Natural Products: *Total Synthesis*

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Resources

‘Organic Chemistry’ by Clayden, Greeves, Warren and Wothers.

‘Classics in Total Synthesis’ by Nicolaou and Sorensen

http://www.york.ac.uk/res/pac/teaching/natprods.html

Scope of the Course

In the limited time available we will look at how synthetic chemists have been inspired by complex natural products to developed new methods for acyclic stereocontrol in order to synthesise these, and other, entities in the laboratory.

Particular emphasis will be placed on understanding the retrosynthetic strategies employed and the stereoselectivity of the key reactions which are used to install the stereogenic centres in the target molecule. These points will be illustrated by the consideration of the total syntheses of the polyether antibiotic monensin.

Learning Objectives

1) To appreciate the general strategies used by synthetic chemists for the total synthesis of monensin.

2) To understand the concept of $A_{1,3}$ strain and to apply it to the stereoselective synthesis of some natural product sub-units.

3) To understand the concept of Felkin-Anh and chelation controlled addition to carbonyl groups and to apply it to the stereoselective synthesis of some natural product sub-units

Course Outline

Introduction to monensin and historical context.

Kishi's Synthesis

$A_{1,3}$ strain as a tool for stereocontrol

Application of the avoidance of $A_{1,3}$ strain to the total synthesis monensin

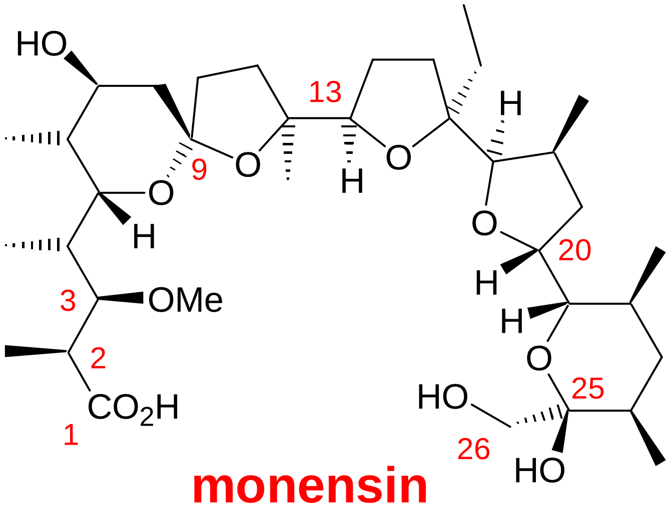
Still's Synthesis

Felkin-Anh model for addition of nucleophiles to chiral aldehydes

Cram chelation control model for addition of nucleophiles to chiral aldehydes

Application of Felkin-Anh and Cram models to the total synthesis monensin

Introduction and Historical Context



monensin

Isolated and characterised in 1967, from a strain of *Streptomyces cinamonensis*.
Exhibits broad spectrum anticoccidial activity.
Since 1971, it has been used to prevent coccidial infections in poultry and cattle.

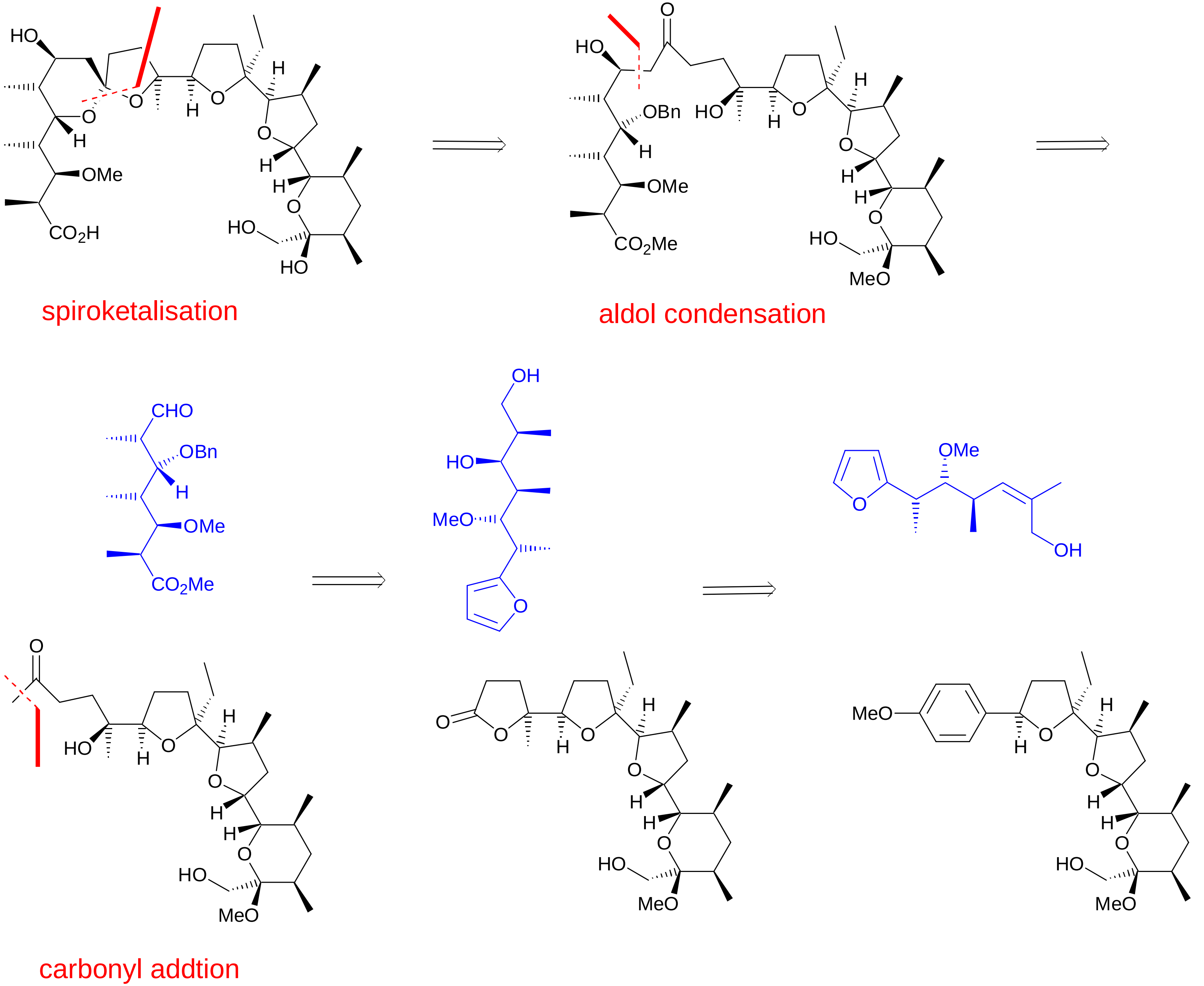
Monensin assumes a cyclic structure which is maintained by two intramolecular hydrogen bonds between the terminal C-1 CO_2H and the C-25 and C-26 OH groups.
Monensin's exterior is hydrocarbon-like, but its interior is rich in Lewis-basic O atoms, and its cyclic conformation make it ideal for the complexation and transportation of metal ions through biological membranes.

