Total Synthesis of (+)-Pleuromutilin

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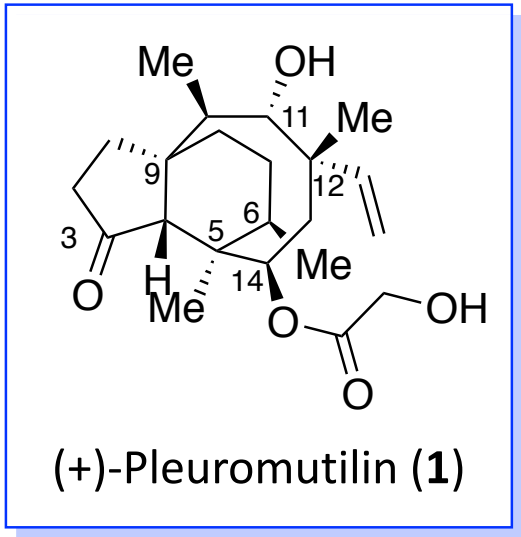
JACS asap



(+)-Pleuromutilin (**1**)

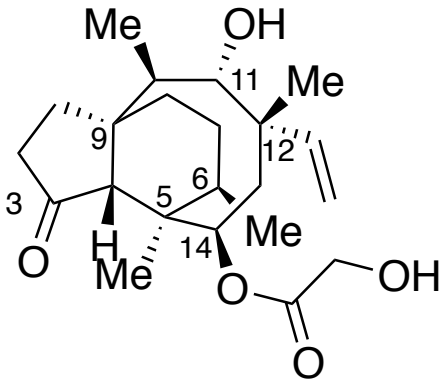
Ruiting Liu

Wipf Group Current Literature

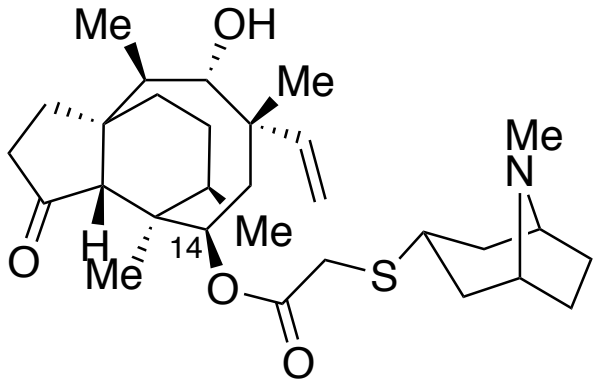
01/27/2018

(+)-Pleuromutilin

- (+)-Pleuromutilin is a diterpene natural product first isolated from the fungus Clitopilus passeckerianus in 1951 and shown to inhibit the growth of Gram- positive bacteria
- Thousands of semisynthetic derivatives has been made in which the C14 ester have been identified as potent antibiotics
- Retapamulin was approved in 2007 by FDA as topical antibiotic



