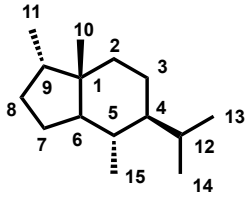
Synthesis of picrotoxanes

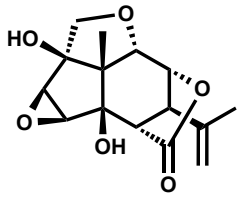
Shenvi Lab Group Meeting

5/9/2016

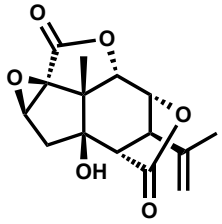
Picrotoxanes



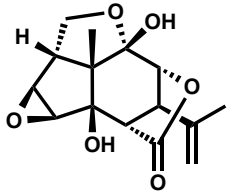
Picrotoxane skeleton



Corianin

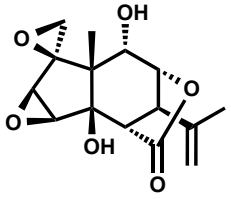


Picrotoxinin
162$/250 mg(aldrich)

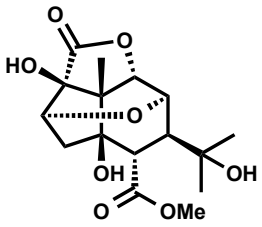


asteromurin

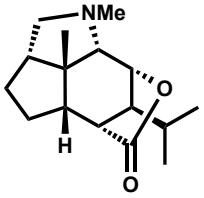
sold as picrotin powder
1:1 mixture
41.6$/1g



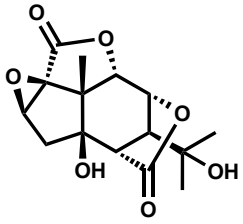
Tutin



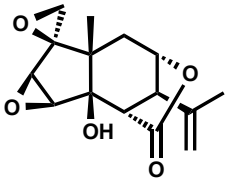
Methyl
Picrotoxate



Dendrobine



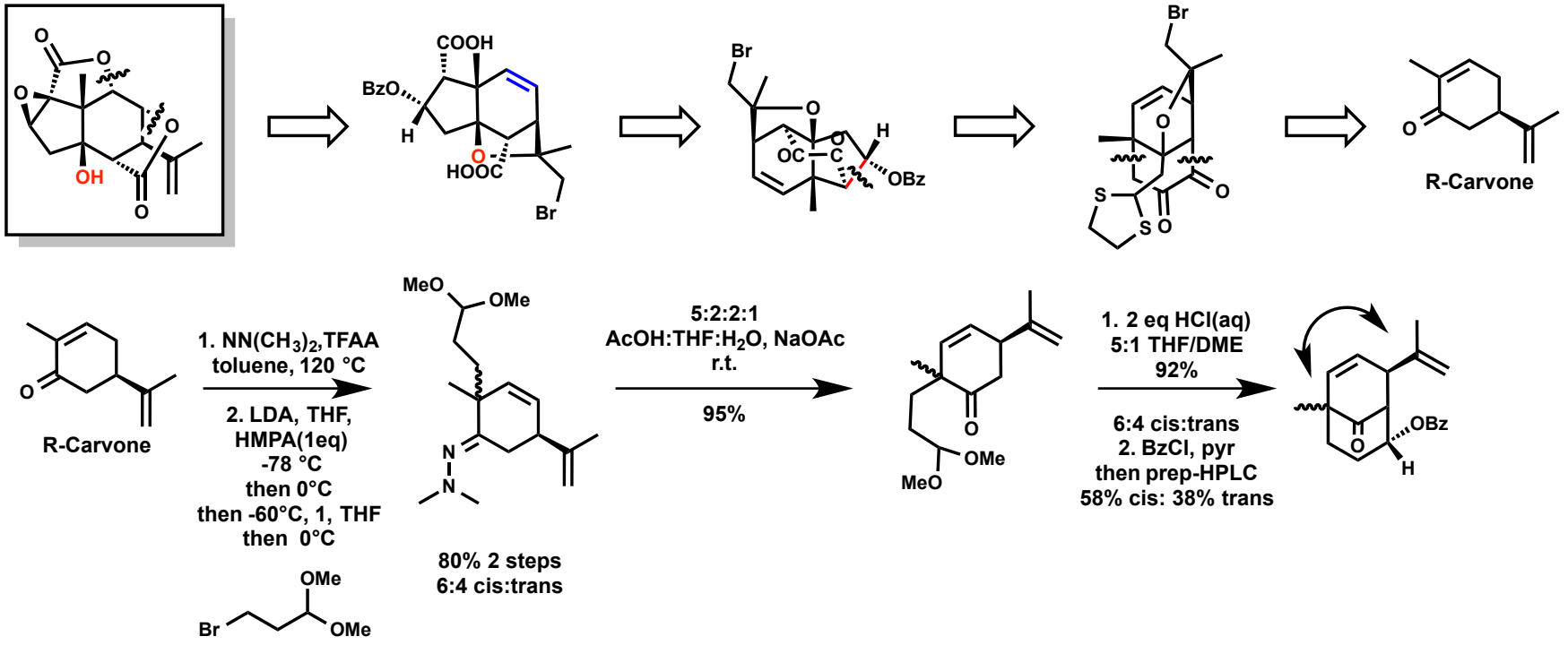
Picrotin
162$/250 mg(aldrich)



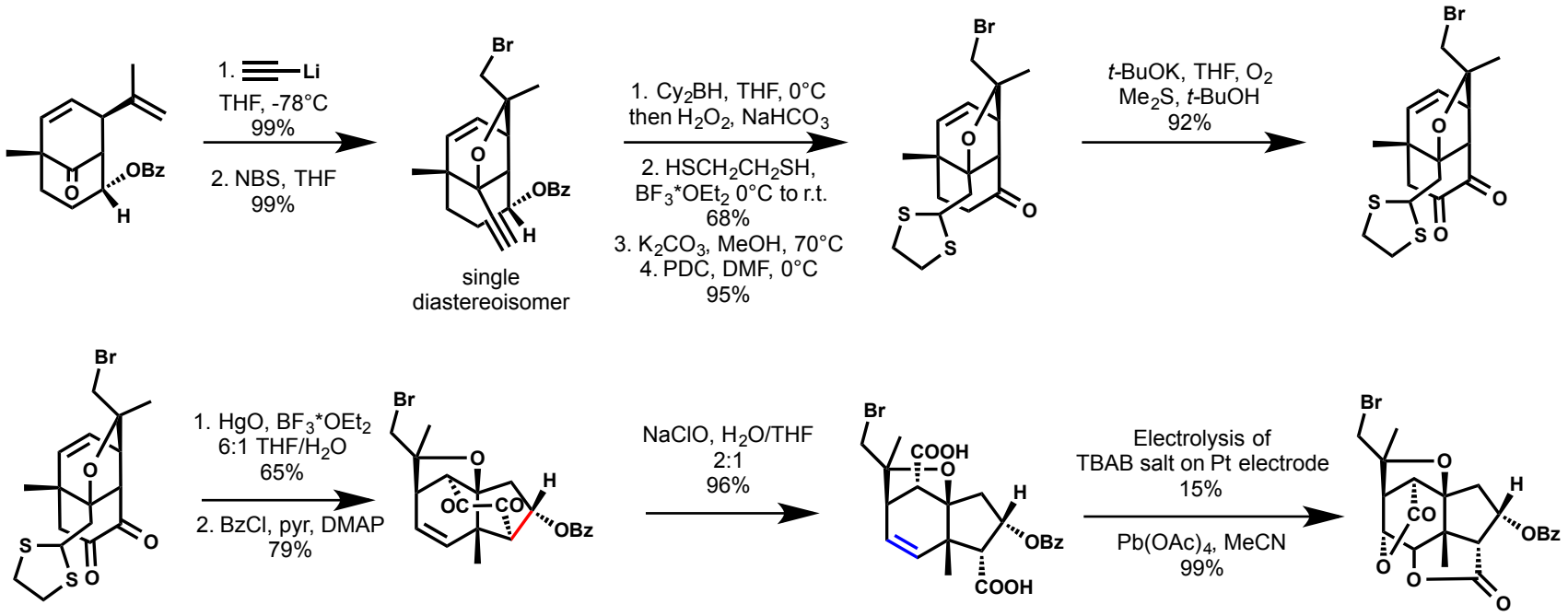
Coriamyrtin

Found primarily in the fruit of the climbing plant *Anamirta cocculus*
Non-competitive Gabba A receptor antagonist

