Tandem Nazarov Reaction by Prof. Tu's Group

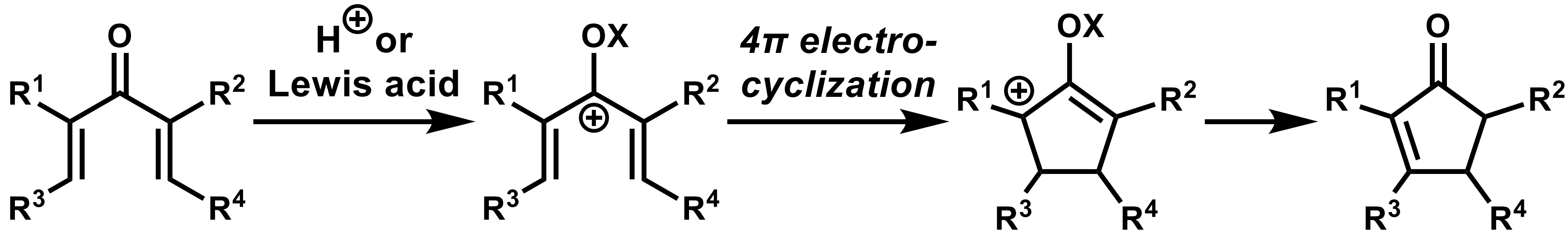
Literature Seminar
2023/09/16
Wentao Wang

Contents

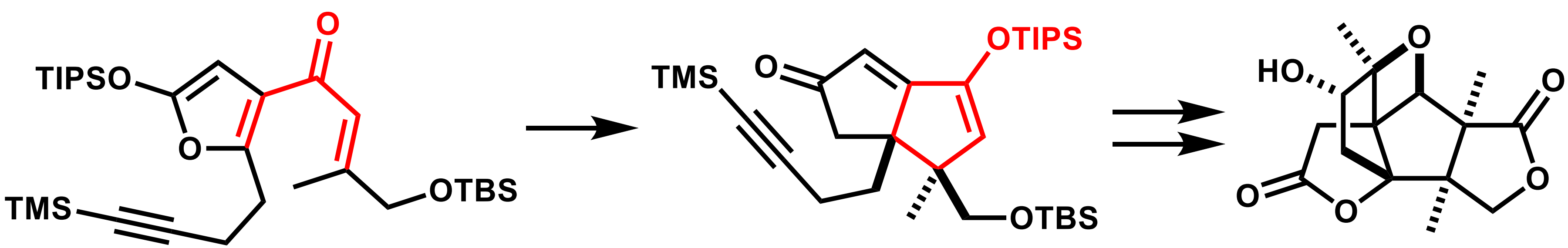
Contents

Nazarov Cyclization

Classical Nazarov cyclization:

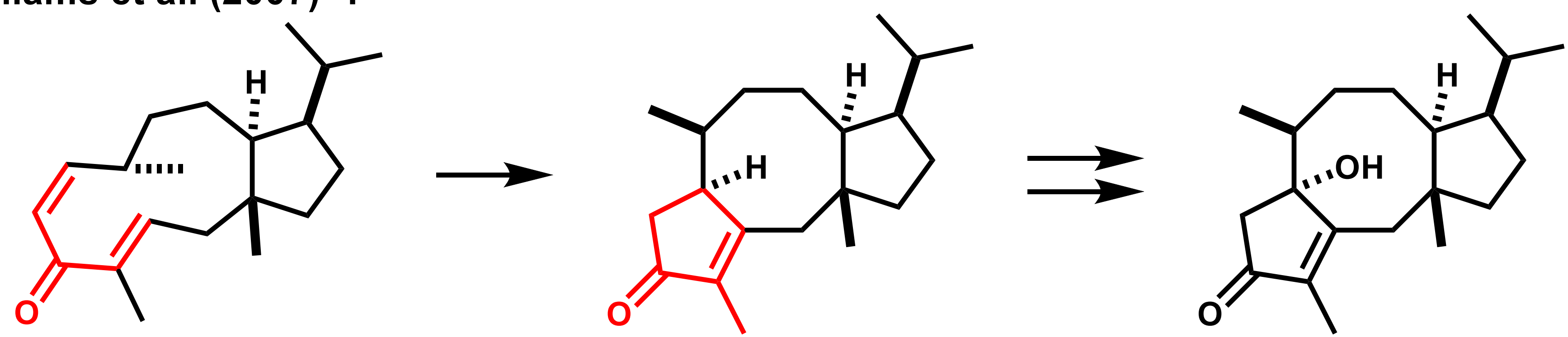


Frontier et al. (2007)[3]:



merrilactone A

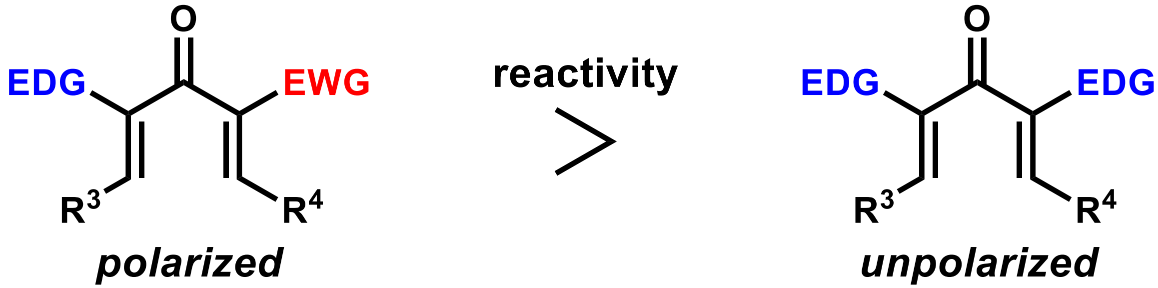
Williams et al. (2007)[4]:



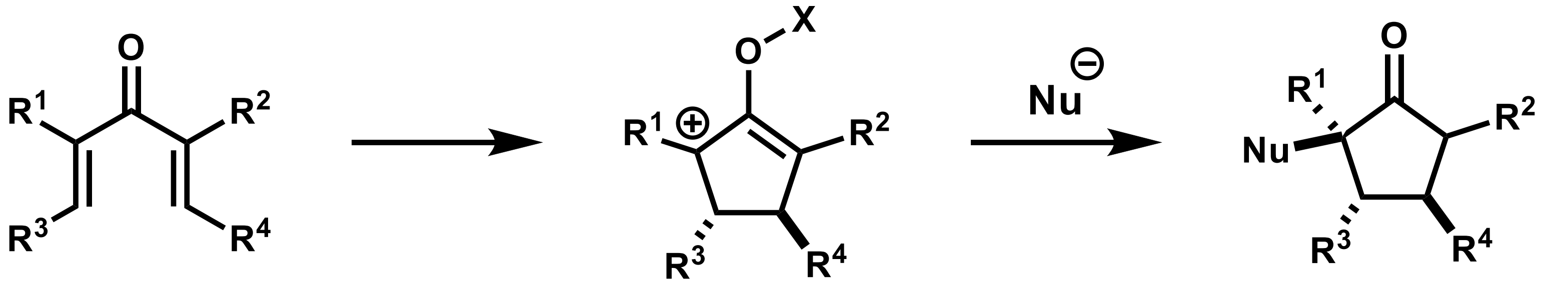
fusicoauritone

Nazarov Cyclization

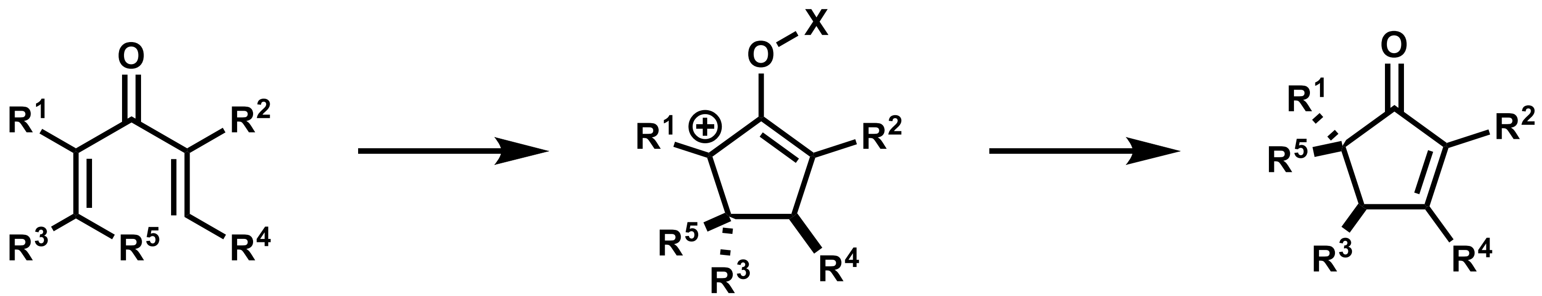
Polarized model by Frontier et al.[5]:



Interrupted Nazarov cyclization:

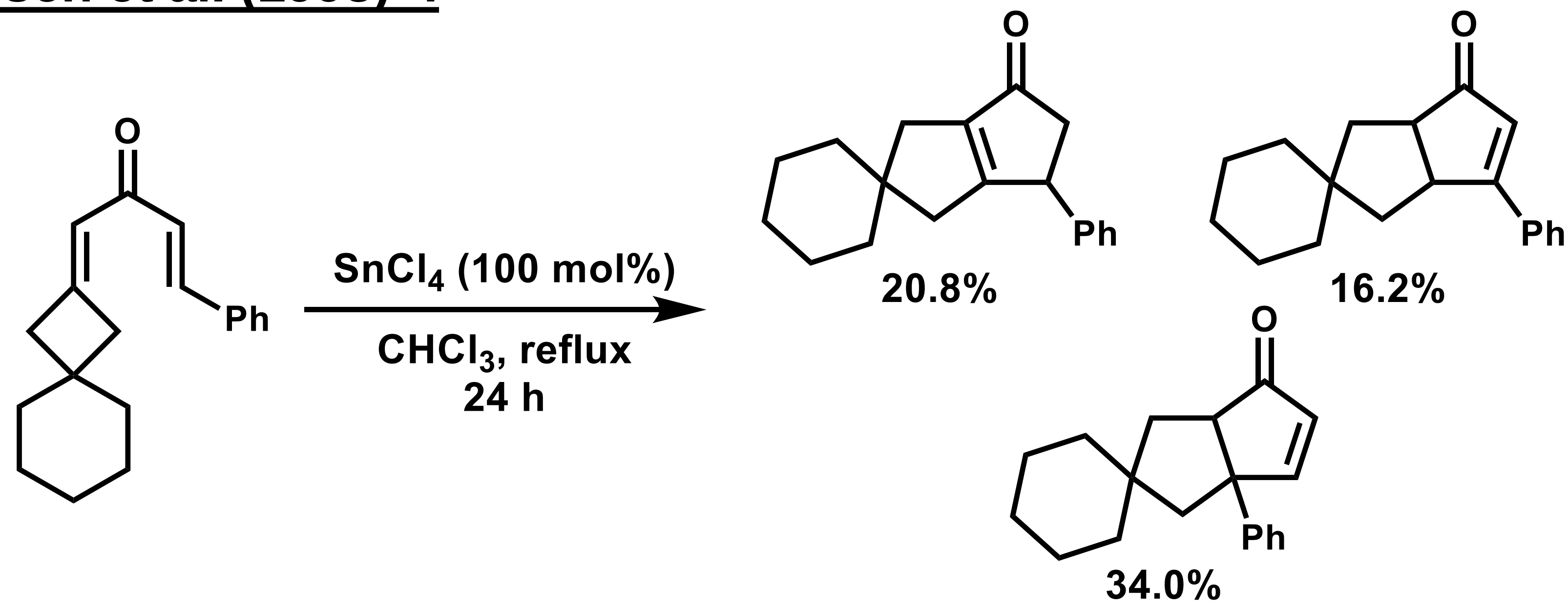


Followed by Wagner-Meerwein rearrangement:

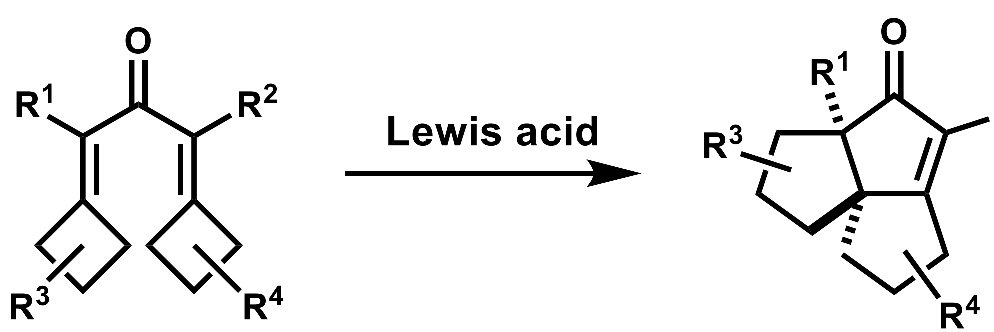


Nazarov Cyclization

Reusch et al. (1993)[6]:



Tu et al. (2022)[1]:



Introduction of Prof. Yong-Qiang Tu

Education & Academic Career:

- 1982: B.S. @ Lanzhou University, China
- 1985: M.S. @ S/A (Prof. Wen-Kui Huang)
- 1989: Ph.D. @ S/A (Prof. Yao-Zu Chen)
- 1993-1995: Postdoctoral Fellow @ University of Queensland, Australia (Prof. William Kitching)
- 1995-present: Full Professor @ Lanzhou University, China
- 2004-2005: Visiting Professor @ Bielefield University, Germany

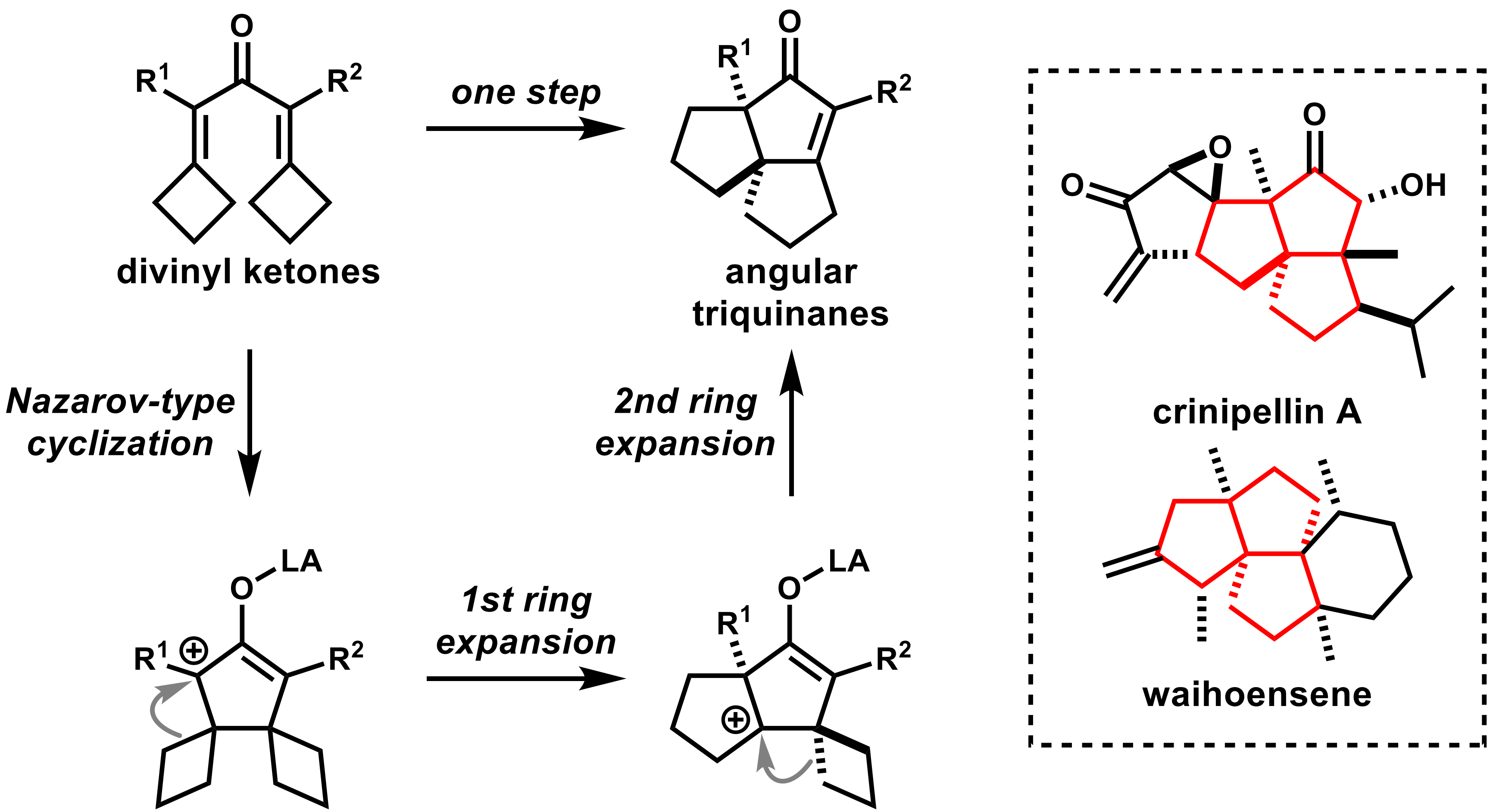
Research Interests:

