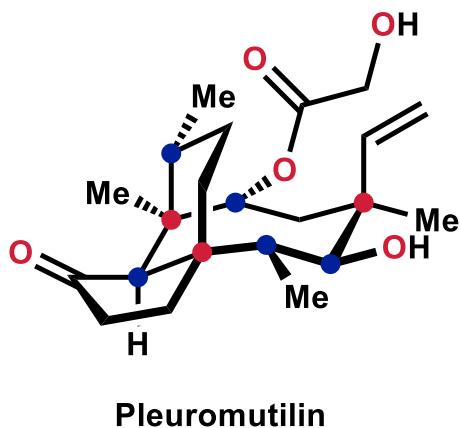


Total Synthesis of Pleuromutilin



Reporter: Qitao Lu

Supervisor: Prof. Quan Cai

Content

- **Introduction**
- **Total Synthesis of Pleuromutilin**
 - ✓ Gibbons, E. G.
 - ✓ Boeckman, R. K.
 - ✓ Procter, D. J.
 - ✓ Herzon, S. B.
 - ✓ Reisman, S. E.
 - ✓ Pronin, S. V.
 - ✓ Luo, T.
- **Summary**

Content

➤ Introduction

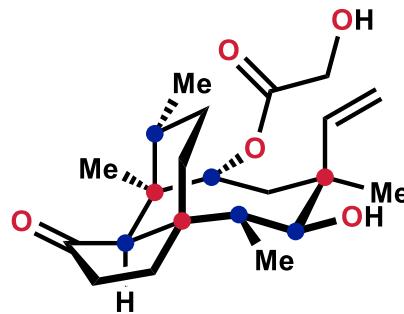
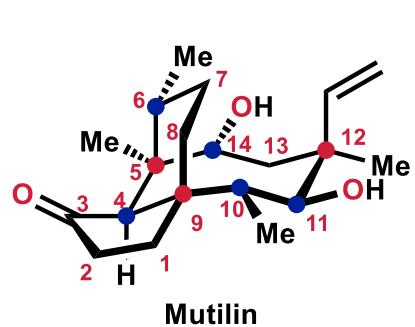
➤ Total Synthesis of Pleuromutilin

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- ✓ Reisman, S. E.
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- ✓ Luo, T.

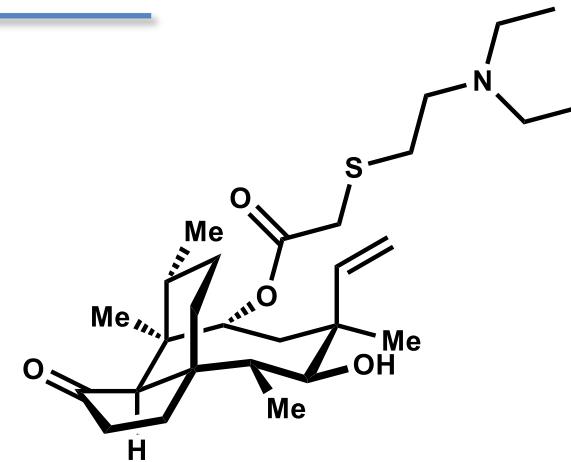
➤ Summary

Introduction

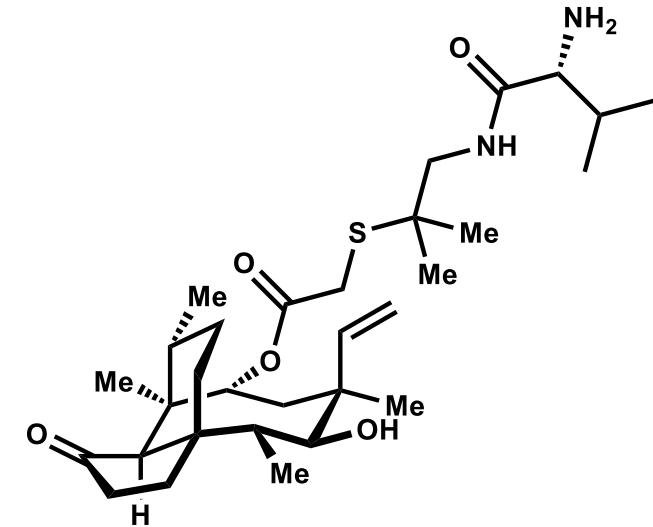
1. Isolation and R&D History



Pleuromutilin (截短侧耳素), 1951
inhibitor of bacterial protein synthesis



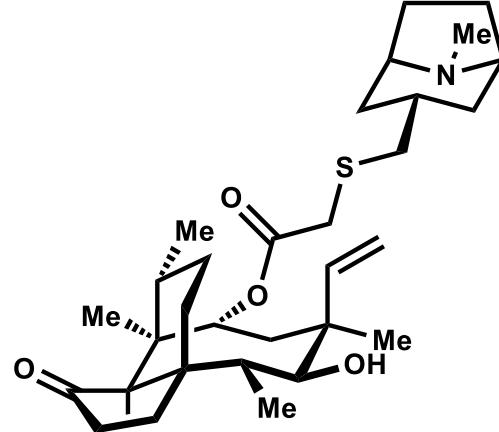
Tiamulin (泰妙菌素), 1979
veterinary antibiotics



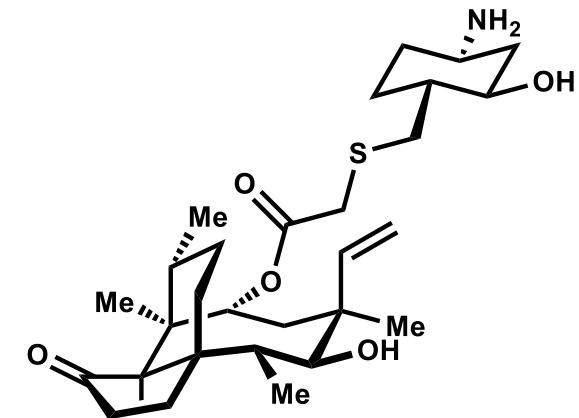
Valnemulin (沃尼妙林), 1999
veterinary antibiotics



Pleurotus mutilus
侧耳菌



Retapamulin (瑞他帕林), 2007
approved for topical treatment of infections
IC50 Value: 3 nM (Kd, E.coli) Target: ribosome



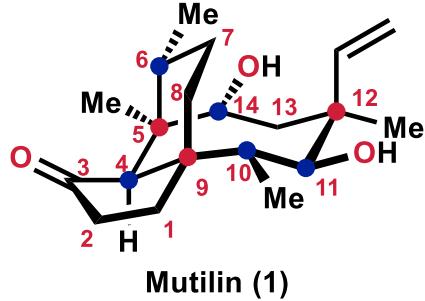
Lefamulin (来法莫林), 2019
approved for systemic treatment of infections

Kavanagh, F.; Hervey, A.; Robbins, W. J. *Proc. Natl. Acad. Sci. U.S.A.* **1951**, 37, 570.

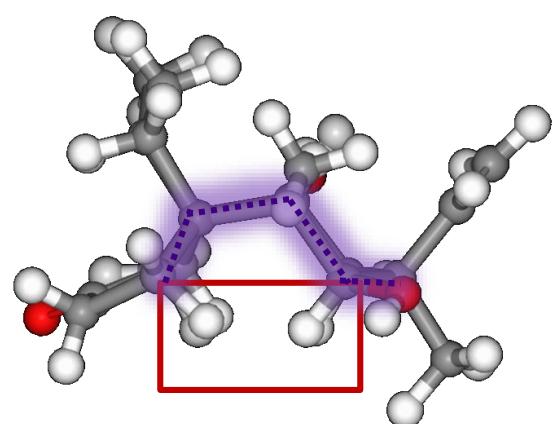
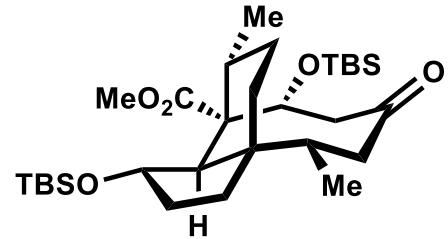
Arigoni, D. *Gazz. Chim. Ital.* **1962**, 92, 884.

Introduction

2. Structural features



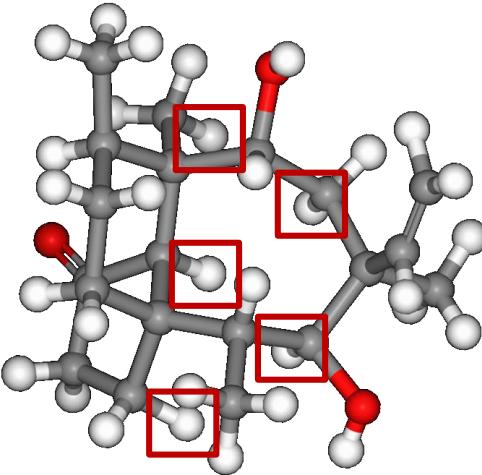
- 5,6,8-tricyclic scaffold
- 8 stereogenic centers
- 3 all-carbon quaternary carbons



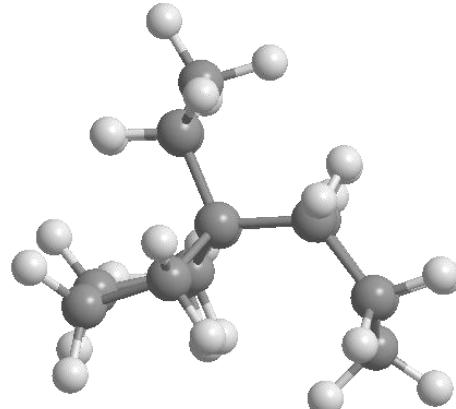
view from front to back

CCDC-126124

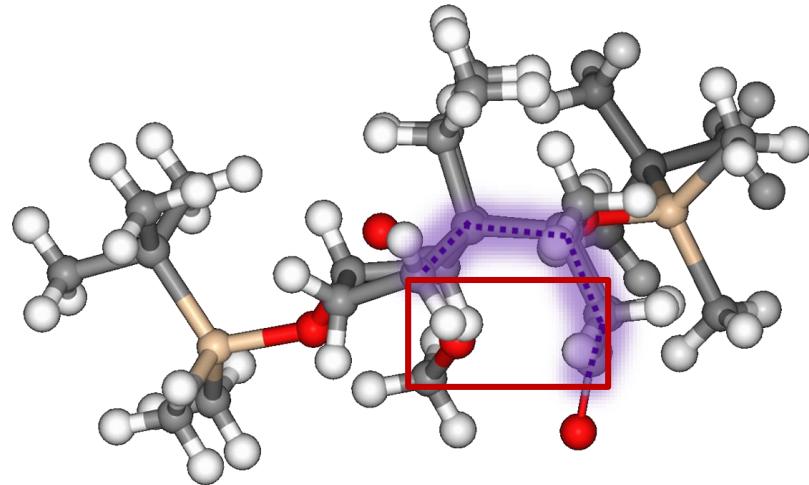
sp³-C12 boat-chair



view from top to bottom



computed conformation
sp³-C12 boat-boat



CCDC-913369
sp²-C12 boat-boat

Content

➤ Introduction

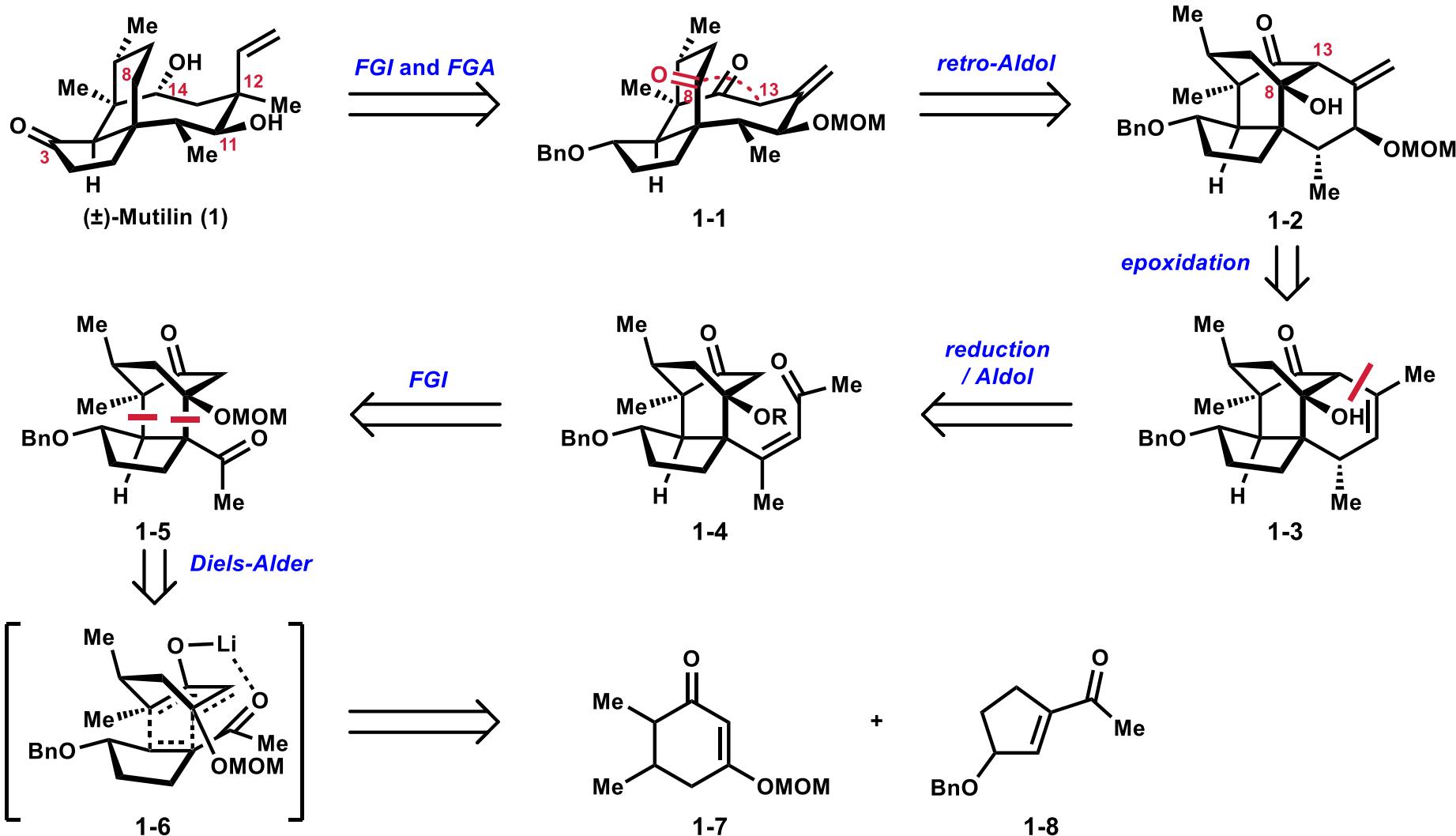
➤ Total Synthesis of Pleuromutilin

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- ✓ Boeckman, R. K.
- ✓ Procter, D. J.
- ✓ Herzon, S. B.
- ✓ Reisman, S. E.
- ✓ Pronin, S. V.
- ✓ Luo, T.

