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Article

Total Synthesis of (+)-Cyclobutastellettolide B

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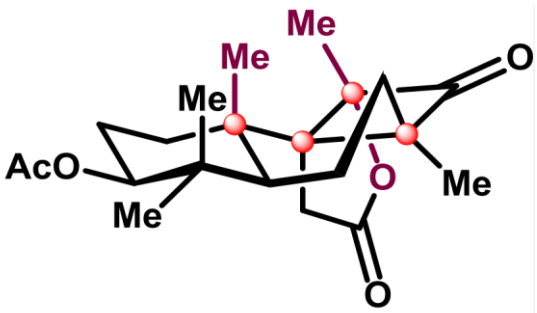
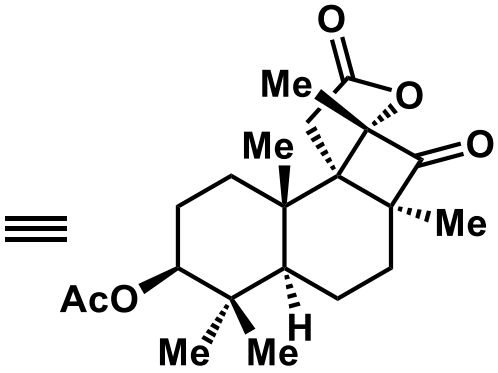


cyclobutastellettolide B (**1**)



isolated from a *Stelletta* sp. By Stonik et al. in 2019

an unusual 6/6/4-fused tricyclic core

six stereocenters（three contiguous quaternary stereocenters）

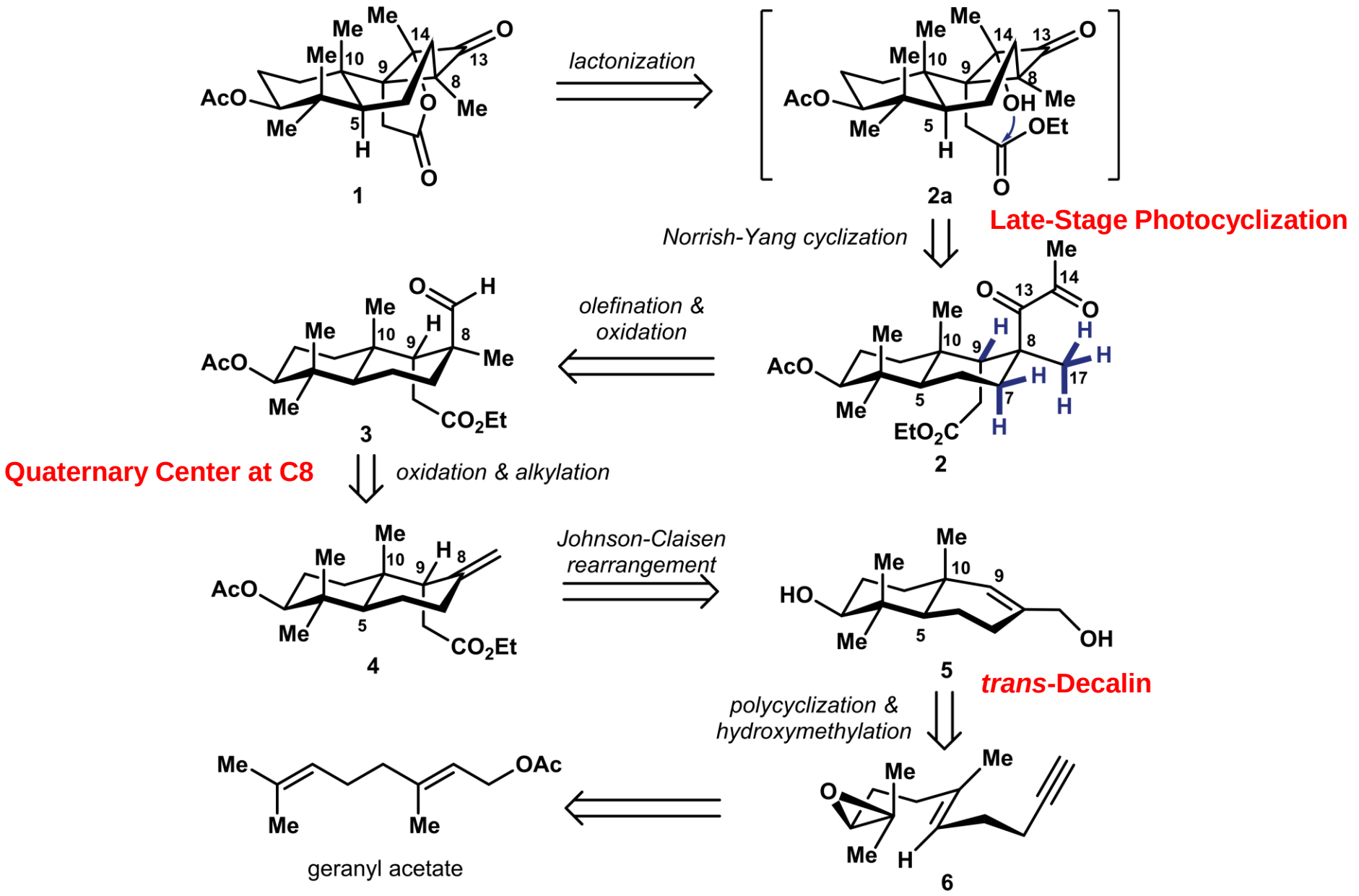
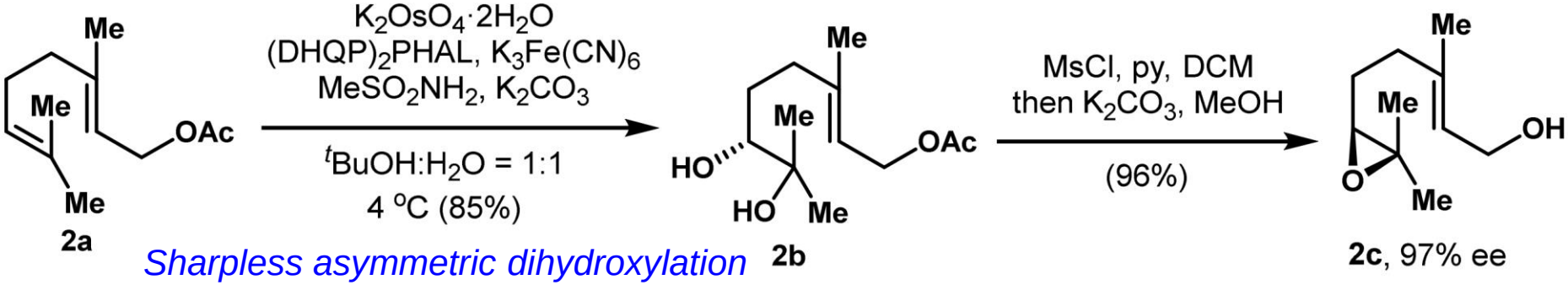
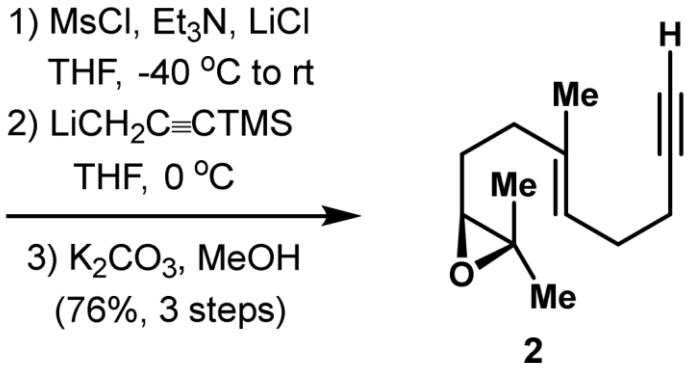


