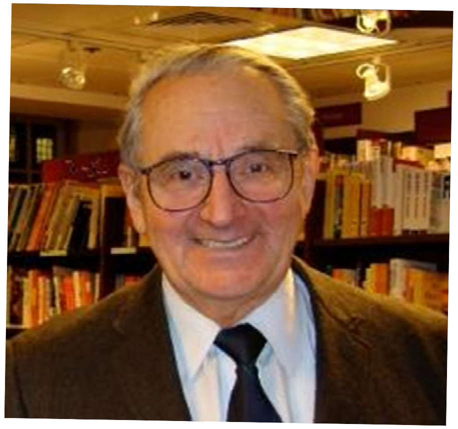
Methodologies

New reagents
New convertions
New reactivities
...



miscellaneous

CADD
Biochemical researches
Enzyme chemistry
...

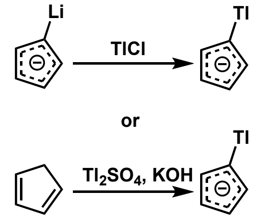
Total syntheses

Prostaglandins
Leukotrienes
Gibberellic acid
...

"...To them and to those starting careers in chemistry, I would offer the following advice: Never underestimate what you can accomplish if you prepare yourself well, continue to learn, work hard and optimistically, and value your integrity."

Thallous Cyclopentadienide

JACS, 1971, 93, 1489



Advantages:

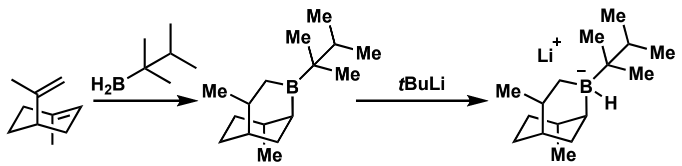
1. More stable than sodium/lithium
2. The anion is relatively difficult to isomerize

Disadvantage:

Highly toxic!!

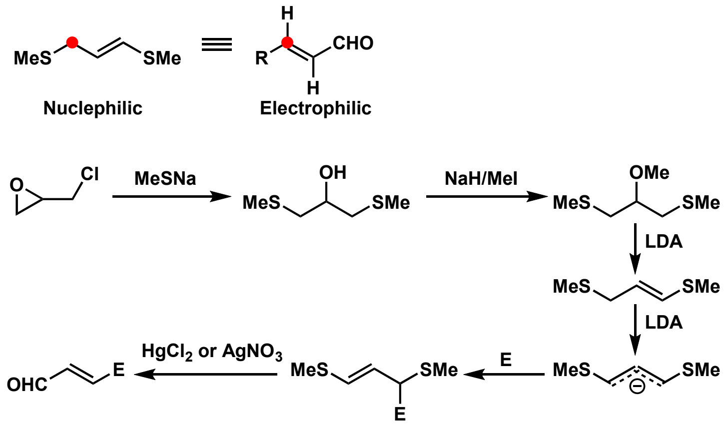
Stereoselective Reduction Reagent

JACS, 1971, 93, 1491



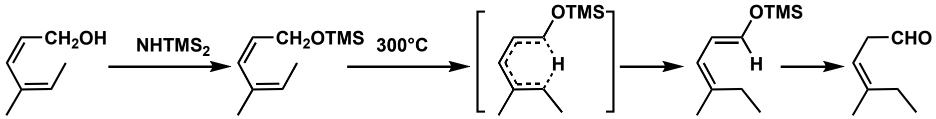
1,3-bis(methylthio)allyllithium

JACS, 1971, 93, 1724



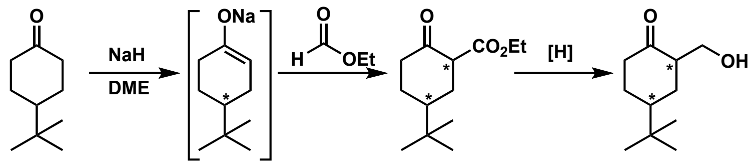
Trisubstituted Olefins synthesis by 1,5-prototropic Shift

TL, 1971, 20, 1641



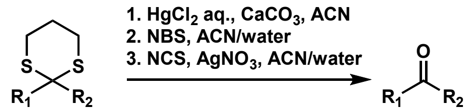
Hydroxymethylation of Ketone

JOC, 1971, 36, 3070



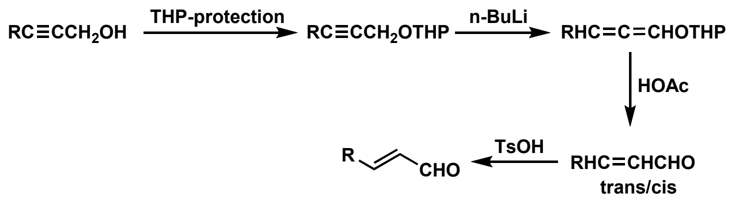
Oxidative Hydrolysis of 1,3-Dithiane

JOC, 1971, 36, 3553



Preparation of α,β-Unsaturated Aldehyde by Propargylic Alcohol

TL, 1972, 18, 1815



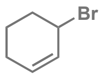
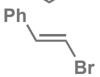
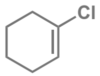
Organocopper Reagent

JACS, 1967, 89, 3911
JACS, 1968, 90, 5615
JACS, 1969, 91, 1851
JACS, 1970, 92, 395
TL, 1970, 11, 315

General Formula

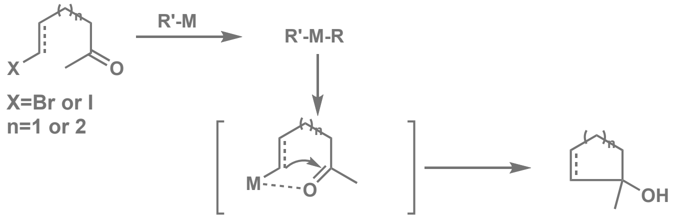
Features:

1. *cis* addition when reacts in THF at -80°C while a mixture of *cis*/*trans* product was formed in Et_2O
2. when equivalent of [Cu] is less than 0.5 eq. of [Li], 1,2-addition will dominate.
3. when R=Me, coppor-halogen exchange will become a serious side reaction.
4. carboxylic acid and amide are tolerated

$C_{10}H_{21}I$	80%
$C_7H_{15}Cl$	75%
	60%
	65%
	60%
	60%
$I(CH_2)_{10}CO_2H$	76%
$I(CH_2)_{10}CON(Me)Ph$	82%
PhI	75%

Other metal ion(Manganese\cobalt) were also tested, leading to a unsatisfactory resluts

Intramolecular Cyclization



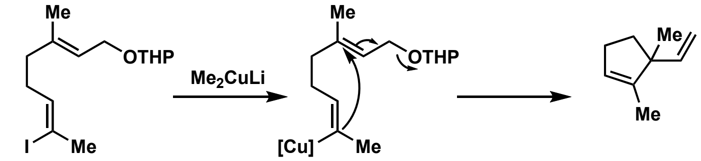
X=Br or I
n=1 or 2

Bu_2CuLi ⇨	C_{sp2} halides
$NiTPP^{2-}$ ⇨	C_{sp3} halides

nickel tetraphenylporphine —(Li-Nap)→ $NiTPP^{2-}$

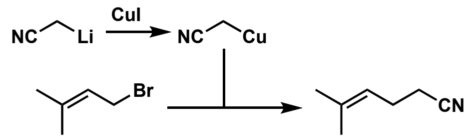
Cyclization with Allyl-THP Ether

JOC, 1972, 37, 1441



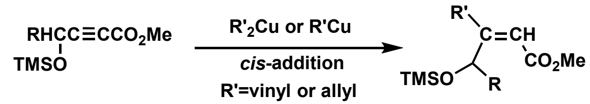
γ,δ-Unsaturated Nitrile Synthesis

TL, 1972, 6, 487

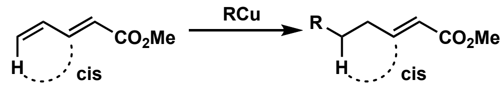


1,3- or 1,4-Diene Synthesis

JACS, 1972, 94, 4395

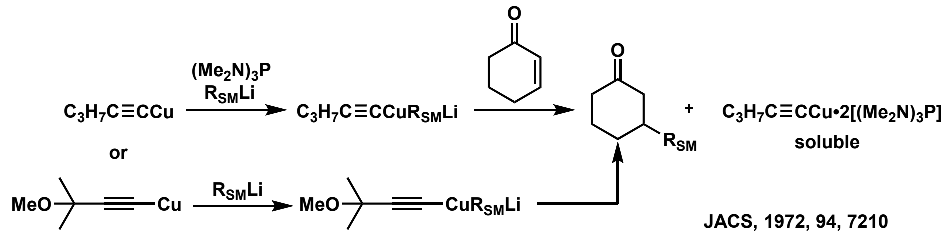


Addition to $\Delta^{2,4}$-dienoic esters



Mixed Cuprate Reagents of Type $RR_{SM}CuLi$

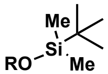
To avoid wasting high-value starting material, cheaper R was employed



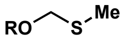
JACS, 1972, 94, 7210
JOC, 1978, 43, 3418

Protection Group

1. Hydroxyl Group:

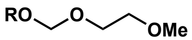
TBS- 

JACS, 1972, 94, 6190

MTM- 

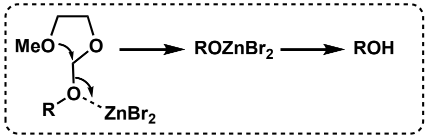
TL, 1975, 38, 3269

Stable in acidic, basic, nucleophilic conditions
Cleavage by $HgCl_2$ or $AgNO_3$

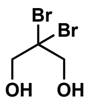
MEM- 

TL, 1976, 17, 809

Stable in strong basic, reducing, oxidazing, organometallic, mild acidic conditions
Cleavage by Lewis acids:$ZnBr_2$...

