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Communication

Total Synthesis of Hypersampsone M

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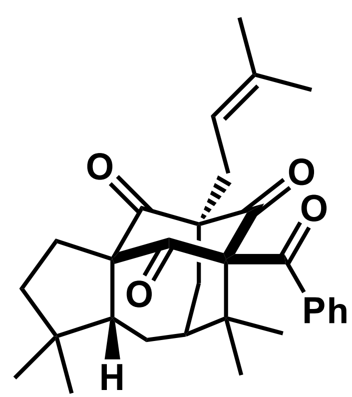
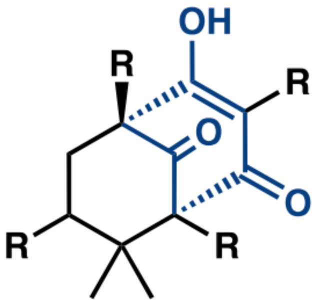
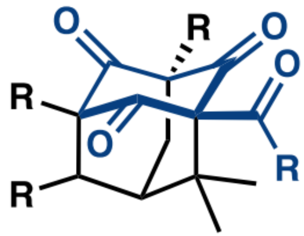


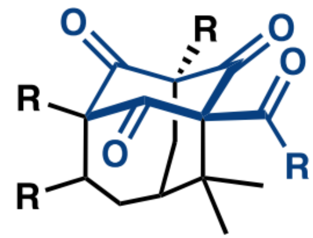
Hypersampsone M



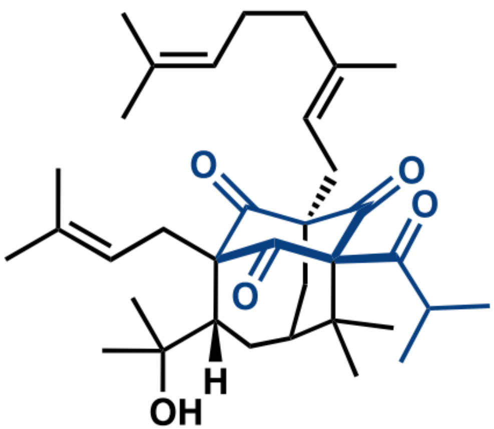
BPAPs
>250 compounds
>20 syntheses



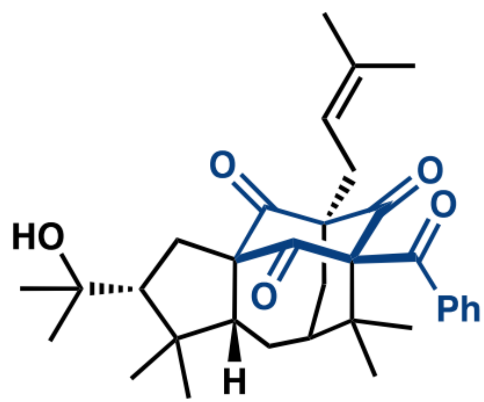
Adamantane PPAPs
>40 compounds
3 syntheses



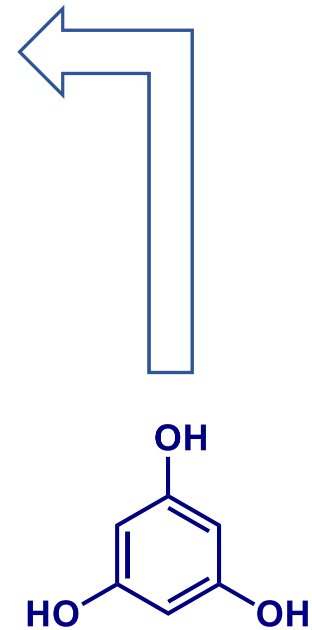
Homoadamantane PPAPs
>70 compounds
no syntheses



Pseudohenone F

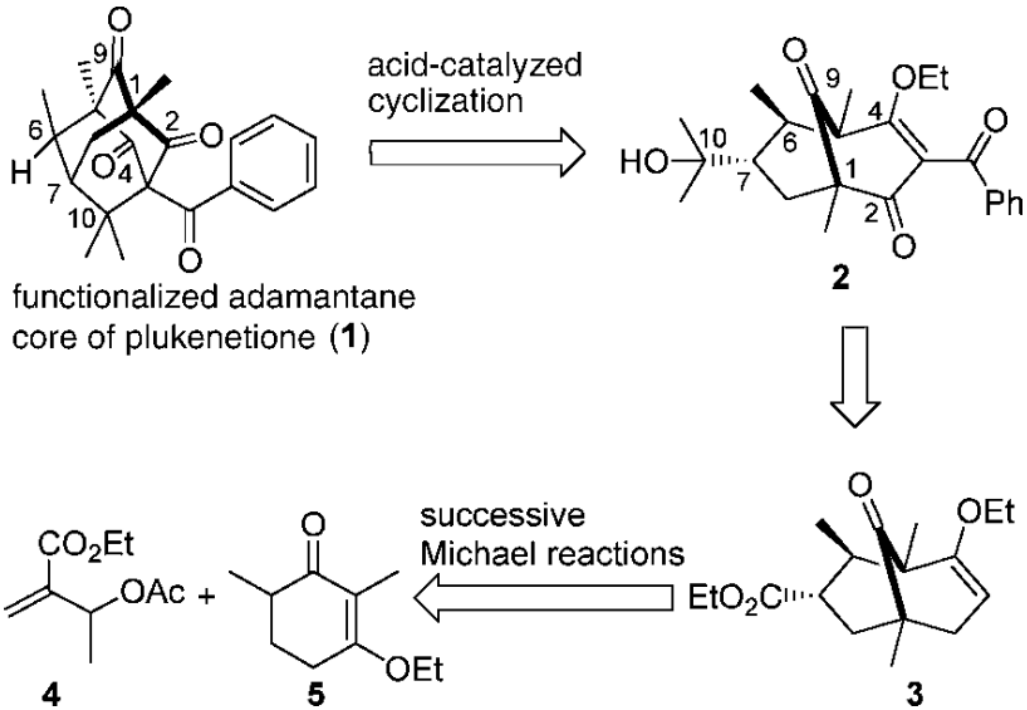


Hypersampsone Q

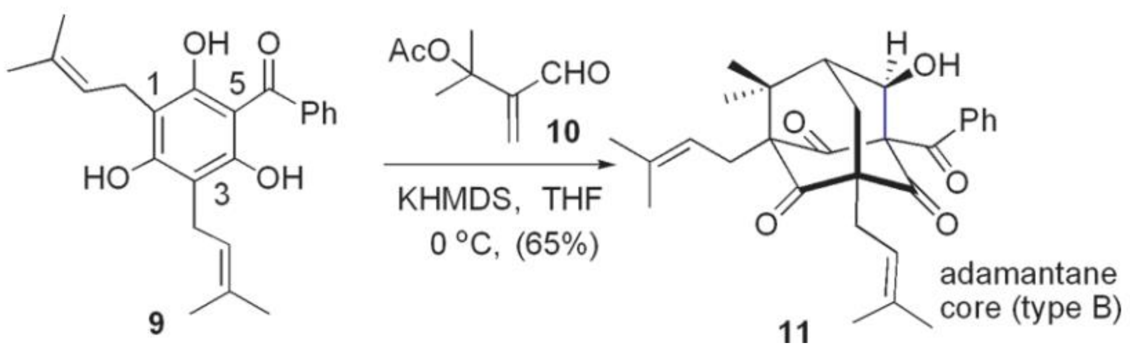


phloroglucinol

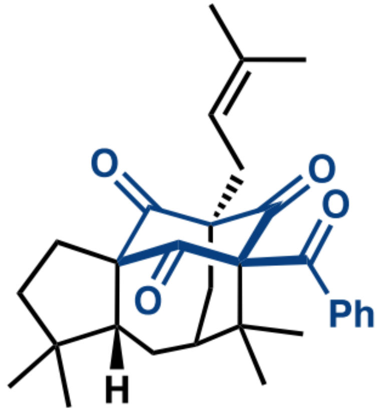
PPAP: polycyclic polyprenylated acylphloroglucinol
BPAP: bicyclic polyprenylated acylphloroglucinol