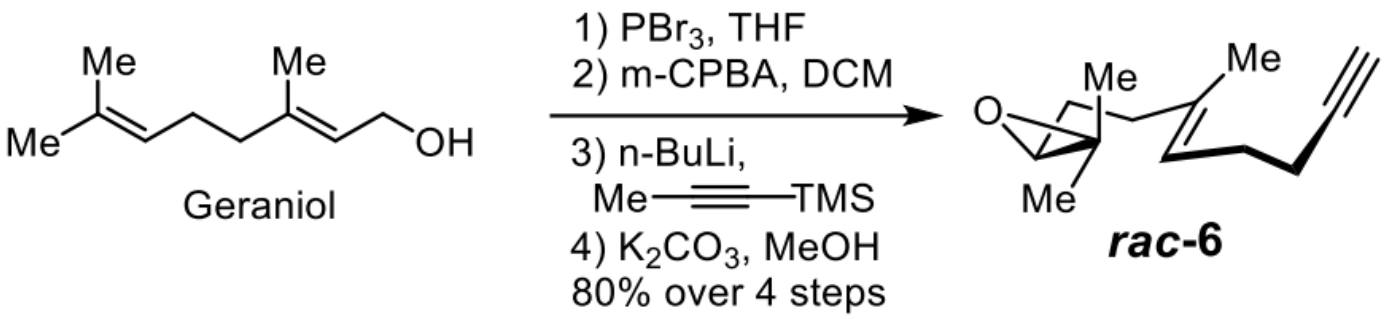
Figure 1. Retrosynthetic analysis of cyclobutastellettolide B (**1**).

Synthetic route of the known epoxide 2 in asymmetric form:



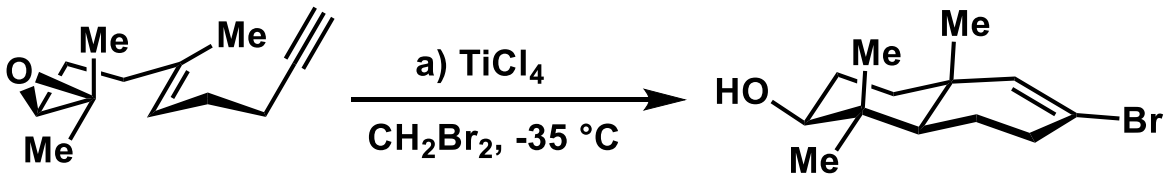
Sharpless asymmetric dihydroxylation





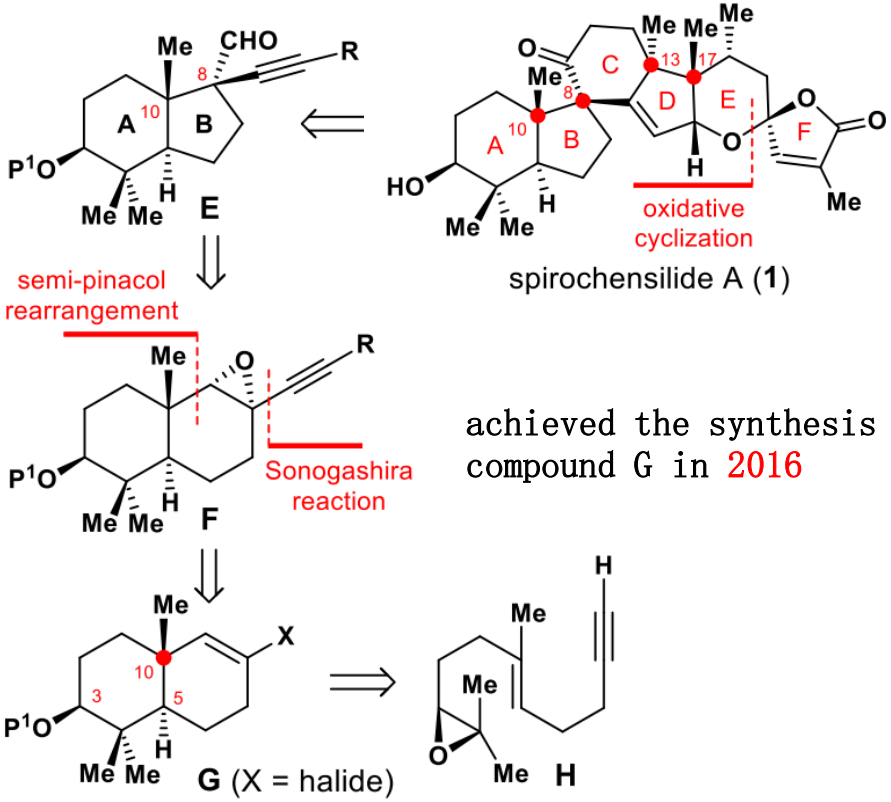
J. Am. Chem. Soc. **2020**, *142*, 8116.

