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WILEY-VCH

RESEARCH ARTICLE

Total Syntheses of Kopsaporine, Kopsinol and Kopsiloscine A

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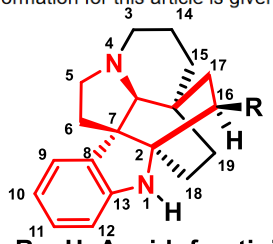
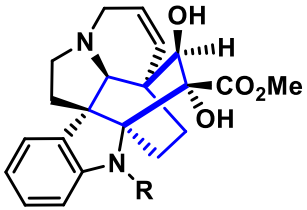
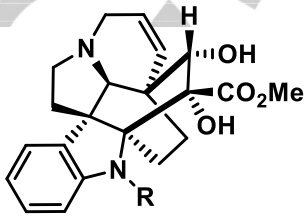
Supporting information for this article is given via a link at the end of the document.



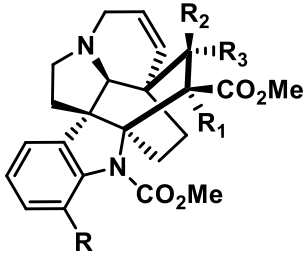
1: R = H, Aspidofractinine
2: R = CO_2Me, Kopsinine



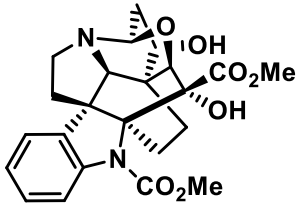
3: R = CO_2Me, Kopsaporine
4: R = H, Kopsinol



5: R = CO_2Me, Kopsiloscine A
6: R = H, Kopsiloscine H

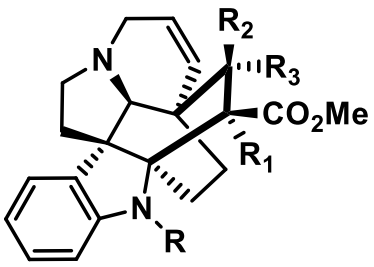


7: R = R_1 = R_3 = H, R_2 = OH, N-Carbomethoxy-17-hydroxy-Δ-14,15-kopsinine
8: R = OMe, R_1 = R_2 = OH, R_3 = H, Kopsaporine
9: R_1 = H, R_2/R_3=O, Yunnanoffine D

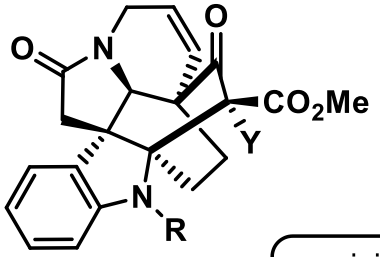


10: Singapurensine A

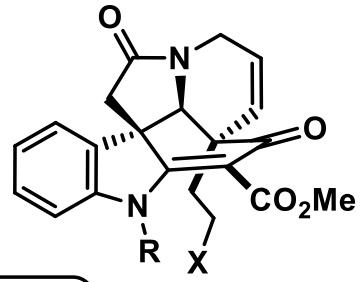
Retrosynthetic Analysis



Kopsaporine related alkaloids

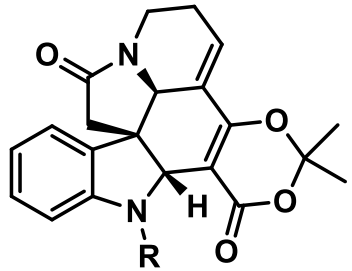


11

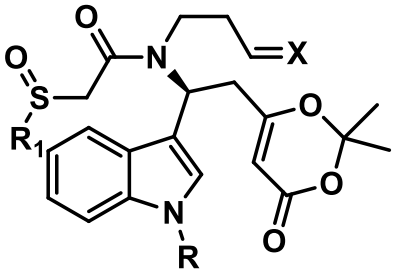


12

visible light induced radical cyclization towards *Kopsia* alkaloids

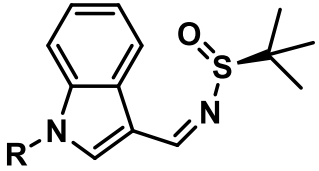


13. key pentacyclic structure unit



14

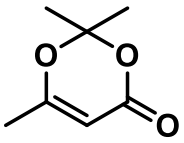
Thionium ion induced cyclization / aza-Prins cyclization cascade towards *Aspidosperma* alkaloids



