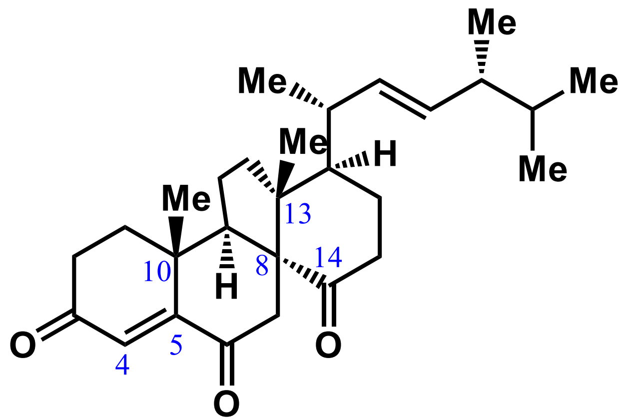
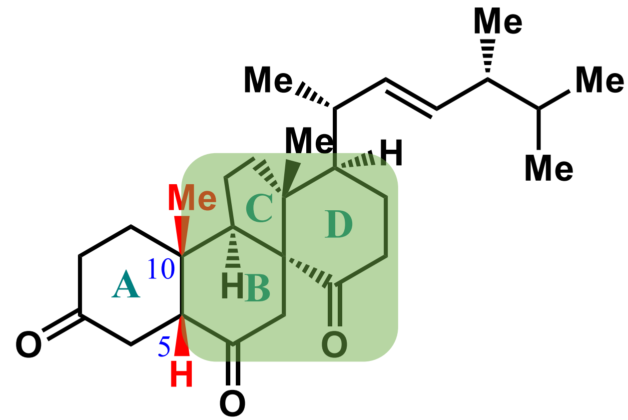
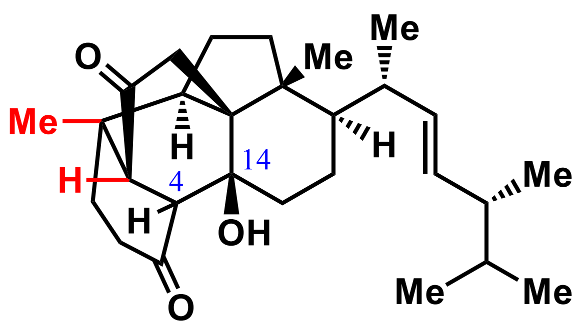
Asymmetric Total Synthesis of Dankasterones A and B and Periconiastone A Through Radical Cyclization



Dankasterones A (**1a**)



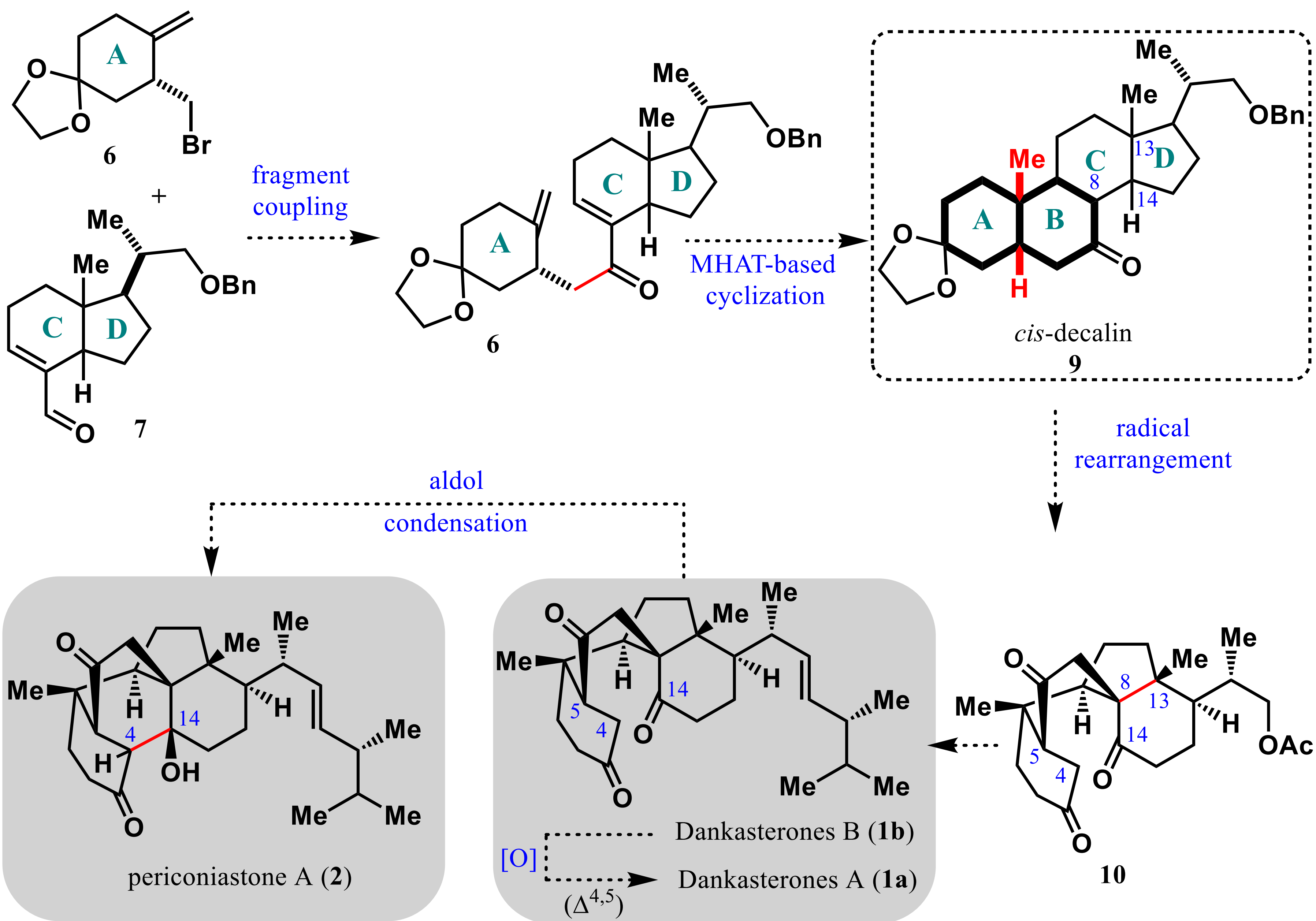
Dankasterones B (**1b**)



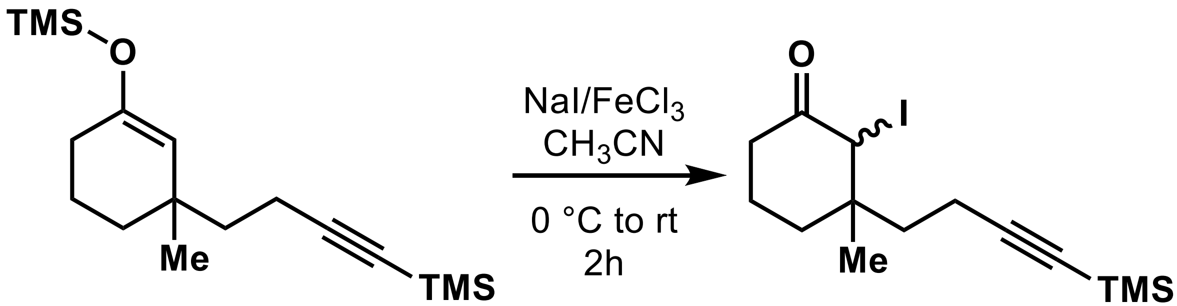
Periconiastone A (**2**)

DOI:10.1002/anie.202013881.

Synthetic analysis of dankasterones A and B (1) and periconiastone A (2).

