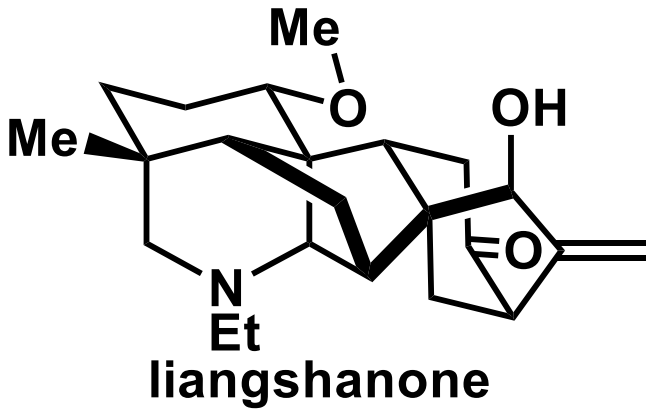
Total Synthesis of Liangshanone

Hong-Xiu Huang, Fen Mi, Chunxin Li, Huan He, Feng-Peng Wang, Xiao-Yu Liu,* and Yong Qin*

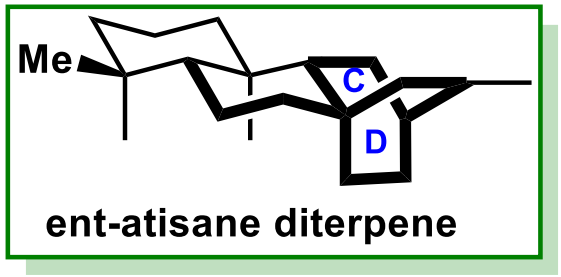


liangshanone

- OD/DA sequence
- Alkene cleavage/Mannich
- Robinson-type annulation
- Aldol addition

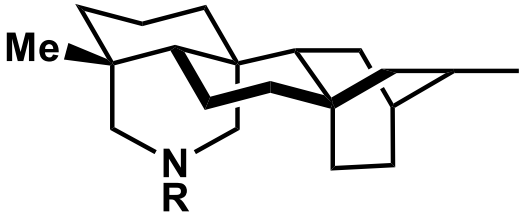
Angew. Chem. Int. Ed. 10.1002/anie.202011923

A) Diterpenoid alkaloids derived from *ent-atisanes* [total synthesis: *well-studied*]

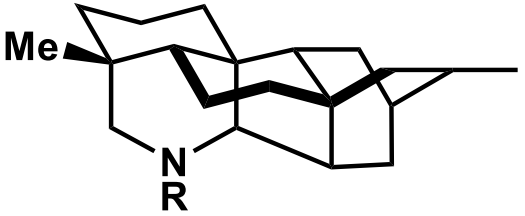


ent-atisane diterpene

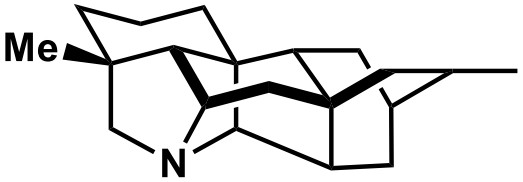
bicyclo[2.2.2]octane C/D rings



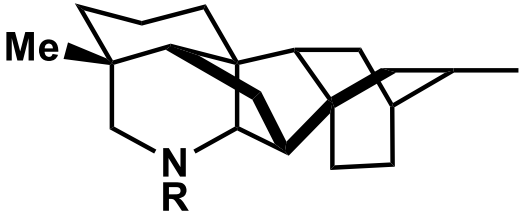
atisine skeleton



hetidine skeleton

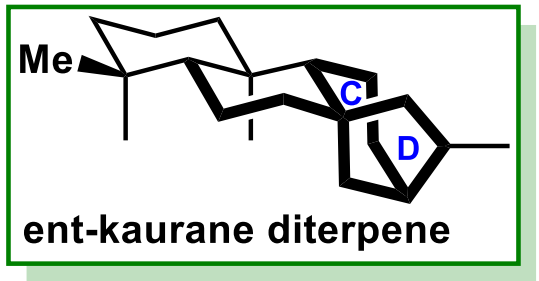


hetisine skeleton



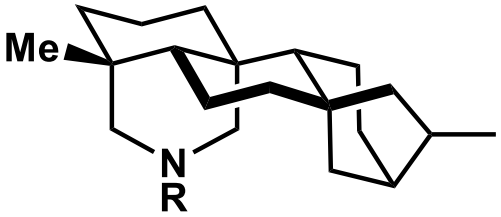
denudatine skeleton

B) Diterpenoid alkaloids derived from *ent-kauranes* [total synthesis: *underexplored*]

