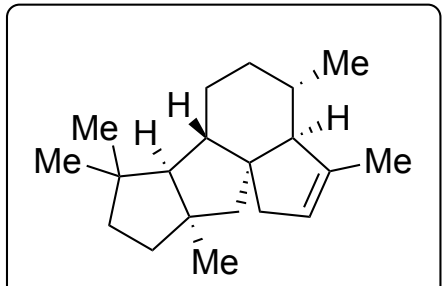
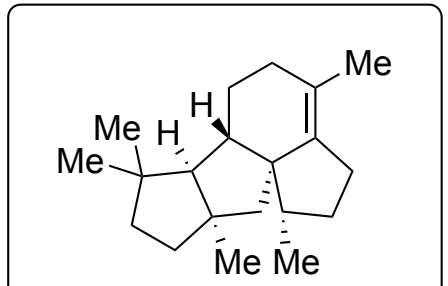
Total Syntheses of Polycyclic Diterpenes Phomopsene, Methyl Phomopsenonate, and *iso*-Phomopsene via Reorganization of C–C Single Bonds

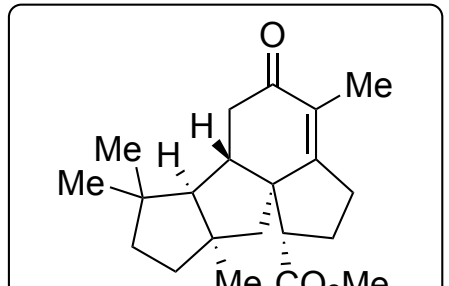
S.- H. Hou, Y.- Q. Tu, *J. Am. Chem. Soc,* **2023**. *145,* 21170–21175.



1
***iso*-phomopsene**



2
phomopsene



3
methyl phomopsenonate

- Phomopsene diterpenes **1–3** were isolated from the fermentation of fungi
- First total synthesis report of **1–3**, leading to the structural revision of **1**
- Strategic ring expansions to access fused 5/5/6/5 tetracyclic rings
- 5–6 consecutive stereogenic centers, including two quaternary carbon centers

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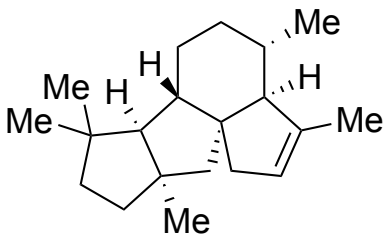
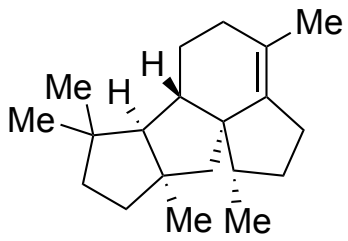
2024/02/28

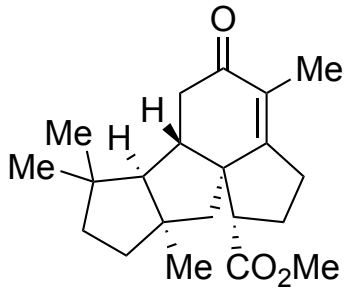
Retrosynthetic Analysis



***iso*-phomopsene**

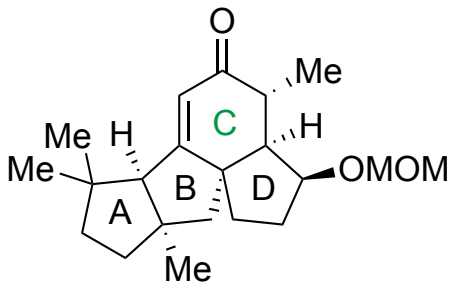


phomopsene

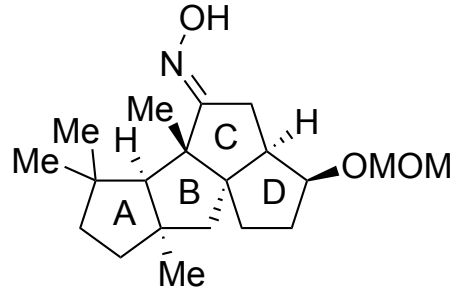


methyl phomopsenonate

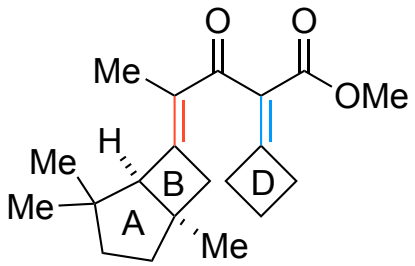
Late-stage Diversification



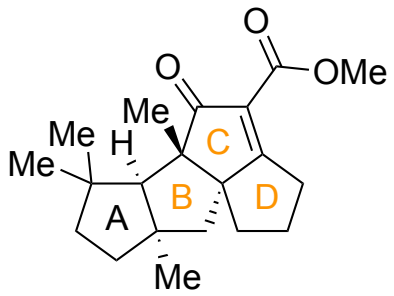
Ring Expansion



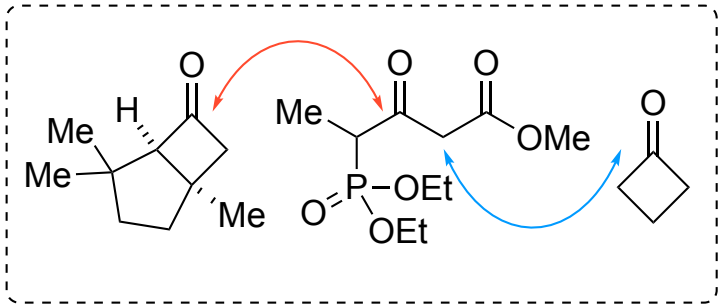
FGI



Nazarov Cyclization & Ring Expansions

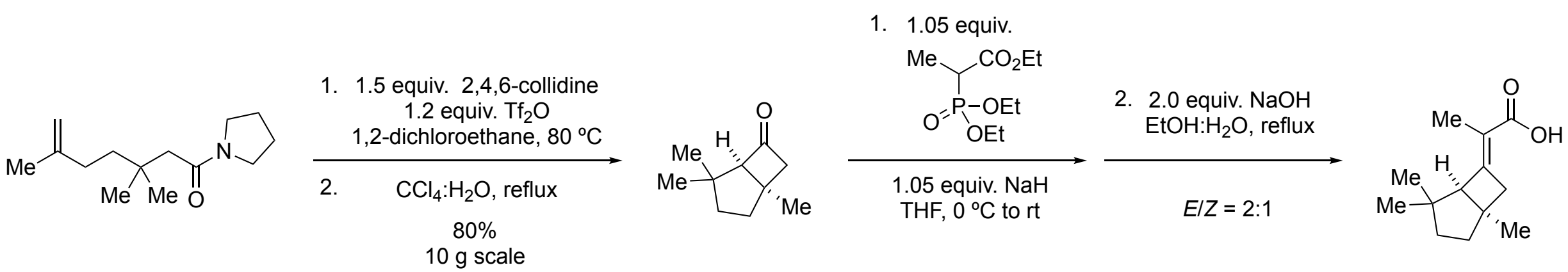


c.f.) Tu, *Nat Comm*., **2022**, *13*, 2335.

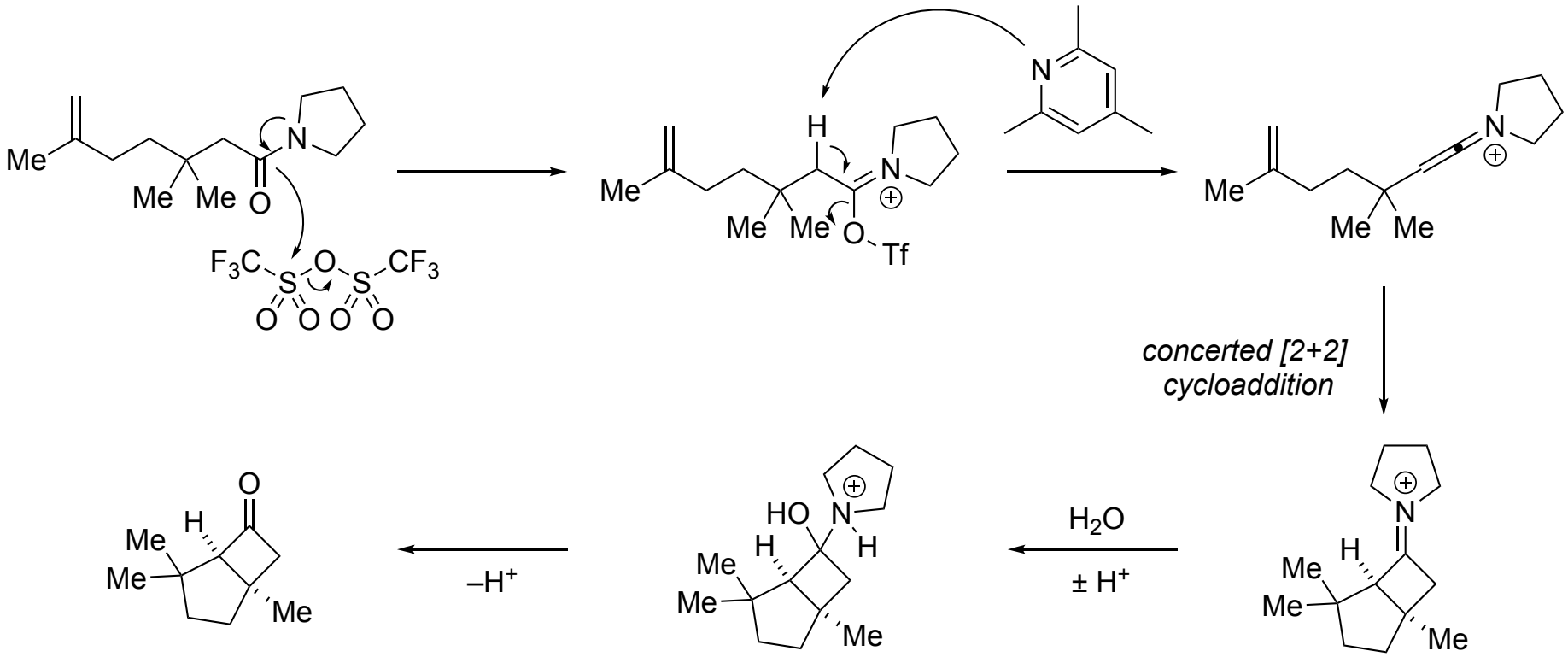


5/5/6/5 tetracycles was generated from sequential ring expansions

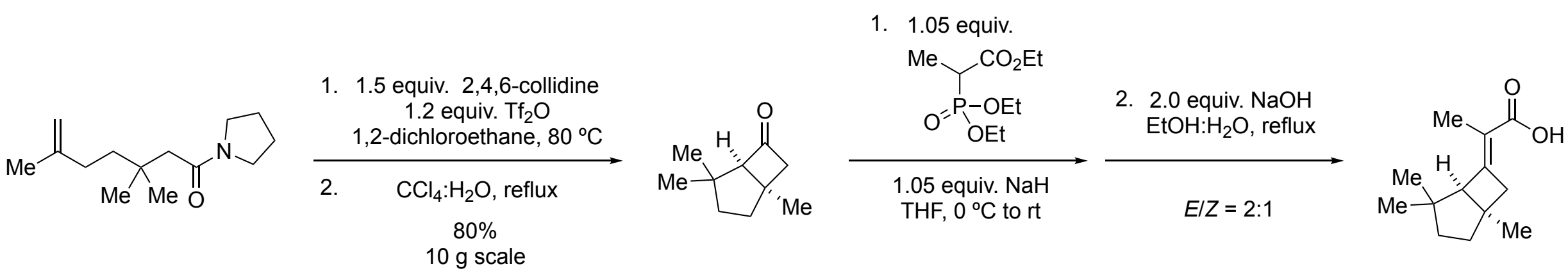
Key Steps:
Nazarov cyclization/Ring expansions