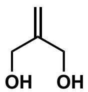


2. Carbonyl Group:

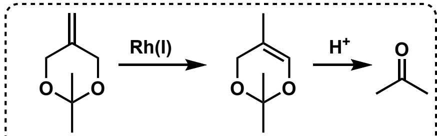
2,2-dibromo-1,3-propanediol 

TL, 1976, 17, 4577

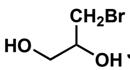
Cleavage by Zn/$AgNO_3$

2,2-methylene-1,3-propanediol 

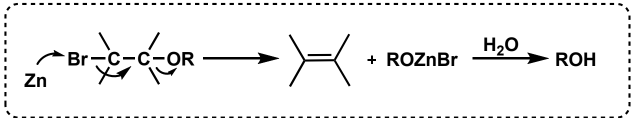
TL, 1975, 16, 3775



Cleavage by Rh(I) then acid

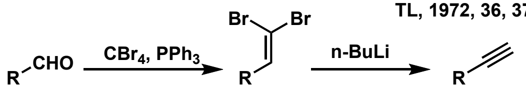
1,2-dihydroxy-3-bromo-propane 

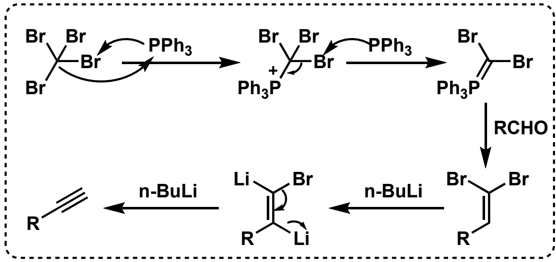
JOC, 1973, 38, 834



Corey-Fuchs Reaction

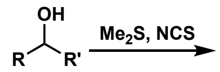
TL, 1972, 36, 3769

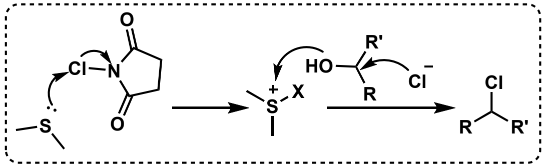




Allylic/Benzylic Alcohaol to Halide

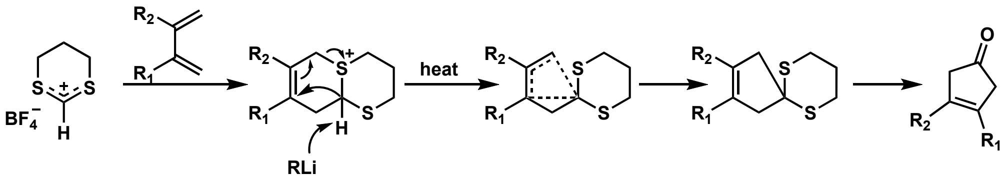
TL, 1972, 42, 4339



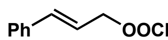


Δ^3-Cyclopentenone Synthesis by 1,3-Dithienium Fluoroborate

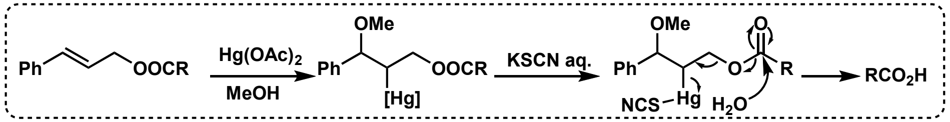
JACS, 1972, 94, 8932

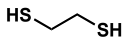


3. Carbonyl derivatives:

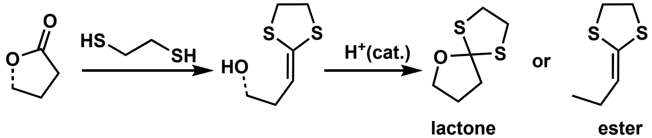
Cinnamyl 

TL, 1977, 24, 2081



1,2-ethanedithiolate 

JACS, 1973, 95, 5829

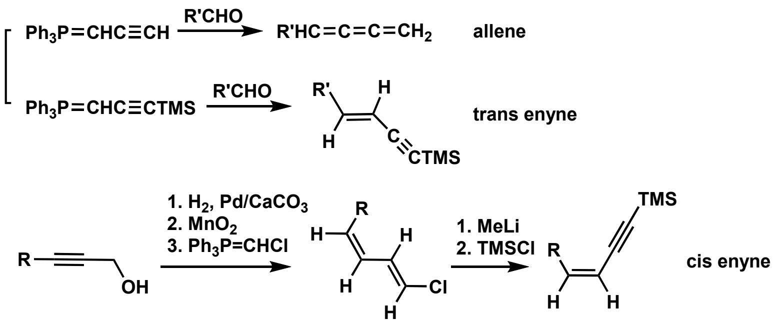


Cleavage by HgO/BCl_3

Corey's Career Review (1971-1980)

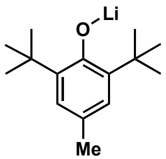
Stereocontrolled cis&trans Enyne Synthesis

TL, 1973, 14, 1495



Hindered Phenolic Lithium

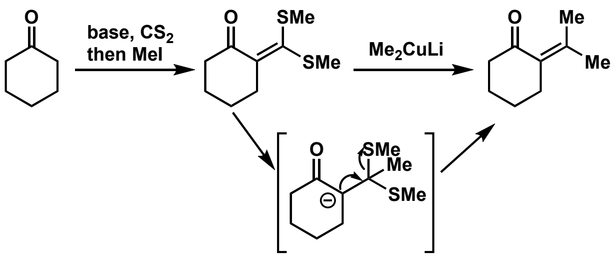
JOC, 1973, 38, 4086
TL, 1973, 39, 3817



To enolize ketone and react with CO_2

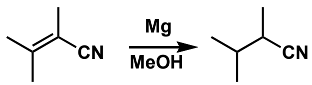
- Hard to react with CO_2
- Inefficient to less acidic substrates

To form dithiomethylene ketone and convert into others



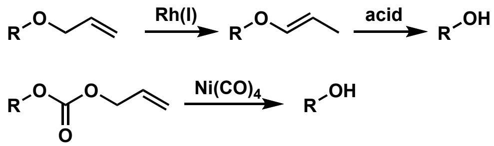
1,4-Reduction of Conjugated Nitrile

JOC, 1975, 40, 127



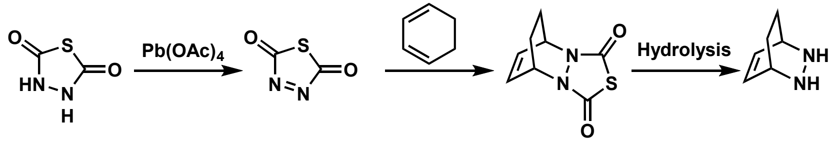
Deprotection of Alcohol with Allyl group