J. Org. Chem., **2008**, *73*, 9320.



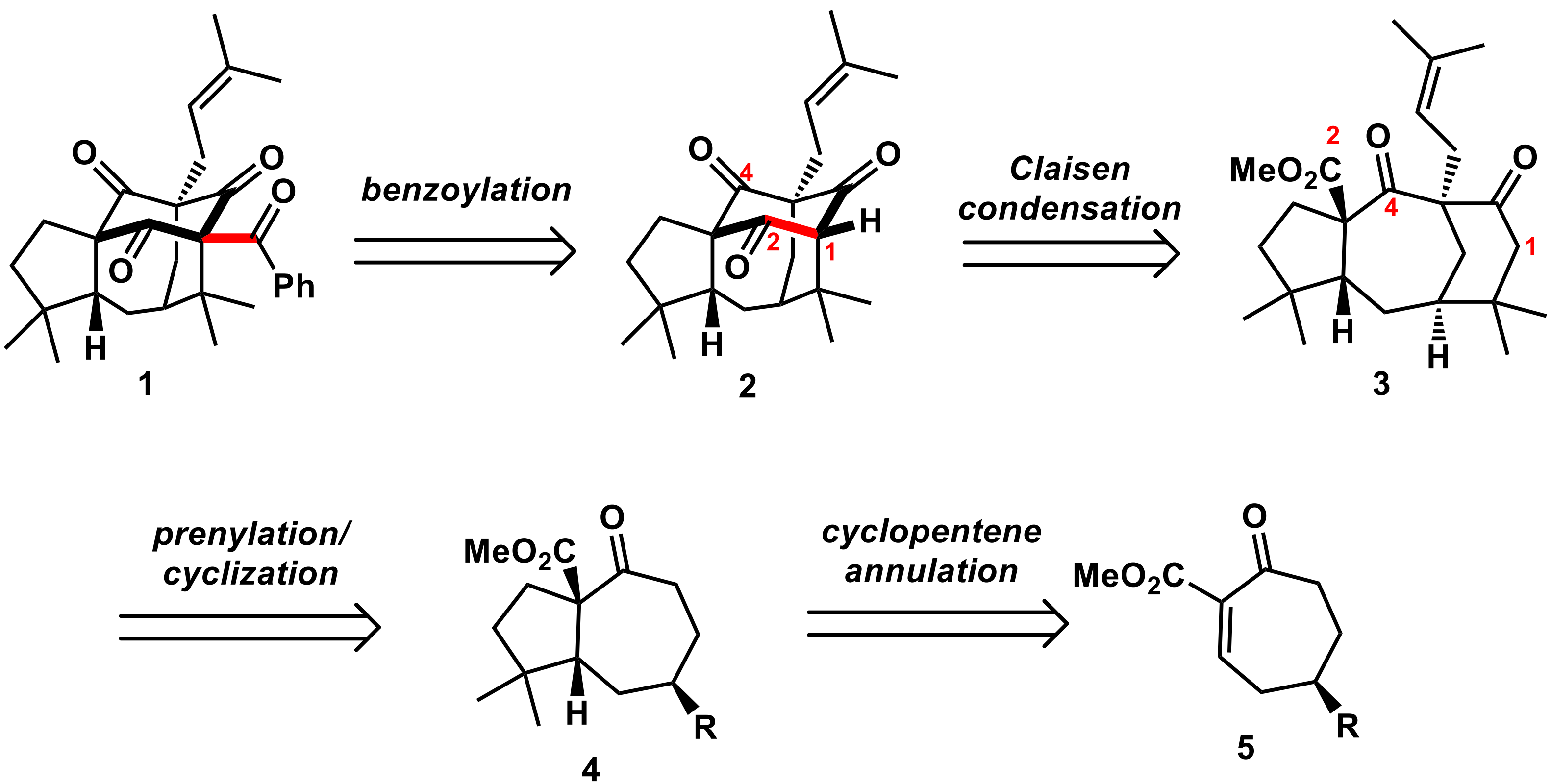
J. Am. Chem. Soc., **2010**, *132*, 14212.

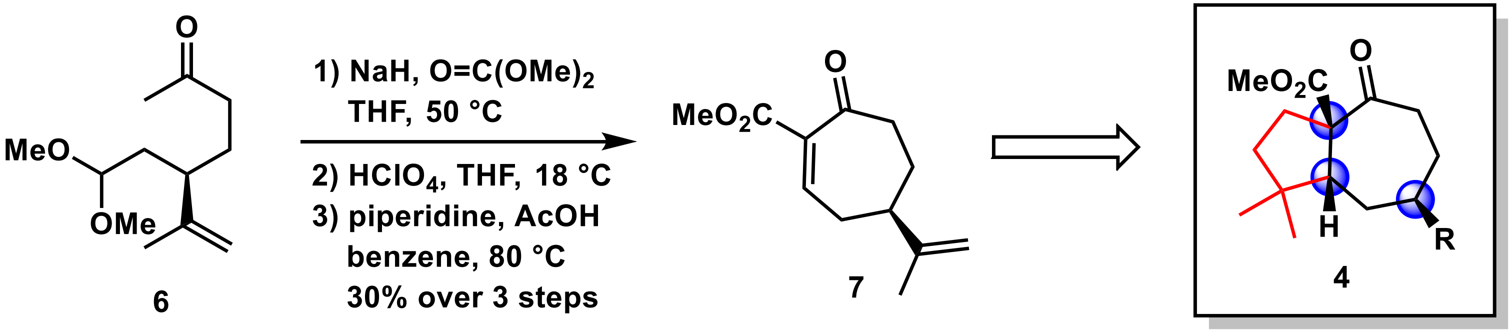


Hypersampsone M (1)