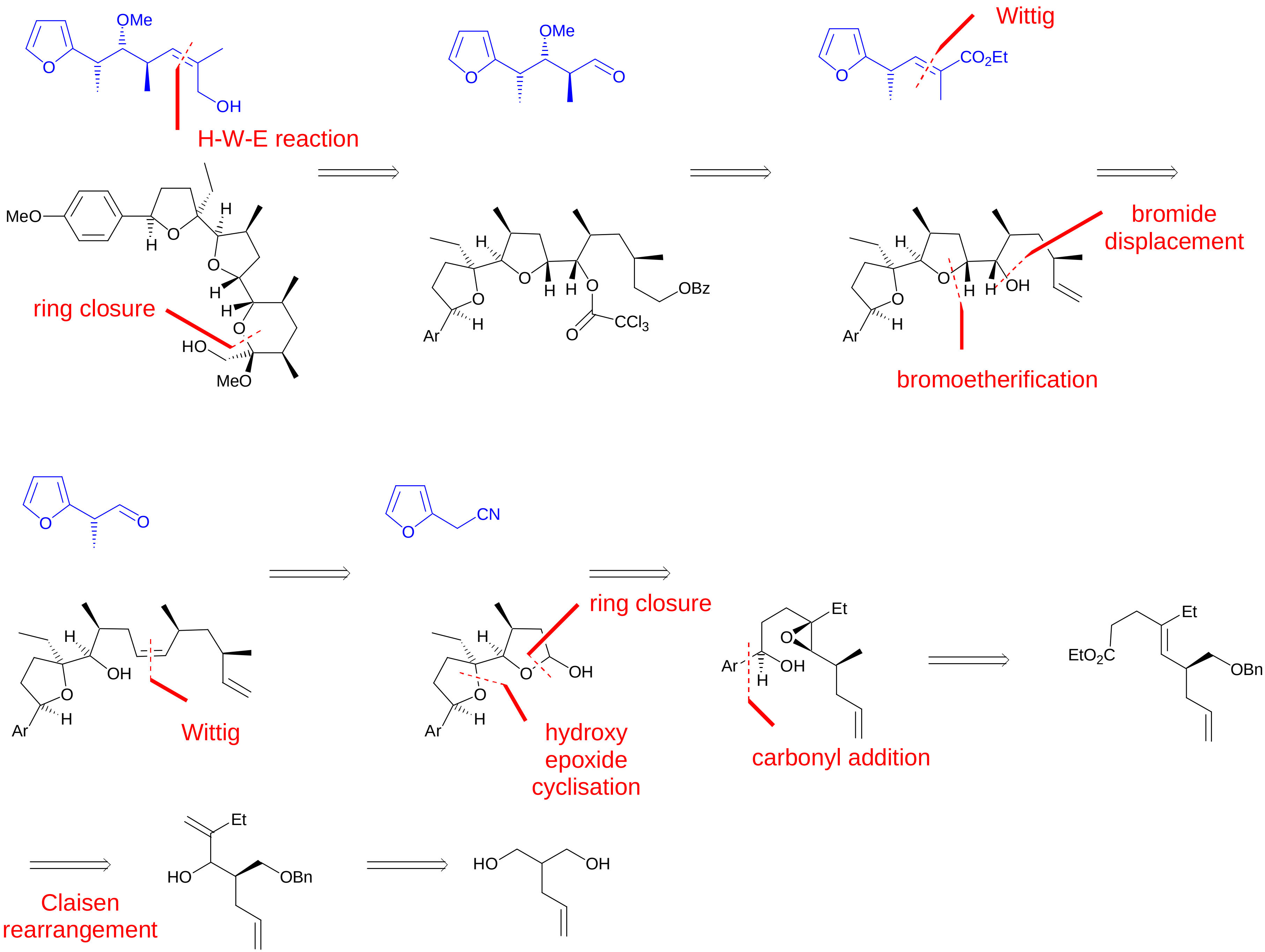
It is difficult to overestimate the role that polyether antibiotics, particularly monensin, have played in the development of acyclic stereocontrol. In fact much of our understanding of factors controlling acyclic stereoselectivity for such fundamental processes as hydroboration, epoxidation, halocyclisations, Claisen rearrangements, additions to carbonyls and aldol reactions arise from studies into the synthesis of polyethers.

Kishi’s Synthesis

Allylic 1,3 ($A_{1,3}$) Strain

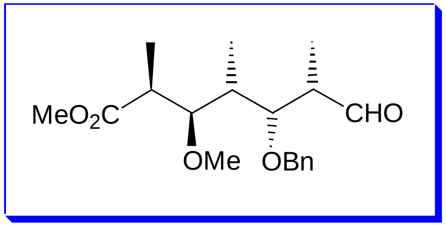
Retrosynthesis

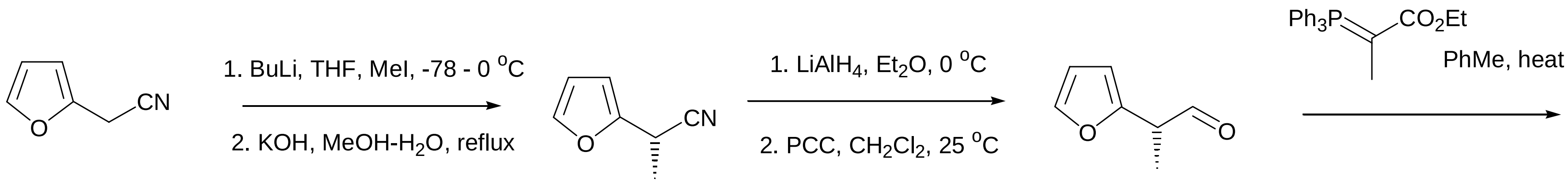


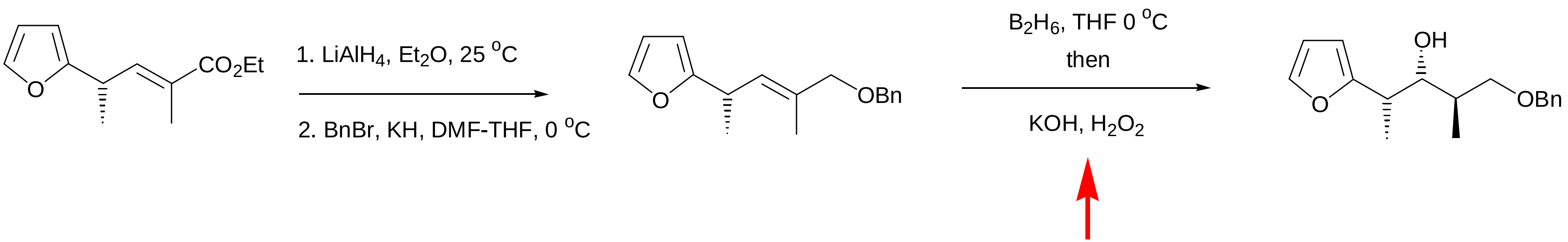


H-W-E reaction
Wittig
ring closure
bromide displacement
bromoetherification
Wittig
ring closure
hydroxy epoxide cyclisation
carbonyl addition
Claisen rearrangement

Synthesis

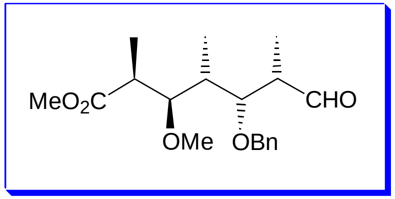


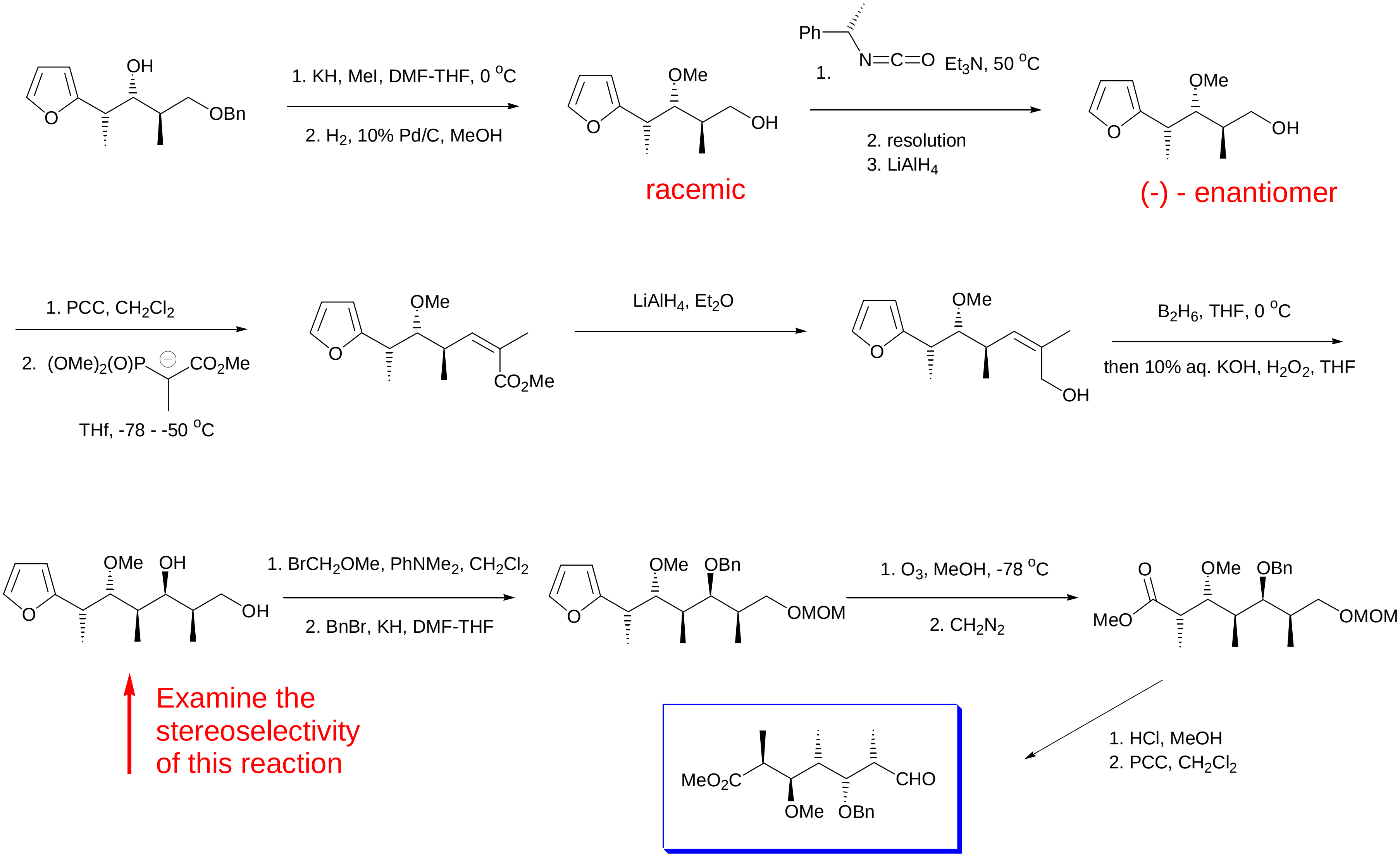




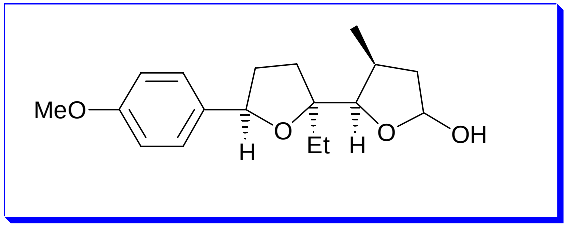
Let's examine the mechansim and stereoselectivity of this reaction

