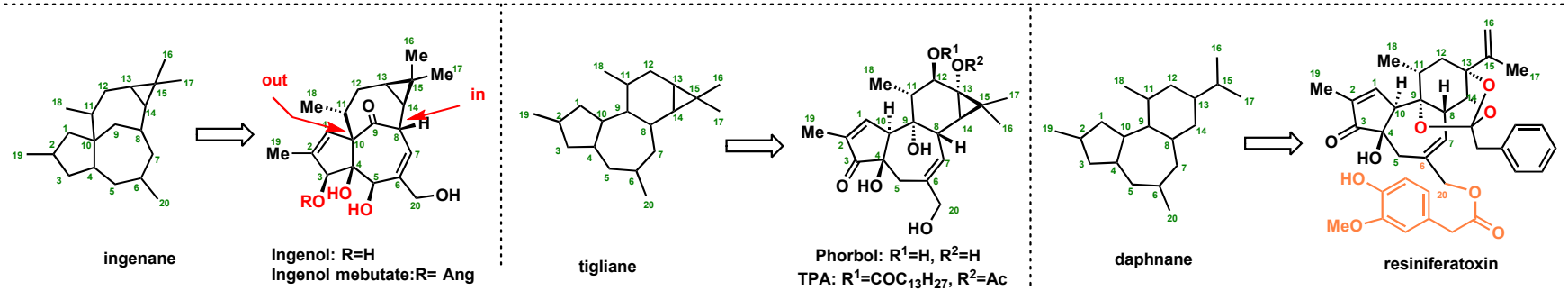
Representative Molecule Diterpenoid from Euphorbia



ingenane

Ingenol: R=H
Ingenol mebutate:R= Ang

tigliane

Phorbol: R^1=H, R^2=H
TPA: R^1=$COC_{13}H_{27}$, R^2=Ac

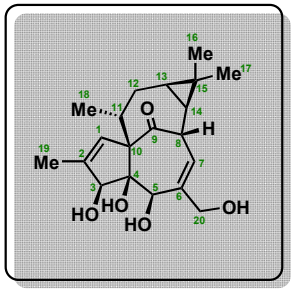
daphnane

resiniferatoxin

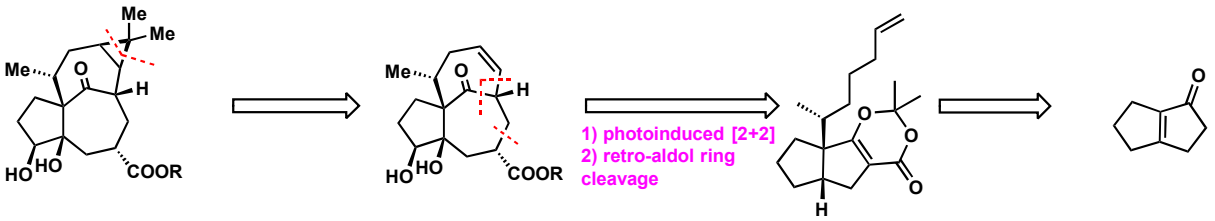
- 1968 Hecker isolated Ingenol from from Euphorbia ingens
- Ingenol mebutate (Picato®): a first-in-class drug for the treatment of the precancerous skin condition actinic keratosis (approved by FDA in 2012)
- Ingenol is a PKC activator ((Ki =30 μM)
- highly oxygenated trans-fused 5/ 6/ 7/ 3-membered ABC-ring system.
- 2002:First total synthesis by Winkler (44 steps)
- 2003: Total synthesis by Kuwajima (45 steps)
- 2004: Formal total synthesis by Kigoshi (34 steps)
- 2004: Total synthesis by Wood (37 steps)
- 2013: Total synthesis by Baran (14 steps)

- 1934, Swiss chemists Bonifaz Flaschenträger and Rudolf von Wolffersdorff isolated it from hydrolyzed croton oil
- Phorbol 12-myristate 13-acetate (TPA): often employed in biomedical research to activate the protein kinase C (Ki =2.6 nM)
- different phorbol diesters exhibit a variety of biological functions: anti-inflammatory, antitumor and anti-HIV activity
- 1989: First total synthesis by Wender (52 steps)
- 1990: Formal synthesis by Wender (42 steps)
- 1997: First formal asymmertric synthesis by Wender (40 steps)
- 2001: Formal asymmertric synthesis by Cha (44 steps)
- 2016: Total synthesis by Baran (19 steps)
- 2024: Total synthesis by Inoue (22 steps)

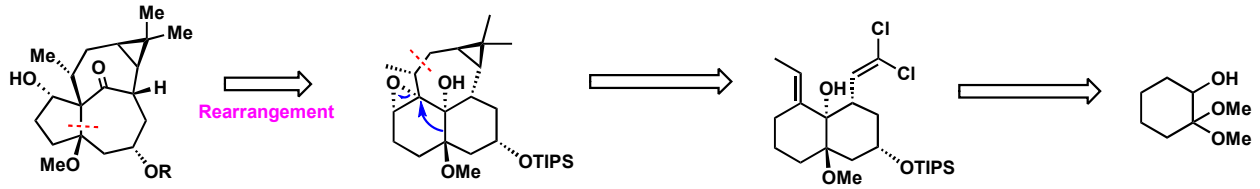
- 1975, Hecker et al. isolated resiniferatoxin from the latex of Euphorbia resinifera.
- 1982 revealed it belongs to a daphnane diterpenoid family
- potent activator of transient receptor potential vanilloid 1 ($TRPV_1$), an ion channel protein of sensory neurons that perceives pain.
- highly oxygenated trans-fused 5/ 6/ 7-membered ABC-ring system.
- 1997: First total synthesis by Wender (44 steps)
- 2017: total synthesis by Inoue(41 steps)
- 2021: total synthesis by Inoue (20 steps)
- 2022: total synthesis by Maimone (15 steps)
- 2022: formal synthesis by Inoue (27 steps)



