Total Synthesis of (+)-Euphorikanin A Via an Astropospecific Cascade By Prof. Carreira's group

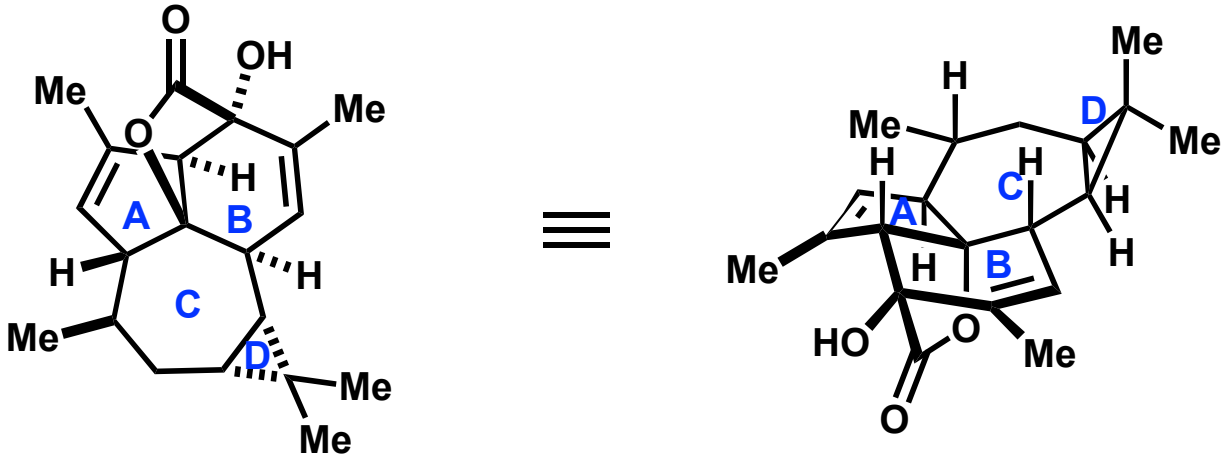
Literature Seminar

2023/12/25

Takuya Ishii

Contents

(+)-Euphorikanin A



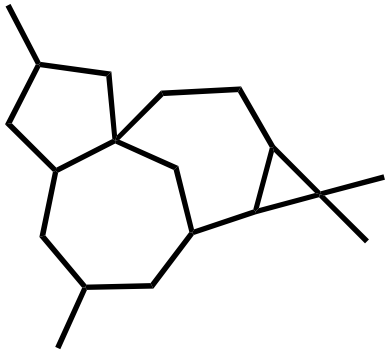
Isolation: the roots of *Euphorbia kansui* in 2016 by Zhang[1]

Biological activity: cytotoxicity against human tumor cell (NCI-446 and HeLa)

Structual features: unprecedented 5/6/7/3-fused tetracyclic skelton and lactone bridge,contiguous eight stereocenters, most likely a rearranged ingenane diterpenoids

Total synthesis: Carreira (2021)[2] (2023)[3] and Jia (2022)[4]

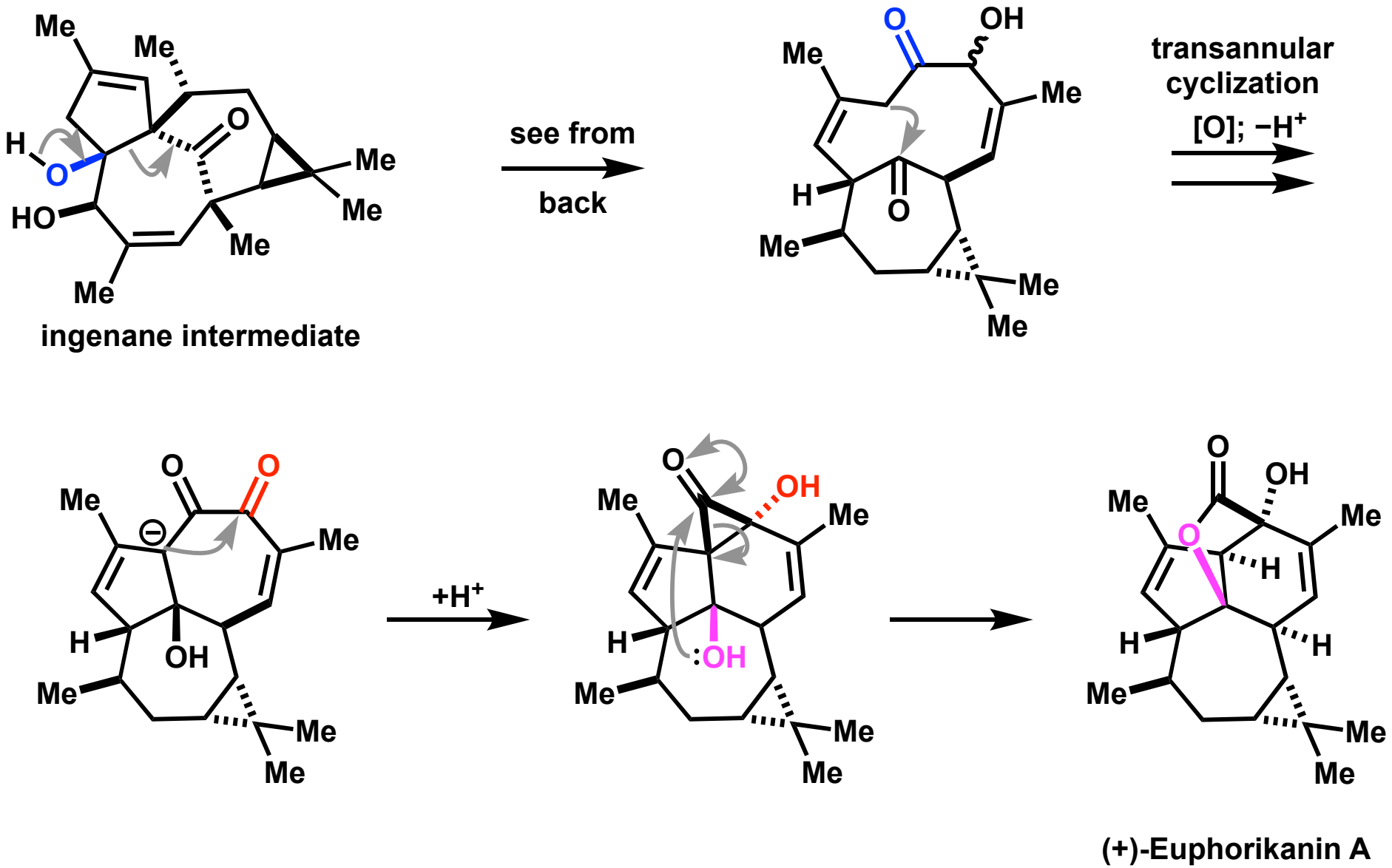
For detail, please see also 220430_PS_Hiromu_Kakizawa



ingenane skeleton

1) D.-Q. Fei; L.-L. Dong; F.-M. Qi; G.-X. Fan; H.-H. Li; Z.-Y. Li; Z.-X. Zhang. *Org. Lett.* **2016**, *18*, 2844.
2) M. J. Classen; M. N. A. Böcker; R. Roth; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2021**, *143*, 8261.
3) Z. Chen; K. Zhao; Y. Jia. *Angew. Chem. Int. Ed.* **2022**, *51*, e202200576

Proposed Biosynthetic Pathway by Zhang



1) D.-Q. Fei; L.-L. Dong; F.-M. Qi; G.-X. Fan; H.-H. Li; Z.-Y. Li; Z.-X. Zhang. *Org. Lett.* **2016**, *18*, 2844.

Contents

Introduction of Prof. Erick M. Carreira

Education & Academic Career:

1984 B.S., @ University of Illinois at Urbana-Champaign (Prof. Denmark)
1990 Ph.D., @ Harvard University (Prof. Evans)
1990- Postdoctoral fellow @ California Institute of Technology (Prof. Dervan)
1992- Assistant Professor @ California Institute of Technology
1996- Associate Professor @ California Institute of Technology
1997- Professor @ California Institute of Technology
1998- Professor @ ETH Zürich

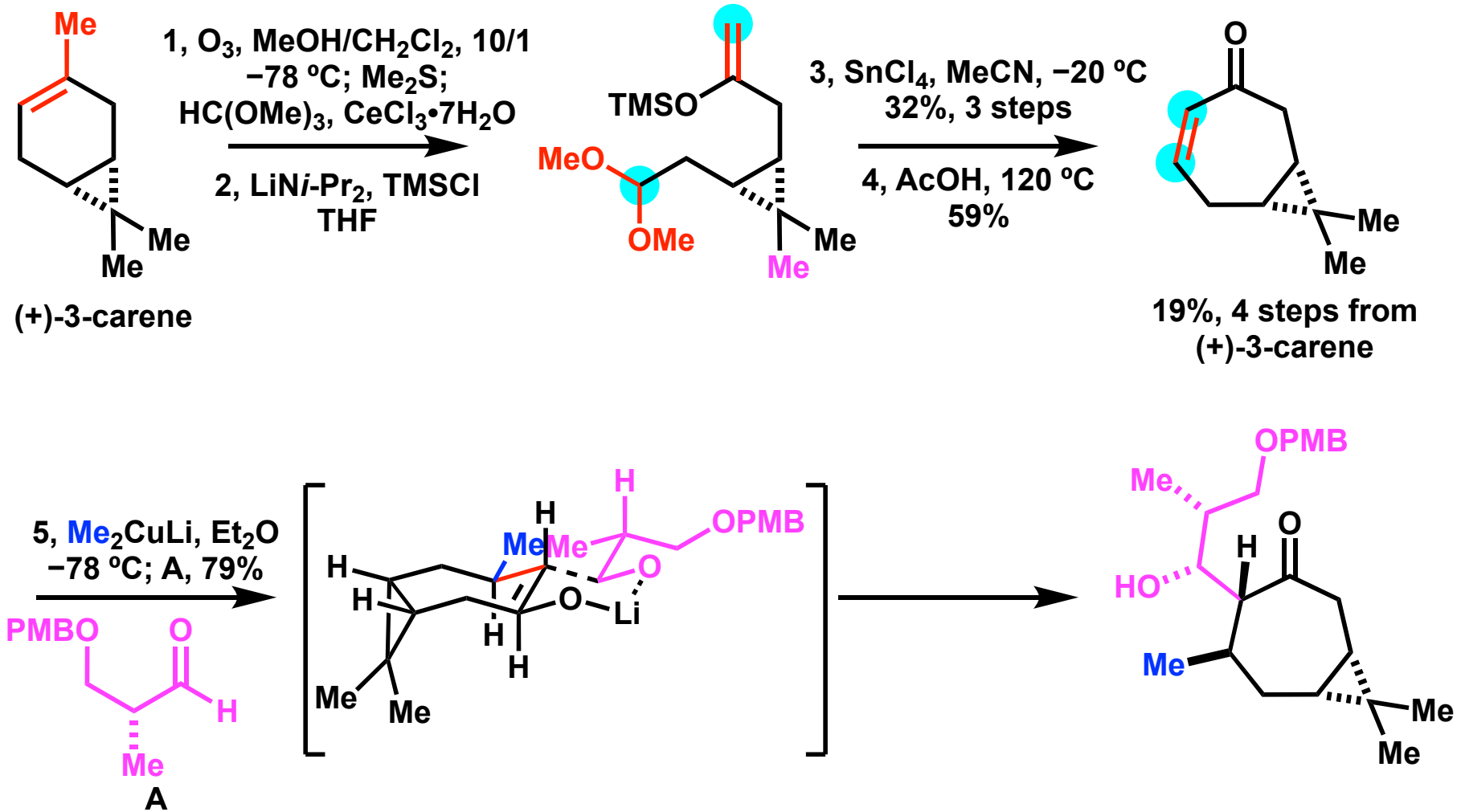
Research topic: Asymmetric synthesis of biologically active, stereo-chemically complex, natural product

Recent PS and LS: 231115_PS_Manaka_Matsumoto
230623_PS_Junhao_Fu
220430_PS_Hiromu_Kakizawa
221029_LS_Manaka_Matsumoto

