Total Syntheses of Illisimonin A and Merrilactone A

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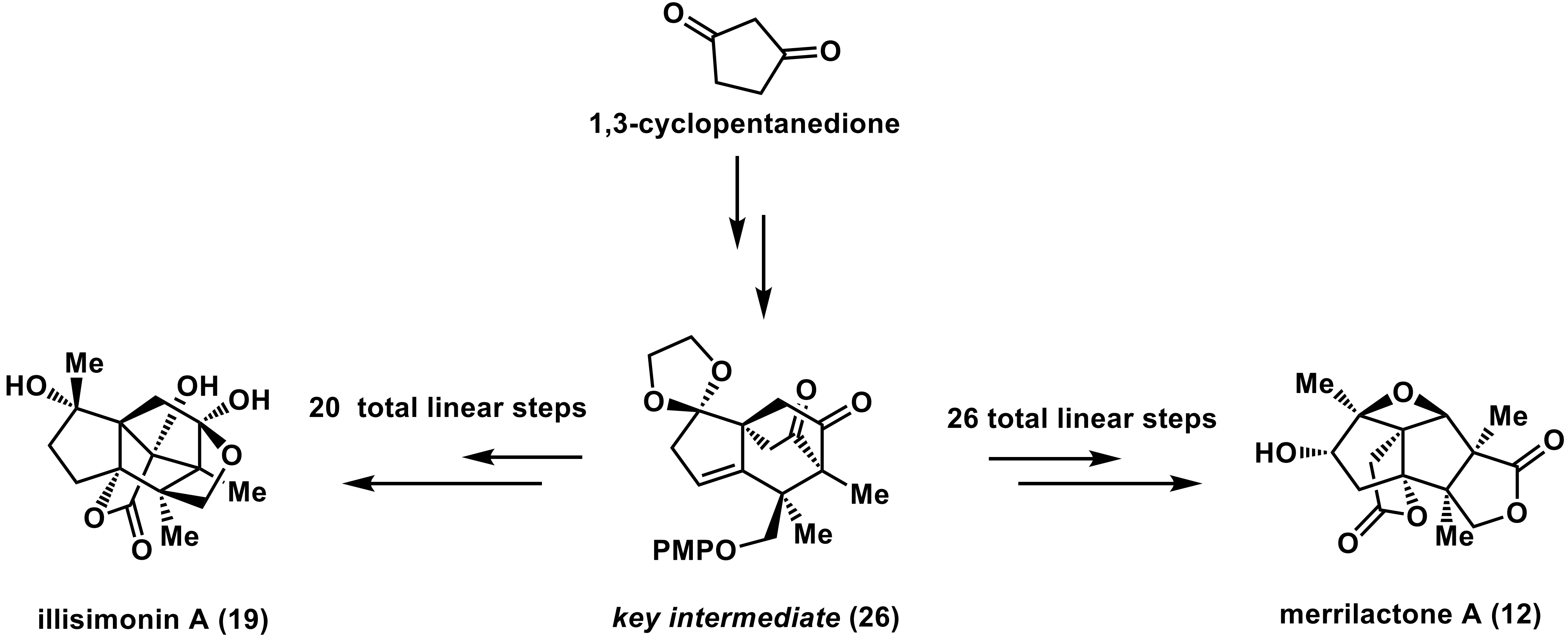
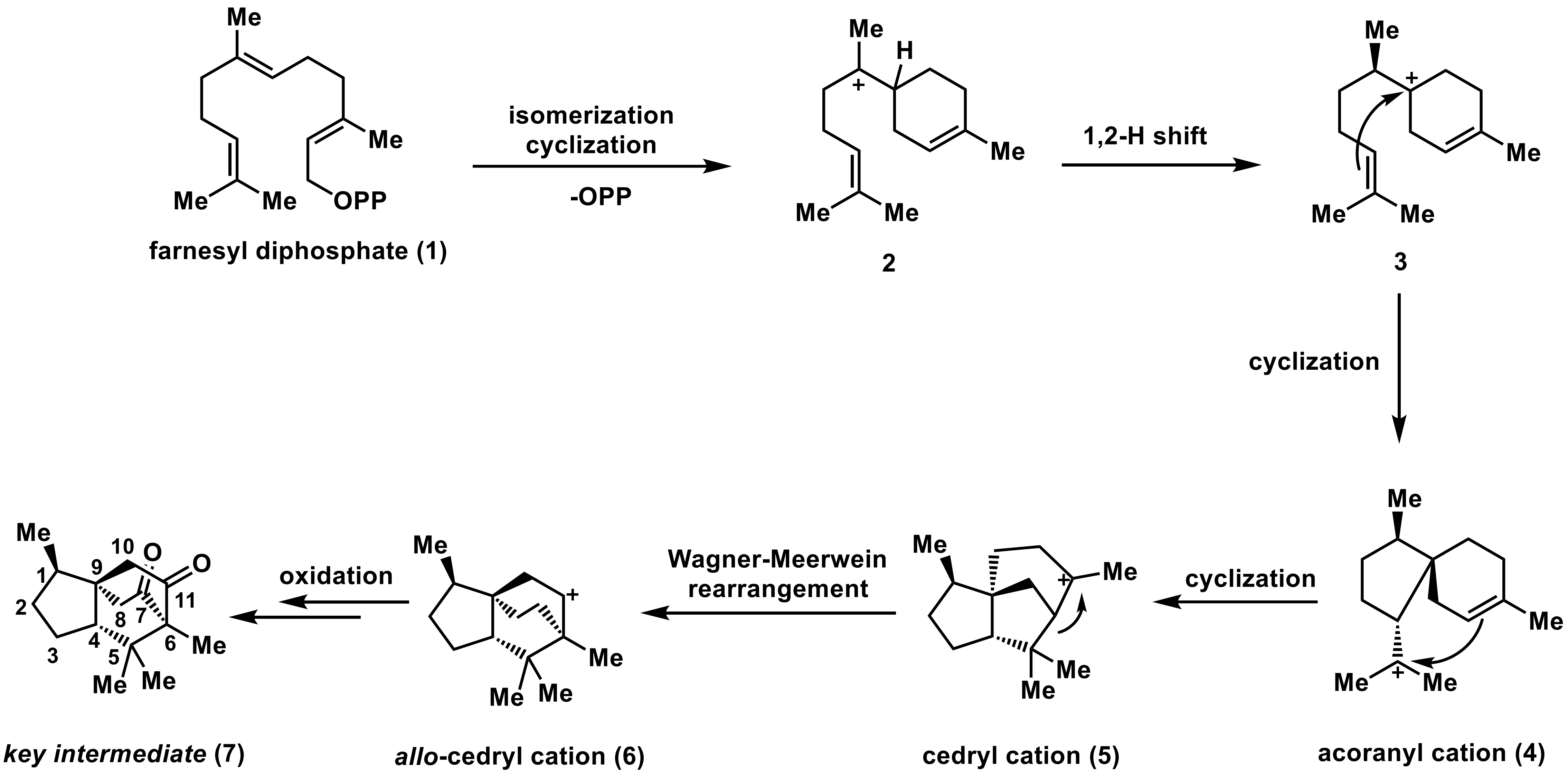
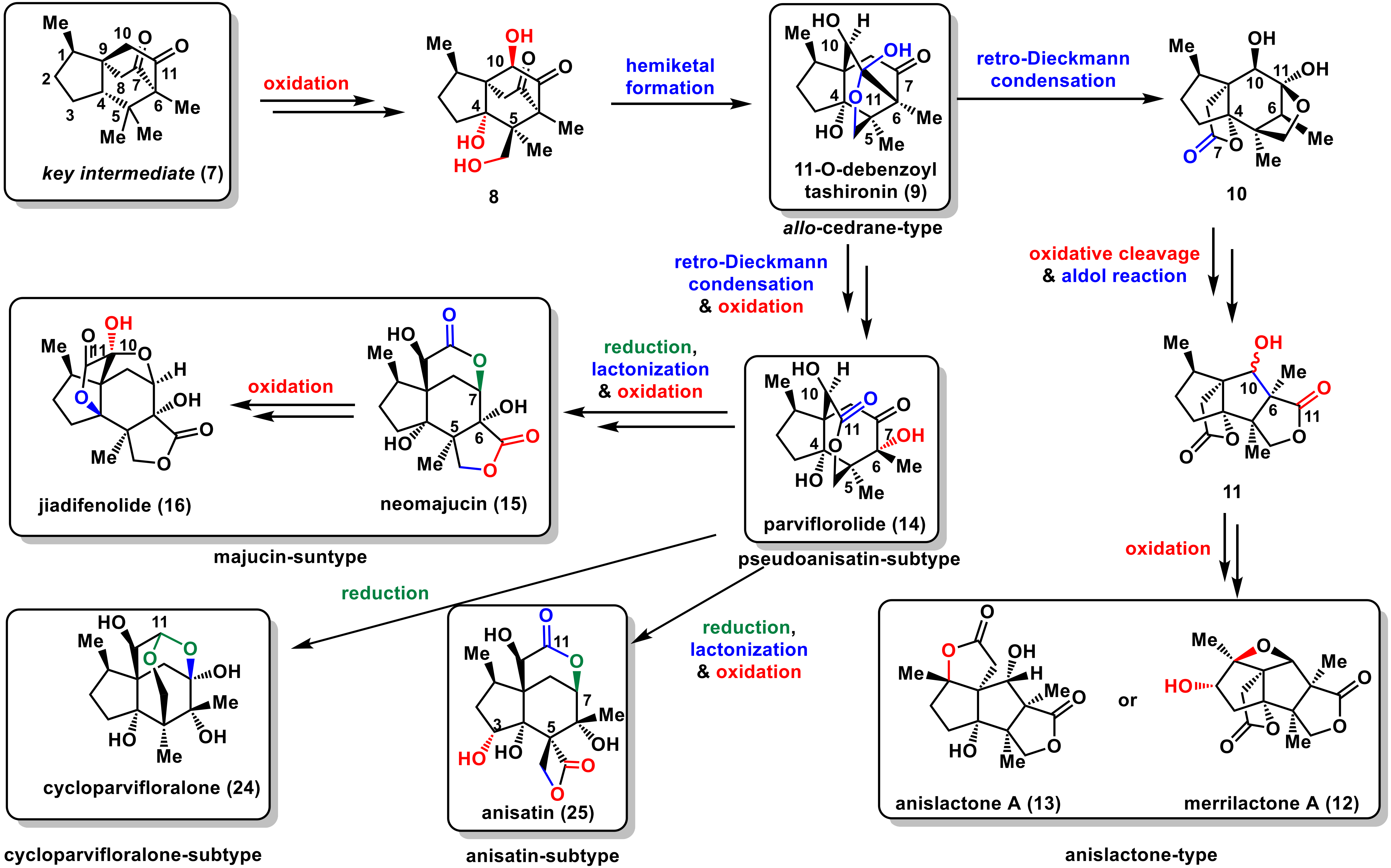
Dedicated to Professor Yong-Qiang Tu on the occasion of his 65th birthday.



