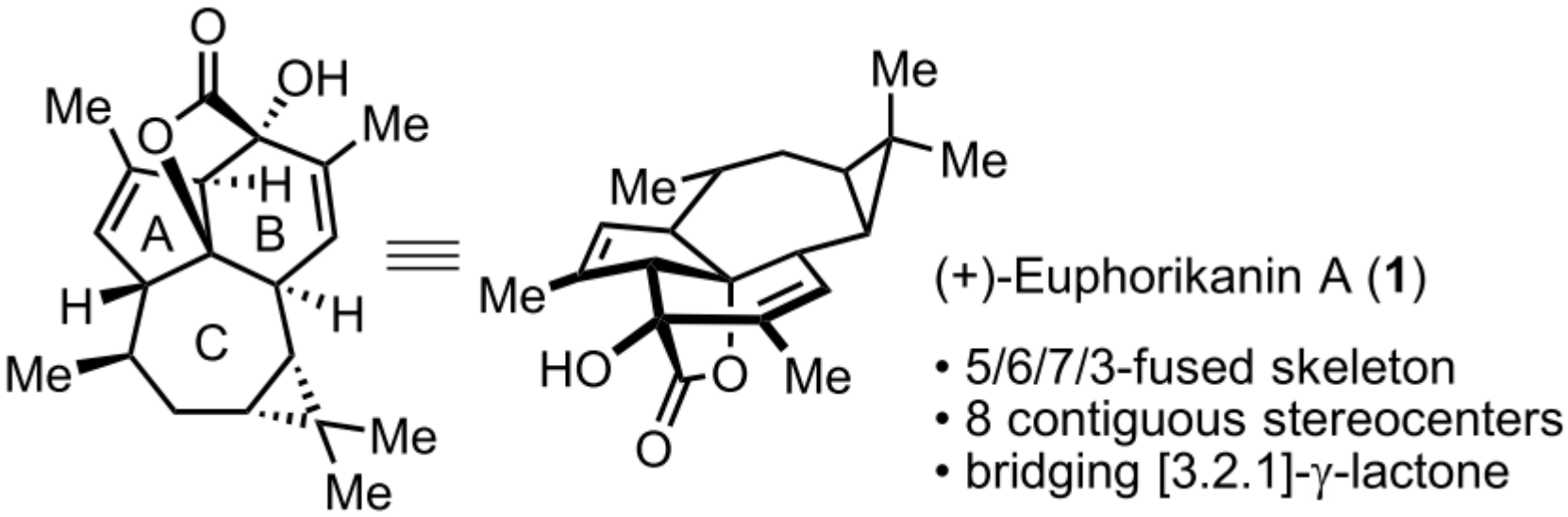
Total Synthesis of (+)-Euphorikanin A via an Atropospecific Cascade

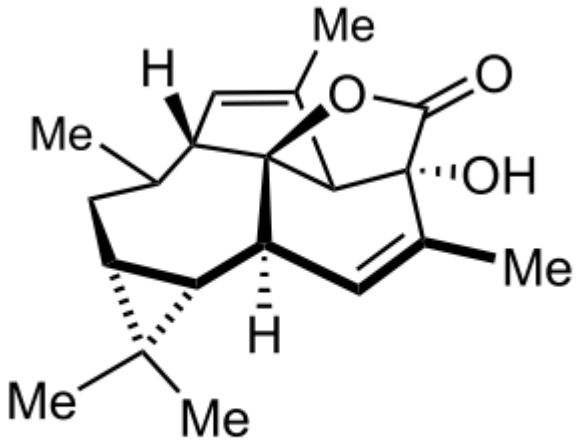
Moritz J. Classen,[‡] Bilal Kicin,[‡] Vincent A. P. Ruf,[‡] Alexander Hamminger, Loélie Ribadeau-Dumas, Willi M. Amberg, and Erick M. Carreira*



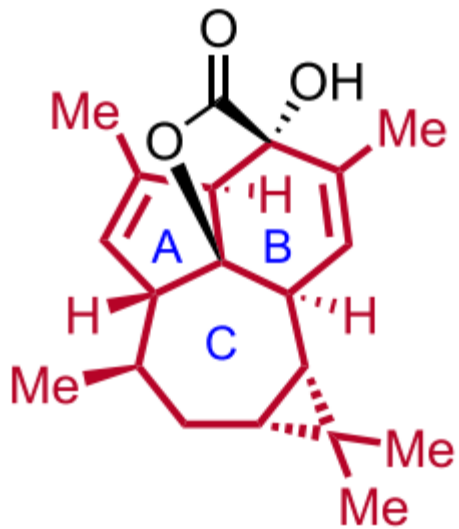
(+)-Euphorikanin A (**1**)

- 5/6/7/3-fused skeleton
- 8 contiguous stereocenters
- bridging [3.2.1]-γ-lactone

J. Am. Chem. Soc., **2023**, *145*, 27225.



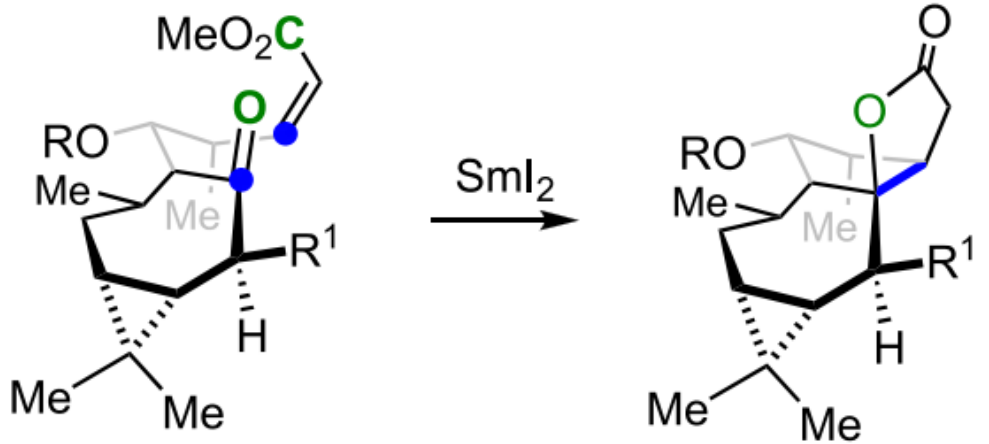
(+)-Euphorikanin A (**1**)



