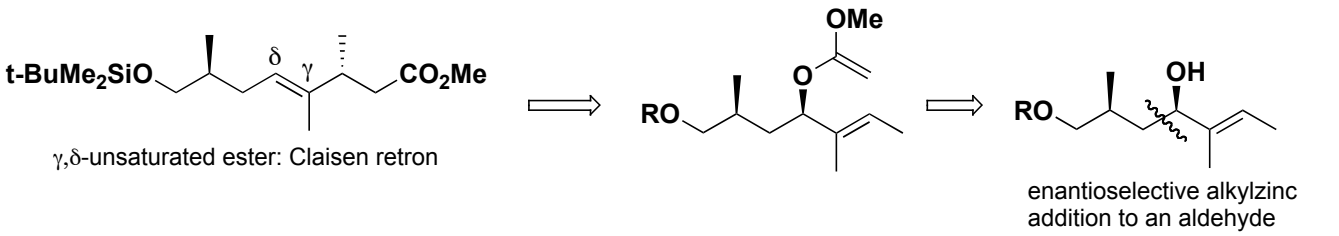
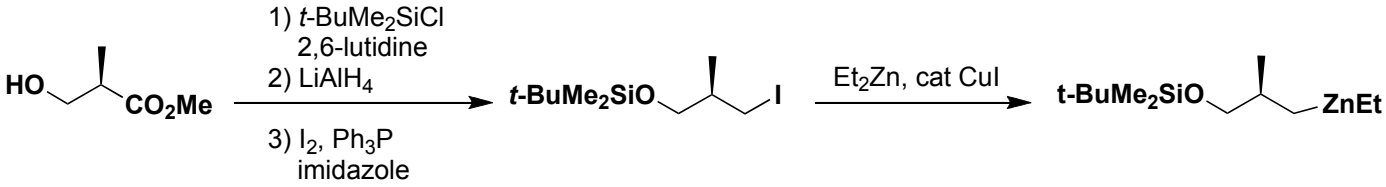
Massachusetts Institute of Technology
Organic Chemistry 5.511

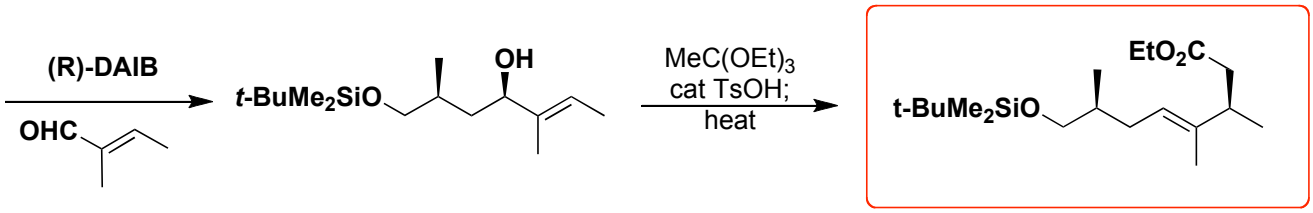
Nov. 17, 2007

Problem Set 8 Solutions
Stereocontrolled Addition to Carbonyl Compounds

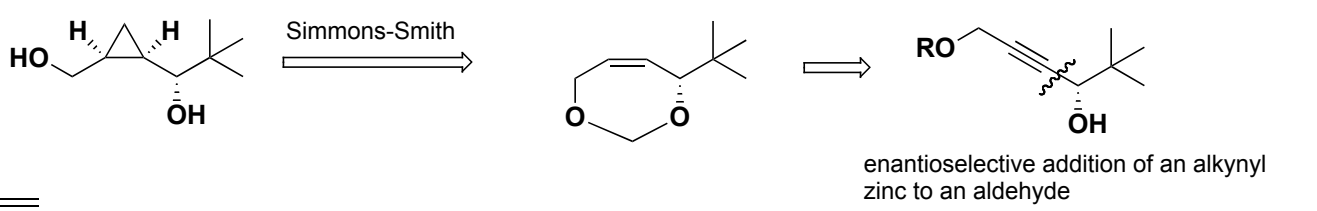
(1)

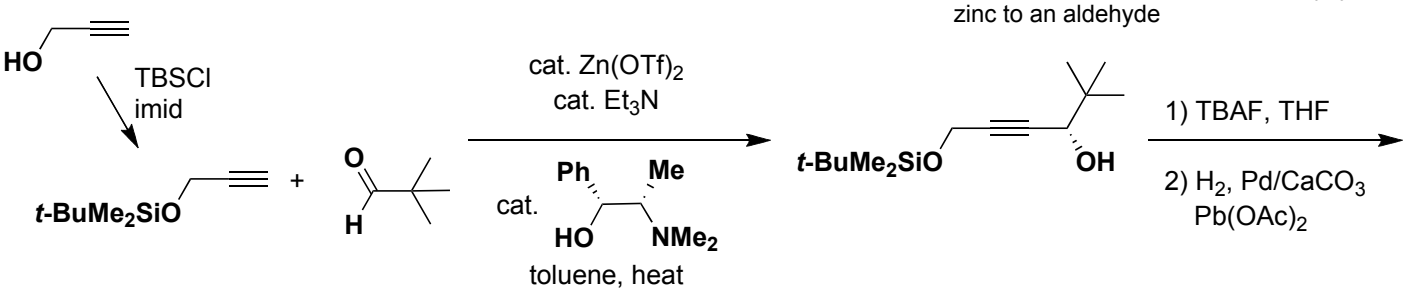


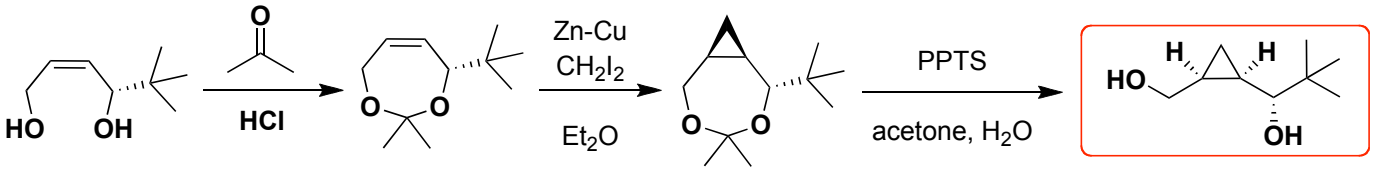




(2)







