

# Total Synthesis and Target Identification of the Curcusone Diterpenes

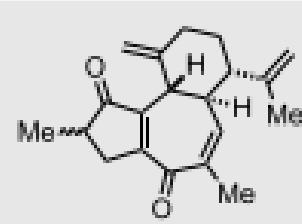
Chengsen Cui,<sup>\$</sup> Brendan G. Dwyer,<sup>\$</sup> Chang Liu, Daniel Abegg, Zhong-Jian Cai, Dominic G. Hoch, Xianglin Yin, Nan Qiu, Jie-Qing Liu, Alexander Adibekian,\* and Mingji Dai\*



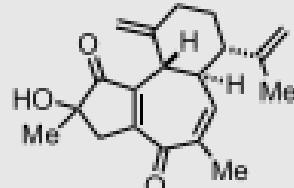
Cite This: *J. Am. Chem. Soc.* 2021, 143, 4379–4386



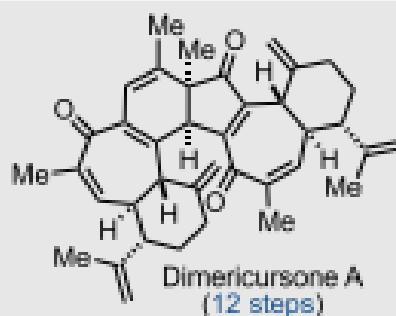
Read Online



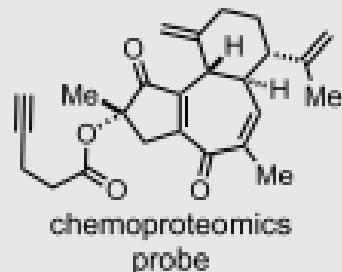
Curcusone A (2S)  
Curcusone B (2R)  
(9 steps)



Curcusone C (2R)  
Curcusone D (2S)  
(10 steps)



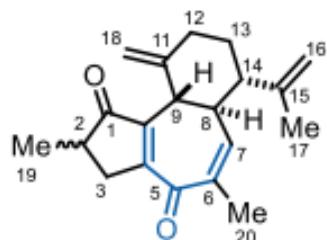
Dimericurusone A  
(12 steps)



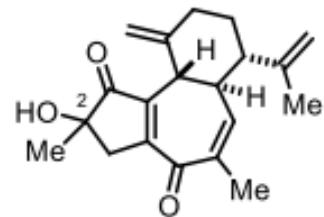
chemoproteomics  
probe

## BRCA1-associated ATM activator 1 (BRAT1)

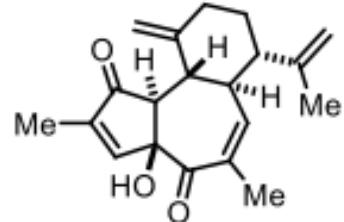
- Target undruggable oncogenic protein
- Inhibit cancer cell proliferation
- Suppress cancer cell migration
- Impair DNA damage response
- Potentiate activity of etoposide



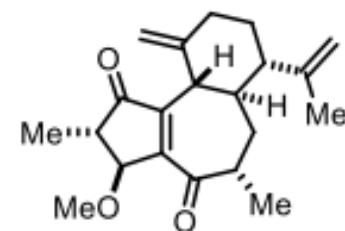
anti cancer cell proliferation and antimetastatic



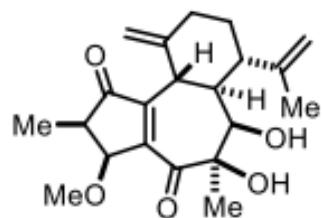
Curcusone C (**1c**: 2*R*)  
Curcusone D (**1d**: 2*S*)



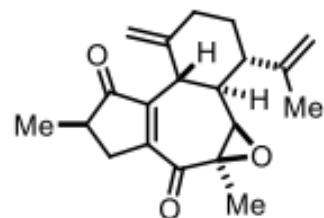
Curcusone E (**1e**)



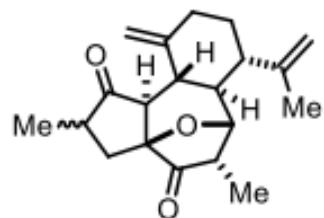
Curcusone F (**1f**)



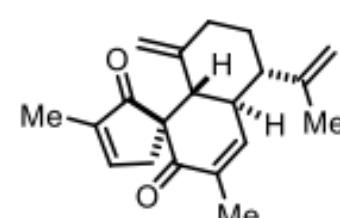
Curcusone G (**1g**)



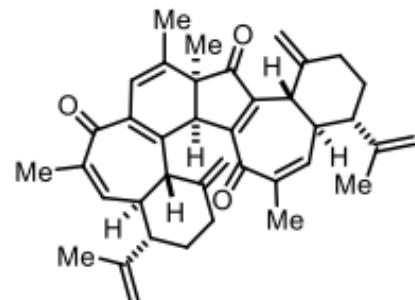
Curcusone H (**1h**)



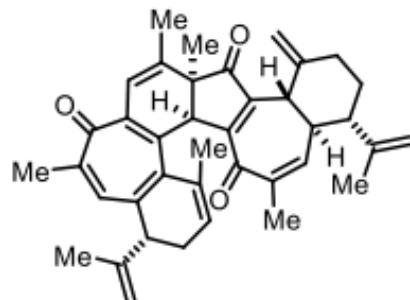
Curcusone I (**1i**: 2*S*)  
Curcusone J (**1j**: 2*R*)  
putative structures



Spirocurcasone (**3**)

