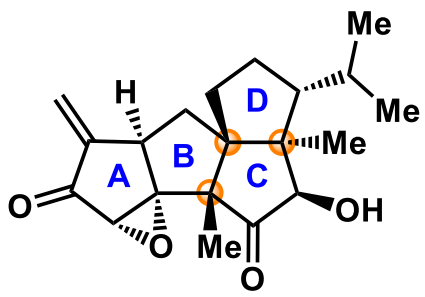
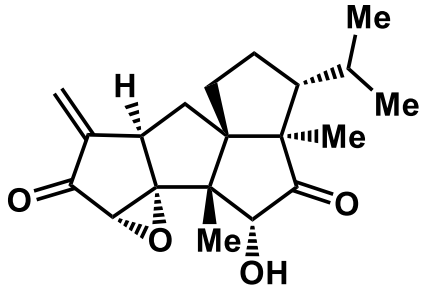
Divergent Total Syntheses of (−)-Crinipellins Facilitated by a HAT-Initiated Dowd−Beckwith Rearrangement

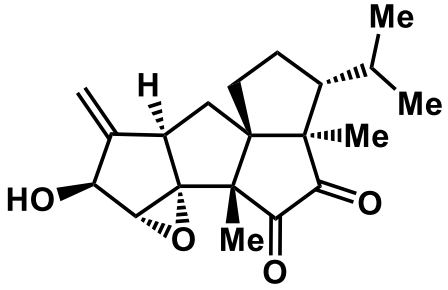
Yifan Zhao,[#] Jialei Hu,[#] Ruyi Chen,[#] Fengping Xiong, Hujun Xie,* and Hanfeng Ding*



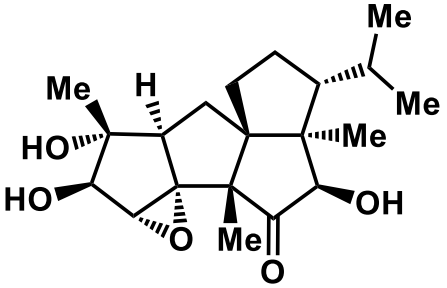
crinipellin A (1)



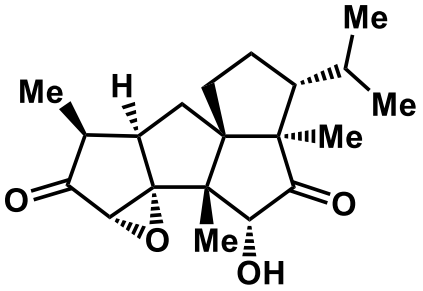
crinipellin B (2)



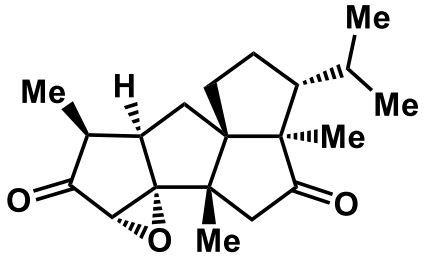
crinipellin C (3)



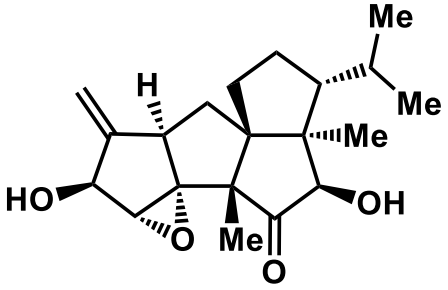
crinipellin D (4)
[revised structure]



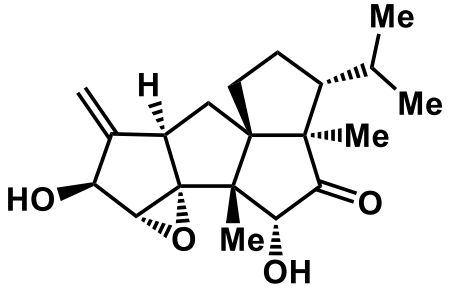
crinipellin E (5)



crinipellin F (6)



(-)-dihydrocrinipellin A (1a)



(-)-dihydrocrinipellin B (2a)

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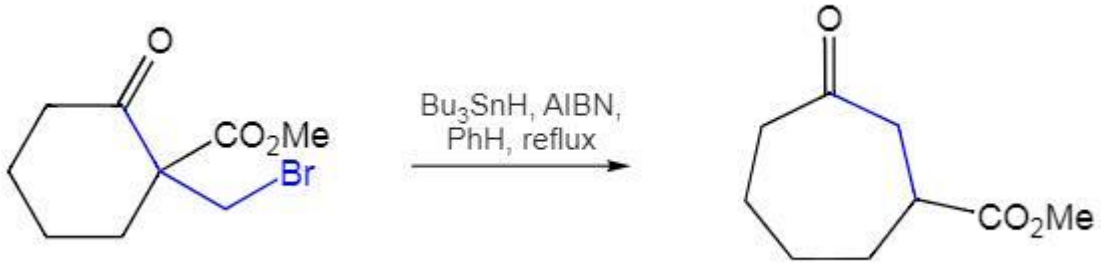
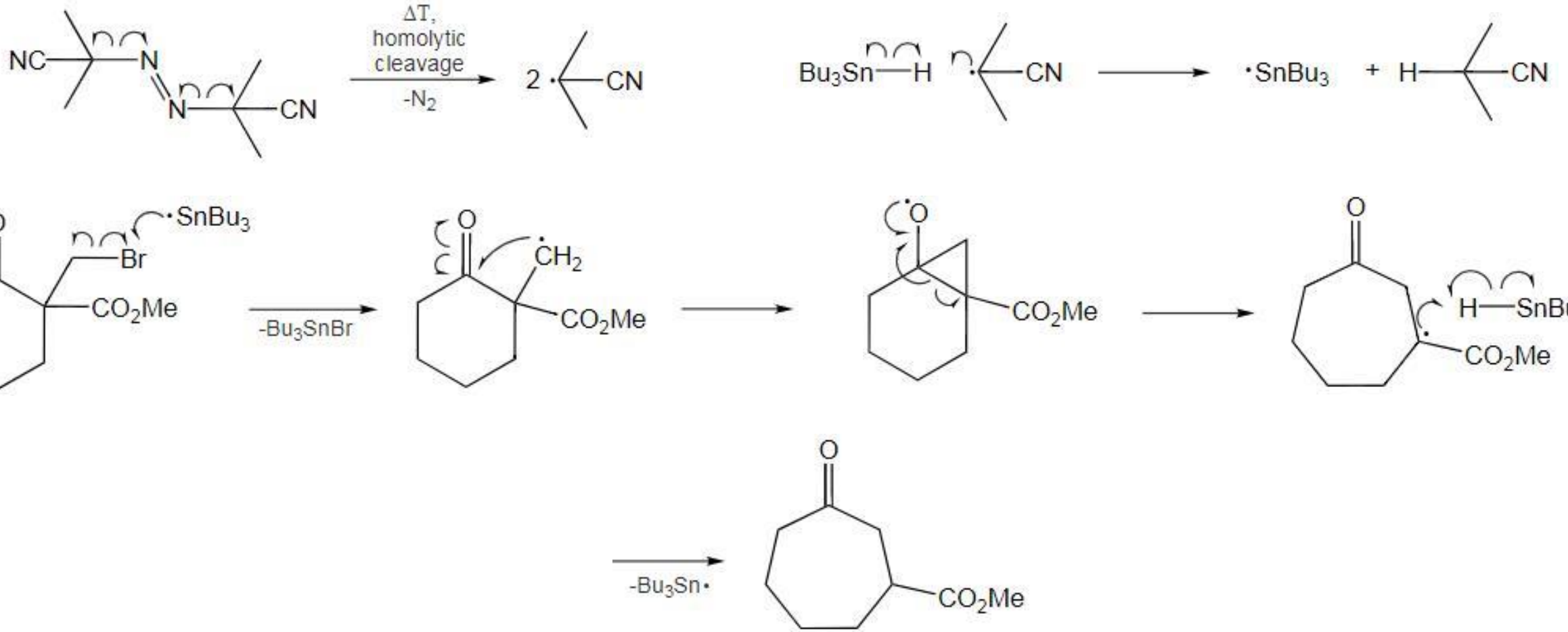
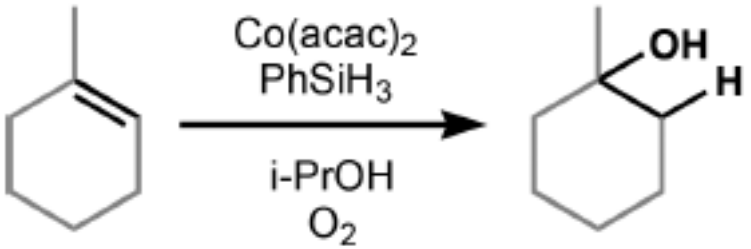
Dowd–Beckwith Rearrangement