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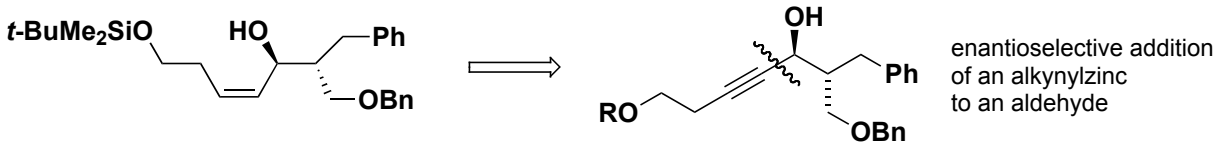

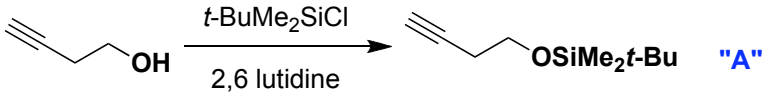

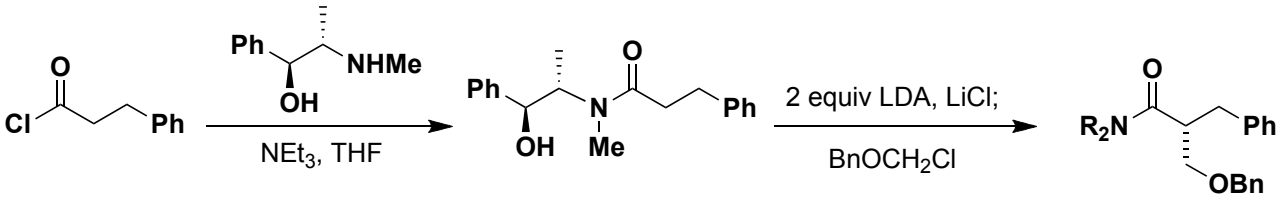

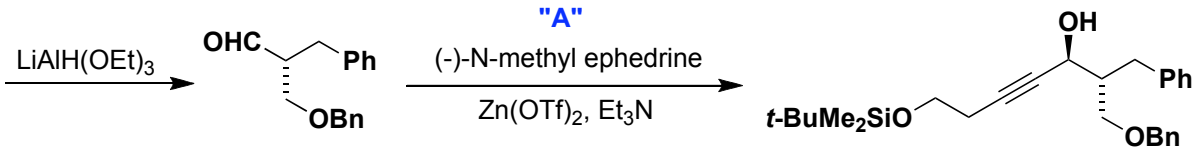

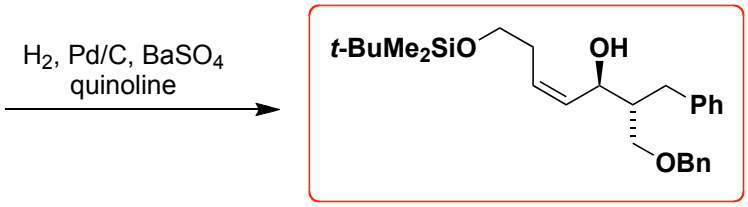

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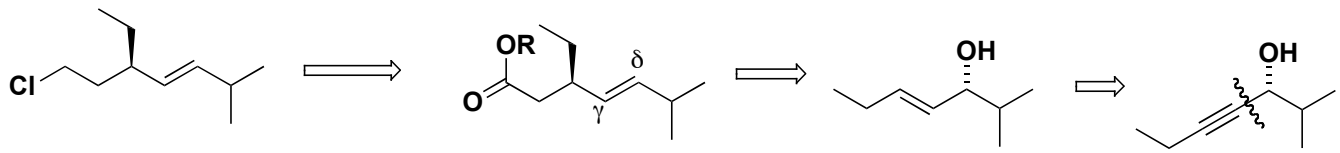
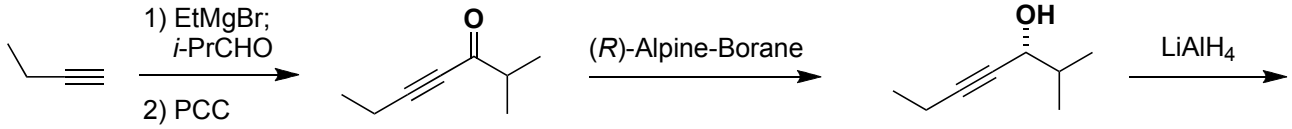
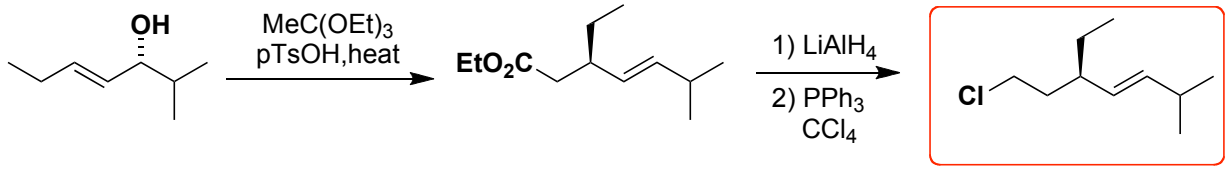