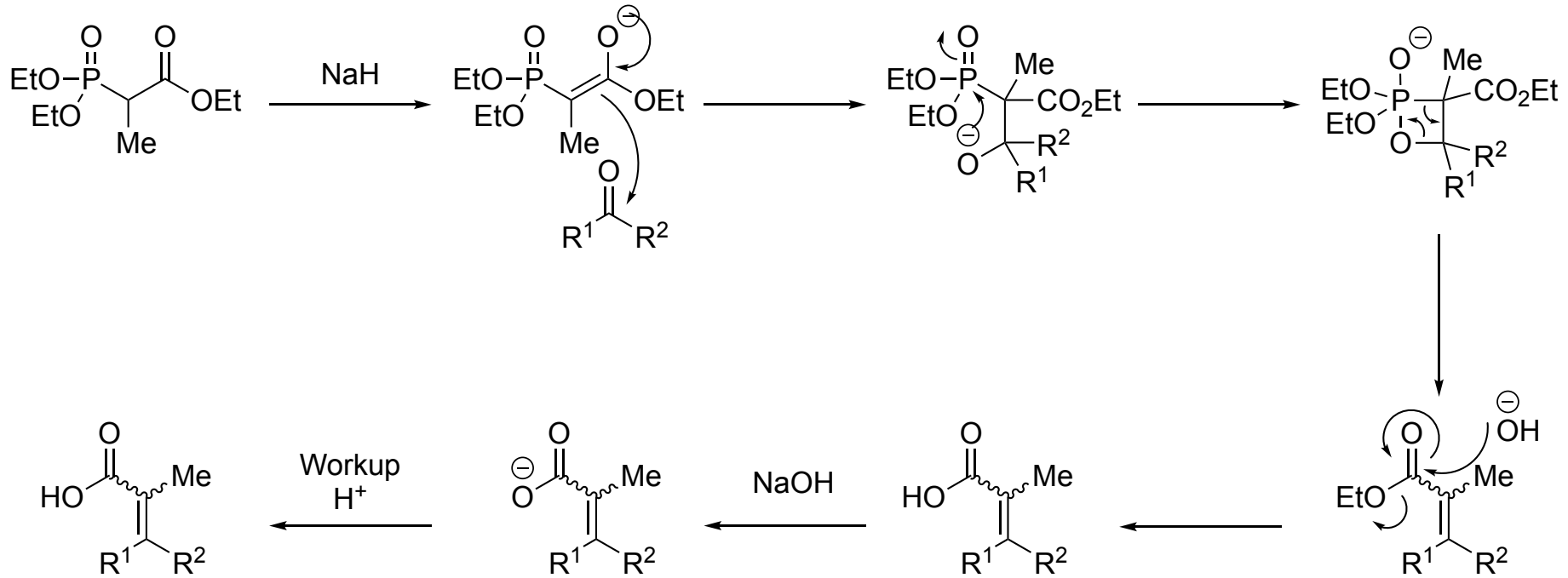
Intramolecular [2+2] cyclization between keteniminium salt with alkene (Ghosez cycloaddition)

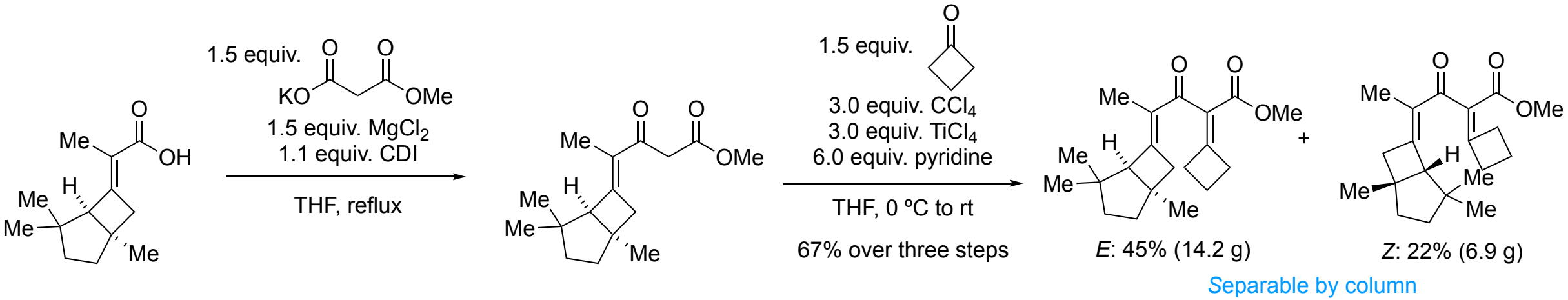


L. Ghosez, *J. Am. Chem. Soc.*, **1972**, *94*, 2870–2872.

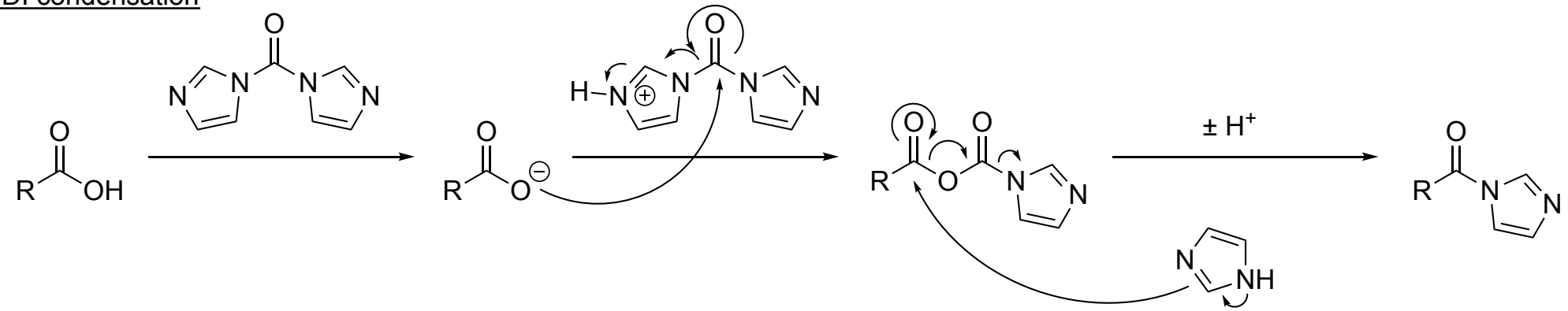


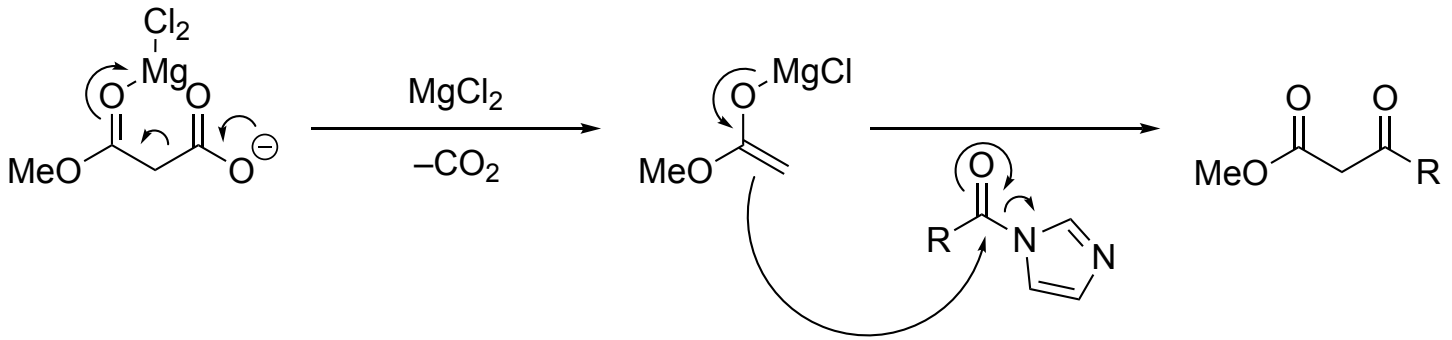
Horner-Wadsworth-Emmons reaction & hydrolysis