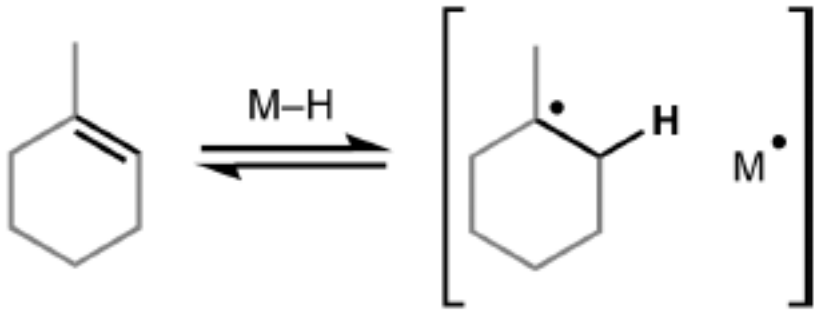


MHAT

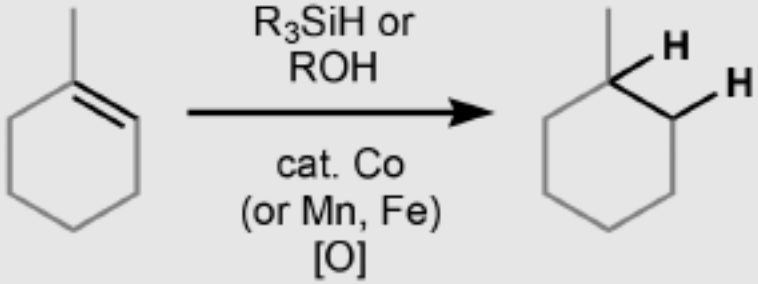
Drago-Mukaiyama hydration



MHAT elementary step



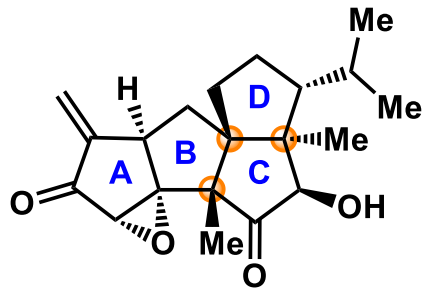
HAT Hydrogenation



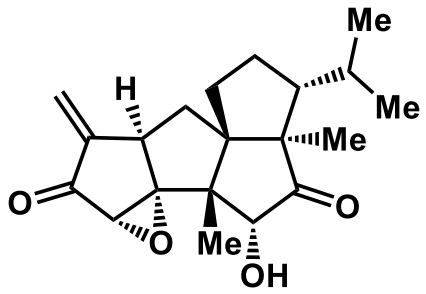
- no hydrogen gas is required
- abundant first row transition metals
- stereoselectivity is often reversed compared to other common methods

Acc. Chem. Res. **2018**, *51*, 2628.

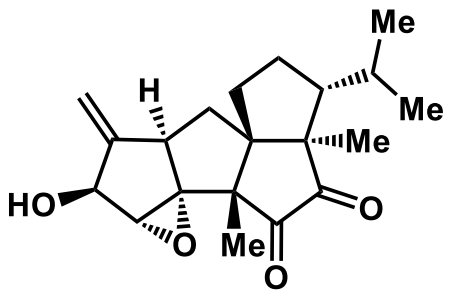
Structures and Retrosynthetic Analysis of (−)-Crinipellins A−F (1−6)



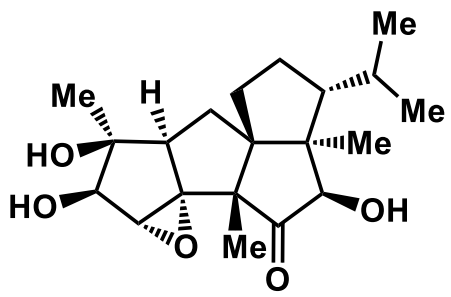
crinipellin A (1)



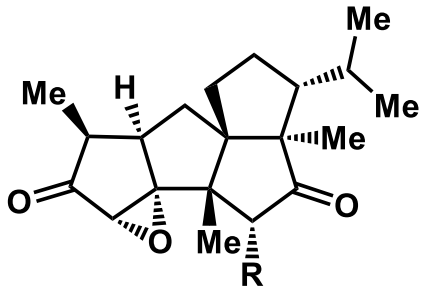
crinipellin B (2)



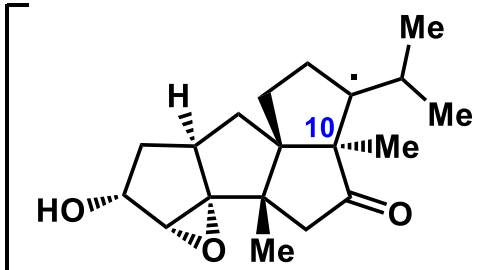
crinipellin C (3)



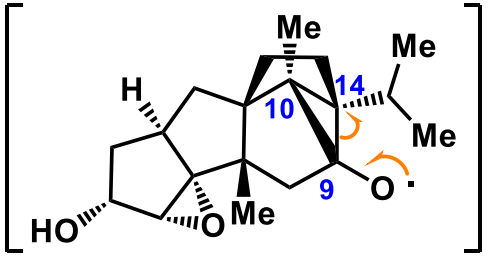
crinipellin D (4)
[originally assigned]



R = OH: crinipellin E (5)
R = H: crinipellin F (6)

