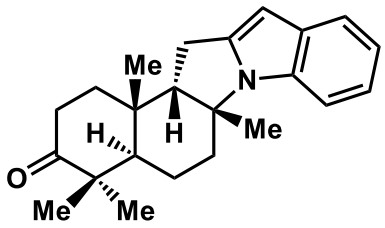
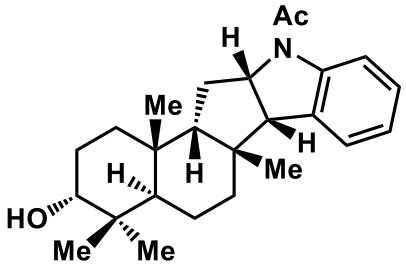
A Chiral-Pool-Based Strategy to Access trans-syn-Fused Drimane Meroterpenoids: Chemoenzymatic Total Syntheses of Polysin, N-Acetyl-polyveoline and the Chrodrimanins

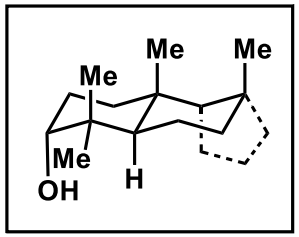
Fuzhuo Li and Hans Renata*



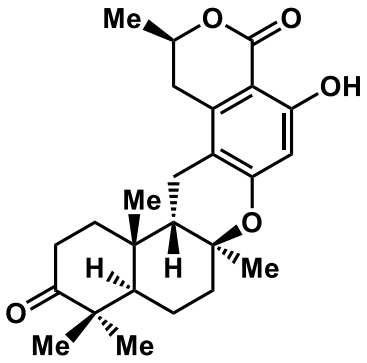
polysin (1)



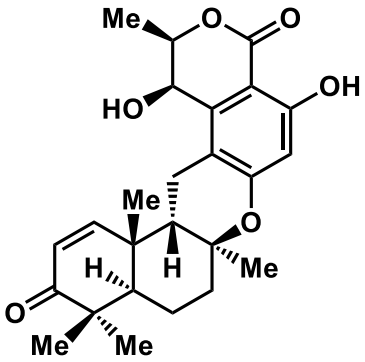
N-acetyl-polyveoline (2)



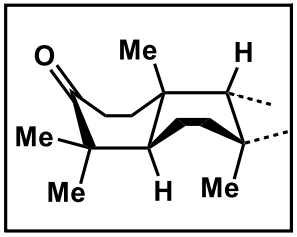
trans-syn-cis fusion



chrodrimanin C (3)



chrodrimanin T (4)



trans-syn-trans fusion

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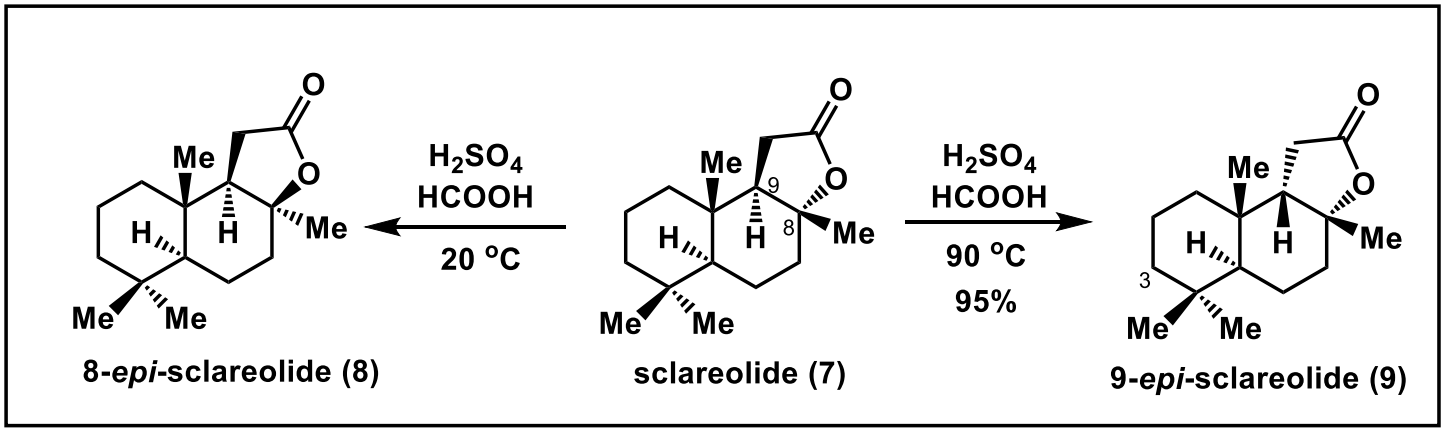
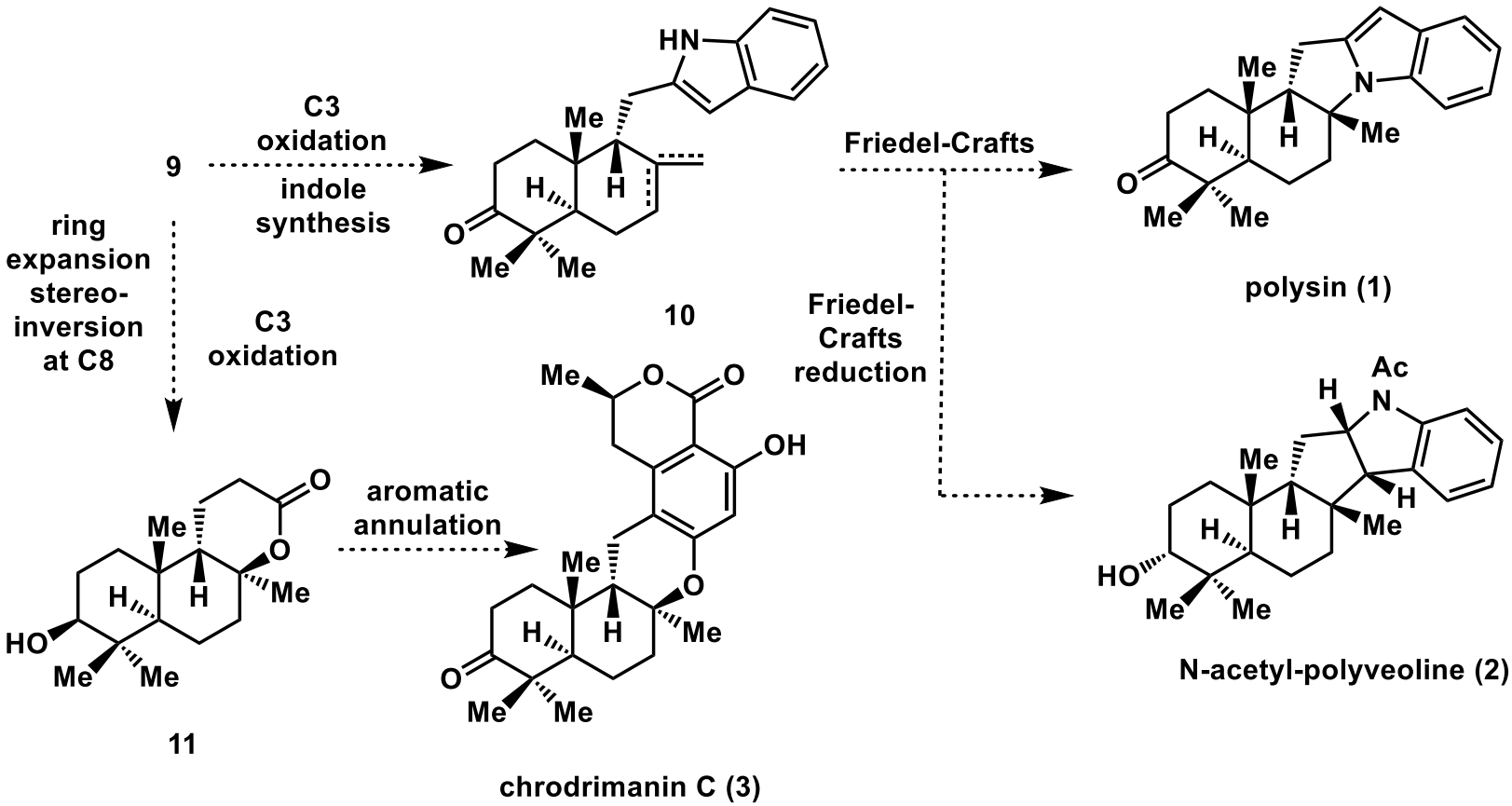
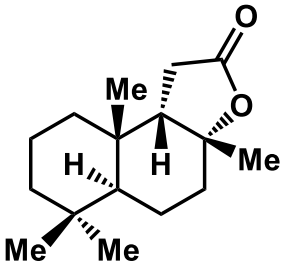
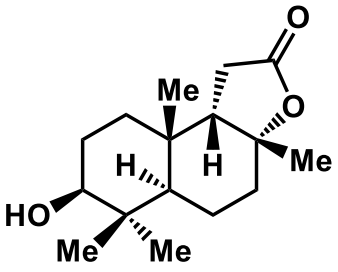