➤ Summary

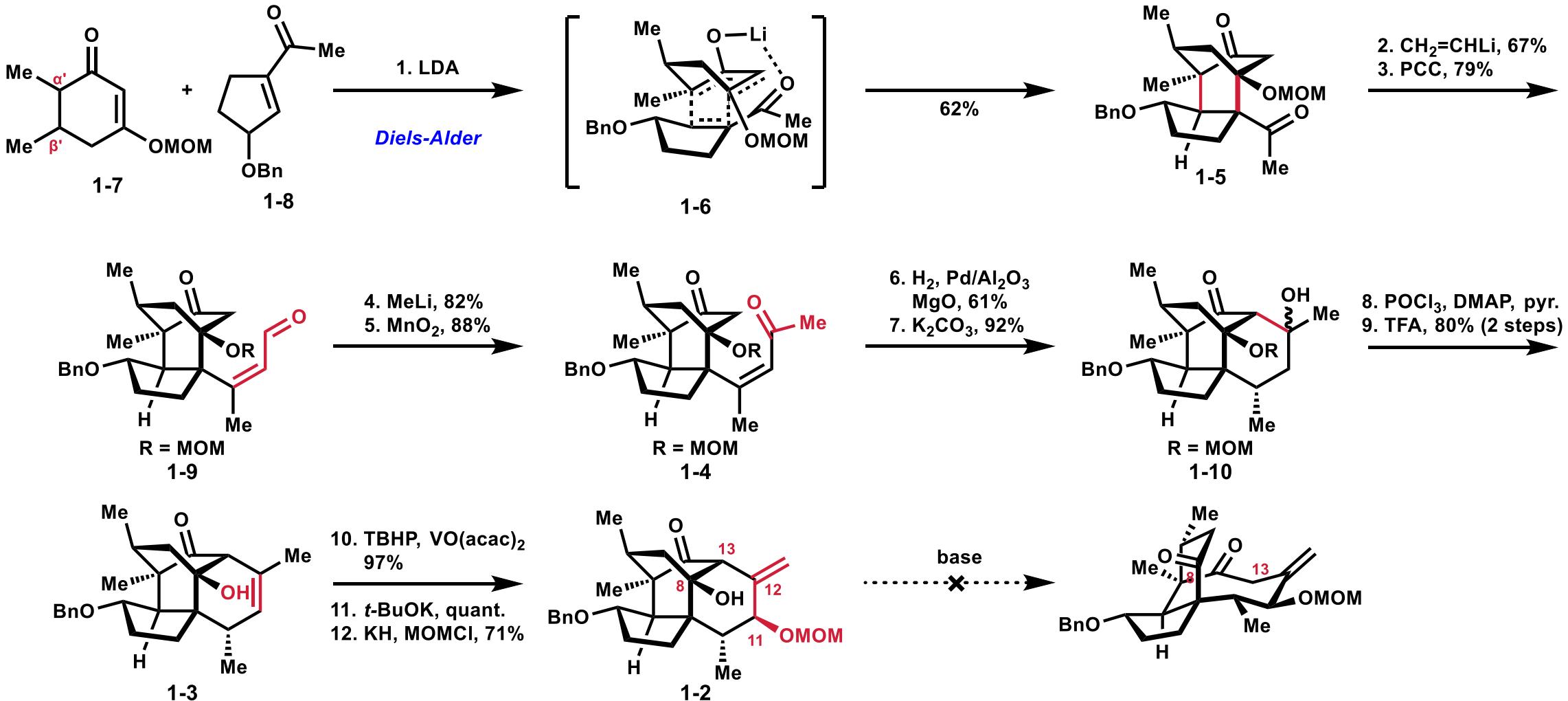
Total Synthesis of (\pm)-Pleuromutilin — Gibbons (1982)

1. Retrosynthetic Analysis



Total Synthesis of (\pm)-Pleuromutilin — Gibbons (1982)

2. Preparation of the retro-Aldol Precursor 1-2

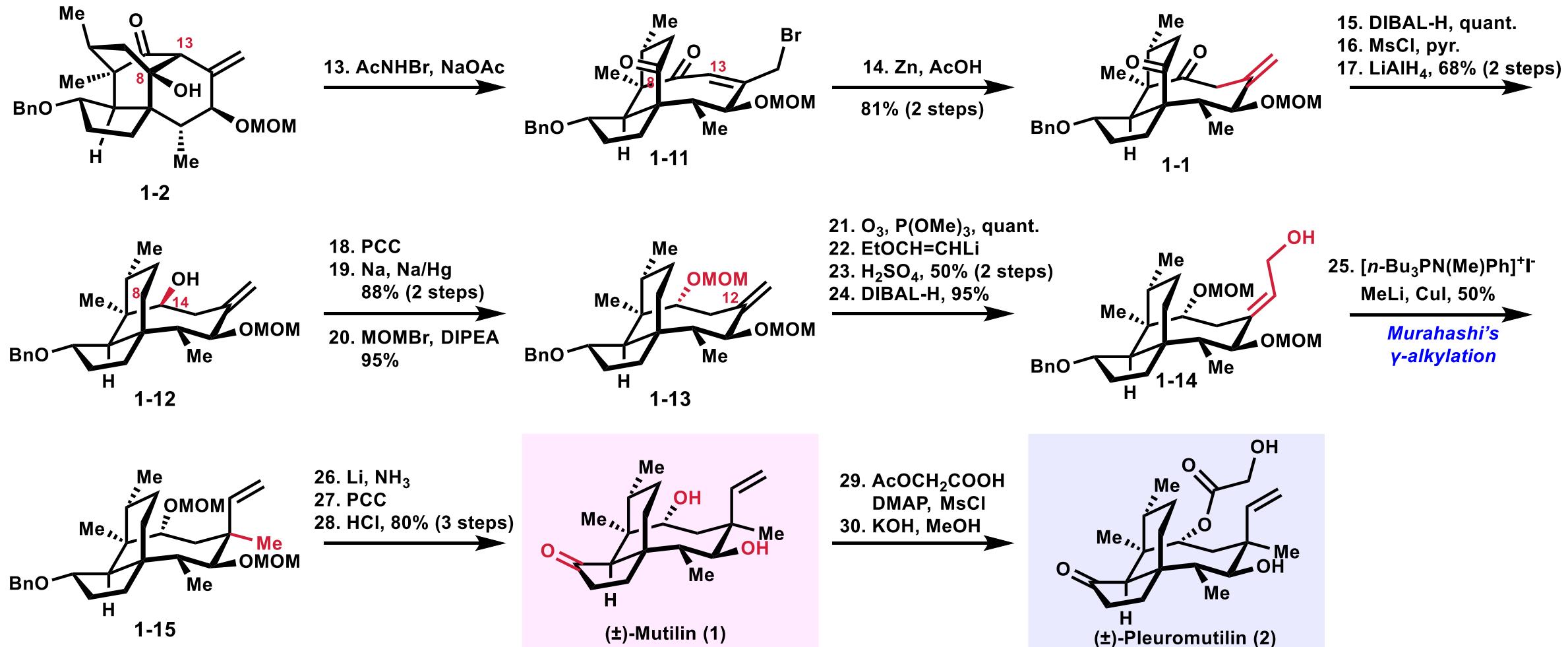


Gibbons, E. G. *J. Org. Chem.* **1980**, *45*, 1540.

Gibbons, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 1767.

Total Synthesis of (\pm)-Pleuromutilin — Gibbons (1982)

3. Synthesis of (\pm)-Pleuromutilin

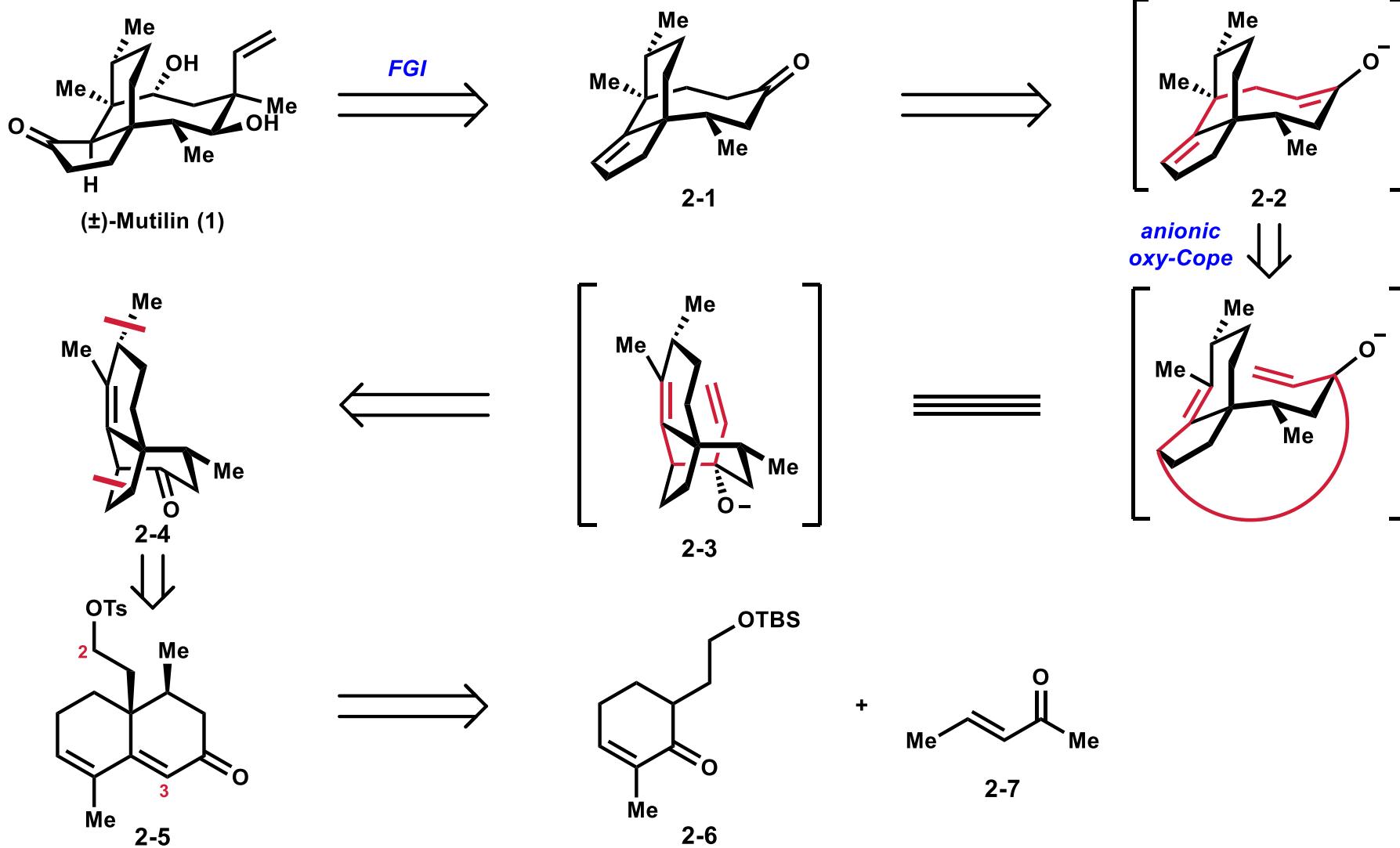


Tanigawa, Y.; Ohta, H.; Sonoda, A.; Murahashi, S. *J. Am. Chem. Soc.* **1978**, *100*, 4610.

Brewster, J. H.; Ciotti, C. J. *J. Am. Chem. Soc.* **1955**, *77*, 6214.

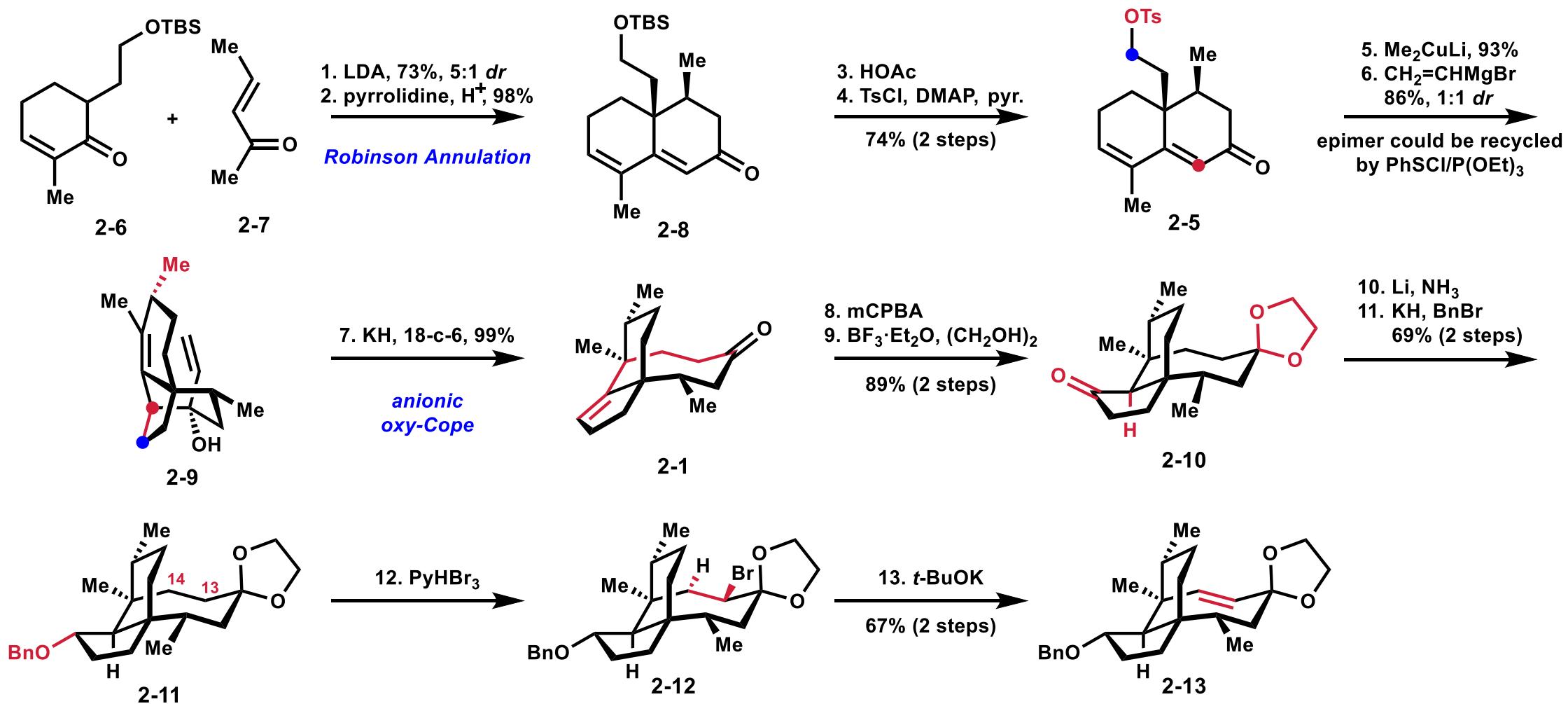
Total Synthesis of (\pm)-Pleuromutilin — Boeckman (1989)

1. Retrosynthetic Analysis



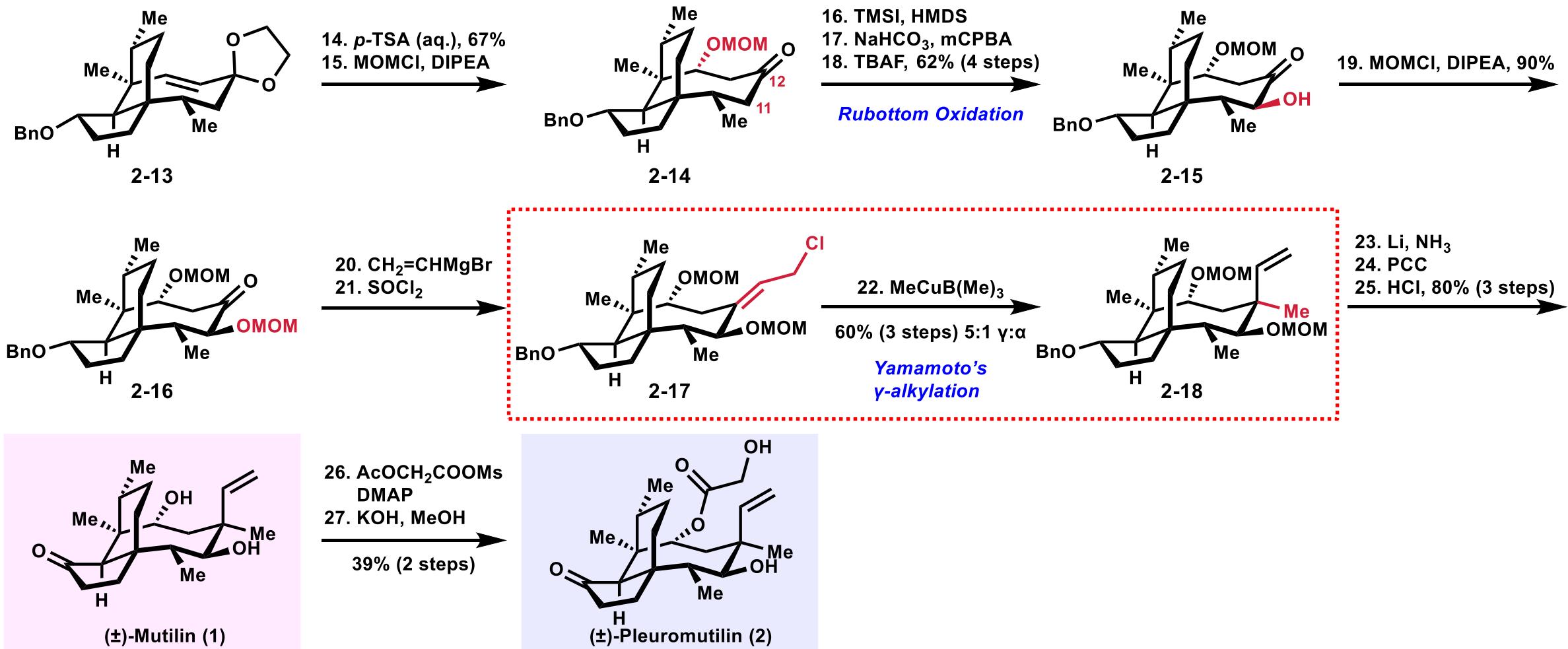
Total Synthesis of (\pm)-Pleuromutilin — Boeckman (1989)