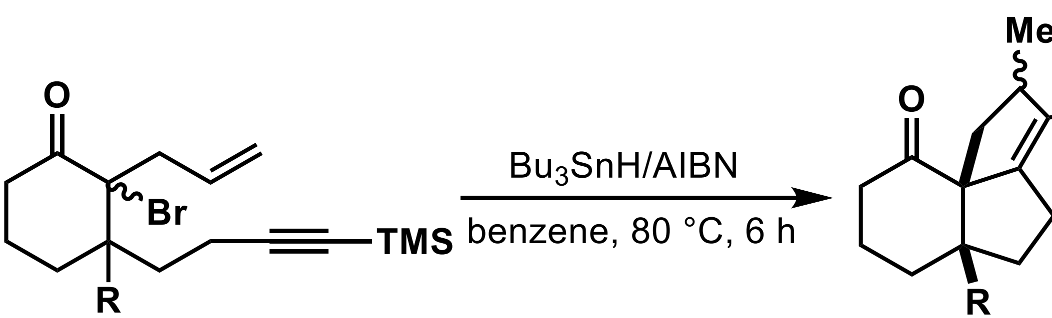


Mohanakrishnan’s group:



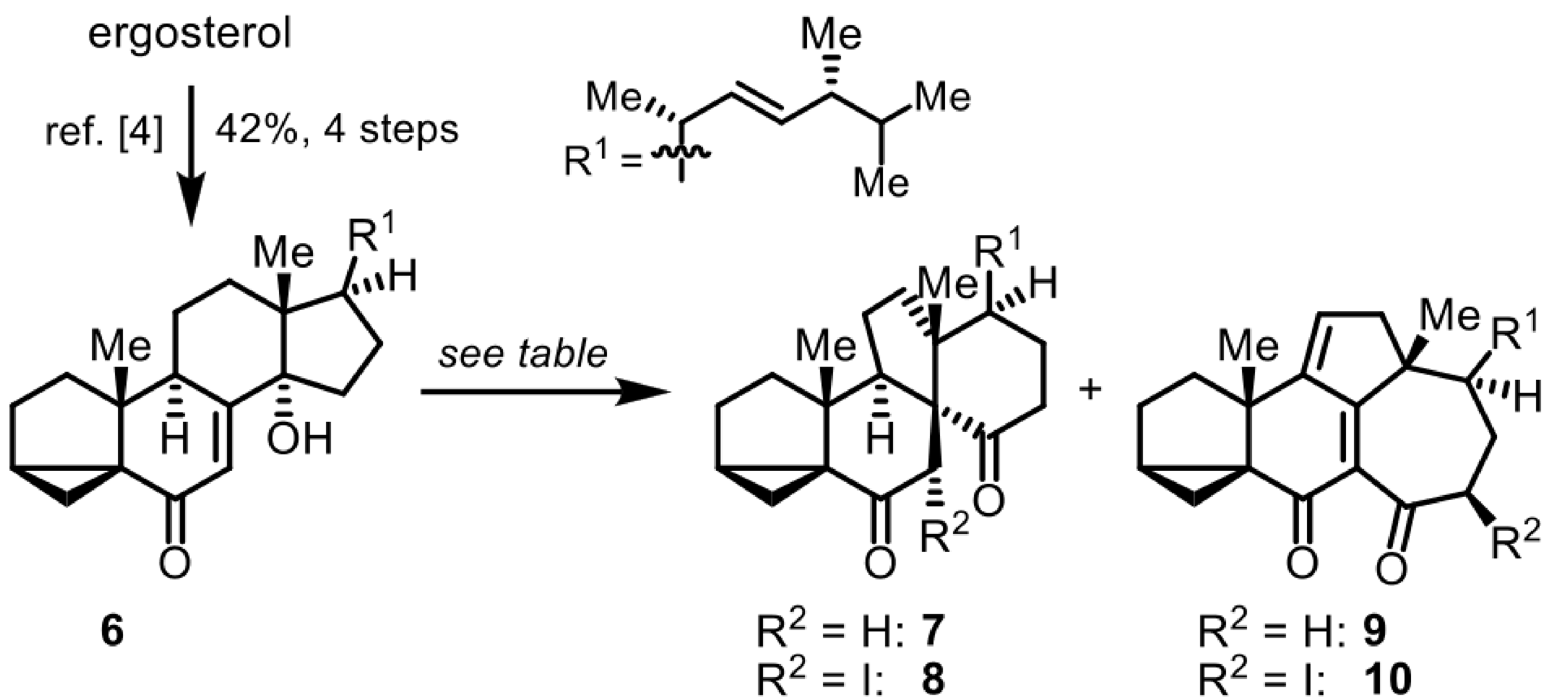
$$NaX + 2\ FeCl_3 \longrightarrow XCl + NaCl + 2\ FeCl_2$$

DOI: 10.1016/j.tet.2006.01.067.



DOI: 10.1002/ejoc.200700986.

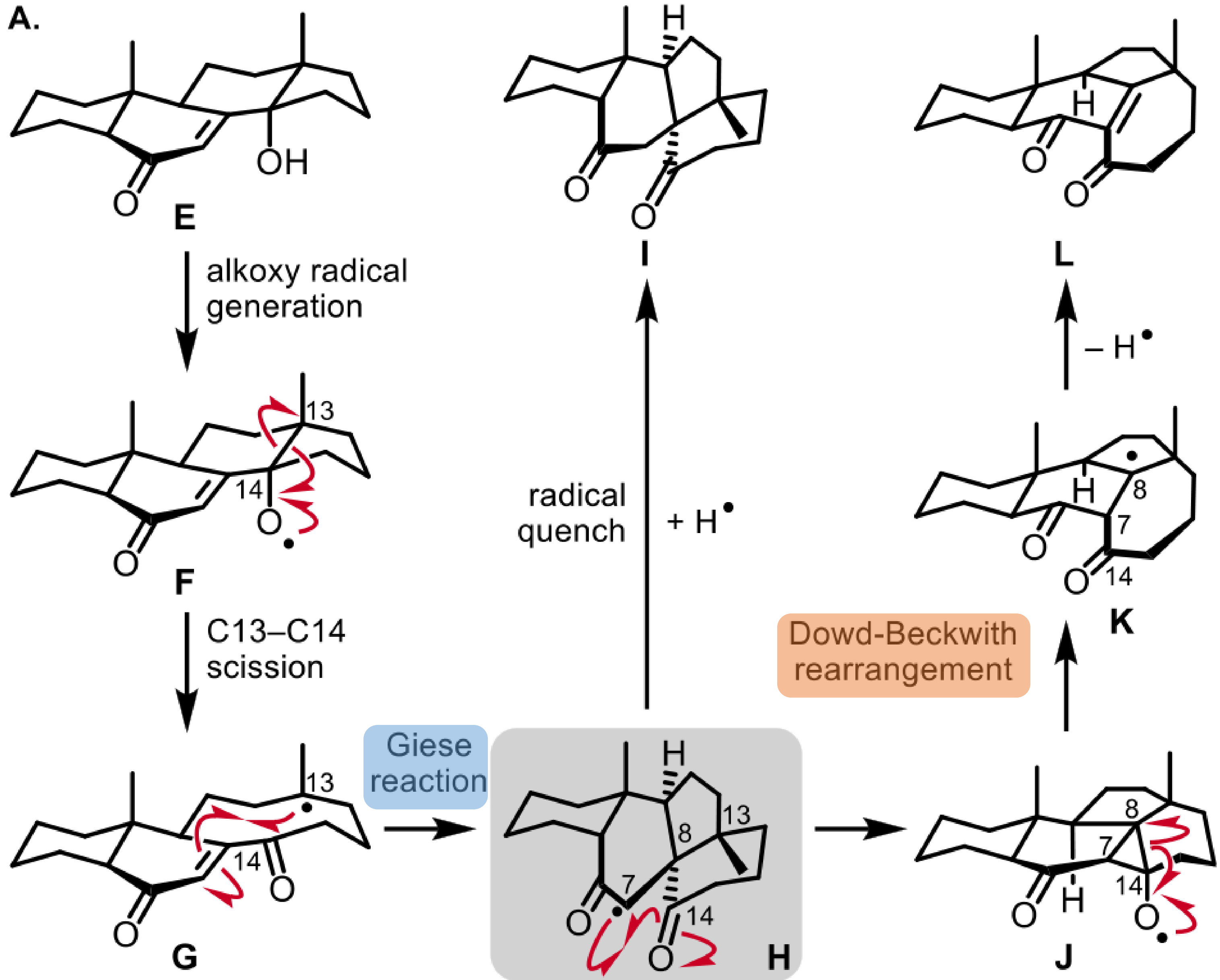
Heretsch's group:



no.	reagents[a]	isolated yields 7	8	9	10
1	$Pb(OAc)_4$, I_2[b]	15%	8%	52%	10%
2	$PhI(OAc)_2$, I_2	n.o.	76%	n.o.	n.o.
3	HgO, I_2	n.o.	<5%	68%	n.o.

[a]Conditions: C_6H_6, 0.025 M. [b]$CaCO_3$ was added. n.o.: not observed.