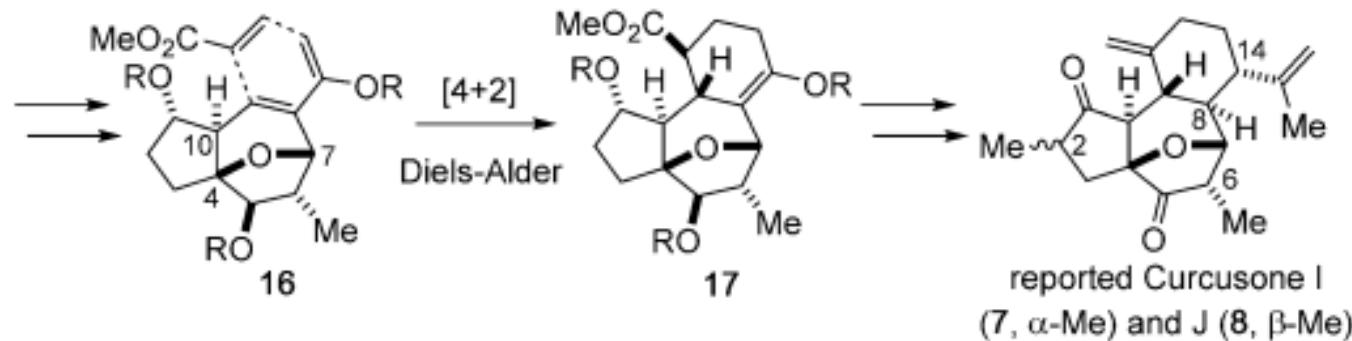
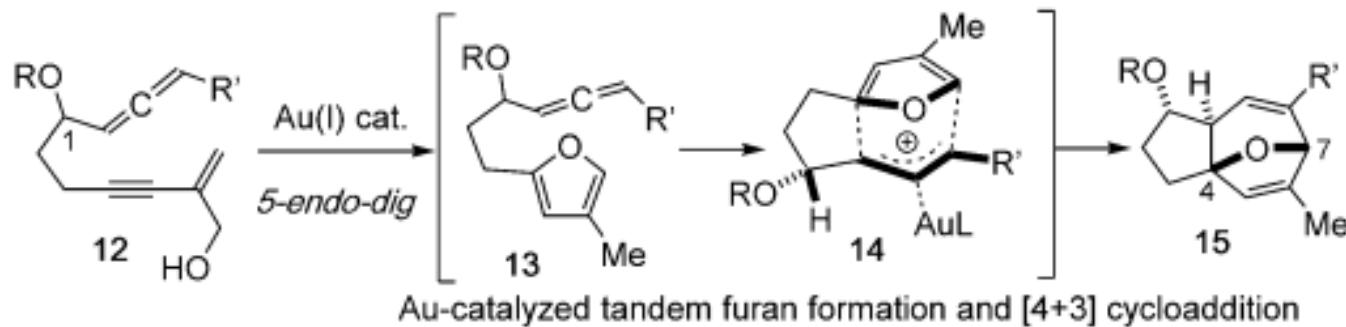
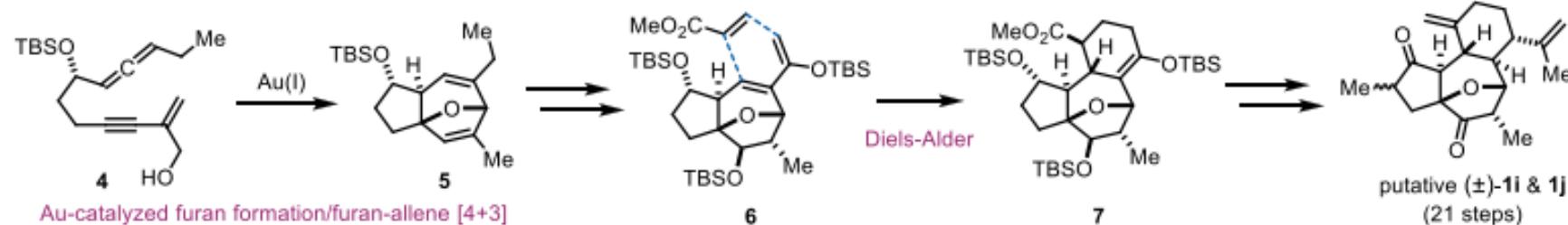


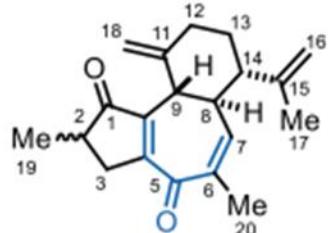
Dimericurcione A (**2a**)



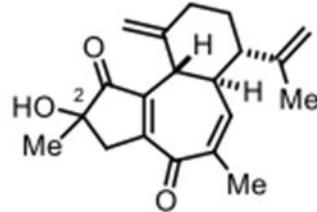
Dimericurcione B (**2b**)

## B Our Previous Total Syntheses of Curcusones I and J

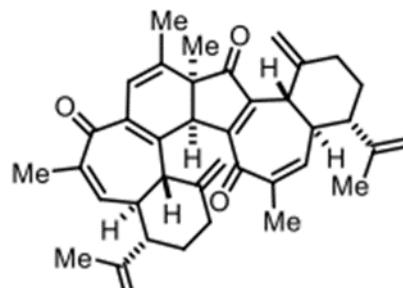




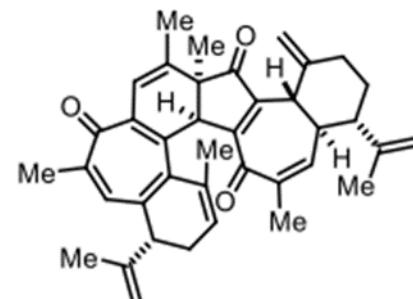
Curcusone A (**1a**: 2*S*)  
Curcusone B (**1b**: 2*R*)



Curcusone C (**1c**: 2*R*)  
Curcusone D (**1d**: 2*S*)



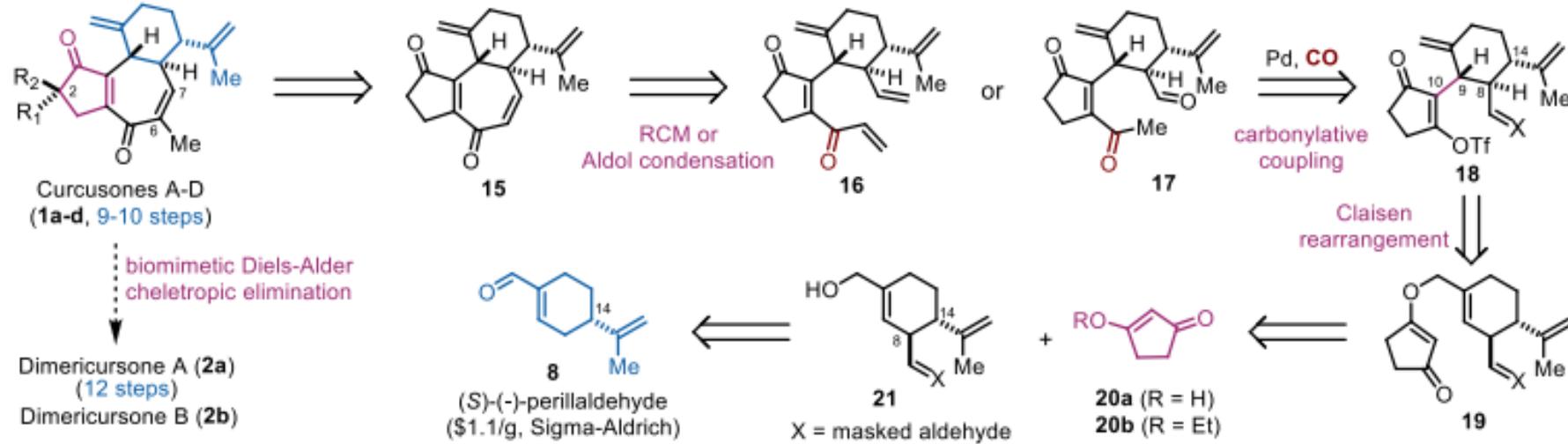
Dimericurcione A (**2a**)

