Total Synthesis of *Sarcandrolide J* and *Shizukaol D*

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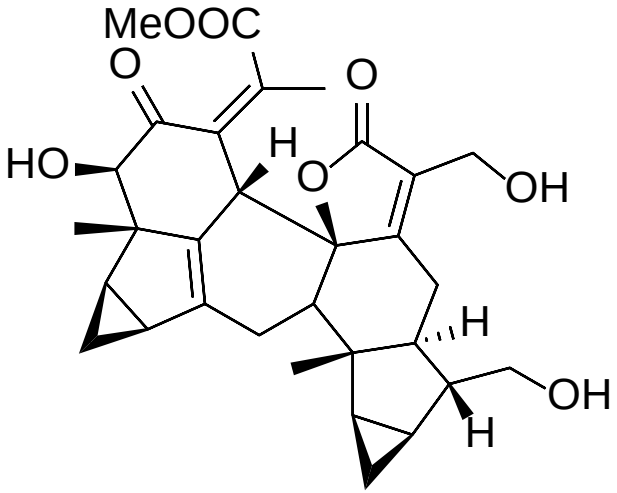
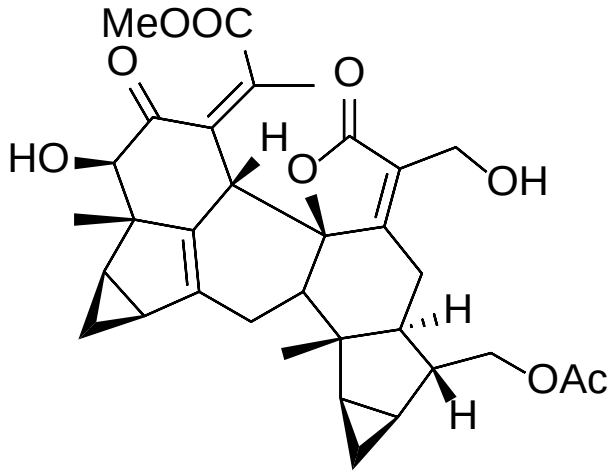
Angew. Chem. Int. Ed. **2017,** *56,* 637–640

Pohan Lin

Structure



sarcandrolide J



shizukaol D

Isolation & Biological Application

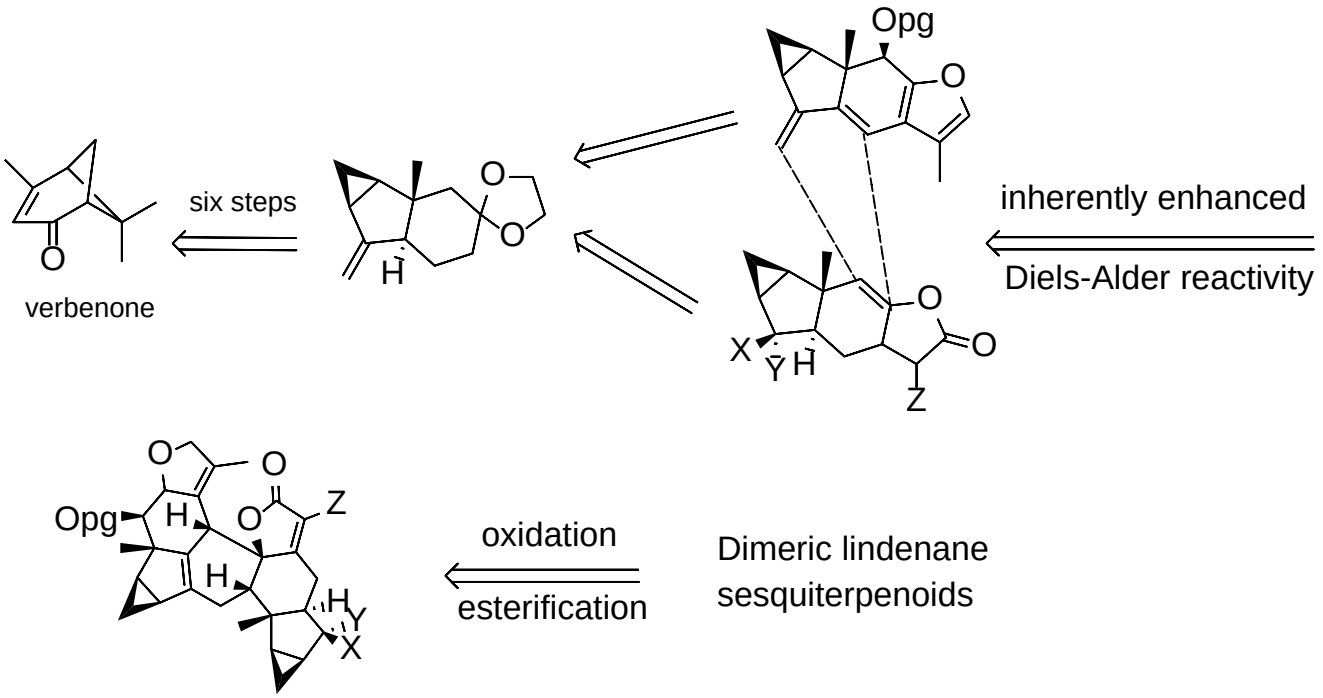
- Shizukaol D can activate AMP-activated protein kinase, increase ACC phosphorylation in HepG2 cells, and repress the growth of human liver cancer cells.
- Interestingly, sarcandrolide J shares the same
- molecular architecture as Shizukaol D, although they were isolated from *Sarcandra glabra* and *Chloranthus serratus*, respectively.