γ,δ-unsaturated ester: Claisen retron

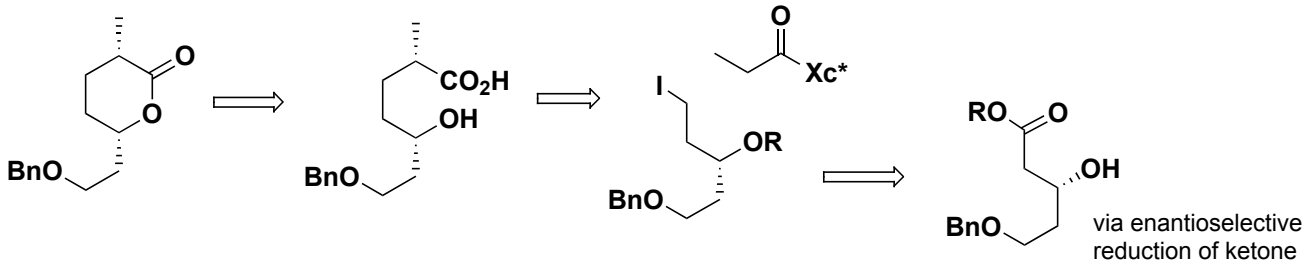
enantioselective addition of an alkynylzinc to an aldehyde

The target compound was used as an intermediate in the synthesis of (-)-talaromycin A by Evans in *J. Am. Chem. Soc.* **1995**, *117*, 3454.

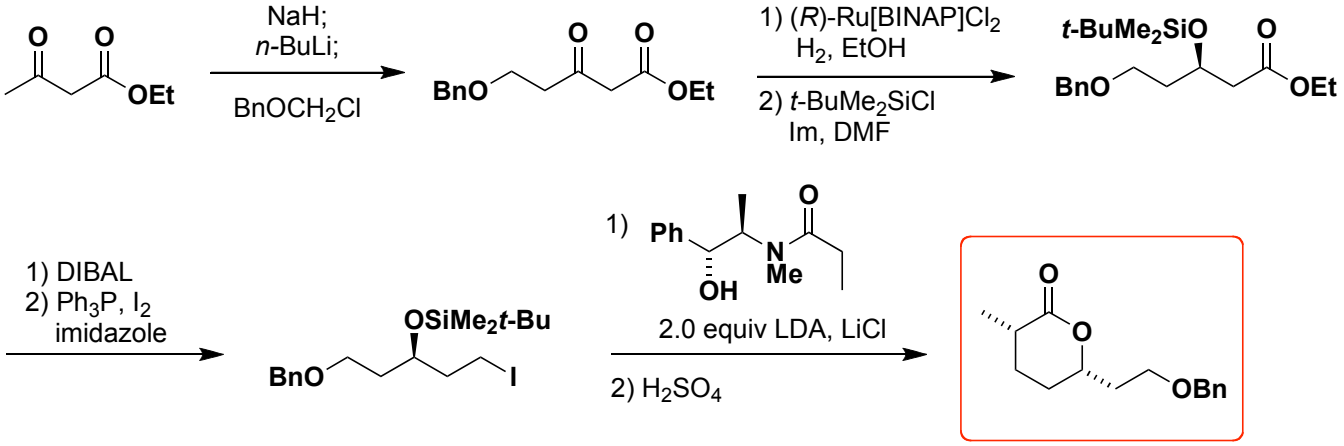




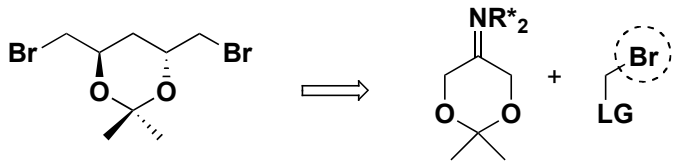
(5)



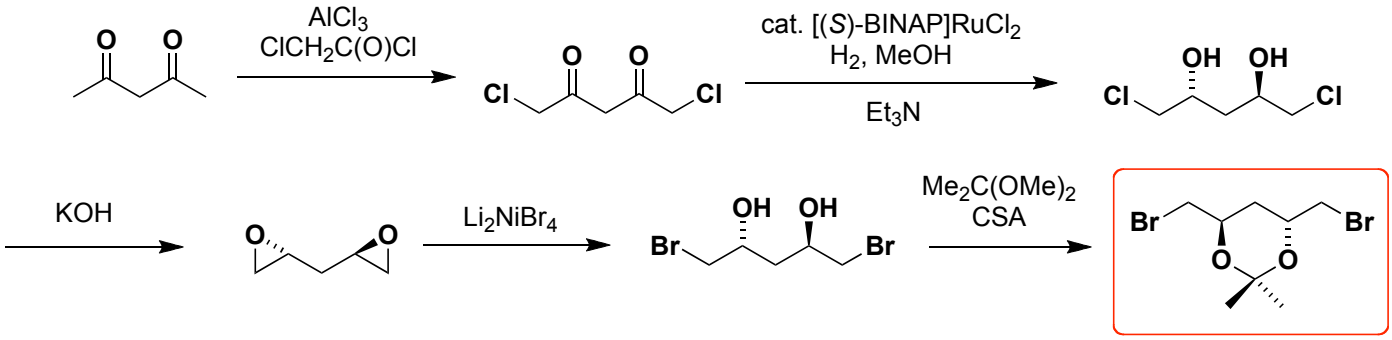
The target compound was used as an intermediate in the synthesis of leucasandrolide A by Rychnovsky (*J. Am. Chem. Soc.* **2001**, *123*, 8420).