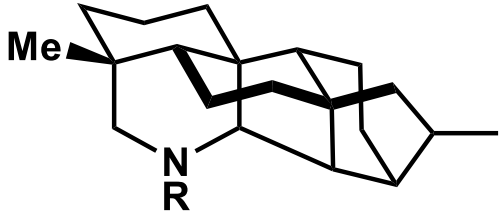


ent-kaurane diterpene

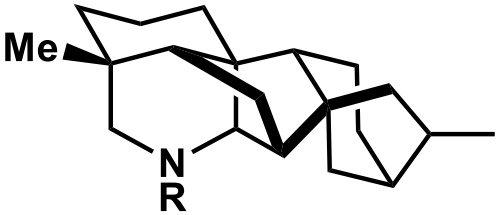
bicyclo[3.2.1]octane C/D rings



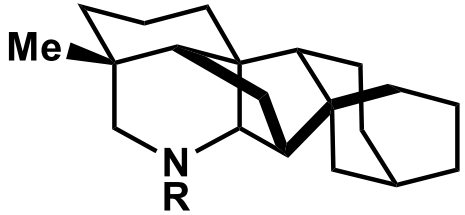
veatchine skeleton



anopterine skeleton

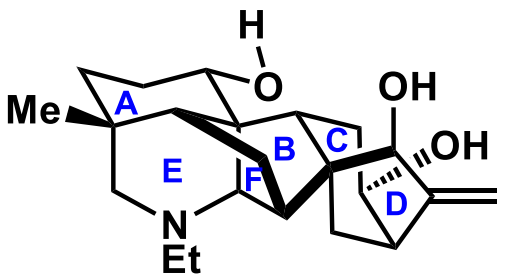


napelline skeleton

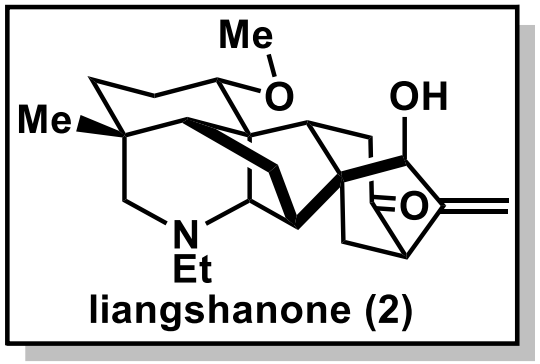


aconicarmisulfonine skeleton

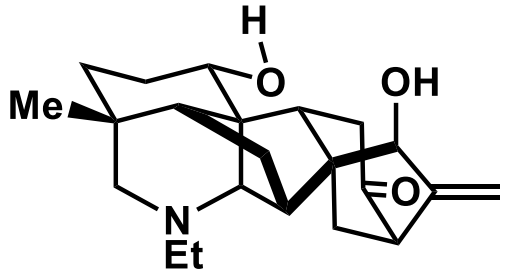
C) Selected members of the napelline-type C_{20}-diterpenoid alkaloids



napelline (1)



liangshanone (2)



songorine (3)

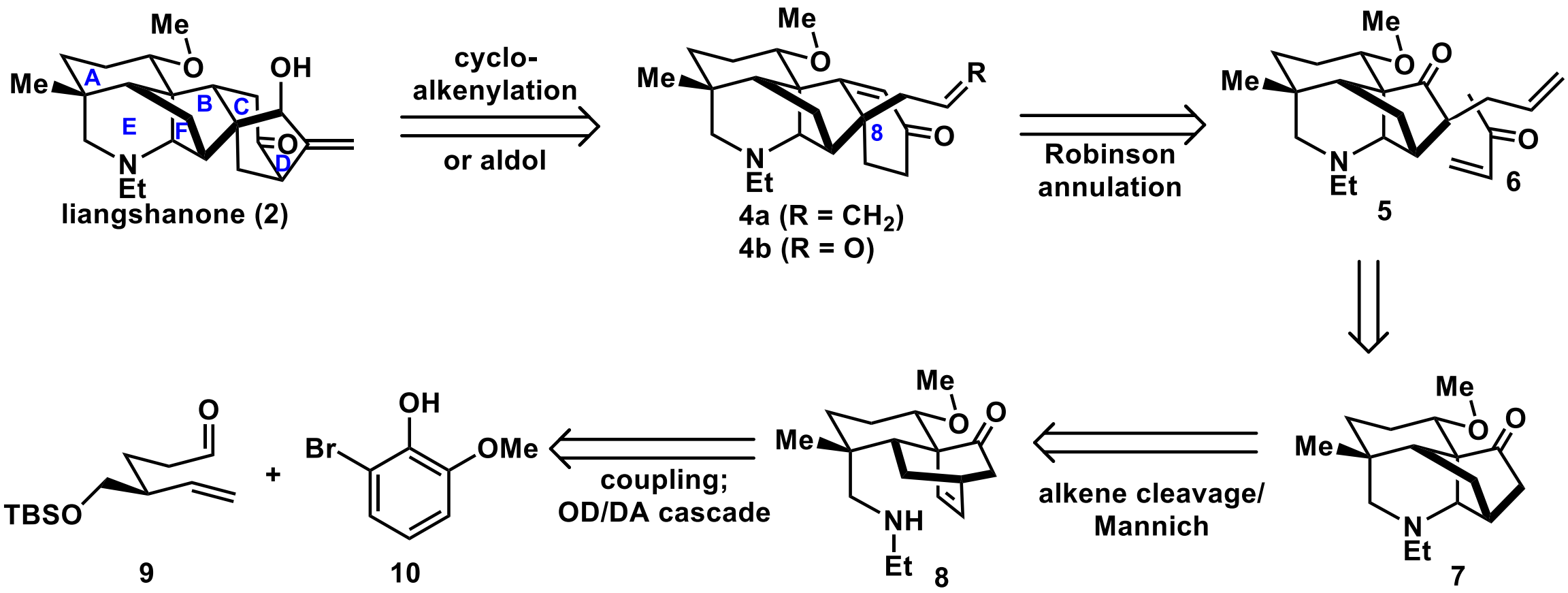
Compact hexacyclic framework：

- an azabicyclo[3.3.1] nonane (A/E rings),
- a bicyclo[2.2.1]heptane (B/F rings),
- and a bicyclo[3.2.1]octane (C/D rings) moieties.

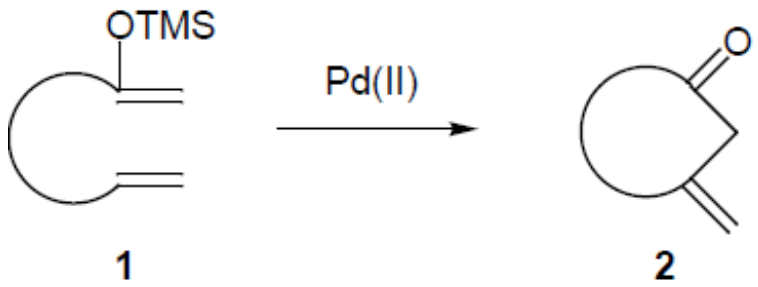
A wide spectrum of pharmacological effects：

- antiarrhythmic,
- anti-inflammatory,
- anti-nociceptive,
- anxiolytic activities.

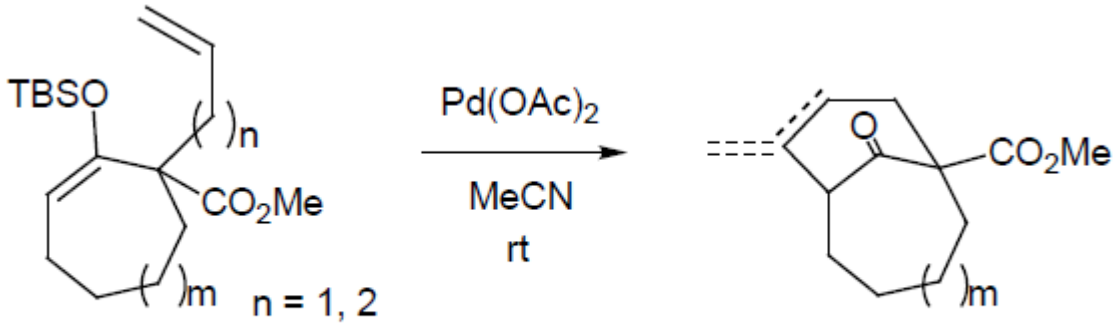
Retrosynthetic analysis of liangshanone (2).