Isolation

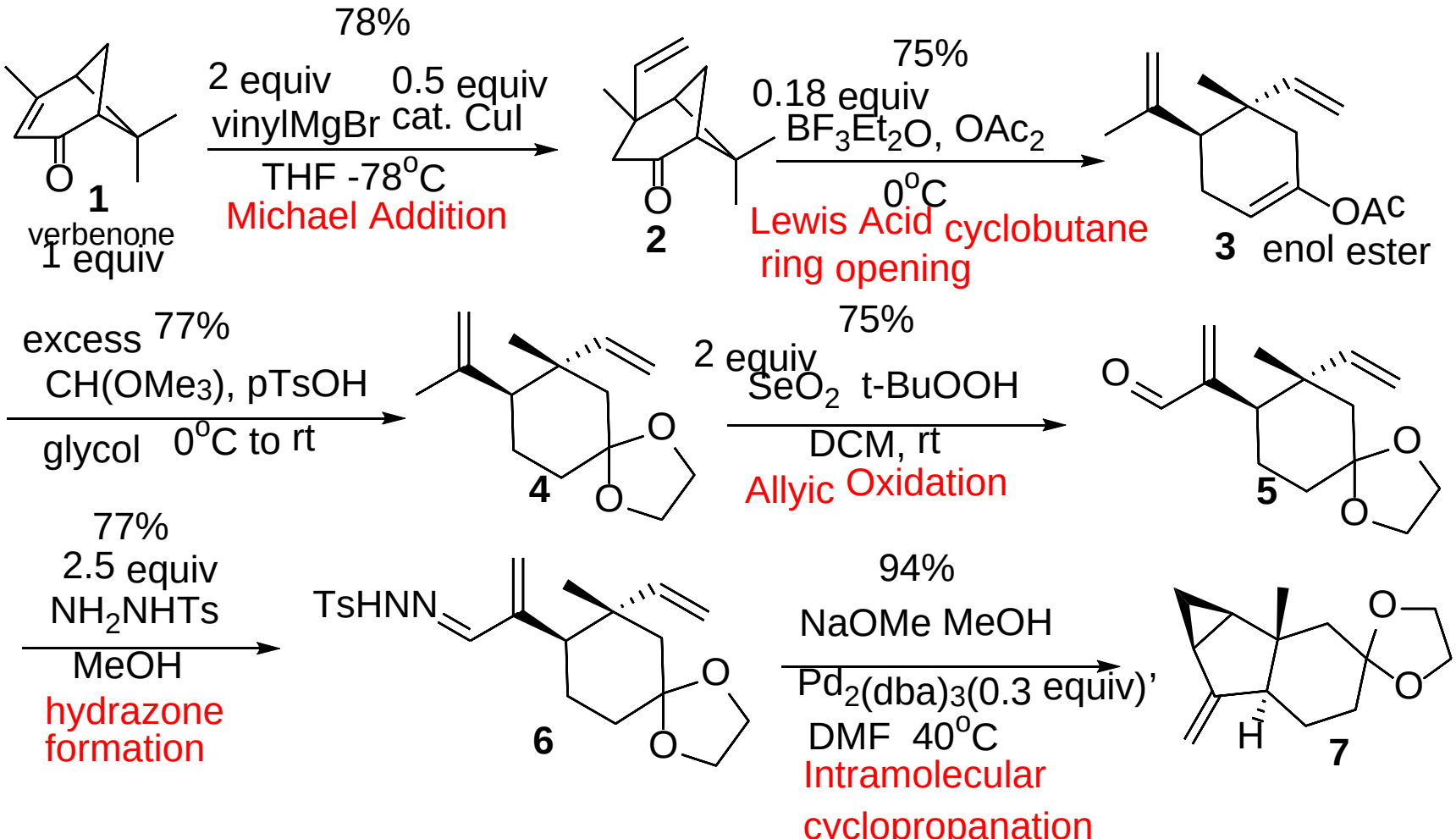
Sarcandra glabra

Chloranthus serratus

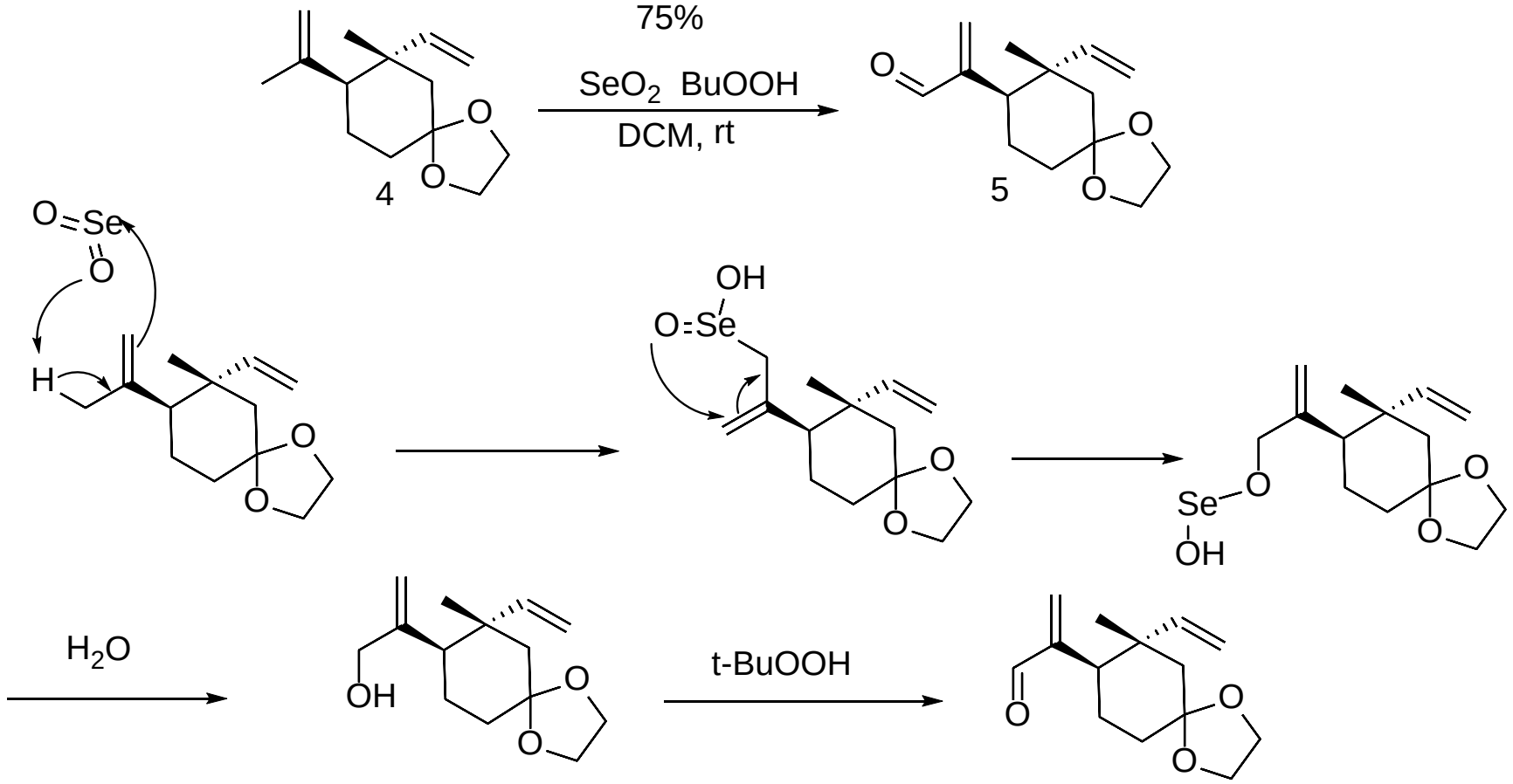
Retrosynthetic Analysis



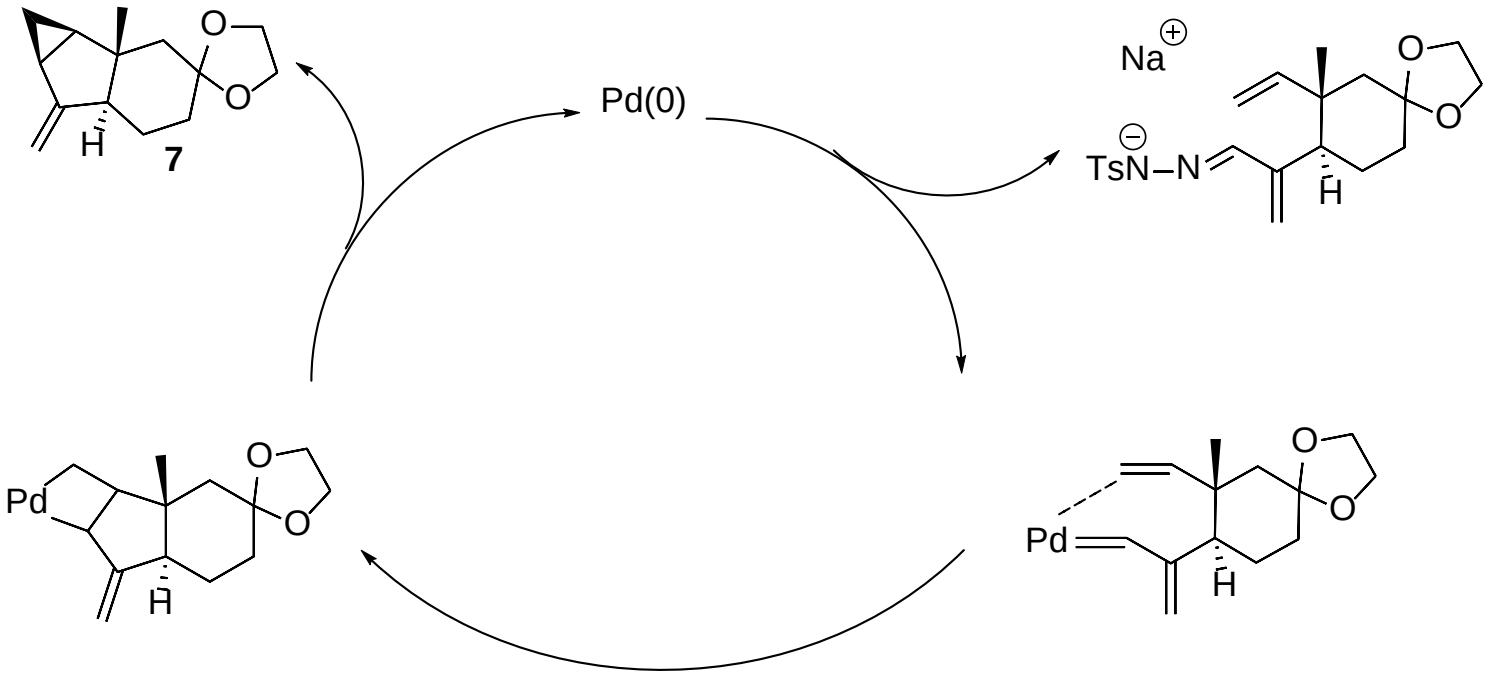
Precursor 7


78%
2 equiv vinylMgBr
0.5 equiv cat. CuI
THF -78°C
Michael Addition
1
verbenone
1 equiv
2
75%
0.18 equiv BF_3Et_2O, OAc_2
0°C
Lewis Acid cyclobutane ring opening
OAc
3 enol ester
excess $CH(OMe_3)$, pTsOH
glycol
77%
0°C to rt
4
75%
2 equiv SeO_2 t-BuOOH
DCM, rt
Allyic Oxidation
5
77%
2.5 equiv NH_2NHTs
MeOH
hydrazone formation
TsHNN
6
94%
NaOMe MeOH
$Pd_2(dba)_3$(0.3 equiv)'
DMF 40°C
Intramolecular cyclopropanation
H
7