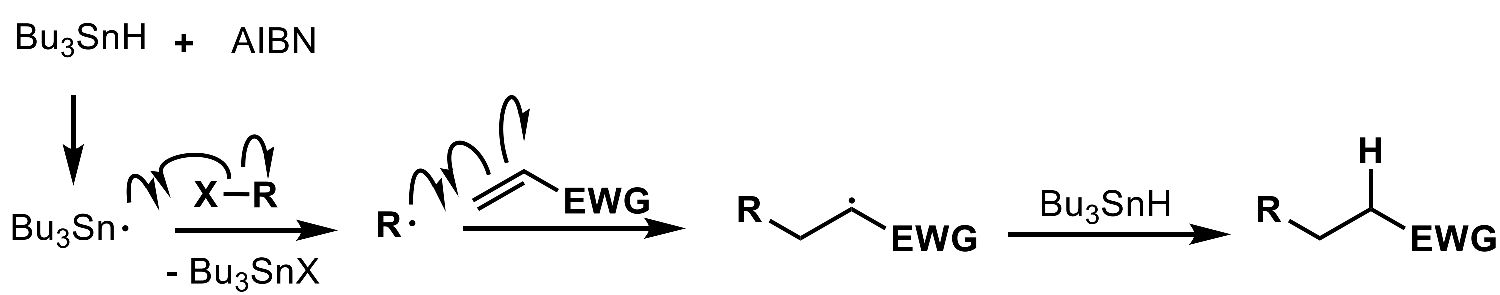
DOI: 10.1021/jacs.9b12899.



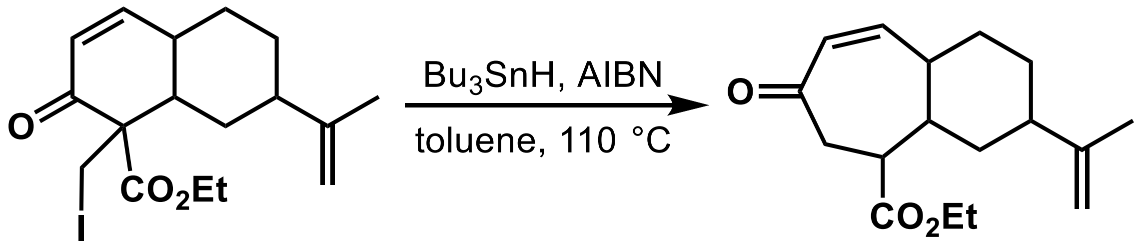
A.
OH
O
E
alkoxy radical
generation
13
14
O
F
C13–C14
scission
G
Giese
reaction
H
8
7
14
radical
quench
+ H•
I
Dowd-Beckwith
rearrangement
J
K
– H•
L

Giese Radical Addition

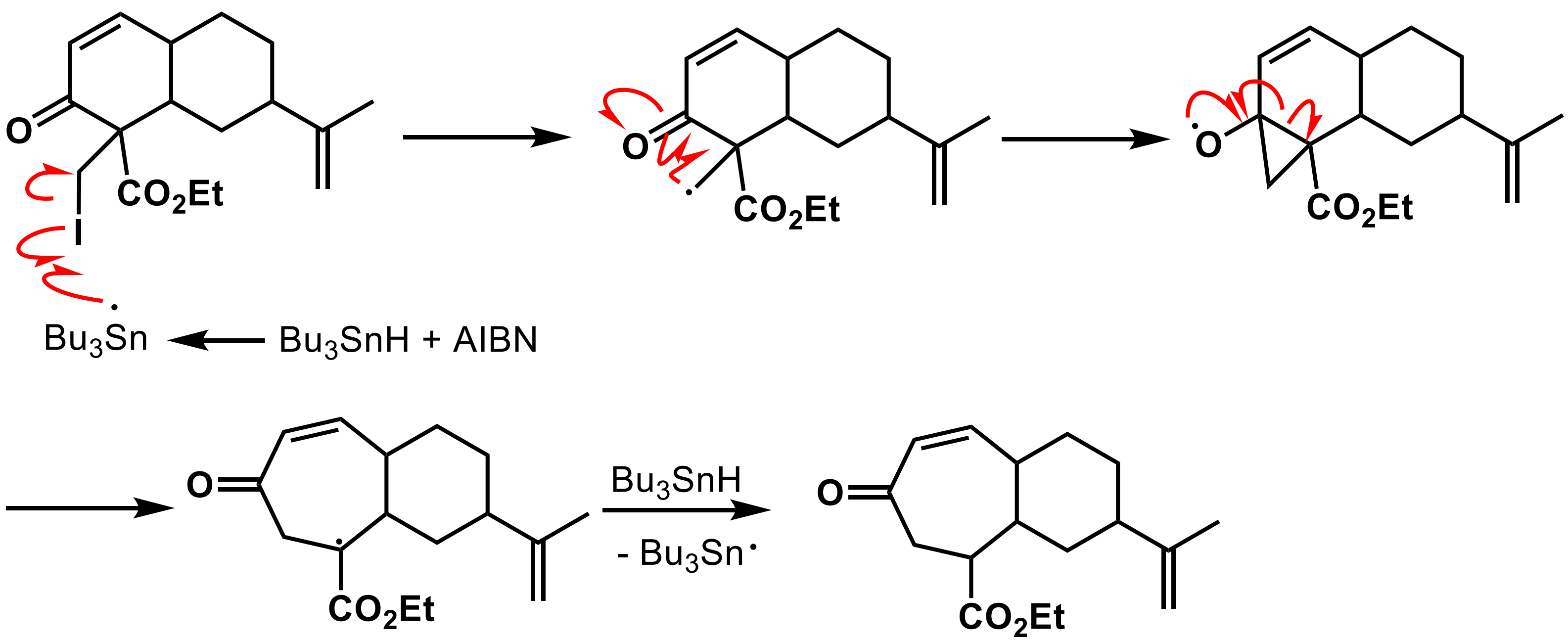
像含卤素・硫化合物等可以与自由基起始剂反应形成碳自由基，进而与各种自由基捕获剂反应。在这些反应中，对于缺电子的烯烃作为底物的形成C-C键的反应通常被称为**Giese反应**。在反应中生成的亲核α碳自由基还可以应用于串联性的反应。该反应在天然产物全合成中特别是分子内环化反应中作用巨大。



Dowd–Beckwith rearrangement

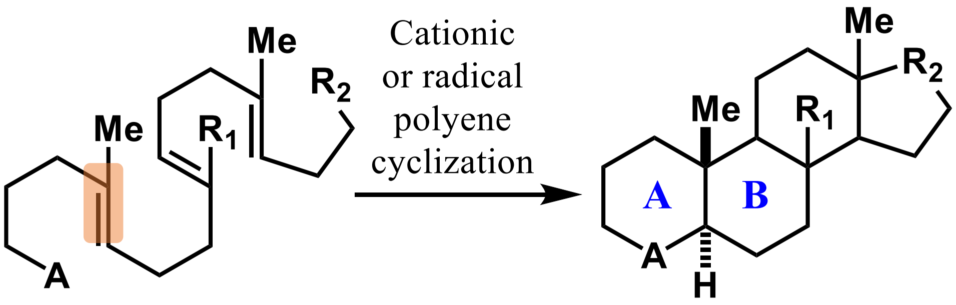


DOI: 10.1016/0040-4039(95)02178-7.



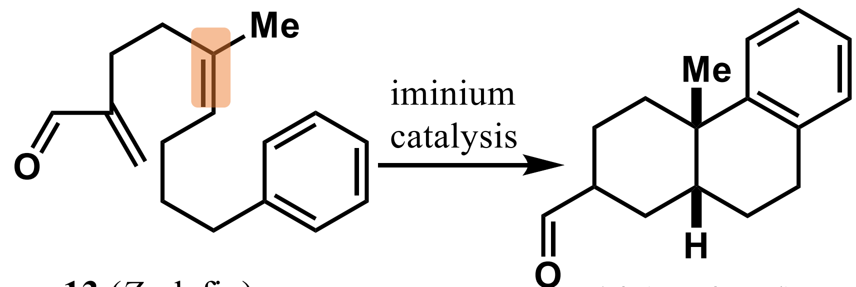
Synthetic approaches to trans- and cis-decalins

a. Result from *E*-olefin



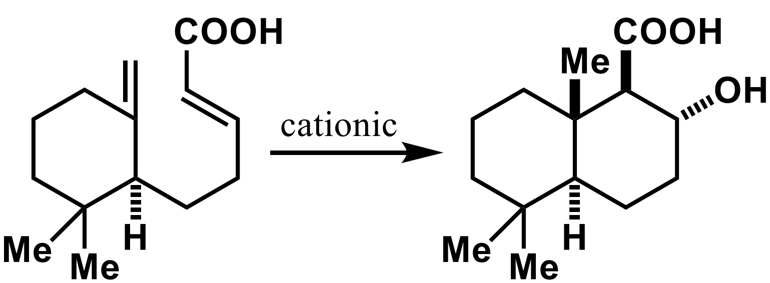
11 (*E*-olefin) **12** (*trans*-fused)

b. Result from *Z*-olefin



13 (*Z*-olefin) **14** (*cis*-fused)