H_2SO_4
HCOOH
20 °C
H_2SO_4
HCOOH
90 °C
95%
8-*epi*-sclareolide (8)
sclareolide (7)
9-*epi*-sclareolide (9)


9
C3
oxidation
indole
synthesis
10
Friedel-Crafts
polysin (1)
ring
expansion
stereo-
inversion
at C8
C3
oxidation
Friedel-
Crafts
reduction
aromatic
annulation
11
chrodrimanin C (3)
N-acetyl-polyveoline (2)

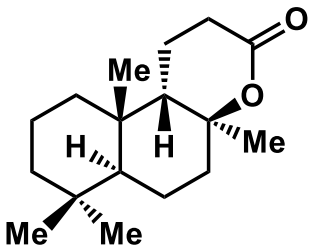


9

P450BM3
variant
Opt13



13



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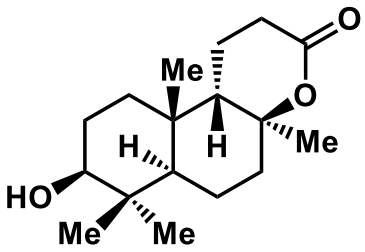
P450BM3
variant
Opt13



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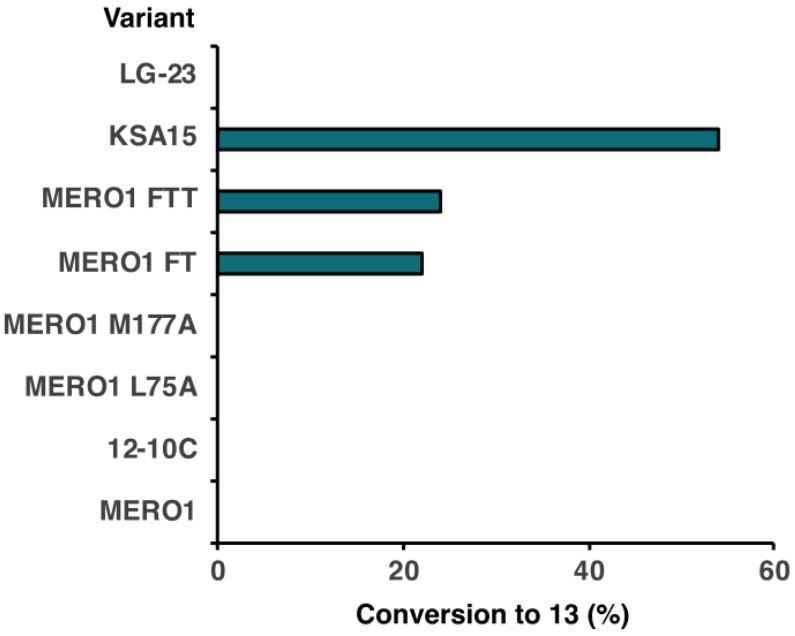
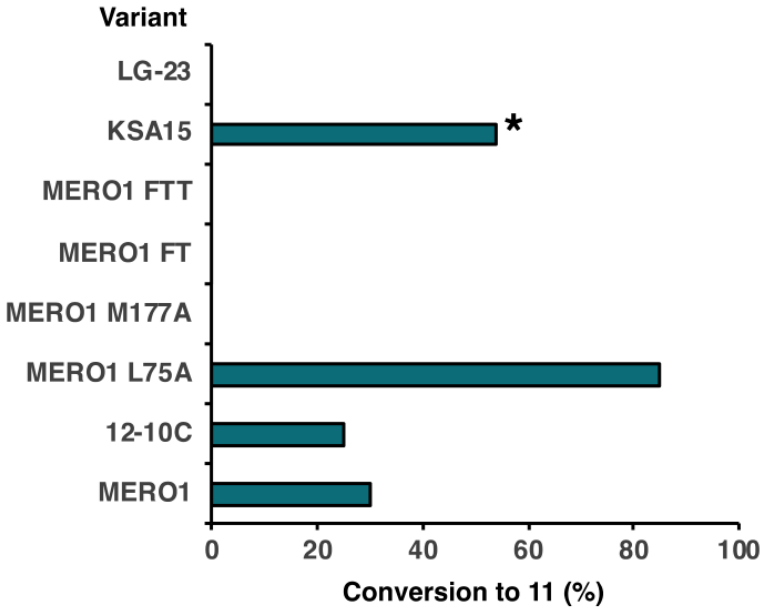
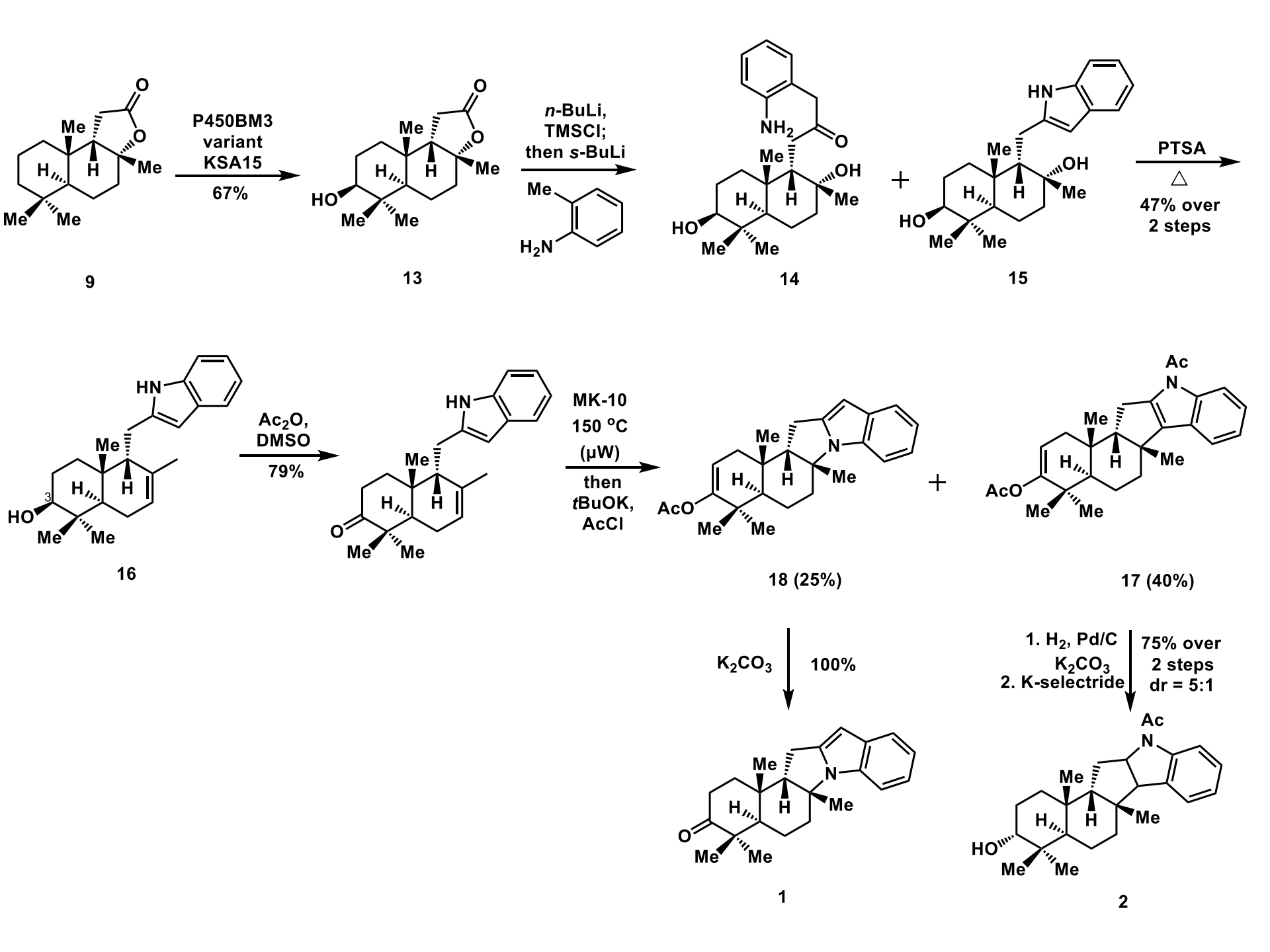
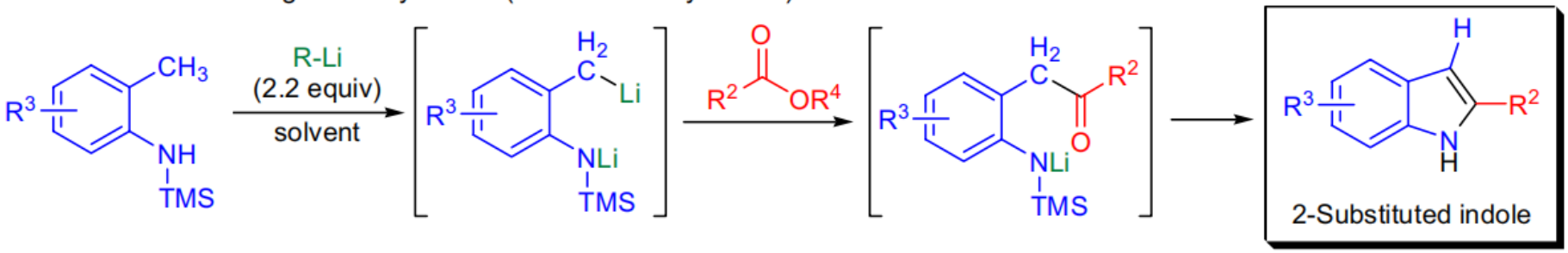