Synthesis of *trans*-Decalin



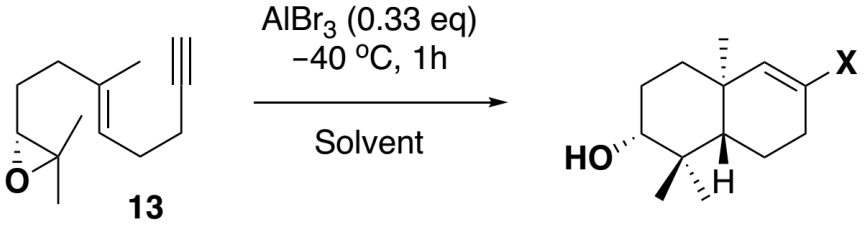
6
97% *ee*

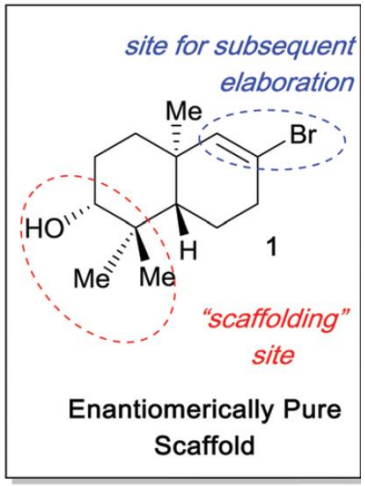
7
decagram scale prepared



achieved the synthesis of compound G in 2016

J. Am. Chem. Soc. **2020**, *142*, 8116.



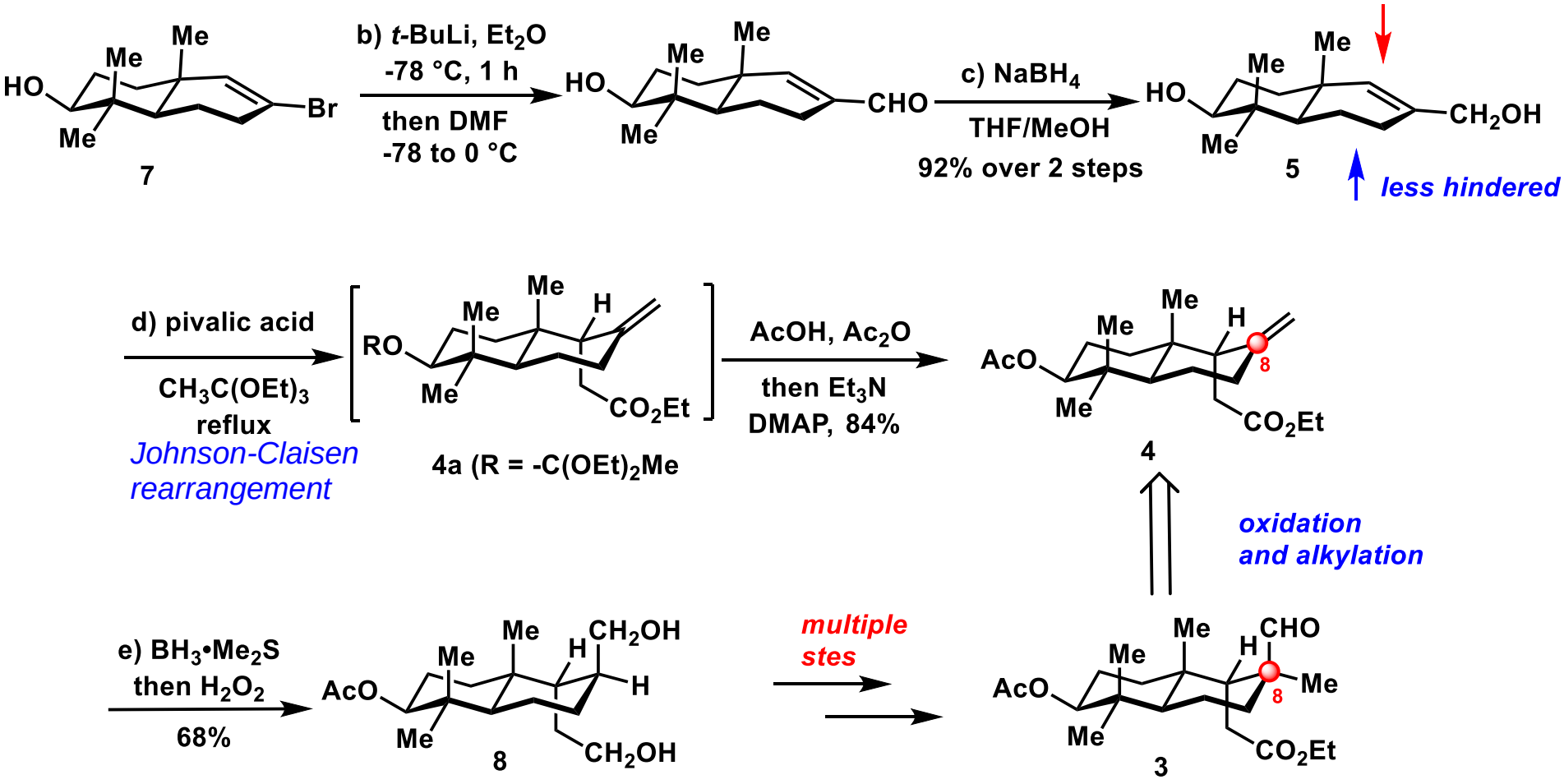


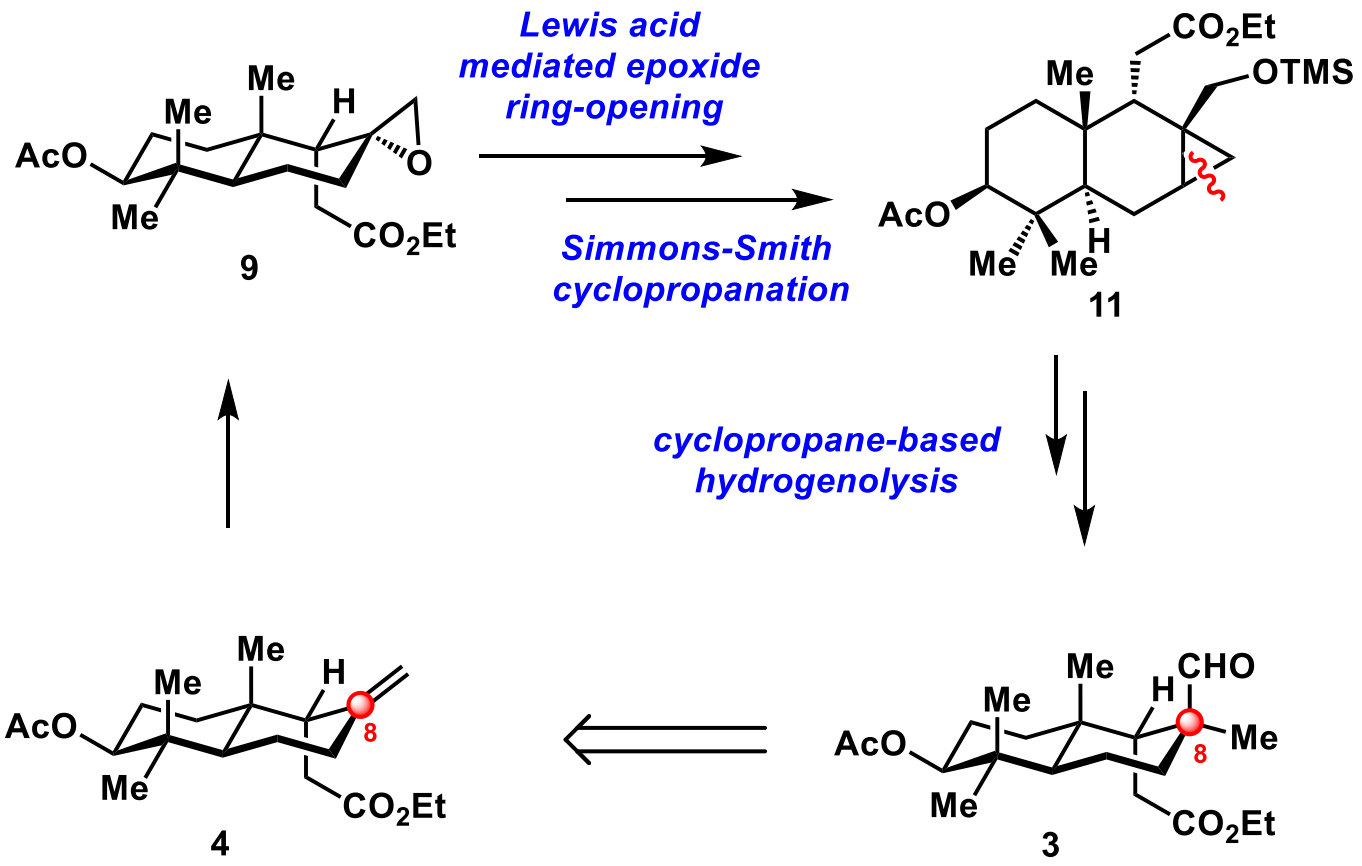
Solvent

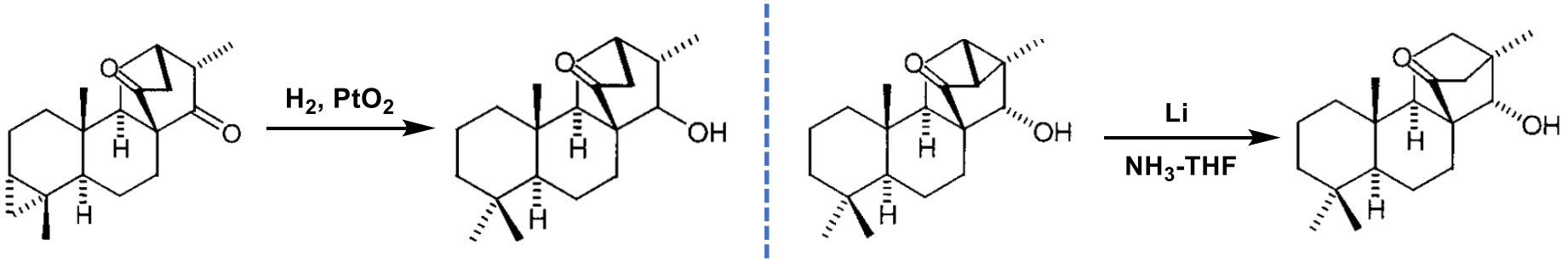
$CH_2\mathbf{Br_2}$	**1** (X = Br); 83%
$CH_2\mathbf{Cl_2}$	**14** (X = Cl); 70%
$CH_3\mathbf{I}$	**15** (X = I); 74%