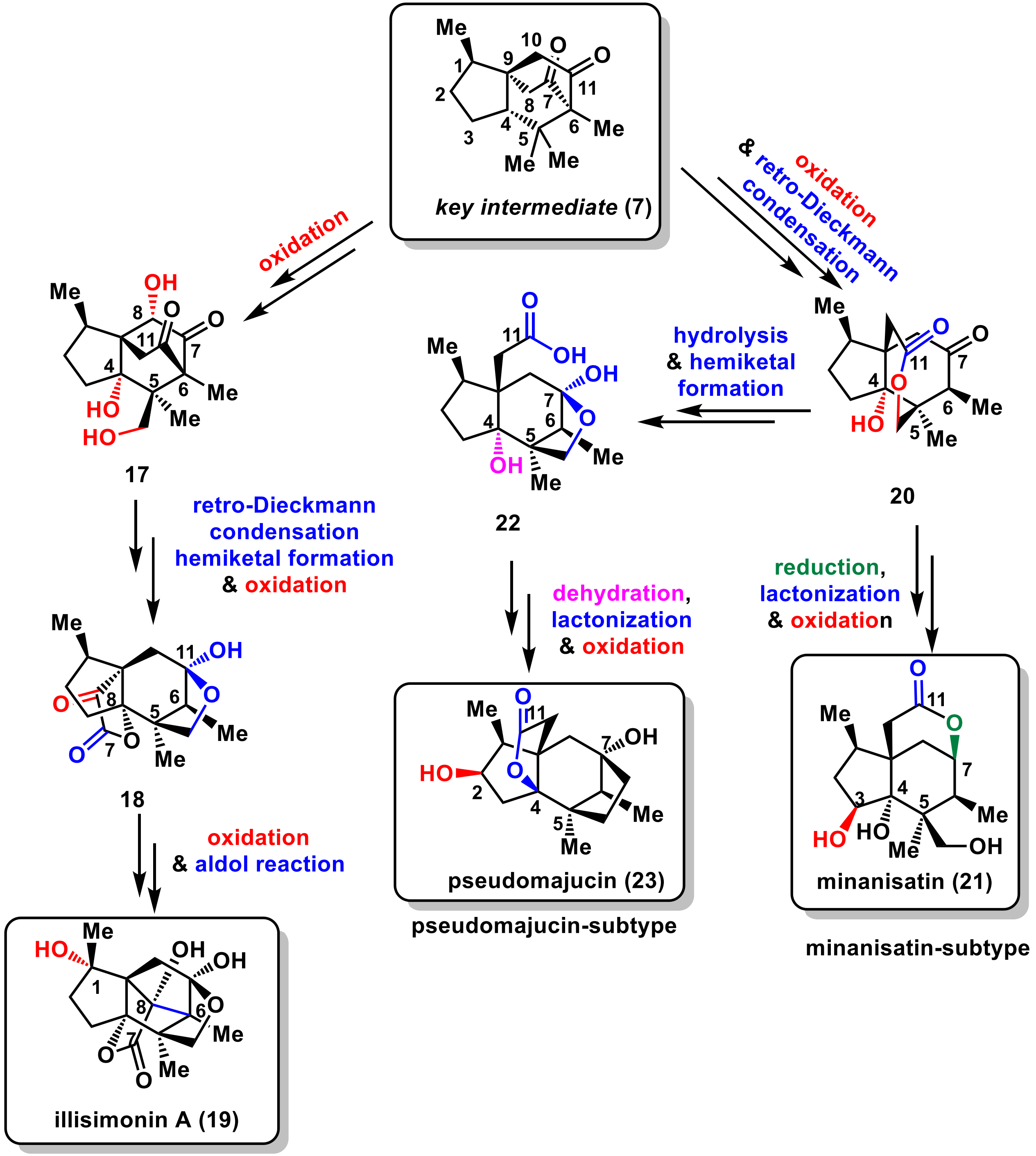
Angew. Chem. Int. Ed., **2023**, e202306367.