P450BM3
variant
KSA15
67%
n-BuLi,
TMSCl;
then s-BuLi
PTSA
△
47% over
2 steps
Ac2O,
DMSO
79%
MK-10
150 °C
(μW)
then
tBuOK,
AcCl
K2CO3
100%
1. H2, Pd/C
K2CO3
2. K-selectride
75% over
2 steps
dr = 5:1
9
13
14
15
16
18 (25%)
17 (40%)
1
2

Smith-modified Madelung indole synthesis (Smith indole synthesis):

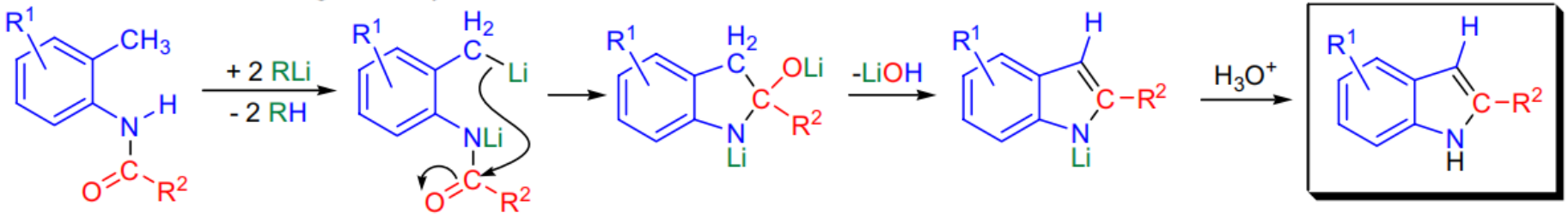


R^1 = H, alkyl, aryl, typically EDG; R^2 = alkyl, aryl; R^3 = alkyl, O-alkyl, O-aryl, Cl, F; R^4 = Me, Et; EWG = CN, CO_2R

strong base: KOEt, NaOEt, $NaNH_2$, Na(O-alkyl); alkyllithium, aryllithium; solvent: hexanes, THF

Mechanism: [4,11]

Mechanism of the Madelung indole synthesis:



Mechanism of the Smith indole synthesis:

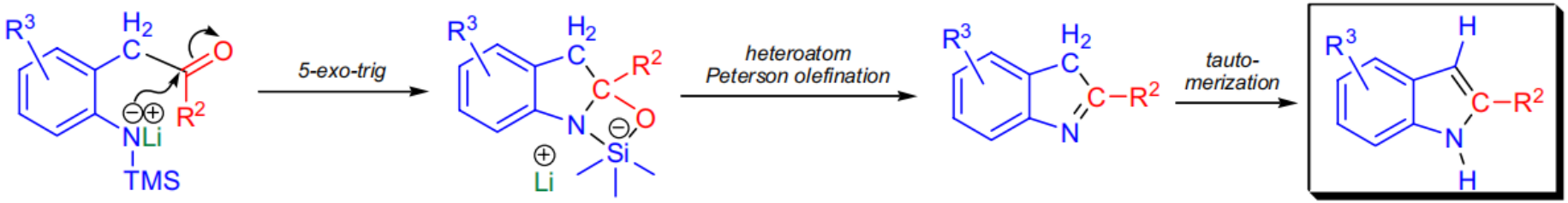
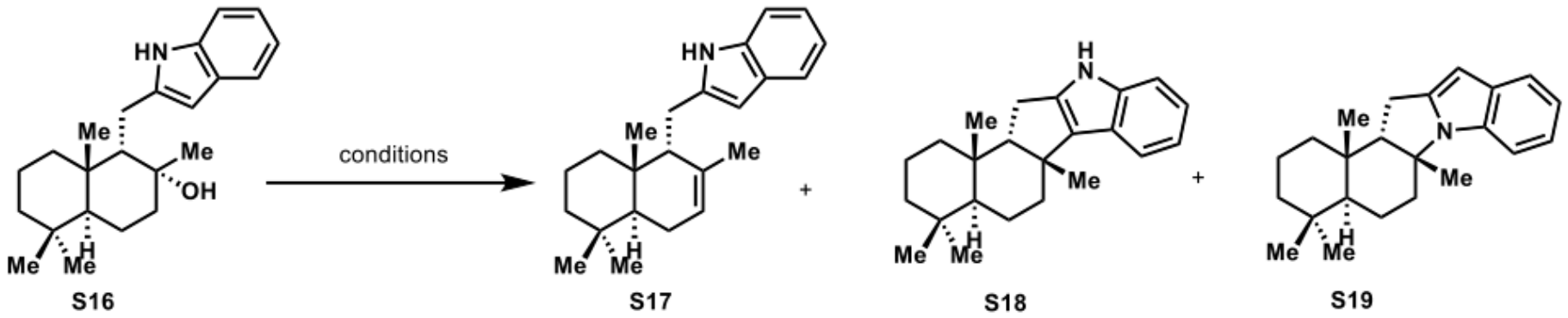