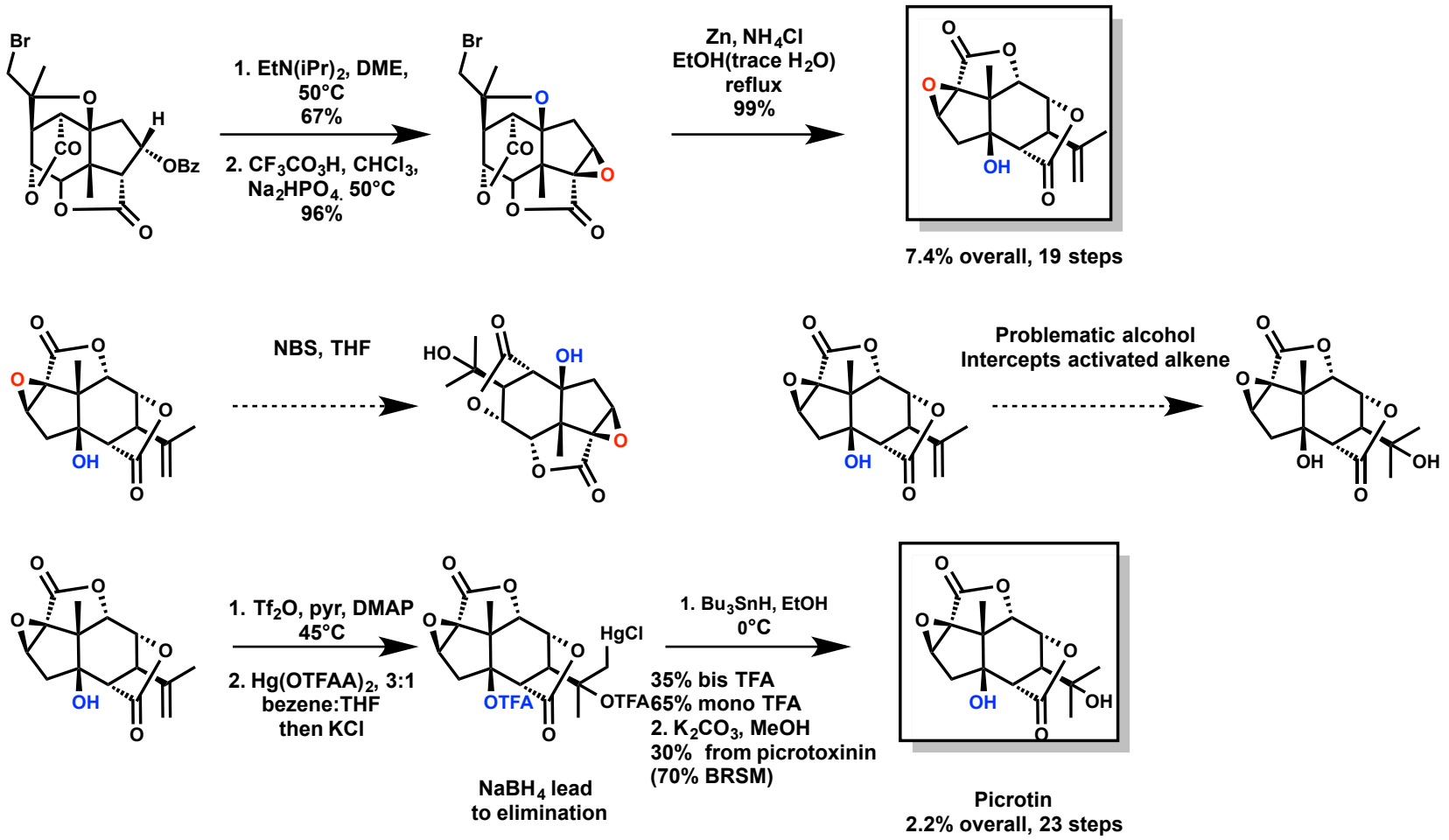
Corey Route


R-Carvone
1. NN(CH3)2,TFAA
toluene, 120 °C
2. LDA, THF,
HMPA(1eq)
-78 °C
then 0°C
then -60°C, 1, THF
then 0°C
80% 2 steps
6:4 cis:trans
5:2:2:1
AcOH:THF:H2O, NaOAc
r.t.
95%
1. 2 eq HCl(aq)
5:1 THF/DME
92%
6:4 cis:trans
2. BzCl, pyr
then prep-HPLC
58% cis: 38% trans
R-Carvone

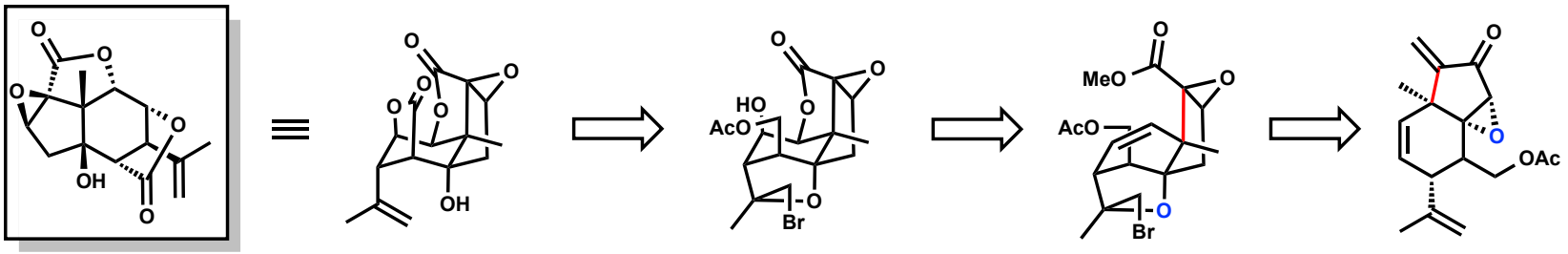
Corey Route Cont



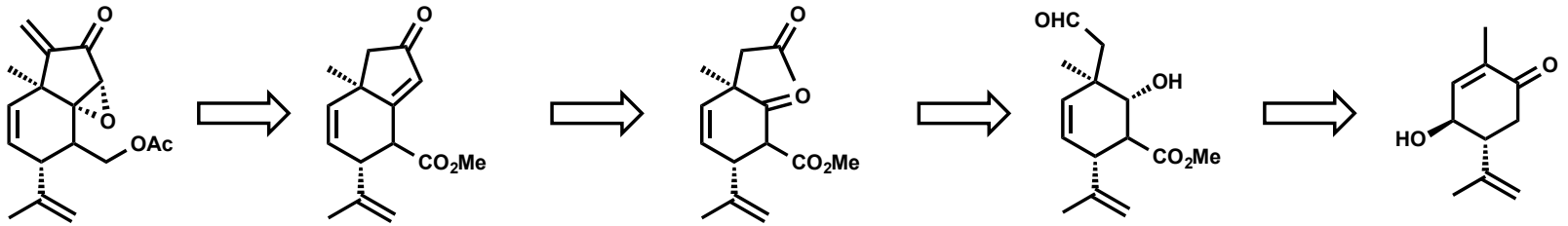
Corey Route Cont.



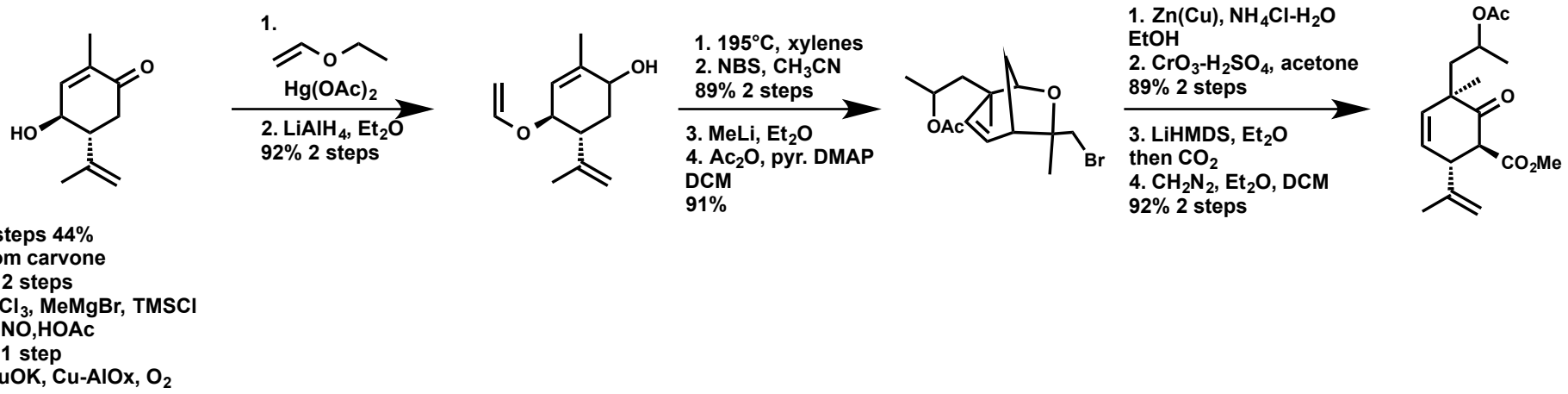
Yoshikoshi Route



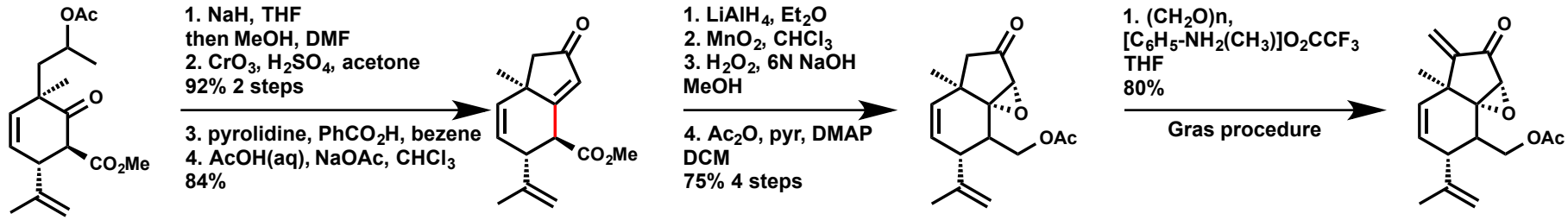
Base leads to trans lactonization to more stable delta lactone



Yoshikoshi Route Cont.



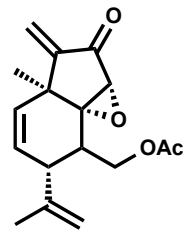
9 steps 44%
from carvone
or 2 steps
$FeCl_3$, MeMgBr, TMSCl
PhNO,HOAc
or 1 step
tBuOK, Cu-AlOx, O_2



K_2CO_3/MeOH lead to stable acetal formation
Generation of bis enolate anion and addition to jones reagent circumvented this issue
Some gamma unsaturated isomer formed could be isomerized with Al_2O_3 and benzene

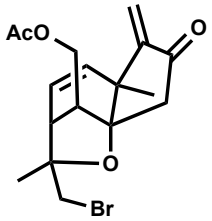
Direct epoxidation failed due to enol formation
in presence of base

Yoshikoshi Route Cont.