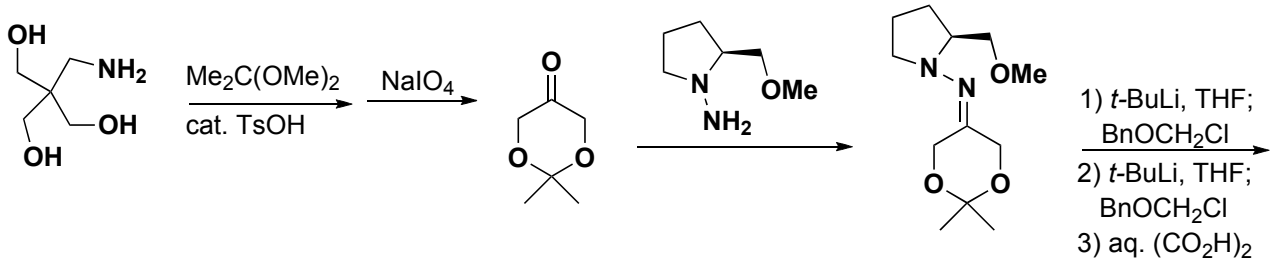
(6)

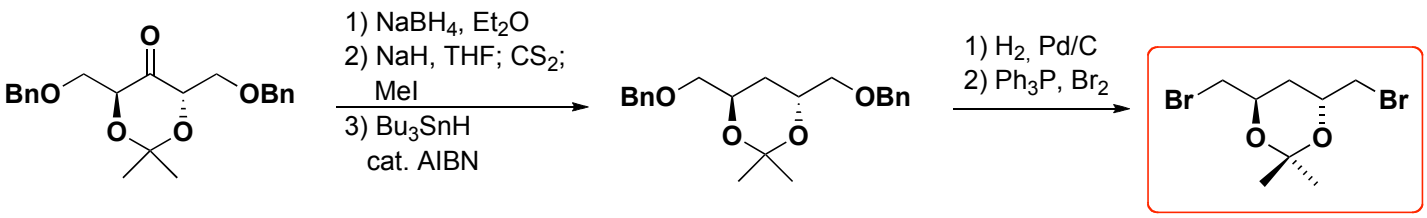


The synthesis used by S. Rychnovsky et al. is shown below (*J. Am. Chem. Soc.* **1994**, *116*, 1753)

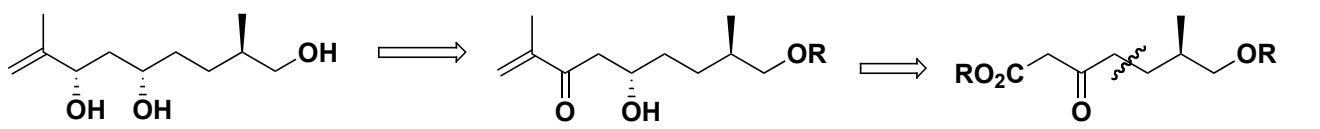


An alternate route:





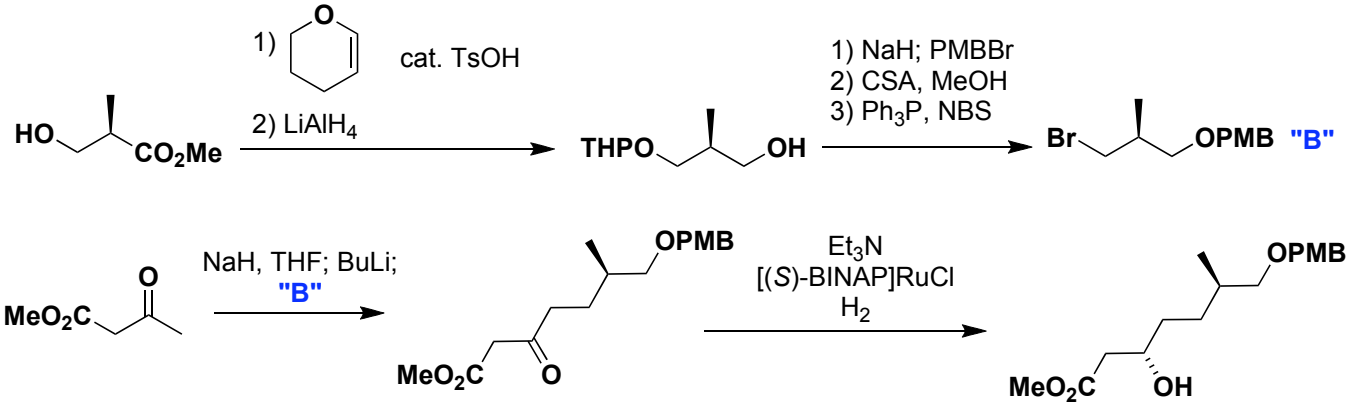
(7)