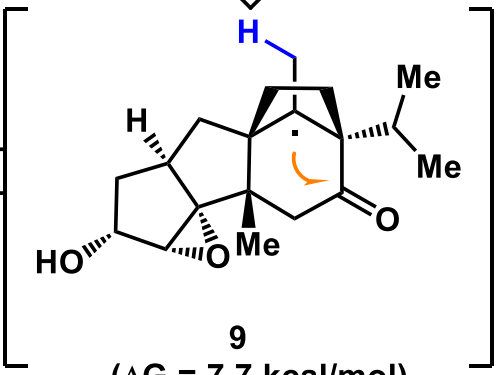


7
(ΔG = 0.0 kcal/mol)



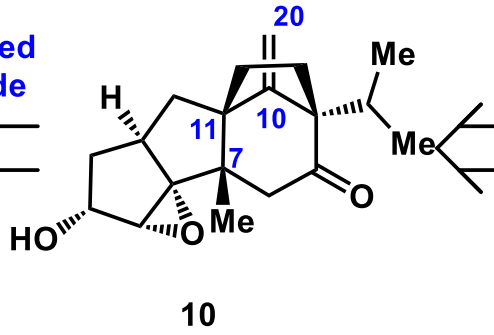
8

HAT-initiated
Dowd-Beckwith
rearrangement

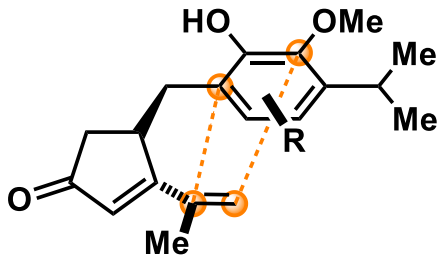


9
(ΔG = 7.7 kcal/mol)

diastereocontrolled
ODI-[5+2] cascade

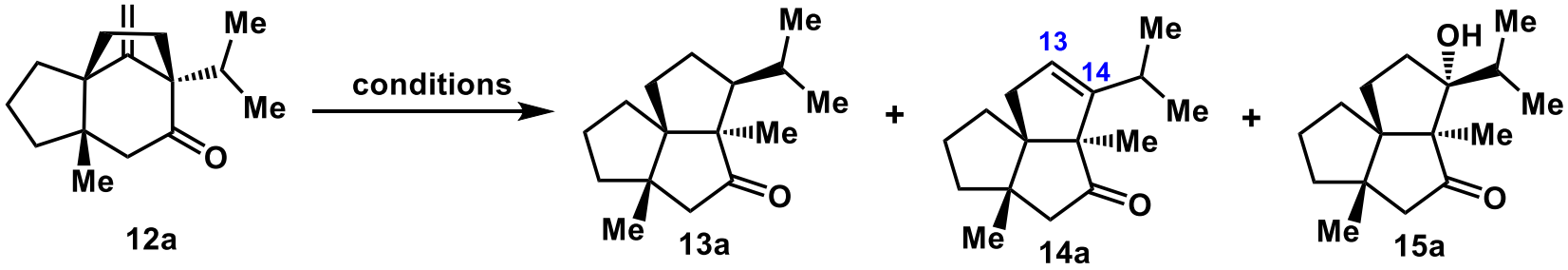


10



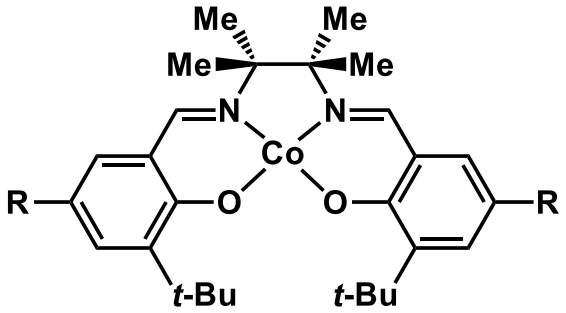
11

Optimization of the HAT-Initiated Dowd–Beckwith Rearrangement

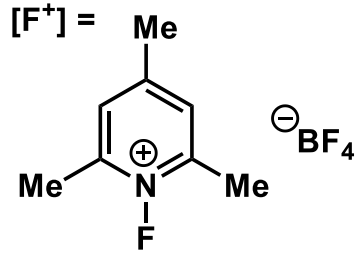


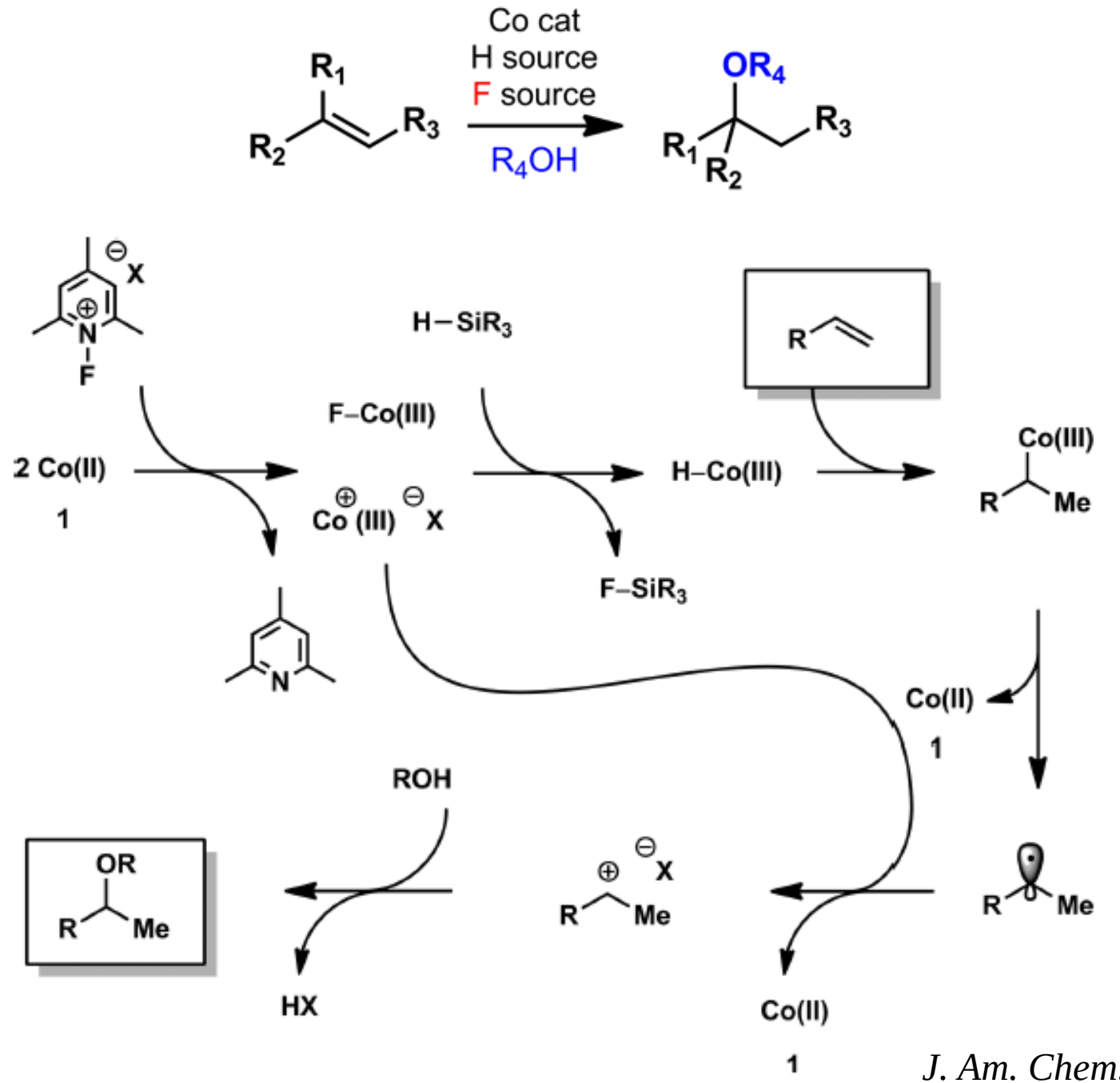
entry	conditions	yield (%)[b] 13a	14a	15a
1	$Mn(dpm)_3$, $PhSiH_3$, TBHP, EtOH	84	<5	0
2[c]	$Fe(acac)_3$, $Fe(acac)_2$, $PhSiH_3$, THF	40	33	0
3	$Co(acac)_2$, TMDSO, TBHP, *i*-PrOH	<5	45	24
4	C1–5, $PhSiH_3$, TBHP, *i*-PrOH	<5	20–81	<5
5	C6, $PhSiH_3$, TBHP, *i*-PrOH	11	83(98)[d]	<5
6[e]	C6, $PhSiH_3$, $[F^+]$, HFIP	<5	90	0