https://carreira.ethz.ch/the-group/people/prof-dr-erick-m-carreira

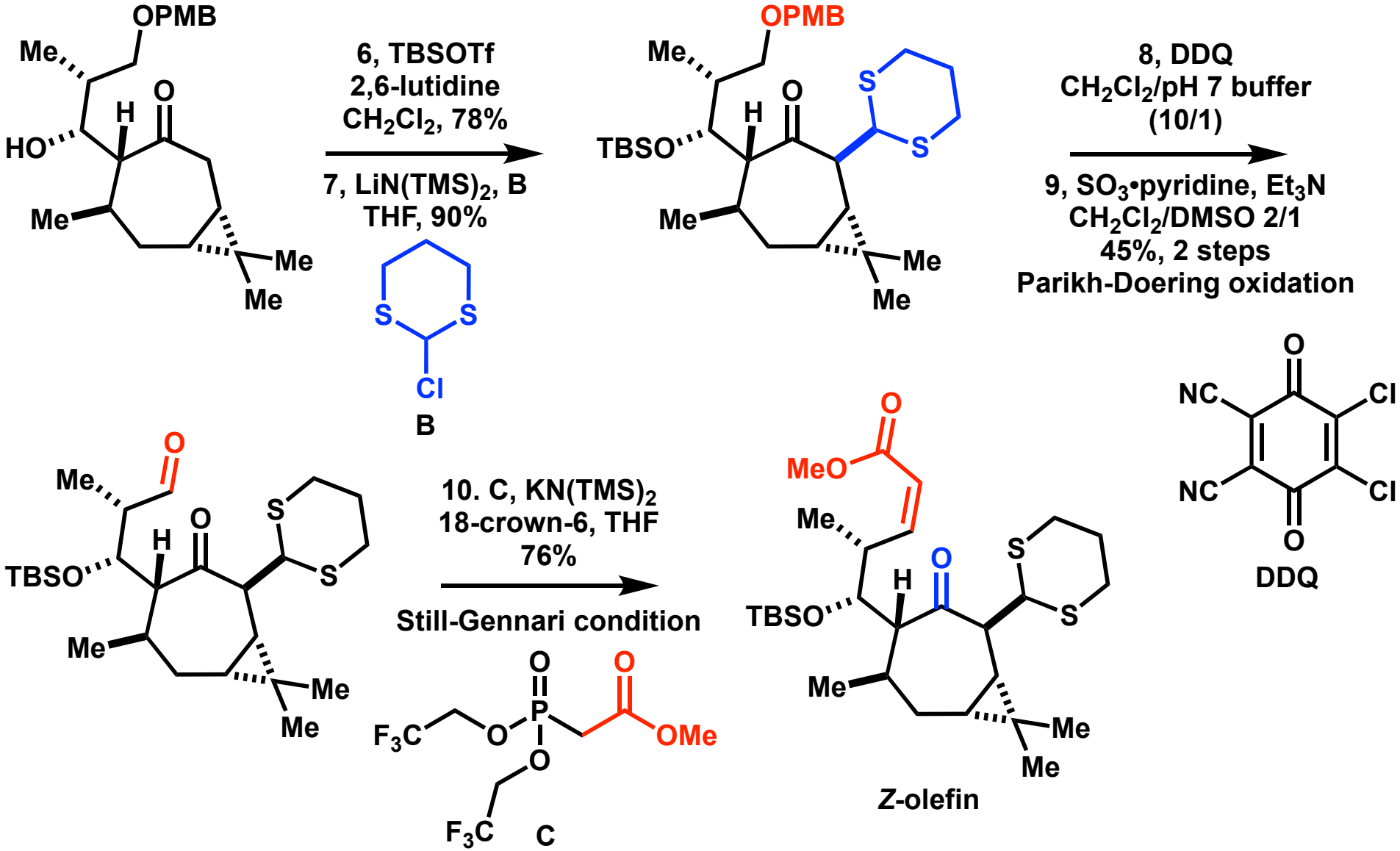
C-ring Functinalization

Carreira (2021): 19 steps, 0.12 %



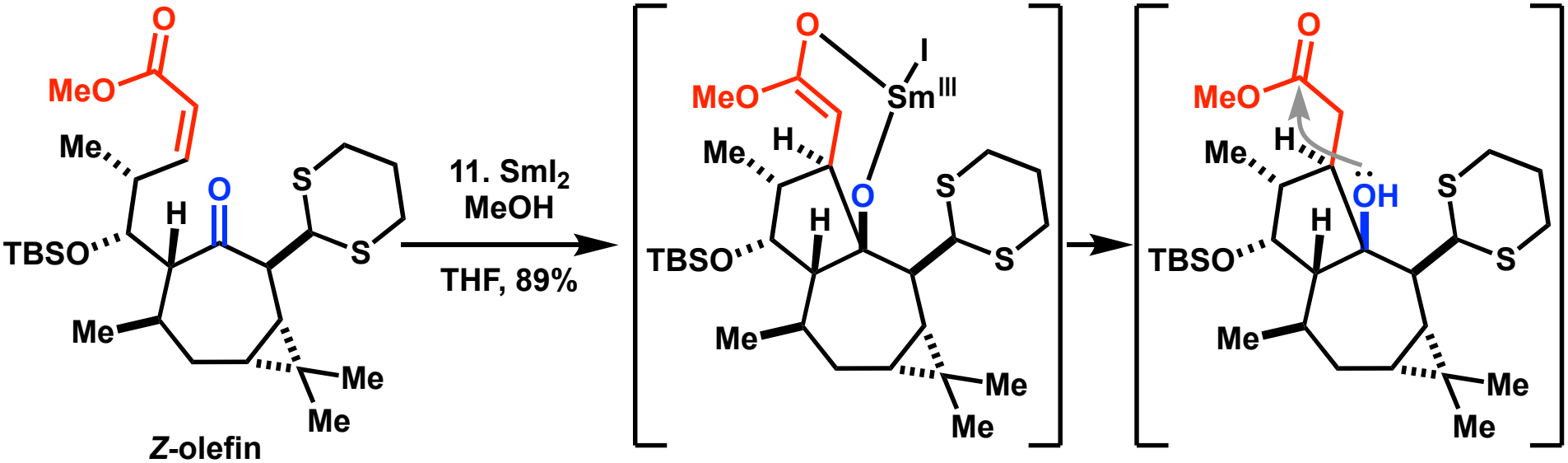
1) M. J. Classen; M. N. A. Böcker; R. Roth; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2021**, *143*, 8261.
2) T. Satoh; Kaneko. Y; Okura. T; Uwaya. S; Yamakawa. K. *Chem. Pharm. Bull.* **1984**, 32, 3452_3460.
3) 220430_PS_Hiromu_Kakizawa

A-ring Construction

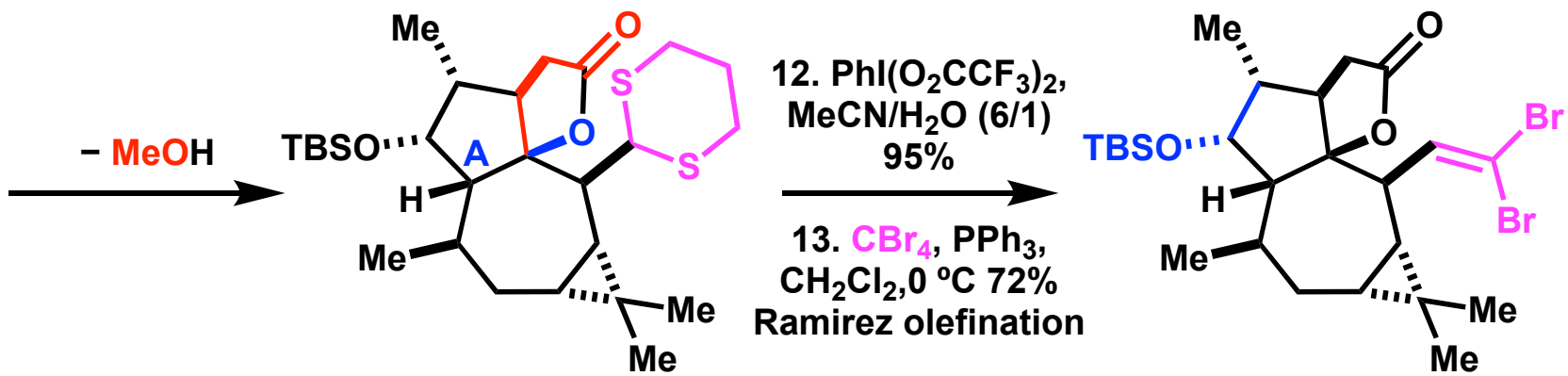


1) M. J. Classen; M. N. A. Böcker; R. Roth; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2021**, *143*, 8261.
2) 220430_PS_Hiromu_Kakizawa

A-ring Construction

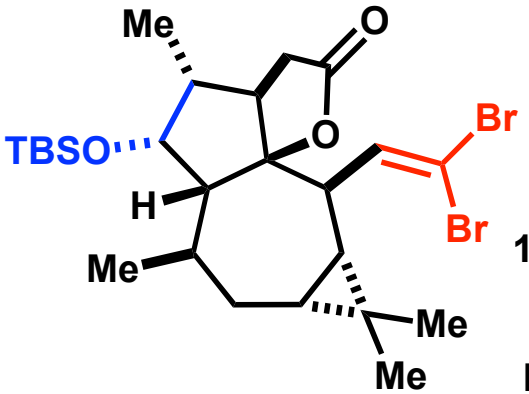


in detail: 220430_PS_Hiromu_Kakizawa



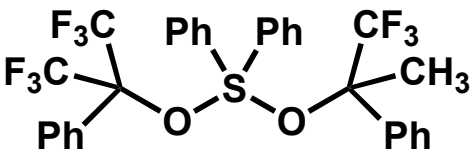
1) M. J. Classen; M. N. A. Böcker; R. Roth; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2021**, *143*, 8261.
2) 220430_PS_Hiromu_Kakizawa
3) Desai. N. B; McKelvie. N; Ramirez. F. *J. Am. Chem. Soc.* **1973**, *95*, 793.

B-ring Construction

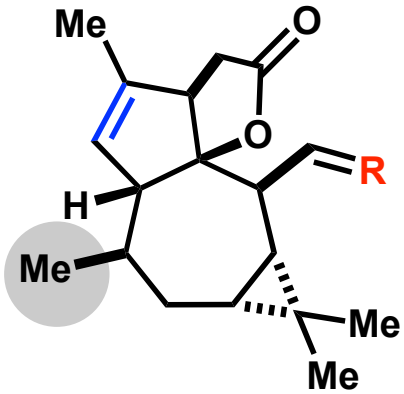


14. *n*-Bu_4NF
THF, 95%

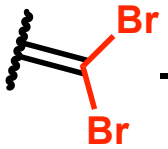
15. Martin's sulfurane
CH_2Cl_2, 0 ºC 42%



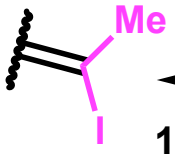
Martin's sulfurane



R =



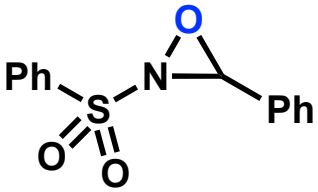
R =



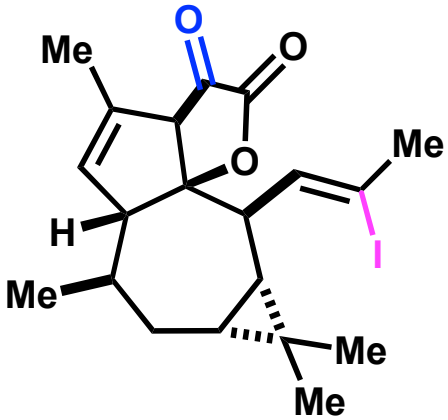
16. Me_2CuLi, Et_2O
−78 ºC; I_2 (74%)

17. $KN(TMS)_2$,
Davis's oxaziridine
THF, −78 ºC

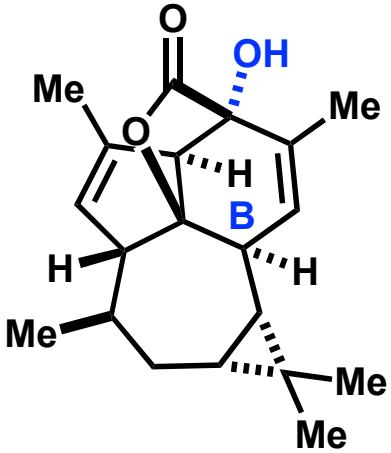
18. Dess-Martin Periodinane
CH_2Cl_2, 49%, 2 steps



Davis's oxaziridine



19. *t*-BuLi,
Et_2O,
−78 ºC, 40%



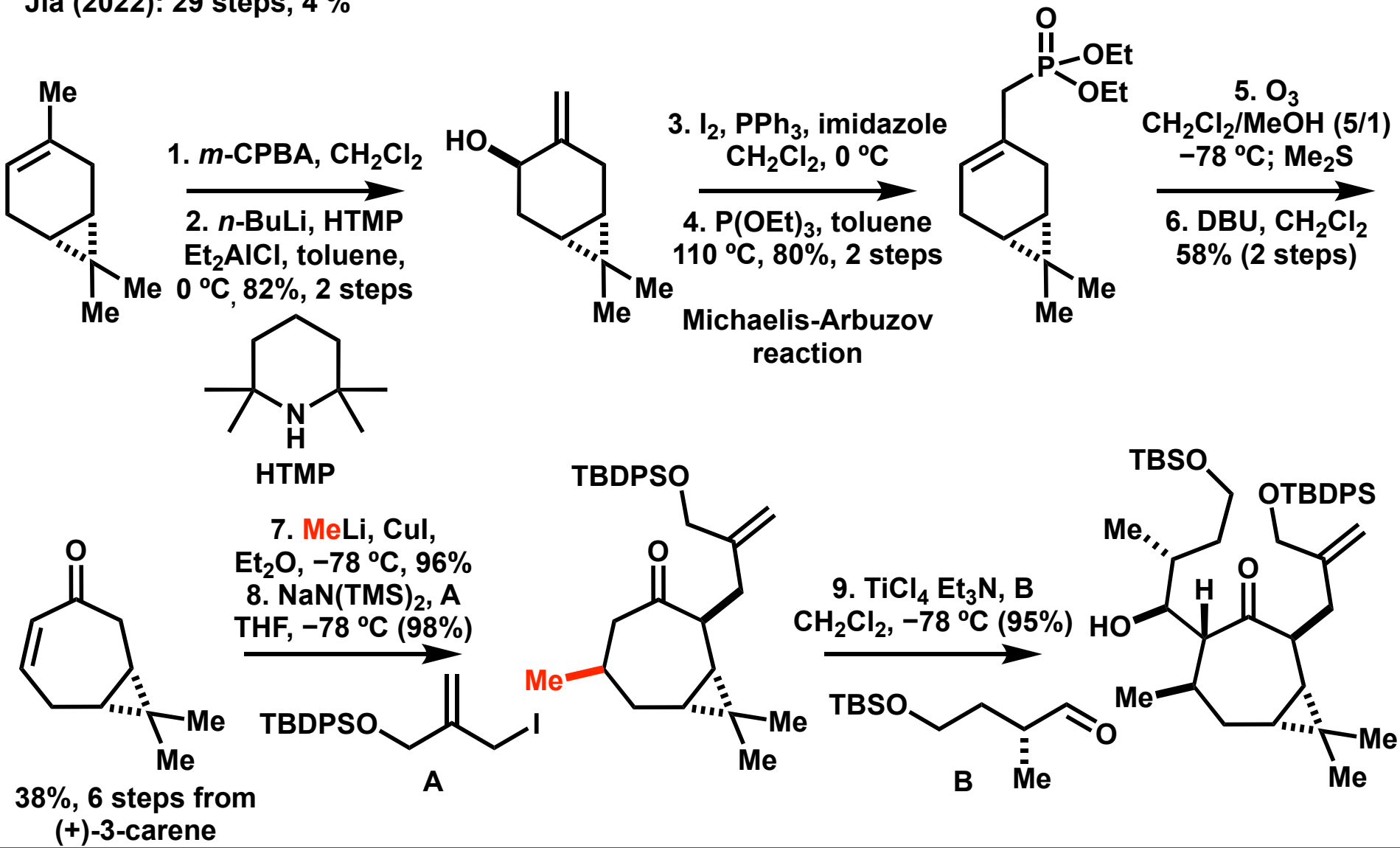
(+)-Euphorikanin A

19 steps, 0.12 %

1) M. J. Classen; M. N. A. Böcker; R. Roth; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2021**, *143*, 8261.
2) 220430_PS_Hiromu_Kakizawa
3) Tanino. K; Arakawa. K; Satoh. M; Iwata. Y; Miyashita. M. *Tetrahedron Lett.* **2006**, 47, 861

