

Literature Report 3

Total Synthesis of (+)-Pleuromutilin

Reporter: Zhou-Hao Zhu

Checker: Yang Zhao

Date: 2018-07-09

Farney, E. P.; Feng, S. S.; Schäfers, F.; **Reisman, S. E.***
J. Am. Chem. Soc. **2018**, *140*, 1267

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CV of Prof. Sarah E. Reisman



Sarah E. Reisman

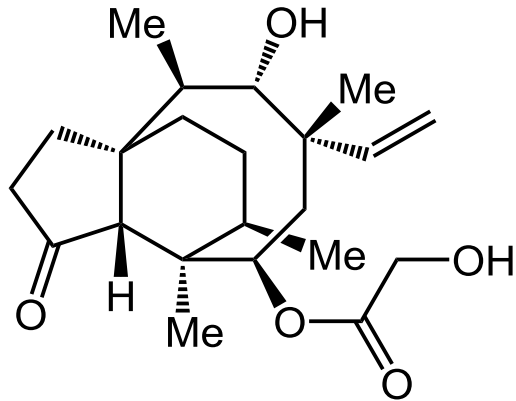
Background:

- 1997-2001 B.S., Connecticut College
- 2001-2006 Ph.D., Yale University
- 2006-2008 Postdoctoral Fellow, Harvard University (with Prof. Jacobsen)
- 2008-2014 Assistant Professor, Caltech
- 2014-now Professor, Caltech

Research Interests:

Natural product synthesis with an emphasis on the development of new synthetic methods that facilitate the construction of complex molecules

Introduction



(+)-Pleuromutilin

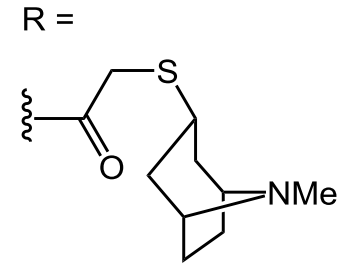
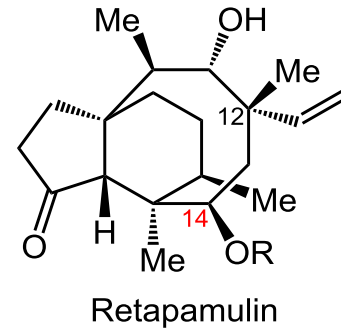
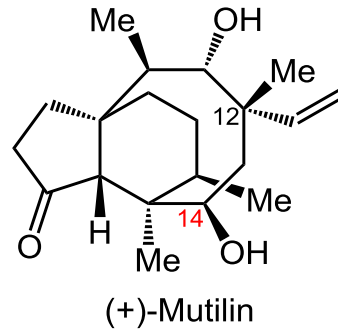
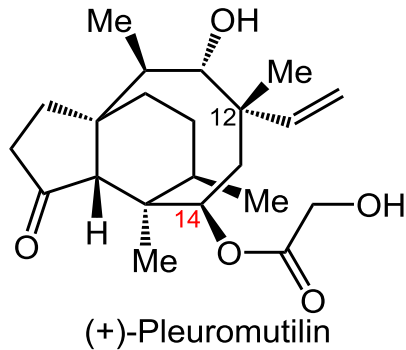


Clitopilus passeckerianus

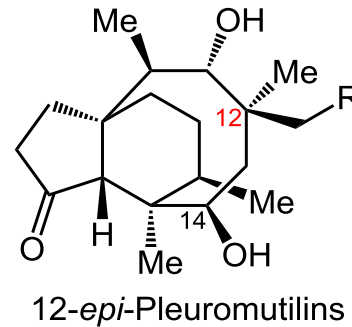
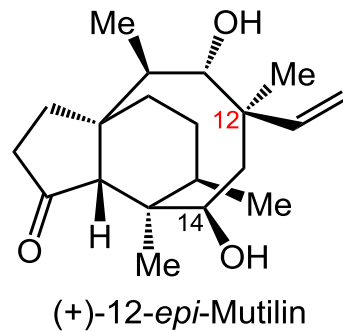
- A diterpene natural product first isolated from the fungus *Clitopilus passeckerianus* in 1951;
- Binding to the highly-conserved peptidyl transferase center of the bacterial ribosome arising from its tricyclic core;
- Slow resistance to Pleuromutilin, and displaying minimal cross-resistance with existing antibiotics.

Robbins, W. J. *et al. Proc. Natl. Acad. Sci. U. S. A.* **1951**, 37, 570

Introduction

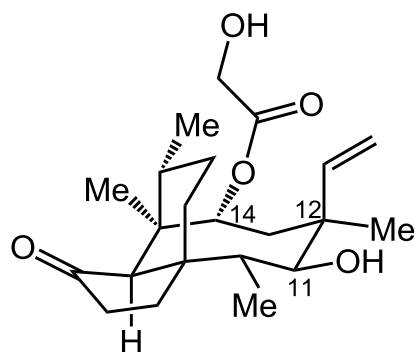


Inhibiting the growth of predominantly Gram-positive pathogens(GPPs)

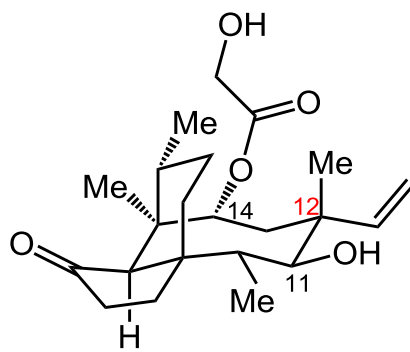


Extended activity against Gram-negative pathogens(GNPs)

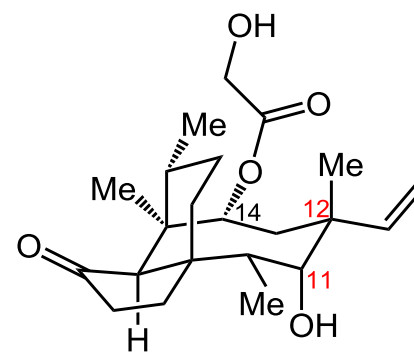
Total Synthesis of (+)-Pleuromutilins by Herzon



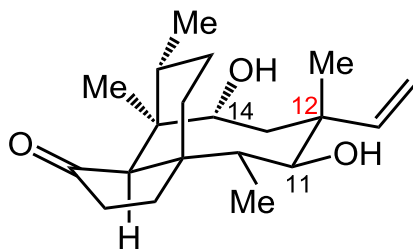
(+)-Pleuromutilin



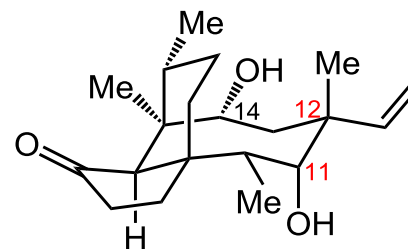
(+)-12-*epi*-Pleuromutilin



(+)-11,12-*di-epi*-Pleuromutilin



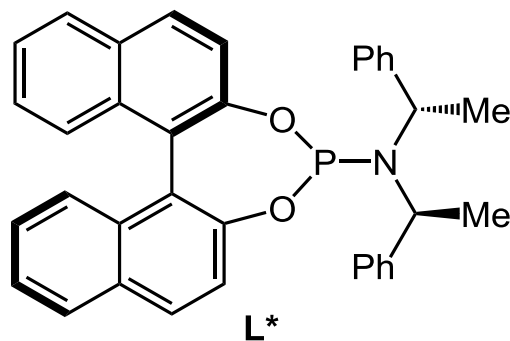
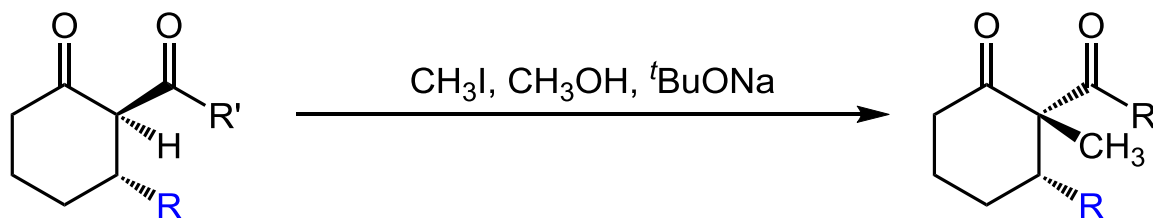
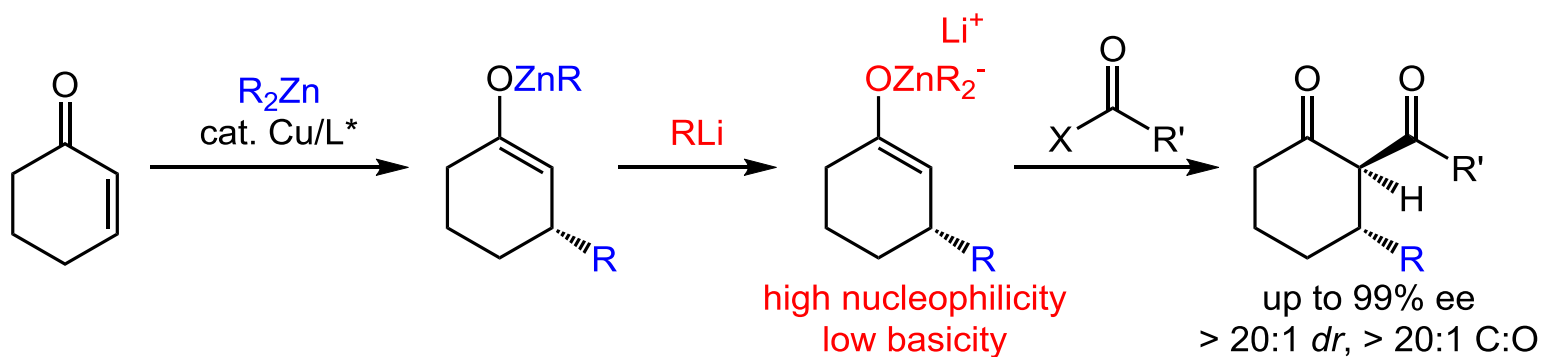
(+)-12-*epi*-Mutilin