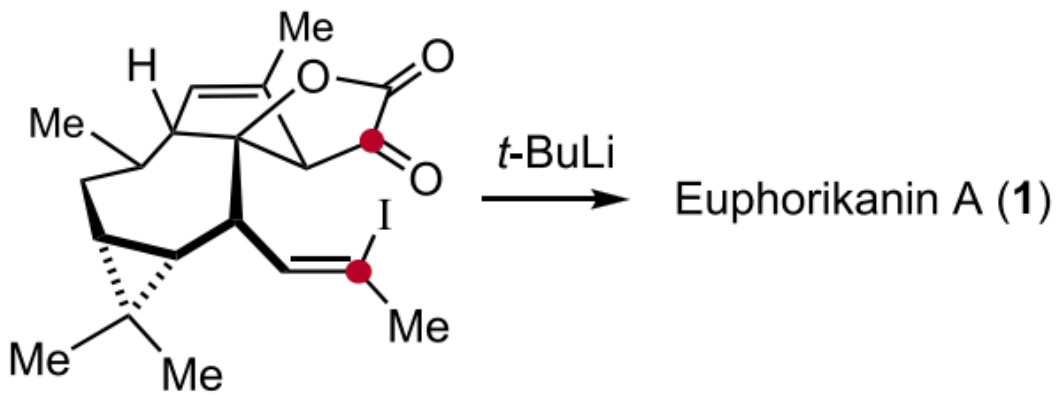
5/6/7/3-fused skeleton

Key Transformations

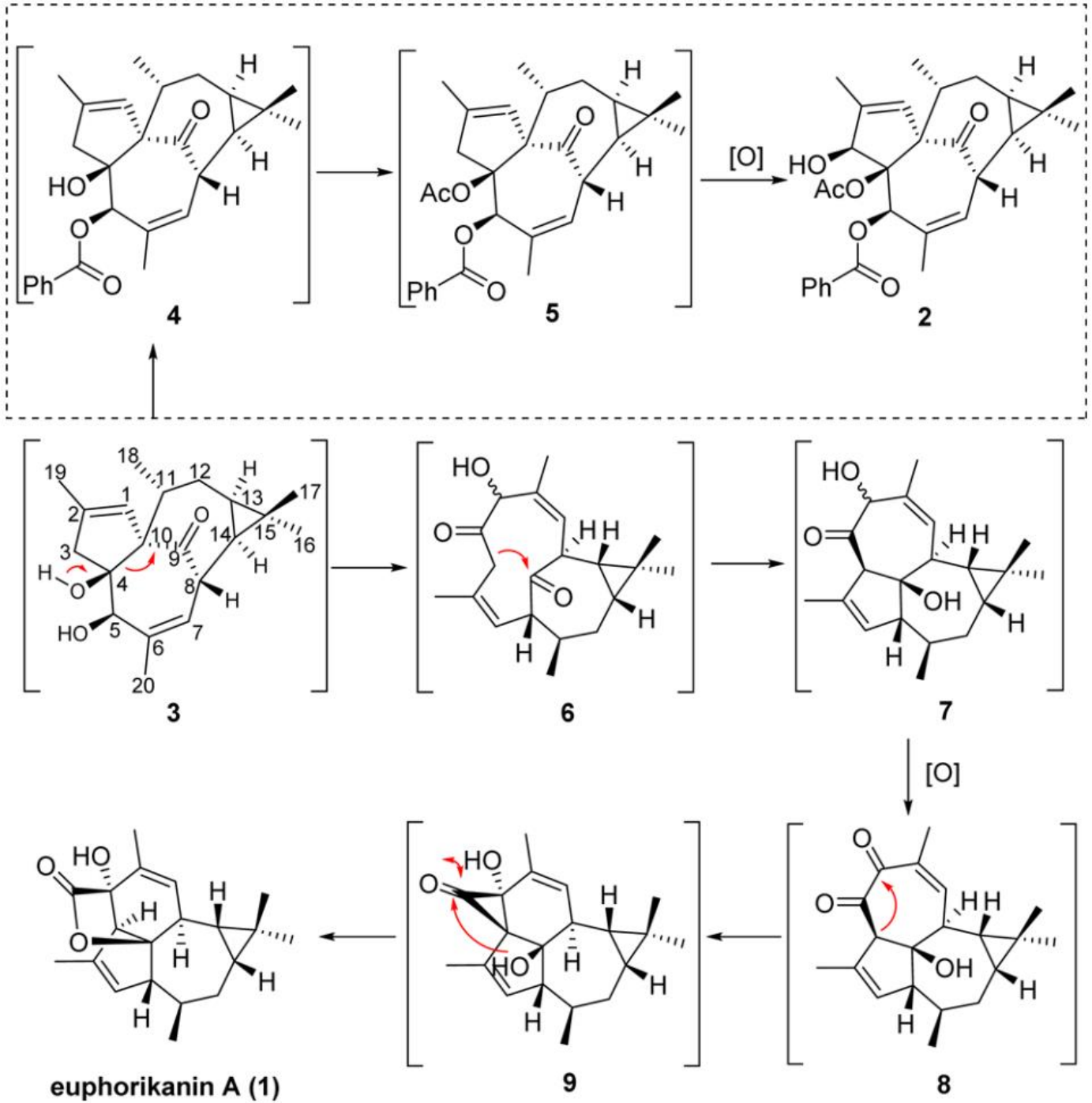
✓ *1-step Formation of A Ring & Lactone*



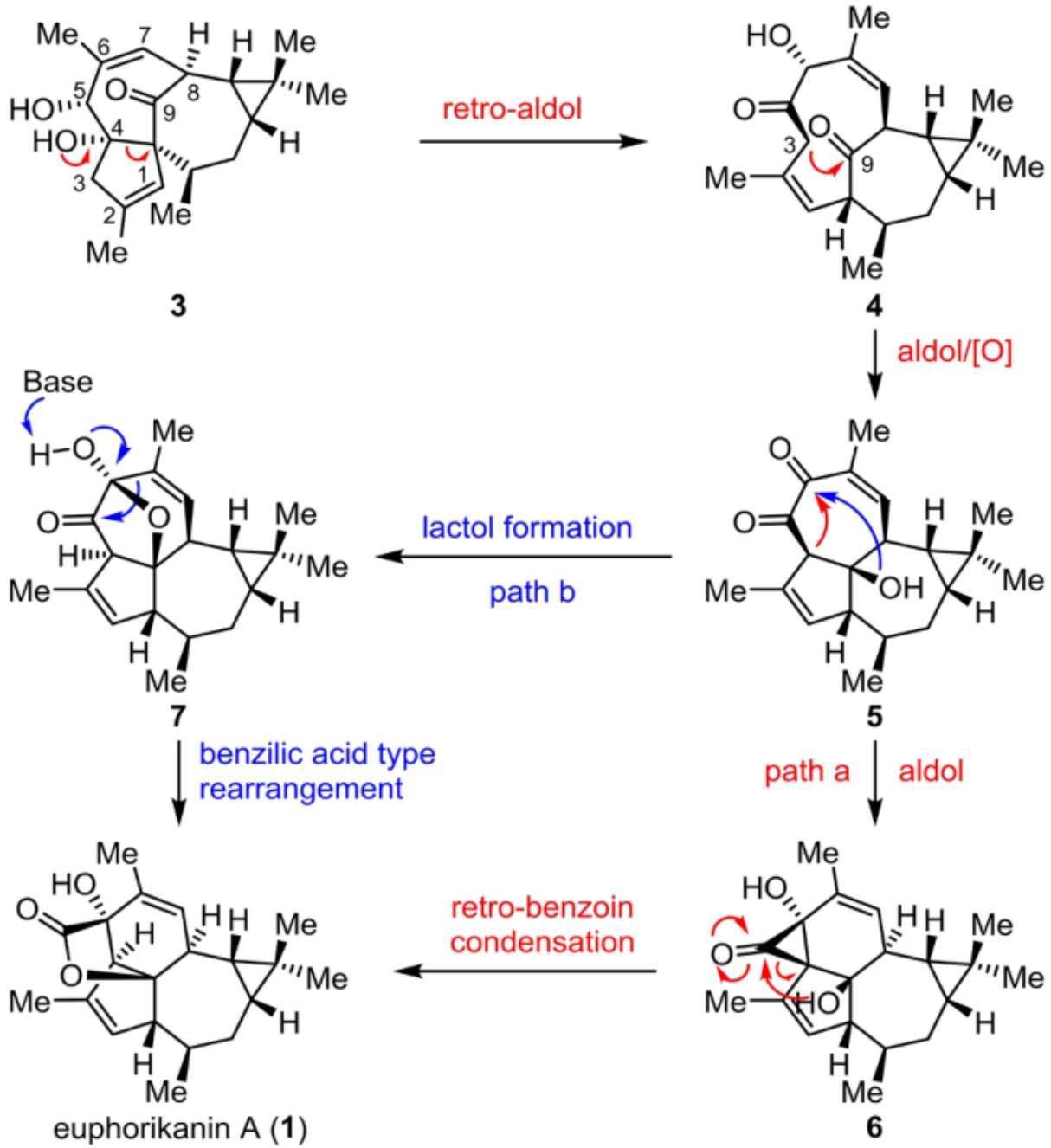
✓ *Metallation and Chemoselective Addition*



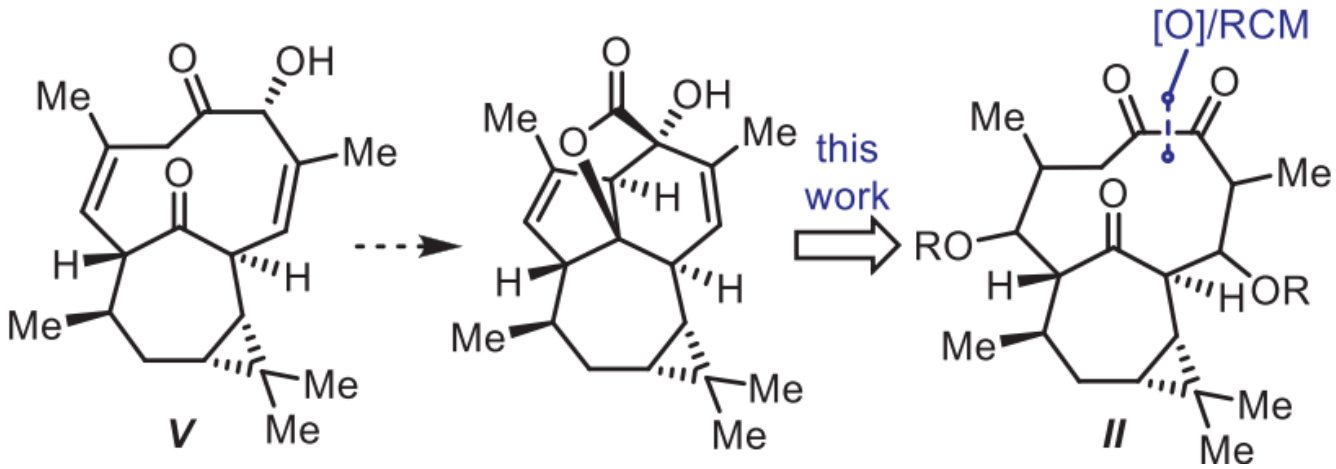
J. Am. Chem. Soc., **2021**, *143*, 8261.

