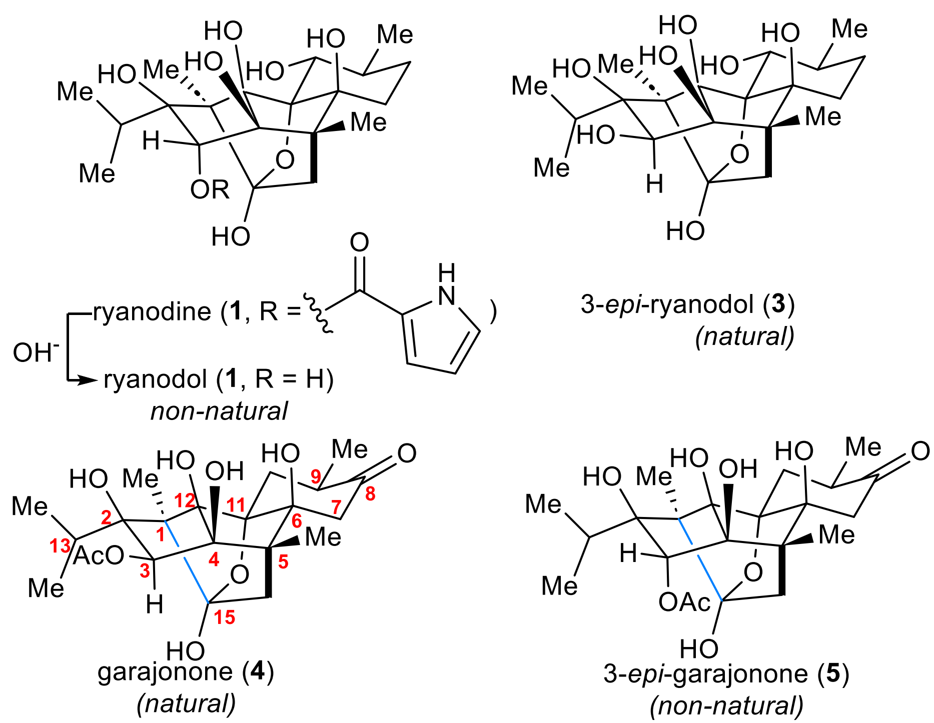
 10.1002/ange.202417647

WILEY-VCH

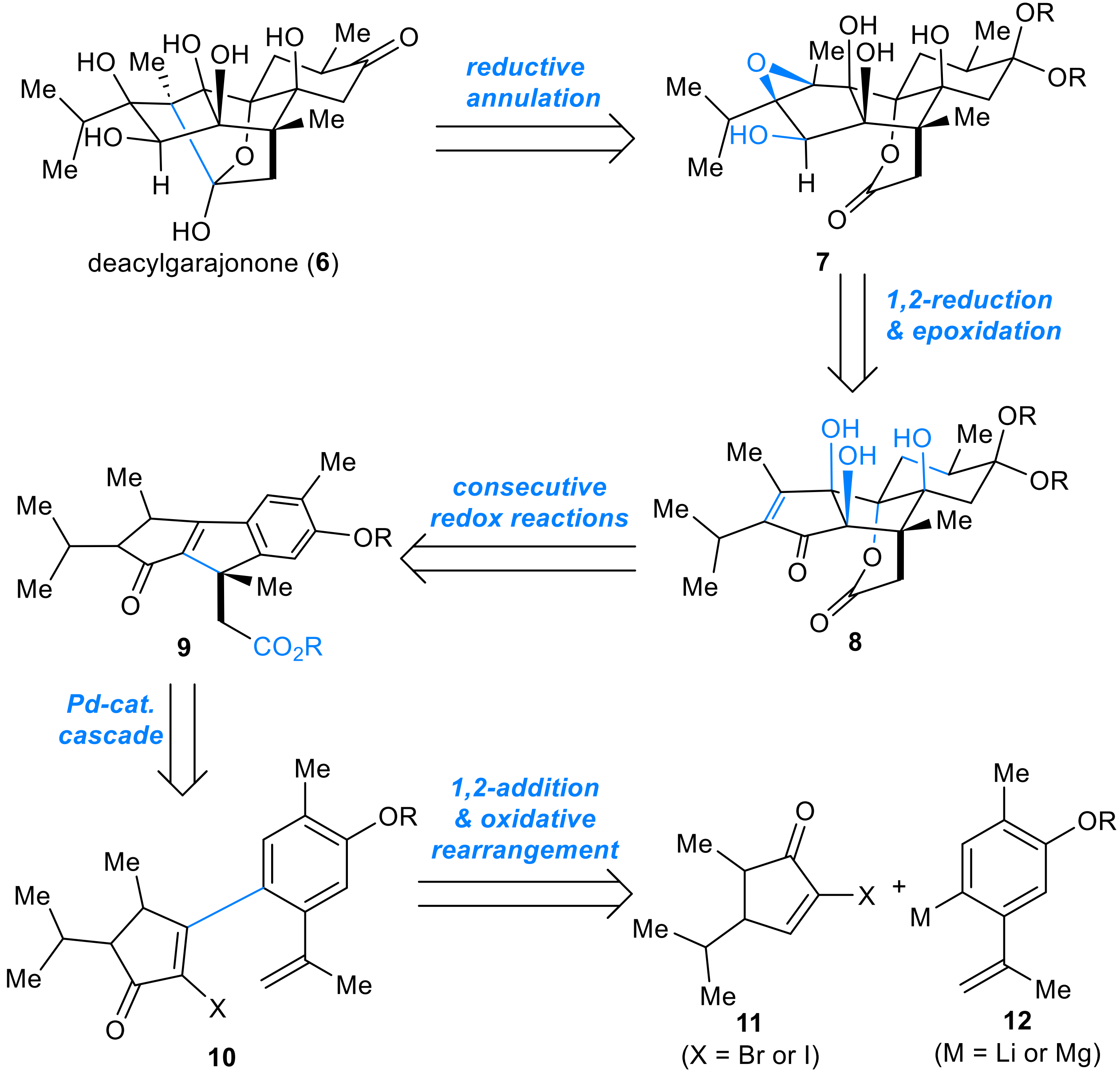
RESEARCH ARTICLE

Total Synthesis of Ryanodane Diterpenoids Garajonone and 3-*epi*-Garajonone

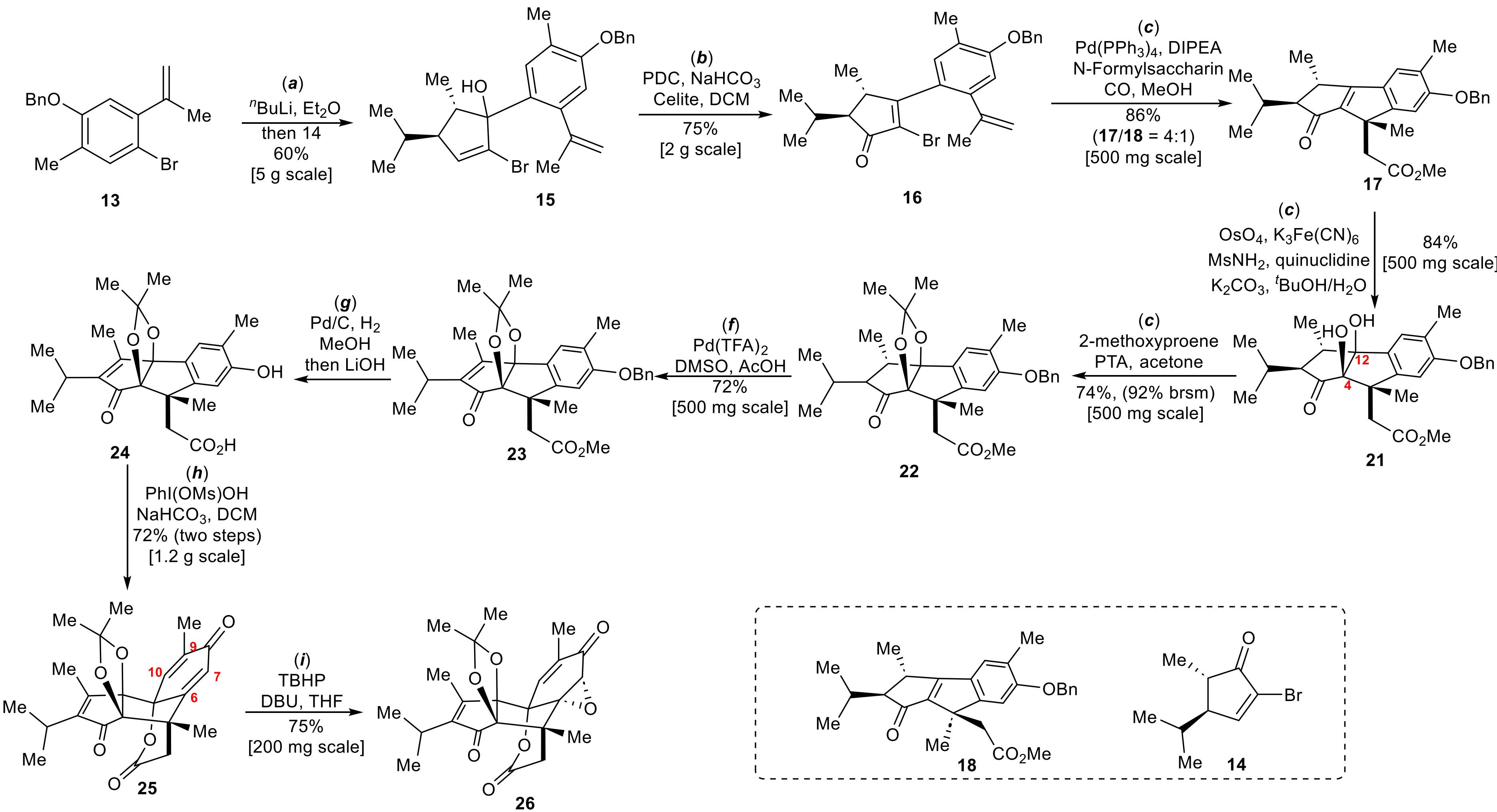
Jin-Bao Qiao,[§,a] Long Meng,[§,a] Jia-Yi Pei,[a] Hui Shao,[a] and Yu-Ming Zhao[*,a]

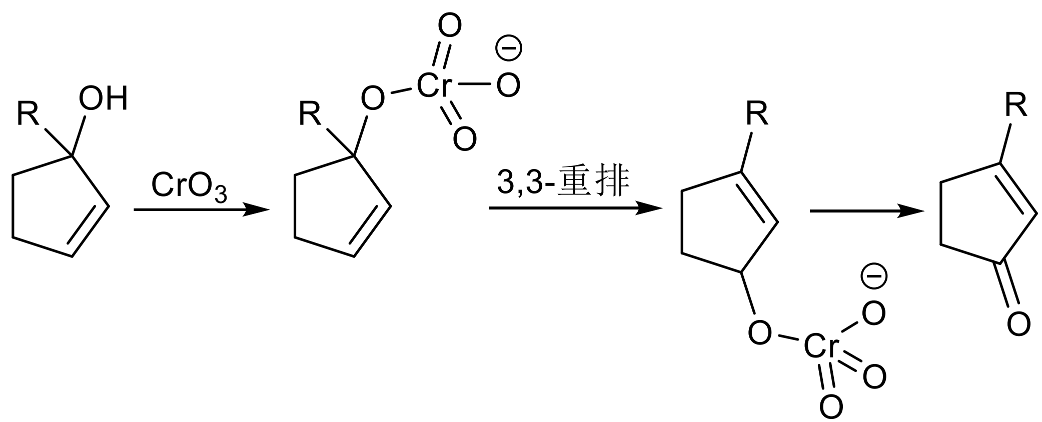


DOI: 10.1002/ange.202417647.



deacylgarajonone (6)
reductive annulation
7
1,2-reduction & epoxidation
8
consecutive redox reactions
9
Pd-cat. cascade
10
1,2-addition & oxidative rearrangement
11
(X = Br or I)
12
(M = Li or Mg)

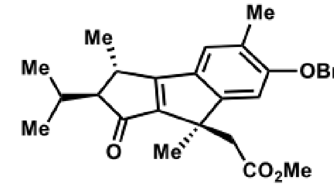

13
(a)
nBuLi, Et2O
then 14
60%
[5 g scale]
15
(b)
PDC, NaHCO3
Celite, DCM
75%
[2 g scale]
16
(c)
Pd(PPh3)4, DIPEA
N-Formylsaccharin
CO, MeOH
86%
(17/18 = 4:1)
[500 mg scale]
17
(c)
OsO4, K3Fe(CN)6
MsNH2, quinuclidine
K2CO3, tBuOH/H2O
84%
[500 mg scale]
21
(c)
2-methoxyproene
PTA, acetone
74%, (92% brsm)
[500 mg scale]
22
(f)
Pd(TFA)2
DMSO, AcOH
72%
[500 mg scale]
23
(g)
Pd/C, H2
MeOH
then LiOH
24
(h)
PhI(OMs)OH
NaHCO3, DCM
72% (two steps)
[1.2 g scale]
25
(i)
TBHP
DBU, THF
75%
[200 mg scale]
26
18
14


