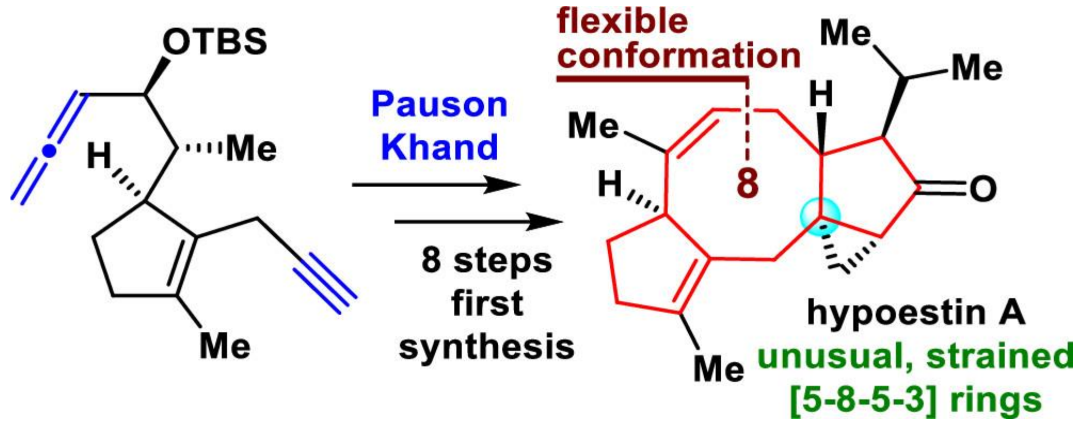
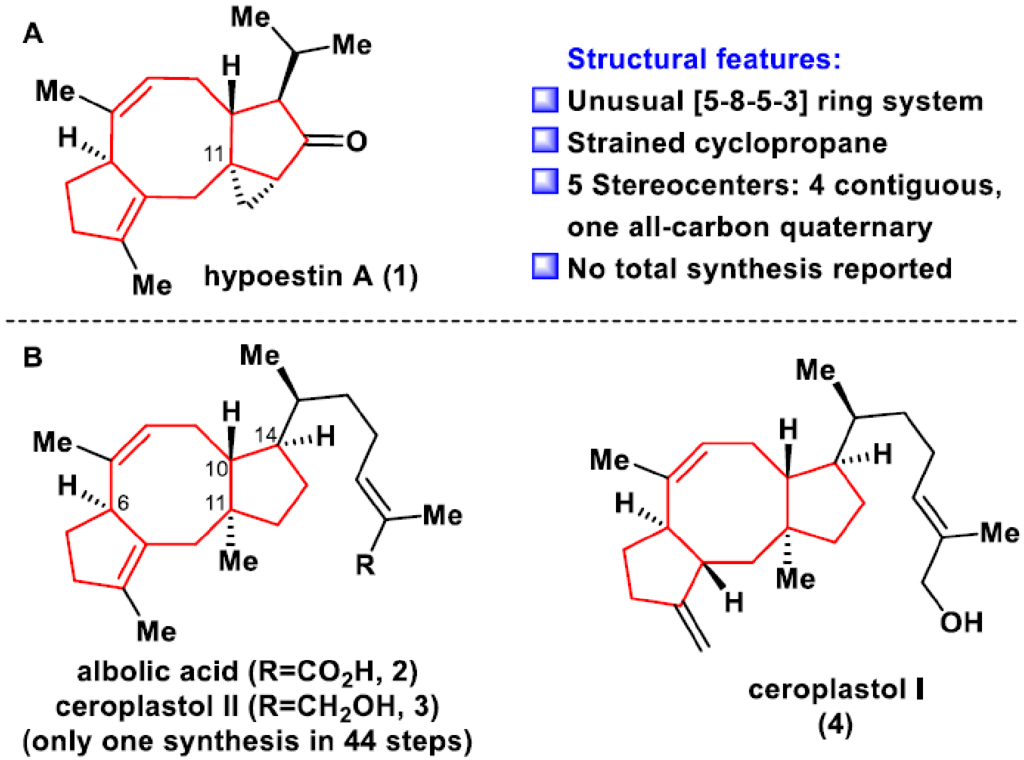
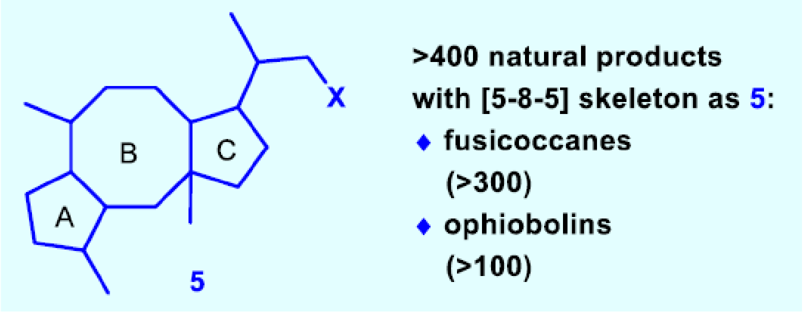
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Asymmetric Total Syntheses of Hypoestin A, Albolic Acid, and Ceroplastol II

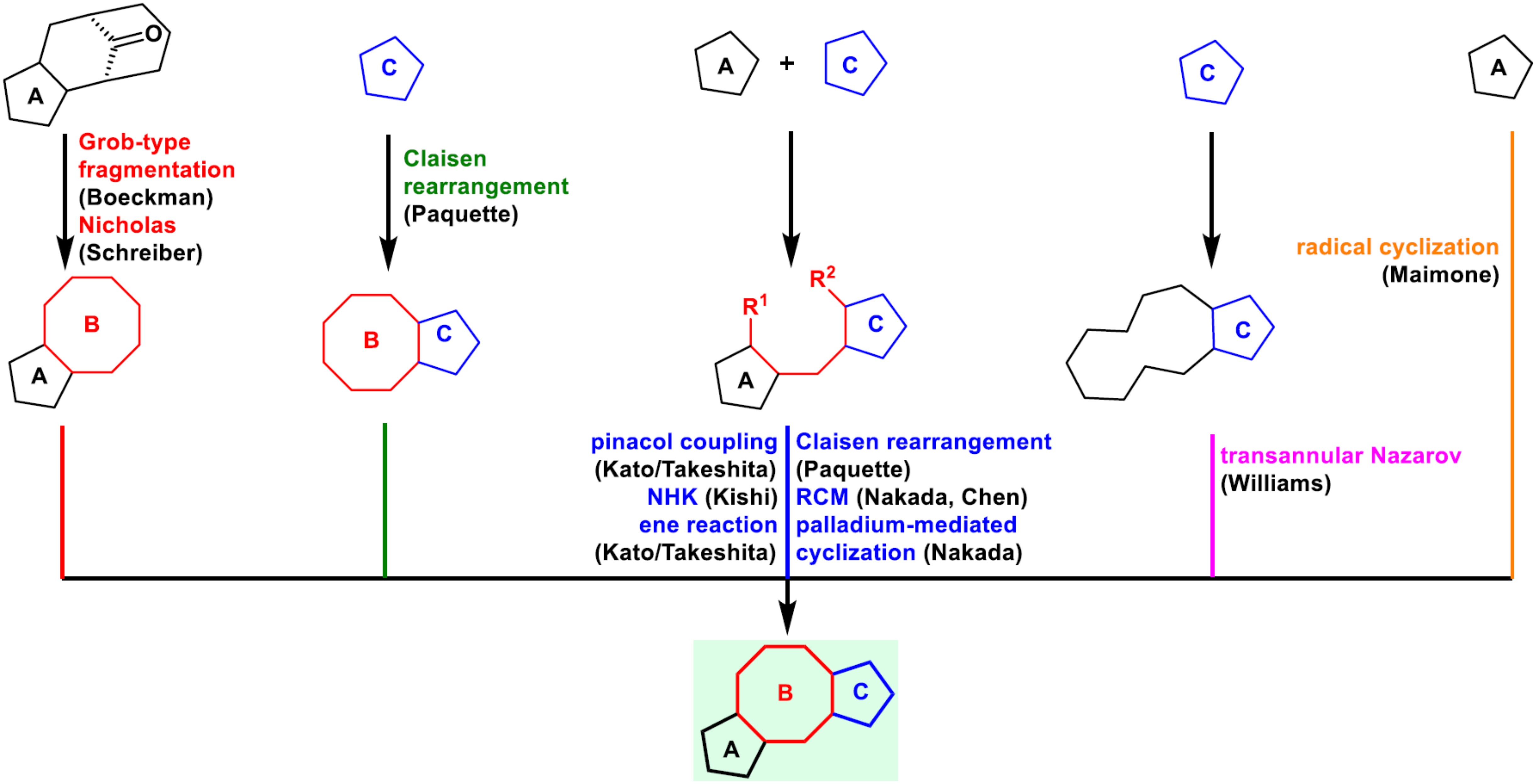
Yong-Qiang Wang, Kunhua Xu, Long Min, and Chuang-Chuang Li*