JOC, 1973, 38, 3223
JOC, 1973, 38, 3224



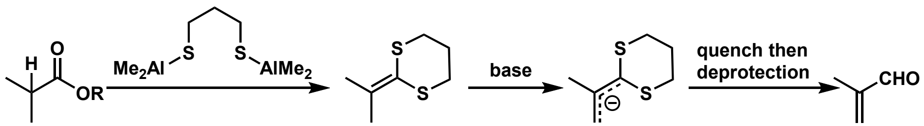
New DA Dienophile

JOC, 1973, 38, 3632



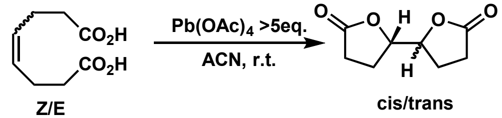
Ester to Unsaturated Aldehyde or Ketone

TL, 1975, 11, 925



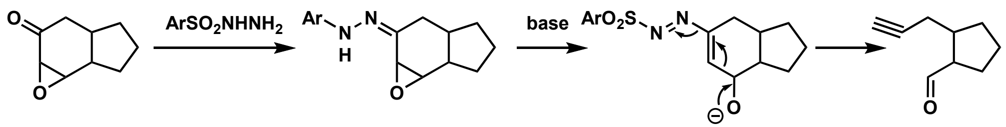
Conversion of diacid into bi-lactone

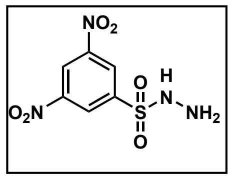
TL, 1980, 21, 1819



Eschenmoser Cleavage enabled by Hydrazine

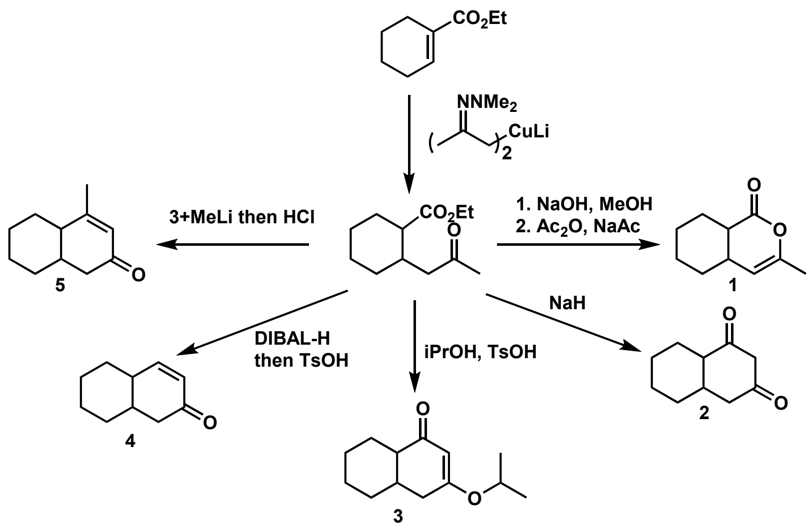
JOC, 1975, 40, 579





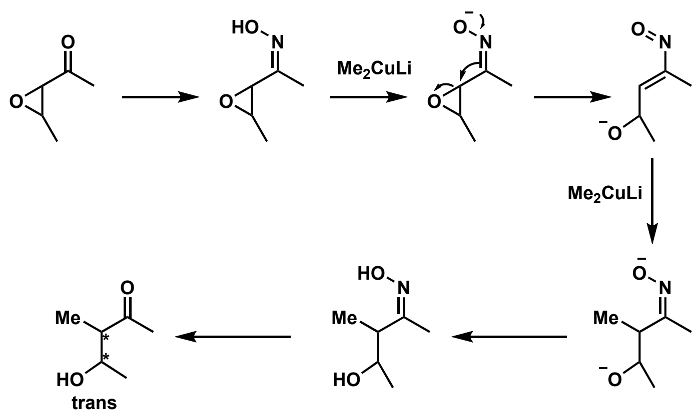
Synthesis of Fused Cyclohexenone Units

TL, 1978, 47, 4597



α-Alkylation of α,β-Epoxy Ketone

TL, 1976, 36, 3117



Catalytic Dehalogenations via Trialkyltin Hydride

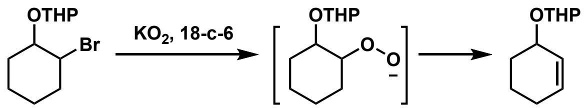
JOC, 1975, 40, 2554

R_3SnH + R'-X ⟶ R_3SnX + R'-H

R_3SnX + $NaBH_4$ ⟶ R_3SnH + NaCl + B_2H_6

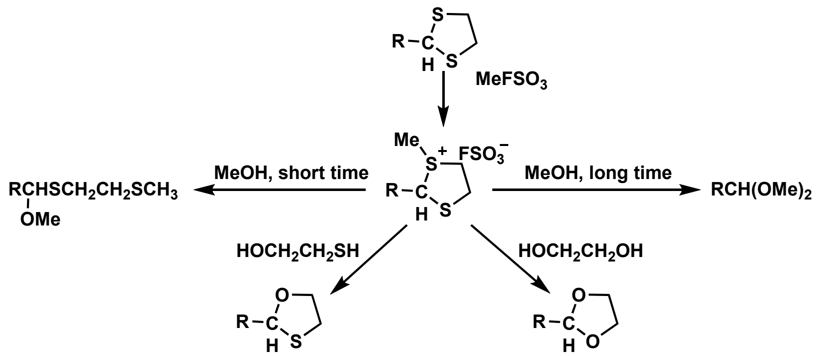
KO_2 As a Oxygen Nucleophile

TL, 1975, 37, 3183



Thioacetal-Hemithioacetal-Acetal Interchange

TL, 1975, 38, 3267



Conversion of Azides to Amine

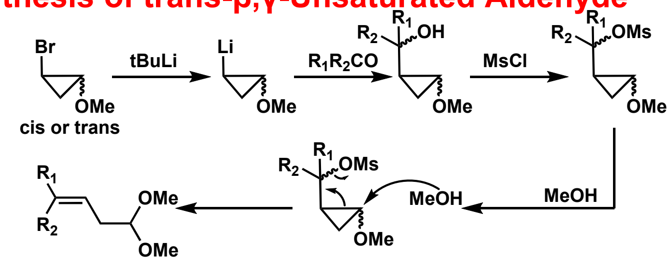
Synthesis, 1975, 590

$R\text{-}N_3$ $\xrightarrow{\text{Lindlar, } H_2}$ $R\text{-}NH_2$

carbon-carbon unsaturation, carbonyl groups were not effected

Synthesis of trans-β,γ-Unsaturated Aldehyde

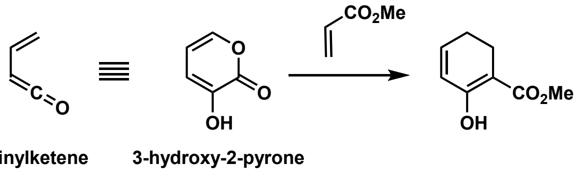
TL, 1975, 43, 3685



Equivalents in synthesis

Equivalent of Vinylketene

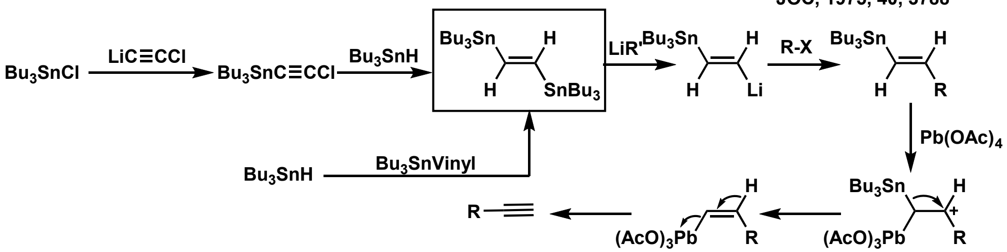
TL, 1975, 28, 2389



trans

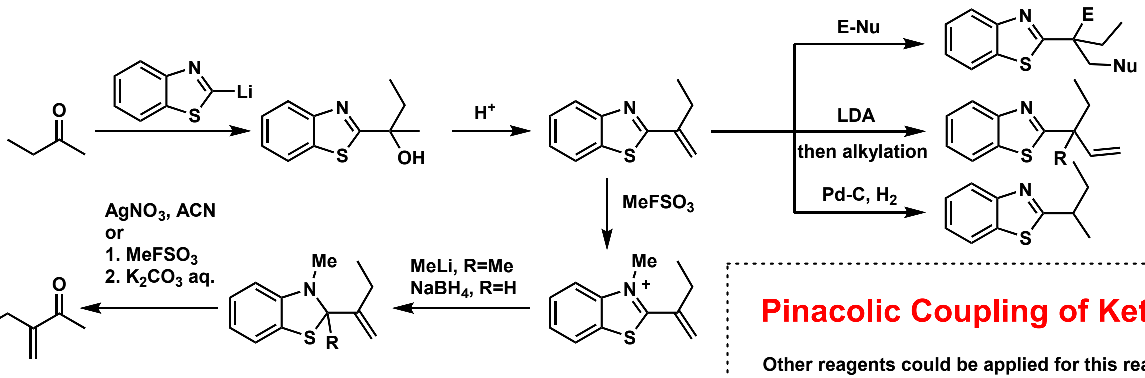
Nucleophilic Ethynyl Group Equivalent

JACS, 1974, 96, 5581
JOC, 1975, 40, 3788



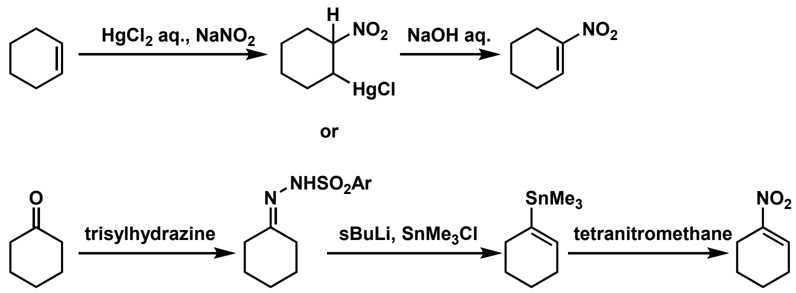
Benzothiazole as Carbonyl Anion Equivalent

TL, 1978, 19, 5
TL, 1978, 19, 9
TL, 1978, 19, 13



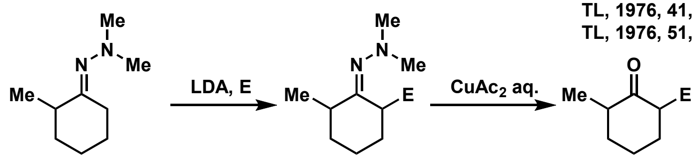
Synthesis of Conjugated Nitro Cyclo Olefin

JACS, 1978, 100, 1294
TL, 1980, 21, 1113



Hydrazone Chemistry

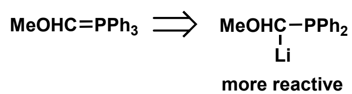
TL, 1976, 1, 3
TL, 1976, 1, 7
TL, 1976, 1, 11
TL, 1976, 41, 3667
TL, 1976, 51, 4687



- Higher reactivity than enolate
- Only monosubstitution was observed
- Substitution at less hinder position
- Less side reactions like aldol, C=O addition...

Synthesis of Aldehyde from ketone

TL, 1980, 21, 3535



Pinacolic Coupling of Ketone and Aldehyde by $CpTiCl_3$-LAH

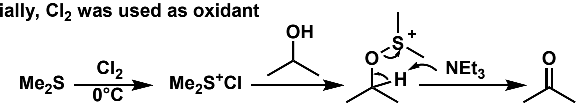
JOC, 1976, 41, 260

Other reagents could be applied for this reaction: Mg(Hg)-$TiCl_4$, LAH-$TiCl_3$(olefin), Zn-$TiCl_4$, Mg-$TiCl_3$, Al(Hg)

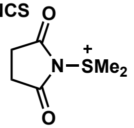
Oxidation Methodologies

Corey-Kim Oxidation

Initially, Cl_2 was used as oxidant JOC, 1972, 94, 7586

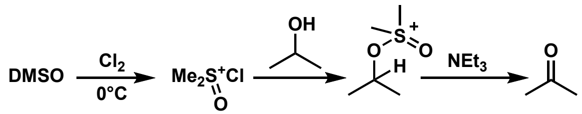


Then change Cl_2 by NCS

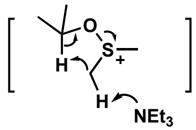


Subsequently, DMSO was choosen to be sulfur source and used in the synthesis of prostaglandins

TL, 1973, 12, 919
JOC, 1973, 38, 1233

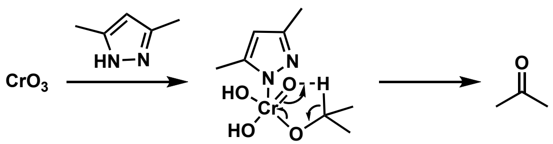


Again, they explored the mechanism TL, 1974, 3, 287



CrO_3-3,5-Dimethylpyrazole Complex Oxidation

TL, 1973, 45, 4499

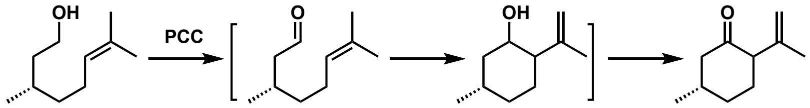


PCC/PDC Oxidation

TL, 1975, 31, 2647

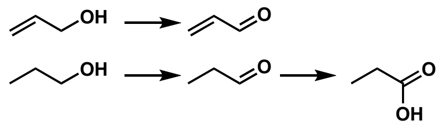
Initially, based on the weak acidity, an oxidation followed by cationic cyclization occurred.
Then they extended the substrate scope

JOC, 1976, 41, 380
TL, 1978, 28, 2461



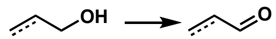
As for less acidic PDC, a lot of useful procedures were established

- PDC in DMF: TL, 1979, 5, 399



no isomerization of olefin

- PDC in DCM:



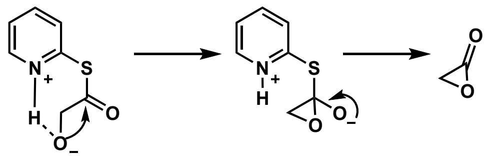
no over-oxidized product
but isomerization could happen

Subsequently, PDC finished the oxidation of aldehyde into acid assisted by TMSCN

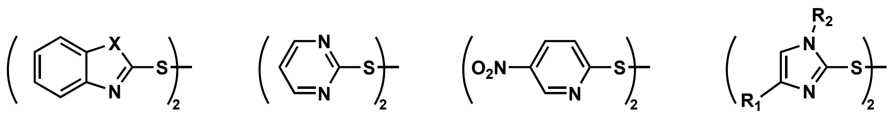
TL, 1980, 21, 731

Corey-Nicolaou Lactonization

JACS, 1974, 96, 5614
TL, 1976, 38, 3405
TL, 1976, 38, 3405



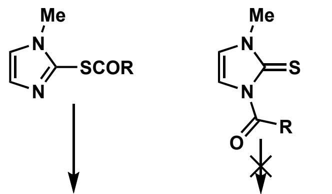
other derivatives:



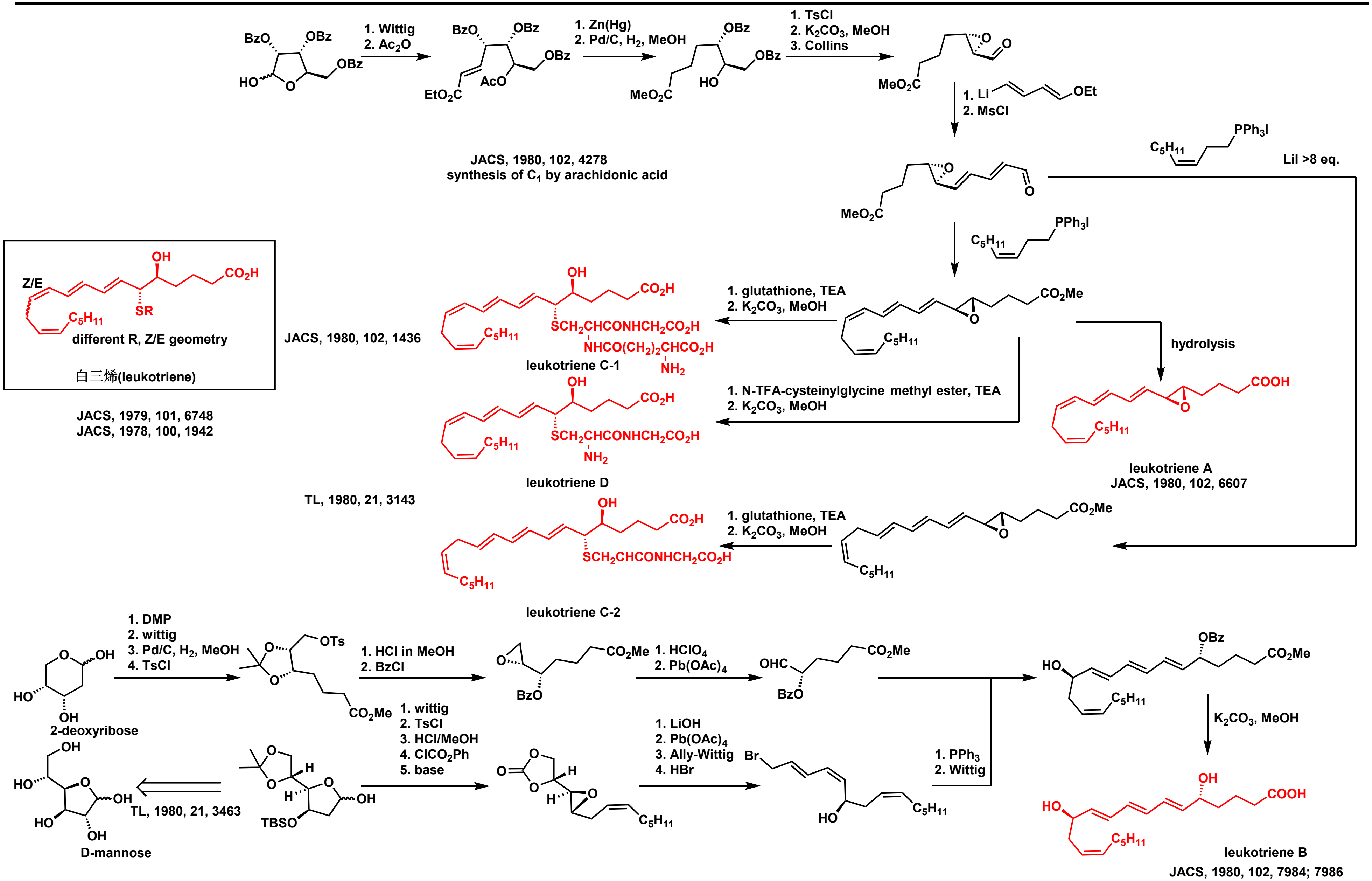
X=NMe, O, S

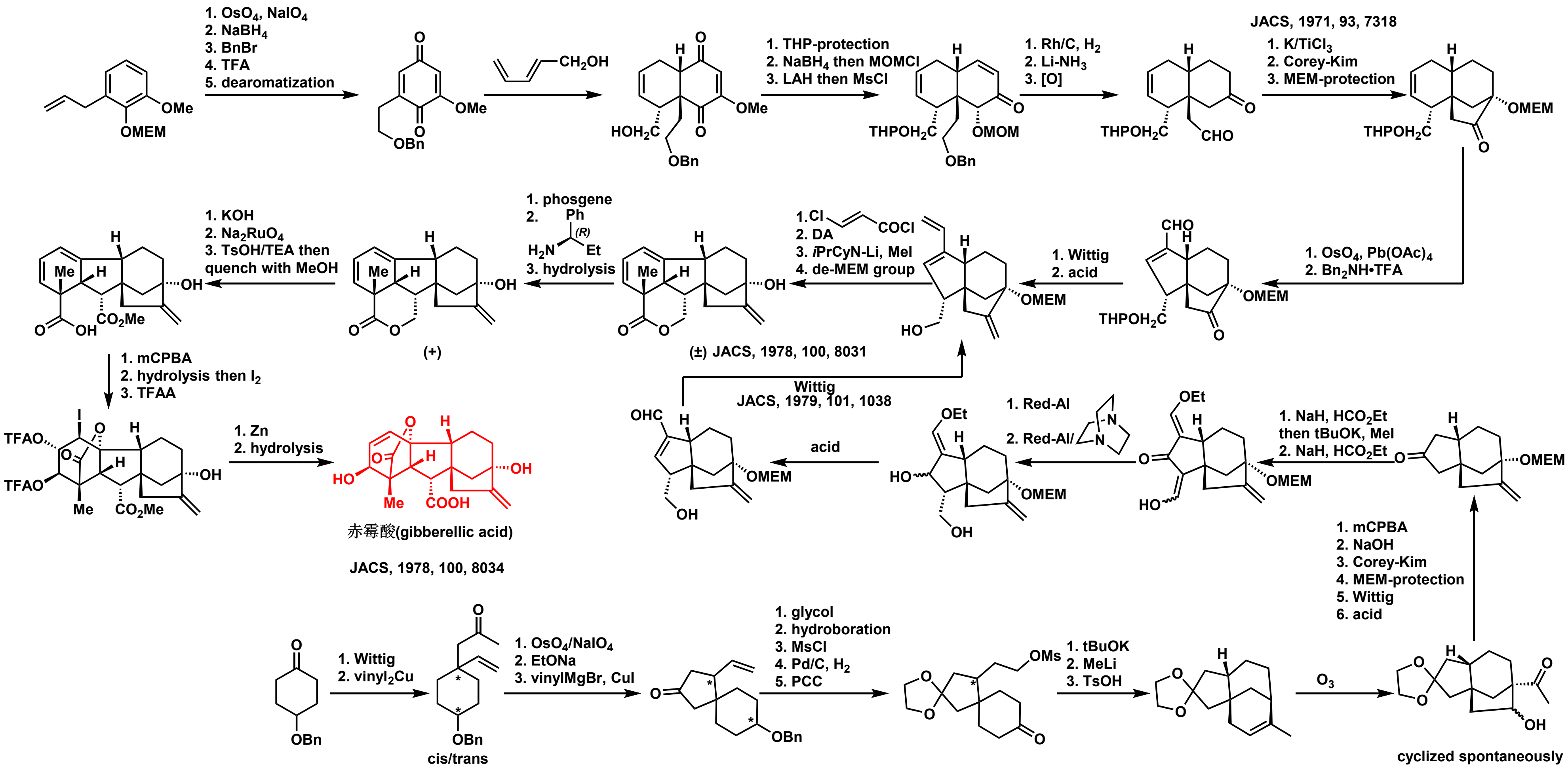
R_1=H, R_2=Me
R_1=H, R_2=tBu
R_1=tBu, R_2=Me
R_1=tBu, R_2=iPr

Side reaction could happen:

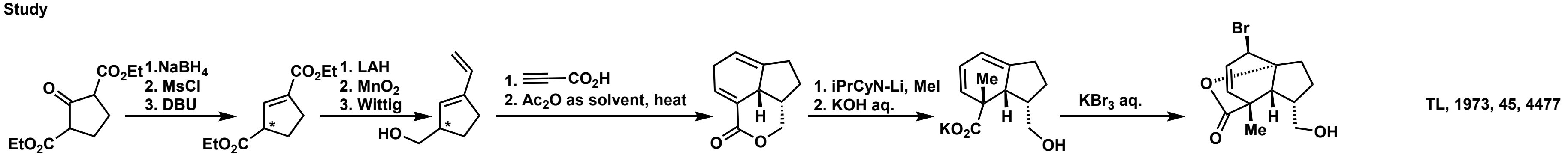


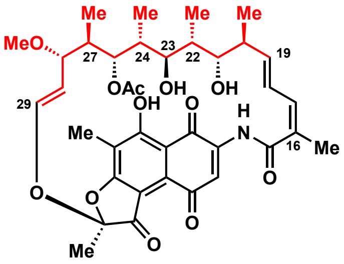
lactonization lactonization


1. Wittig
2. Ac2O
1. Zn(Hg)
2. Pd/C, H2, MeOH
1. TsCl
2. K2CO3, MeOH
3. Collins
1. Li
2. MsCl
JACS, 1980, 102, 4278
synthesis of C1 by arachidonic acid
LiI >8 eq.
Z/E
different R, Z/E geometry
白三烯(leukotriene)
JACS, 1979, 101, 6748
JACS, 1978, 100, 1942
JACS, 1980, 102, 1436
1. glutathione, TEA
2. K2CO3, MeOH
leukotriene C-1
hydrolysis
1. N-TFA-cysteinylglycine methyl ester, TEA
2. K2CO3, MeOH
leukotriene D
leukotriene A
JACS, 1980, 102, 6607
TL, 1980, 21, 3143
1. glutathione, TEA
2. K2CO3, MeOH
leukotriene C-2
1. DMP
2. wittig
3. Pd/C, H2, MeOH
4. TsCl
2-deoxyribose
1. HCl in MeOH
2. BzCl
1. HClO4
2. Pb(OAc)4
D-mannose
TL, 1980, 21, 3463
1. wittig
2. TsCl
3. HCl/MeOH
4. ClCO2Ph
5. base
1. LiOH
2. Pb(OAc)4
3. Ally-Wittig
4. HBr
1. PPh3
2. Wittig
K2CO3, MeOH
leukotriene B
JACS, 1980, 102, 7984; 7986

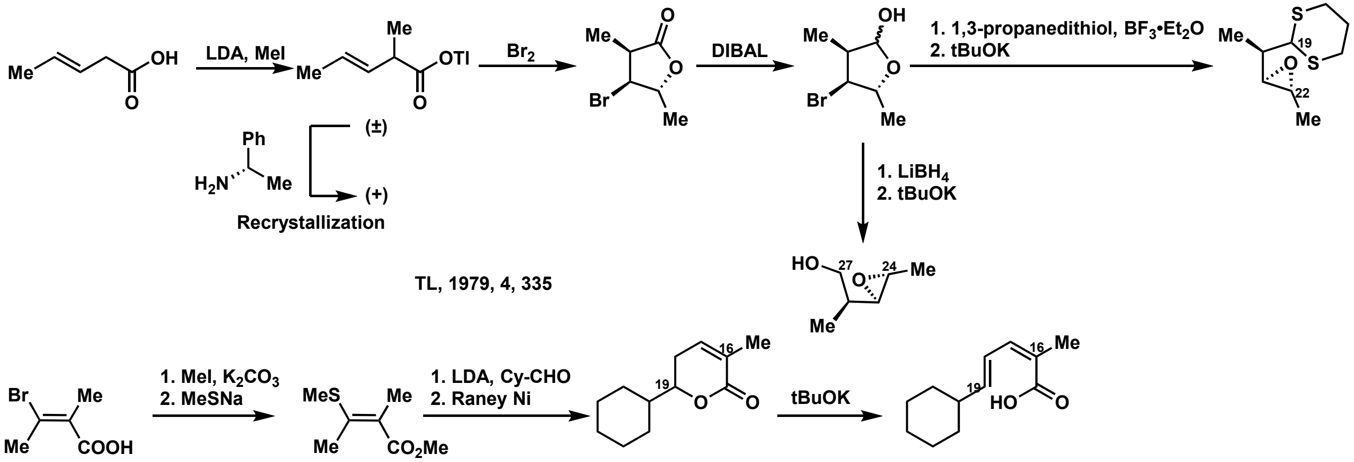

1. OsO_4, $NaIO_4$
2. $NaBH_4$
3. BnBr
4. TFA
5. dearomatization
CH_2OH
1. THP-protection
2. $NaBH_4$ then MOMCl
3. LAH then MsCl
1. Rh/C, H_2
2. Li-NH_3
3. [O]
JACS, 1971, 93, 7318
1. K/TiCl$_3$
2. Corey-Kim
3. MEM-protection
1. OsO_4, $Pb(OAc)_4$
2. Bn_2NH•TFA
1. Wittig
2. acid
1. Cl COCl
2. DA
3. *i*PrCyN-Li, MeI
4. de-MEM group
(±) JACS, 1978, 100, 8031
1. phosgene
2. Ph (R) H_2N Et
3. hydrolysis
(+)
1. KOH
2. Na_2RuO_4
3. TsOH/TEA then quench with MeOH
1. mCPBA
2. hydrolysis then I_2
3. TFAA
1. Zn
2. hydrolysis
赤霉酸(gibberellic acid)
JACS, 1978, 100, 8034
Wittig
JACS, 1979, 101, 1038
acid
1. Red-Al
2. Red-Al/
1. NaH, HCO_2Et then tBuOK, MeI
2. NaH, HCO_2Et
1. mCPBA
2. NaOH
3. Corey-Kim
4. MEM-protection
5. Wittig
6. acid
1. Wittig
2. vinyl$_2$Cu
cis/trans
1. OsO_4/$NaIO_4$
2. EtONa
3. vinylMgBr, CuI
1. glycol
2. hydroboration
3. MsCl
4. Pd/C, H_2
5. PCC
1. tBuOK
2. MeLi
3. TsOH
O_3
cyclized spontaneously