[a]Reaction conditions: **12a** (0.2 mmol), [M] (5 mol %), [Si] (2.5 equiv), TBHP (1.5 equiv), solvent (2 mL), 25 °C. [b]Isolated yields. [c]$[Fe^{III}]$ (50 mol %), $[Fe^{II}]$ (50 mol %), MeOH (10 equiv), 40 °C. [d][M] (1 mol %), [Si] (0.2 equiv), TBHP (0.2 equiv). [e]$[F^+]$ (2.5 equiv).



R = H: C1
R = Br: C2
R = CF_3: C3
R = NO_2: C4
R = OMe: C5
R = *t*-Bu: C6





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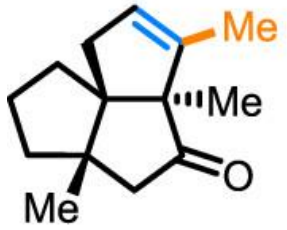
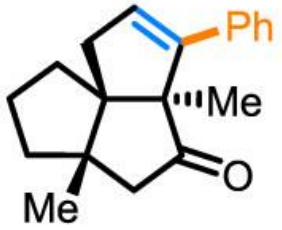
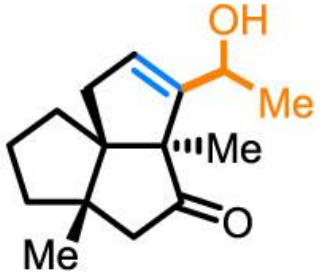


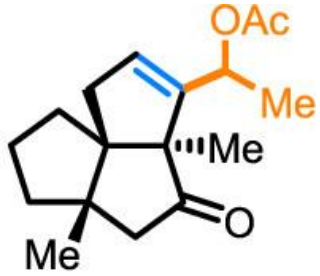
14b, 95%[a]



14c, 70%[a,c]

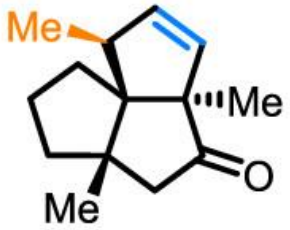


14d, 62%[a]

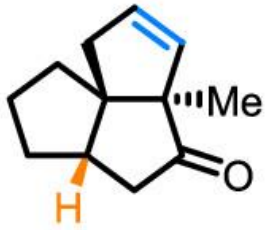


14e, 60%[a]

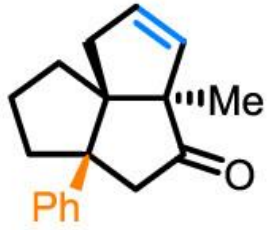
14f, 78%[b](18%)[a]



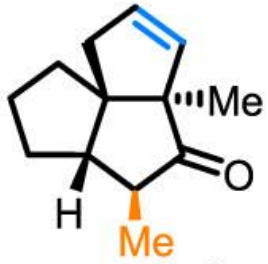
14g, 84%[b]



14h, 96%[b]

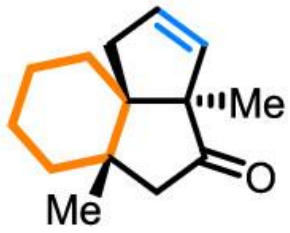


14i, 87%[b]

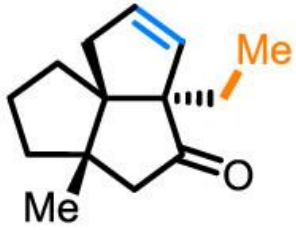


14j, 81%[b]

14k, 68%[b]



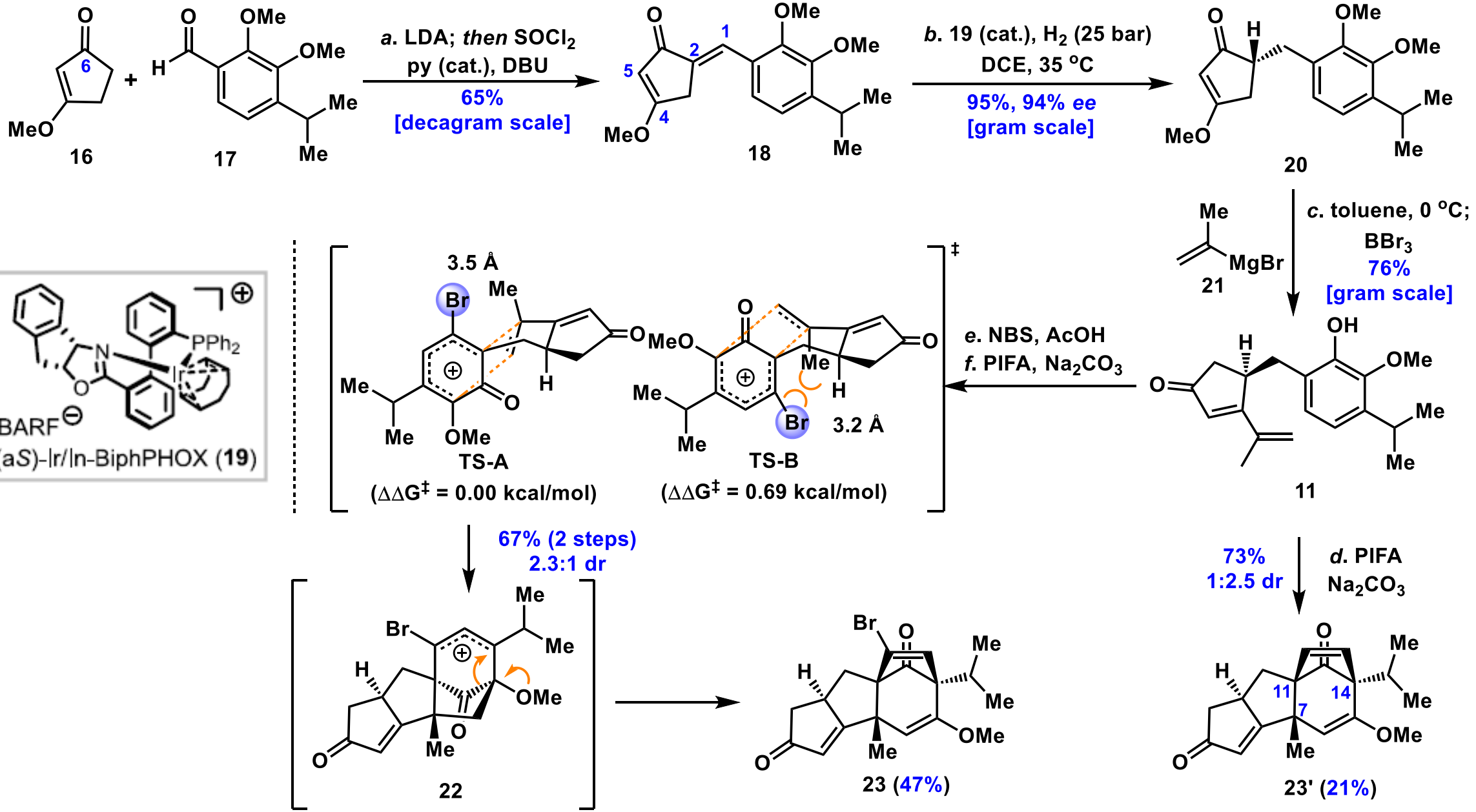
14l, 72%[b]