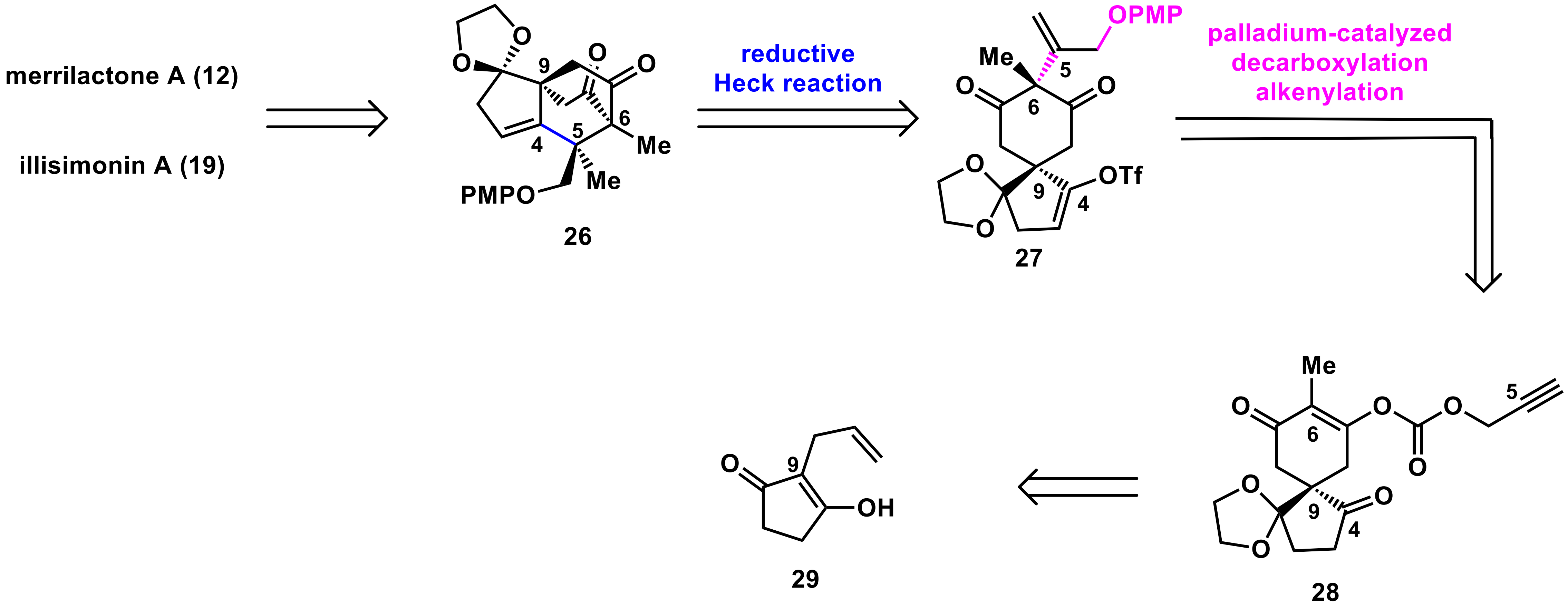


Me
Me
Me
Me
OPP
farnesyl diphosphate (1)
isomerization
cyclization
-OPP
Me
H
Me
Me
Me
2
1,2-H shift
Me
Me
Me
Me
3
cyclization
Me
Me
Me
Me
acoranyl cation (4)
cyclization
Me
Me
Me
Me
cedryl cation (5)
Wagner-Meerwein
rearrangement
Me
Me
Me
Me
allo-cedryl cation (6)
oxidation
Me
10
O
O
9
1
11
2
8
7
4
6
3
5
Me
Me
Me
key intermediate (7)

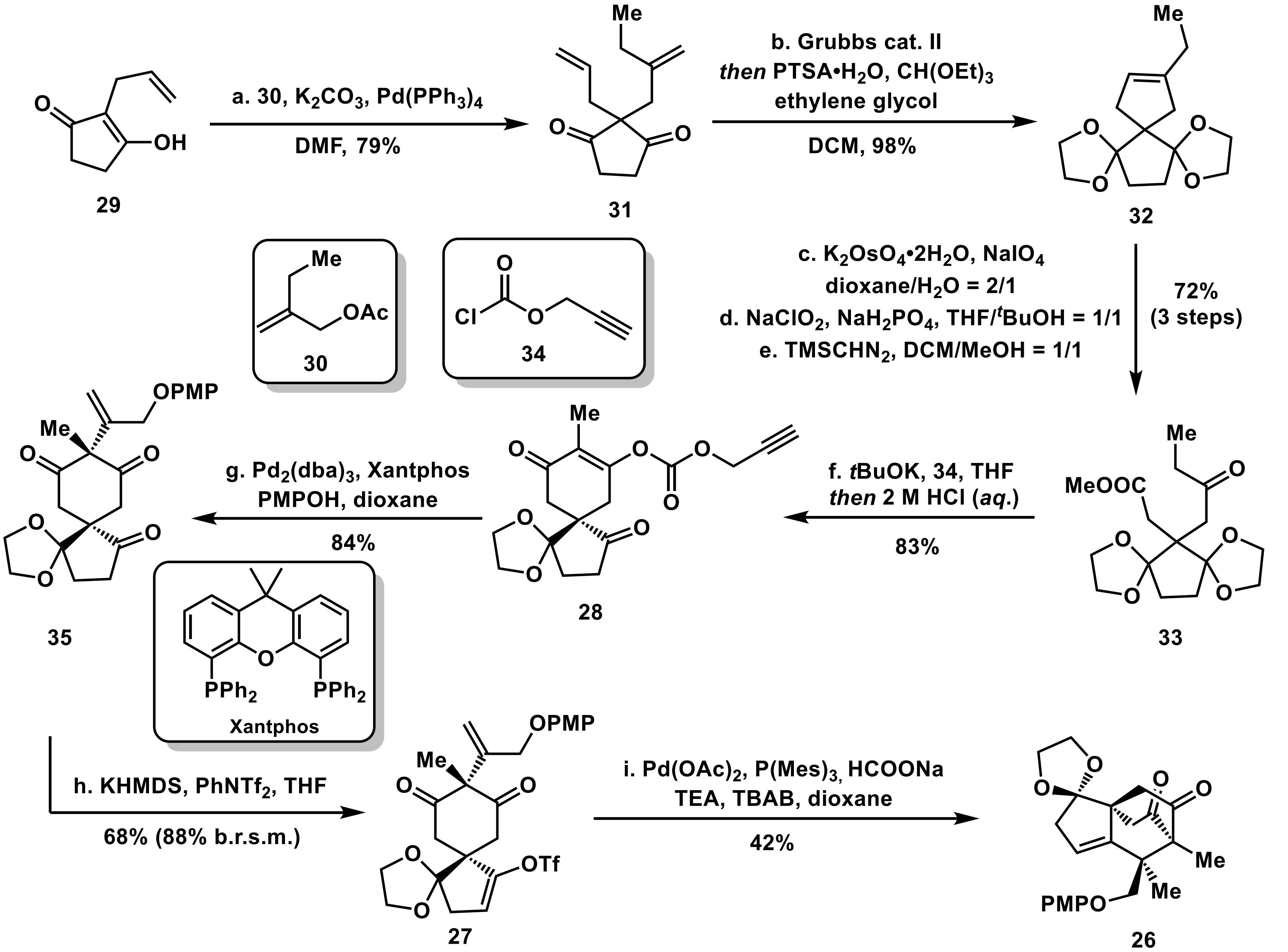


key intermediate (7)
oxidation
8
hemiketal formation
11-O-debenzoyl tashironin (9)
allo-cedrane-type
retro-Dieckmann condensation
10
retro-Dieckmann condensation & oxidation
oxidative cleavage & aldol reaction
11
reduction, lactonization & oxidation
parviflorolide (14)
pseudoanisatin-subtype
neomajucin (15)
oxidation
jiadifenolide (16)
majucin-suntype
reduction
cycloparvifloralone (24)
cycloparvifloralone-subtype
anisatin (25)
anisatin-subtype
reduction, lactonization & oxidation
oxidation
anislactone A (13)
or
merrilactone A (12)
anislactone-type

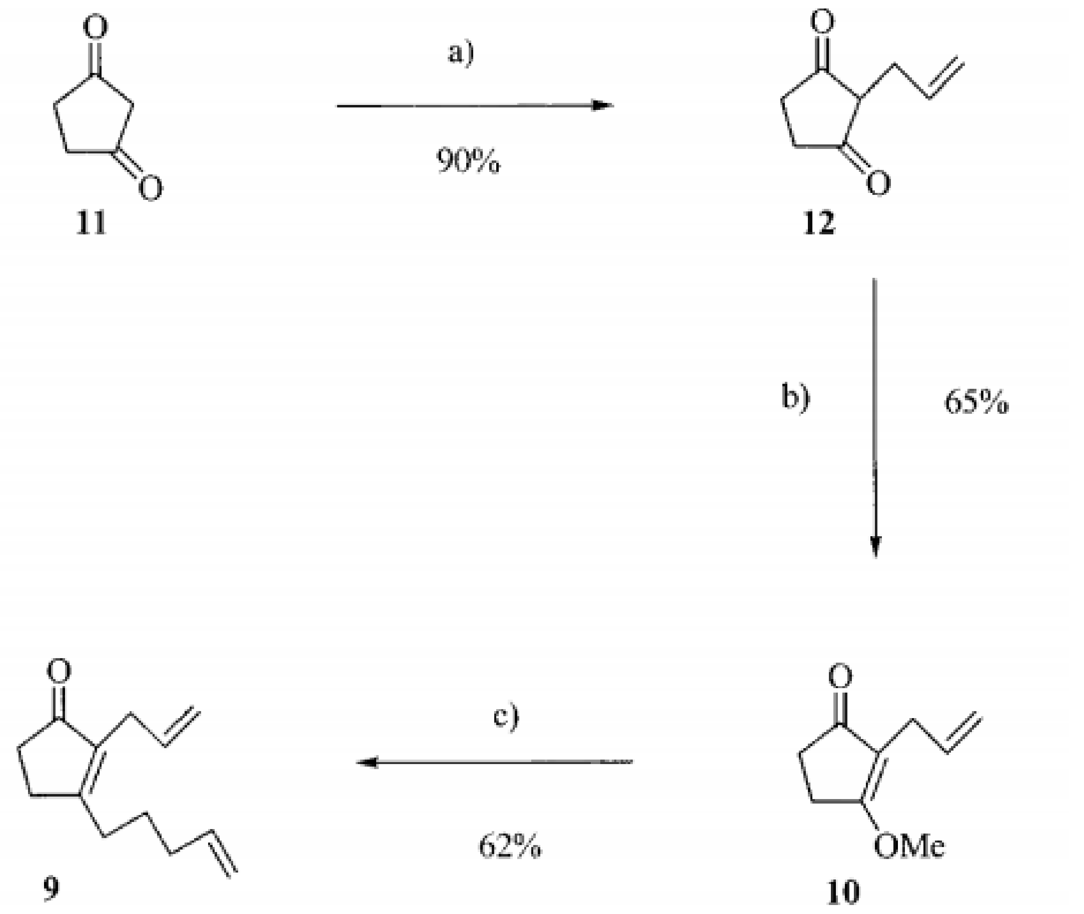

key intermediate (7)
oxidation
& retro-Dieckmann condensation
17
retro-Dieckmann condensation
hemiketal formation
& oxidation
18
oxidation
& aldol reaction
illisimonin A (19)
22
hydrolysis
& hemiketal formation
20
dehydration,
lactonization
& oxidation
pseudomajucin (23)
pseudomajucin-subtype
reduction,
lactonization
& oxidation
minanisatin (21)
minanisatin-subtype



merrilactone A (12)
illisimonin A (19)
26
reductive
Heck reaction
27
palladium-catalyzed
decarboxylation
alkenylation
28
29