R
OH
CrO3
R
O
Cr
O
O
O
3,3-重排
R
O
Cr
O
O
O
R
O

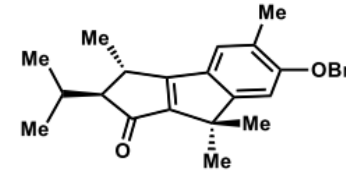
16 17

Entry	Catalyst	Ligand	Base	Additive	T (°C)	Combined yield (17/18, ratio)	Yield (19)	Yield (20)
1	$Pd(dba)_2$	PCy_3	K_3PO_4	-	rt to 100	0	36%	60%
2	$Pd(OAc)_2$	PPh_3	NEt_3	-	rt to 100	43% (2.5:1)	16%	35%
3	$Pd(PPh_3)_4$	-	NEt_3	-	100	59% (3.7:1)	13%	20%
4	$Pd(TFA)_2$	PPh_3	NEt_3	-	100	66% (2.6:1)	12%	18%
5	$Pd_2(dba)_3$	PPh_3	NEt_3	-	100	52% (4.0:1)	27%	18%
6	$Pd(TFA)_2$	PPh_3	NEt_3	S3	100	80% (2.9:1)	<5%	<5%
7	$Pd(TFA)_2$	PPh_3	NEt_3	S4	100	65% (3:1)	11%	19%
8	$Pd(TFA)_2$	PPh_3	NEt_3	S5	100	75% (3:1)	<5%	<5%
9	$Pd(TFA)_2$	PPh_3	Na_2CO_3	S3	100	28% (3.6:1)	<5%	<5%
10	$Pd(TFA)_2$	PPh_3	DIPEA	S3	100	60% (3.1:1)	10%	25%
11[d]	$Pd(TFA)_2$	PPh_3	NEt_3	S3	100	0	0	28%
12	$Pd(TFA)_2$	-	NEt_3	S3	100	0	0	0
13	$Pd(TFA)_2$	PPh_3	-	S3	100	23% (3:1)	<5%	<5%
14[d]	$Pd(PPh_3)_4$	-	NEt_3	S3	100	0	0	24%
15	$Pd(PPh_3)_4$	-	NEt_3	S3	100	84% (3.3:1)	<5%	<5%
16	$Pd(PPh_3)_4$	-	K_3PO_4	S3	100	48% (4:1)	22%	13%
17	$Pd(PPh_3)_4$	-	DIPEA	S3	100	86% (4:1)	<5%	<5%

[a] All reactions were carried on 0.02 mmol, catalyst (10 mol%), ligand (20 mol%) in MeOH (2 mL) and were purged with carbon monoxide (CO balloon) for 20 seconds then placed into a preheated 100 °C oil bath. [b] Using the CH_2Br_2 as an internal standard to determine the yield of all reactions. [c] The ratio of stereoisomer was determined by H-NMR. [d] Replace CO source with S3.



18 (*minor diastereomer*)



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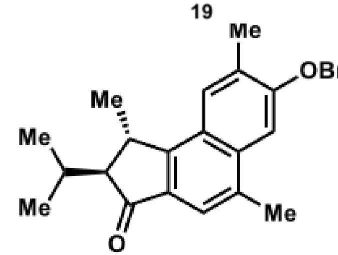
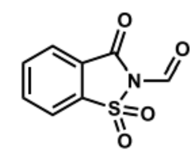
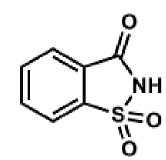


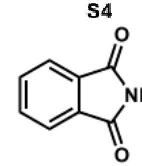
20 (*via* 6-endo-type Heck)



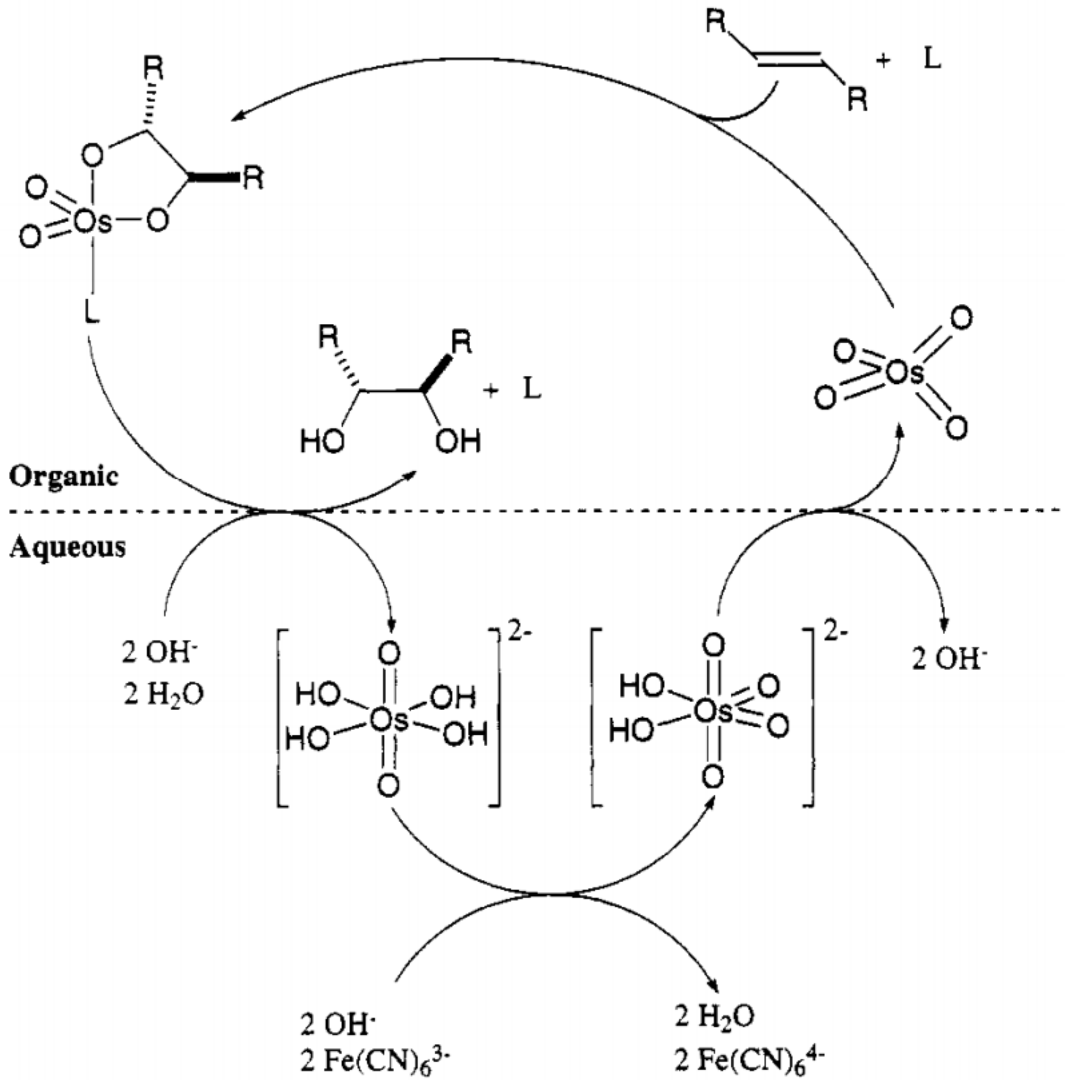
S3



S4



S5

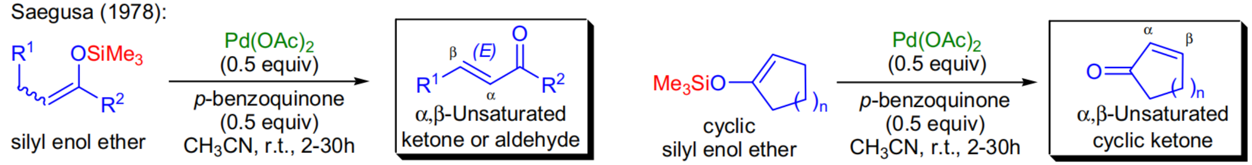


Chem. Rev., **1994**, *94*, 2483.