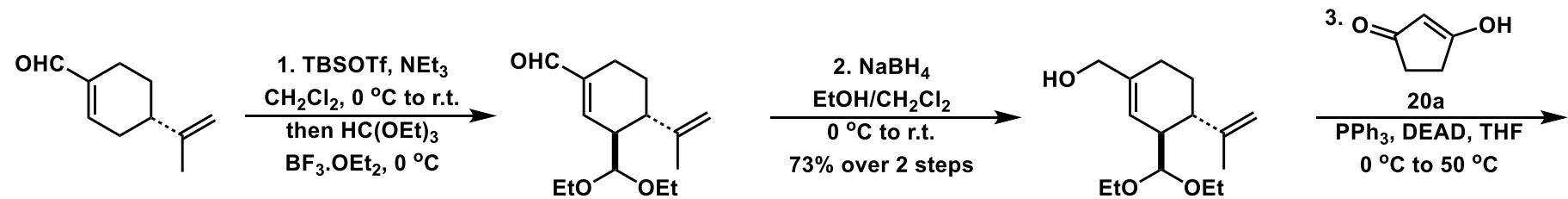


Dimericurcione B (**2b**)

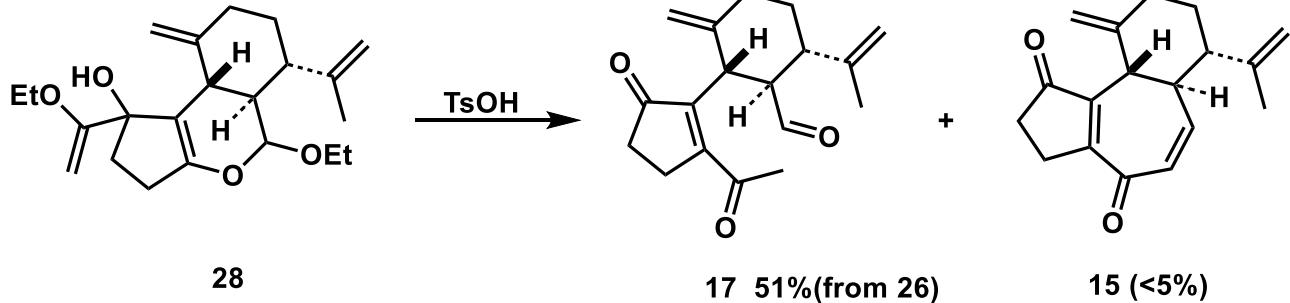
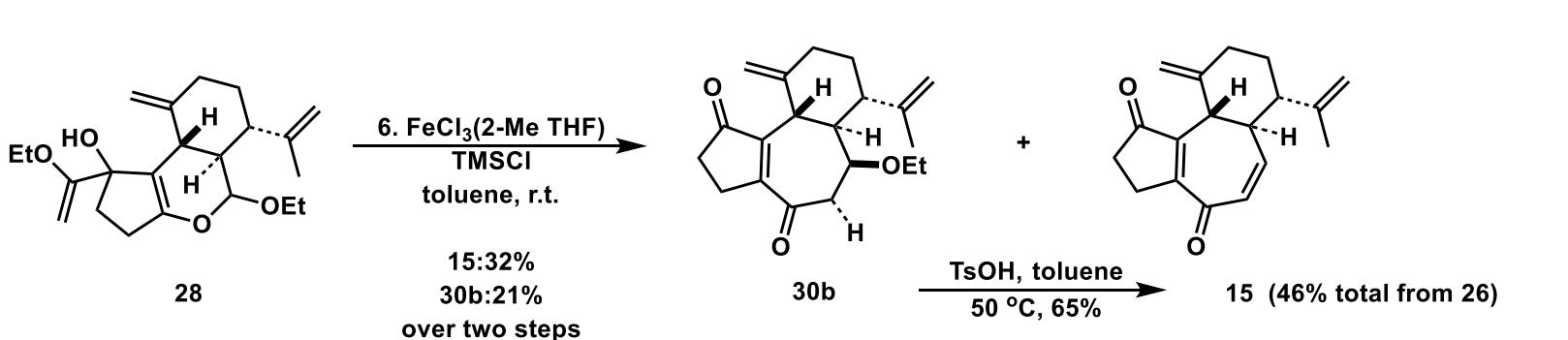
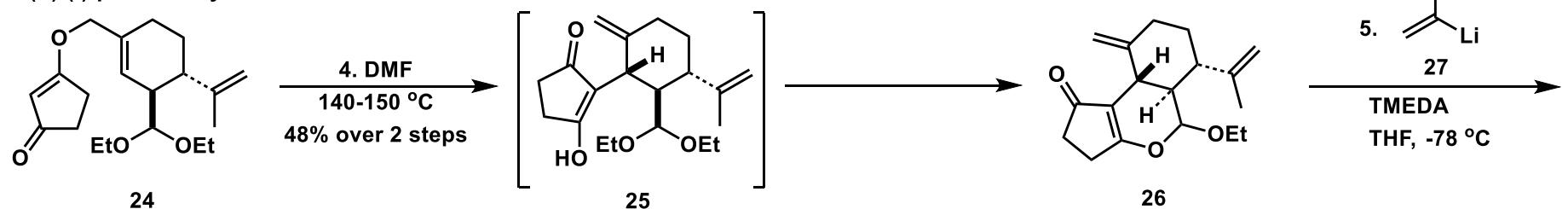
anti cancer cell proliferation and antimetastatic

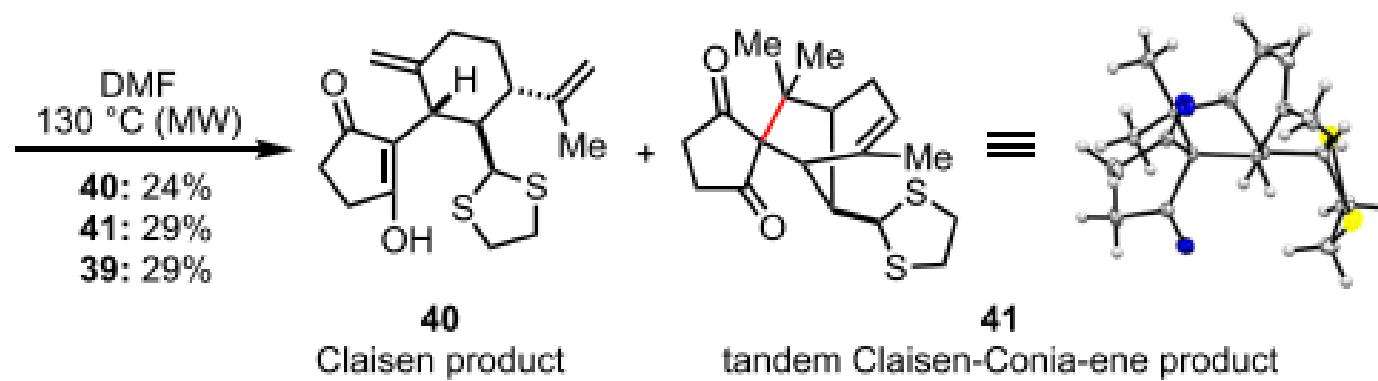
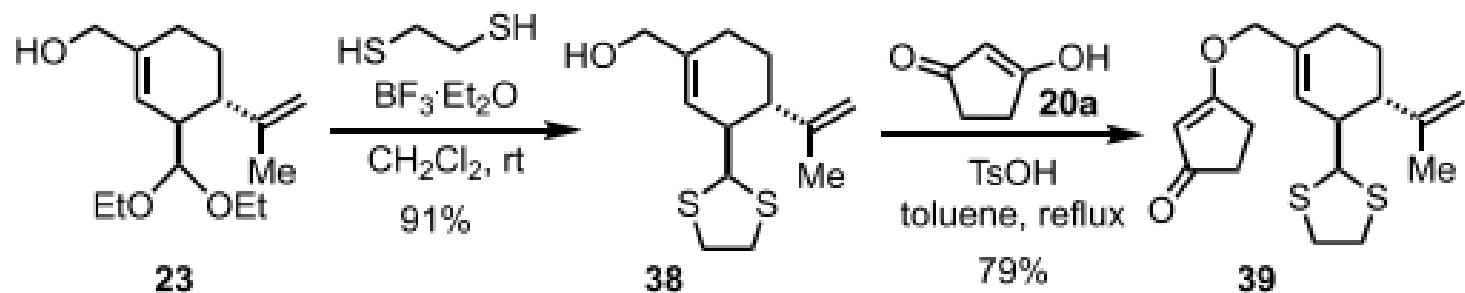
#### D Retrosynthetic Analysis