- Organic synthetic methodology
- Total synthesis of natural products and pharmaceutical molecules
- Organometallic chemistry

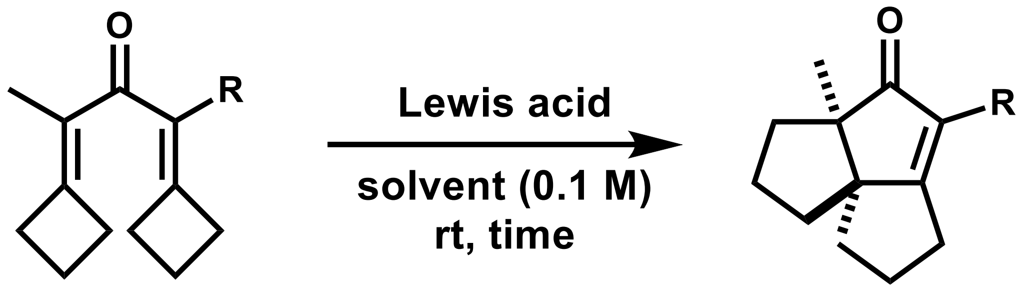
Contents

1. Introduction
2. **Tandem Nazarov Reaction**[1)]
3. Application to Total Synthesis
    1) Total Synthesis of Waihoensene[1)]
    2) Total Syntheses of Phomopsene Diterpenes[2)]
4. Summary

Design of Reaction



Optimization of Conditions



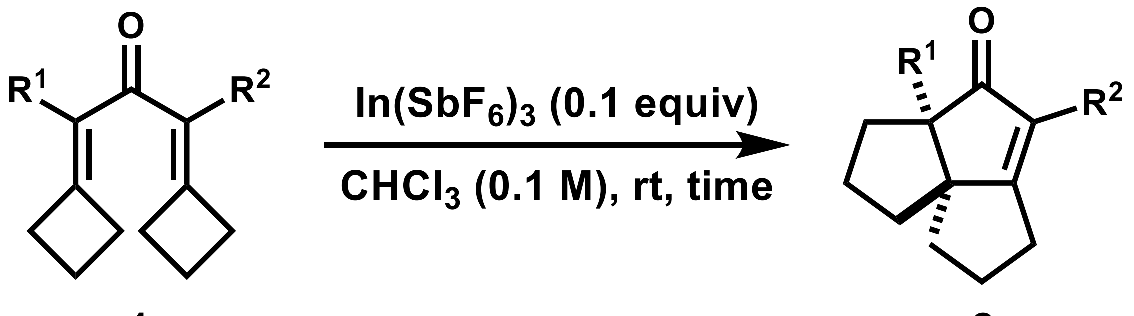
1a: R = Me
1b: R = CO_2Me

2a: R = Me
2b: R = CO_2Me

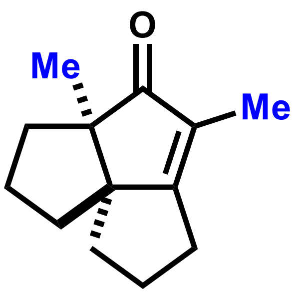
Table 1

entry	substrate	Lewis acid (equiv)	solvent	time (h)	yield (%)
1	1a	$Cu(OTf)_2$ (0.2)	CH_2Cl_2	24	71 (93 brsm)
2	1a	$BF_3 \cdot Et_2O$ (1.0)	CH_2Cl_2	0.25	96
3	1a	$In(SbF_6)_3$ (0.1)	Et_2O	0.25	97
4	1a	$In(SbF_6)_3$ (0.1)	$CHCl_3$	0.5	95
5	1b	$Cu(OTf)_2$ (0.2)	CH_2Cl_2	24	not detected
6	1b	$BF_3 \cdot Et_2O$ (1.0)	CH_2Cl_2	24	75
7	1b	$In(SbF_6)_3$ (0.2)	Et_2O	12	not detected
8	1b	$In(SbF_6)_3$ (0.1)	$CHCl_3$	12	81
9	1b	$TiCl_4$ (1.0)	CH_2Cl_2	48	49 (71 brsm)

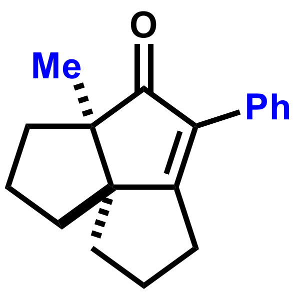
Scope of Substrates



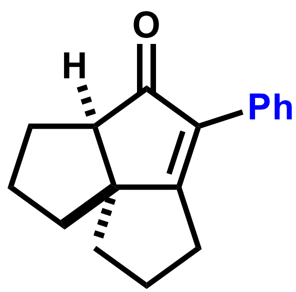
1 **2**



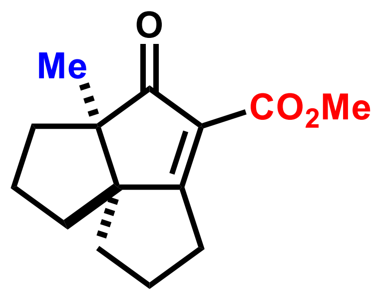
0.5 h, 95%



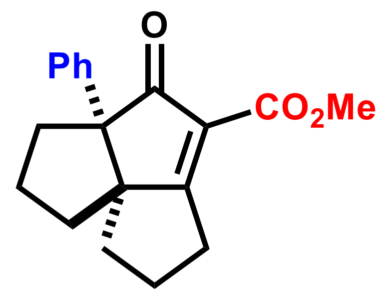
0.5 h, 75%



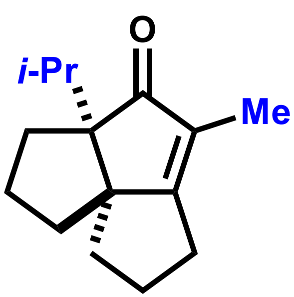
4 h, 71%



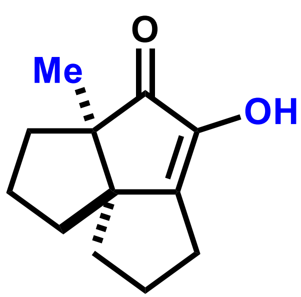
12 h, 81%



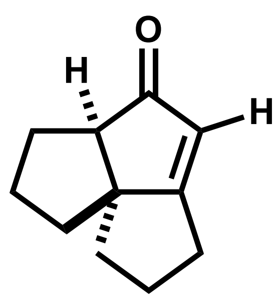
12 h, 85%



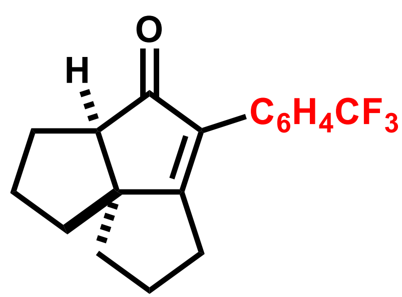
0.5 h, 80%



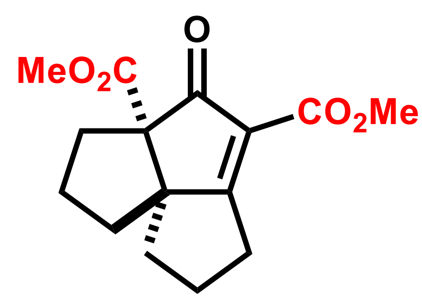
1 h, 80%



no reaction

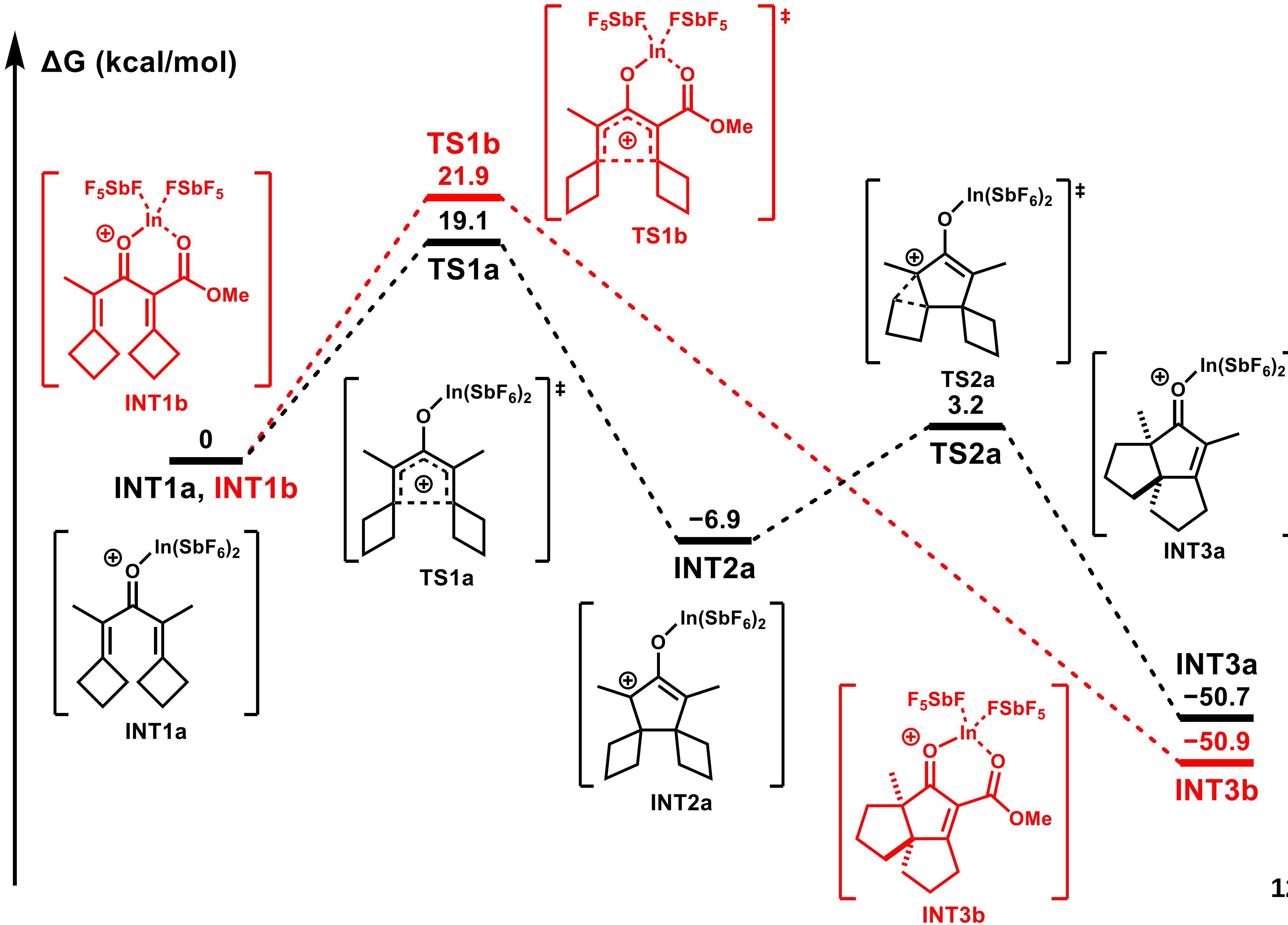


48 h, 51%



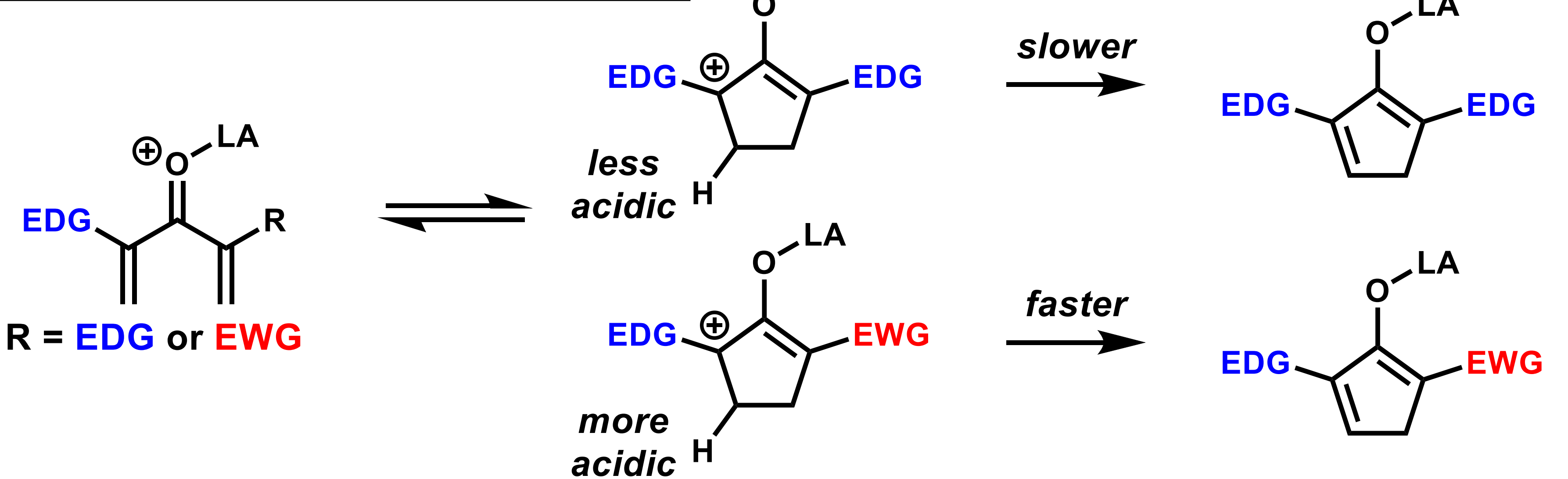
no reaction

Mechanism Study by DFT Calculation

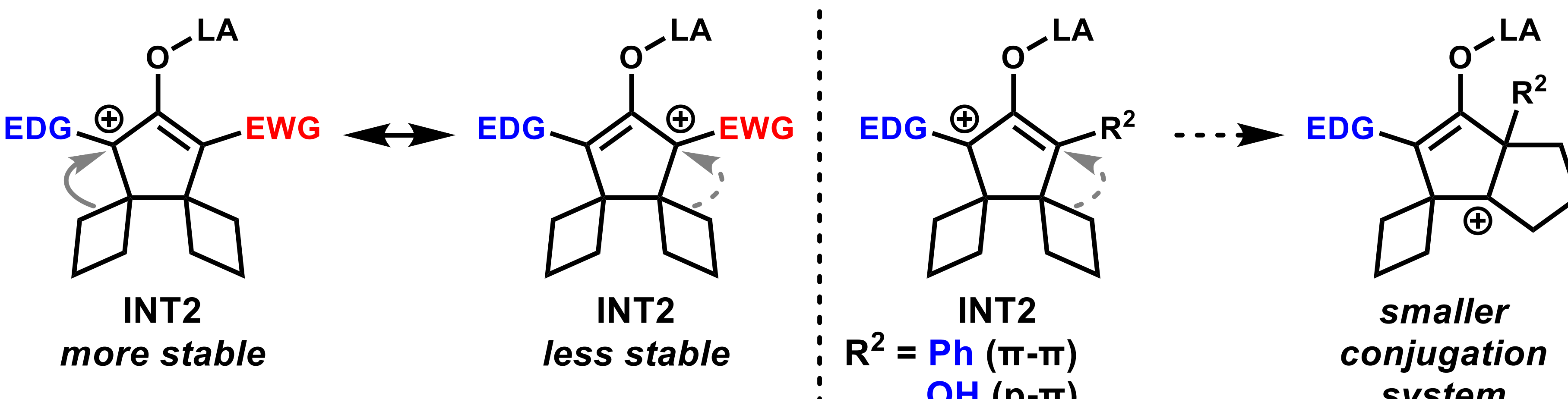


Proposed Mechanism

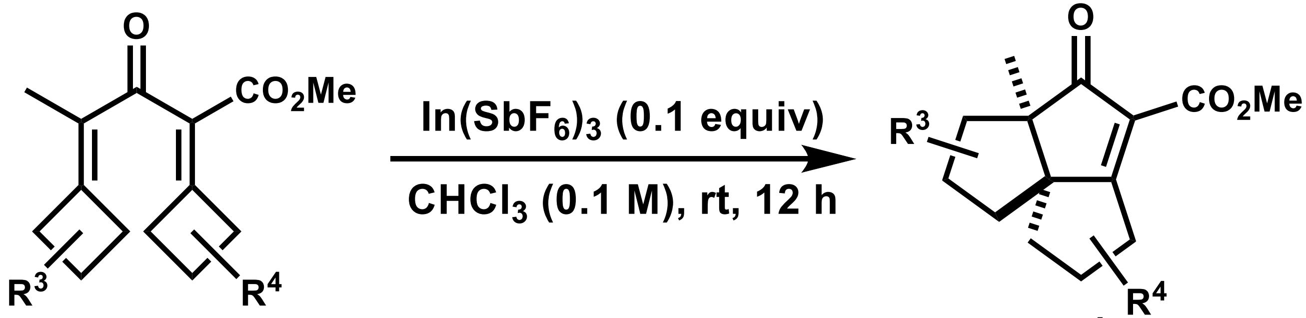
In classical Nazarov cyclization:



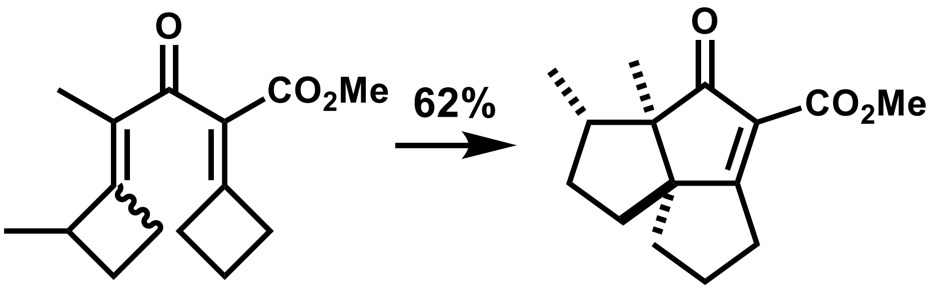
Regioselectivity of ring expansion:

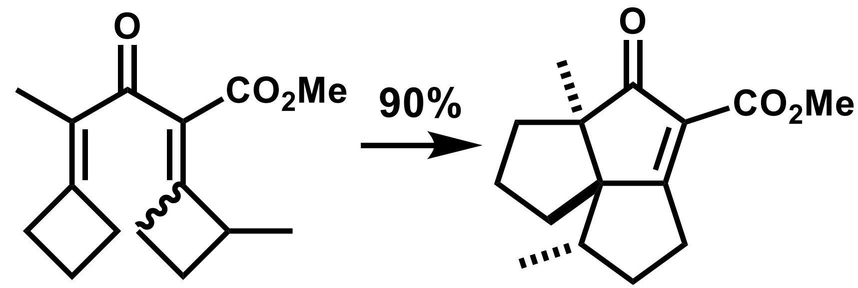


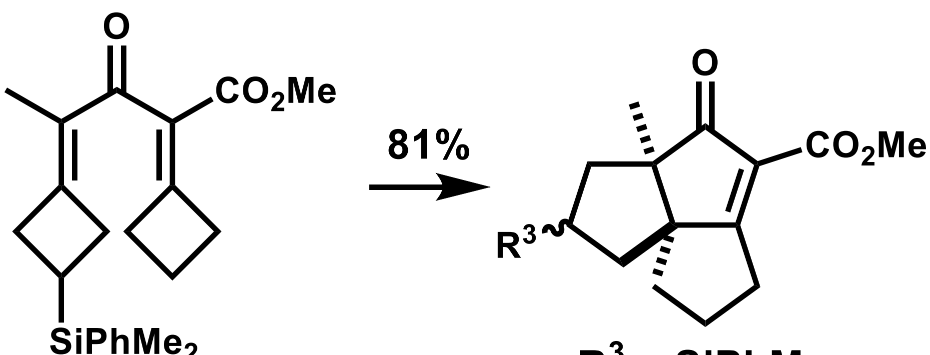
Scope of Substrates



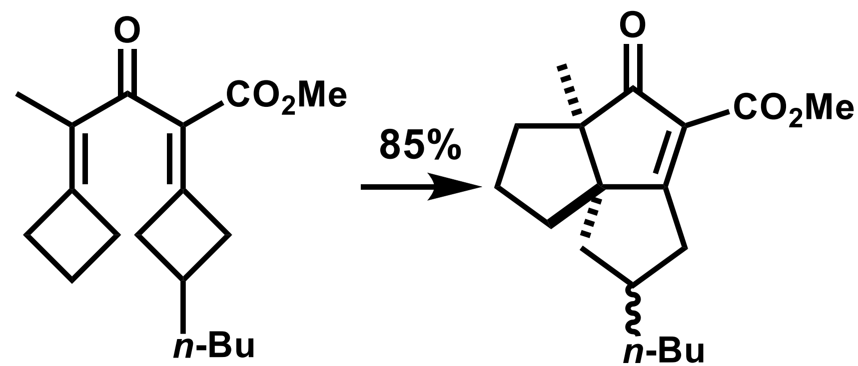
3 4





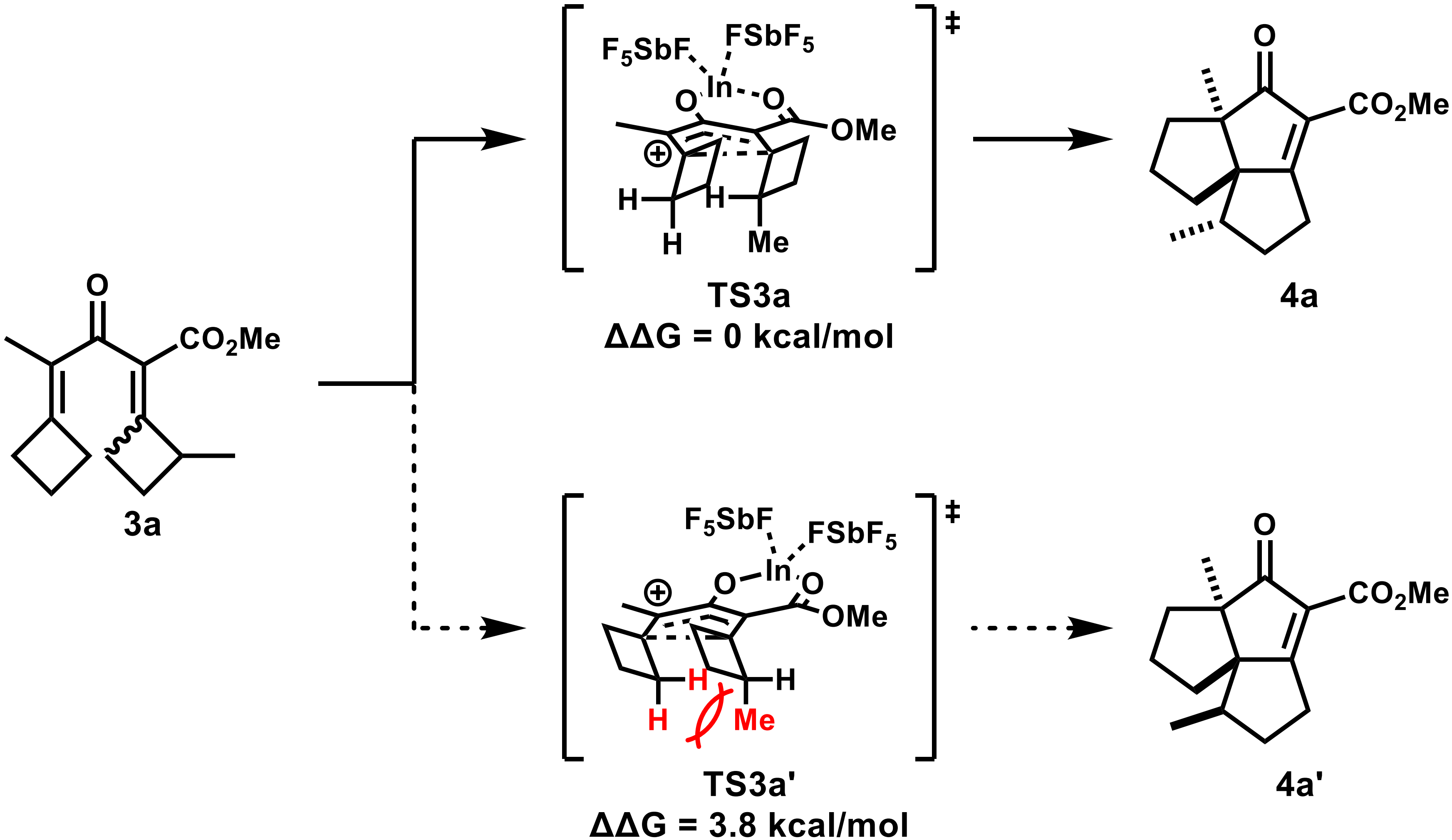


R^3 = $SiPhMe_2$
α/β = 1/4

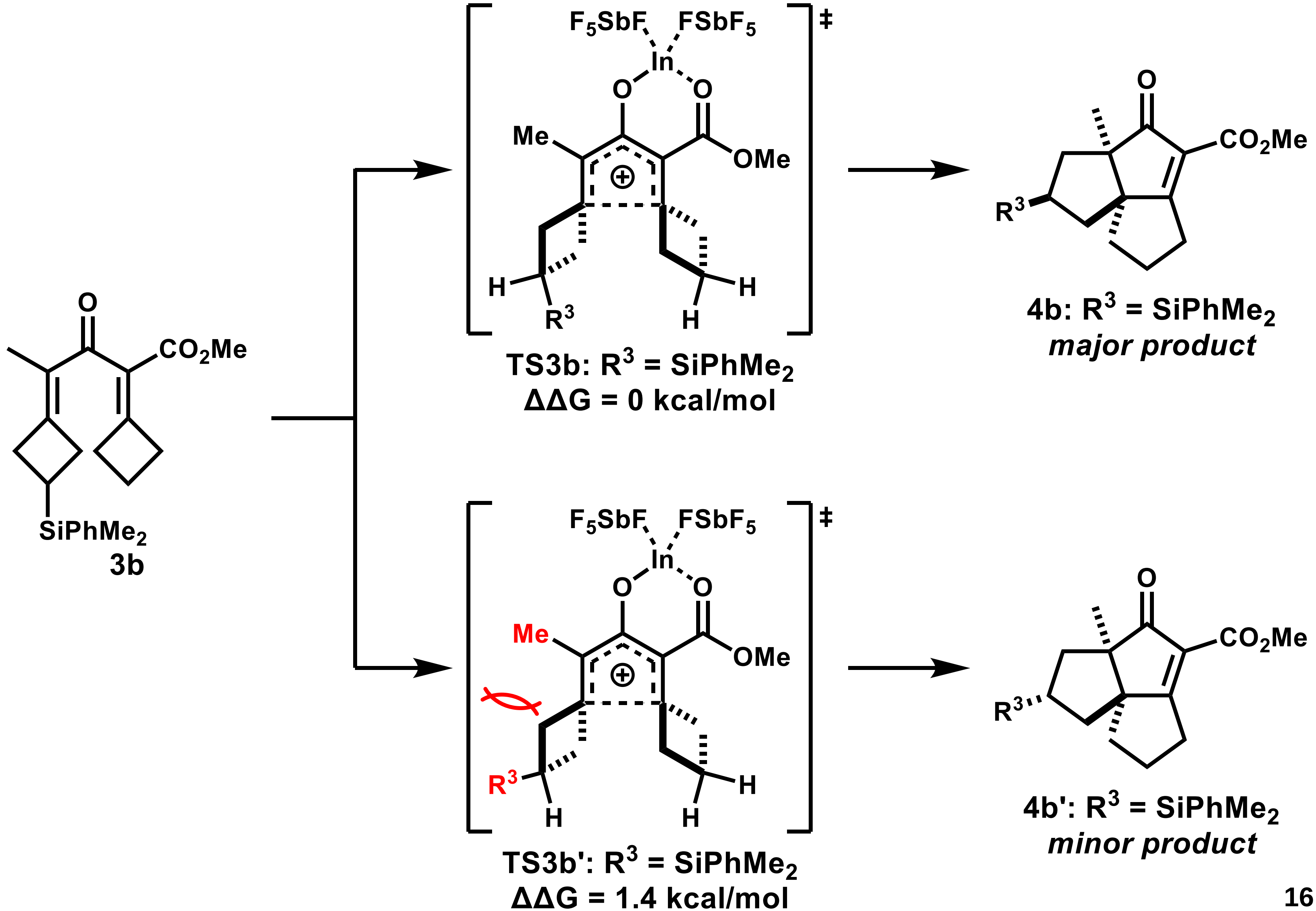


α/β = 1/3

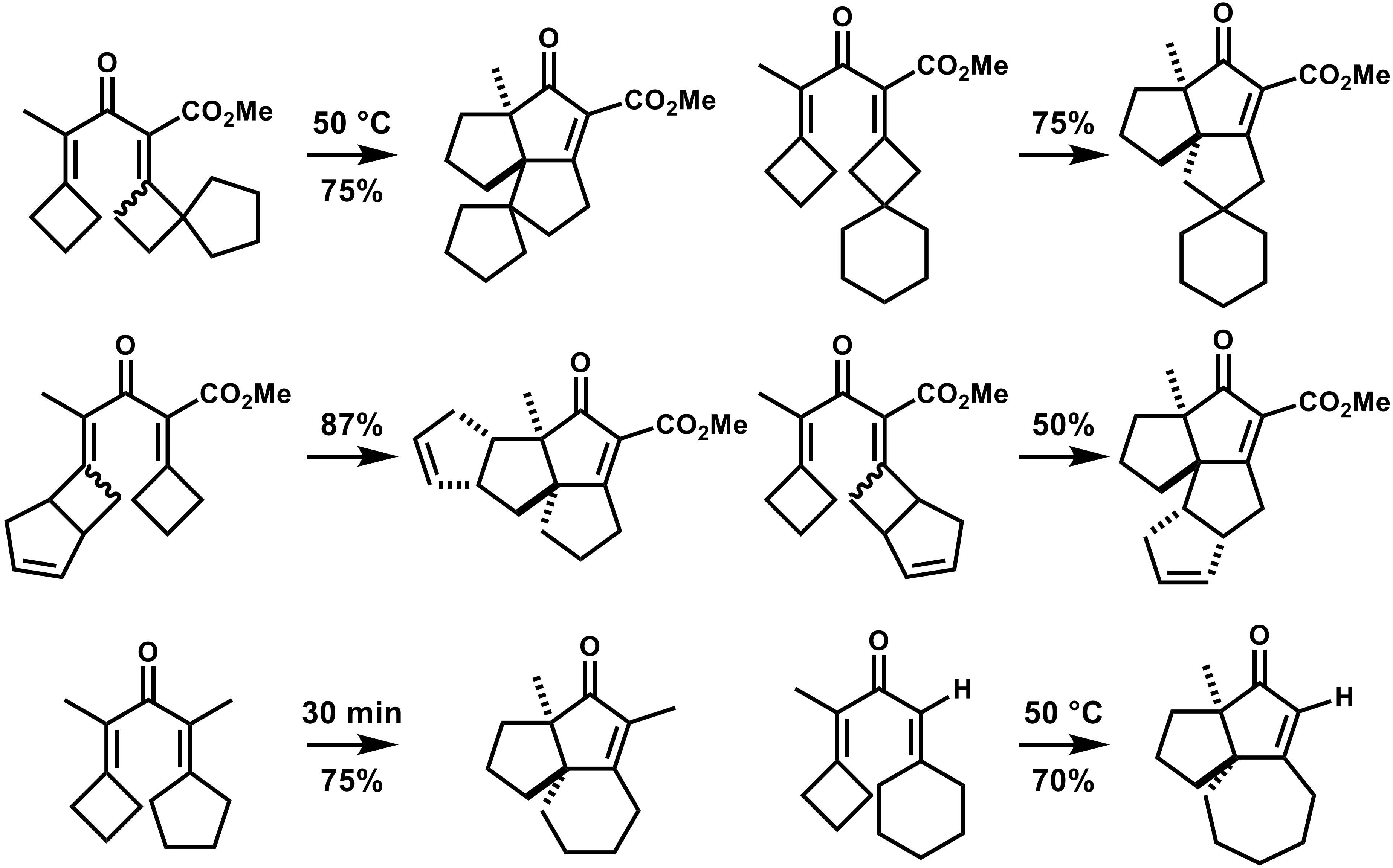
Proposed Mechanism



Proposed Mechanism



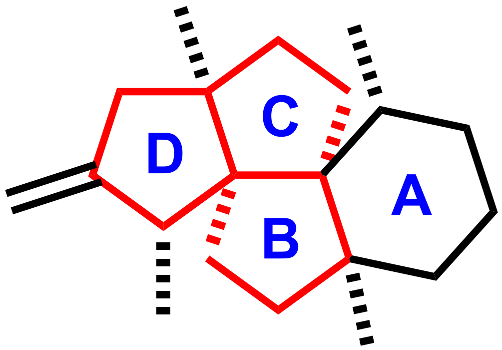
Scope of Substrates



Conditions (unless noted): $In(SbF_6)_3$ (0.1 equiv), $CHCl_3$ (0.1 M), rt, 12 h

Contents

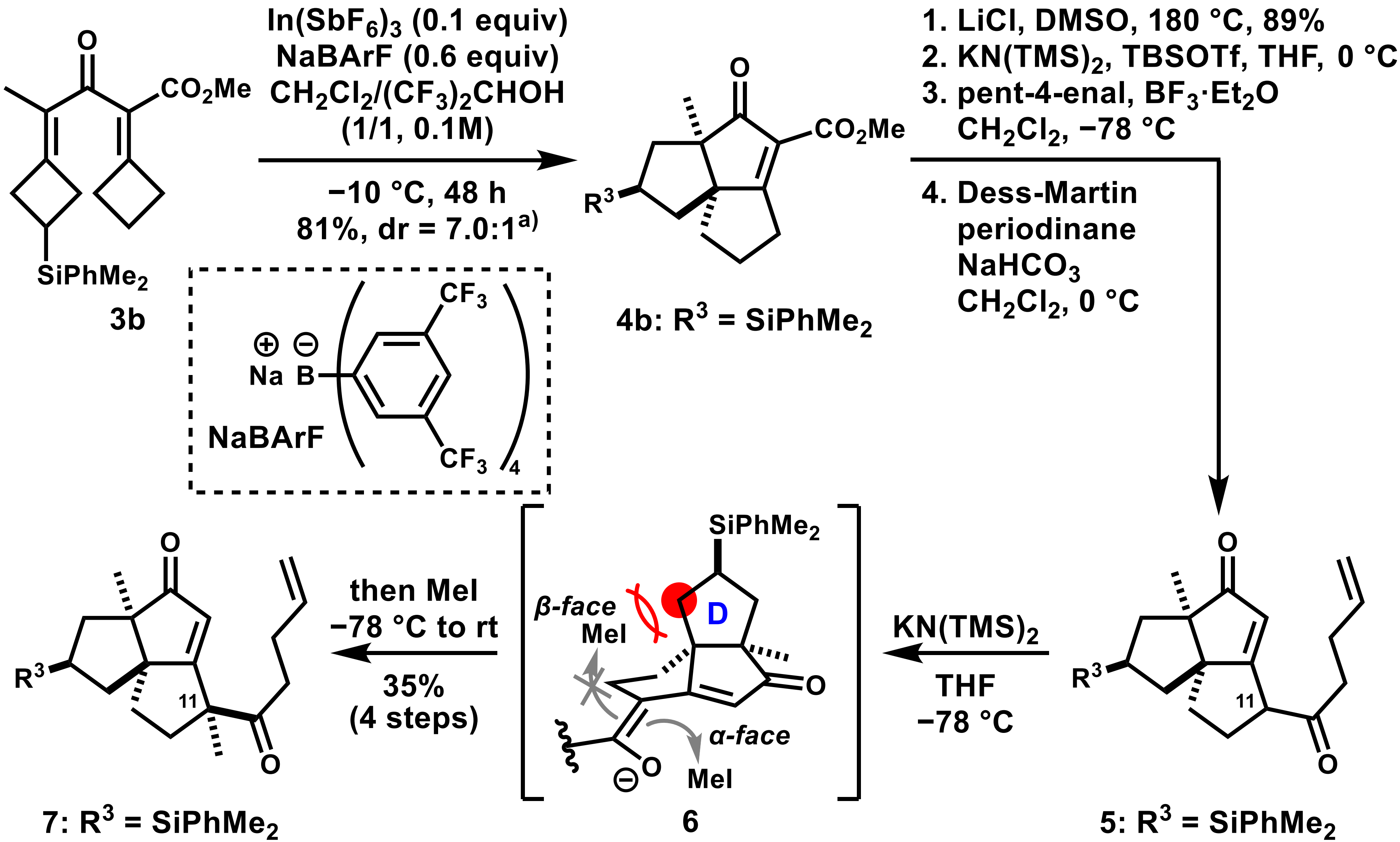
Waihoensene



Isolation: plant ***Podocarpus totara var. waihoensis***
Biological activity: not reported
Structural features:
- **6/5/5/5 tetracyclic core**
- **angularly fused A/B/C ring and B/C/D ring**
- **4 quaternary centers**
- **6 contiguous stereocenters**