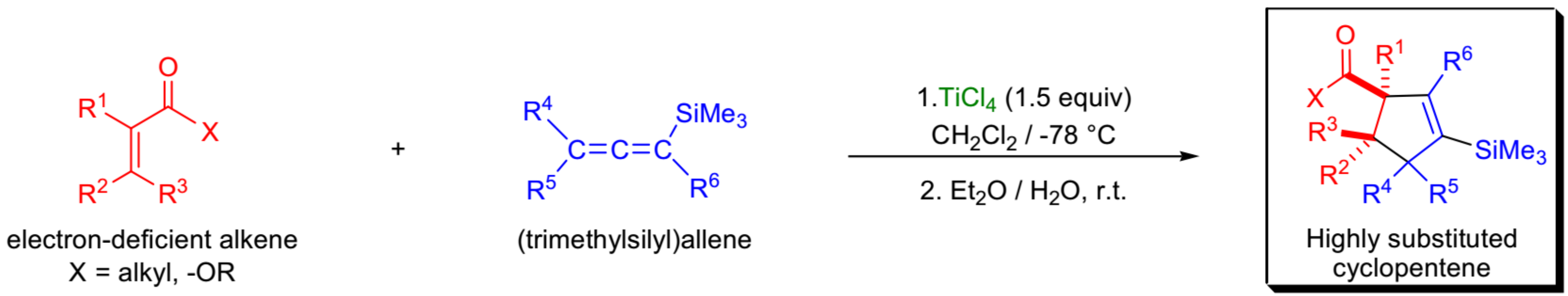
- *–Prototypical homoadamantane PPAP*
- *–Fully substituted cyclohexatrione core*
- *–No prior syntheses in class*

Retrosynthetic Strategy

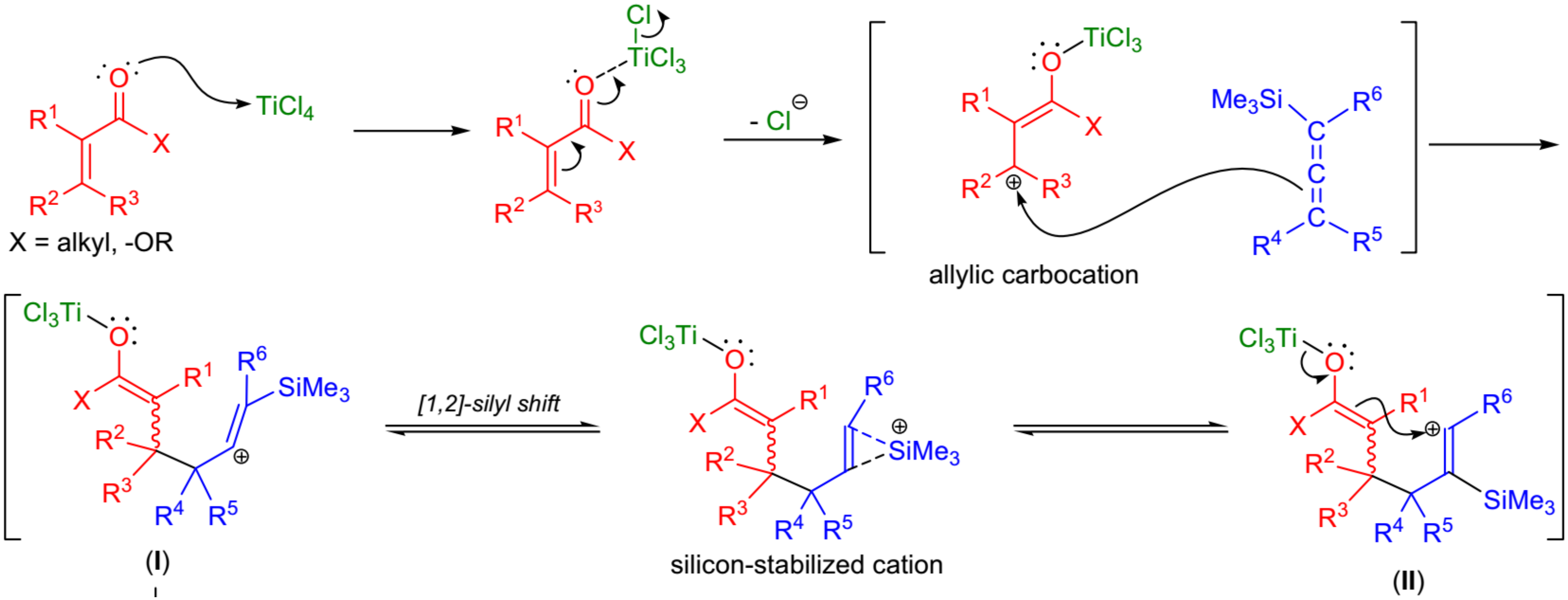




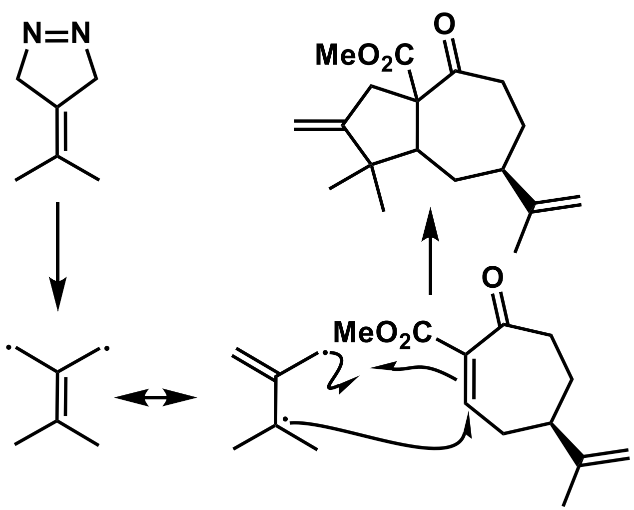
Danheiser cyclopentene annulation



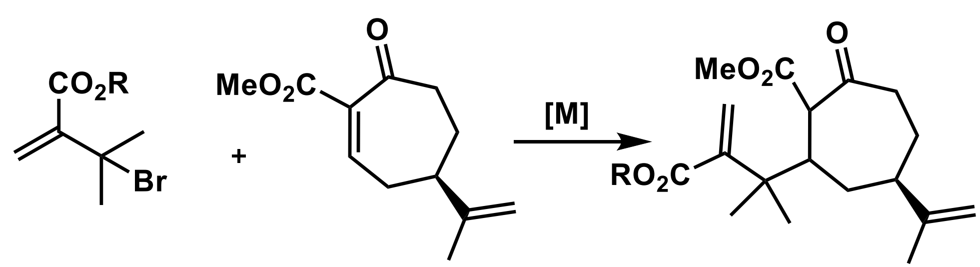
Danheiser cyclopentene annulation (mechanism)