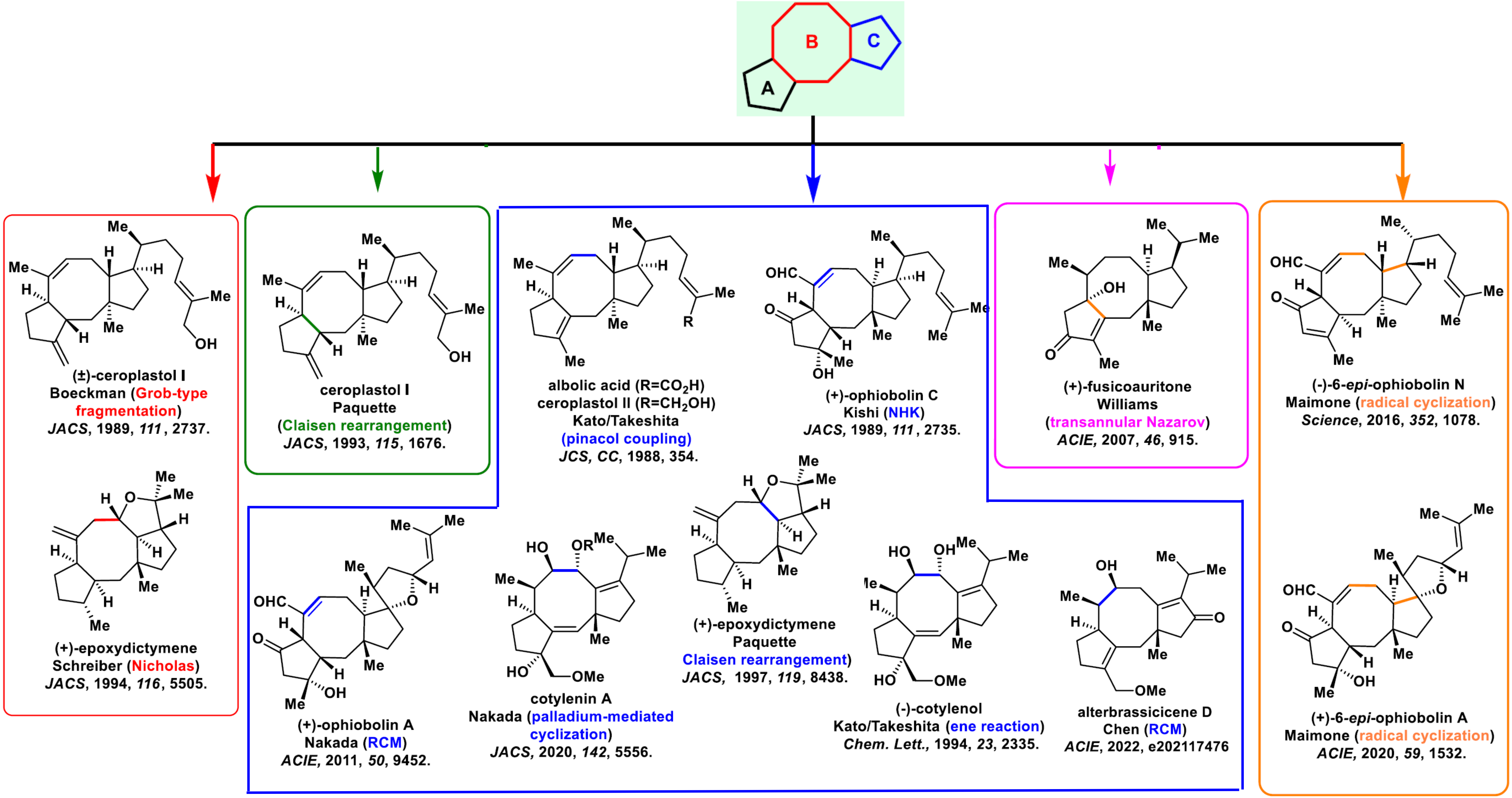




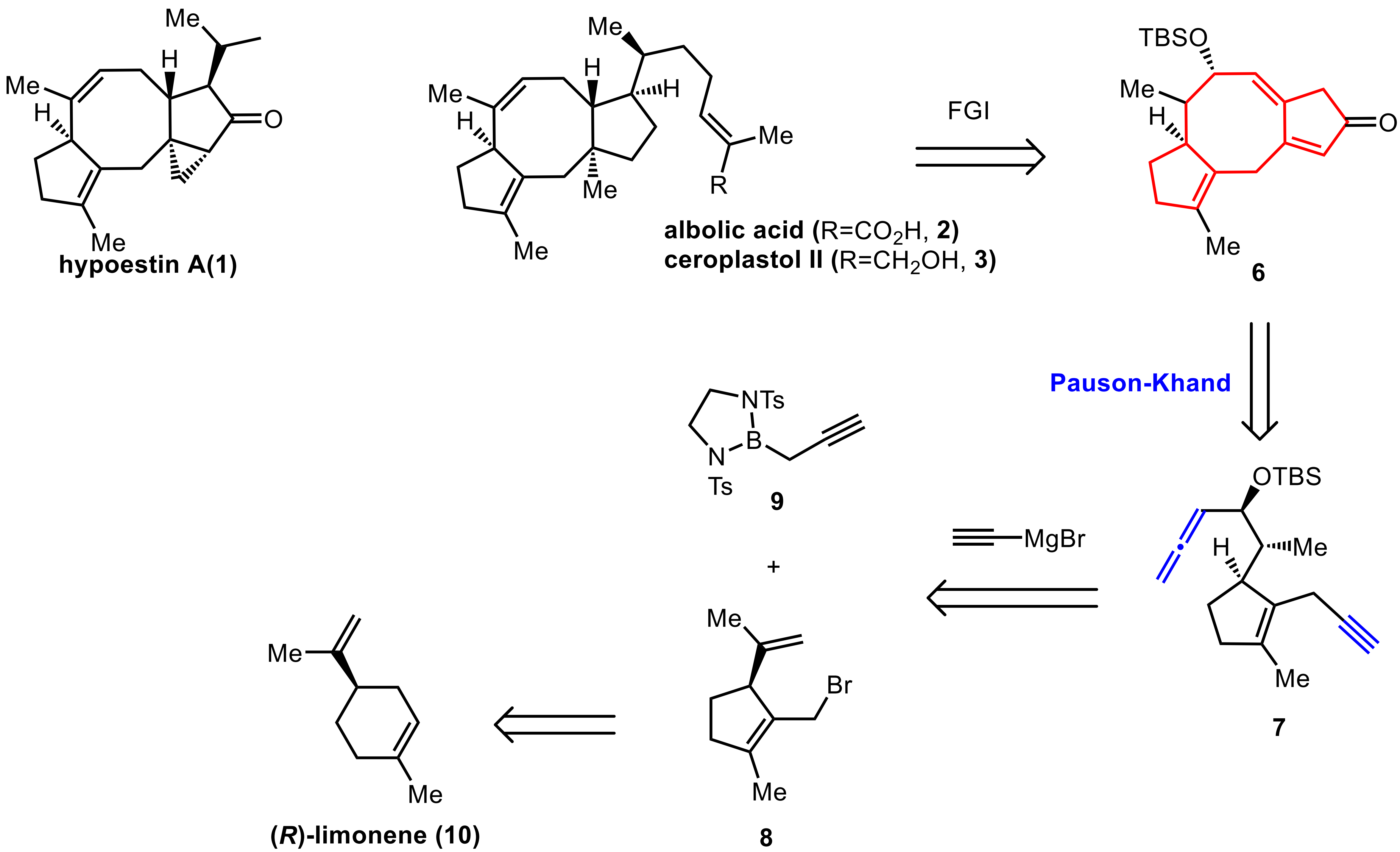
DOI: 10.1021/jacs.2c04633.