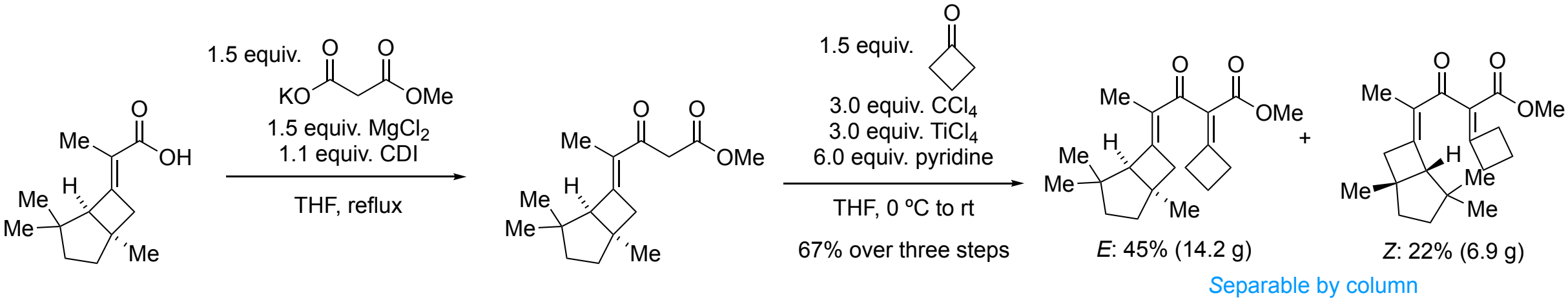




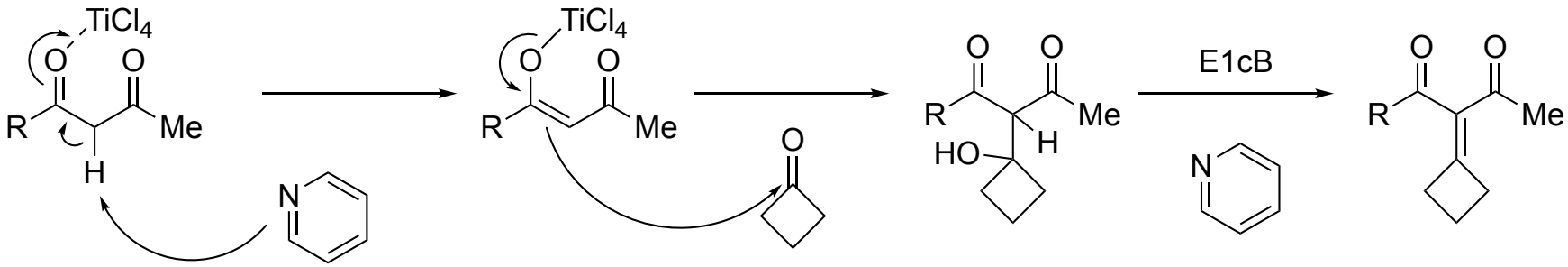
CDI condensation

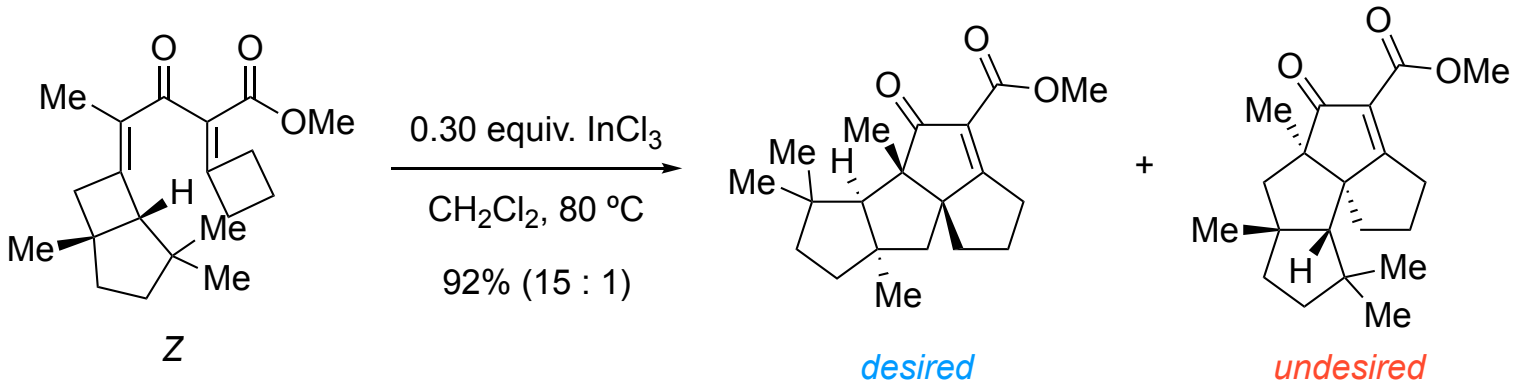




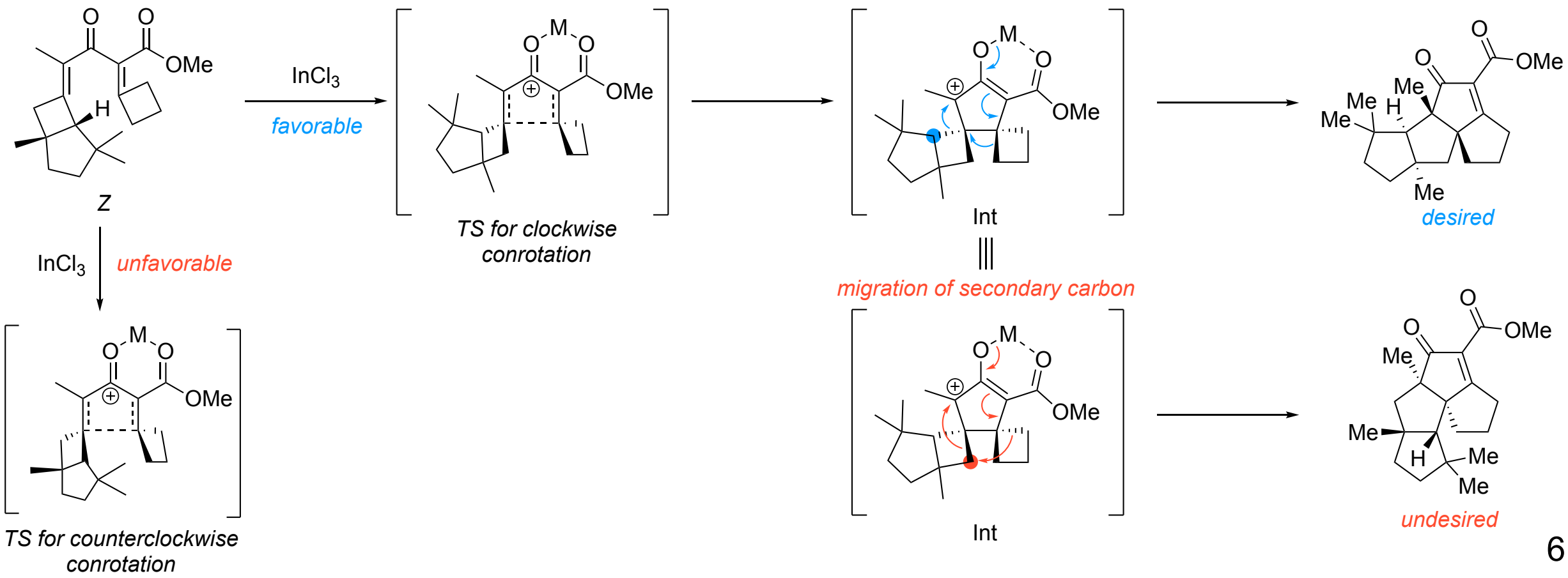


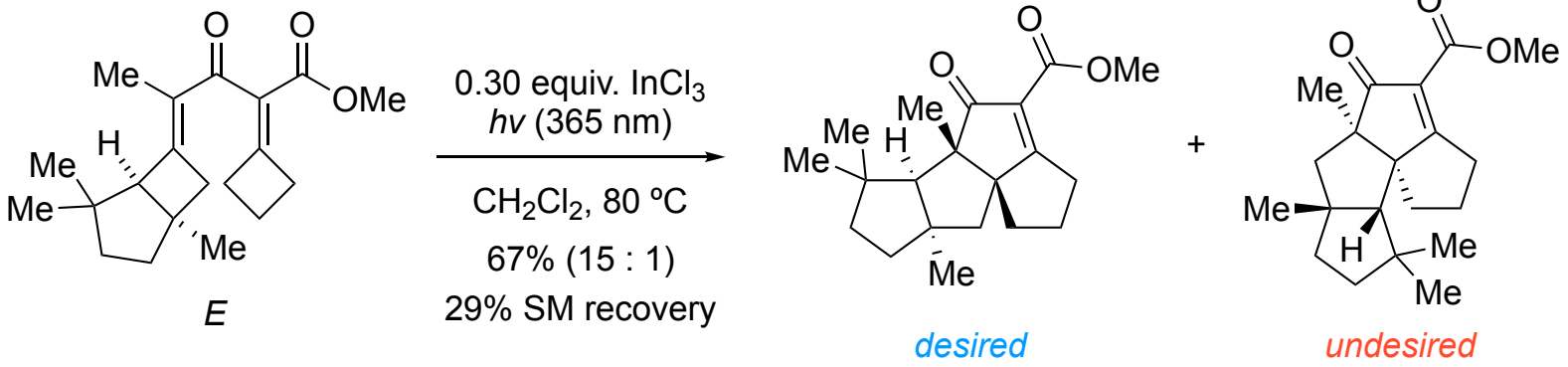
Knoevenagel Condensation



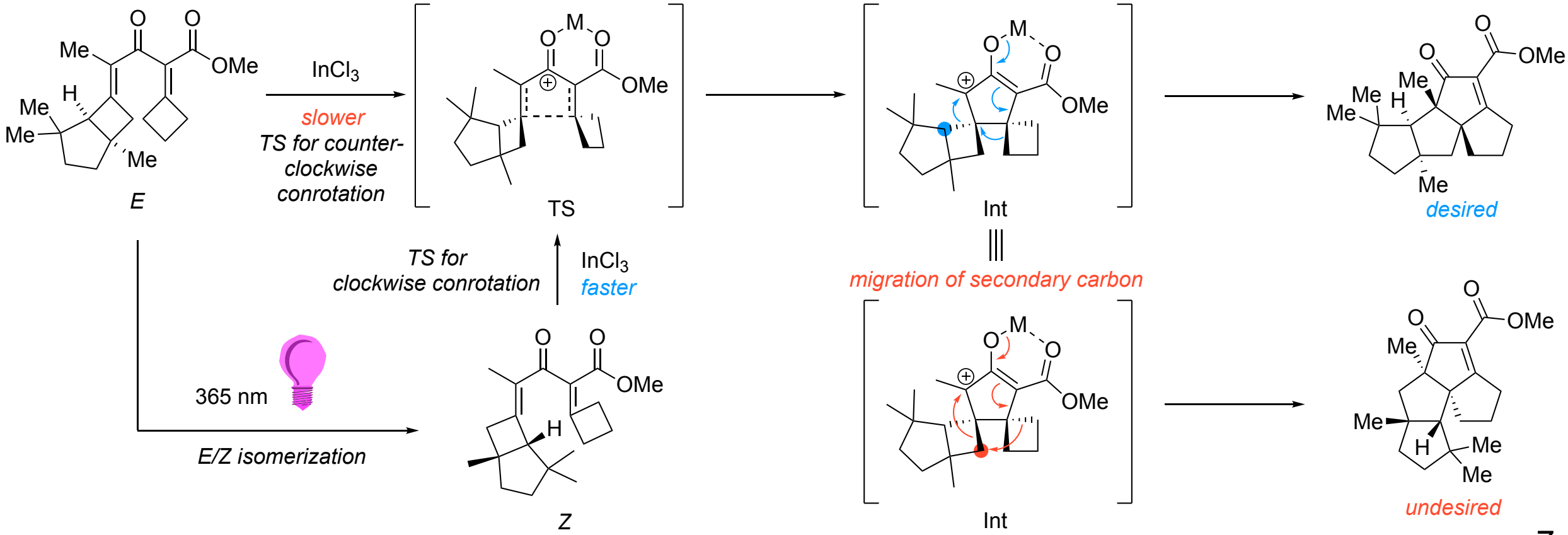


Nazarov cyclization/Double ring expansion (From Z-isomer)

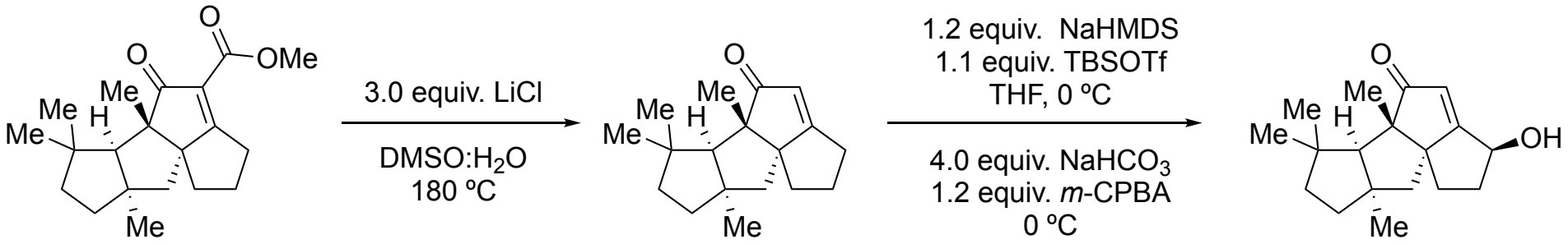




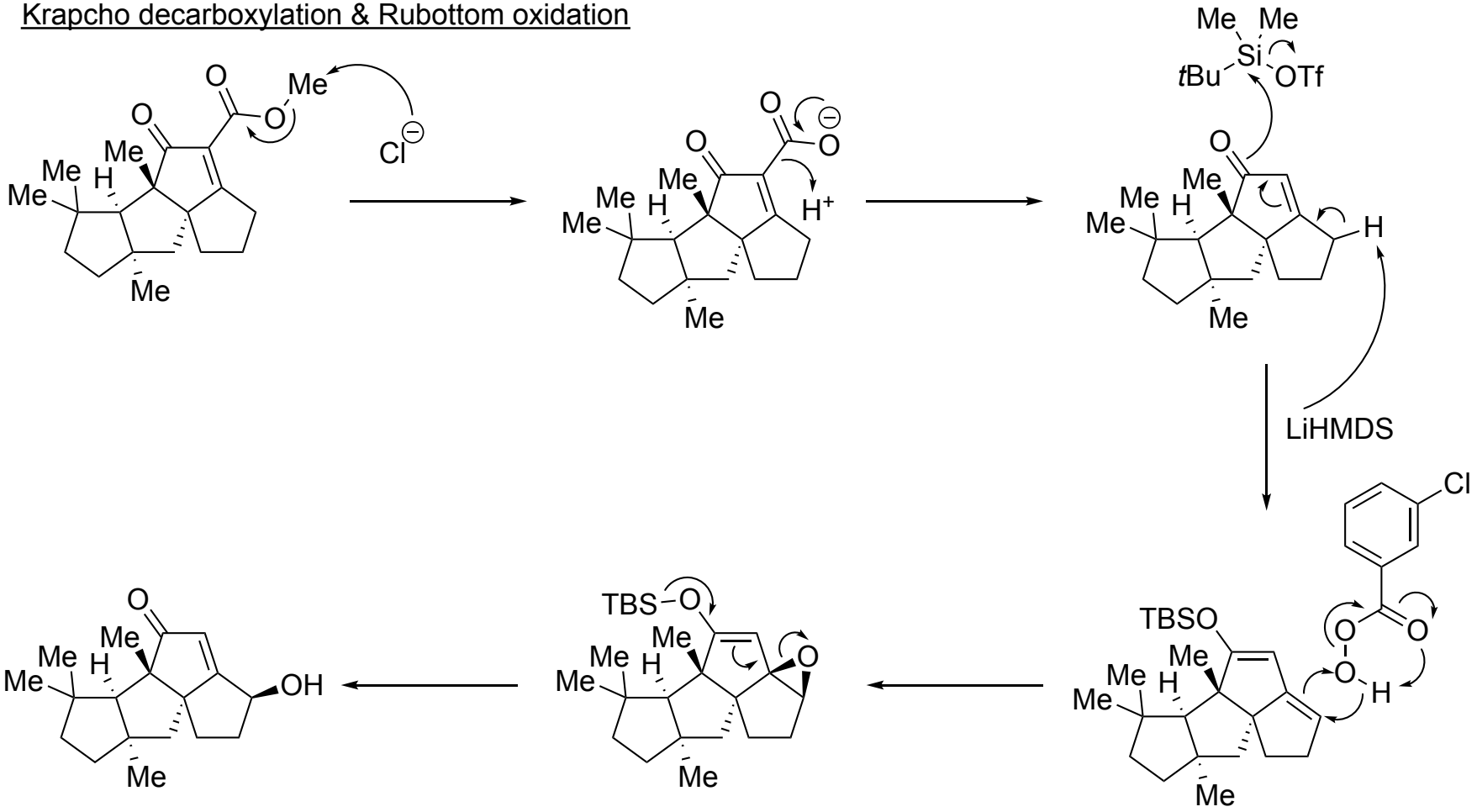
Nazarov cyclization/Double ring expansion (From E-isomer)