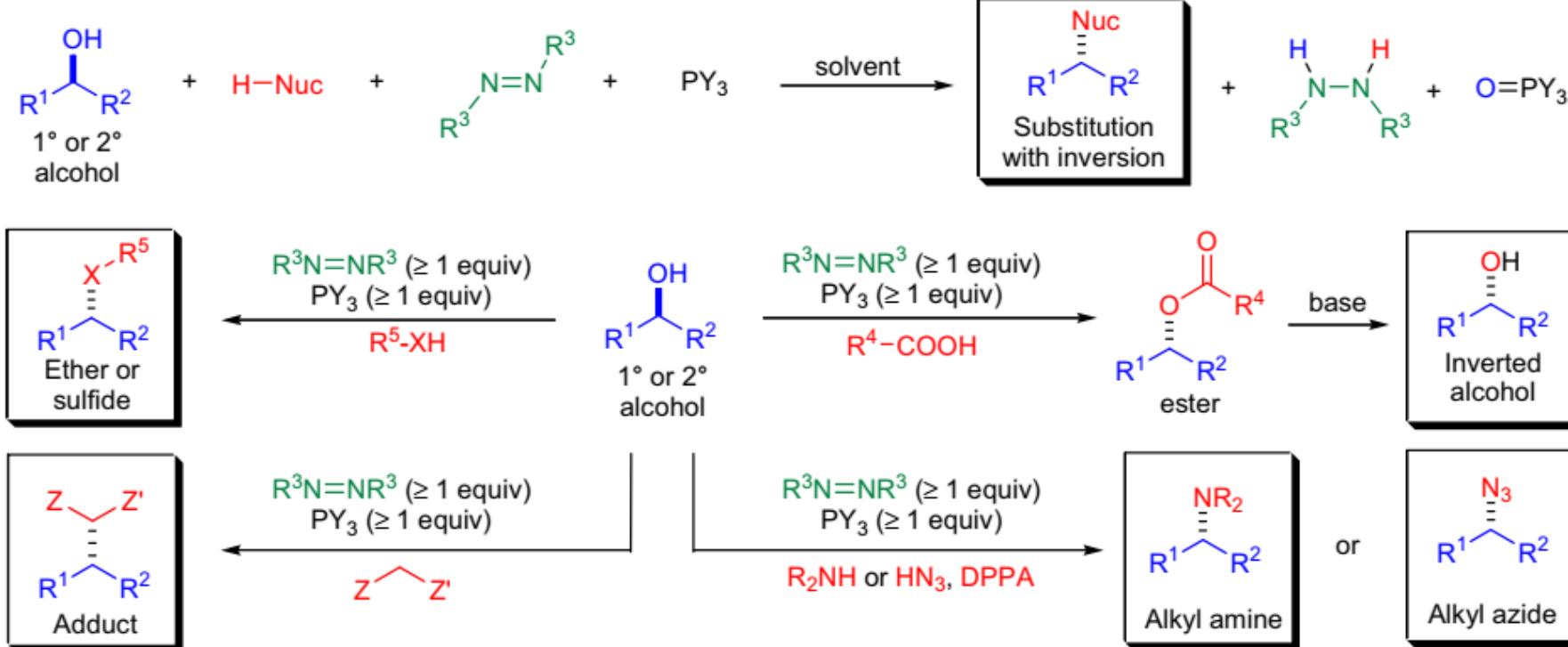


8  
(S)-(-)-perillaldehyde

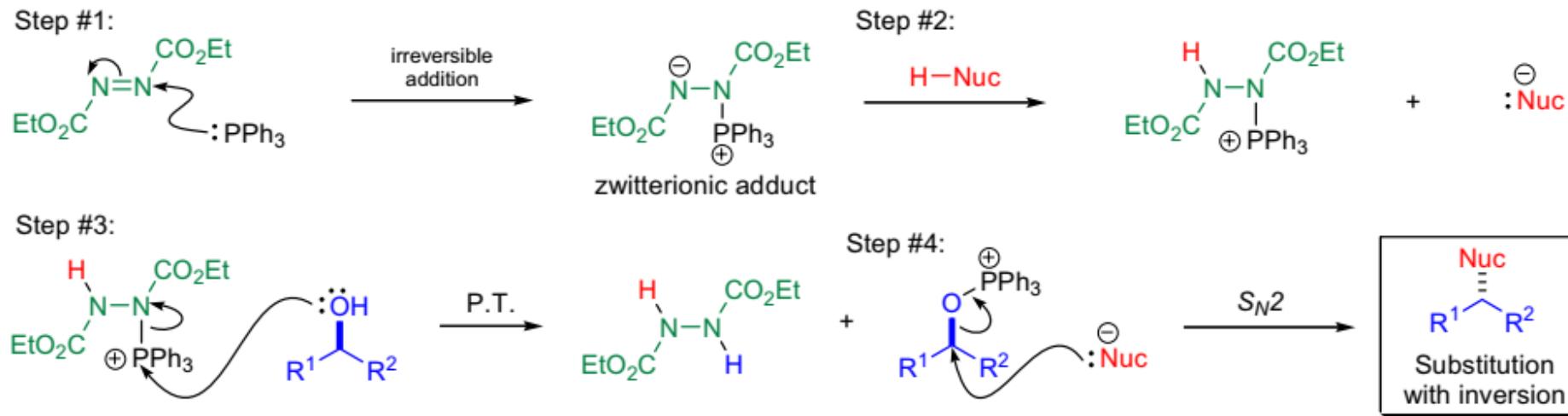




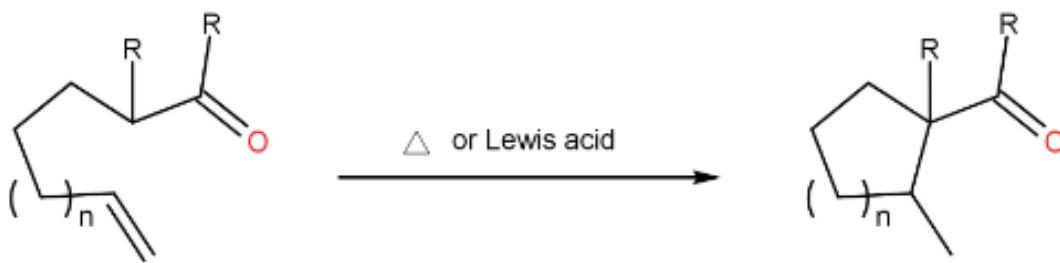
# MITSUNOBU REACTION



**Mechanism:**<sup>25-45</sup>



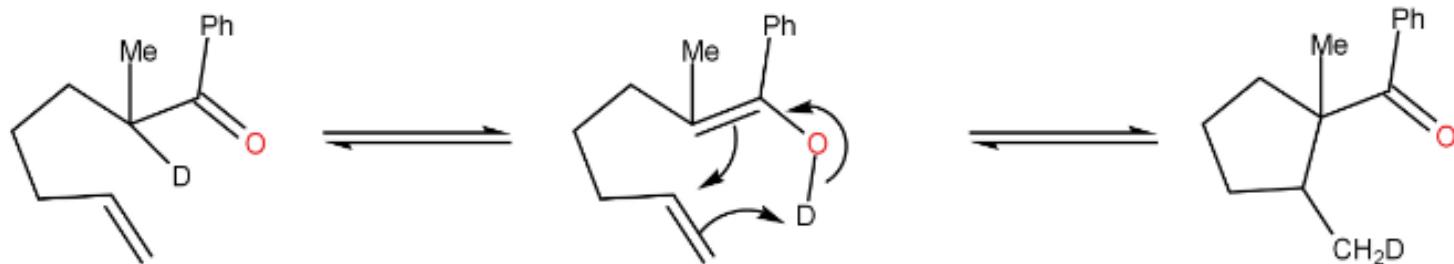
## Conia-Ene环化反应

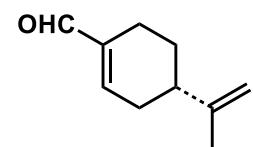


Conia-ene环化反应是在加热或者路易斯酸的催化下，烯酮和炔酮等不饱和羰基化合物所发生的分子内环化反应，是一种重要的合成环状化合物的方法。

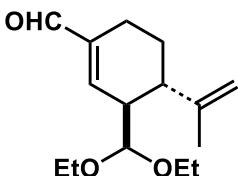
## Conia-Ene环化反应机理

反应的机理是酮烯醇化，烯醇氢迁移形成C-C键，因此Conia-Ene反应是分子间Ene反应的分子内变体。Conia-ene反应适用于合成五元和六元环状化合物。含有端烯和端炔的环酮可以用于制备桥环、螺环和稠环化合物。

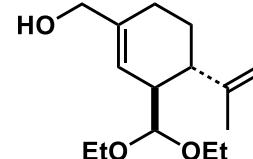




1. TBSOTf, NEt<sub>3</sub>  
CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to r.t.  
then HC(OEt)<sub>3</sub>  
BF<sub>3</sub>·OEt<sub>2</sub>, 0 °C

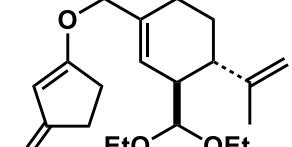