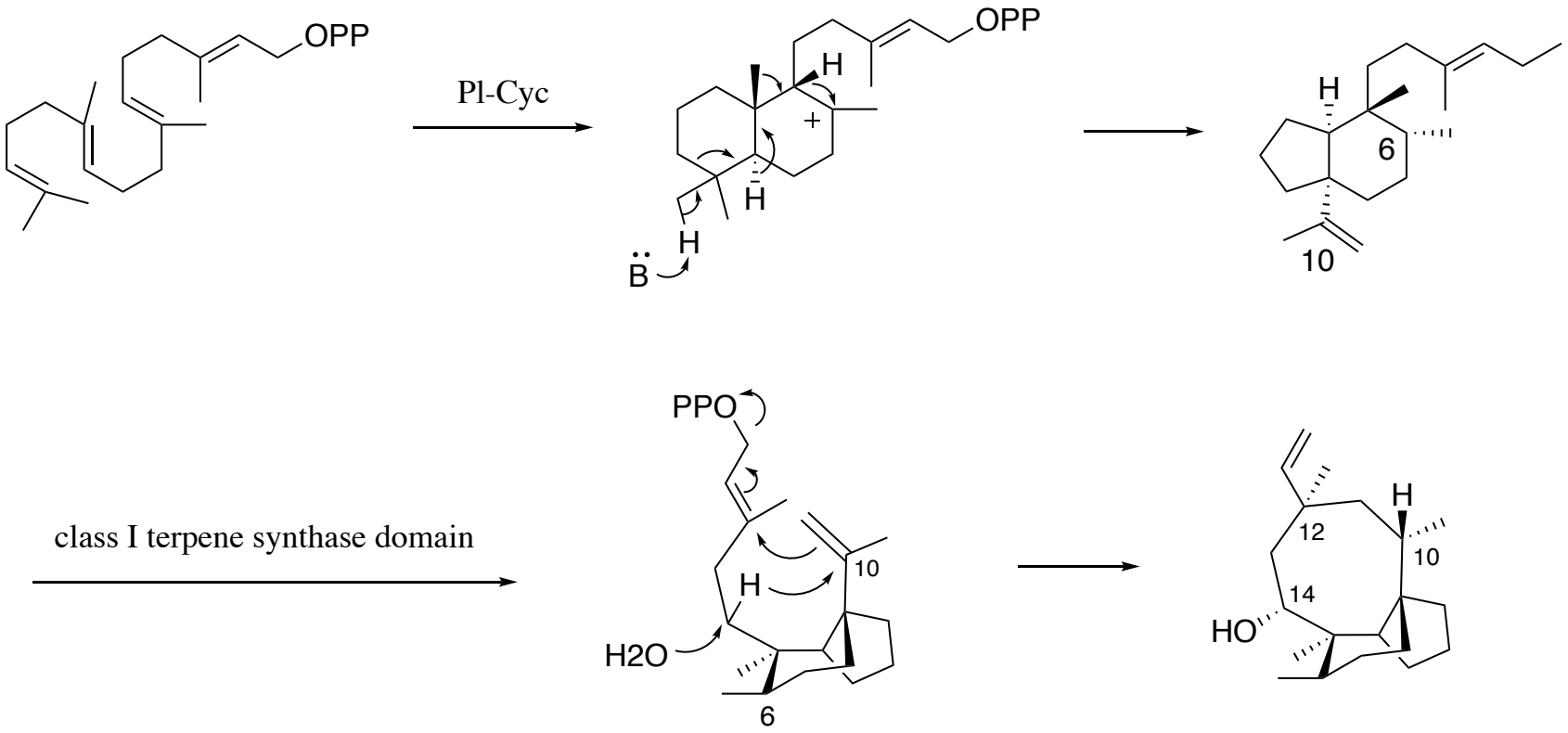
(+)-Pleuromutilin (**1**)



Retapamulin

Proc. Natl. Acad. Sci. U. S. A. 1951, 37, 570
Antimicrob. Agents Chemother. 2006, 50, 3882
Tetrahedron 2014, 70, 6911