(+)-11,12-*di-epi*-Mutilin

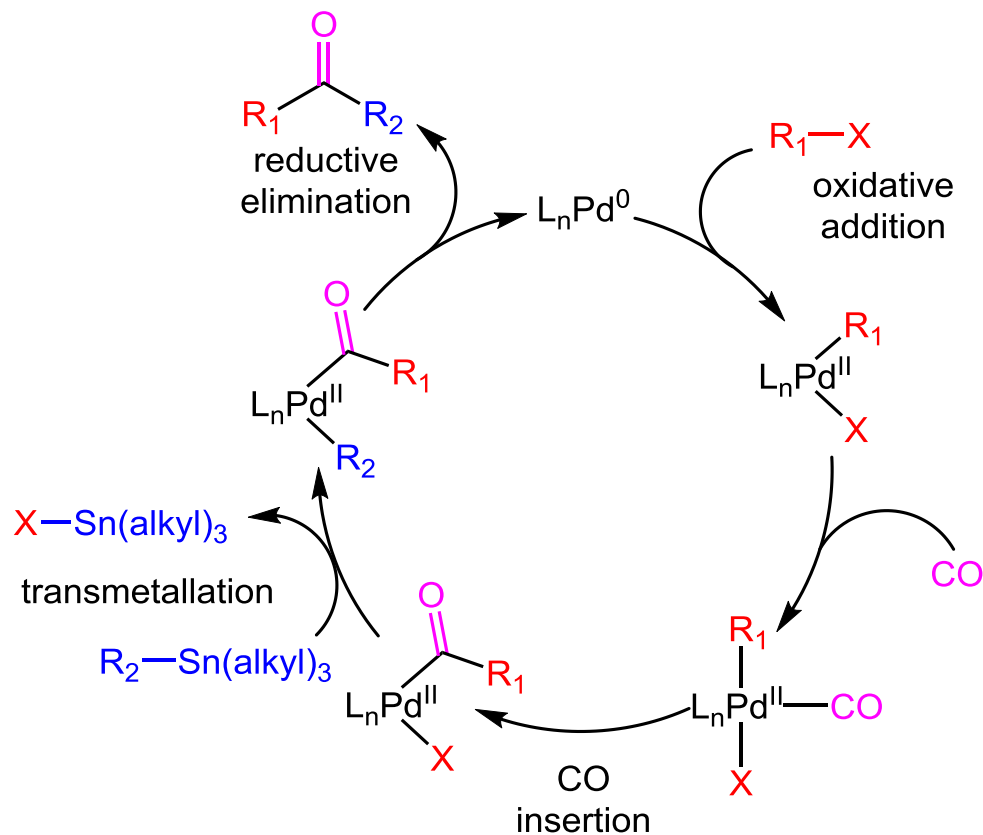
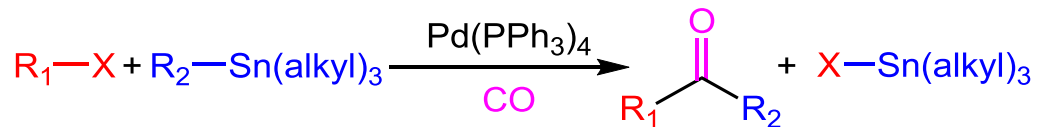
Murphy, S. K.; Zeng, M.; Herzon, S. B.* *Science*. 2017, 356, 956

Conjugate Addition-C-Acylation

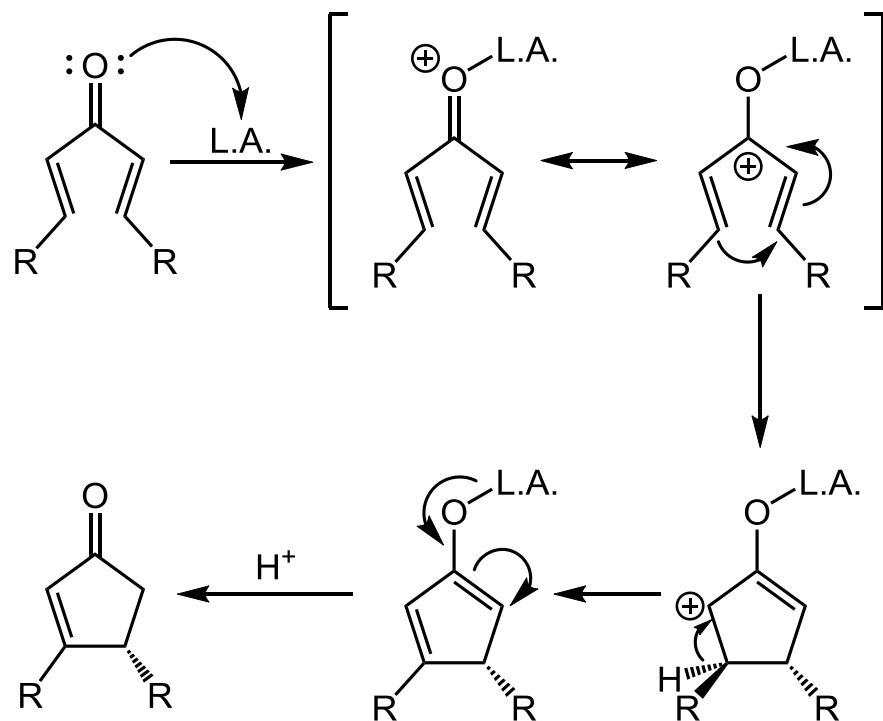
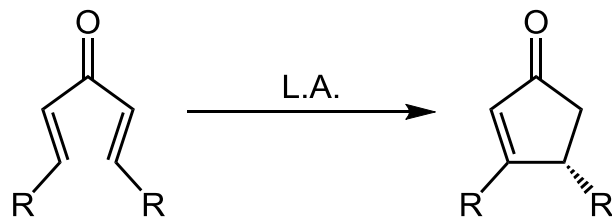