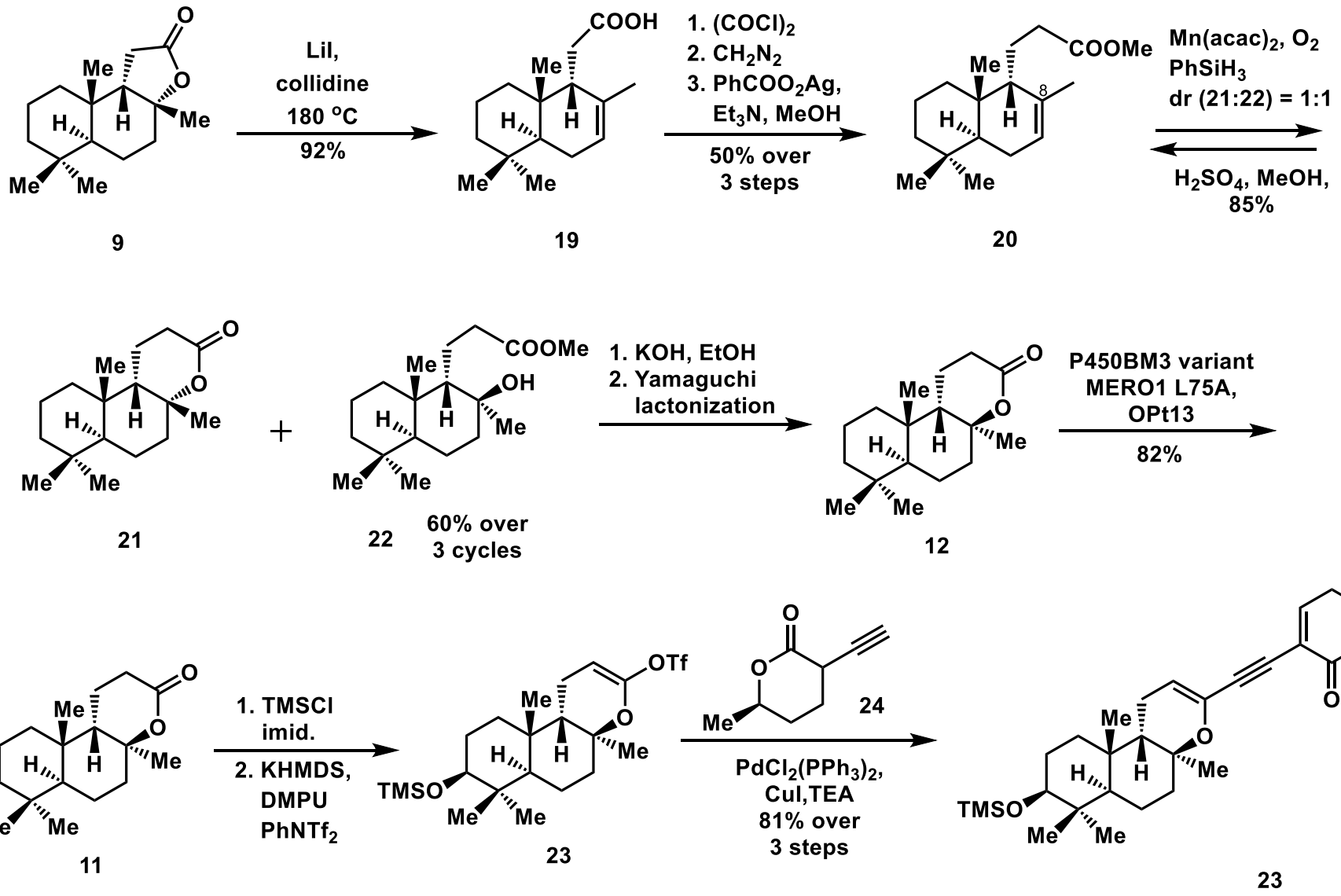
Table S4. Condition Screening for Friedel-Crafts Cyclization on Model Compound S16