Chem. Commun., **2018**, *54*, 11025.

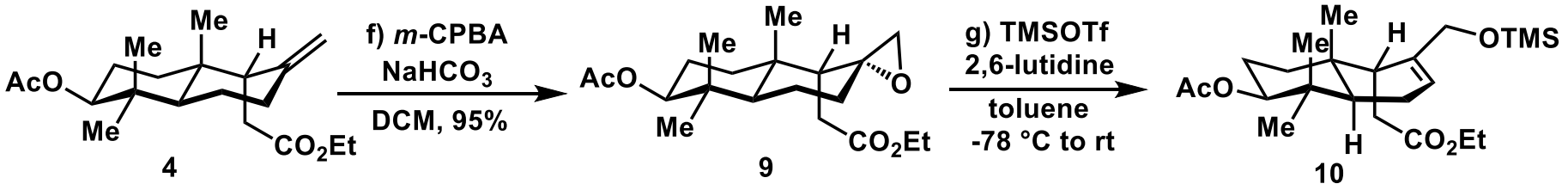
Efforts to Install a Quaternary Center at C8

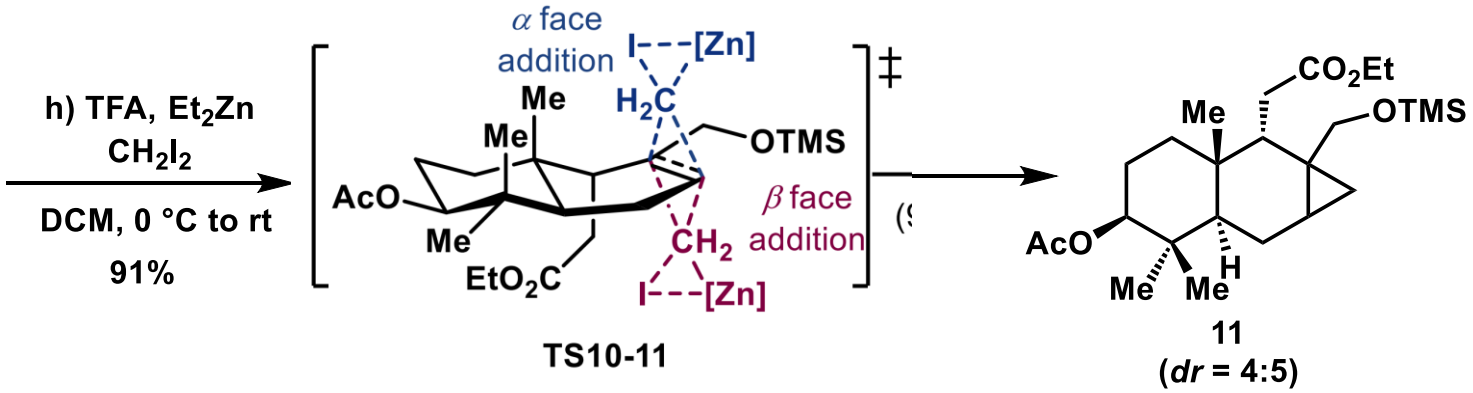


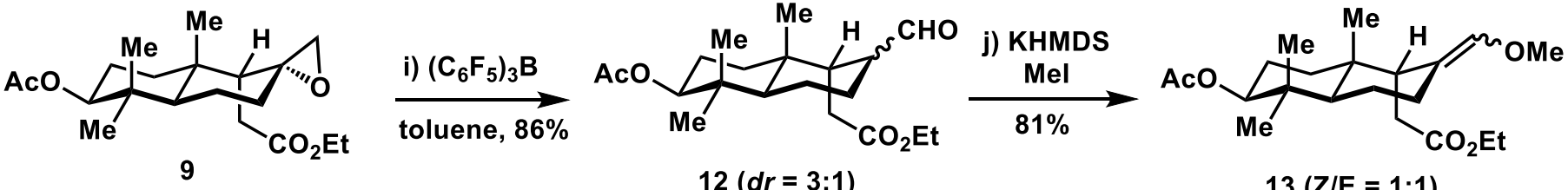

Lewis acid
mediated epoxide
ring-opening
Simmons-Smith
cyclopropanation
cyclopropane-based
hydrogenolysis
AcO
Me
H
O
CO2Et
9
CO2Et
OTMS
11
8
4
CHO
3



Synlett **2001**, 349







12 was reacted with a variety of methylating agents under different basic conditions