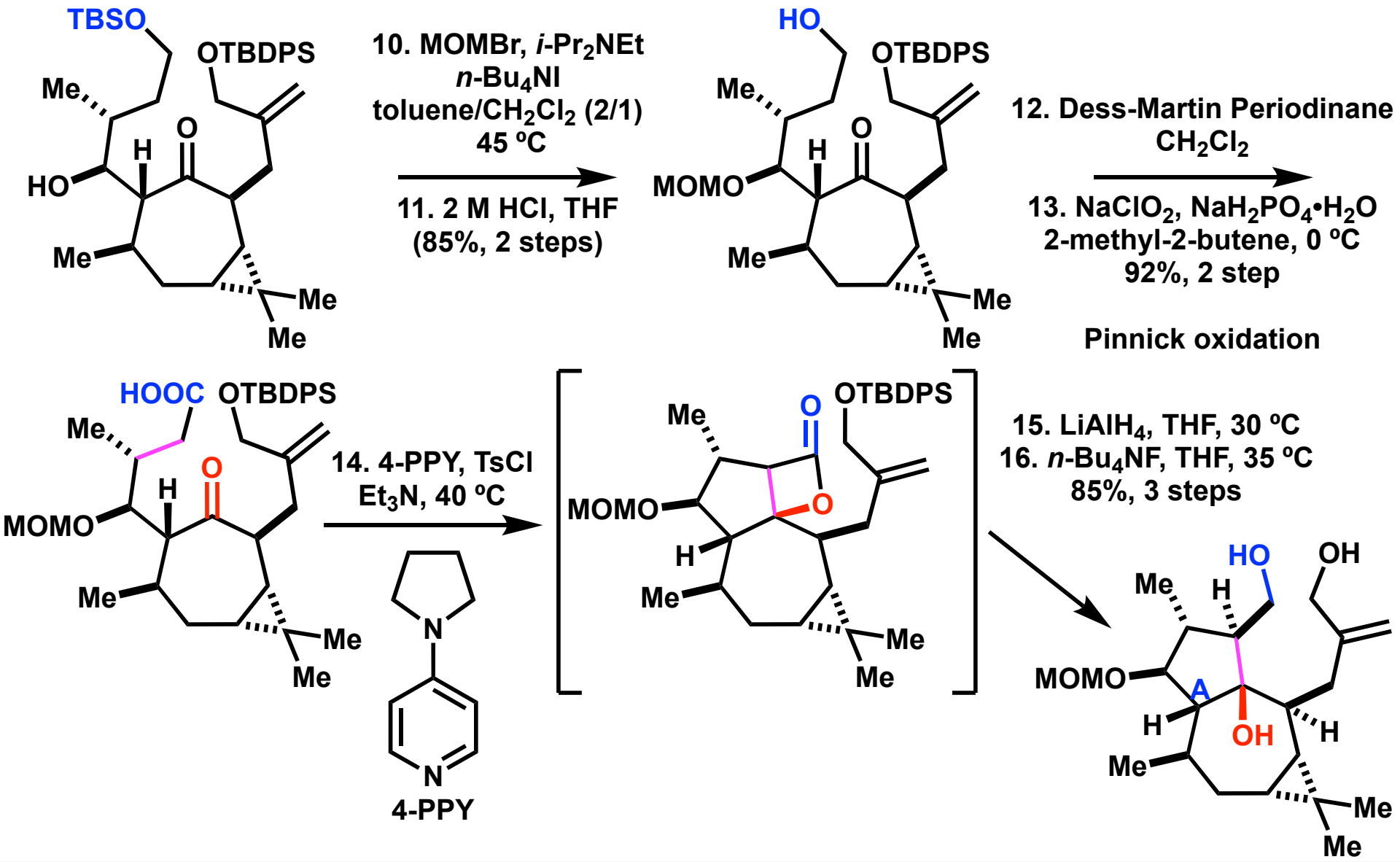
C-ring Functionalization

Jia (2022): 29 steps, 4 %



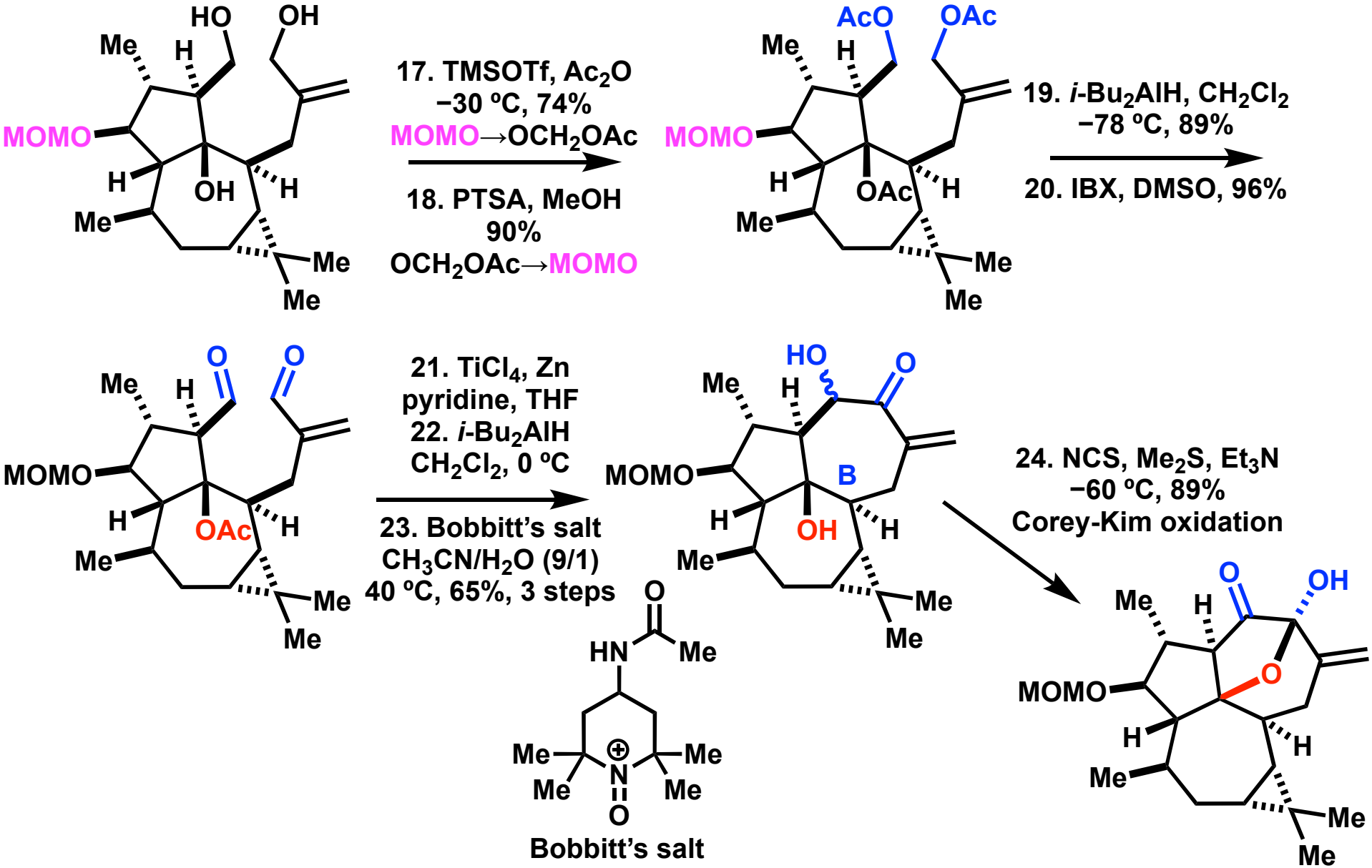
1) Z. Chen; K. Zhao; Y. Jia. *Angew. Chem. Int. Ed.* **2022**, *51*, e202200576
2) 220430_PS_Hiromu_Kakizawa

A-ring Construction



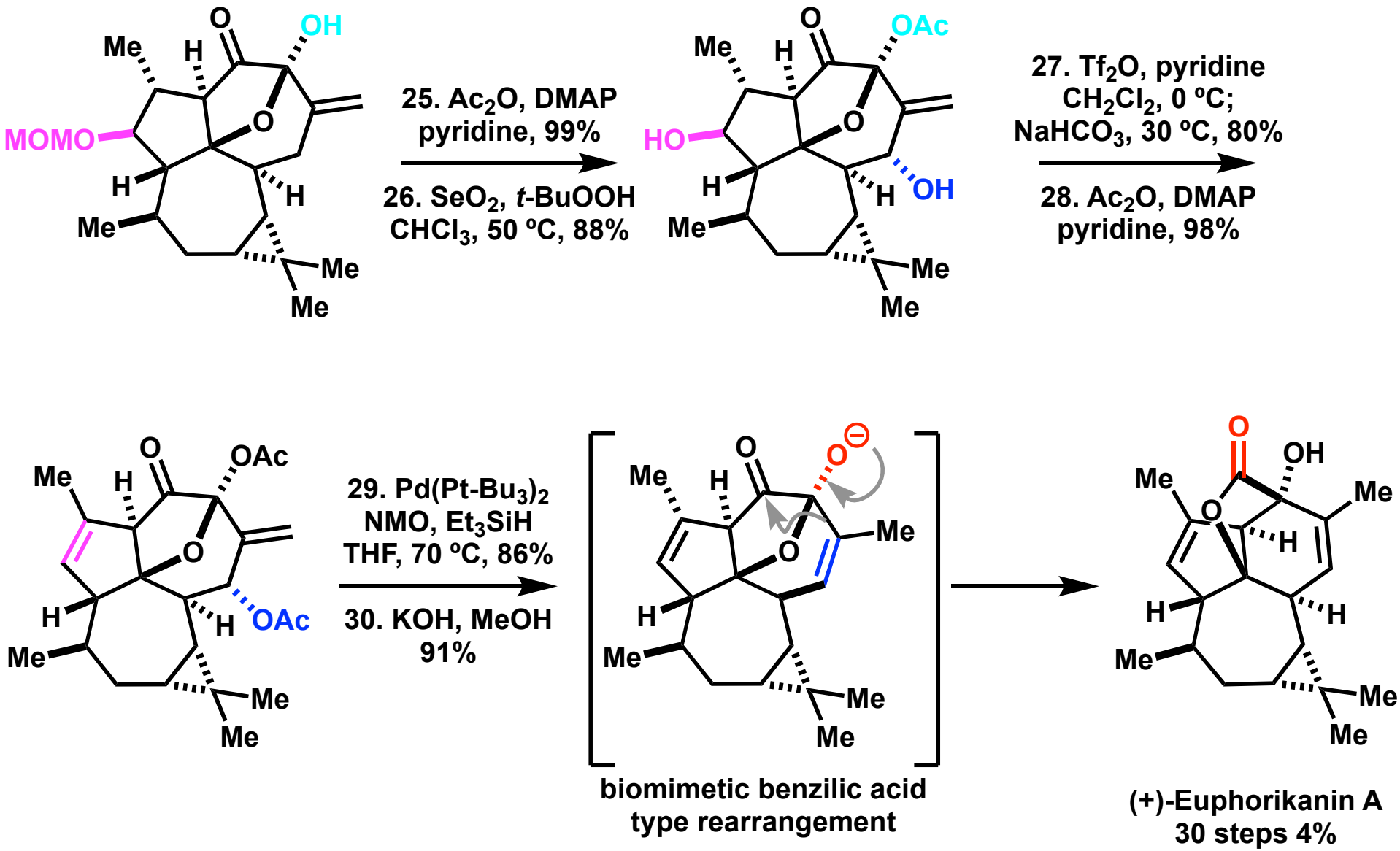
1) Z. Chen; K. Zhao; Y. Jia. *Angew. Chem. Int. Ed.* **2022**, *51*, e202200576
2) 220430_PS_Hiromu_Kakizawa
3) H. Henry-Riyad; C. Lee; V. C. Purohit; D. Romo. *Org. Lett.* **2006**, *8, 4363*

B-ring Construction



1) Z. Chen; K. Zhao; Y. Jia. *Angew. Chem. Int. Ed.* **2022**, *51*, e202200576
2) 220430_PS_Hiromu_Kakizawa

B-ring Construction

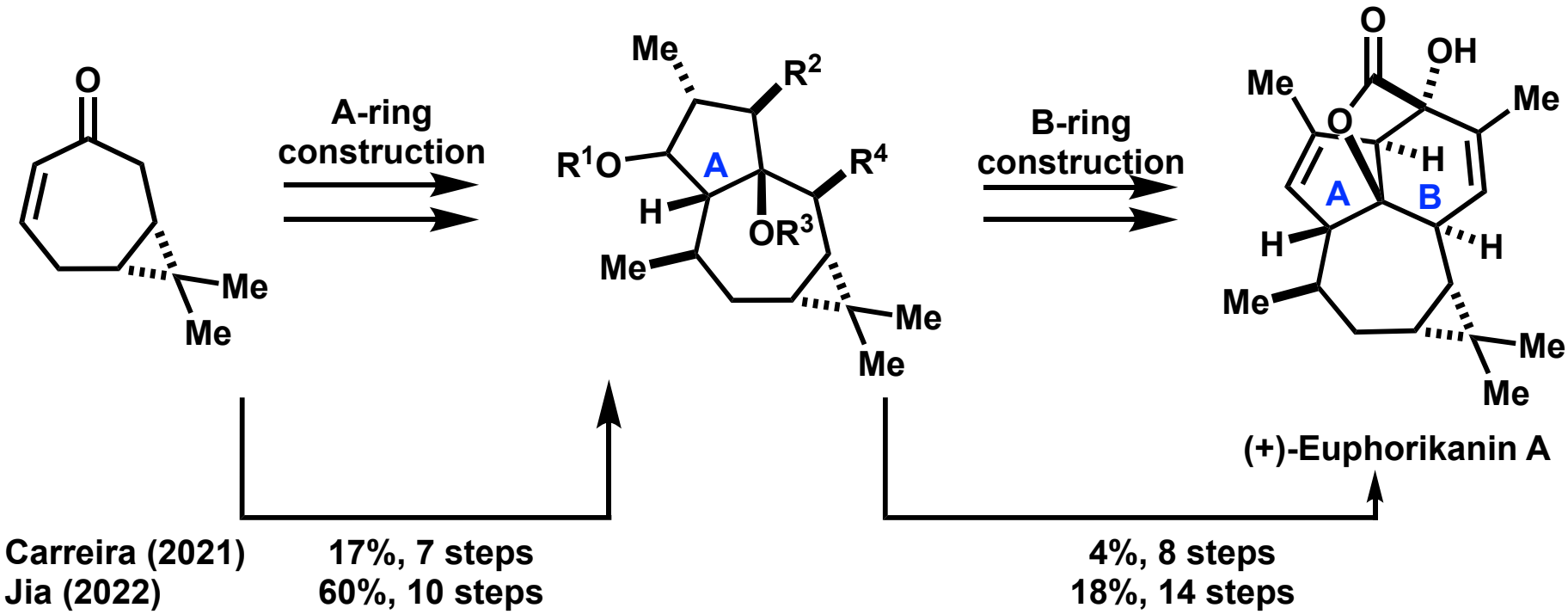


1) Z. Chen; K. Zhao; Y. Jia. *Angew. Chem. Int. Ed.* **2022**, *51*, e202200576
2) 220430_PS_Hiromu_Kakizawa
3) N. K. Garg; D. D. Caspi; B. M. Stoltz. *J. Am. Chem. Soc.* **2005,** *127*, 5970