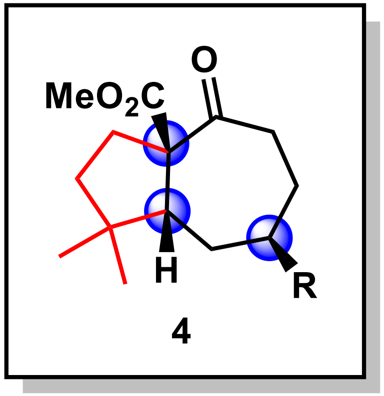


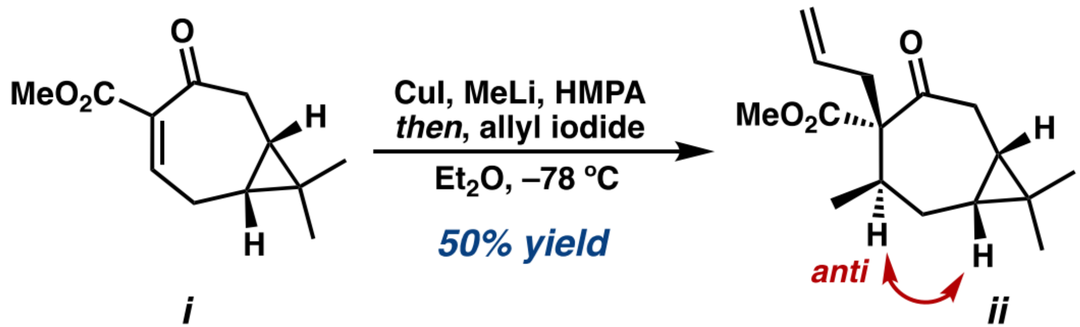
Trimethylenemethane cycloaddition



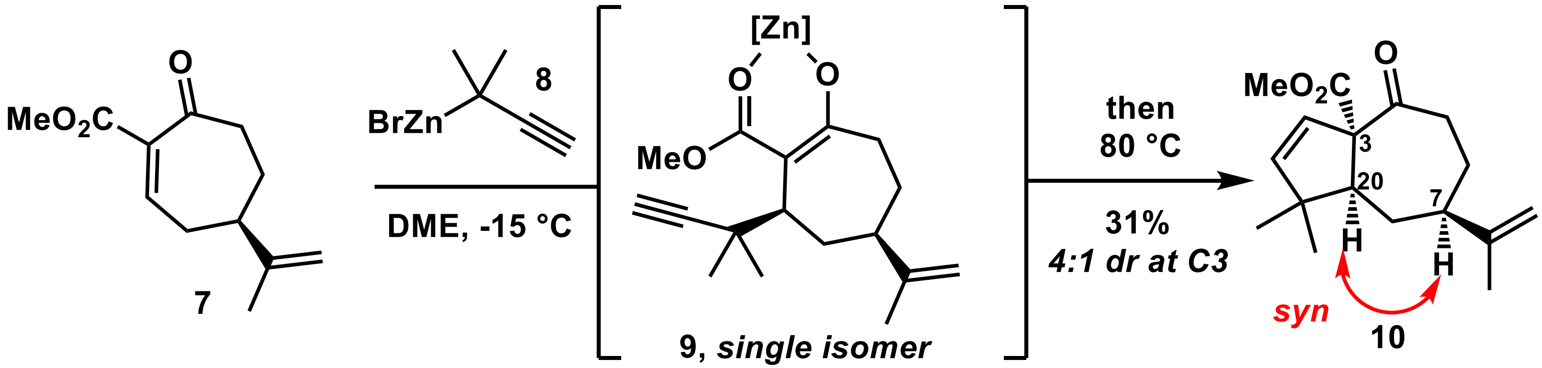
Additions of 2-(bromoisopropyl)acrylates