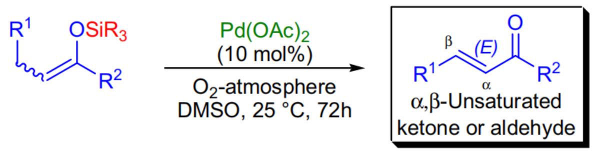
SAEGUSA OXIDATION

(References are on page 667)

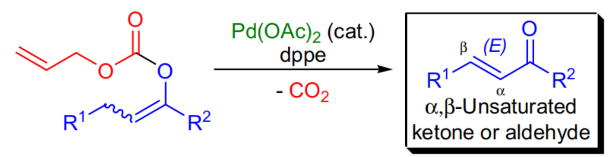
Saegusa (1978):



Catalytic process (*Larock modification*,1995):



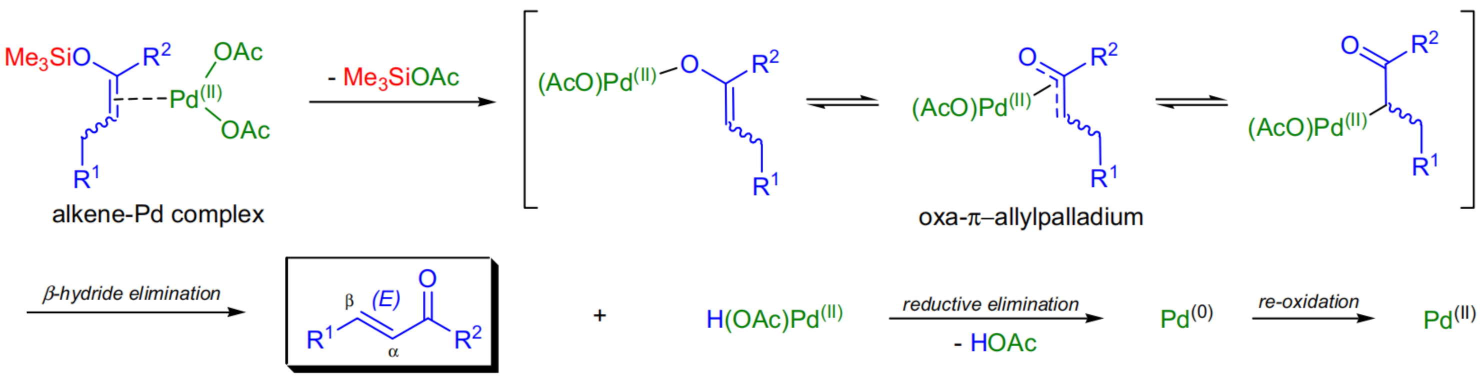
Allyl enol carbonate modification:



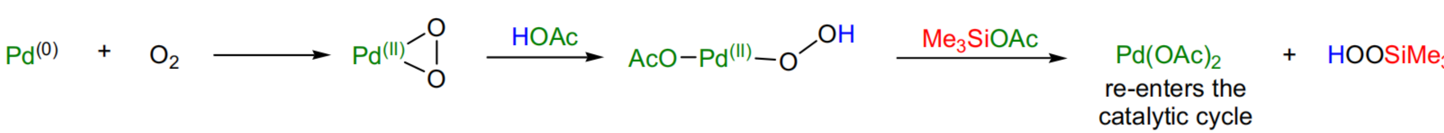
R^{1-2} = H, alkyl, aryl; SiR_3 = TMS, TBDMS; n = 1-7

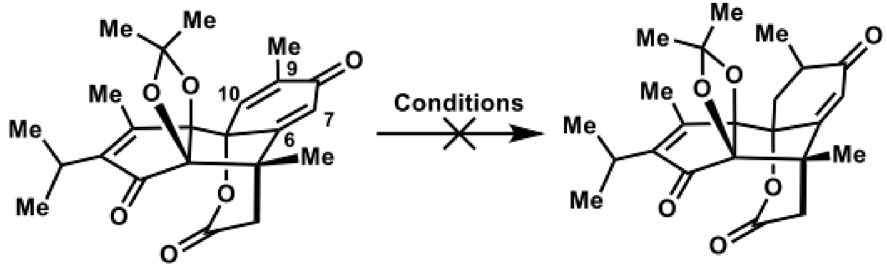
Mechanism: [15,7]

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



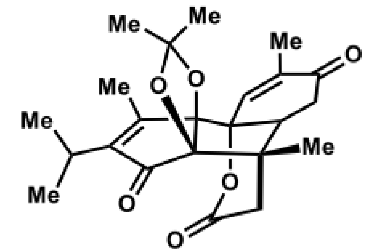
When the oxidation takes place under an oxygen atmosphere with catalytic amounts of $Pd(OAc)_2$:



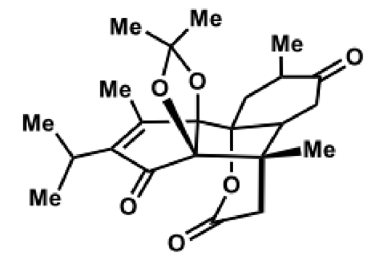


Entry	Conditions	Result[a]
1	Ipr.HCl, CuCl, ^{t}BuONa, $(EtO)_3SiH$, PhMe, 23 °C	**S9** (40%) + **S10** (26%)
2	L-Selectride, THF, -78 °C	Decomp.
3	MAD, L-Selectride, PhMe, -78°C to 23 °C	NR
4	$[(Ph_3P)CuH]_6$, $PhSiH_3$, PhMe, 23 °C	**S9** (58%) + **S10** (24%)
5	$RhCl(PPh_3)_3$, Et_3SiH, DCE, 0°C to 35 °C	**S9** (70%) + **S10** (13%)
6	$RhCl(PPh_3)_3$, H_2 balloon, DCM, 23 °C	**S9** (68%) + **S10** (10%)
7	Crabtree catalyst, H_2 balloon, DCM, 23 °C	NR
8	Crabtree catalyst, H_2 (3.0 Mpa), DCM, 23 °C	NR
9	$KO_2CN{=}NCO_2K$, HOAc, $MeNO_2$, 0 to 60 °C	NR
10	$NiCl_2·6H_2O$, $NaBH_4$, MeOH, 0 °C	**24** (86%)
11	Pd/C, H_2 balloon, acetone, 0 to 23 °C	**24** (90%)

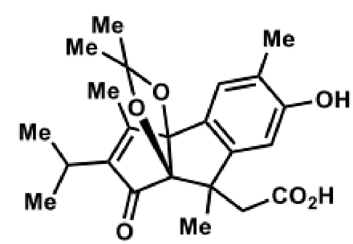
[a] NR = no reaction, MAD = methylaluminum bis(4-bromo-2,6-di(tert-butylphenoxide).