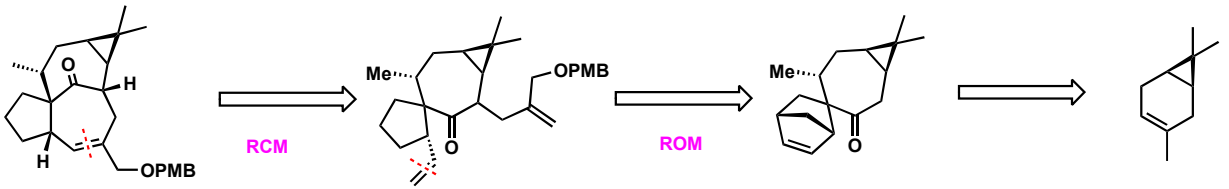
Winkler's strategy



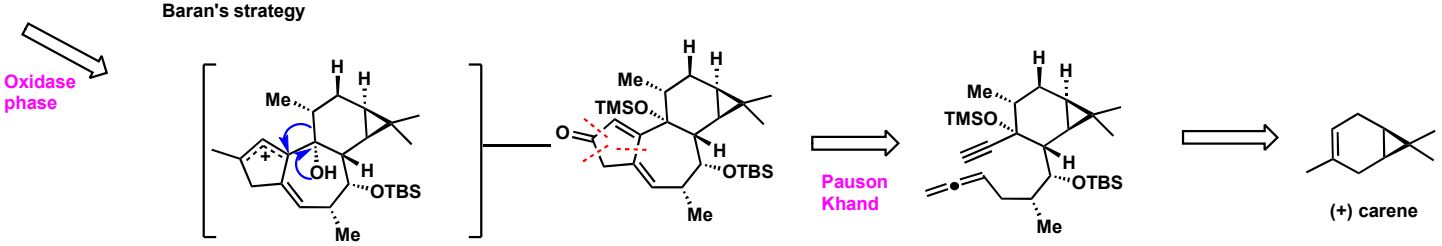
Kuwajima's strategy

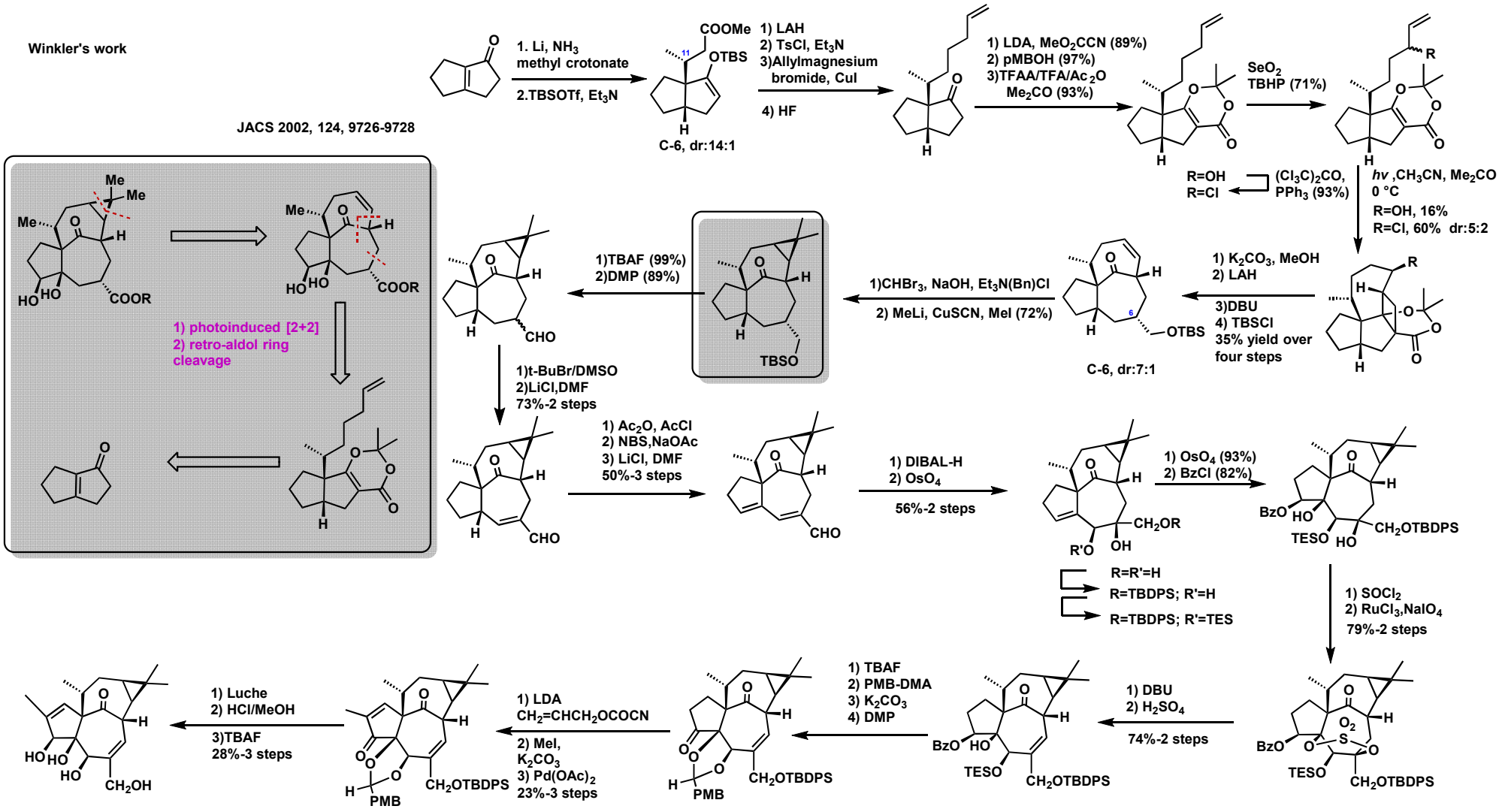


Wood's strategy



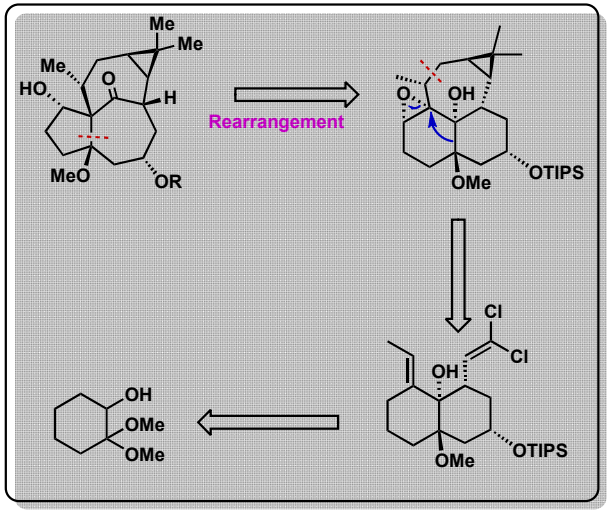
Baran's strategy

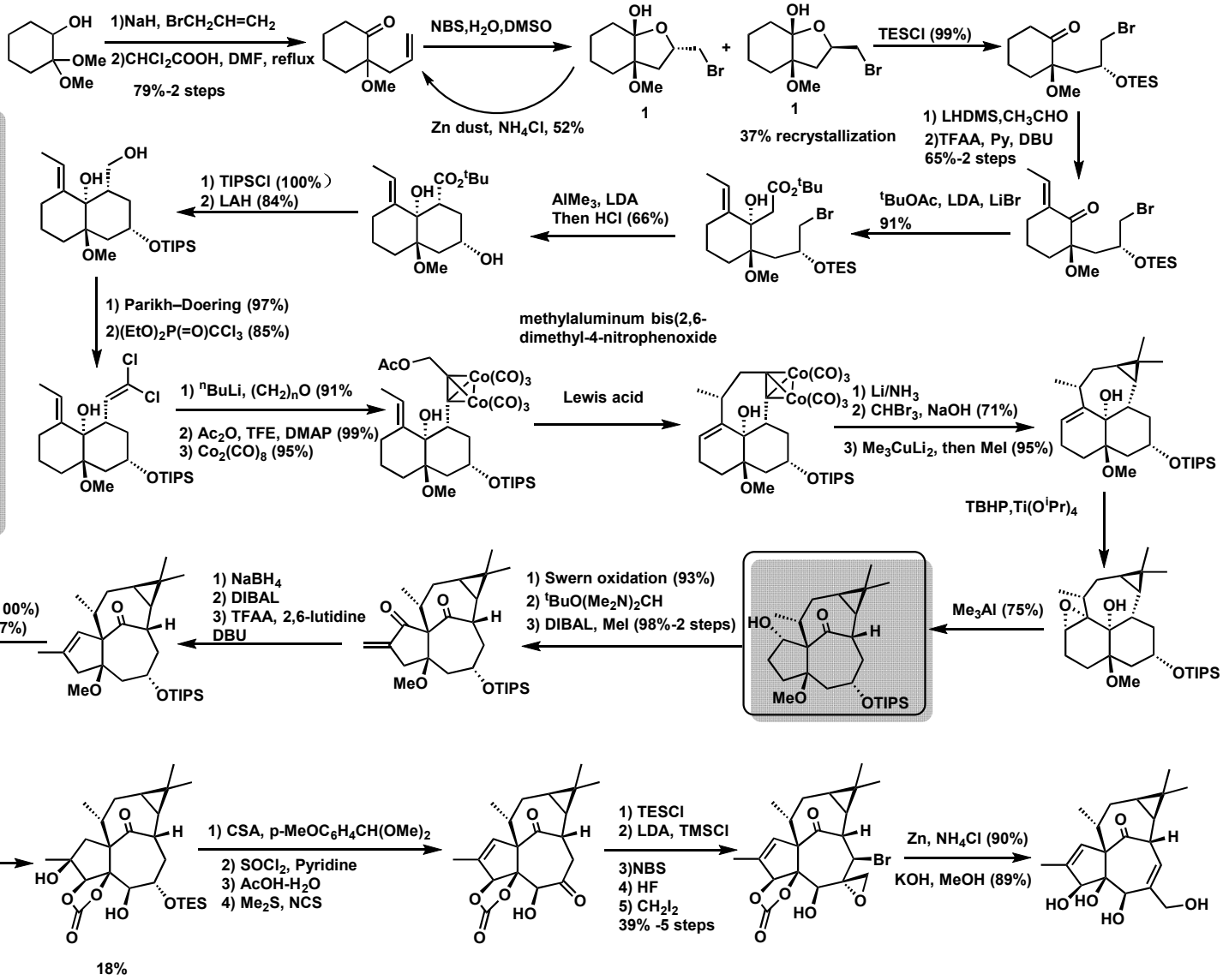



Winkler's work
JACS 2002, 124, 9726-9728
1) photoinduced [2+2]
2) retro-aldol ring cleavage
1. Li, NH3
methyl crotonate
2.TBSOTf, Et3N
C-6, dr:14:1
1) LAH
2) TsCl, Et3N
3)Allylmagnesium bromide, CuI
4) HF
1) LDA, MeO2CCN (89%)
2) pMBOH (97%)
3)TFAA/TFA/Ac2O
Me2CO (93%)
SeO2
TBHP (71%)
R=OH
R=Cl
(Cl3C)2CO,
PPh3 (93%)
hv ,CH3CN, Me2CO
0 °C
R=OH, 16%
R=Cl, 60% dr:5:2
1) K2CO3, MeOH
2) LAH
3)DBU
4) TBSCl
35% yield over four steps
C-6, dr:7:1
1)CHBr3, NaOH, Et3N(Bn)Cl
2) MeLi, CuSCN, MeI (72%)
1)TBAF (99%)
2)DMP (89%)
1)t-BuBr/DMSO
2)LiCl,DMF
73%-2 steps
1) Ac2O, AcCl
2) NBS,NaOAc
3) LiCl, DMF
50%-3 steps
1) DIBAL-H
2) OsO4
56%-2 steps
1) OsO4 (93%)
2) BzCl (82%)
R=R'=H
R=TBDPS; R'=H
R=TBDPS; R'=TES
1) SOCl2
2) RuCl3,NaIO4
79%-2 steps
1) DBU
2) H2SO4
74%-2 steps
1) TBAF
2) PMB-DMA
3) K2CO3
4) DMP
1) LDA
CH2=CHCH2OCOCN
2) MeI,
K2CO3
3) Pd(OAc)2
23%-3 steps
1) Luche
2) HCl/MeOH
3)TBAF
28%-3 steps