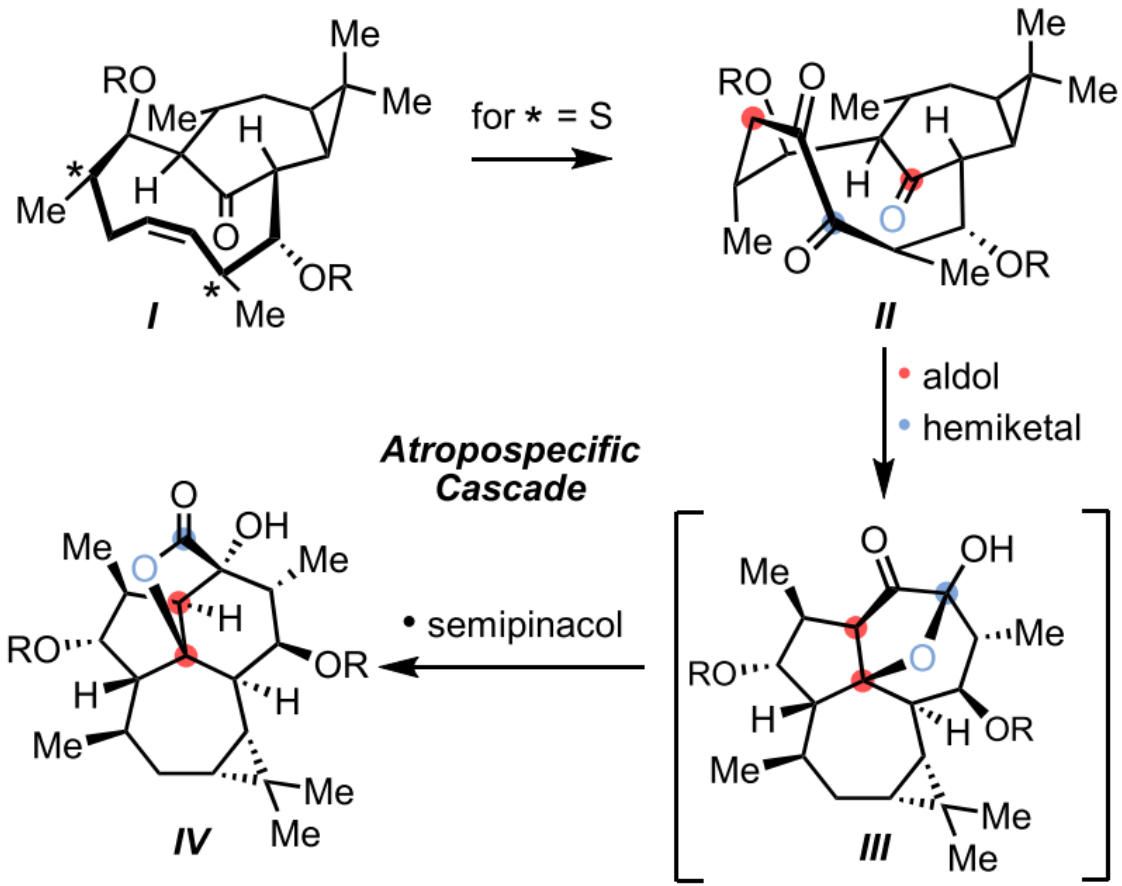


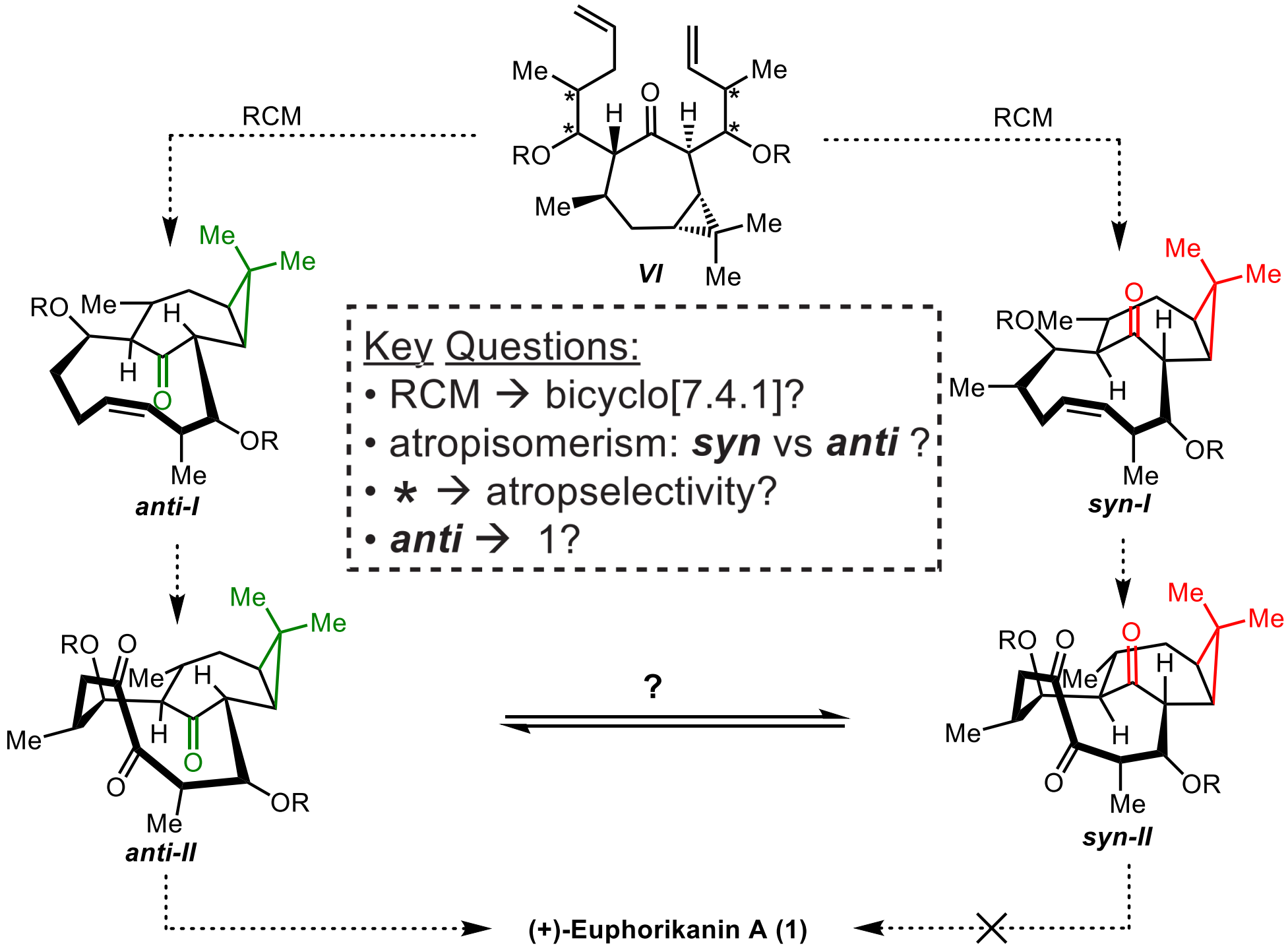
Org. Lett., **2016**, *18*, 2844.