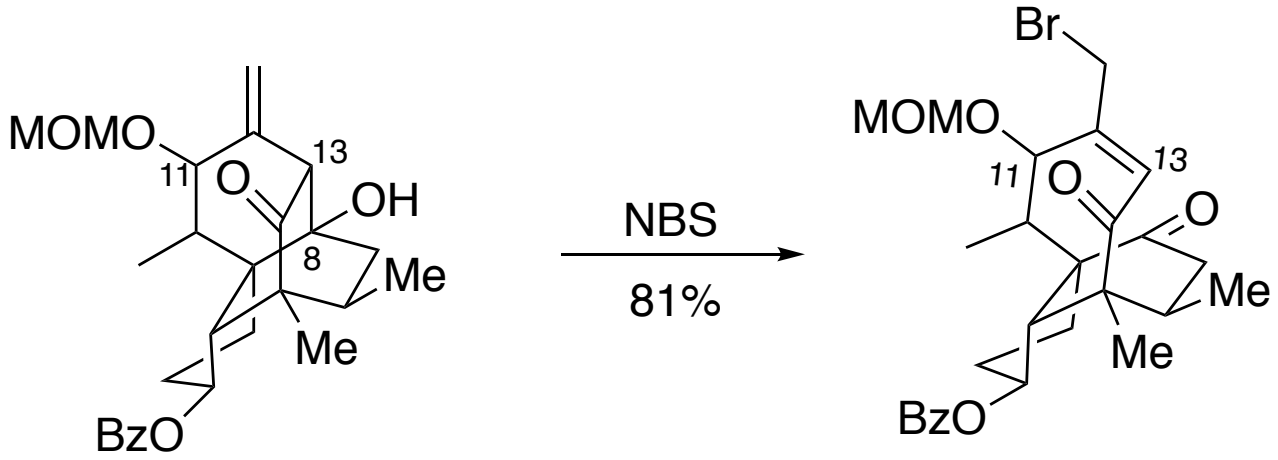
Proposed Biosynthesis



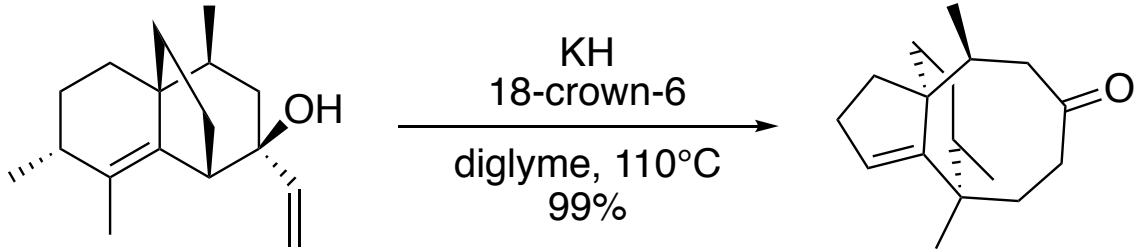
Gazz. Chim. Ital. 92, 884–901 (1962).
Pure Appl. Chem. 17, 331–348 (1968).
Tetrahedron 22, 359–387 (1966).

8-Membered Ring Construction

- Grob fragmentation by Gibbons



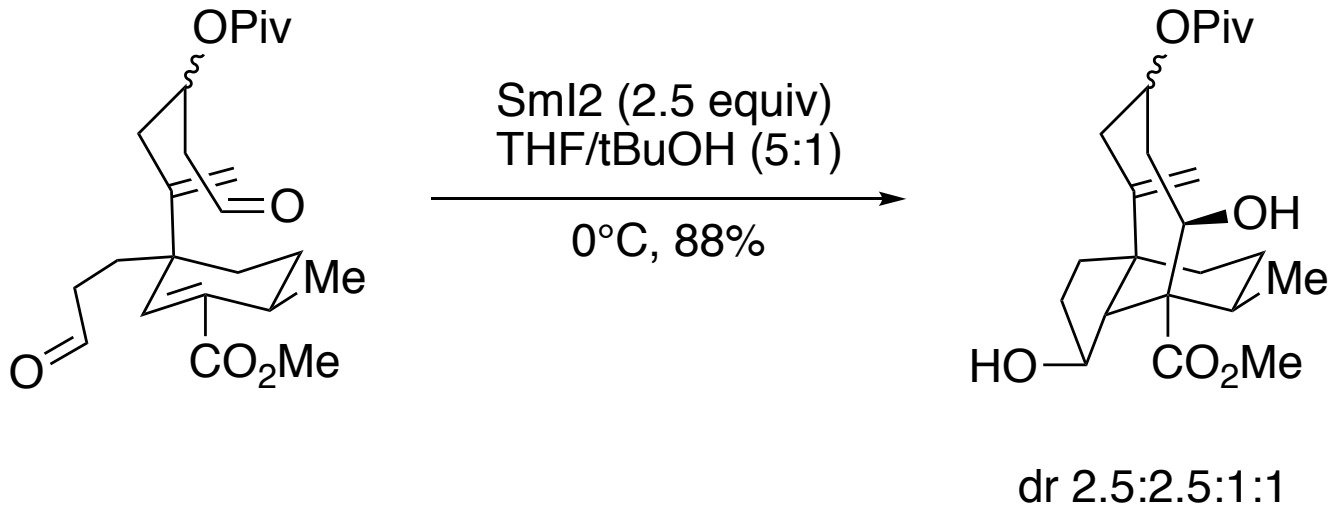
- Oxy-Cope rearrangement by Boeckman etc



JACS.**1982, *104,*** 1767
J. Am. Chem. Soc. 1989, 111, 8284.