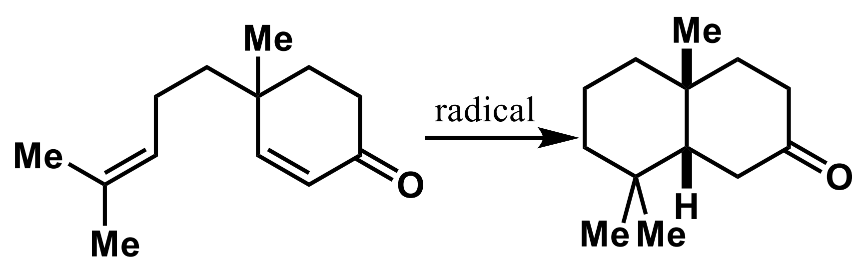
c. Result from exocyclic olefin unsaturated acid substrate:cationic



15 (enantiomerically enriched)

16 (racemic) (*trans*-fused)

d. Result from Baran's olefin enone substrate: radical



17

18 (*cis*-fused)

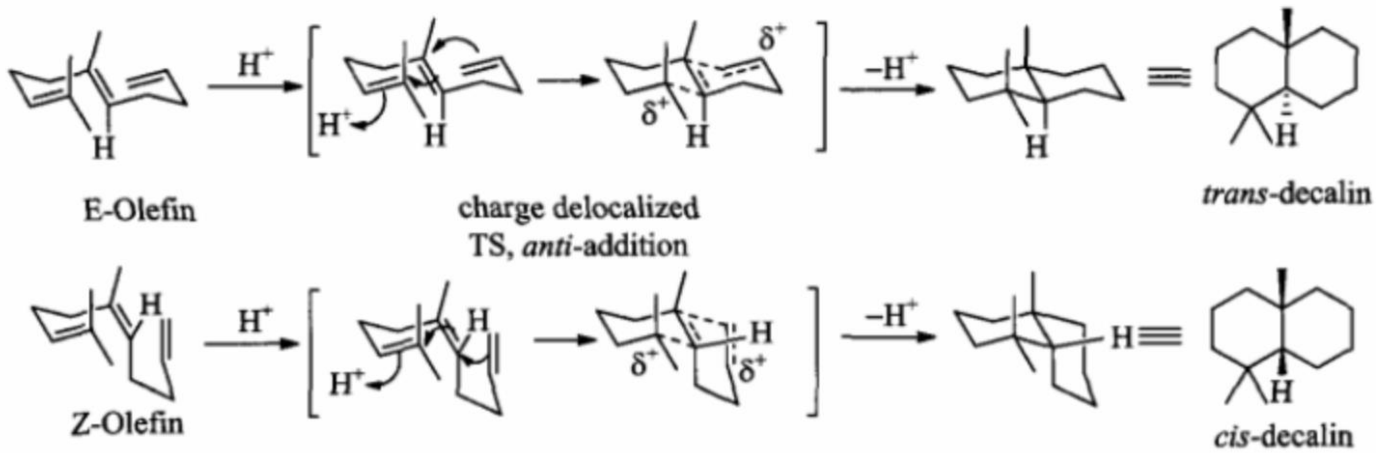


图 2 Stork-Eschenmoser 理论

Fig. 2 Stork-Eschenmoser principle

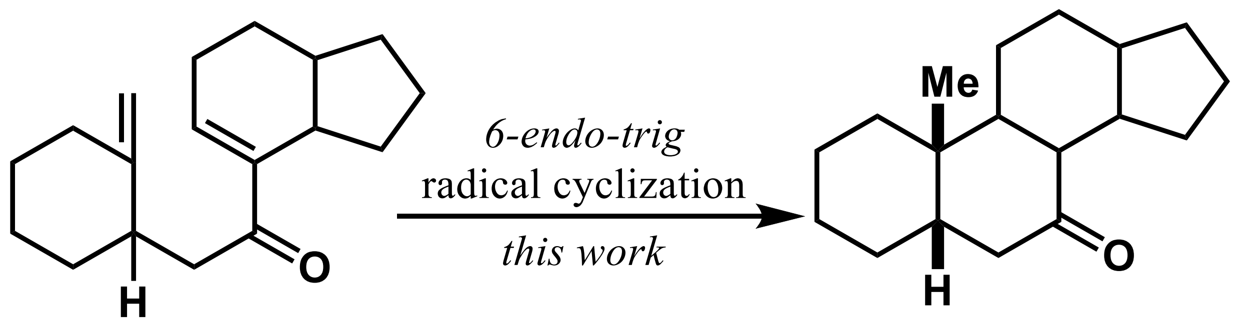
Stork-Eschenmoser 理论：

1. 链状多烯化合物在溶液中折叠成椅式构象，顺式烯烃将会环化为Cis-构型的十氢萘双环化合物；反式烯烃则会环化为Trans-构型的十氢萘双环化合物。

2. 亲电试剂和亲核试剂与中心烯烃加成时往往选择平伏键的位置，以此来减小1,3-位取代基的轴向相互排斥作用。

Synthetic approaches to trans- and cis-decalins

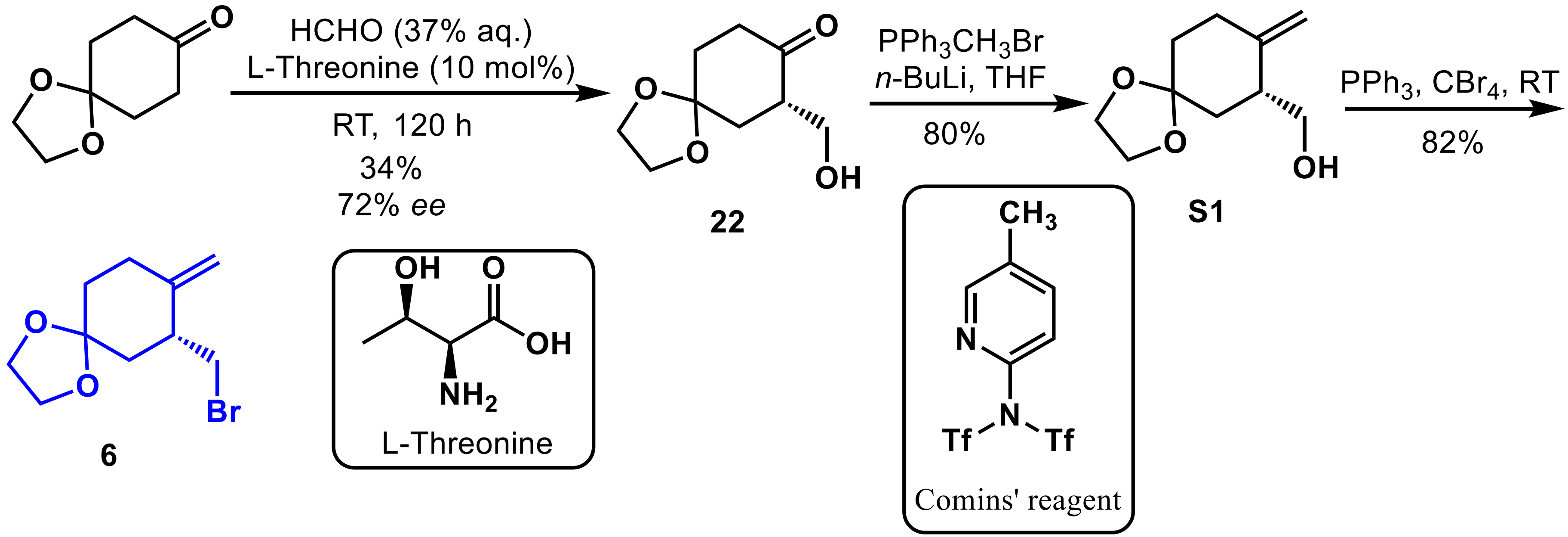
e. Result from exocyclic olefin enone substrate: radical