Allyic Oxidation

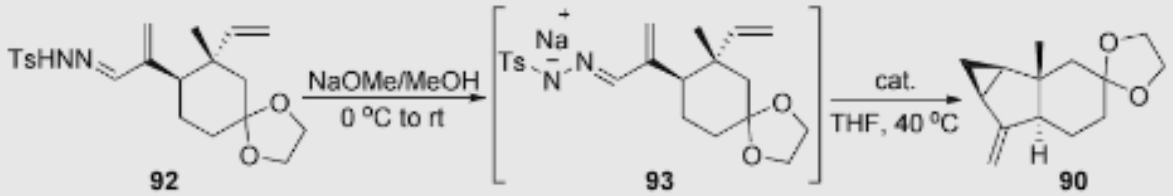


Cyclopropanation Mechanism



- *Chem. Commun.,* 2015,**51**, 6179-6182

TABLE 4 Optimization of Intramolecular Cyclopropanation of 92[a]



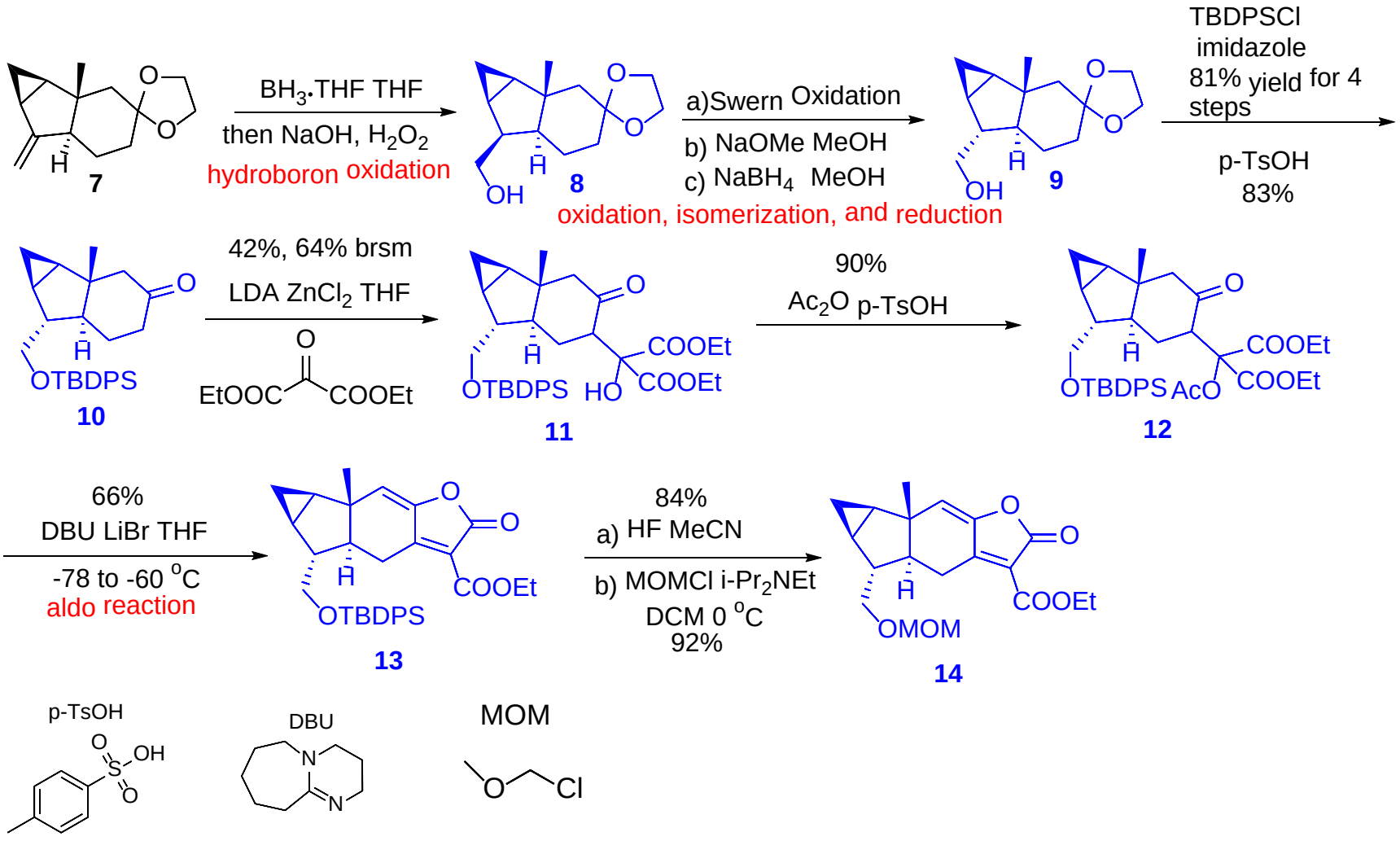
Entry	Base (1.5 eq)	Cat. (15 mol%)	Solvent	Yield (%)[b]
1	NaOMe	–	DMF	0
2	NaOMe	AgOTf[c]	DMF	0
3	NaOMe	$Cu(acac)_2$[c]	DMF	0
4	NaOMe	Ir(cod)Cl[c]	DMF	37
5	NaOMe	$Rh_2(OAc)_4$	DMF	63
6	NaOMe	$Pd(cod)Cl_2$[c]	DMF	55
7	NaOMe	$Pd(MeCN)_2Cl_2$[c]	DMF	48
8	NaOMe	$Pd_2dba_3 \cdot CHCl_3$	DMF	73
9	NaOMe	$Pd(dba)_2$	DMF	42
10	NaOMe	$Pd(PPh_3)_4$	DMF	0
11	**NaOMe**	**Pd_2dba_3**	**DMF**	**81**
12	NaOMe	Pd_2dba_3[d]	DMF	45
13	**NaOMe**	**Pd_2dba_3**[e]	**DMF**	**88**

14	NaH[f]	Pd_2dba_3	DMF	65
15	NaHMDS[f]	Pd_2dba_3	DMF	49
16	KHMDS[f]	Pd_2dba_3	DMF	63
17	LiHMDS[f]	Pd_2dba_3	DMF	52
18	NaOMe	Pd_2dba_3	DMA	36
19	NaOMe	Pd_2dba_3	NMP	55
20	NaOMe	Pd_2dba_3	Ether	31
21	**NaOMe**	**Pd_2dba_3[e]**	**THF**	**65**
21	NaOMe	Pd_2dba_3	DCM	50
22	NaOMe	Pd_2dba_3	Toluene	39

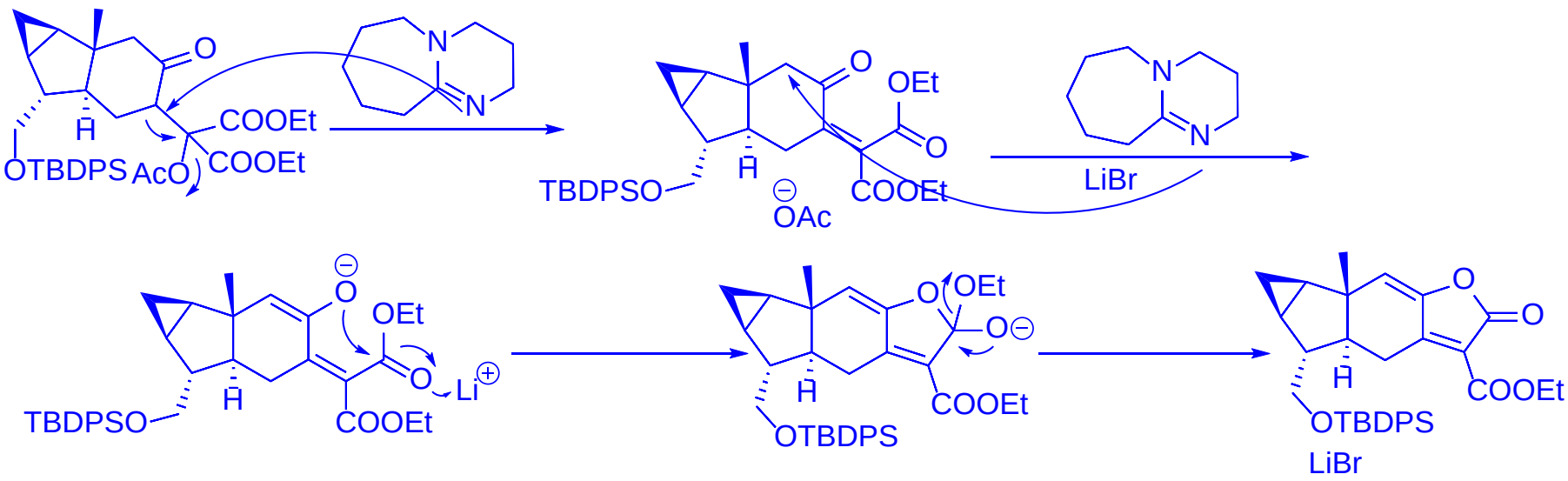
*[a]Conditions: (1) **92** base/MeOH, 5 min at 0 °C then 15 min at rt, remove solvent; (2) 15 mol% metal catalyst, DMF, 35 °C, TLC monitoring until full conversion of **92**.*
*[b]Isolated yield of **90**.*
[c]30 mol%.
[d]7 mol%.
[e]50 mol%.
[f]THF was used instead of MeOH.