8-Membered Ring Construction

- Cascade cyclization by Procter etc

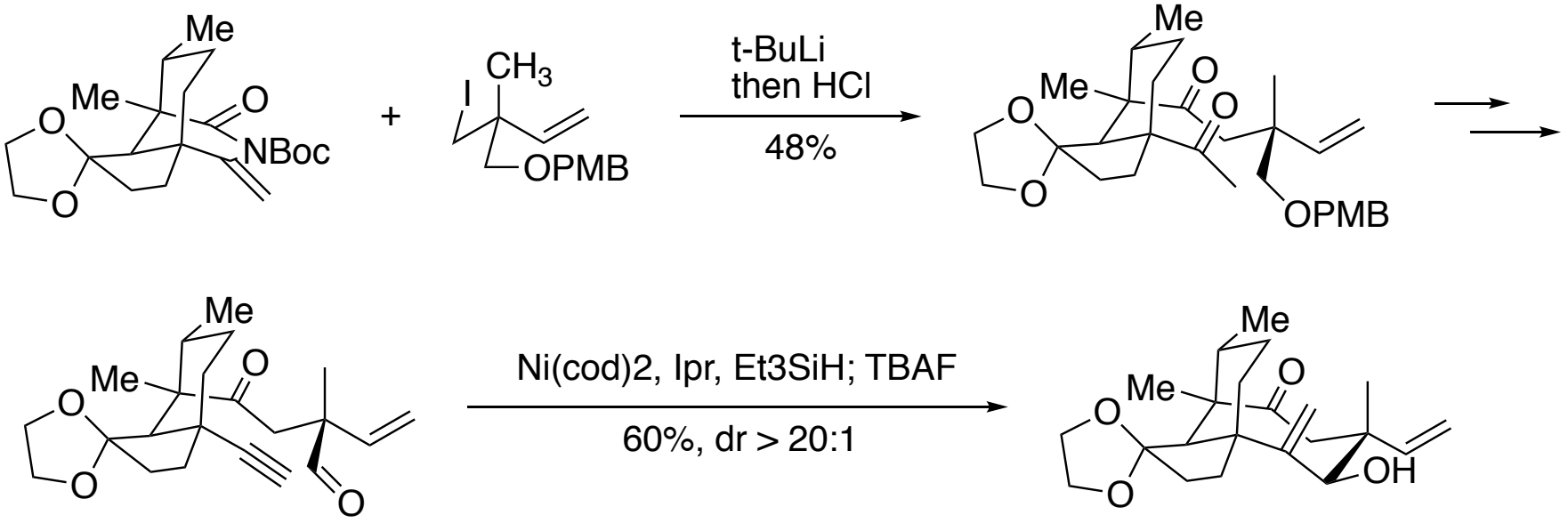


dr 2.5:2.5:1:1

Chem. - Eur. J. 2013, 19, 6718.