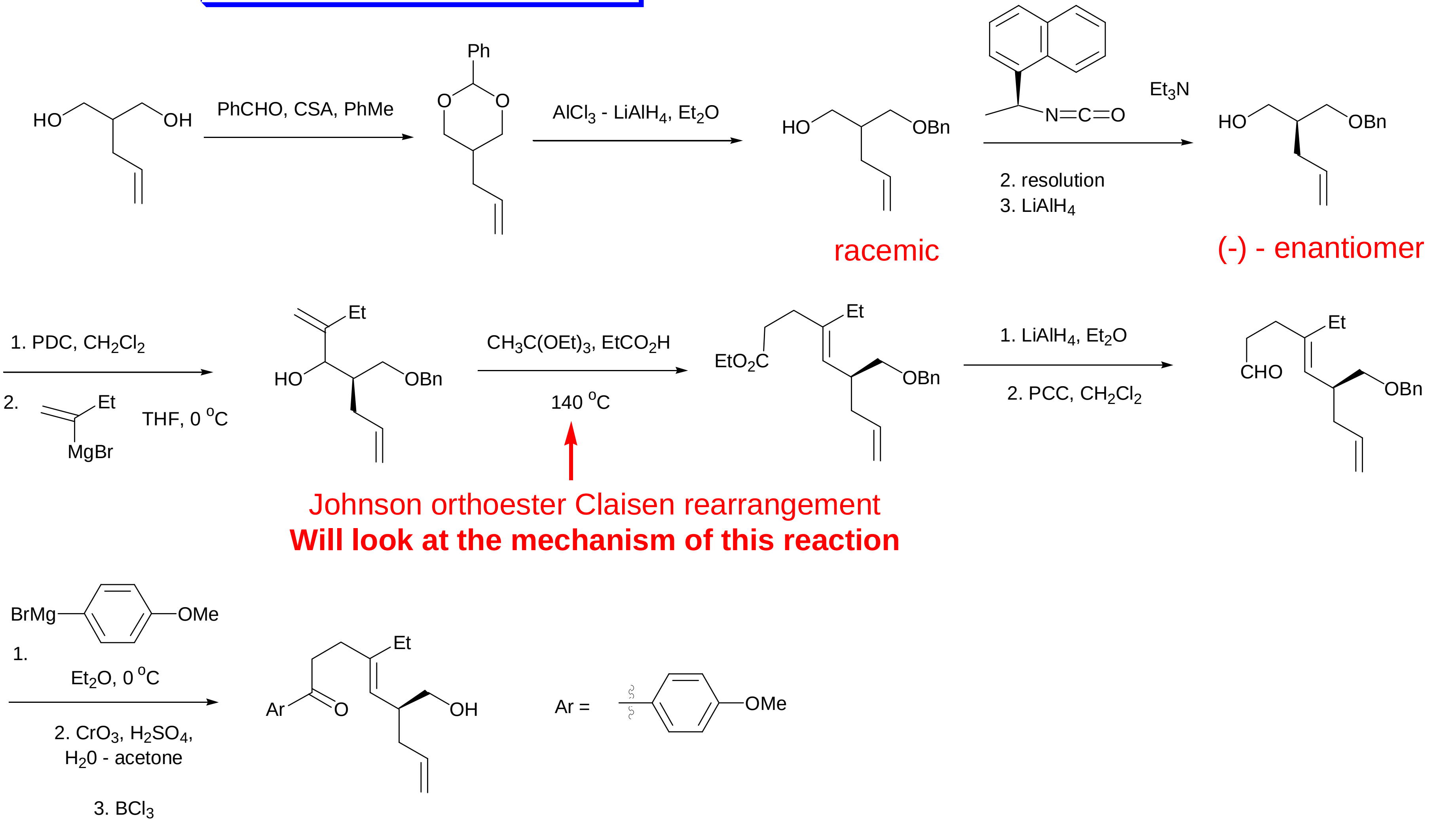
Synthesis


MeO2C
CHO
OMe
OBn

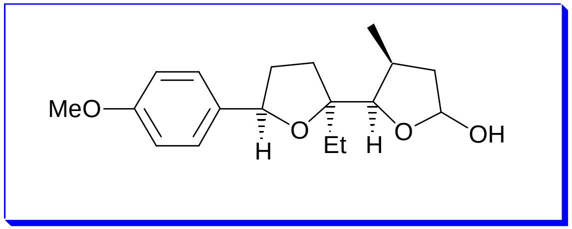

OH
OBn
1. KH, MeI, DMF-THF, 0 °C
2. H2, 10% Pd/C, MeOH
OMe
OH
racemic
Ph
N=C=O
1.
Et3N, 50 °C
2. resolution
3. LiAlH4
(-) - enantiomer
1. PCC, CH2Cl2
2. (OMe)2(O)P
CO2Me
THf, -78 - -50 °C
CO2Me
LiAlH4, Et2O
B2H6, THF, 0 °C
then 10% aq. KOH, H2O2, THF
OMe
OH
1. BrCH2OMe, PhNMe2, CH2Cl2
2. BnBr, KH, DMF-THF
OBn
OMOM
1. O3, MeOH, -78 °C
2. CH2N2
O
MeO
Examine the stereoselectivity of this reaction
1. HCl, MeOH
2. PCC, CH2Cl2
MeO2C
CHO

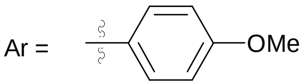
Synthesis

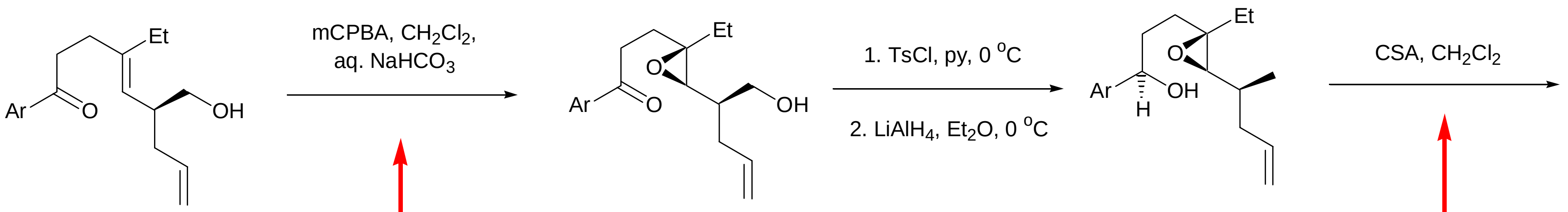

MeO
H
O
Et
H
O
OH


HO
OH
PhCHO, CSA, PhMe
Ph
O
O
AlCl3 - LiAlH4, Et2O
HO
OBn
racemic
N=C=O
Et3N
2. resolution
3. LiAlH4
HO
OBn
(-) - enantiomer
1. PDC, CH2Cl2
2.
Et
MgBr
THF, 0 oC
Et
HO
OBn
CH3C(OEt)3, EtCO2H
140 oC
Johnson orthoester Claisen rearrangement
Will look at the mechanism of this reaction
Et
EtO2C
OBn
1. LiAlH4, Et2O
2. PCC, CH2Cl2
Et
CHO
OBn
BrMg
OMe
1.
Et2O, 0 oC
2. CrO3, H2SO4,
H20 - acetone
3. BCl3
Et
Ar
O
OH
Ar =
OMe