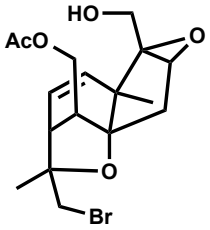
1. $[Na(PhSeB(OEt)_3)]^-$
AcOH, EtOH
92%

2. NBS, THF
88%



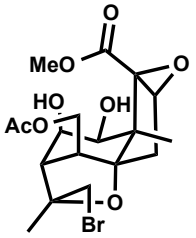
1. $NaBH_4$, $CeCl_3$, MeOH
2. MsCl, pyr
3. OsO_4, pyr
then H_2S, $CHCl_3$

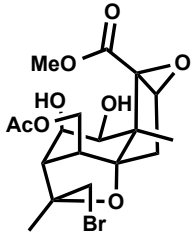
4. DBU, DMF
81% 4 steps



1. CrO_3-pyr, DCM
2. $NaClO_2$, NaH_2PO_4
H_2O $(H_3C)_2C{=}CHCH_3$
tBuOH, then CH_2N_2

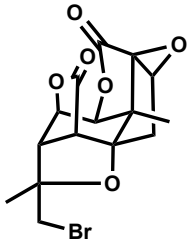
81%
3. OsO_4, pyr
then H_2S, $CHCl_3$
86%





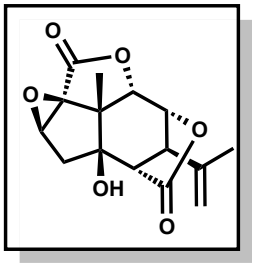
Diol is very hindered

1. NaH, MeOH
then AcOH
2. PCC, DCM
41% 2 steps

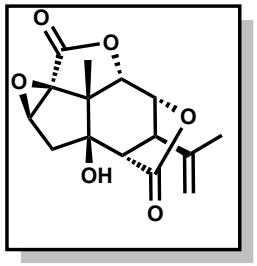


Zn(Cu), NH_4Cl
H_2O, EtOH

100%

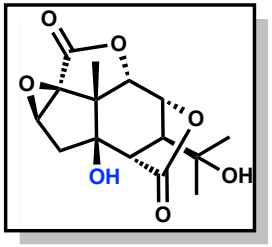


31 steps
from 5-hydroxycarvone
5% overall



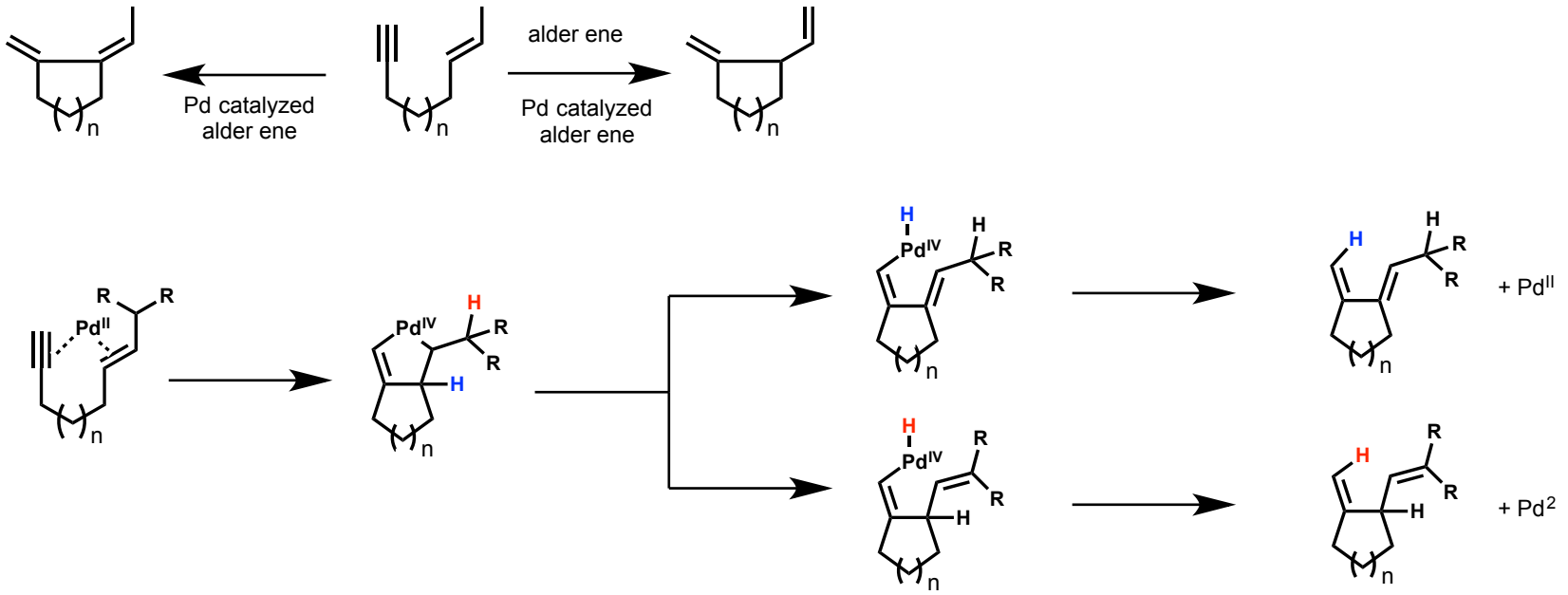
1. mCPBA, DCM
2. $[Na(PhSeB(OEt)_3)]^-$,
AcOH, EtOH