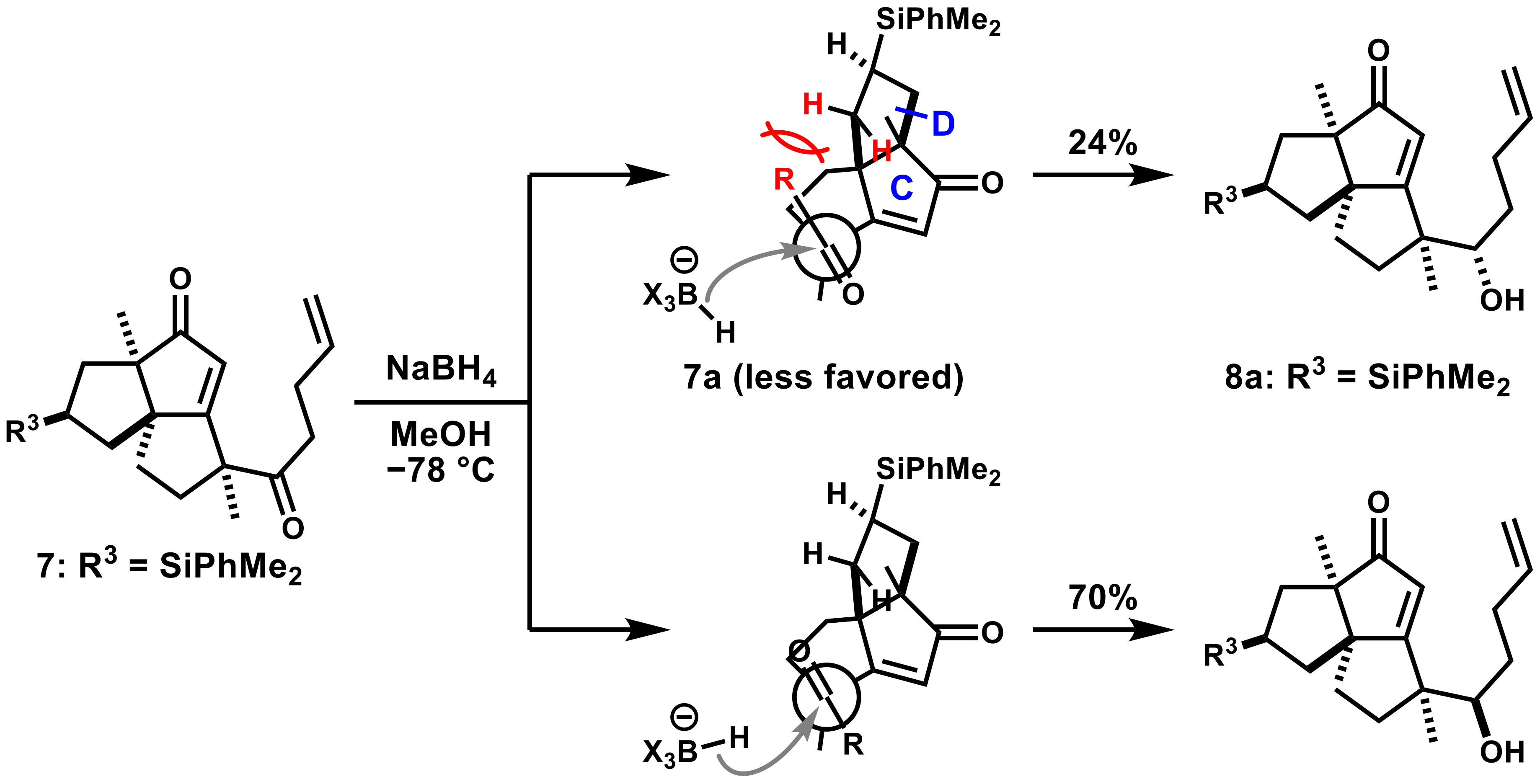
Total synthesis: **(5 examples)**
- **Lee et al. (2017, racemic)[7)] ⇒ 200919_PS_Yuma_Komori**
- **Yang et al. (2020, asymmetric)[8)] ⇒ 200919_PS_Yuma_Komori**
- **Snyder et al. (2020, asymmetric)[9)]**
- **Gaich et al. (2021, racemic & asymmetric)[10)]**
- **Tu et al. (2022, racemic)[1)]**

Synthesis of Waihoensene



a) Previous conditions: In$(SbF_6)_3$ (0.1 equiv), $CHCl_3$ (0.1 M), rt, 12 h, 81%, dr = 4:1

Synthesis of Waihoensene



7: R^3 = $SiPhMe_2$

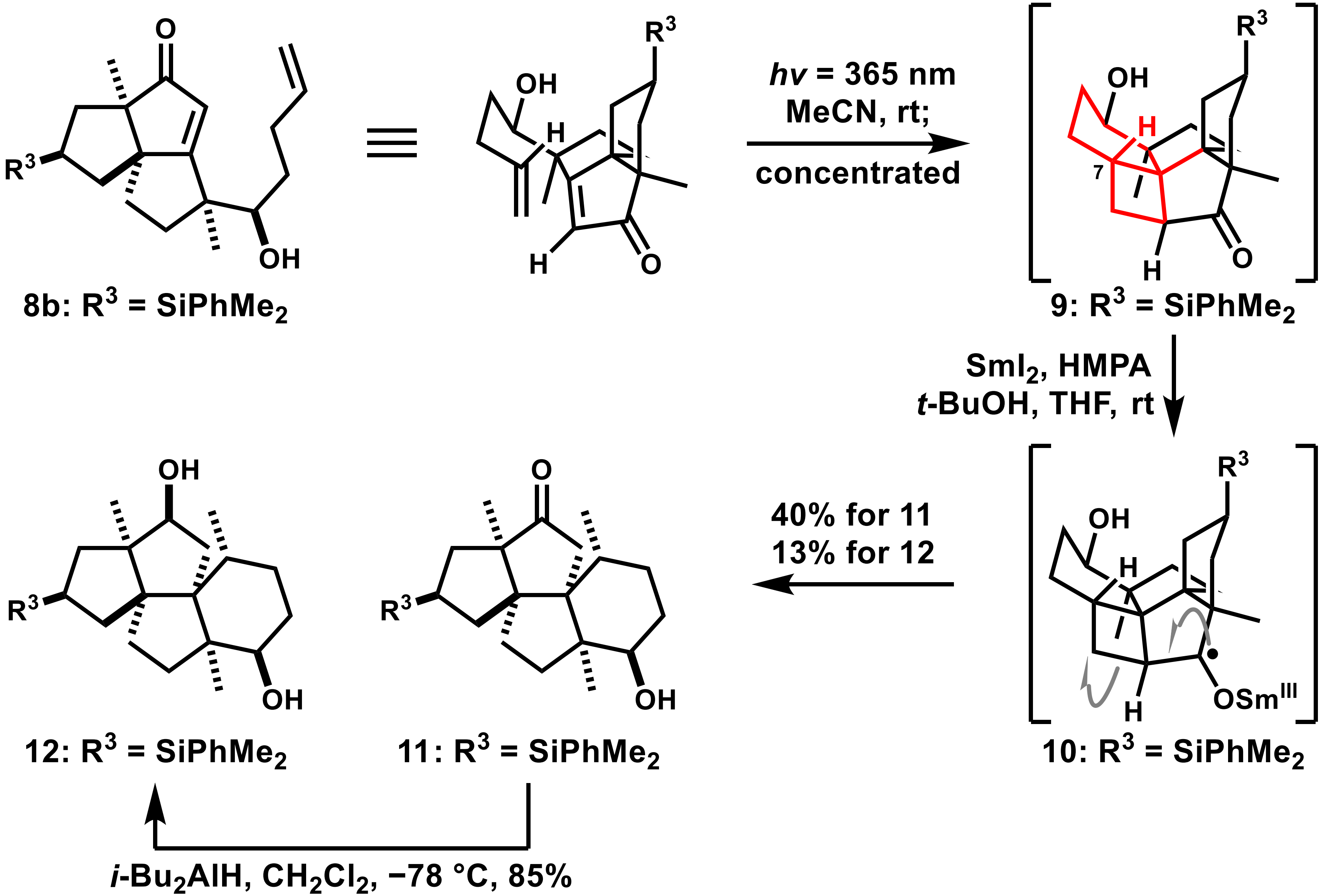
7a (less favored)

7b (more favored)

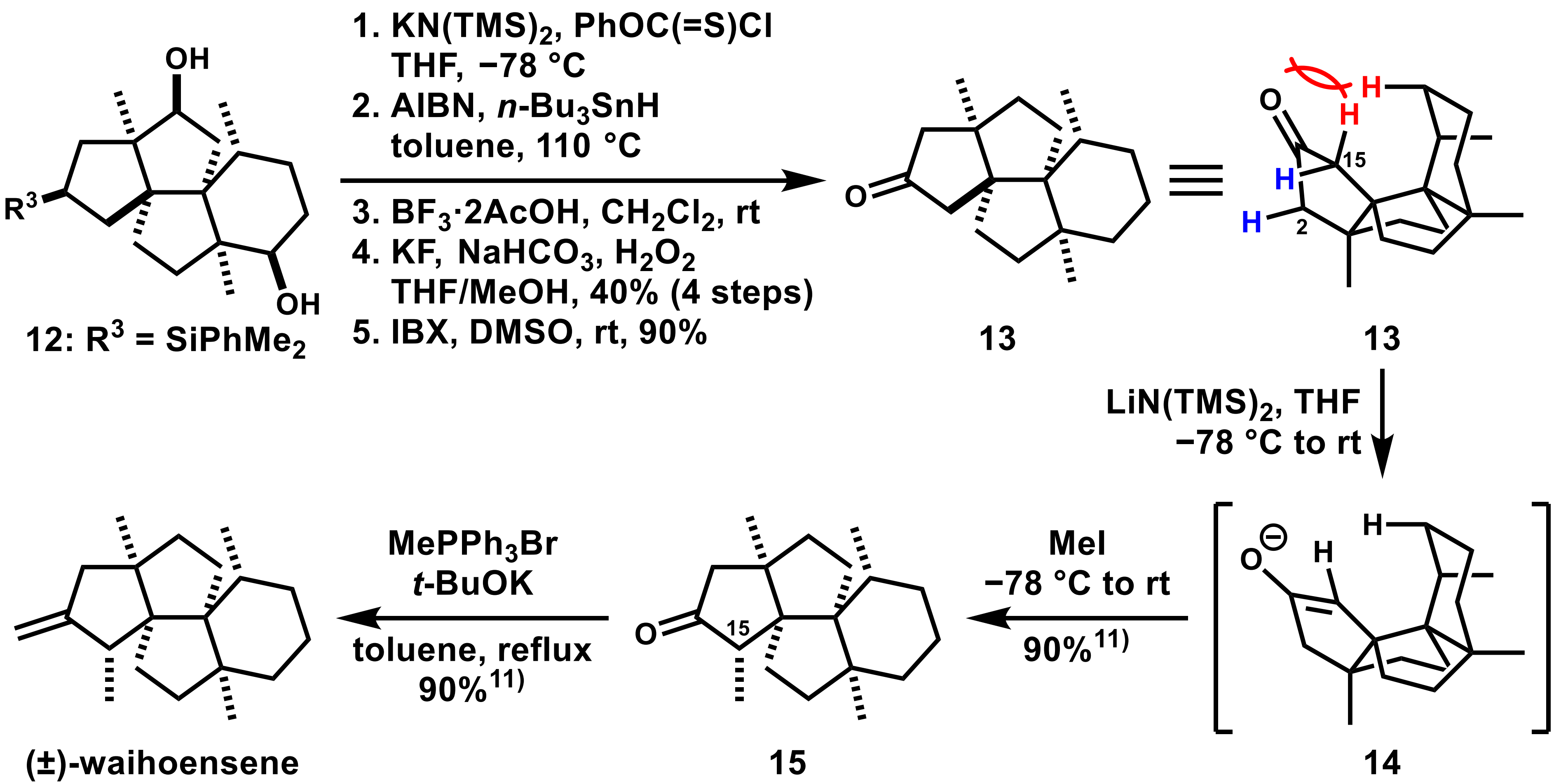
8a: R^3 = $SiPhMe_2$

8b: R^3 = $SiPhMe_2$

Synthesis of Waihoensene



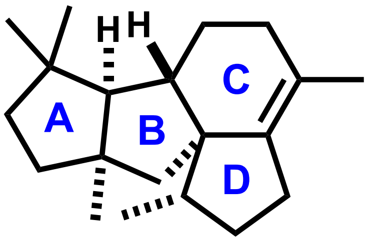
Synthesis of Waihoensene



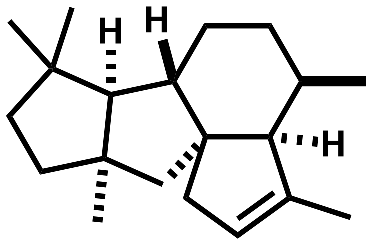
11) Qu, Y.; Wang, Z.; Zhang, Z.; Zhang, W.; Huang, J.; Yang, Z. *J. Am. Chem. Soc.* **2020**, *142*, 6511.