Synthesis

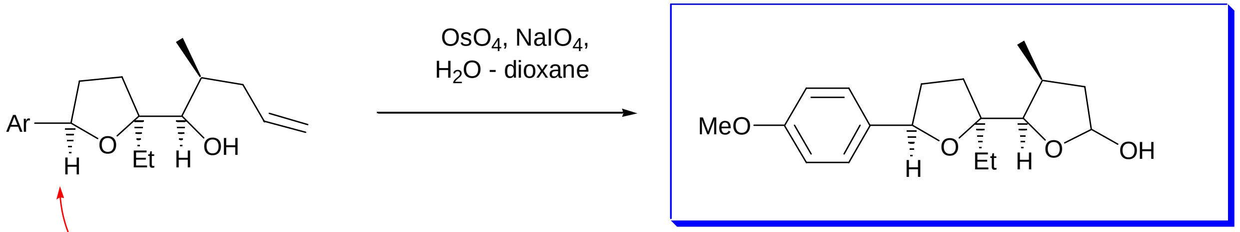






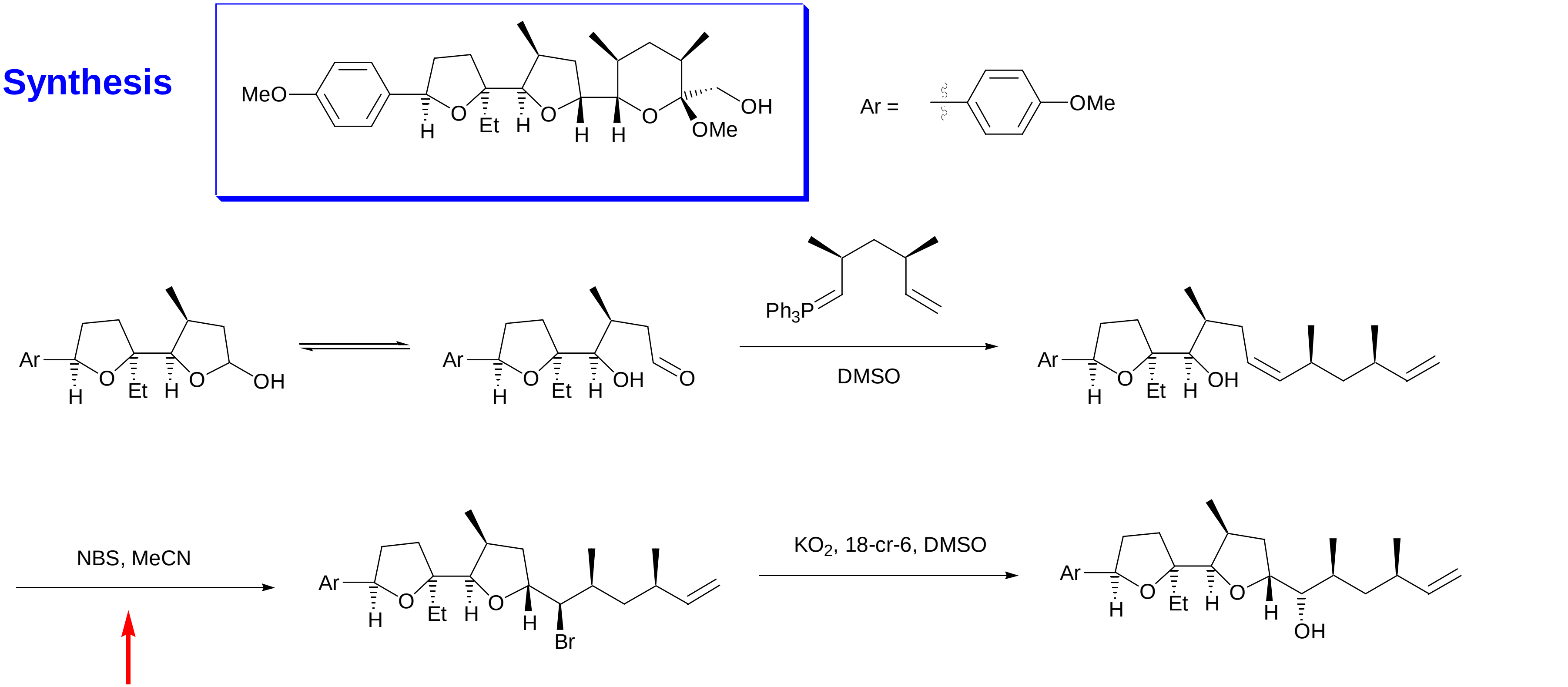
Examine the selectivity in this reaction