Murphy, S. K.; Zeng, M.; Herzon, S. B.* *Org. Lett.* **2016**, *18*, 4880

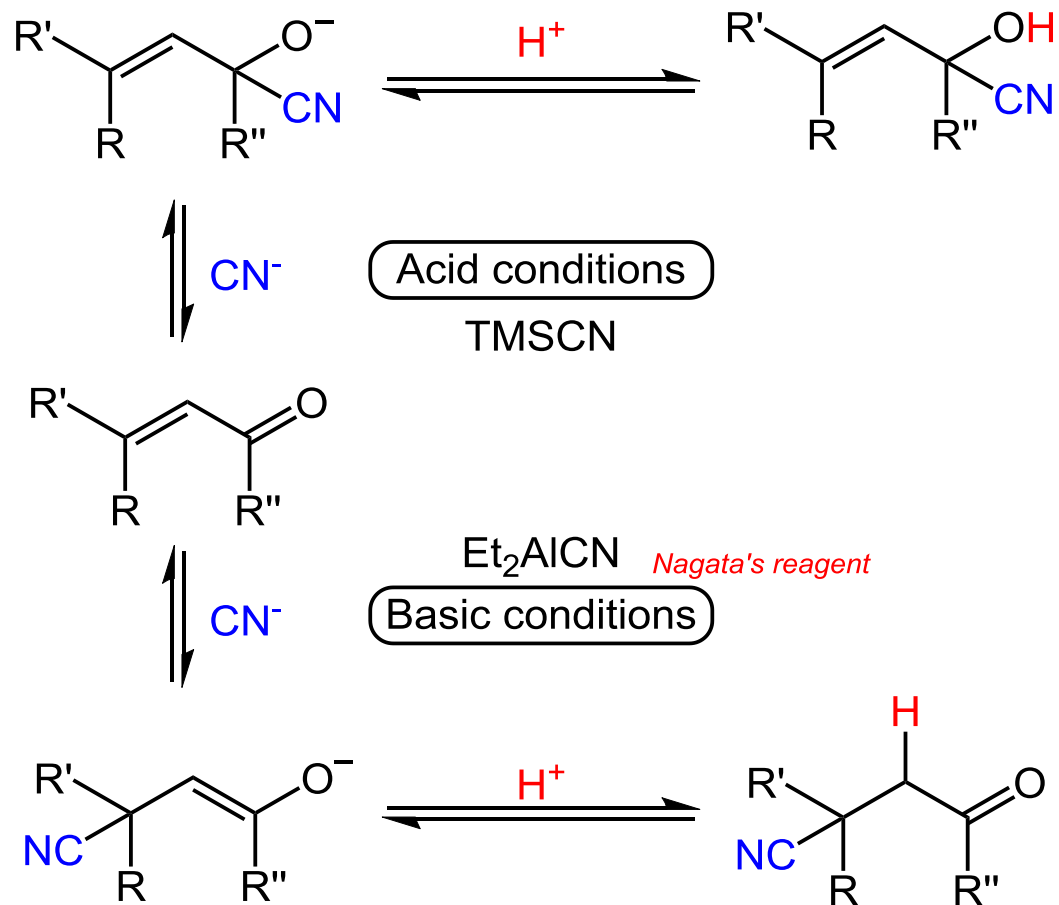
Stille-Carbonylative Cross-Coupling



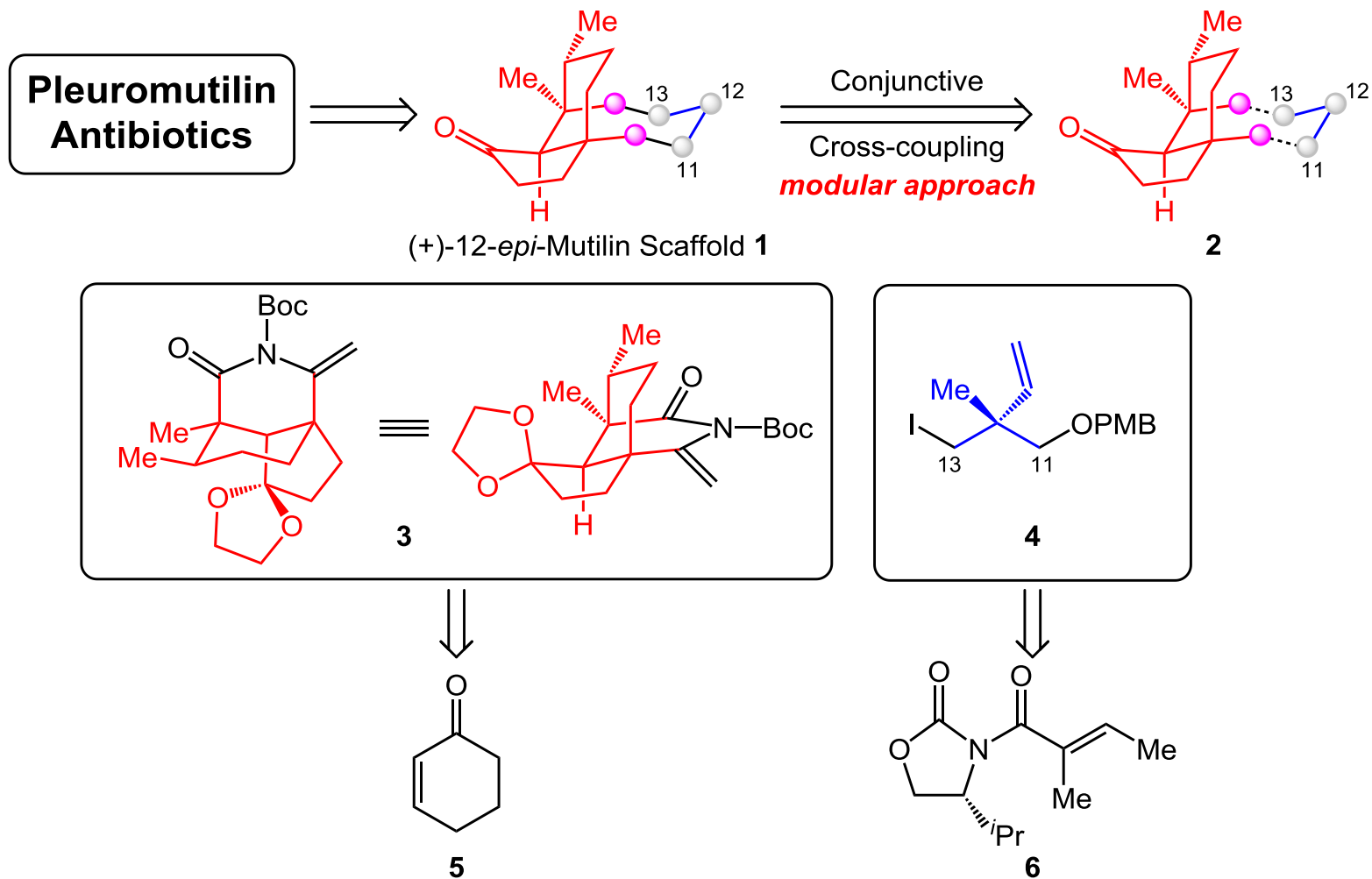
Nazarov Cyclization



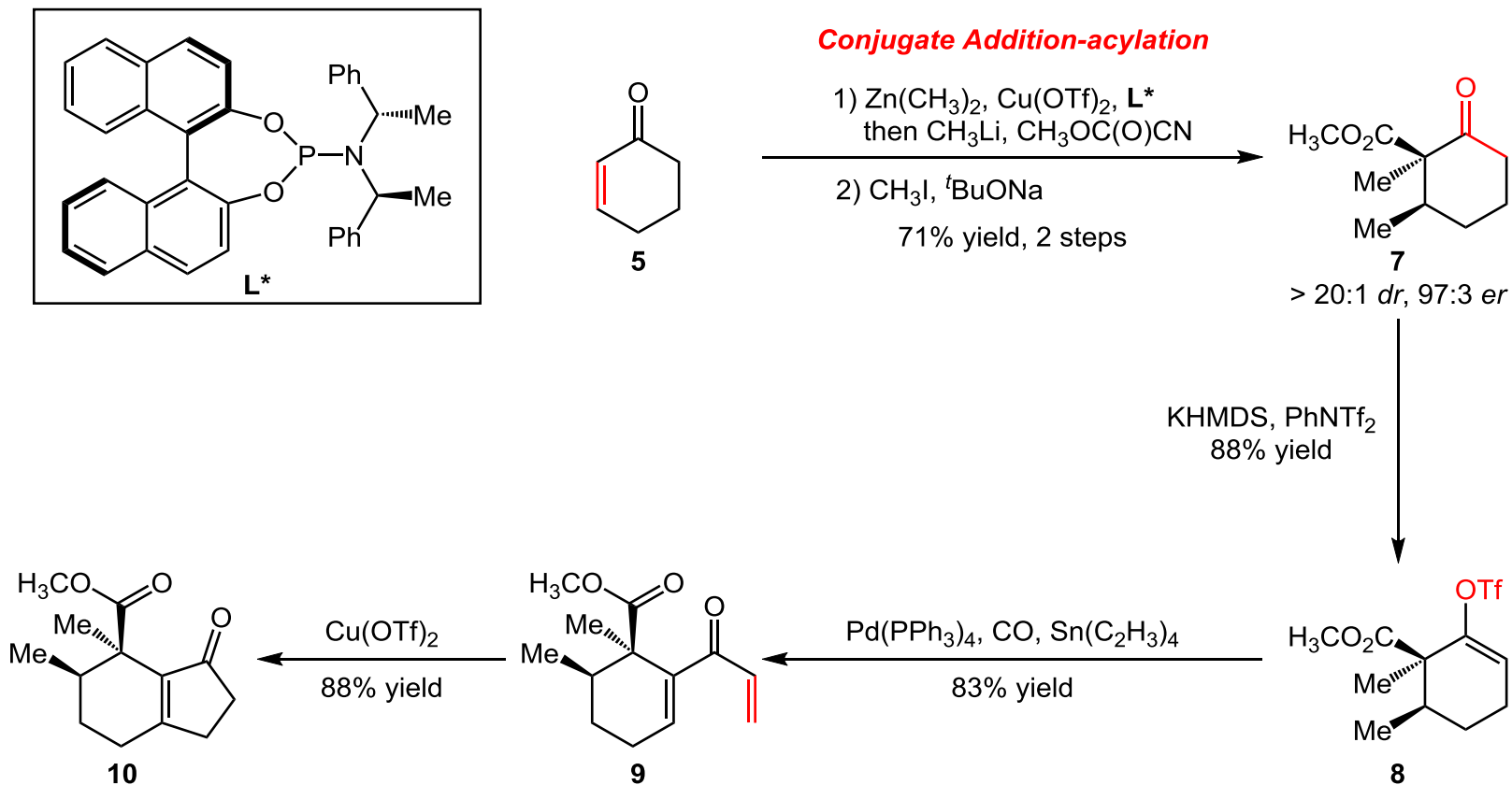
Nagata Hydrocyanation



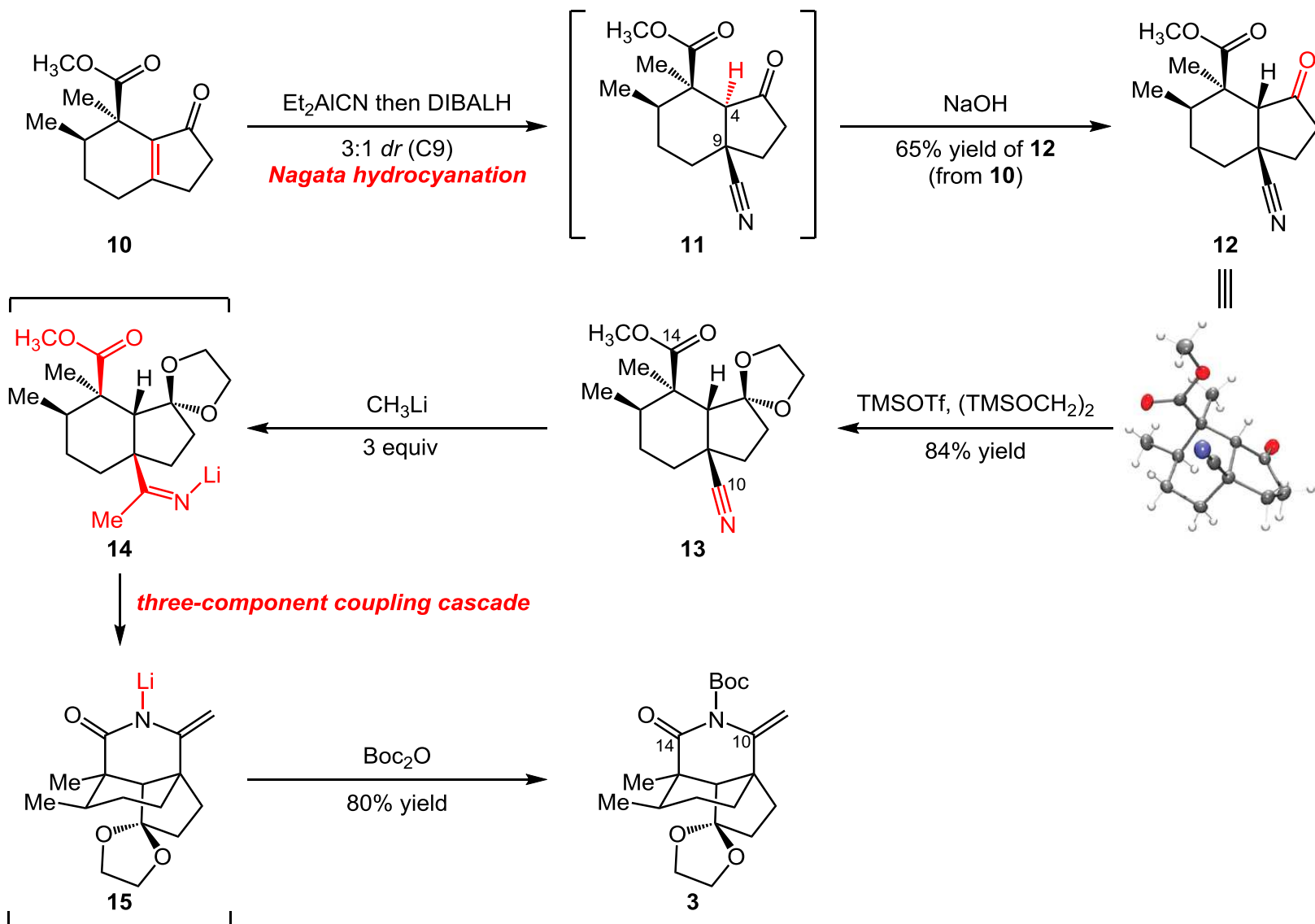