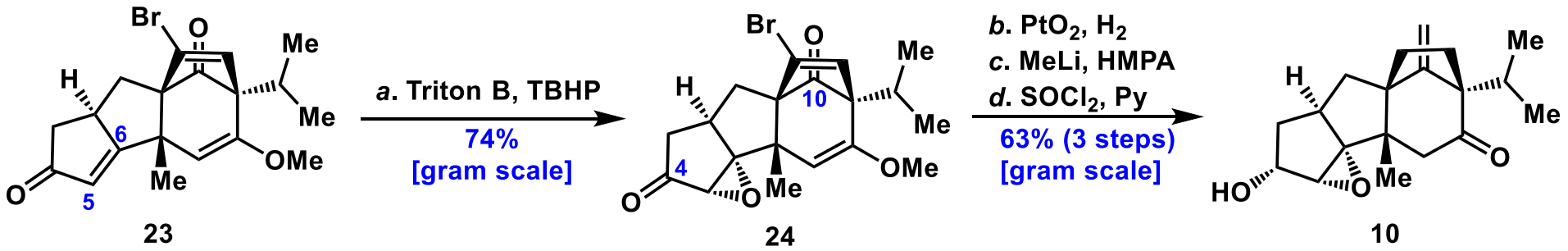
14m, 76%[b]

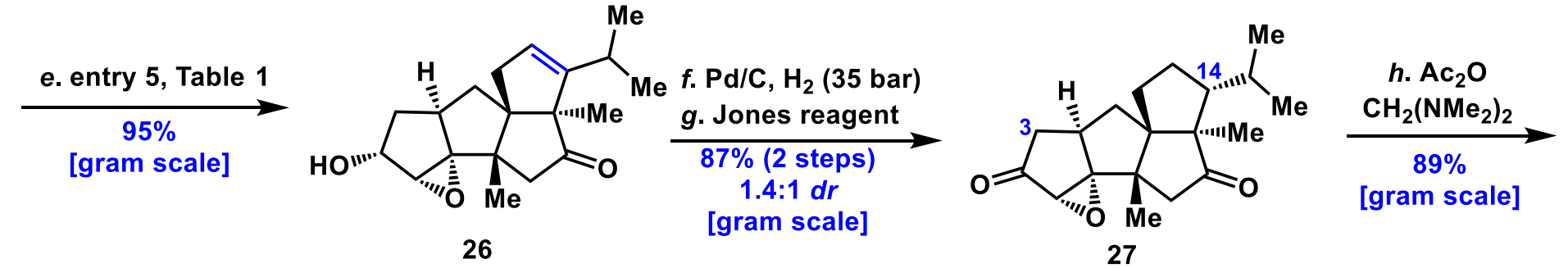
Scope of the rearrangement. Reaction conditions: [a]entry 5, Table 1 and [b]entry 6, Table 1. [c]Ph_2SiH_2 (0.6 equiv) was used.

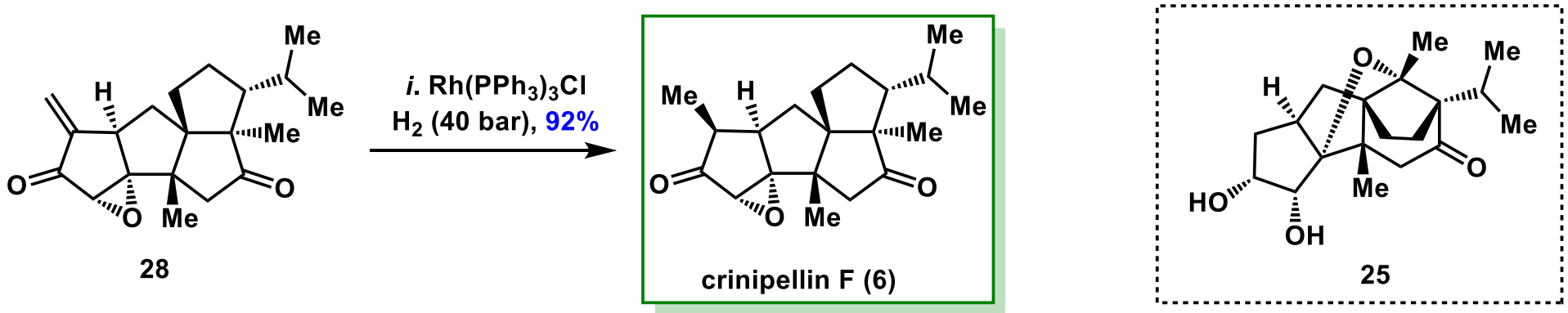
Construction of the 5/5/6/5 Tetracyclic Skeleton