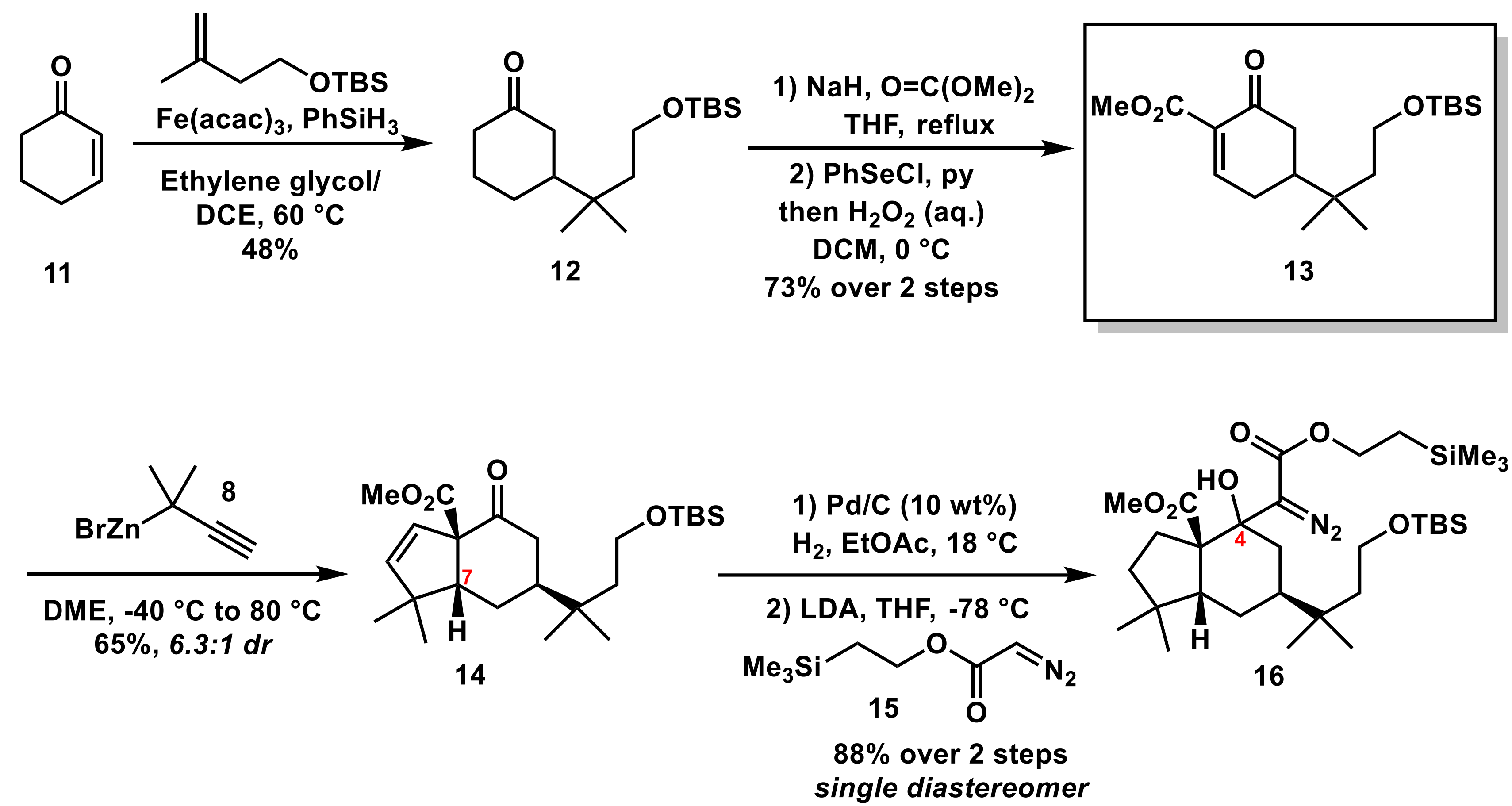






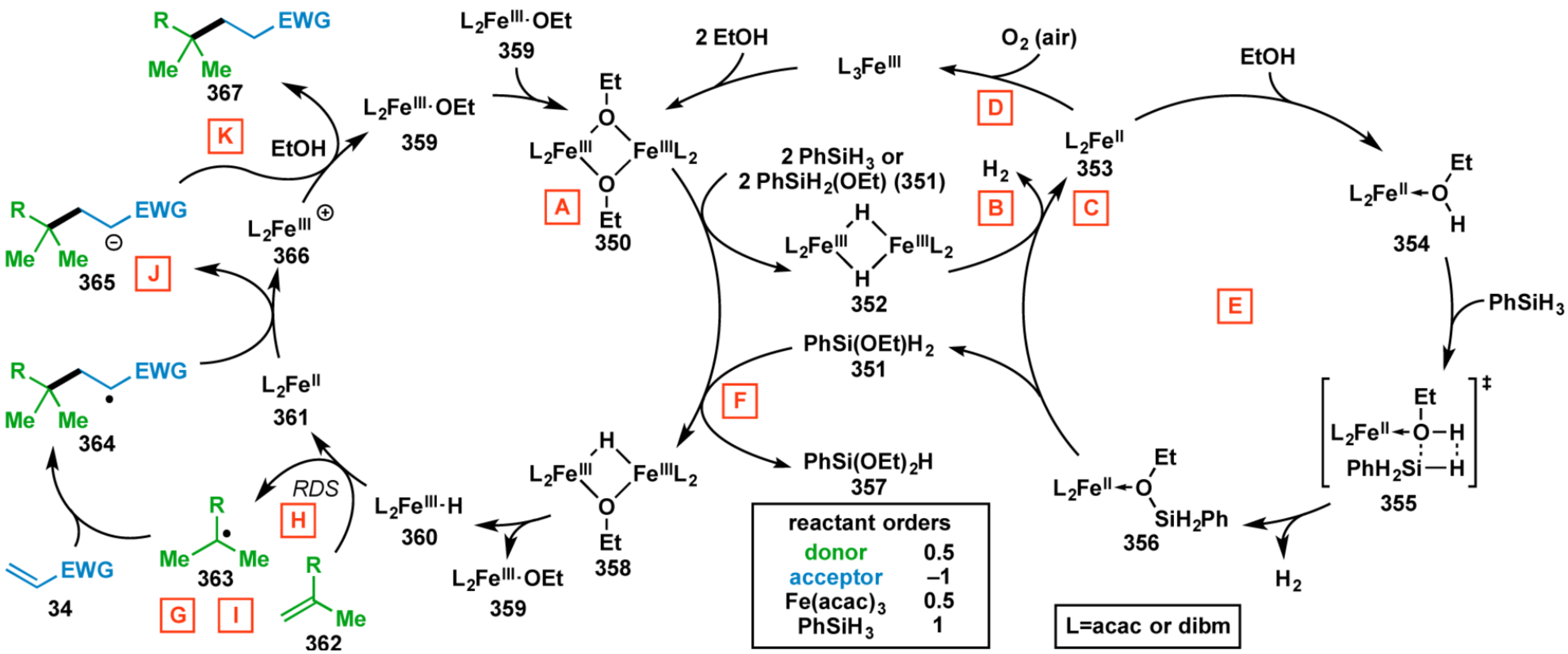
Chem.Commun., **2020**, *56*, 531.





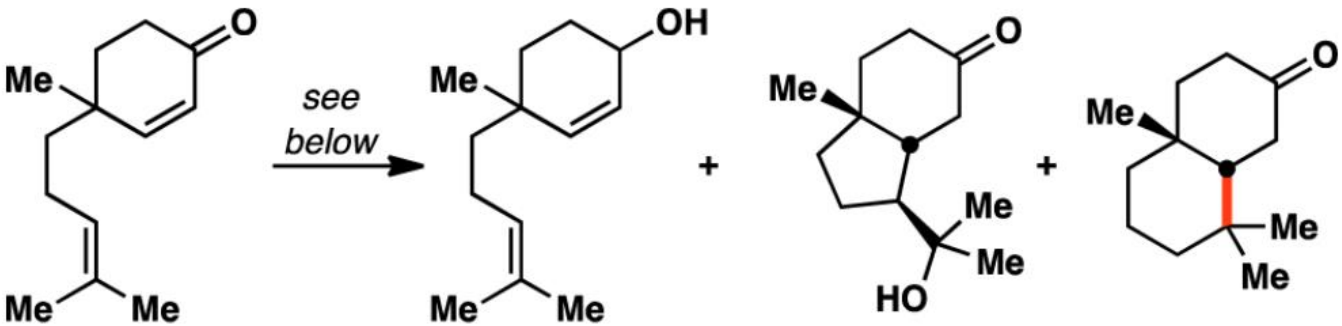
OTBS
Fe(acac)3, PhSiH3
Ethylene glycol/
DCE, 60 °C
48%
11
OTBS
12
1) NaH, O=C(OMe)2
THF, reflux
2) PhSeCl, py
then H2O2 (aq.)
DCM, 0 °C
73% over 2 steps
MeO2C
OTBS
13
BrZn
8
DME, -40 °C to 80 °C
65%, 6.3:1 dr
MeO2C
OTBS
7
H
14
1) Pd/C (10 wt%)
H2, EtOAc, 18 °C
2) LDA, THF, -78 °C
Me3Si
N2
15
88% over 2 steps
single diastereomer
SiMe3
HO
MeO2C
N2
4
OTBS
H
16

A. Mechanistic proposal for the olefin cross-coupling (boxed, red letters indicate steps with supporting evidence).



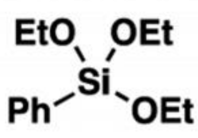
J. Am. Chem. Soc., **2017**, *139*, 2484.

Table 1. Optimization of the Reductive Diene Cyclization



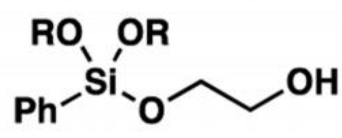
25 → 36 + 37 + 38

Entry	[Fe(III)] (equiv)	Reductant	Solvent	Temp (°C)	25[a]	36[a]	37[a]	38[a]
1	$Fe_2(ox)_3 \cdot 6H_2O$ (2.0)	$NaBH_4$	$EtOH/H_2O$	0	20	5	0	75
2	$Fe_2(ox)_3 \cdot 6H_2O$ (2.0)	$NaBH(OAc)_3$	THF/H_2O	0 to rt	89	0	5	6
3	$Fe_2(ox)_3 \cdot 6H_2O$ (2.0)	$(TMS)_3SiH$	THF/H_2O	0 to 60	23	0	77	0
4	$Fe_2(ox)_3 \cdot 6H_2O$ (2.0)	Et_3SiH	THF/H_2O	0 to 60	0	0	100	0
5	$Fe_2(ox)_3 \cdot 6H_2O$ (2.0)	$PhSiH_3$	$EtOH/H_2O$	0 to rt	15	0	11	74
6	$Fe(acac)_3$ (1.0)	Et_3SiH	EtOH	60	100	0	0	0
7	$Fe(acac)_3$ (1.0)	$PhSiH_3$	EtOH	60	0	0	0	100
8	$Fe(acac)_3$ (0.3)	$PhSiH_3$	$EtOH/(CH_2OH)_2$	60	0	0	0	100