Retrosynthetic Analysis



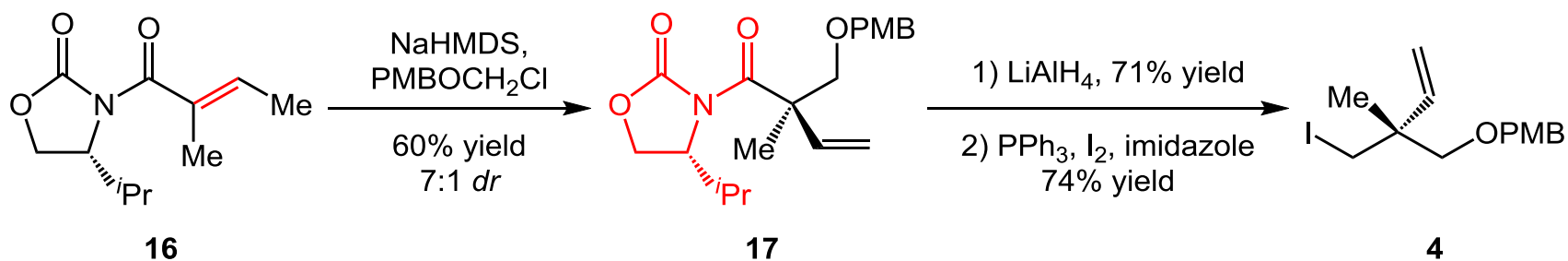
Synthesis of Modular 3



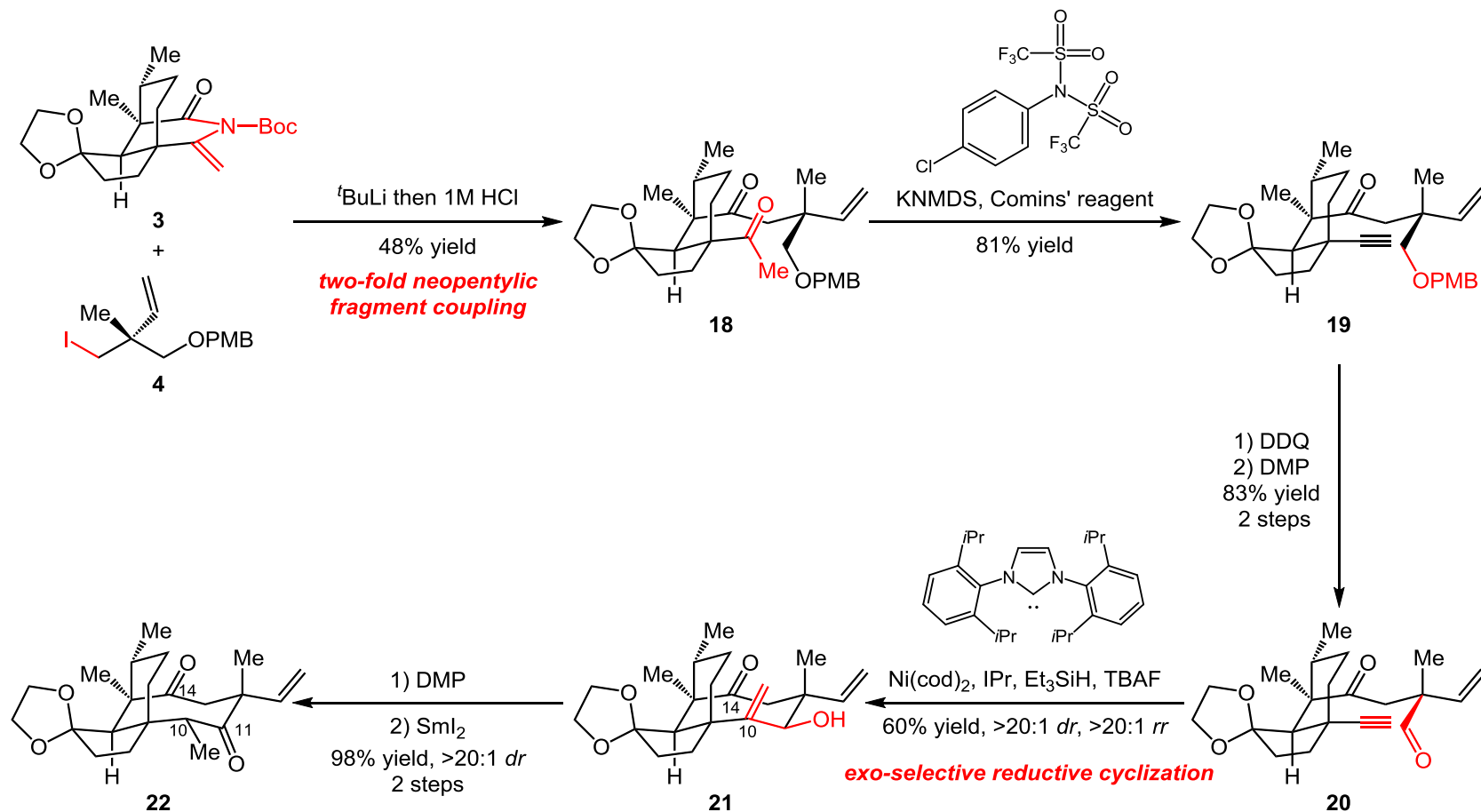
Synthesis of Modular 3



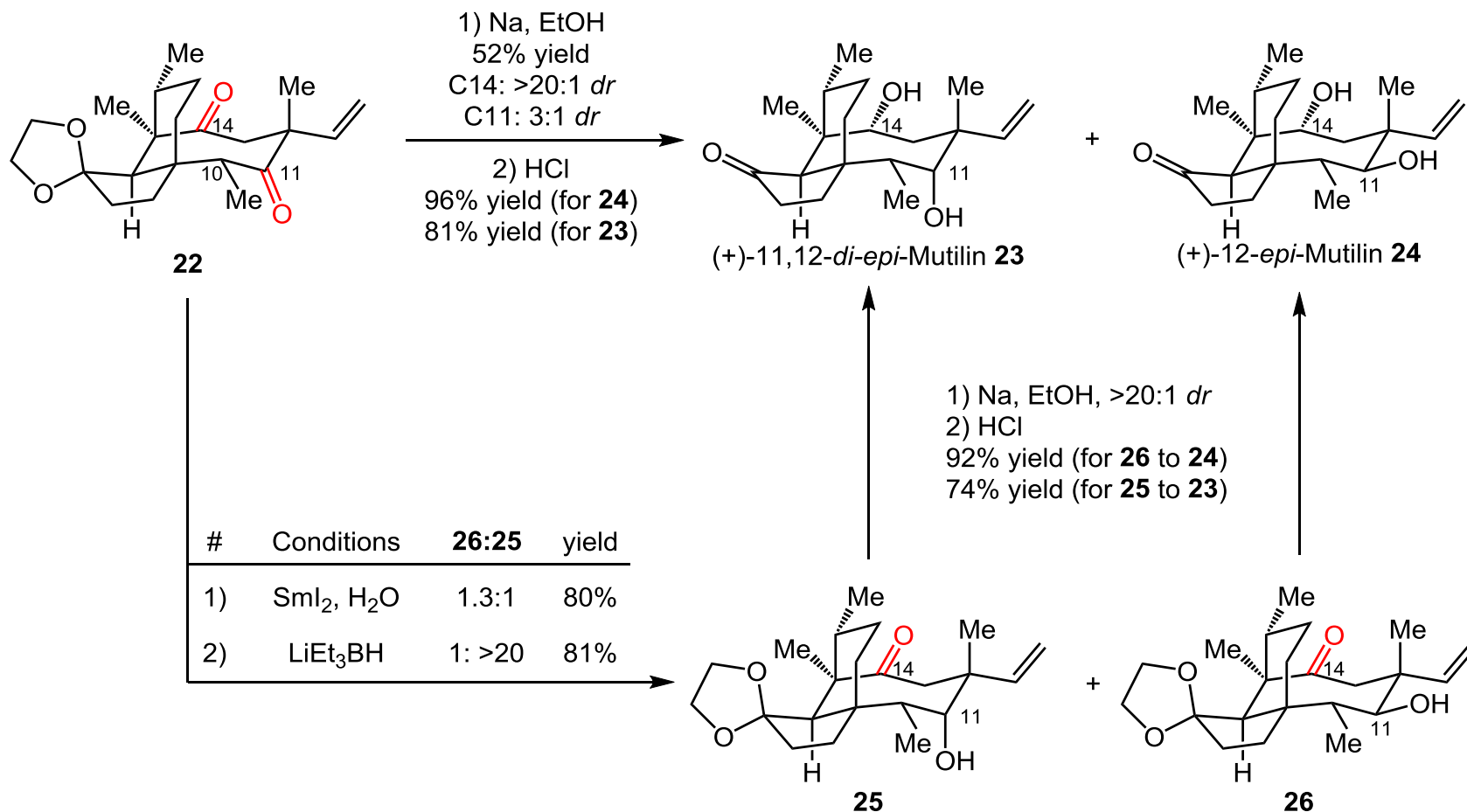
Synthesis of Modular 4



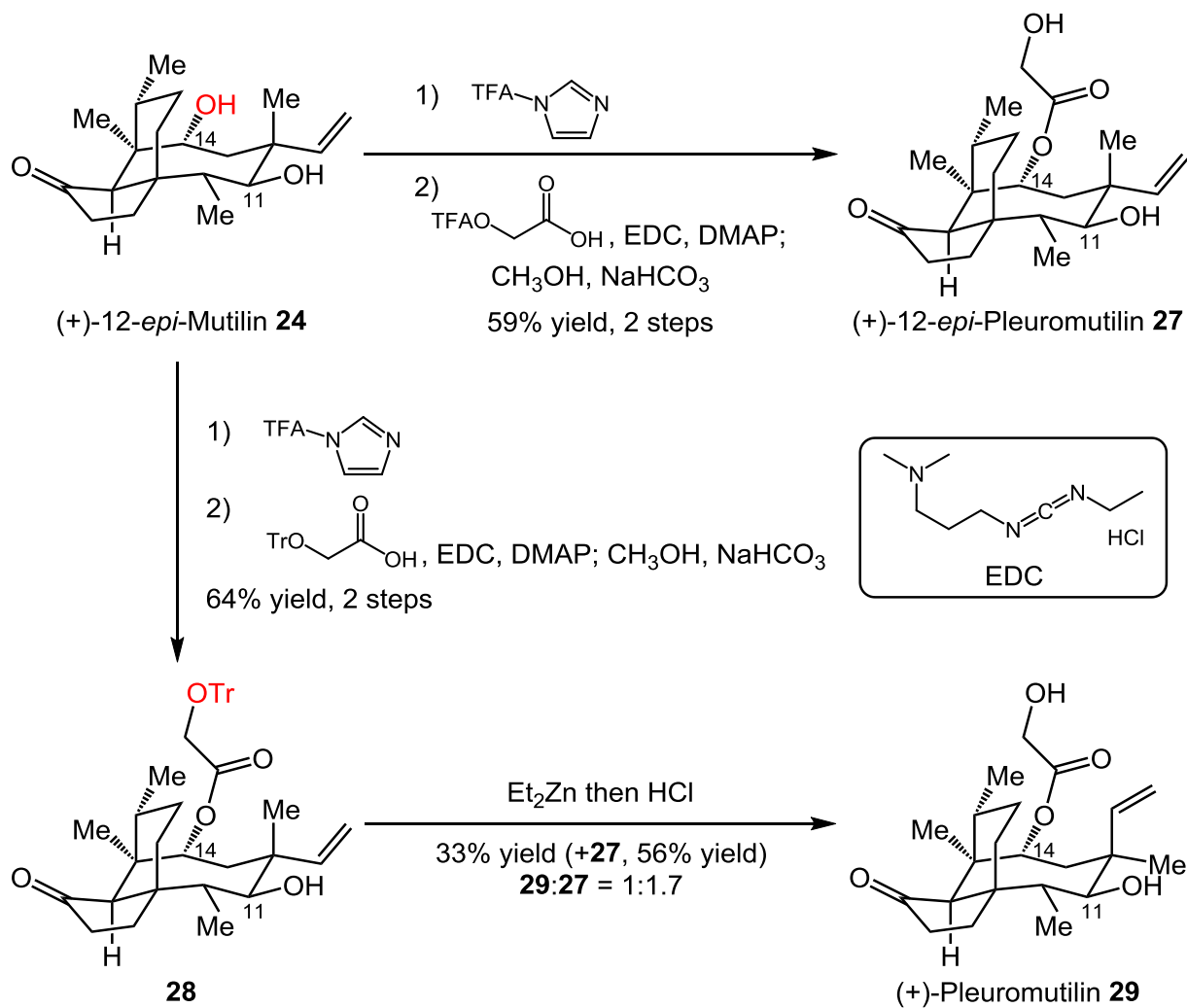
Synthesis of (+)-Pleuromutilins