2. Synthesis of 2-13



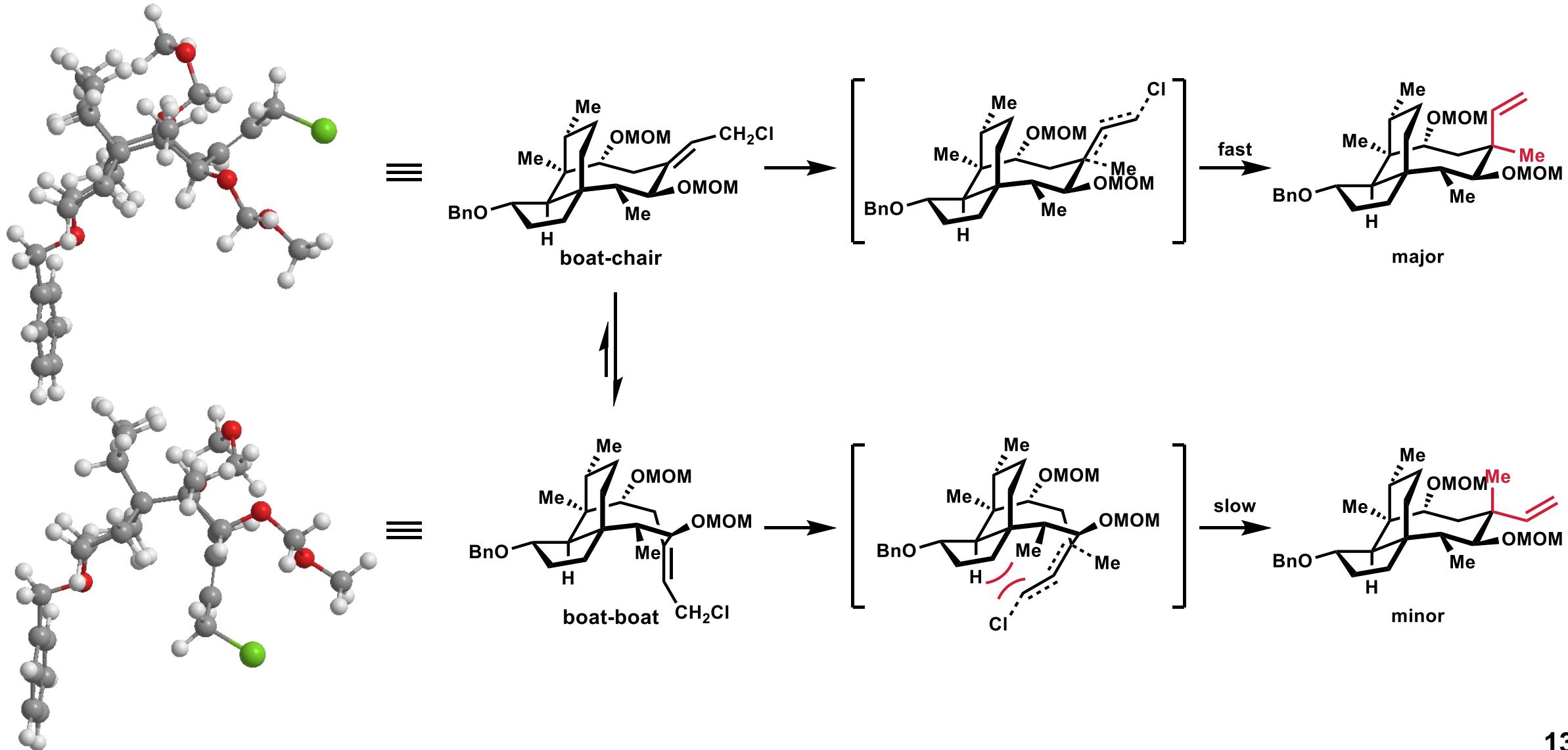
Total Synthesis of (\pm)-Pleuromutilin — Boeckman (1989)

3. Synthesis of (\pm)-Pleuromutilin



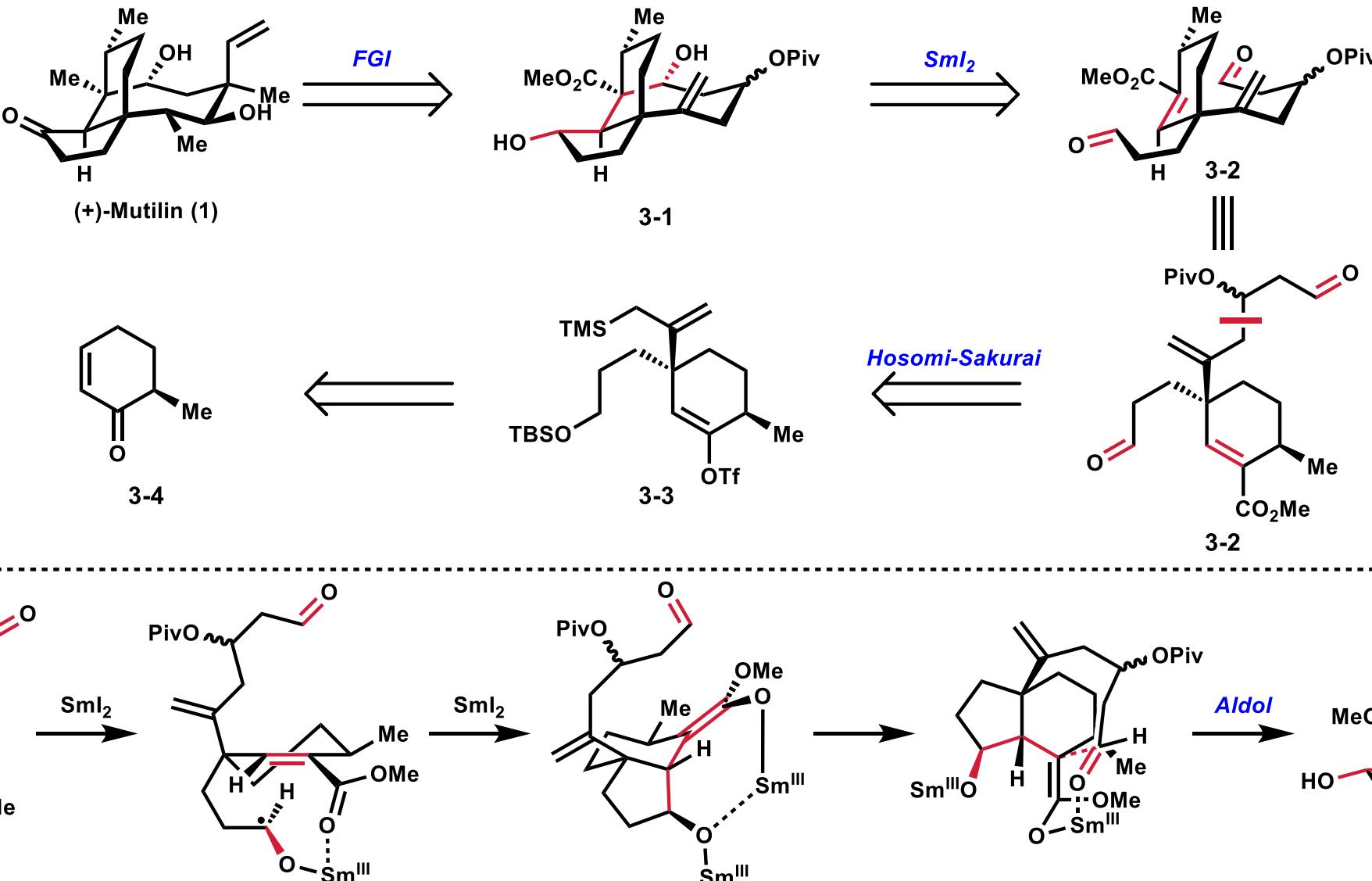
Total Synthesis of (\pm)-Pleuromutilin — Boeckman (1989)

4. Selectivity of the γ -Alkylation — Curtin-Hammett



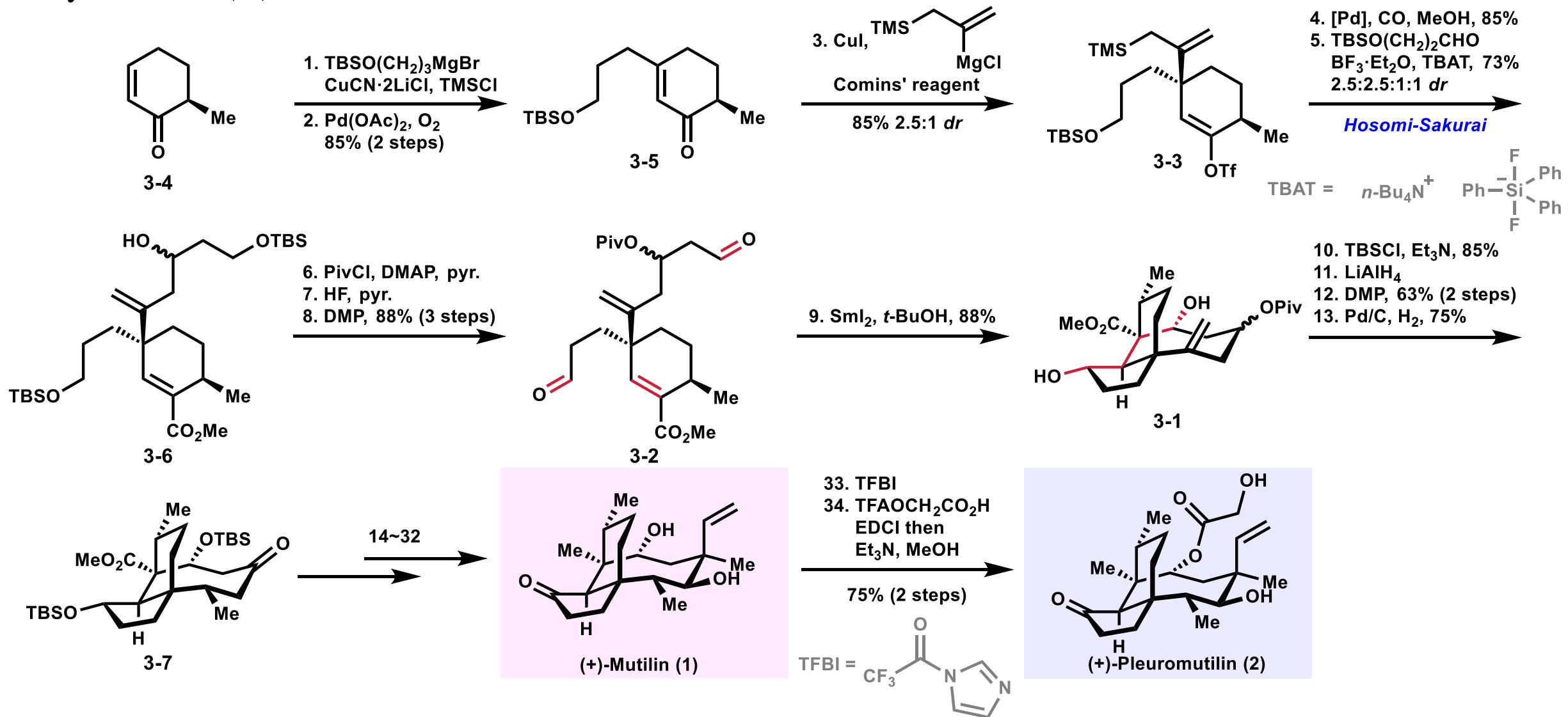
Total Synthesis of (+)-Pleuromutilin — Procter (2013)

1. Retrosynthetic Analysis



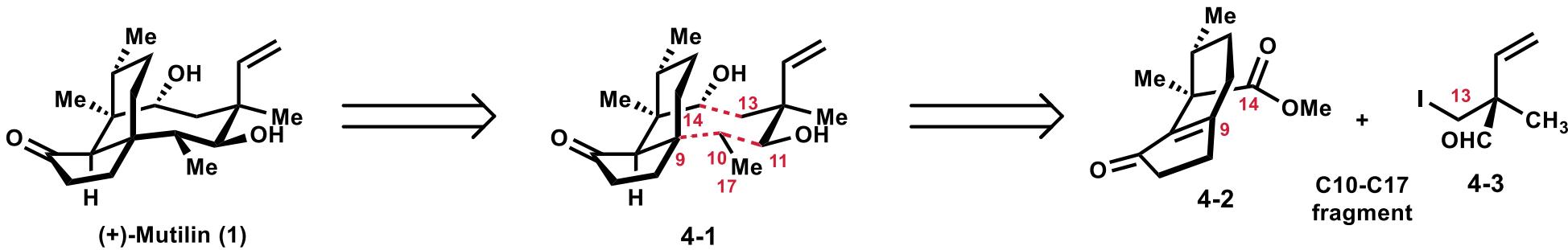
Total Synthesis of (+)-Pleuromutilin — Procter (2013)

2. Synthesis of (+)-Pleuromutilin

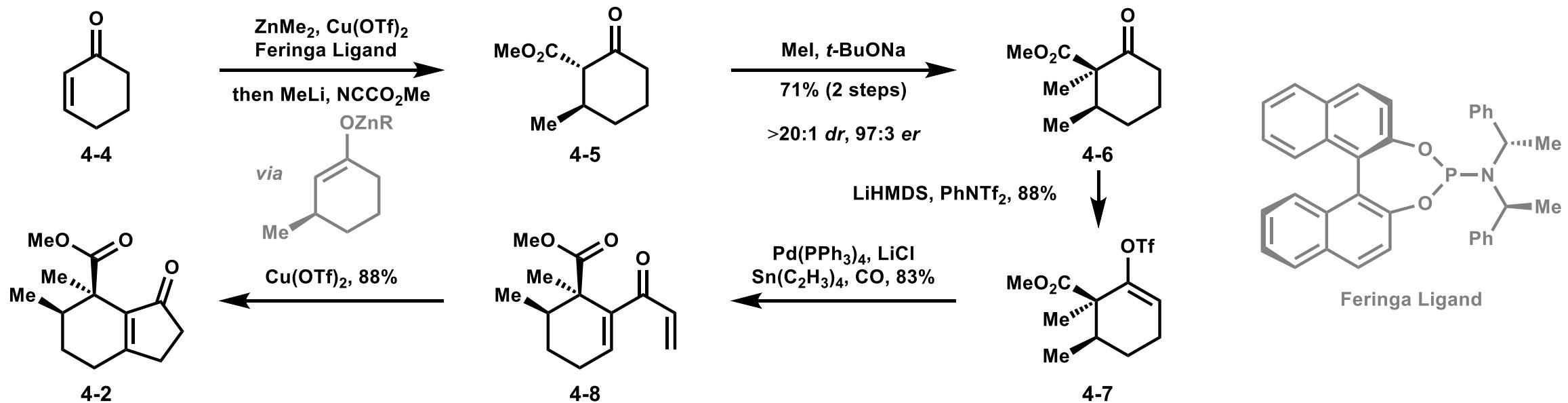


Total Synthesis of (+)-Pleuromutilin — Herzon (2017)