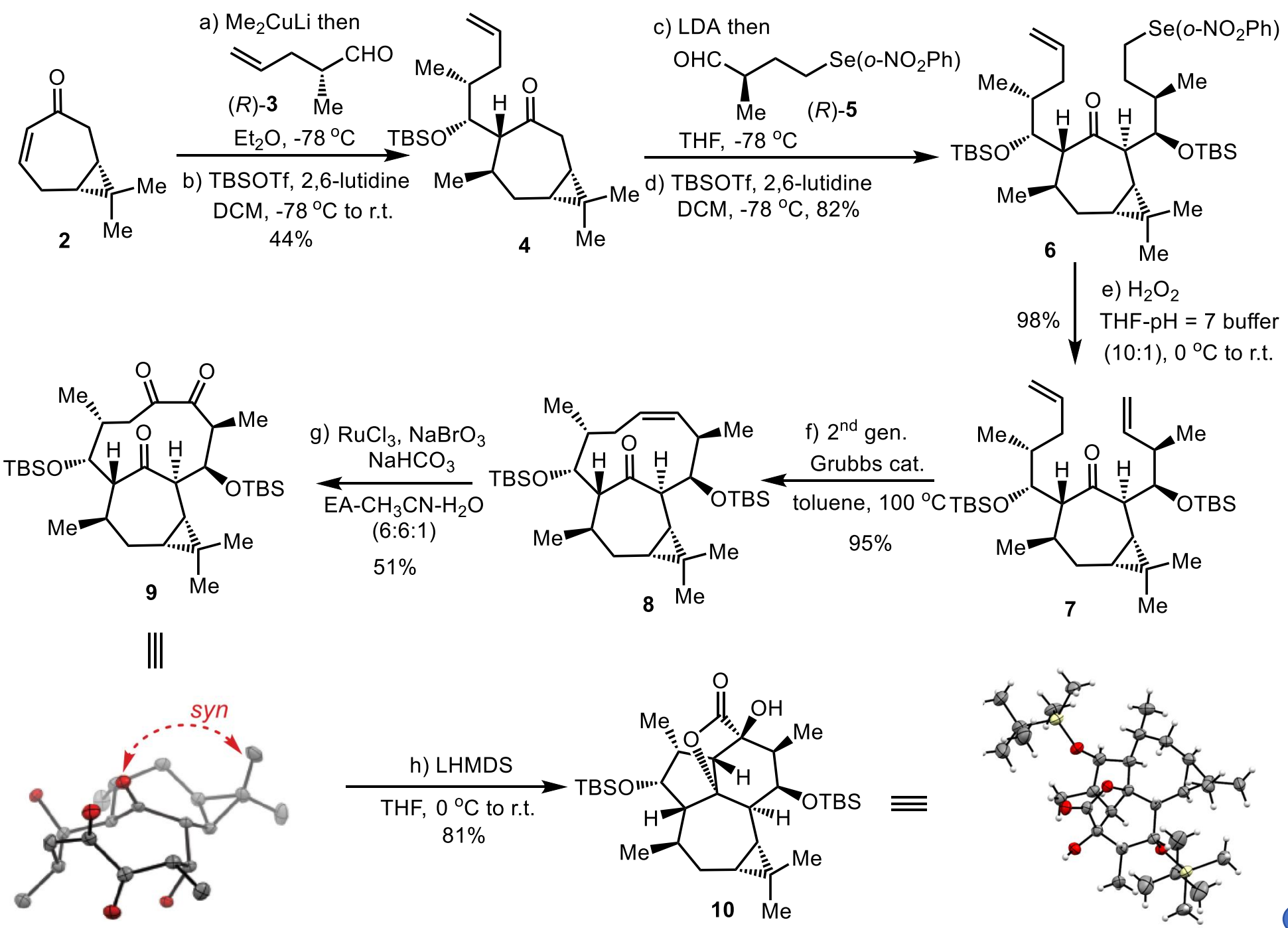


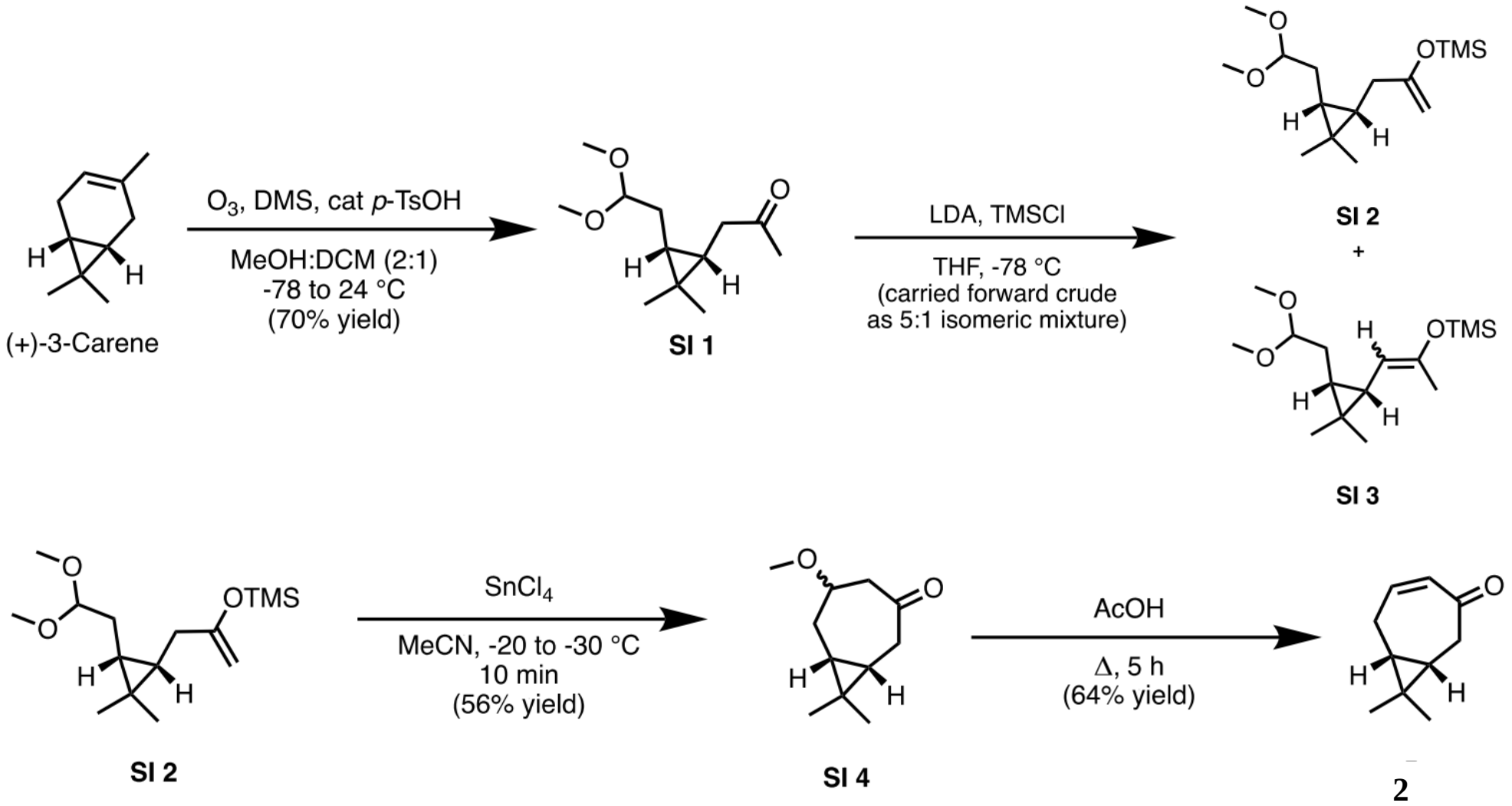
Angew. Chem. Int. Ed., **2022,** *61*, e202200576.


[O]/RCM
this work
V
II

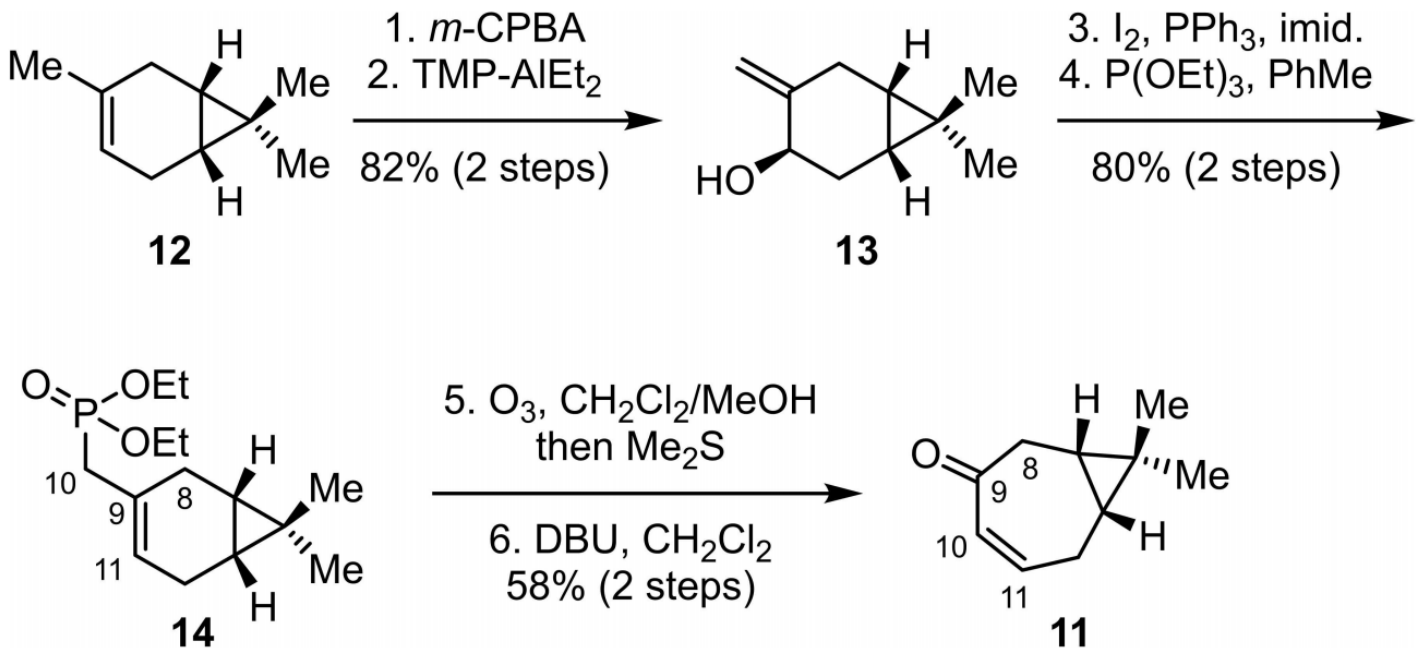

for * = S
I
II
• aldol
• hemiketal
Atropospecific Cascade
• semipinacol
III
IV


RCM
RCM
VI
anti-I
syn-I
anti-II
syn-II
Key Questions:
• RCM → bicyclo[7.4.1]?
• atropisomerism: syn vs anti ?
• * → atropselectivity?
• anti → 1?
?
(+)-Euphorikanin A (1)

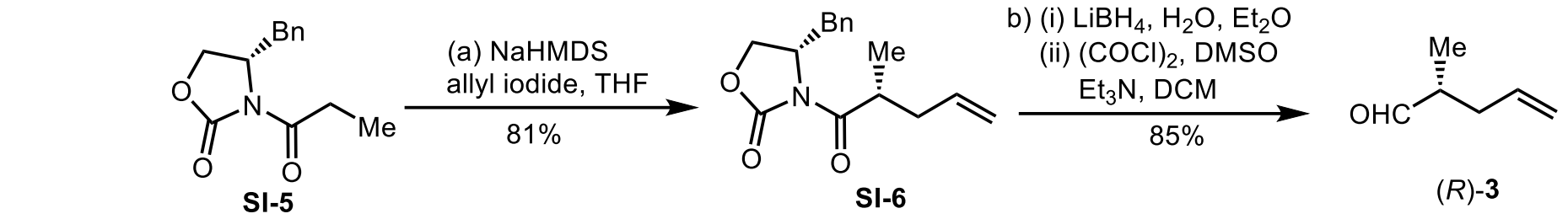

a) Me2CuLi then
(R)-3
Et2O, -78 °C
b) TBSOTf, 2,6-lutidine
DCM, -78 °C to r.t.
44%
2
4
c) LDA then
(R)-5
THF, -78 °C
d) TBSOTf, 2,6-lutidine
DCM, -78 °C, 82%
6
98%
e) H2O2
THF-pH = 7 buffer
(10:1), 0 °C to r.t.
7
f) 2nd gen.
Grubbs cat.
toluene, 100 °C
95%
8
g) RuCl3, NaBrO3
NaHCO3
EA-CH3CN-H2O
(6:6:1)
51%
9
syn
h) LHMDS
THF, 0 °C to r.t.
81%
10