3. Bu_3SnH, AIBN, toluene
87%

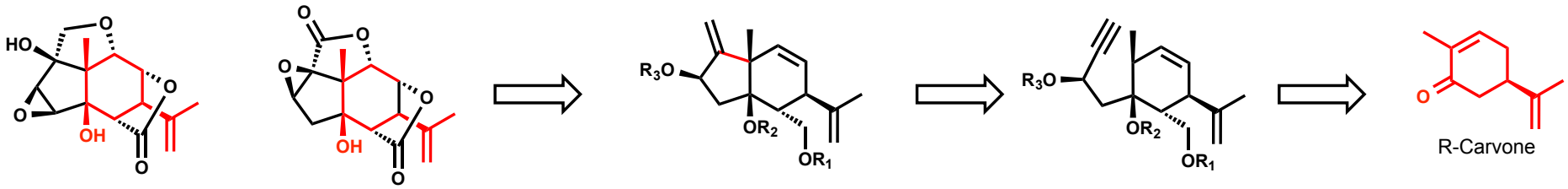


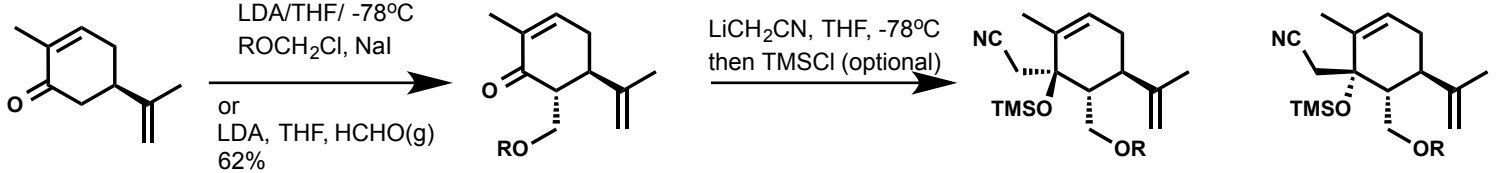
34 steps
4.3% overall

Trost Route: Preface



Trost Route

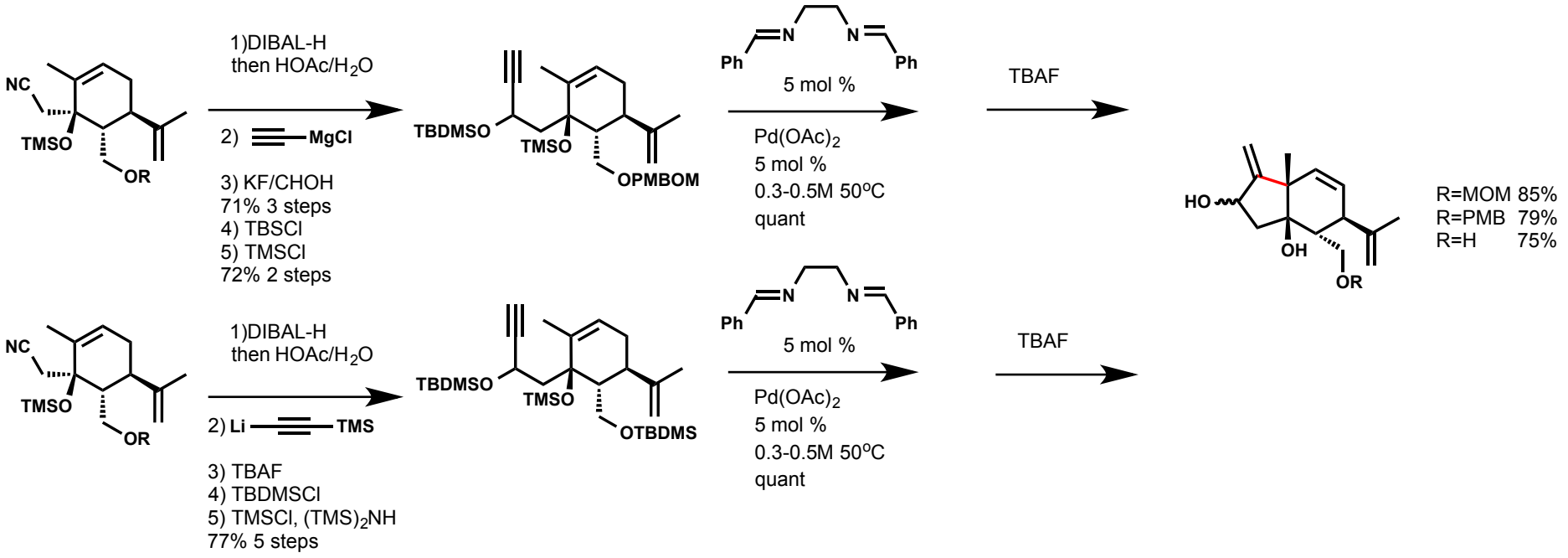




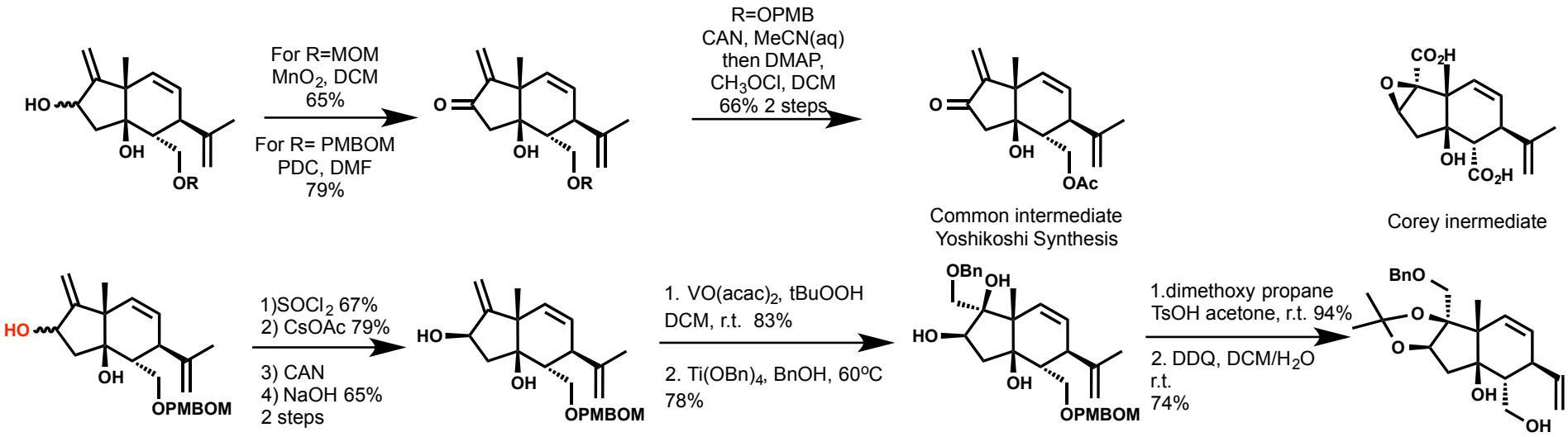
10:1 41% for R=PMB
5:1 75% for R=MOM
14:1 75% for R=PMBOM
5:1 86% for R=TBDMS

R=TBDMS separated
72% yeild desired 14% undesired

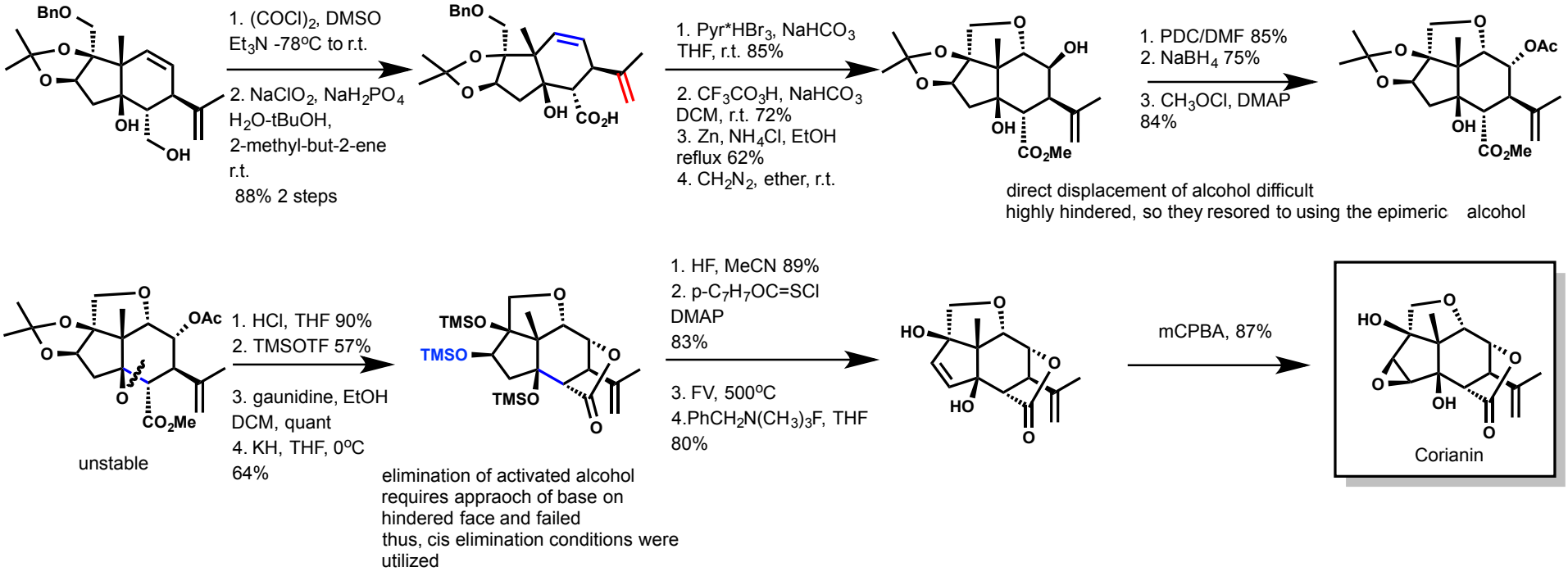
Trost Route


NC
TMSO
OR
1)DIBAL-H
then HOAc/H2O
2) MgCl
3) KF/CHOH
71% 3 steps
4) TBSCl
5) TMSCl
72% 2 steps
TBDMSO
TMSO
OPMBOM
Ph
N
N
Ph
5 mol %
Pd(OAc)2
5 mol %
0.3-0.5M 50°C
quant
TBAF
HO
OH
OR
R=MOM 85%
R=PMB 79%
R=H 75%
NC
TMSO
OR
1)DIBAL-H
then HOAc/H2O
2) Li TMS
3) TBAF
4) TBDMSCl
5) TMSCl, (TMS)2NH
77% 5 steps
TBDMSO
TMSO
OTBDMS
Ph
N
N
Ph
5 mol %
Pd(OAc)2
5 mol %
0.3-0.5M 50°C
quant
TBAF