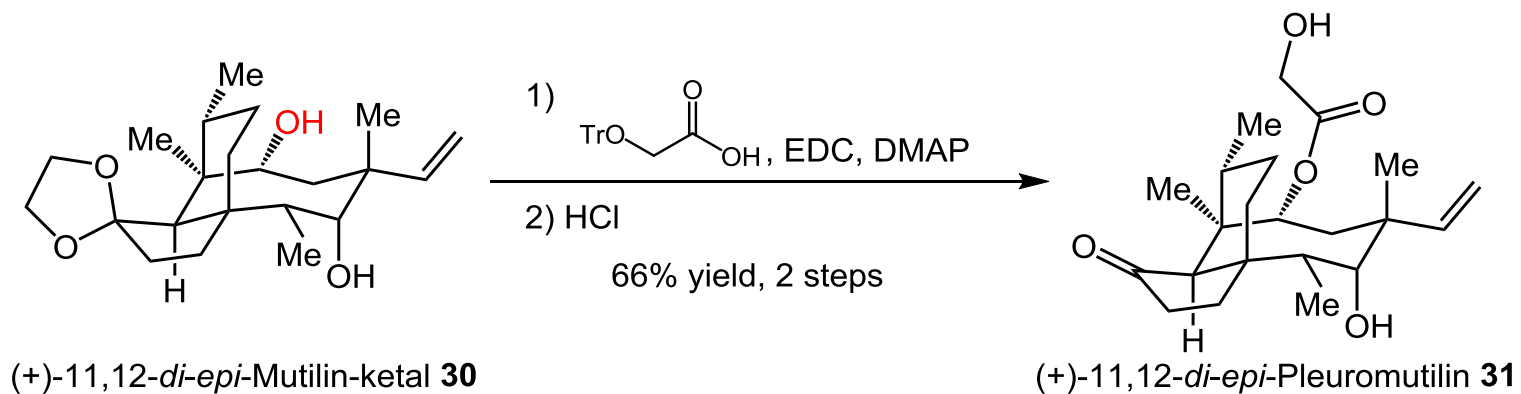
Synthesis of (+)-Pleuromutilins



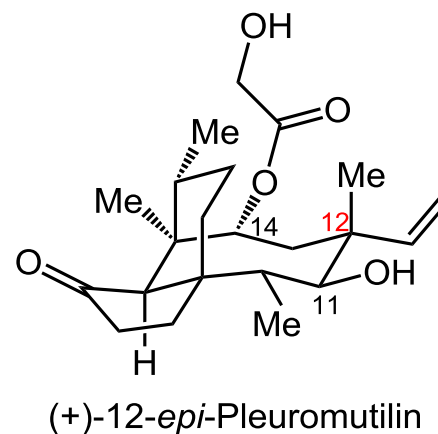
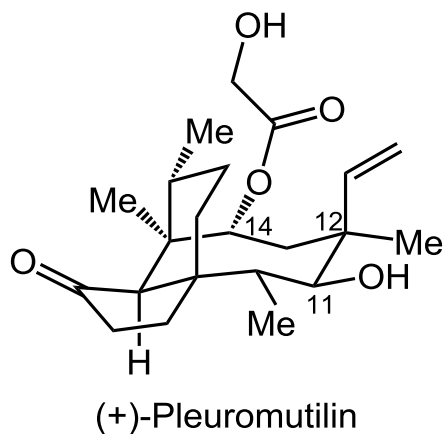
Synthesis of (+)-Pleuromutilins



Synthesis of (+)-Pleuromutilins

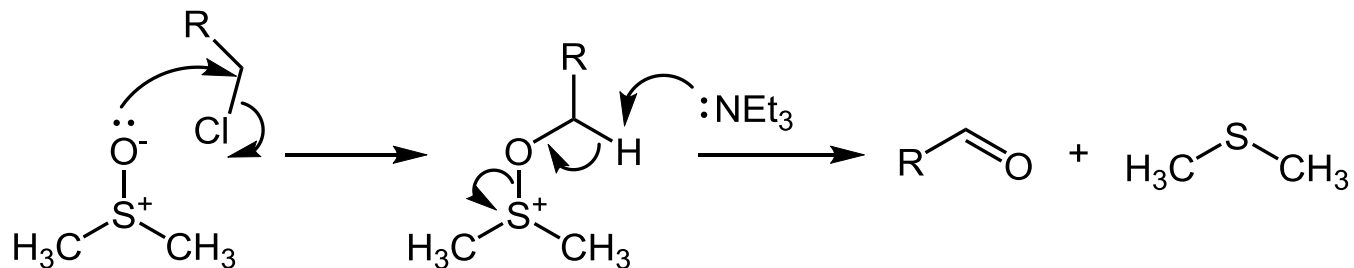
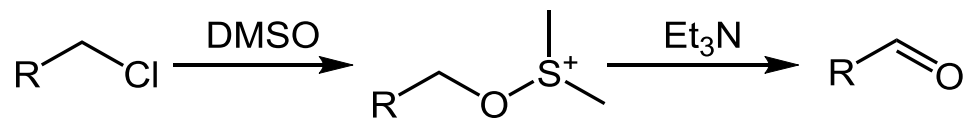