1. Retrosynthetic Analysis



2. Attempted Synthesis — Synthesis of **4-2**



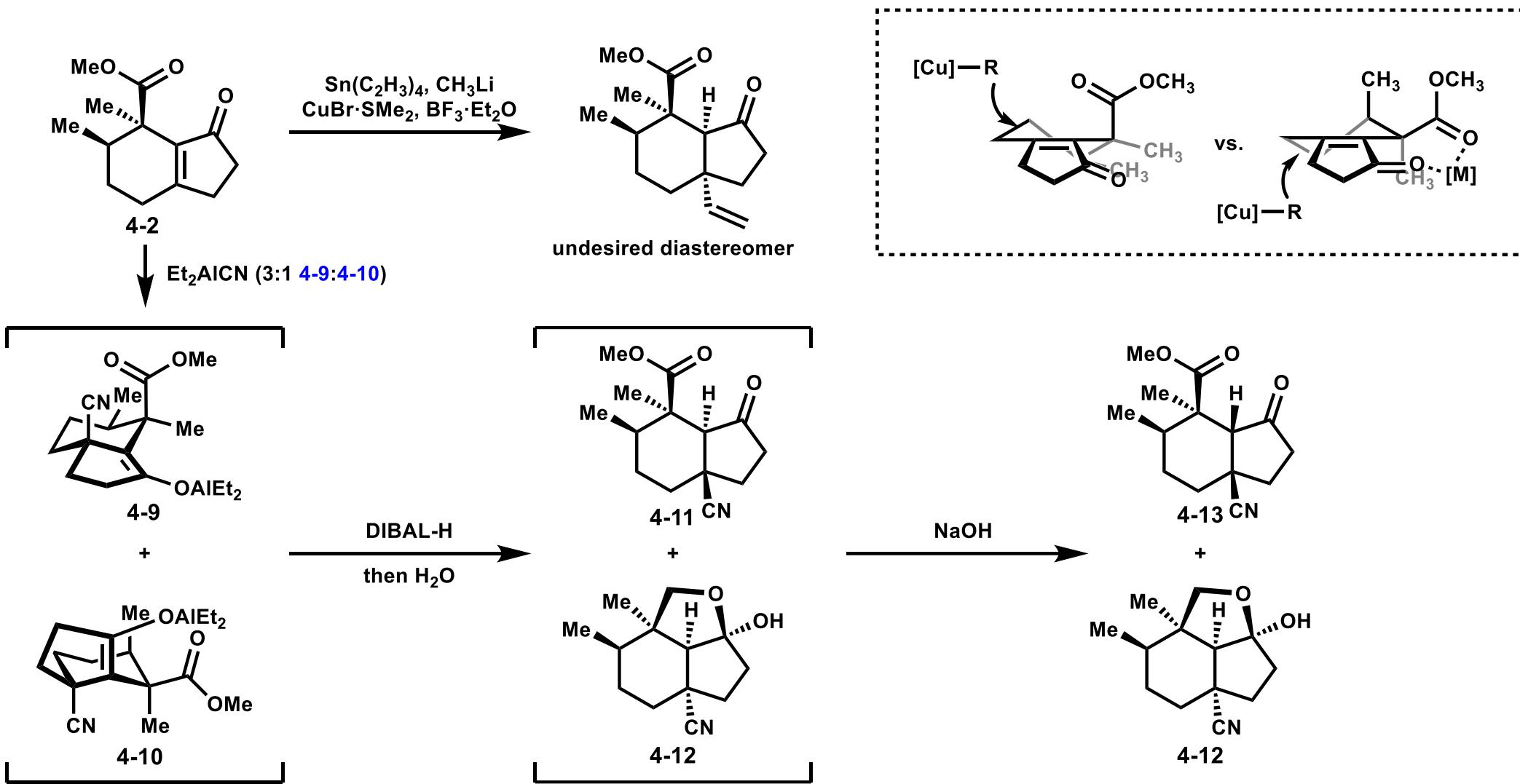
Murphy, S. K.; Zeng, M.; Herzon, S. B. *Org. Lett.* **2016**, *18*, 4880.

Murphy, S. K.; Zeng, M.; Herzon, S. B. *Science* **2017**, *356*, 956.

Zeng, M.; Murphy, S. K.; Herzon, S. B. *J. Am. Chem. Soc.* **2017**, *139*, 16377.

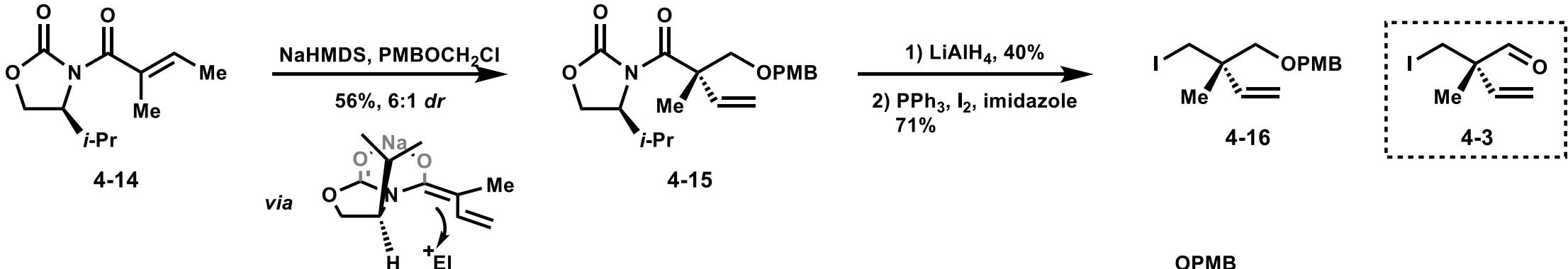
Total Synthesis of (+)-Pleuromutilin — Herzon (2017)

2. Attempted Synthesis — Installation of the C10-C17 Fragment

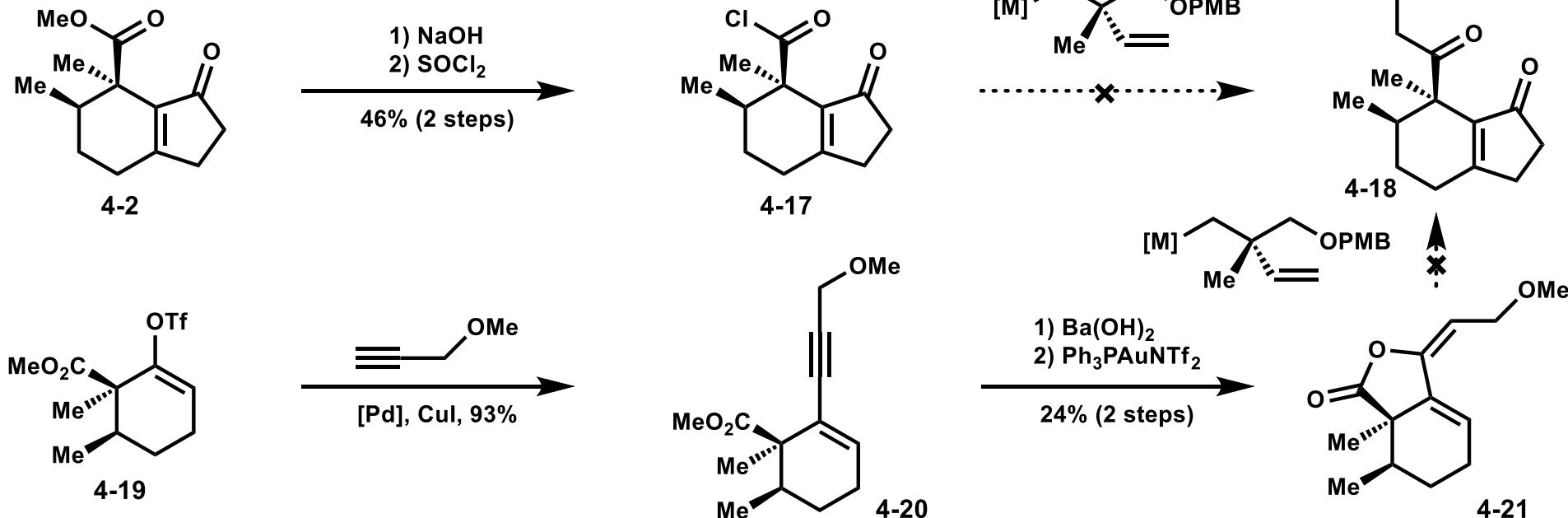


Total Synthesis of (+)-Pleuromutilin — Herzon (2017)

2. Attempted Synthesis — Synthesis of the 4-3 Fragment

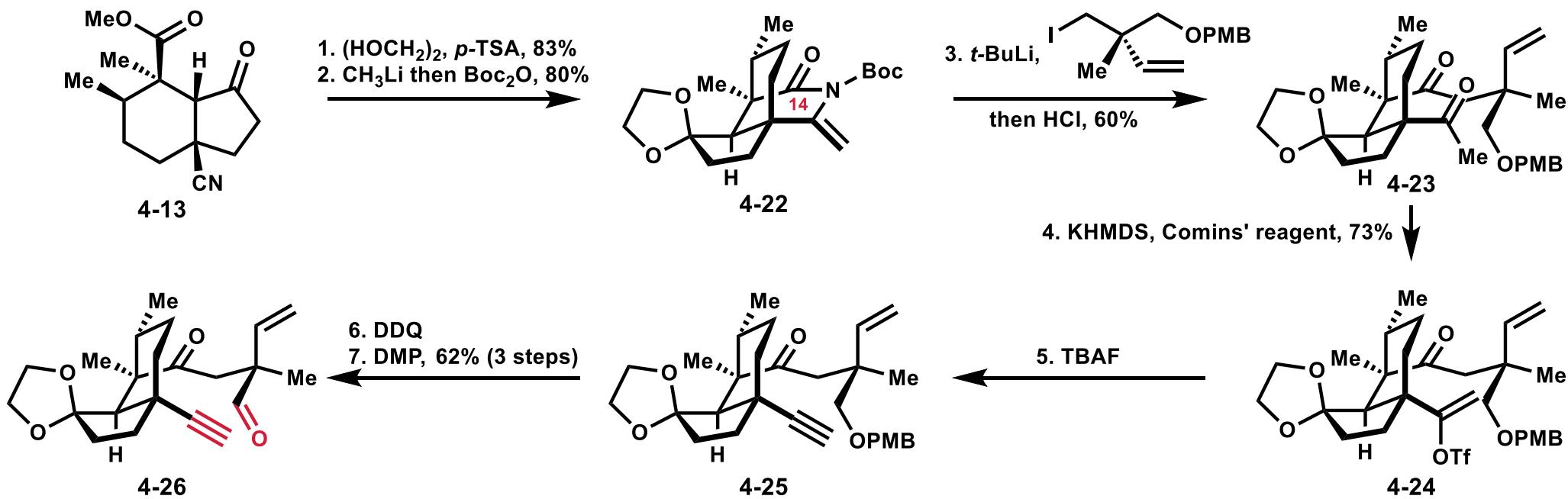
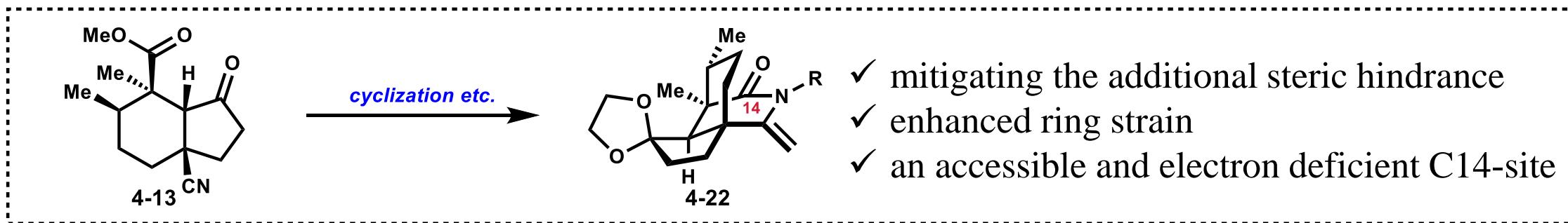


2. Attempted Synthesis — Installation of the 4-3 Fragment (*failed*)



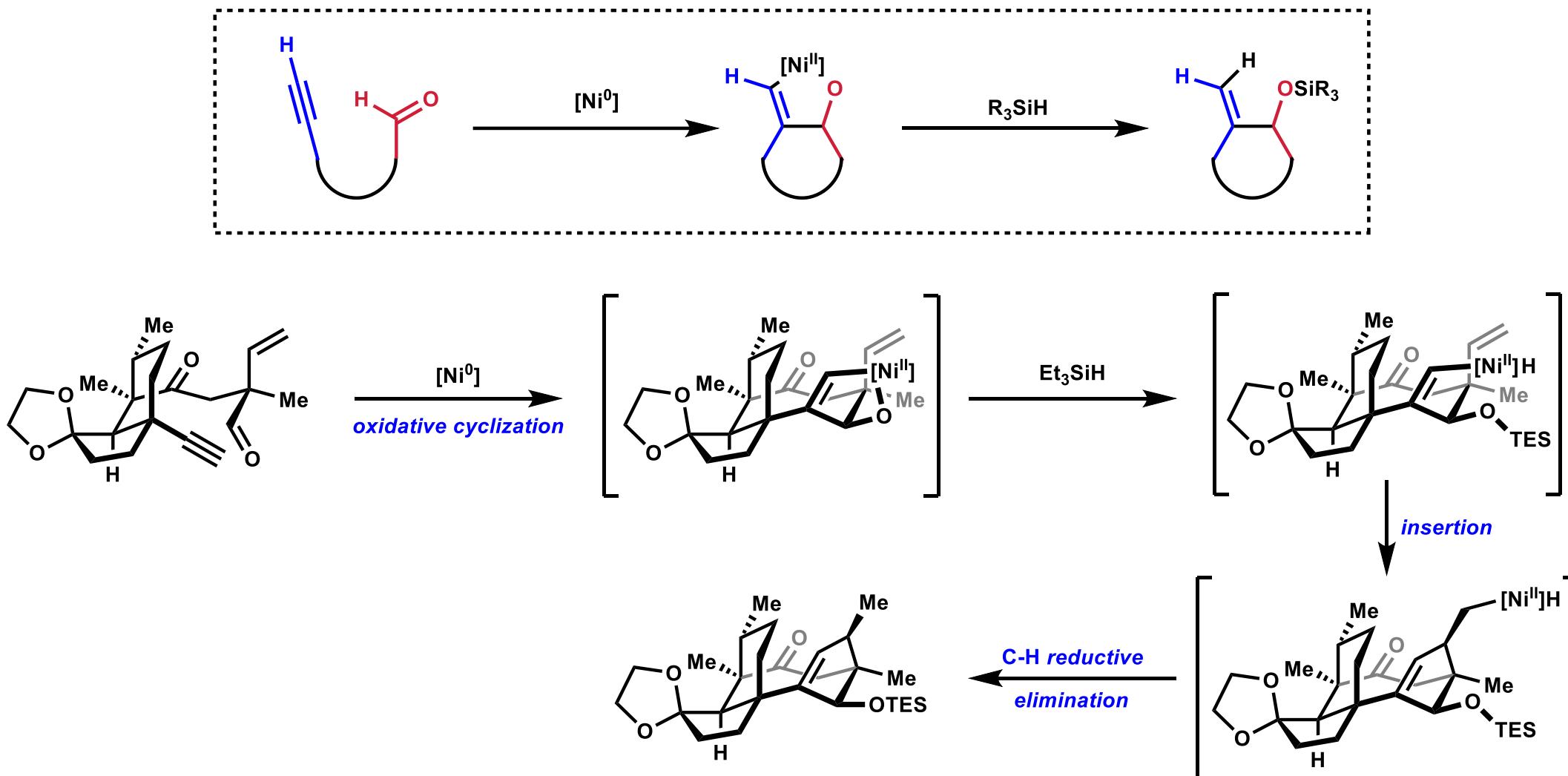
Total Synthesis of (+)-Pleuromutilin — Herzon (2017)