S9



S10



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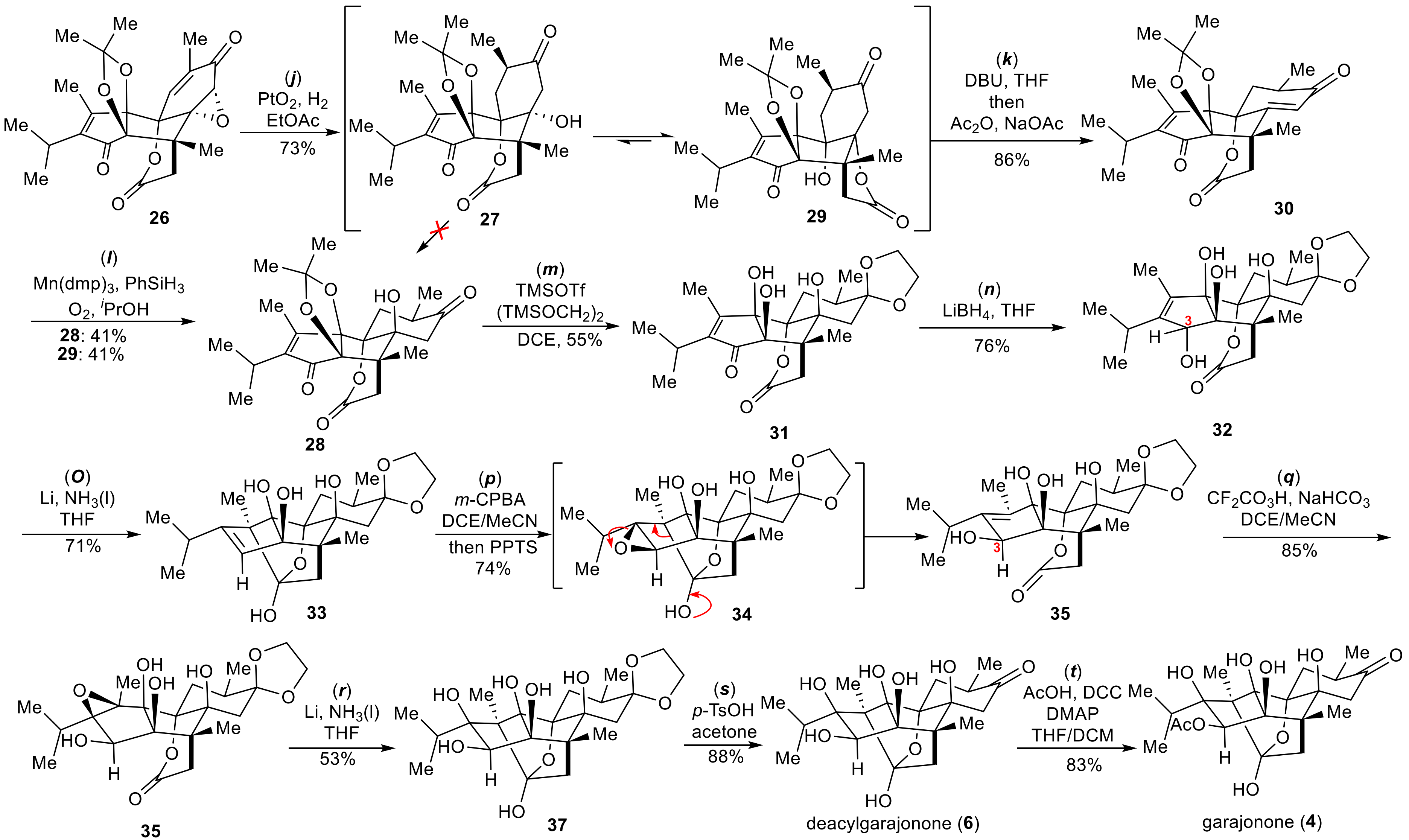
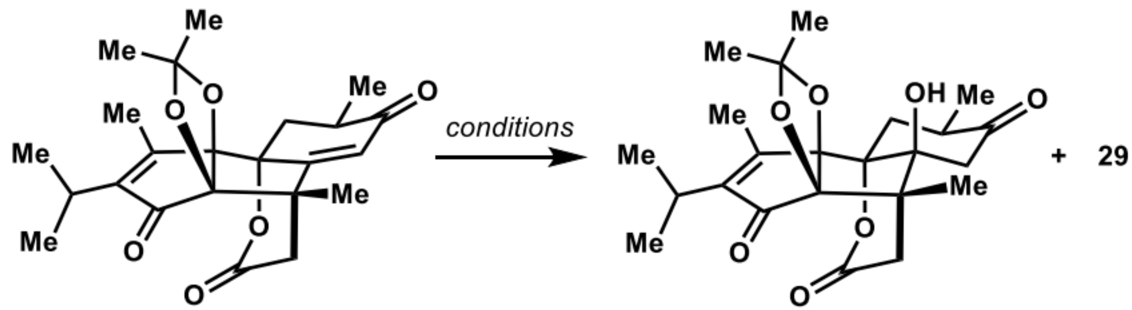

26
(j)
PtO2, H2
EtOAc
73%
27
29
(k)
DBU, THF
then
Ac2O, NaOAc
86%
30
(l)
Mn(dmp)3, PhSiH3
O2, iPrOH
28: 41%
29: 41%
28
(m)
TMSOTf
(TMSOCH2)2
DCE, 55%
31
(n)
LiBH4, THF
76%
32
(O)
Li, NH3(l)
THF
71%
33
(p)
m-CPBA
DCE/MeCN
then PPTS
74%
34
35
(q)
CF3CO3H, NaHCO3
DCE/MeCN
85%
35
(r)
Li, NH3(l)
THF
53%
37
(s)
p-TsOH
acetone
88%
deacylgarajonone (6)
(t)
AcOH, DCC
DMAP
THF/DCM
83%
garajonone (4)