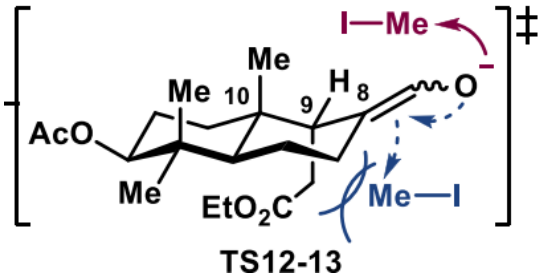
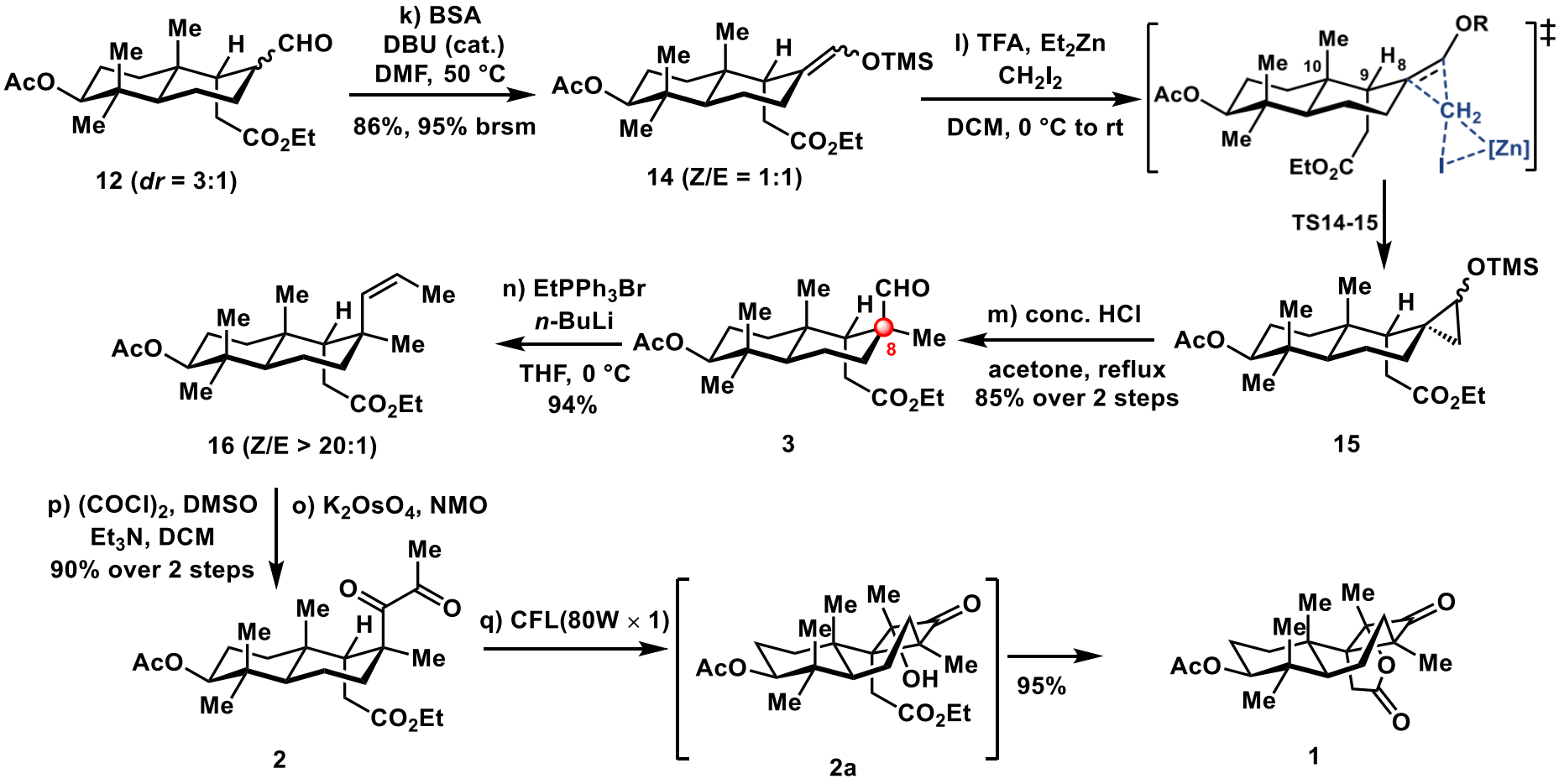
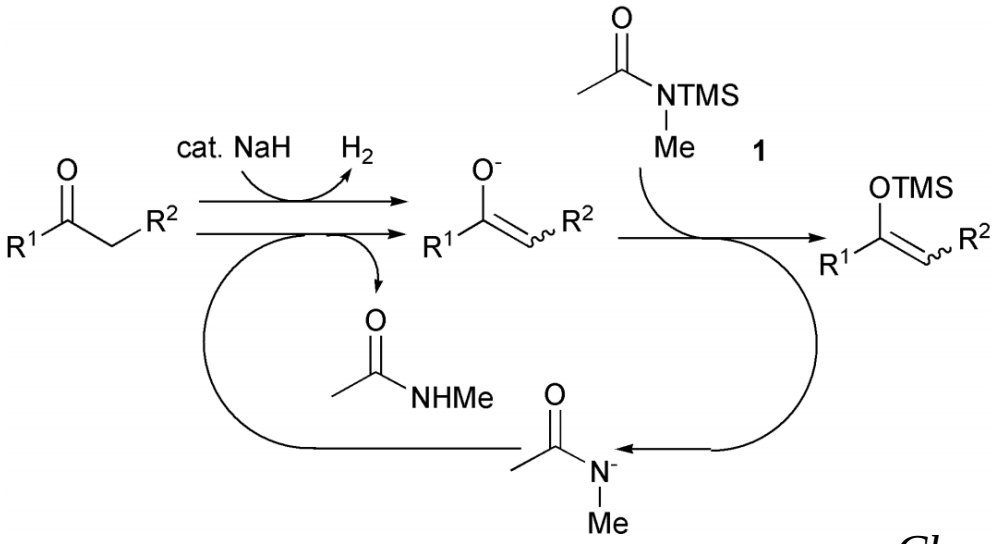


Table S1. Conditions screening of semi-pinacol rearrangement.

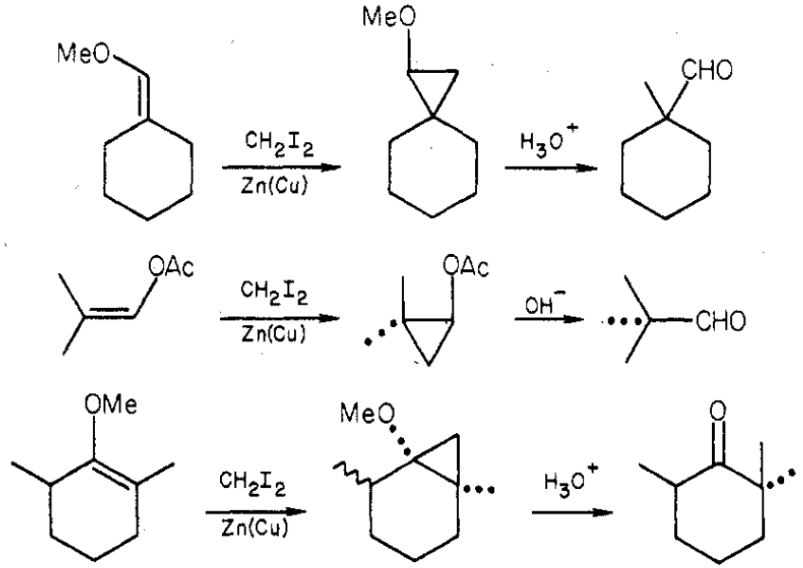
Entry	LA	equiv.	sol.	Temp	Time	yield
1	$BF_3{\cdot}OEt_2$	2.0 eq.	DCM	0 °C to r.t.	0.5 h	48 %
2	$BF_3{\cdot}OEt_2$	2.0 eq.	toluene	0 °C to r.t.	0.5 h	61 %
3	$BF_3{\cdot}OEt_2$	6.0 eq.	Et_2O	0 °C to r.t.	3.0 h	64 %
4	$(C_6F_5)_3B$	0.5 eq.	DCM	r.t.	4.0 h	71 %
5	$(C_6F_5)_3B$	0.5 eq.	toluene	r.t.	4.0 h	92 %

Cyclopropanation/oxycycloproane ring-opening reaction strategy

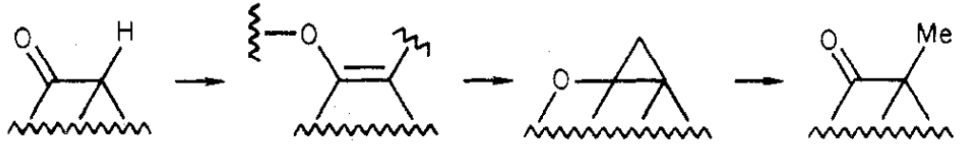




Chem. Commun. **2002**, 1628.