2. NaBH<sub>4</sub>  
EtOH/CH<sub>2</sub>Cl<sub>2</sub>  
0 °C to r.t.  
73% over 2 steps

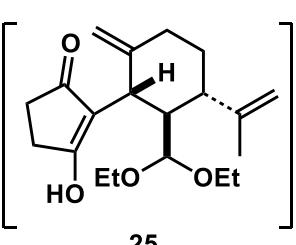


3. O=Cyclopentadiene-1,4-diol  
20a  
PPh<sub>3</sub>, DEAD, THF  
0 °C to 50 °C

8  
(S)-(-)-perillaldehyde



4. DMF  
140-150 °C  
48% over 2 steps

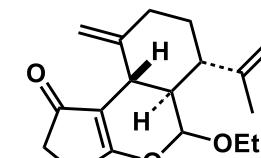


25

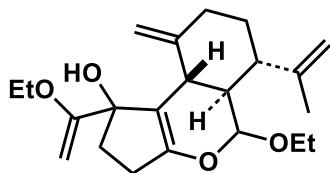
23

5. EtO-C≡Li  
27

TMEDA  
THF, -78 °C



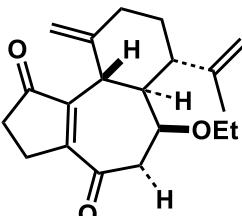
26



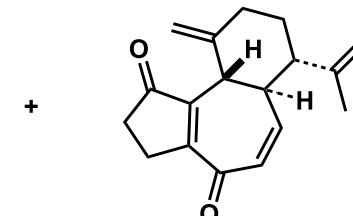
28

6. FeCl<sub>3</sub>(2-Me THF)  
TMSCl  
toluene, r.t.

15:32%  
30b:21%  
over two steps

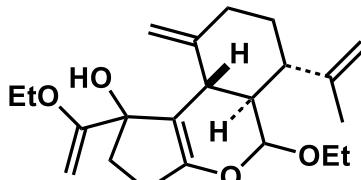


30b

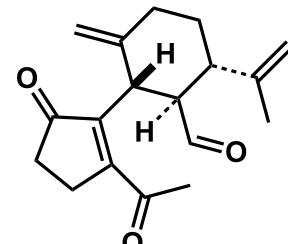


TsOH, toluene  
50 °C, 65%

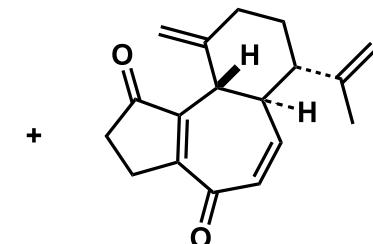
15 (46% total from 26)