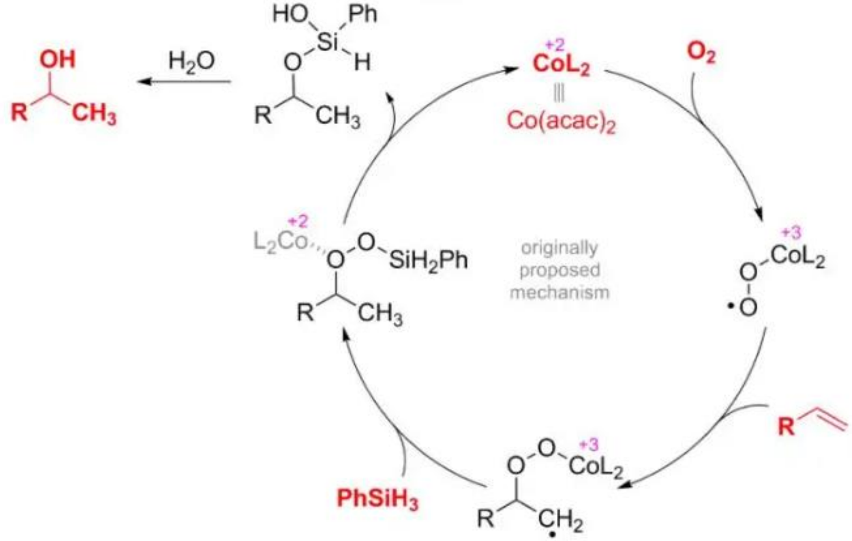
30 28

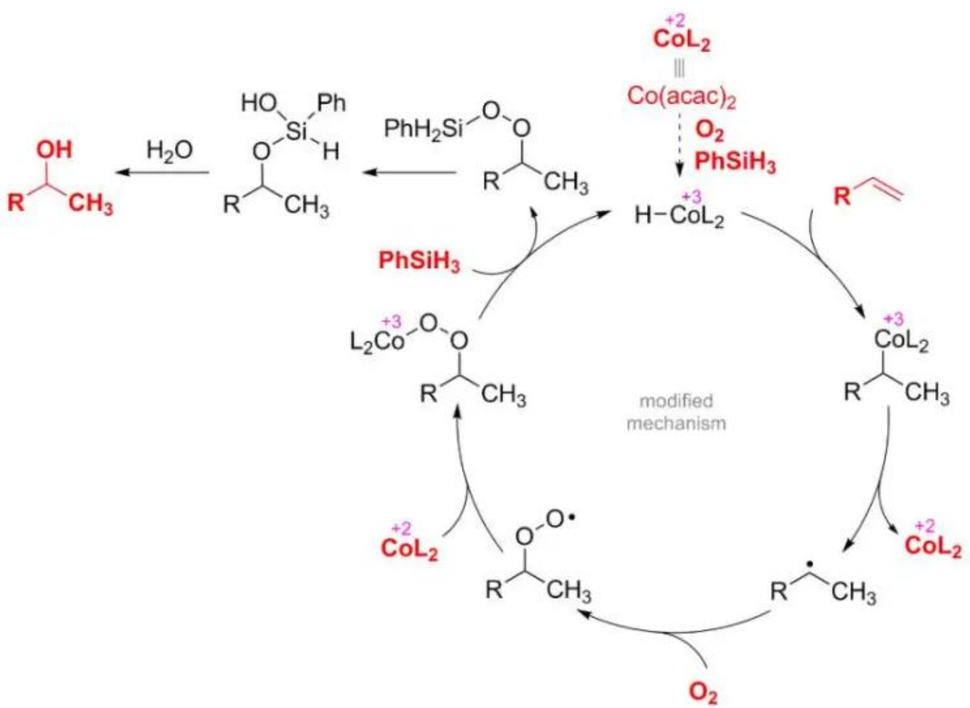
Entry	Conditions	Ratio[b] **28**/**29**	Yield[c]
1	Fe(dmp)$_3$, PhSiH$_3$, O$_2$, ^{i}PrOH, rt	--	NR
2	Co(acac)$_2$, PhSiH$_3$, O$_2$, ^{i}PrOH, rt	1:1.2	48%
3	Mn(dmp)$_3$, PhSiH$_3$, O$_2$, ^{i}PrOH, rt	1:1	82%
4	Mn(dmp)$_3$, Ph$_2$SiH$_2$, O$_2$, ^{i}PrOH, rt	1:1	36%
5	Mn(dmp)$_3$, (EtO)$_3$SiH, O$_2$, ^{i}PrOH, rt	--	NR
6	Mn(dmp)$_3$, ^{i}Pr$_3$SiH, O$_2$, ^{i}PrOH, rt	--	NR
7	Mn(dmp)$_3$, Ph(^{i}PrO)SiH$_2$, O$_2$, ^{i}PrOH, rt	1:1	80%
8	Mn(dmp)$_3$, PhSiH$_3$, O$_2$, 1,4-dioxane, rt	1:1	15%

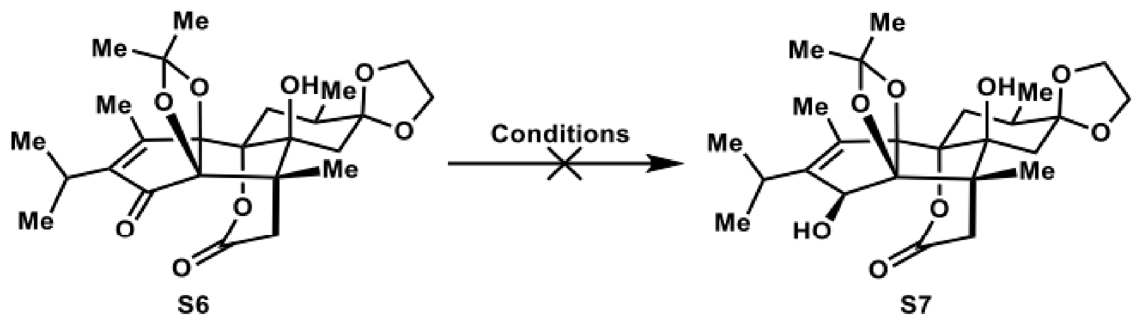
[a] All reactions were performed on a 0.005 mmol scale. [b] Ratio determined by crude ^{1}H-NMR. [c] Combined yield of **28** and **29**. Mn(dpm)$_3$ = tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III); NR = no reaction.

Mukaiyama Hydration

[1989]