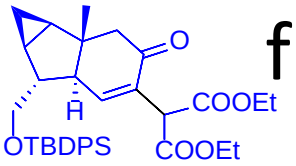
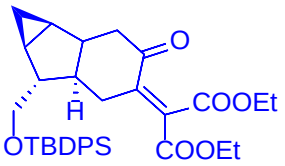
Chem. Commun., 2015,**51**, 6179-6182

Precursor 14

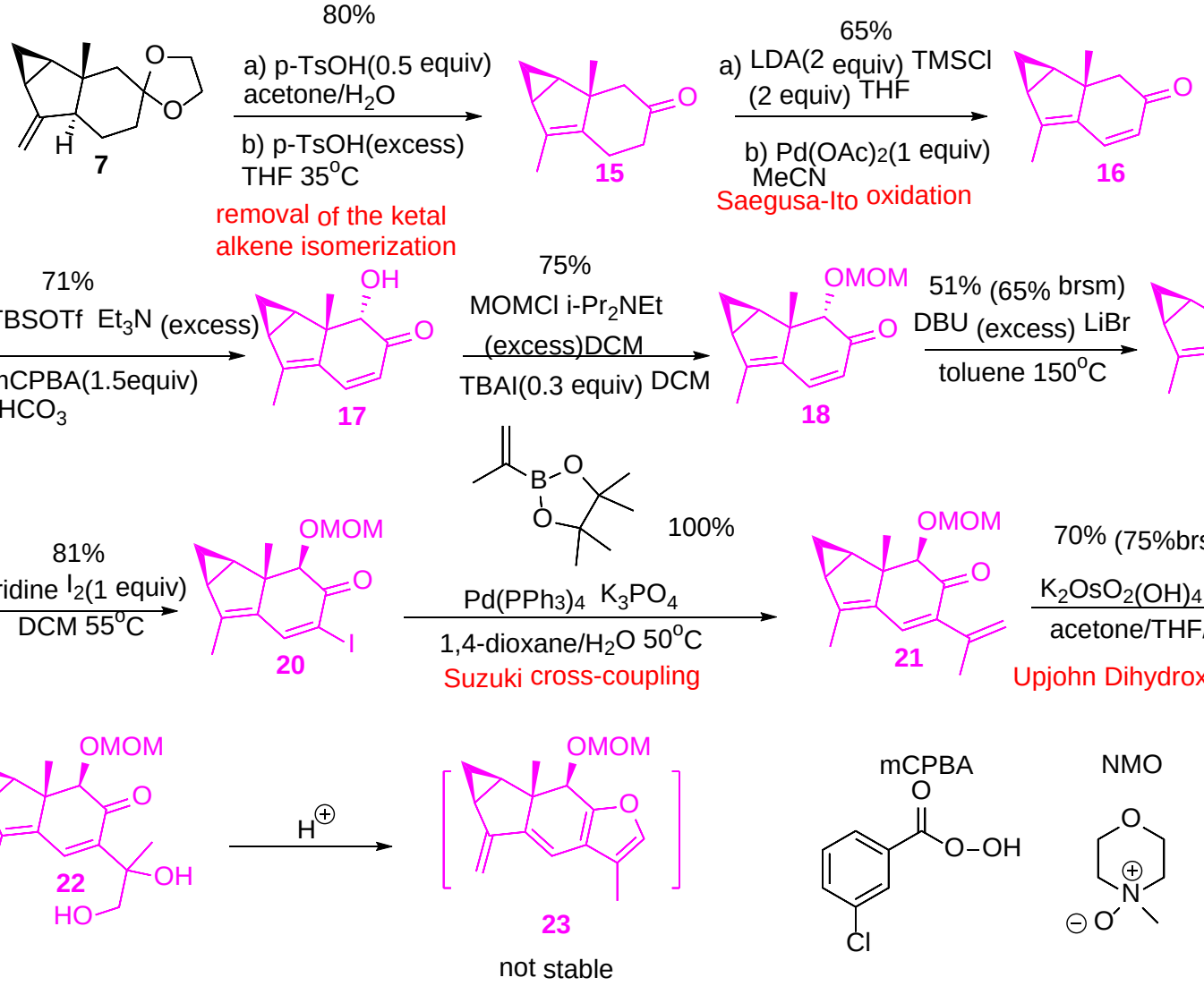


Ring formation Mechanism

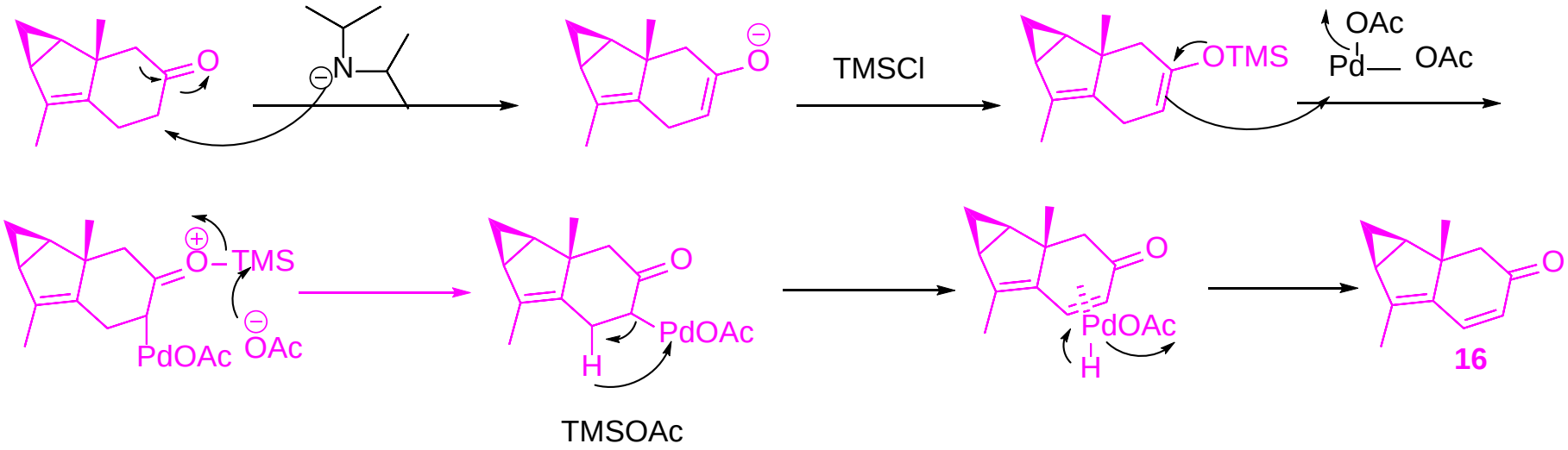


The presence of LiBr is crucial to avoid the competitive formation of  from  .