Kuwajima' work

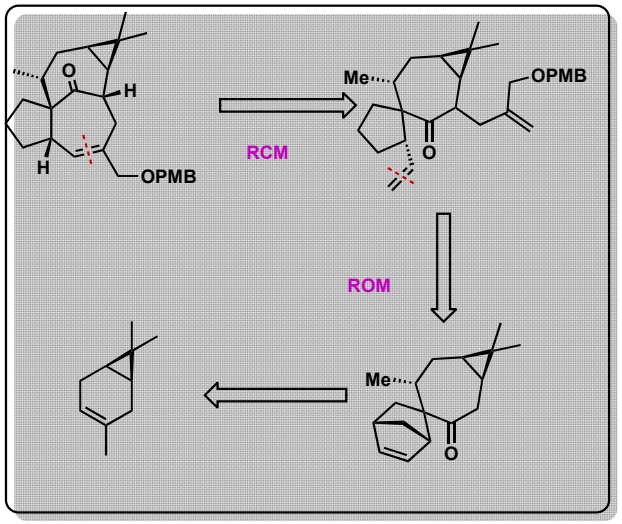
JACS. 2003, 125, 1498-1500

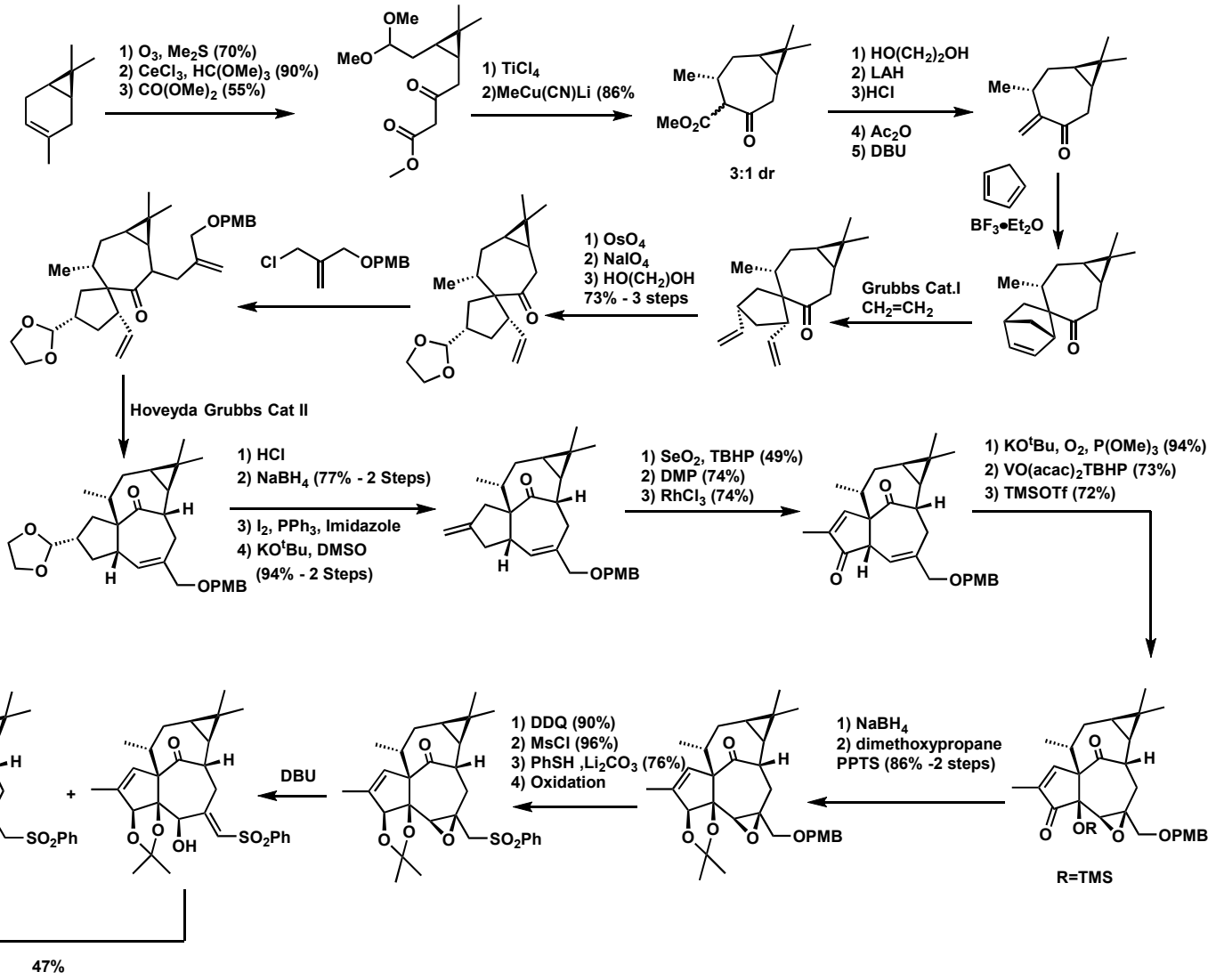




Wood's work

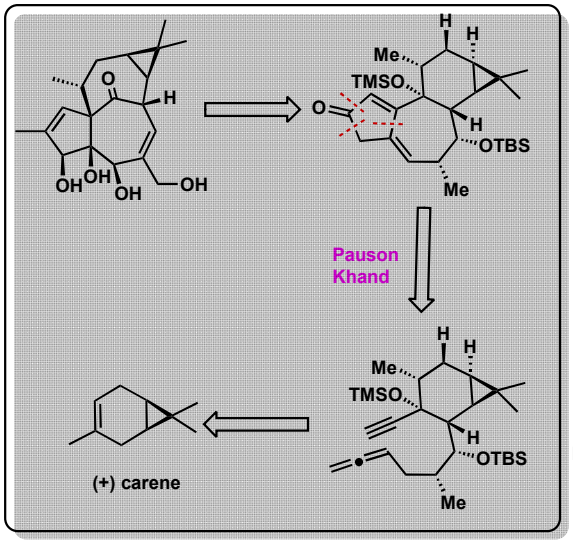
JACS. 2004, 126, 16300 -16301

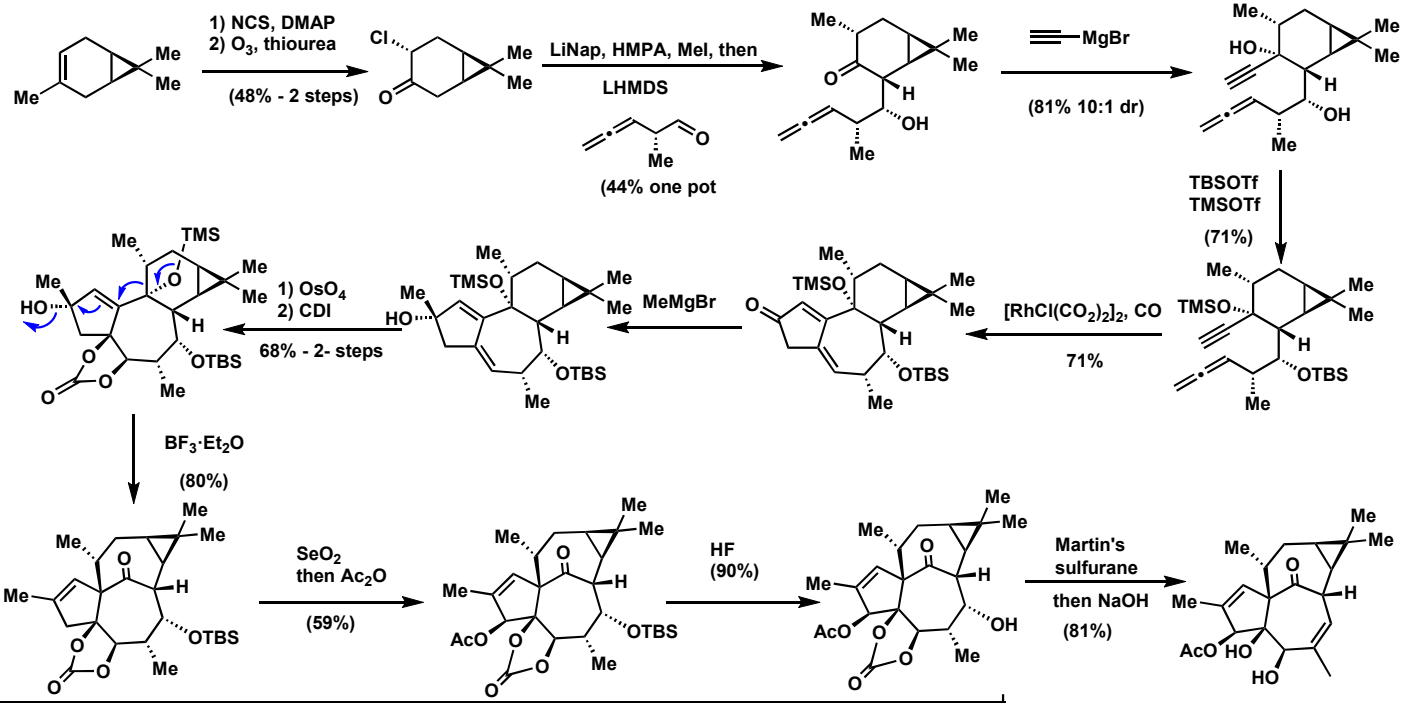




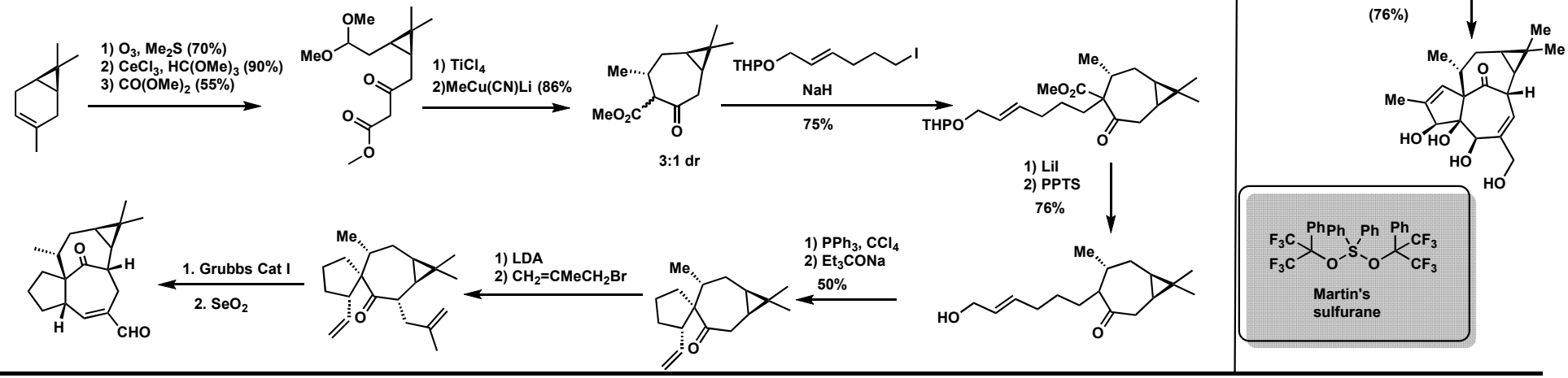
Baran's work

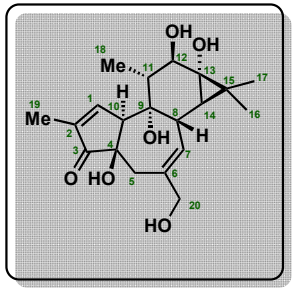
10.1126/science.1241606



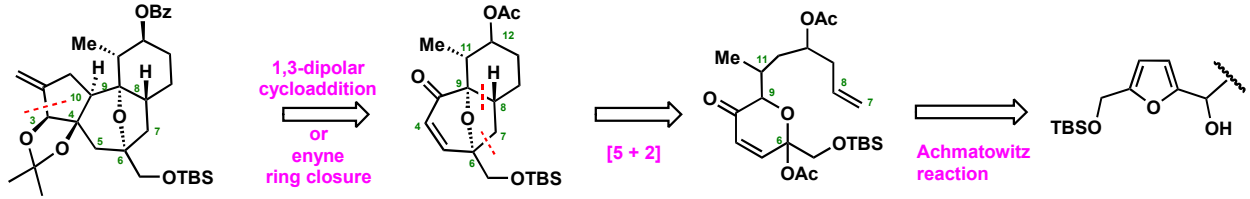


Kigoshi' work JOC 2004, 69, 7802-7808