Contents

Previous Approach's Problem

The previous approaches:



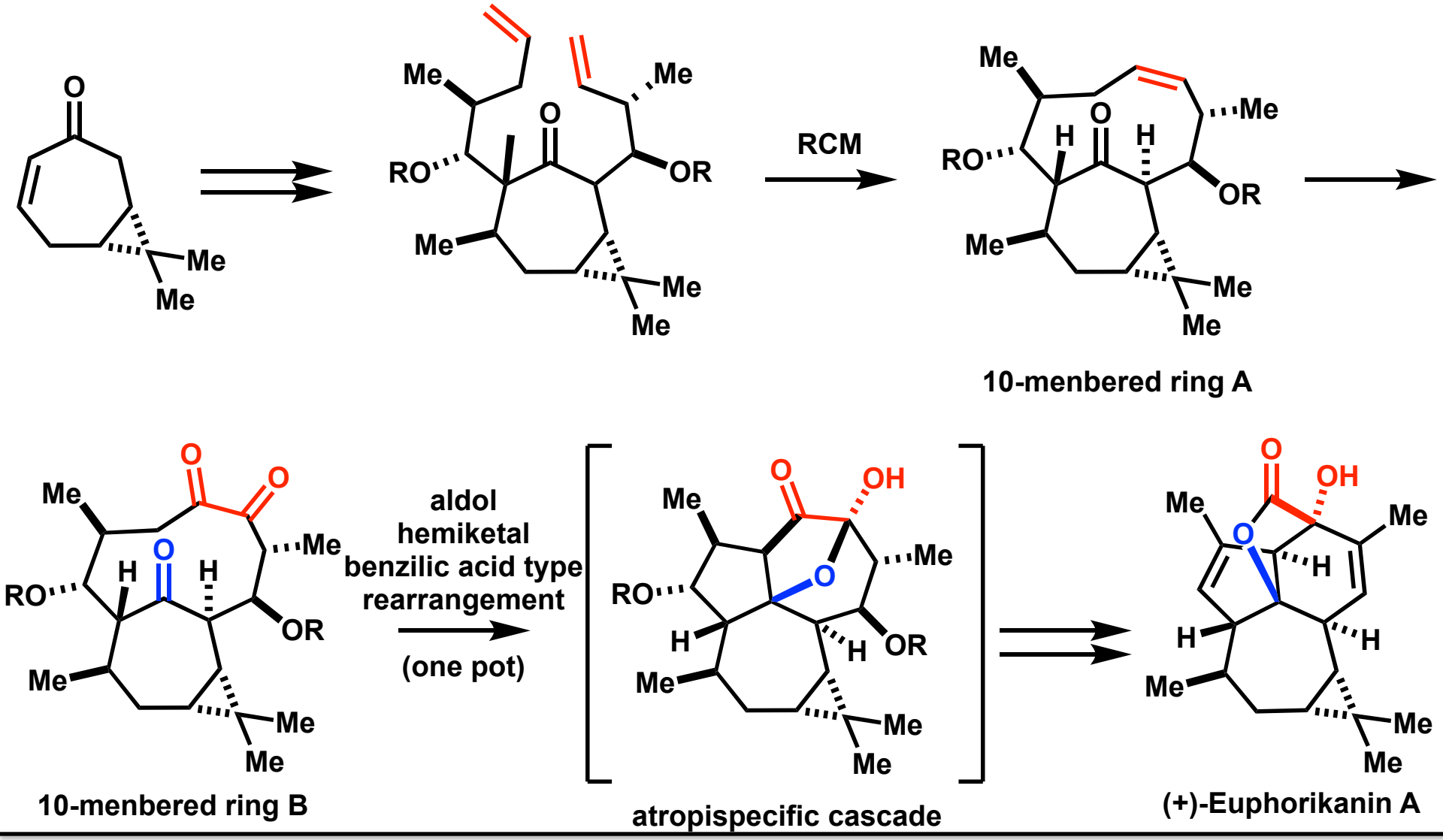
the assembly of the A ring and B ring in a <u>sequential manner in common</u>.

problems: low yield, step count

1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

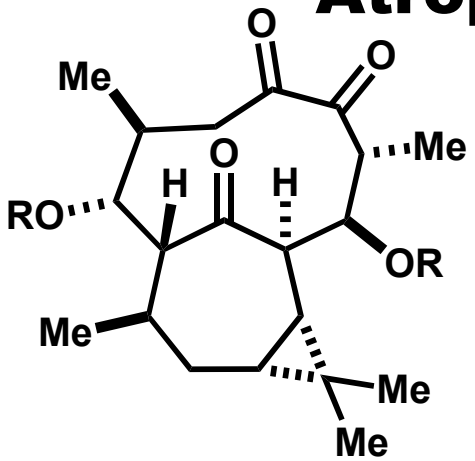
Carreira's New Approach

Carreira's new approache:

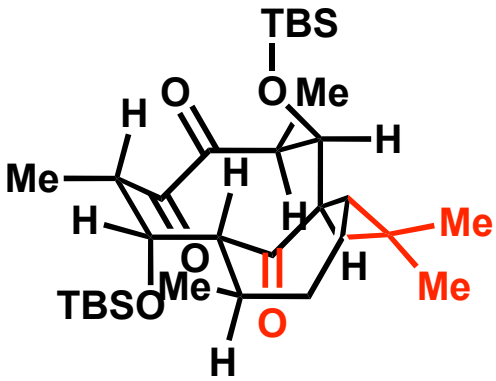


1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

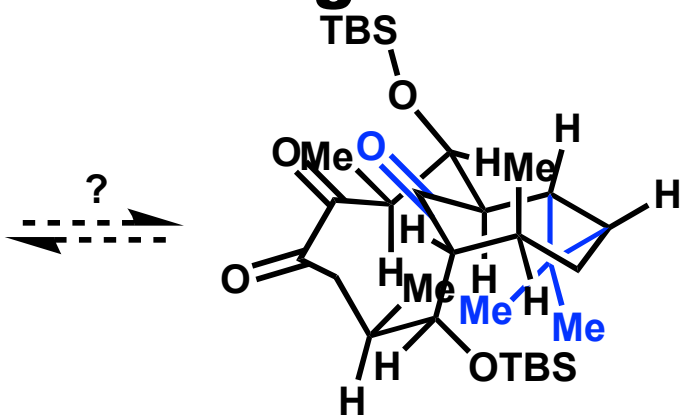
Atropisomeric 10-membered Ring



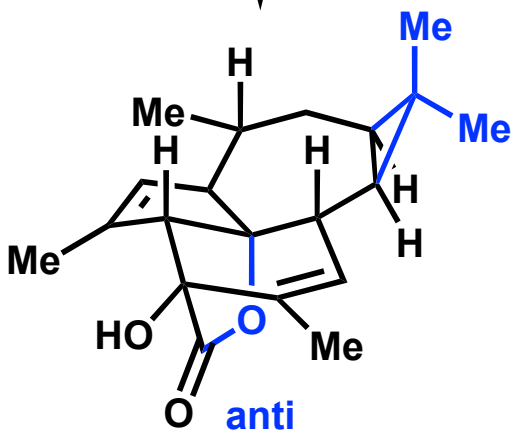
10-menbered ring B



syn



anti



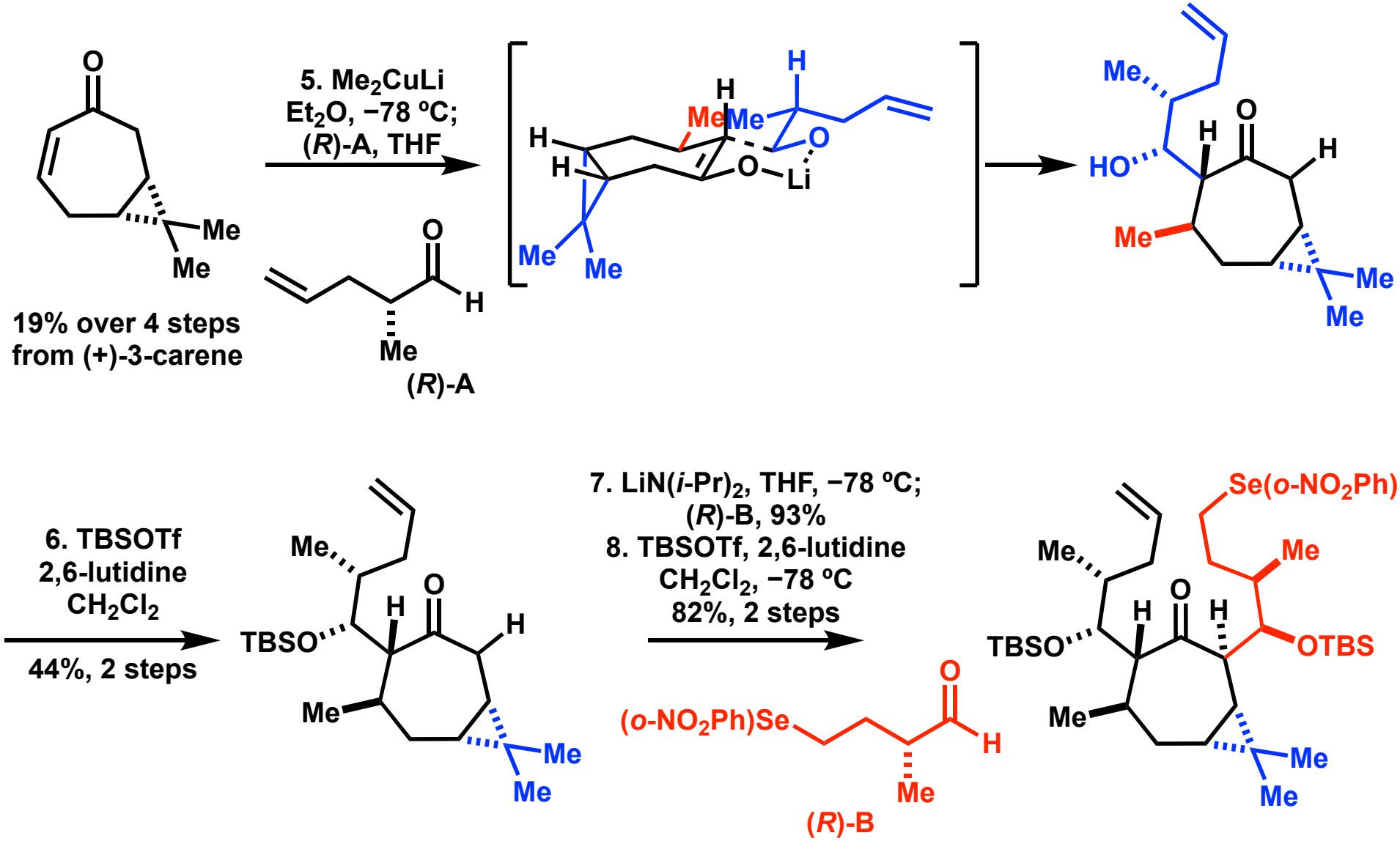
(+)-Euphorikanin A

key question

RCM→bicyclo[7.4.1]?
atropisomerism: syn vs anti?
what effect atropselectivity? side chains?

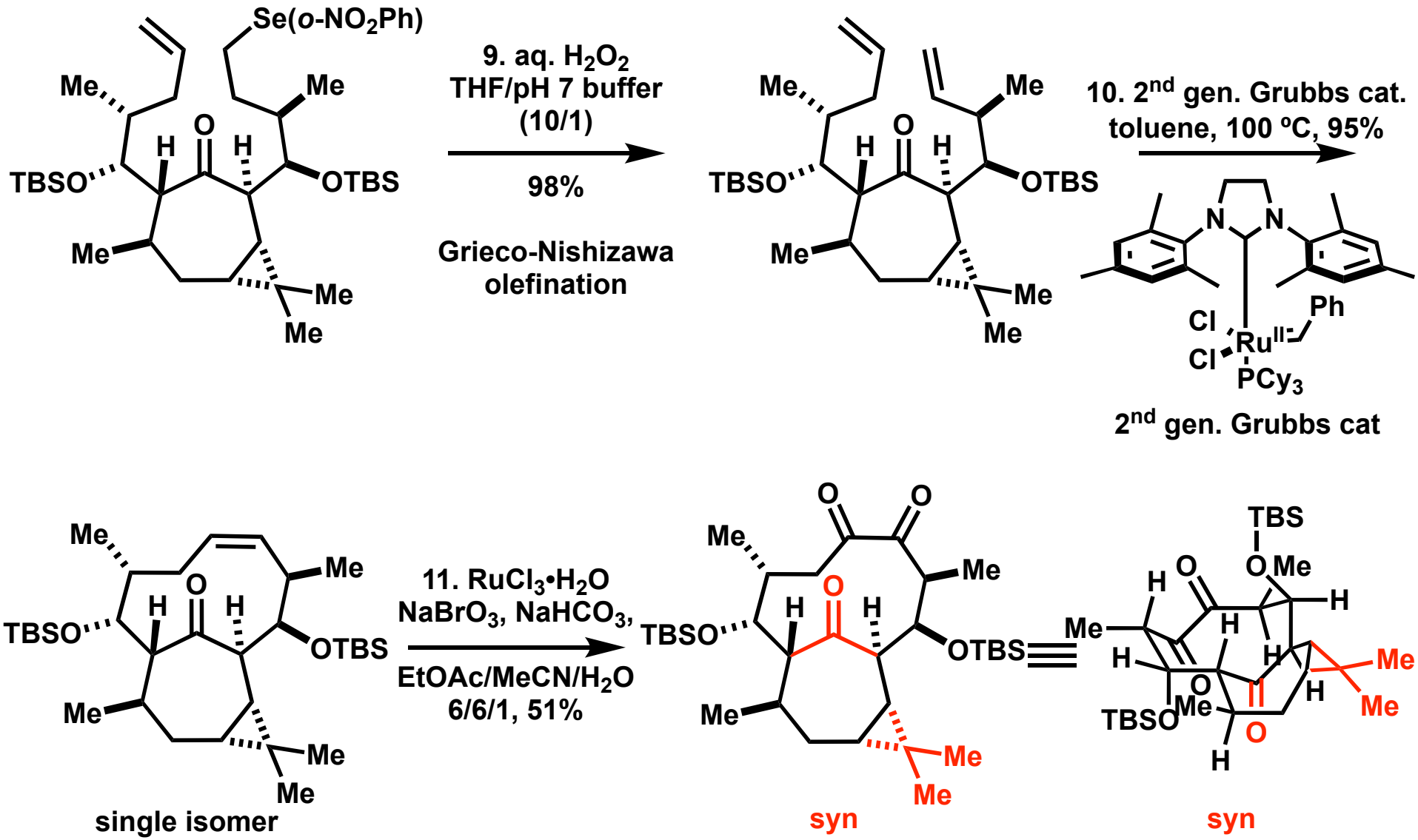
1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