Intramolecular cycloalkenylation



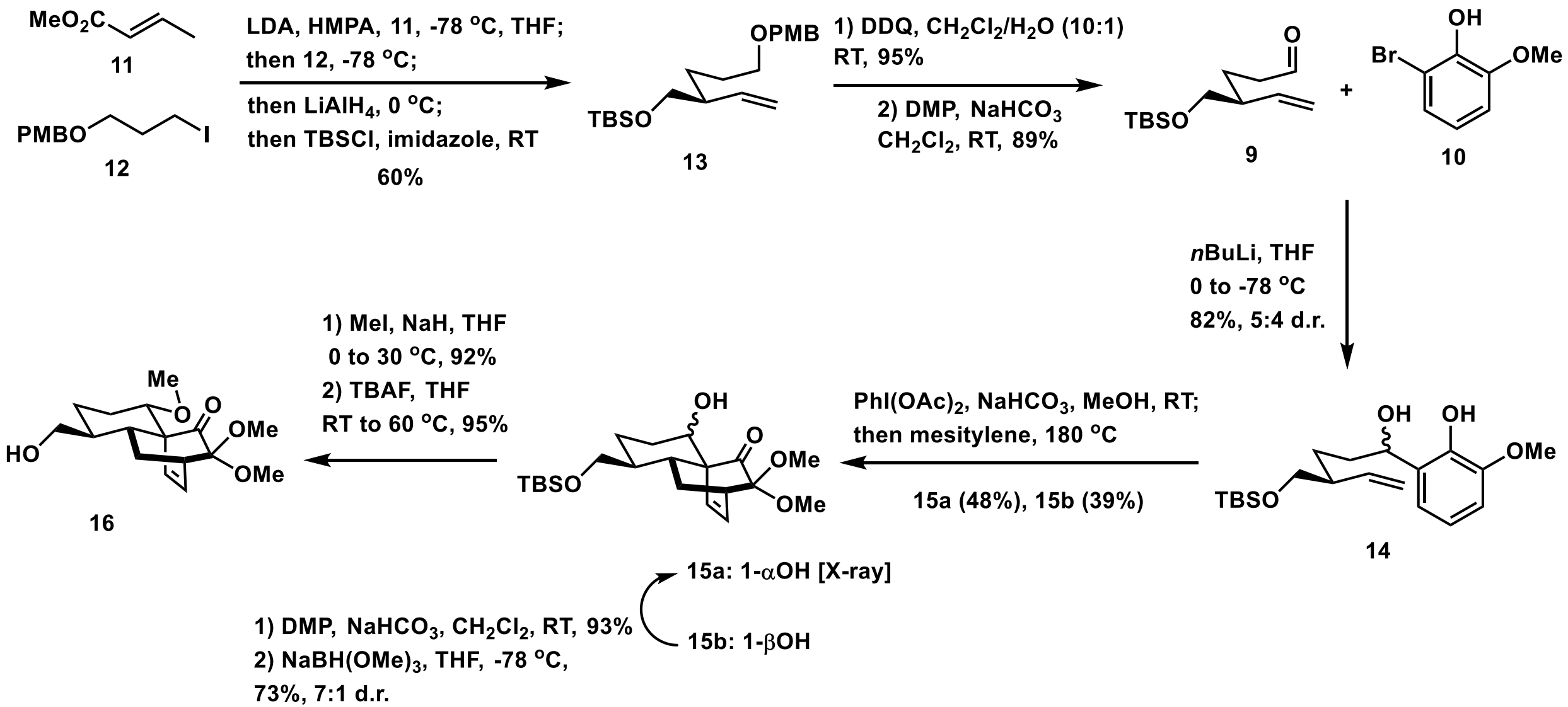
1 2

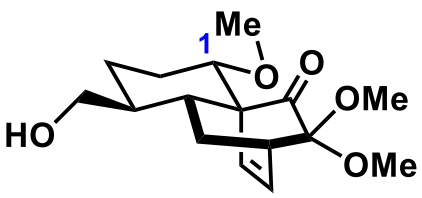


n = 1, 2
m =1, 2 and 7

30 31

Construction of the A/B/E/F tetracycle 7.

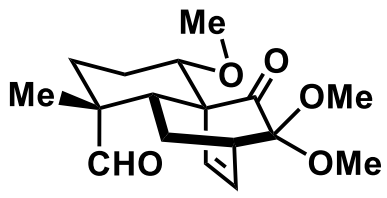




16

1) DMP, $NaHCO_3$
CH_2Cl_2, RT, 90%

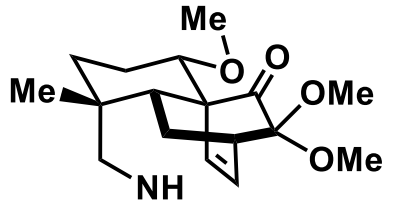
2) MeI, *t*BuOK
THF, -10 °C, 80%



17

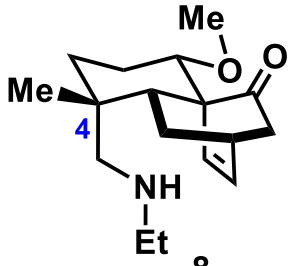
$EtNH_2$•HCl, Et_3N
HOAc, MeCN, RT;

then $NaBH_3CN$
RT, 88%



18

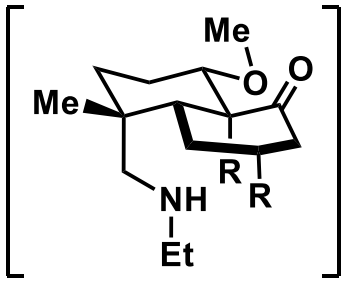
SmI_2, MeOH
THF, 0 °C, 93%



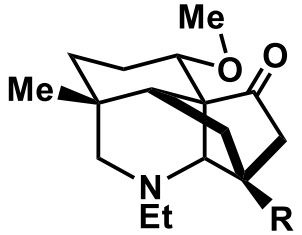
8

TFA, O_3, -78 °C, CH_2Cl_2;
then PPh_3, 0 °C;

then *t*BuNH_2, RT, 80%



19
R = CHO



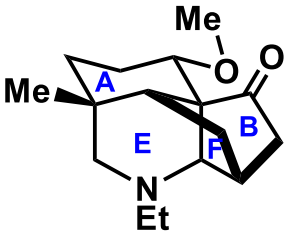
20a (R = CHO)