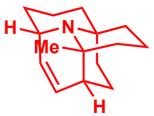
Model Study


1.$NaBH_4$
2. MsCl
3. DBU
1. LAH
2. MnO_2
3. Wittig
1. ≡—CO_2H
2. Ac_2O as solvent, heat
1. iPrCyN-Li, MeI
2. KOH aq.
KBr_3 aq.
TL, 1973, 45, 4477

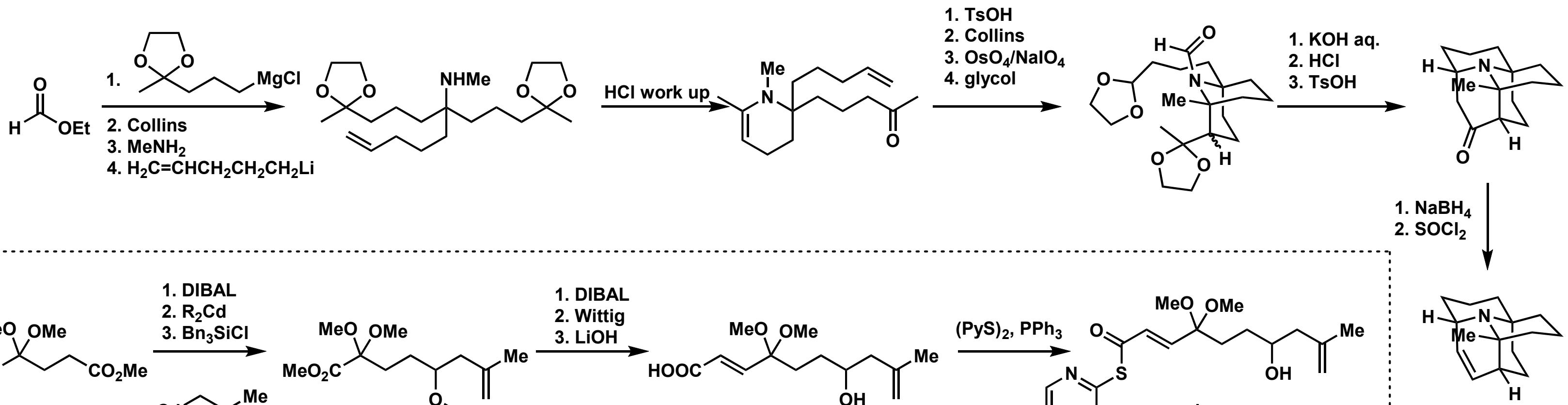


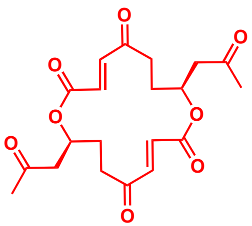
利福霉素(rifamycin)