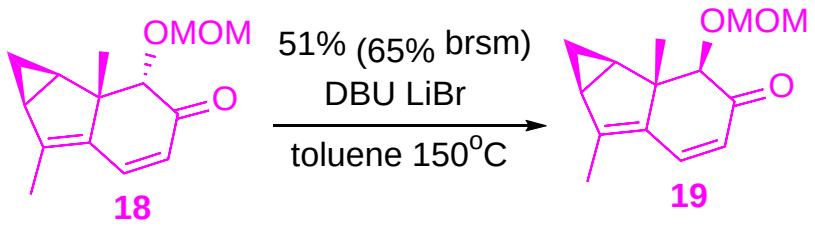
Precursor 22



Saegusa-Ito oxidation
Atsushi Nishida Modification

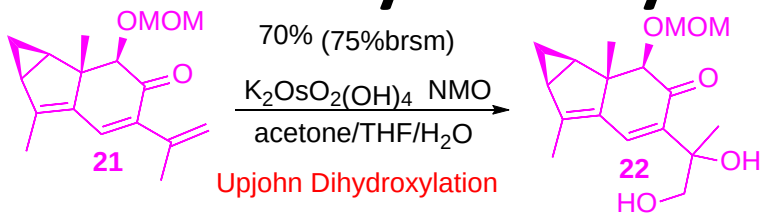


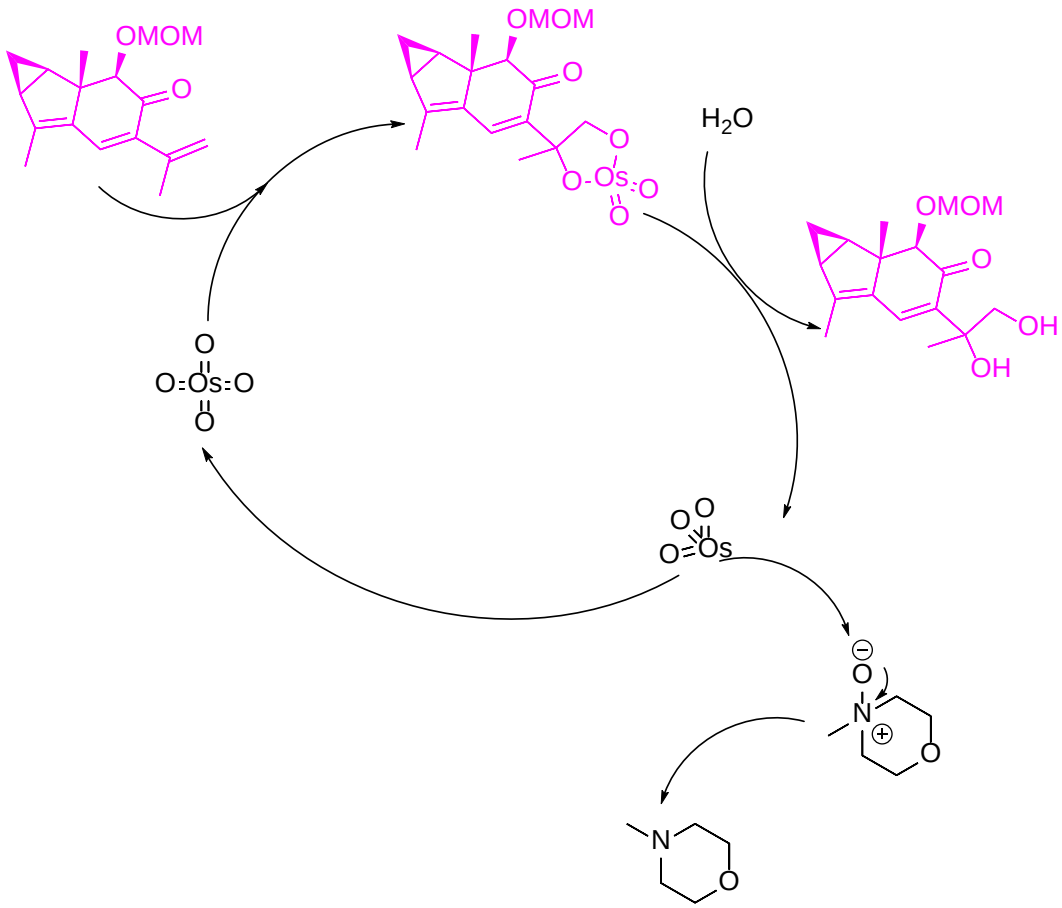
Stereochemistry Inversion



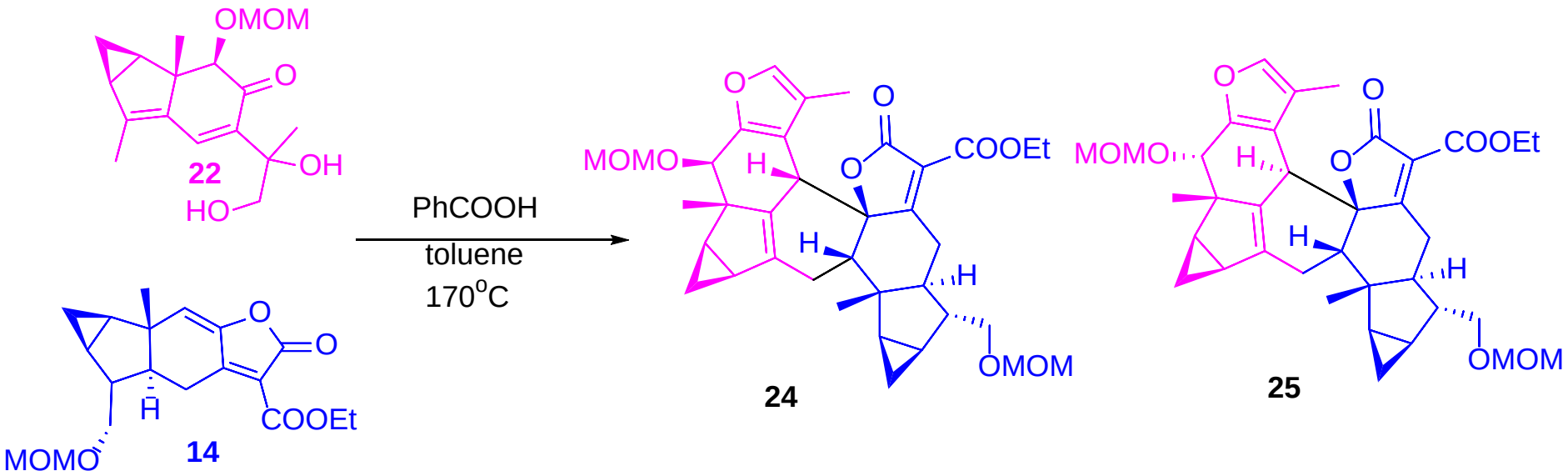
- 18 was subjected to thermal conditions in the presence of both DBU and LiBr to achieve equilibrium.
- The presence of a catalytic amount of a lithium salt (20 mol%) was essential. Otherwise, only trace amounts of 19 could be obtained, even with 10 equivalents of DBU

Upjohn Dihydroxylation

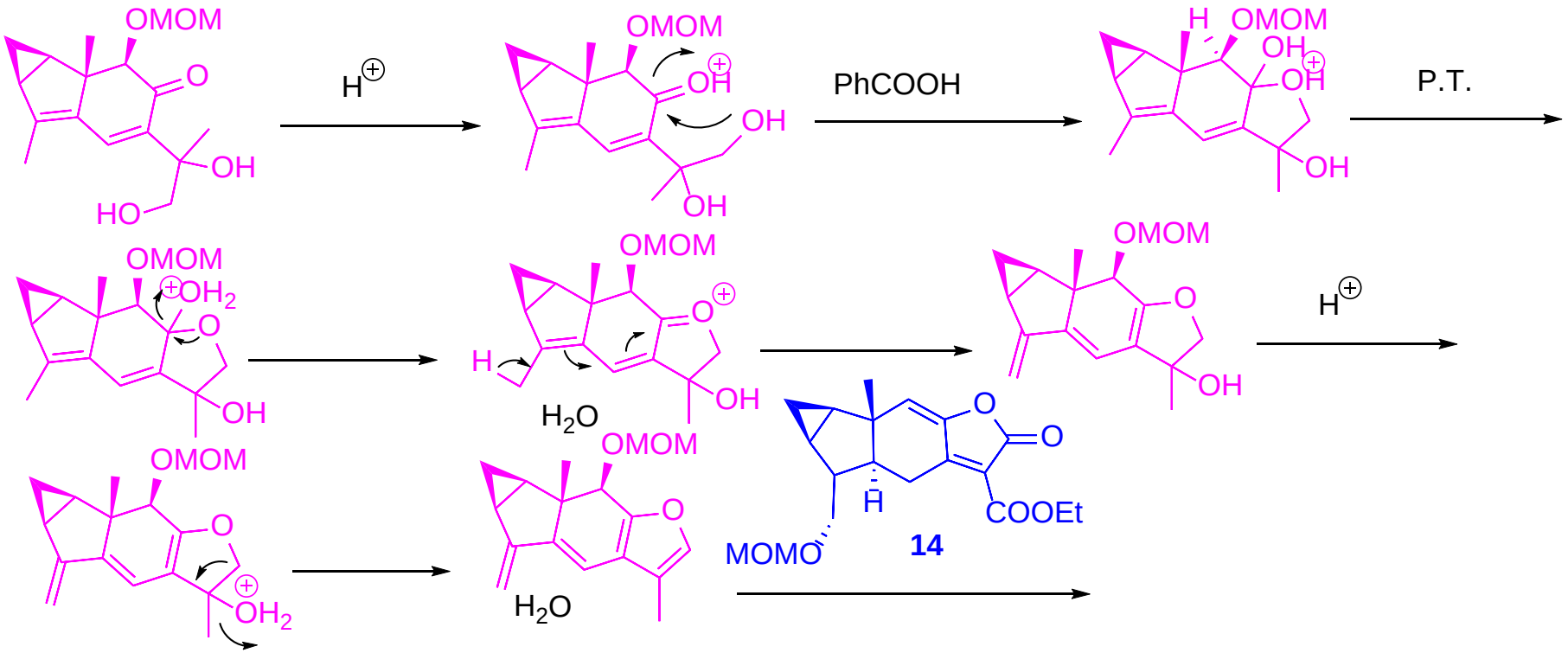




Diels-Alder[4+2]