20b (R = COOH) [X-ray]

$NaClO_2$, NaH_2PO_4
2-methyl-2-butene
*t*BuOH/H_2O (1:1),
RT, 95%

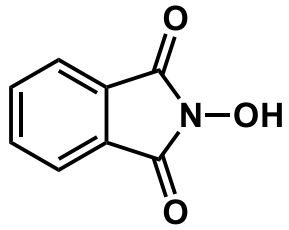
NHPI, DIC, DMAP, CH_2Cl_2, RT;
then Zn, $NiCl_2$•$6H_2O$/di-*t*Bubipy,

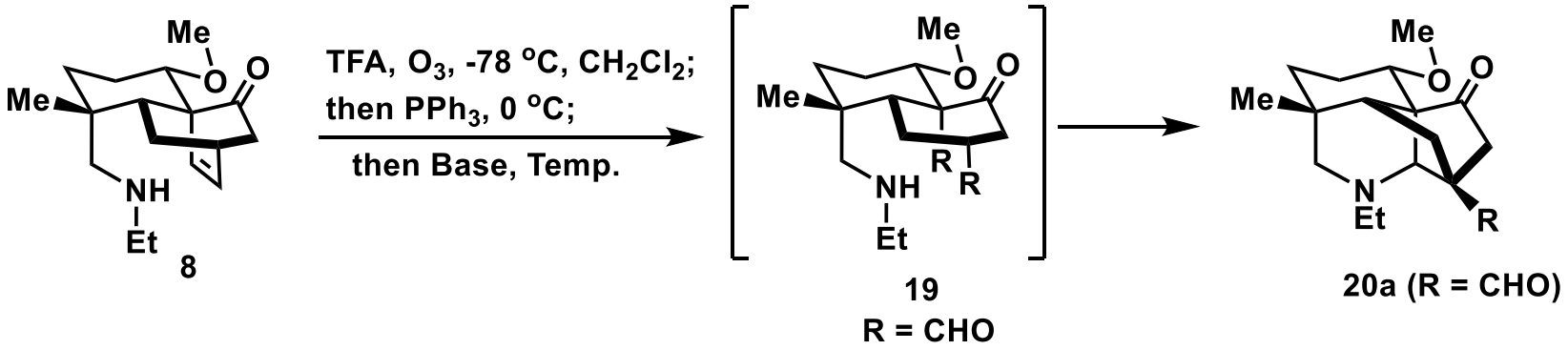
$PhSiH_3$, DMF, THF, 50 °C, 53%



7

NHPI:

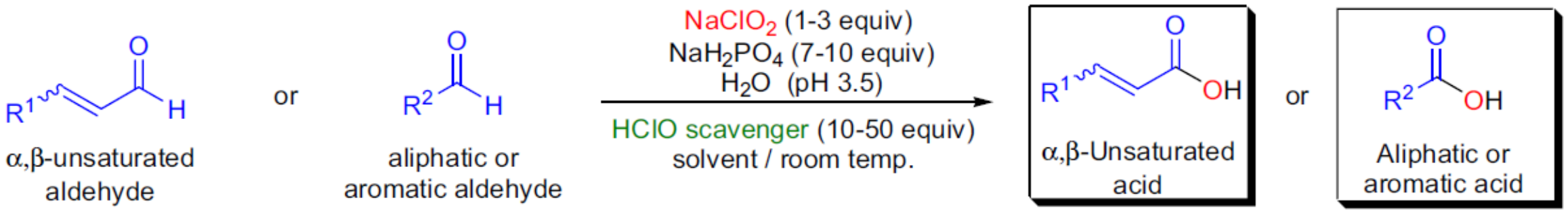




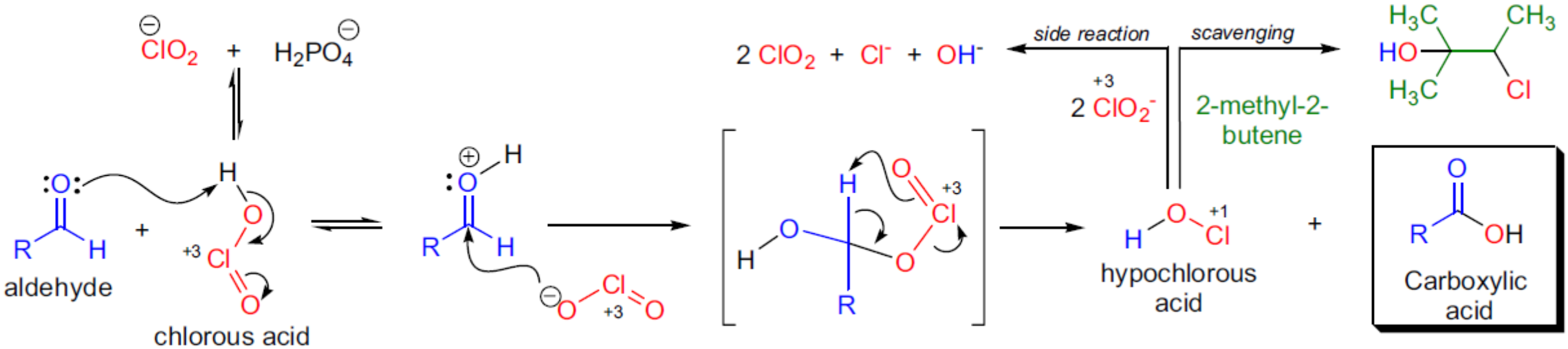
Entry	Acid	Base	Temperature	Yield%[b]
1	--	Et_3N	60 °C	trace
2	TFA	Et_3N	60 °C	28%
3	TFA	iPr_2NH	60 °C	24%
4	TFA	Na_2SO_3	60 °C	23%
5	TFA	TMG	60 °C	63%
6	TFA	DABCO	60 °C	52%
7	TFA	$tBuNH_2$	60 °C	72%
8	TFA	$tBuNH_2$	RT	80%