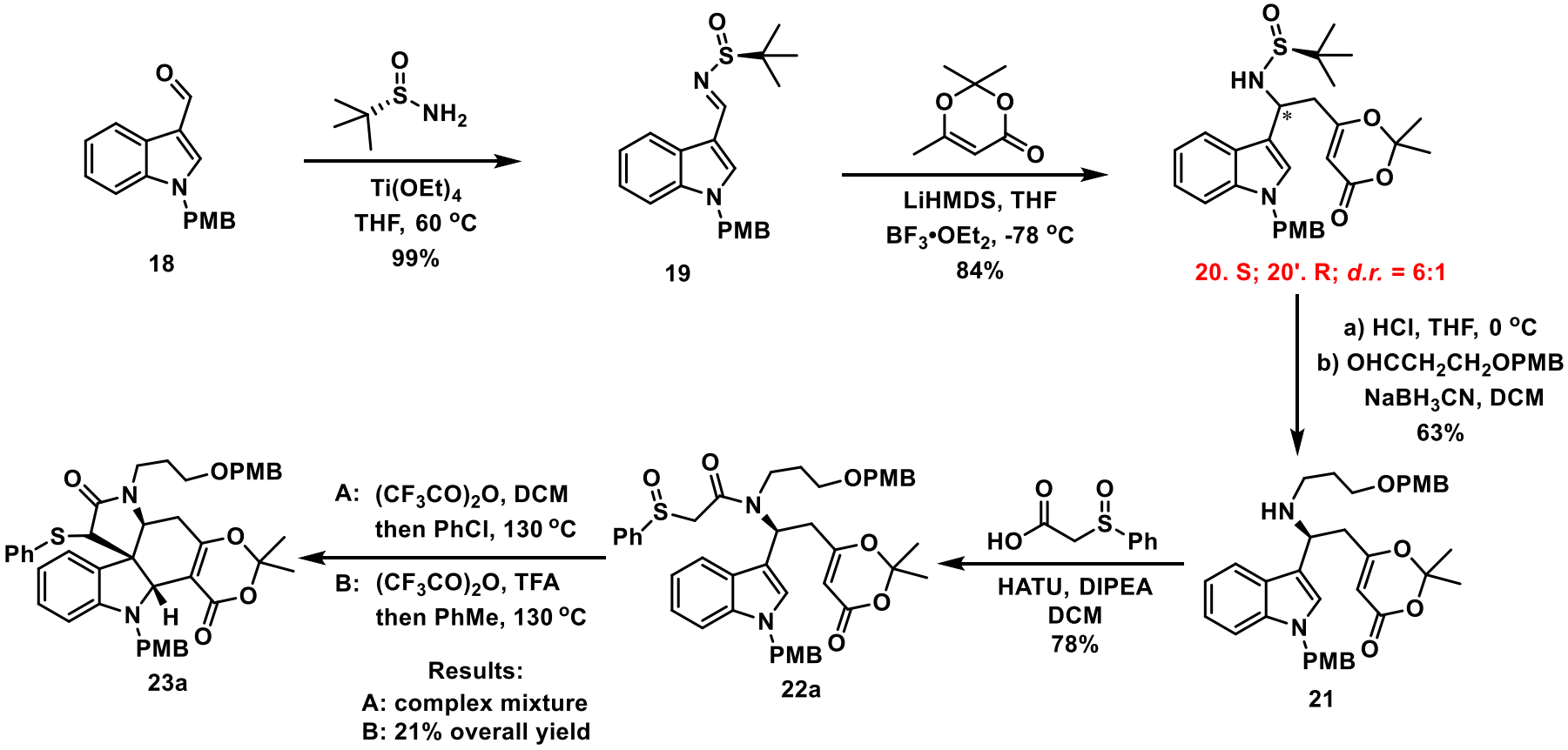
15

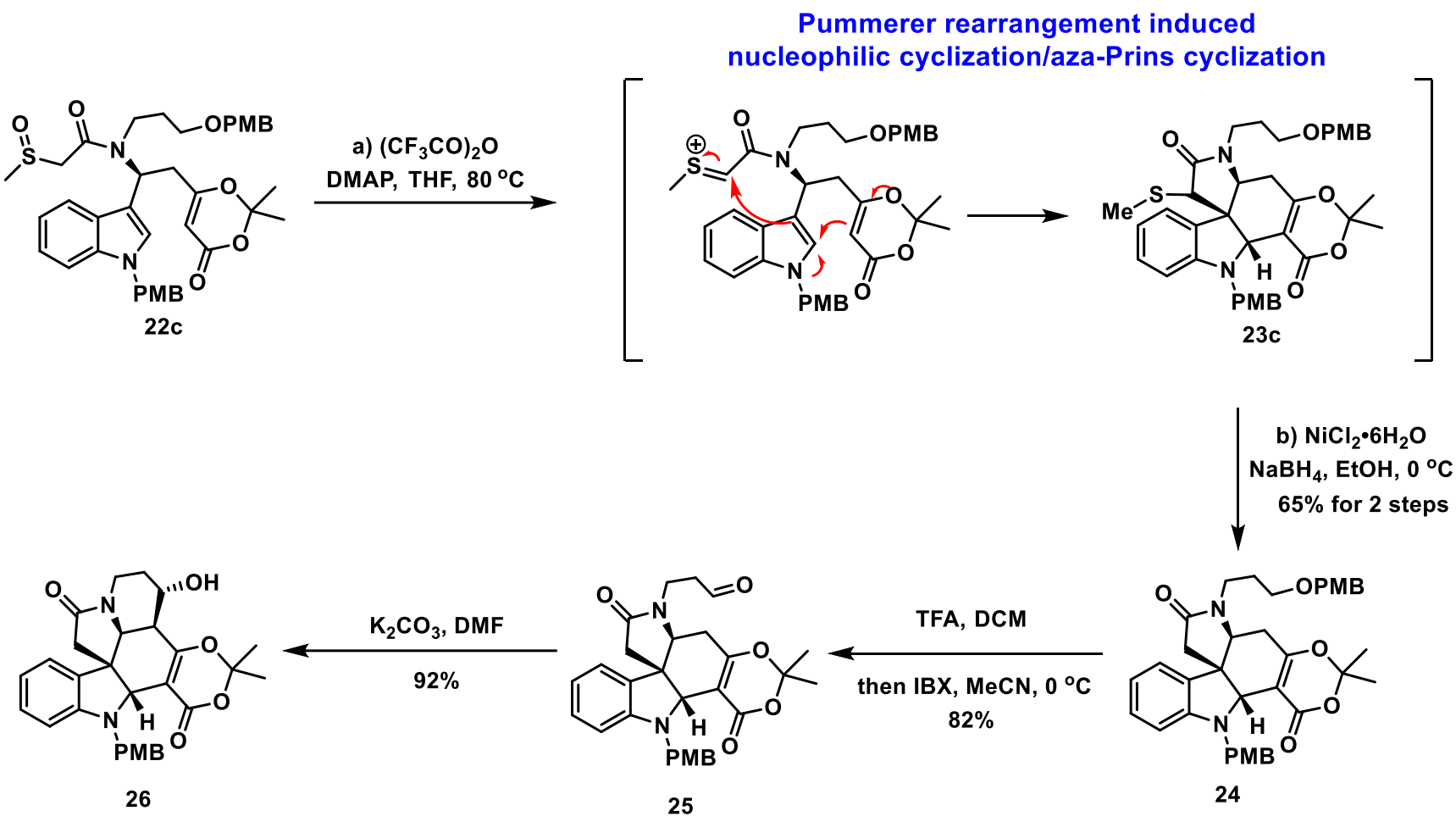
+

16:

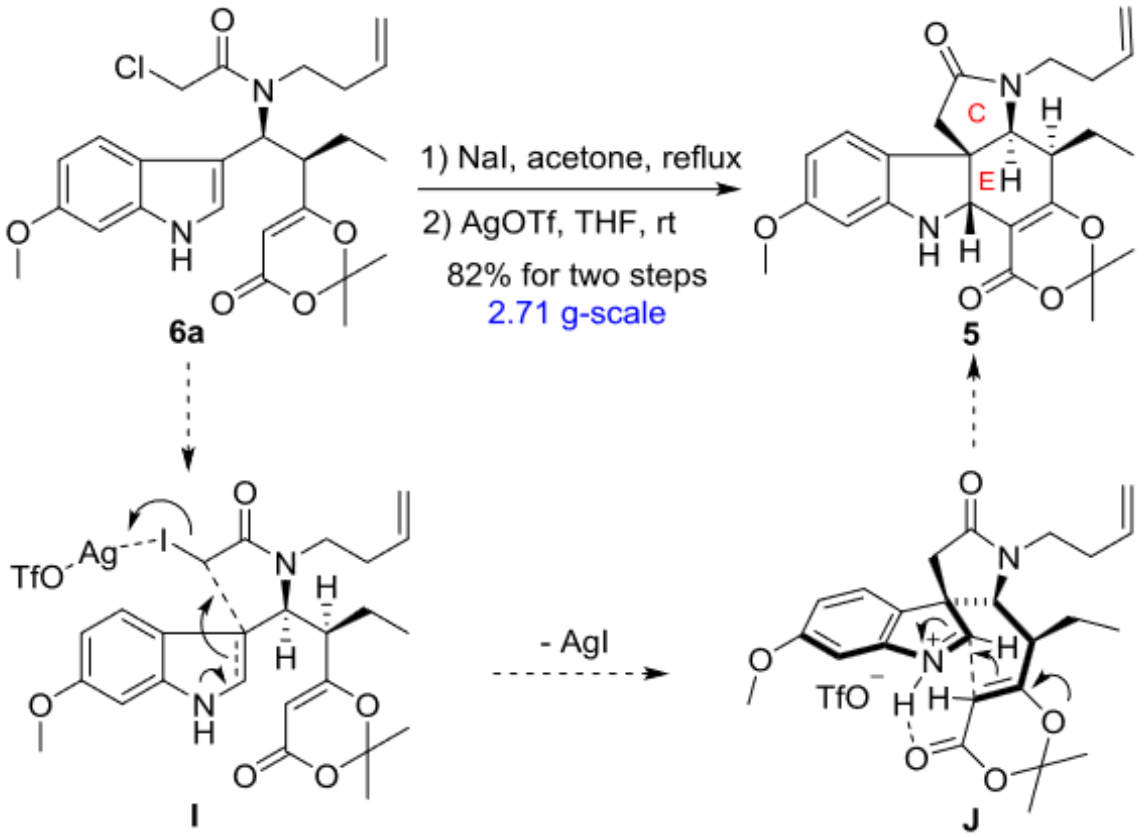


17: $RSOCH_2COOH$


18
Ti(OEt)4
THF, 60 °C
99%
19
LiHMDS, THF
BF3•OEt2, -78 °C
84%
20. S; 20'. R; d.r. = 6:1
a) HCl, THF, 0 °C
b) OHCCH2CH2OPMB
NaBH3CN, DCM
63%
21
HATU, DIPEA
DCM
78%
22a
A: (CF3CO)2O, DCM
then PhCl, 130 °C
B: (CF3CO)2O, TFA
then PhMe, 130 °C
23a
Results:
A: complex mixture
B: 21% overall yield


Pummerer rearrangement induced
nucleophilic cyclization/aza-Prins cyclization
a) (CF3CO)2O
DMAP, THF, 80 °C
22c
23c
b) NiCl2•6H2O
NaBH4, EtOH, 0 °C
65% for 2 steps
24
TFA, DCM
then IBX, MeCN, 0 °C
82%
25
K2CO3, DMF
92%
26