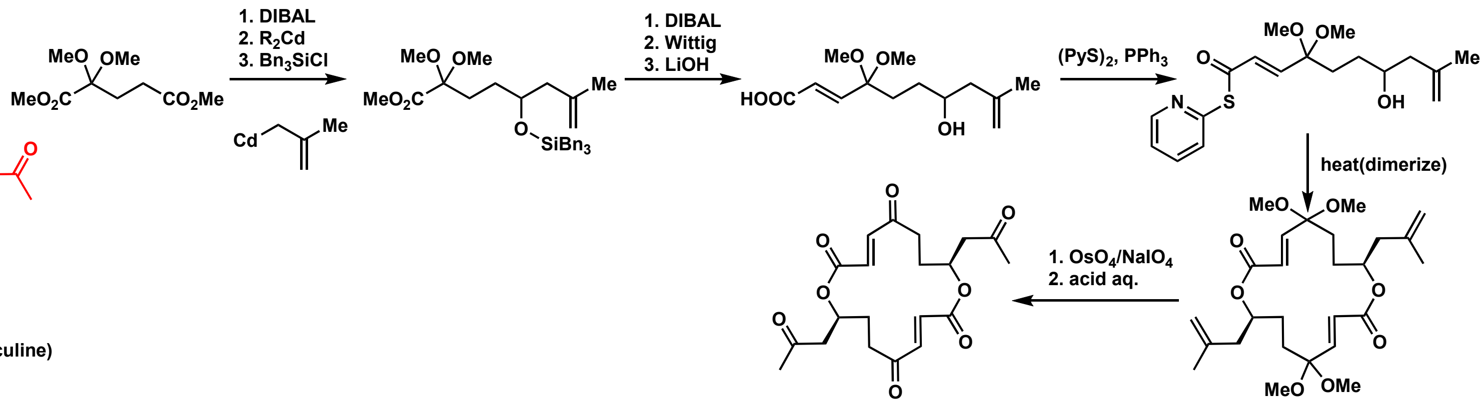


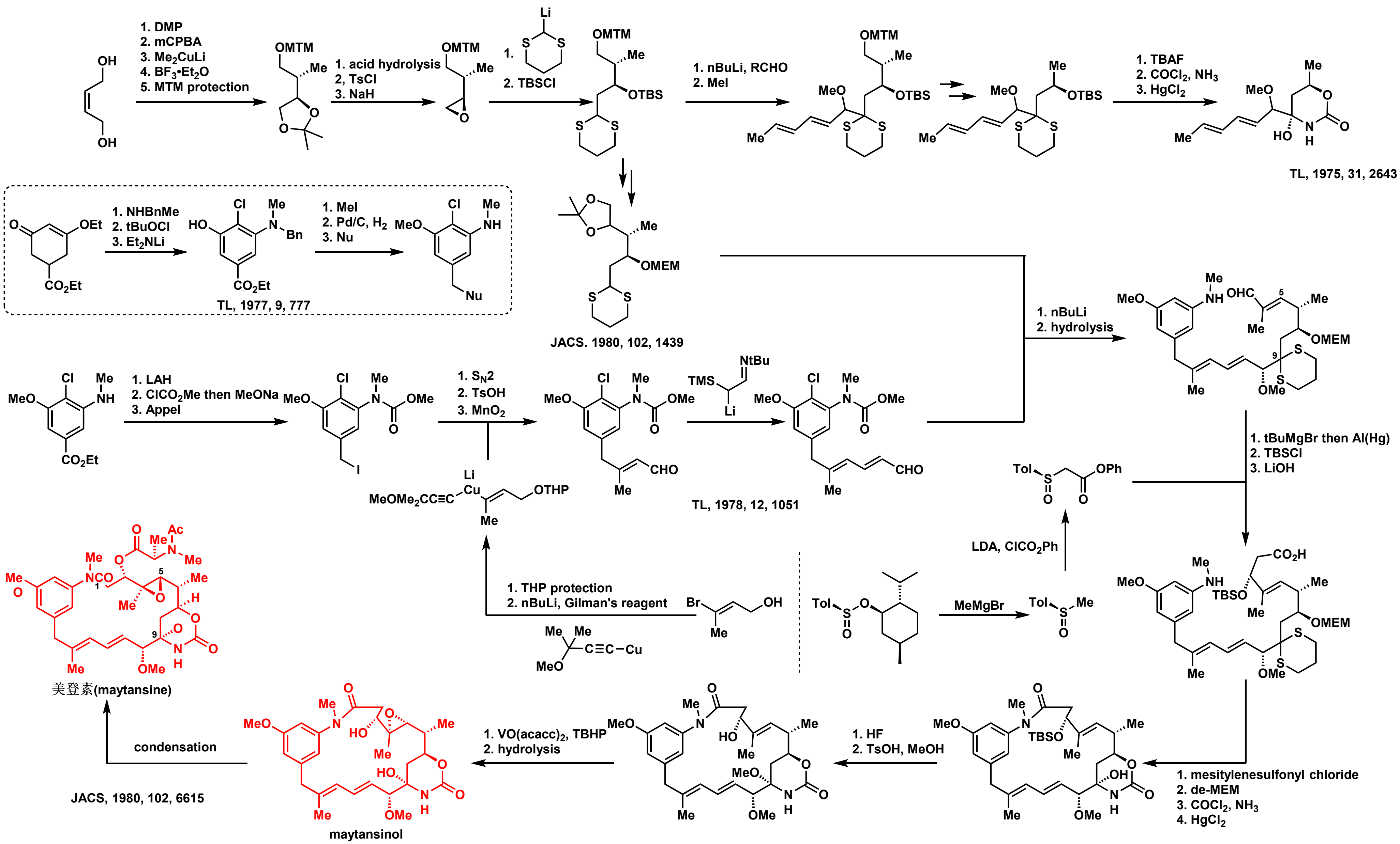
(±) porantherine
JACS, 1974, 96, 6516



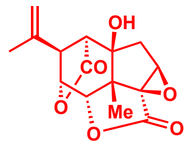


(±)蠕形青霉素(vermiculine)
JACS, 1975, 97, 2287

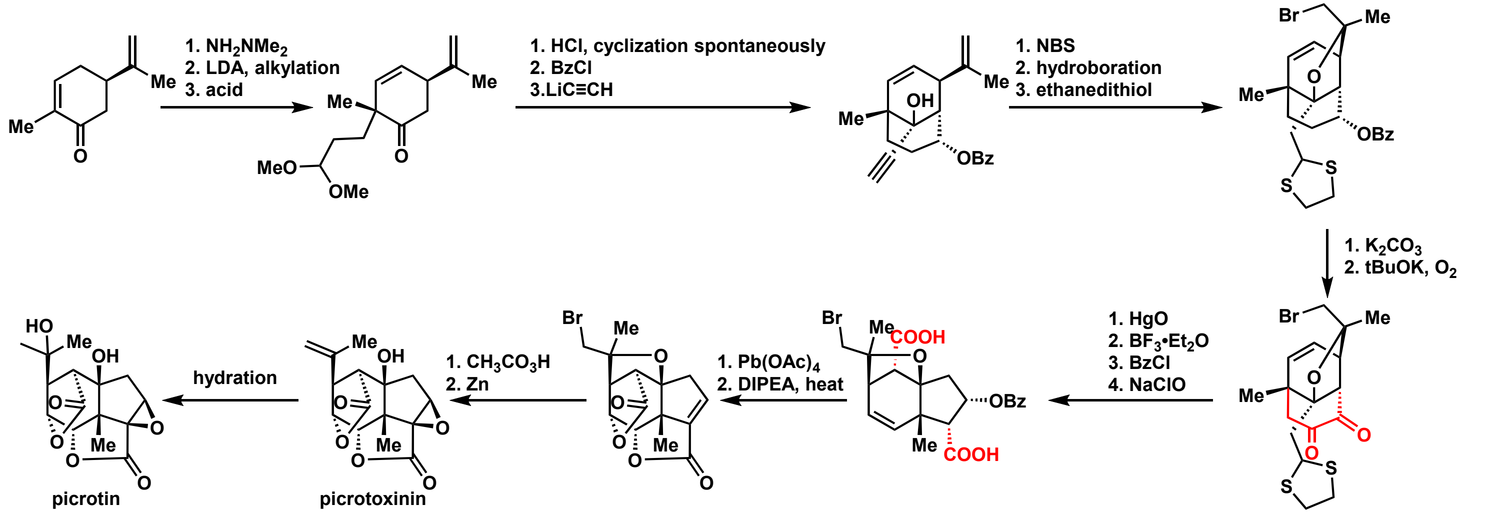


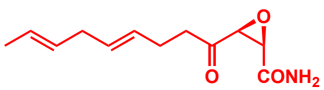


1. DMP
2. mCPBA
3. Me2CuLi
4. BF3•Et2O
5. MTM protection
OH
OH
OMTM
Me
1. acid hydrolysis
2, TsCl
3. NaH
Li
1.
S
S
2. TBSCl
OTBS
1. nBuLi, RCHO
2. MeI
MeO
1. TBAF
2. COCl2, NH3
3. HgCl2
HO
TL, 1975, 31, 2643
1. NHBnMe
2. tBuOCl
3. Et2NLi
OEt
CO2Et
Cl
N
Bn
1. MeI
2. Pd/C, H2
3. Nu
NH
Nu
TL, 1977, 9, 777
OMEM
JACS. 1980, 102, 1439
1. nBuLi
2. hydrolysis
OHC
1. LAH
2. ClCO2Me then MeONa
3. Appel
OMe
1. SN2
2. TsOH
3. MnO2
NtBu
TMS
CHO
MeOMe2CC≡C
Cu
OTHP
TL, 1978, 12, 1051
1. tBuMgBr then Al(Hg)
2. TBSCl
3. LiOH
Tol
OPh
LDA, ClCO2Ph
CO2H
TBSO
1. THP protection
2. nBuLi, Gilman's reagent
Br
MeMgBr
C≡C−Cu
Ac
美登素(maytansine)
condensation
JACS, 1980, 102, 6615
1. VO(acacc)2, TBHP
2. hydrolysis
maytansinol
1. HF
2. TsOH, MeOH
1. mesitylenesulfonyl chloride
2. de-MEM
3. COCl2, NH3
4. HgCl2

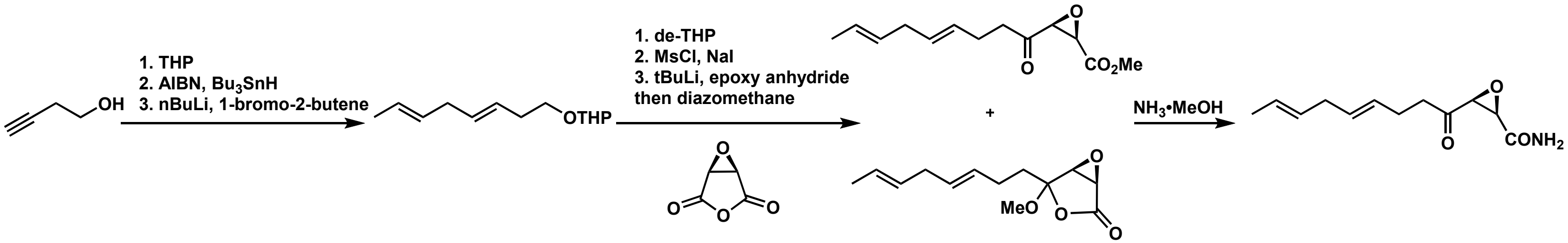


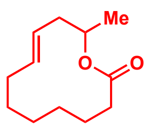
木防己苦毒宁(Picrotoxinin)
JACS, 1979, 101, 5841



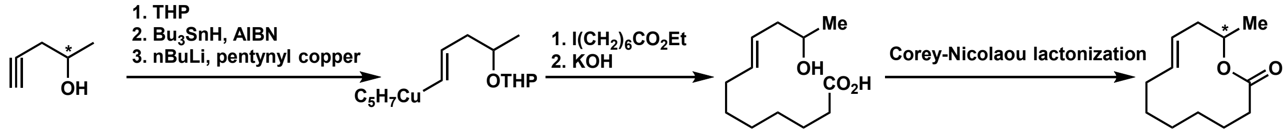


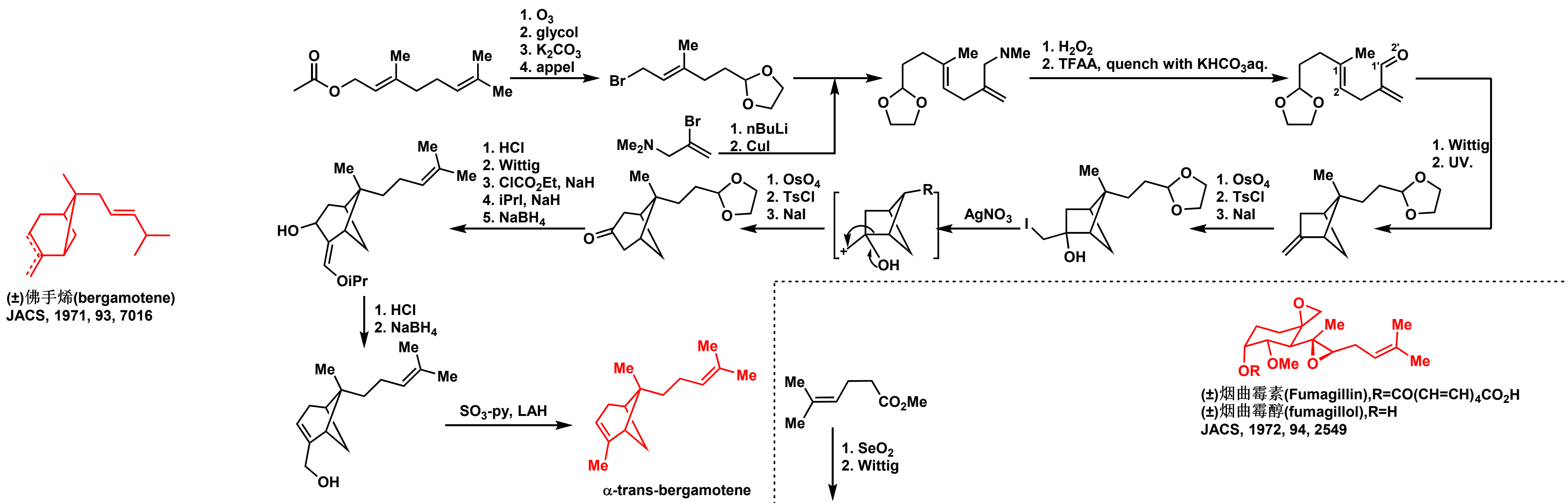
(±)浅蓝菌素(cerulenin)
TL, 1977, 44, 3847

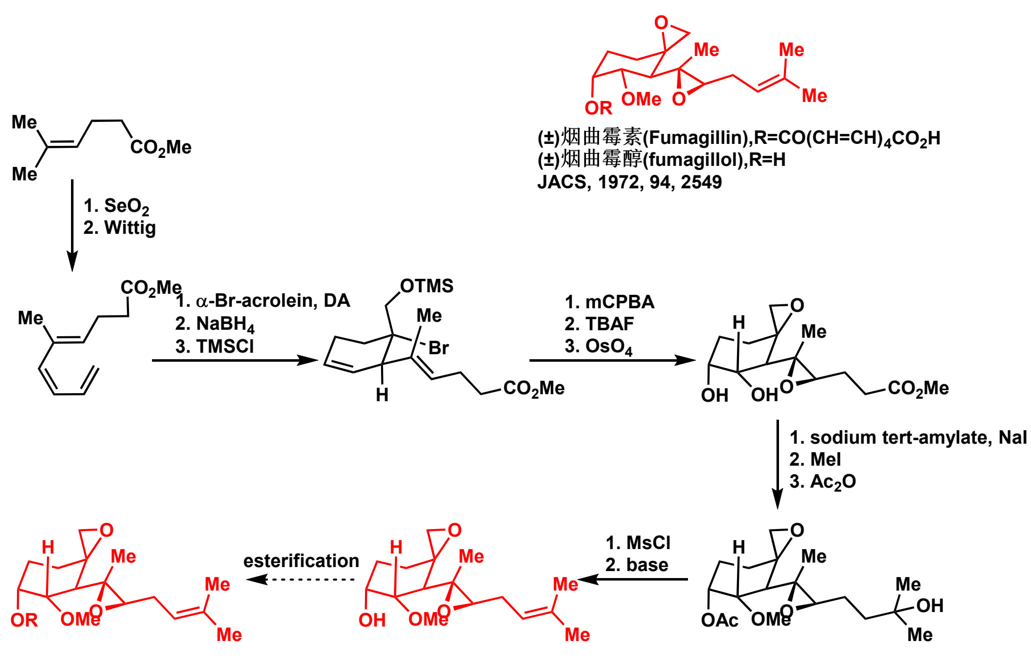


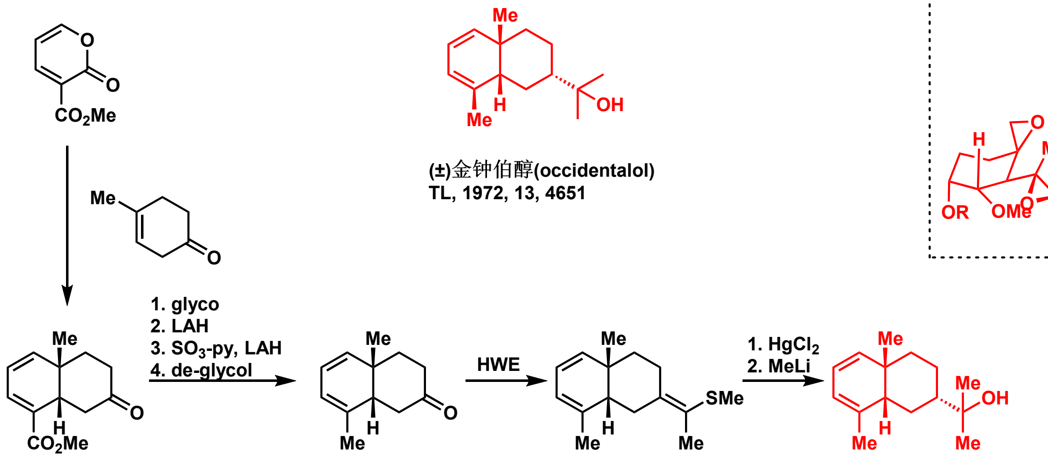


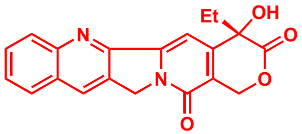
(±)-11 -Hydroxy-trans- 8-dodecenoic acid lactone
JACS, 1976, 98, 222