Initial Synthesis of Key Intermediate



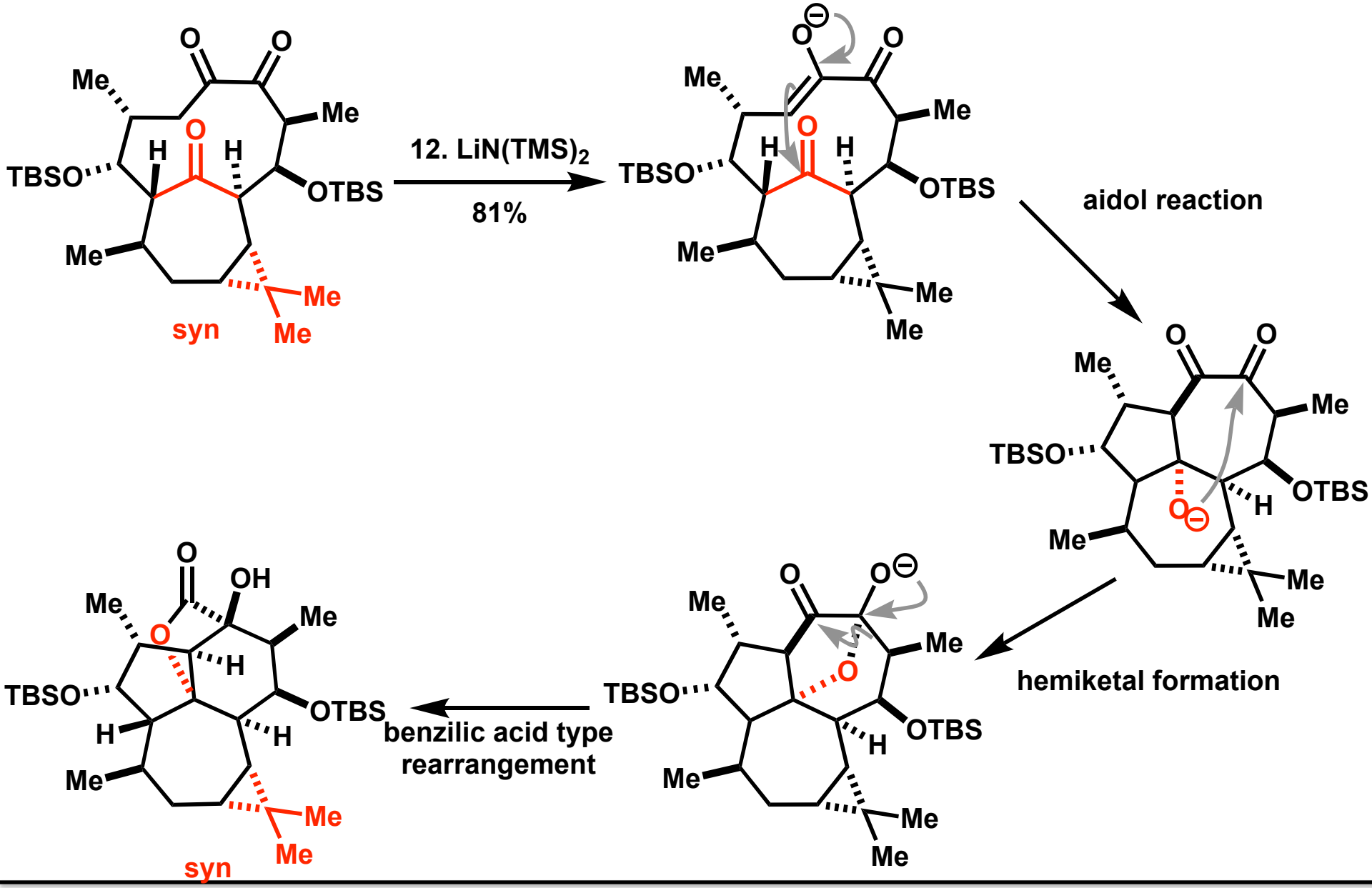
1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

Initial Synthesis of Key Intermediate



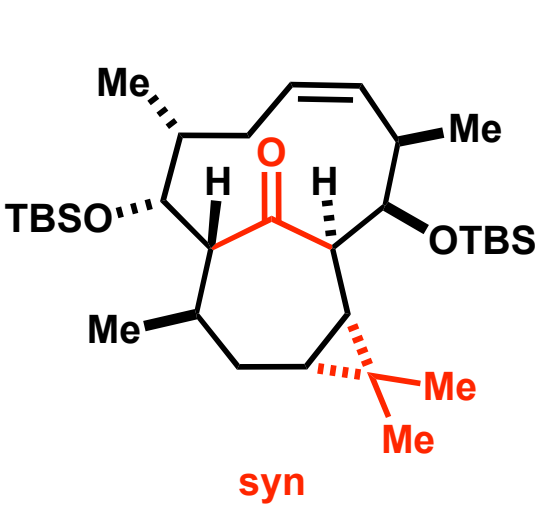
1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

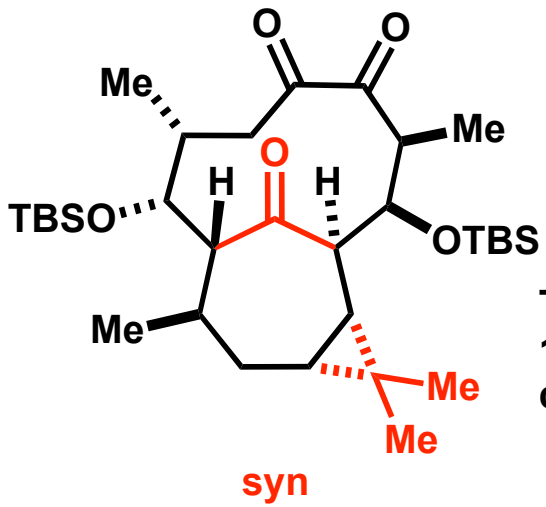
Cascade Reactions



1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

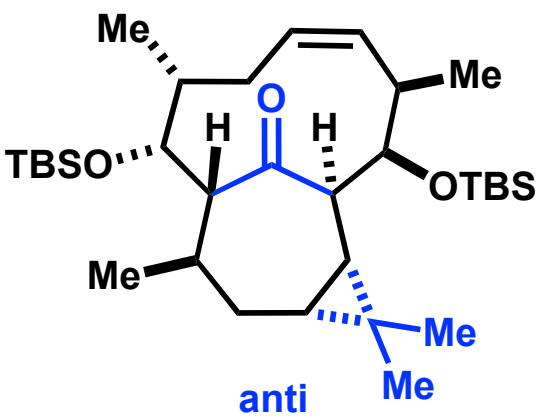
Undesired Atropisomerism

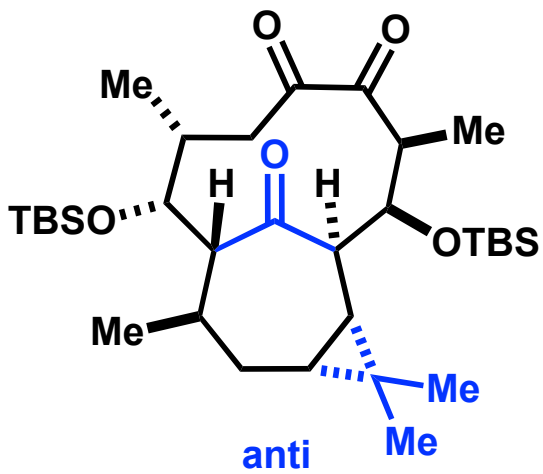


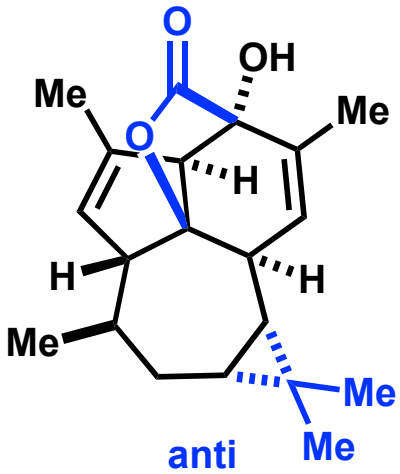


The repulsion between ketone and 10 menbered ring, and whole structural change might prevent atropisomerization

20 ºC to 100 ºC in d^8-toluene atropisomerization did not occur



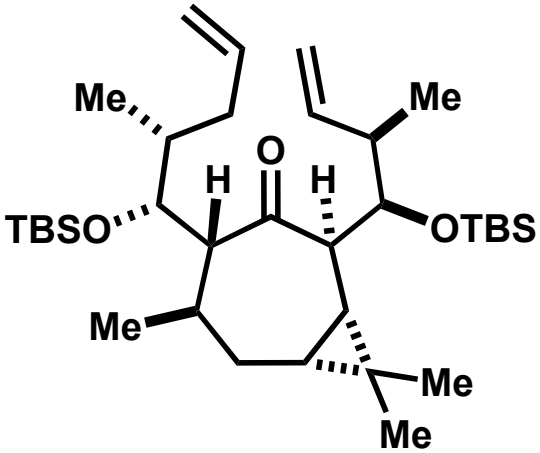




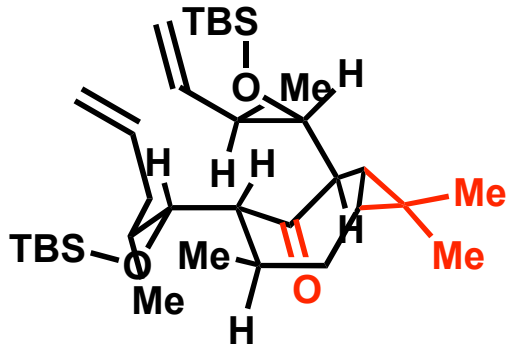
(+)-Euphorikanin A

1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

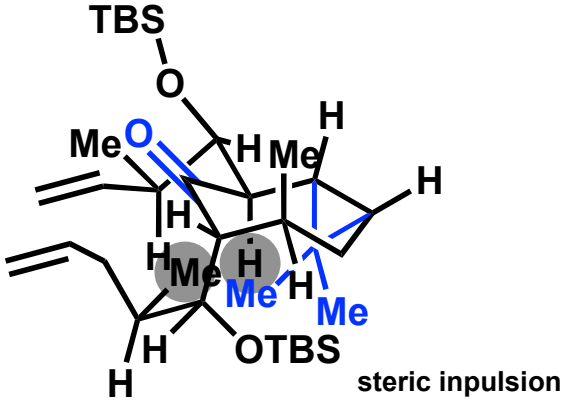
Undesired Atropisomerism



≡



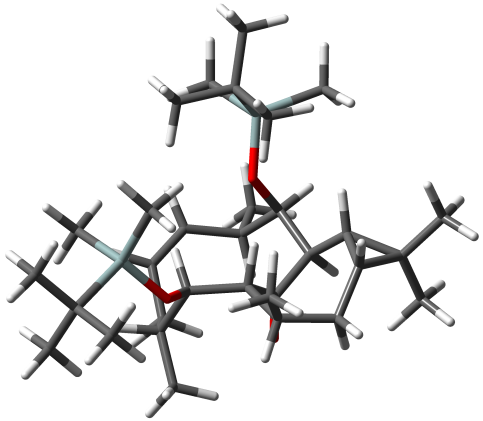
syn



steric inpulsion

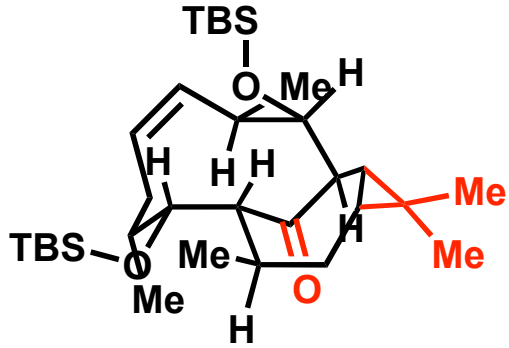
anti

2nd gen.
Grubbs cat.