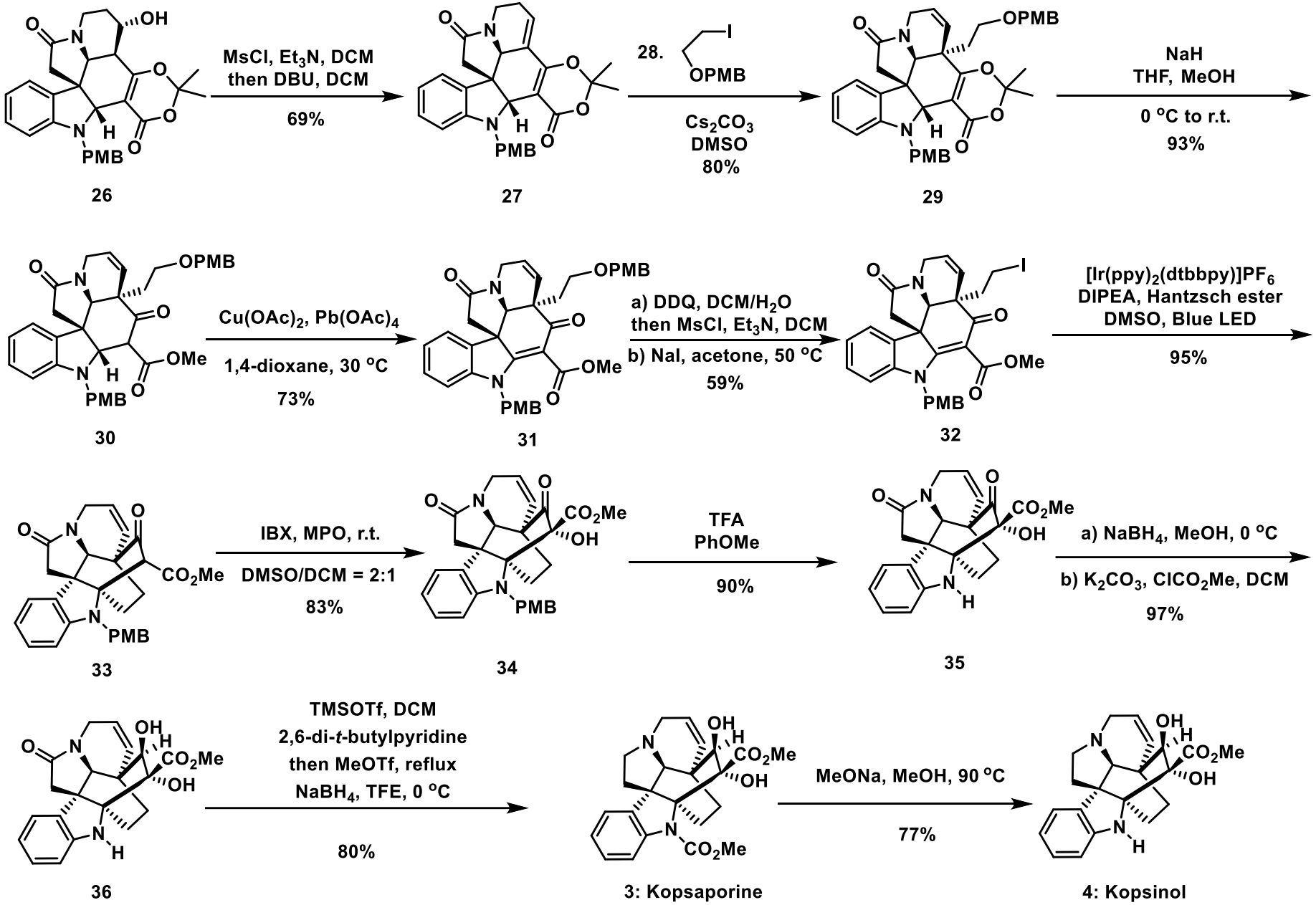
Heathcock/aza-Prins cyclizations

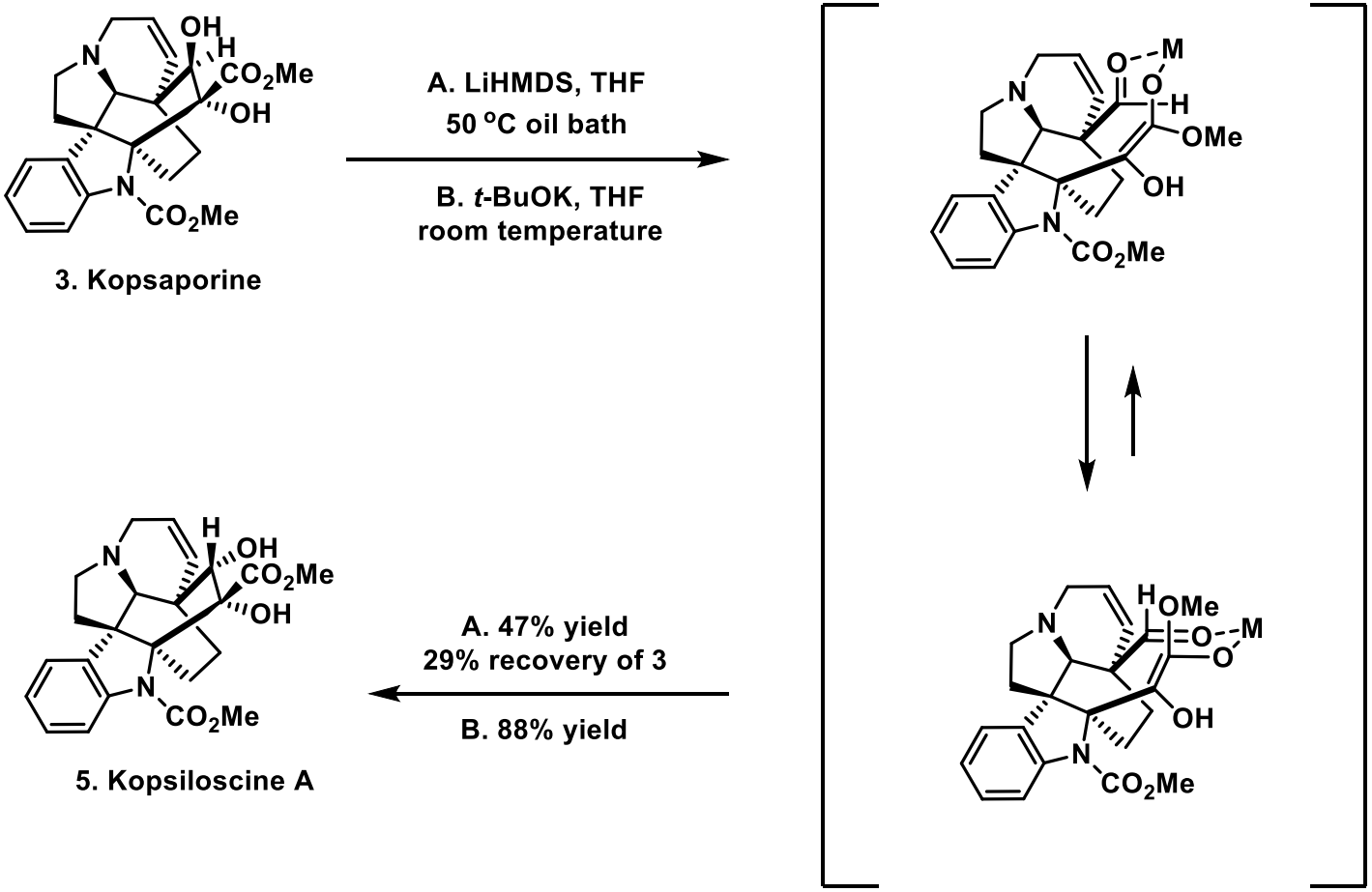


Scheme 4. The key Heathcock/aza-Prins cyclization. Tf = trifluoromethanesulfonyl.

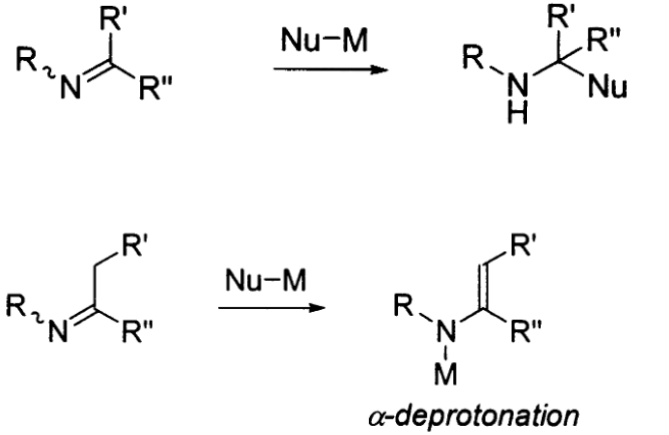
Angew. Chem. Int. Ed., **2017**, *56*, 12327.

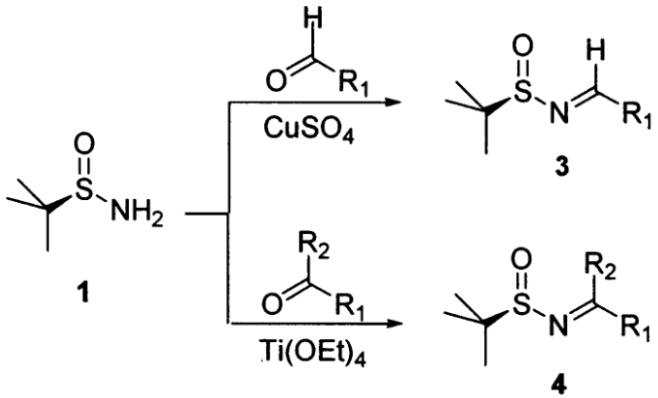
Tetrahedron, **2019**, *75*, 1751.


MsCl, Et3N, DCM
then DBU, DCM
69%
28.
I
OPMB
Cs2CO3
DMSO
80%
NaH
THF, MeOH
0 °C to r.t.
93%
Cu(OAc)2, Pb(OAc)4
1,4-dioxane, 30 °C
73%
a) DDQ, DCM/H2O
then MsCl, Et3N, DCM
b) NaI, acetone, 50 °C
59%
[Ir(ppy)2(dtbbpy)]PF6
DIPEA, Hantzsch ester
DMSO, Blue LED
95%
IBX, MPO, r.t.
DMSO/DCM = 2:1
83%
TFA
PhOMe
90%
a) NaBH4, MeOH, 0 °C
b) K2CO3, ClCO2Me, DCM
97%
TMSOTf, DCM
2,6-di-t-butylpyridine
then MeOTf, reflux
NaBH4, TFE, 0 °C
80%
MeONa, MeOH, 90 °C
77%
26
27
29
30
31
32
33
34
35
36
3: Kopsaporine
4: Kopsinol

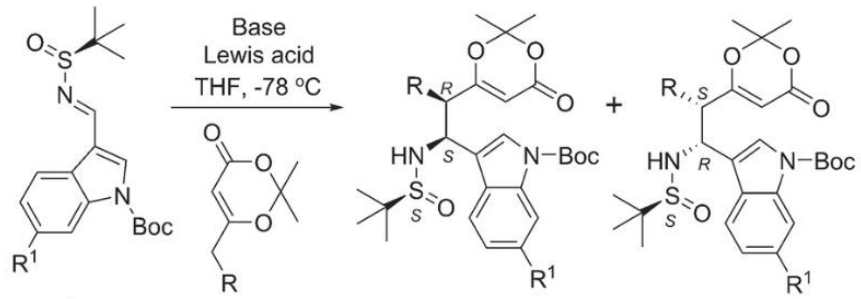

OH
H
CO2Me
OH
N
N
CO2Me
3. Kopsaporine
A. LiHMDS, THF
50 °C oil bath
B. t-BuOK, THF
room temperature
O
M
O
H
OMe
OH
N
N
CO2Me
H
OMe
O
M
O
OH
N
N
CO2Me
A. 47% yield
29% recovery of 3
B. 88% yield
H
OH
CO2Me
OH
N
N
CO2Me
5. Kopsiloscine A