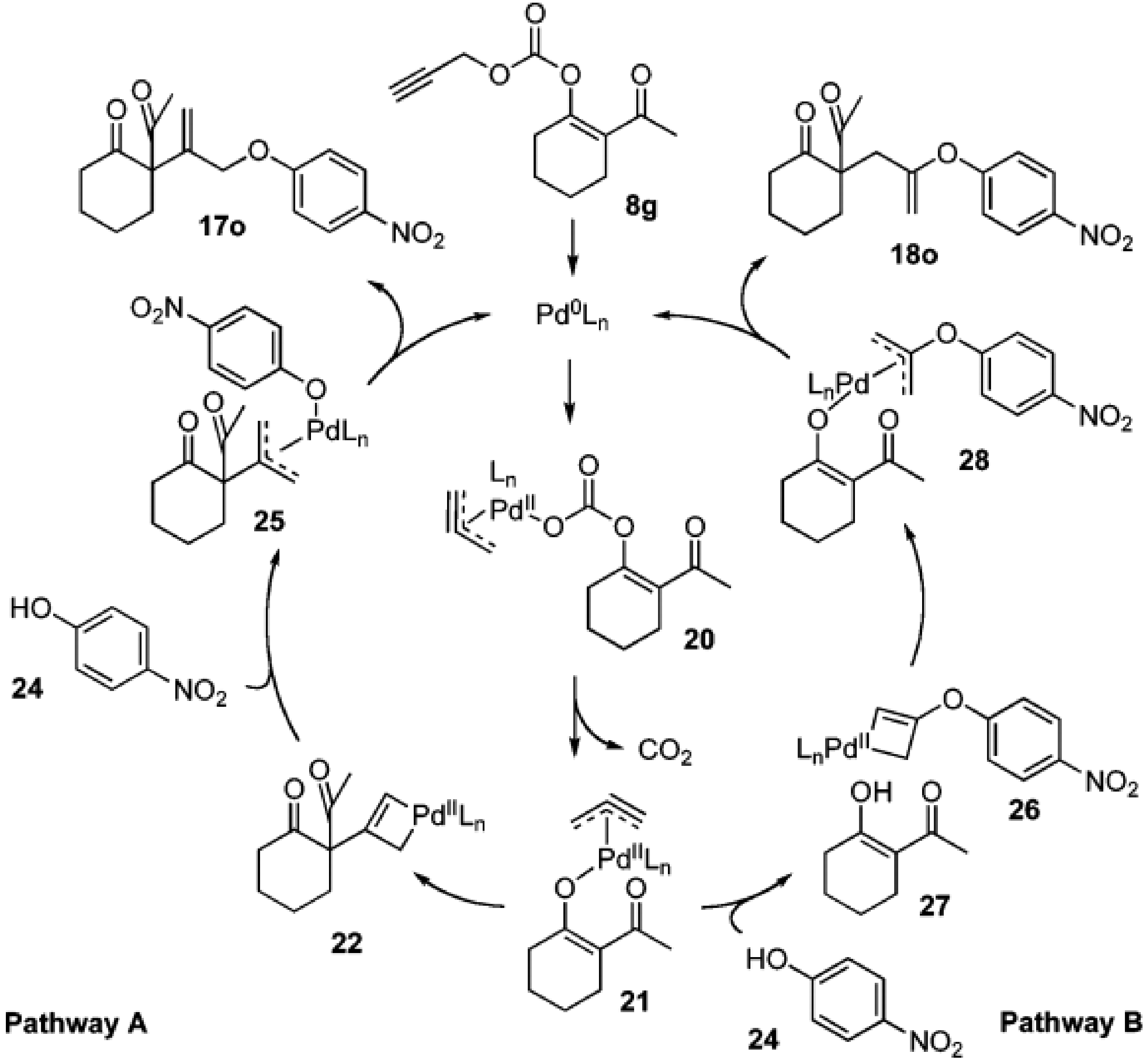


a. 30, K2CO3, Pd(PPh3)4
DMF, 79%
b. Grubbs cat. II
then PTSA•H2O, CH(OEt)3
ethylene glycol
DCM, 98%
c. K2OsO4•2H2O, NaIO4
dioxane/H2O = 2/1
d. NaClO2, NaH2PO4, THF/tBuOH = 1/1
e. TMSCHN2, DCM/MeOH = 1/1
72%
(3 steps)
f. tBuOK, 34, THF
then 2 M HCl (aq.)
83%
g. Pd2(dba)3, Xantphos
PMPOH, dioxane
84%
Xantphos
h. KHMDS, PhNTf2, THF
68% (88% b.r.s.m.)
i. Pd(OAc)2, P(Mes)3, HCOONa
TEA, TBAB, dioxane
42%
29
31
32
30
34
33
28
35
27
26