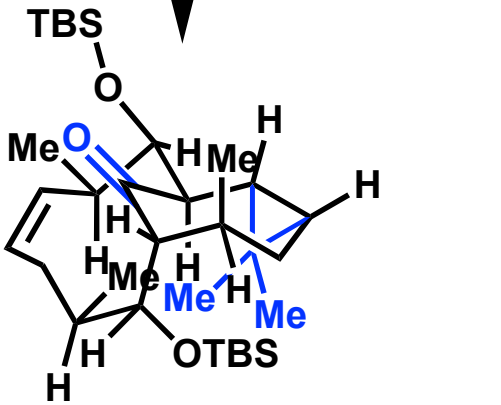


syn

≡



syn

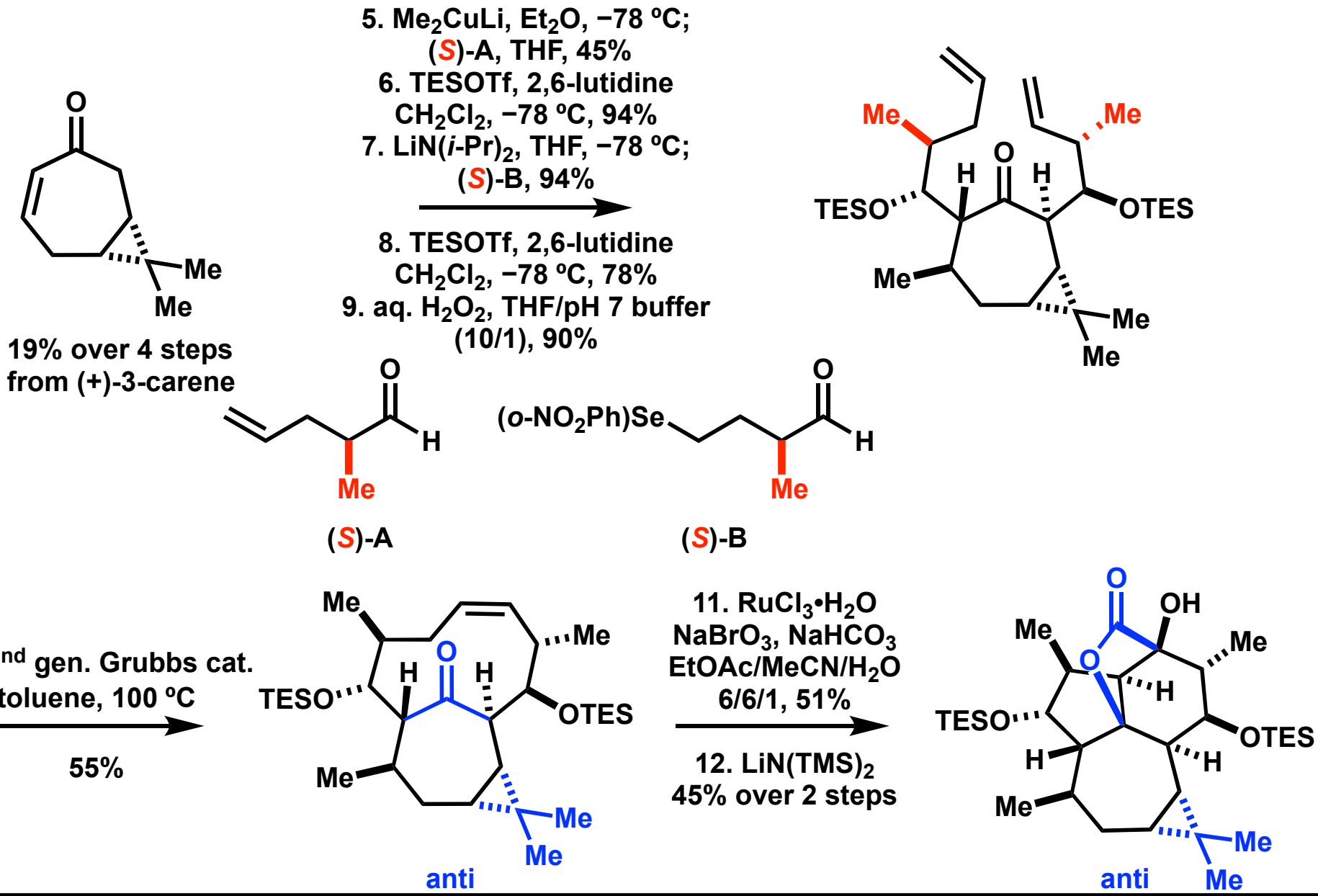


anti

Carreira next attempted to change side chain, the enantiomeric Metyl

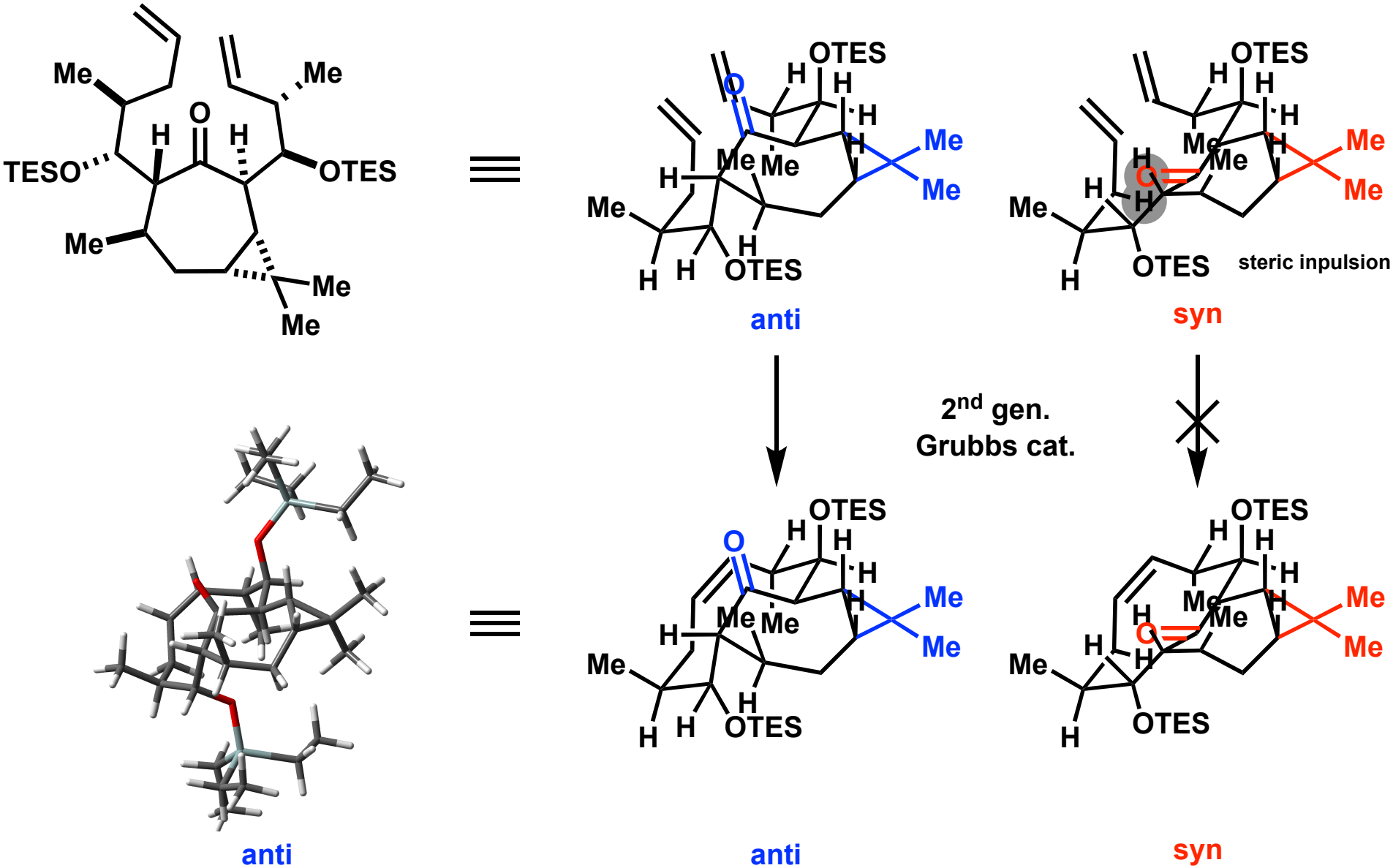
1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

Second Synthesis of Key Intermediate



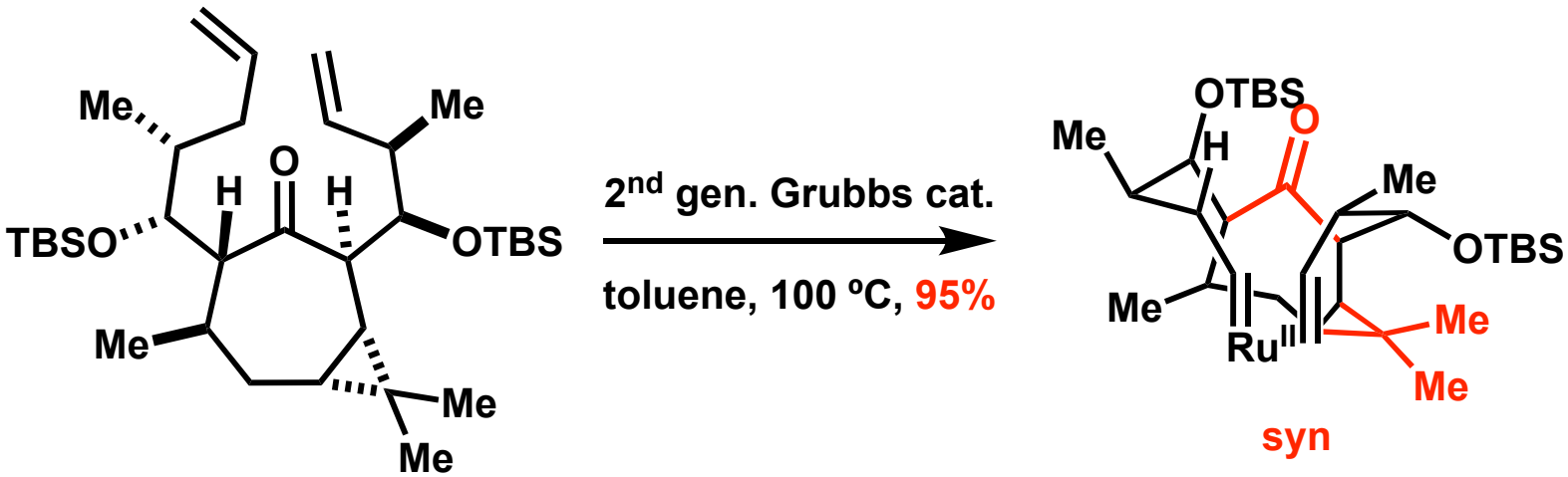
1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