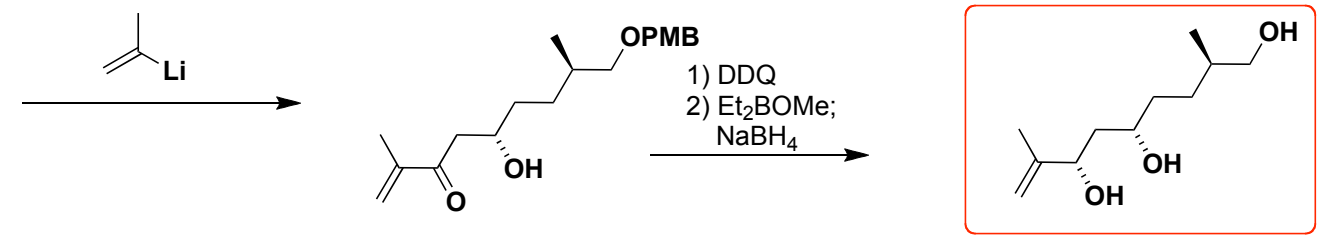


substrate-controlled reduction

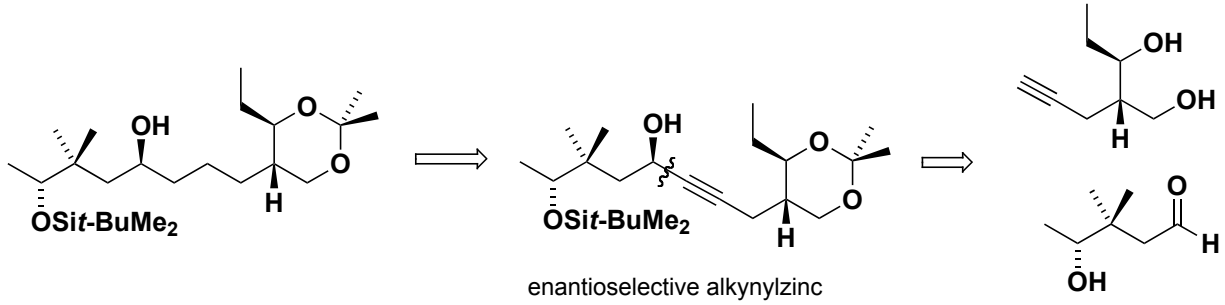
dianion alkylation then enantioselective reduction of ketone

See S.L. Schreiber *J. Org. Chem.* **1992**, *57*, 5058.