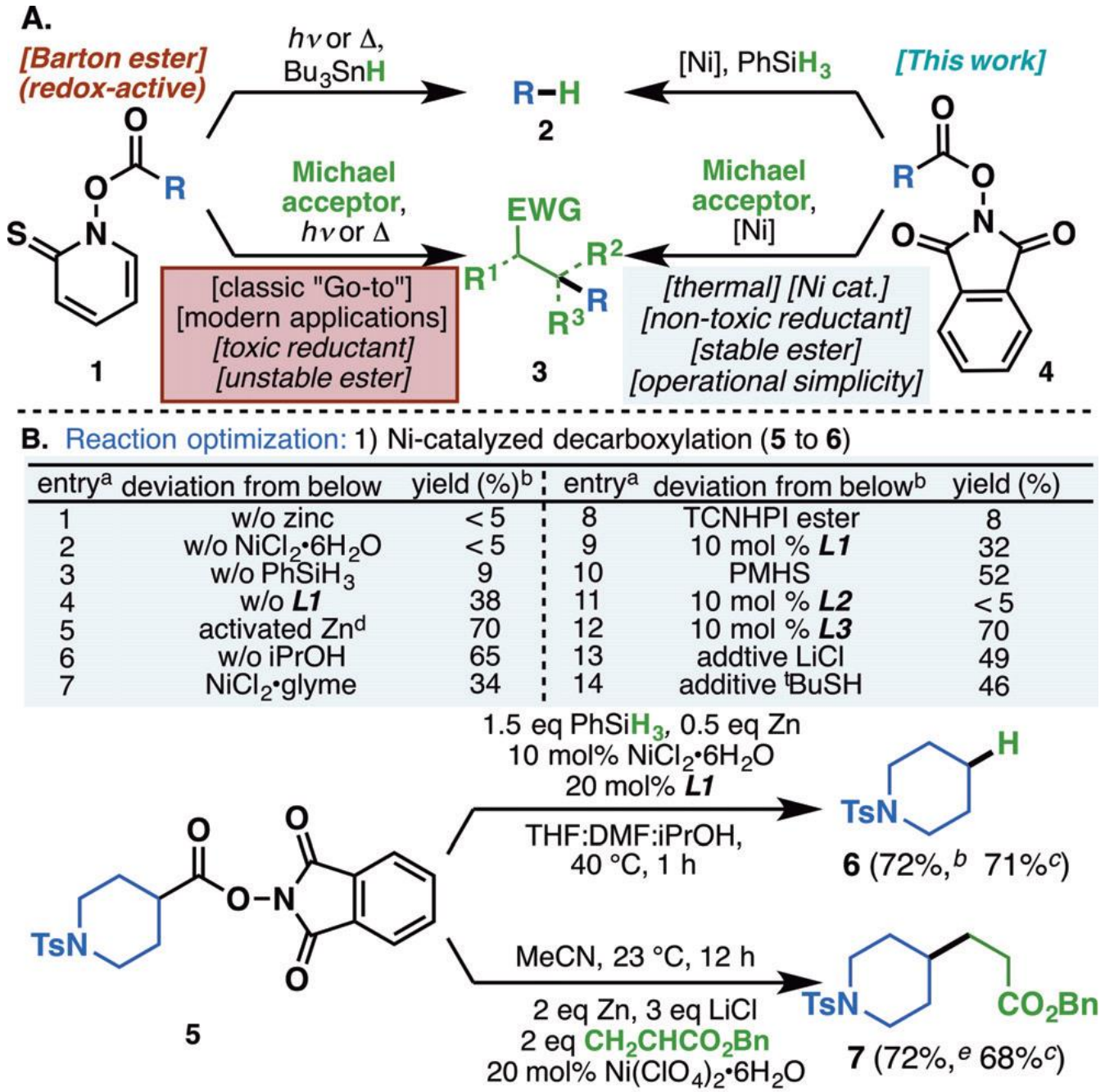
[a]Unless otherwise noted, reactions were performed with **8** (30 mg, 0.108 mmol, 1 eq), TFA (40 μL, 0.541 mmol, 5eq), PPh_3 (56.9 mg, 0.217 mmol, 2 eq) and base (1.08 mmol, 10 eq) in CH_2Cl_2 (30 mL) .[b] Yield of isolated product.

Pinnick oxidation



R^1 = H, alkyl, aryl, alkenyl, allyl; R^2 = alkyl, aryl, allyl, homoallyl; scavenger = 2-methyl-2-butene, H_2O_2, H_2NSO_3H, *m*-$C_6H_4(OH)_2$, DMSO; solvent = *t*-BuOH, *t*-BuOH/THF