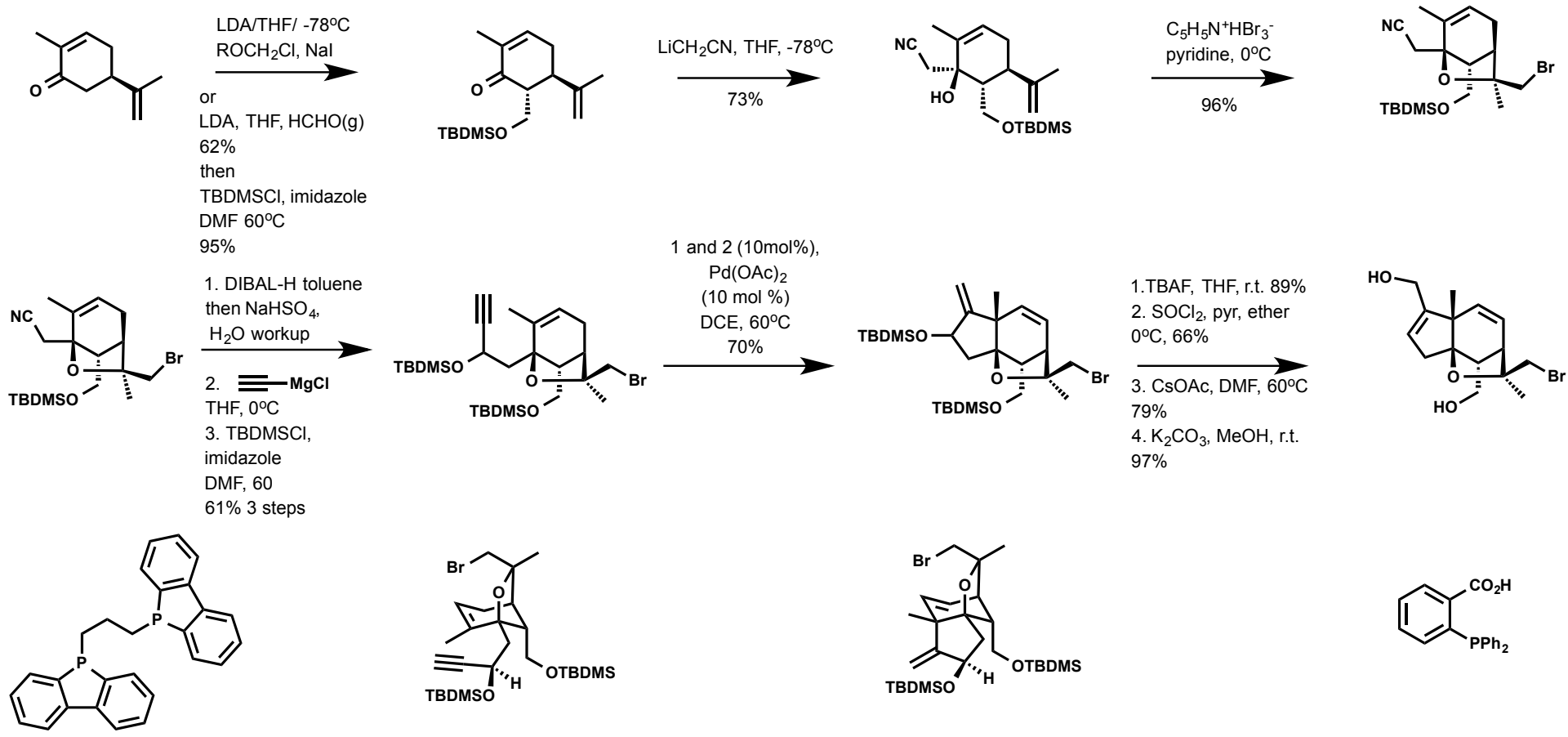
Trost Route: Formal Synthesis



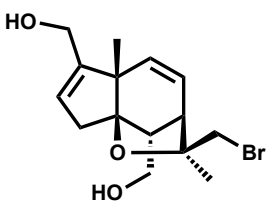
Trost Route


BnO
1. (COCl)2, DMSO
Et3N -78ºC to r.t.
2. NaClO2, NaH2PO4
H2O-tBuOH,
2-methyl-but-2-ene
r.t.
88% 2 steps
CO2H
1. Pyr*HBr3, NaHCO3
THF, r.t. 85%
2. CF3CO3H, NaHCO3
DCM, r.t. 72%
3. Zn, NH4Cl, EtOH
reflux 62%
4. CH2N2, ether, r.t.
CO2Me
1. PDC/DMF 85%
2. NaBH4 75%
3. CH3OCl, DMAP
84%
OAc
direct displacement of alcohol difficult
highly hindered, so they resored to using the epimeric alcohol
unstable
1. HCl, THF 90%
2. TMSOTF 57%
3. gaunidine, EtOH
DCM, quant
4. KH, THF, 0ºC
64%
TMSO
elimination of activated alcohol
requires appraoch of base on
hindered face and failed
thus, cis elimination conditions were
utilized
1. HF, MeCN 89%
2. p-C7H7OC=SCl
DMAP
83%
3. FV, 500ºC
4.PhCH2N(CH3)3F, THF
80%
HO
mCPBA, 87%
Corianin

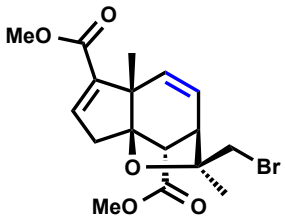
Trost Route: 1995



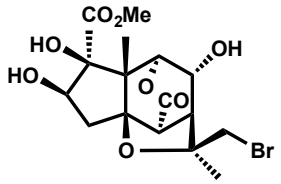
Trost Route: 1995



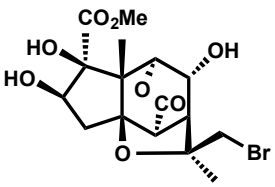
1. $(COCl)_2$, DMSO, Et_3N, DCM, -78°C
2. $NaClO_2$
   $(H_3C)_2C{=}CHCH_3$
   NaH_2PO_4, *t*BuOH
   0°C
3. CH_2N_2, ether, 0°C
   79% 3 steps



1. CH_3CO_3H, CSA, DCM reflux, 63%
2. OsO_4, pyridine, r.t. 75%
3. KOH, CH_3OH, H_2O r.t then CH_2N_2, ether, 0°C 91%

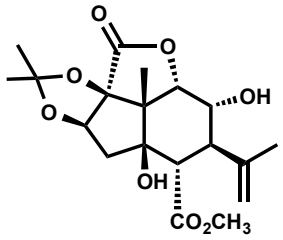


Direct bis lactonization failed
6 membered lactone favored with cyclic ether
5 membered lactone favored if bromoether is not present

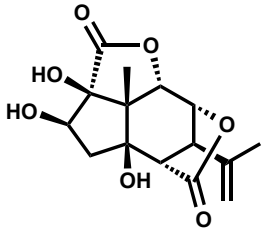


1. Zn, HOAC, CH_3OH 96%
2. $(CH_3)_2C(OCH_3)_2$ CH_3COCH_3, TsOH 70%
3. KOH, CH_3OH, H_2O r.t. then CH_2N_2, ether, 0°C

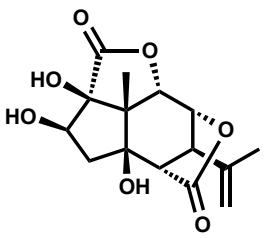
lactone closure sensitive to protecting groups on diol
cyclic PG lead to no reaction,
TMS ethers allowed cyclization



1. CH_3COCl, Et_3N DMAP, DCM 86%
2. HCl, H_2O, THF, r.t 67%
3. TMSOTf, lutidine, DCE r.t. 85%
4. NaCN, MeOH, THF, r.t. 90%
5. *t*BuOLi, *t*BuOH, toluene 100°C, 68%
6. HF, H_2O, MeCN, 100°C 92%

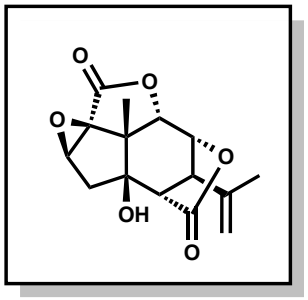


Trost Route 1995

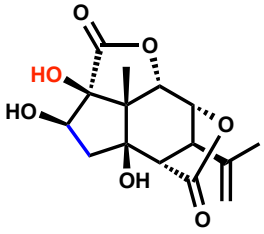


1. $(CH_3)_2NCH(OCH_3)_2$
Ac_2O, 100°C
68%

2. LiHMDS, *t*BuOOH
THF, 0°C, 71%

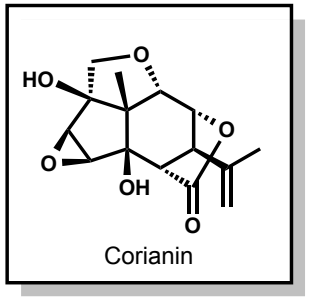


32 steps



1. $(CF_3SO_2)_2O$
N-methylimidazole
100°C

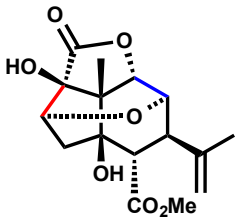
2. $LiBH_4$, HOAc, THF
0°C, 71%
3. PHSH, CH_3CN
TMSCl(cat), r.t.
98%
4. Ph_3SnH, AIBN
toluene, reflux 84%
5. mCPBA, DCM, 0°C
87%