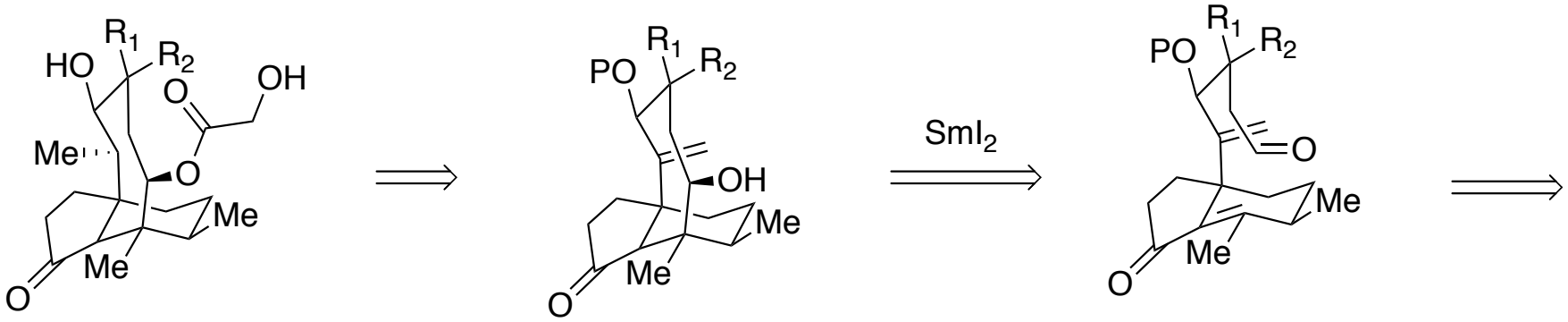
8-Membered Ring Construction

- Reductive cyclization by Herzon etc

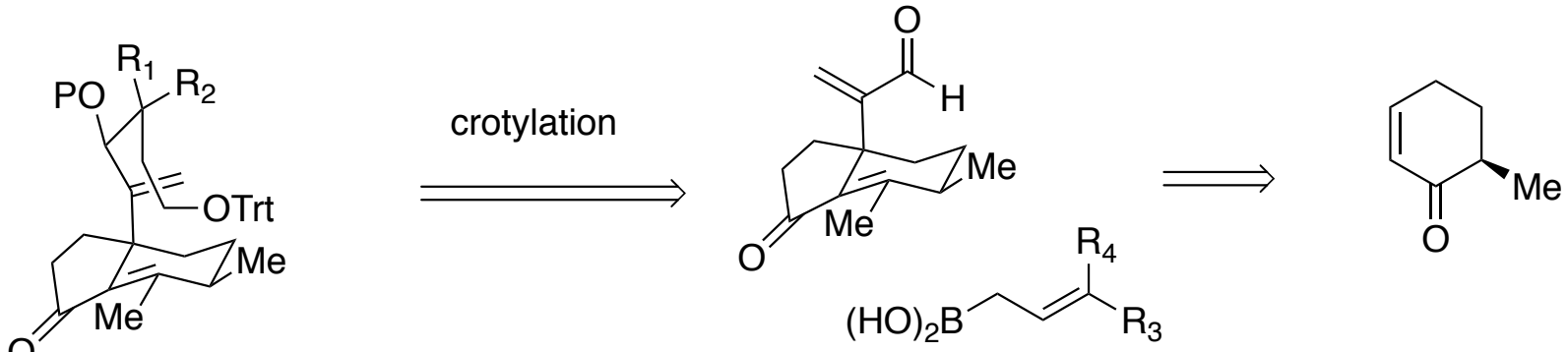


Science 356, 956–959 (2017)