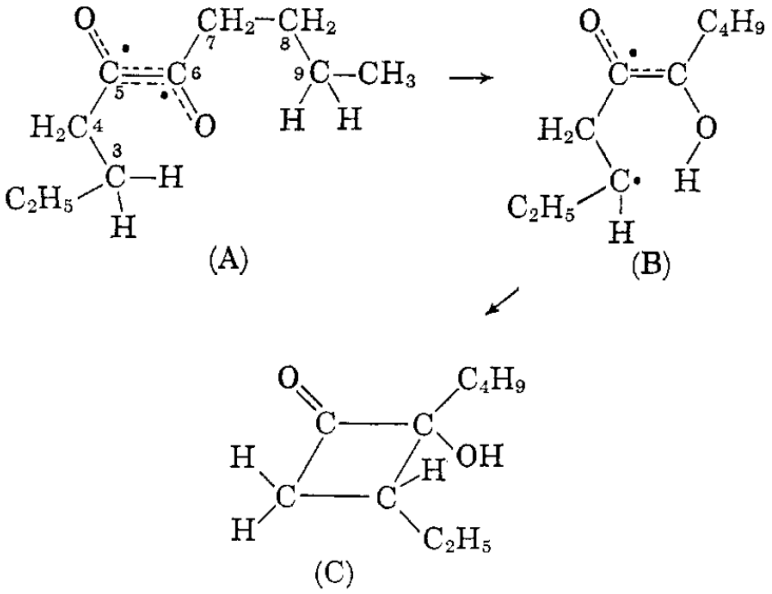


masked keto systems, the combination of oxycyclopropane synthesis and acid-induced unravelling represents an interesting three-step equivalent of the α-alkylation of carbonyl compounds (vide infra), especially of relevance to the formation of α-keto quaternary centers and to angular methylation of terpenes and steroids.

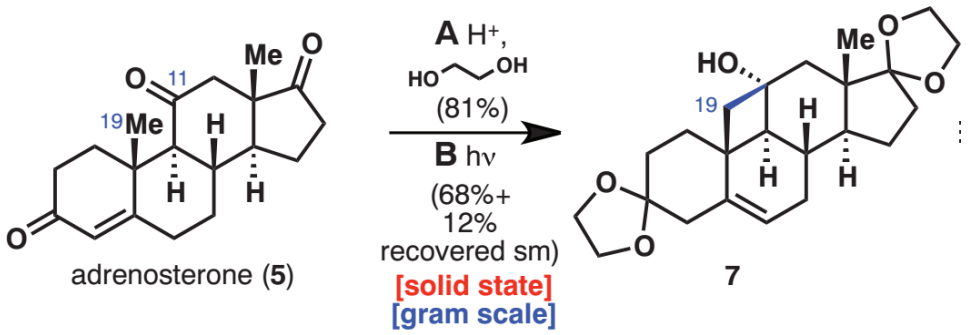


Acc. Chem. Res. **1980**, *13*, 27.

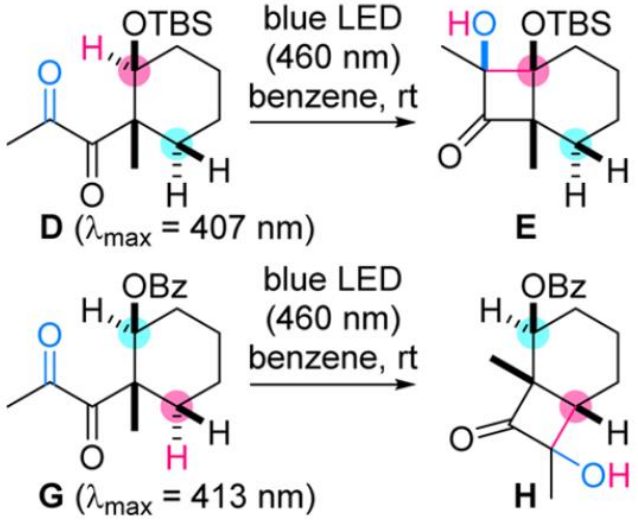
Norrish-Yang photocyclization



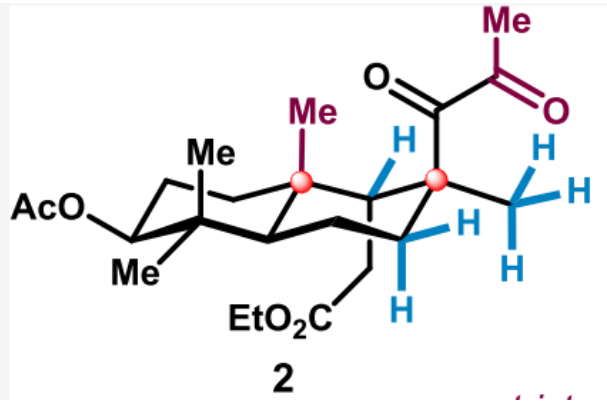
J. Am. Chem. Soc. **1962**, *84*, 118.



Science **2013**, *339*, 59.



J. Am. Chem. Soc. **2017**, *139*, 1814.



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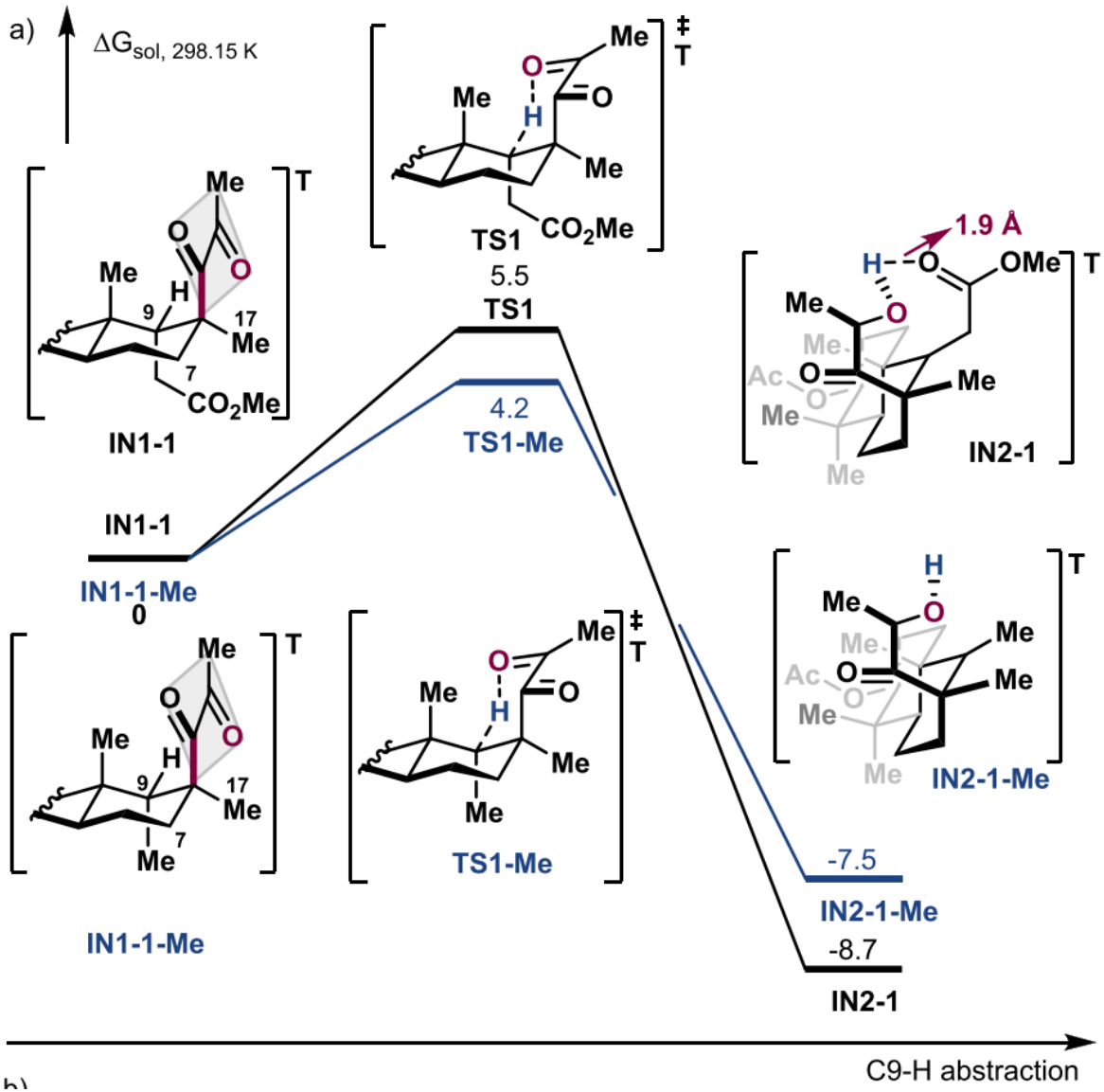