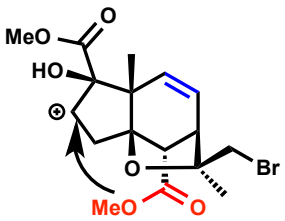
Corianin

34 steps

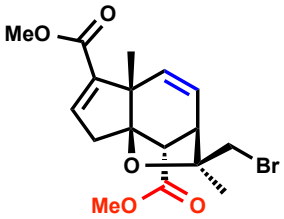
Trost: Methyl Picrotoxate

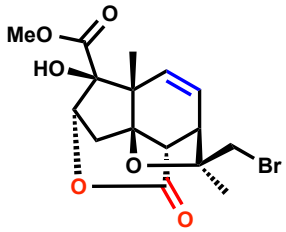


Methyl Picrotoxate

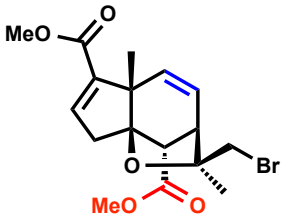


Alkene very hindered with bromoether linkage intact

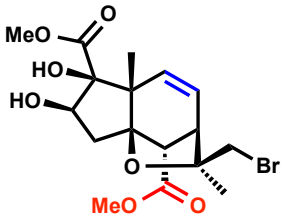


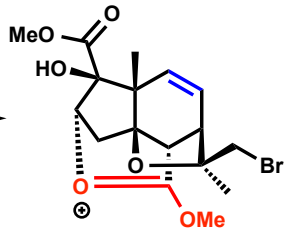


1. Tf_2O, pyr r.t.
89%

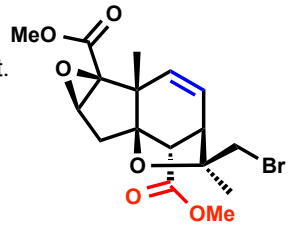


1. OsO_4, pyr, r.t.
89%

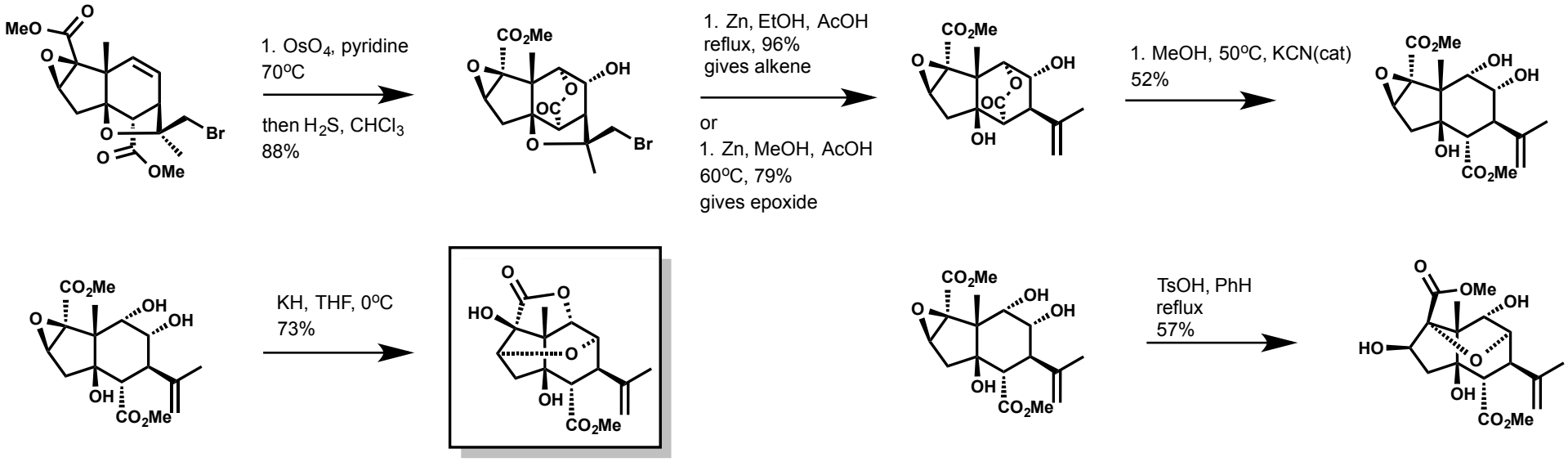




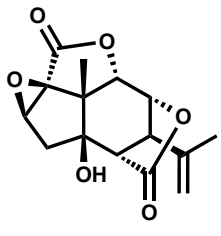
1. Tf_2O, DMAP r.t.
88%



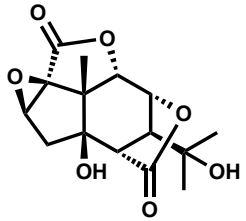
Trost: Methyl Picrotoxate



Trost: Picrotoxin Studies

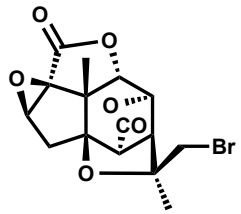


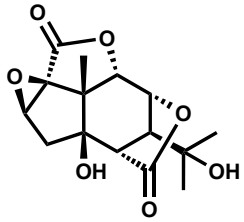
Picrotoxinin



Picrotin

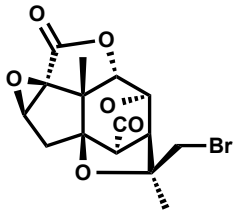
Br_2, H_2O
reflux



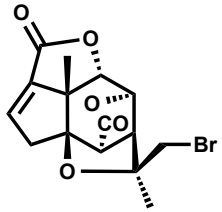


Picrotin

convenient for separation

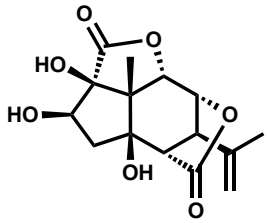


WCl_6, BuLi
THF-Et_2O
r.t. 52%



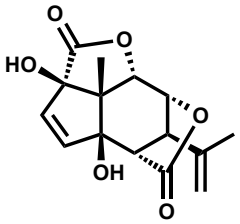
1. OsO_4, pyr
then aq $NaHSO_3$
73%

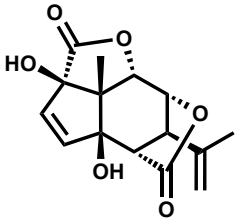
2. Zn, MeOH, AcOH
60°C



N-methylimdazole
Tf_2O, 100°C

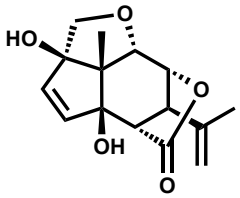
85%





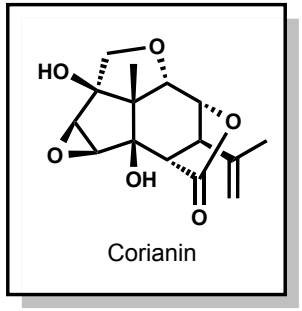
1. $LiBH_4$, AcOH, THF
0°C 71%

2. PhSH, TMSCl(cat)
MeCN, r.t. 98%
3. $PhSn_3H$, AIBN(cat)
toluene reflux
84%



mCPBA, DCM
0°C

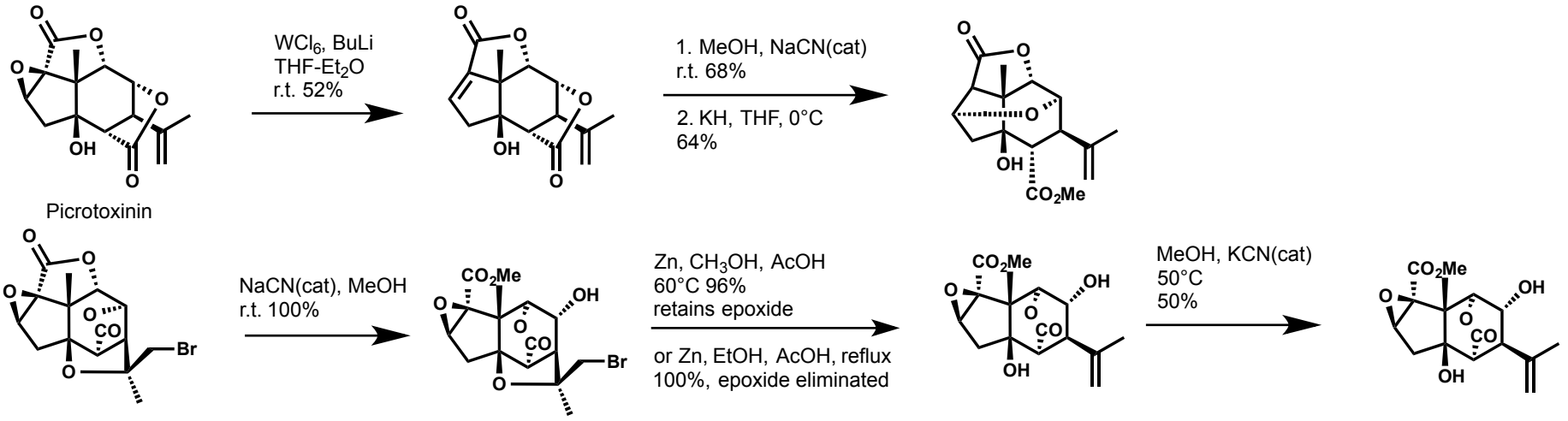