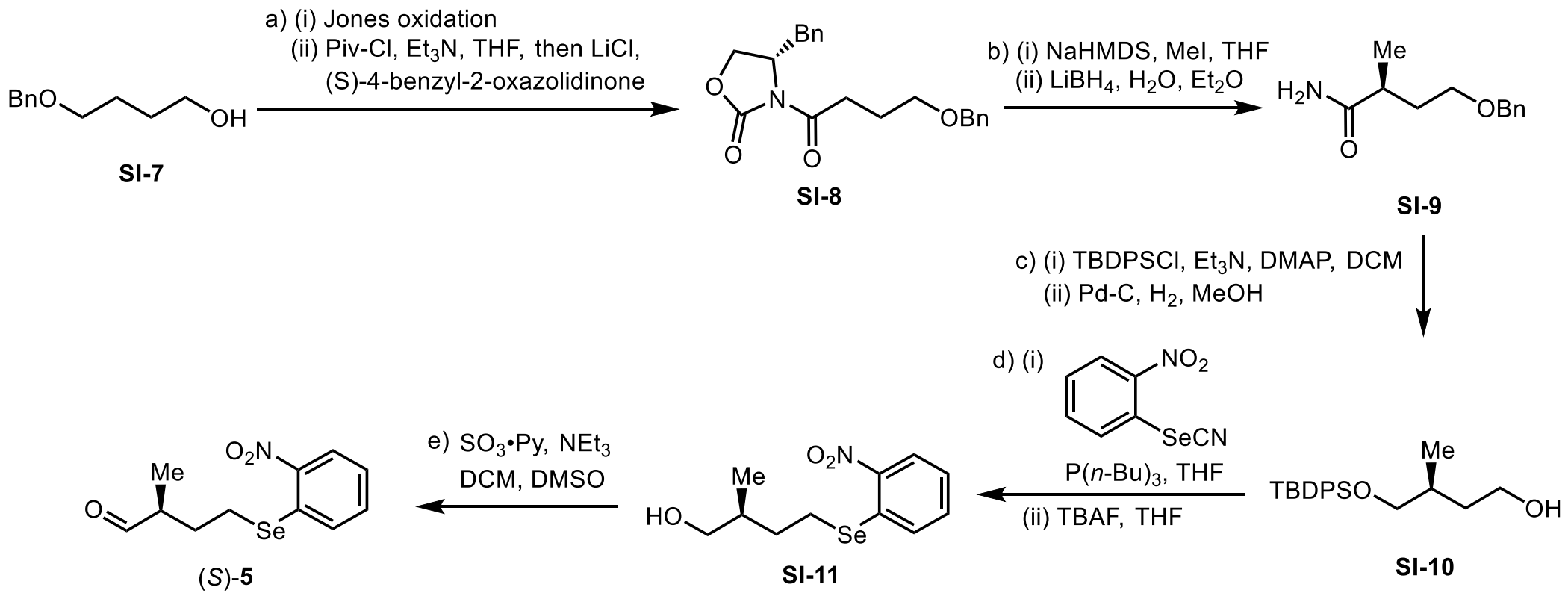


Org. Lett., **2021**, *23*, 1243.

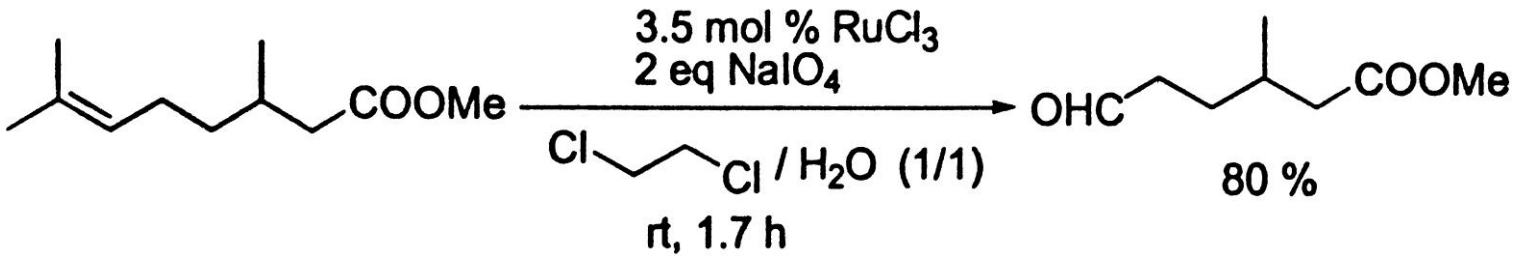


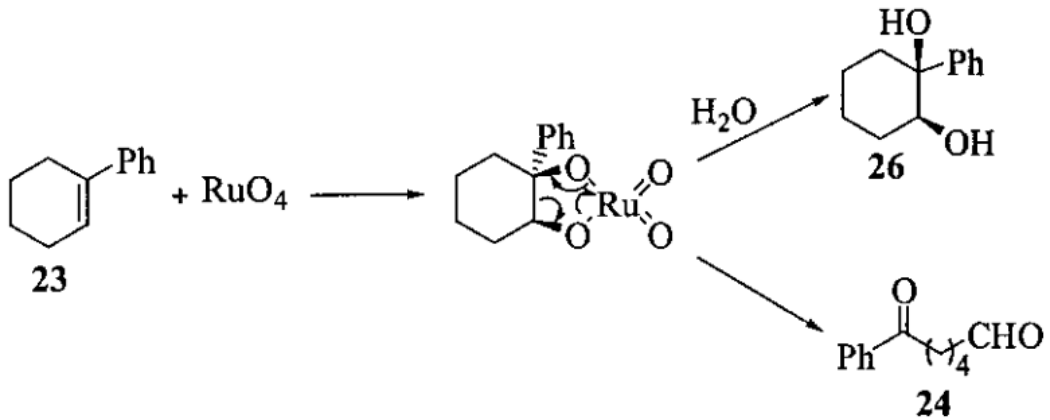
Angew. Chem. Int. Ed., **2022,** *61*, e202200576.



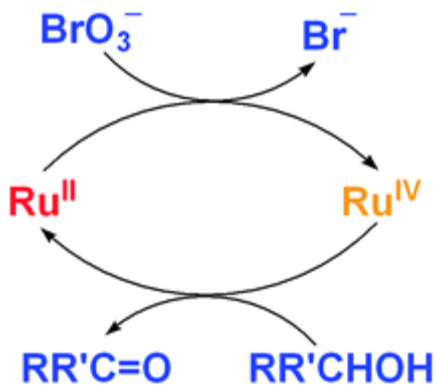


Tetrahedron Lett., **1998**, *39*, 7775.