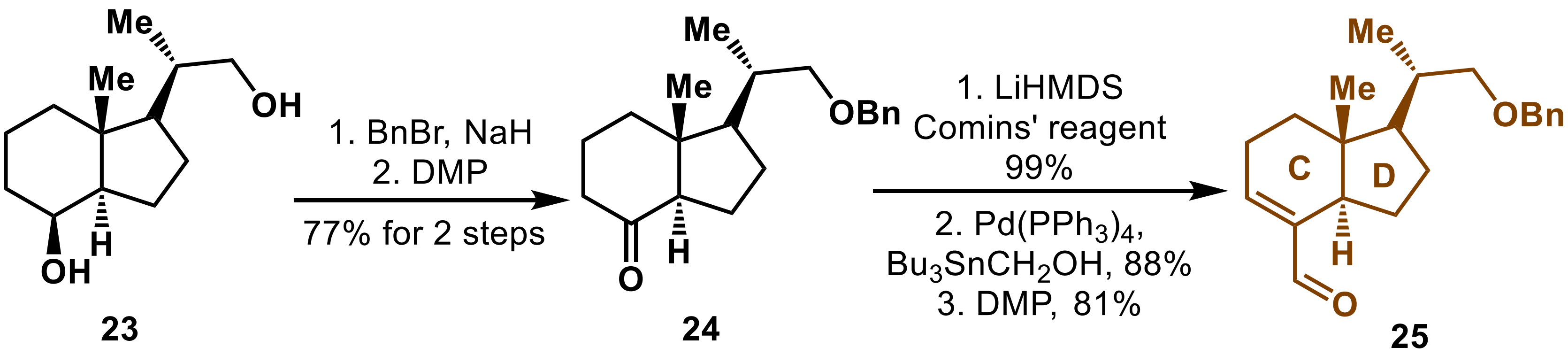
19

20 (*cis*-fused)

