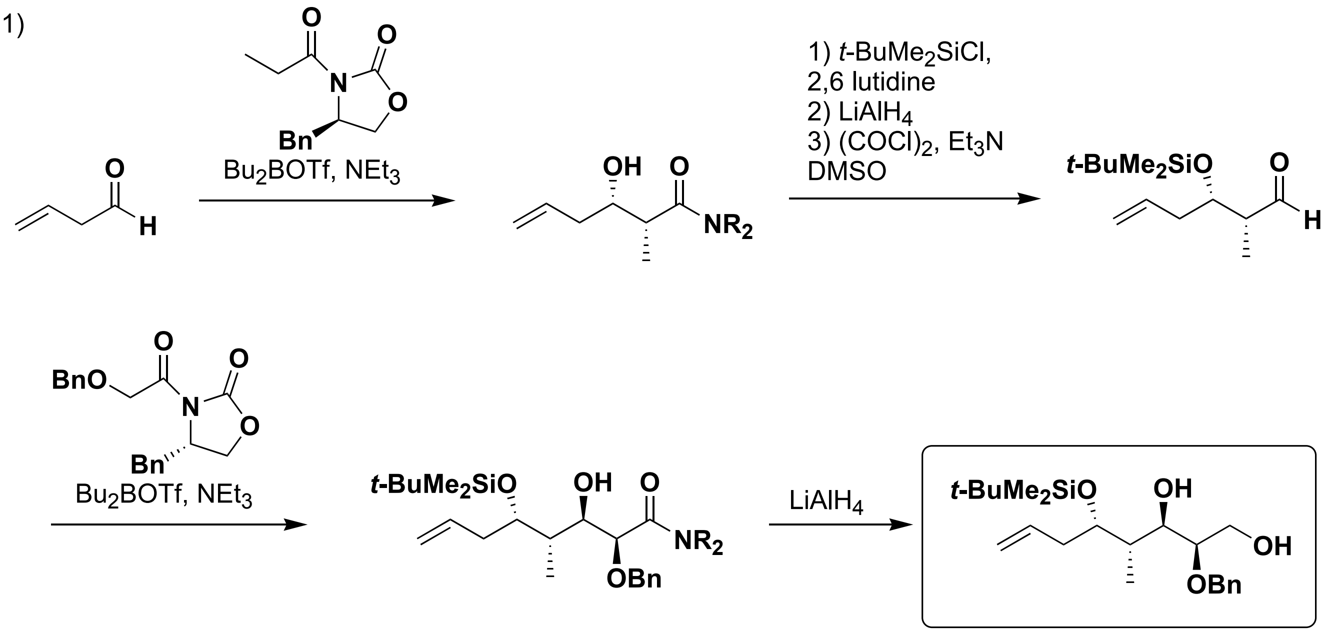
NC
1) LDA, Allyl bromide
2) MeLi; HCl, H₂O
O
cat.
Ph
Ph
O
N
B
Bu
BH₃-Me₂S
OH
1) t-BuMe₂SiCl, imidazole
2) O₃; Me₂S
OSit-BuMe₂
CHO
1) cat.
NMe₂
Ph
OH
cat. Zn(OTf)₂
Et₃N, "A"
2) H₂, Pd/C
OH
O
O
H
OSit-BuMe₂
O
CO₂Et
H₂, RuCl₂
BINAP
OH
CO₂Et
2 eq LDA;
Propargyl bromide
OH
CO₂Et
1) LiAlH
2) Me₂C(OMe)₂
O
O
H
"A"

(30)