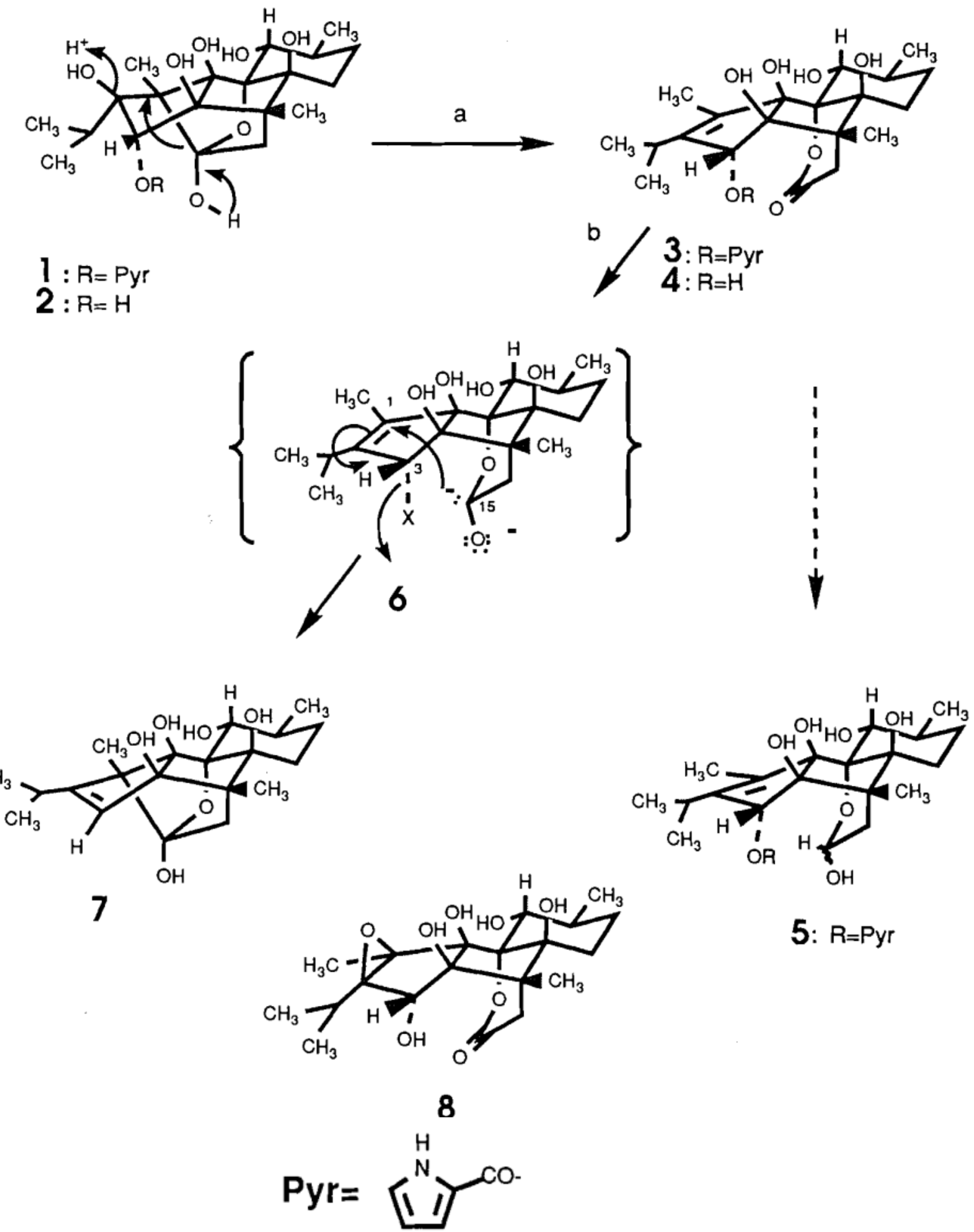






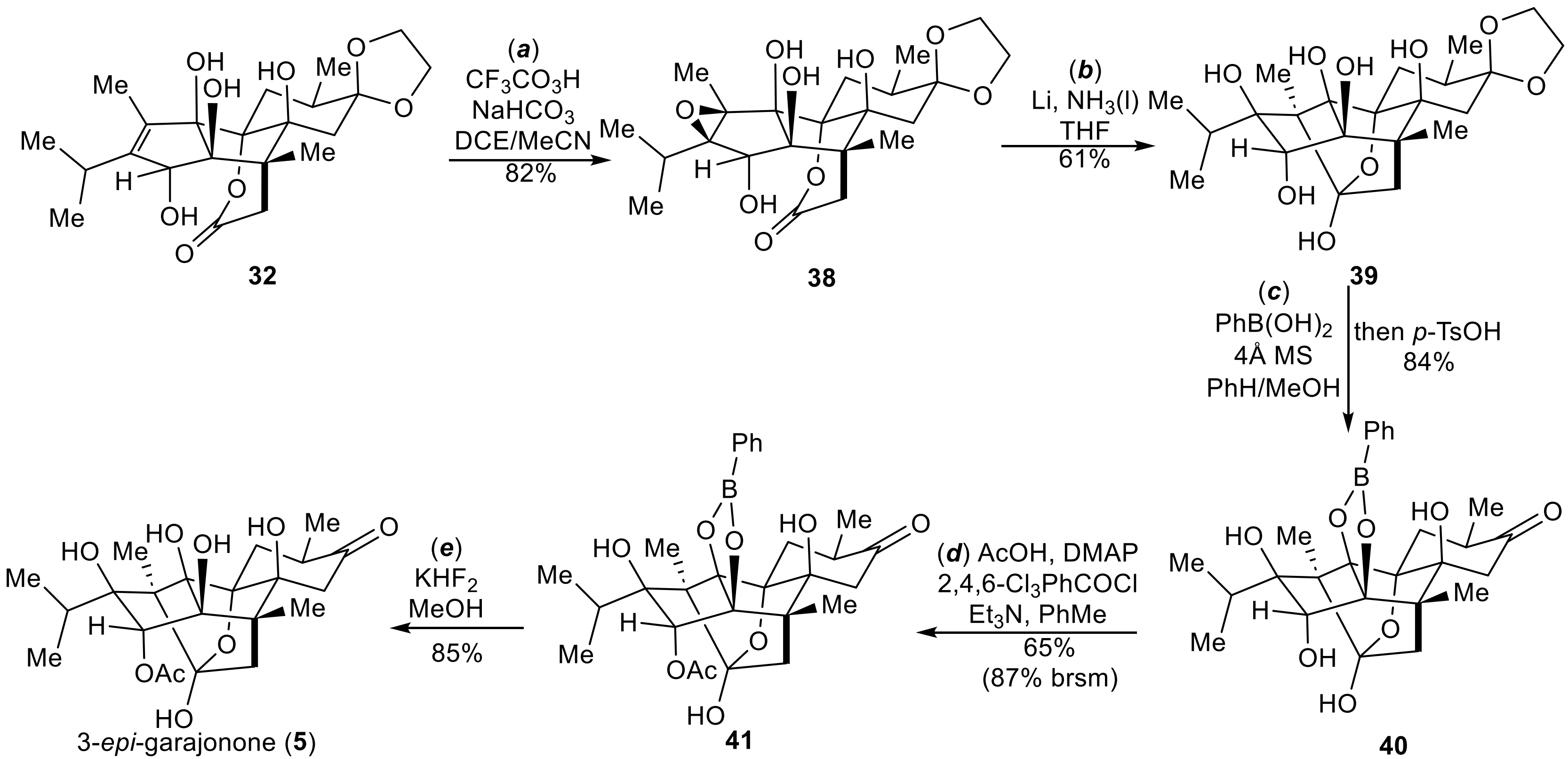
Entry	Conditions	Result[a]
1	$LiBH_4$, THF, -15 °C to 0°C	NR
2	$NaBH_4$, MeOH, 0 °C to 23°C	NR
3	$NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C to 23°C	NR
4	L-selectride, THF, -15 °C to 0 °C	NR

[a] NR = no reaction



a: H_2SO_4, 2 N; b: Li, NH_3, THF, −78°C, 20–100 min

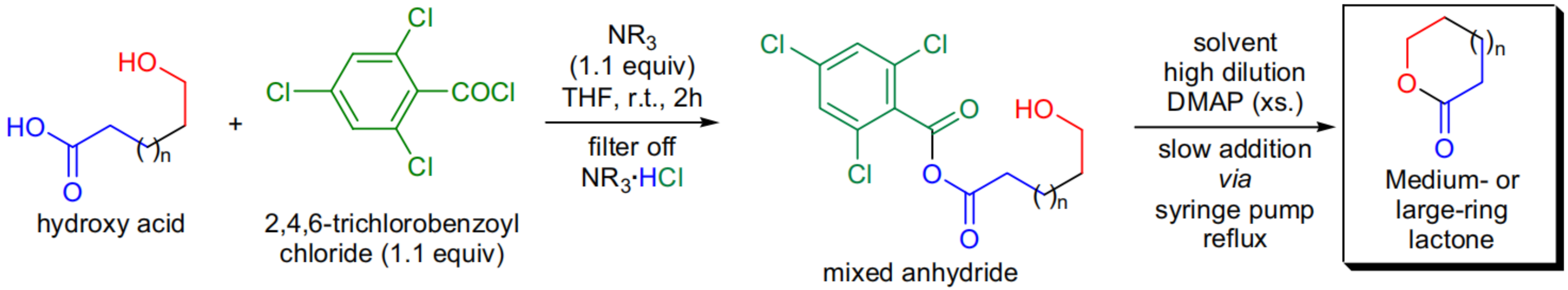
Can. J. Chern., **1993**, *71*, 634.