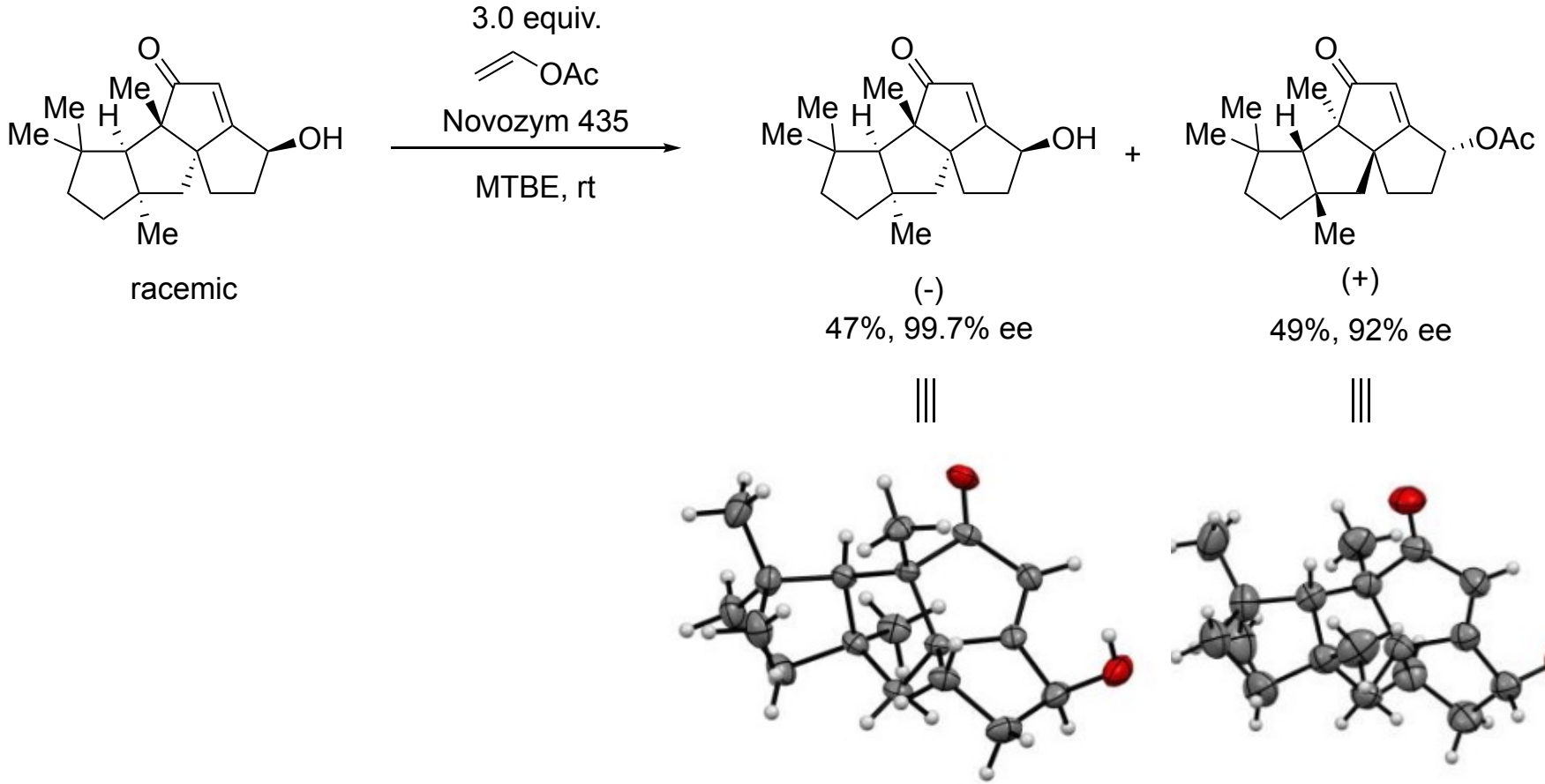
Z's ground state has higher energy than E



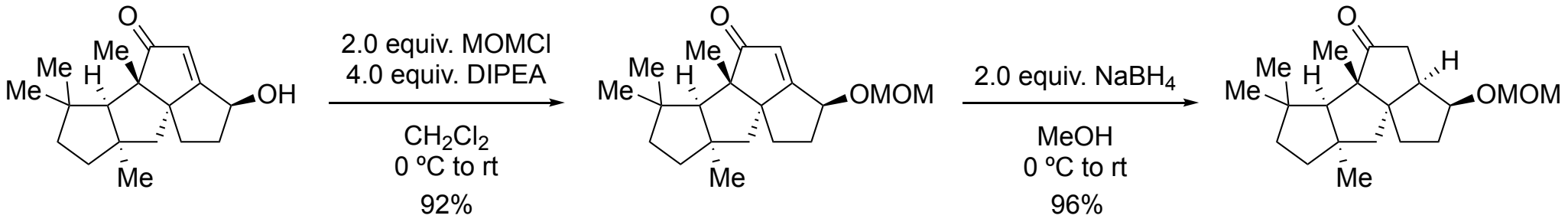
Krapcho decarboxylation & Rubottom oxidation



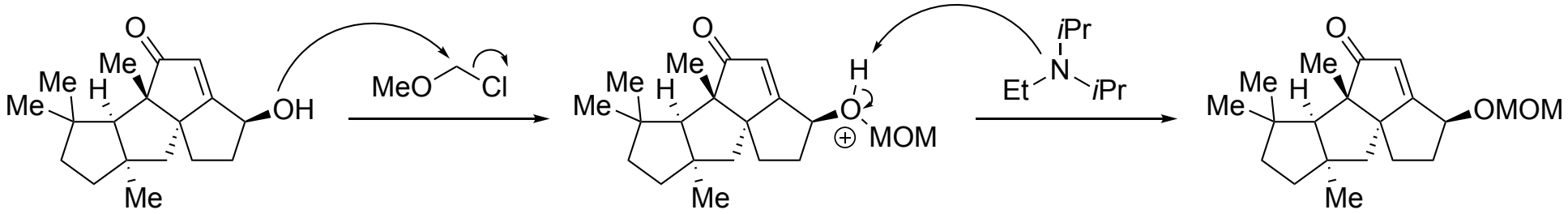
Enzymatic kinetic resolution



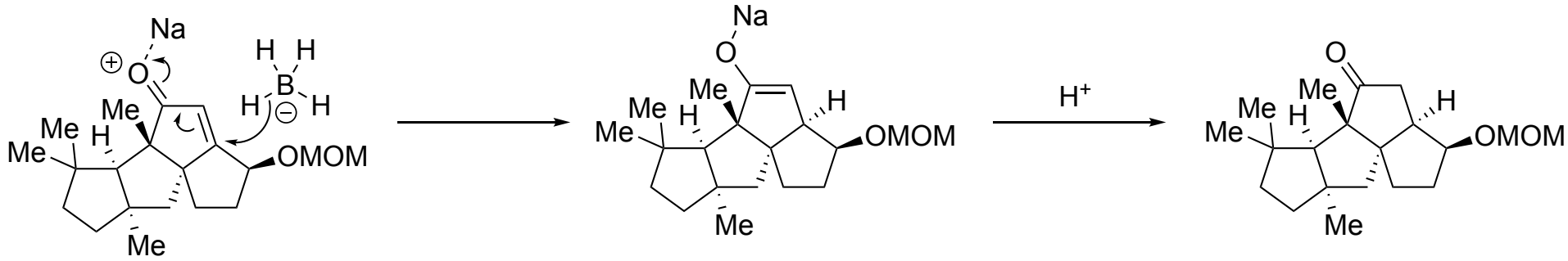
c.f.) Catal. Sci. Technol. **2019**, *9*, 2380−2420.
J. Am. Chem. Soc. **2021**, *143*, 11951−11956.

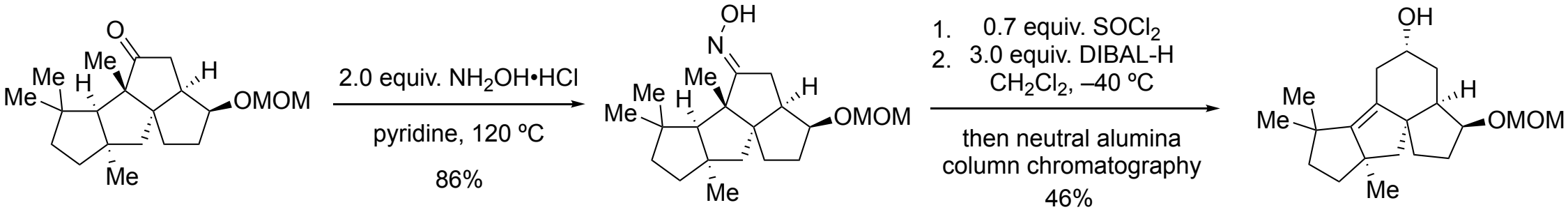


MOM protection of alcohol

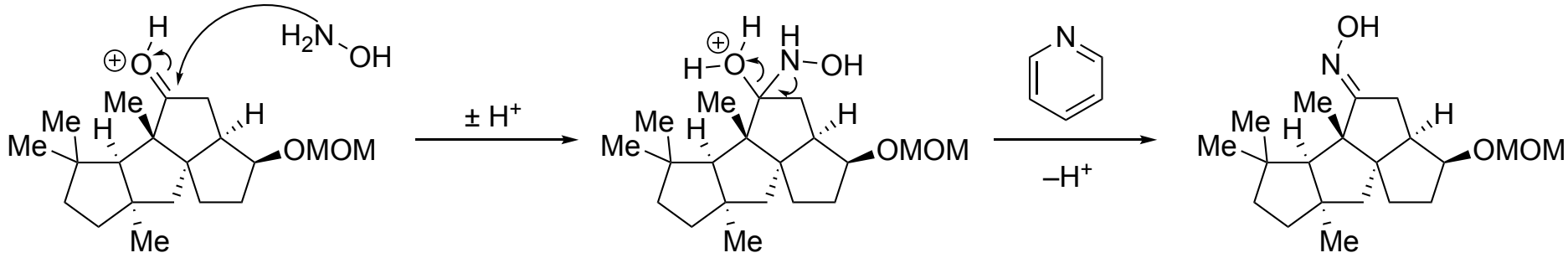


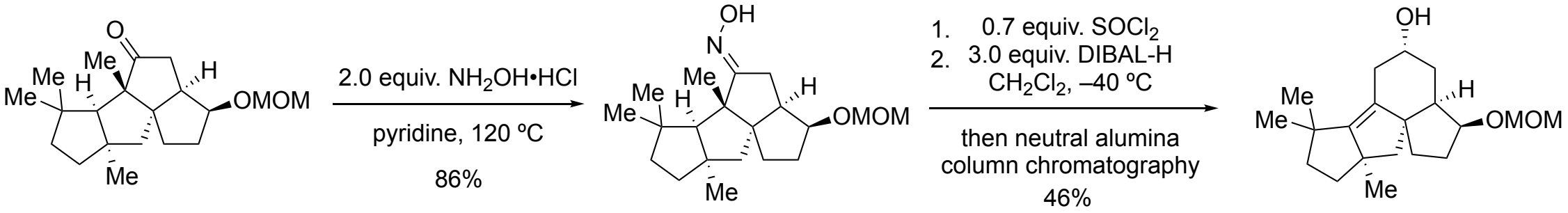
1,4-Reduction



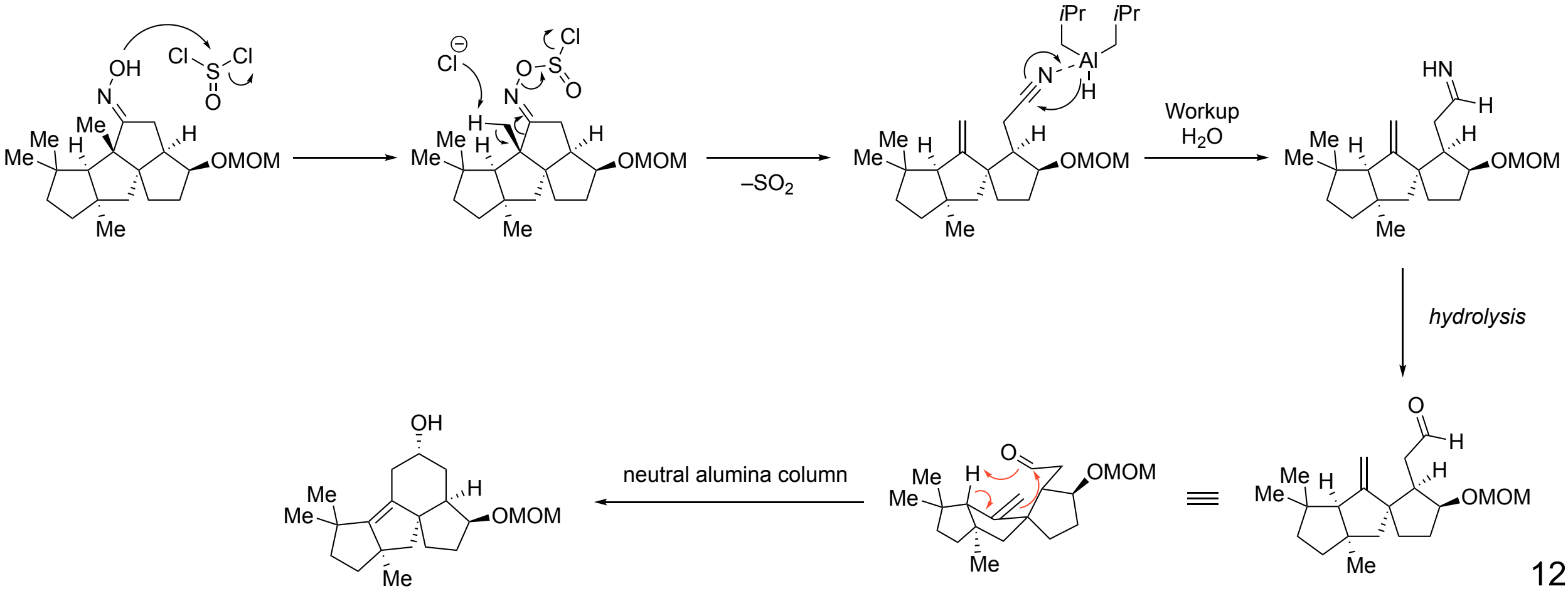

2.0 equiv. NH2OH•HCl
pyridine, 120 ºC
86%
1. 0.7 equiv. SOCl2
2. 3.0 equiv. DIBAL-H
CH2Cl2, –40 ºC
then neutral alumina
column chromatography
46%