Contents

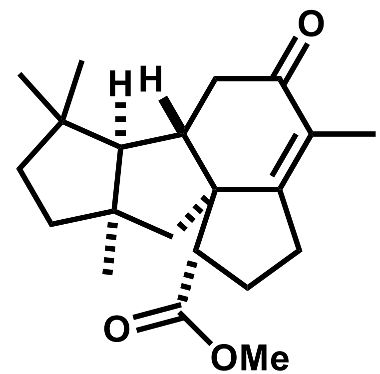
Phomopsene Diterpenes



phomopsene



iso-phomopsene
(originally proposed)



methyl
phomopsenonate

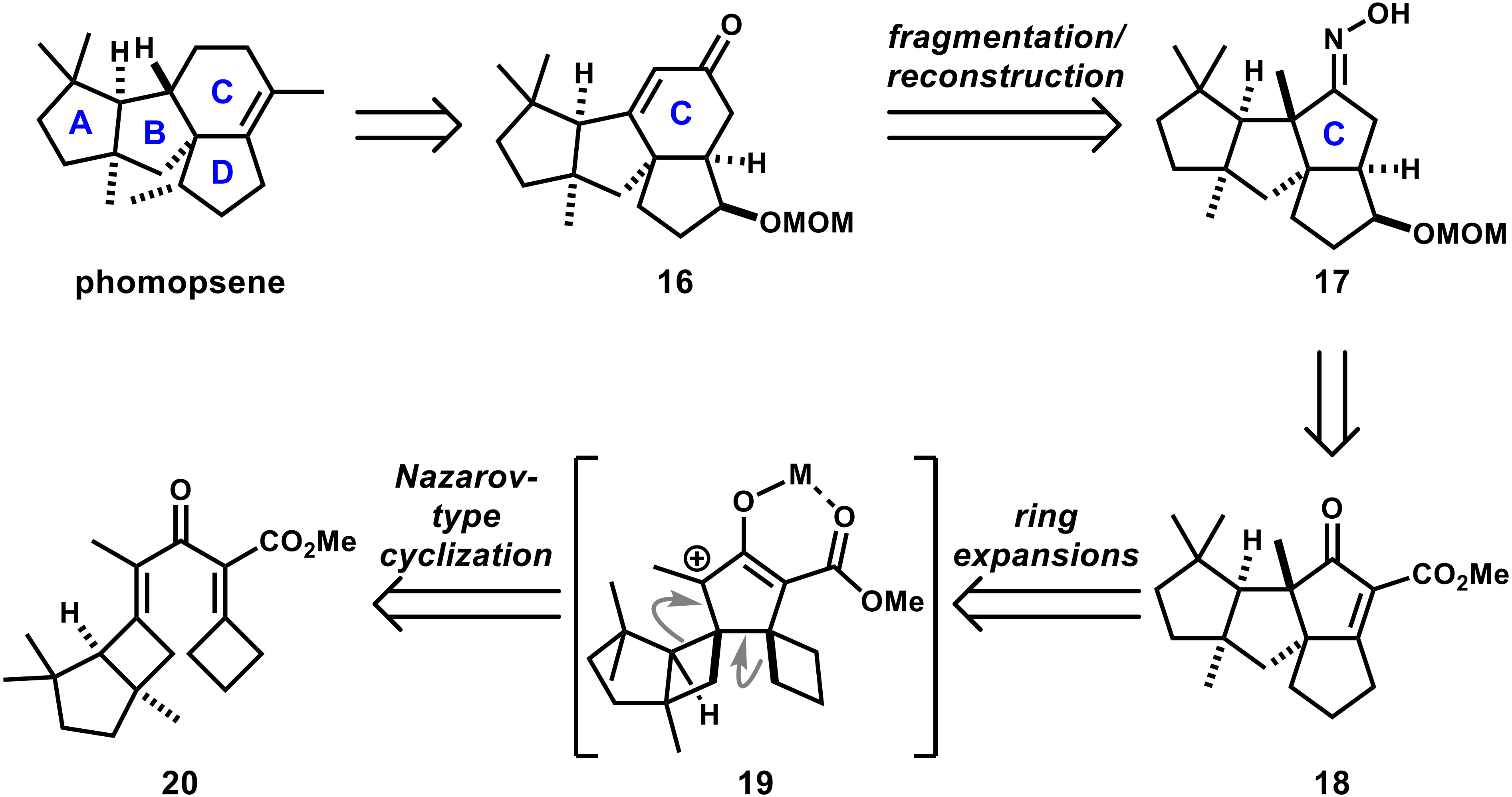
Isolation: fugus *Phomopsis amygdali*
Biological activity: not reported
Structural features:

- unique 5/5/6/5 tetracyclic core
- 3 quaternary centers
- 5-6 contiguous stereocenters

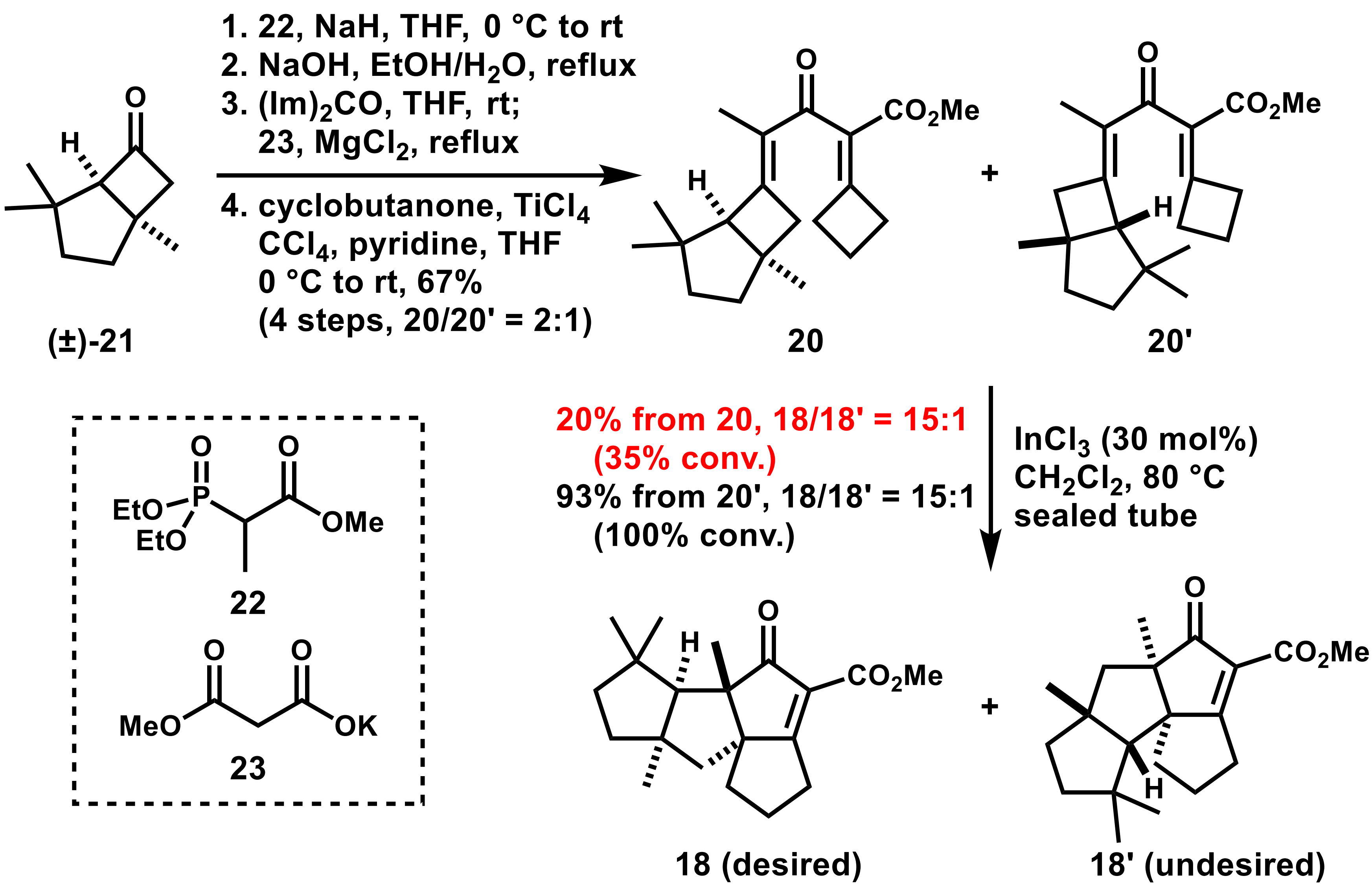
Total sythesis: (1 example)

- Tu et al. (2023, racemic and asymmetric)[2)]