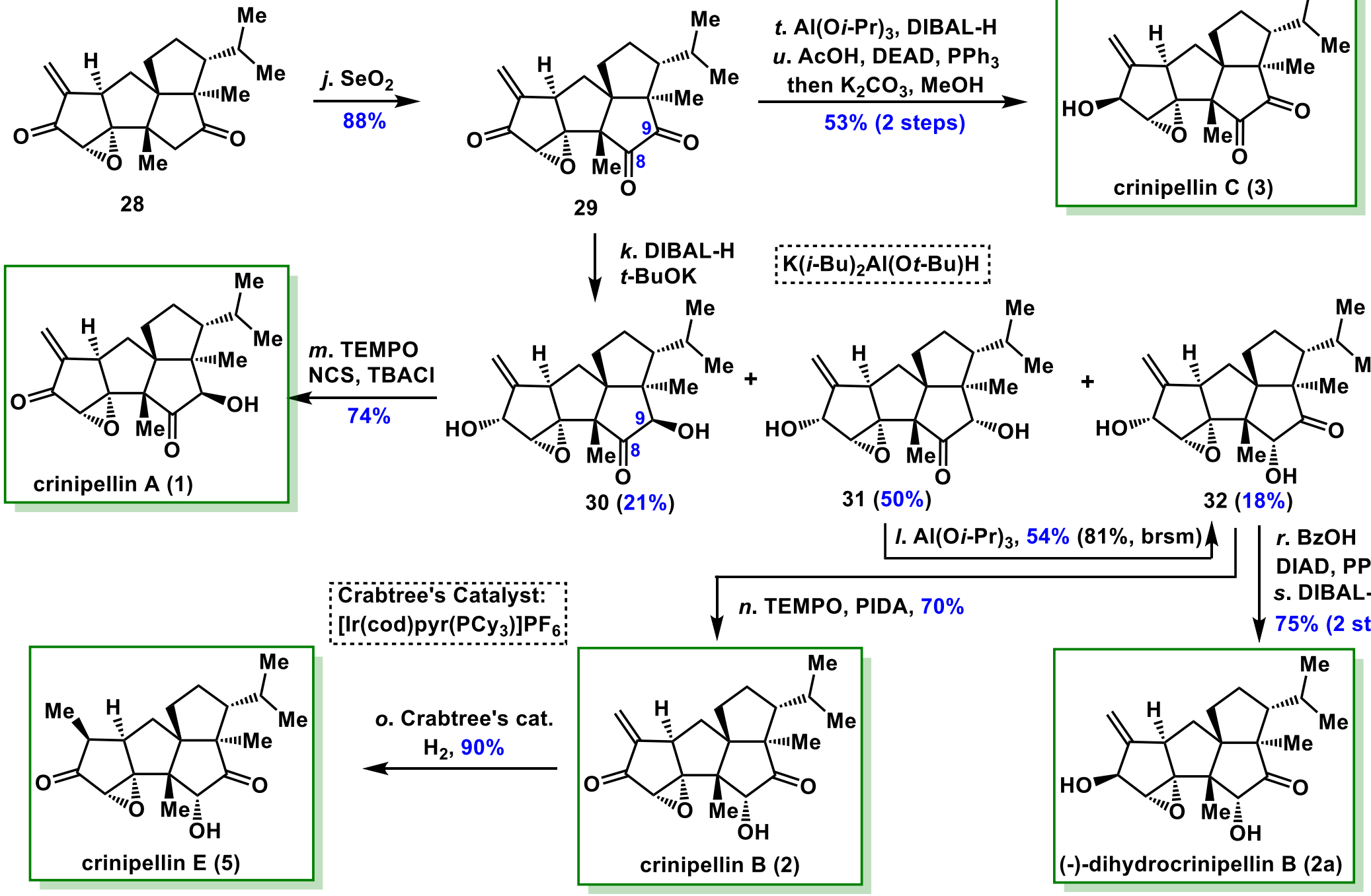


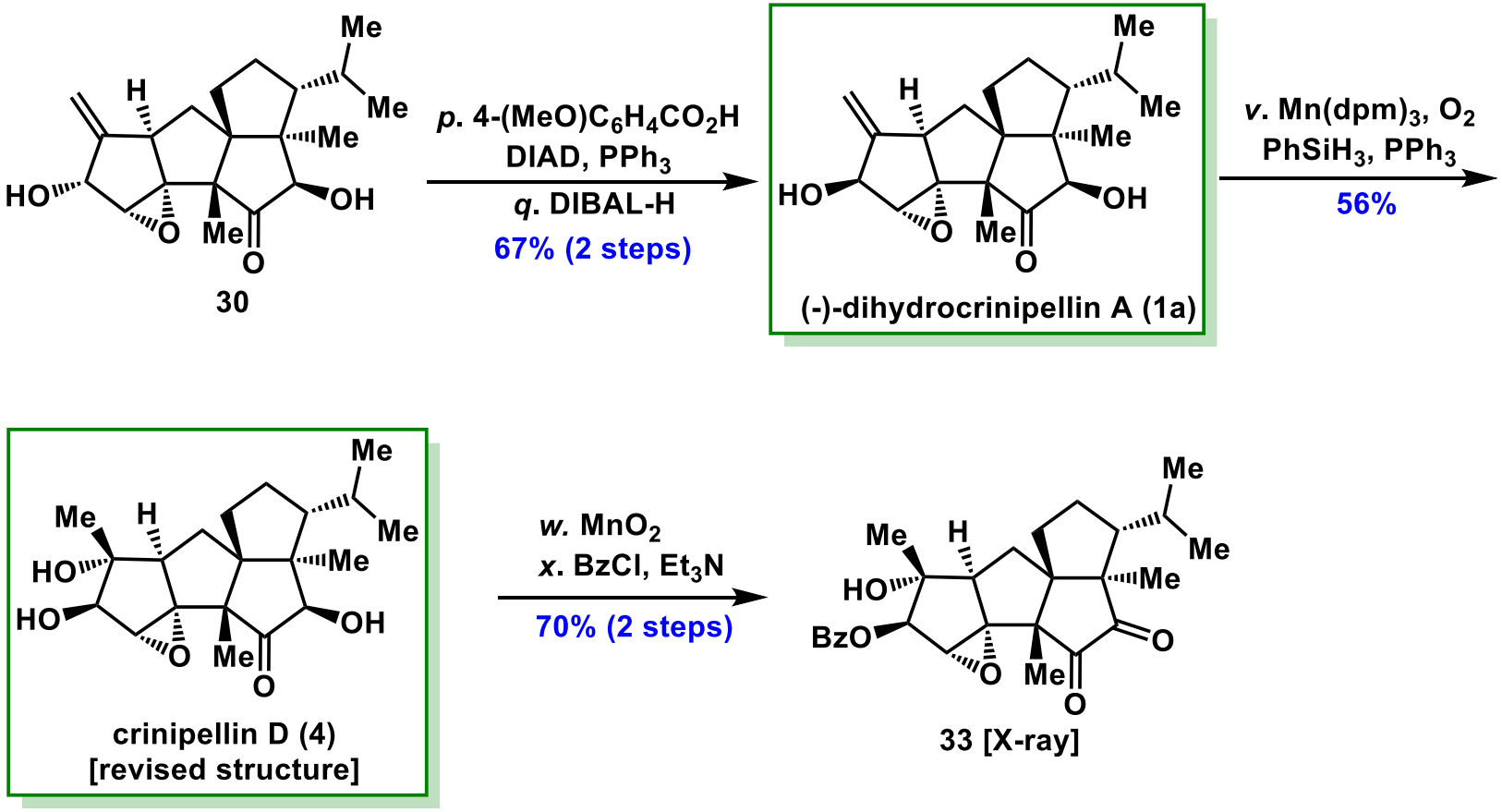
Divergent Total Syntheses of (−)-Crinipellins A−F and (−)-Dihydrocrinipellins A and B