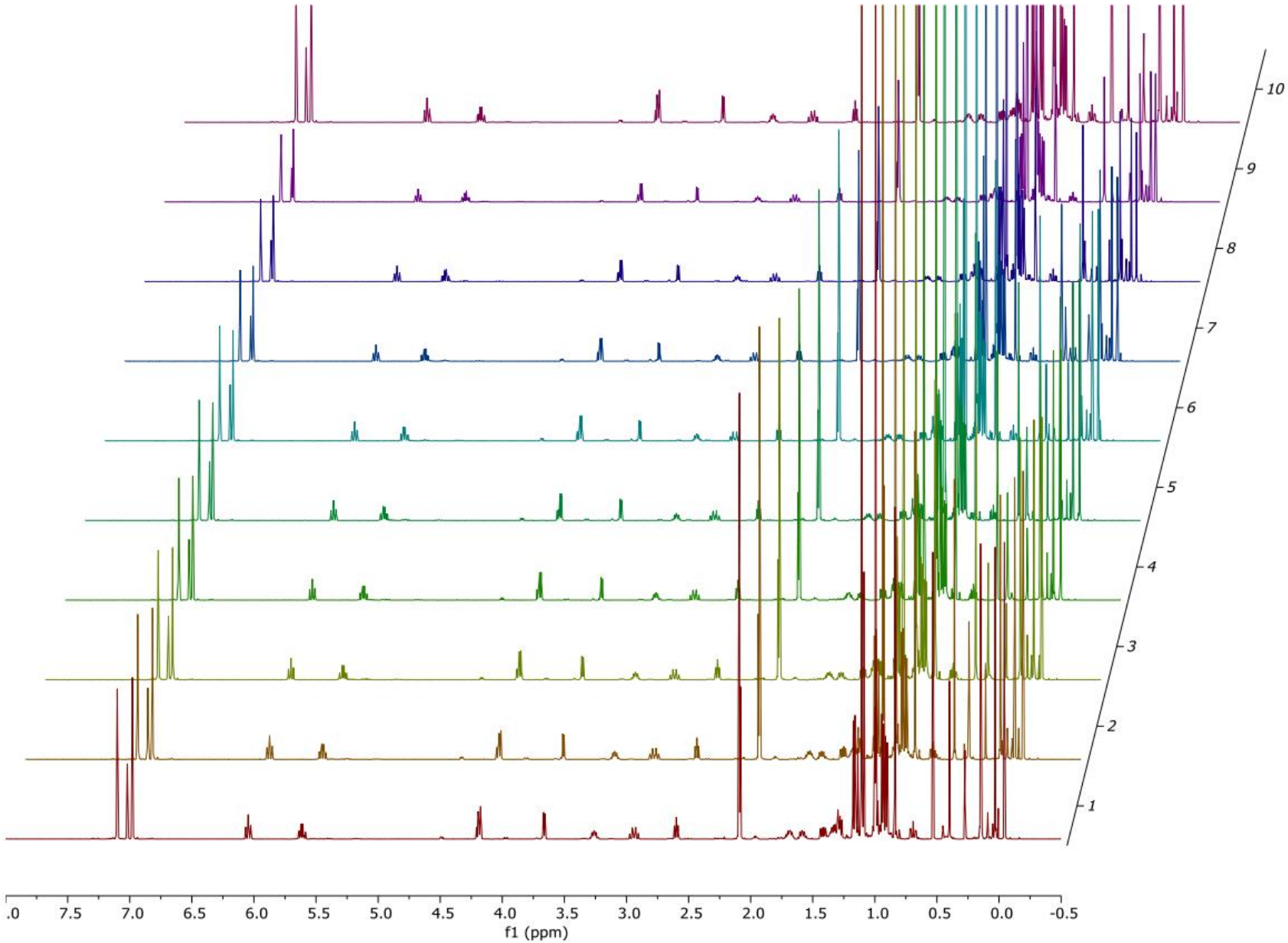


J. Org. Chem., **2001**, *66*, 4814.



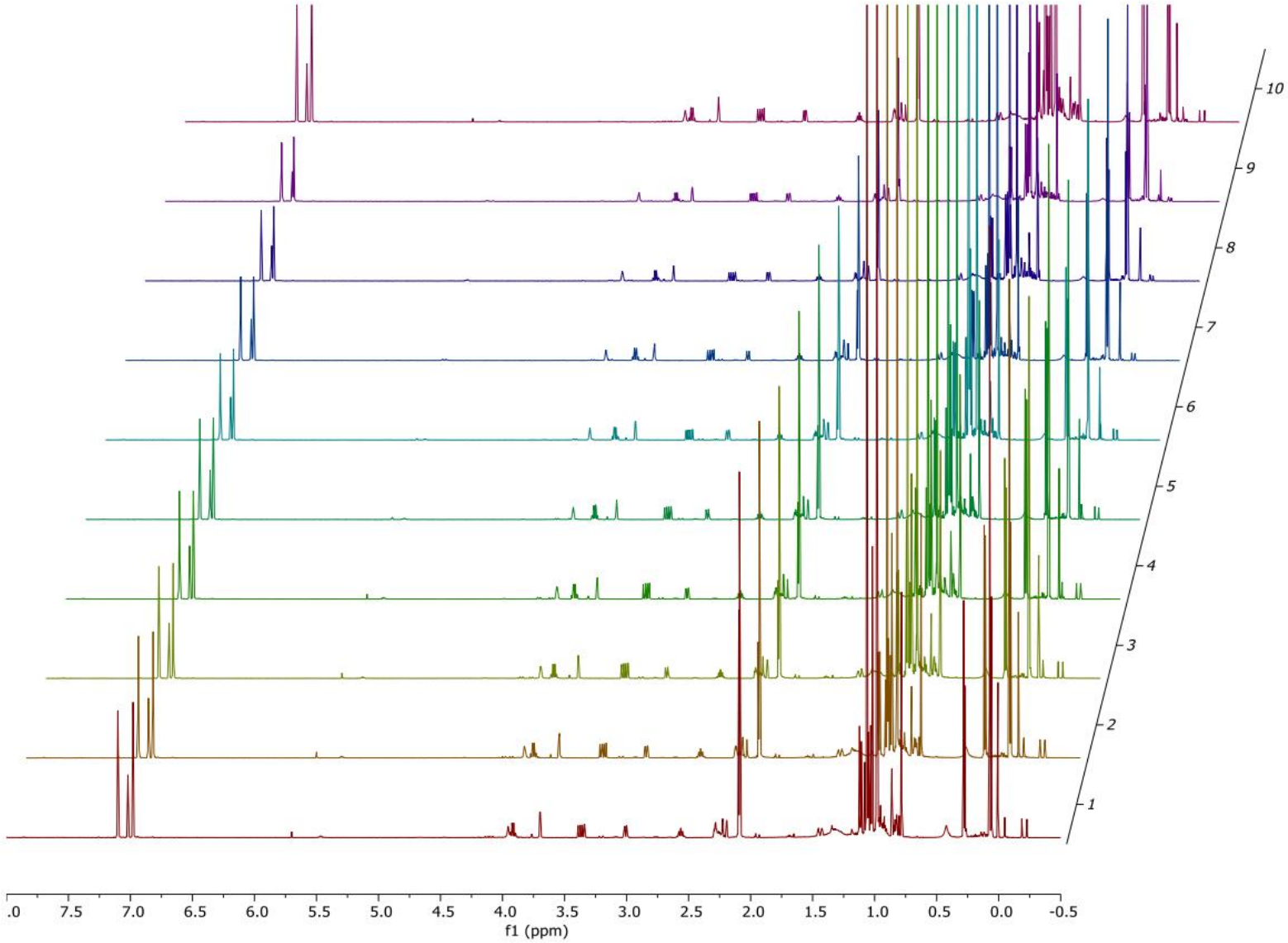
New J. Chem., **2013**, *37*, 1707.

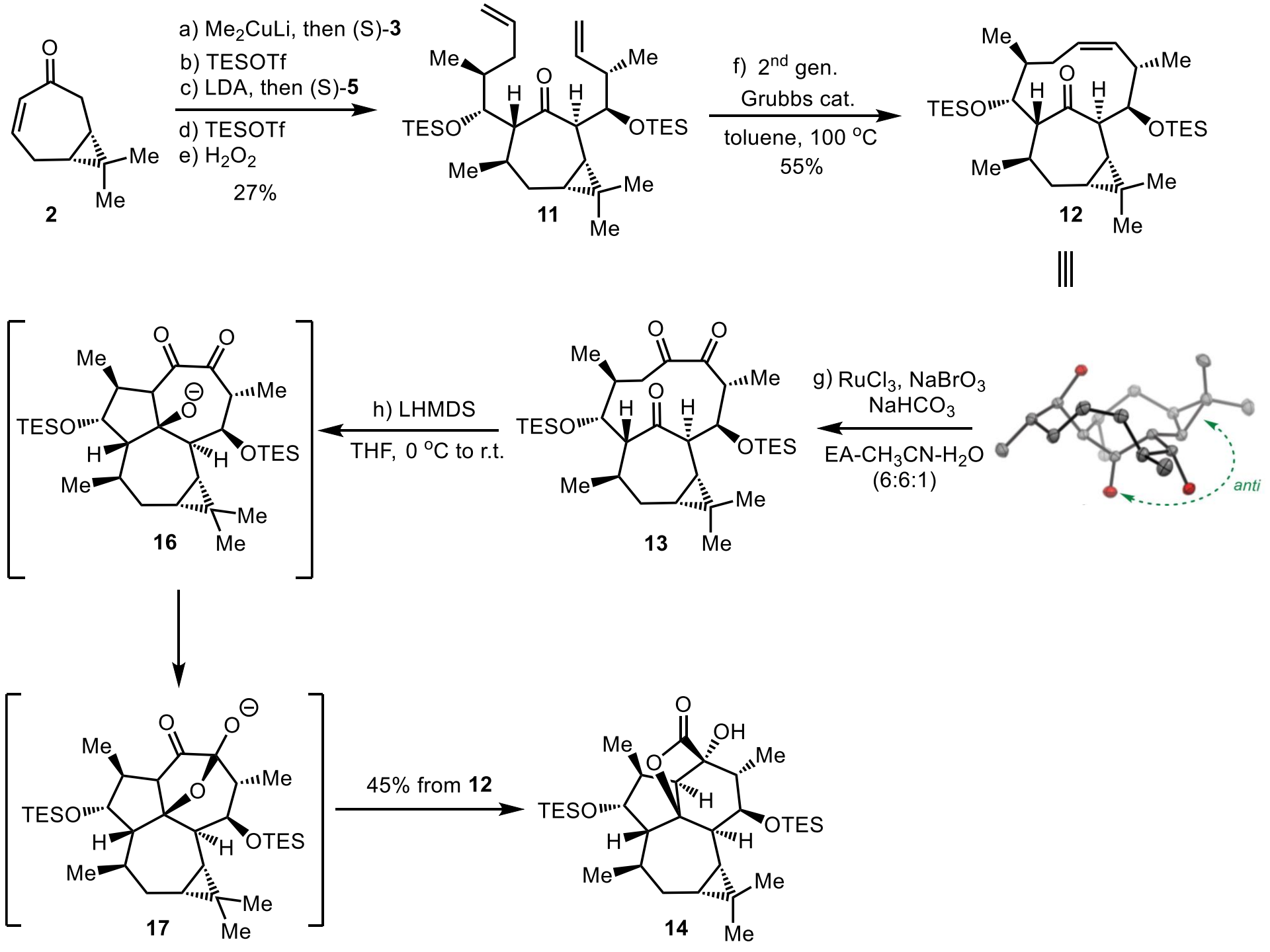
No change for **8**, except the thermal induced ppm shift, was observed during the various temperature experiments.

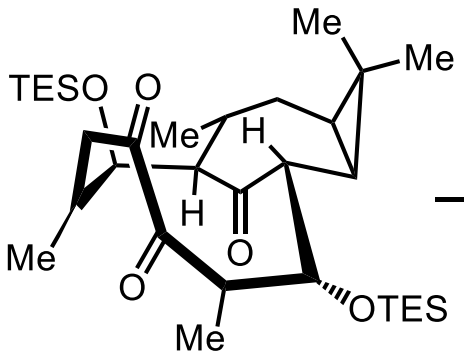


No change for **9**, except the thermal induced ppm shift was observed during the various temperature experiments.

When **9** was heated to higher temperatures, it started to undergo transannular aldol addition and slow decomposition.