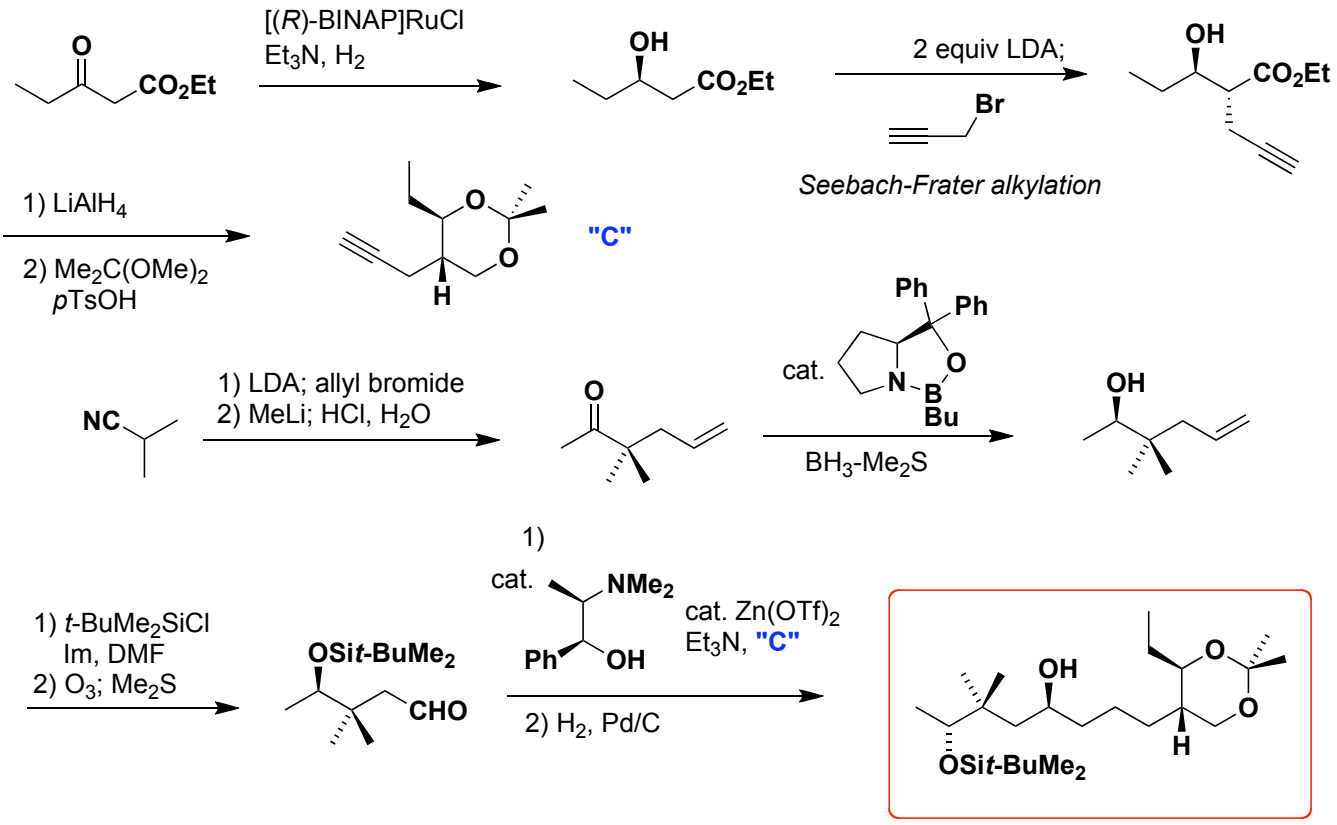


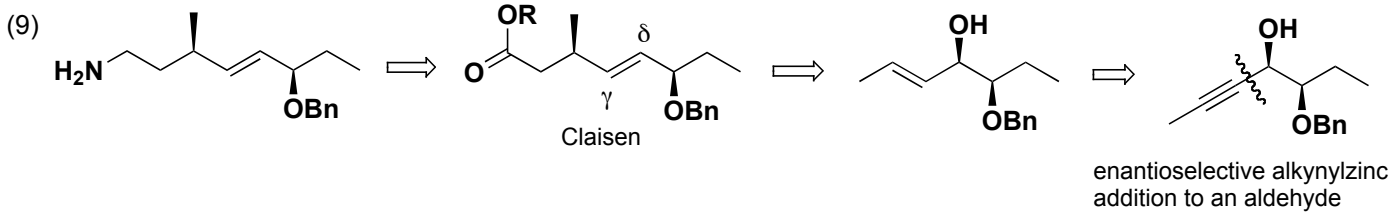


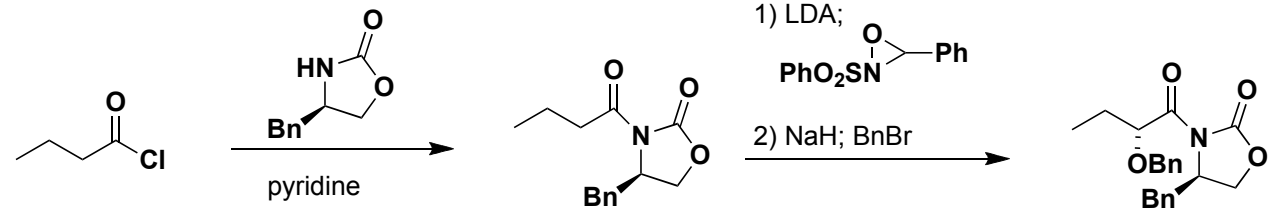
(8)

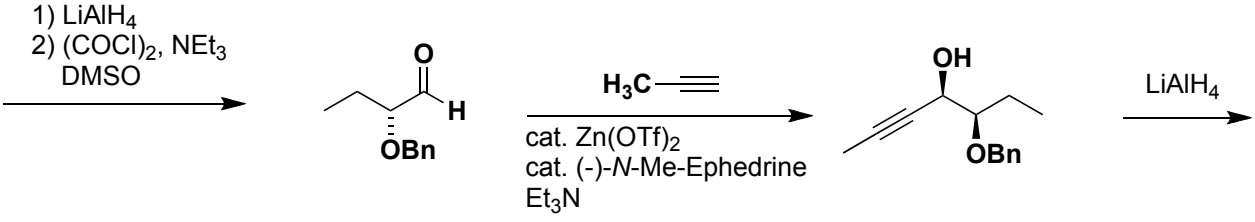


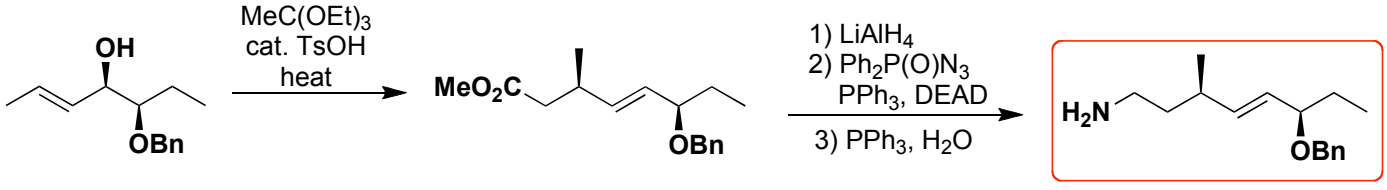
enantioselective alkynylzinc addition to an aldehyde


[(R)-BINAP]RuCl
Et3N, H2
2 equiv LDA;
Br
Seebach-Frater alkylation
1) LiAlH4
2) Me2C(OMe)2
pTsOH
"C"
1) LDA; allyl bromide
2) MeLi; HCl, H2O
cat.
BH3-Me2S
1) t-BuMe2SiCl
Im, DMF
2) O3; Me2S
1)
cat. Zn(OTf)2
Et3N, "C"
2) H2, Pd/C