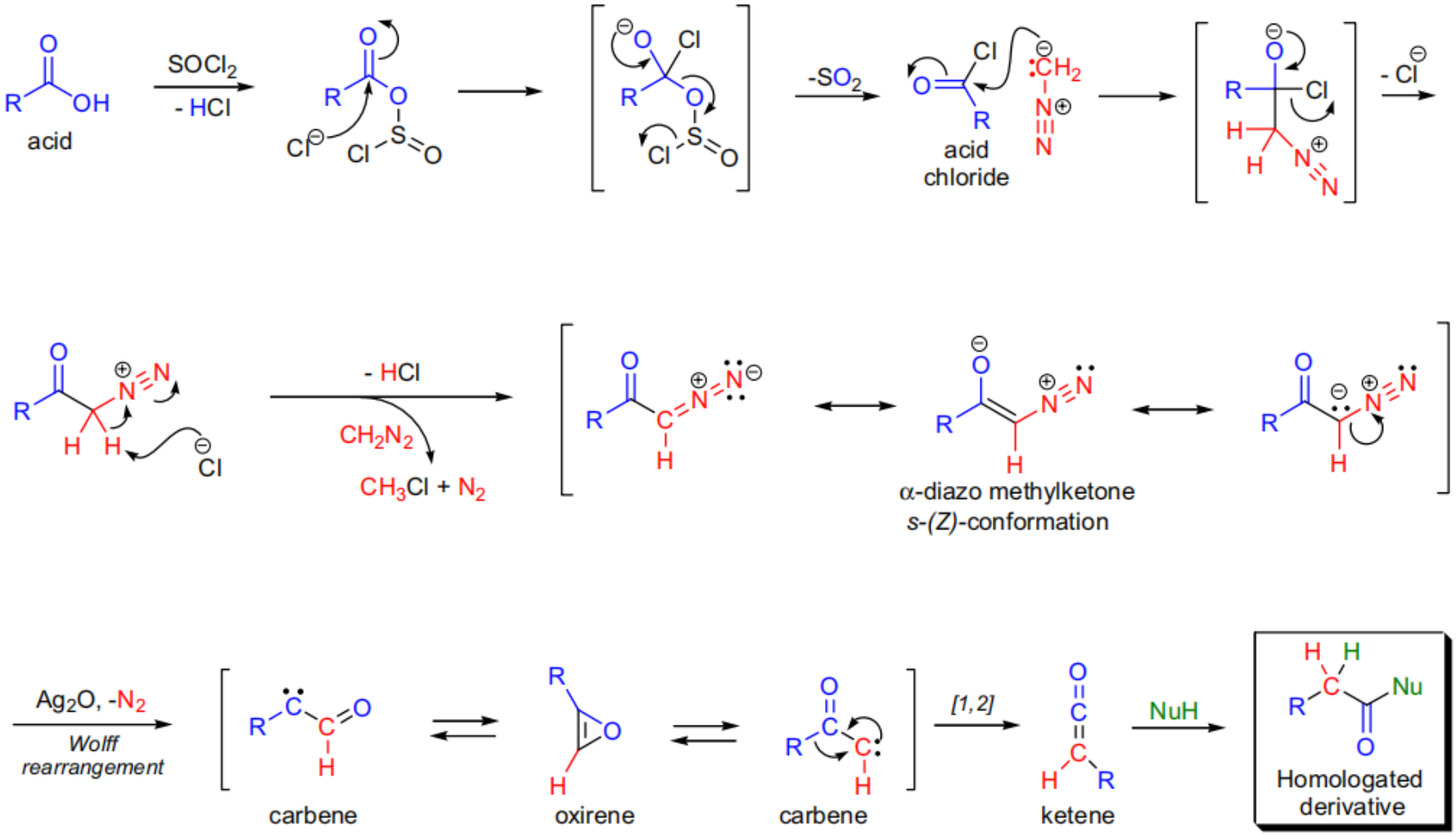
S16 S17 S18 S19

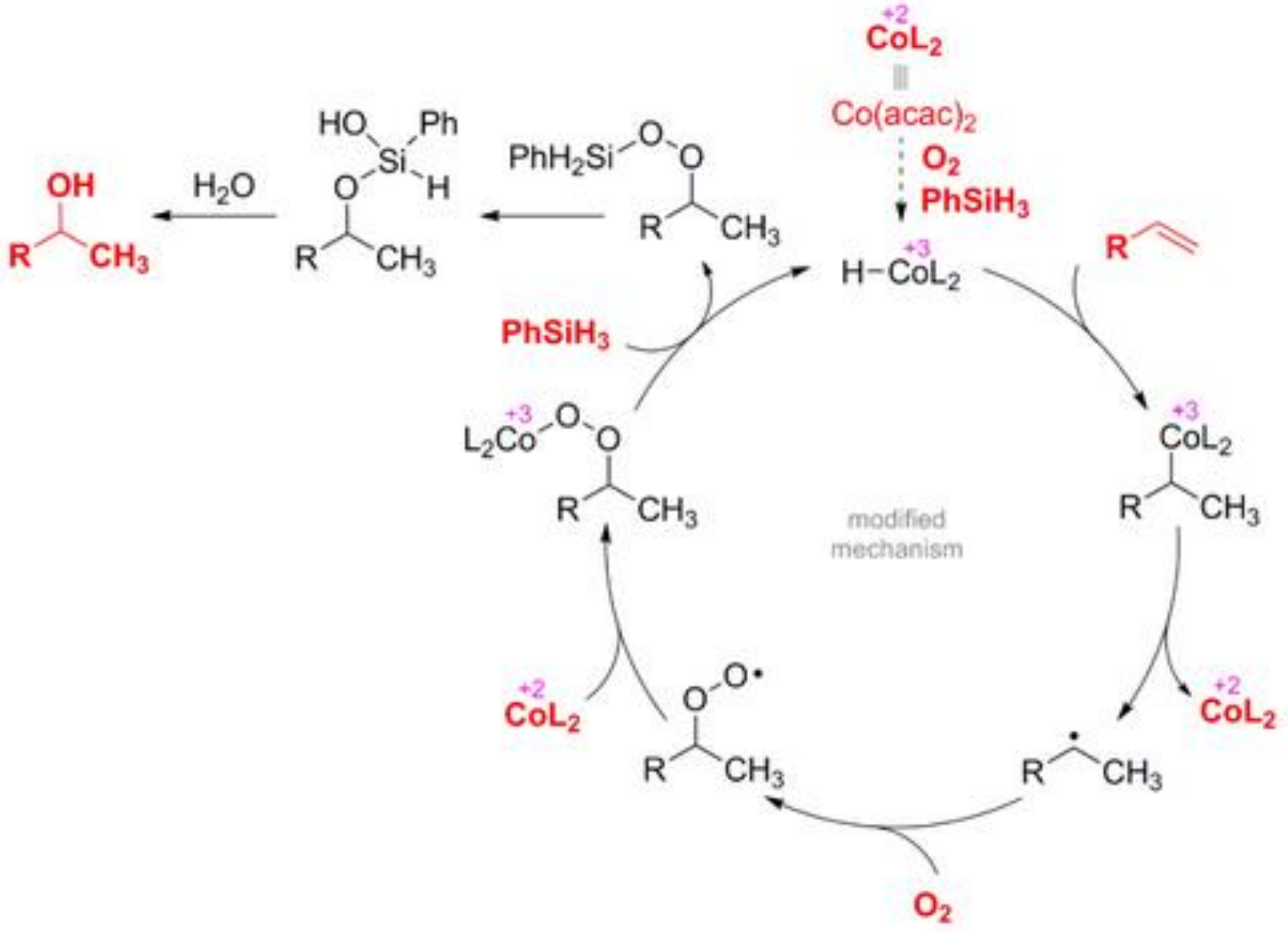
Entry	Conditions	Results
1	$AlCl_3$, DCM, 0 °C to rt	**S17**
2	$BF_3{\cdot}Et_2O$, DCM, 0 °C	**S17**
3	TFA, DCM, 0 °C	*Messy*
4	$SnCl_4$, DCM, 0 °C	**S17** (major)
5	$FeCl_3$, $AgSbF_6$, DCE, 80 °C	**S17**
6	$BF_3{\cdot}Et_2O$ or $SnCl_4$, $MeNO_2$, 0 °C to rt	*Messy*
7	TFA, DCM, 0 °C	*Messy*
8	TfOH, DCM, 0 °C	**S17**
9	TFSI-H, DCM, rt	*N.R.*
10	PTSA, toluene, 125 °C	**S17**
11	montmorillonite K–10, DCE, 120 °C, *mw*	**S18** (45%)[a] **S19** (23%)