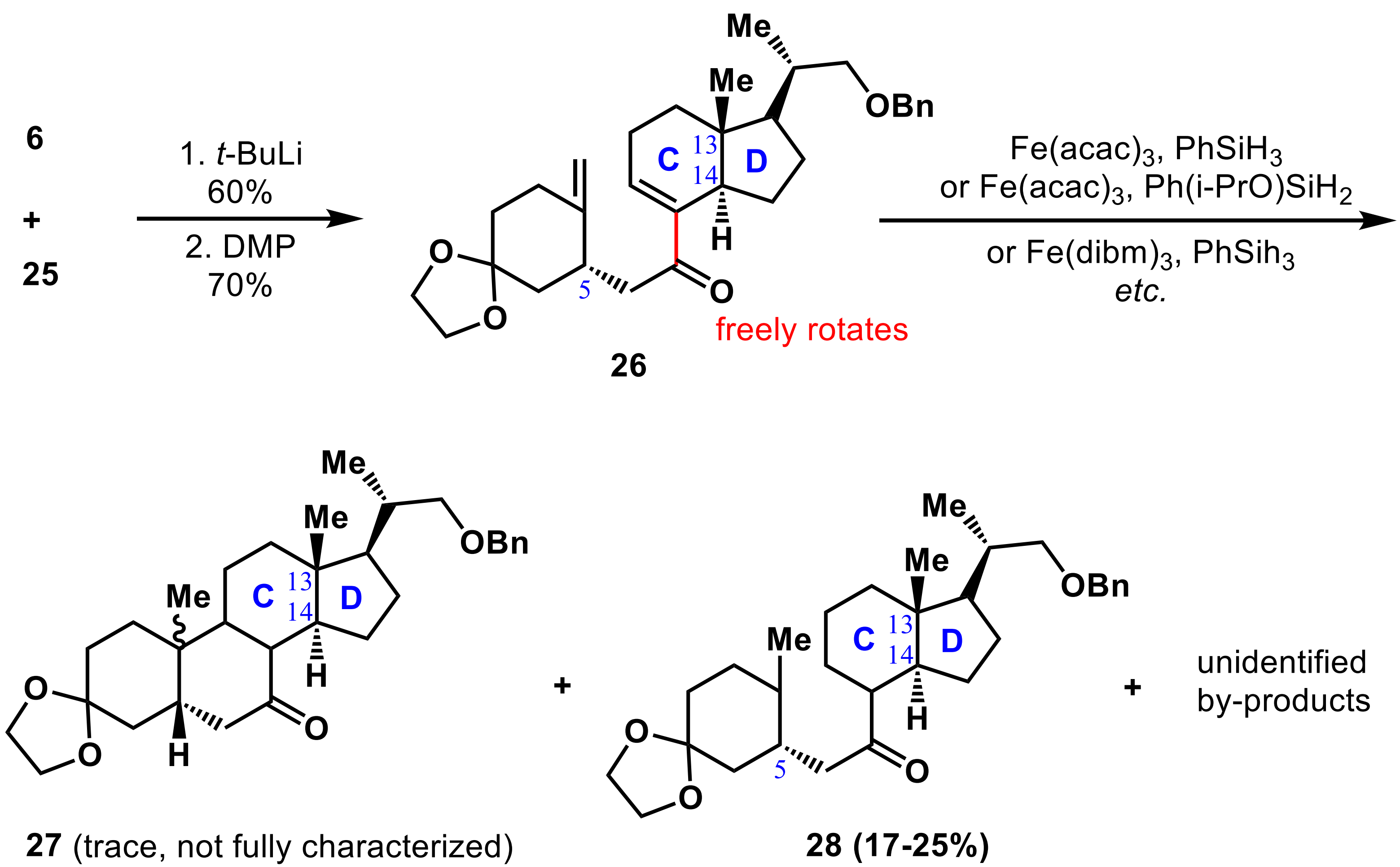
(A). Synthesis of coupling fragment 6



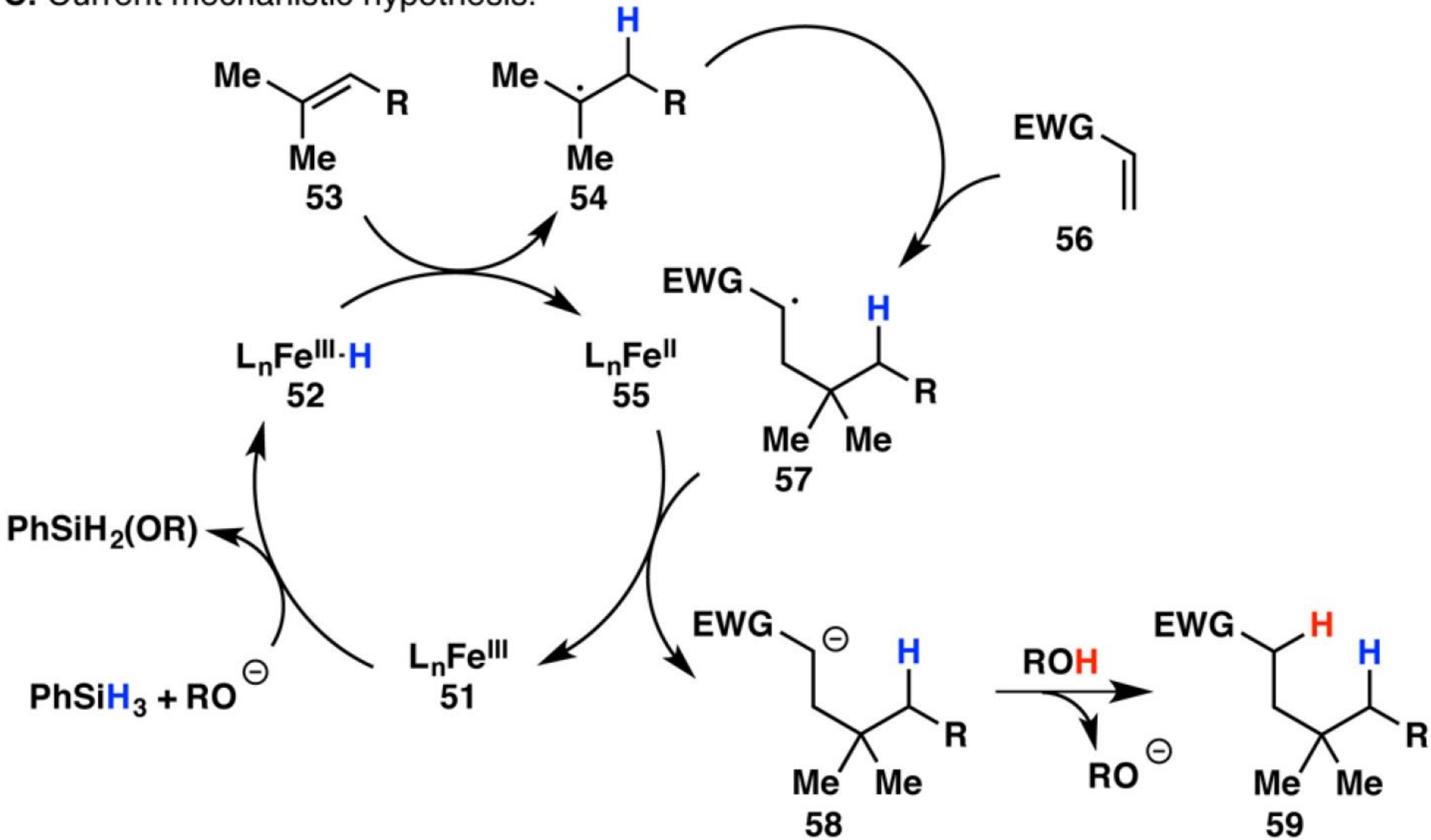
(B). Synthesis of coupling fragment 25



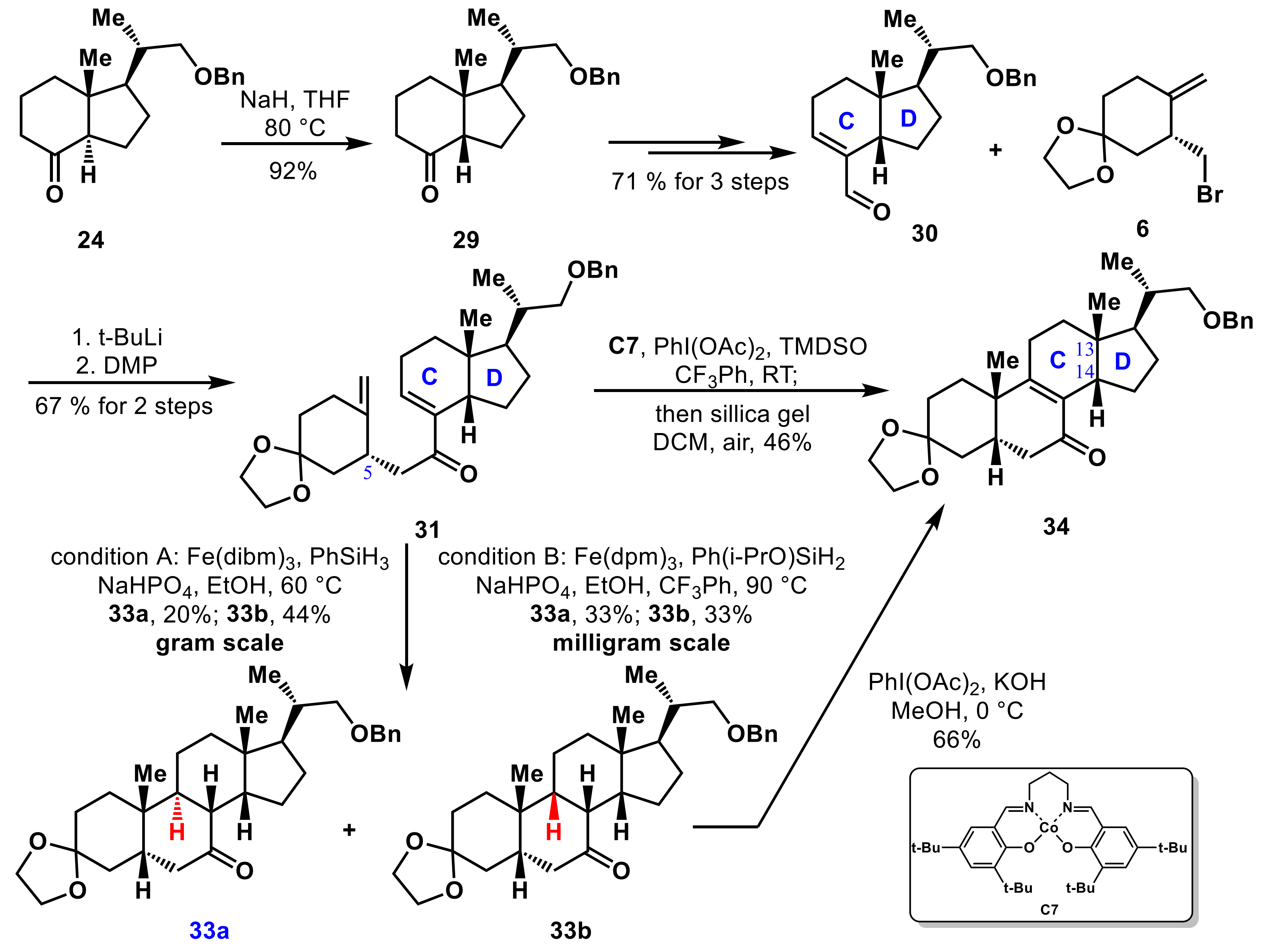
(C). Failed MHAT attempt with 26 containing trans-fused C/D ring



C. Current mechanistic hypothesis.



DOI: 10.1021/ja4117632.

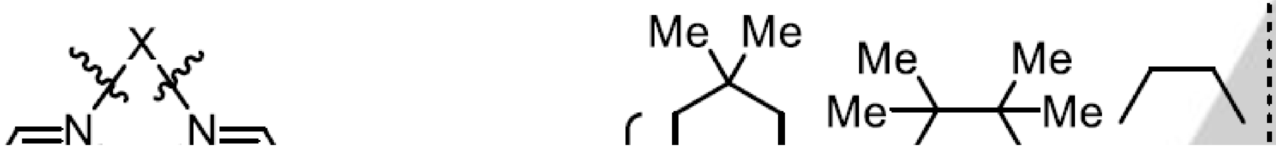


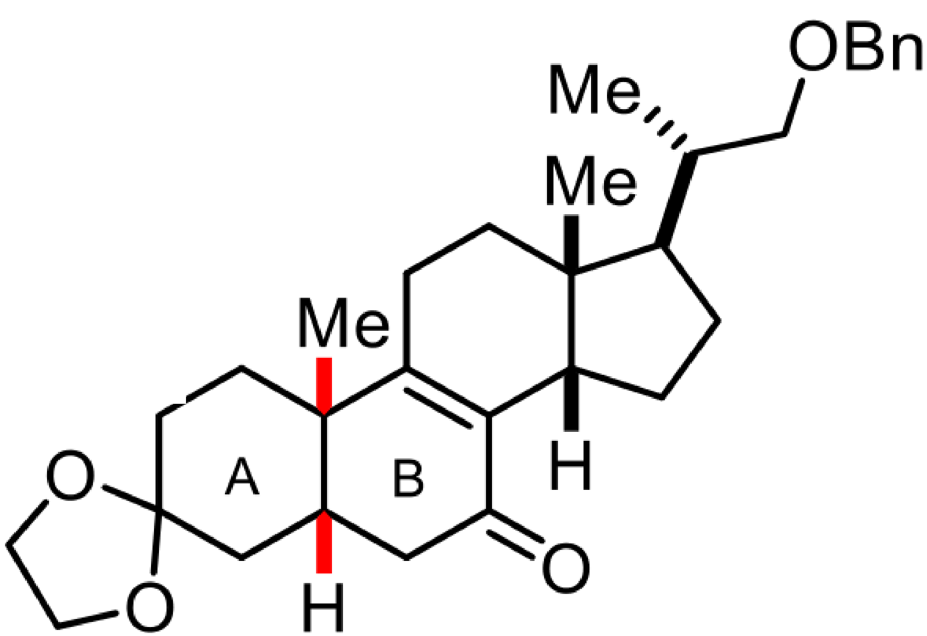
NaH, THF
80 °C
92%
71 % for 3 steps
1. t-BuLi
2. DMP
67 % for 2 steps
C7, PhI(OAc)2, TMDSO
CF3Ph, RT;
then sillica gel
DCM, air, 46%
condition A: Fe(dibm)3, PhSiH3
NaHPO4, EtOH, 60 °C
33a, 20%; 33b, 44%
gram scale
condition B: Fe(dpm)3, Ph(i-PrO)SiH2
NaHPO4, EtOH, CF3Ph, 90 °C
33a, 33%; 33b, 33%
milligram scale
PhI(OAc)2, KOH
MeOH, 0 °C
66%
24
29
30
6
31
34
33a
33b
C7

Table 1. Conditions of Radical Cyclization of **31**.