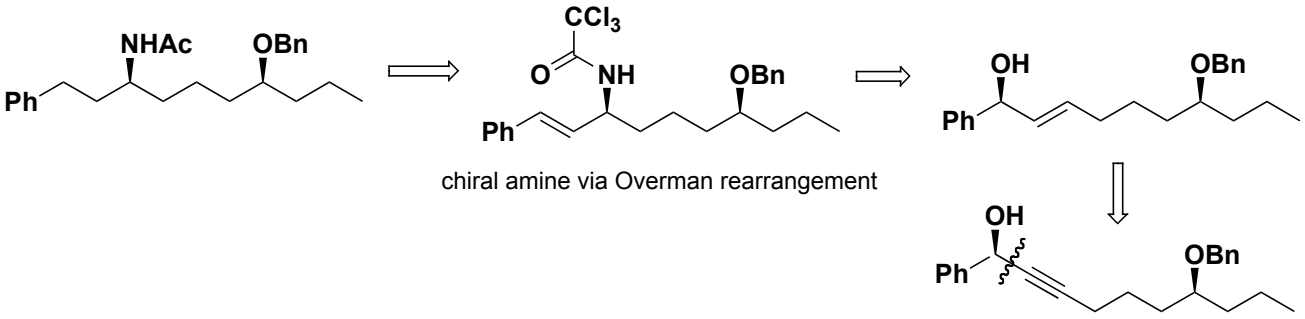

(9)
Claisen
enantioselective alkynylzinc
addition to an aldehyde

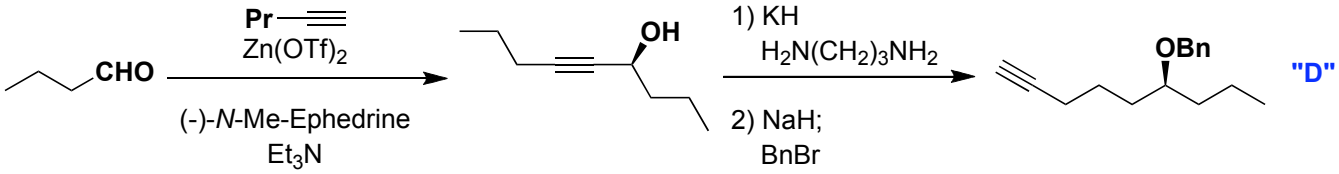

1) LDA;
2) NaH; BnBr
pyridine

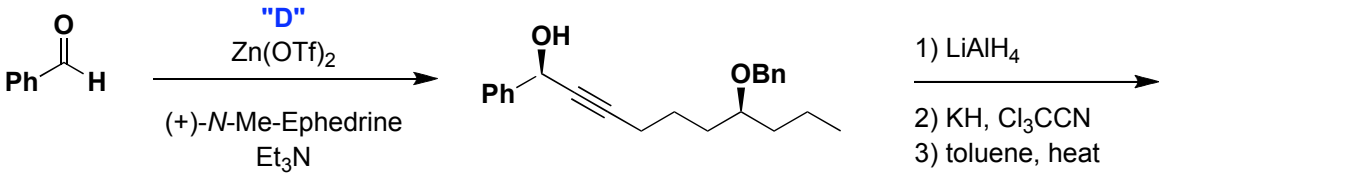

1) LiAlH4
2) (COCl)2, NEt3
DMSO
cat. Zn(OTf)2
cat. (-)-N-Me-Ephedrine
Et3N
LiAlH4

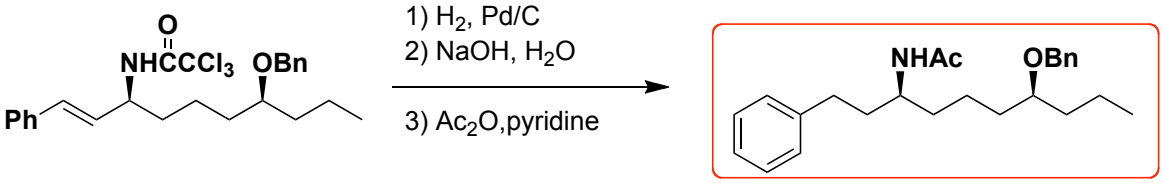

MeC(OEt)3
cat. TsOH
heat
1) LiAlH4
2) Ph2P(O)N3
PPh3, DEAD
3) PPh3, H2O

(10)

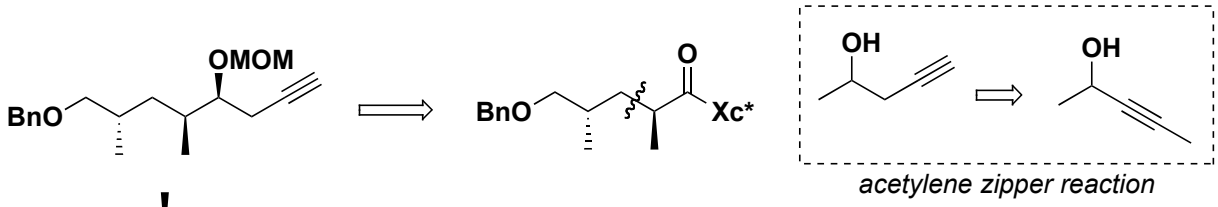

NHAc
OBn
Ph
CCl3
O
NH
chiral amine via Overman rearrangement
OH

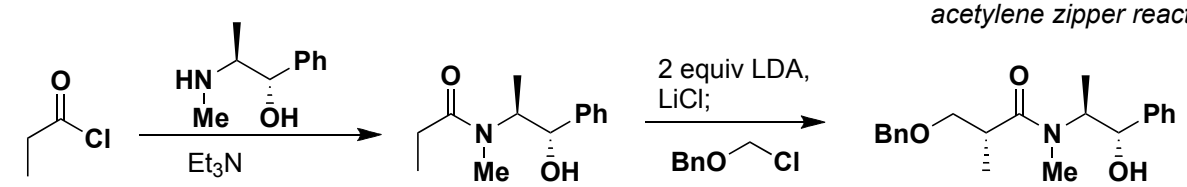

Pr
Zn(OTf)2
CHO
(-)-N-Me-Ephedrine
Et3N
OH
1) KH
H2N(CH2)3NH2
2) NaH;
BnBr
OBn
"D"

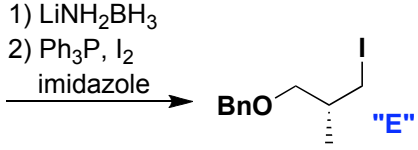

O
Ph
H
"D"
Zn(OTf)2
(+)-N-Me-Ephedrine
Et3N
OH
OBn
1) LiAlH4
2) KH, Cl3CCN
3) toluene, heat