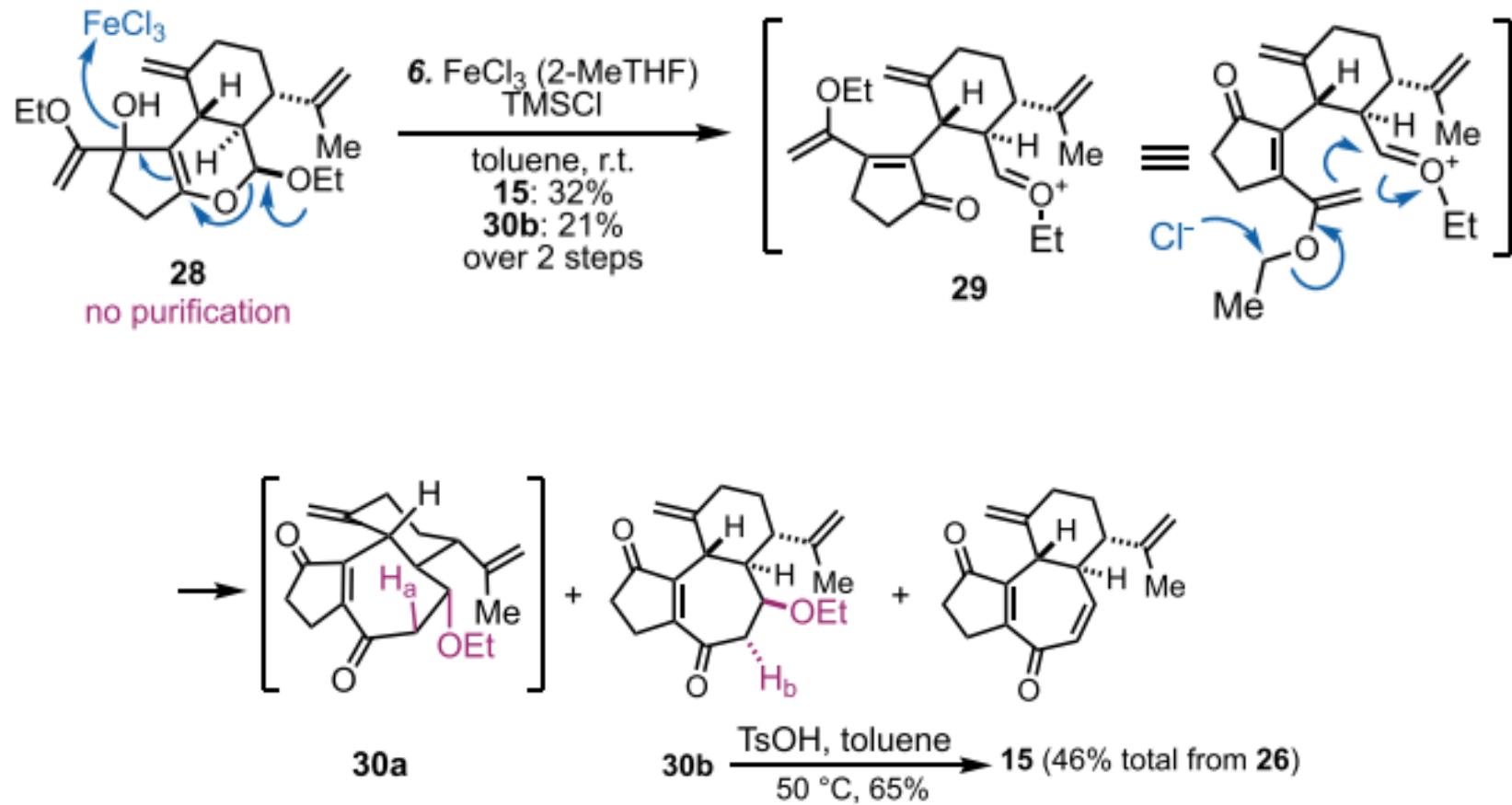
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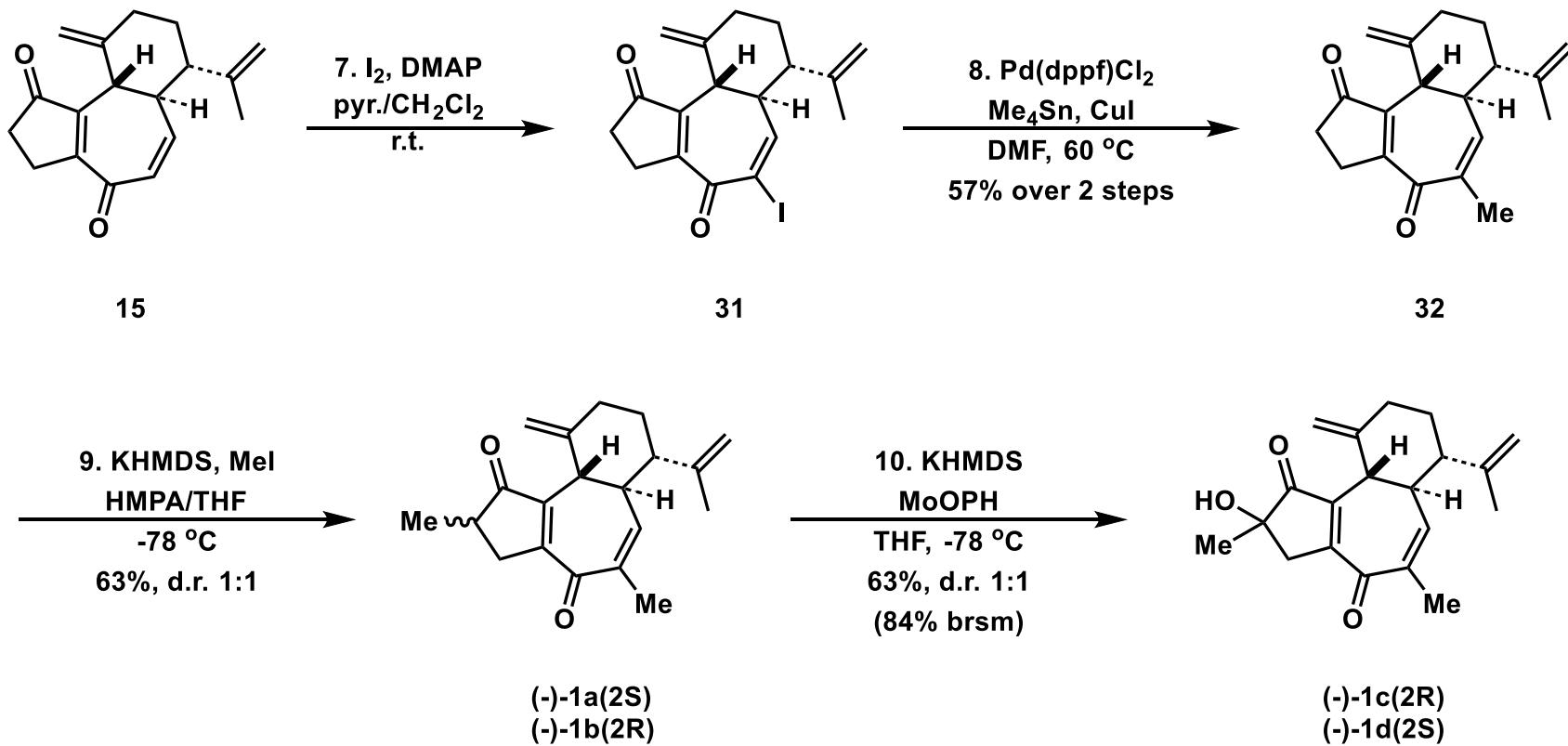