87%



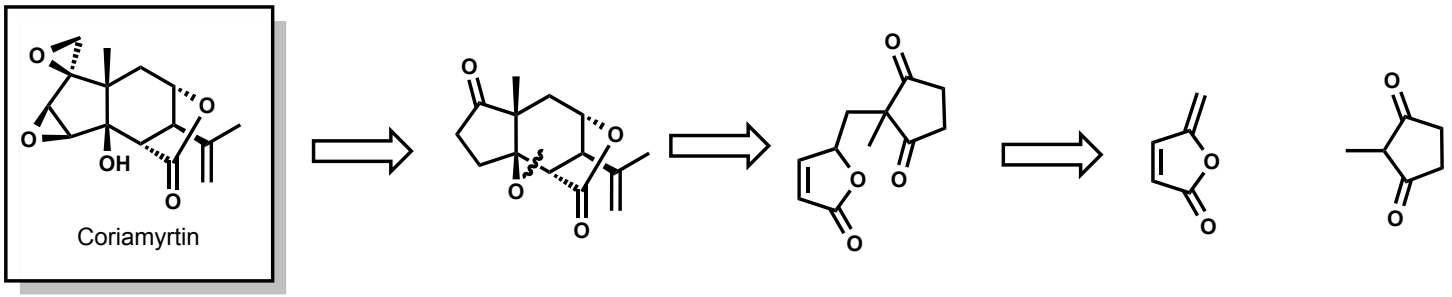
Corianin

Trost: Picrotoxin Studies

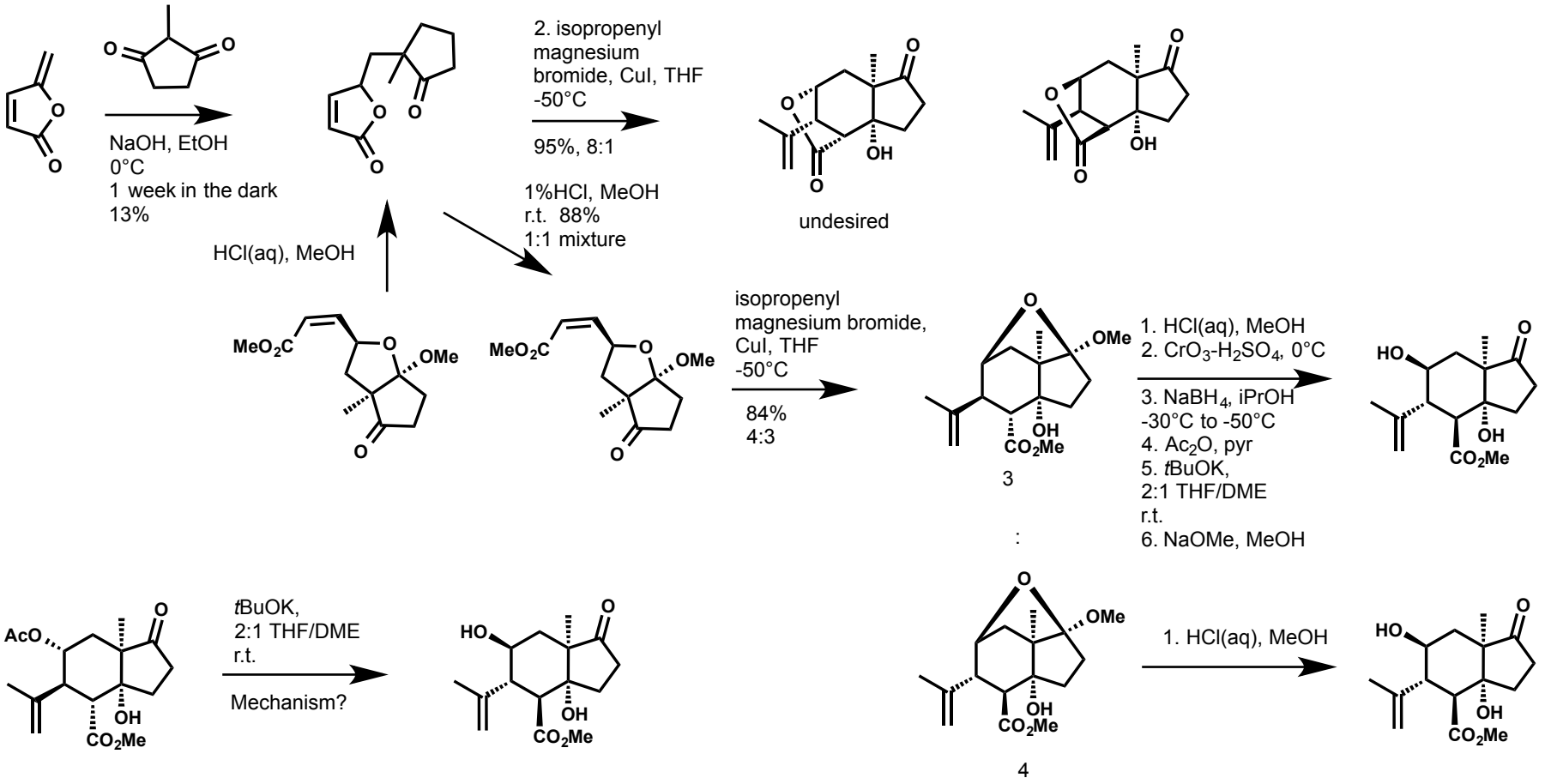
analogue synthesis



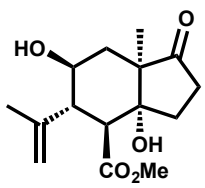
Coriamyrtin: Inubushi



Coriamyrtin: Inubushi

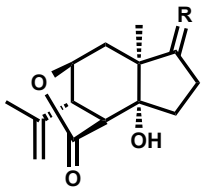


Coriamyrtin: Inubushi



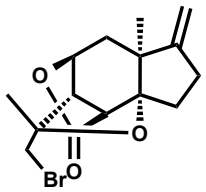
1. dihydrofuran
PPTS(cat), DCM
reflux

2. PPh_3CH_3Br, *t*-AmOK
t-AmOH, toluene, reflux
(used only for $R=CH_2$)
3. oxalic acid, MeOH(aq)
4. 1N NaOH, MeOH
reflux
5. 2,4,6-chlorobenzoyl chloride
Et_3N, toluene, reflux
43% 4 steps R=O
36% 5 steps $R=CH_2$



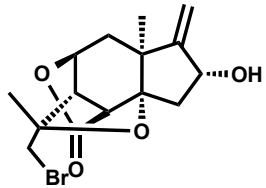
R =O
or
$R=CH_2$

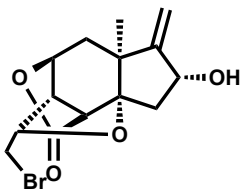
1. NBS, THF
87% R=O
98% $R=CH_2$



installation of methylene
unit late stage failed
due to hindrance

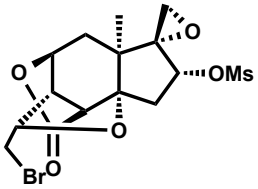
*t*BUOOH, SeO_2
DCM, r.t.
48% and 49% RSM





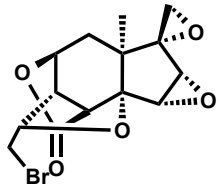
1. *t*BUOOH
$VO(acac)_2$, bezene
r.t. 64%

2. MsCl, DMAP, pyr
0°C
98%



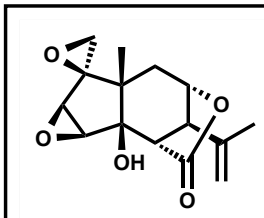
1. DBU, toluene
reflux 98%

2. mCPBA, Na_2HPO_4
DCM, reflux
3%



Zn-Cu couple
NH_4Cl, EtOH
H_2O, reflux

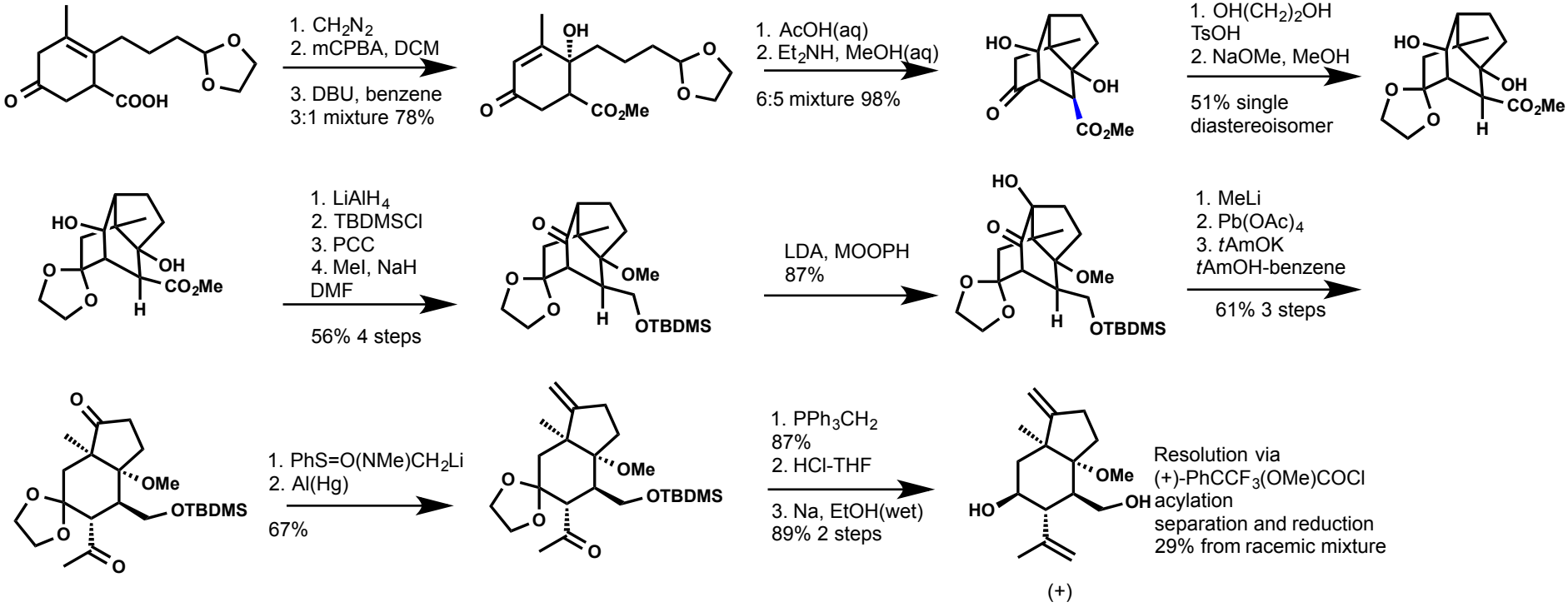
58%



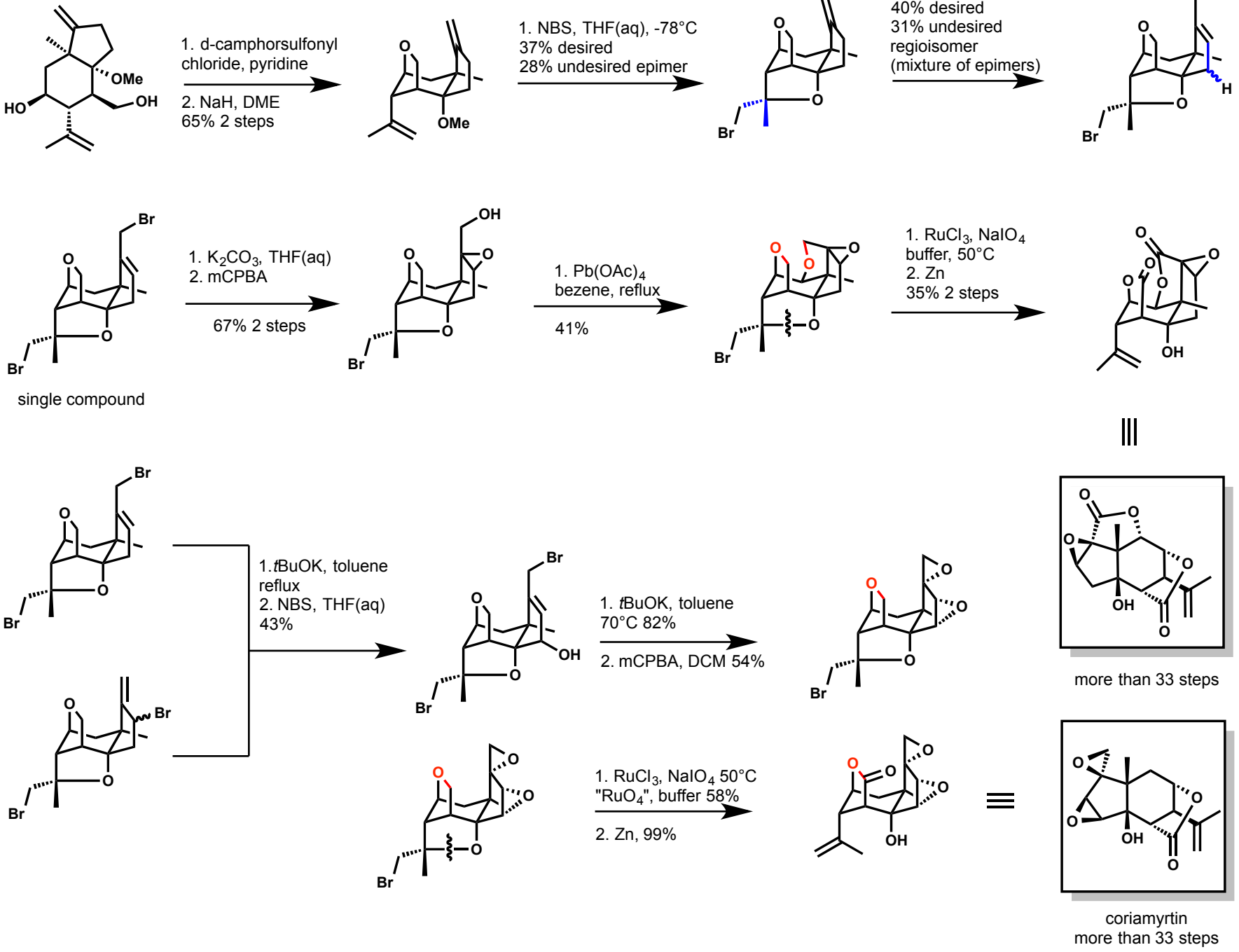
Coriamyrtin

15 steps

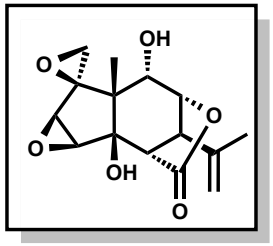
Picrotoxinin Yamada



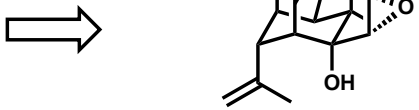
double olefination low yielding
split over 3 steps instead