5-exo cyclisation
cf. radical course yr 3

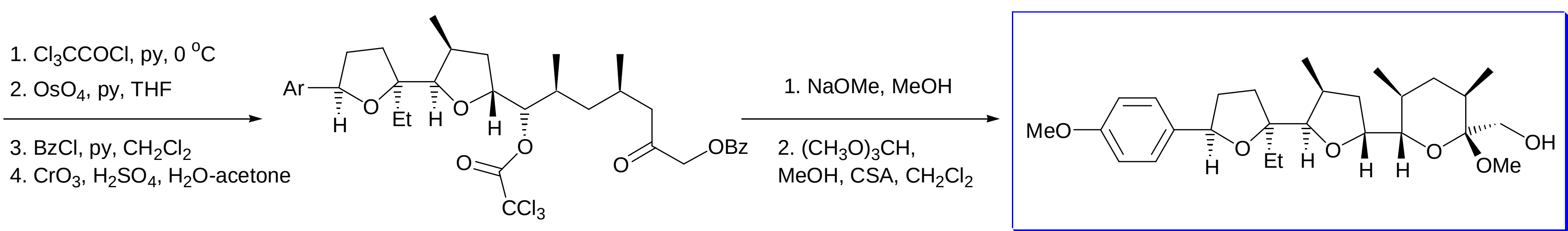


7:2 mix of epimers in favour of this one

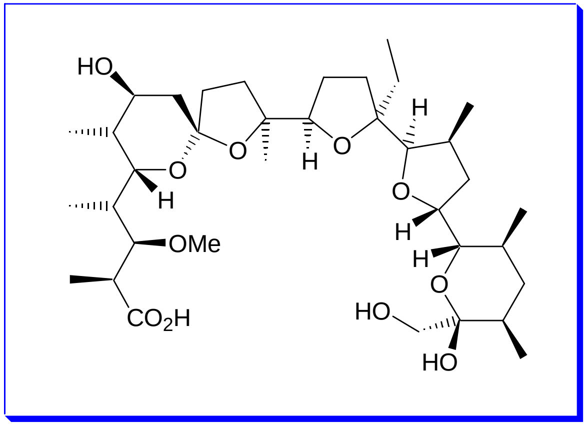
Synthesis

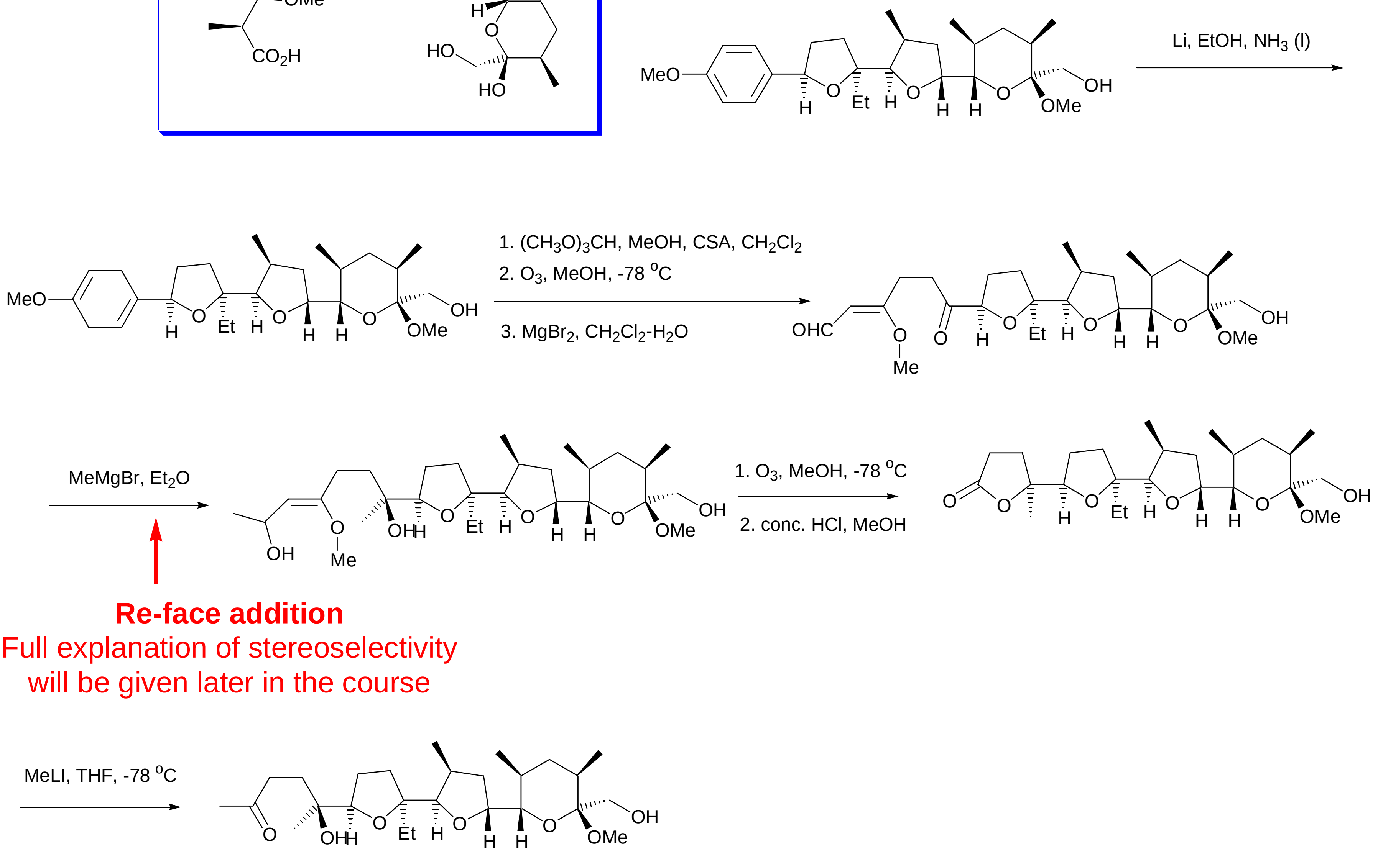


bromoetherification.
Let's examine the selectivity

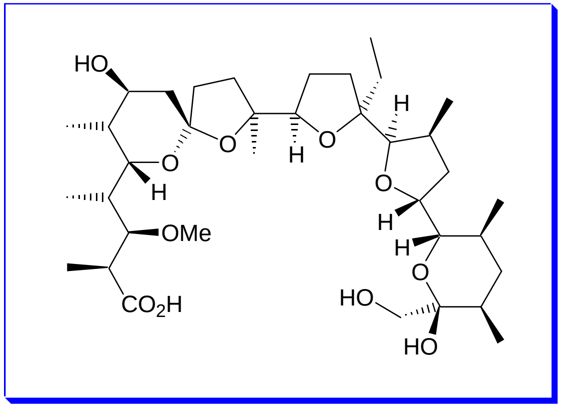


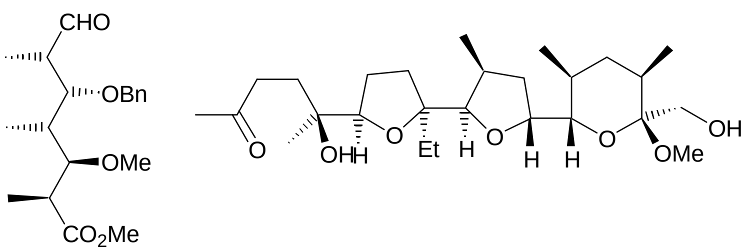
Synthesis


HO
OMe
CO2H
HO
HO

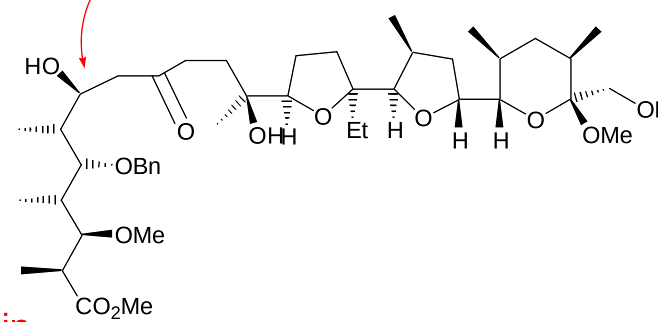

Li, EtOH, NH3 (l)
1. (CH3O)3CH, MeOH, CSA, CH2Cl2
2. O3, MeOH, -78 °C
3. MgBr2, CH2Cl2-H2O
MeMgBr, Et2O
1. O3, MeOH, -78 °C
2. conc. HCl, MeOH
MeLI, THF, -78 °C
Re-face addition
Full explanation of stereoselectivity
will be given later in the course

Synthesis





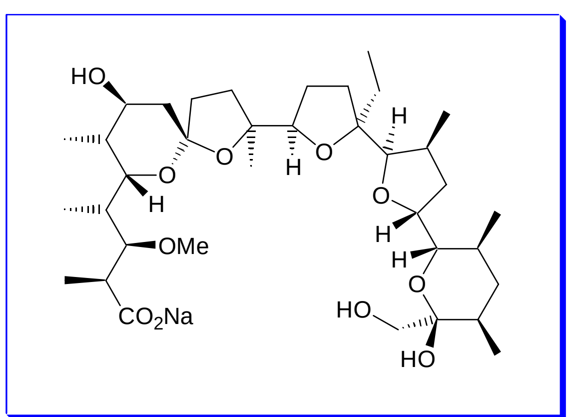
$^{i}Pr_2NMgBr$, THf, -78 ^oC



8:1 mix of diastereomers in favour of this one

aldol reaction
Explain stereoselectivity later in course

1. H_2, 10% Pd/C, MeOH - AcOH
2. CSA, H_2O, CH_2Cl_2 - Et_2O
3. 1N NaOH - MeOH



spiroketalisation
Explanation of the selectivity

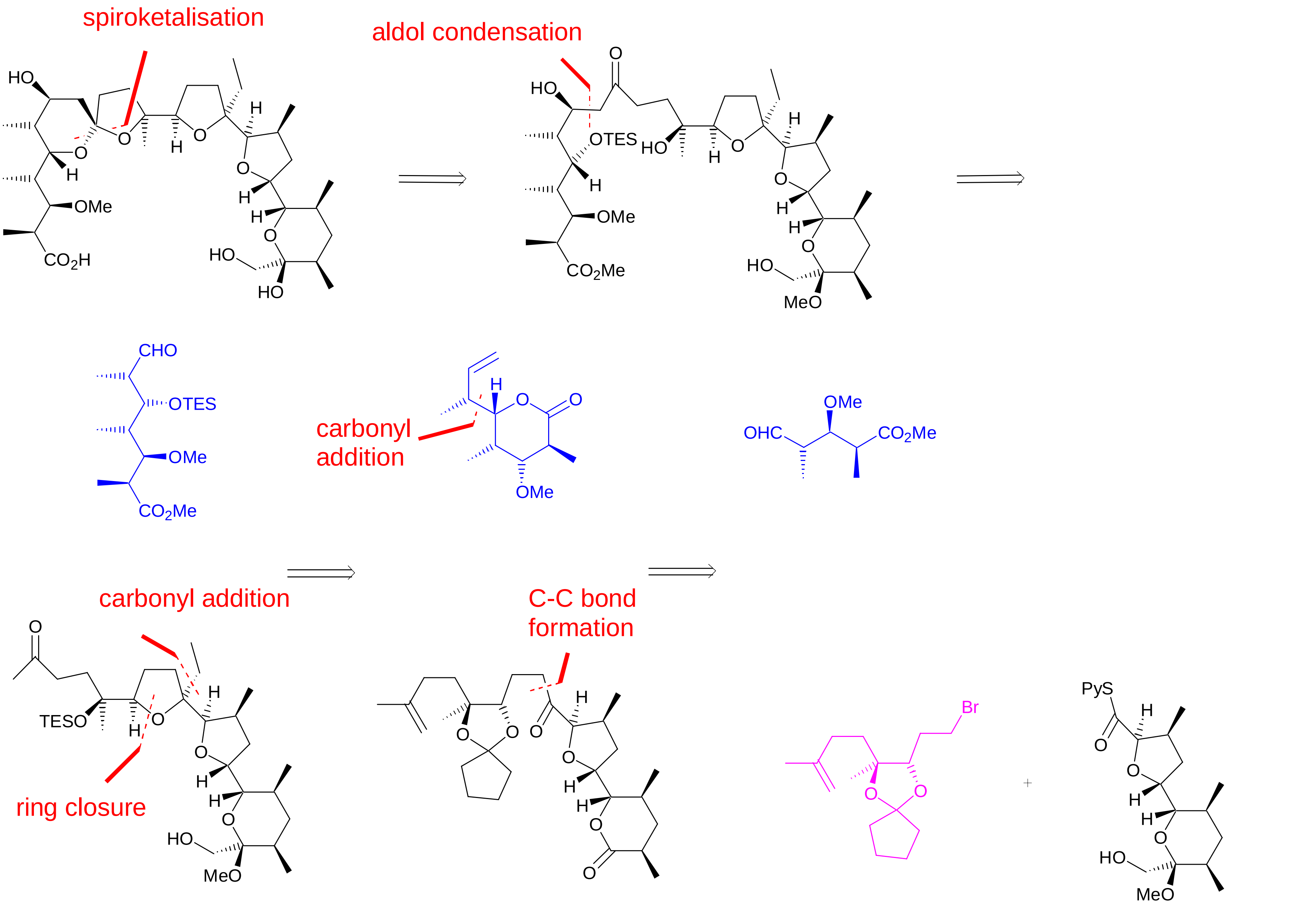
Summary of Kishi's Synthesis

The first total synthesis of monensin by Kishi is one of the great achievements in acyclic stereocontrol. Retrosynthetic analysis allowed the molecule to be divided into two sectors to be unified by a crossed aldol reaction. The left hand sector containing vicinal stereocentres is set up under the guiding influence of a pre-existing seterocentre by the use of two hydroboration reactions. While the right hand sector possesses both vicinal and remote stereocentres which are set up using a combination of stereo-defining principles. However, the main highlight of Kishi's synthesis is the use of the avoidance of allylic 1,3 strain as a stereocontrolling factor, and he used it to install 6 out of the 17 stereogenic centres present in monensin.