39

byproduct formed in pure EtOH

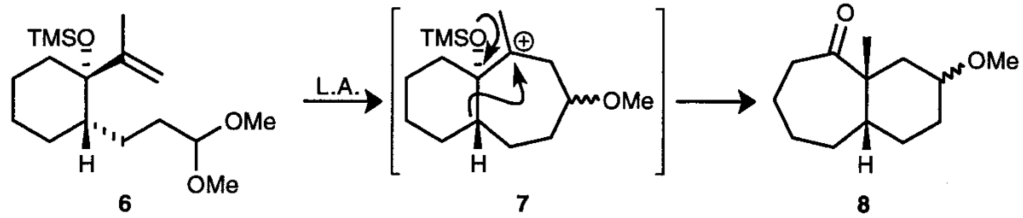


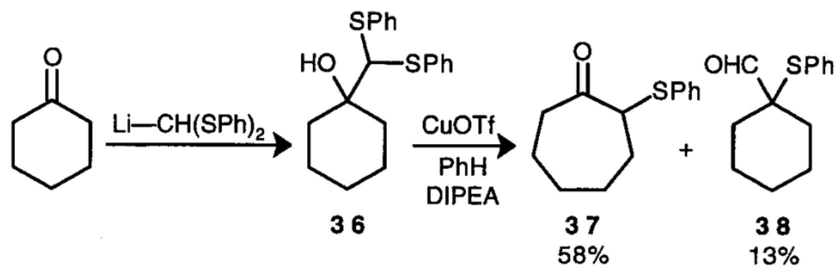
40

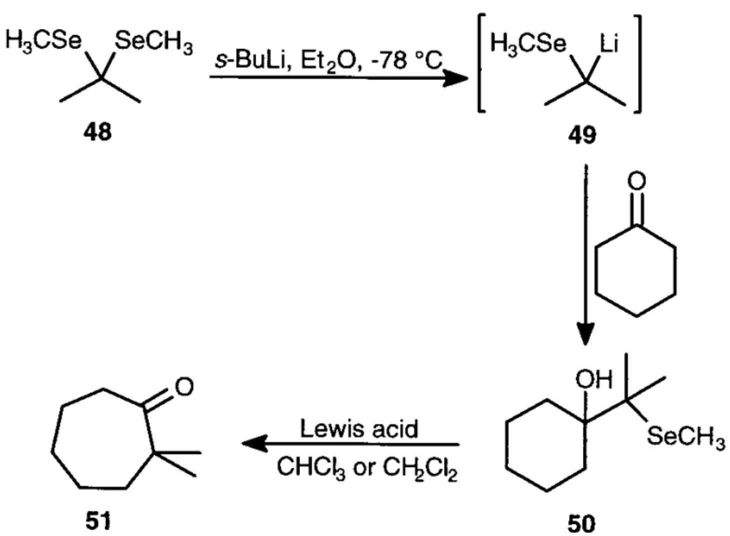
analogous byproduct using $(CH_2OH)_2$ cosolvent

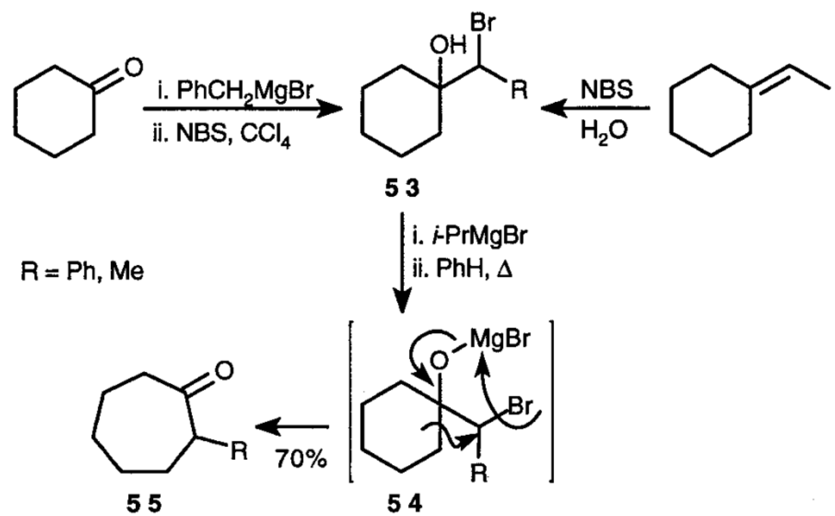
J. Am. Chem. Soc., **2017**, *139*, 2484.