ELLMAN 亚胺&手性选择





Accounts. Chem. Res., **2002**, *35*, 984



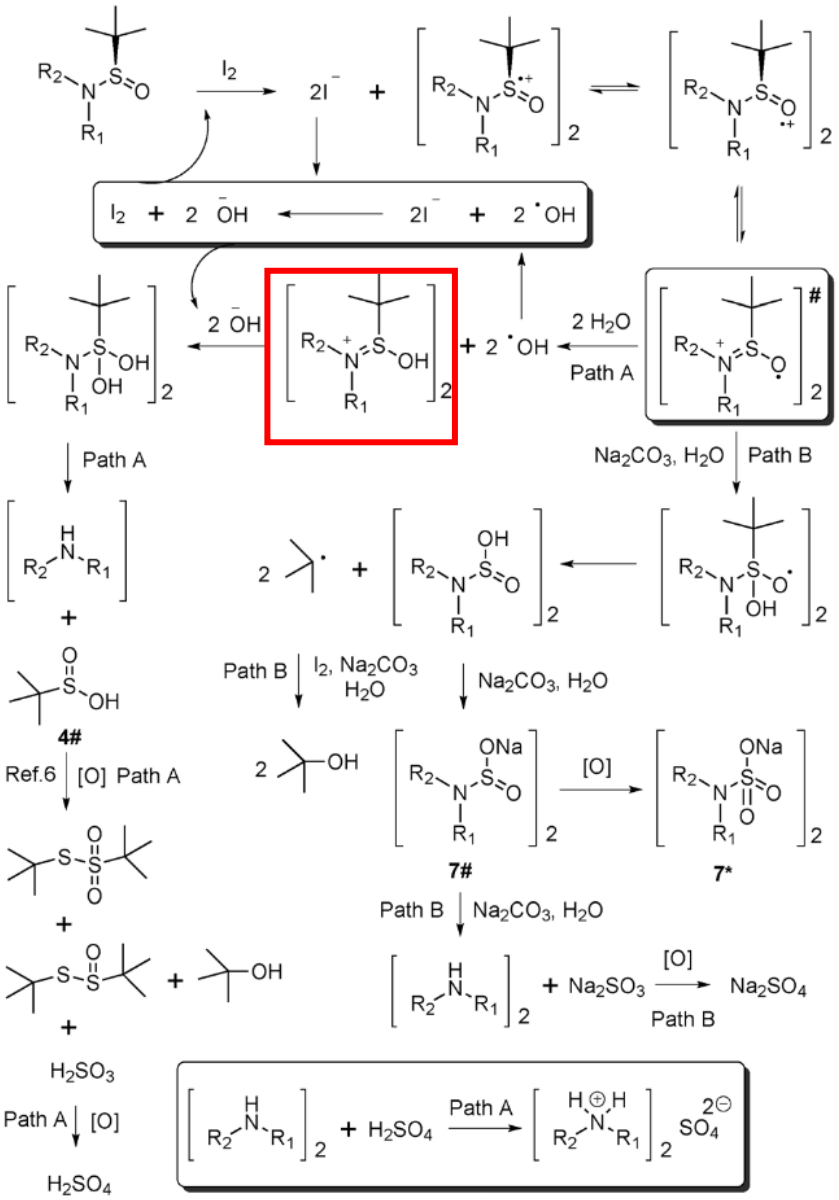
13a,**13a'**: R, R^1 = H; **13c**,**13c'**: R^1 = OMe, R = Et;
13b,**13b'**: R^1 = H, R = Et; **13d**,**13d'**: R^1 = OMe, R = H

Entry	Bases	Lewis acids	Products and Yields[a]	d.r.
1: **9a** + **12**	LDA	none	**13a** +**13a'** 8%	3 : 1
2: **9a** + **12**	$LiN(SiMe_3)_2$	none	**13a** +**13a'** 27%	3.5 : 1
3: **9a** + **12**	$LiN(SiMe_3)_2$	$ZnCl_2$	no desired product	
4: **9a** + **12**	$LiN(SiMe_3)_2$	CuOTf	complex mixture	
5: **9a** + **12**	$LiN(SiMe_3)_2$	AgOTf	complex mixture	
6: **9a** + **12**	$LiN(SiMe_3)_2$	BF_3-Et_2O	**13a**: 86%; **13a'**: 2%	>40 : 1
7: **9a** + **10**	$LiN(SiMe_3)_2$	BF_3-Et_2O	**13b**: 83%; **13b'**: 11%	7.6 : 1
8: **9b** + **10**	$LiN(SiMe_3)_2$	BF_3-Et_2O	**13c**: 84%; **13c'**: 13%	6.5 : 1
9: **9b** + **12**	$LiN(SiMe_3)_2$	BF_3-Et_2O	**13d**: 85%; **13d'**: 2%	>40 : 1

[a] Yields represent yields of isolated products. Reactions were conducted on gram-scale in THF at -78 °C (acetone-dry ice bath).

Angew. Chem. Int. Ed., **2017**, *129*, 12495.

ELLMAN 亚胺的脱除



Scheme 5 Proposed pathway for iodine mediated deprotection of *tert*-butanesulfinyl units.

Chem. Commun., **2014**, *50*, 6259.

HATU缩合

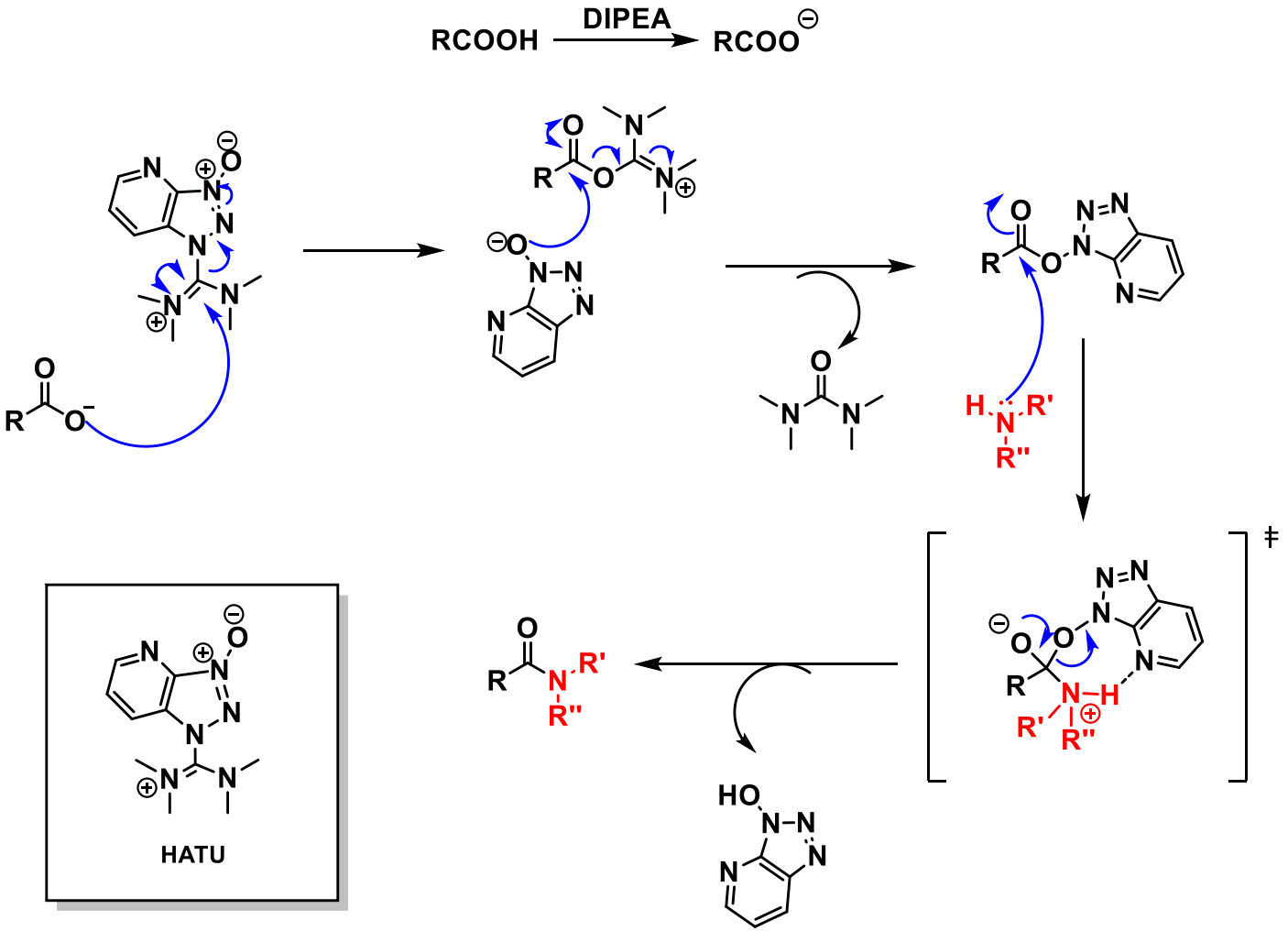
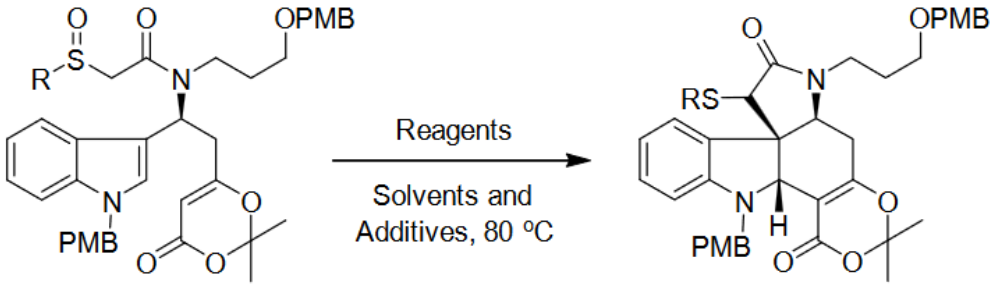