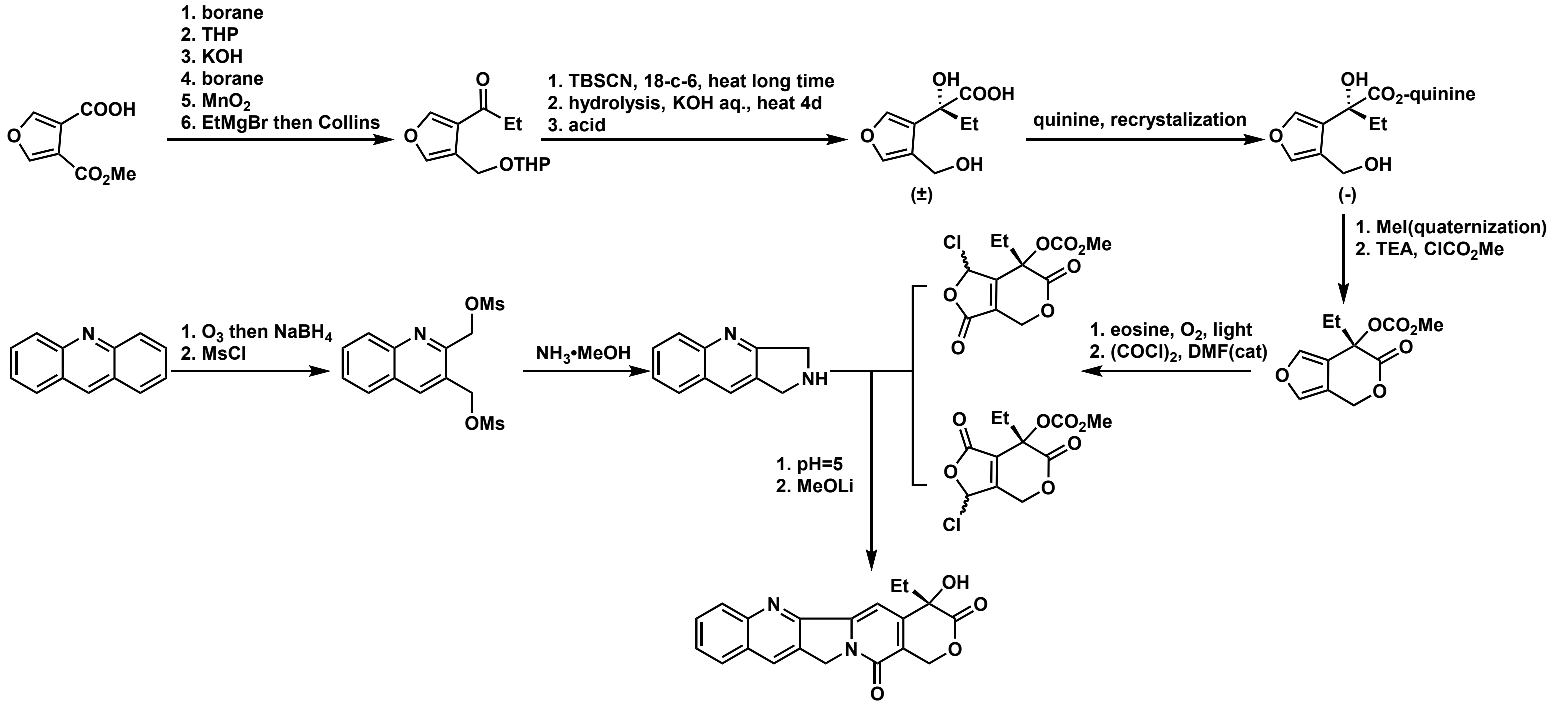

1. O3
2. glycol
3. K2CO3
4. appel
Br
Me2N
1. nBuLi
2. CuI
NMe
1. H2O2
2. TFAA, quench with KHCO3aq.
1. Wittig
2. UV.
1. OsO4
2. TsCl
3. NaI
AgNO3
1. HCl
2. Wittig
3. ClCO2Et, NaH
4. iPrI, NaH
5. NaBH4
HO
OiPr
OH
1. HCl
2. NaBH4
SO3-py, LAH
α-trans-bergamotene
(±)佛手烯(bergamotene)
JACS, 1971, 93, 7016

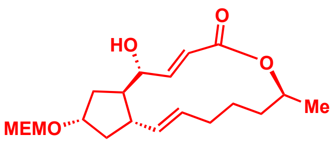

(±)烟曲霉素(Fumagillin),R=CO(CH=CH)4CO2H
(±)烟曲霉醇(fumagillol),R=H
JACS, 1972, 94, 2549
CO2Me
1. SeO2
2. Wittig
1. α-Br-acrolein, DA
2. NaBH4
3. TMSCl
OTMS
1. mCPBA
2. TBAF
3. OsO4
1. sodium tert-amylate, NaI
2. MeI
3. Ac2O
1. MsCl
2. base
esterification
OAc
OMe
OR


(±)金钟伯醇(occidentalol)
TL, 1972, 13, 4651
CO2Me
1. glyco
2. LAH
3. SO3-py, LAH
4. de-glycol
HWE
SMe
1. HgCl2
2. MeLi
OH

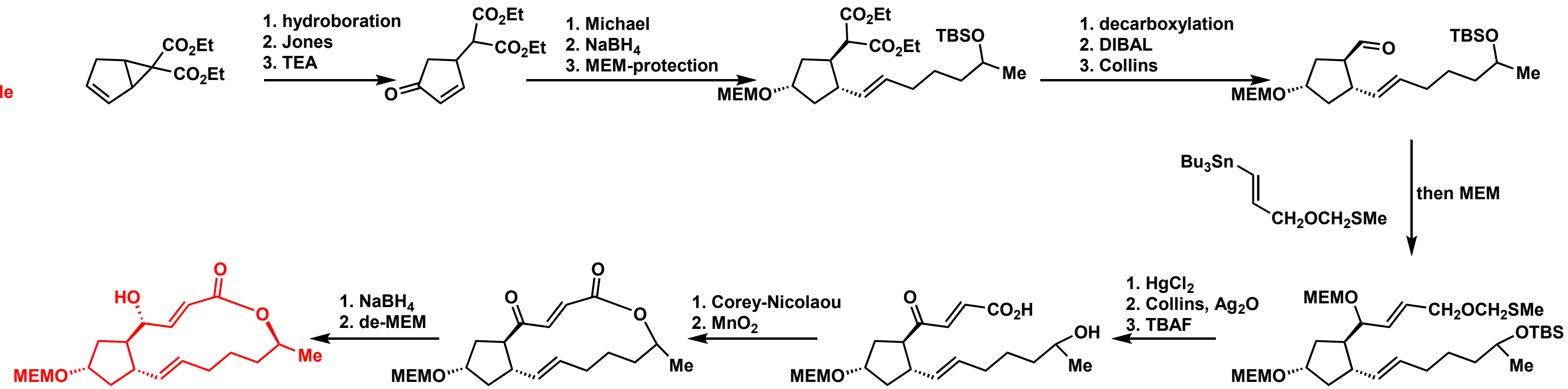


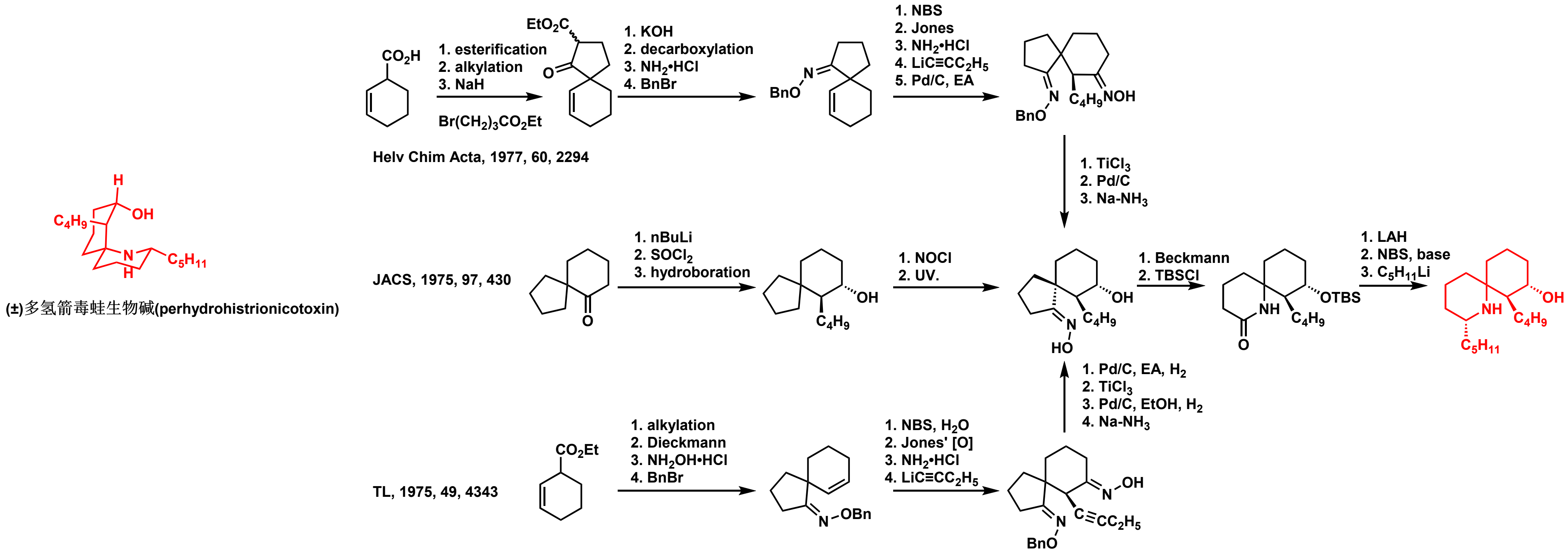
喜树碱(20(S)-Camptothecin)
JOC, 1975, 40, 2140