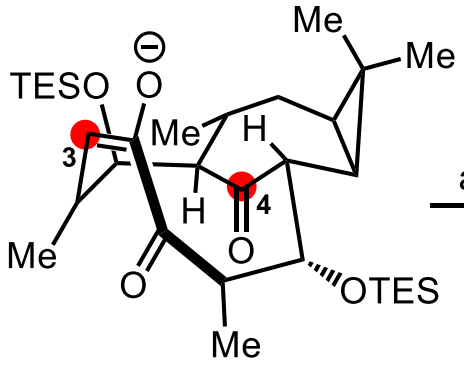



a) Me2CuLi, then (S)-3
b) TESOTf
c) LDA, then (S)-5
d) TESOTf
e) H2O2
27%
2
11
f) 2nd gen.
Grubbs cat.
toluene, 100 °C
55%
12
g) RuCl3, NaBrO3
NaHCO3
EA-CH3CN-H2O
(6:6:1)
13
anti
h) LHMDS
THF, 0 °C to r.t.
16
17
45% from 12
14



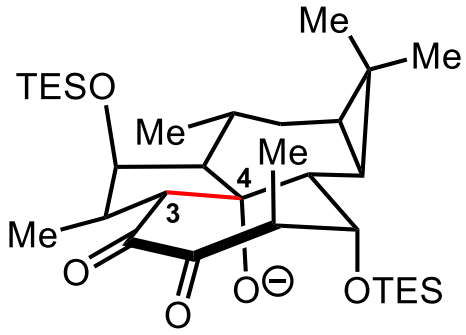
13

enolization



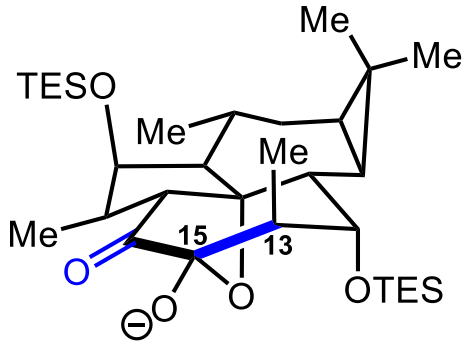
15

transanular
aldol additon



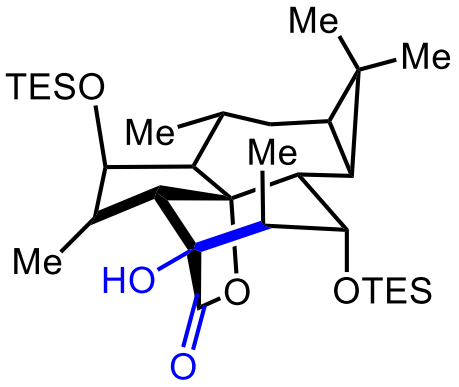
16

hemiketal
formation



17

semipinacol
rearrangement



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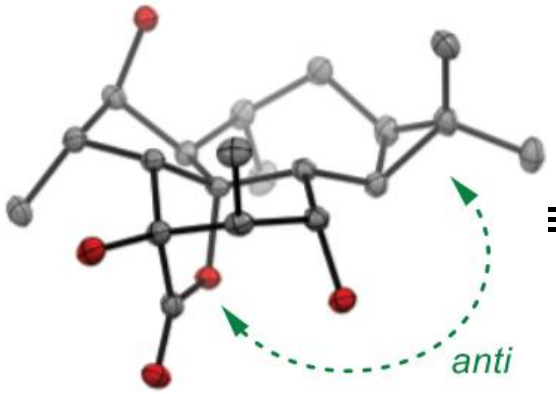
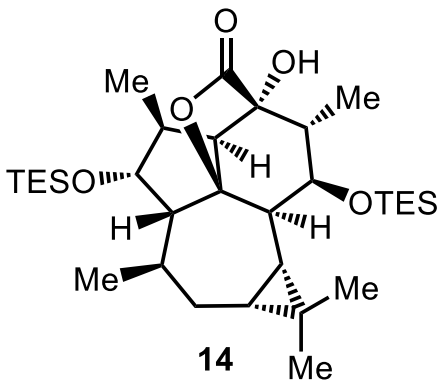


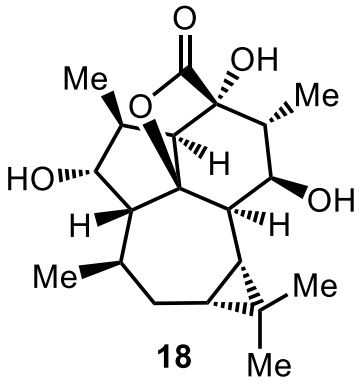


14

a) TBAF

THF, 0 °C to r.t.