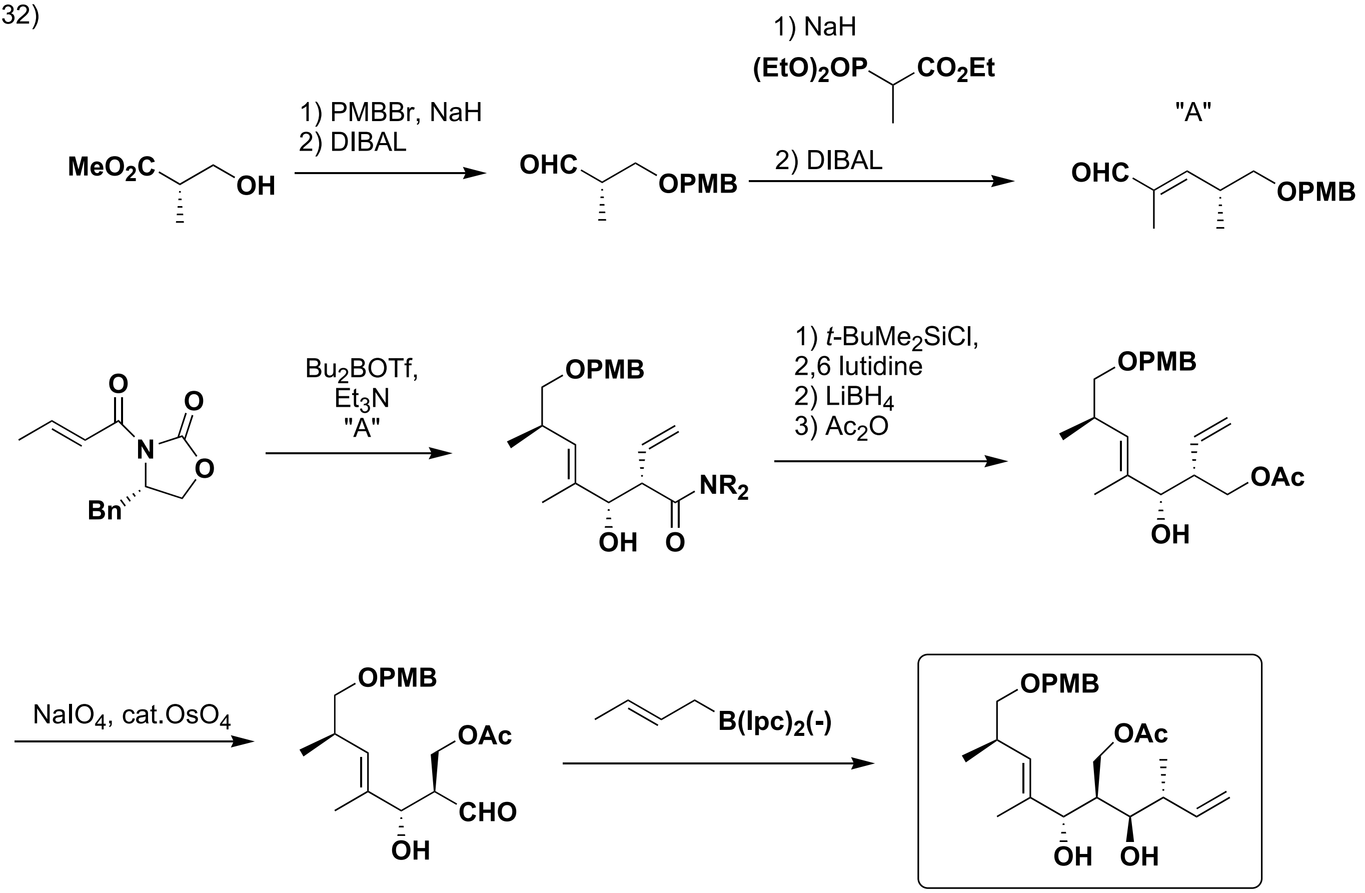


OH
(-)-DET, Ti(Oi-Pr)₄
1 eq TBHP
OH
O
BnBr, NaH
OBn
O
CH₃CO₂Et, LDA
O
OBn
EtO
OH
cat. TsOH
OBn
O
O