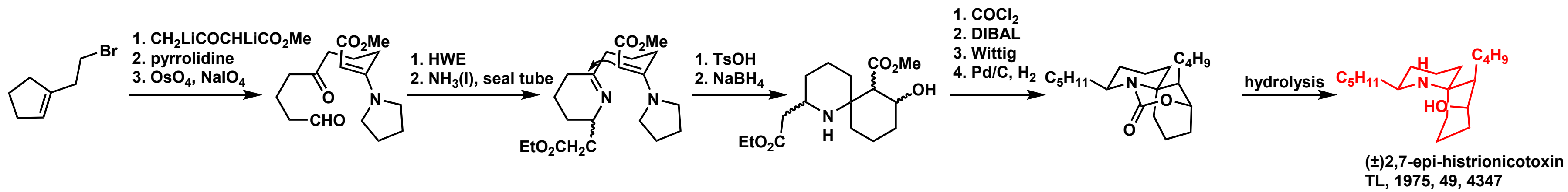


(±)布雷非德菌素(brefeldin A)
TL, 1976, 17, 4705

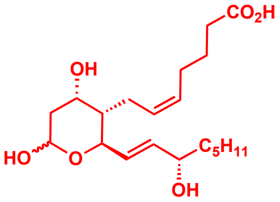




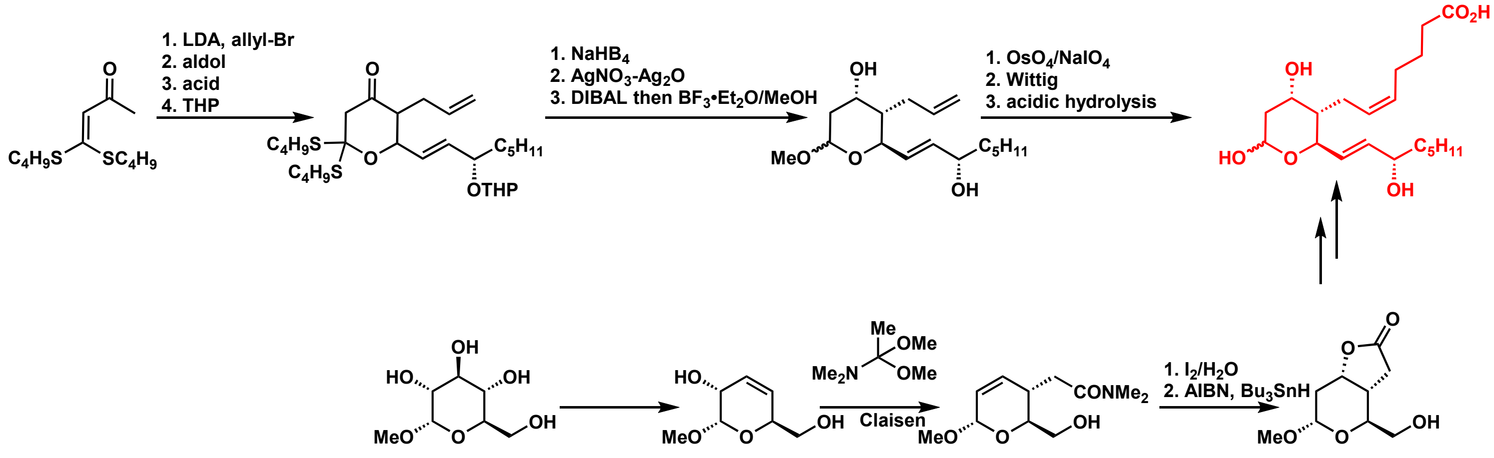
(±)多氢箭毒蛙生物碱(perhydrohistrionicotoxin)
1. esterification
2. alkylation
3. NaH
Br(CH2)3CO2Et
Helv Chim Acta, 1977, 60, 2294
1. KOH
2. decarboxylation
3. NH2•HCl
4. BnBr
1. NBS
2. Jones
3. NH2•HCl
4. LiC≡CC2H5
5. Pd/C, EA
1. TiCl3
2. Pd/C
3. Na-NH3
JACS, 1975, 97, 430
1. nBuLi
2. SOCl2
3. hydroboration
1. NOCl
2. UV.
1. Beckmann
2. TBSCl
1. LAH
2. NBS, base
3. C5H11Li
1. Pd/C, EA, H2
2. TiCl3
3. Pd/C, EtOH, H2
4. Na-NH3
TL, 1975, 49, 4343
1. alkylation
2. Dieckmann
3. NH2OH•HCl
4. BnBr
1. NBS, H2O
2. Jones' [O]
3. NH2•HCl
4. LiC≡CC2H5



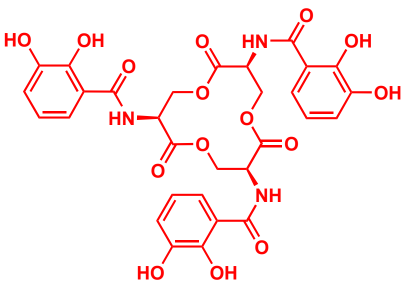
1. CH2LiCOCHLiCO2Me
2. pyrrolidine
3. OsO4, NaIO4
1. HWE
2. NH3(l), seal tube
1. TsOH
2. NaBH4
1. COCl2
2. DIBAL
3. Wittig
4. Pd/C, H2
hydrolysis
(±)2,7-epi-histrionicotoxin
TL, 1975, 49, 4347



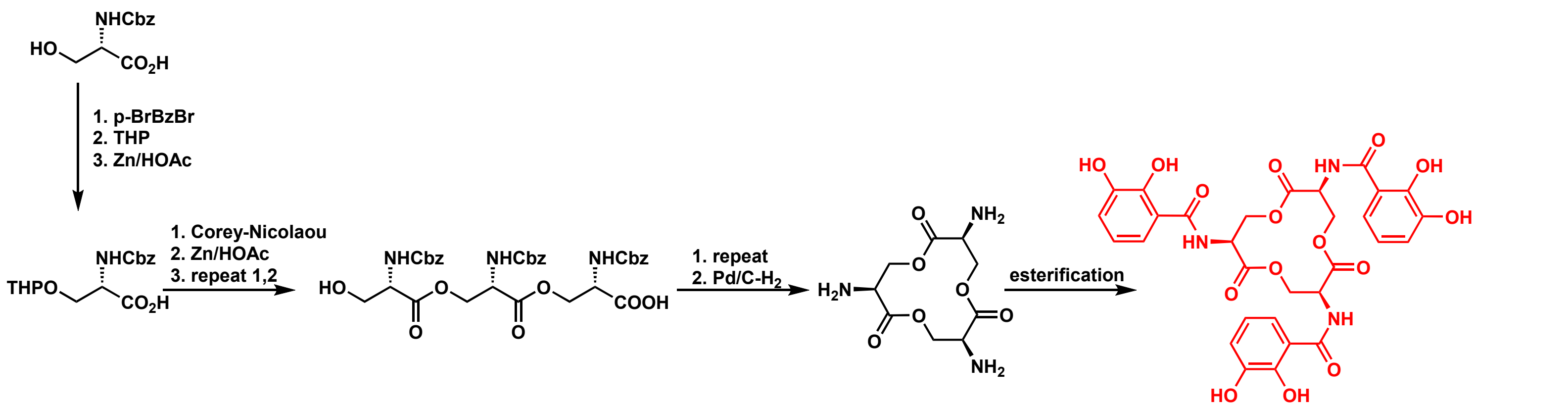
血栓素B_2(thromboxane B_2)
TL, 1977, 18, 785
TL, 1977, 18, 1625

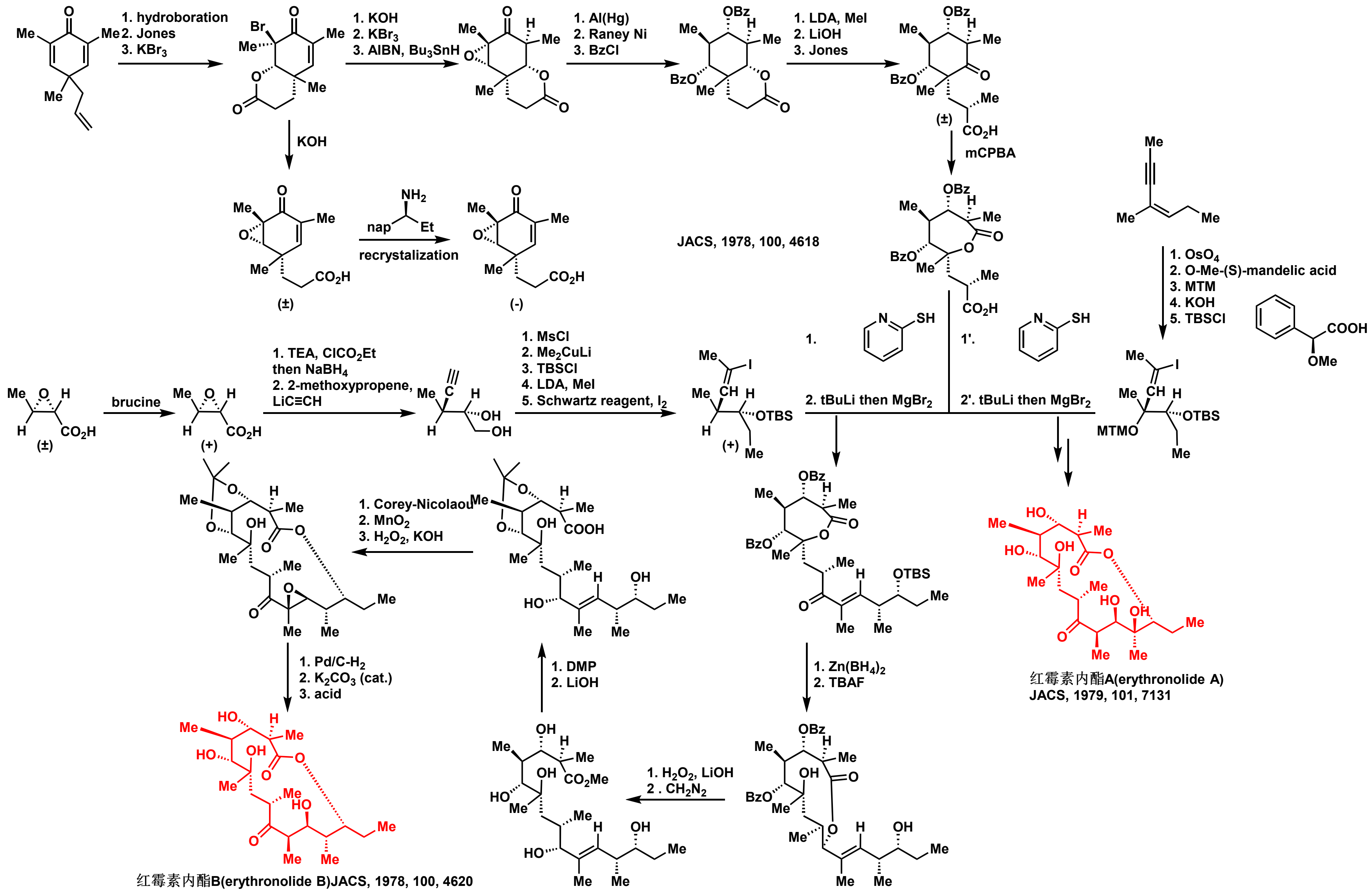


Can. J. Chem., 1973, 51, 3357



肠杆菌素(enterobactin)
TL, 1977, 45, 3919




1. hydroboration
2. Jones
3. KBr_3
1. KOH
2. KBr_3
3. AIBN, Bu_3SnH
1. Al(Hg)
2. Raney Ni
3. BzCl
1. LDA, MeI
2. LiOH
3. Jones
KOH
recrystalization
mCPBA
JACS, 1978, 100, 4618
1. OsO_4
2. O-Me-(S)-mandelic acid
3. MTM
4. KOH
5. TBSCl
brucine
1. TEA, $ClCO_2Et$ then $NaBH_4$
2. 2-methoxypropene, LiC≡CH
1. MsCl
2. Me_2CuLi
3. TBSCl
4. LDA, MeI
5. Schwartz reagent, I_2
2. tBuLi then $MgBr_2$
2'. tBuLi then $MgBr_2$
1. Corey-Nicolaou
2. MnO_2
3. H_2O_2, KOH
1. Pd/C-H_2
2. K_2CO_3 (cat.)
3. acid
1. DMP
2. LiOH
1. $Zn(BH_4)_2$
2. TBAF
1. H_2O_2, LiOH
2. CH_2N_2
红霉素内酯A(erythronolide A)
JACS, 1979, 101, 7131
红霉素内酯B(erythronolide B)JACS, 1978, 100, 4620