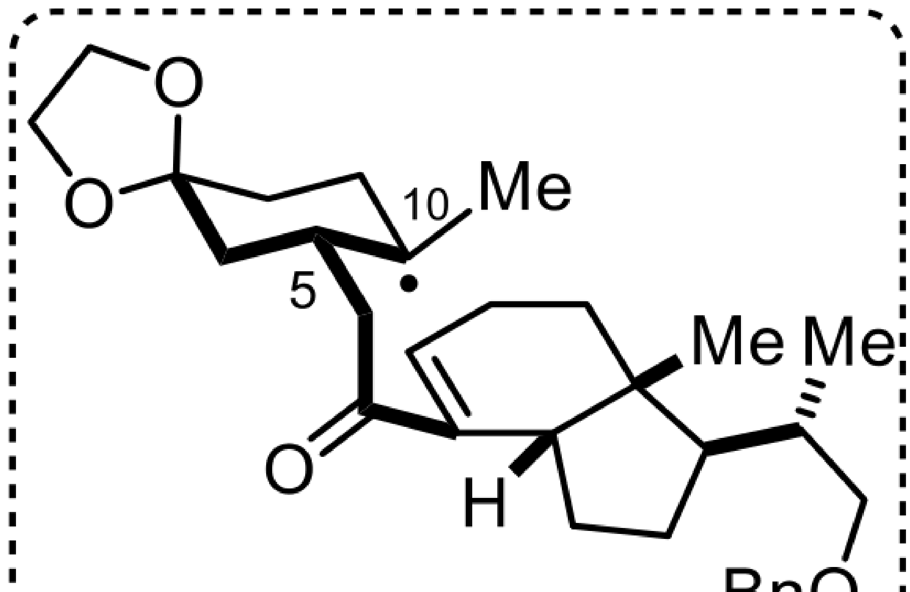
Entry	Conditions[a]	**33a**[b] + **33b**[b] (**33a**:**33b**)	**34**[b]
1	$Fe(acac)_3$, $PhSiH_3$, EtOH, 60 °C	43% (1:2.9)	-
2	$Fe(dibm)_3$, $PhSiH_3$, EtOH, 60 °C	62% (1:2)	-
3	$Fe(dibm)_3$, $PhSiH_3$, Na_2HPO_4, EtOH, 60 °C	72% (1:1.6)	-
4	$Fe(dpm)_3$, $PhSiH_3$, Na_2HPO_4, EtOH, 60 °C	58% (1:1.6)	-
5	$Fe(dibm)_3$, $PhSiH_3$, Na_2HPO_4, EtOH, CF_3Ph, 90 °C	64% (1:1.2)	-
6	$Fe(dibm)_3$, Ph(*i*-PrO)SiH_2, Na_2HPO_4, EtOH, CF_3Ph, 90 °C	69% (1:1.3)	-
7	$Fe(dpm)_3$, Ph(*i*-PrO)SiH_2, Na_2HPO_4, EtOH, CF_3Ph, 90 °C	66% (1:1)	-
8	**C1** or **C7**, **F1**, TMDSO, CF_3Ph, rt	-	23-27%[c]

9	**C2** or (**C3**, **C4**), **F1**, TMDSO, CF_3Ph, rt	-	7-16%[c]
10	**C5** or **C6**, **F1**, TMDSO, CF_3Ph, rt	-	21-23%[c]
11	**C8** or (**C9**, **C10**), **F1**, TMDSO, CF_3Ph, rt	-	0-27%[c]
12	**C7**, **F1**, $PhI(OAc)_2$, TMDSO, CF_3Ph, rt	-	26%[c]
13	**C7**, $PhI(OAc)_2$, TMDSO, CF_3Ph, rt	-	39%[c]
14	**C7, $PhI(OAc)_2$, TMDSO, CF_3Ph, rt; then silica gel, DCM, air**	-	**46%**[c]
15	10 mol% **C11**, $PhSiH_3$, TBHP,	**33b** (22%)[d]	-
16	**C12** or **C13**, **F1**, TMDSO, CF_3Ph,	-	<13%[c]
17	34 mol% **C14**, TMDSO, EtOH, rt or (10 mol% **C15**, $Co(BF_4)_2 \cdot 6H_2O$), $PhSiH_3$, TBHP,	-	messy