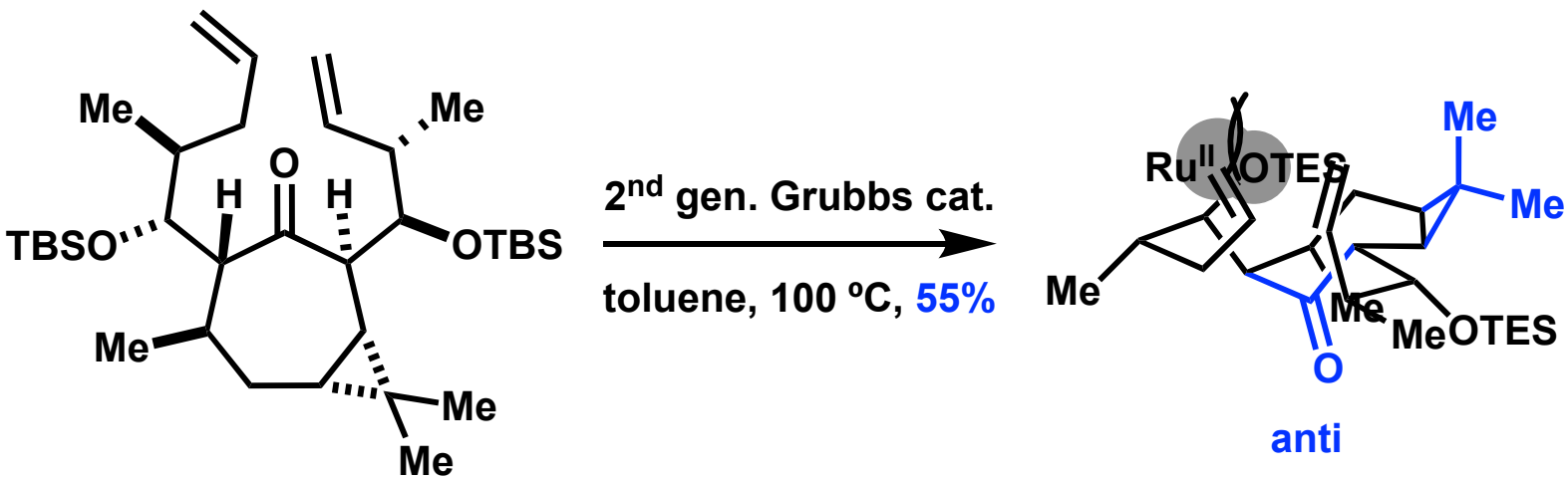
Desired atropisomerism



1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

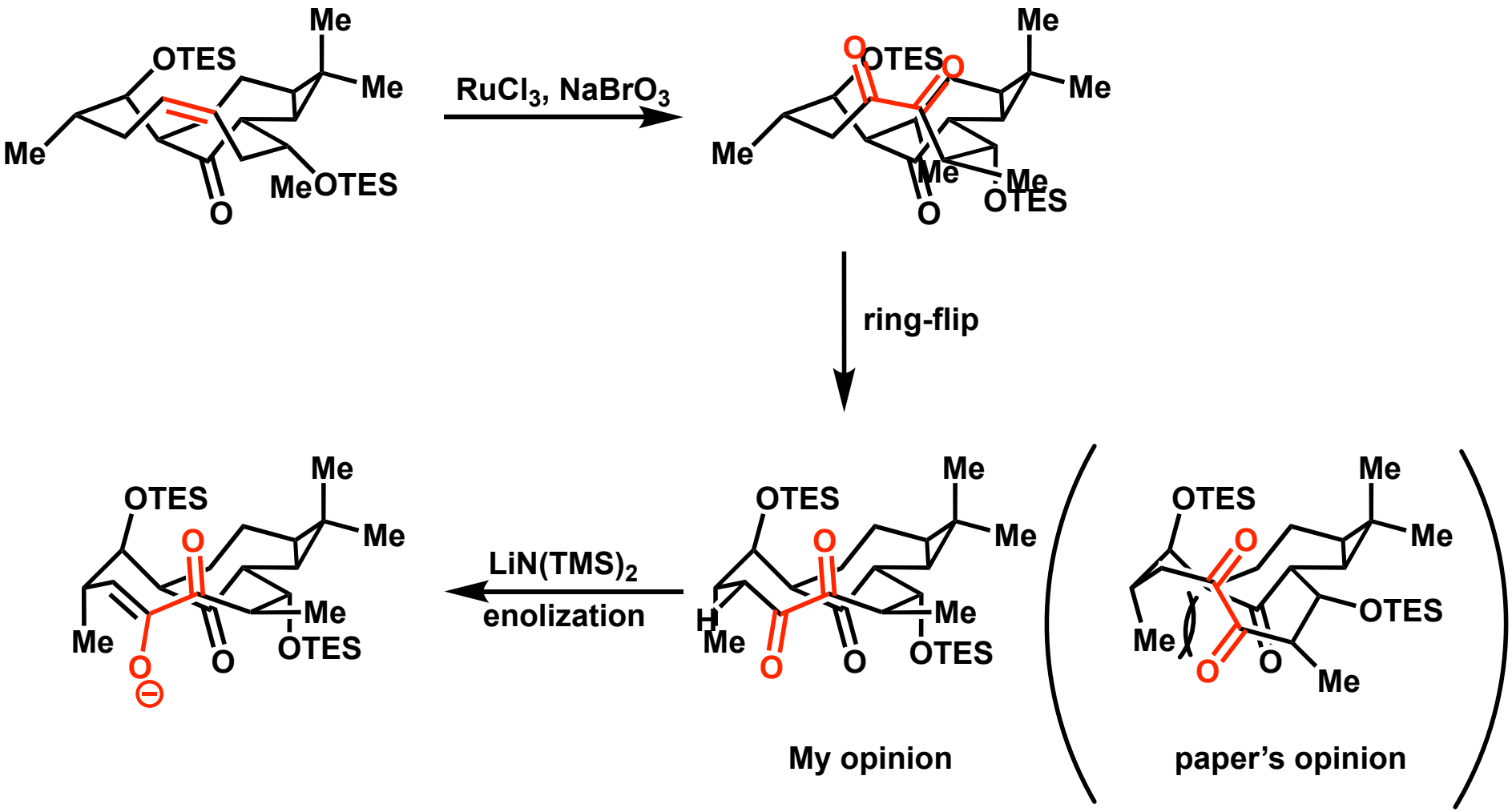
Yield of Ring-Crosing-Metathesis





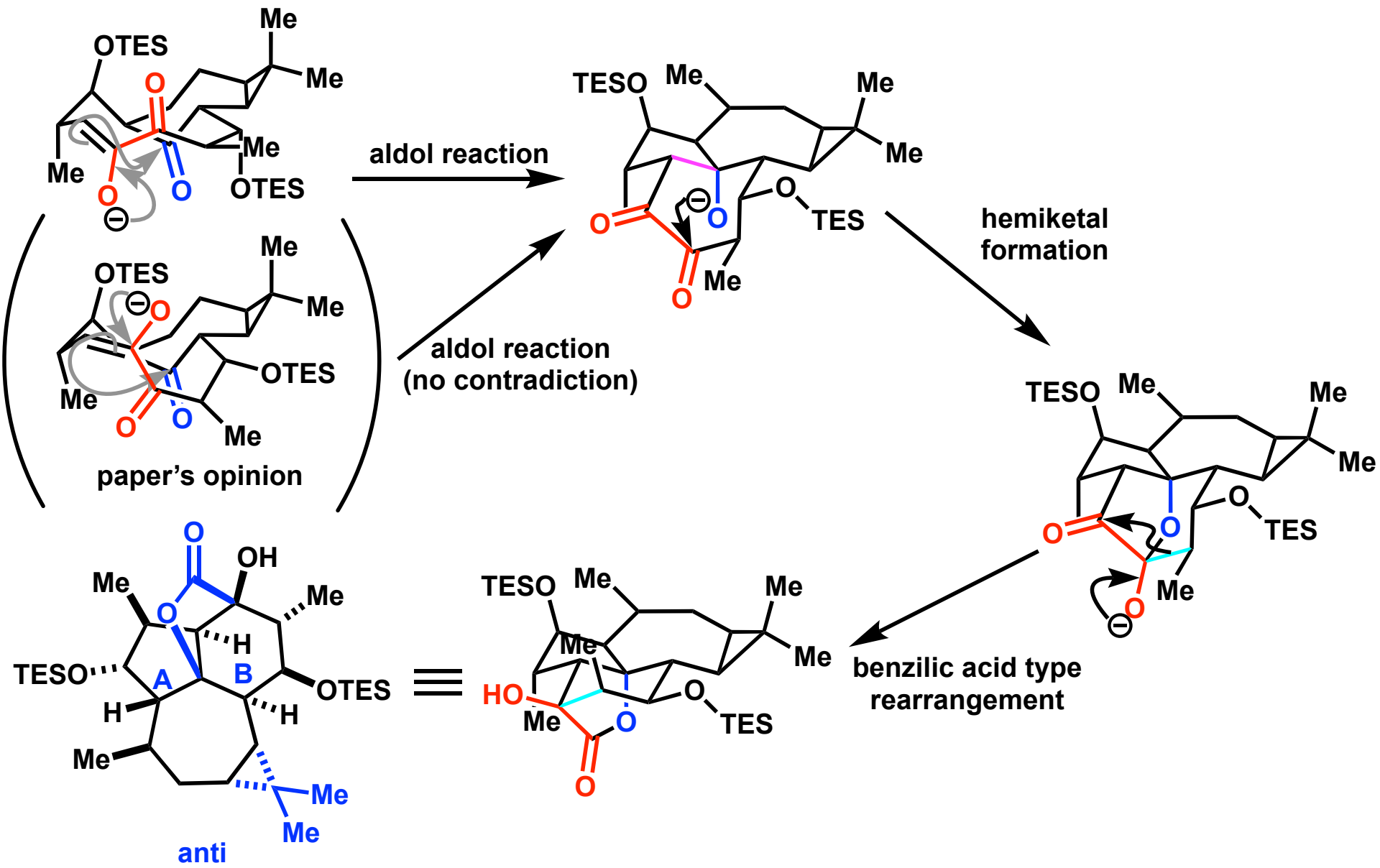
1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

Cascade Reactions



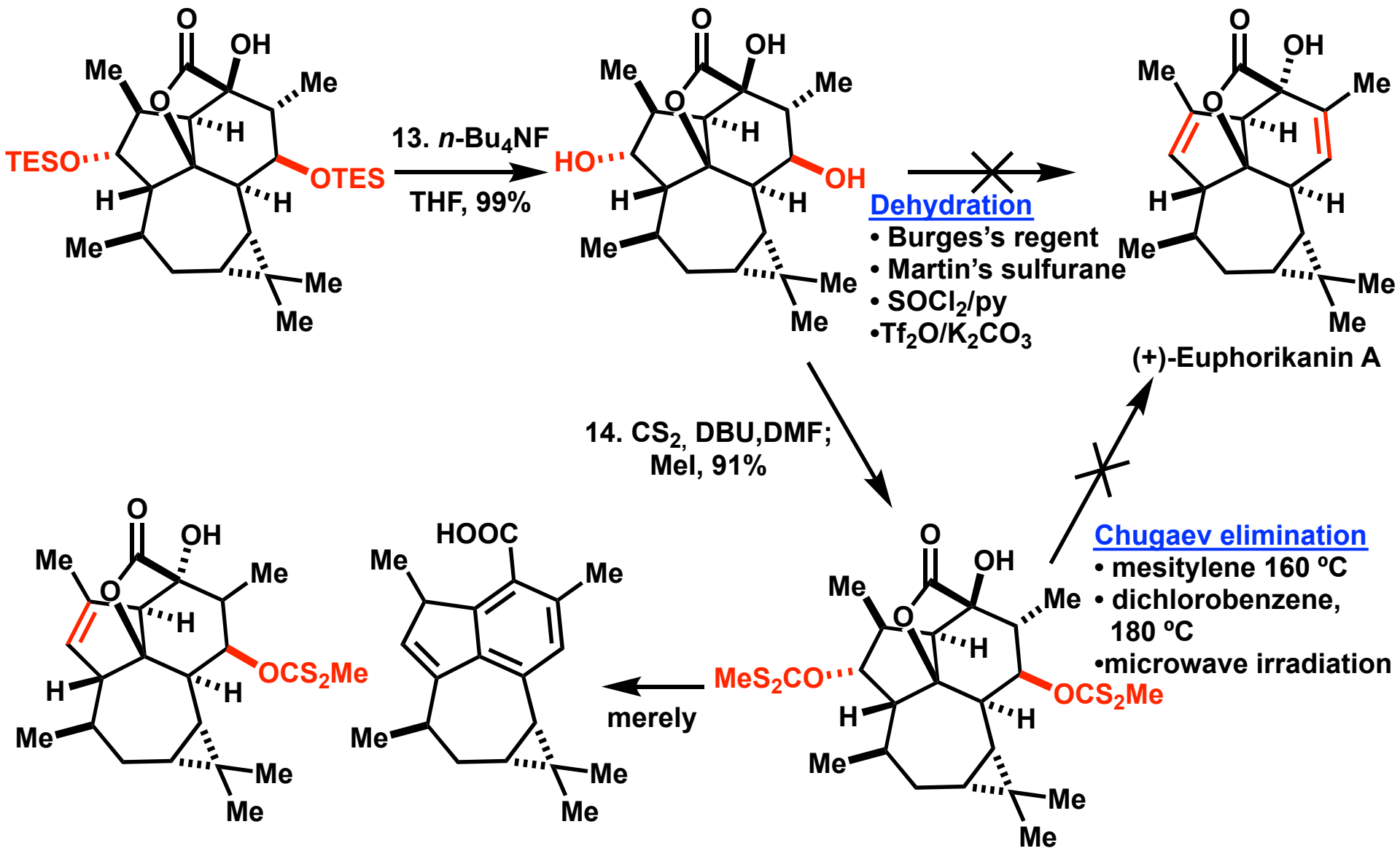
1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

Cascade Reactions



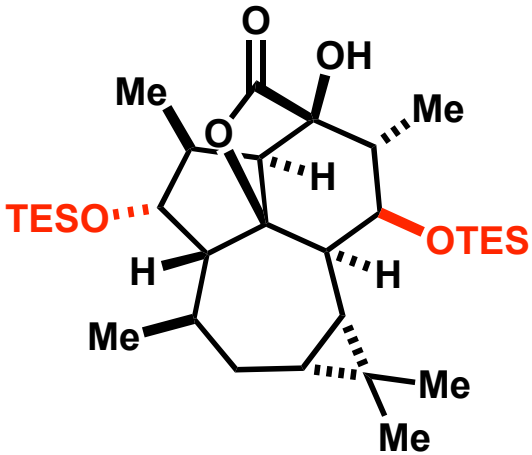
1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

Fail to Complete of the Synthesis



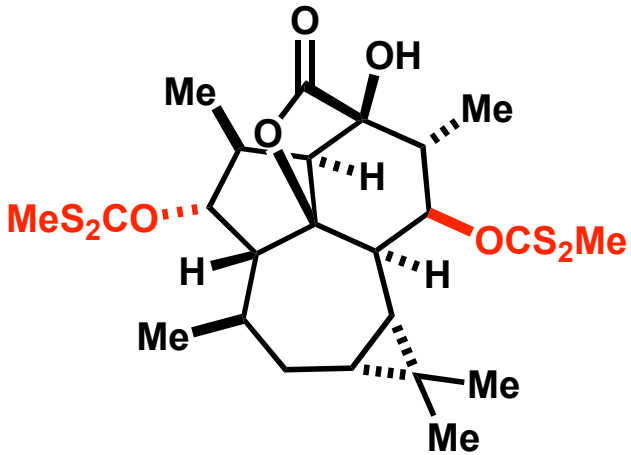
1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