99%

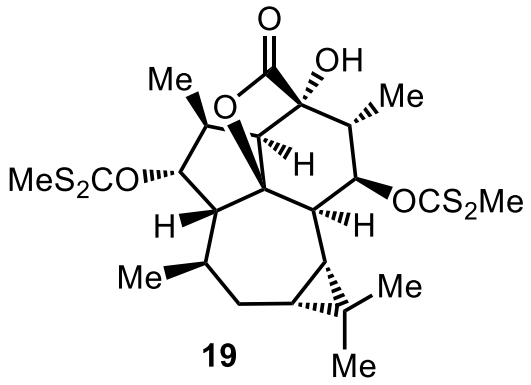


18

b) DBU, CS_2, DMF

then MeI

91%



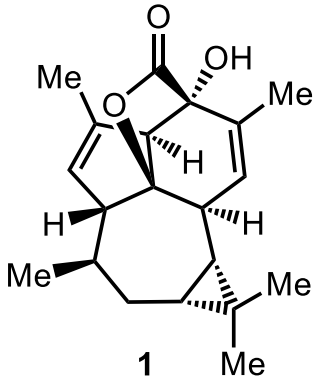
19

c) Δ FVP

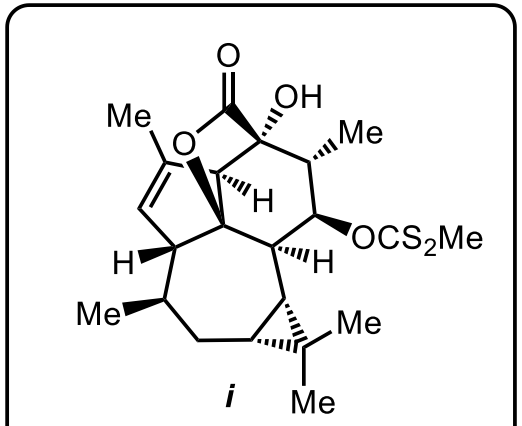
bis-methylxanthated

pyrrolysis

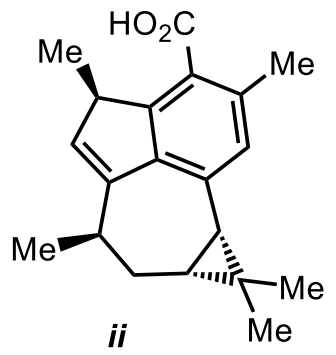
68%



1



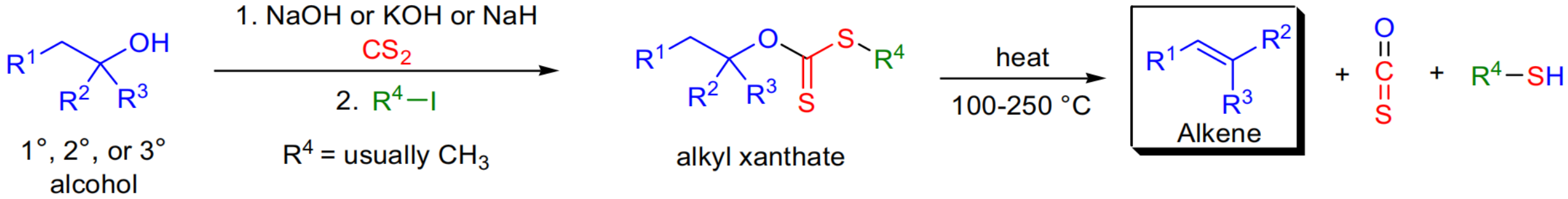
i



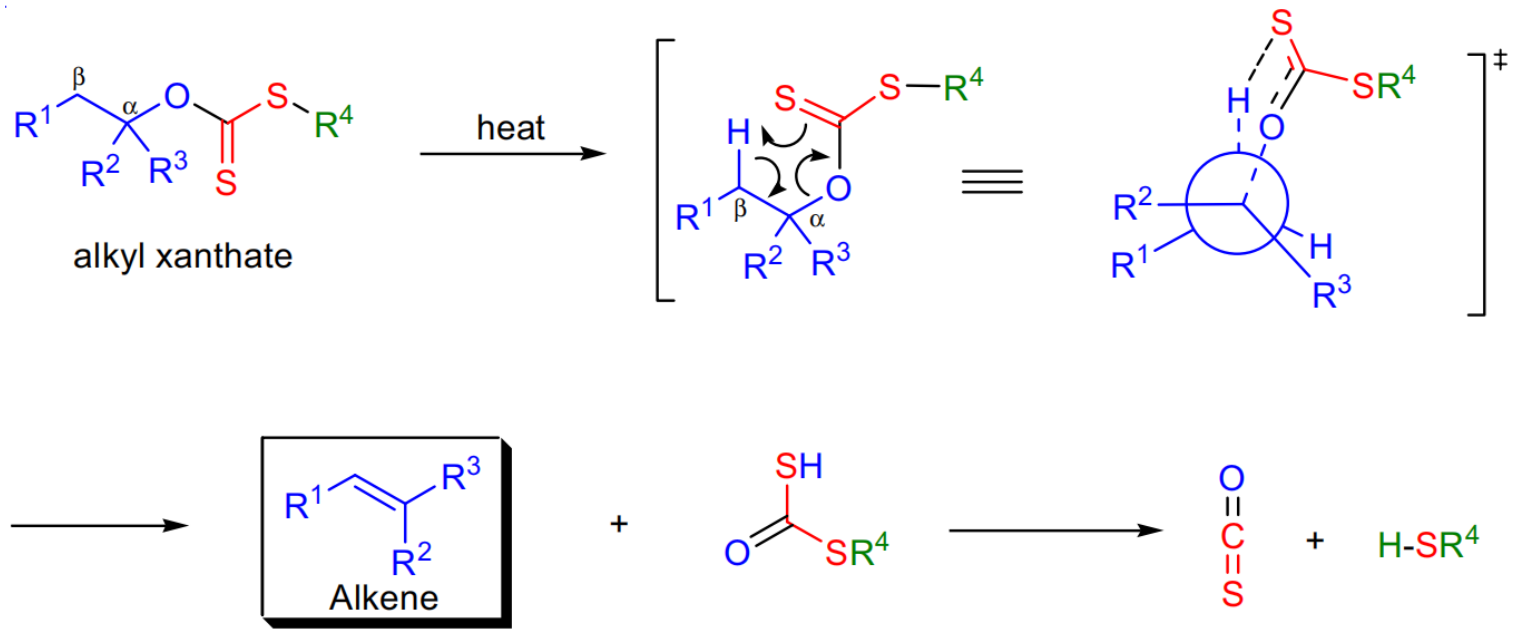
ii

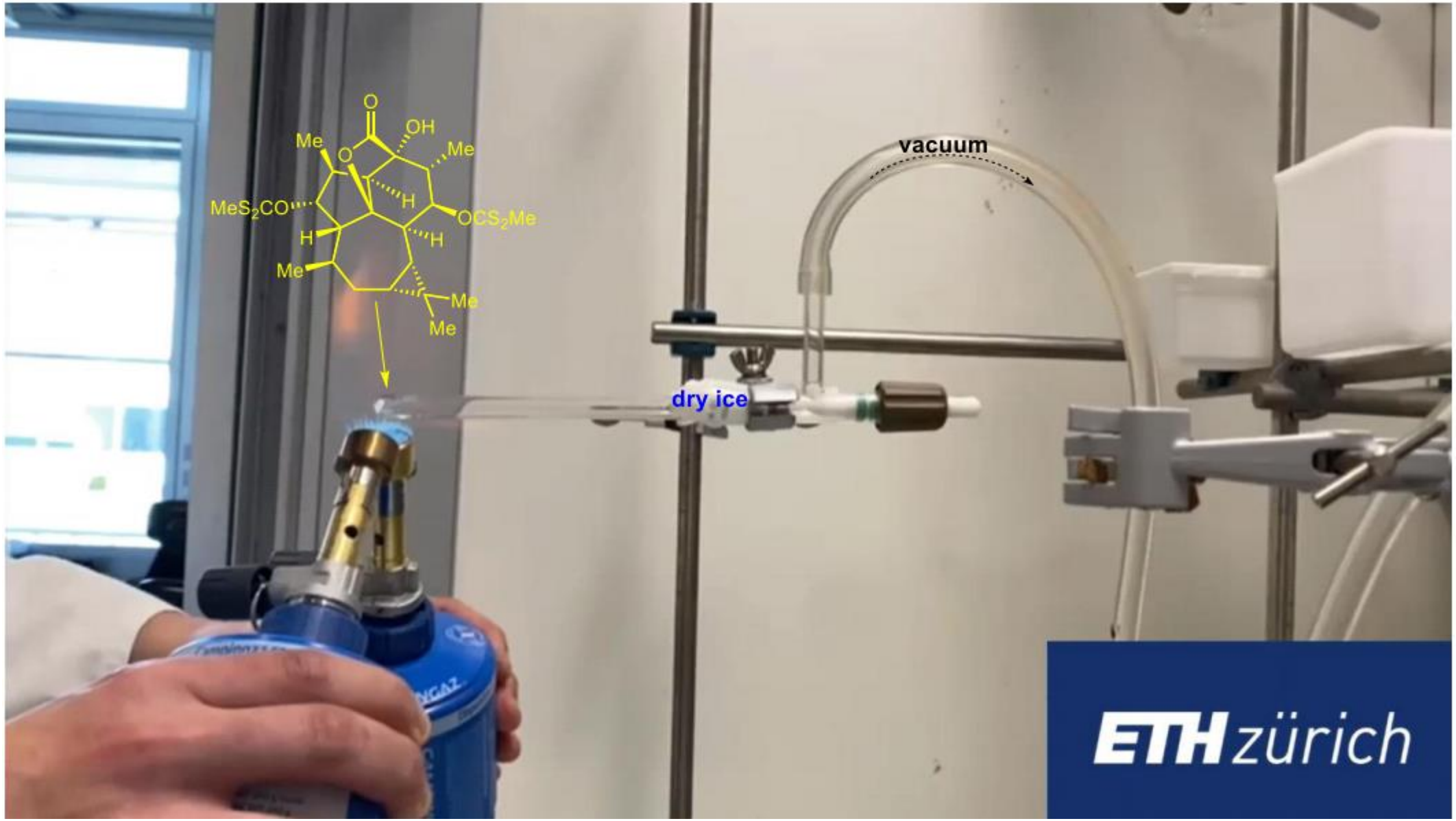
CHUGAEV ELIMINATION REACTION
(XANTHATE ESTER PYROLYSIS)

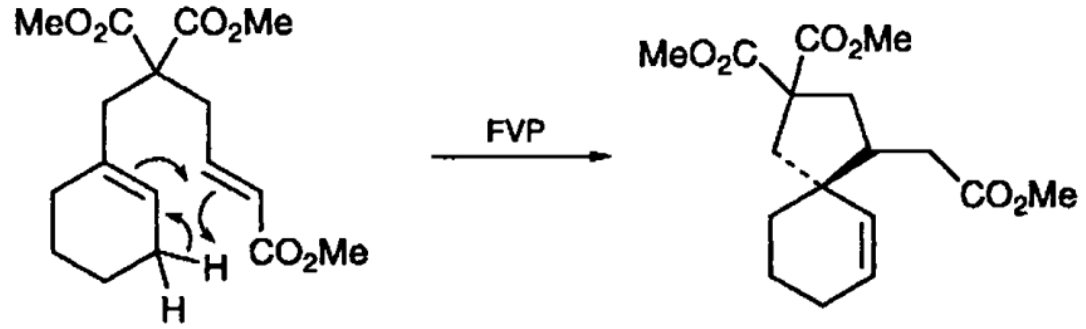
(References are on page 559)



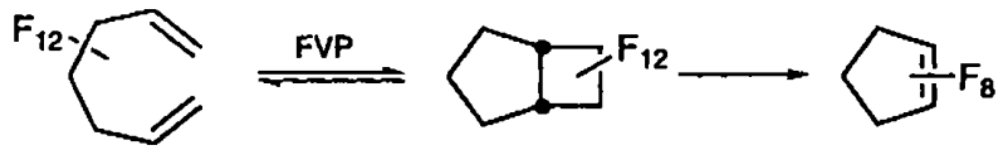
Mechanism:




O
OH
Me
Me
O
H
MeS2CO
OCS2Me
H
H
Me
Me
Me
vacuum
dry ice
ETH zürich

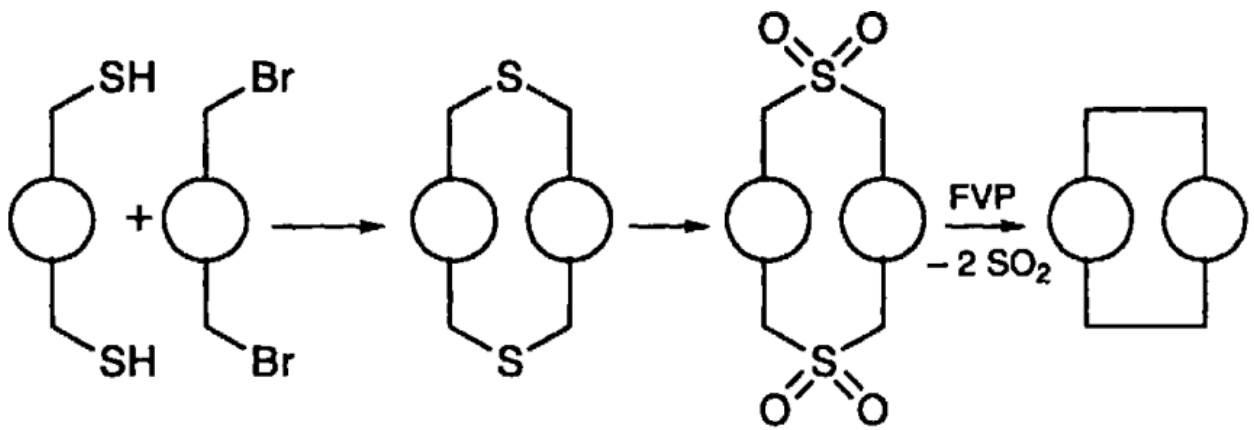


Scheme 1



1 **2** **3**

Scheme 2



Scheme 3

Org. Syn., **1996**, *3*, 373.