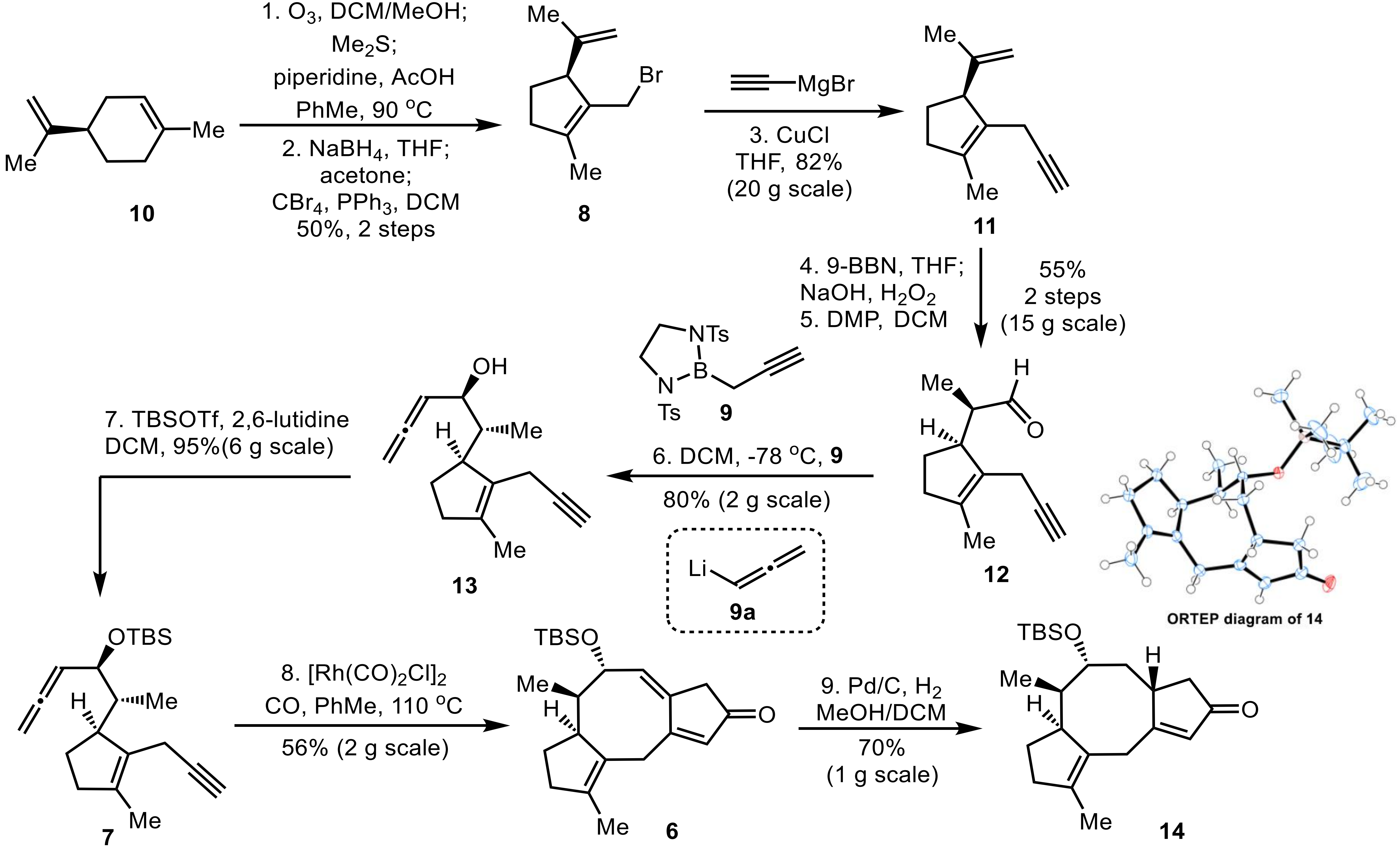


O
A
Grob-type fragmentation (Boeckman)
Nicholas (Schreiber)
B
C
Claisen rearrangement (Paquette)
A + C
R1
R2
pinacol coupling (Kato/Takeshita)
NHK (Kishi)
ene reaction (Kato/Takeshita)
Claisen rearrangement (Paquette)
RCM (Nakada, Chen)
palladium-mediated cyclization (Nakada)
transannular Nazarov (Williams)
radical cyclization (Maimone)



A
B
C
(±)-ceroplastol I
Boeckman (Grob-type fragmentation)
JACS, 1989, 111, 2737.
ceroplastol I
Paquette
(Claisen rearrangement)
JACS, 1993, 115, 1676.
albolic acid (R=CO2H)
ceroplastol II (R=CH2OH)
Kato/Takeshita
(pinacol coupling)
JCS, CC, 1988, 354.
(+)-ophiobolin C
Kishi (NHK)
JACS, 1989, 111, 2735.
(+)-fusicoauritone
Williams
(transannular Nazarov)
ACIE, 2007, 46, 915.
(-)-6-epi-ophiobolin N
Maimone (radical cyclization)
Science, 2016, 352, 1078.
(+)-epoxydictymene
Schreiber (Nicholas)
JACS, 1994, 116, 5505.
(+)-ophiobolin A
Nakada (RCM)
ACIE, 2011, 50, 9452.
cotylenin A
Nakada (palladium-mediated cyclization)
JACS, 2020, 142, 5556.
(+)-epoxydictymene
Paquette
Claisen rearrangement)
JACS, 1997, 119, 8438.
(-)-cotylenol
Kato/Takeshita (ene reaction)
Chem. Lett., 1994, 23, 2335.
alterbrassicicene D
Chen (RCM)
ACIE, 2022, e202117476
(+)-6-epi-ophiobolin A
Maimone (radical cyclization)
ACIE, 2020, 59, 1532.


Me
H
Me
H
O
Me
hypoestin A(1)
Me
Me
H
H
H
Me
Me
R
Me
albolic acid (R=CO2H, 2)
ceroplastol II (R=CH2OH, 3)
FGI
TBSO
Me
H
O
Me
6
Pauson-Khand
NTs
B
N
Ts
9
+
MgBr
OTBS
H
Me
Me
7
Me
Br
Me
8
Me
Me
(R)-limonene (10)



1. O3, DCM/MeOH; Me2S; piperidine, AcOH PhMe, 90 °C
2. NaBH4, THF; acetone; CBr4, PPh3, DCM 50%, 2 steps
10
8
MgBr
3. CuCl THF, 82% (20 g scale)
11
4. 9-BBN, THF; NaOH, H2O2
5. DMP, DCM
55% 2 steps (15 g scale)
12
9
6. DCM, -78 °C, 9
80% (2 g scale)
9a
13
7. TBSOTf, 2,6-lutidine DCM, 95%(6 g scale)
7
8. [Rh(CO)2Cl]2 CO, PhMe, 110 °C
56% (2 g scale)
6
9. Pd/C, H2 MeOH/DCM
70% (1 g scale)
14
ORTEP diagram of 14

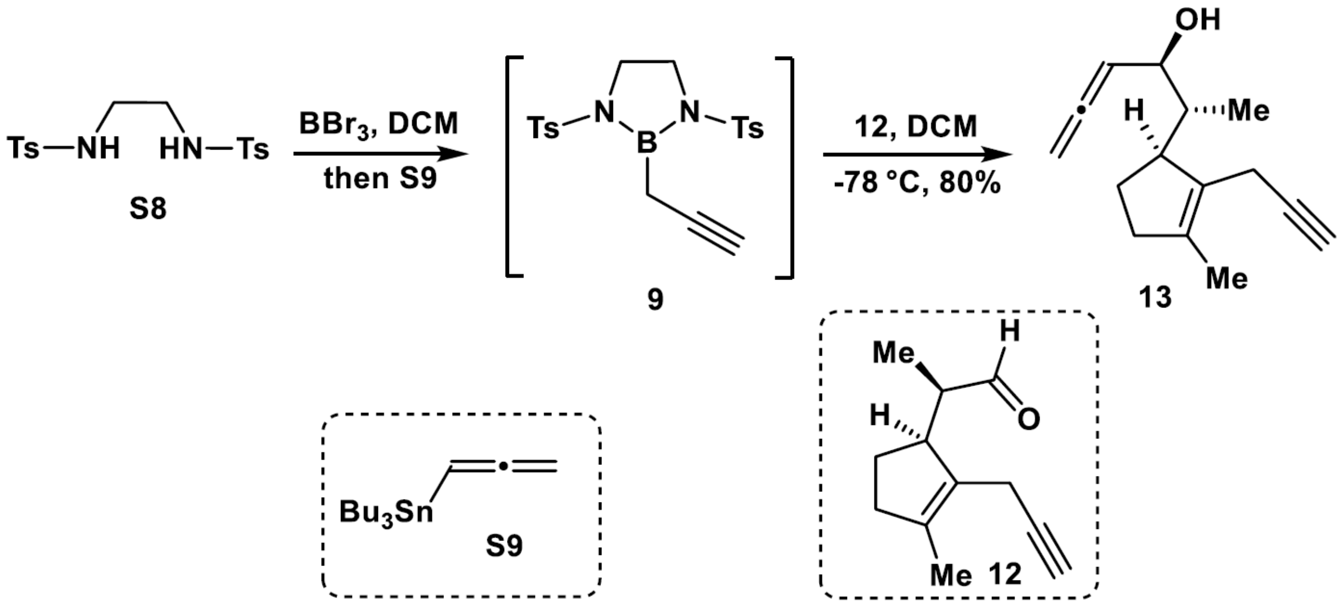
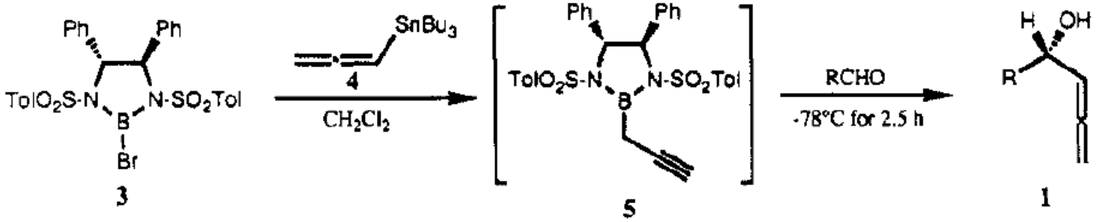
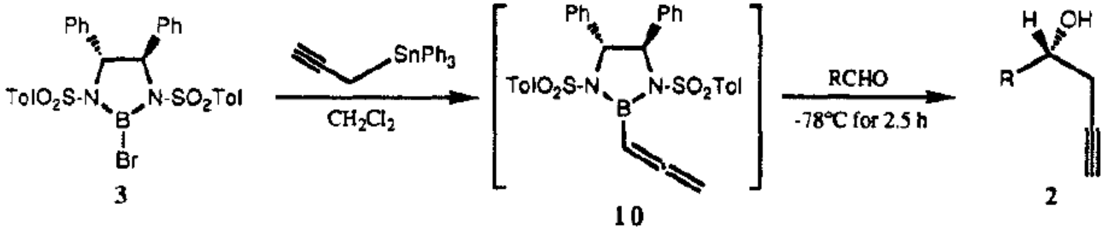