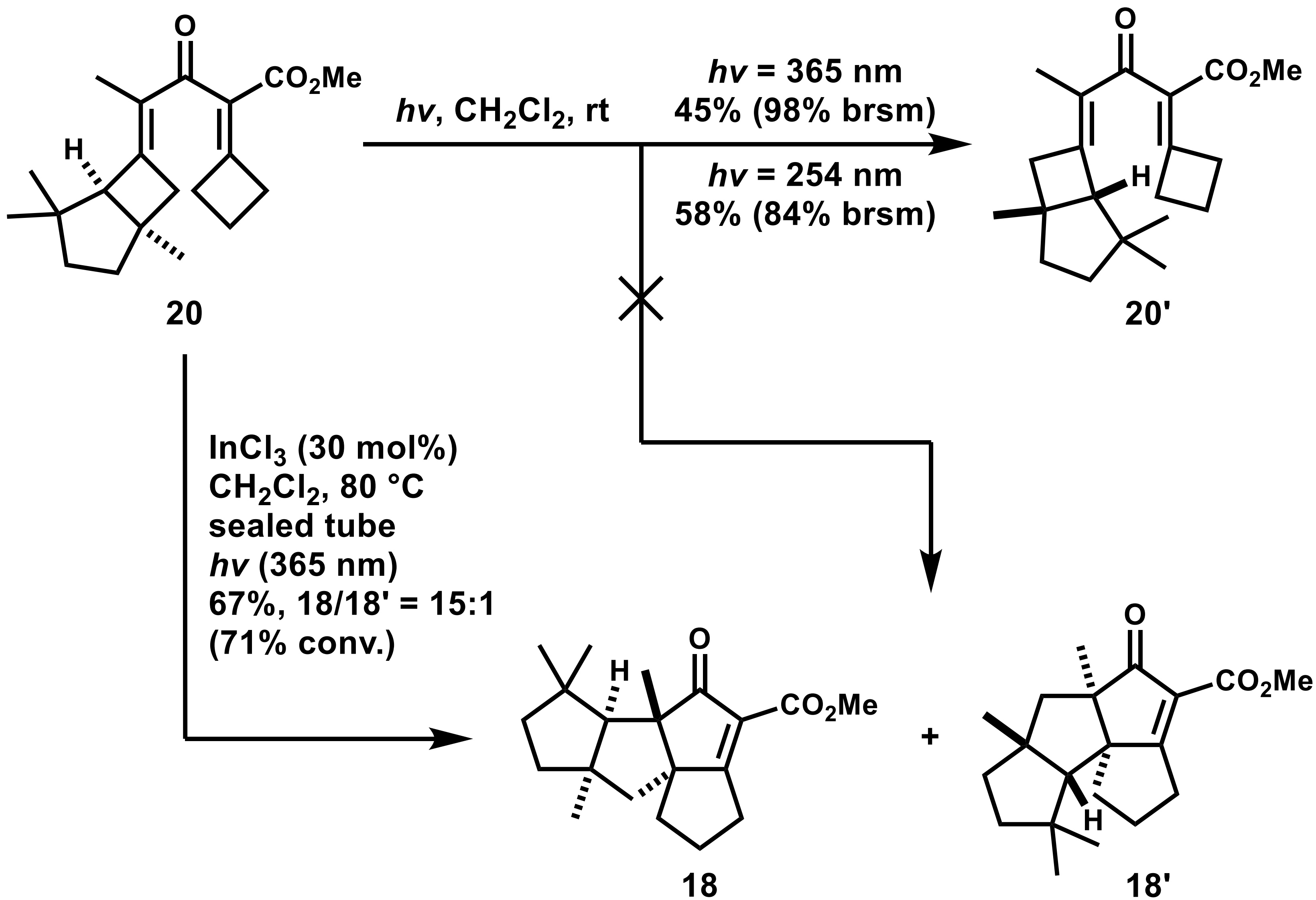
Retrosynthetic Analysis



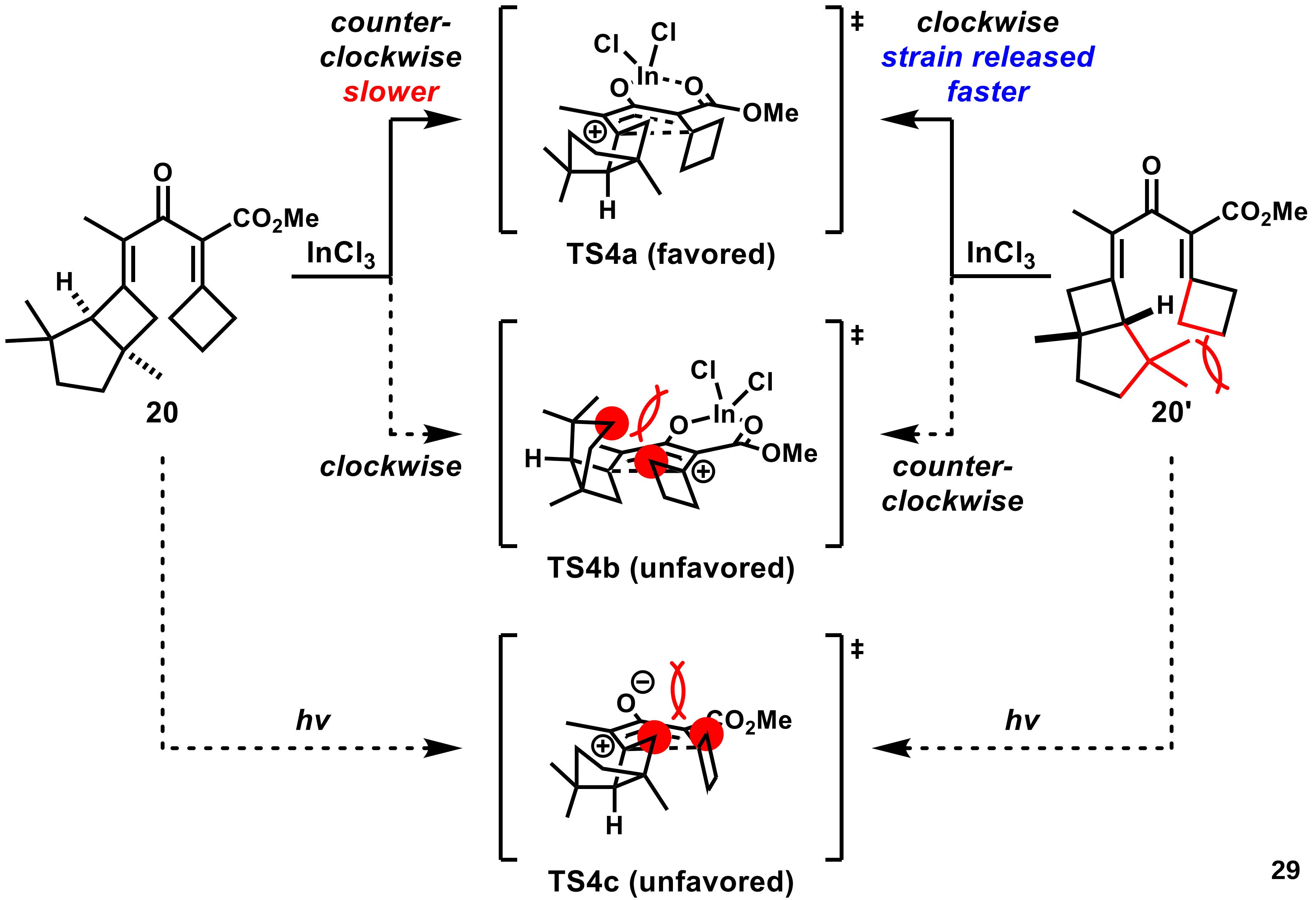
Synthesis of Tetracyclic Core



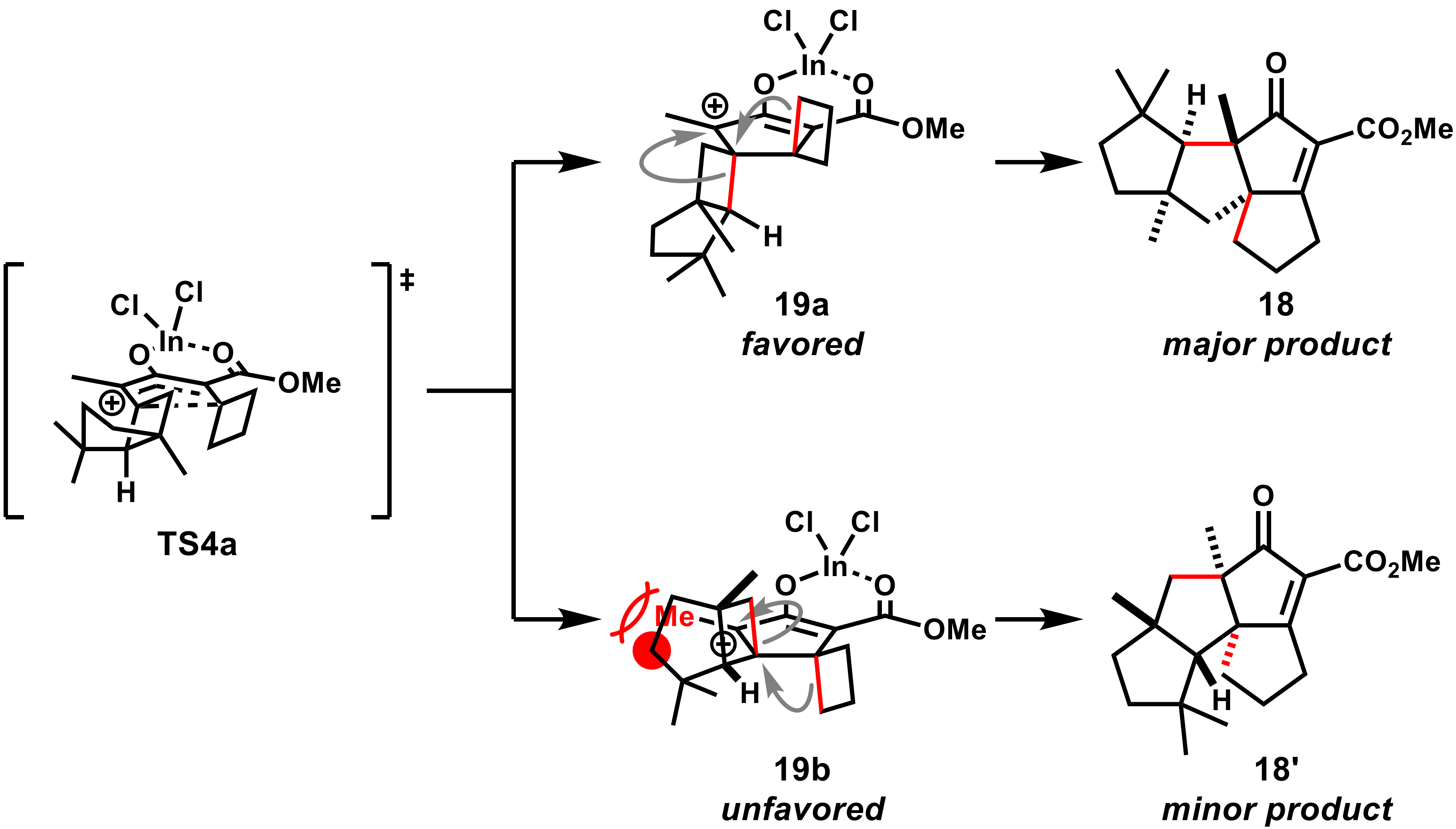
Synthesis of Tetracyclic Core



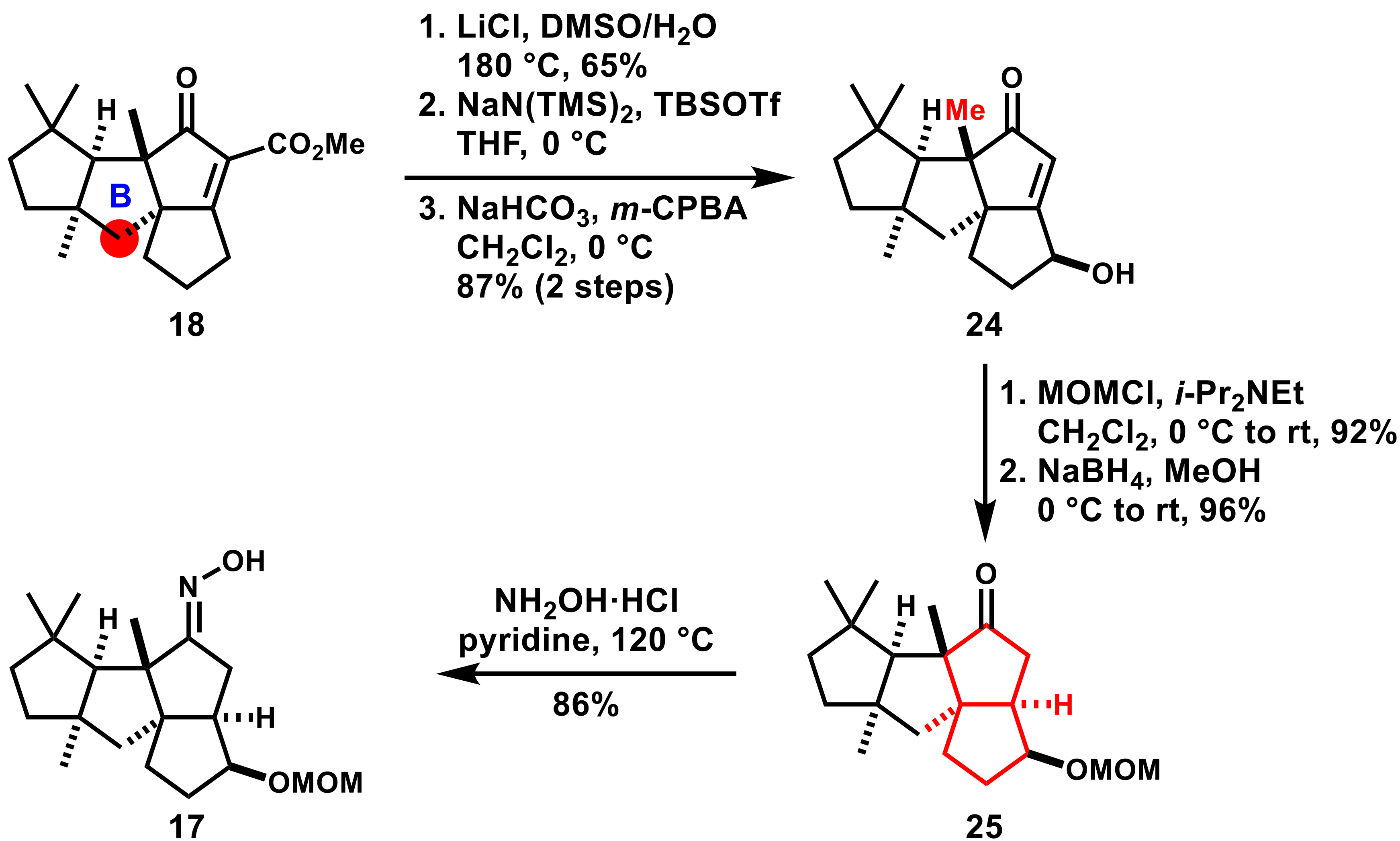
Proposed Mechanism



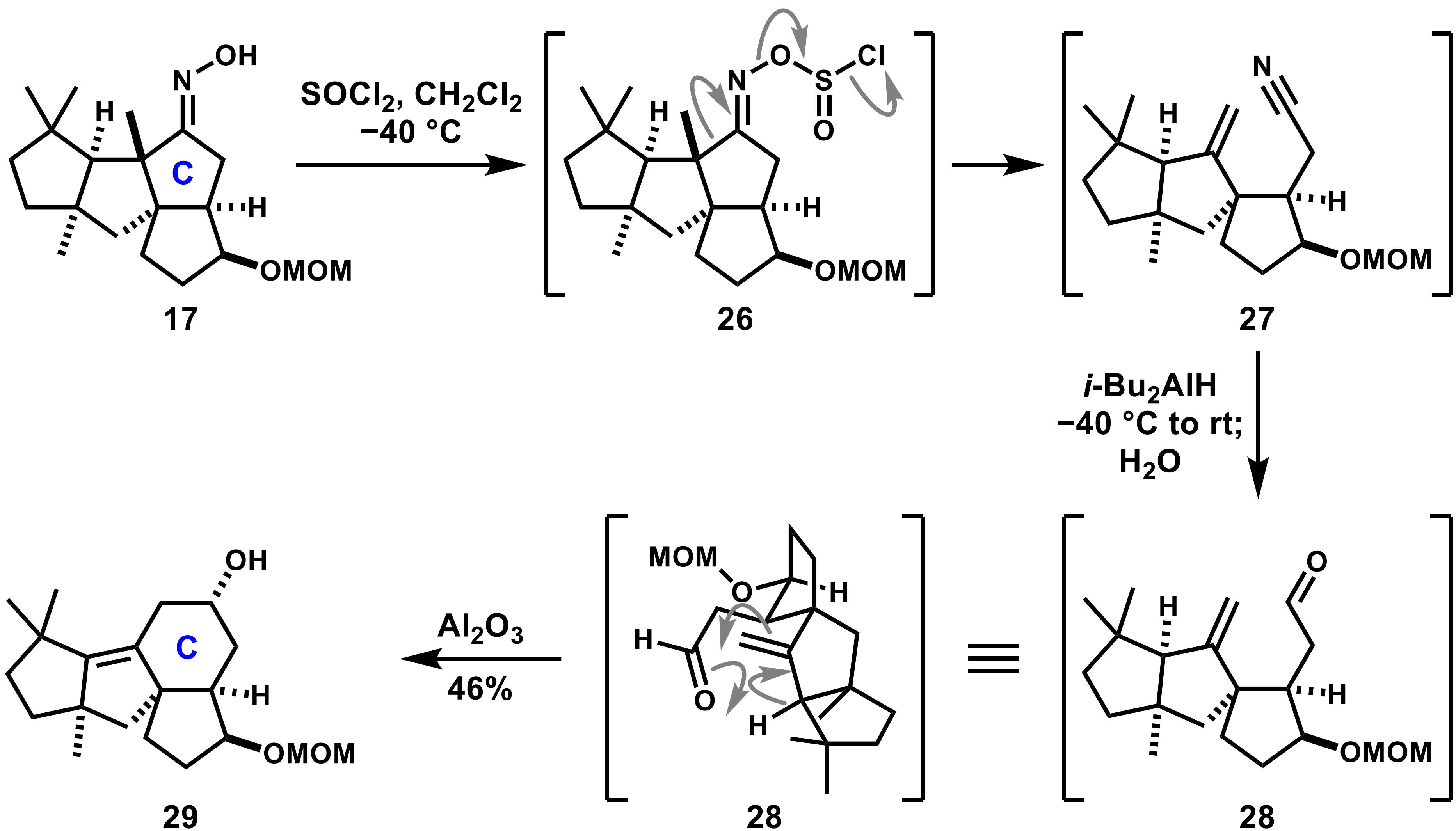
Proposed Mechanism



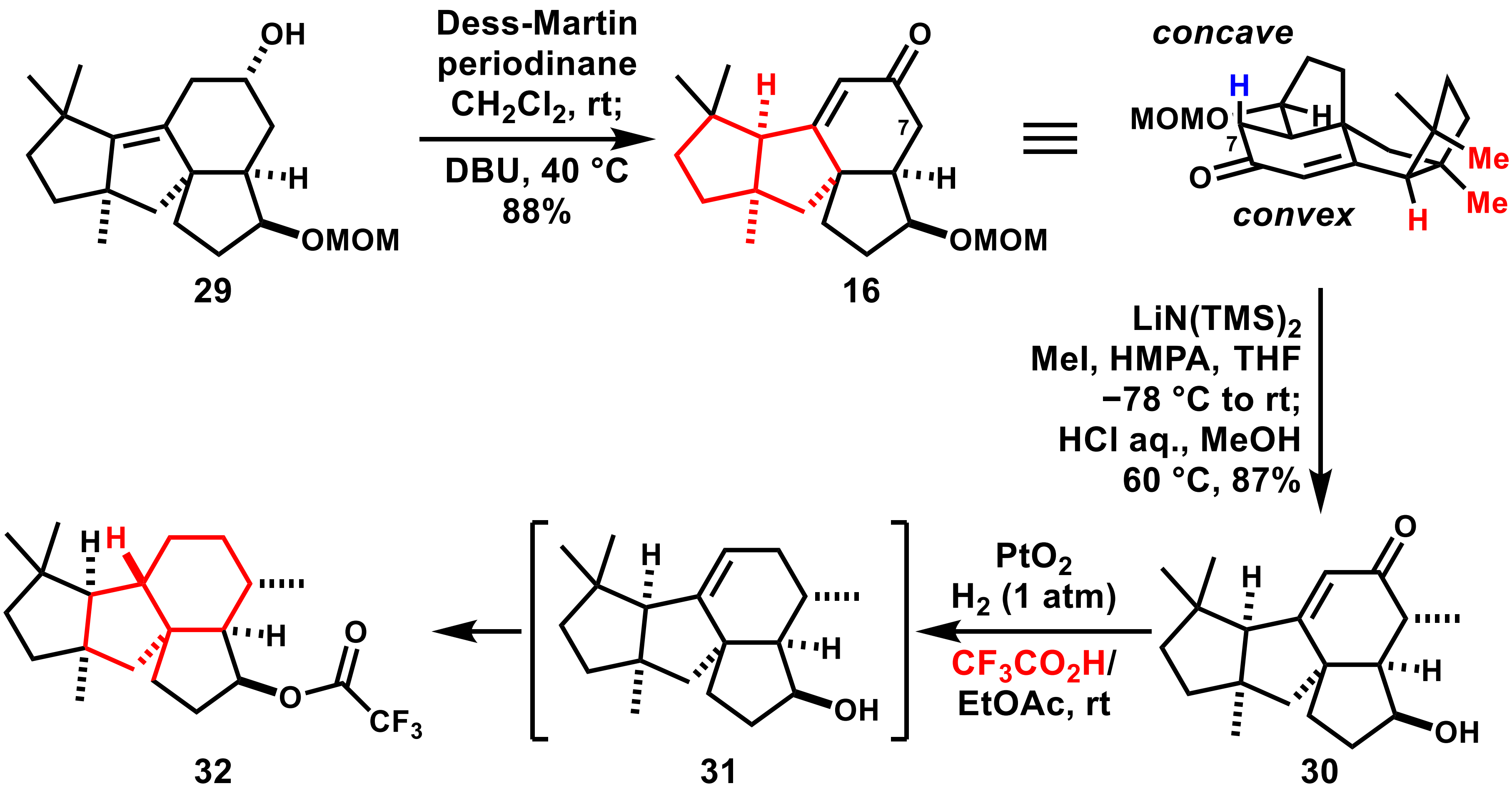
Functionalization



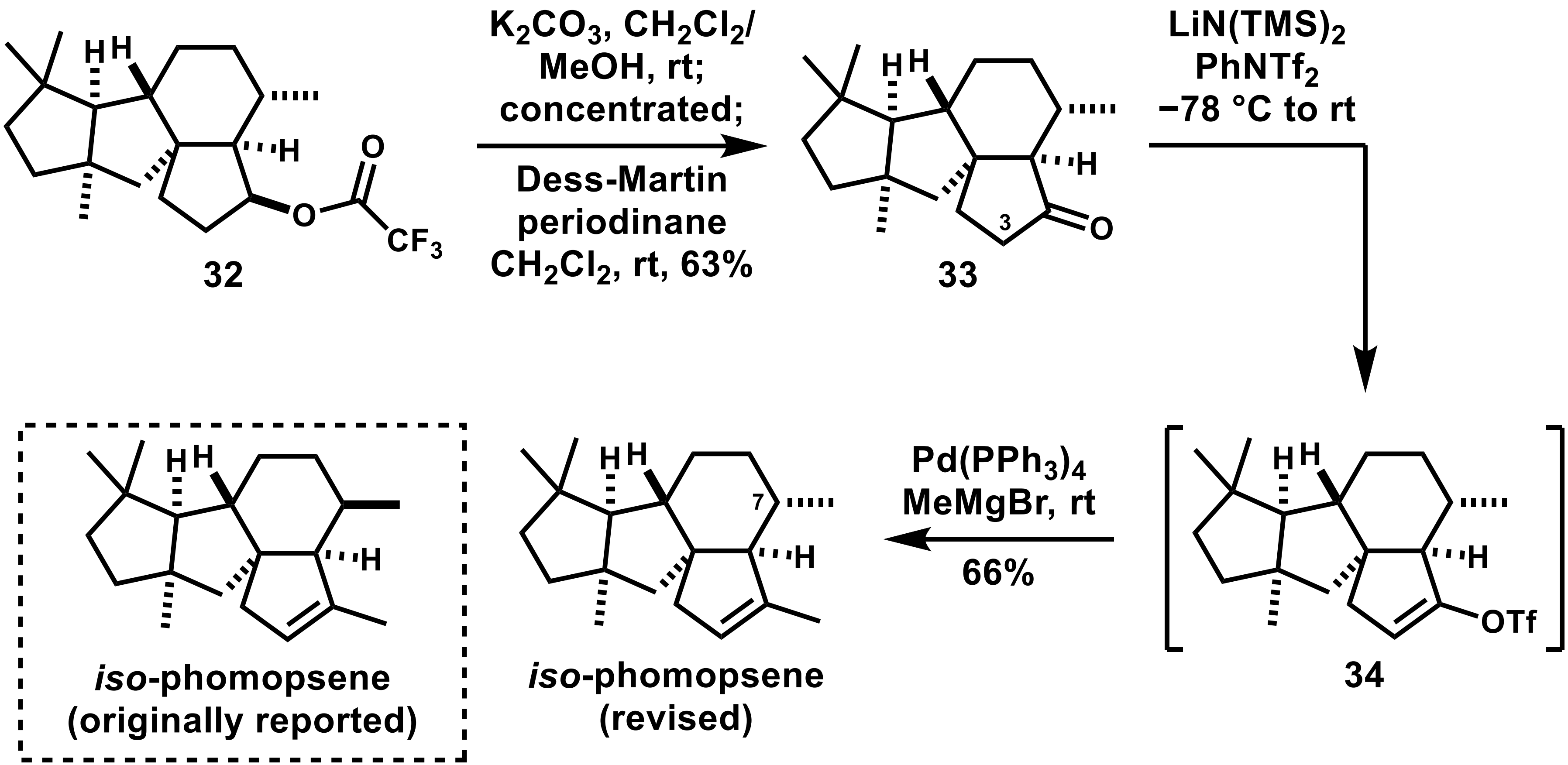
C-Ring Expansion



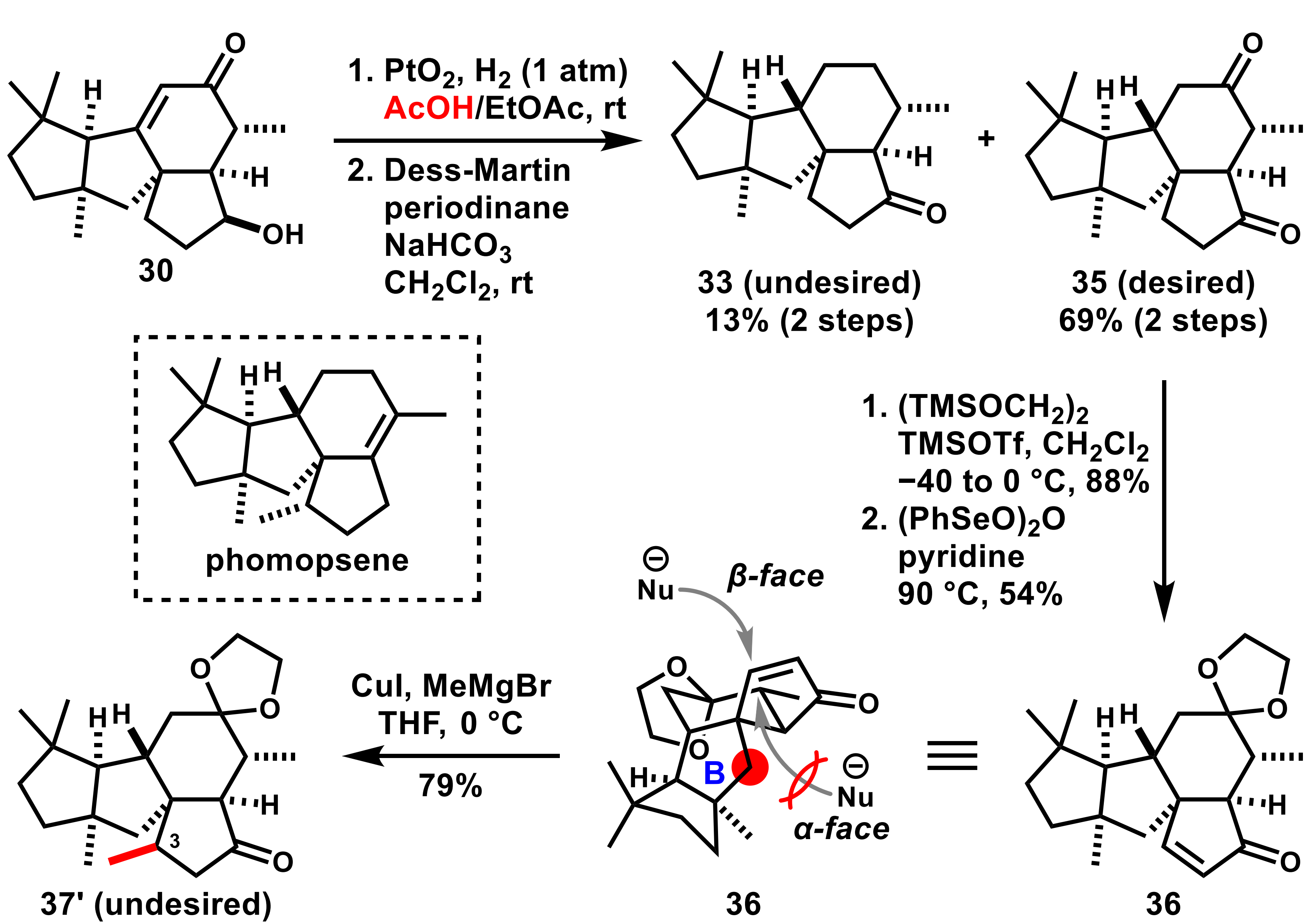
Total Synthesis of *iso*-Phomopsene



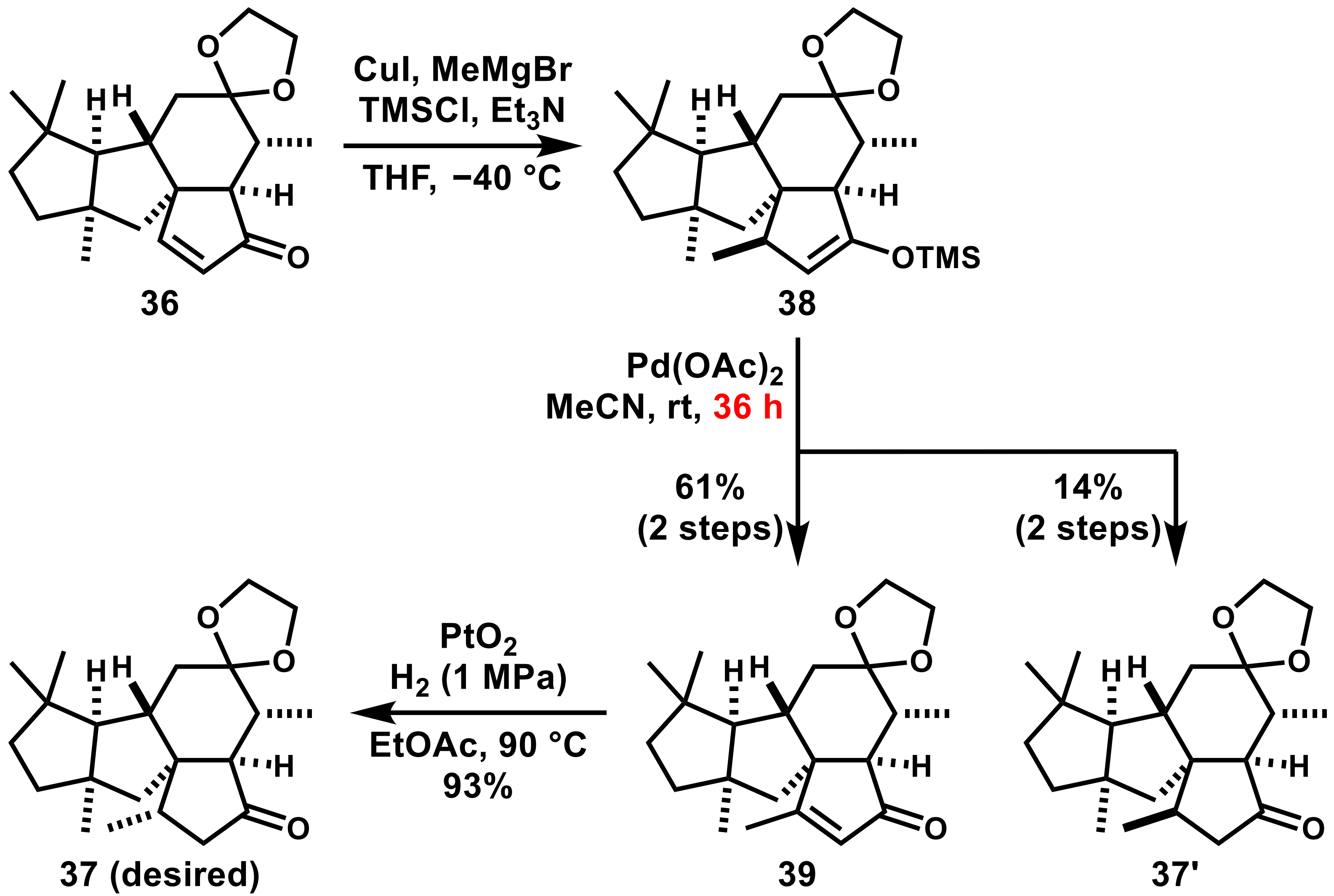
Total Synthesis of *iso*-Phomopsene



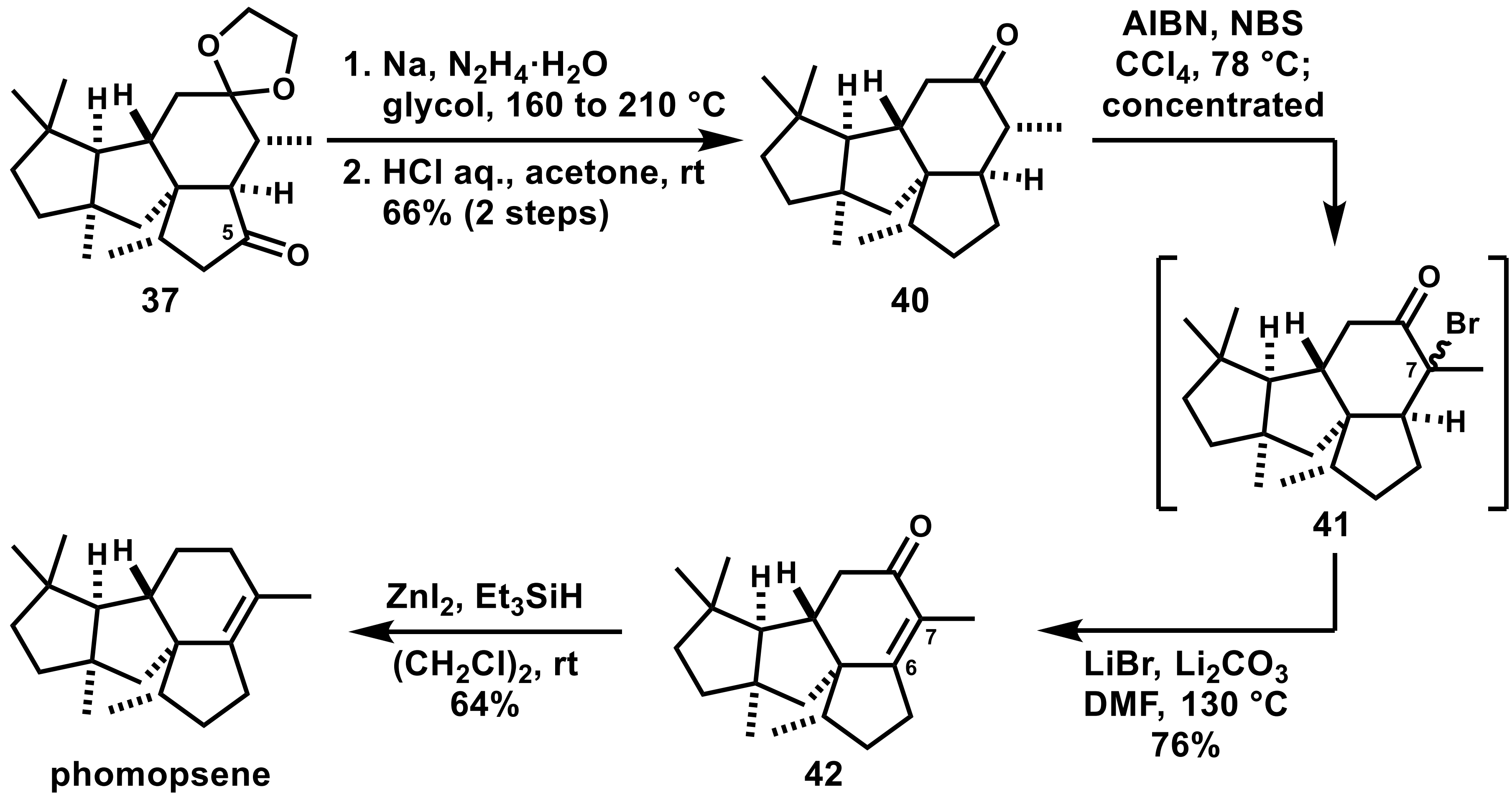
Total Synthesis of Phomopsene



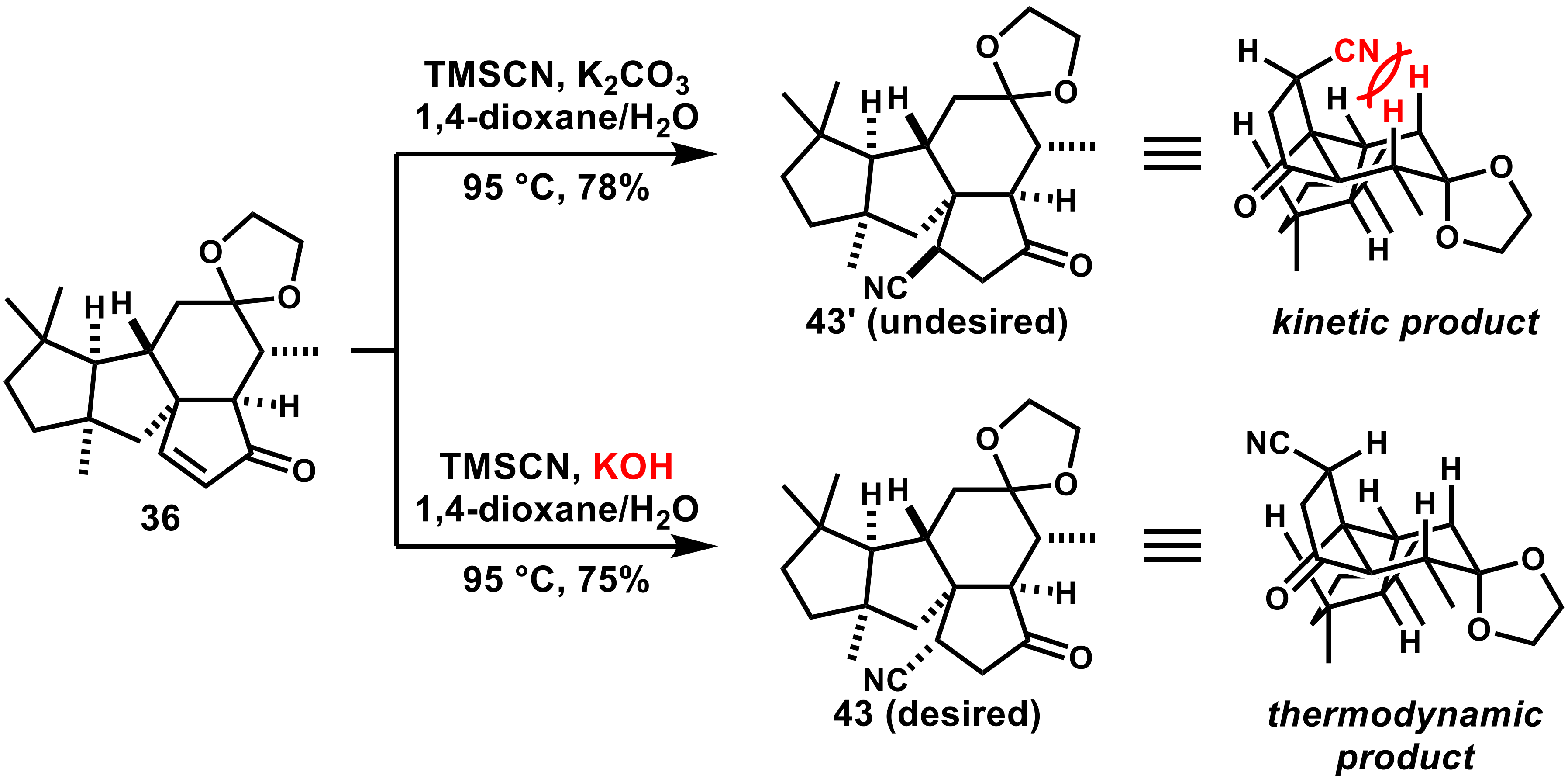
Total Synthesis of Phomopsene



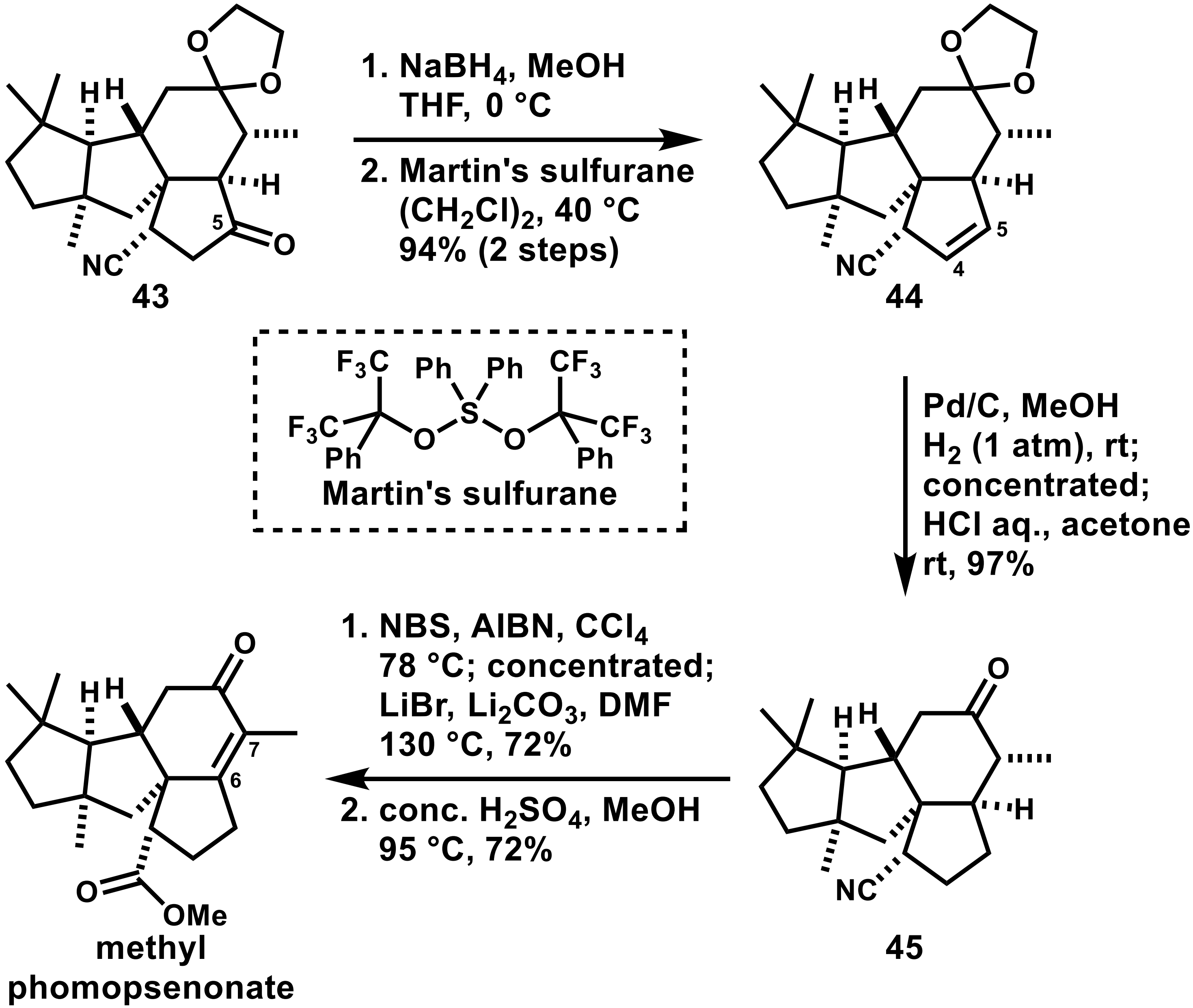
Total Synthesis of Phomopsene



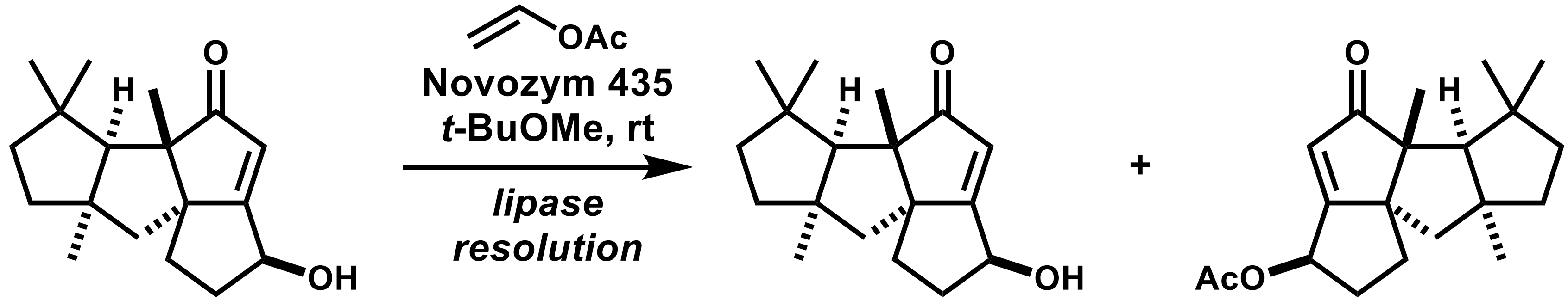
Total Synthesis of Methyl Phomopsenonate



Total Synthesis of Methyl Phomopsenonate



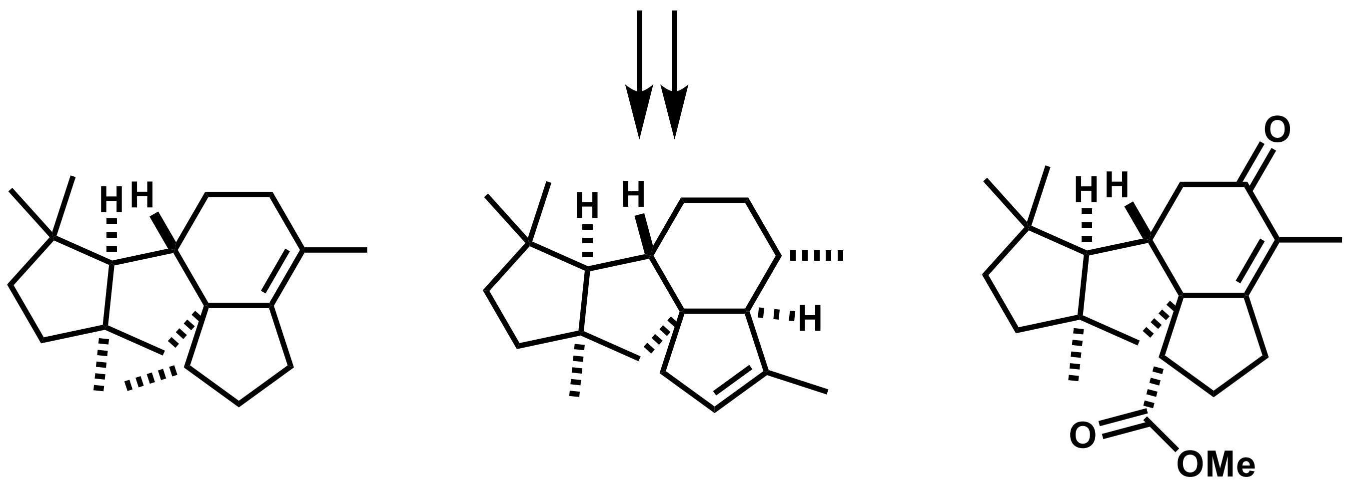
Asymmetric Total Syntheses