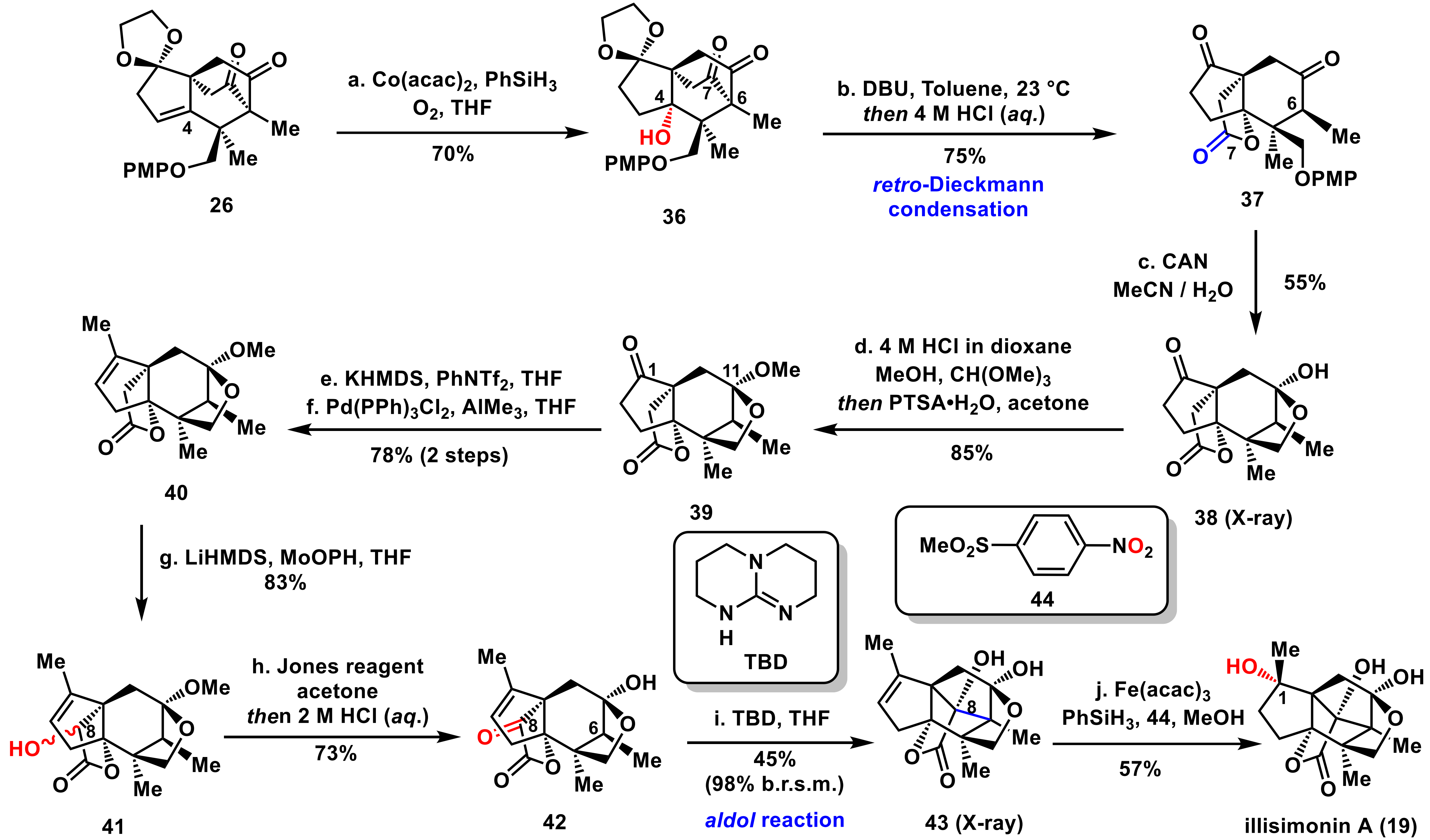


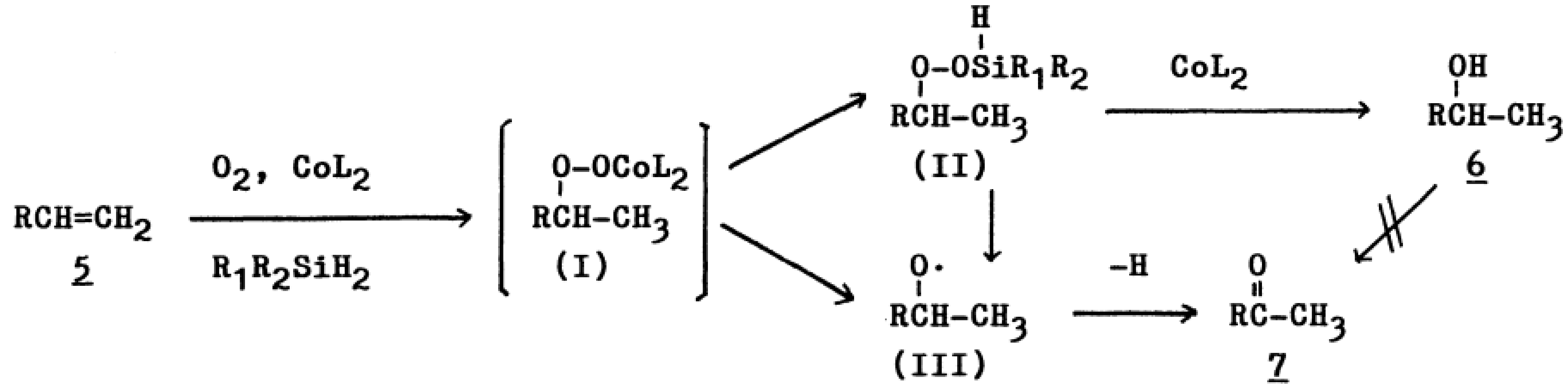
Scheme 2. Synthesis of RCM precursor **9**; reagents and conditions: a) allyl acetate, $[Pd(C_3H_5)Cl_2]_2$, BSA [BSA = $Me_3SiN=C(CH_3)O$-$SiMe_3$], cat. NaOAc, THF, reflux 24 h; b) $(MeO)_3CH$, conc. H_2SO_4, MeOH, reflux 1 h; c) (i) pentenylmagnesium bromide, Et_2O, 0 °C to room temp. 12 h, (ii) 2 M HCl, room temp. 30 min.

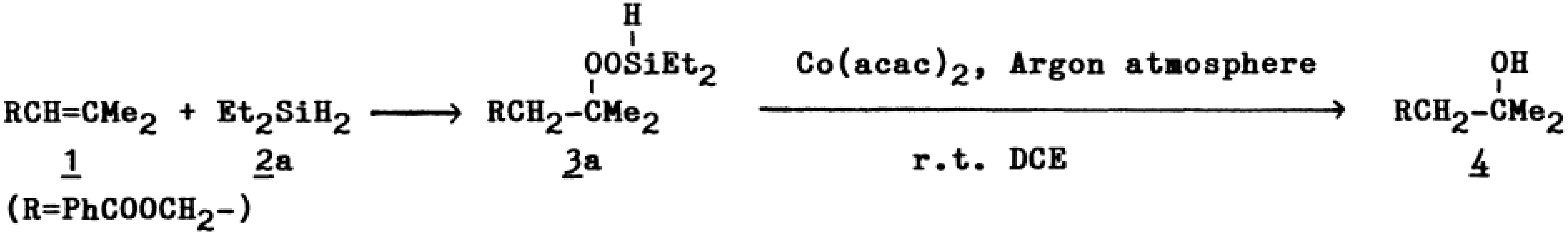
Eur. J. Org. Chem., **2002**, 3145.



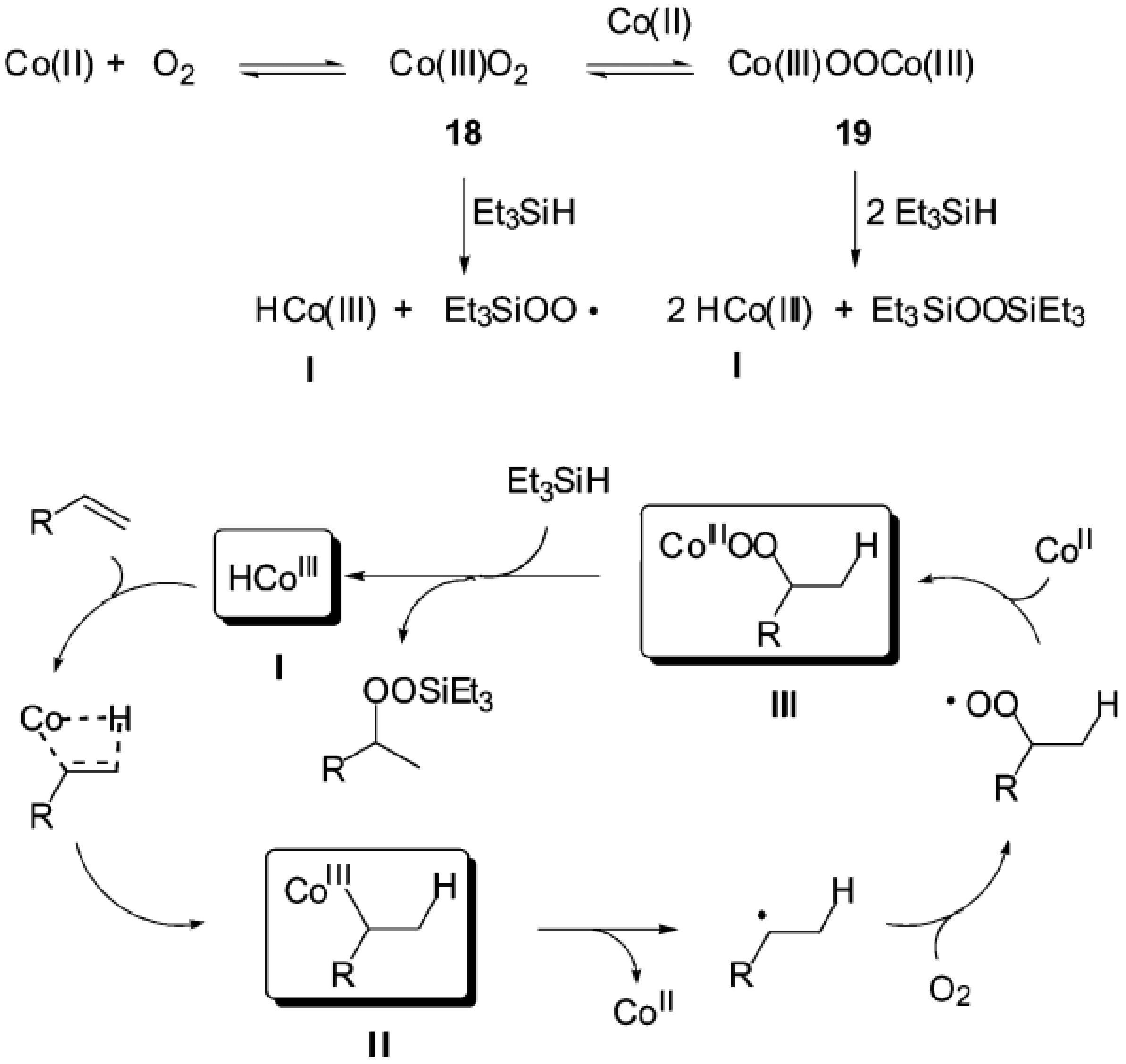
Org. Lett., **2013**, *15*, 3778.