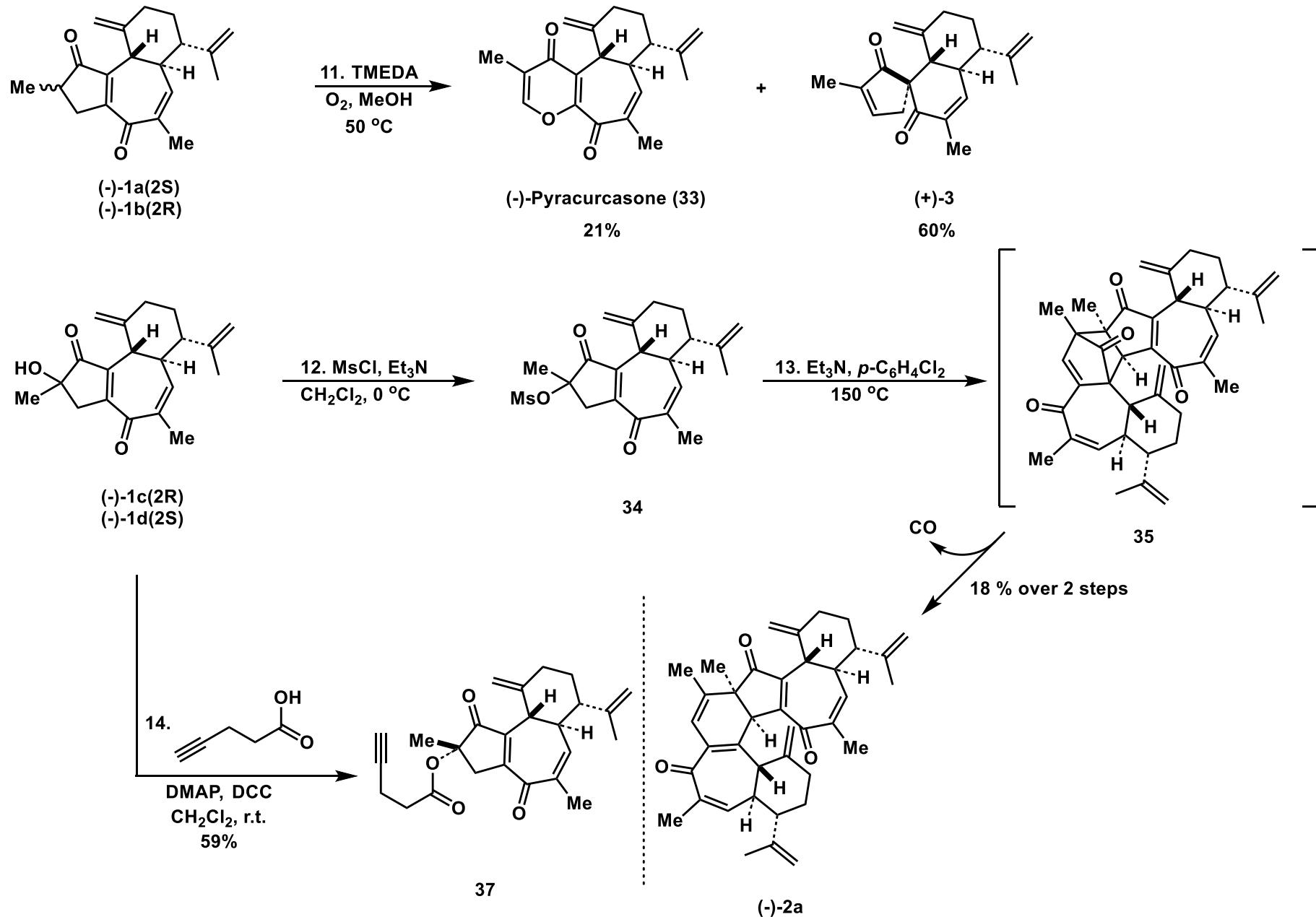
17 51%(from 26)



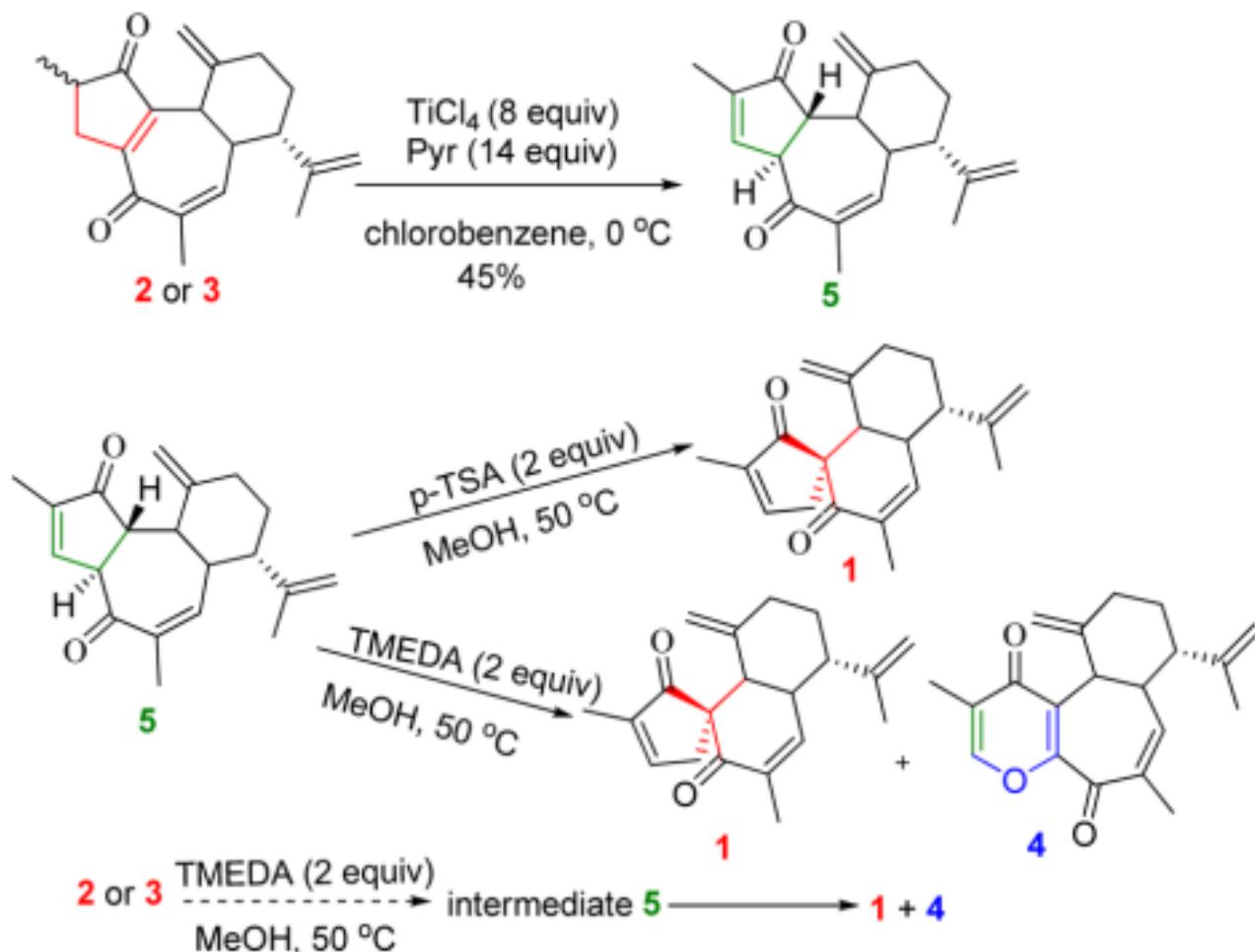
15 (<5%)