Total Synthesis of (+)-Pleuromutilins by Reisman

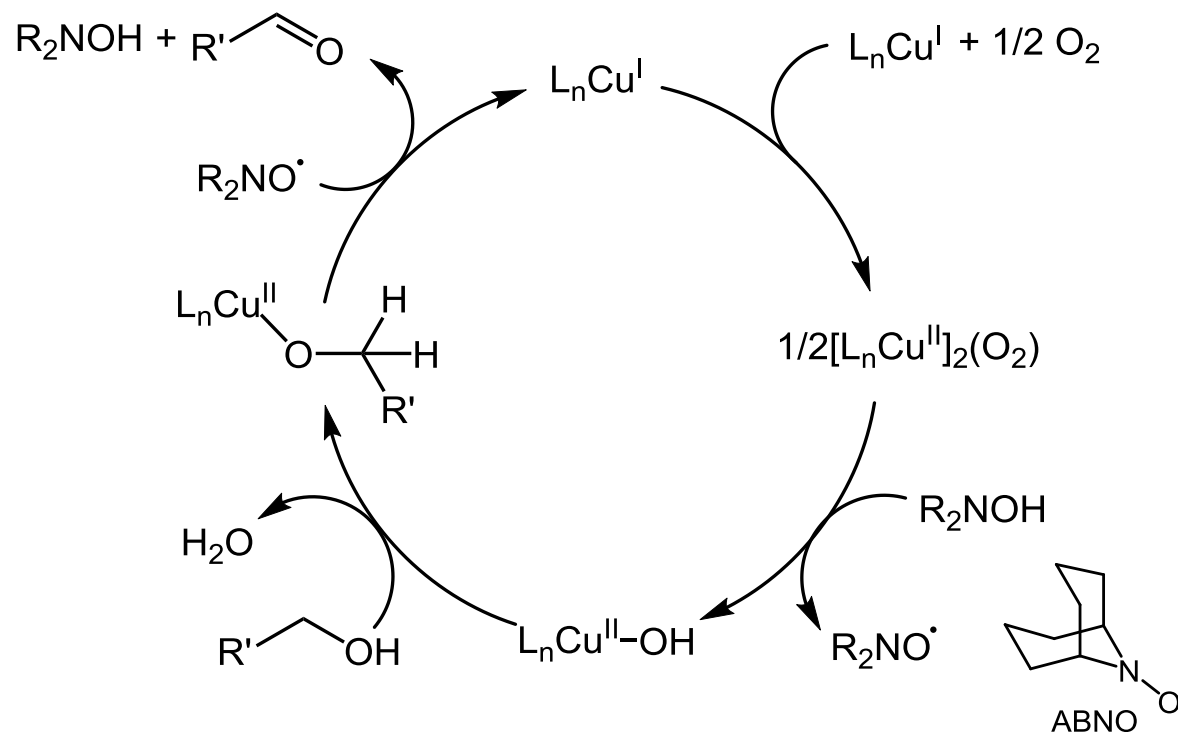
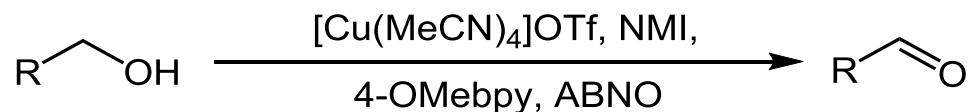


Farney, E. P.; Feng, S. S.; Reisman, S. E.* *et al. J. Am. Chem. Soc.* **2018**, *140*, 1267