Table I



aldehyde	isolated yield, %	% ee of **1**	abs config
n-$C_5H_{11}CHO$	82	>99	*S*
$(CH_3)_2CHCHO$	74	>99	*S*
c-$C_6H_{11}CHO$	78	>99	*S*
$(CH_3)_3CCHO$	78	>99	*S*
PhCHO	72	>99	*R*
PhCH═CHCHO	74	>99	*S*

Table II

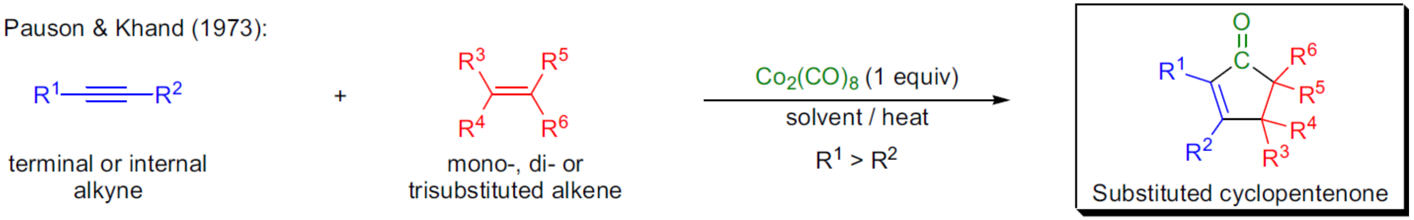


aldehyde	isolated yield, %	% ee of **2**	abs config
n-$C_5H_{11}CHO$	81	91	*S*
$(CH_3)_2CHCHO$	76	94	*R*
c-$C_6H_{11}CHO$	82	92	*R*
$(CH_3)_3CCHO$	74	98	*R*
PhCHO	76	96	*R*
PhCH═CHCHO	79	98	*R*

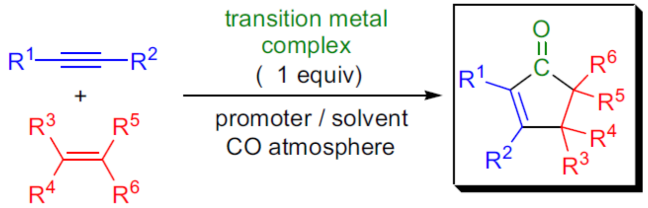
PAUSON-KHAND REACTION

(References are on page 647)

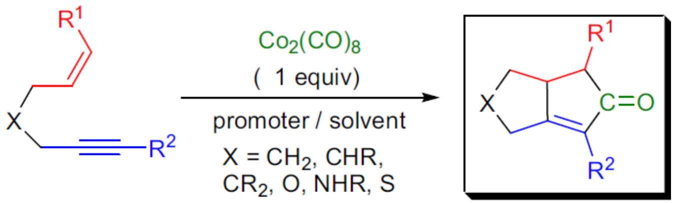
Pauson & Khand (1973):



Modified P-K reaction:



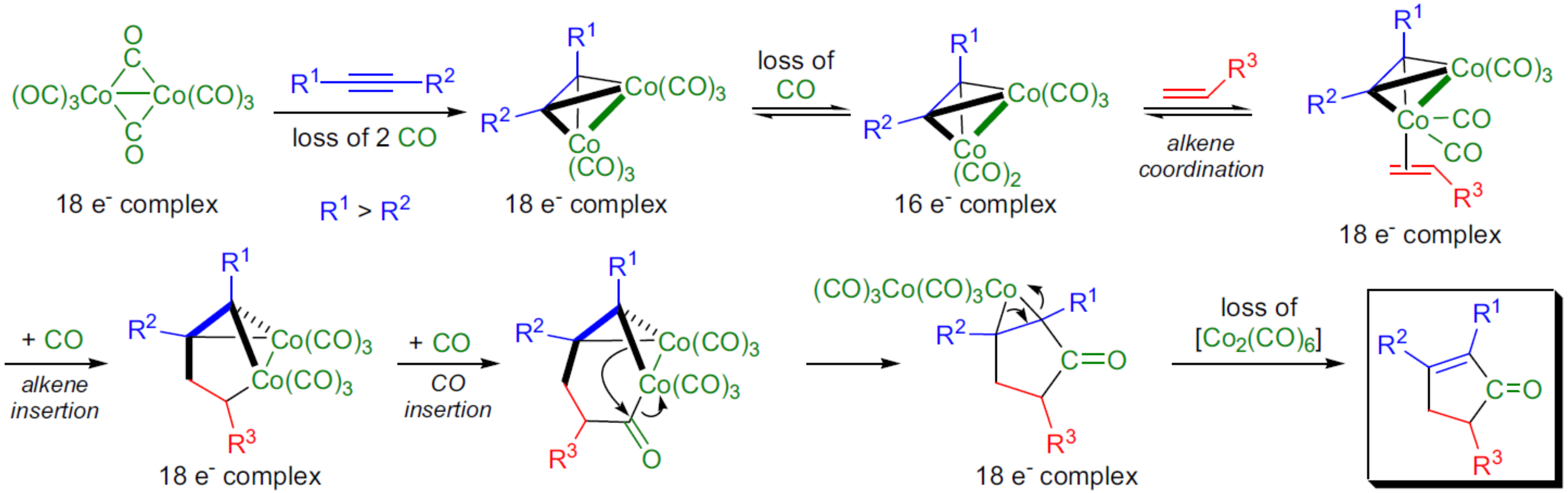
Intramolecular variant:

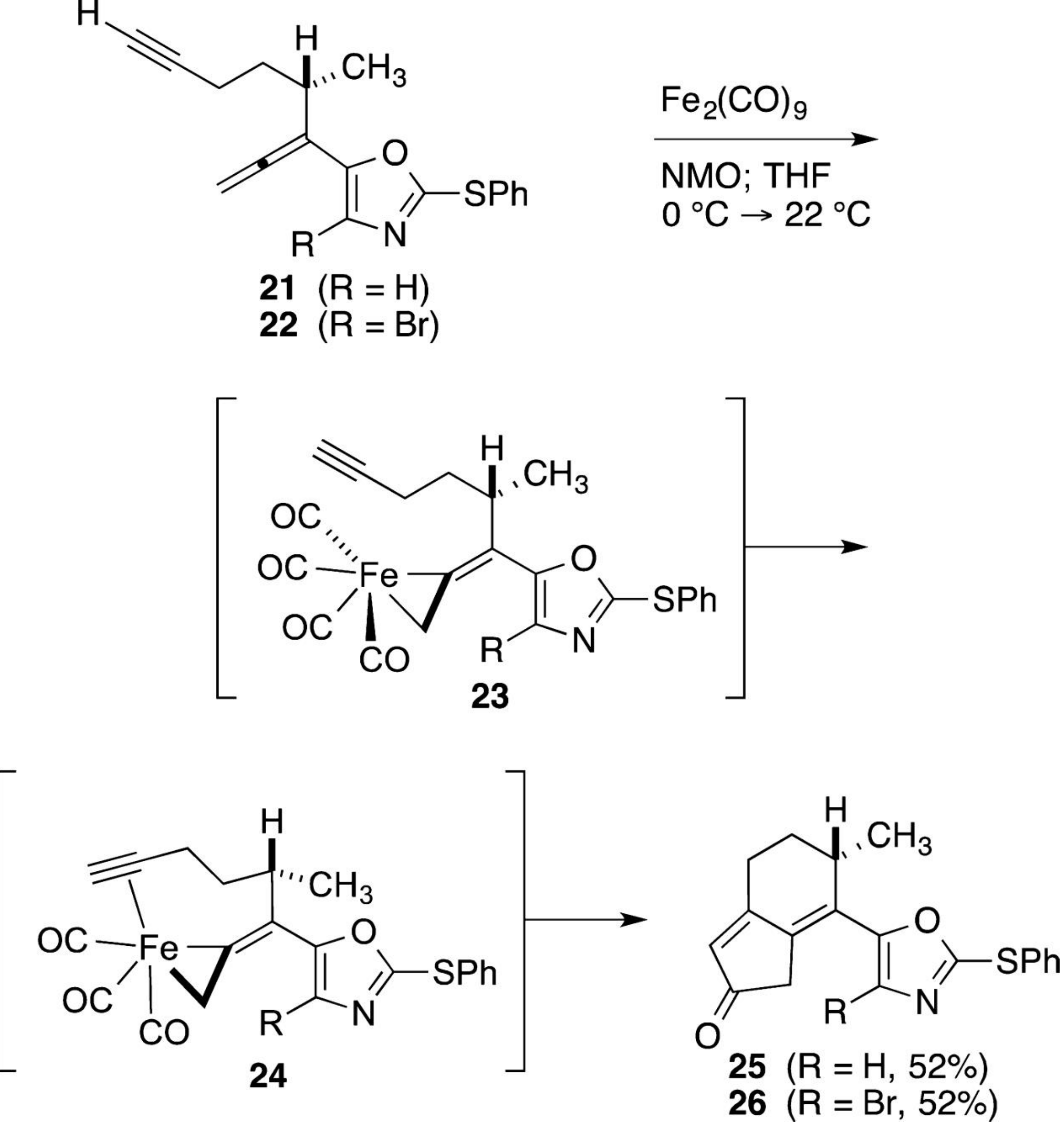


R^{1-6} = H, alkyl, aryl, substituted alkyl and aryl; <u>transition metal complex:</u> $Co_2(CO)_8$, $Fe(CO)_5$, $Ru_2(CO)_{12}$, Cp_2TiR_2, $Ni(COD)_2$, $W(CO)_6$, $Mo(CO)_6$, $[RhCl(CO)_2]_2$; <u>promoter:</u> NMO, TMAO, $RSCH_3$, high-intensity light/photolysis, "hard" Lewis base

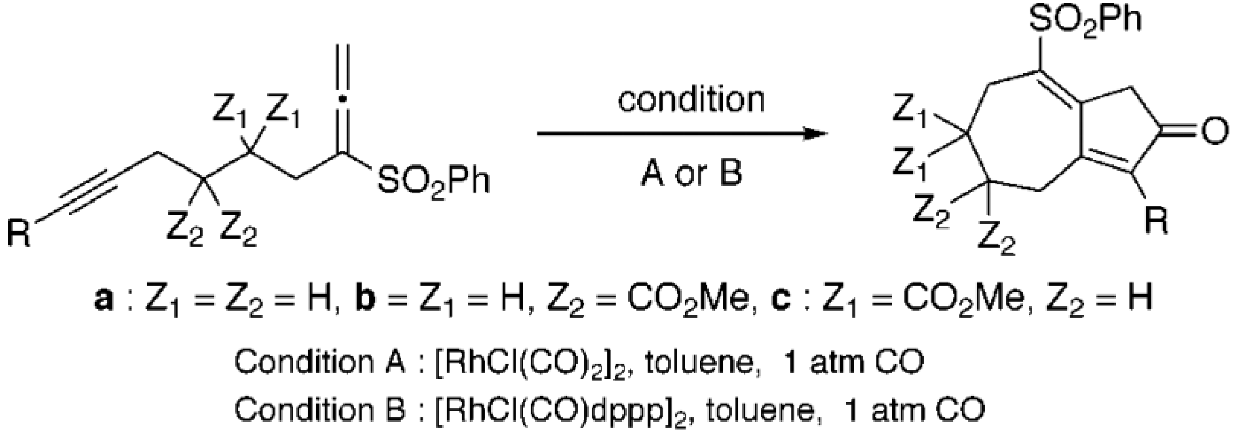
Mechanism: [48-62]

The mechanism of the *Pauson-Khand reaction* has not been fully elucidated. However, based on the regio- and stereochemical outcome in a large number of examples, a reasonable hypothesis has been inferred.

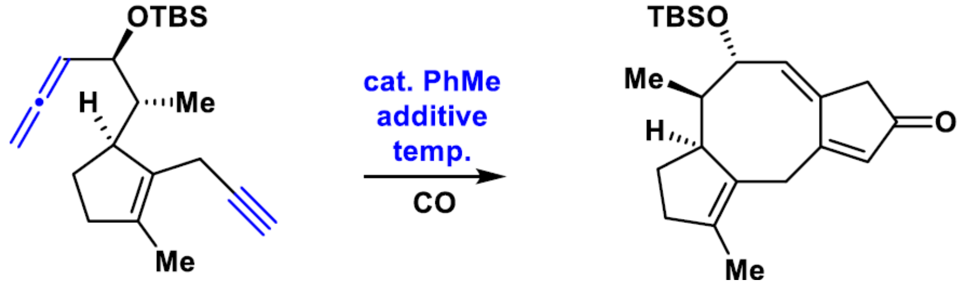




J. Am. Chem. Soc., **2014**, *136*, 8829.



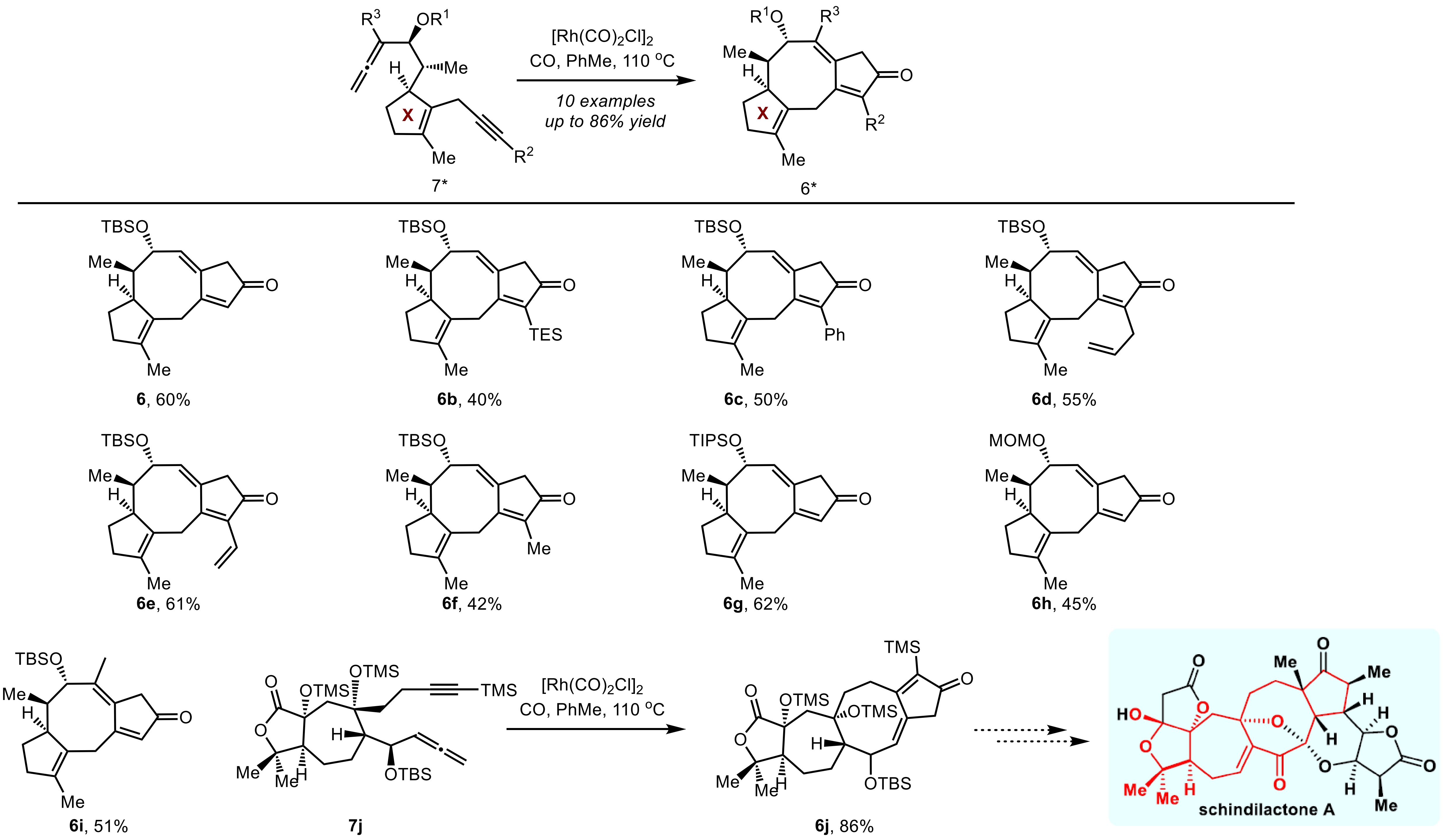
Org. Lett., **2002**, *4*, 1755.