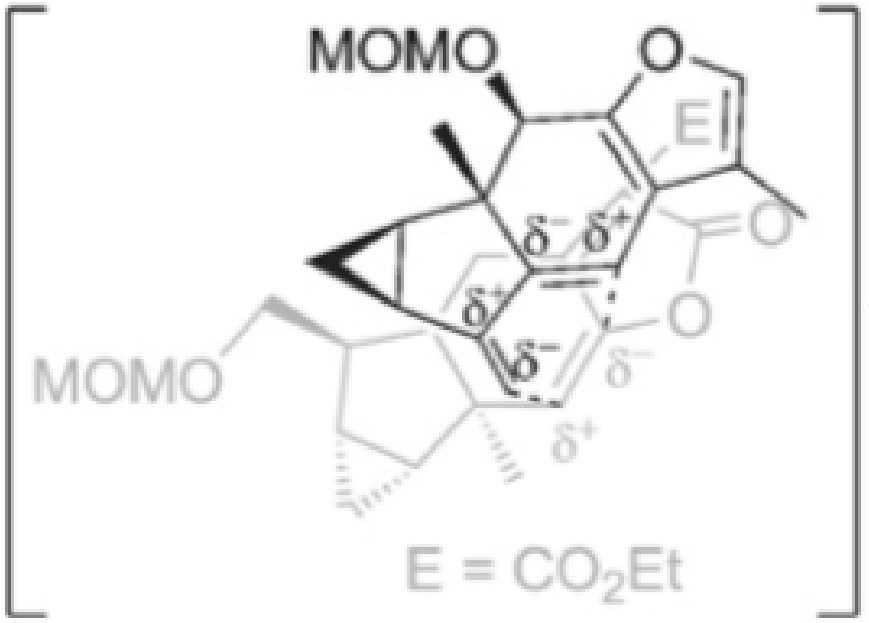


Mechanism of the product 24



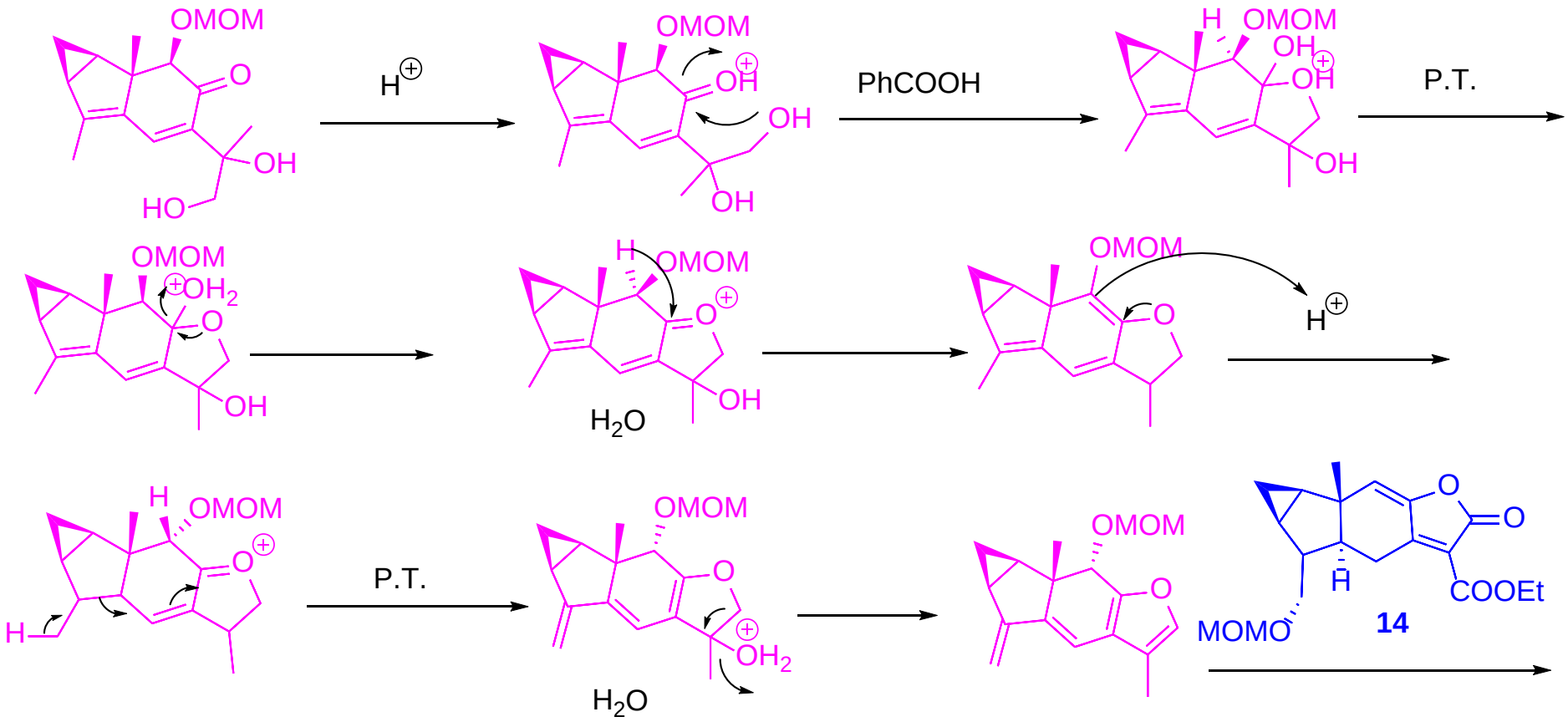
Mechanism of the product 24

endo-type Diels-Alder



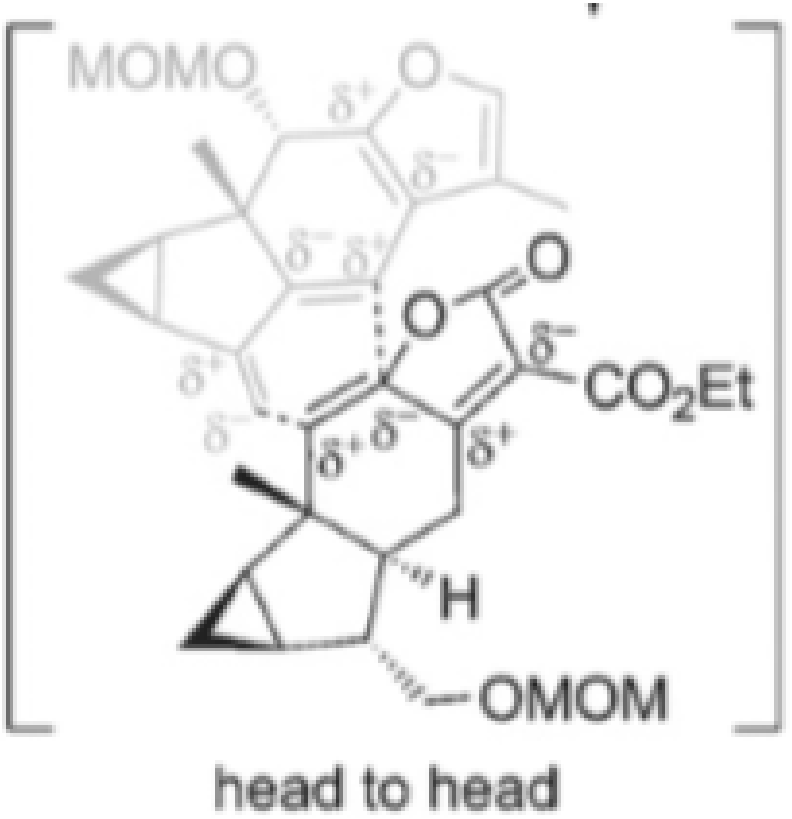
head to head

Mechanism of the product 25

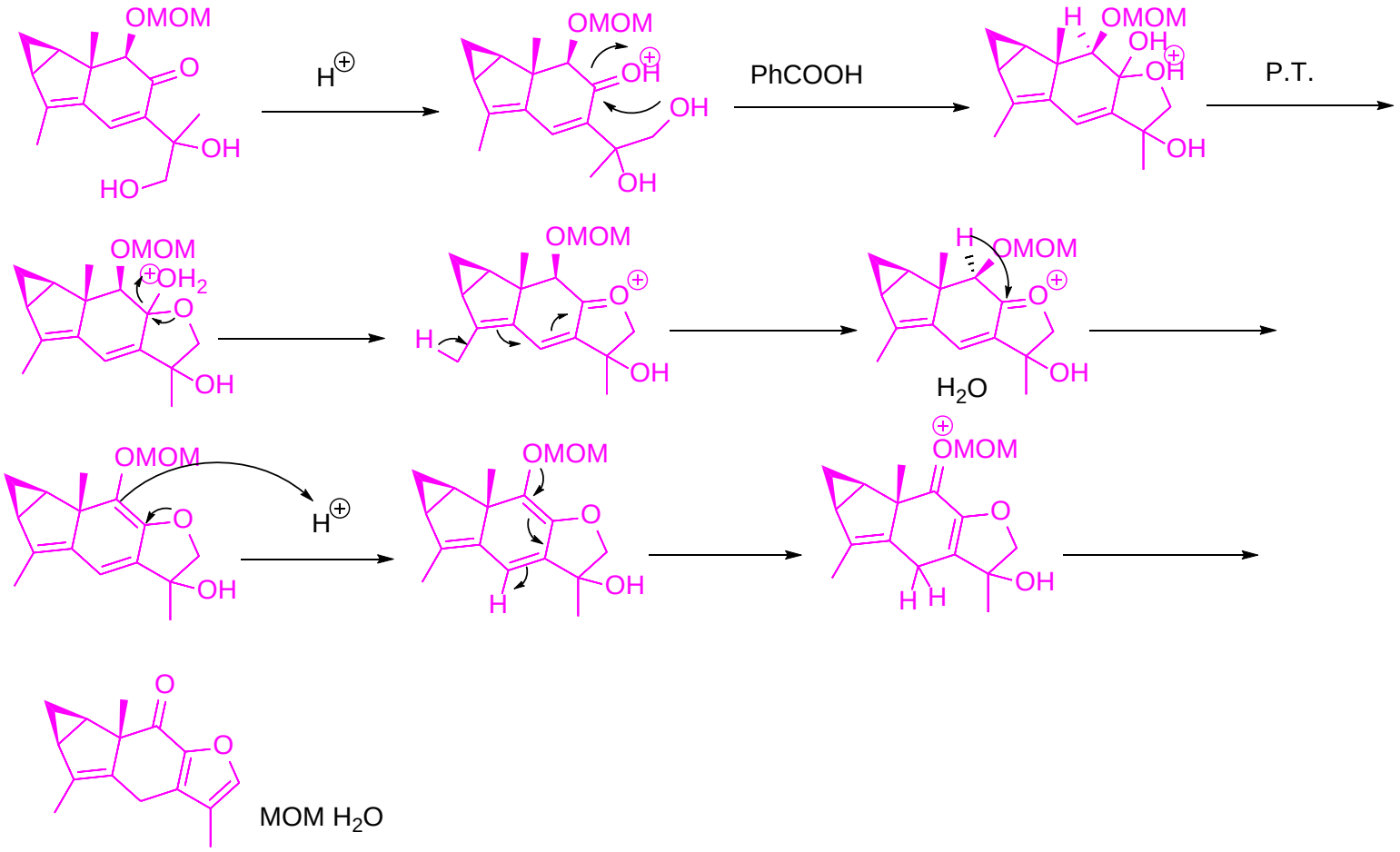


Mechanism of the product 25

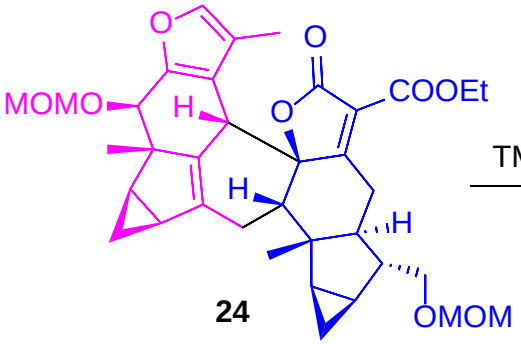
exo-type Diels-Alder



Another Byproduct Mechanism