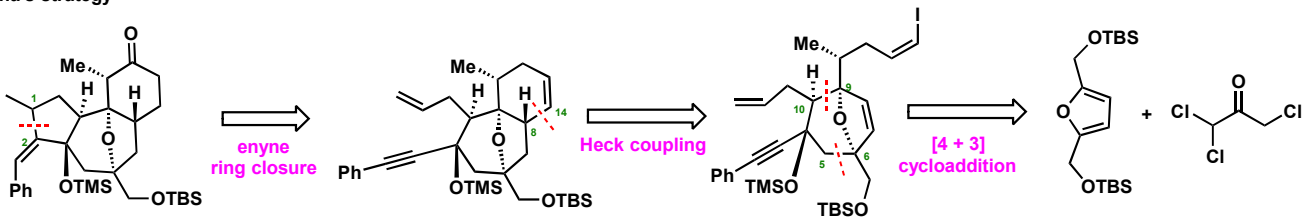




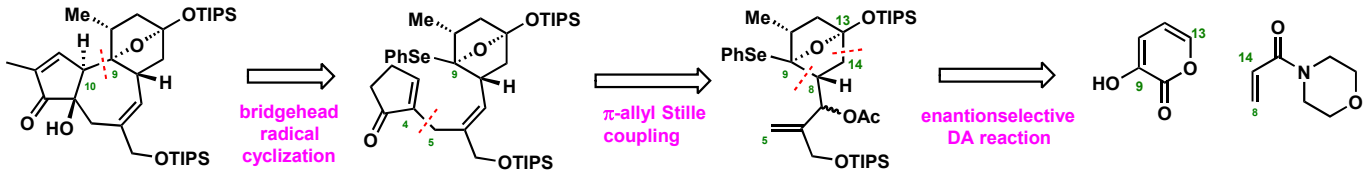
Wender's strategy



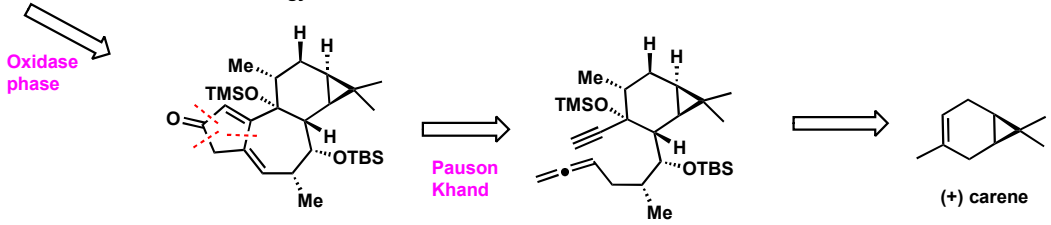
Cha's strategy



Inoue's strategy

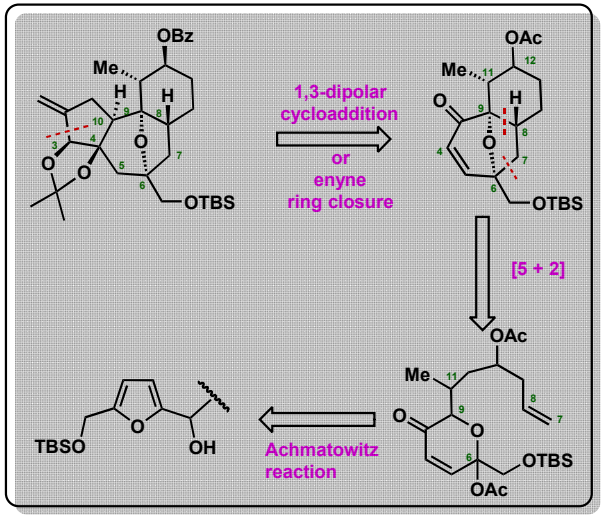


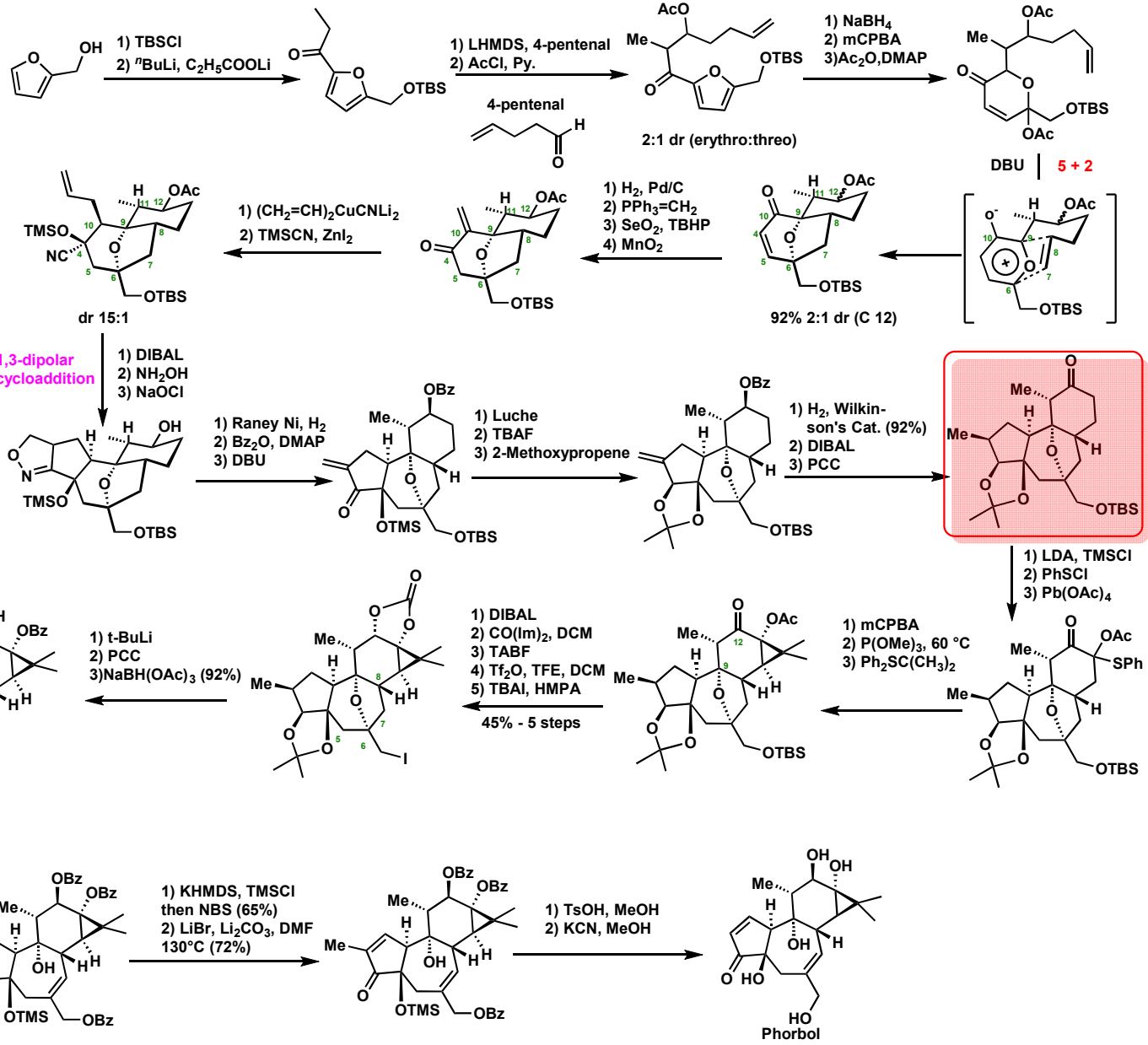
Baran's strategy



Wender's work

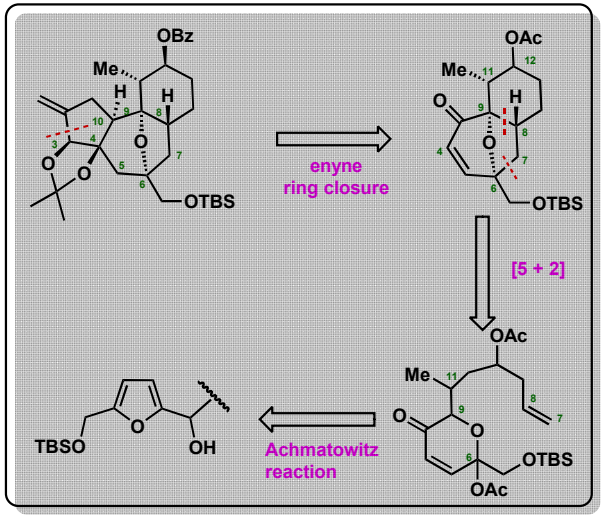
Wender, J. Am. Chem. Soc. 1989, 111, 8954-8957
Wender, J. Am. Chem. Soc. 1989, 111, 8957-8958