2. Attempted Synthesis



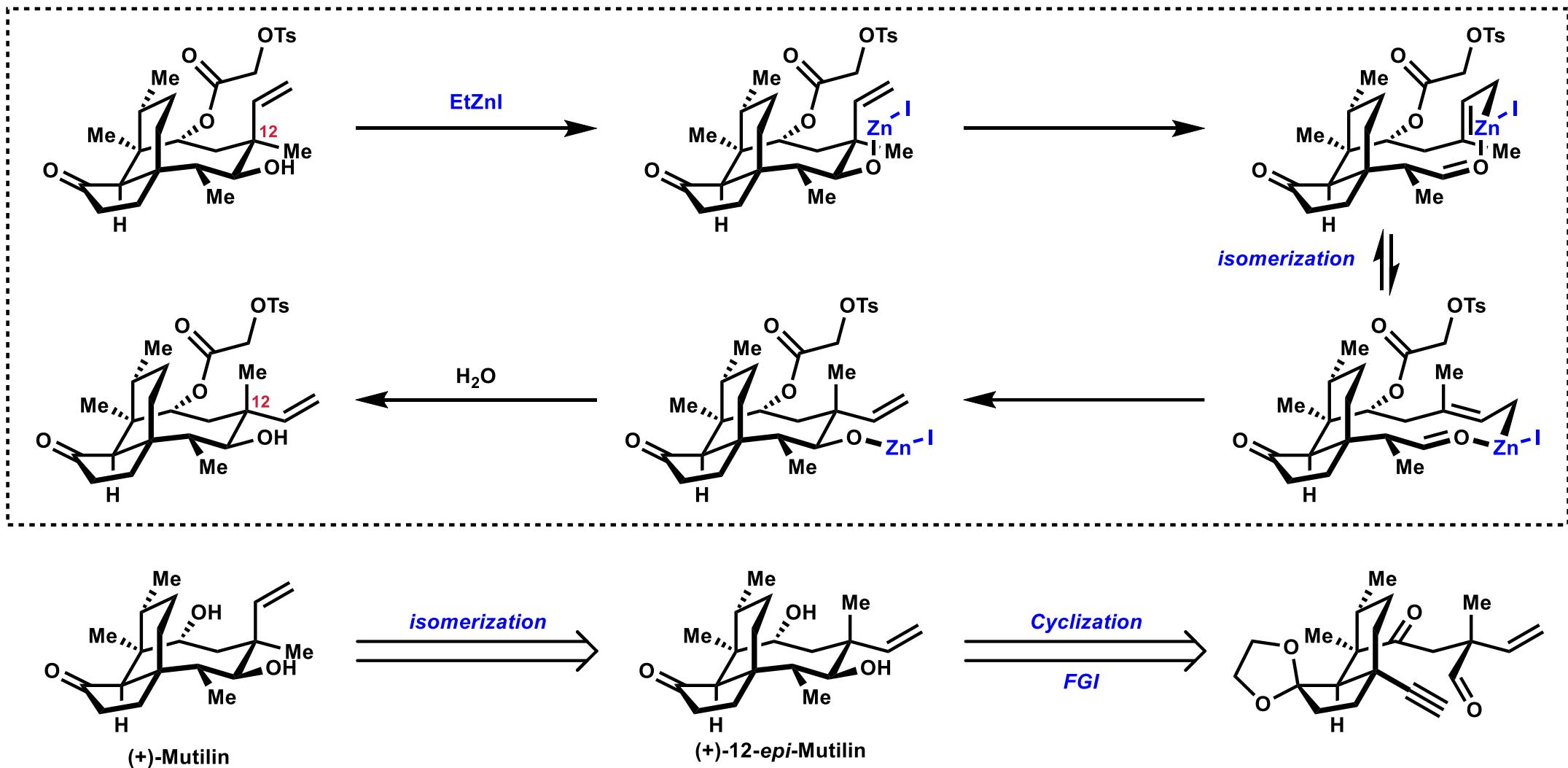
Total Synthesis of (+)-Pleuromutilin — Herzon (2017)

2. Attempted Synthesis — Cyclization (*failed*)



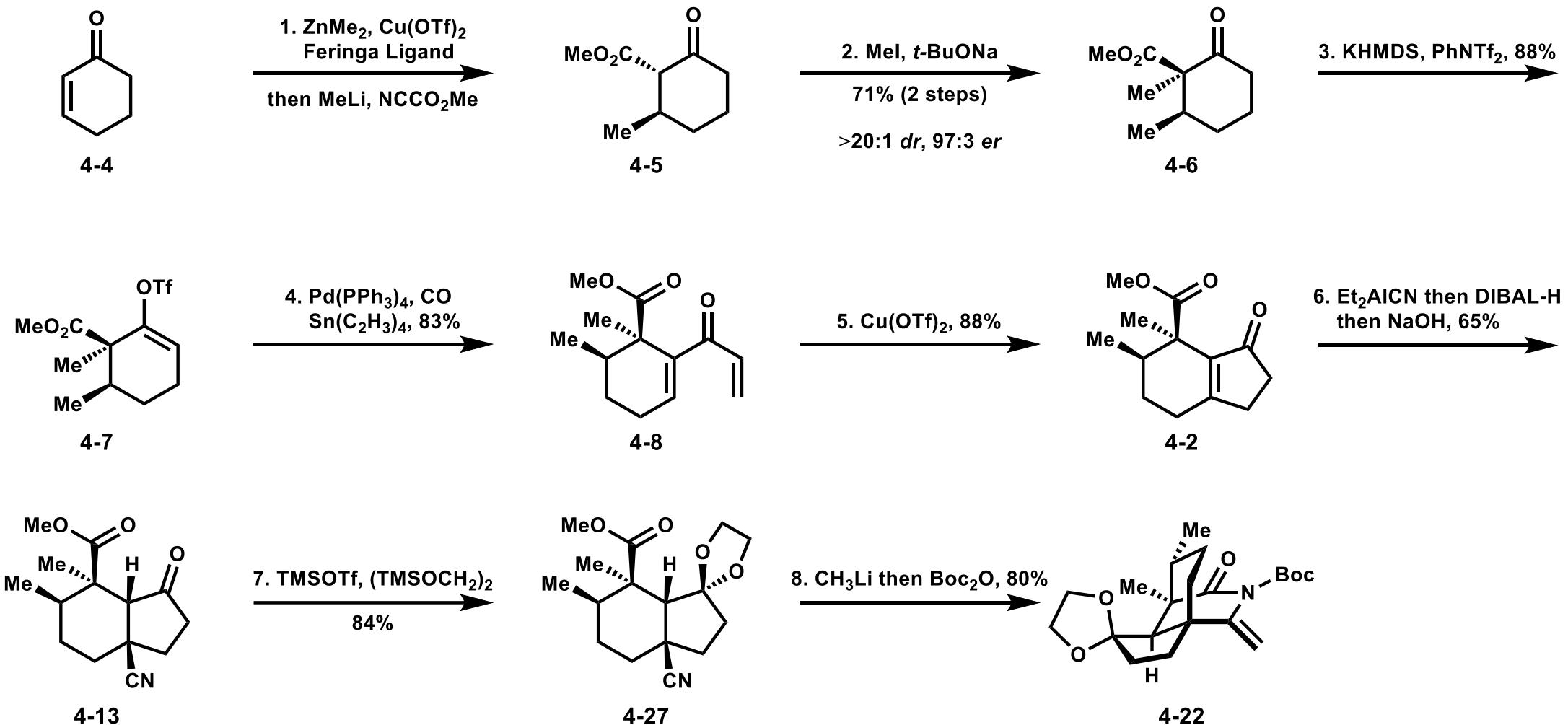
Total Synthesis of (+)-Pleuromutilin — Herzon (2017)

2. Attempted Synthesis — Cyclization



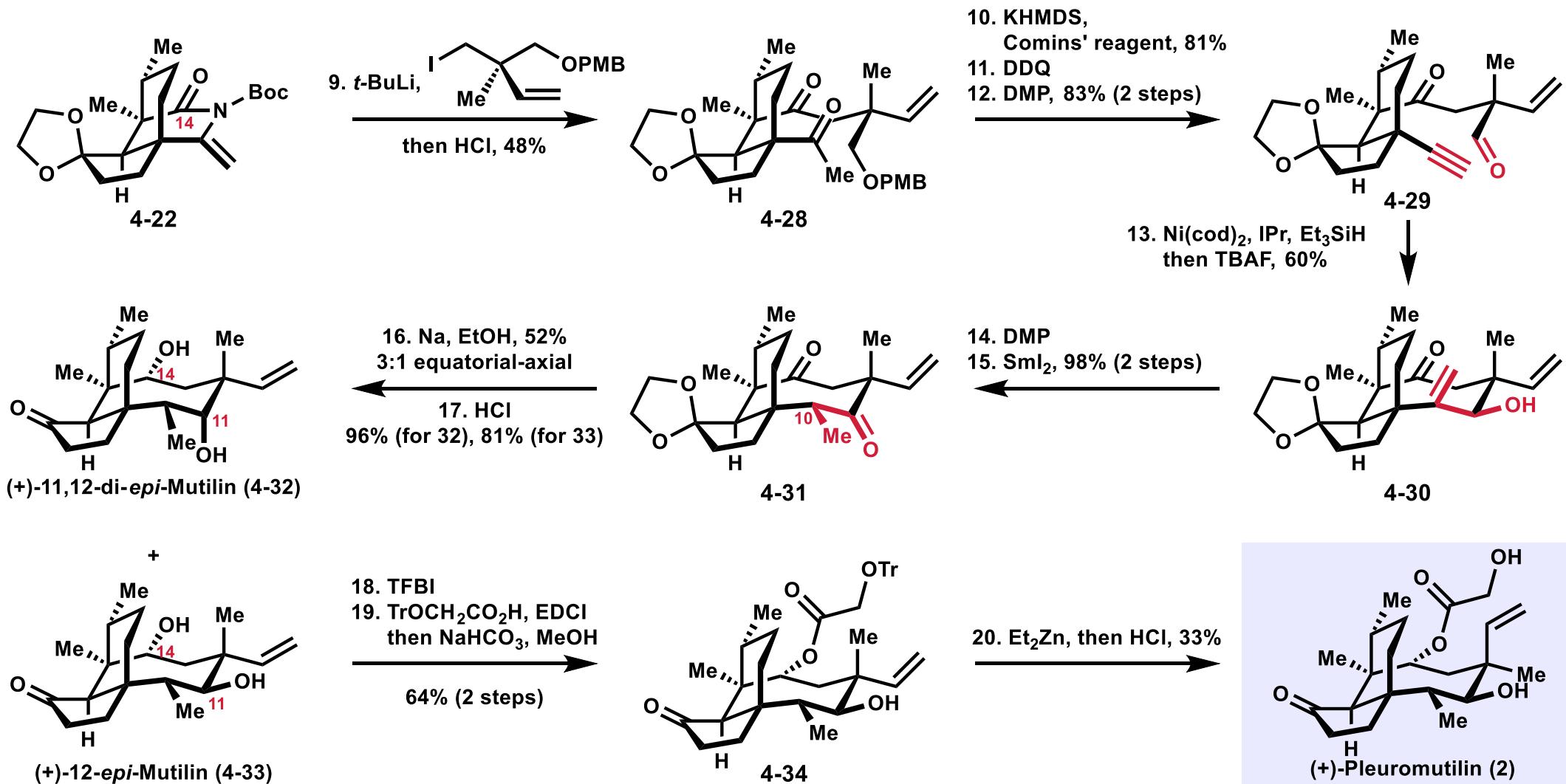
Total Synthesis of (+)-Pleuromutilin — Herzon (2017)

3. Synthesis of the Cyclic Enimide 4-22



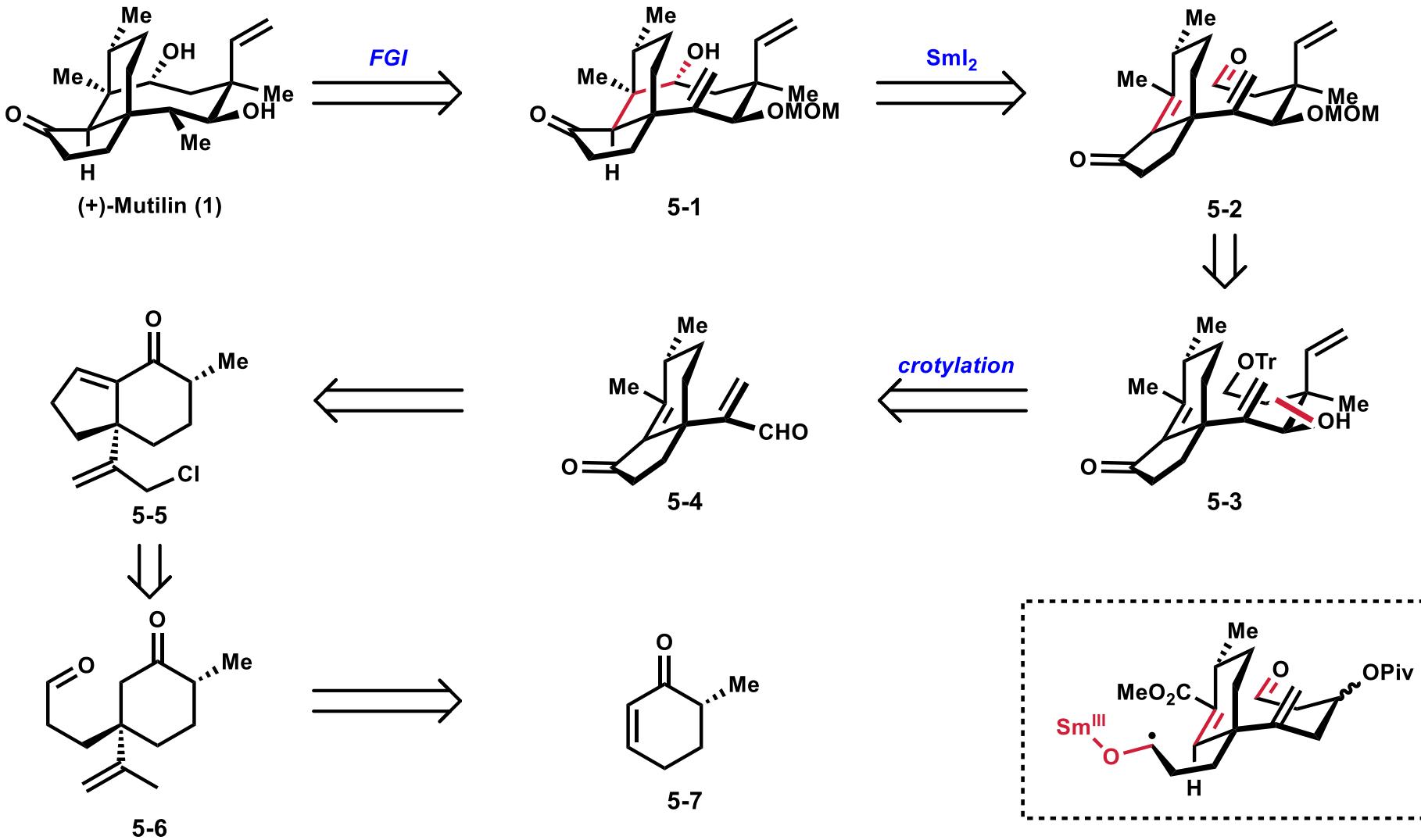
Total Synthesis of (+)-Pleuromutilin — Herzon (2017)