a)
ΔG sol, 298.15 K
IN1-1
TS1
5.5
TS1
4.2
TS1-Me
IN1-1
IN1-1-Me
0
IN1-1-Me
TS1-Me
1.9 Å
IN2-1
IN2-1-Me
-7.5
IN2-1-Me
-8.7
IN2-1
C9-H abstraction

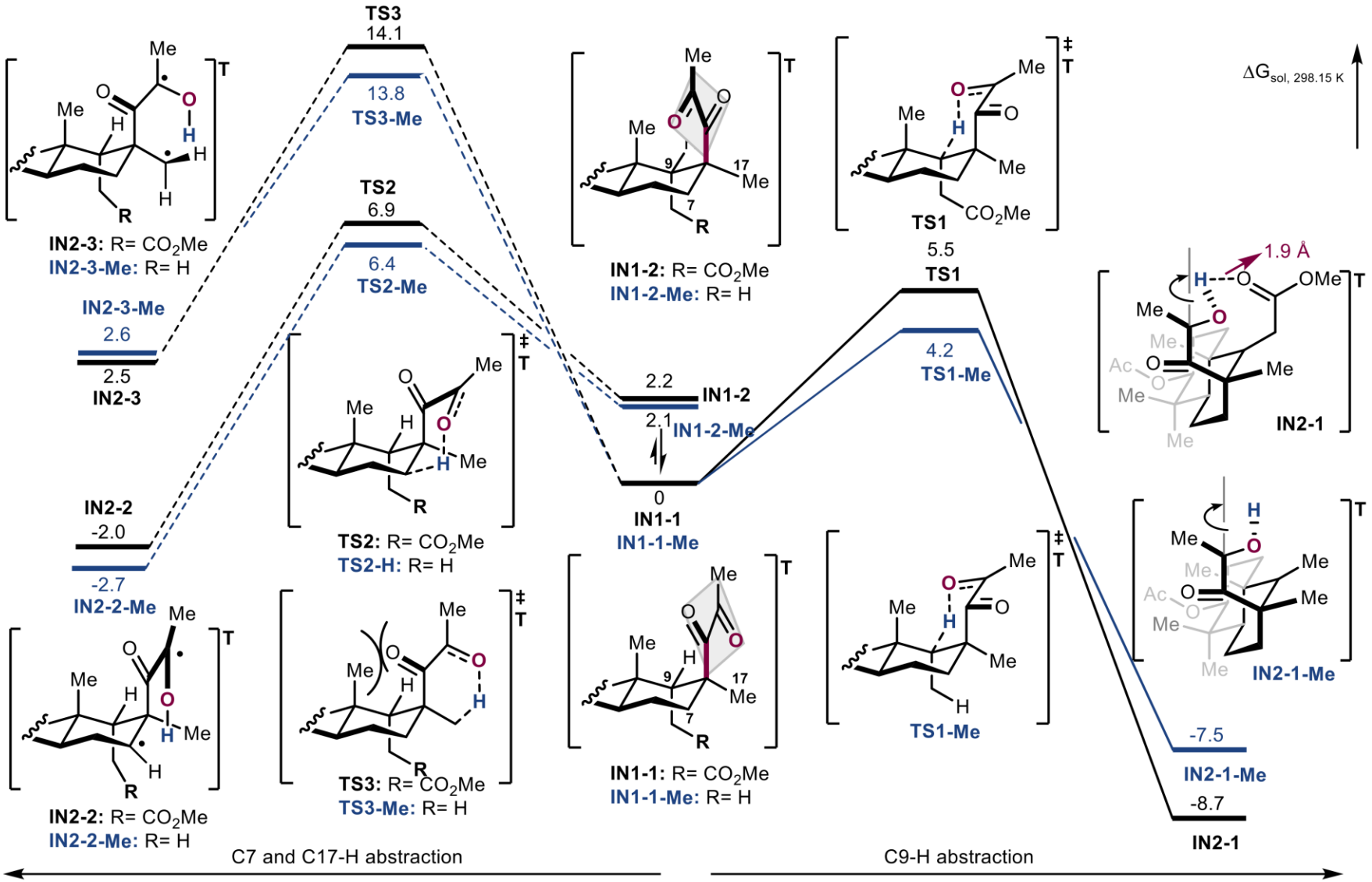
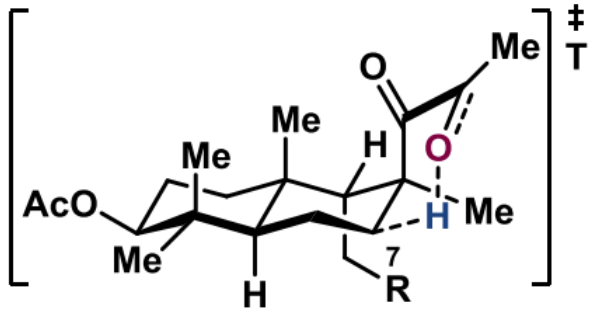


Figure S2. Energy profiles of 1,5-hydrogen shift of **IN1-1 and IN1-1-Me** via C9-H, C7-H and C17-H abstraction.