Table 1 Studies on the cascade cyclizations of compounds **22a**, **22b** and **22c**



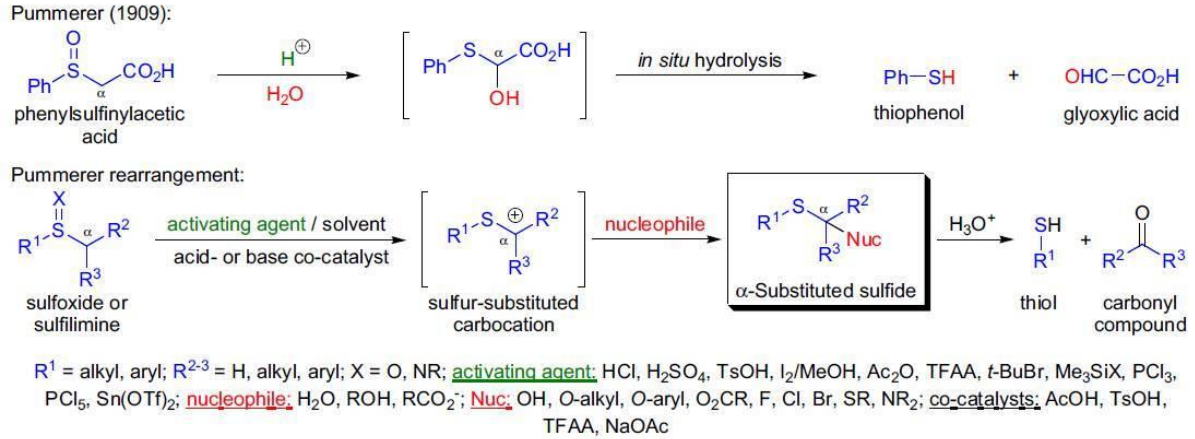
22a: R = Ph; **22b**: R = *t*-Bu; and **22c**: R = Me

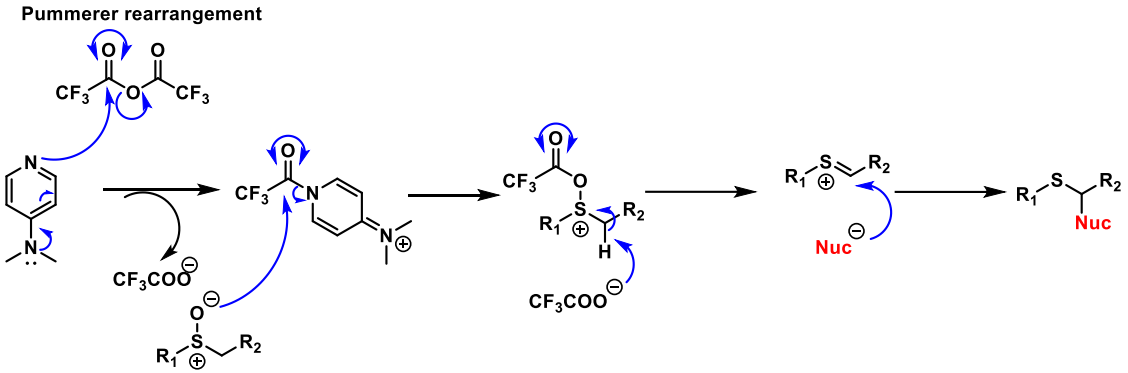
23a: R = Ph; **23b**: R = *t*-Bu; and **23c**: R = Me

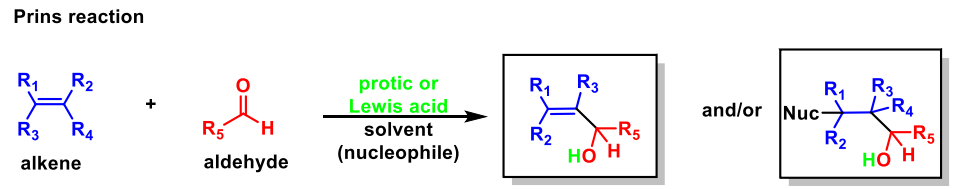
entry	solvents	substrates, reagents (eq.)	yields
1	DCE	**22a**, TFAA (4), TFA (3)	**23a**: 11% [b]
2	THF	**22a**, TFAA (4), TFA (3)	**23a**: 25%[b]
3	THF	**22a**, $POCl_3$ (4)	complex
4	THF	**22a**, TFAA (4), DABCO (3)	**23a**: 38%[c]
5	THF	**22a**, TFAA (4), DMAP (3)	**23a**: 41%[c]
6	THF	**22b**, TFAA (4), DMAP (3)	**23b**: 82% [b]
7	THF	**22c**, TFAA (4), DMAP (3)	**23c**: 81% [c]

[a] Reactions were conducted with 0.1 mmol of **22a**, **22b** or **22c** in solvents (5 mL). Yields represent isolated yields (as mixtures of C6-isomers). DCE = dichloroethane, DMAP = *N*,*N*-4-dimethylaminopyridine.

Pummerer 重排引发的分子内 Prins 反应







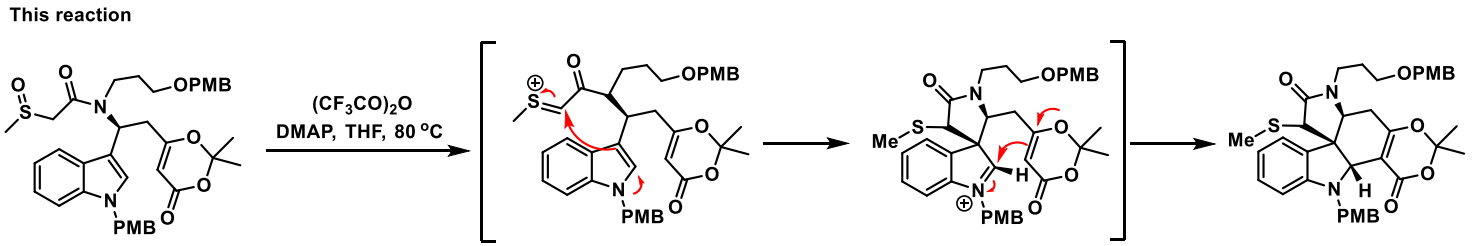
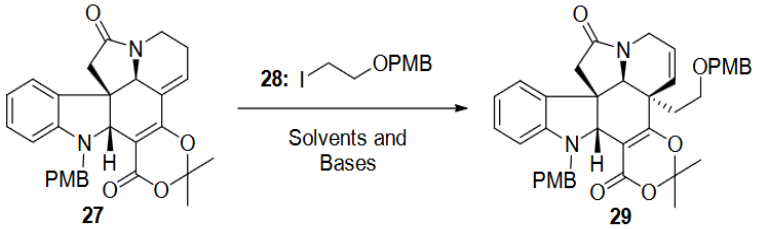