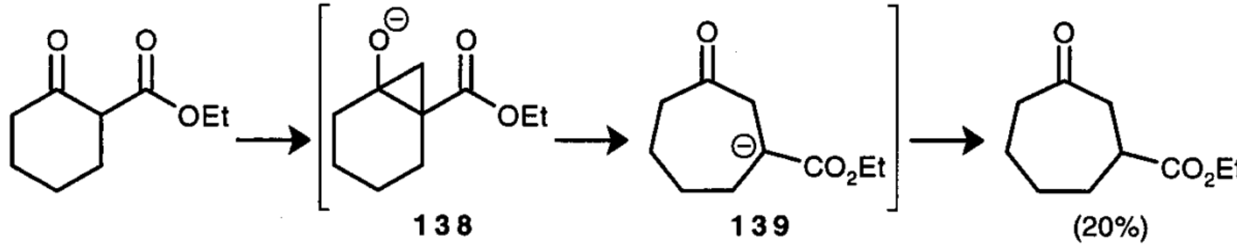
Ring expansion

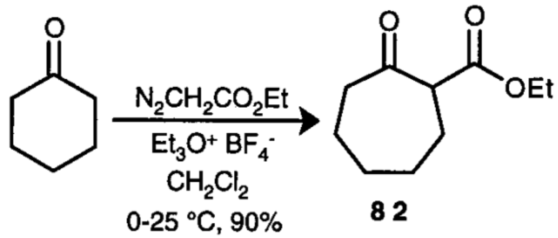


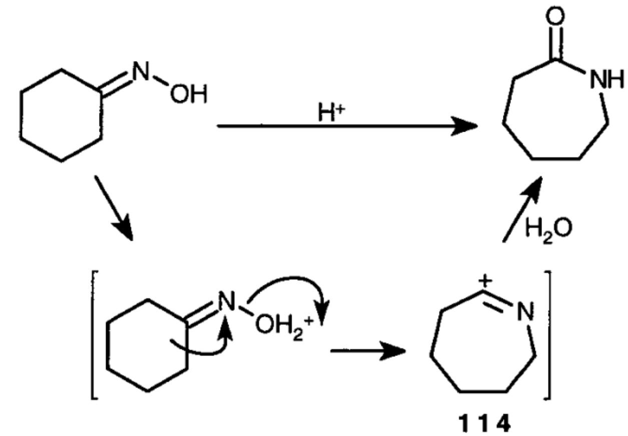


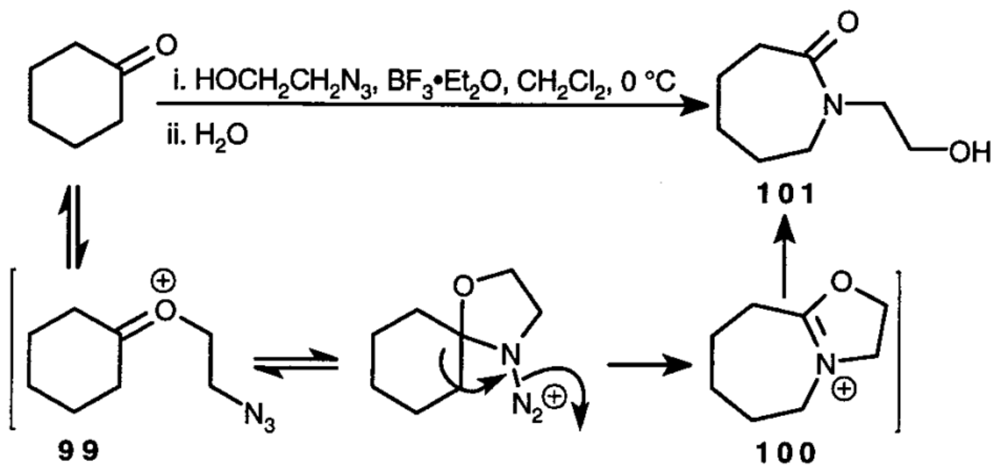


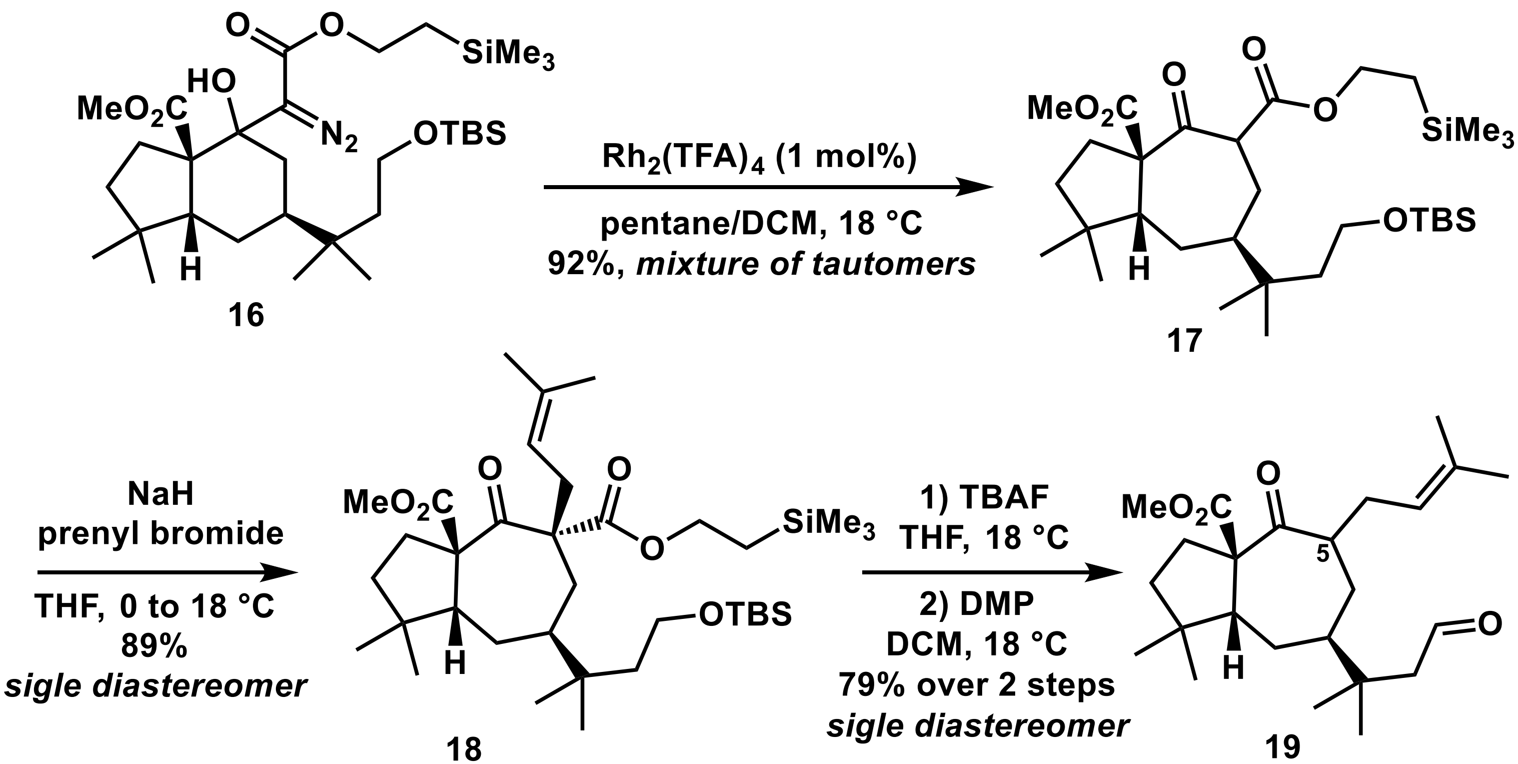



OEt
OEt
CO_2Et
CO_2Et
138
139
(20%)

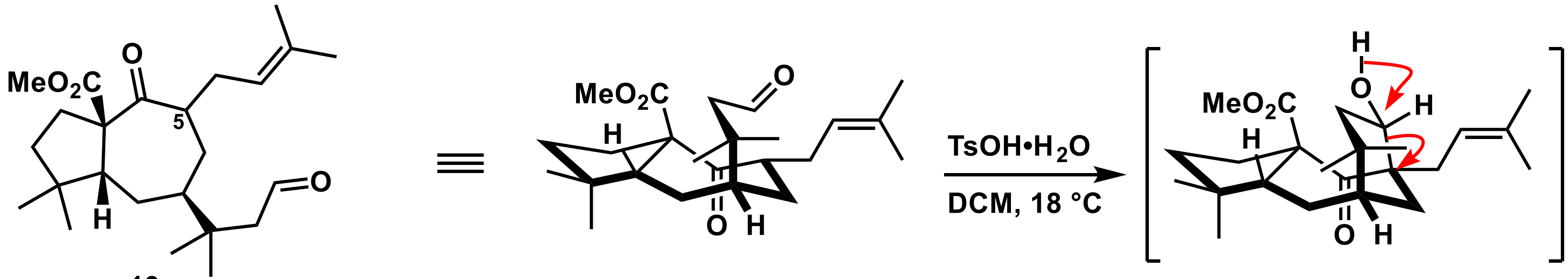

$N_2CH_2CO_2Et$
$Et_3O^+ BF_4^-$
CH_2Cl_2
0-25 °C, 90%
OEt
82


N
OH
H^+
NH
H_2O
OH_2^+
N
114


i. $HOCH_2CH_2N_3$, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C
ii. H_2O
N
OH
101
N_3
99
N_2
100



MeO$_2$C
HO
O
O
SiMe$_3$
N$_2$
OTBS
H
16
Rh$_2$(TFA)$_4$ (1 mol%)
pentane/DCM, 18 °C
92%, *mixture of tautomers*
MeO$_2$C
O
O
O
SiMe$_3$
OTBS
H
17
NaH
prenyl bromide
THF, 0 to 18 °C
89%
sigle diastereomer
MeO$_2$C
O
O
O
SiMe$_3$
OTBS
H
18
1) TBAF
THF, 18 °C
2) DMP
DCM, 18 °C
79% over 2 steps
sigle diastereomer
MeO$_2$C
O
5
O
H
19