Retrosynthetic Analysis

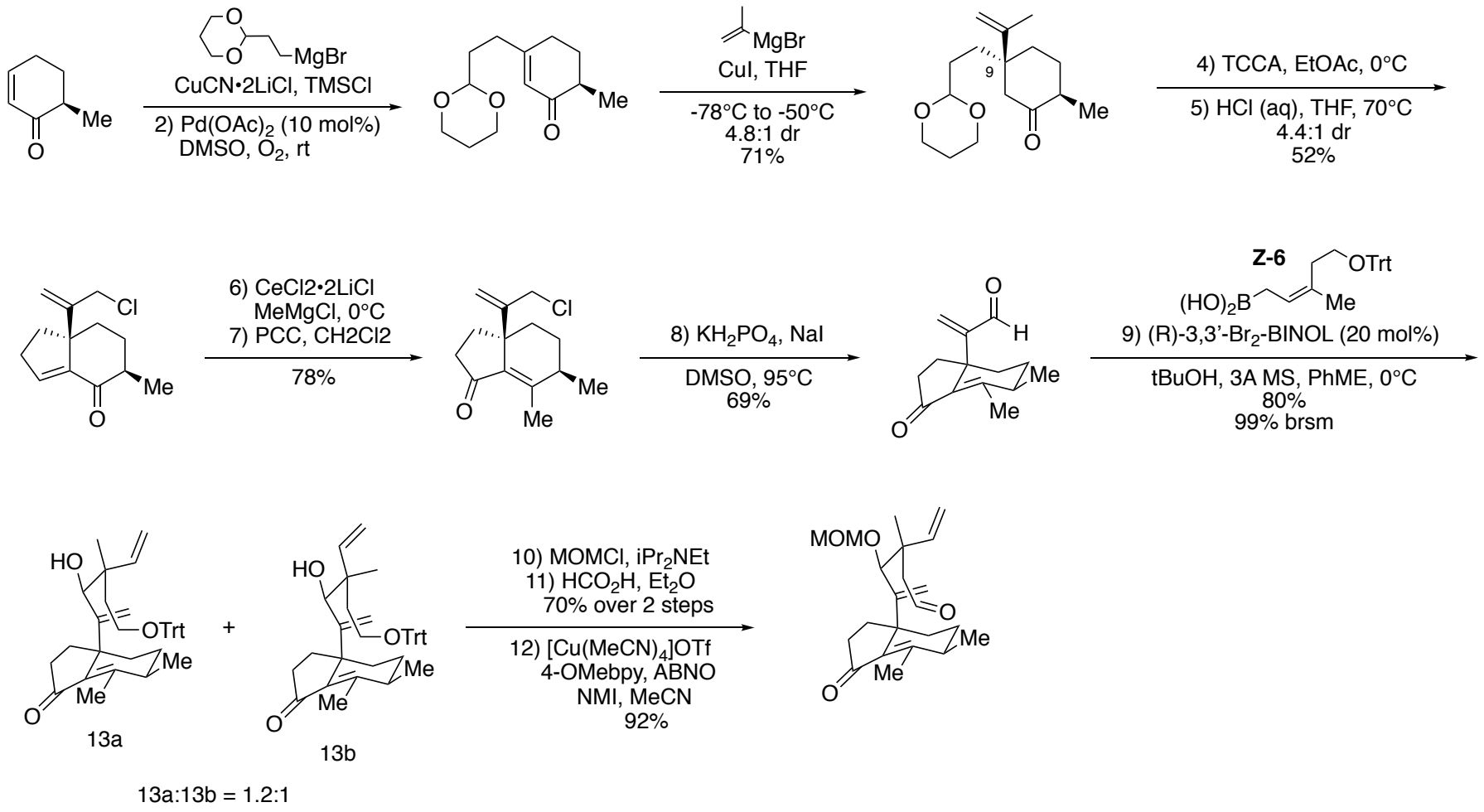


1: R_1 = Me, R_2 = vinyl
12-epi-**1** : R_1 = vinyl, R_2 = Me

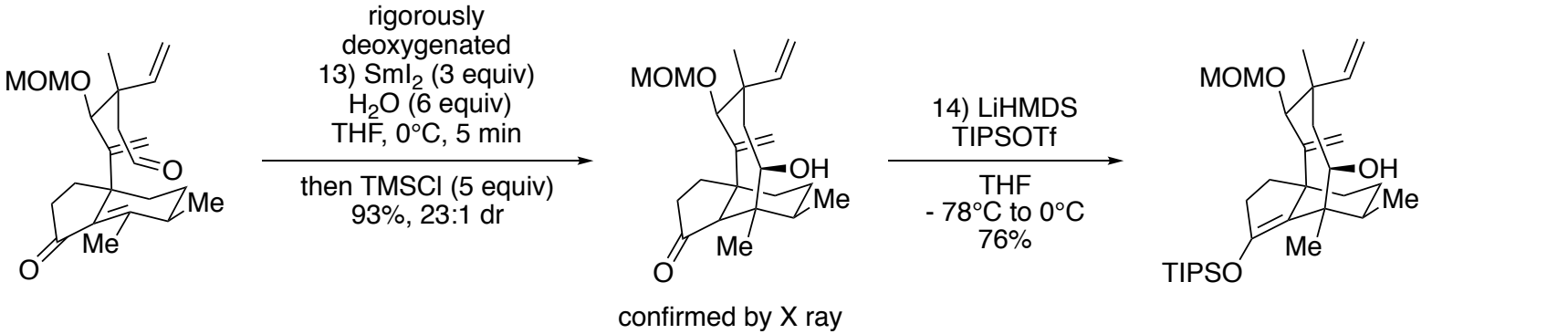


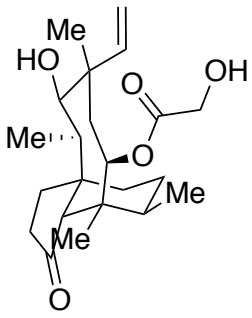
Z-6: R_3 = Me, R_4 = CH_2CH_2OTrt
E-6: R_3 = CH_2CH_2OTrt, R_4 = Me