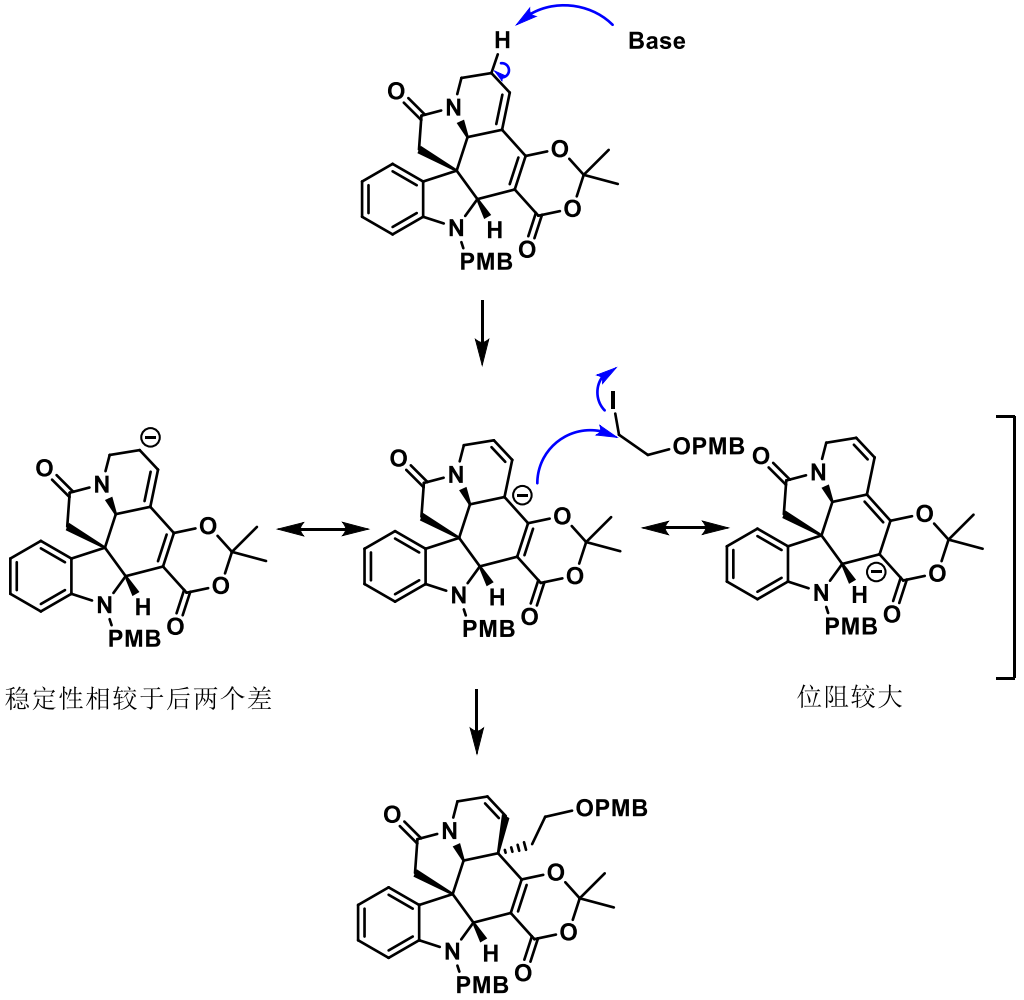
Table 2 Evaluation of the vinylogous alkylation of intermediate **27**



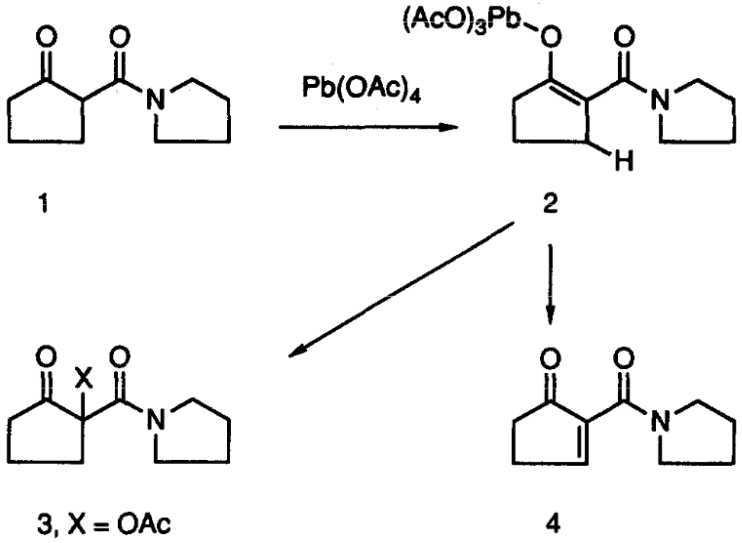
entry	solvents	Bases and additives (eq.)	yields
1	DMF	*t*-BuOK (2), None	30%
2	DMF	NaH (2), DMAP (0.1)	30%
3	DMF	K_2CO_3 (2), None	10%
4	DMF	Cs_2CO_3 (2), None	46%
5	DMSO	Cs_2CO_3 (2), None	80%

[a] All reactions were conducted with 12 mg of **27** in solvents (1 mL). Yields represent isolated yields. DMSO = dimethyl sulfoxide.

文中：高温加强碱性会使得底物分解



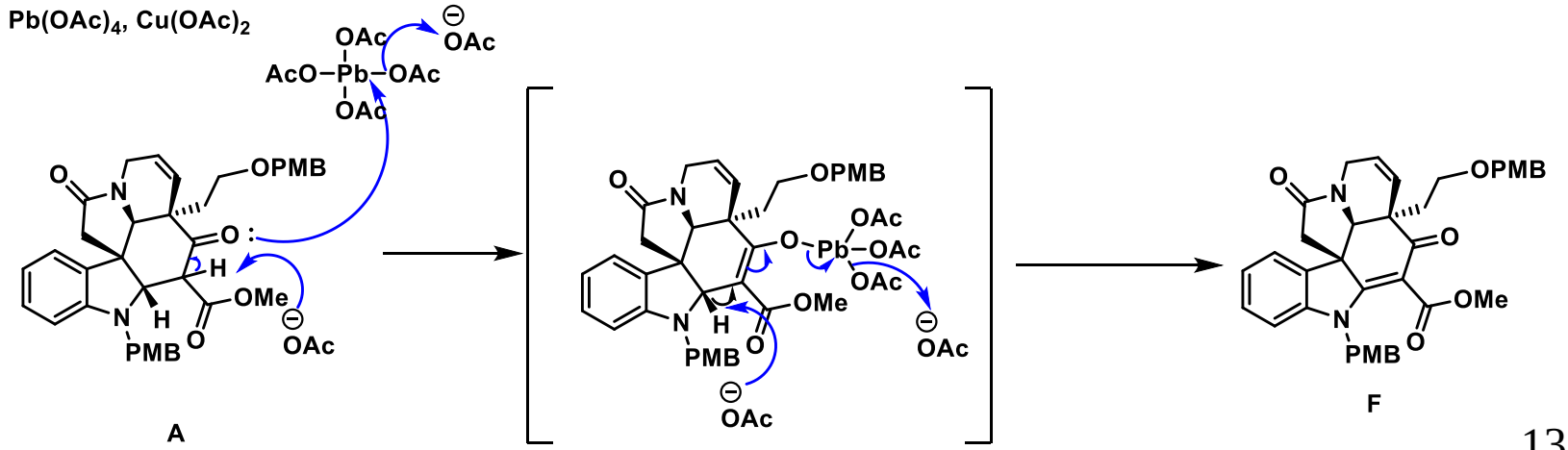
Scheme 1

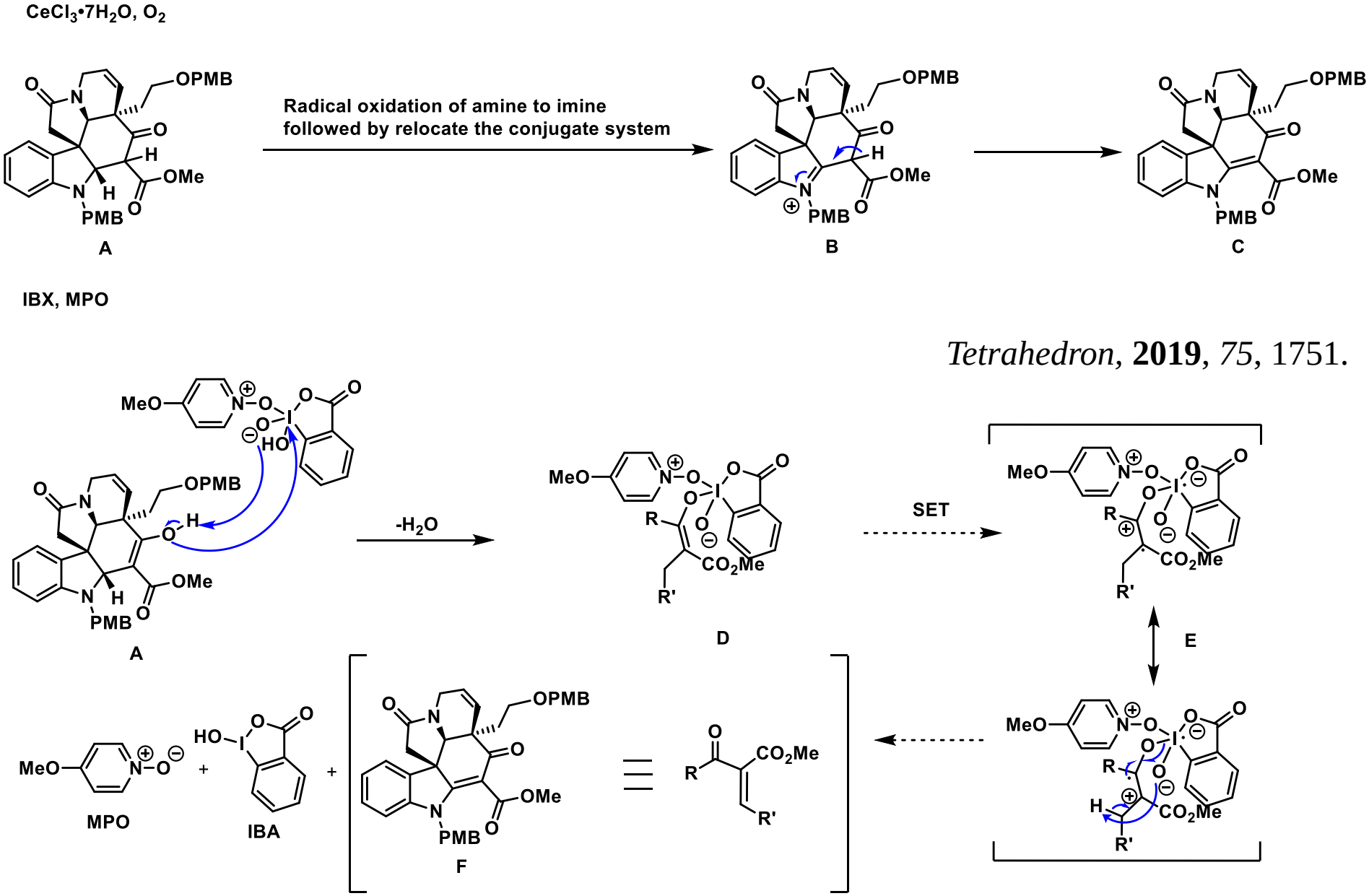


Reaction Conditions	3 (% Yield)	4 (% Yield)
$Pb(OAc)_4$ in HOAc	42	6
$Pb(OAc)_4$ in benzene	15	29
$Pb(OAc)_4 + Cu(OAc)_2$ in benzene	5	67