Final steps

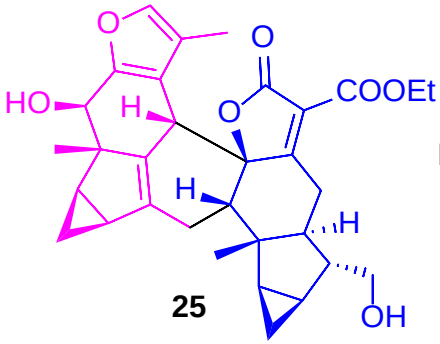


24

70%

TMSBr(excess) DCM

-60 to -45°C

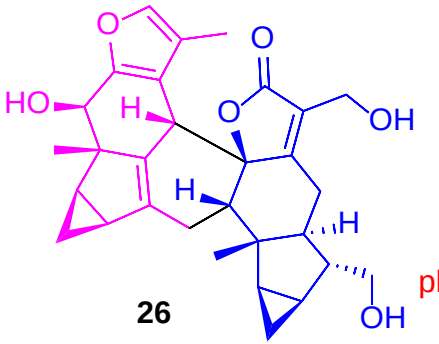


25

89%

$LiEt_3BH$(10 equiv)

-35°C



26

47%

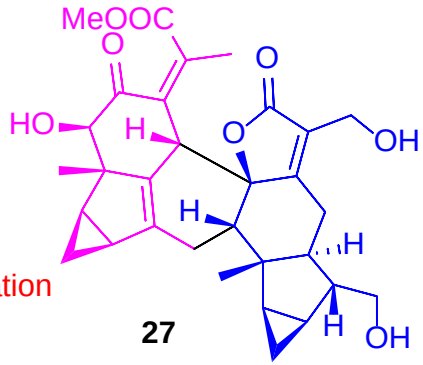
TPP, iPr_2NEt O_2

DCM, hv -78°C

then $TMSCHN_2$

MeOH

photo-triggered oxidation



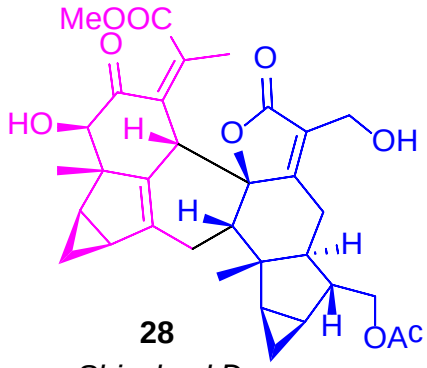
27

Sarcandrolide J

31%(49%brsm)