Synthesis of 5,6-membered ring



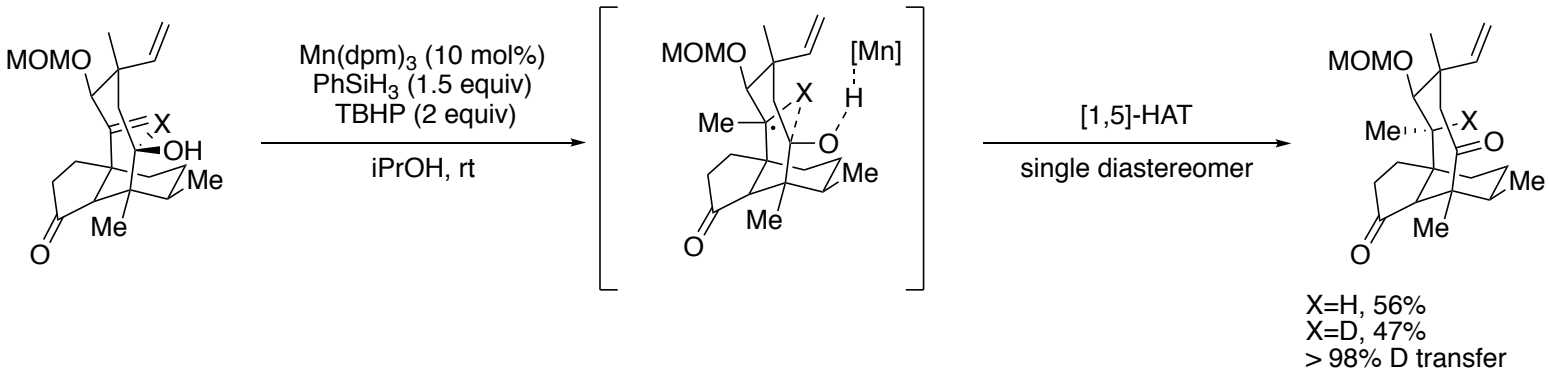
Completion of Synthesis





(+)-Pleuromutilin

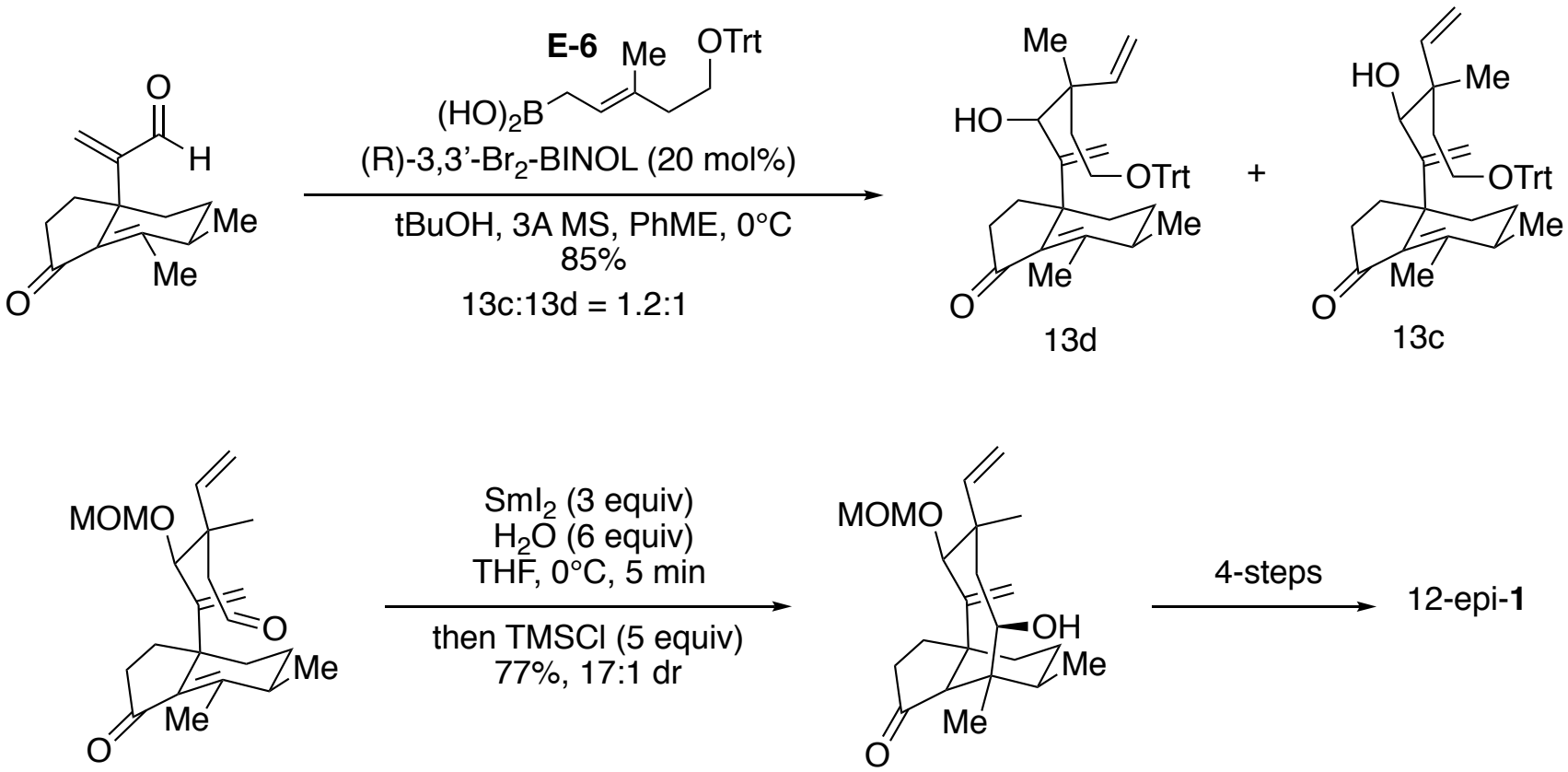
Redox Relay by Transannular [1,5]-HAT



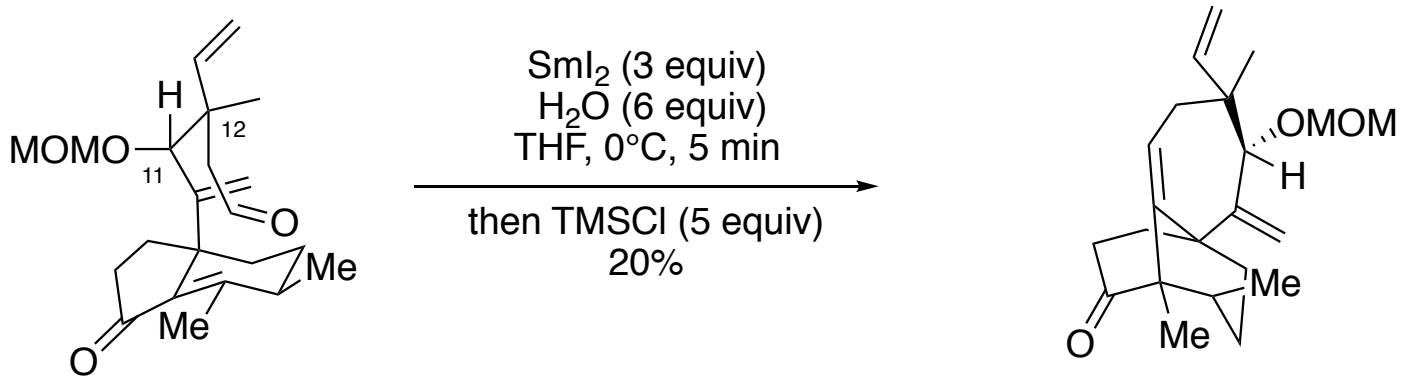
- Standard hydrogenation conditions employing cationic transition metal complexes gave rapid and exclusive reduction of the more sterically accessible vinyl group
- The protected C14 alcohol perform poorly under the HAT conditions suggests that cleavage of the O−H bond to form the C14 ketone serves as a driving force for this transformation