This reaction

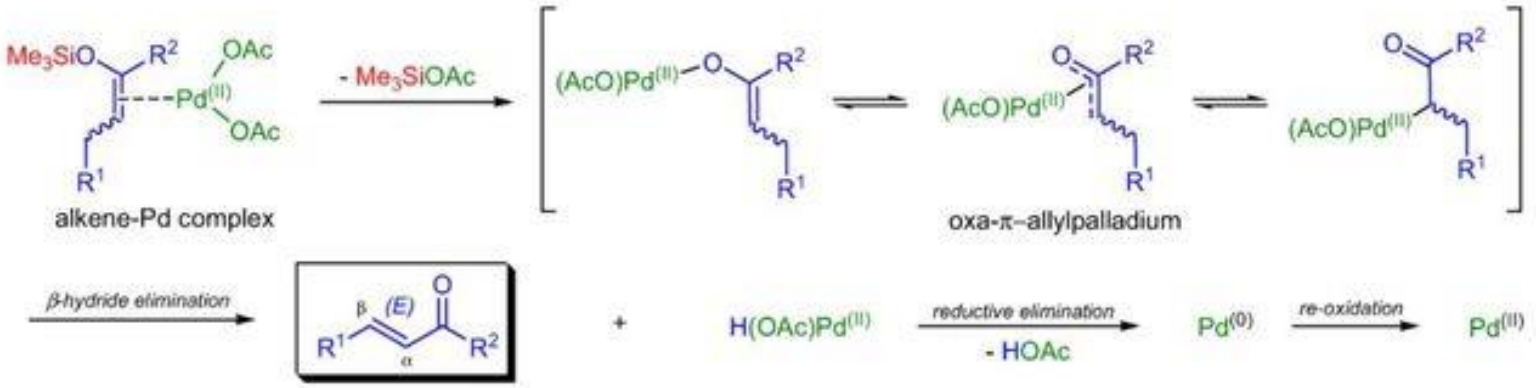
Tetrahedron, **1993**, *34*, 3021.



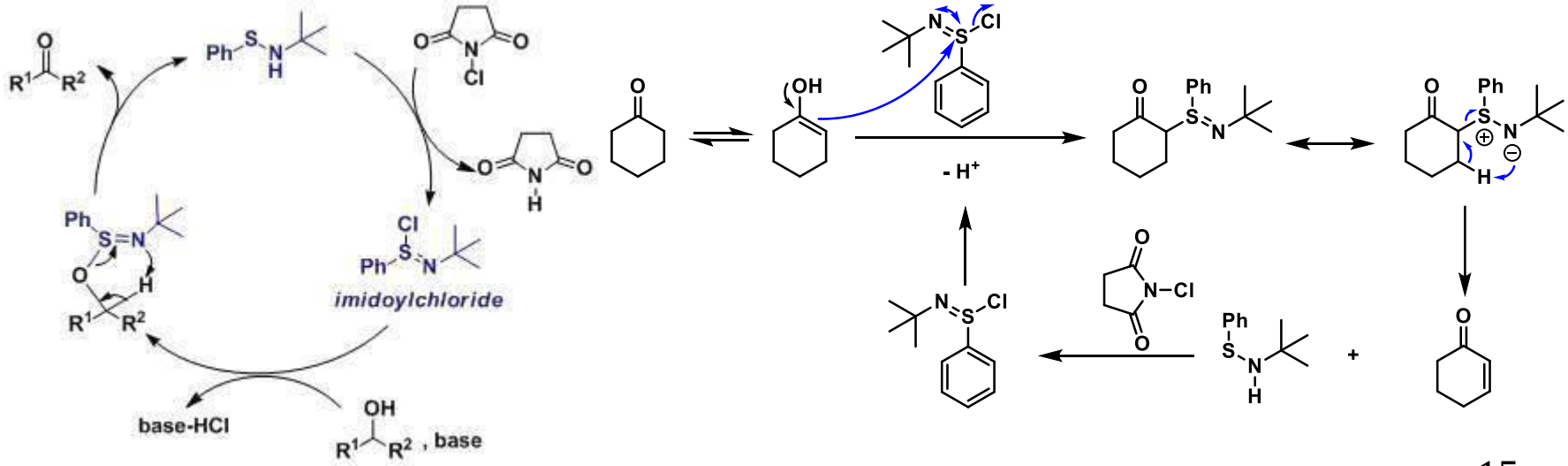

CeCl3•7H2O, O2
OPMB
OMe
PMB
A
Radical oxidation of amine to imine
followed by relocate the conjugate system
B
C
IBX, MPO
Tetrahedron, 2019, 75, 1751.
MeO
HO
-H2O
D
SET
E
MPO
IBA
F
CO2Me
R
R'
Angew. Chem. Int. Ed., 2002, 41, 996.

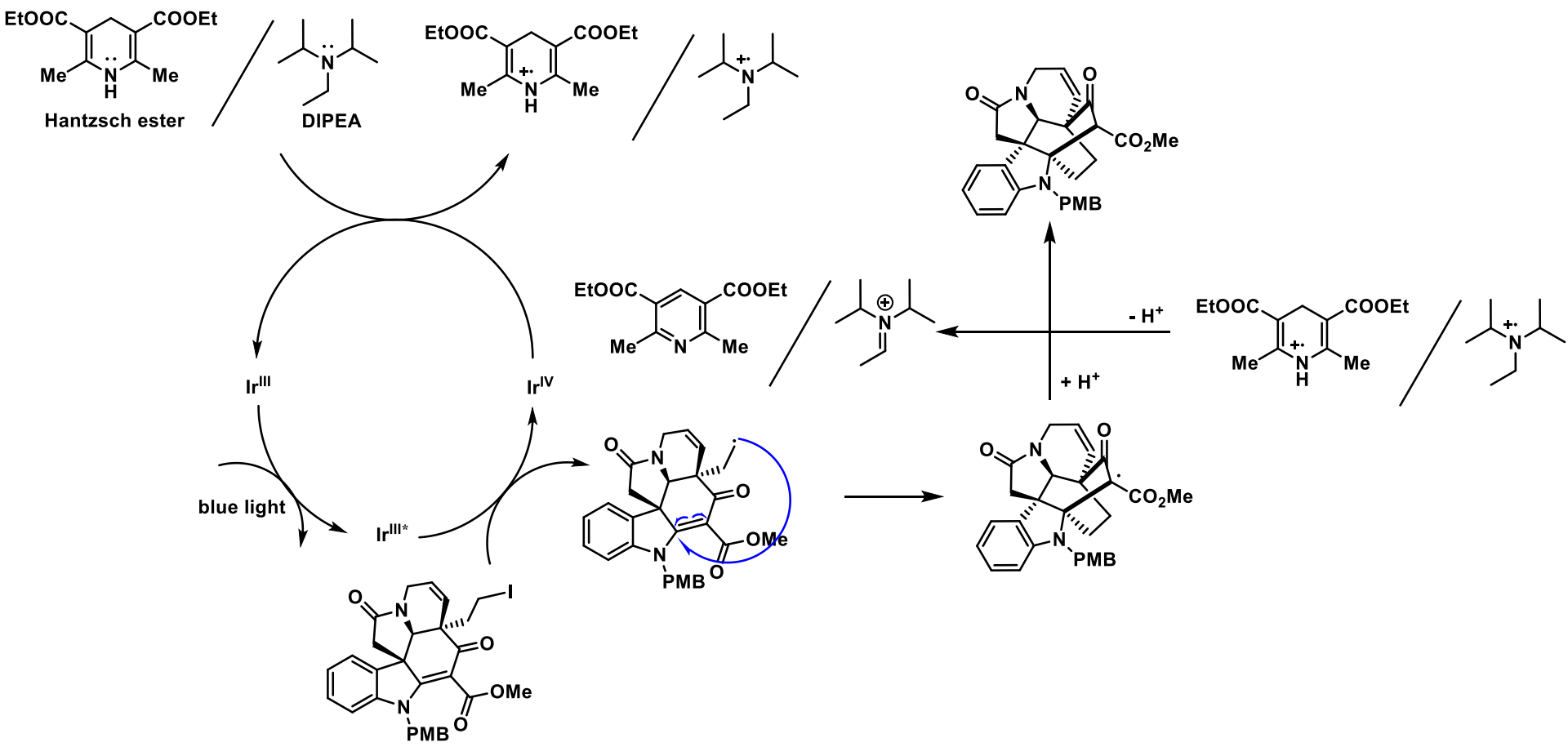
Saegusa 氧化反应

When substoichiometric/stoichiometric amounts of $Pd(OAc)_2$ is used:



Mukaiyama 氧化反应





Eur. J. Org. Chem., **2017**, *15*, 1993.