Complete of the Synthesis



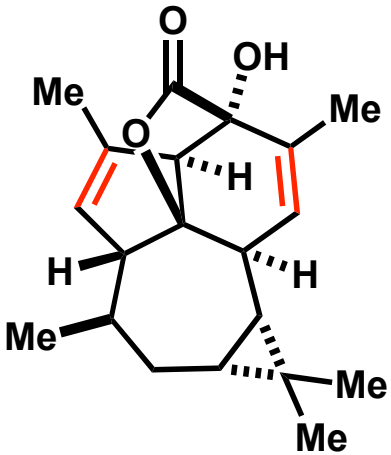
13. *n*-Bu_4NF
THF, 99%

14. CS_2, DBU,DMF;
MeI, 91%



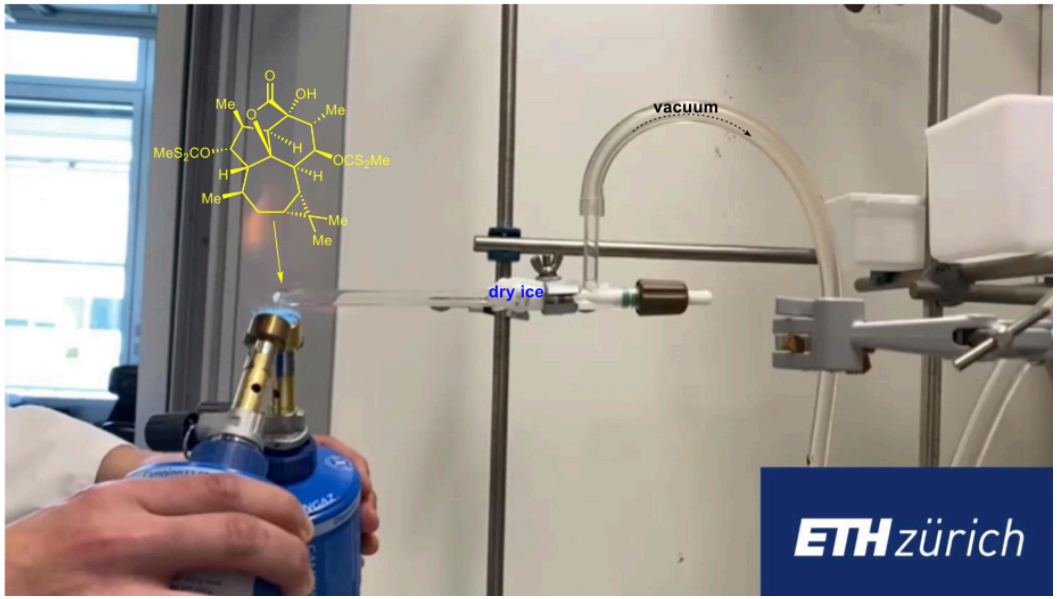
15. Δ (Bunsen buner)
0.36 mbar, 68%

Chugaev elimination



(+)-Euphorikanin A

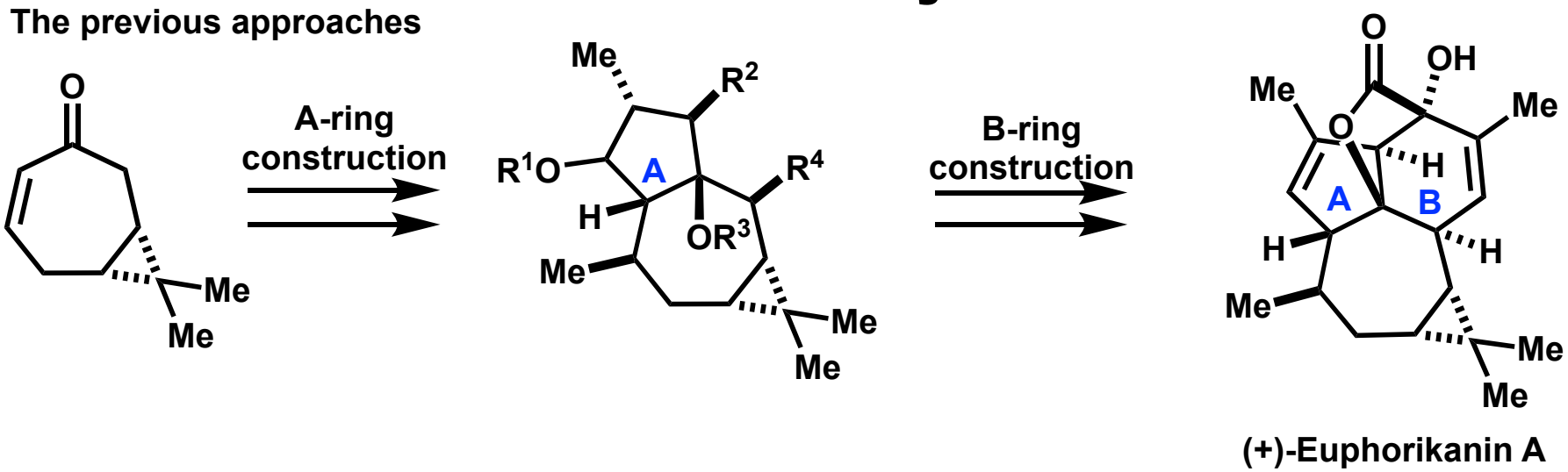
15 steps, 0.8%



1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

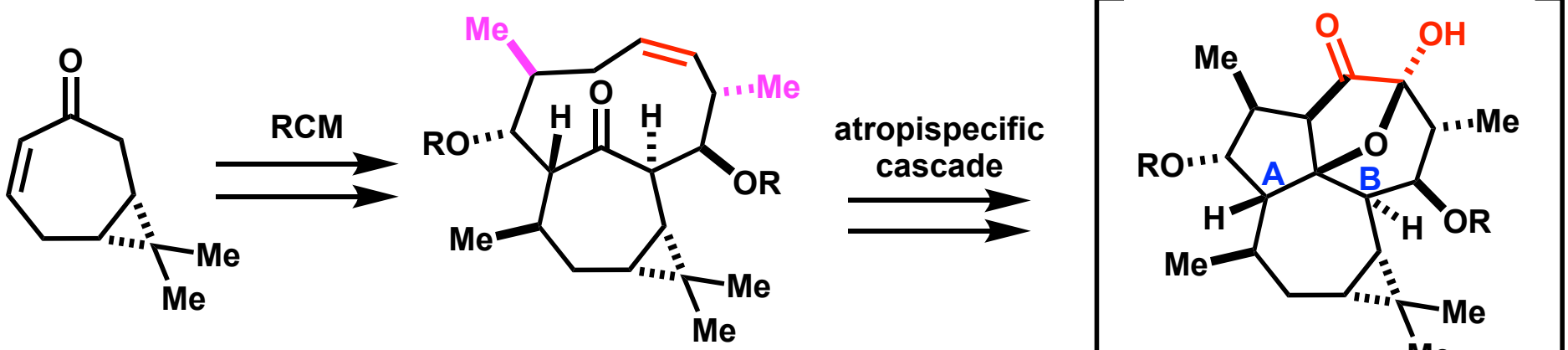
Summary

The previous approaches



(+)-Euphorikanin A

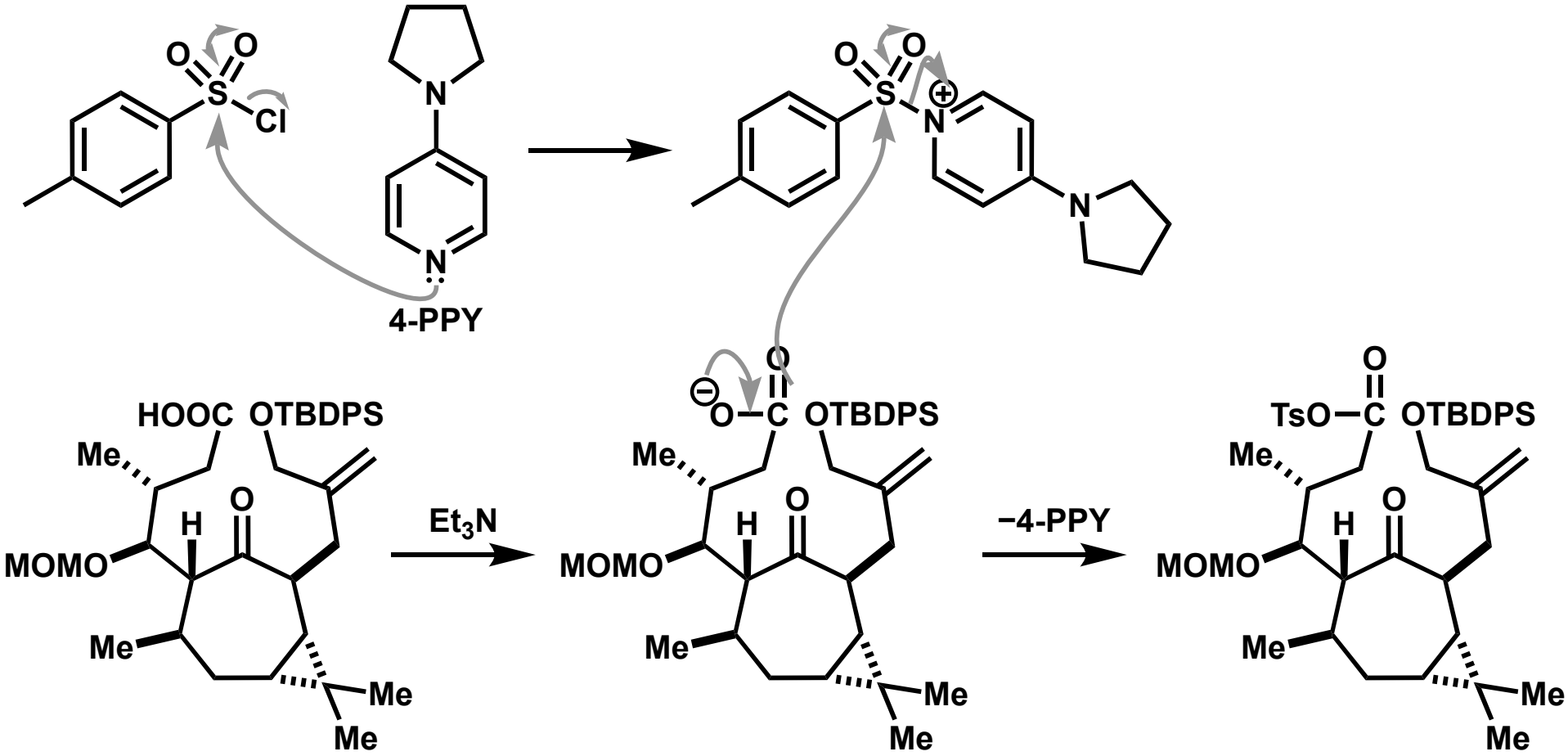
Carreira's new approach



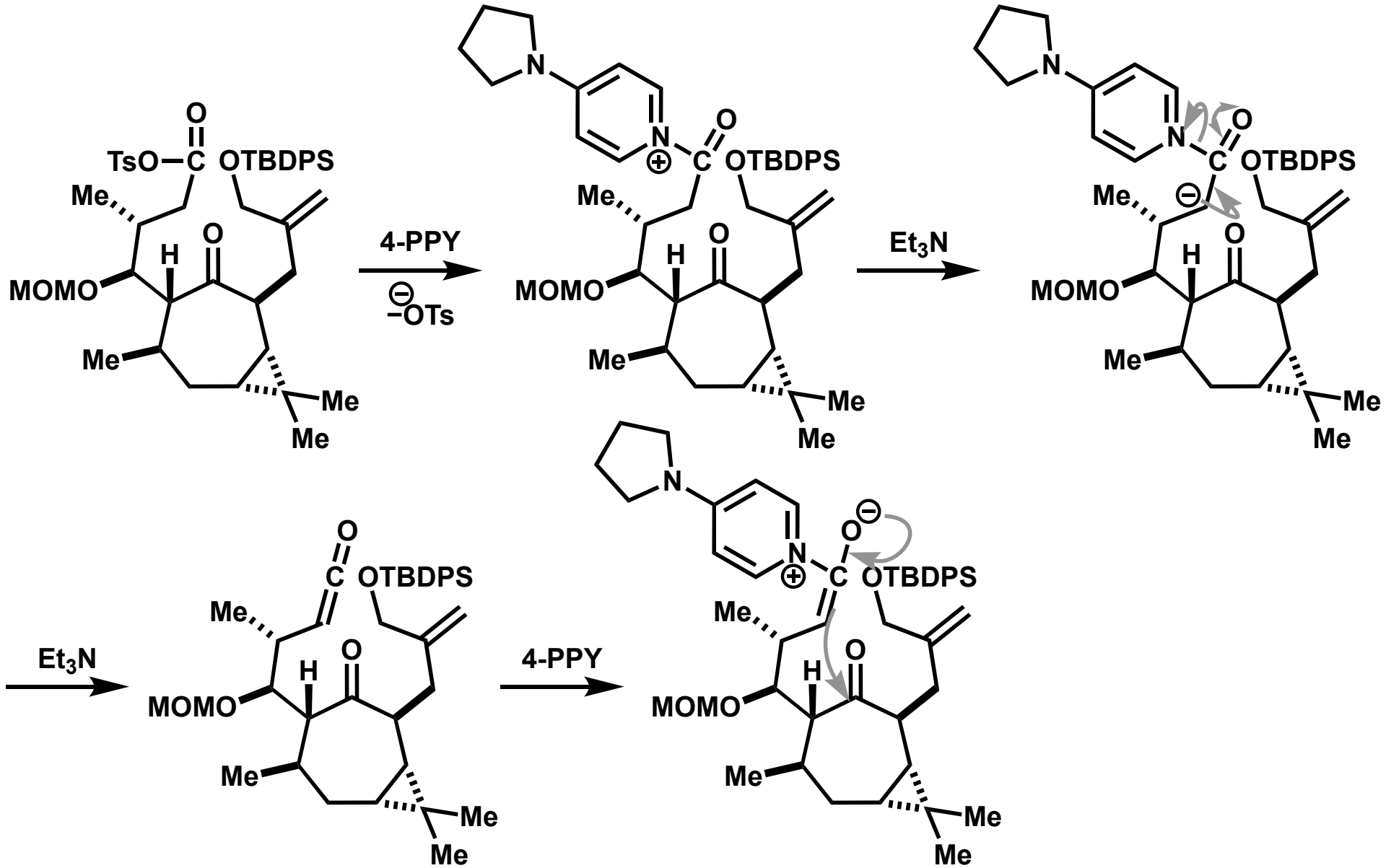
10-menbered ring
astroselective by Me

1) M. J. Classen; B. Kicin; V. A. P. Ruf; A. Hamminger; L. Ribadeau-Dumas; W. M. Amberg; E. M. Carreira. *J. Am. Chem. Soc.* **2023**, *in press.*

Appendix

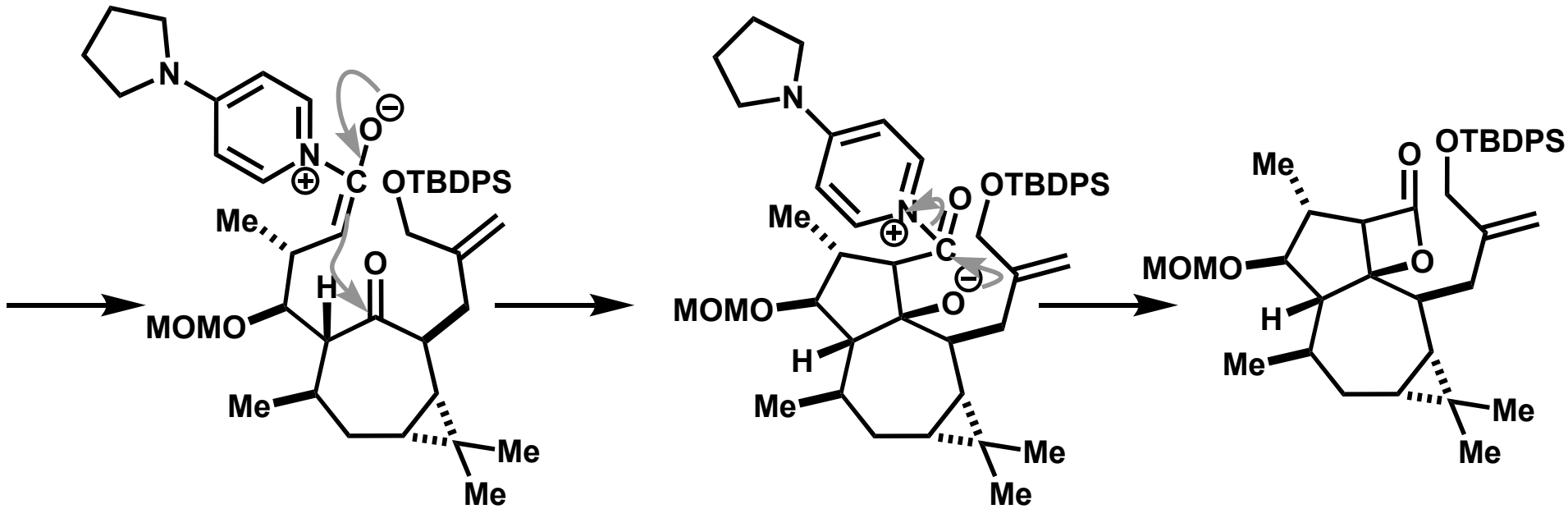

O
O
S
Cl
N
N
4-PPY
O
O
S
N
N
HOOC
OTBDPS
Me
H
O
MOMO
Me
Me
Me
Et3N
O
O
C
OTBDPS
Me
H
O
MOMO
Me
Me
Me
−4-PPY
O
TsO
C
OTBDPS
Me
H
O
MOMO
Me
Me
Me

Appendix



1) 220430_PS_Hiromu_Kakizawa

Appendix



stereoselectivity
→ 220430_PS_Hiromu_Kakizawa

1) 220430_PS_Hiromu_Kakizawa