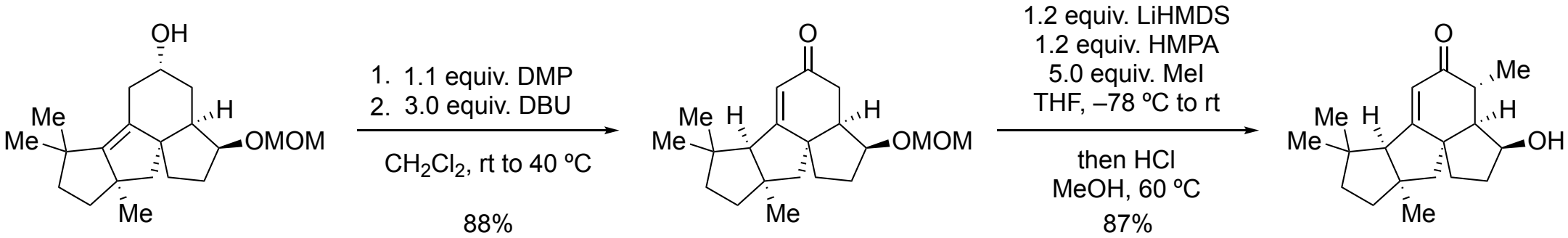
Oximation


± H+
–H+



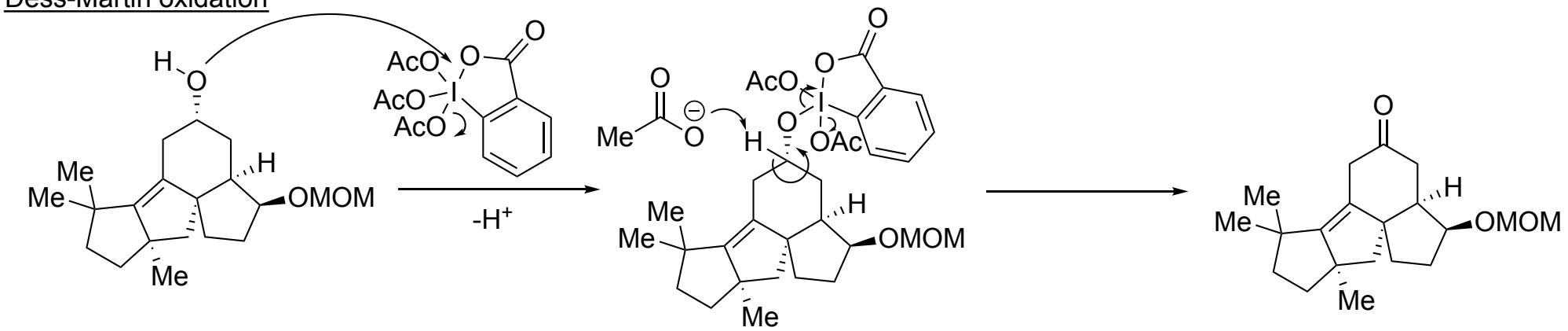
Beckmann Fragmentation & carbonyl-ene cyclization