Kornblum Oxidation

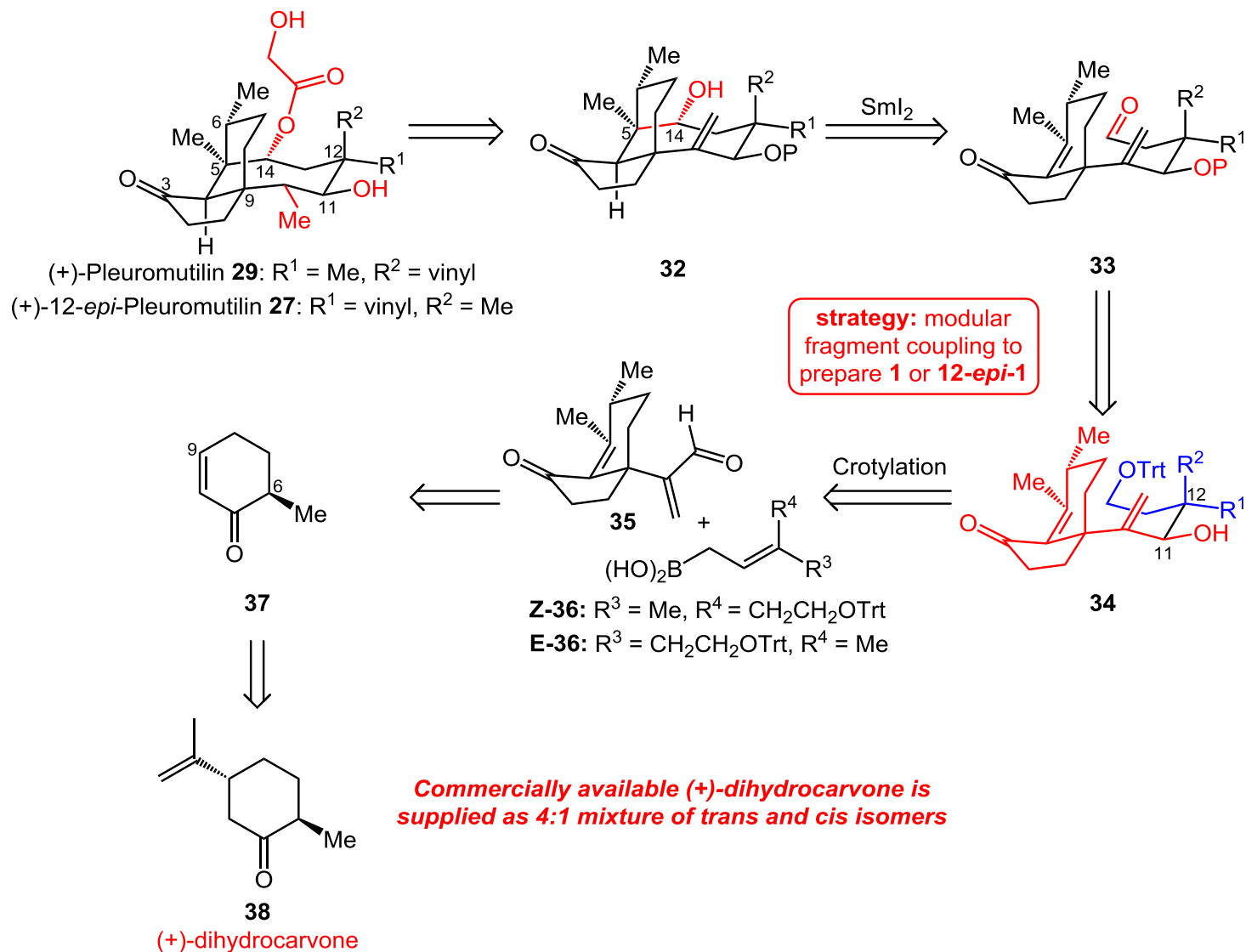


Oxidation by Stahl

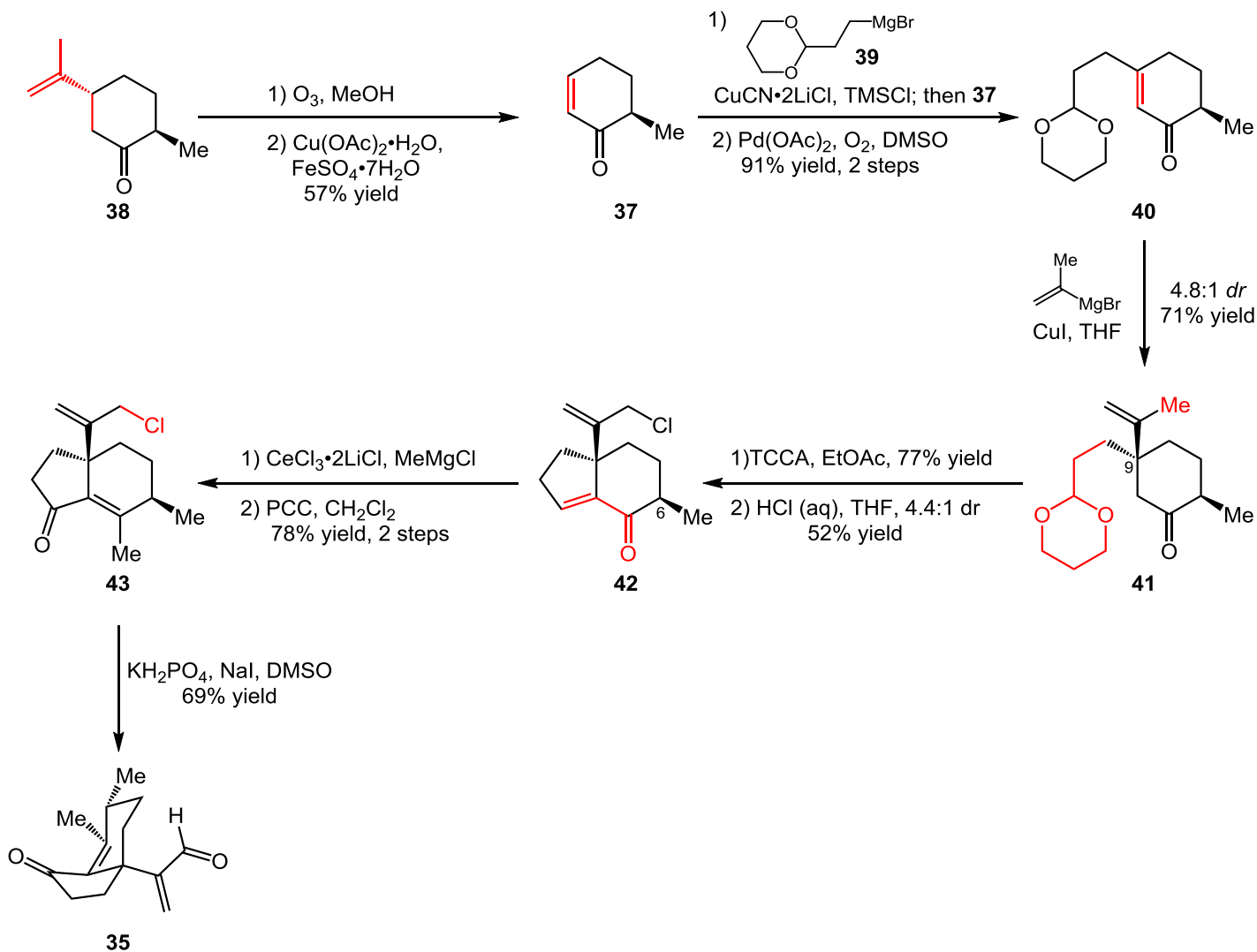


Steves, J. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 15742

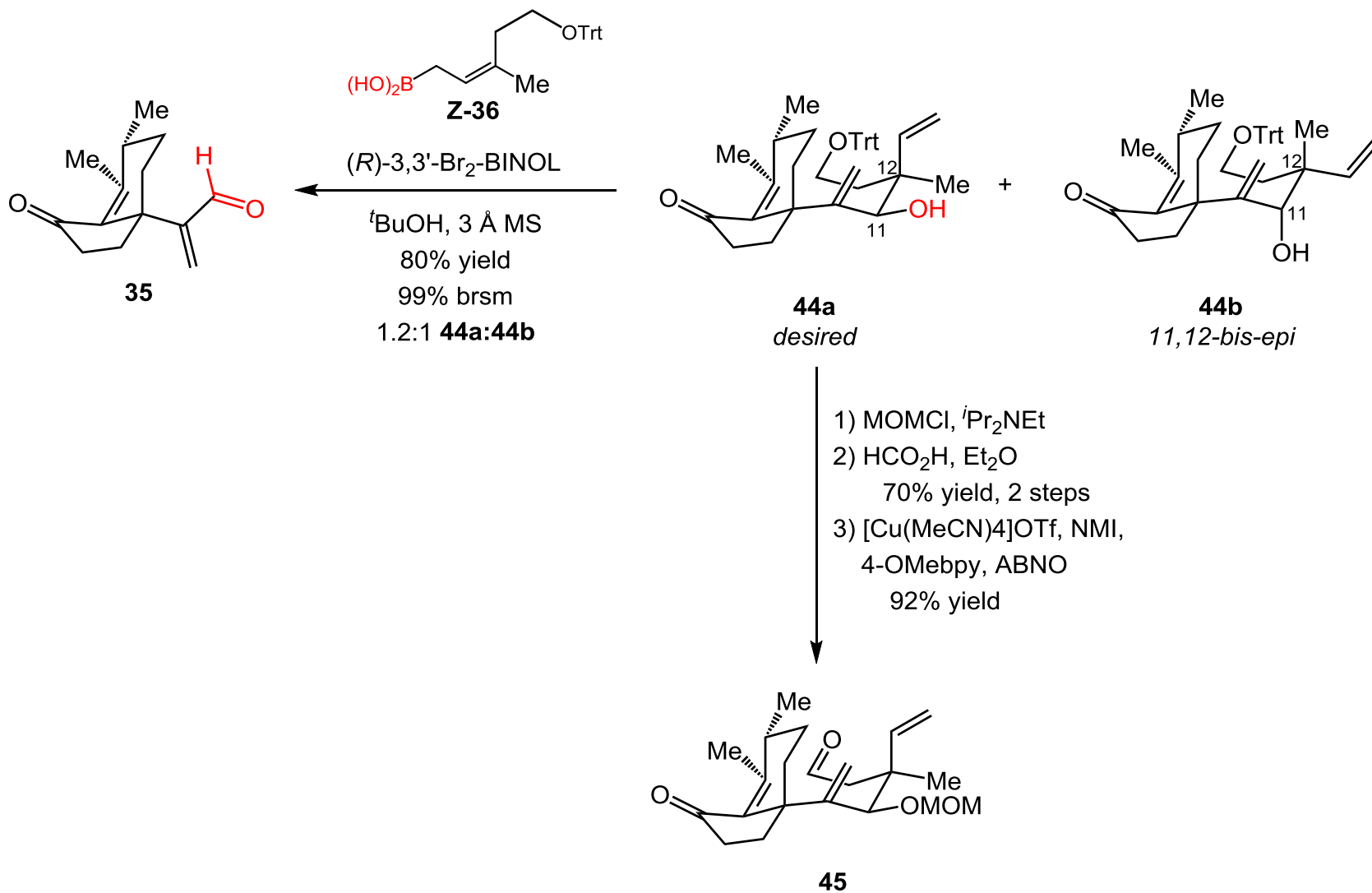
Retrosynthetic Analysis



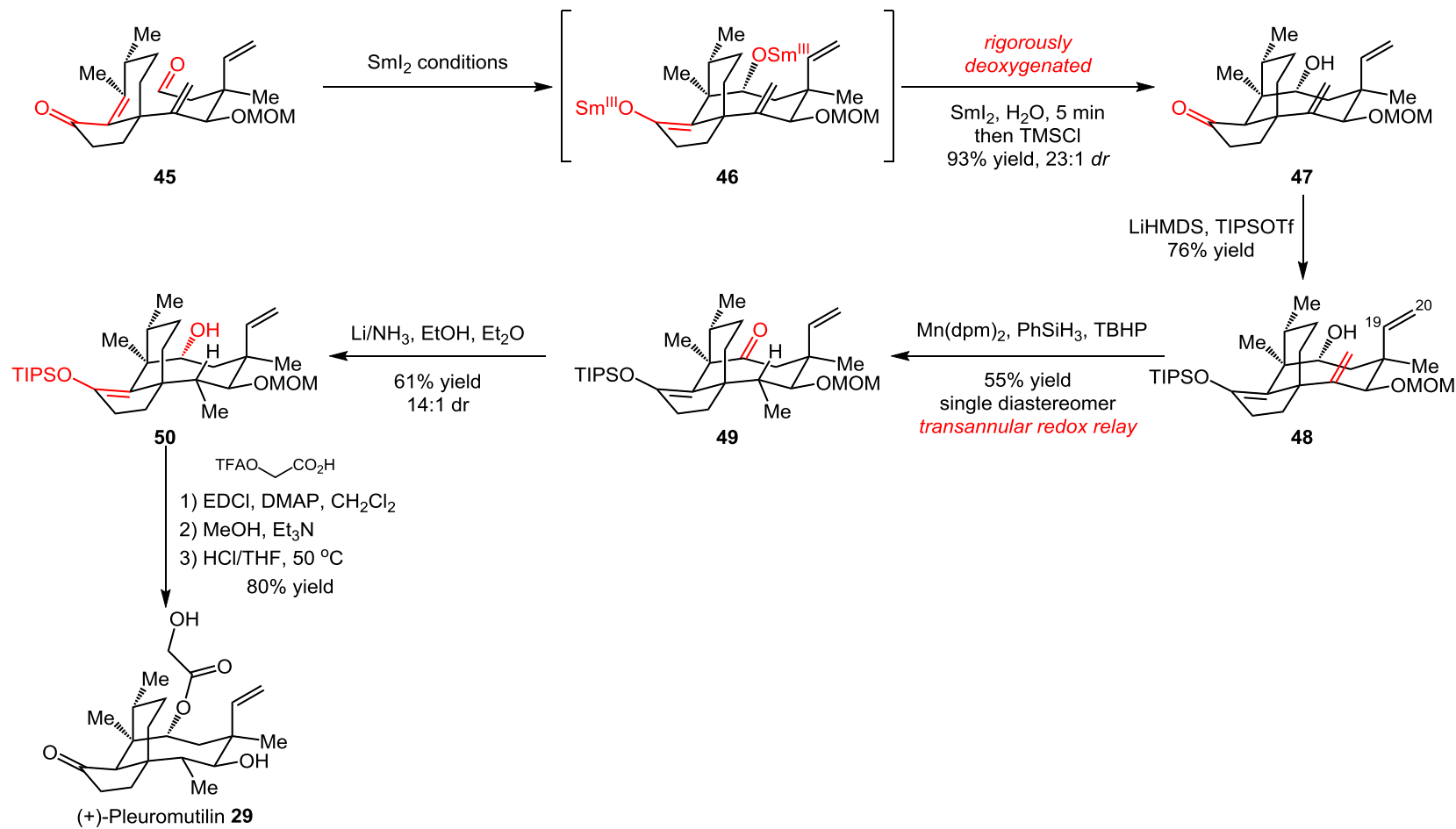
Synthesis of a Cyclization Substrate



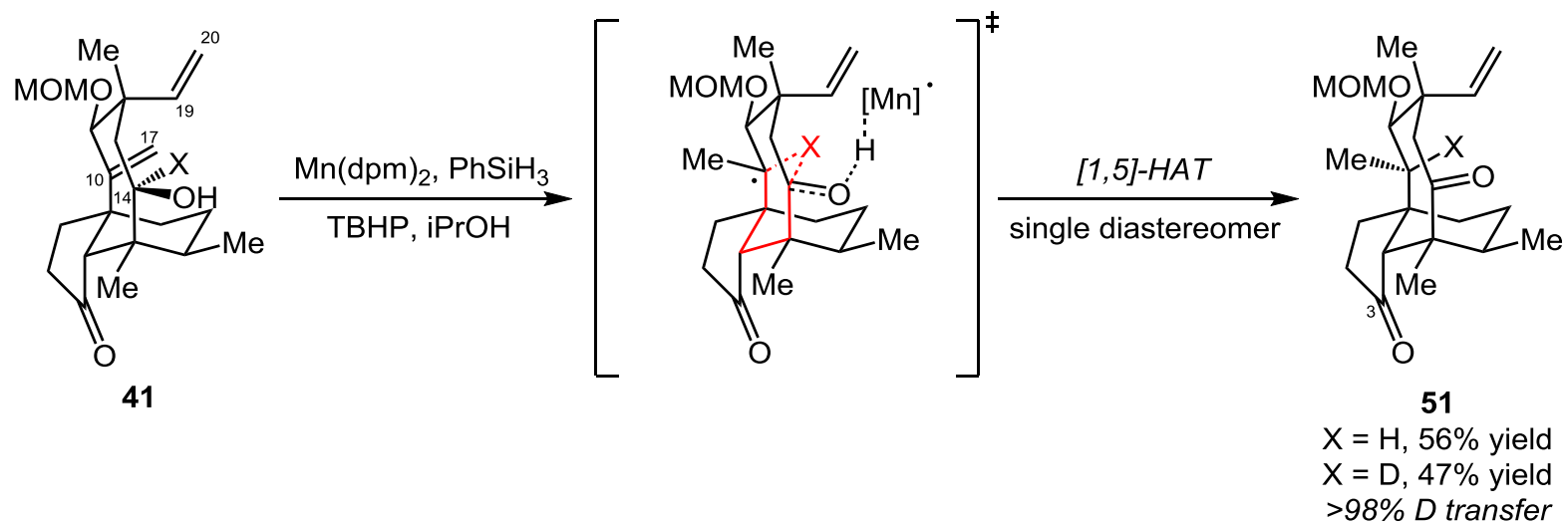
Synthesis of a Cyclization Substrate



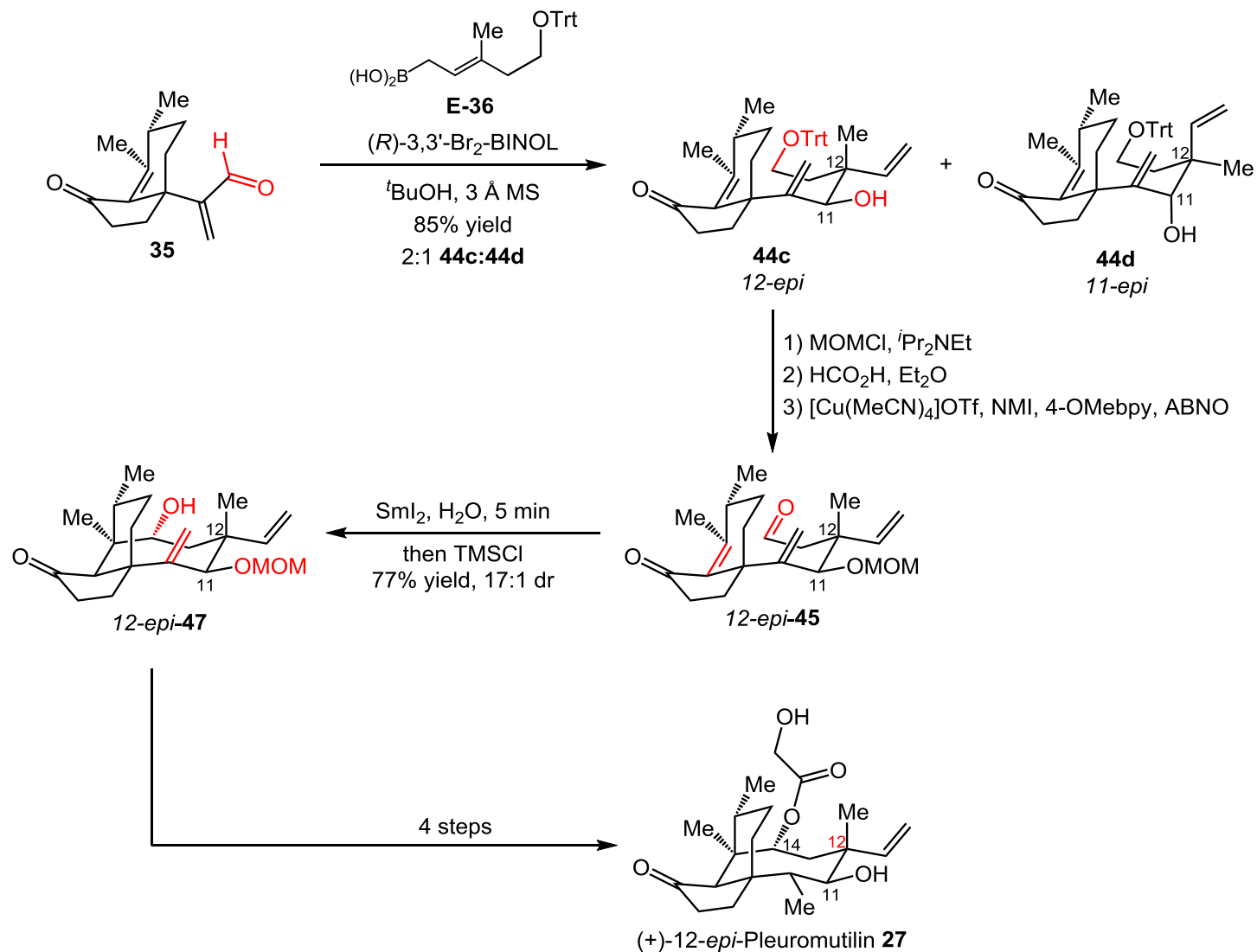
Synthesis of (+)-Pleuromutilin (29)



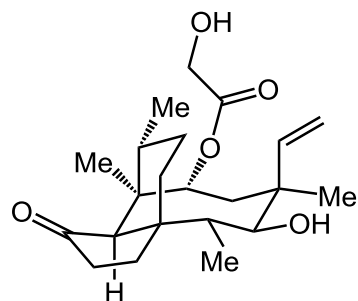
Redox Relay by Transannular [1,5]-HAT



Synthesis of (+)-12-*epi*-Pleuromutilin (27)



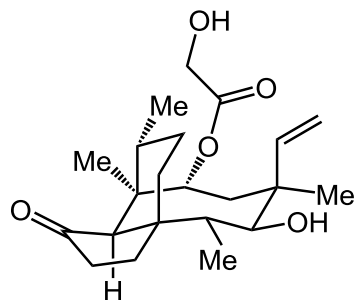
Summary



(+)-Pleuromutilin
(+)-12-*epi*-Pleuromutilin
(+)-11,12-*di-epi*-Pleuromutilin
(+)-12-*epi*-Mutilin
(+)-11,12-*di-epi*-Mutilin

- 17-20 Steps, 0.4-2.3% overall yield;
- A modular synthesis of pleuromutilins by the convergent union of an enamide with a bifunctional iodoether;
- An unusual zinc-mediated retroallylation-allylation reaction;

Herzon, S. B. *et al. Science* **2017**, 356, 956



(+)-Pleuromutilin
(+)-12-*epi*-Pleuromutilin

- 18 Steps, 1.4% overall yield;
- A highly stereoselective SmI_2 -mediated cyclization to establish the eight-membered ring;
- A stereospecific transannular [1,5]-hydrogen atom transfer to set the C10 stereocenter;

Reisman, S. E. *et al. J. Am. Chem. Soc.* **2018**, 140, 1267

The first paragraph