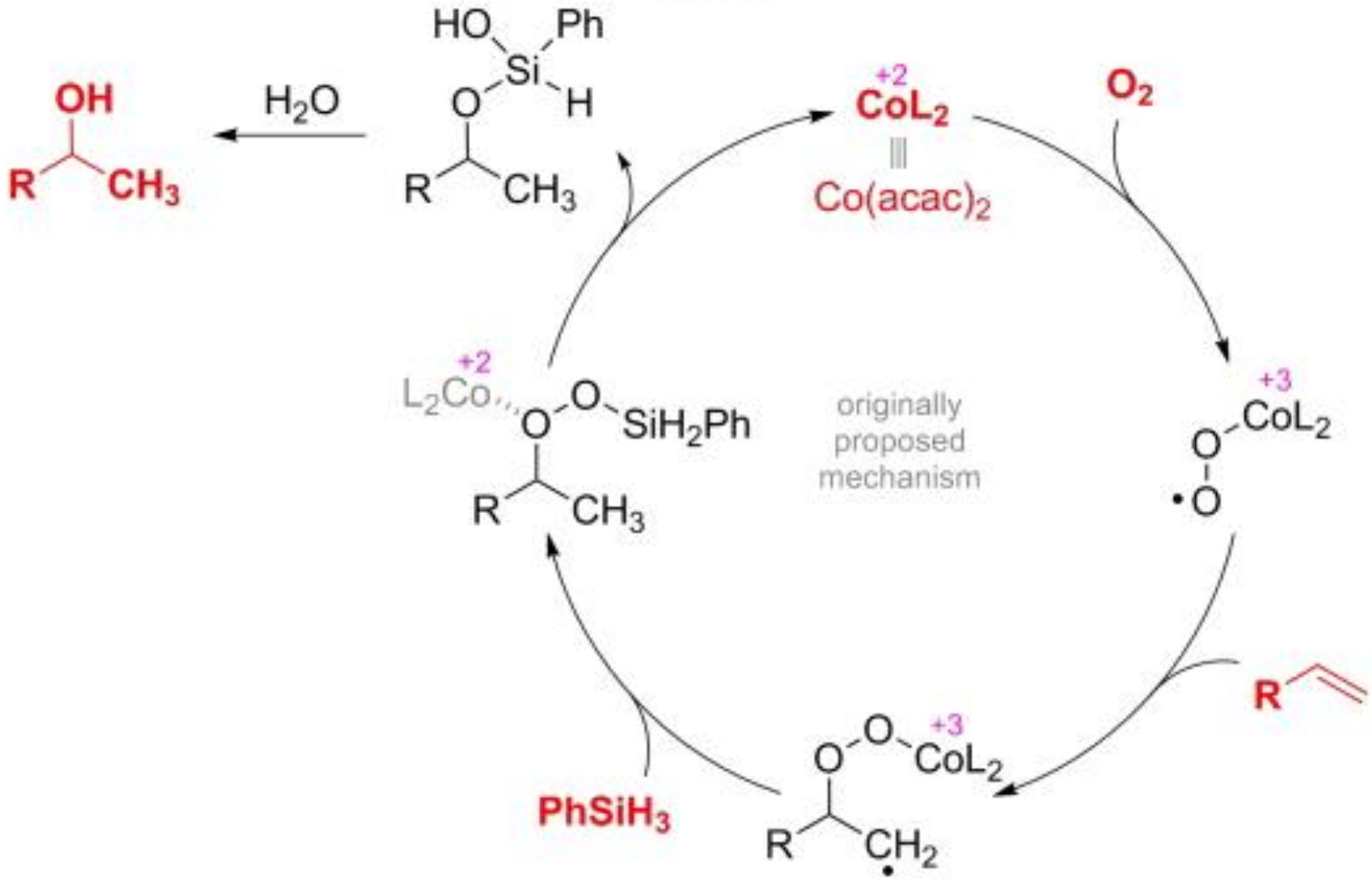


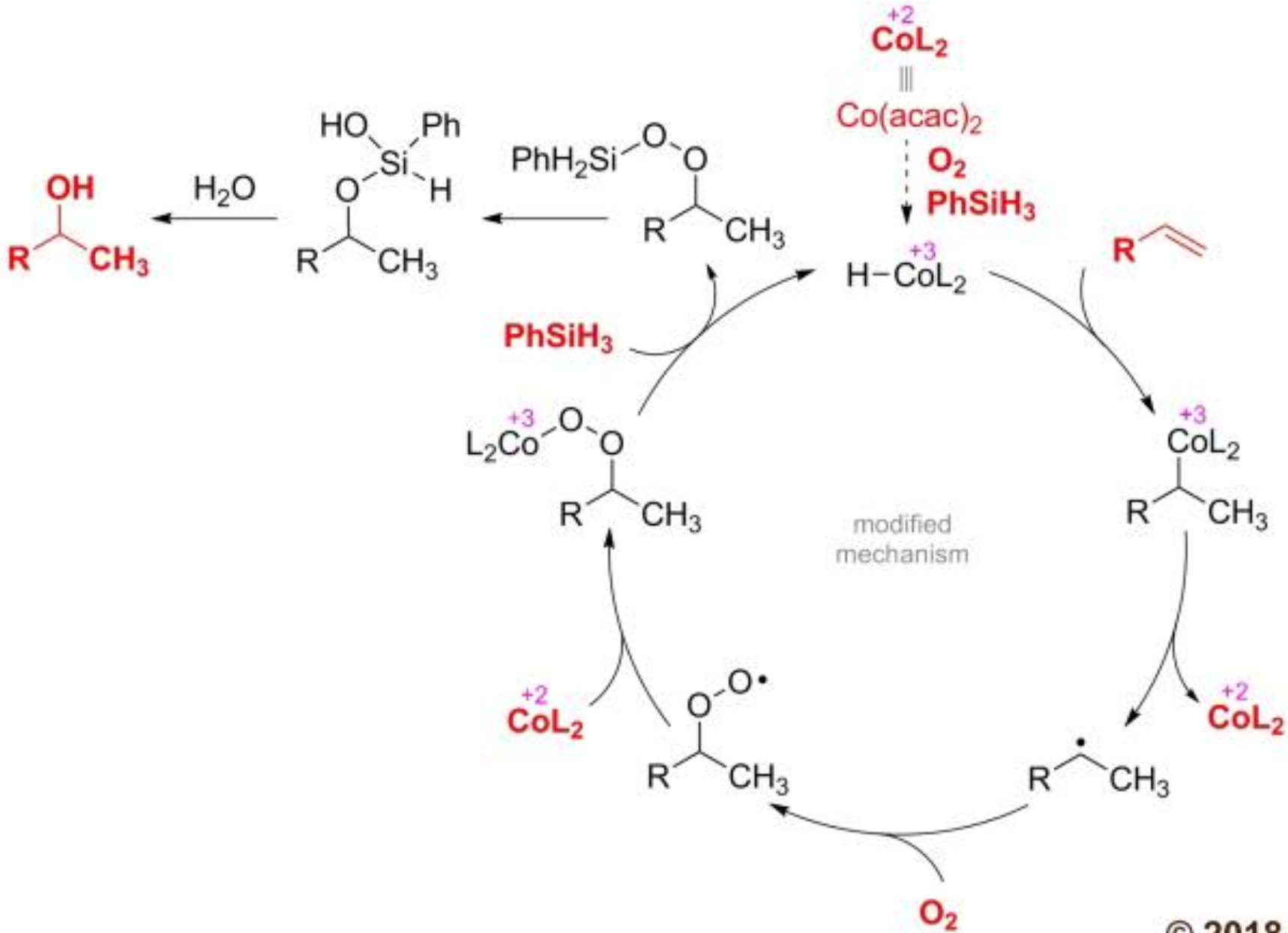

28
j. SeO2
88%
29
t. Al(Oi-Pr)3, DIBAL-H
u. AcOH, DEAD, PPh3
then K2CO3, MeOH
53% (2 steps)
crinipellin C (3)
k. DIBAL-H
t-BuOK
K(i-Bu)2Al(Ot-Bu)H
m. TEMPO
NCS, TBACl
74%
crinipellin A (1)
30 (21%)
31 (50%)
32 (18%)
l. Al(Oi-Pr)3, 54% (81%, brsm)
r. BzOH
DIAD, PPh3
s. DIBAL-H
75% (2 steps)
n. TEMPO, PIDA, 70%
Crabtree's Catalyst:
[Ir(cod)pyr(PCy3)]PF6
o. Crabtree's cat.
H2, 90%
crinipellin E (5)
crinipellin B (2)
(-)-dihydrocrinipellin B (2a)