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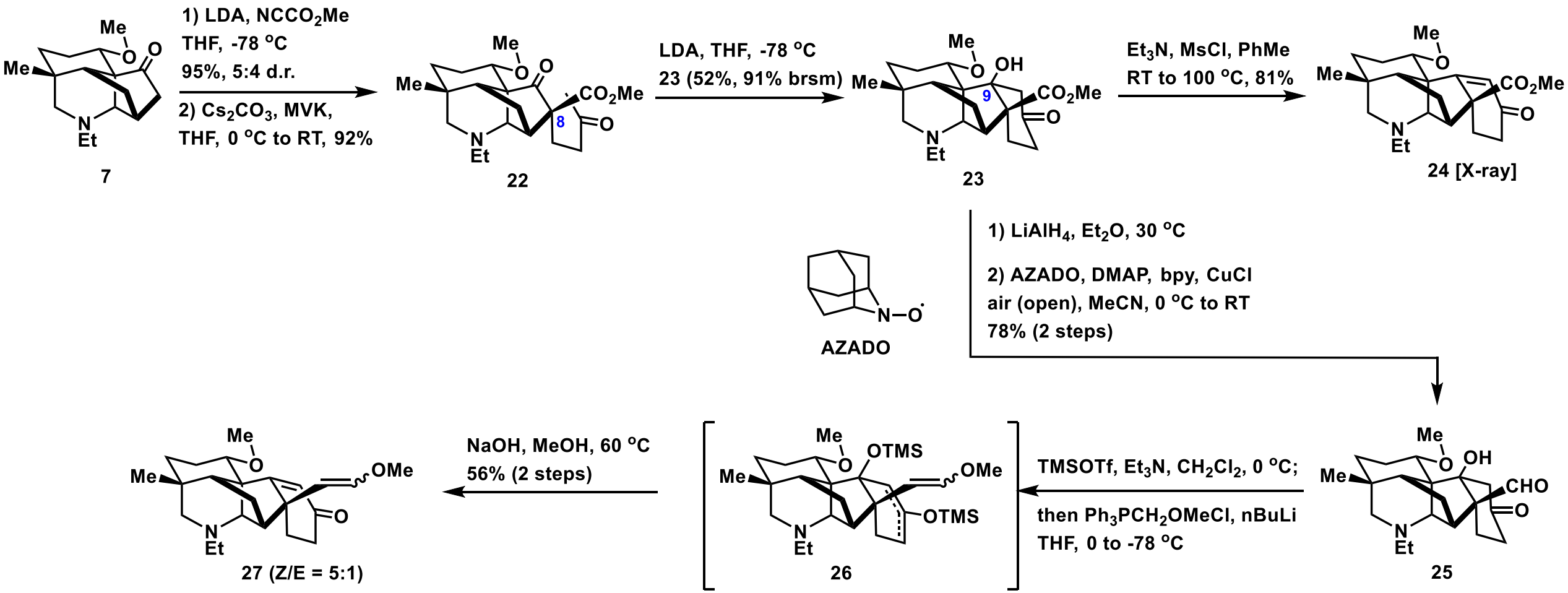
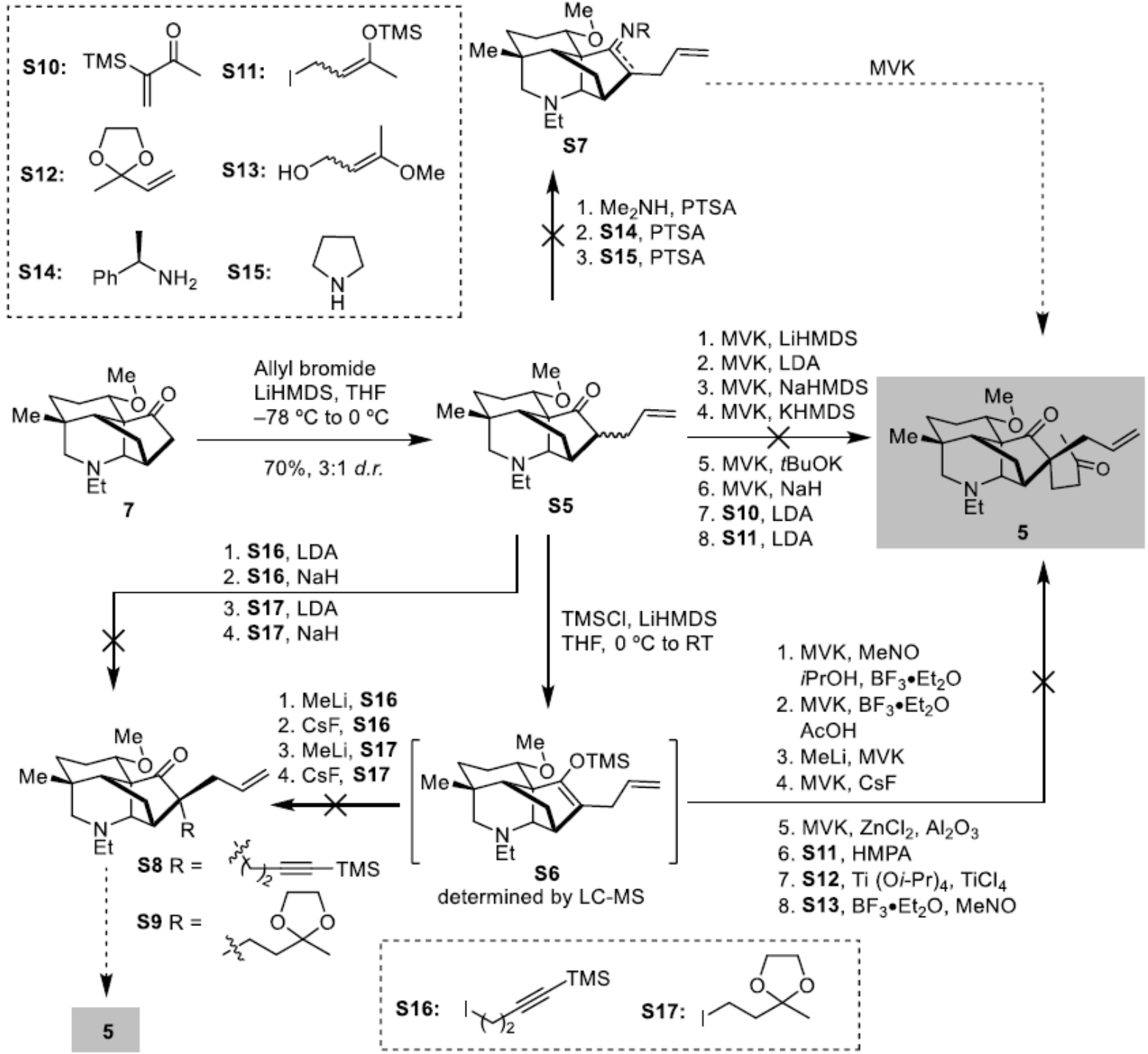
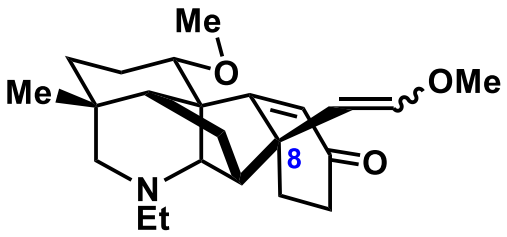
Completion of the total synthesis of liangshanone (2).

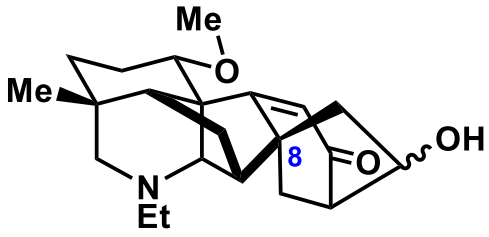



S10:
TMS
S11:
OTMS
S12:
S13:
HO
OMe
S14:
Ph
NH2
S15:
N
H
Me
O
NR
Me
N
Et
S7
MVK
1. Me2NH, PTSA
2. S14, PTSA
3. S15, PTSA
Me
O
O
Me
N
Et
7
Allyl bromide
LiHMDS, THF
–78 °C to 0 °C
70%, 3:1 d.r.
Me
O
O
Me
N
Et
S5
1. MVK, LiHMDS
2. MVK, LDA
3. MVK, NaHMDS
4. MVK, KHMDS
5. MVK, tBuOK
6. MVK, NaH
7. S10, LDA
8. S11, LDA
Me
O
O
Me
N
Et
5
1. S16, LDA
2. S16, NaH
3. S17, LDA
4. S17, NaH
TMSCl, LiHMDS
THF, 0 °C to RT
1. MVK, MeNO
iPrOH, BF3•Et2O
2. MVK, BF3•Et2O
AcOH
3. MeLi, MVK
4. MVK, CsF
5. MVK, ZnCl2, Al2O3
6. S11, HMPA
7. S12, Ti (Oi-Pr)4, TiCl4
8. S13, BF3•Et2O, MeNO
1. MeLi, S16
2. CsF, S16
3. MeLi, S17
4. CsF, S17
Me
O
O
Me
N
Et
R
S8 R =
TMS
S9 R =
Me
O
OTMS
Me
N
Et
S6
determined by LC-MS
5
S16:
TMS
S17:



27

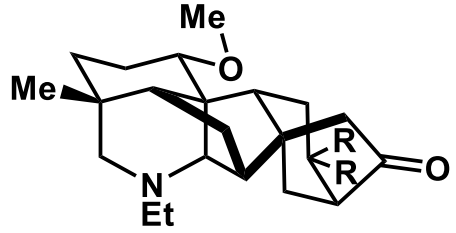
TfOH, MeCN, 40 °C
82%, 1:1.3 d.r.



28

1) Pd/C, HOAc, H_2, EtOH, RT
2) $CH(OEt)_3$, *p*TsOH, ethylene glycol
CH_2Cl_2, RT

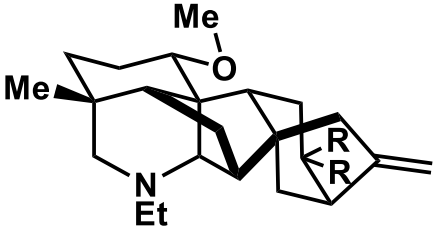
3) DMP, TFA, CH_2Cl_2, 0 °C
57% (3 steps)



R = -O$(CH_2)_2$O-

29

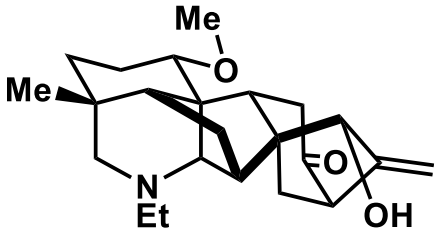
Petasis reagent
THF, 70 °C, 76%



30

SeO_2, TBHP, CH_2Cl_2
0 °C to RT

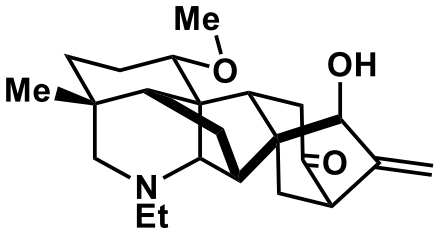
then *p*TsOH, RT, 69%



15-*epi*-liangshanone (31)