4. Synthesis of (+)-Pleuromutilin



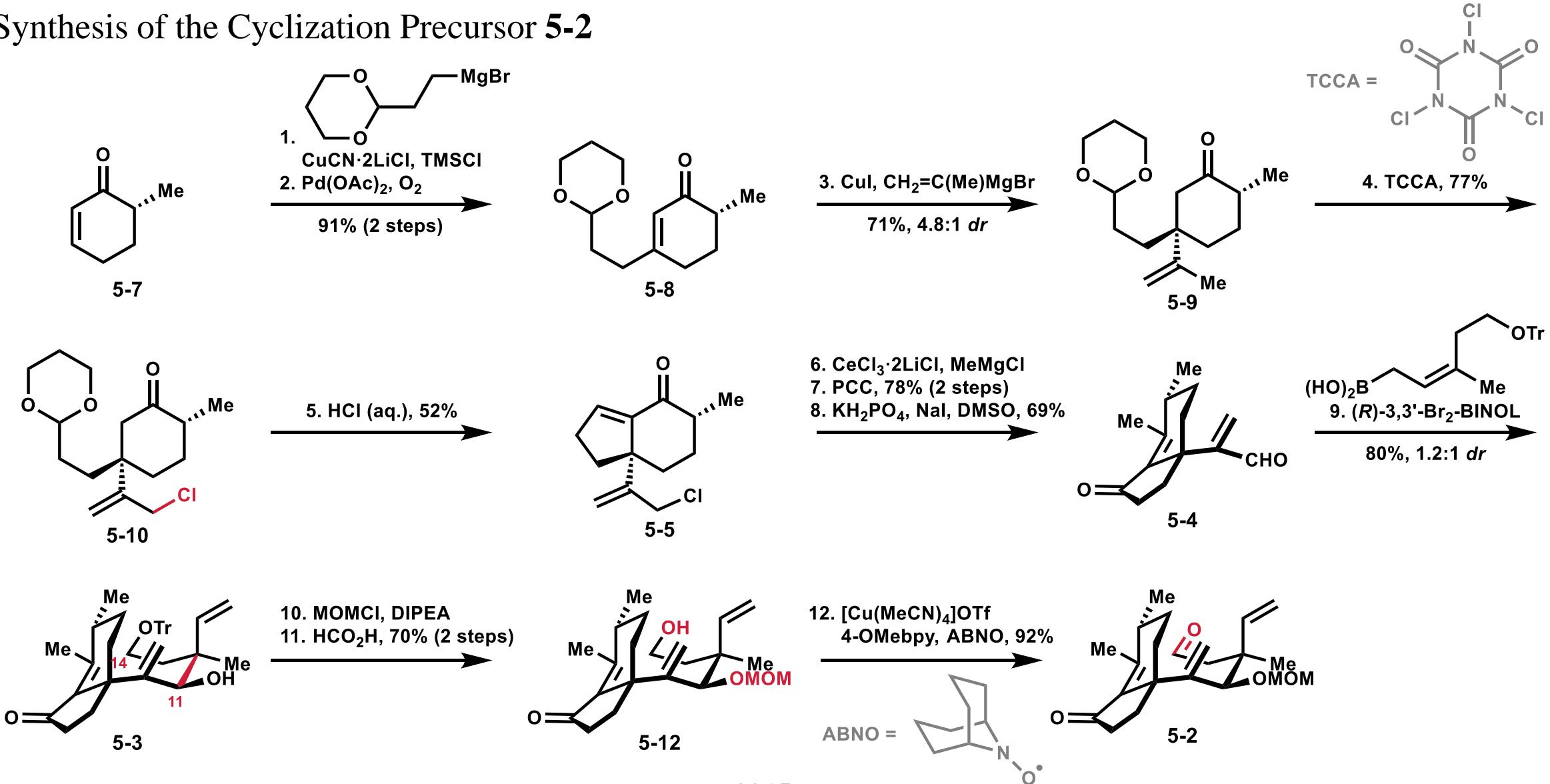
Total Synthesis of (+)-Pleuromutilin — Reisman (2018)

1. Retrosynthetic Analysis



Total Synthesis of (+)-Pleuromutilin — Reisman (2018)

2. Synthesis of the Cyclization Precursor 5-2

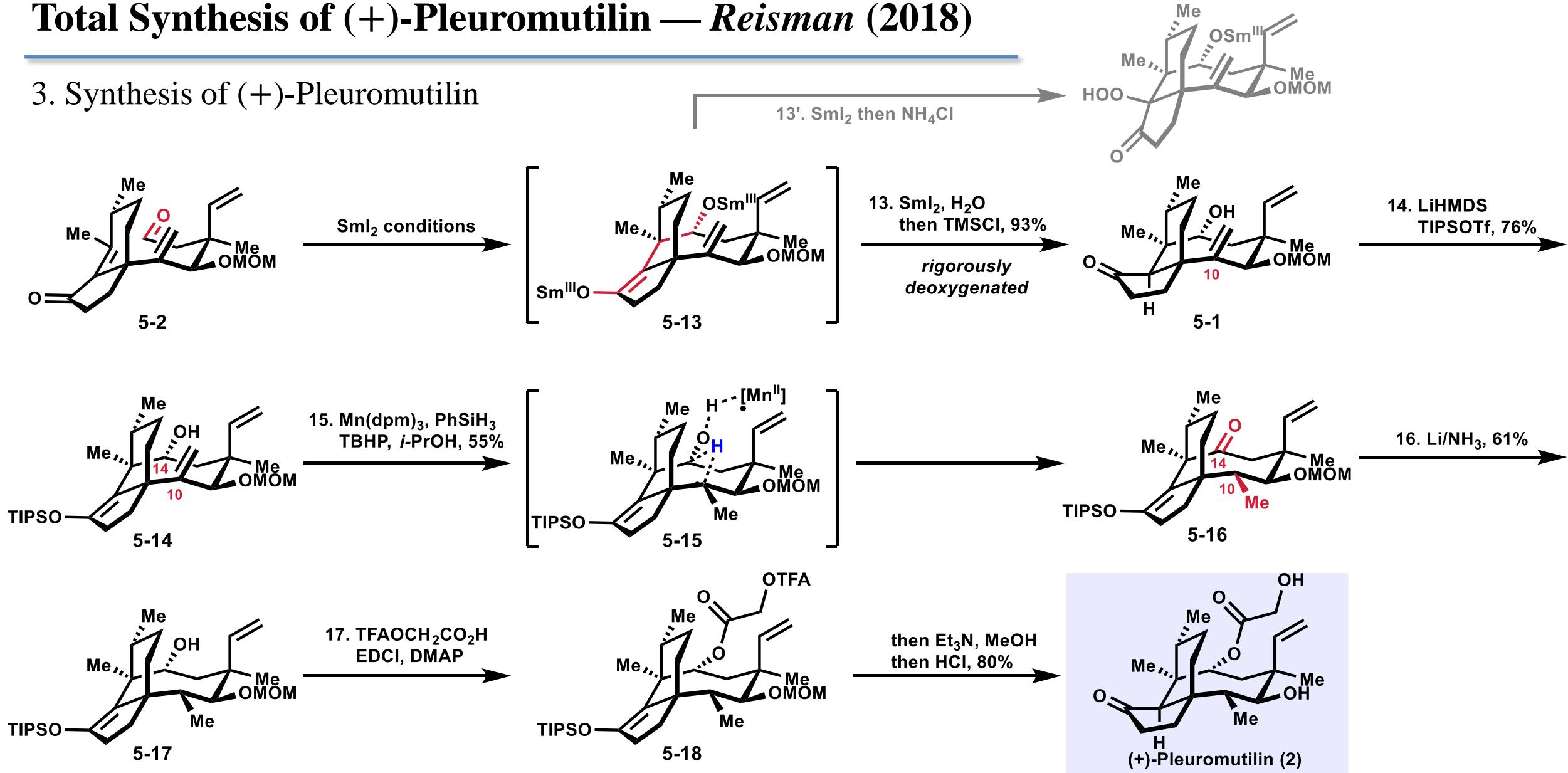


Alam, R.; Vollgraff, T.; Eriksson, L.; Szabo, K. L. *J. Am. Chem. Soc.* **2015**, *137*, 11262.

Steves, J. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 15742.

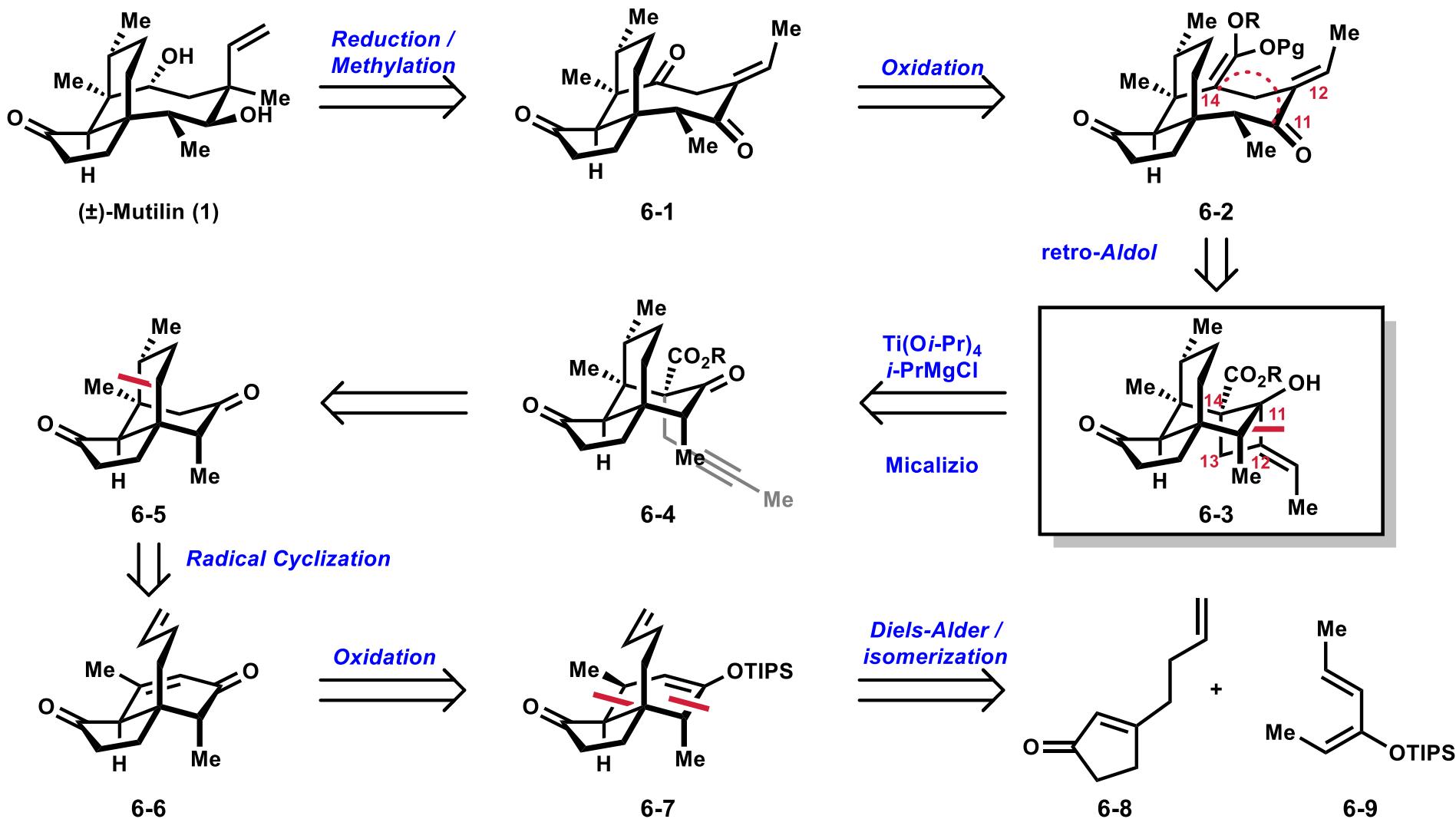
Total Synthesis of (+)-Pleuromutilin — Reisman (2018)

3. Synthesis of (+)-Pleuromutilin



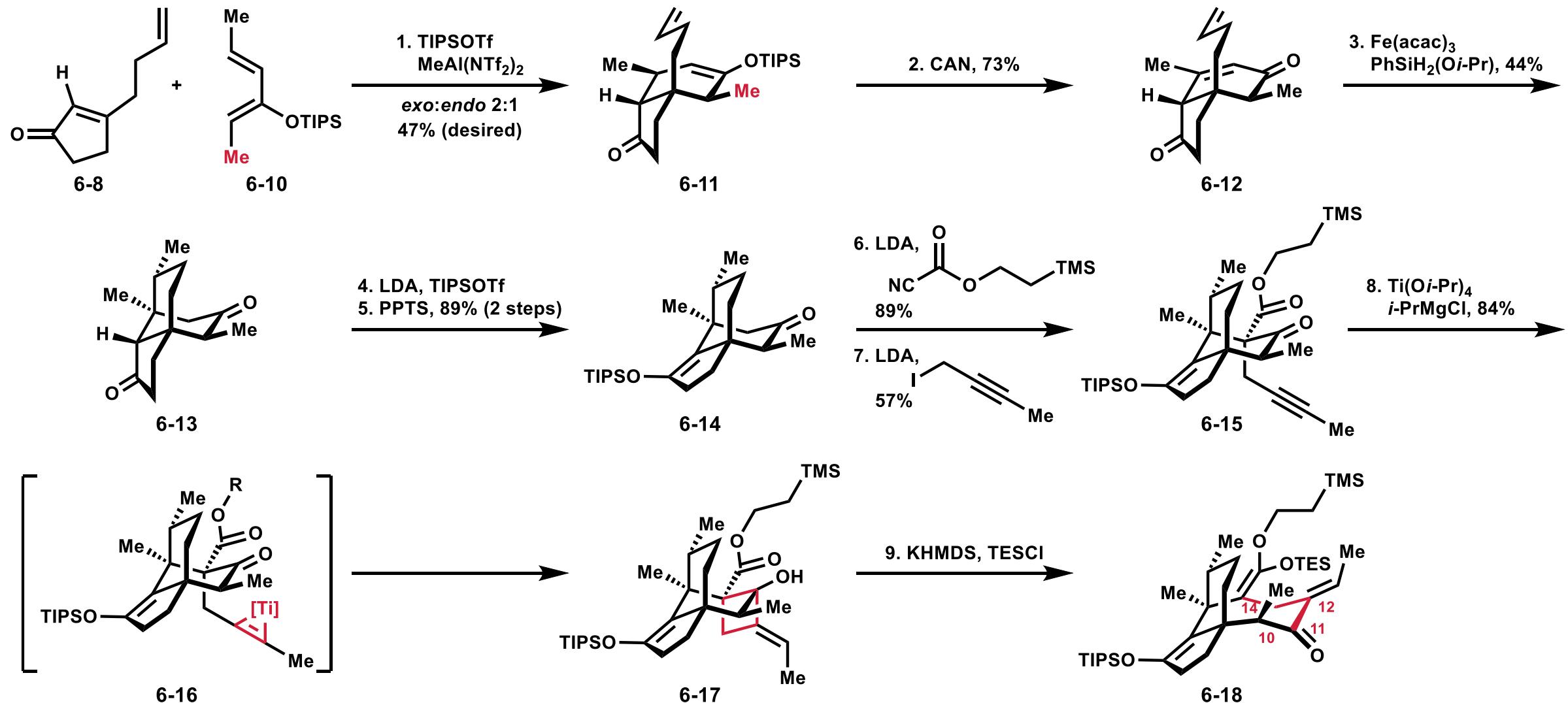
Total Synthesis of (\pm)-Pleuromutilin — Pronin (2022)

1. Retrosynthetic Analysis



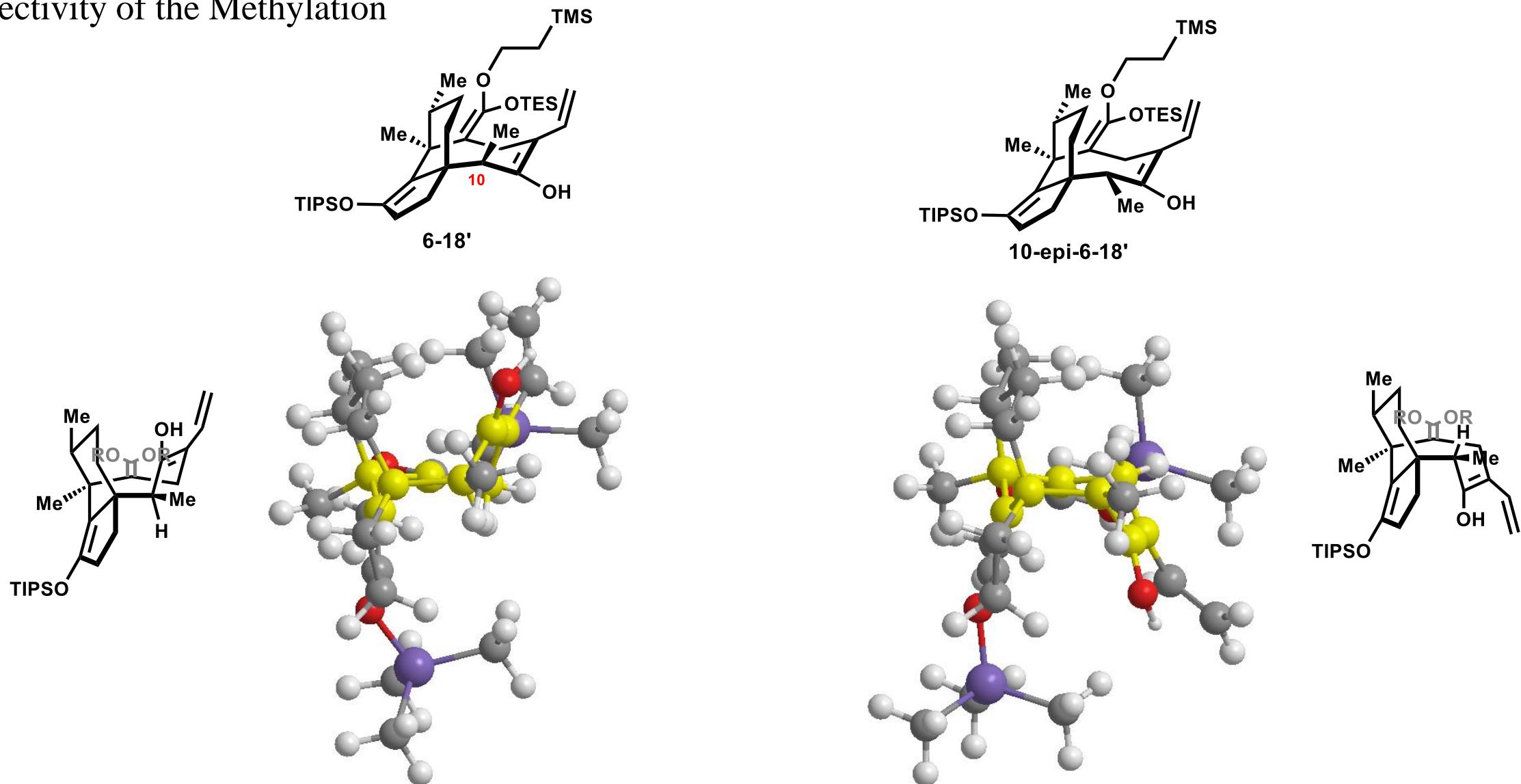
Total Synthesis of (\pm)-Pleuromutilin — Pronin (2022)