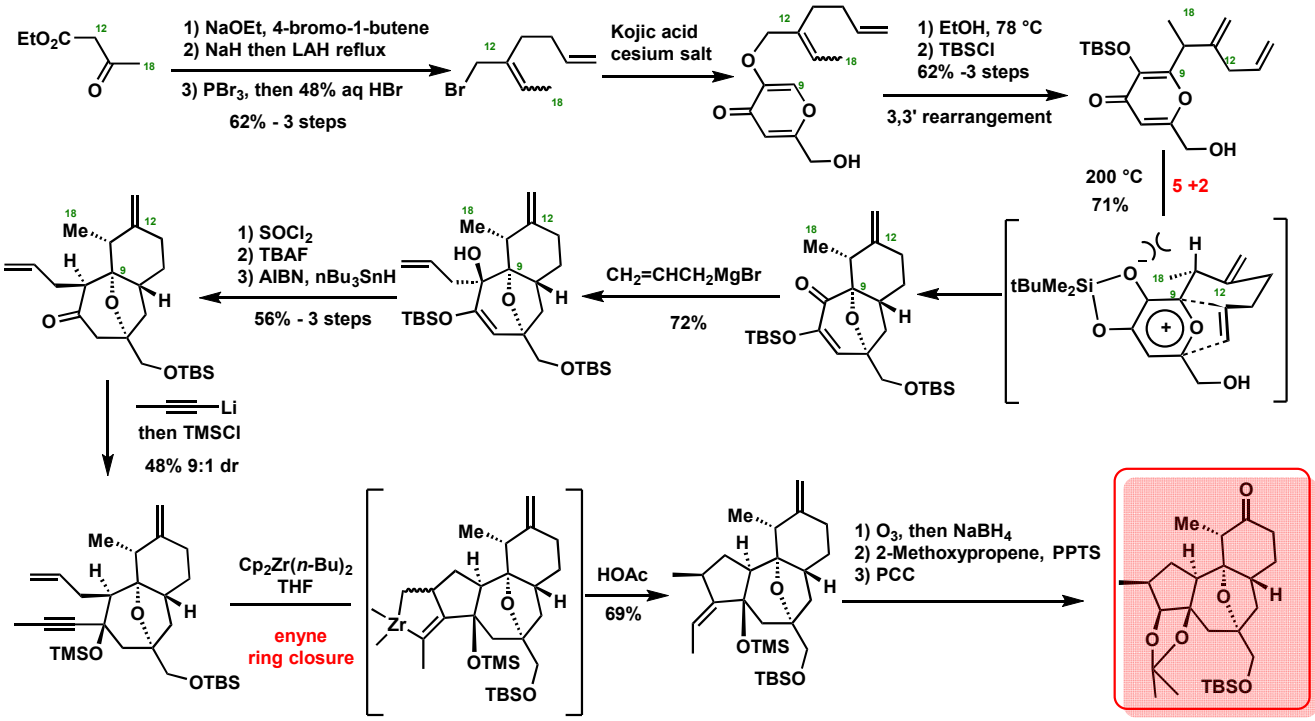


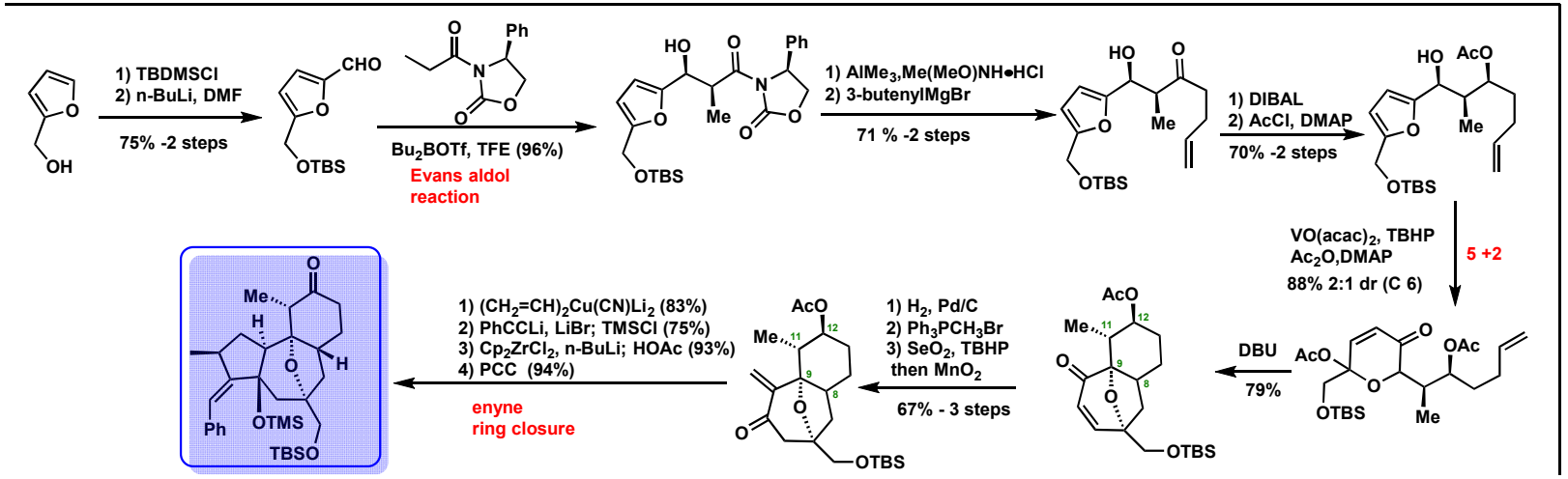


Wender's work

JACS 1990,112,4956-4958
JACS 1997,119,7897-7898

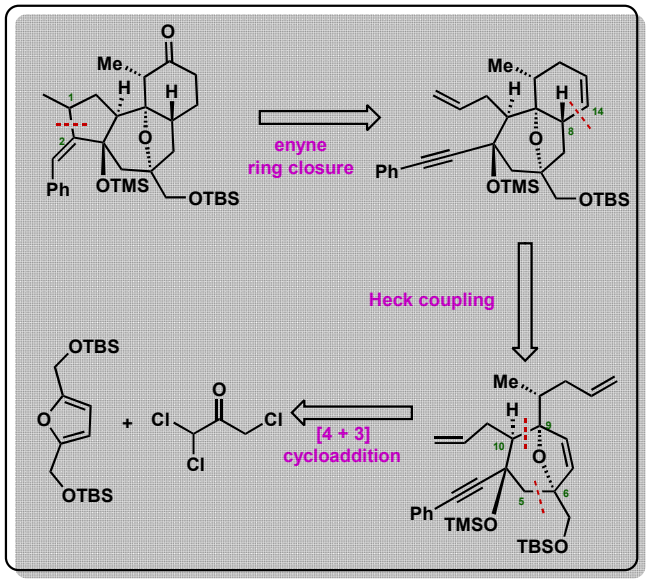


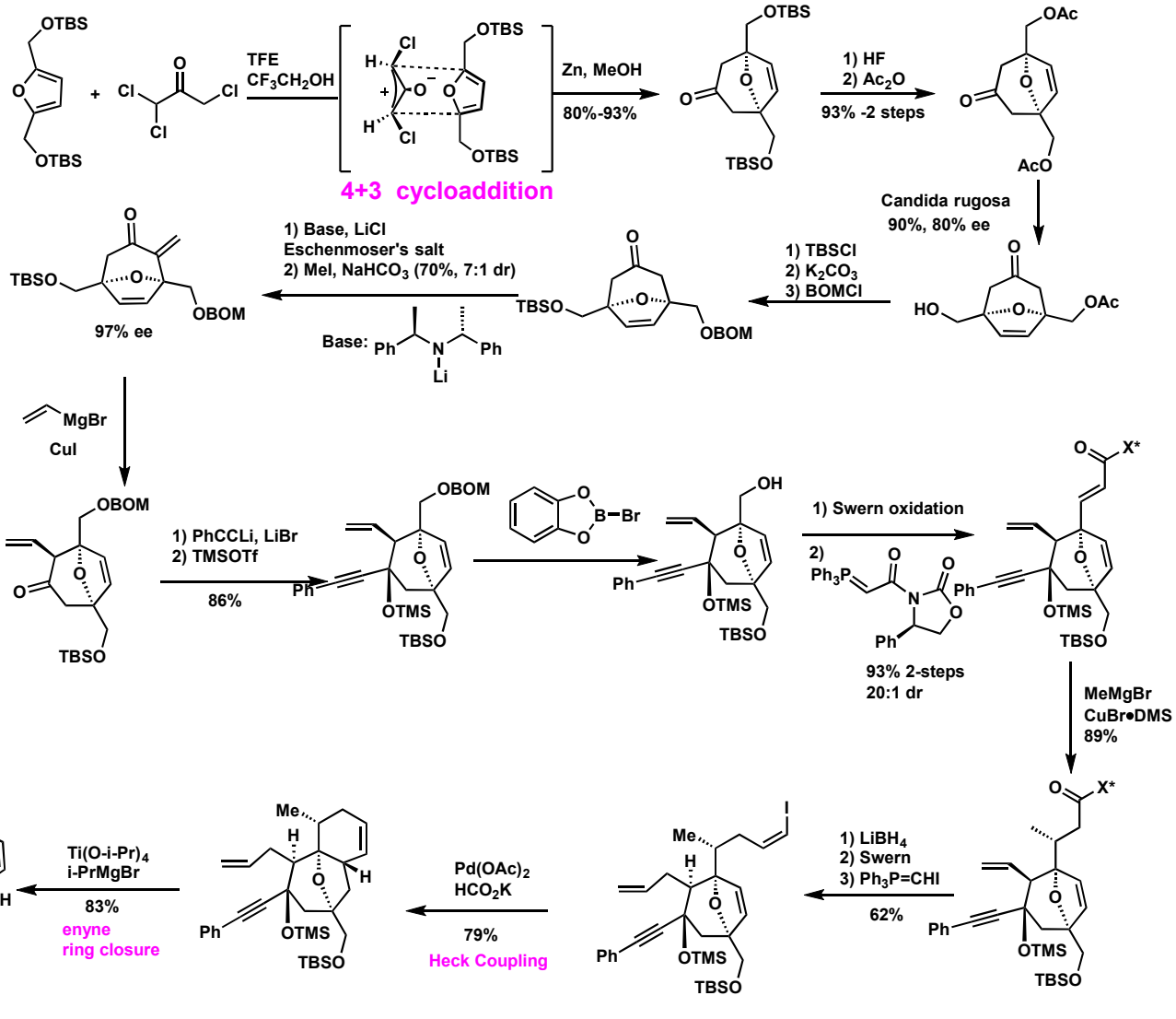




Cha's work

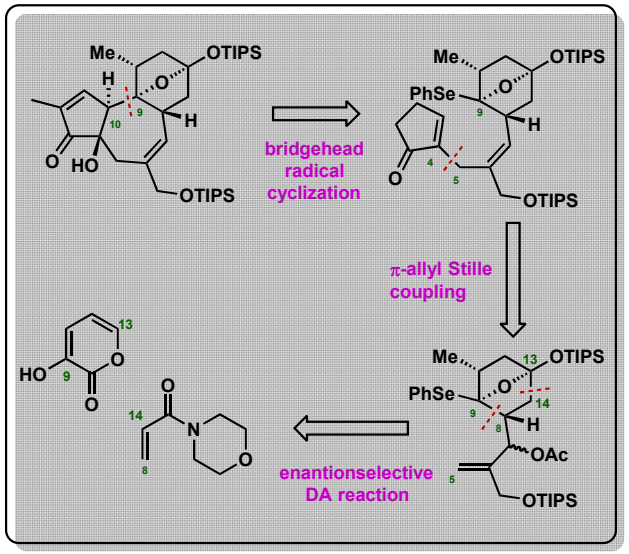
JACS 2001,123,5590-5591

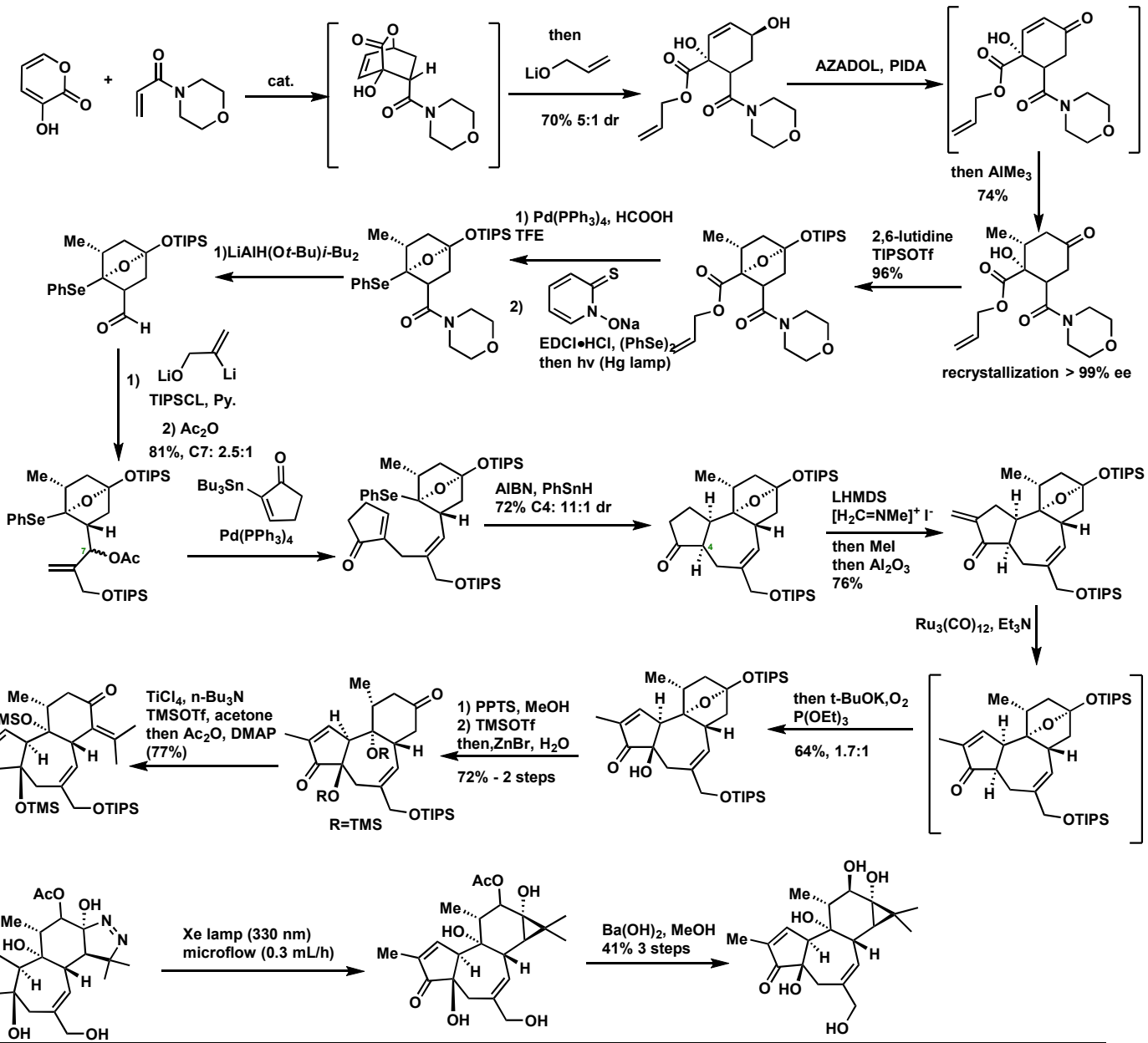




Inoue's work

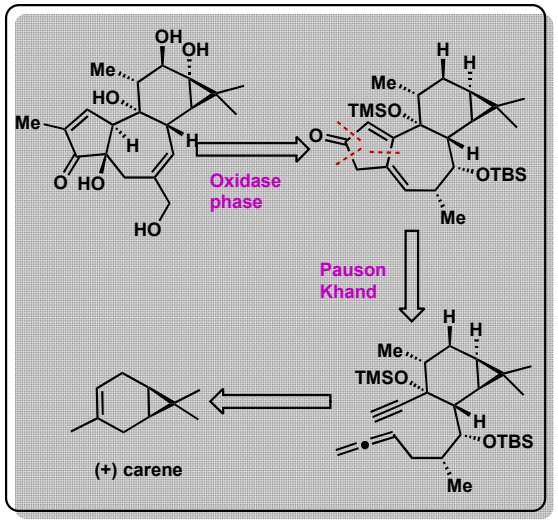
J. Am. Chem. Soc. 2024, 146, 8746−8756

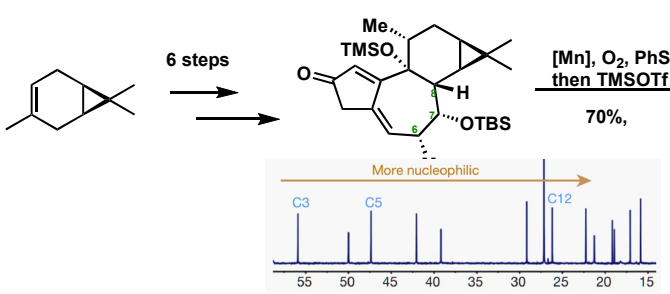




Baran's work

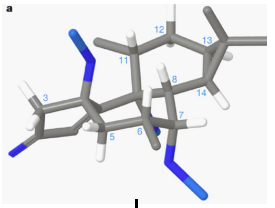
10.1038/nature17153





[Mn], O_2, $PhSiH_3$