Nat. Chem., **2012**, *4*, 854.

Angew. Chem. Int. Ed., **2012**, 51, 12303.

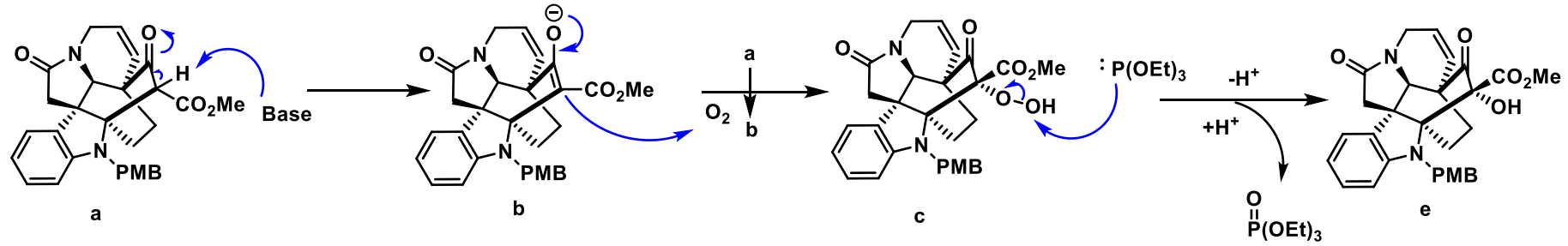
Table 3 Studies on the introduction of hydroxy group towards β-ketoester **33**

33 **34**

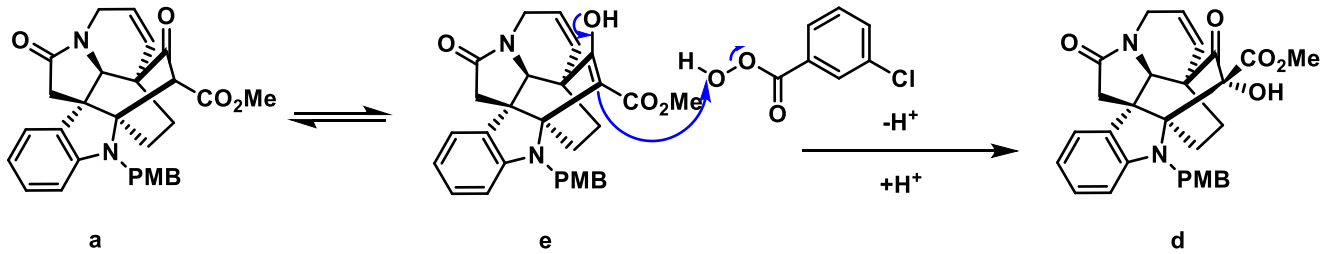
entry	solvents	Reagents (eq.), *T* (°C)	yields [a]
1	*i*-PrOH	$CeCl_3 \cdot 7H_2O$ (4), O_2, 35 °C	trace
2	DCM	*m*-CPBA (4), $NaHCO_3$ (3), rt	10%
3	THF	$P(OEt)_3$ (4), O_2, Cs_2CO_3 (3), rt	0%
4	H_2O/1,4-dioxane (4:1)	Oxone (4), Na_2CO_3 (3), rt	0%
5	DMSO/DCM (2:1)	IBX, MPO (4), rt	83%

[a] Reactions were conducted with 0.06 mmol of **33** in solvents (0.5 mL–2mL). Yields represent isolated yields. *m*-CPBA = 3-chloroperbenzoic acid, MPO = 4-methoxypyridine-*N*-oxide.

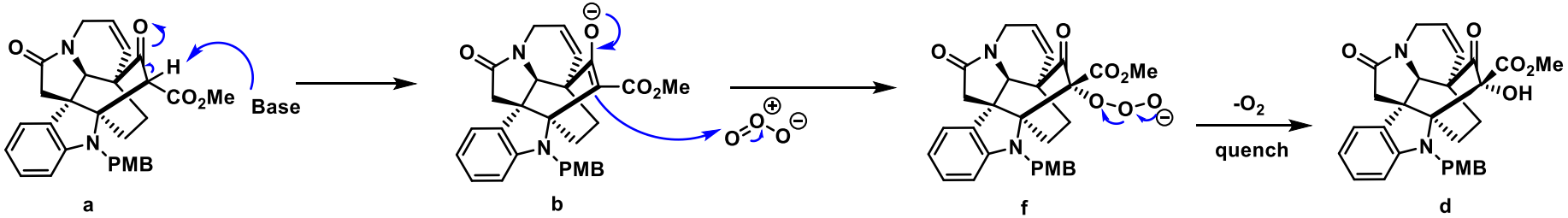
O_2, $P(OEt)_3$, Cs_2CO_3

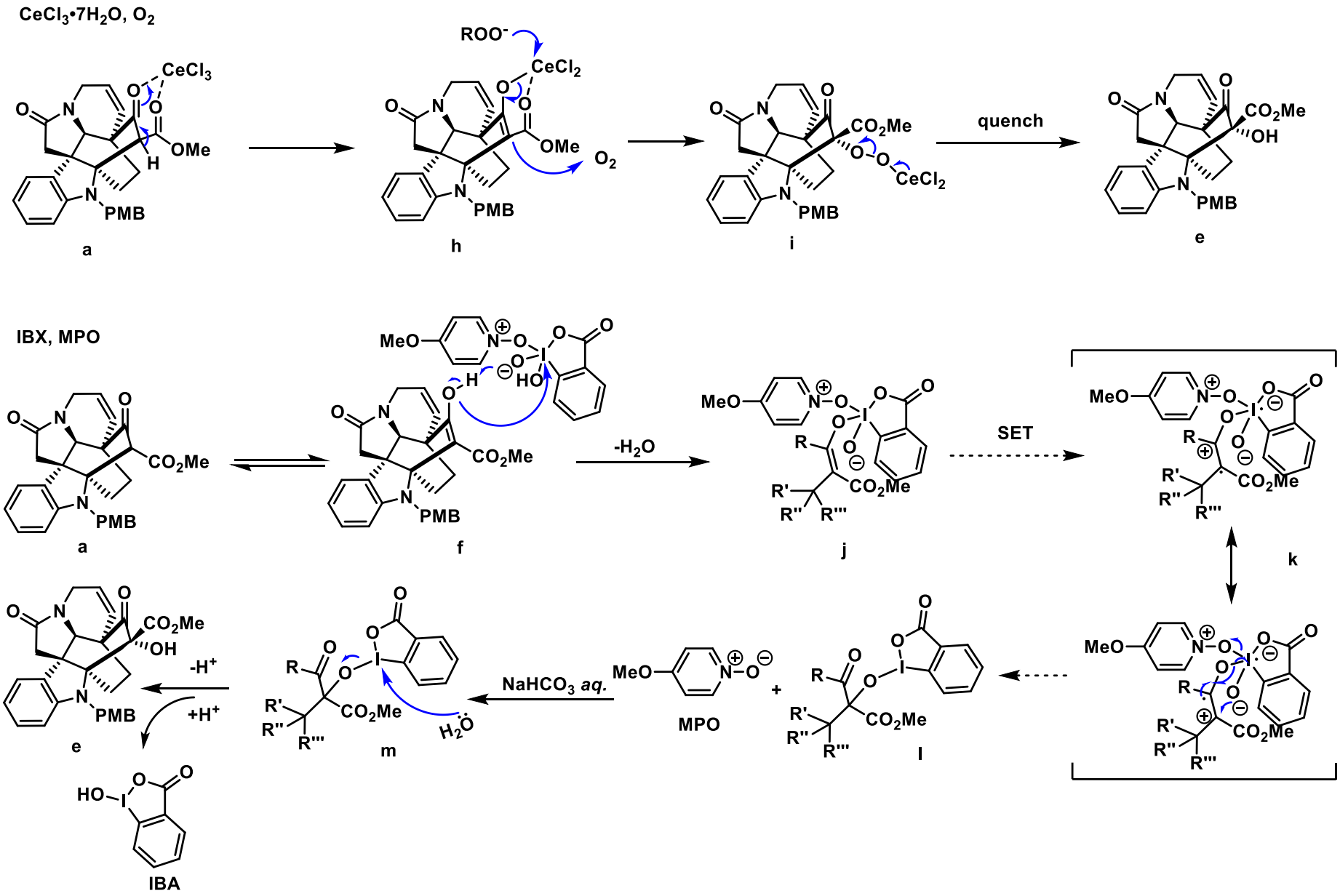


m-CPBA, $NaHCO_3$



O_3, Na_2CO_3




CeCl3•7H2O, O2
CeCl3
OMe
H
PMB
a
ROO-
CeCl2
O2
h
CO2Me
CeCl2
i
quench
OH
e
IBX, MPO
CO2Me
f
-H2O
j
SET
k
-H+
+H+
HO
IBA
NaHCO3 aq.
MPO
m
l
MeO
R
R'
R''
R'''
H2O