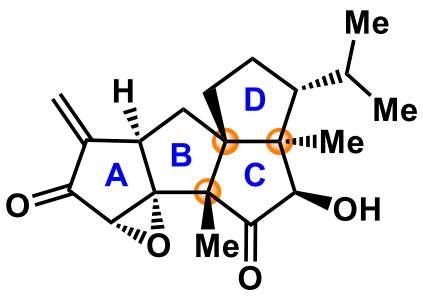

Me
H
Me
Me
HO
OH
O
Me
O
30
p. 4-(MeO)C6H4CO2H
DIAD, PPh3
q. DIBAL-H
67% (2 steps)
(-)-dihydrocrinipellin A (1a)
v. Mn(dpm)3, O2
PhSiH3, PPh3
56%
crinipellin D (4)
[revised structure]
w. MnO2
x. BzCl, Et3N
70% (2 steps)
BzO
33 [X-ray]

Mukaiyama Hydration

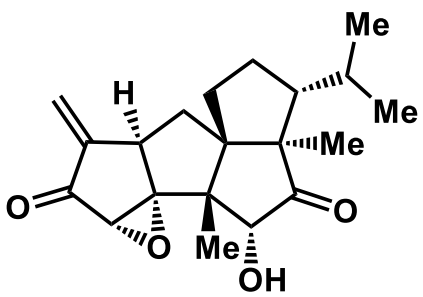
[1989]



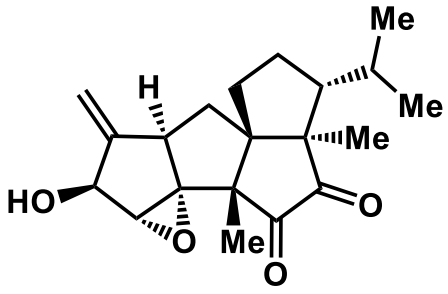

+2
CoL2
Co(acac)2
O2
PhSiH3
+3
H−CoL2
R
+3
CoL2
R
CH3
+2
CoL2
R
CH3
O2
O
O•
R
CH3
+2
CoL2
+3
L2Co
O
O
R
CH3
PhSiH3
PhH2Si
O
O
R
CH3
HO
Ph
Si
O
H
R
CH3
H2O
OH
R
CH3
modified
mechanism
© 2018



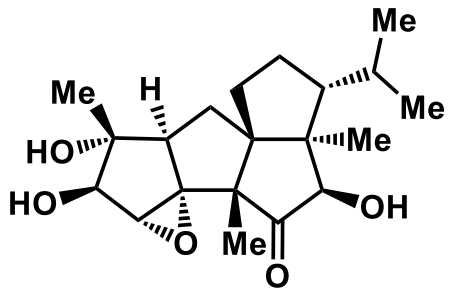
crinipellin A (1)



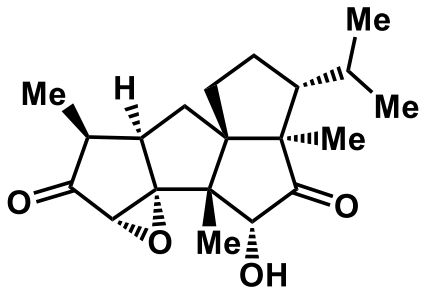
crinipellin B (2)



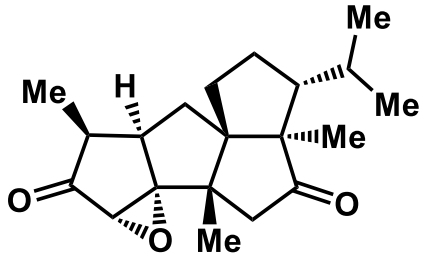
crinipellin C (3)



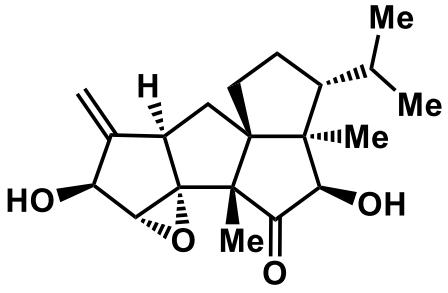
crinipellin D (4)
[revised structure]



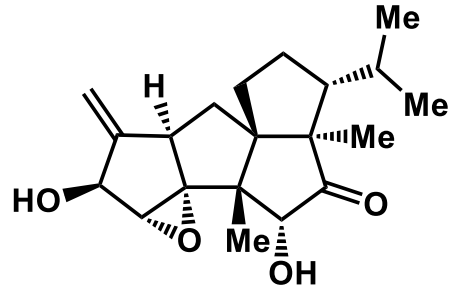
crinipellin E (5)



crinipellin F (6)

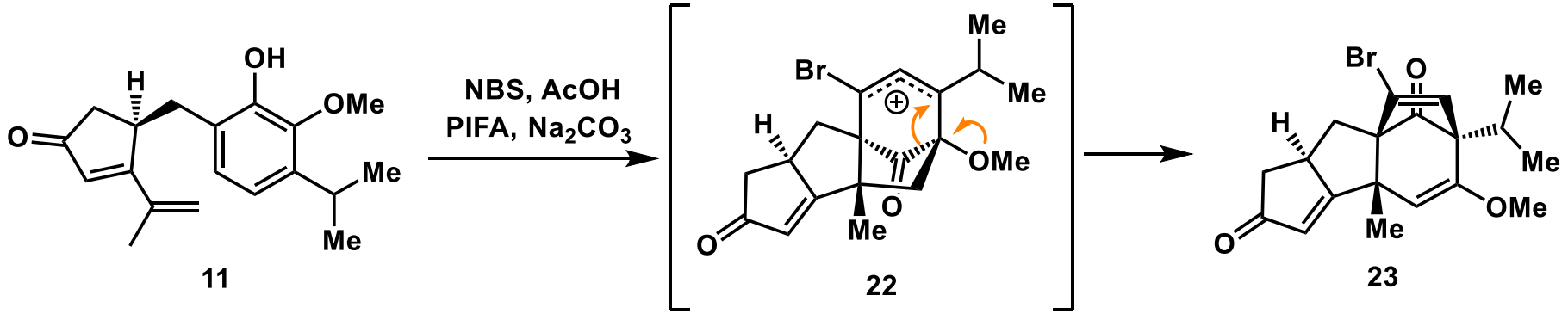


(-)-dihydrocrinipellin A (1a)



(-)-dihydrocrinipellin B (2a)

diastereocontrolled ODI-[5+2] cycloaddition/pinacol rearrangement cascade reaction



HAT-initiated Dowd–Beckwith rearrangement reaction