then TMSOTf
70%,

1) C_6,7,8,11-H: steric shielding
2) hyperconjugation from cyclopropane
3) strain-release
4) C13,14: higher s-character



TFDO

MgI_2,ZnI_2

[Mn], O_2,
$PhSiH_3$, PPh_3
2 steps
51%

$RuCl_3$
$NaBrO_3$
96%

TFAA then Zn

Ac_2O

Et_3N
64%

$TsNHNH_2$
$NaBH_3CN$
40%

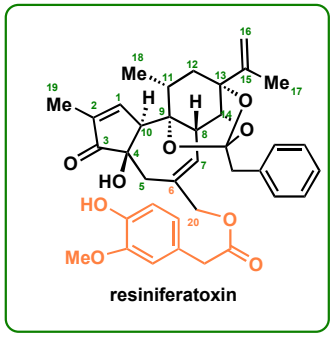
CrO_3
3,5-DMP

1)$TMSN_3$, I_2
2)Me_4Sn, [Pd]
68% 2 Steps

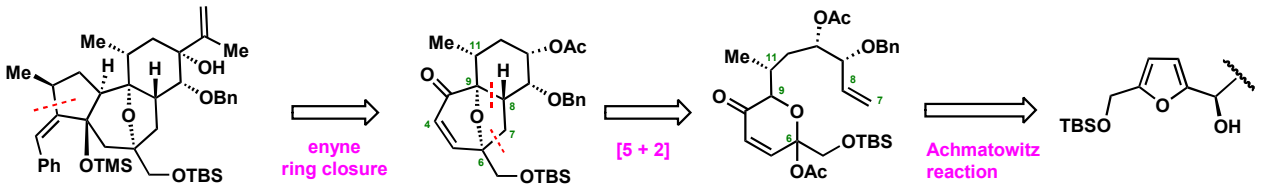
1) HF-Py
2) Martin Sulfurane
then SeO_2
51% 2 Steps

$NaBH_4$ then Ac_2O
93%

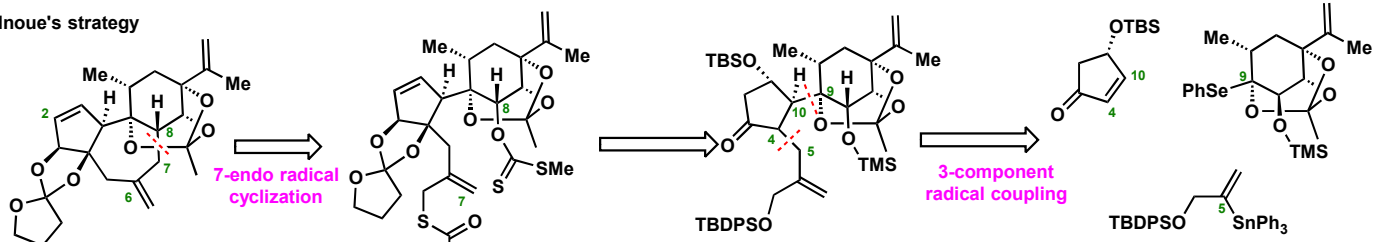
$NaBH(OAc)_3$
then TBAF
then $Ba(OH)_2$
72%