32
(a)
CF3CO3H
NaHCO3
DCE/MeCN
82%
38
(b)
Li, NH3(l)
THF
61%
39
(c)
PhB(OH)2
4Å MS
PhH/MeOH
then p-TsOH
84%
40
(d) AcOH, DMAP
2,4,6-Cl3PhCOCl
Et3N, PhMe
65%
(87% brsm)
41
(e)
KHF2
MeOH
85%
3-epi-garajonone (5)

YAMAGUCHI MACROLACTONIZATION

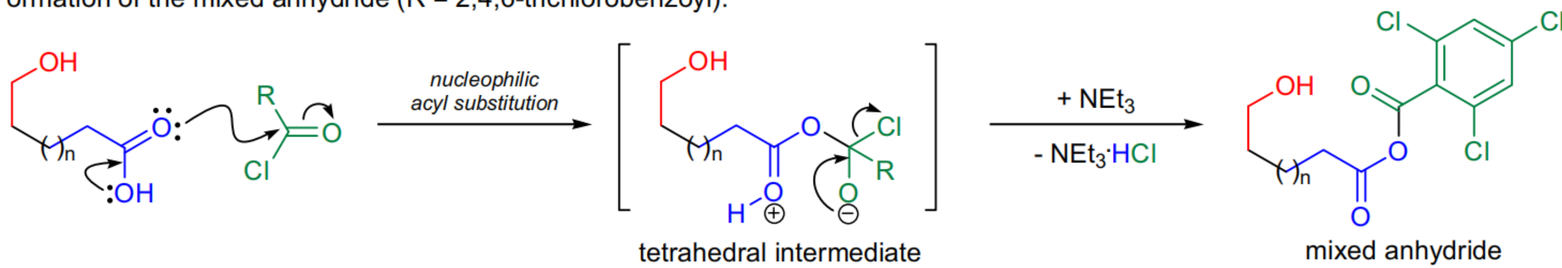
(References are on page 714)

Yamaguchi macrolactonization:

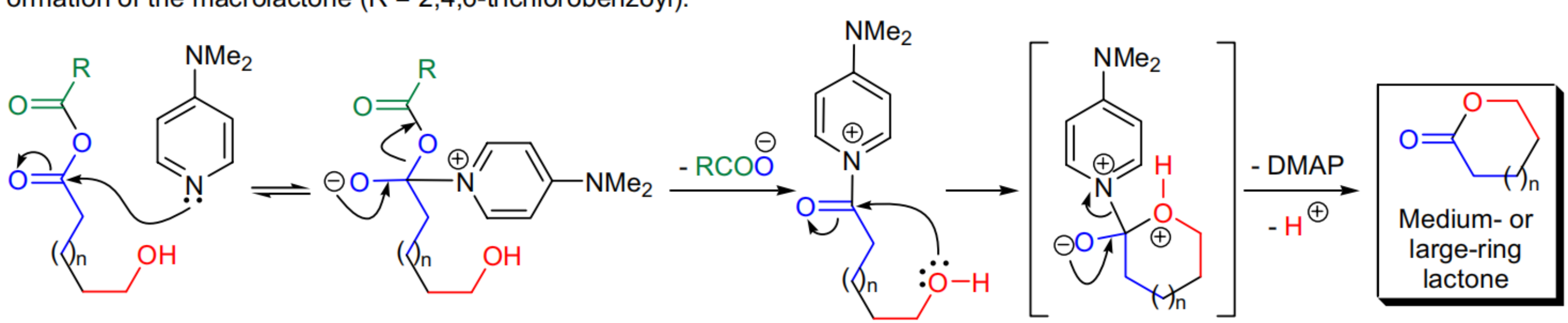


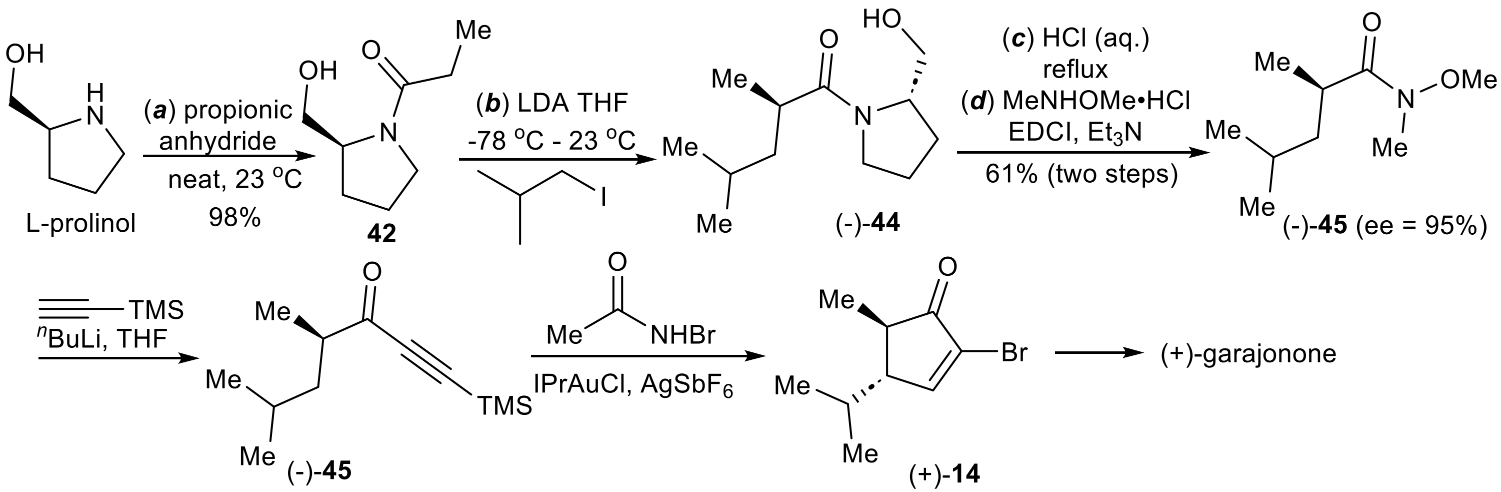
Mechanism:

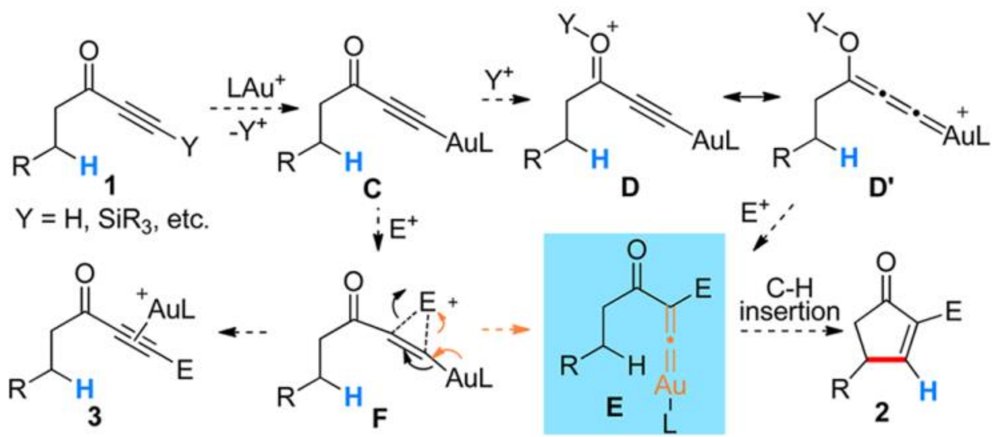
Formation of the mixed anhydride (R = 2,4,6-trichlorobenzoyl):



Formation of the macrolactone (R = 2,4,6-trichlorobenzoyl):







J. Am. Chem. Soc., **2016**, *138*, 7516.