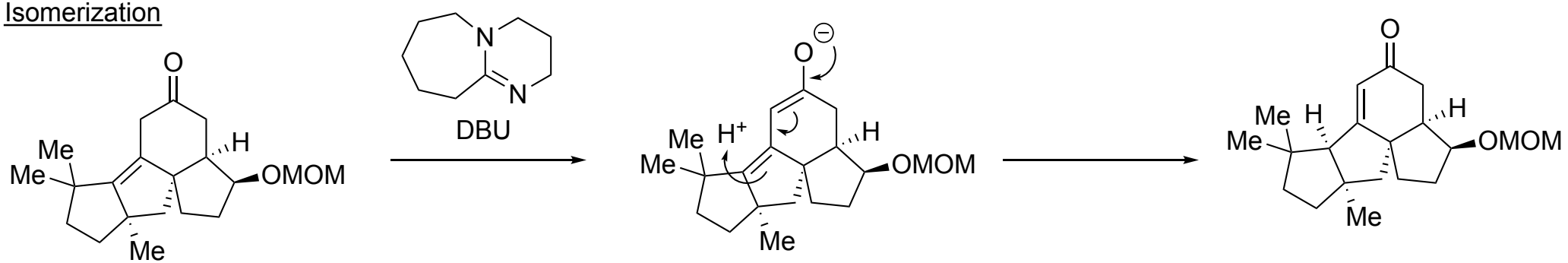


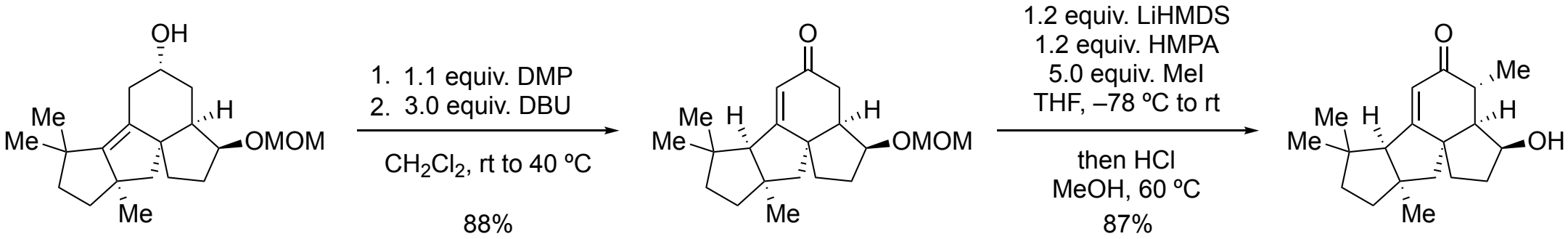
Common Intermediate

Dess-Martin oxidation



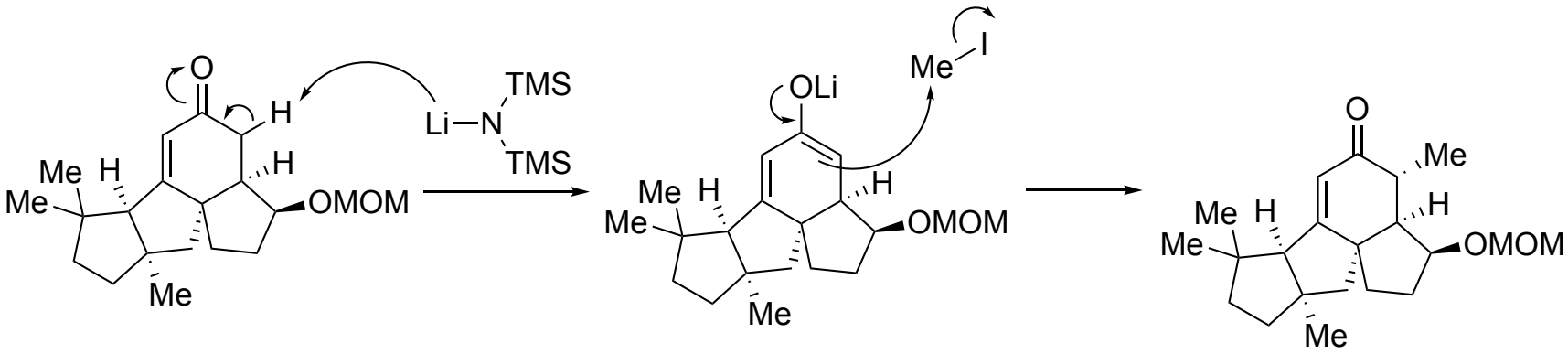
Isomerization



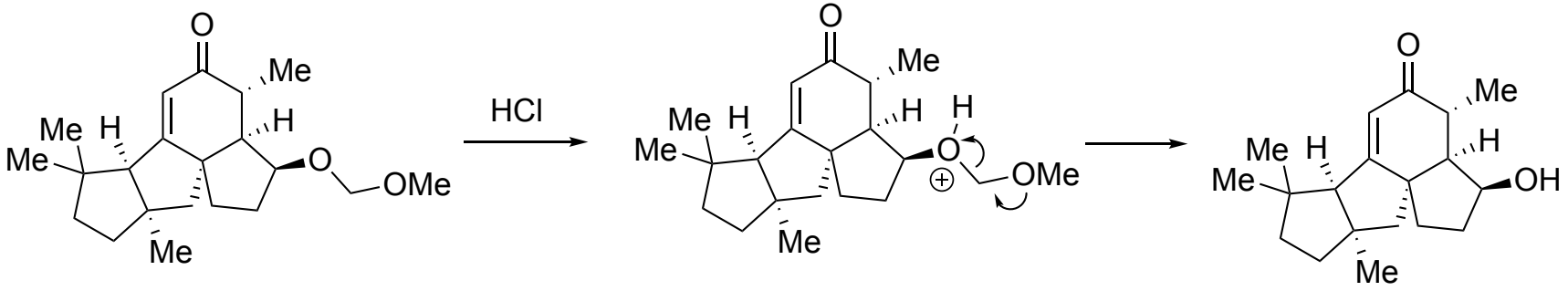


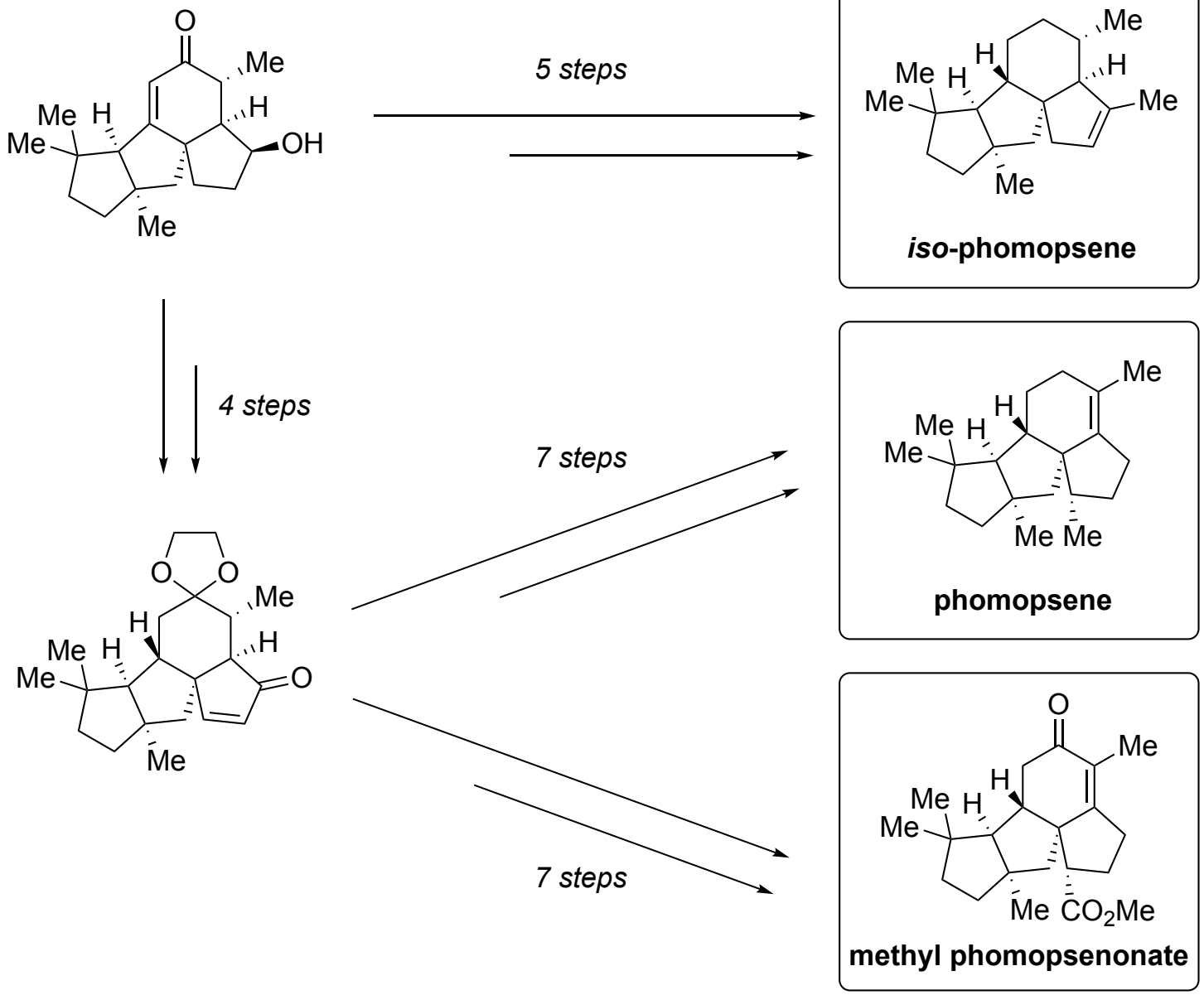
Common Intermediate

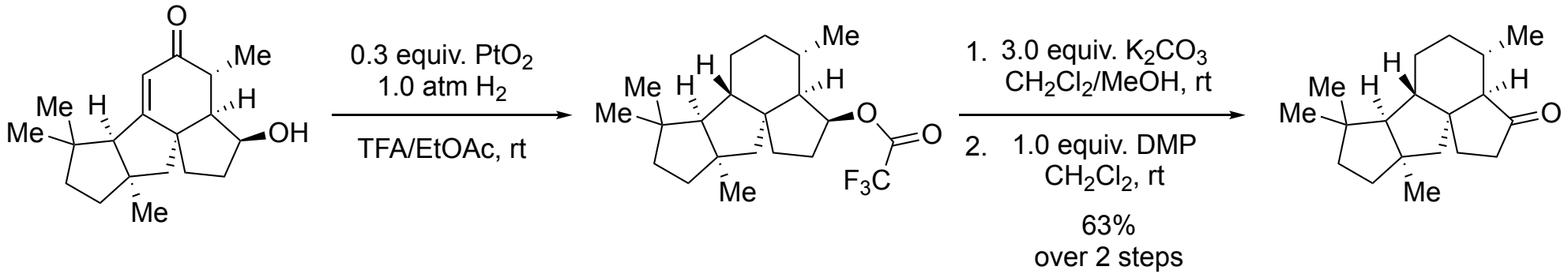
α-Methylation



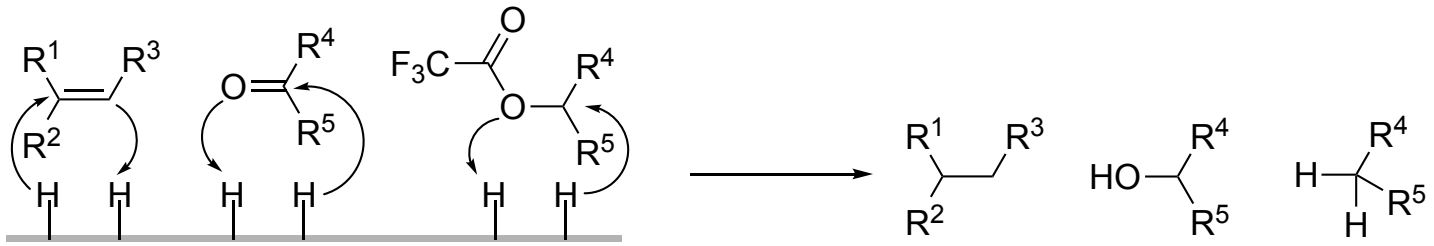
MOM deprotection



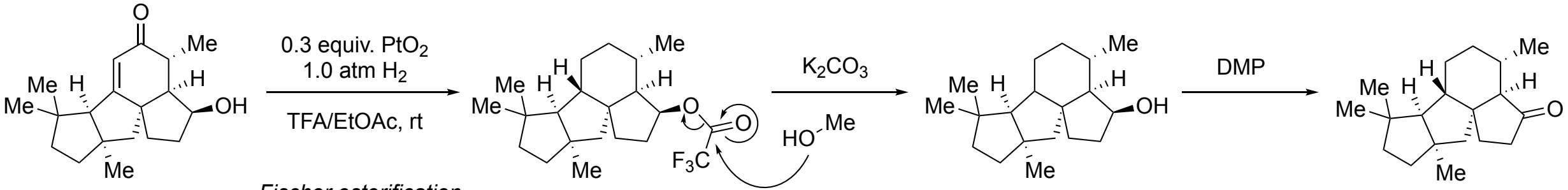

5 steps
4 steps
7 steps
7 steps
iso-phomopsene
phomopsene
methyl phomopsenonate



PtO$_2$-catalyzed reduction

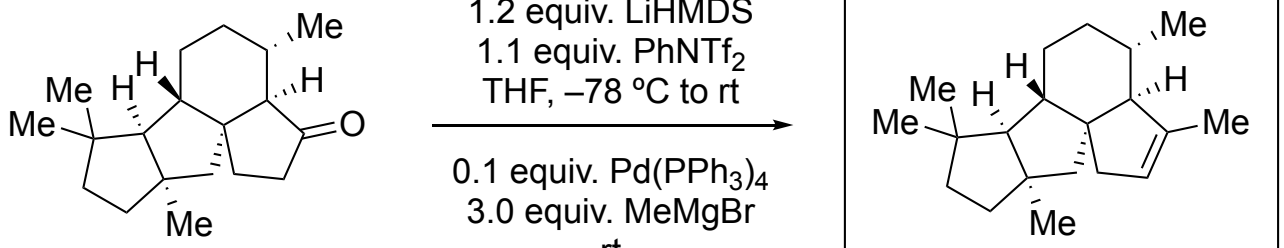


Alcoholysis & DMP oxidation

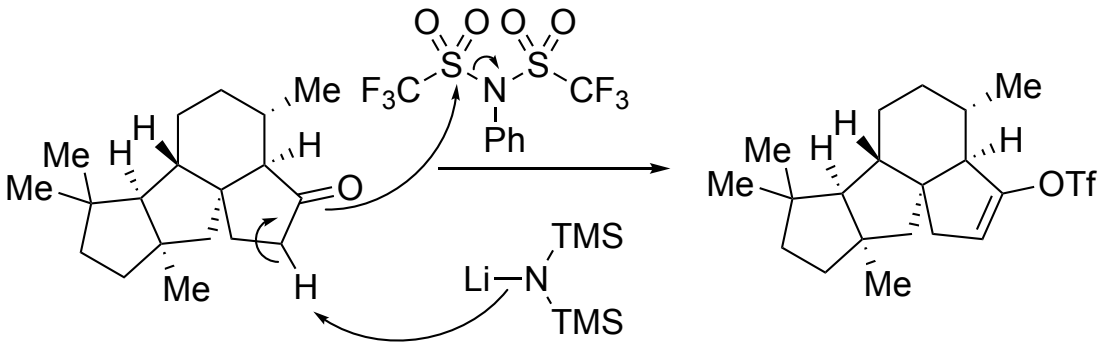


Fischer esterification

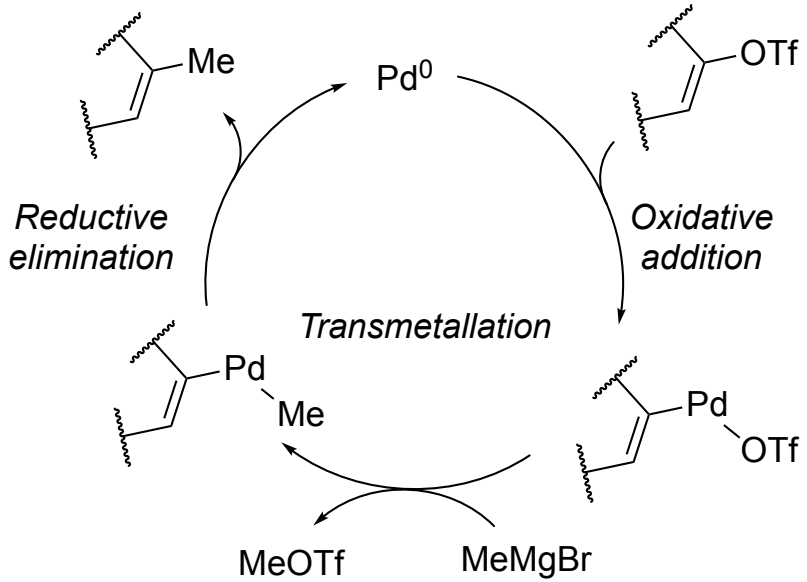
See slide 13 for DMP oxidation mechanism

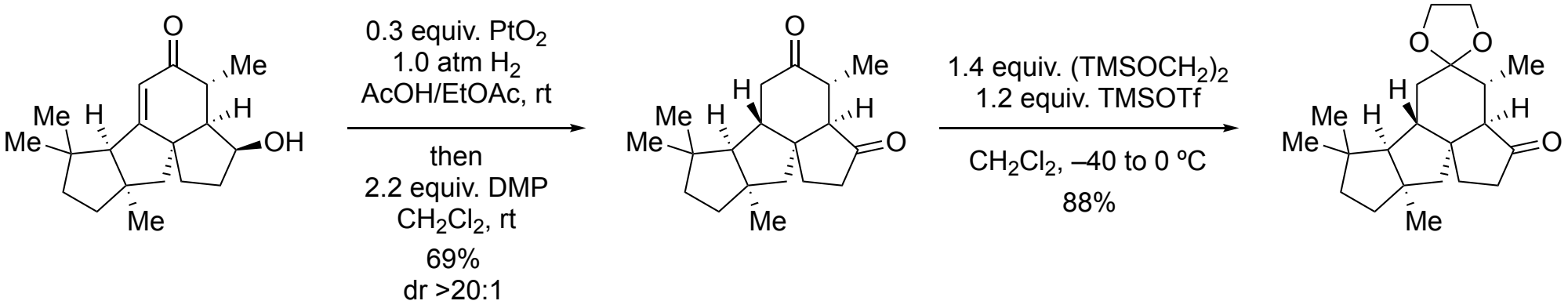


Vinyl triflate formation



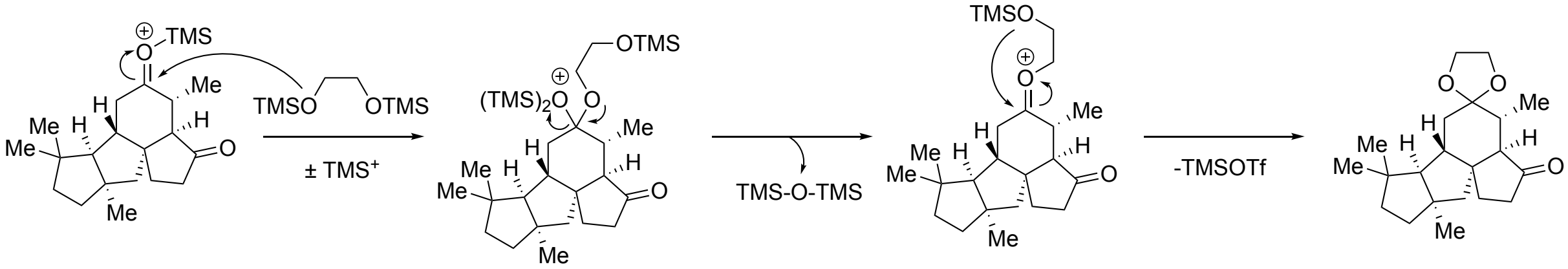
Kumada cross coupling





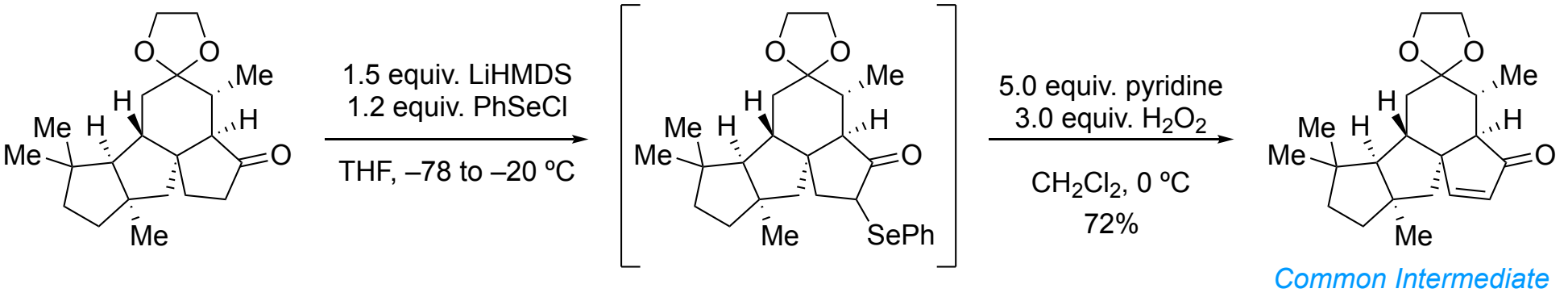
See Slide 13 and 16 for PtO_2 reduction & DMP oxidation mechanism