26
a. $Co(acac)_2$, $PhSiH_3$
O_2, THF
70%
36
b. DBU, Toluene, 23 °C
then 4 M HCl (*aq.*)
75%
retro-Dieckmann
condensation
37
c. CAN
MeCN / H_2O
55%
38 (X-ray)
d. 4 M HCl in dioxane
MeOH, $CH(OMe)_3$
then PTSA•H_2O, acetone
85%
39
e. KHMDS, $PhNTf_2$, THF
f. $Pd(PPh)_3Cl_2$, $AlMe_3$, THF
78% (2 steps)
40
g. LiHMDS, MoOPH, THF
83%
41
h. Jones reagent
acetone
then 2 M HCl (*aq.*)
73%
42
TBD
44
i. TBD, THF
45%
(98% b.r.s.m.)
aldol reaction
43 (X-ray)
j. $Fe(acac)_3$
$PhSiH_3$, 44, MeOH
57%
illisimonin A (19)



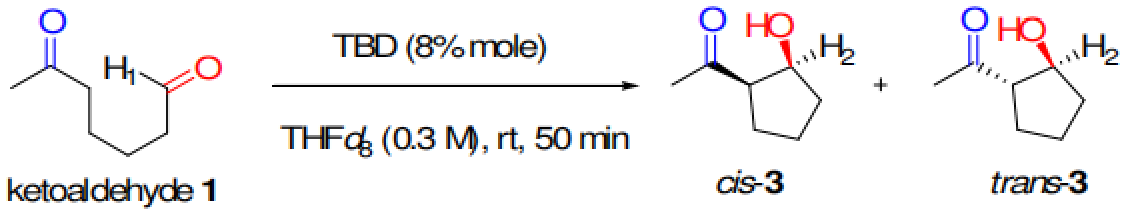


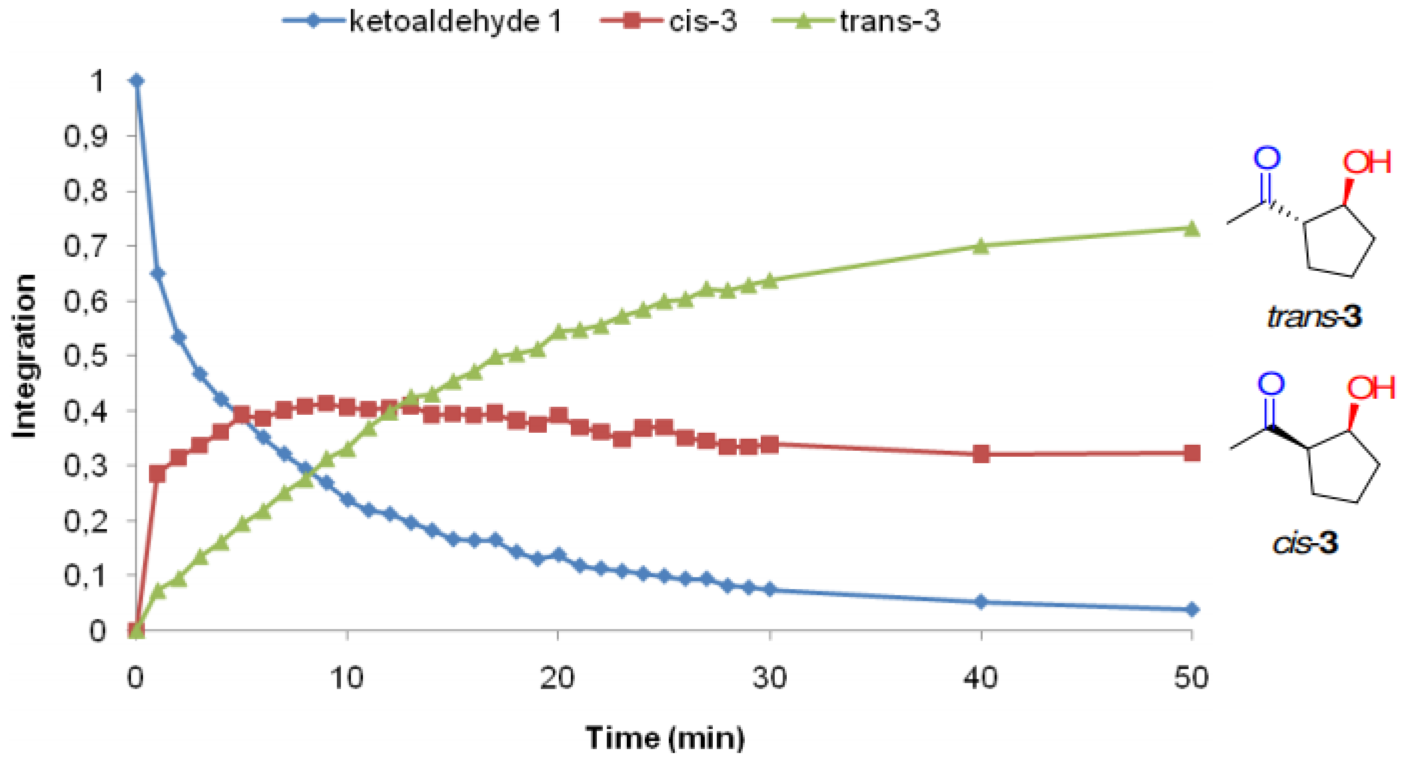
Chem. Lett., **1989**, *18*, 1071.



Org. Lett., **2002**, *4*, 3595.

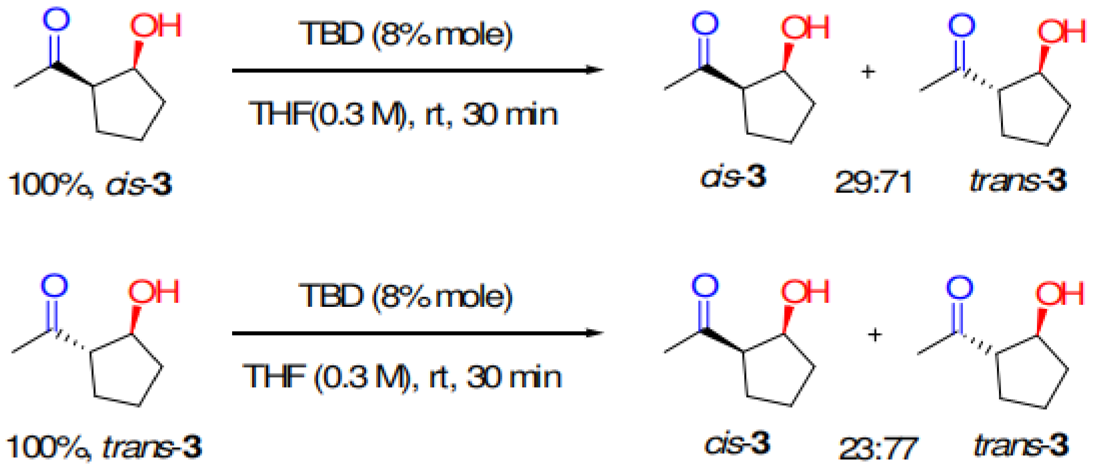
5. Study of the diastereoselectivity of the aldol reaction of ketoaldehyde 1 catalyzed by TBD by ^{1}H NMR spectrometry