19

20

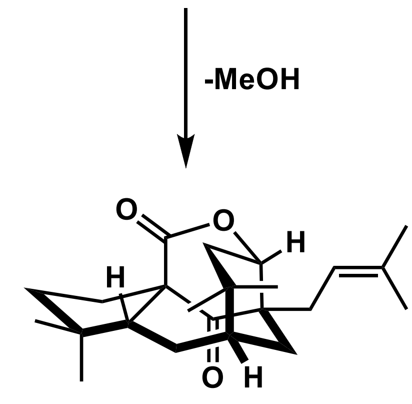


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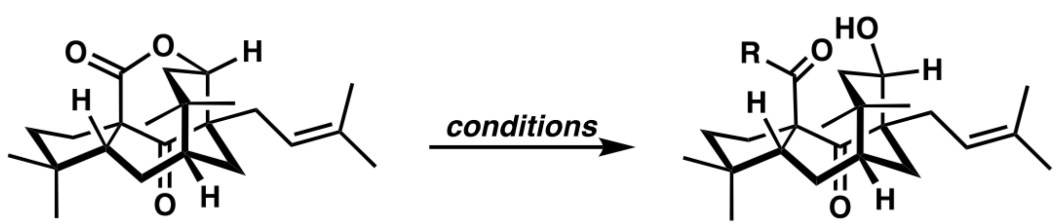
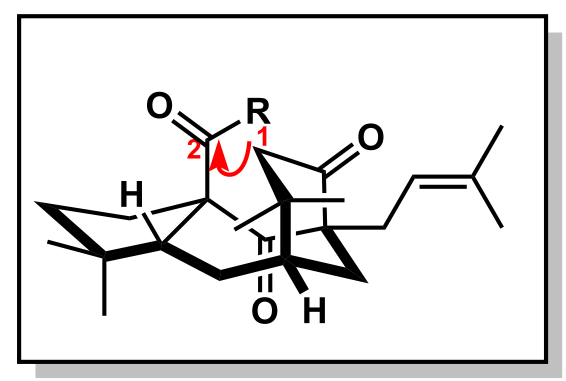
Table 1. Functionalization of Lactone 21: Selected Experiments

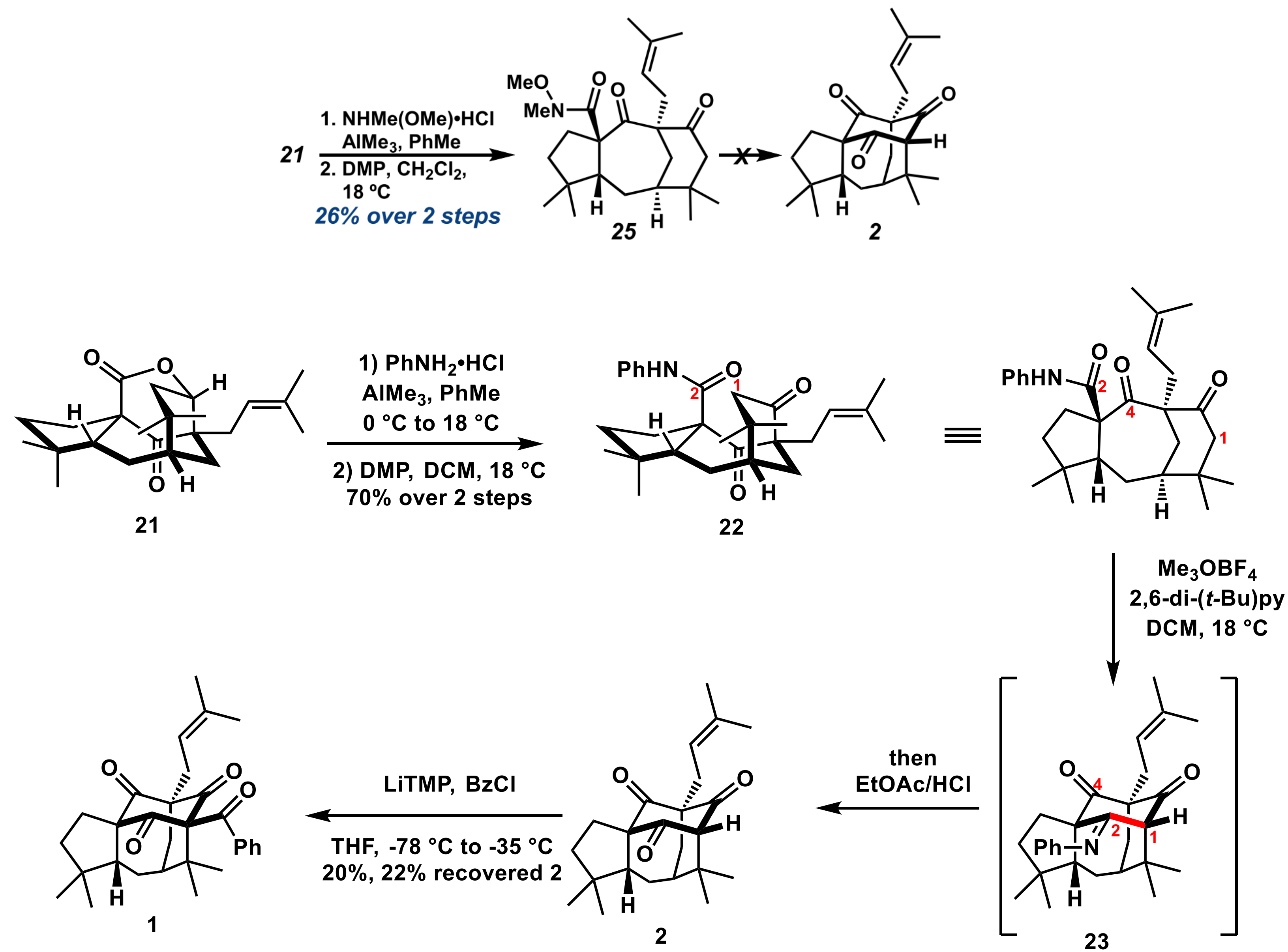


21 *24*

entry	conditions	R	results[a]
1	NaOMe/MeOH	−OMe	decomp
2	Bu_3SnOMe	−OMe	0%
3	$Al(O\textit{i}\text{-}Pr)_3$/MeOH	−OMe	0%
4	KOH/H_2O	−OH	decomp
5	NHMe(OMe)·HCl/$AlMe_3$	−NMe(OMe)	85%
6	$NH_4Cl/AlMe_3$	$-NH_2$	73%
7	$NHMe_2$·HCl/$AlMe_3$	$-NMe_2$	0%
8	$PhNH_2$·HCl/$AlMe_3$	−NHPh	84%[b]

[a]Determined by ^{1}H NMR analysis. [b]Isolated yield.





21
1. NHMe(OMe)•HCl
AlMe3, PhMe
2. DMP, CH2Cl2,
18 °C
26% over 2 steps
MeO
MeN
O
H
25
X
2
1) PhNH2•HCl
AlMe3, PhMe
0 °C to 18 °C
2) DMP, DCM, 18 °C
70% over 2 steps
PhHN
22
Me3OBF4
2,6-di-(t-Bu)py
DCM, 18 °C
Ph
N
23
then
EtOAc/HCl
LiTMP, BzCl
THF, -78 °C to -35 °C
20%, 22% recovered 2
1