Acetal protection of ketone (Noyori condition)



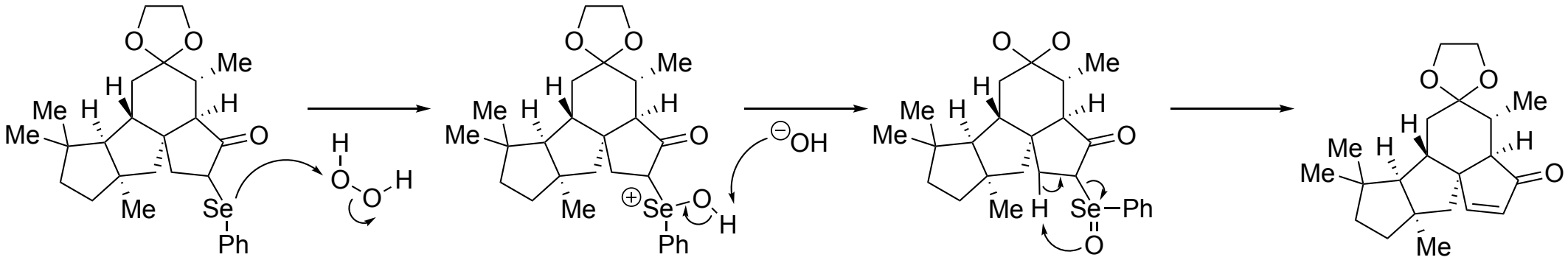
c.f.) Tetrahedron **1981**, *37*, 3899-3910.

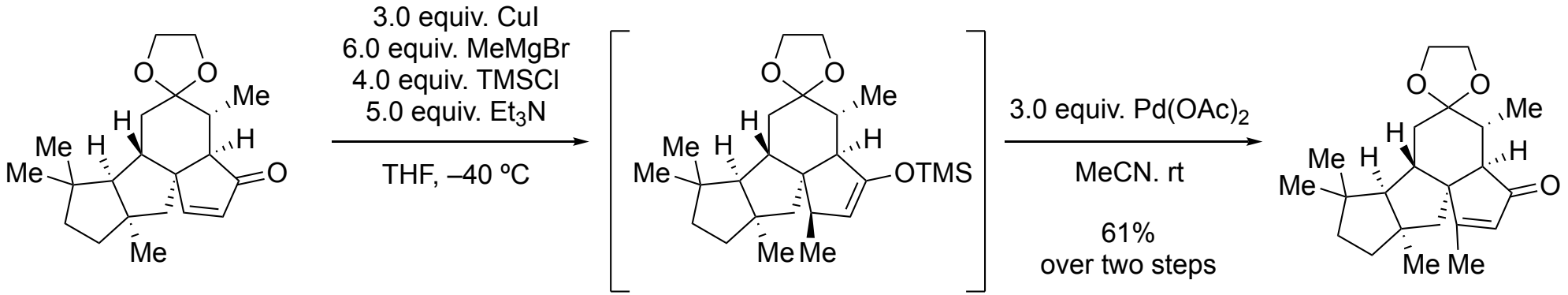
cyclohexanone reacts faster than cyclopentanone



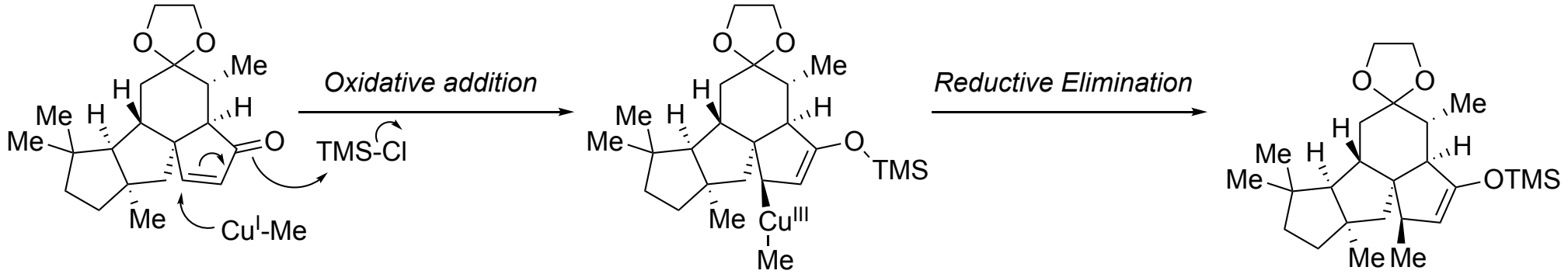
See Slide 14 for α-Selenylation mechanism

Selenoxide elimination

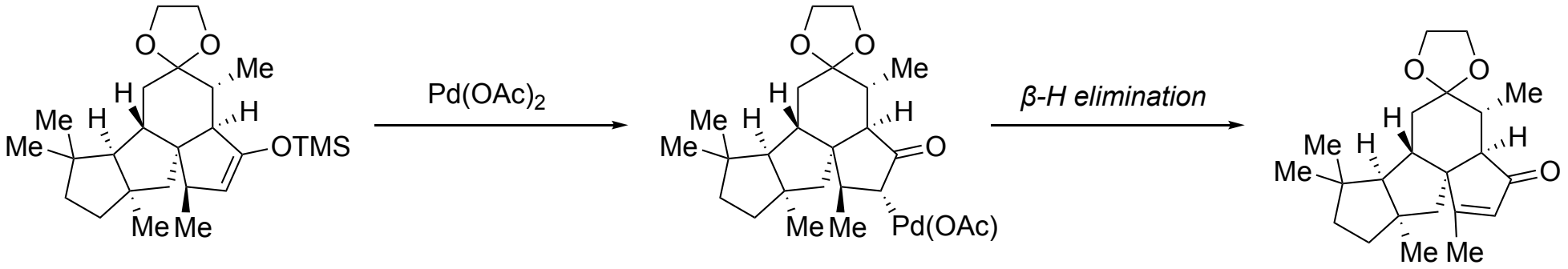


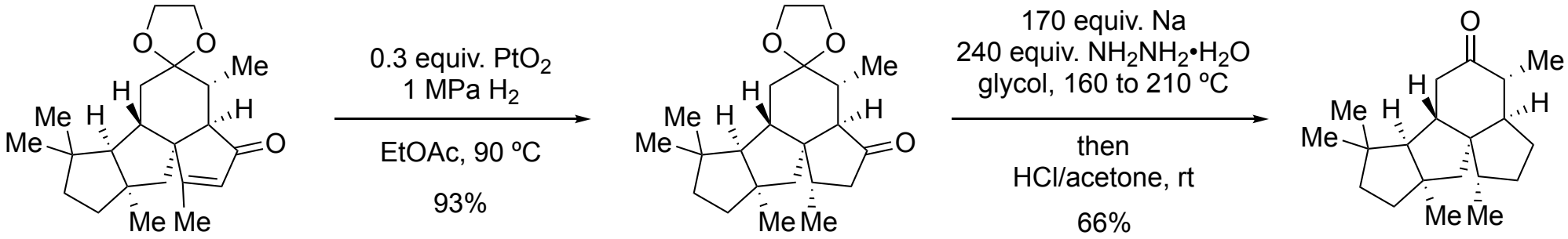


Conjugate addition



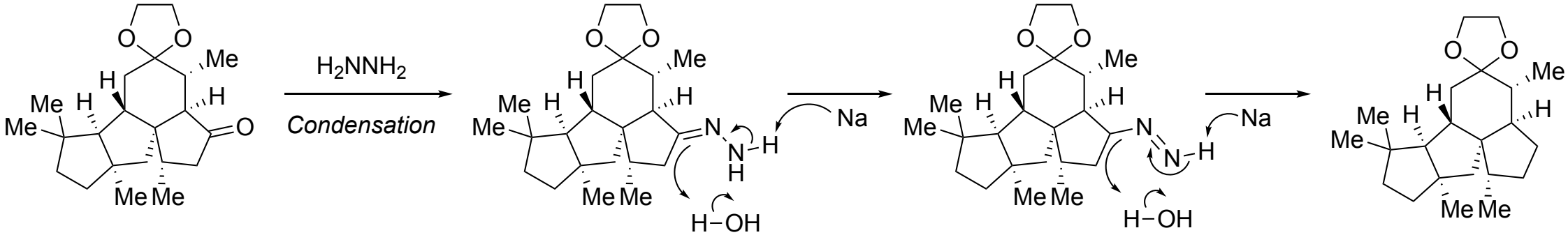
Saegusa-Ito oxidation



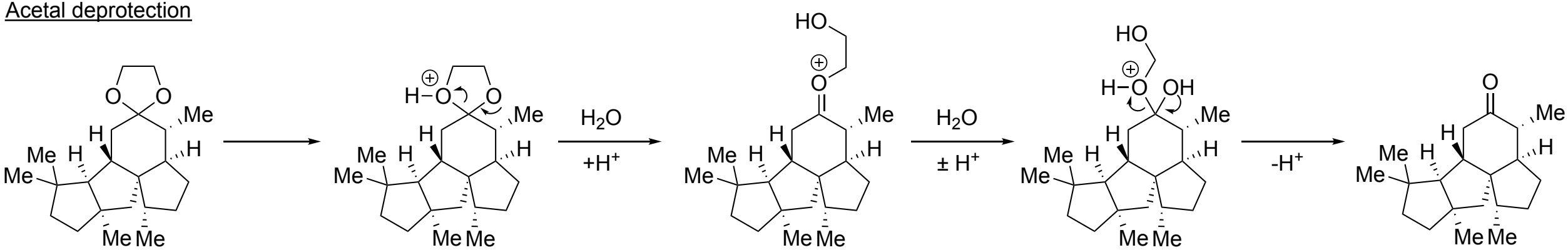


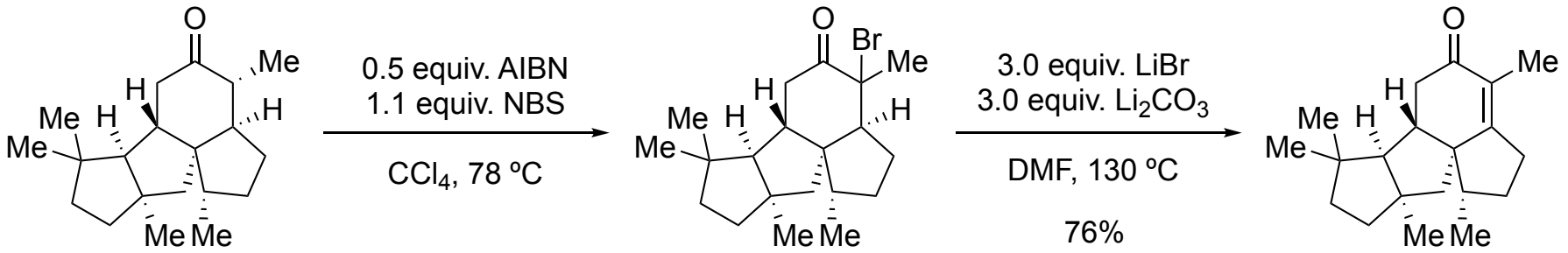
See Slide 13 for PtO_2 reduction mechanism