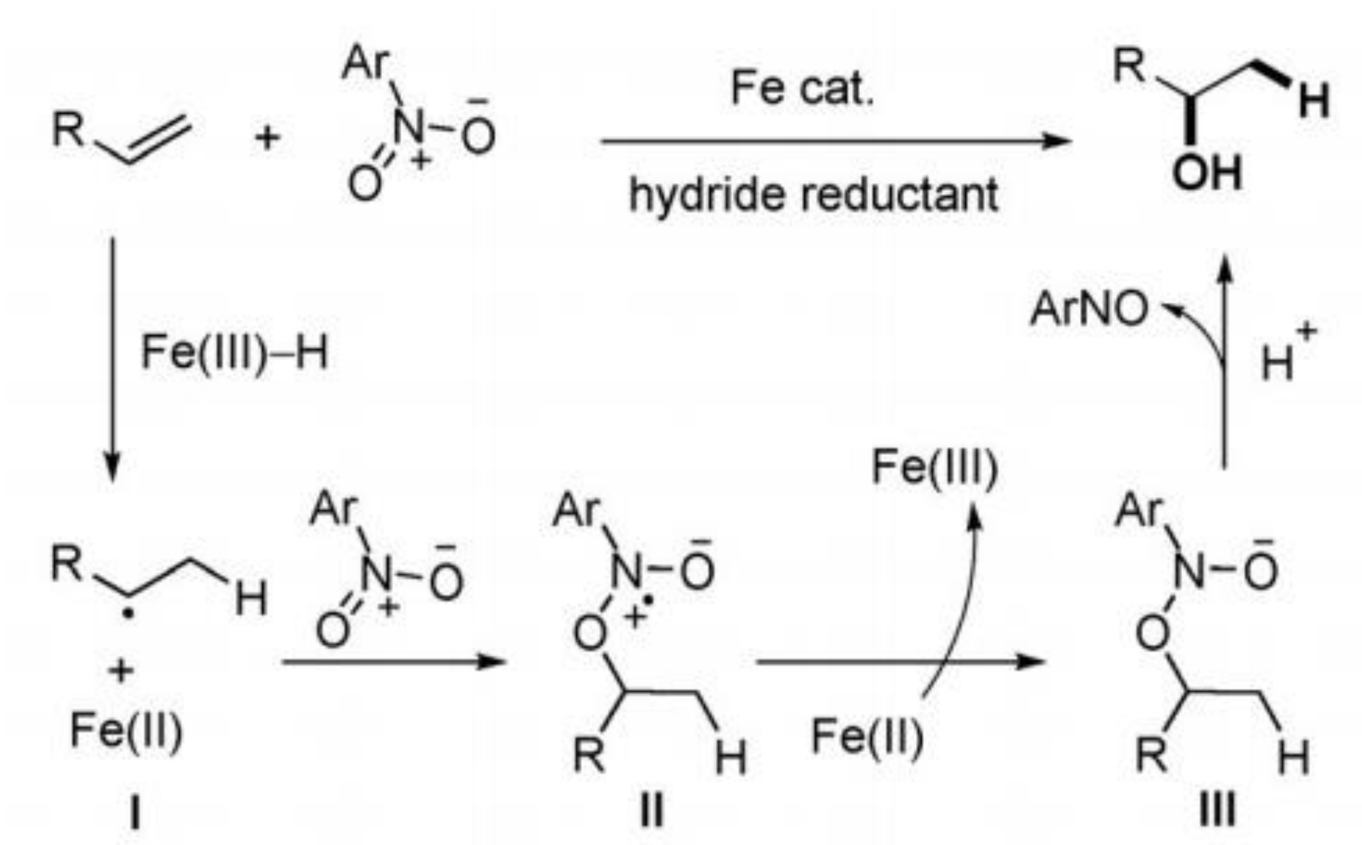
Graphic 1. Kinetic of the intramolecular aldol reaction of ketoaldehyde 1 organocatalyzed by TBD

J. Org. Chem., **2010**, *75*, 4728.



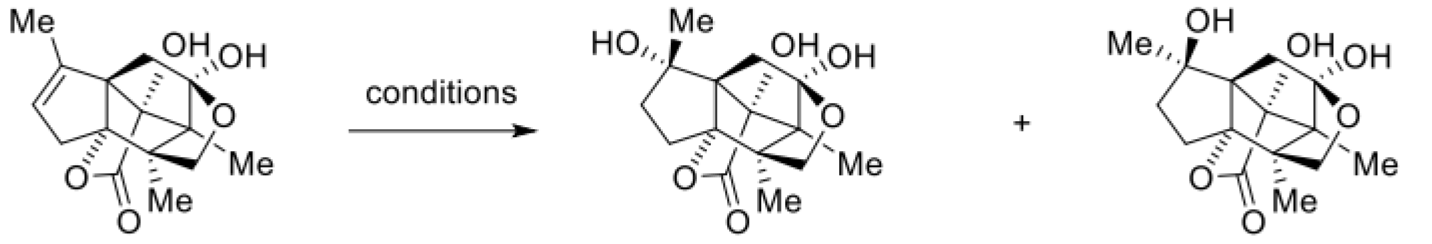
Scheme 1. Thermodynamic equilibrium of the formation of the two diasteroisomers *cis*- and *trans*-3.

J. Org. Chem., **2010**, *75*, 4728.



Angew. Chem. Int. Ed., **2021**, *60*, 8313.

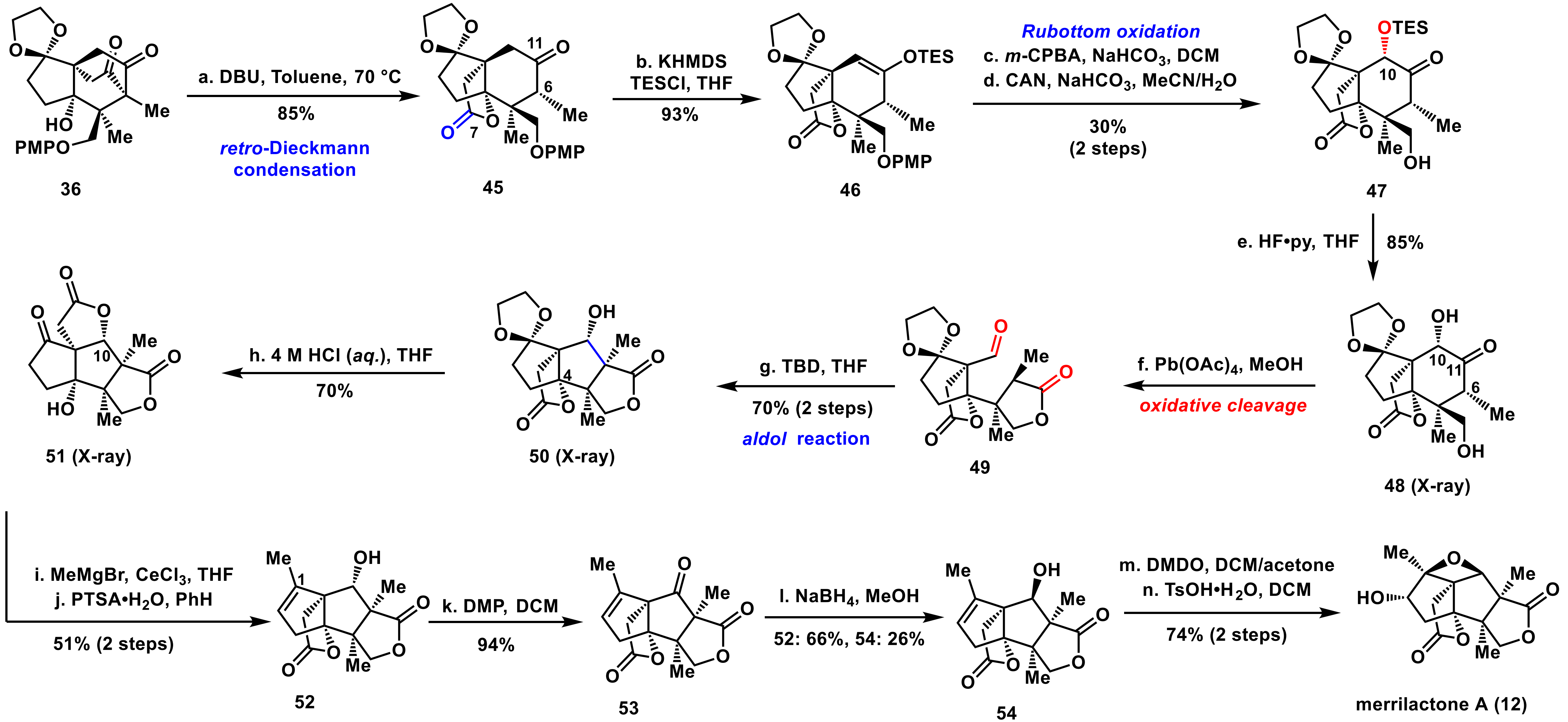
Table S1. Optimization of the Mukaiyama hydration of **43**.



43 illisimonin A (**19**) 1-*epi*-illisimonin A (**19'**)

Entry	**Conditions**[a]	**Temperature (°C)**	**Time (h)**	**d.r. (19:19')**[b]	**Yield (%)**[c]
1	A	23	4	1:1.8	73
2	A	0	14	1:1.3	53
3	B	23	6	>15:1	24
4	B	10	6	>15:1	47
5	B	5	8	>15:1	51
6	**B**	**0**	**8**	**>20:1**	**62**
7	B	-5	9	>20:1	47
8	B	-10	10	6:1	42

[a]Condition A: $Co(acac)_2$ (0.3equiv), $PhSiH_2(O$*i*-Pr) (5.0 equiv), O_2, THF. Condition B: $Fe(acac)_3$ (0.025 equiv), $NaHCO_3$ (2.0 equiv), methyl 4-nitrobenzenesulfonate (1.3 equiv), MeOH.
[b]Determined by ^{1}H NMR spectroscopy.
[c]Isolated yield.