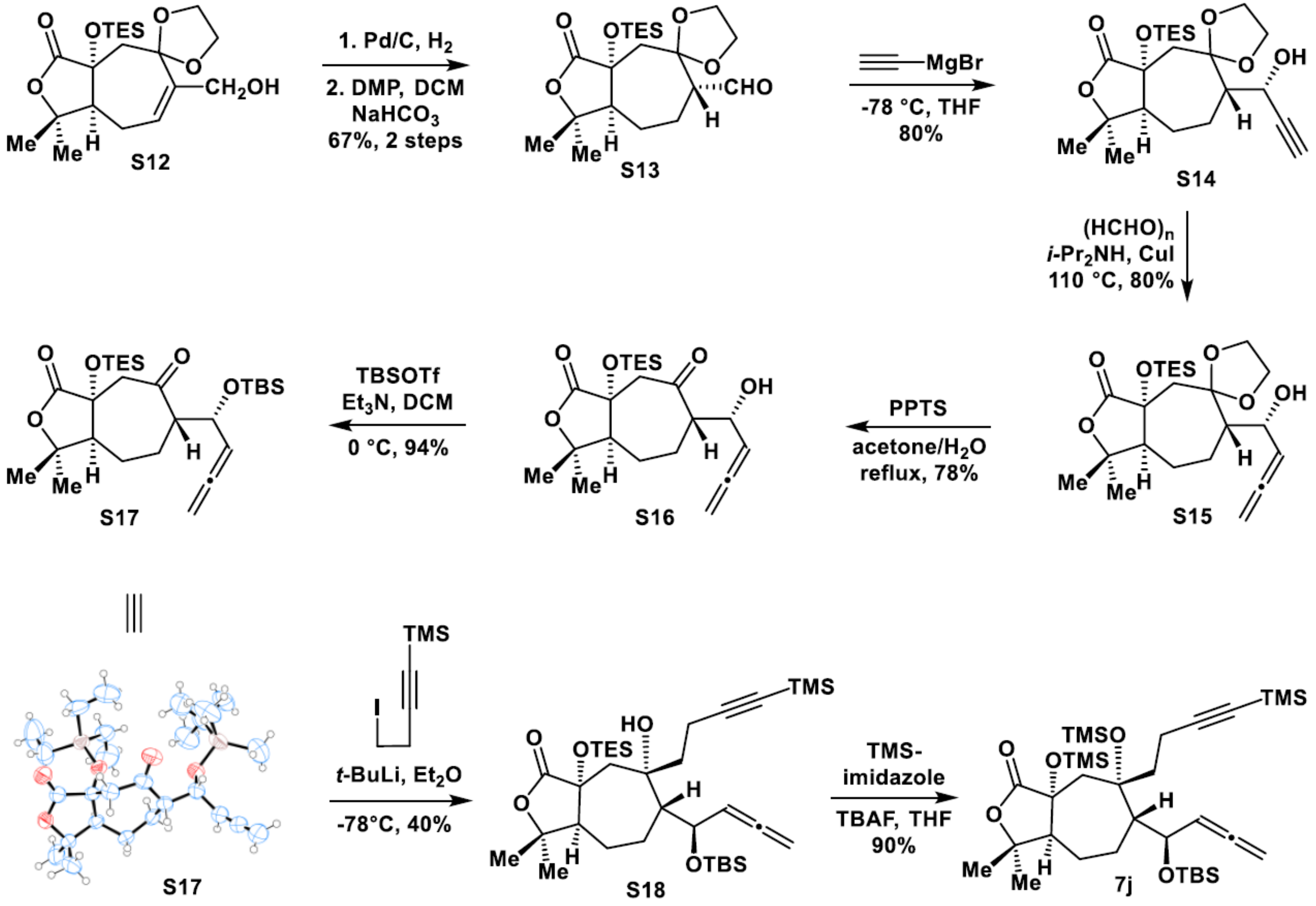
Entry	Catalyst	Additive	Temp./°C	Time/h	Yield/%[b]
1	5%$RhCl_3$	-	110 °C	3	<10%
2	5%$[Rh(OAc)_2]_2$	-	110 °C	3	trace
3	5%$Rh(ethylene)_2(acac)$	-	110 °C	3	<10%
4	5%$RhCl(PPh_3)_2(CO)$	-	110 °C	3	trace
5	5%$[RhCl(cyclooctene)_2]_2$	-	110 °C	3	<10%
6	5%$Rh(MeCN)_2(cod)BF_4$	-	110 °C	3	trace
7	5%$[RhCl(cod)_2]_2$	-	110 °C	3	28%
8	5%$[RhCl(CO)_2]_2$	-	110 °C	3	38%
9	5%$[RhCl(CO)_2]_2$	10%$AgSbF_6$	R.T.	3	0%
10	5%$[RhCl(CO)_2]_2$	10%AgOTs	R.T.	3	0%
11	5%$[RhCl(CO)_2]_2$	10%AgOTf	R.T.	3	0%
12	5%$[RhCl(CO)_2]_2$	50%dppp	110 °C	3	25%

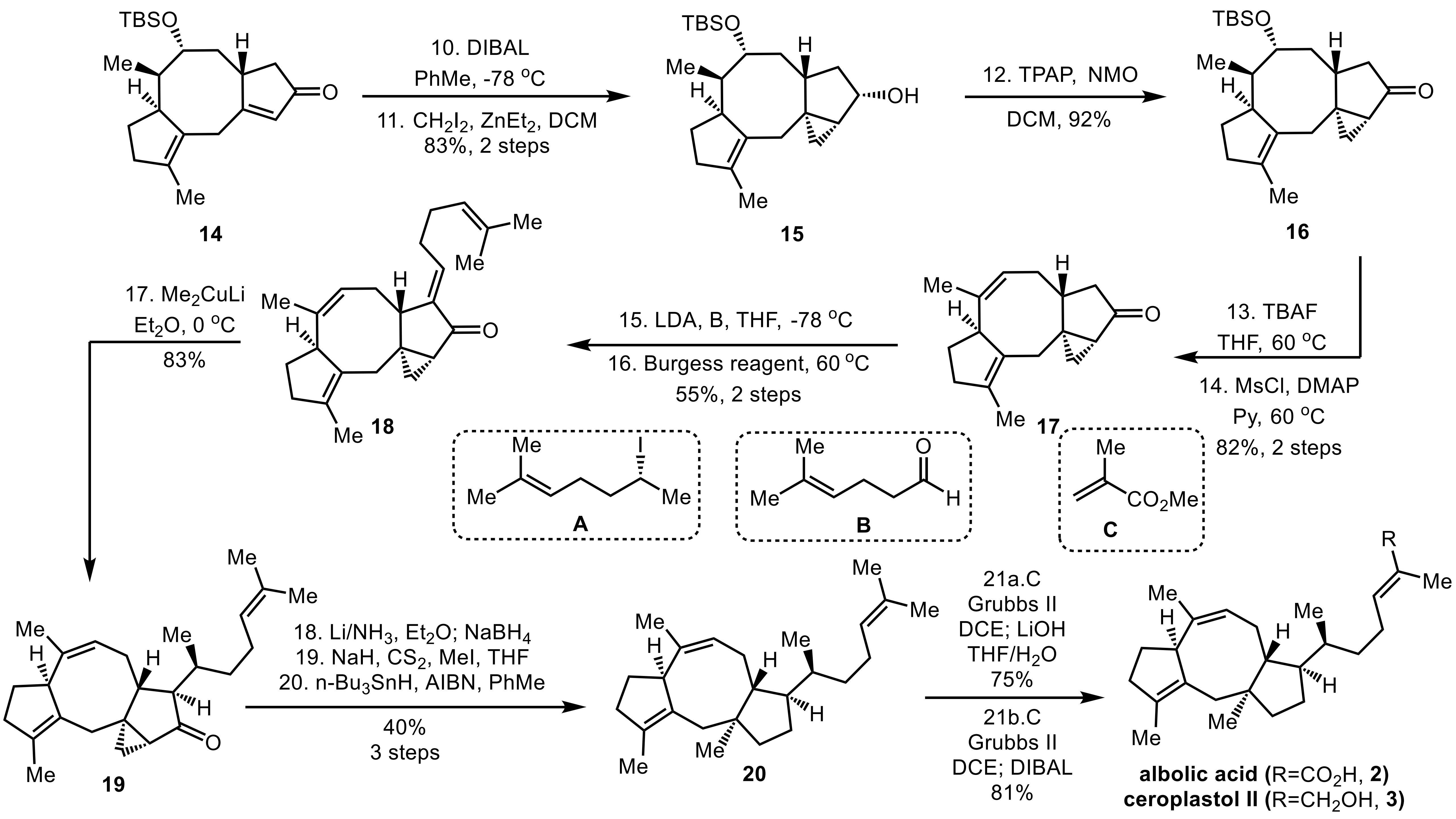
13	5%$[RhCl(cod)_2]_2$	50%dppp	110 °C	3	29%
14[c]	5%$[RhCl(CO)_2]_2$	-	110 °C	3	25%
15[d]	5%$[RhCl(CO)_2]_2$	-	110 °C	3	26%
16[e]	5%$[RhCl(CO)_2]_2$	-	120 °C	3	20%
17	5%$[RhCl(CO)_2]_2$	-	100 °C	3	22%
18[f]	10%$[RhCl(CO)_2]_2$	-	110 °C	3	60%
19[g]	20%$[RhCl(CO)_2]_2$	-	110 °C	3	62%
20[h]	10%$[RhCl(CO)_2]_2$	-	110 °C	overnight	56%