2. Construction of the Cyclooctane Motif



Total Synthesis of (\pm)-Pleuromutilin — Pronin (2022)

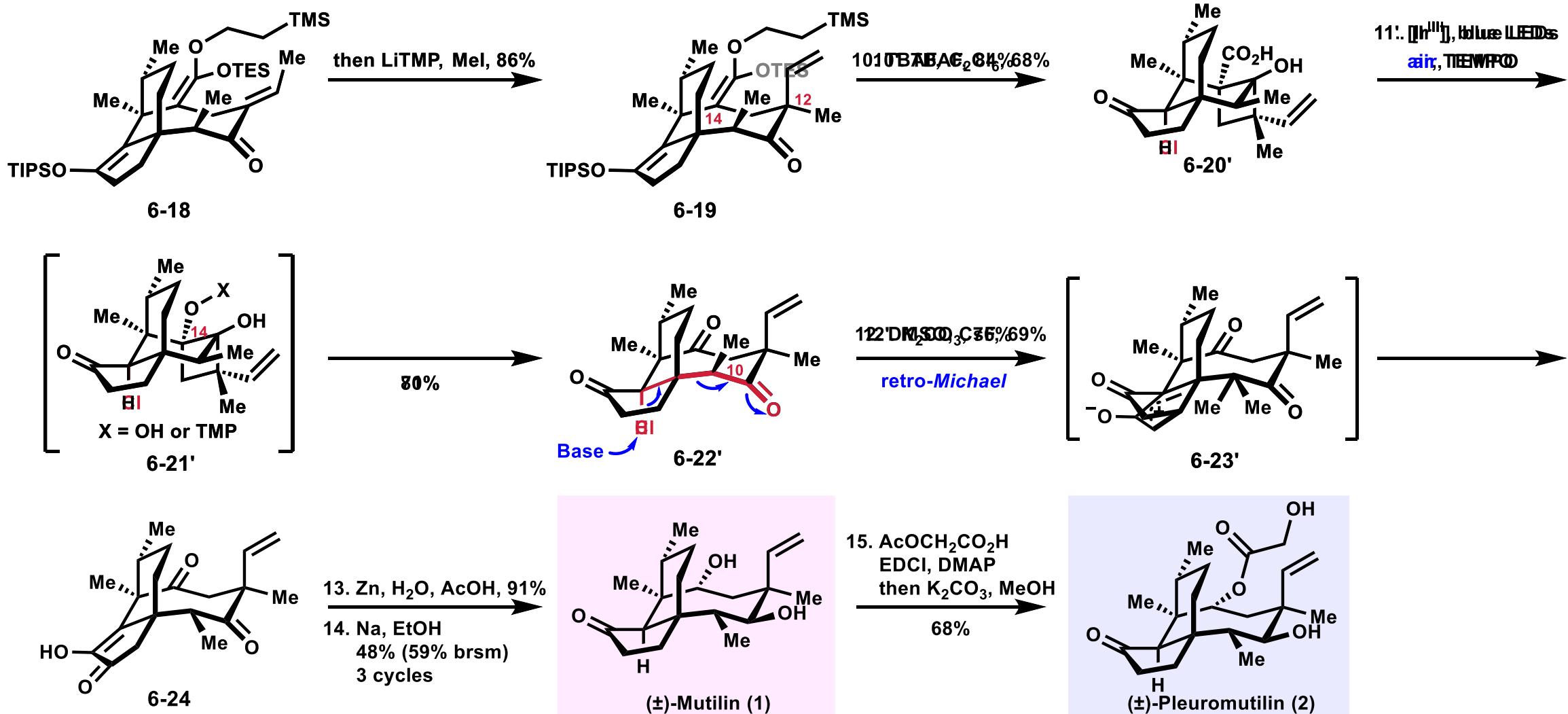
3. Selectivity of the Methylation



Computations were performed at the ω B97X-D/6-31G(d) level of theory

Total Synthesis of (\pm)-Pleuromutilin — Pronin (2022)

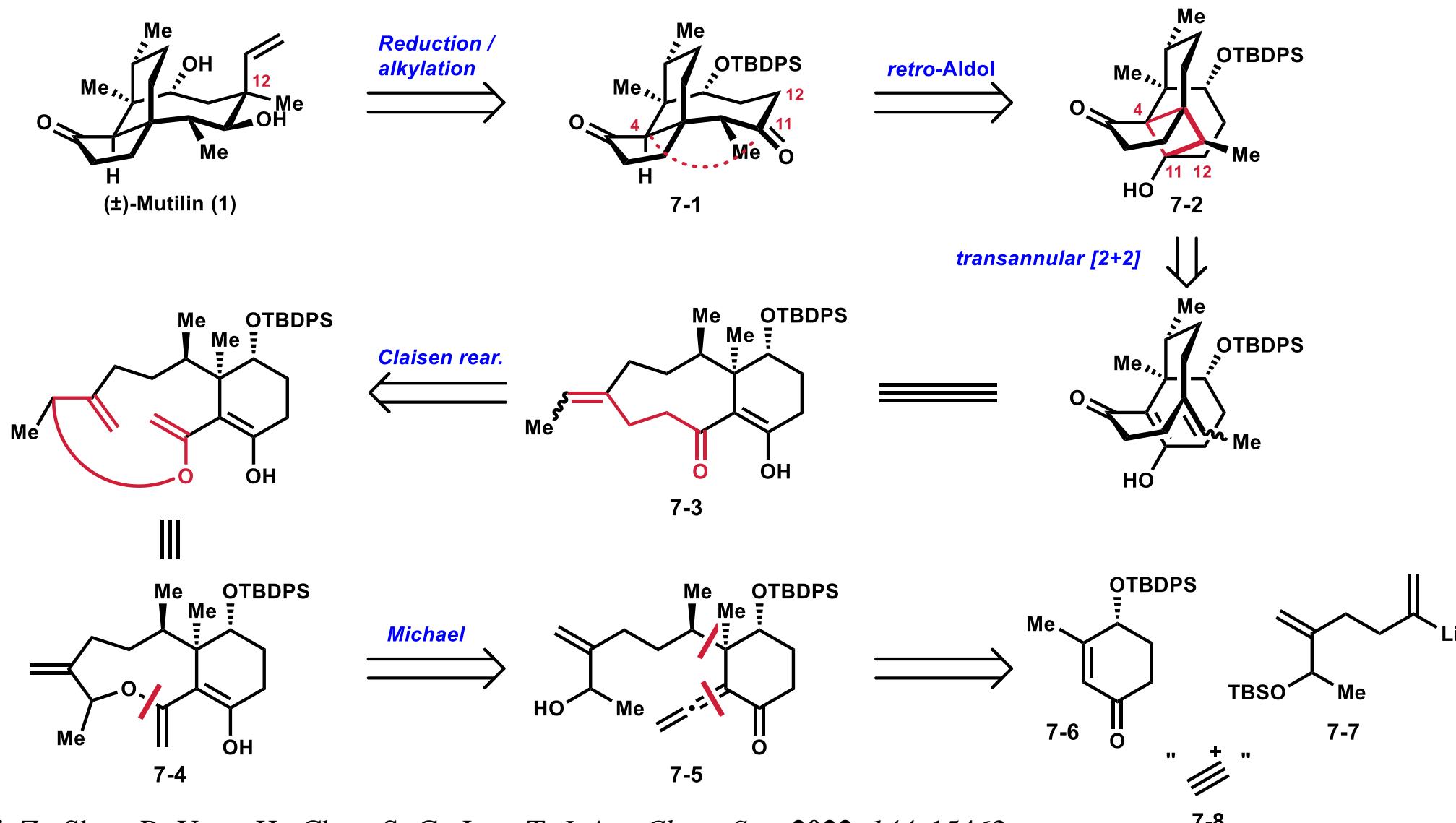
4. Synthesis of (\pm)-Pleuromutilin



Song, H.-T.; Ding, W.; Zhou, Q.-Q.; Liu, J.; Lu, L.-Q.; Xiao, W.-J. *J. Org. Chem.* **2016**, *81*, 7250.
 Majgier-Baranowska, H.; Templeton, J. F. *Tetrahedron* **1999**, *55*, 3717.

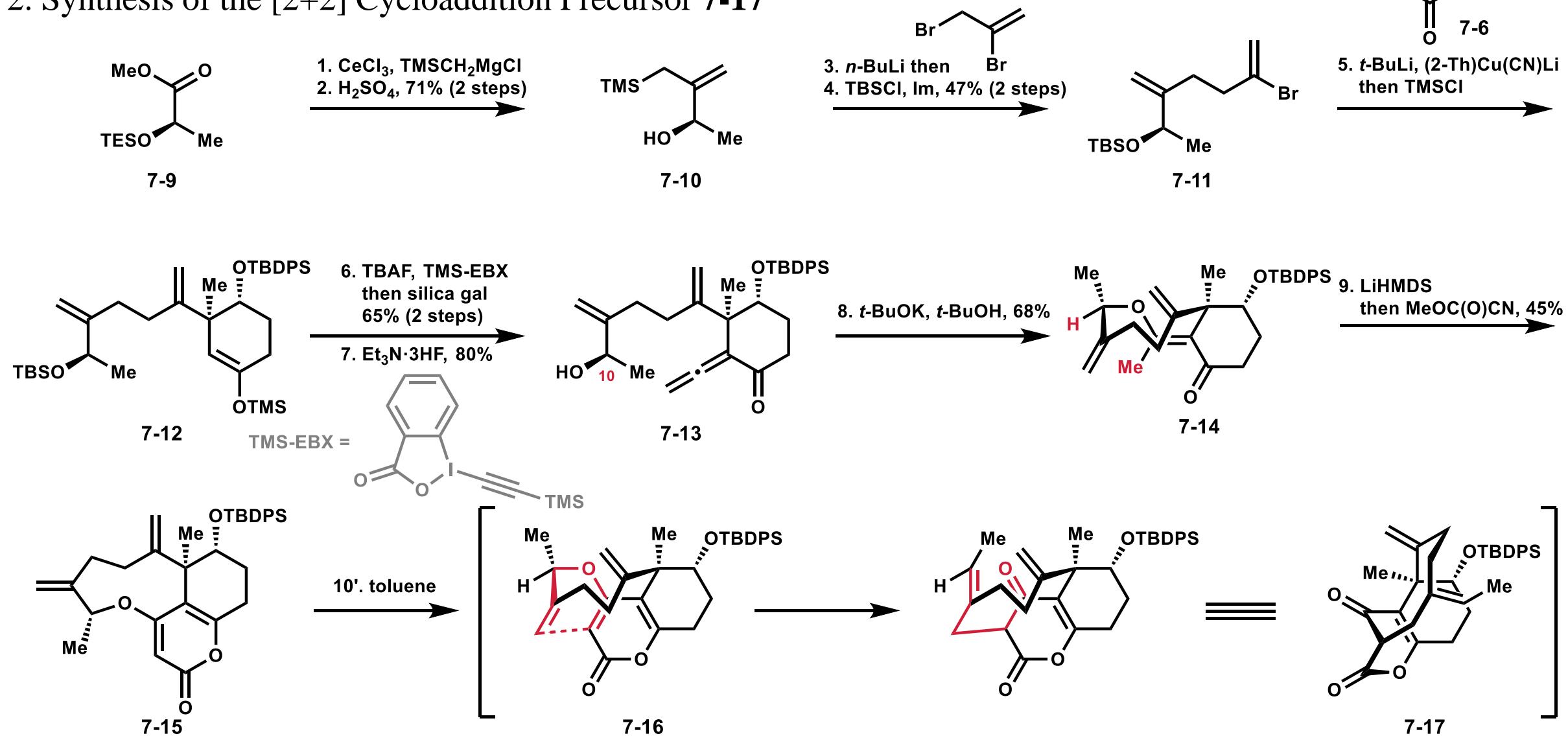
Total Synthesis of (+)-Mutilin — Luo (2022)

1. Retrosynthetic Analysis



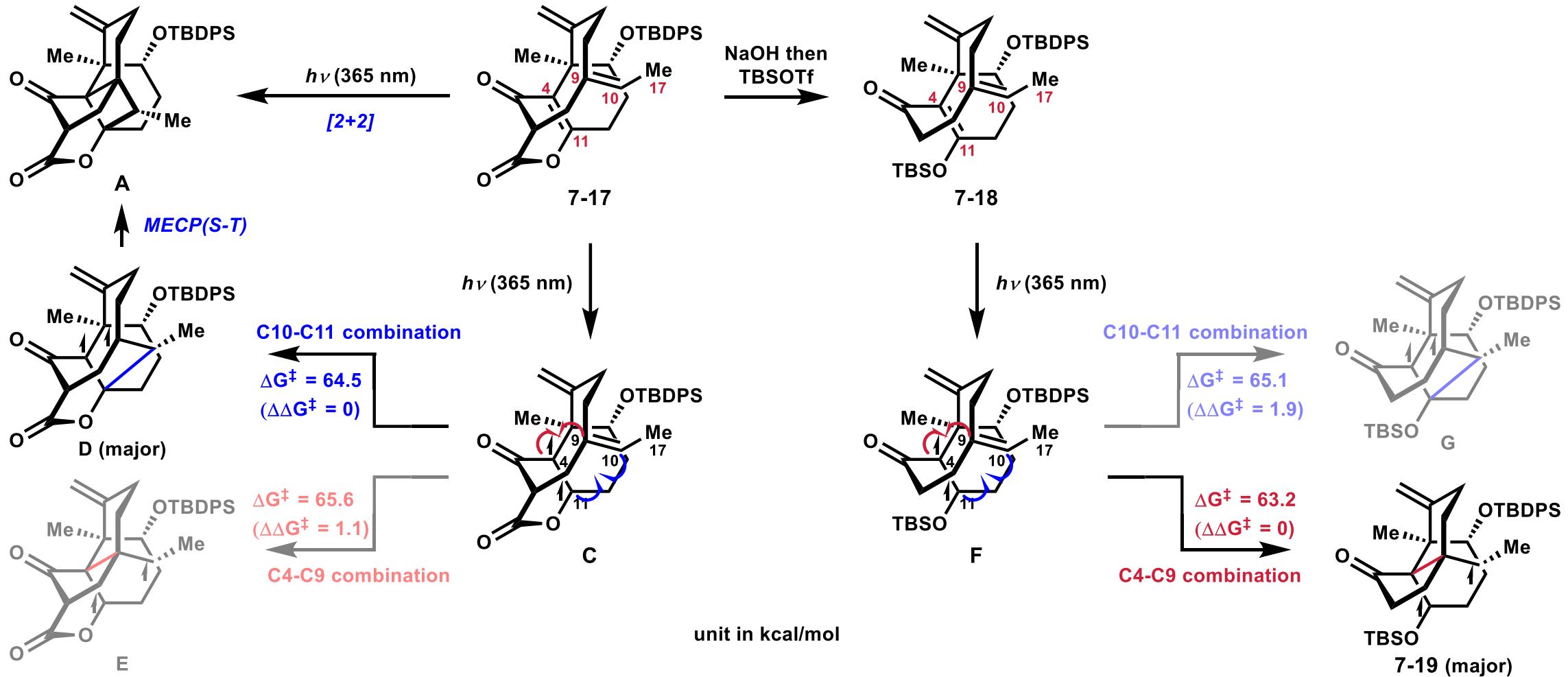
Total Synthesis of (+)-Mutilin — Luo (2022)