(±)-24

(−)-24
47%, 99.7% ee

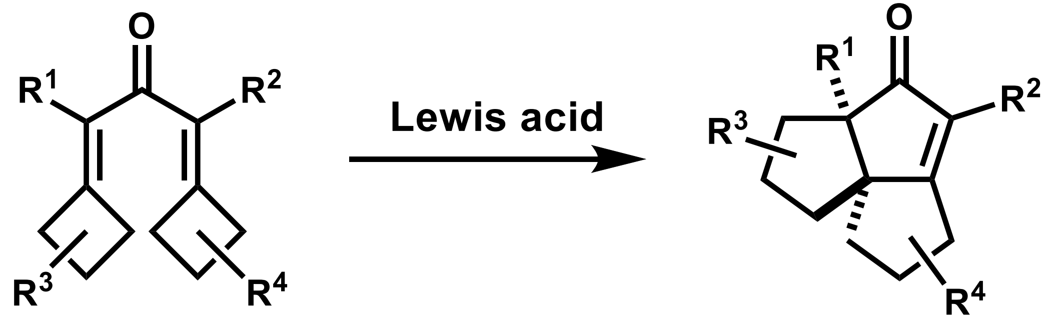
(+)-46
49%, 92% ee

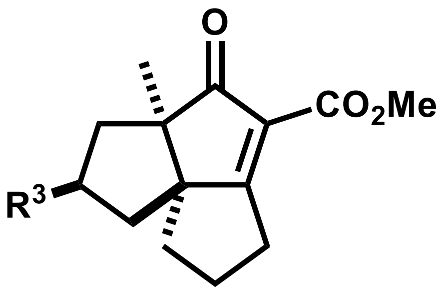


	(−)-phomopsene	(+)-*iso*-phomopsene (revised)	(+)-methyl phomopsenonate
synthetic	−98° (*c* 0.10 , $CHCl_3$)	+15° (*c* 0.10 , $CHCl_3$)	+20.0° (*c* 0.10 , hexane)
reported	−97° (*c* 0.27 , $CHCl_3$)	+12° (*c* 0.50 , $CHCl_3$)	+37.5° (*c* 0.08 , hexane)

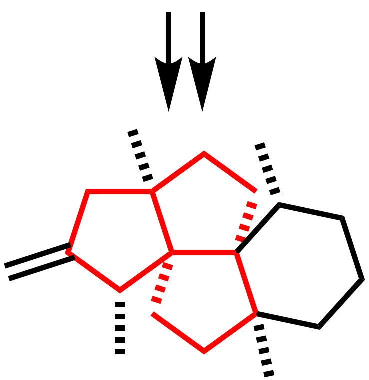
Contents

Summary

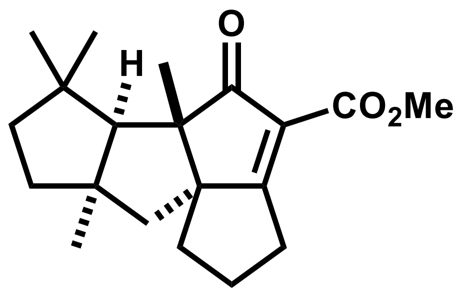




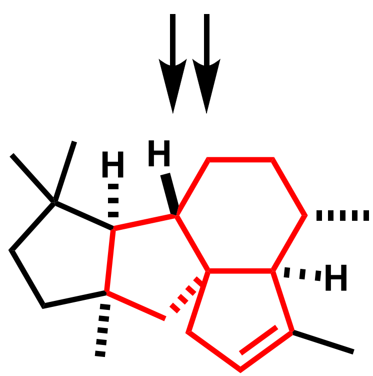
4b: R^3 = $SiPhMe_2$



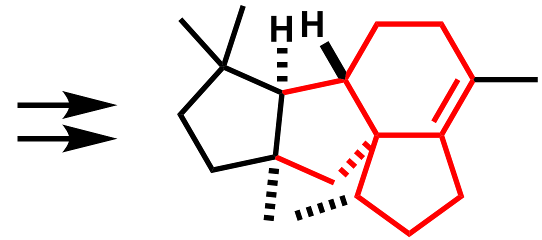
waihoensene
14 or 15 steps



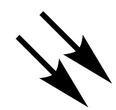
18

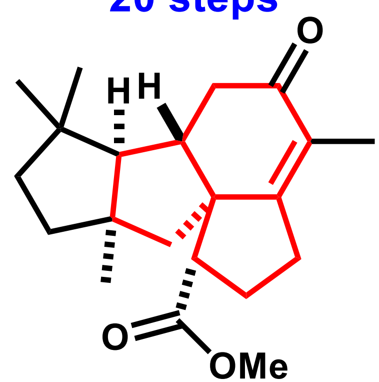


(+)-*iso*-phomopsene
(revised)
12 steps



phomopsene
20 steps



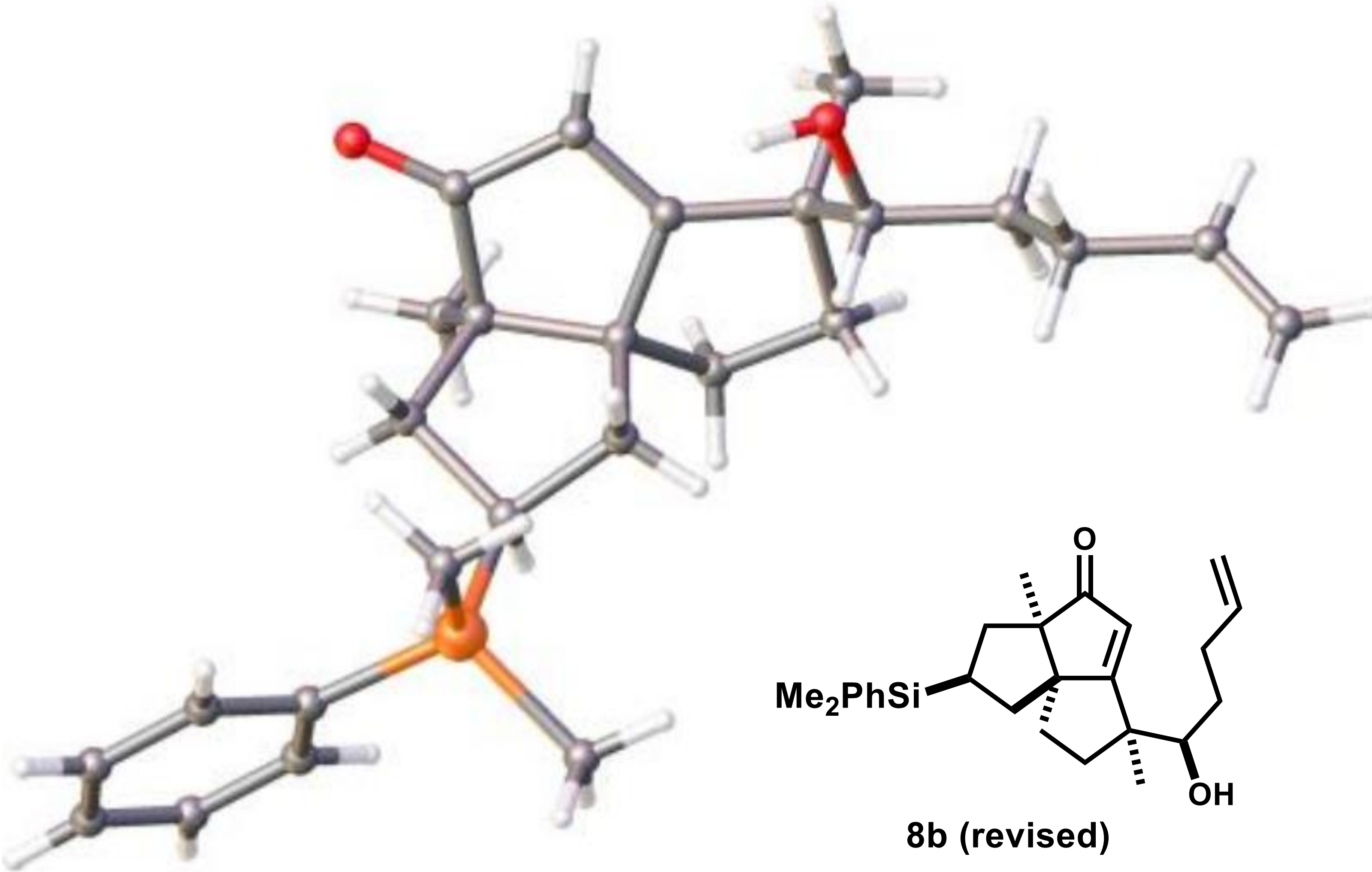


(+)-methyl
phomopsenonate
19 steps

References

1) Wang, Y.-P.; Fang, K.; Tu, Y.-Q.; Yin, J.-J.; Zhao, Q.; Ke, T. An. *Nat. Commun.* **2022**, *13*, 2335.