Wolff-Kishner reduction



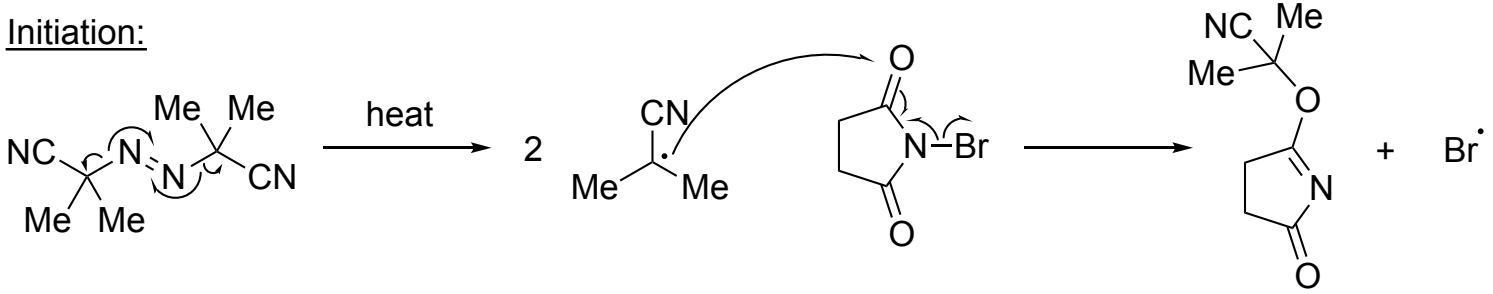
Acetal deprotection



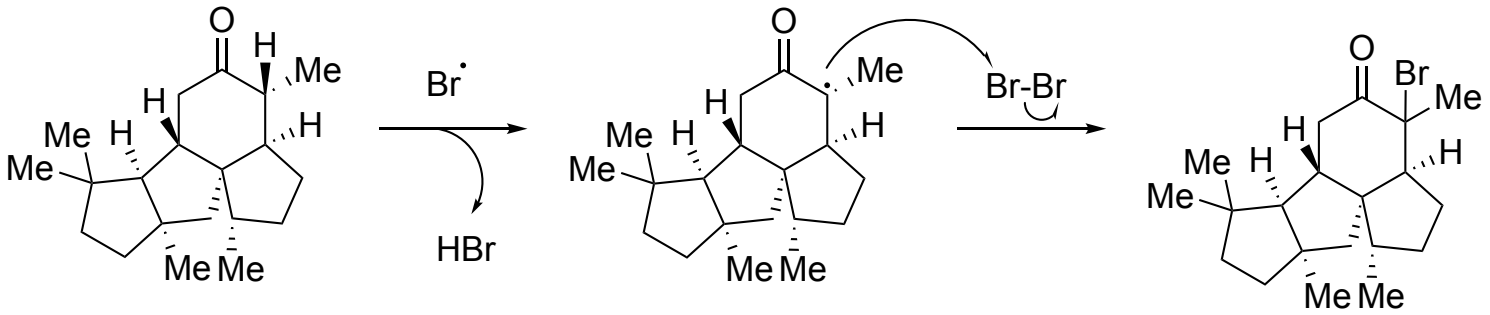


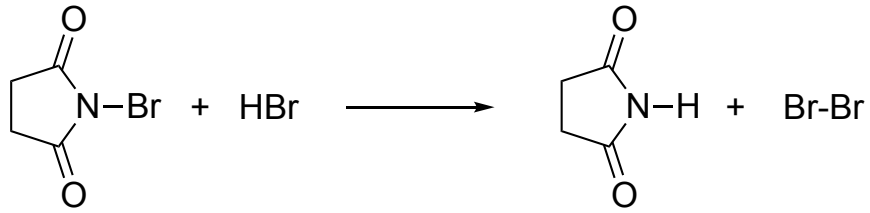
α-Bromination

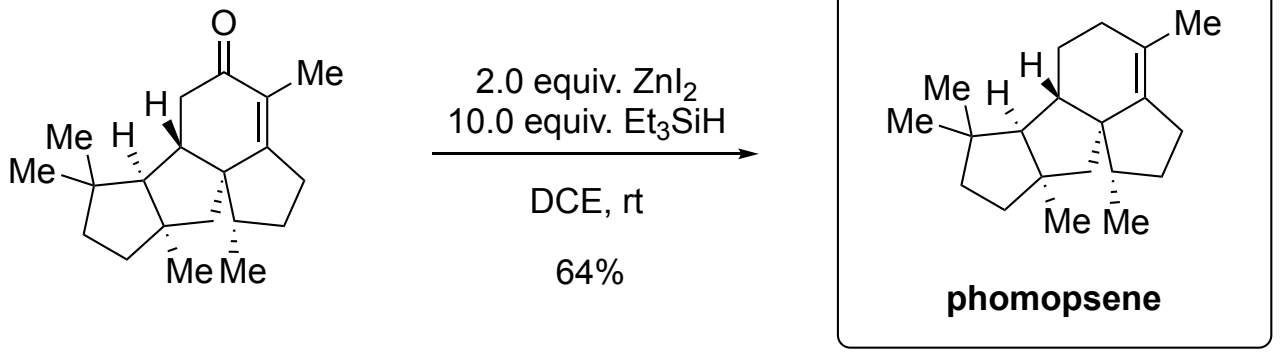
Initiation:



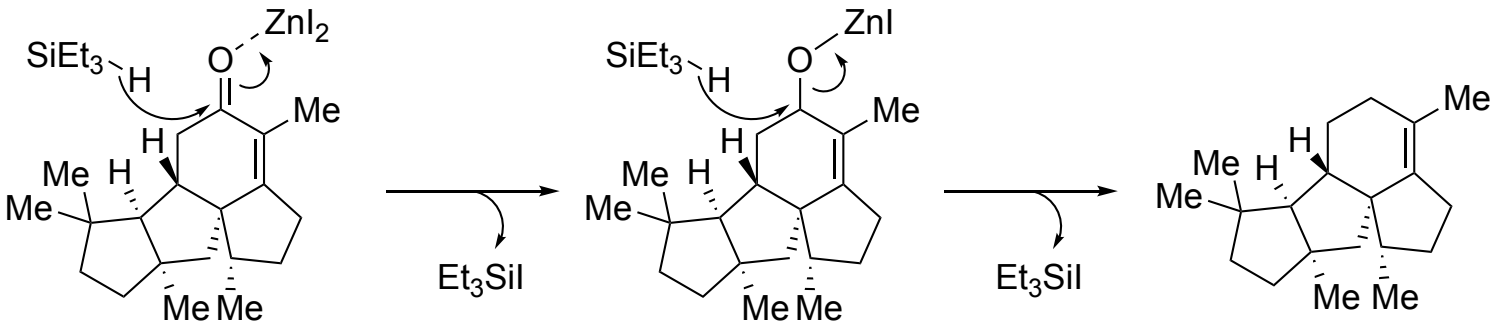
Propagation



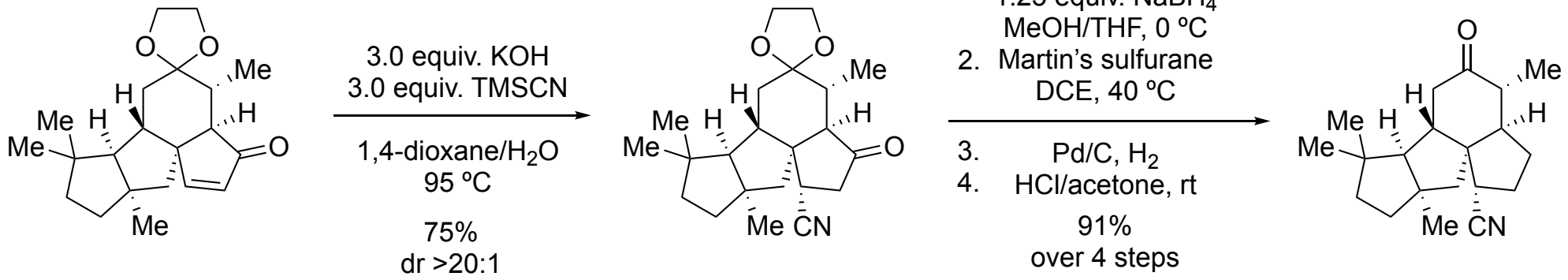




Reduction of ketone

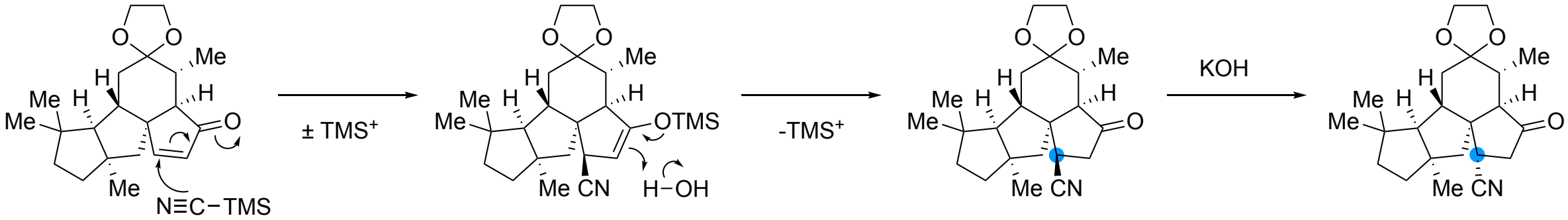


c.f.) Synlett., **2008**, *19*, 3053–3057.

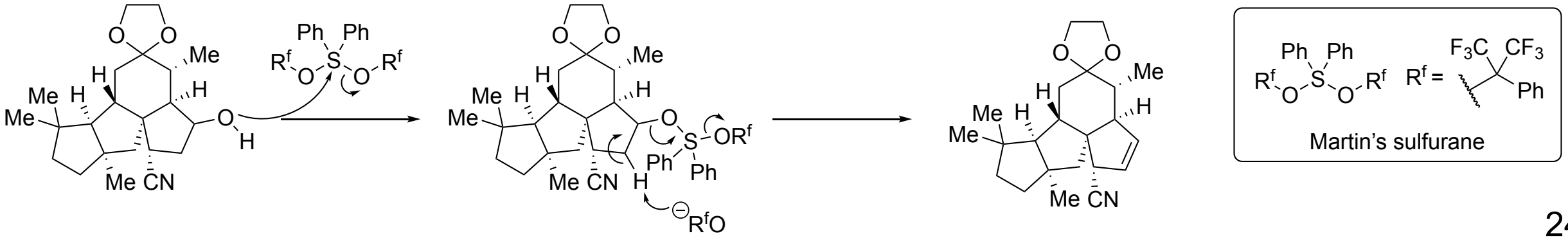


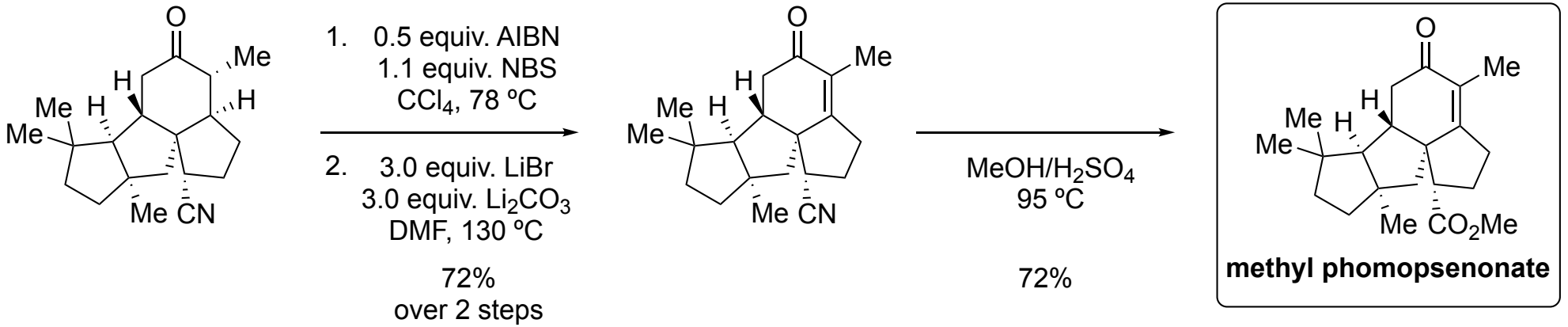
See Slide 10, 13 for reduction, 21 for acetal deprotection mechanism

Conjugate addition & epimerization



Dehydration





See Slide 22 for radical bromination

Alcoholysis of Cyano group