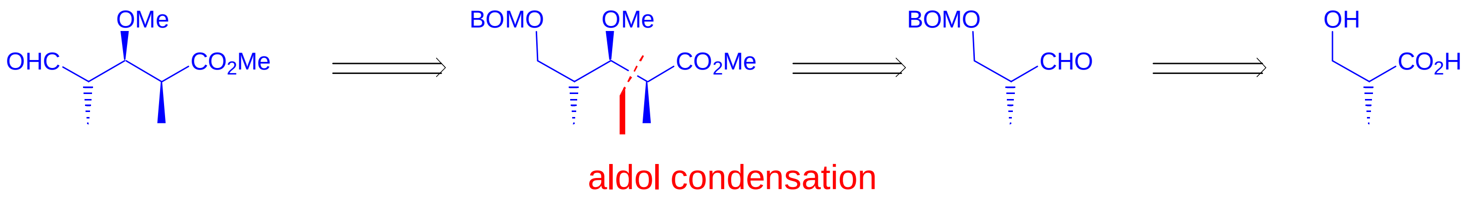
Still’s Synthesis

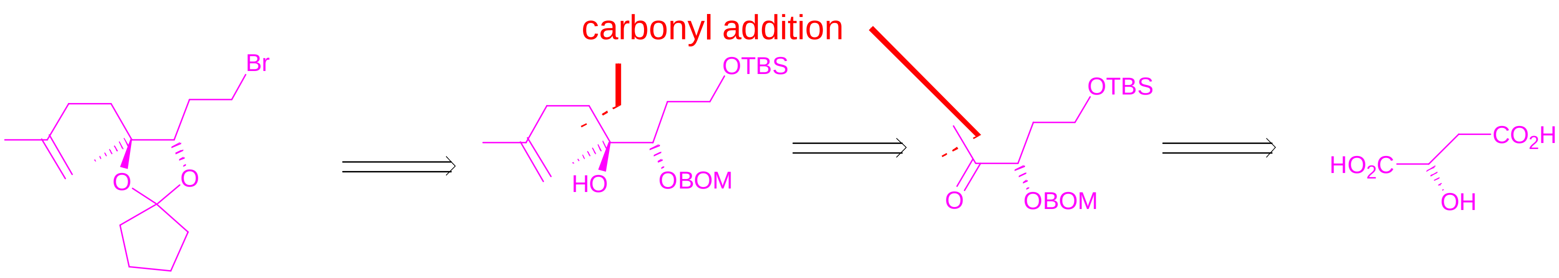
Felkin-Anh and Cram Chelation Models for the Addition of Nucleophiles to Carbonyl Groups

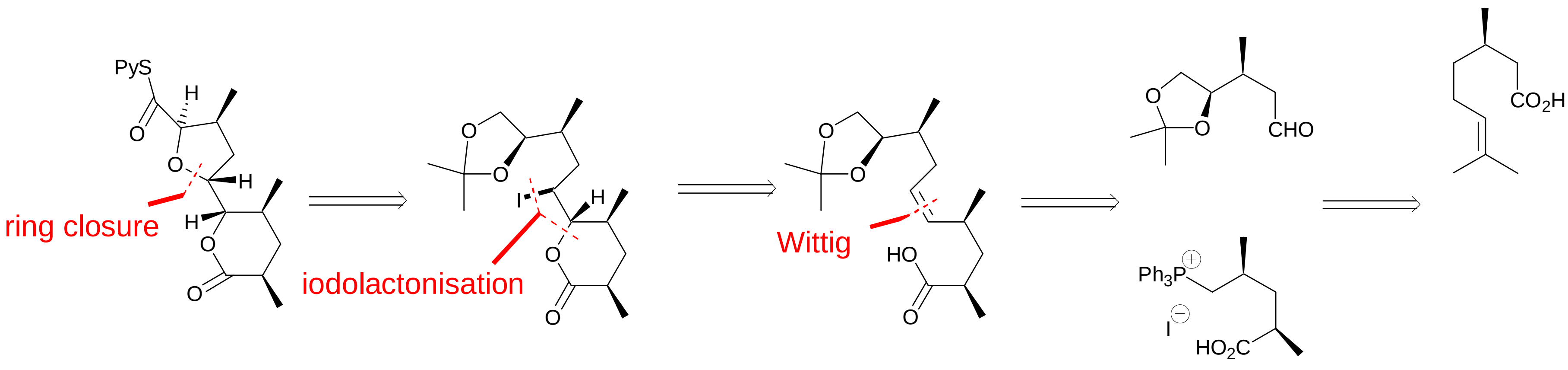
Retrosynthesis



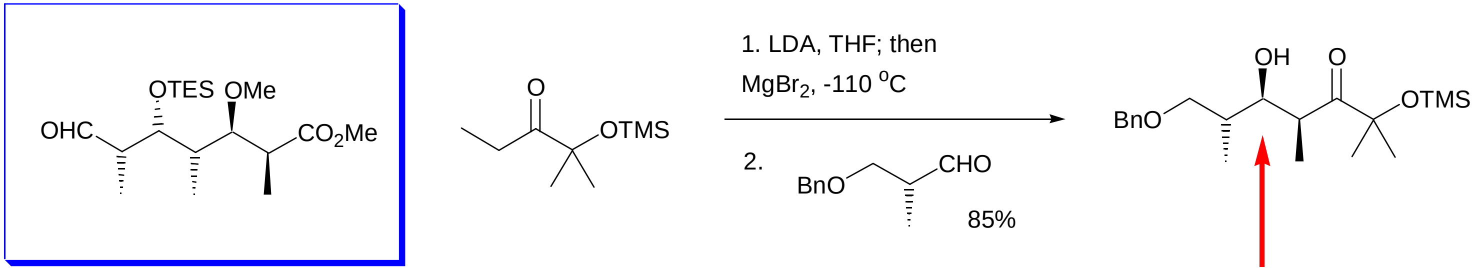
Retrosynthesis







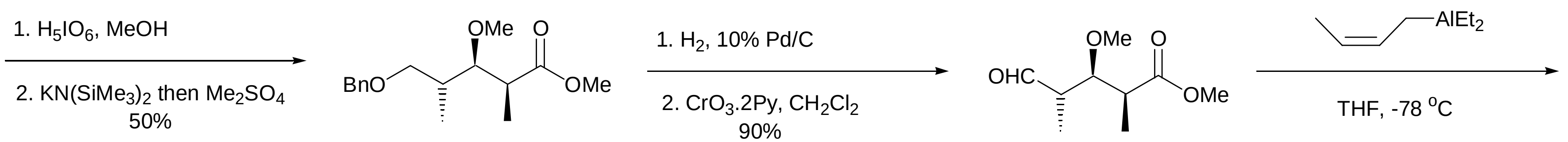
Synthesis

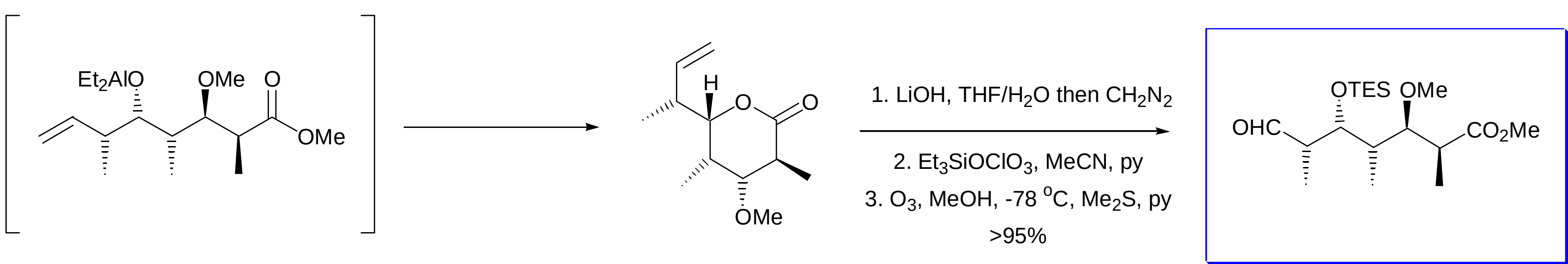


Aldol Reaction

5:1 mix in favour of *syn* diastereomer.