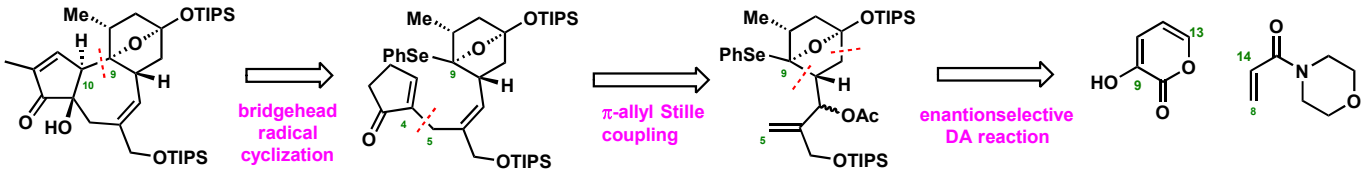
Wender's strategy



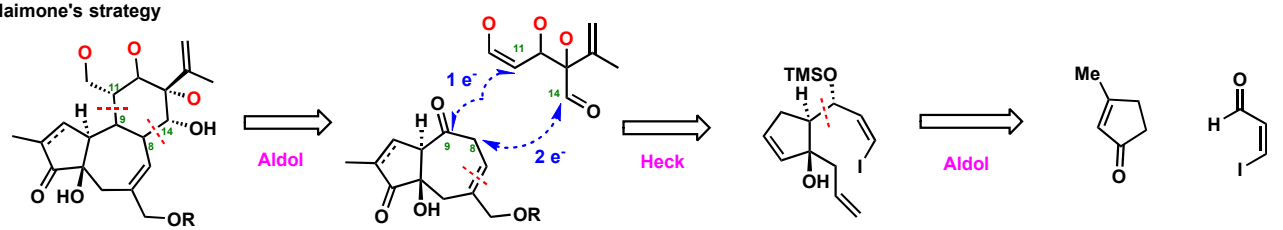
Inoue's strategy

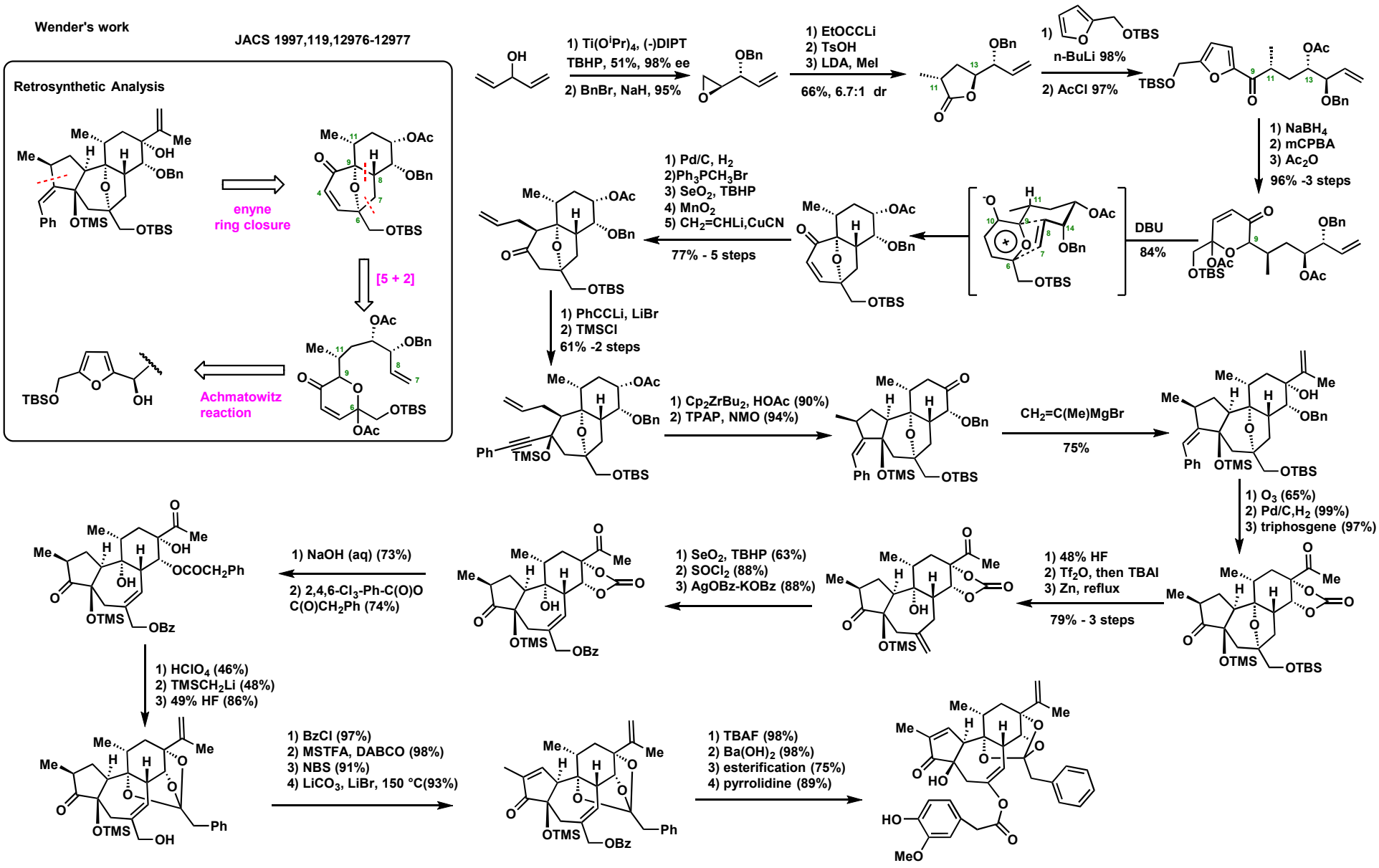


Inoue's strategy

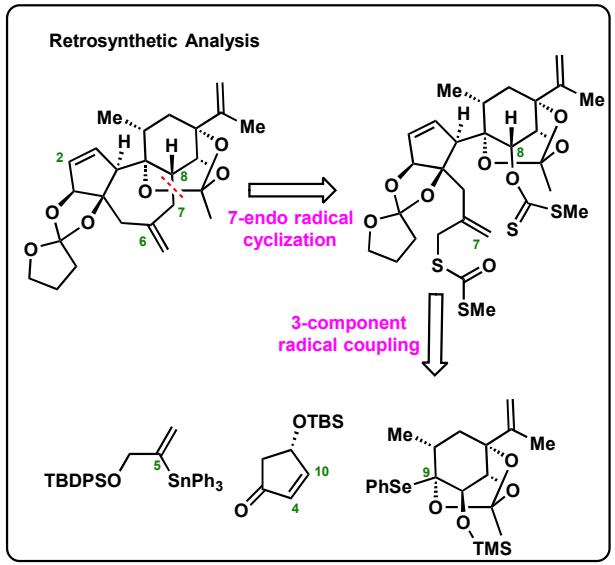


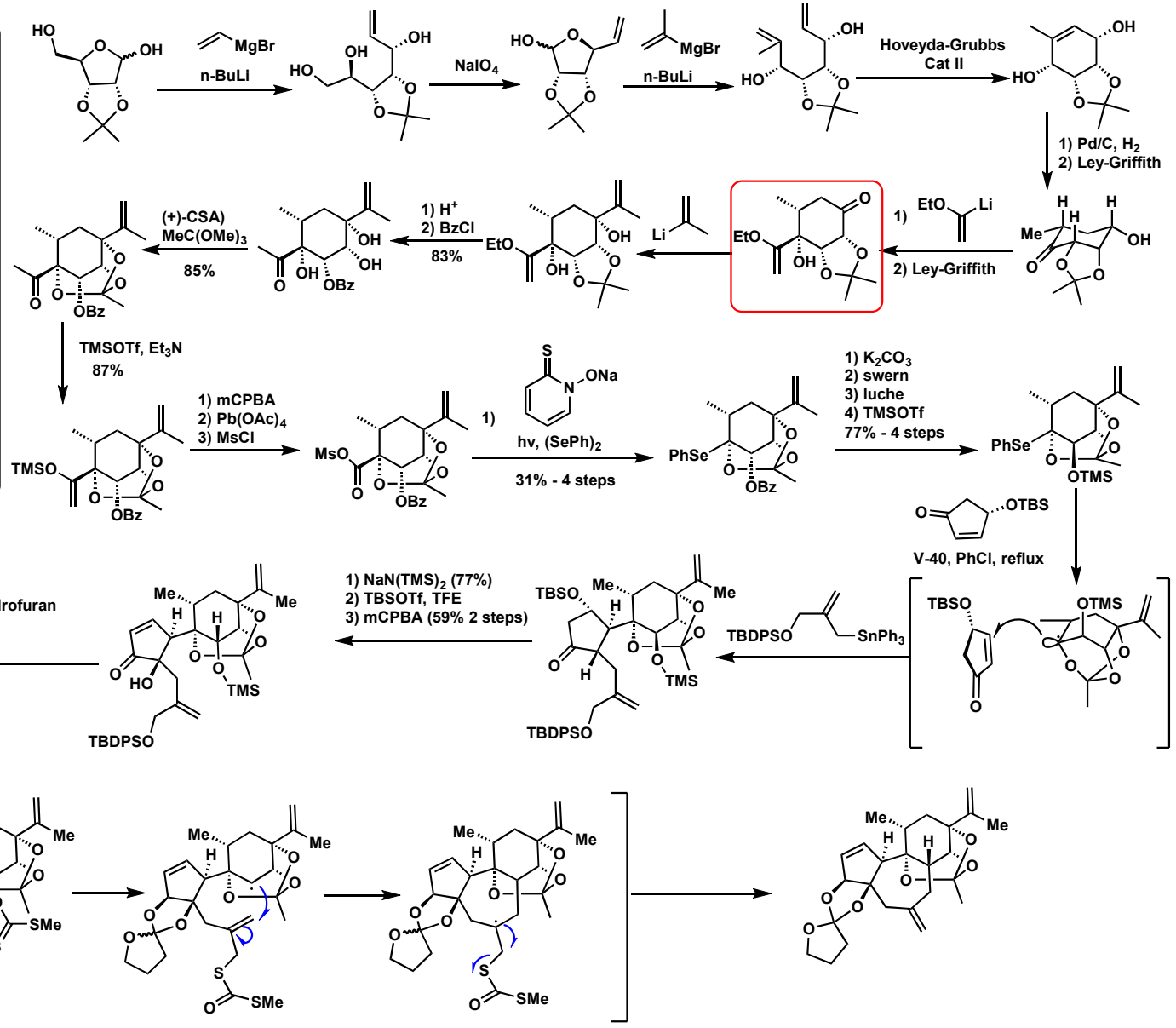
Maimone's strategy

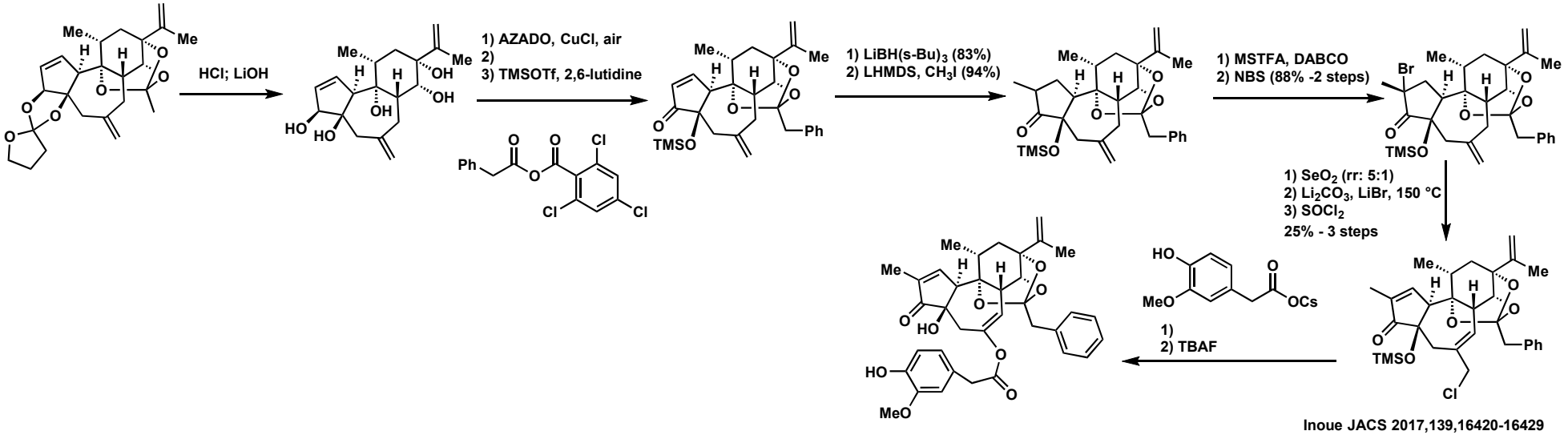



Wender's work
JACS 1997,119,12976-12977
Retrosynthetic Analysis
enyne ring closure
[5 + 2]
Achmatowitz reaction
1) Ti(OiPr)4, (-)DIPT TBHP, 51%, 98% ee
2) BnBr, NaH, 95%
1) EtOCCLi
2) TsOH
3) LDA, MeI
66%, 6.7:1 dr
1) n-BuLi 98%
2) AcCl 97%
1) NaBH4
2) mCPBA
3) Ac2O
96% -3 steps
DBU
84%
1) Pd/C, H2
2)Ph3PCH3Br
3) SeO2, TBHP
4) MnO2
5) CH2=CHLi,CuCN
77% - 5 steps
1) PhCCLi, LiBr
2) TMSCl
61% -2 steps
1) Cp2ZrBu2, HOAc (90%)
2) TPAP, NMO (94%)