(+)-Pleuromutilin is a diterpene natural product first isolated from the fungus *Clitopilus passeckerianus* in 1951. (+)-Pleuromutilin binds to the peptidyl transferase center of bacterial ribosomes, preventing protein synthesis. Semisynthetic derivatives of **1** in which the C14 ester is modified have been identified as potent antibiotics; for example, retapamulin is an FDA-approved topical antibiotic. Recently, derivatives of 12-*epi*-mutilin have been developed as broad-spectrum antibiotics with efficacy against Gram-negative pathogens. In view of its promising antibacterial properties, four total syntheses of **1** have been reported to date, the most recent of which was disclosed by Herzon and co-workers in 2017. Here we report an approach that enables the preparation of (+)-pleuromutilin and (+)-12-*epi*-pleuromutilin in 18 steps from (+)-trans-dihydrocarvone.

The last paragraph

In summary, the total syntheses of (+)-pleuromutilin and (+)-12-*epi*-pleuromutilin were each completed in 18 steps (longest linear sequence) from (+)-trans-dihydrocarvone. These syntheses were enabled by a modular approach that employed a highly diastereoselective SmI_2 -mediated radical cyclization to form the eight-membered ring. In addition, we uncovered a transannular [1,5]-HAT that effects a stereospecific redox relay to set the C10 stereocenter. The brevity and modularity of the route will enable the design and synthesis of new fully synthetic variants of mutilin antibiotics.

***Thanks
for your attention***