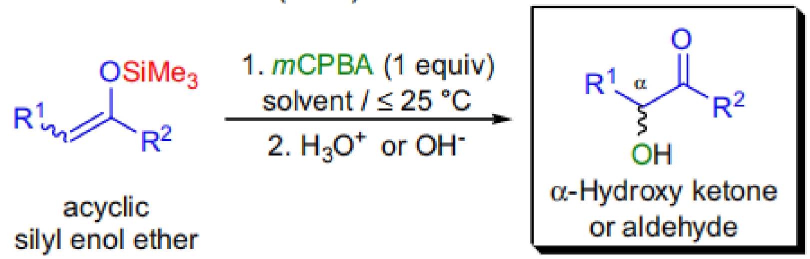


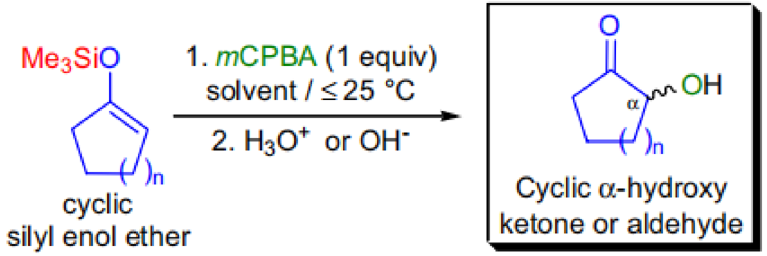
a. DBU, Toluene, 70 °C
85%
retro-Dieckmann condensation
b. KHMDS TESCl, THF
93%
Rubottom oxidation
c. m-CPBA, NaHCO3, DCM
d. CAN, NaHCO3, MeCN/H2O
30% (2 steps)
e. HF•py, THF
85%
f. Pb(OAc)4, MeOH
oxidative cleavage
g. TBD, THF
70% (2 steps)
aldol reaction
h. 4 M HCl (aq.), THF
70%
i. MeMgBr, CeCl3, THF
j. PTSA•H2O, PhH
51% (2 steps)
k. DMP, DCM
94%
l. NaBH4, MeOH
52: 66%, 54: 26%
m. DMDO, DCM/acetone
n. TsOH•H2O, DCM
74% (2 steps)
36
45
46
47
48 (X-ray)
49
50 (X-ray)
51 (X-ray)
52
53
54
merrilactone A (12)

RUBOTTOM OXIDATION

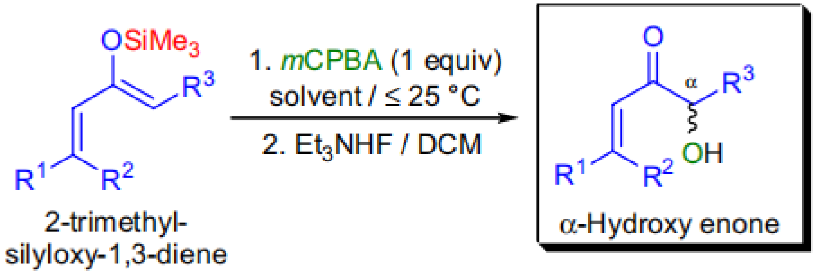
(References are on page 667)

Rubottom & Hassner (1974):

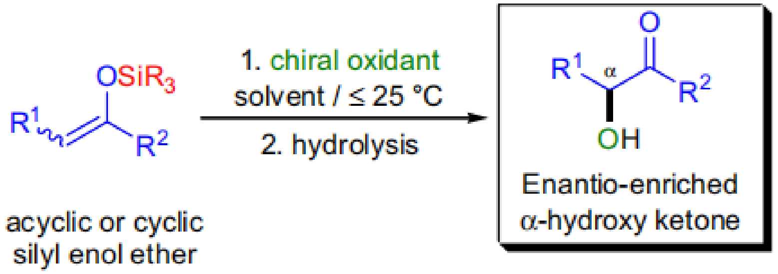




Oxidation of 2-trimethylsilyloxy-1,3-dienes:



Asymmetric modification:



R^{1-3} = H, alkyl, aryl, substituted alkyl and aryl; SiR_3 = $SiMe_3$, $SiMe_2$(t-Bu), $SiEt_3$; solvent: CH_2Cl_2, pentane, toluene; n = 1-3;
chiral oxidant: Davis' chiral oxaziridine, Shi's D-fructose derived ketone/Oxone, (Salen)manganese(III)-complexes/NaOCl or PhIO

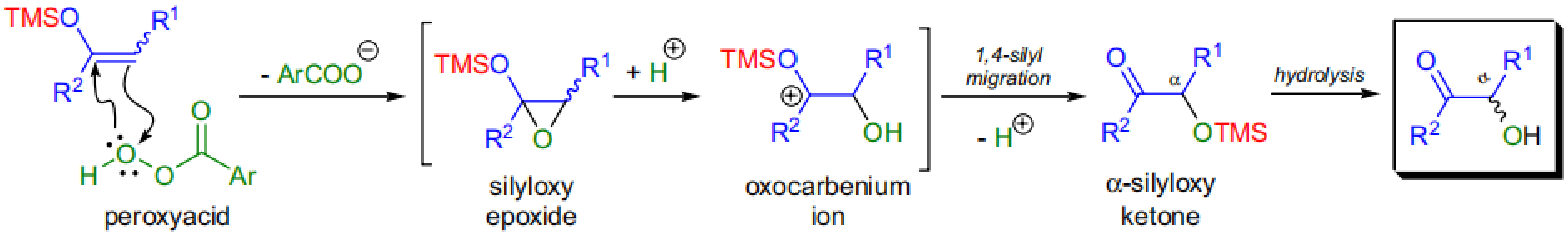
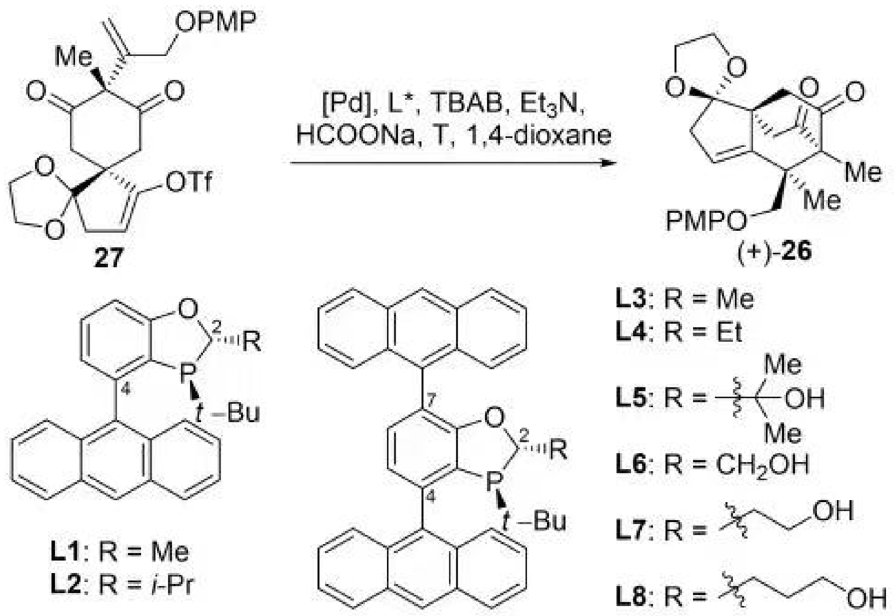


Table S2. Screening the Ligands for the Asymmetric Reductive Heck Reaction of 27.



Entry[a]	[Pd]	L*	T (°C)	Yield (%)[b]	ee (%)[c]
1	$Pd(OAc)_2$	L1	90	37	7
2	$Pd(OAc)_2$	L2	90	39	5
3	$Pd(OAc)_2$	L3	90	33	11
4	$Pd(OAc)_2$	L4	90	32	20
5	$Pd(OAc)_2$	L5	90	30	50
6	$Pd(OAc)_2$	L6	90	31	43
7	$Pd(OAc)_2$	L7	90	23	60
8	$Pd(OAc)_2$	L8	90	27	40
9	$Pd_2(dba)_3$	L7	90	40	30
10	**$Pd_2(dba)_3$**	**L7**	**80**	**23**	**82**
11	$Pd_2(dba)_3$	L7	70	10	60

[a] Conditions: $Pd(OAc)_2$ (10 mol%) or $Pd_2(dba)_3$ (5 mol%), L* (10 mol%), TBAB (2.0 equiv), Et_3N (3.0 equiv), HCOONa (2.0 equiv), 1,4-dioxane. [b] Isolated yield. [c] Determined by Ultra-Performance Convergence Chromatography (UPCC).