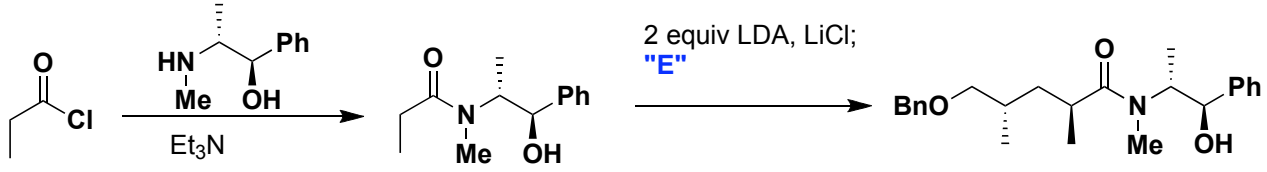

O
NHCCCl3
OBn
Ph
1) H2, Pd/C
2) NaOH, H2O
3) Ac2O,pyridine
NHAc
OBn

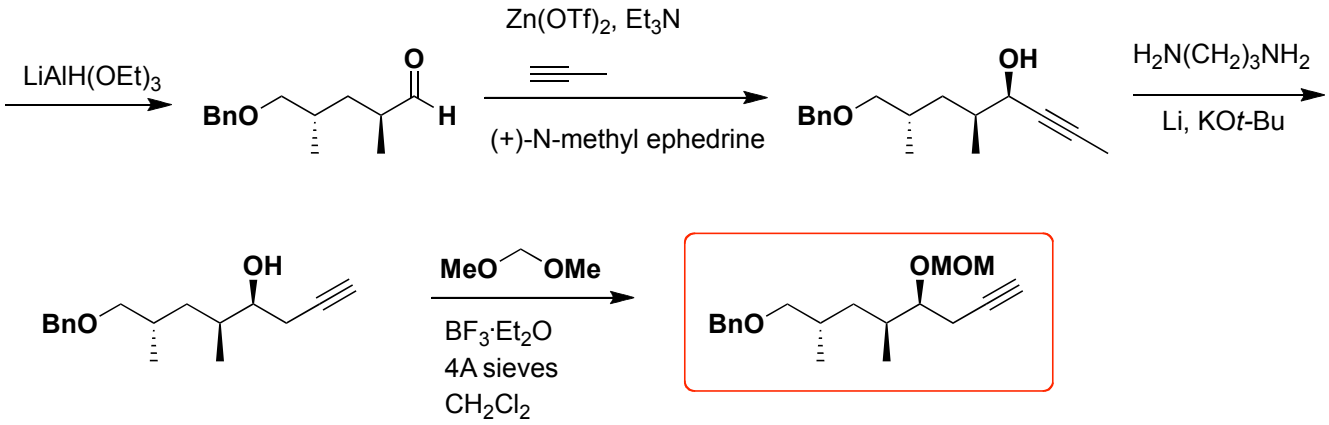
(11)


OMOM
BnO
O
Xc*
OH
OH
acetylene zipper reaction

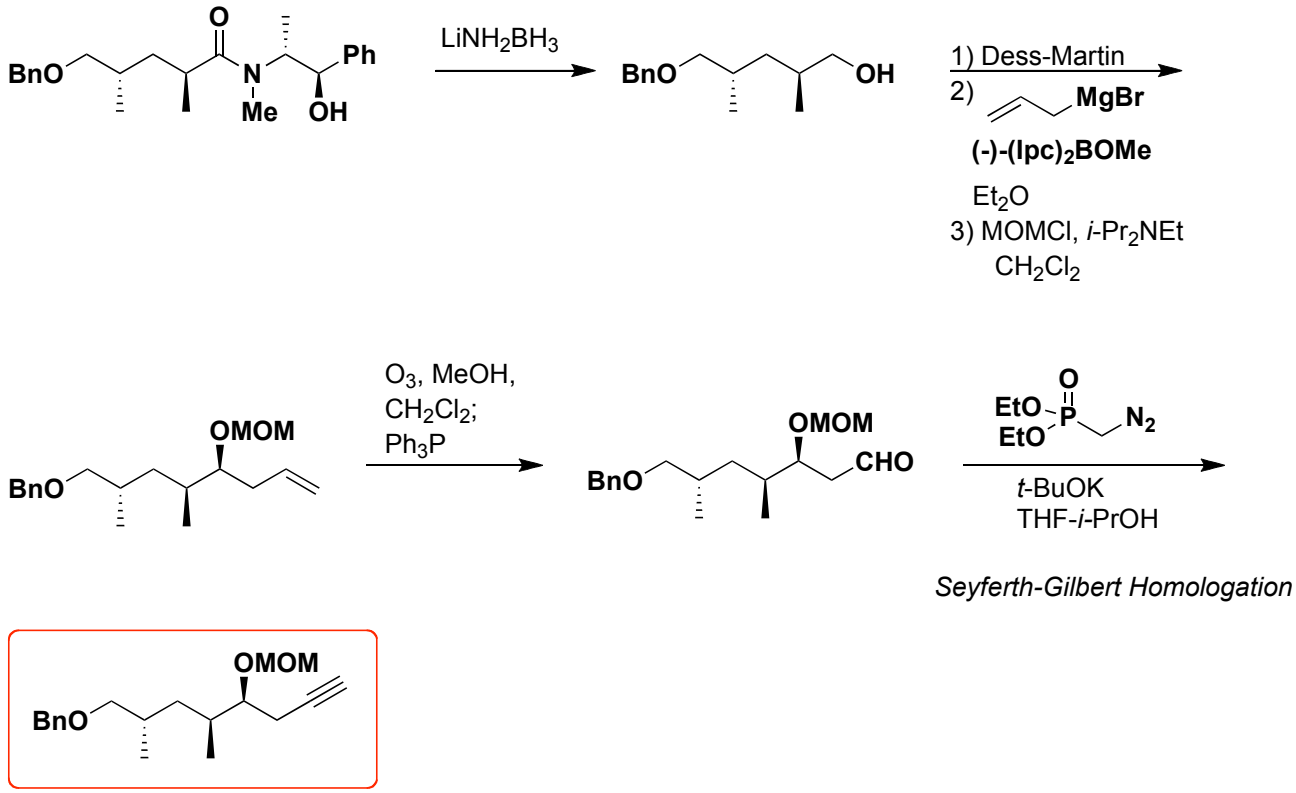

O
Cl
HN
Me
Ph
OH
Et3N
N
2 equiv LDA,
LiCl;
BnO
Cl


1) LiNH2BH3
2) Ph3P, I2
imidazole
BnO
I
"E"


O
Cl
HN
Me
Ph
OH
Et3N
N
2 equiv LDA, LiCl;
"E"
BnO



An alternate route based on chemistry that will be introduced in the next unit is also possible:



Seyferth-Gilbert Homologation