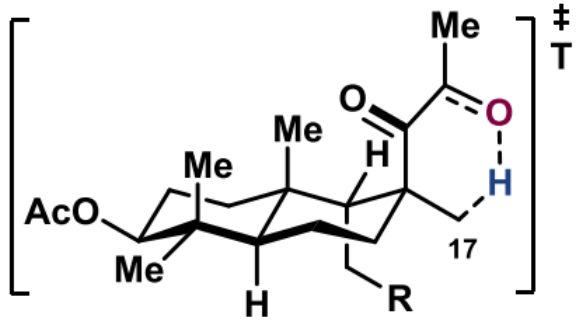
b)



TS2 (R = CO_2Me) **TS2-Me** (R = H)

$\Delta G^{\ddagger}$ = 6.9 $\Delta G^{\ddagger}$ = 6.4

ΔG° = -2.0 ΔG° = -2.7

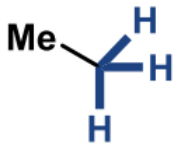


TS3 (R = CO_2Me) **TS3-Me** (R = H)

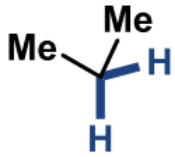
$\Delta G^{\ddagger}$ = 14.1 $\Delta G^{\ddagger}$ = 13.8

ΔG° = +2.6 ΔG° = +2.5

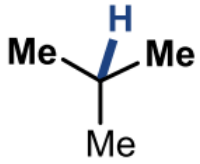
c)



BDE = 100.5 kcal/mol



BDE = 98.1 kcal/mol



BDE = 95.7 kcal/mol

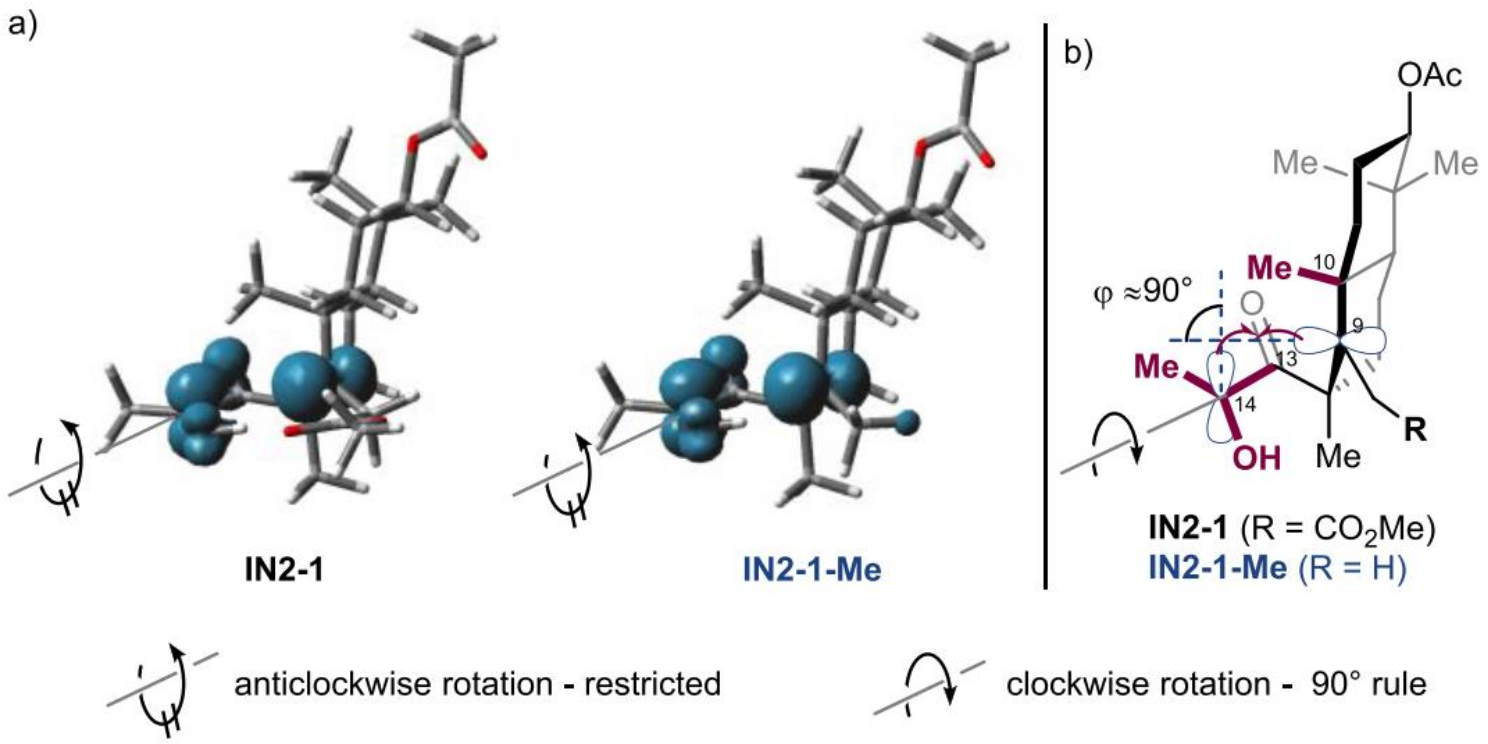
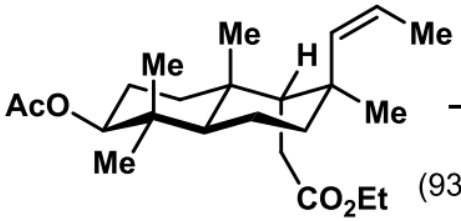


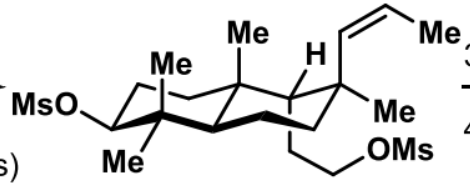
Figure 4. (a) Spin density surfaces of biradical **IN2-1** and **IN2-1-Me** (isovalue = 0.01); (b) schematic representation of the 90° rule.



(±)-**16** (*Z*/*E* > 20:1)

1) LAH

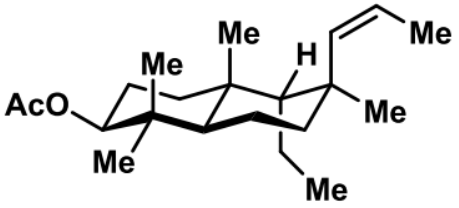
2) MsCl
(93% in two steps)



17

3) LAH (60%)

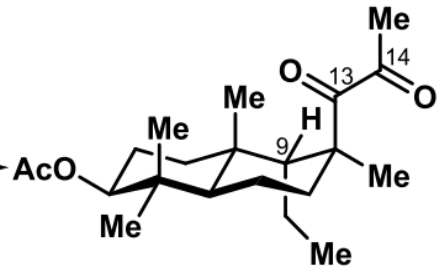
4) Ac_2O (96%)



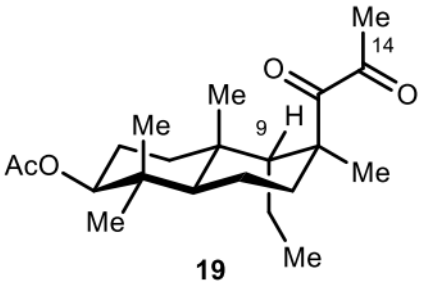
18

5) K_2OsO_4
NMO

6) $(COCl)_2$
DMSO
(85% in two steps)

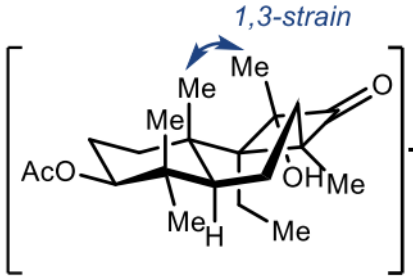


19



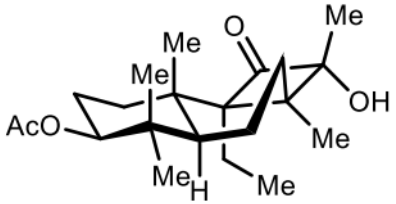
19

7) CFL, $CDCl_3$, rt.



20
inseparable
determined by in-situ NMR study

silica gel
95%



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