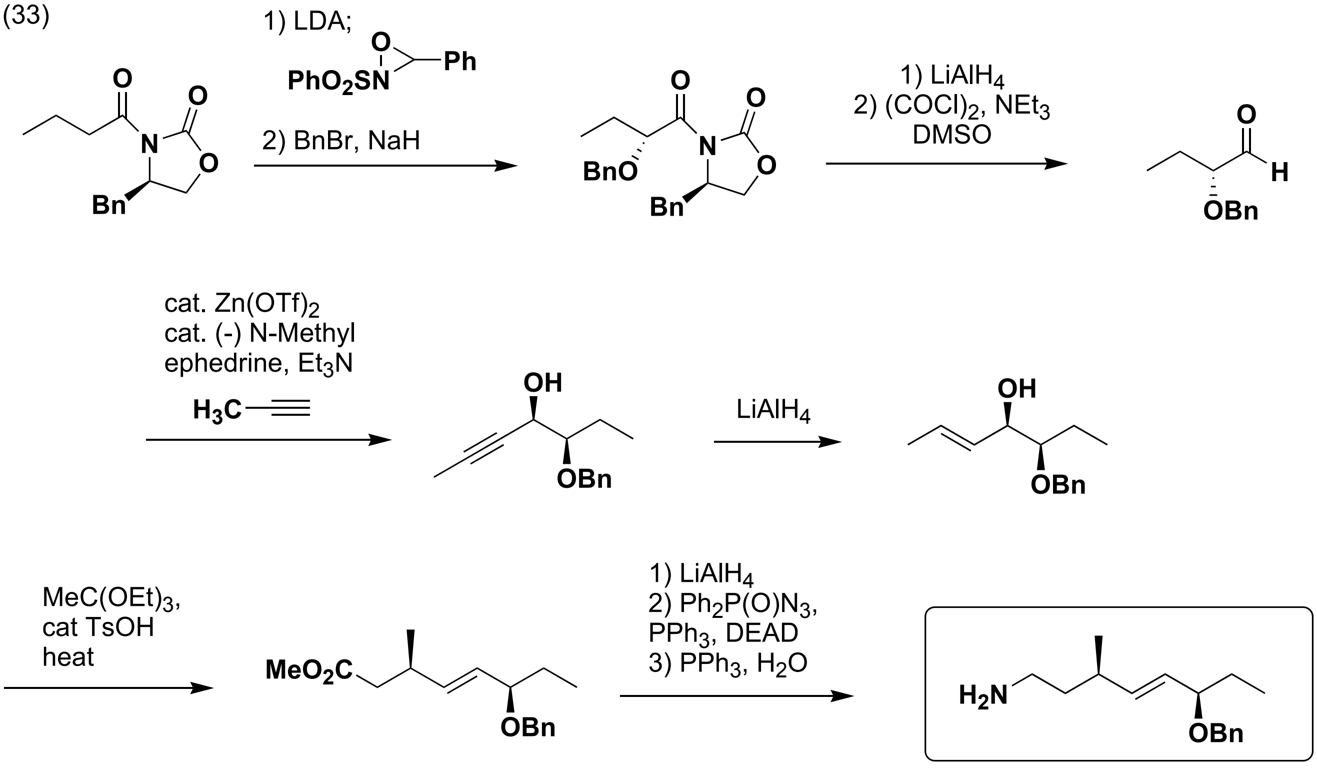
(31)


Bu$_2$BOTf, NEt$_3$
Bn
1) t-BuMe$_2$SiCl, 2,6 lutidine
2) LiAlH$_4$
3) (COCl)$_2$, Et$_3$N DMSO
OH
NR$_2$
t-BuMe$_2$SiO
H
BnO
Bn
Bu$_2$BOTf, NEt$_3$
t-BuMe$_2$SiO
OH
NR$_2$
OBn
LiAlH$_4$
t-BuMe$_2$SiO
OH
OH
OBn

(32)


MeO$_2$C
OH
1) PMBBr, NaH
2) DIBAL
OHC
OPMB
1) NaH
(EtO)$_2$OP
CO$_2$Et
2) DIBAL
"A"
OHC
OPMB
Bn
Bu$_2$BOTf,
Et$_3$N
"A"
OPMB
NR$_2$
OH
1) t-BuMe$_2$SiCl,
2,6 lutidine
2) LiBH$_4$
3) Ac$_2$O
OPMB
OAc
OH
NaIO$_4$, cat.OsO$_4$
OPMB
OAc
CHO
OH
B(Ipc)$_2$(-)
OPMB
OAc
OH
OH

(33)


1) LDA;
PhO2SN
O
Ph
2) BnBr, NaH
O
O
N
O
Bn
BnO
1) LiAlH4
2) (COCl)2, NEt3
DMSO
H
OBn
cat. Zn(OTf)2
cat. (-) N-Methyl
ephedrine, Et3N
H3C
OH
LiAlH4
MeC(OEt)3,
cat TsOH
heat
MeO2C
1) LiAlH4
2) Ph2P(O)N3,
PPh3, DEAD
3) PPh3, H2O
H2N