J. Am. Chem. Soc. 2000, 122, 11660
Science 2015, 349, 1532

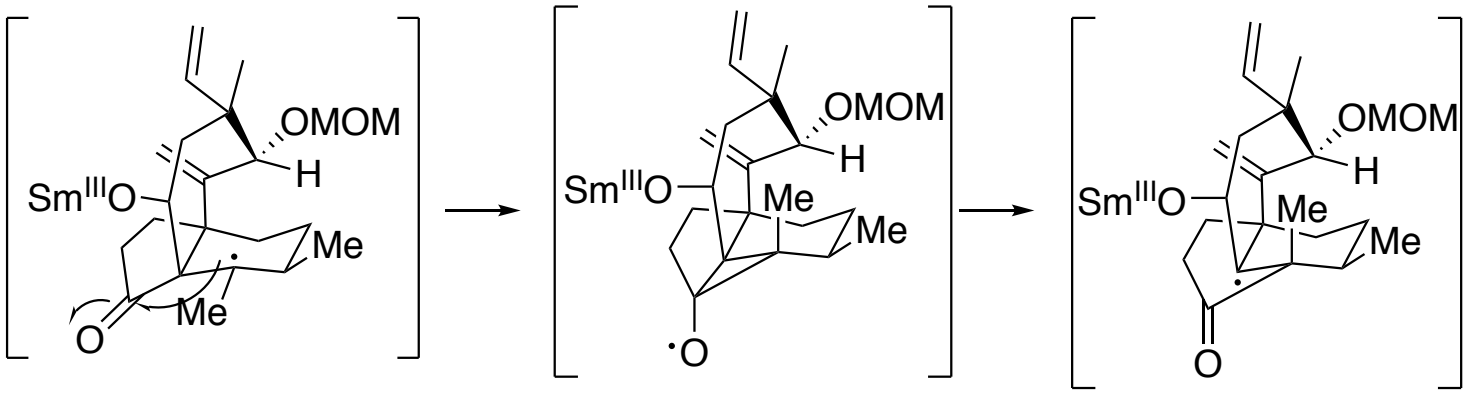
Synthesis of 12-*epi*-**1**



Cyclization of a 11,12-bis-*epi* substrate



11,12-bis-*epi*



Dowd–Beckwith rearrangement

C11 stereochemistry exerts a pronounced effect on the reactivity

Conclusion

- Preparation of (+)-pleuromutilin and (+)-12-epi-pleuromutilin in 18 steps from (+)-trans-dihydrocarvone.
- Highly stereoselective SmI2-mediated cyclization to establish the eight-membered ring and a stereospecific transannular [1,5]-hydrogen atom transfer to set the C10 stereocenter