We will discuss this selectivity



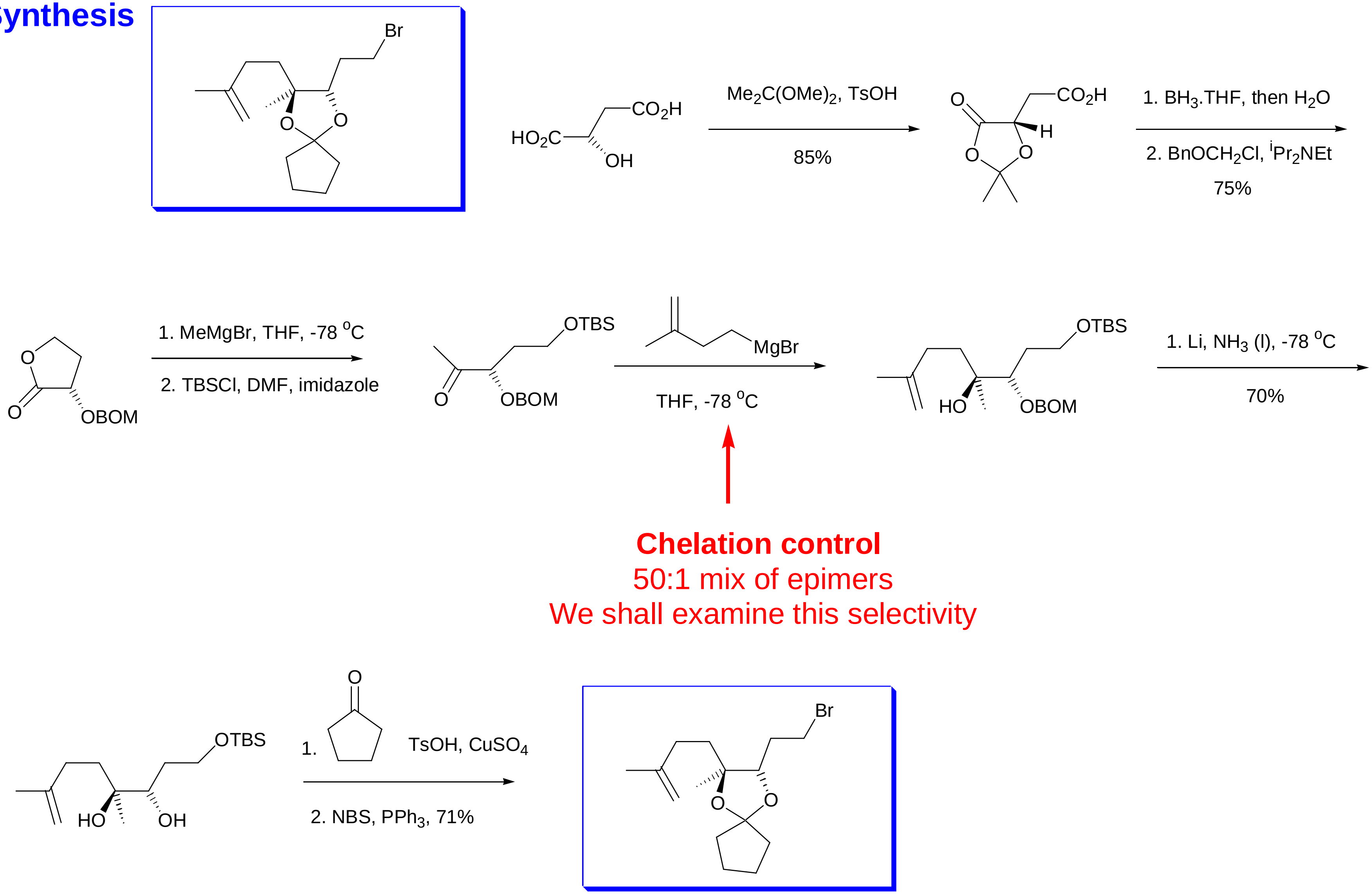


Cram-Felkin-Anh addition

gives this as major diastereomer in 3:1 ratio

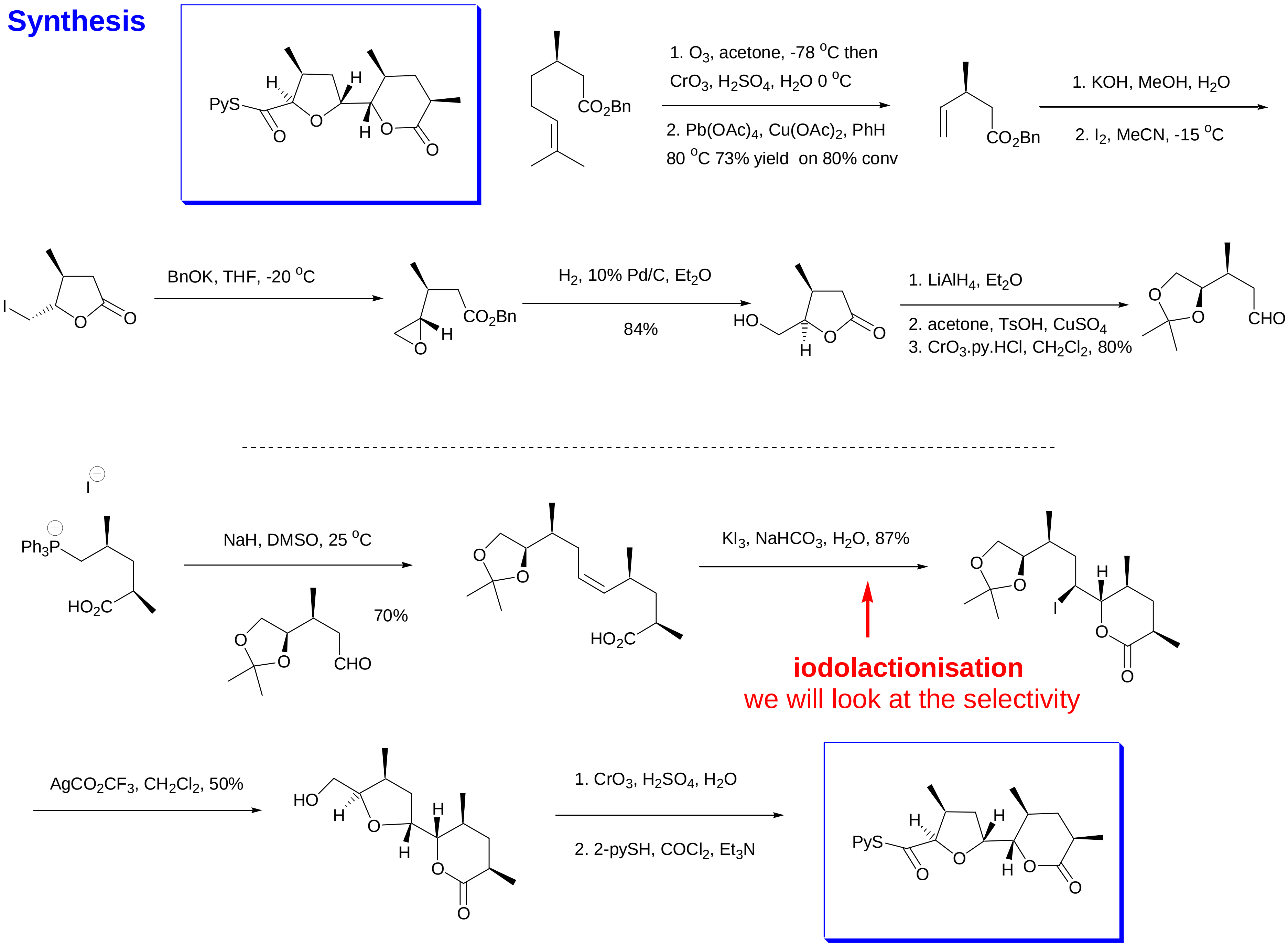
We shall look at this selectivity

Synthesis

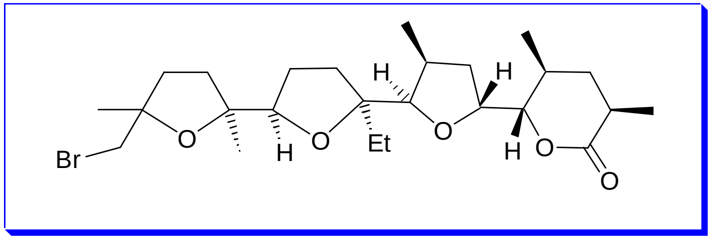


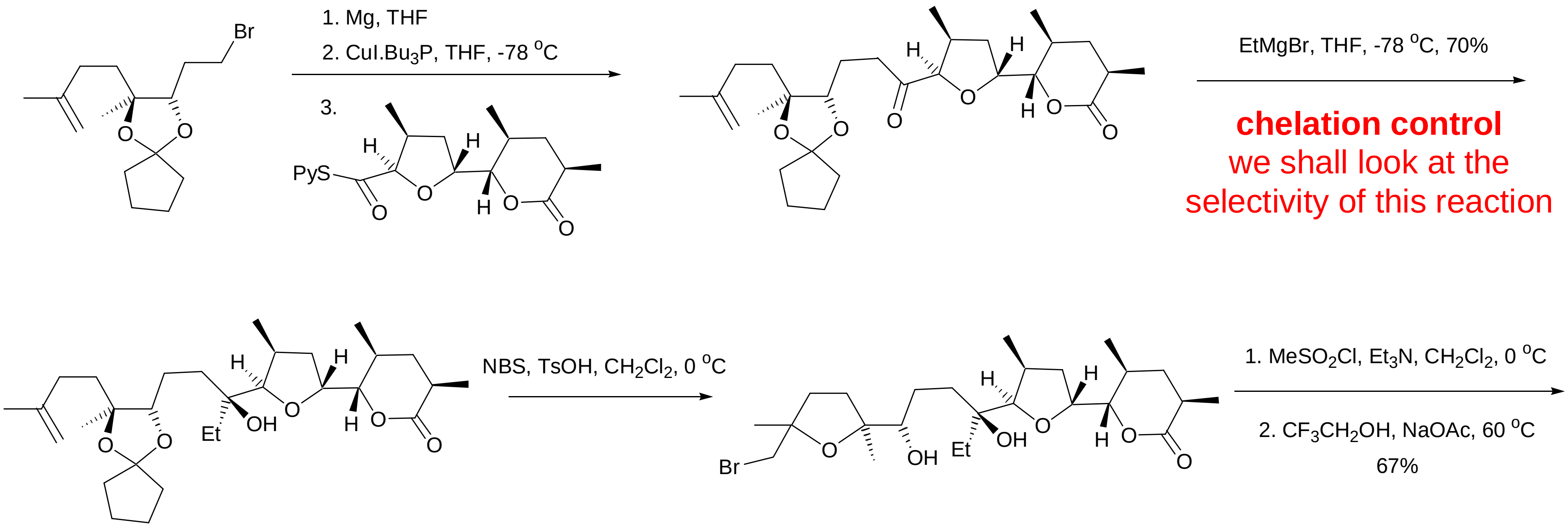
Br
O
O
HO2C
CO2H
OH
Me2C(OMe)2, TsOH
85%
CO2H
H
1. BH3.THF, then H2O
2. BnOCH2Cl, iPr2NEt
75%
OBOM
1. MeMgBr, THF, -78 oC
2. TBSCl, DMF, imidazole
OTBS
MgBr
THF, -78 oC
HO
1. Li, NH3 (l), -78 oC
70%
Chelation control
50:1 mix of epimers
We shall examine this selectivity
OH
1.
TsOH, CuSO4
2. NBS, PPh3, 71%