CH2=C(Me)MgBr
75%
1) O3 (65%)
2) Pd/C,H2 (99%)
3) triphosgene (97%)
1) 48% HF
2) Tf2O, then TBAI
3) Zn, reflux
79% - 3 steps
1) SeO2, TBHP (63%)
2) SOCl2 (88%)
3) AgOBz-KOBz (88%)
1) NaOH (aq) (73%)
2) 2,4,6-Cl3-Ph-C(O)O C(O)CH2Ph (74%)
1) HClO4 (46%)
2) TMSCH2Li (48%)
3) 49% HF (86%)
1) BzCl (97%)
2) MSTFA, DABCO (98%)
3) NBS (91%)
4) LiCO3, LiBr, 150 °C(93%)
1) TBAF (98%)
2) Ba(OH)2 (98%)
3) esterification (75%)
4) pyrrolidine (89%)

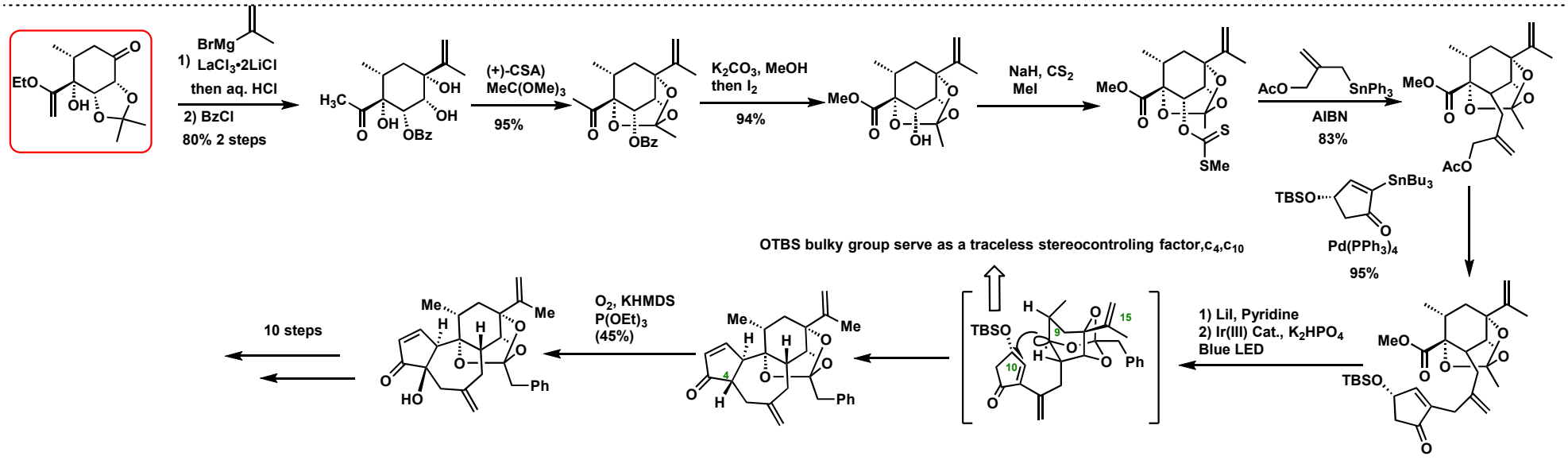
Inoune's work JACS 2017, 139,16420-16429







Inoue JACS 2017,139,16420-16429

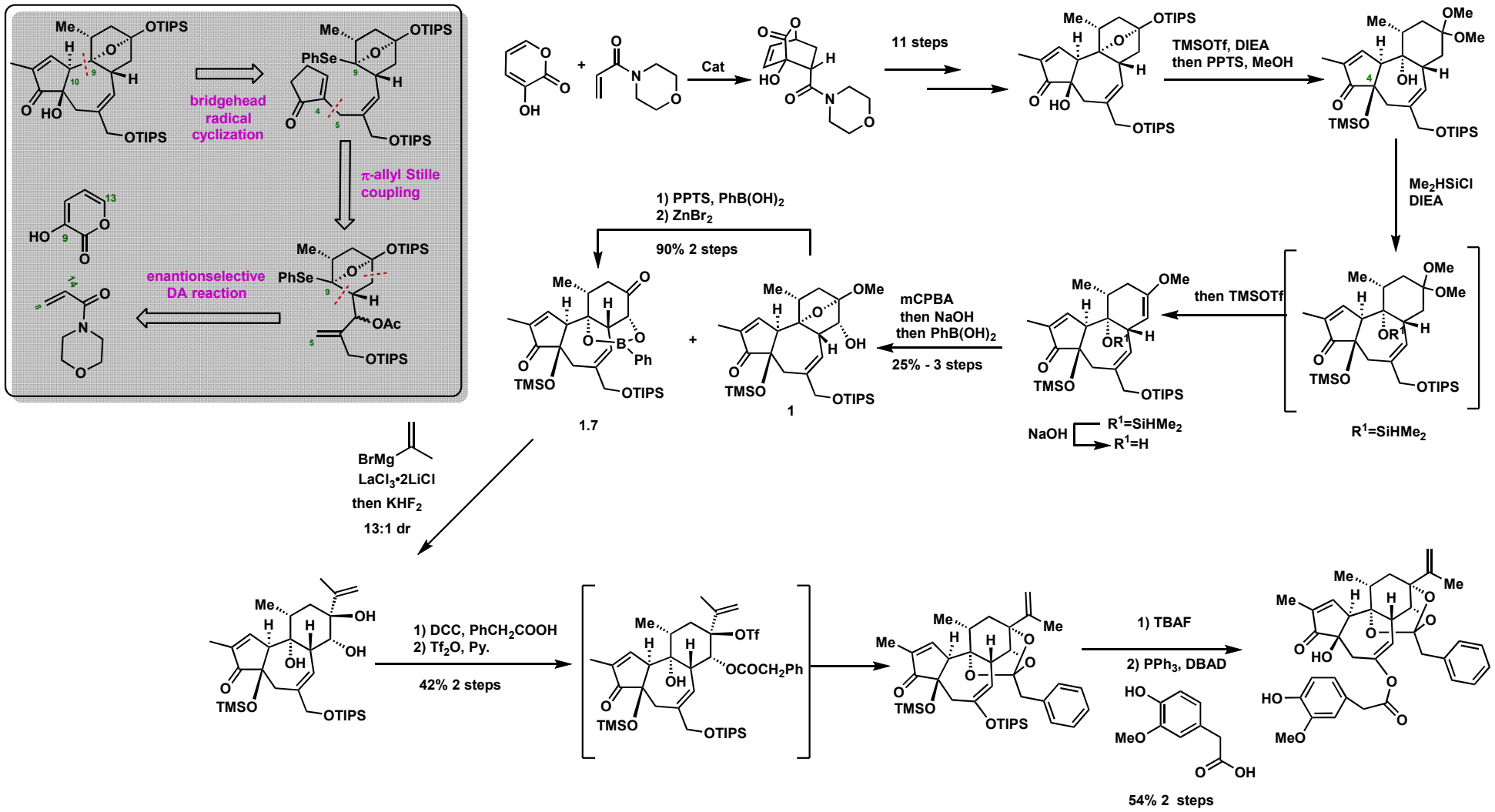


OTBS bulky group serve as a traceless stereocontroling factor,c_4,c_{10}

Inoue OL 2022,24,929-933

Inoue's work

JACS 2021,143,12387-12396



Maimone's work

JACS 2022,144,16332-15337