2) Yin, J.-J.; Wang, Y.-P.; Xue, J.; Zhou, F.-F.; Shan, X.-Q.; Zhu, R.; Fang, K.; Shi, L.; Zhang, S.-Y.; Hou, S.-H.; Xia, W.; Tu, Y.-Q. *J. Am. Chem. Soc.* **2023**. DOI: 10.1021/jacs.3c07044.
3) He, W.; Huang, J.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 300.
4) Williams, D. R.; Robinson, L. A.; Nevill, C. R.; Reddy, J. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 915.
5) a) He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278. b) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003.
6) Gruhn, A. G.; Reusch, W. *Tetrahedron* **1993**, *49*, 8159.
7) Lee, H.; Kang, T.; Lee, H.-Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 8254.
8) Qu, Y.; Wang, Z.; Zhang, Z.; Zhang, W.; Huang, J.; Yang, Z. *J. Am. Chem. Soc.* **2020**, *142*, 6511.
9) Peng, C.; Arya, P.; Zhou, Z.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2020**, *59*, 13521.
10) Rosenbaum, L.-C.; Häfner, M.; Gaich, T. *Angew. Chem. Int. Ed.* **2021**, *60*, 2939.
11) Qu, Y.; Wang, Z.; Zhang, Z.; Zhang, W.; Huang, J.; Yang, Z. *J. Am. Chem. Soc.* **2020**, *142*, 6511.

X-ray for 8b



8b (revised)