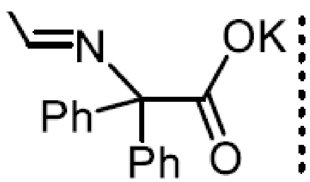




34



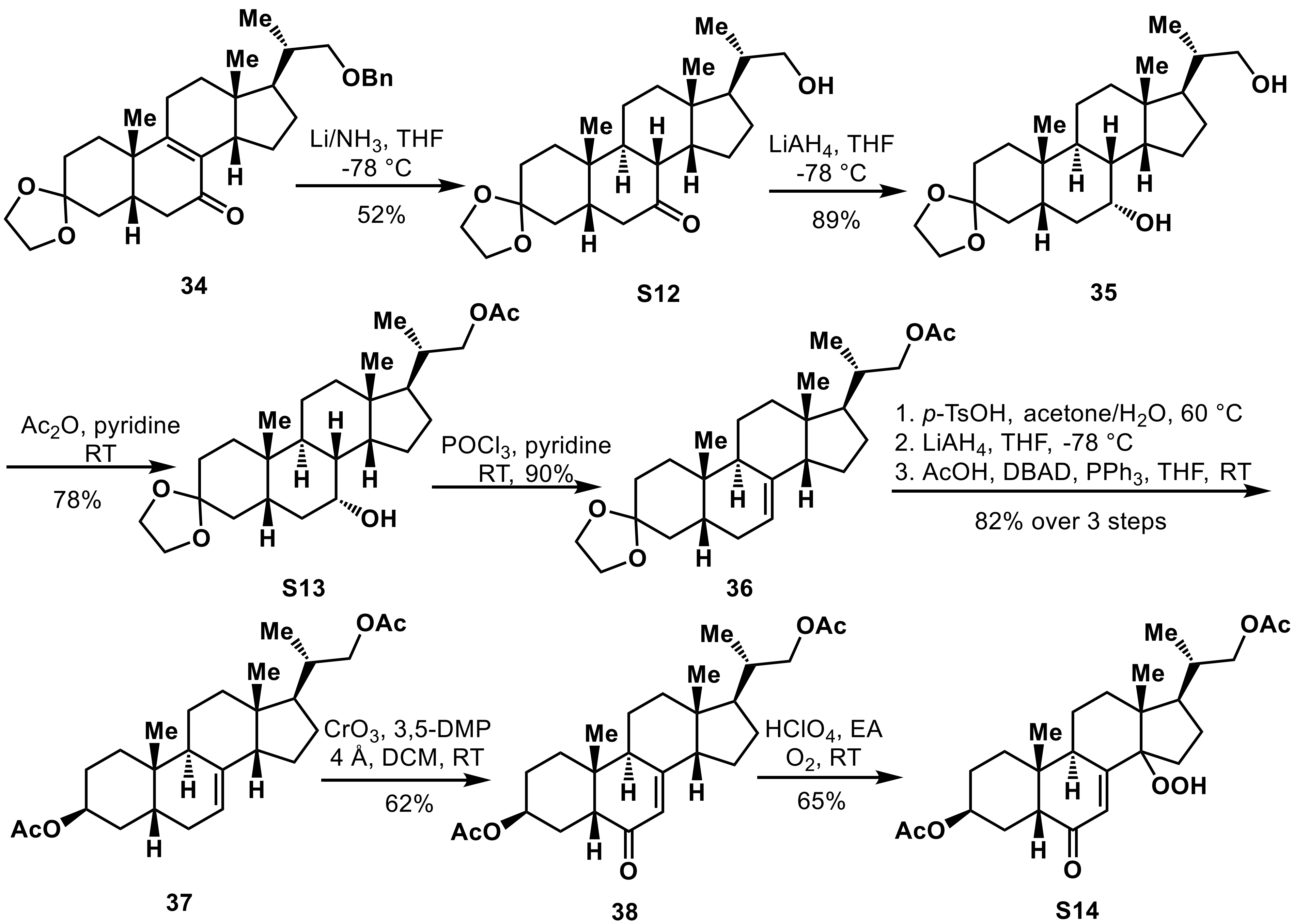
common intermediate 32

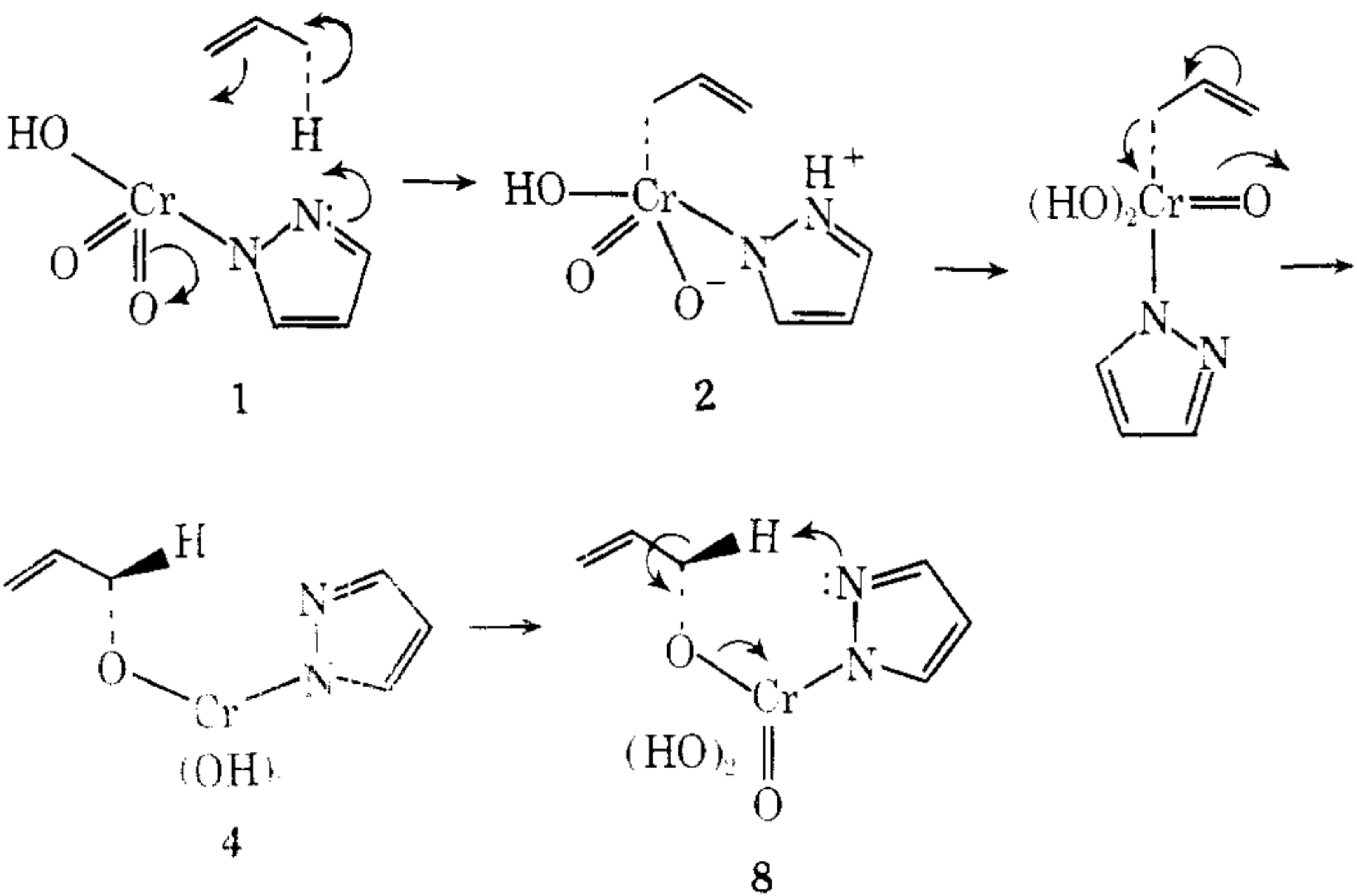


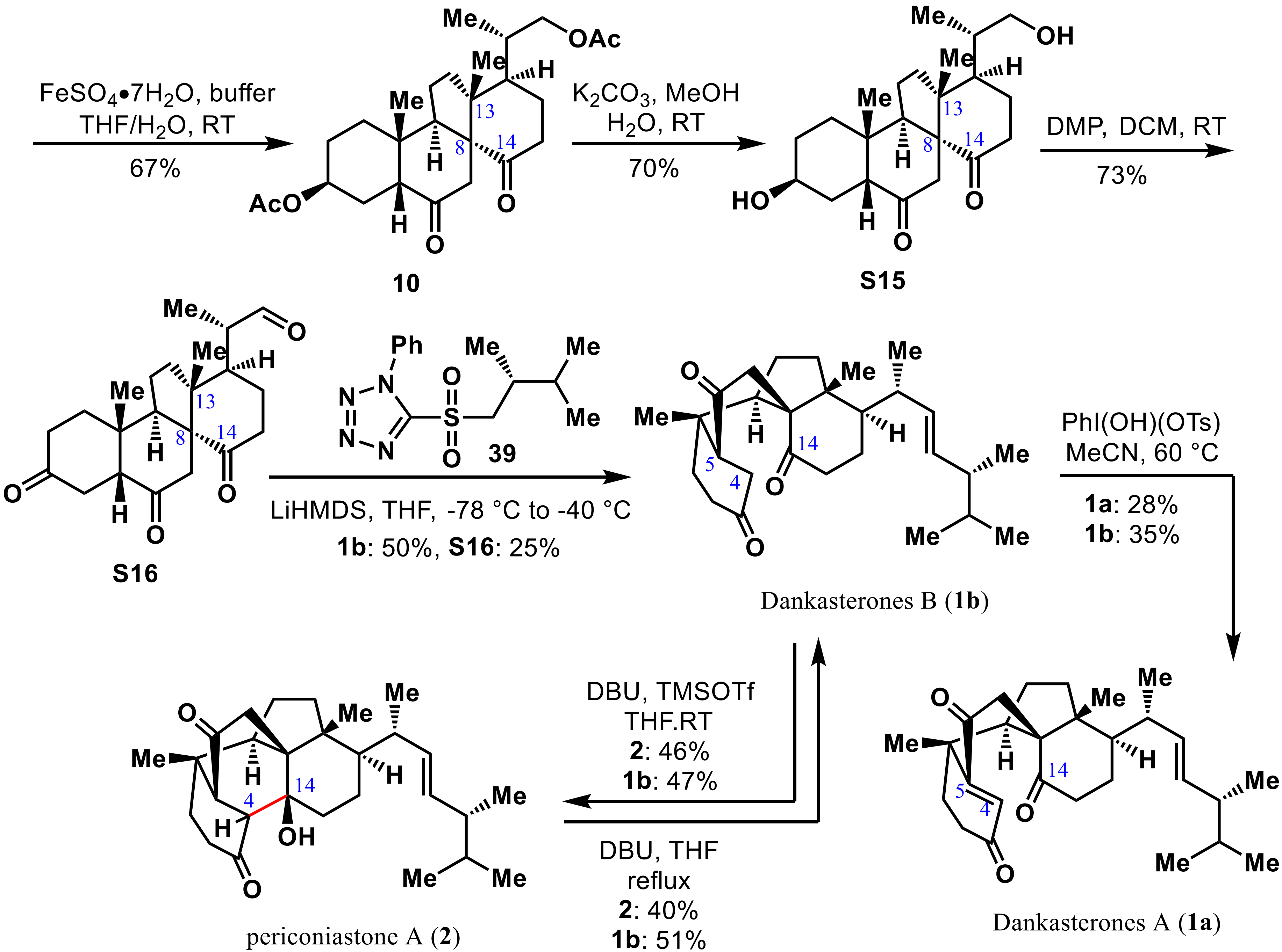
C15

C7 (R = *t*-Bu)
C8 (R = Me)
C9 (R = H)
C10 (R = OMe)

C11 (R^1 = *t*-Bu, R^2 = OAc)
C12 (R^1 = *t*-Bu, R^2 = Cl)
C13 (R^1 = OMe, R^2 = Cl)


Li/NH3, THF
-78 °C
52%
LiAH4, THF
-78 °C
89%
Ac2O, pyridine
RT
78%
POCl3, pyridine
RT, 90%
1. p-TsOH, acetone/H2O, 60 °C
2. LiAH4, THF, -78 °C
3. AcOH, DBAD, PPh3, THF, RT
82% over 3 steps
CrO3, 3,5-DMP
4 Å, DCM, RT
62%
HClO4, EA
O2, RT
65%
34
S12
35
S13
36
37
38
S14


1
2
4
8



FeSO4•7H2O, buffer
THF/H2O, RT
67%
10
K2CO3, MeOH
H2O, RT
70%
S15
DMP, DCM, RT
73%
S16
39
LiHMDS, THF, -78 °C to -40 °C
1b: 50%, S16: 25%
Dankasterones B (1b)
PhI(OH)(OTs)
MeCN, 60 °C
1a: 28%
1b: 35%
Dankasterones A (1a)
DBU, TMSOTf
THF.RT
2: 46%
1b: 47%
DBU, THF
reflux
2: 40%
1b: 51%
periconiastone A (2)