imidazole

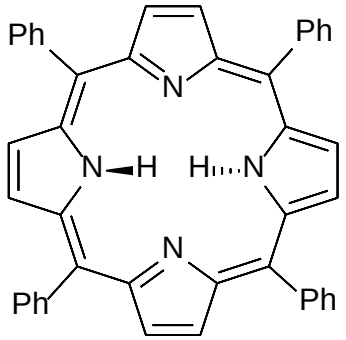
Ac_2O (excess)DCM



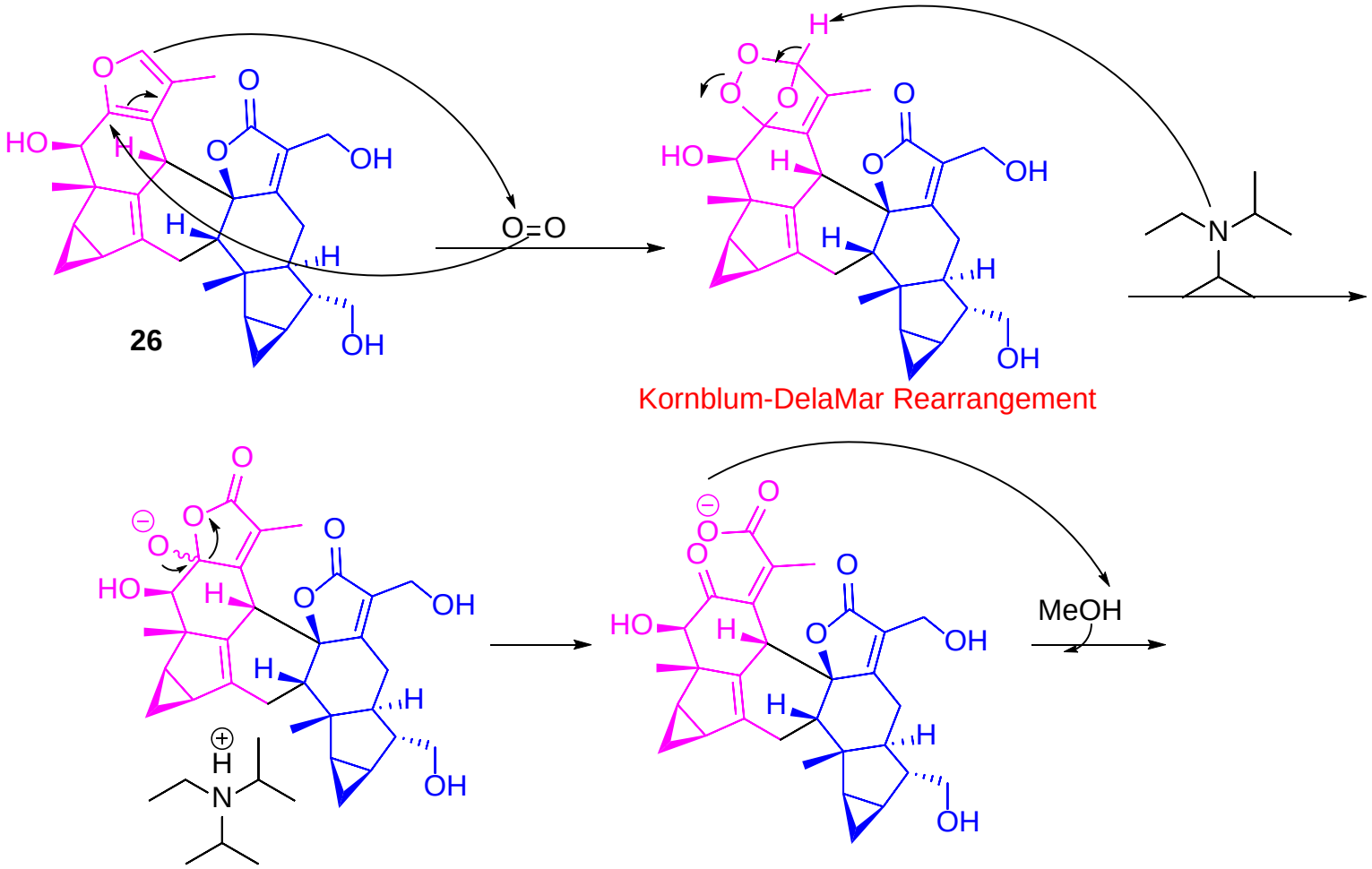
28

Shizukaol D

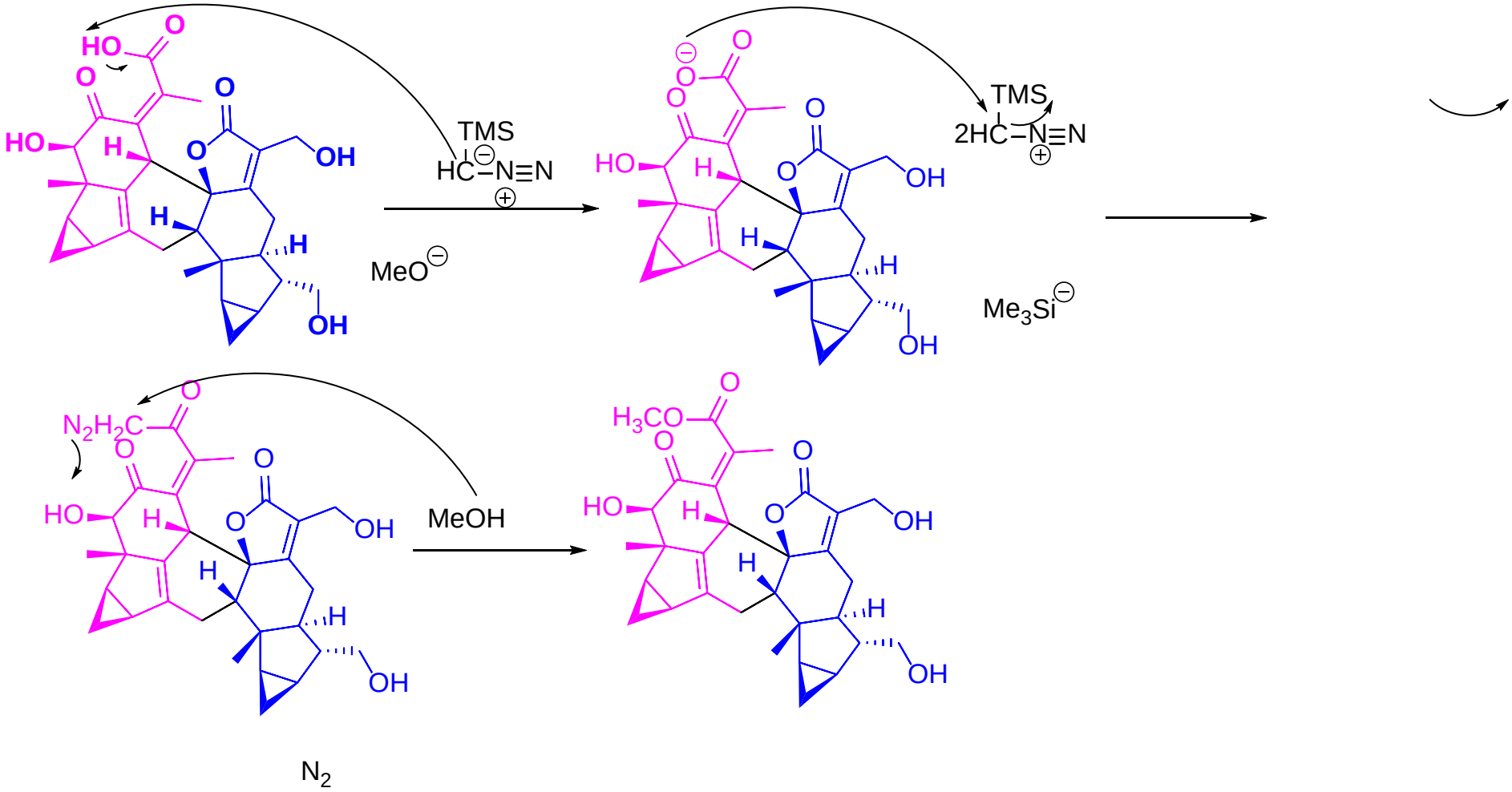
TPP



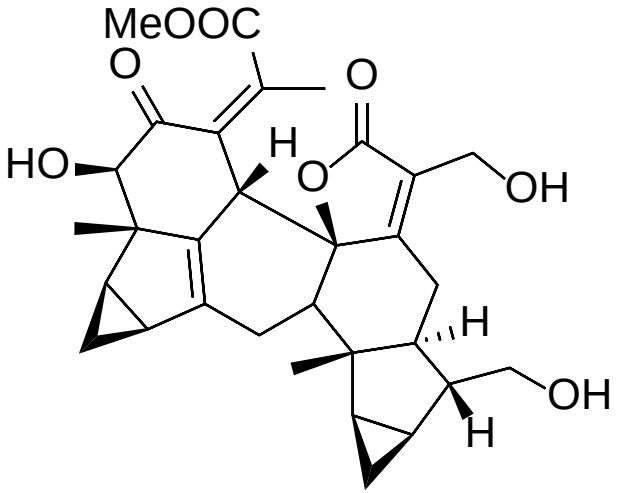
Mechanism of the furan ring opening



Mechanism of the furan ring opening

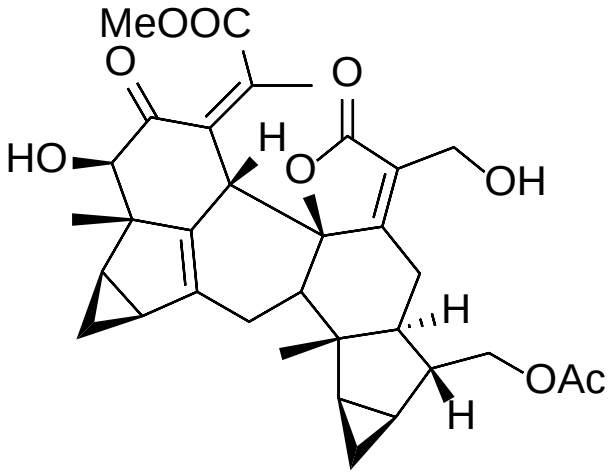


Overall Yield



sarcandrolide J

1.008%



shizukaol D

0.665%

- Thank You!