a). Reaction conditions: To a solution of catalyst (0.00500 mmol, 0.0500 equiv.) and additive (0.0100-0.0500 mmol, 0.100-0.500 equiv.) in PhMe (8.00 mL, 0.01 M) under a balloon pressure of CO was added **7** (33.0 mg, 0.100 mmol, 1.00 equiv.) in PhMe (2.00 mL) and the mixture was stirred for 3 h. b). Isolated yield. c). 1.00 mL PhMe (0.1 M). d). 20.0 mL PhMe (0.005 M). e). Sealed tube. f). The yield was increased to 60% in the presence of 10% mmol catalyst. g). The yield was not improved significantly in the presence of 20% mmol catalyst. h). 2.00 g scale.

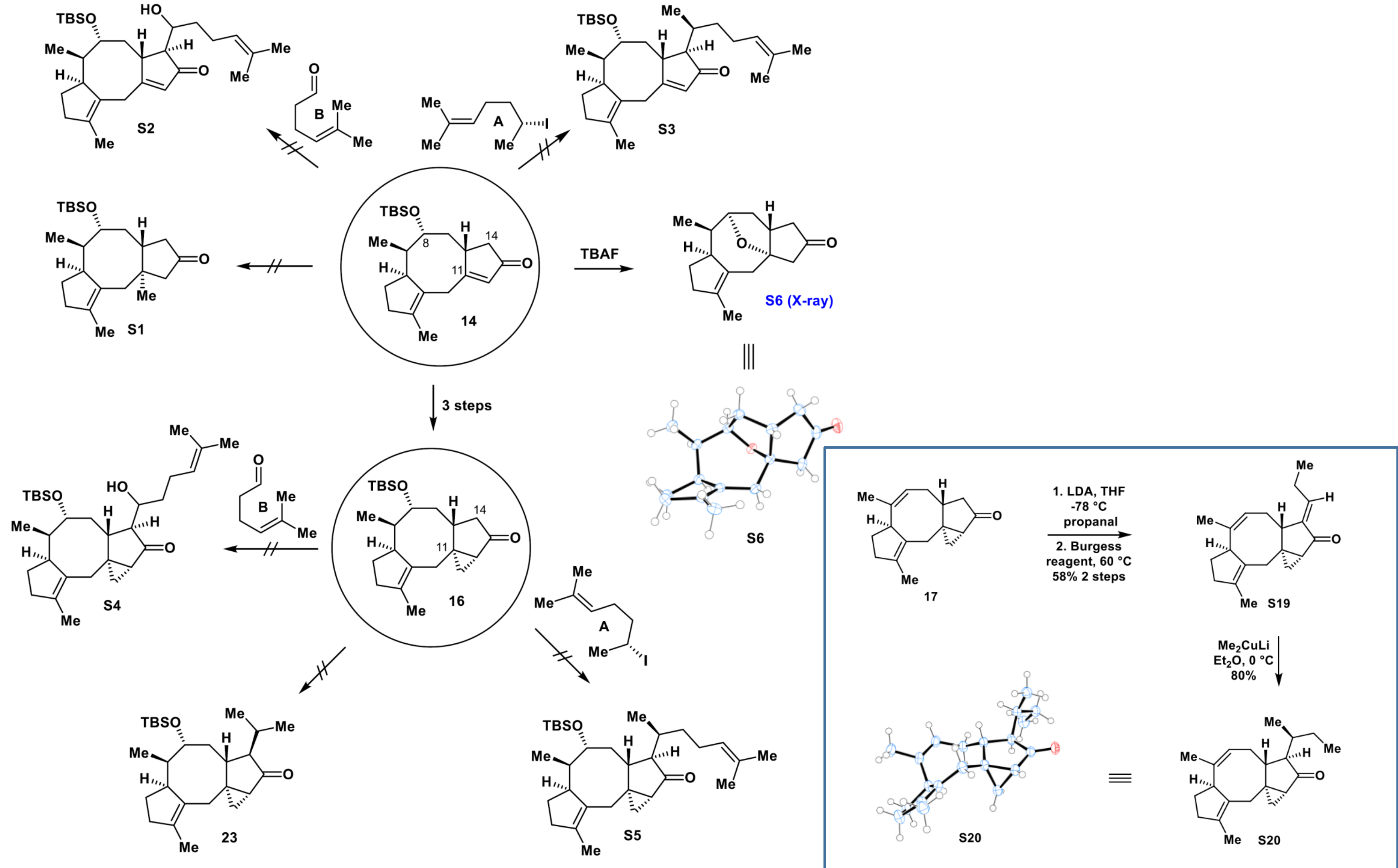

R3
OR1
H
Me
X
Me
R2
7*
[Rh(CO)2Cl]2
CO, PhMe, 110 oC
10 examples
up to 86% yield
R1O
R3
Me
H
X
O
R2
Me
6*
TBSO
Me
H
O
Me
6, 60%
TBSO
Me
H
O
TES
Me
6b, 40%
TBSO
Me
H
O
Ph
Me
6c, 50%
TBSO
Me
H
O
Me
6d, 55%
TBSO
Me
H
O
Me
6e, 61%
TBSO
Me
H
O
Me
Me
6f, 42%
TIPSO
Me
H
O
Me
6g, 62%
MOMO
Me
H
O
Me
6h, 45%
TBSO
Me
H
O
Me
6i, 51%
O
OTMS
OTMS
TMS
O
H
Me
Me
H
OTBS
7j
[Rh(CO)2Cl]2
CO, PhMe, 110 oC
TMS
O
O
OTMS
OTMS
O
H
Me
Me
H
OTBS
6j, 86%
schindilactone A

Scheme S2. Synthetic Route for 7j.



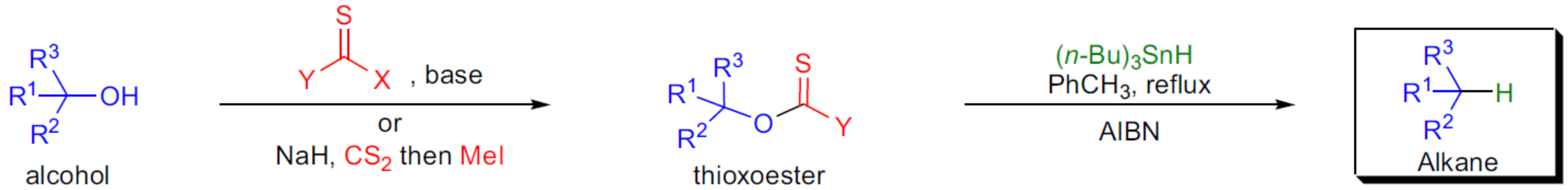

10. DIBAL
PhMe, -78 °C
11. CH2I2, ZnEt2, DCM
83%, 2 steps
12. TPAP, NMO
DCM, 92%
13. TBAF
THF, 60 °C
14. MsCl, DMAP
Py, 60 °C
82%, 2 steps
15. LDA, B, THF, -78 °C
16. Burgess reagent, 60 °C
55%, 2 steps
17. Me2CuLi
Et2O, 0 °C
83%
18. Li/NH3, Et2O; NaBH4
19. NaH, CS2, MeI, THF
20. n-Bu3SnH, AIBN, PhMe
40%
3 steps
21a. C
Grubbs II
DCE; LiOH
THF/H2O
75%
21b. C
Grubbs II
DCE; DIBAL
81%
14
15
16
17
18
19
20
A
B
C
albolic acid (R=CO2H, 2)
ceroplastol II (R=CH2OH, 3)