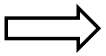

1. d-camphorsulfonyl chloride, pyridine
2. NaH, DME
65% 2 steps
1. NBS, THF(aq), -78°C
37% desired
28% undesired epimer
NBS, THF
40% desired
31% undesired
regioisomer
(mixture of epimers)
single compound
1. K_2CO_3, THF(aq)
2. mCPBA
67% 2 steps
1. $Pb(OAc)_4$
bezene, reflux
41%
1. $RuCl_3$, $NaIO_4$
buffer, 50°C
2. Zn
35% 2 steps
1.tBuOK, toluene
reflux
2. NBS, THF(aq)
43%
1. tBuOK, toluene
70°C 82%
2. mCPBA, DCM 54%
1. $RuCl_3$, $NaIO_4$ 50°C
"RuO_4", buffer 58%
2. Zn, 99%
more than 33 steps
coriamyrtin
more than 33 steps

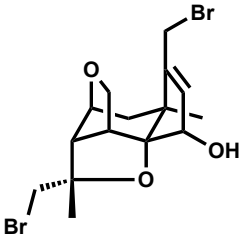
Tutin Yamada

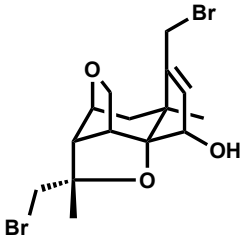


Tutin



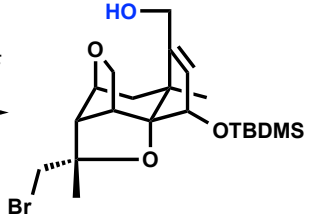






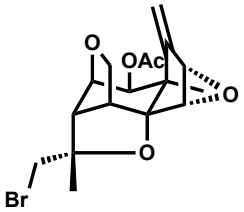
1. TBDMSOTf, pyr
MeCN, 0°C
2. KO_2, DMSO, DMF
0°C

73%



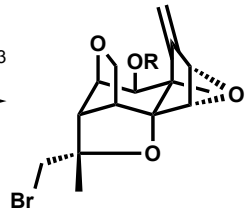
1. $Pb(OAc)_4$, benzene
reflux 57%

2. Acetyl bromide
CaH_2, Bu_4NBr, MECN
84%
3. Bu_4NF, THF, r.t.
99%

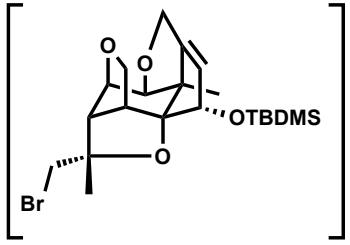


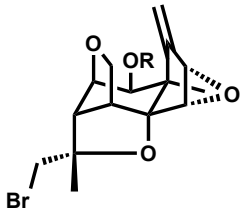
1.K_2CO_3, MeOH
2. pyr. $ClCO_2CH_2CCl_3$
r.t.

89%



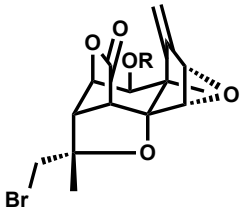
R=$CO_2CH_2CCl_3$



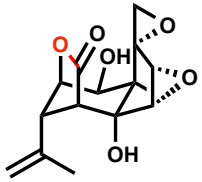


1. CF_3CO_3H, Na_2HPO_4
DCM, 35°C 43%

2. $RuCl_3$, $NaIO_4$
Ph 7 phosphate buffer
$MeCN/CHCl_3$
73%



Zn, NH_4Cl, EtOH
reflux 99%



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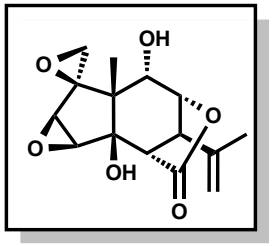
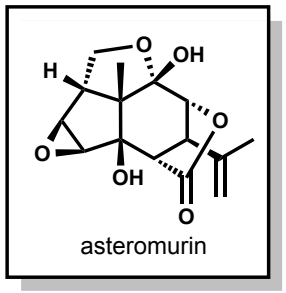
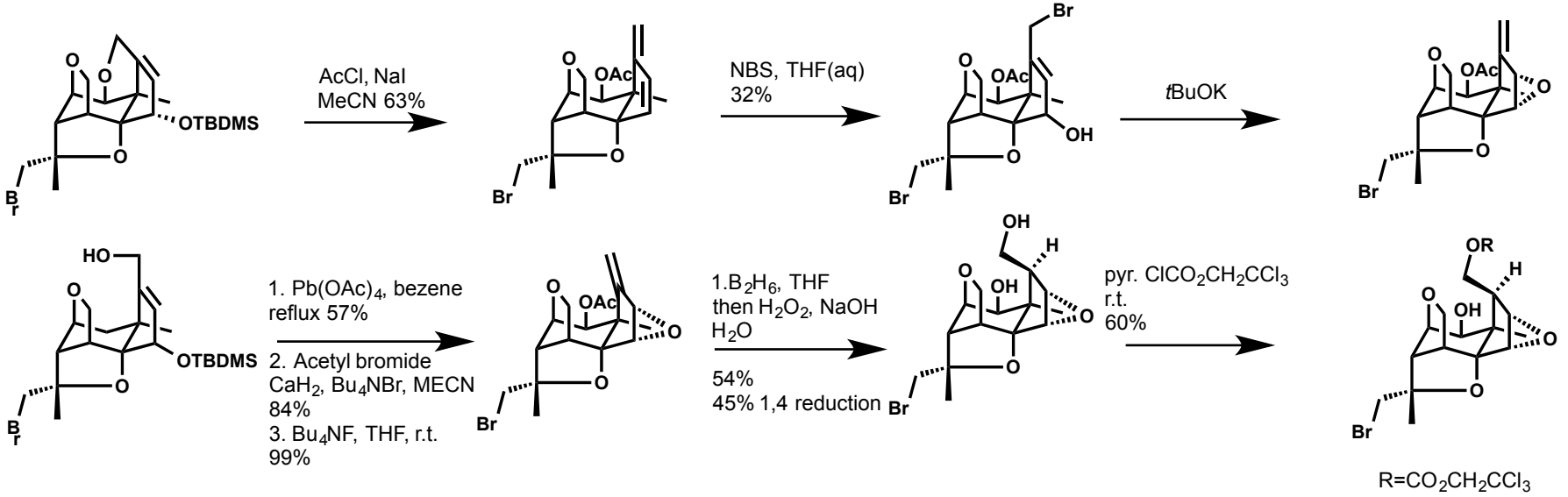
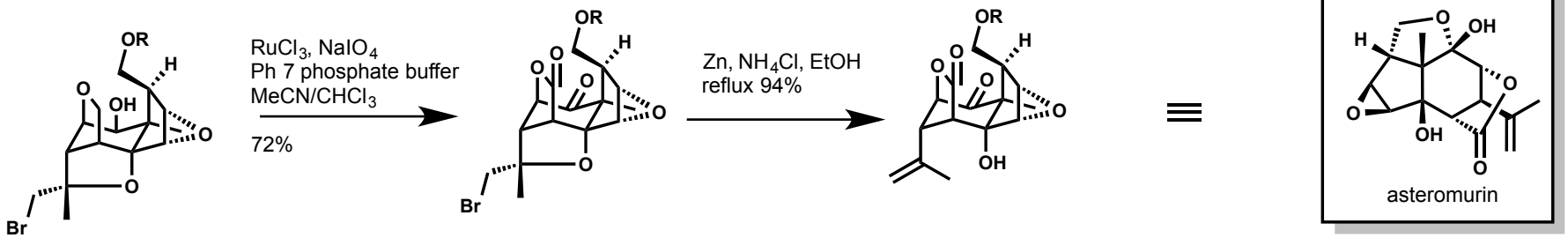


Tutin


asteromurin


OTBDMS
AcCl, NaI
MeCN 63%
OAc
NBS, THF(aq)
32%
Br
OH
tBuOK
HO
1. Pb(OAc)4, bezene
reflux 57%
2. Acetyl bromide
CaH2, Bu4NBr, MECN
84%
3. Bu4NF, THF, r.t.
99%
1.B2H6, THF
then H2O2, NaOH
H2O
54%
45% 1,4 reduction
pyr. ClCO2CH2CCl3
r.t.
60%
OR
R=CO2CH2CCl3


RuCl3, NaIO4
Ph 7 phosphate buffer
MeCN/CHCl3
72%
Zn, NH4Cl, EtOH
reflux 94%
asteromurin