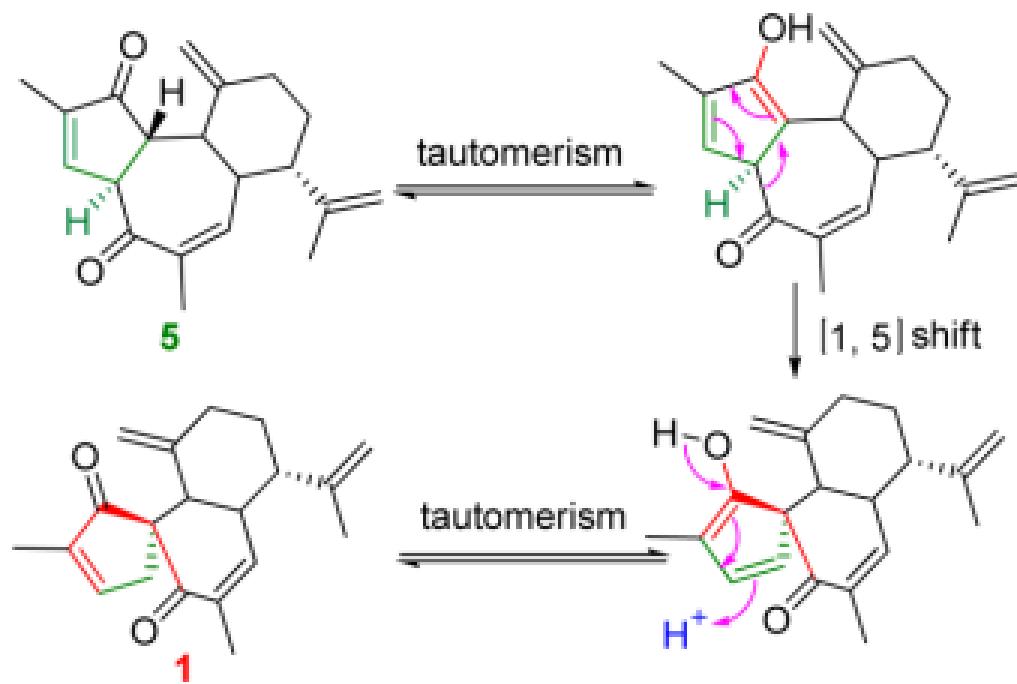




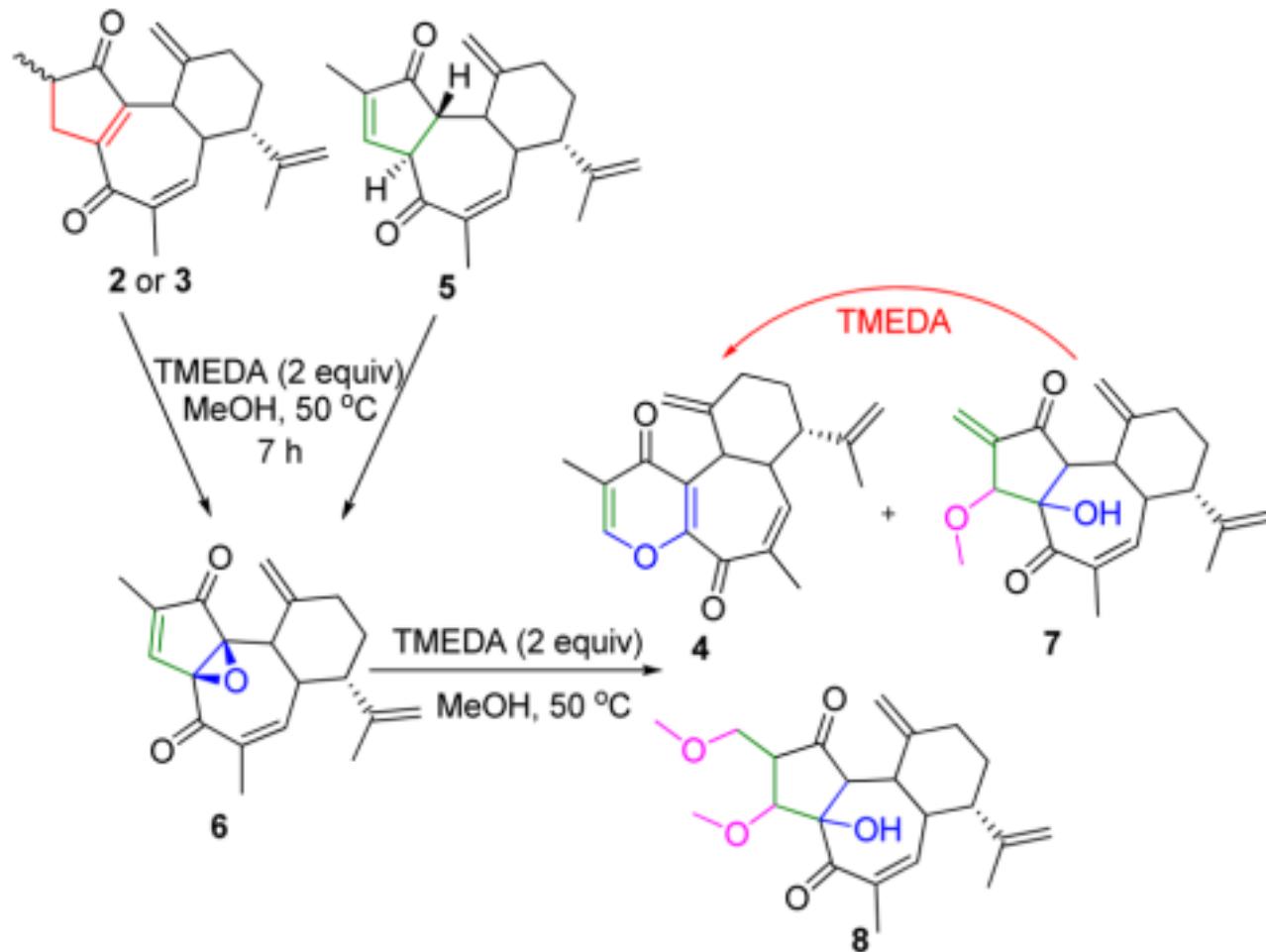
**Scheme 1. Synthesis of Compounds 1 and 4 from 5**



**Scheme 2. Stereospecific Rearrangement of the Rhamnofolane 5**



**Scheme 3. Intermediates of the Formation of Compound 4**



**Scheme 4. Plausible Reaction Mechanism of the Formation of Compound 4**