a. C-cyclization product **S18** is unstable.


LiI,
collidine
180 °C
92%
1. (COCl)2
2. CH2N2
3. PhCOO2Ag,
Et3N, MeOH
50% over
3 steps
Mn(acac)2, O2
PhSiH3
dr (21:22) = 1:1
H2SO4, MeOH,
85%
9
19
20
21
22
60% over
3 cycles
1. KOH, EtOH
2. Yamaguchi
lactonization
12
P450BM3 variant
MERO1 L75A,
OPt13
82%
11
1. TMSCl
imid.
2. KHMDS,
DMPU
PhNTf2
23
24
PdCl2(PPh3)2,
CuI,TEA
81% over
3 steps
23

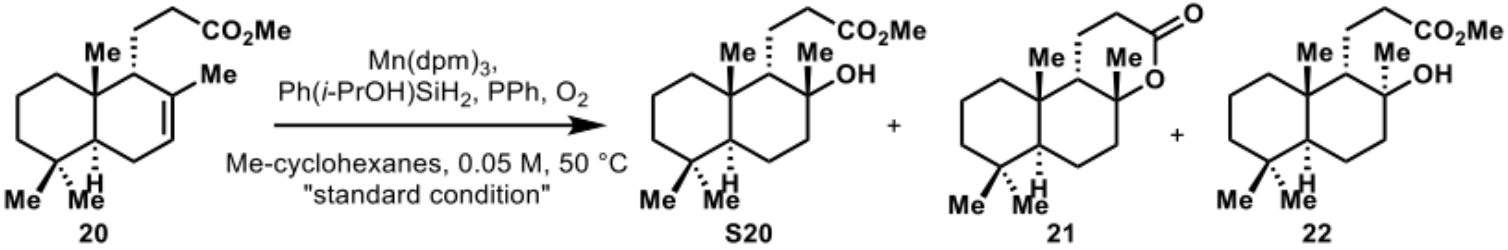
ARNDT-EISTERT HOMOLOGATION / SYNTHESIS





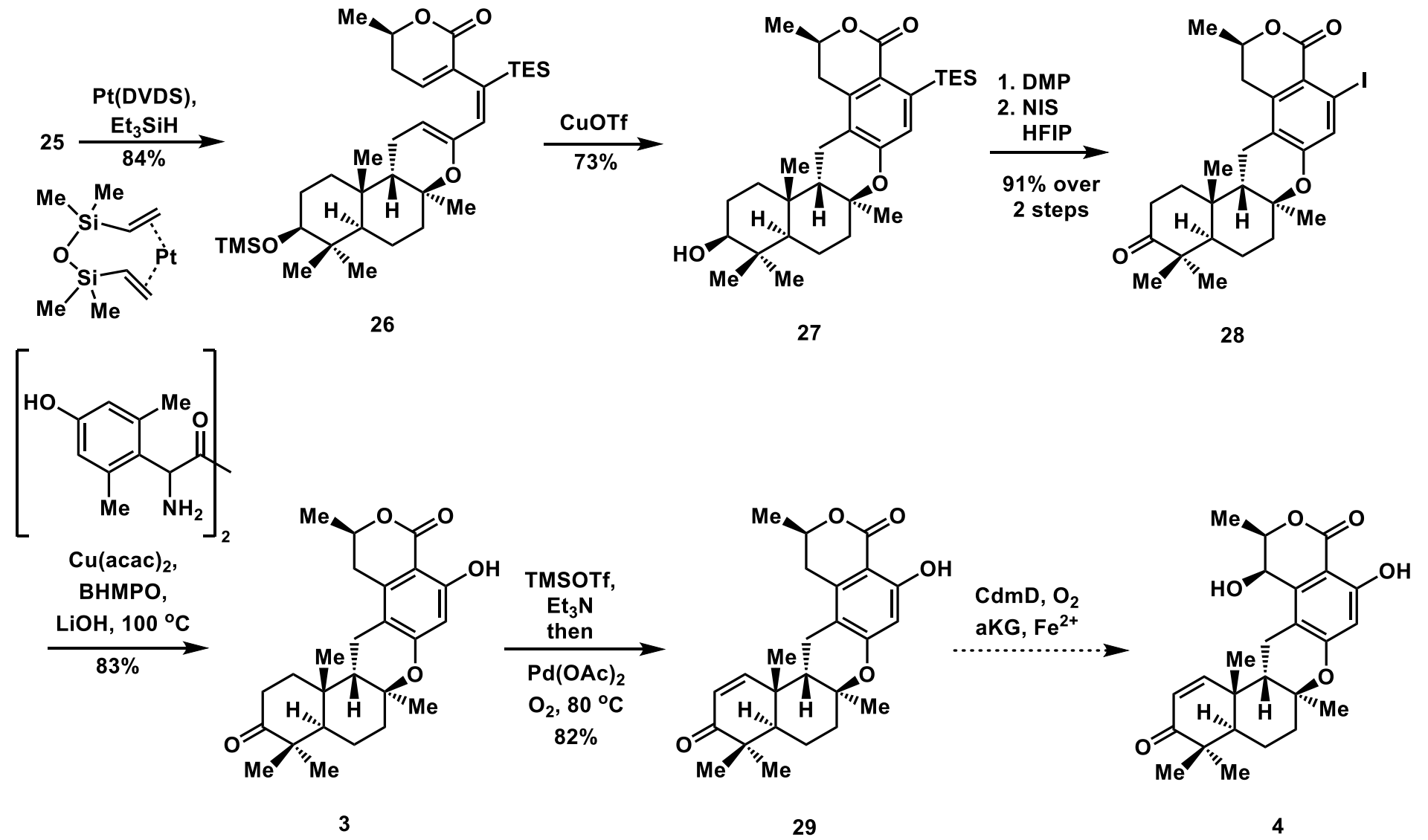
+2
CoL2
Co(acac)2
O2
PhSiH3
+3
H−CoL2
R
+3
CoL2
R
CH3
+2
CoL2
R
CH3
O2
O
O•
R
CH3
+2
CoL2
+3
L2Co
O
O
R
CH3
PhSiH3
PhH2Si
O
O
R
CH3
HO
Ph
Si
O
H
R
CH3
H2O
OH
R
CH3
modified
mechanism