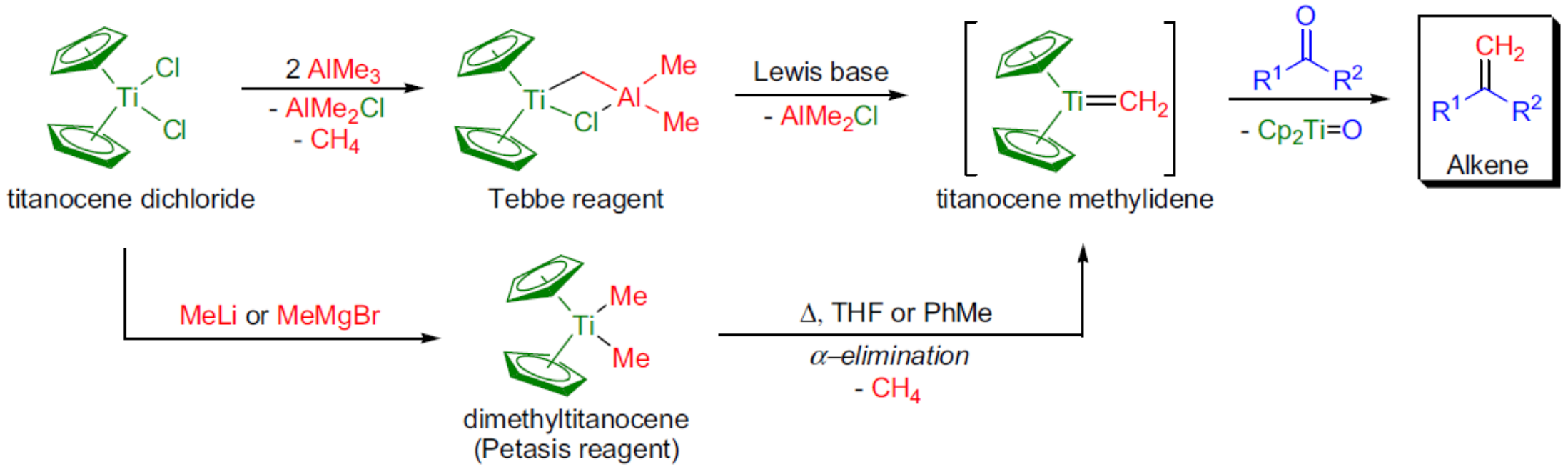
1) DMP, TFA
CH_2Cl_2, 0 °C, 77%

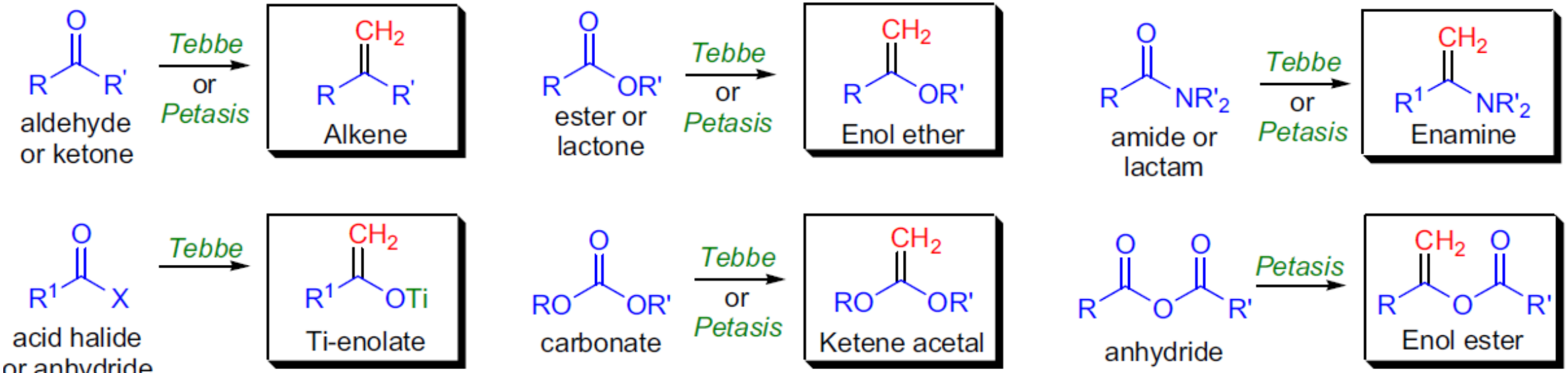
2) $NaBH(OMe)_3$
THF, -78 °C, 91%

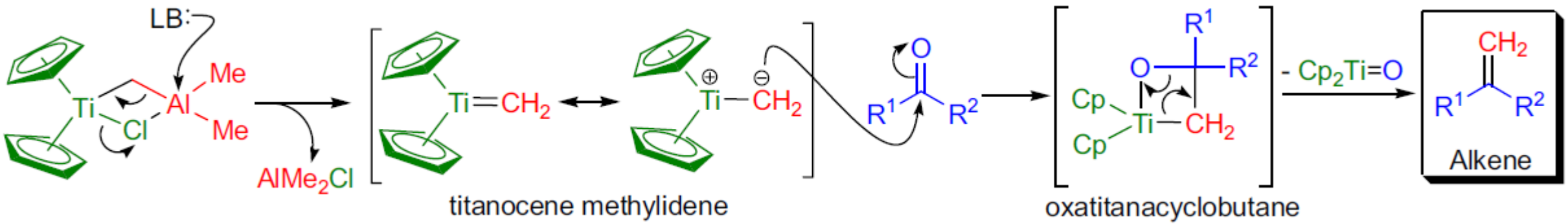


liangshanone (2)

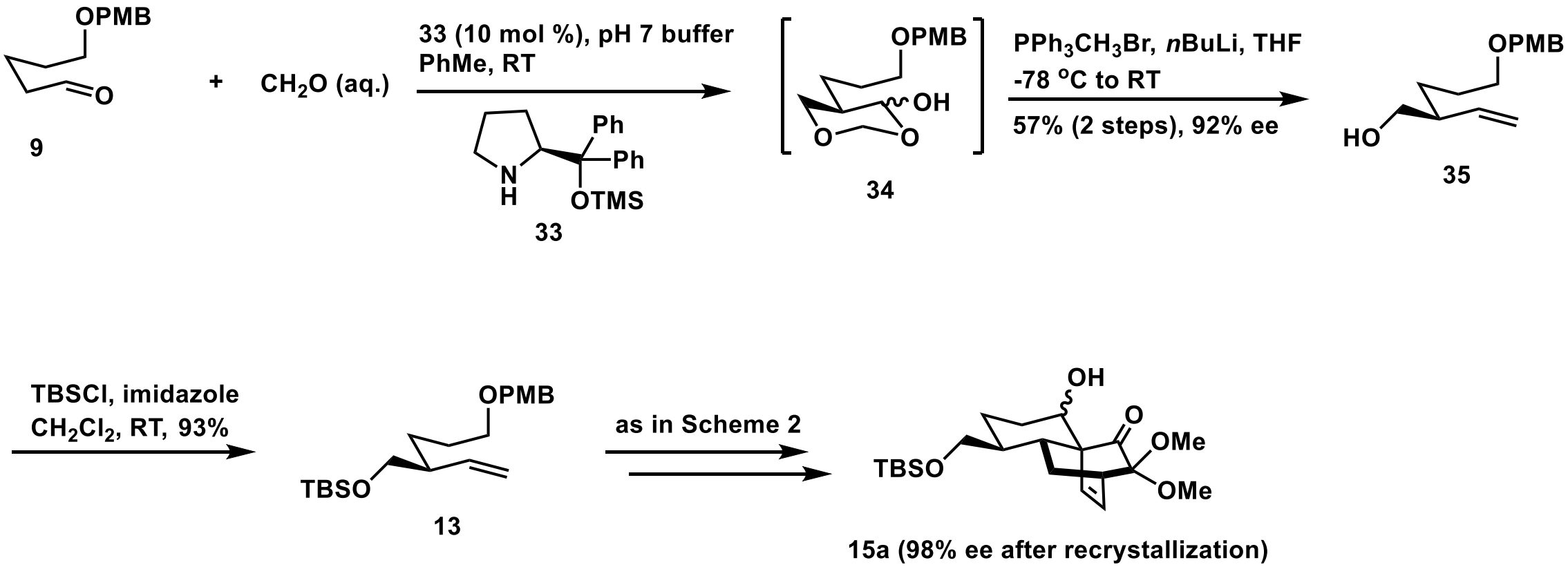
Tebbe Olefination / Petasis-tebbe Olefination

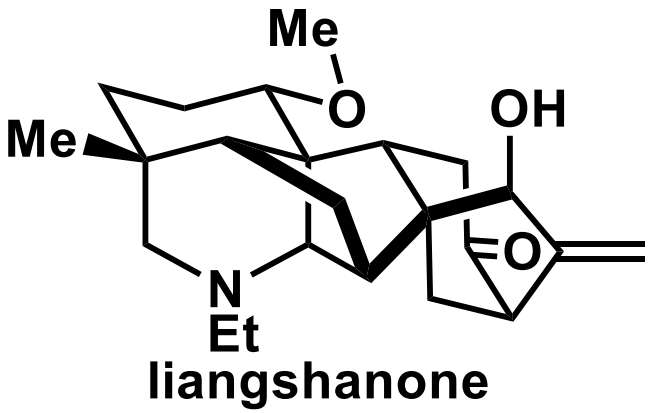





LB:
Ti
Al
Cl
Me
Me
AlMe2Cl
Ti=CH2
Ti—CH2
titanocene methylidene
O
R1
R2
R1
O
R2
Cp
Cp
Ti
CH2
oxatitanacyclobutane
- Cp2Ti=O
CH2
R1
R2
Alkene

Asymmetric synthesis of the advanced tricyclic intermediate 15a.





liangshanone

- OD/DA sequence
- Alkene cleavage/Mannich
- Robinson-type annulation
- Aldol addition