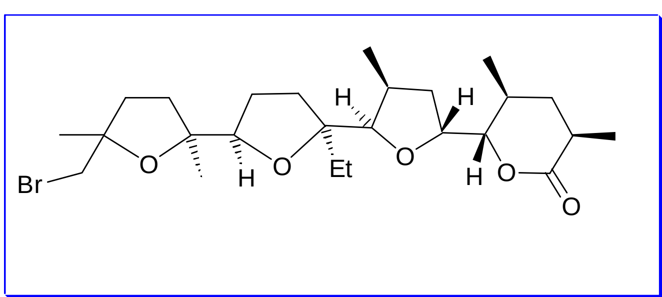
Synthesis


PyS
1. O_3, acetone, -78 °C then
CrO_3, H_2SO_4, H_2O 0 °C
2. $Pb(OAc)_4$, $Cu(OAc)_2$, PhH
80 °C 73% yield on 80% conv
CO_2Bn
1. KOH, MeOH, H_2O
2. I_2, MeCN, -15 °C
BnOK, THF, -20 °C
H_2, 10% Pd/C, Et_2O
84%
1. $LiAlH_4$, Et_2O
2. acetone, TsOH, $CuSO_4$
3. CrO_3.py.HCl, CH_2Cl_2, 80%
CHO
Ph_3P
HO_2C
NaH, DMSO, 25 °C
70%
KI_3, $NaHCO_3$, H_2O, 87%
iodolactionisation
we will look at the selectivity
$AgCO_2CF_3$, CH_2Cl_2, 50%
HO
1. CrO_3, H_2SO_4, H_2O
2. 2-pySH, $COCl_2$, Et_3N

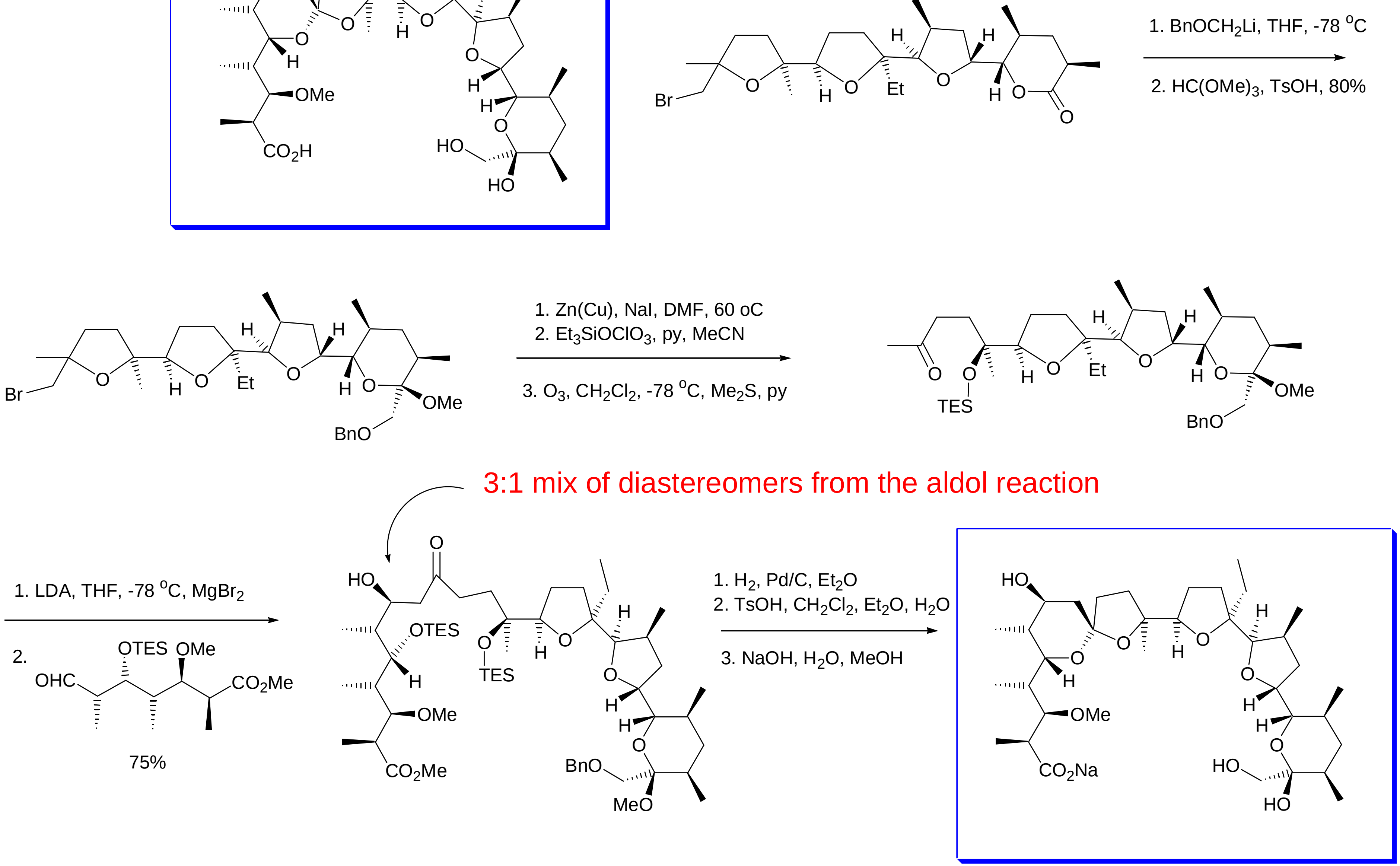
Synthesis


Br
H
H
Et
O
O
O
O
O
H
H
H


Br
1. Mg, THF
2. CuI.Bu$_3$P, THF, -78 ^{o}C
3.
PyS
EtMgBr, THF, -78 ^{o}C, 70%
chelation control
we shall look at the
selectivity of this reaction
OH
Et
NBS, TsOH, CH$_2$Cl$_2$, 0 ^{o}C
1. MeSO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$, 0 ^{o}C
2. CF$_3$CH$_2$OH, NaOAc, 60 ^{o}C
67%


Br
H
H
Et
O
O
O
O
O
H
H
H

Synthesis


1. BnOCH2Li, THF, -78 °C
2. HC(OMe)3, TsOH, 80%
1. Zn(Cu), NaI, DMF, 60 oC
2. Et3SiOClO3, py, MeCN
3. O3, CH2Cl2, -78 °C, Me2S, py
3:1 mix of diastereomers from the aldol reaction
1. LDA, THF, -78 °C, MgBr2
2.
75%
1. H2, Pd/C, Et2O
2. TsOH, CH2Cl2, Et2O, H2O
3. NaOH, H2O, MeOH

Summary of Still's Synthesis

The second total synthesis of monensin by Still is truly one of the great achievements in acyclic stereocontrol and natural product synthesis. Retrosynthetic analysis diveded the molecule into three units of comparable complexity, which allowed for a highly convergent synthesis of the natural product. Of particular note is the fact that only the methyl groups at carbons 4, 18 and 22 are derived from the chiral pool. All other stereogenic centres are fashioned through substrate controlled reactions. A particular highlight of this synthesis is the extensive use of chelation controlled reactions to set the majority of the stereogenic centres present in monensin. This must rank as one of the most impressive total syntheses of the late 20th century.

Course Summary

In this course we have discussed and illustrated the use of acyclic stereocontrol in the total synthesis of the polyether antibiotic monensin. Of particular importance is the avoidance of allylic 1,3 strain employed by Kishi in his synthesis, and the use of Felkin-Anh and Cram chelation control for the installation of stereogenic centres in Still's synthesis.

An understanding of these principles and an ability to apply them in the construction of natural product fragments is expected.