2. Synthesis of the [2+2] Cycloaddition Precursor 7-17



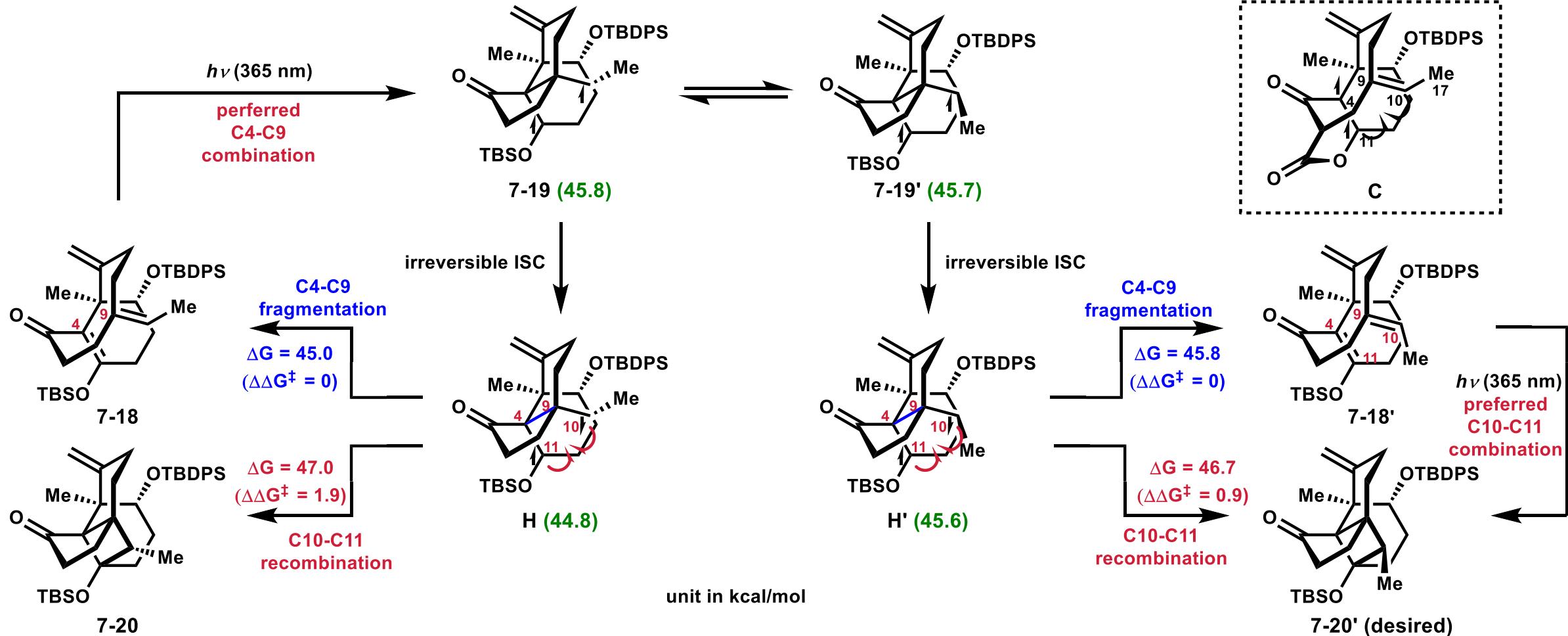
Total Synthesis of (+)-Mutilin — Luo (2022)

3. Attempts of the [2+2] Photocycloaddition



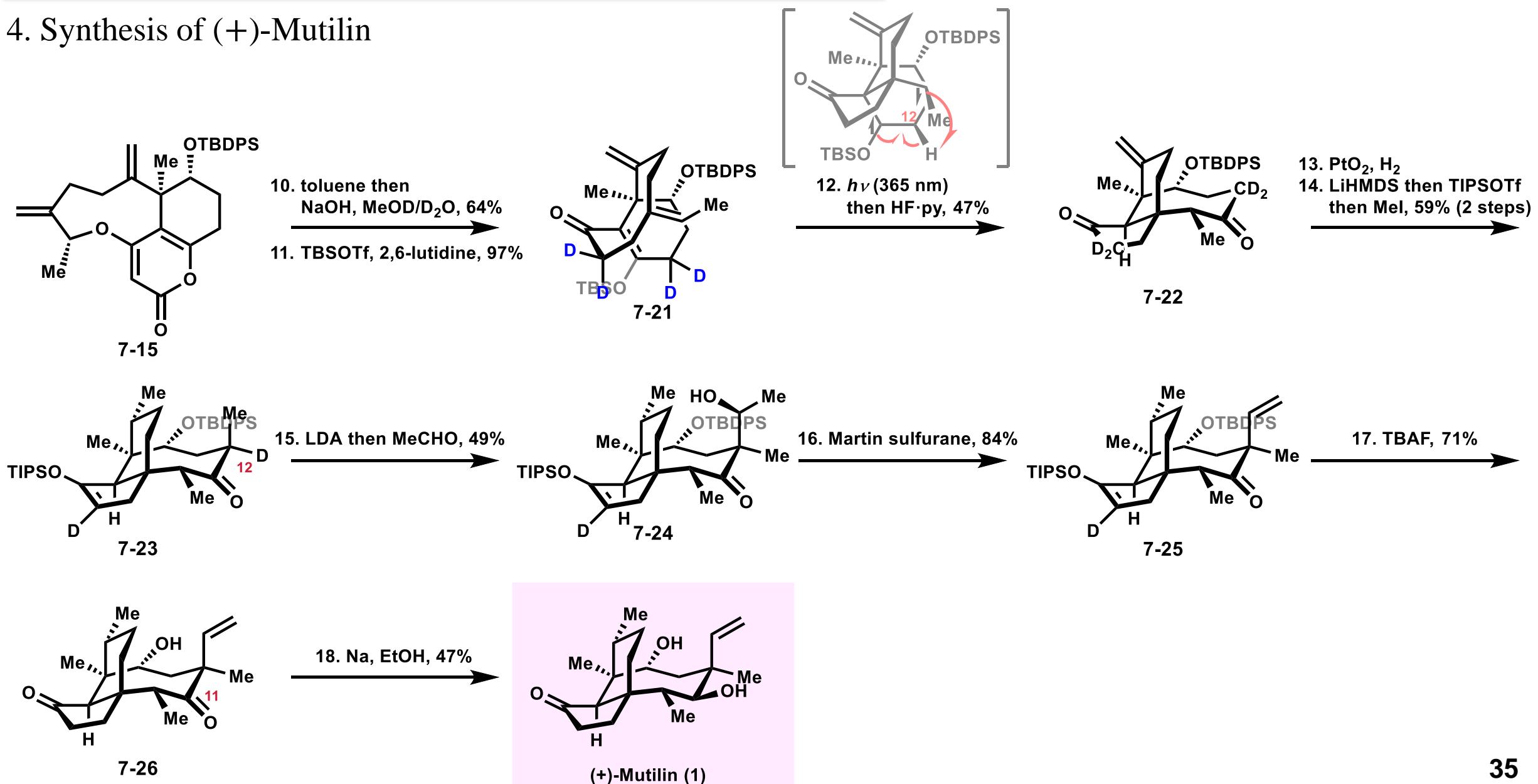
Total Synthesis of (+)-Mutilin — Luo (2022)

3. Attempts of the [2+2] Photocycloaddition



Total Synthesis of (+)-Mutilin — Luo (2022)

4. Synthesis of (+)-Mutilin



Content

➤ **Introduction**

➤ **Total Synthesis of Mutilin and Pleuromutilin**

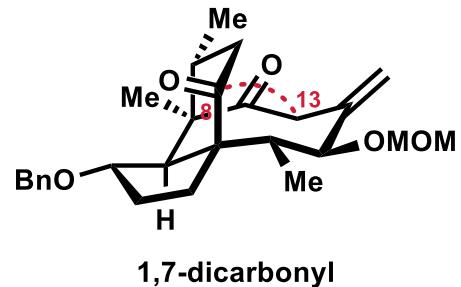
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- ✓ Procter, D. J.
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- ✓ Reisman, S. E.
- ✓ Pronin, S. V.
- ✓ Luo, T.

➤ **Summary**

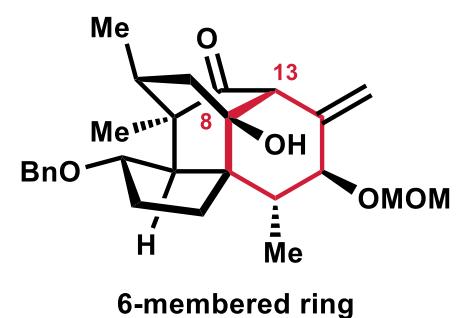
Summary

1. *retro-Aldol* — Ring Expansion

Gibbons

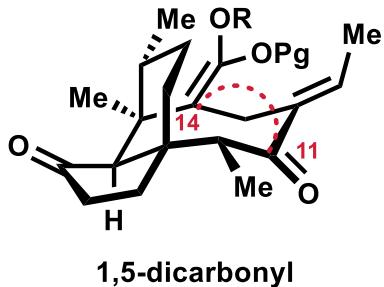


1,7-dicarbonyl

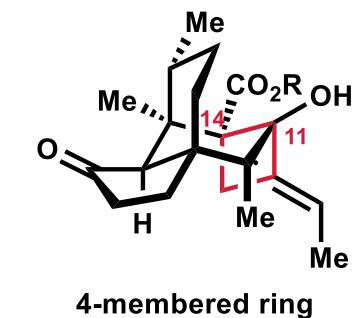


6-membered ring

Pronin

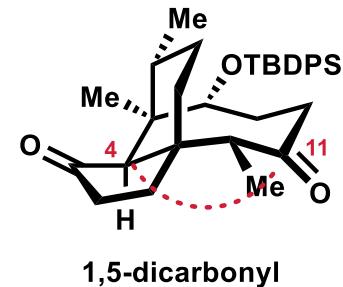


1,5-dicarbonyl

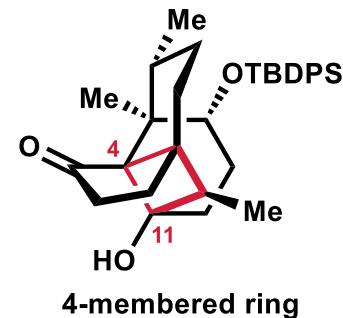


4-membered ring

Luo



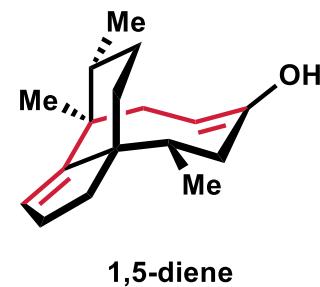
1,5-dicarbonyl



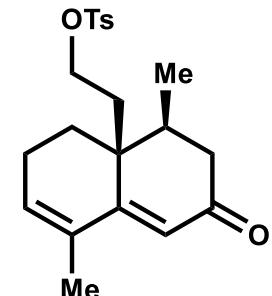
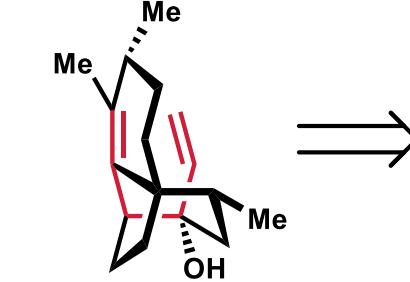
4-membered ring

2. *Cope rearrangement*

Boeckman



1,5-diene



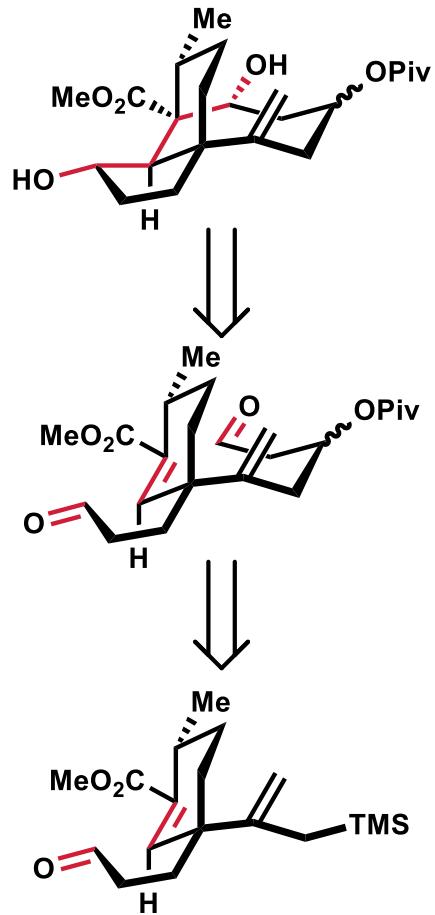
➤ simplified molecules step by step

➤ rapidly simplify molecules
➤ build the core skeleton at an early stage

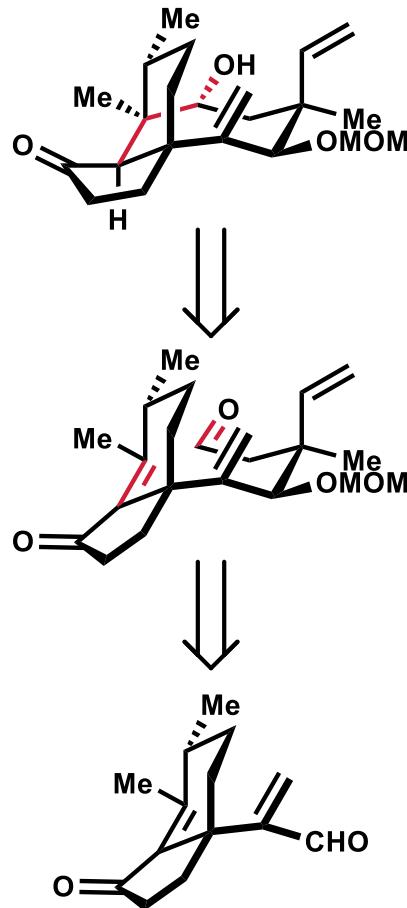
Summary

3. *SmI₂*-mediated Cyclization — Ring Closing

Procter

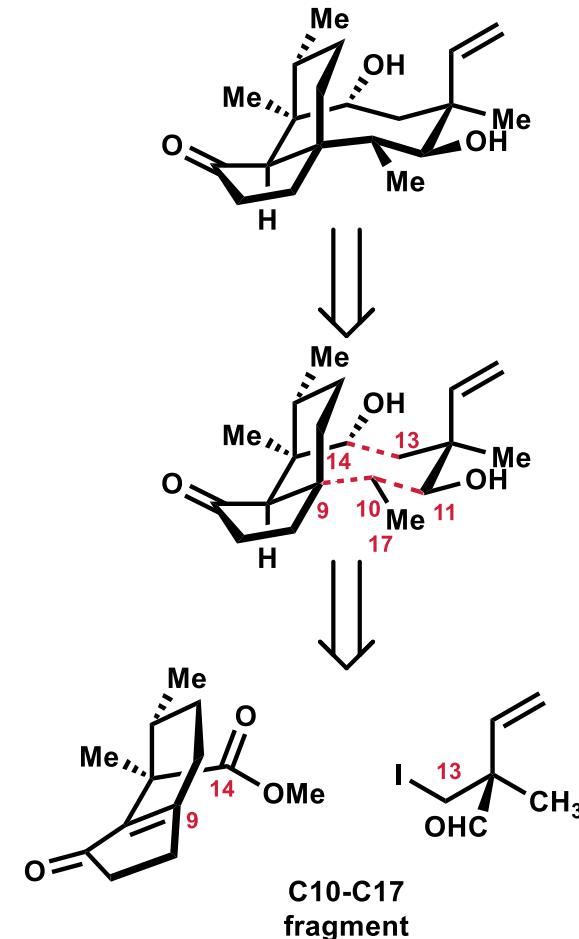


Reisman



4. Modular Synthesis

Herzon



- smooth synthetic route
- high requirements for target molecules

- huge challenge
- potential of divergent synthesis

*Thanks for your
kind attention*