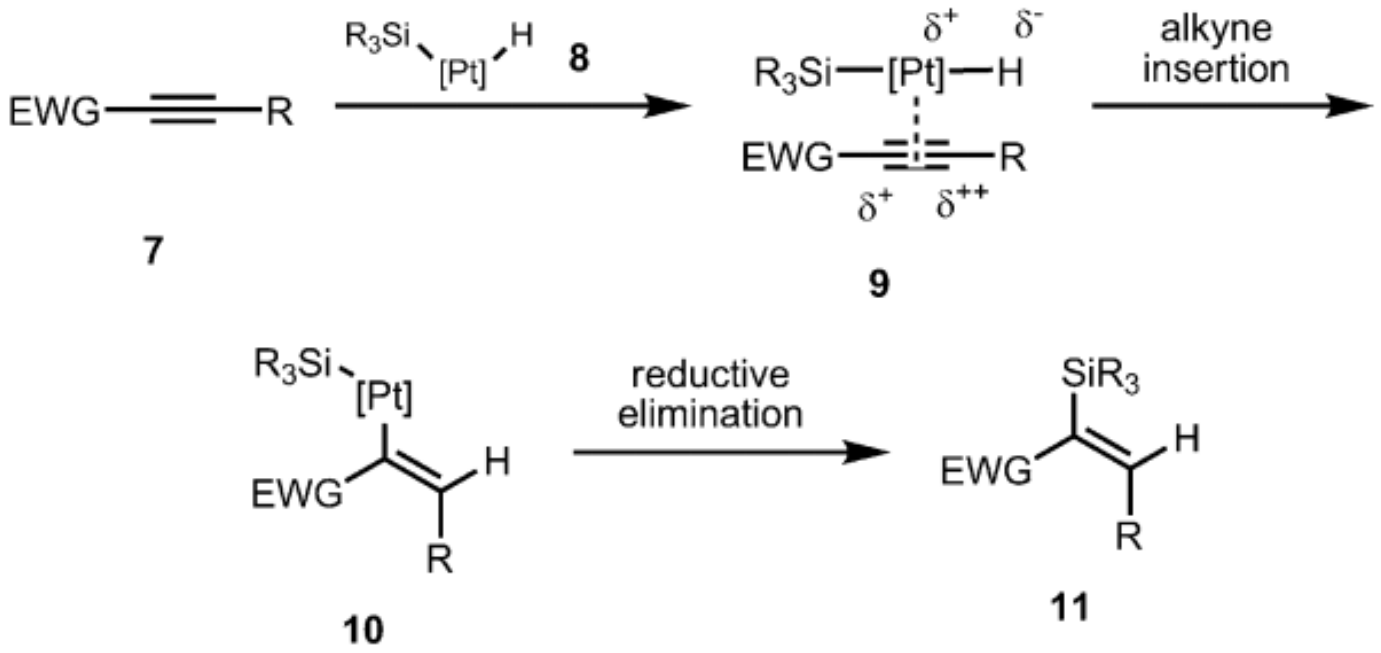
Table S5. Condition Screening of Mukaiyama Hydration on Compound 20



Entry	Deviation from Standard conditions	Ratio of **S20** : **21** : **22**[a]	Yield of **22** (%)
1	None[b]	0.30 : 0.26 : 0.44	30
2	Solvent = THF	0.14 : 0.44 : 0.41	-
3	Solvent = EtOAc	0.24 : 0.35 : 0.41	-
4	Solvent = *t*-BuOMe	0.20 : 0.37 : 0.43	-
5	Solvent = hexane	033 : 0.25 : 0.42	-
6	Solvent = cyclohexane	0 : 0.54 : 0.46	-
7	cyclohexane, rt	0.15 : 0.40 : 0.46	32
8	$Co(acac)_2$, $PhSiH_3$, O_2, *i*-PrOH, rt	0.33 : 0.30 : 0.37	21
9	$Mn(dpm)_3$, $PhSiH_3$, O_2, *i*-PrOH, PPh_3, rt	0.32 : 0.23 : 0.45	32
10	$Mn(acac)_2$, $PhSiH_3$, O_2, *i*-PrOH, THF, rt	0 : 0.50 : 0.50	40

a. Ratio of products was calculated based on ^1H NMR analysis. b. Standard conditions were obtained from Shenvi's report.[6]


25
Pt(DVDS),
Et3SiH
84%
26
CuOTf
73%
27
1. DMP
2. NIS
HFIP
91% over
2 steps
28
Cu(acac)2,
BHMPO,
LiOH, 100 °C
83%
3
TMSOTf,
Et3N
then
Pd(OAc)2
O2, 80 °C
82%
29
CdmD, O2
aKG, Fe2+
4



Scheme 1. Electronic influence on platinum-catalyzed hydrosilylations.