V. Scheme S1. Selected Experiments to Install the Angular Methyl Group and Side-chain at C14.



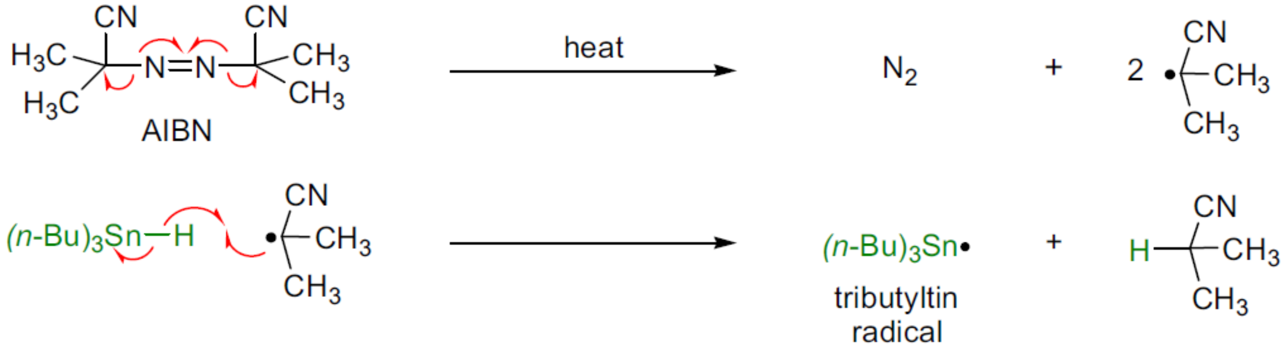
BARTON-McCOMBIE RADICAL DEOXYGENATION REACTION

(References are on page 546)

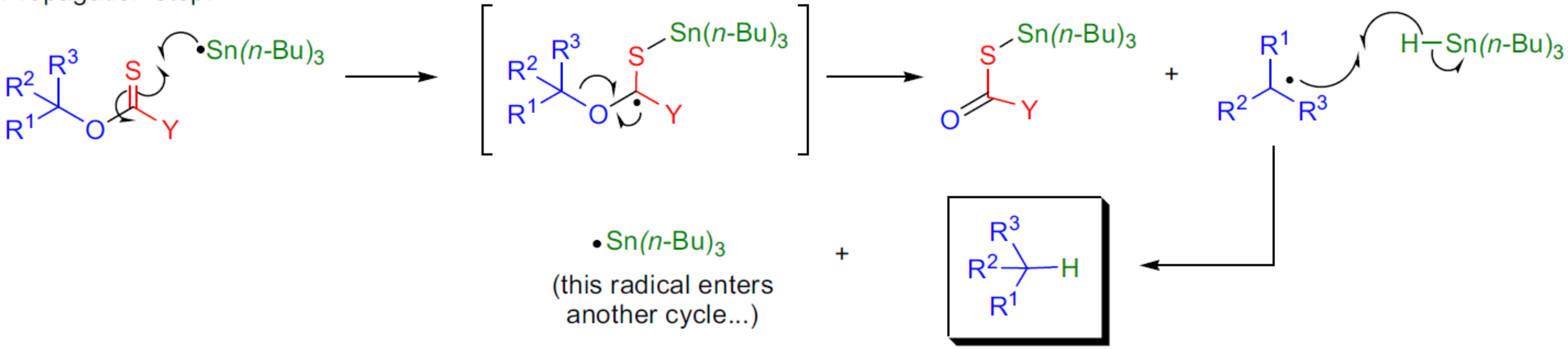


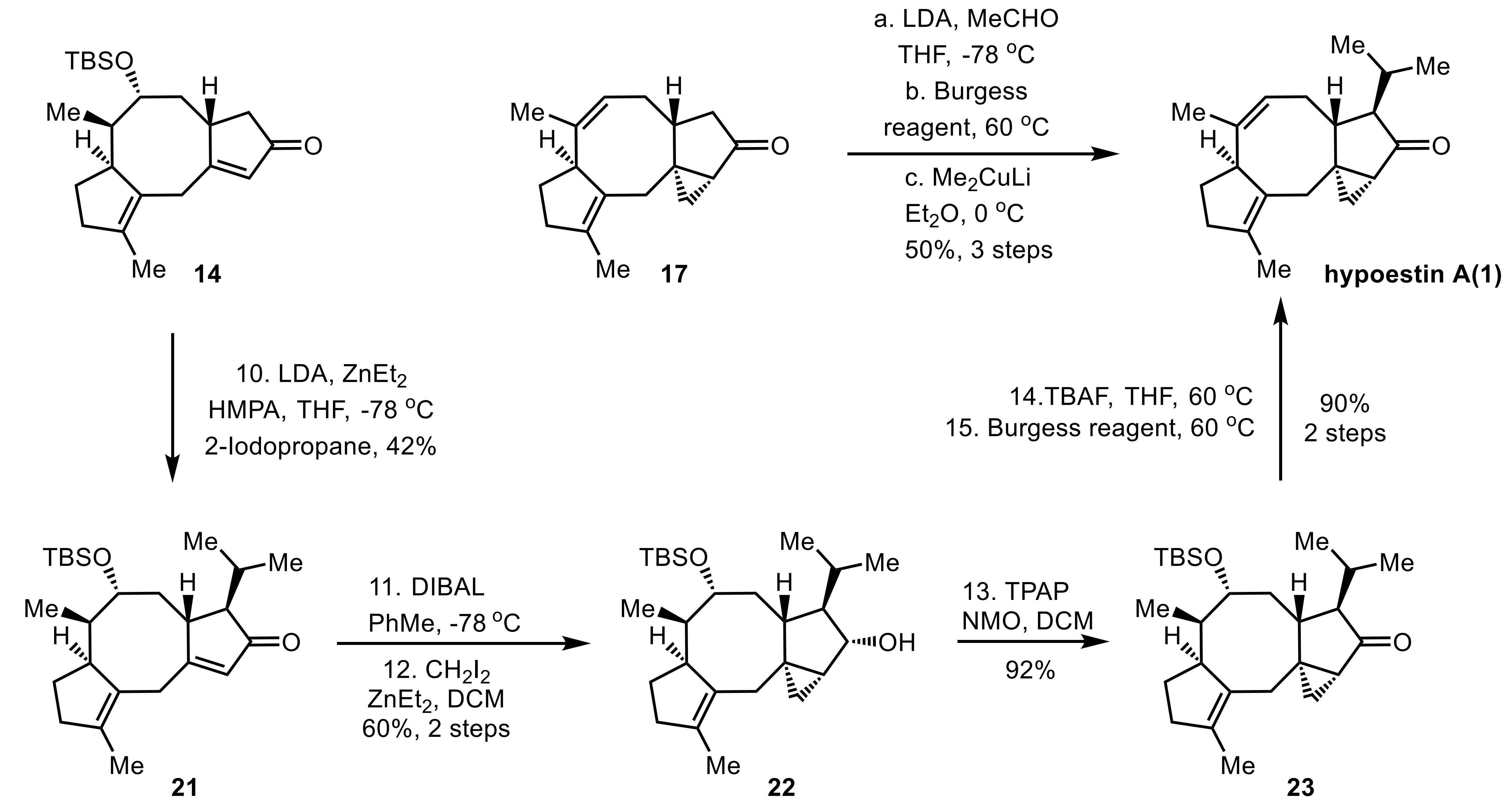
Y = SMe, imidazolyl, OPh, OMe; X = Cl, imidazolyl; <u>base:</u> NaH

Initiation step:



Propagation step:




TBSO
Me
H
O
Me
14
Me
H
O
Me
17
a. LDA, MeCHO
THF, -78 °C
b. Burgess
reagent, 60 °C
c. Me2CuLi
Et2O, 0 °C
50%, 3 steps
Me
Me
Me
H
O
Me
hypoestin A(1)
10. LDA, ZnEt2
HMPA, THF, -78 °C
2-Iodopropane, 42%
14.TBAF, THF, 60 °C
15. Burgess reagent, 60 °C
90%
2 steps
TBSO
Me
Me
Me
H
O
Me
21
11. DIBAL
PhMe, -78 °C
12. CH2I2
ZnEt2, DCM
60%, 2 steps
TBSO
Me
Me
Me
H
OH
Me
22
13. TPAP
NMO, DCM
92%
TBSO
Me
Me
Me
H
O
Me
23