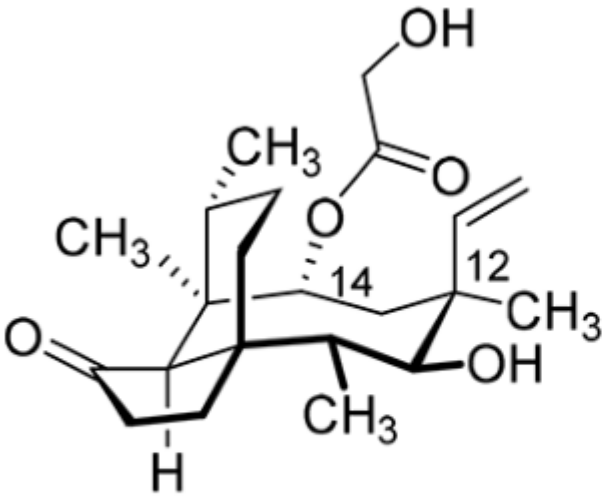
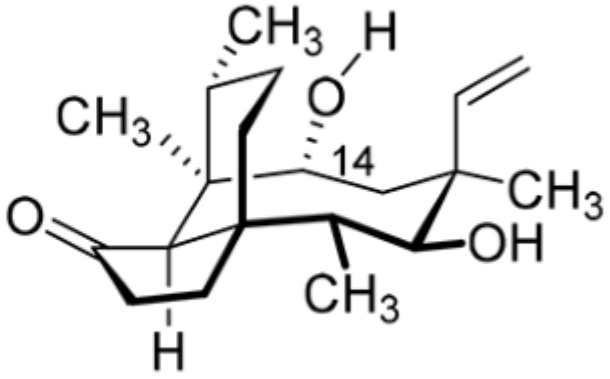
Total Synthesis of (+)-Pleuromutilin

Sarah E. Reisman



(+)-pleuromutilin (**1**)



(+)-mutilin (**2**)

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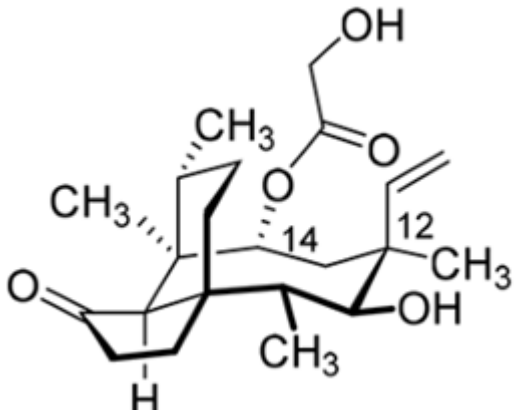
J. Am. Chem. Soc.

Sarah E. Reisman

- 2006-2008： NIH Postdoctoral Fellow, Harvard University, Cambridge, MA (Prof. Eric Jacobsen)
- 2001–2006： Ph.D. Yale University, New Haven, CT (Prof. John Wood)
- 1997–2001： B.A. Connecticut College, New London, CT (Prof. Timo Ovaska)
- Born in Bar Harbor, Maine.

Pleuromutilin



Pleuromutilin 截短侧耳素

Clitopilus passeckerianus

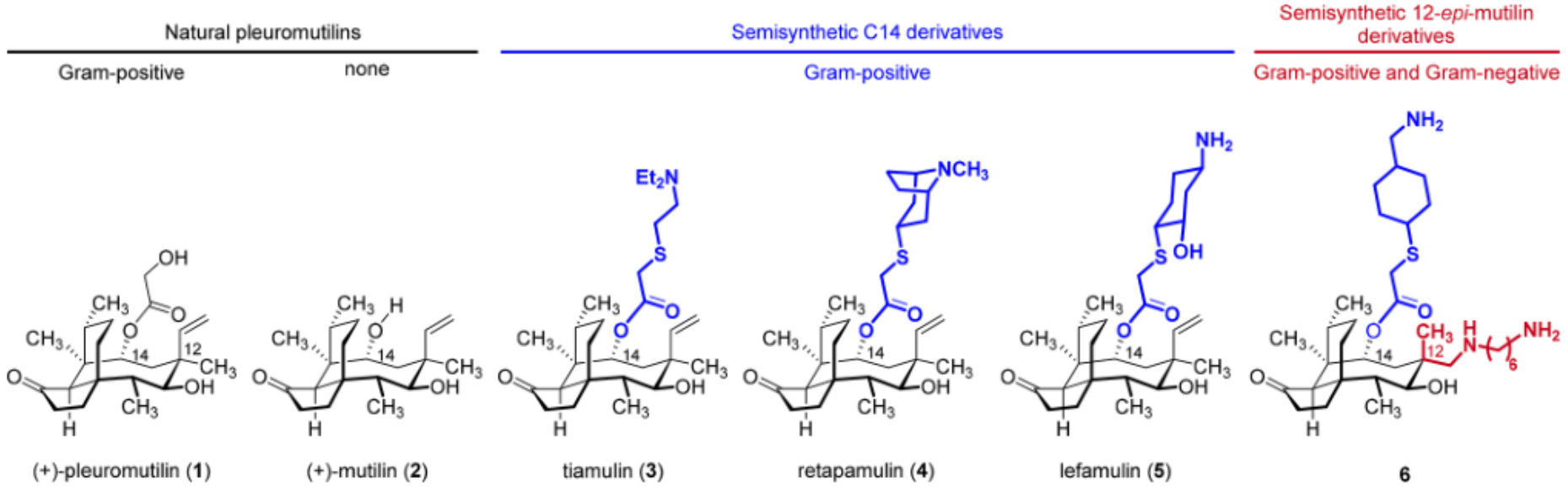
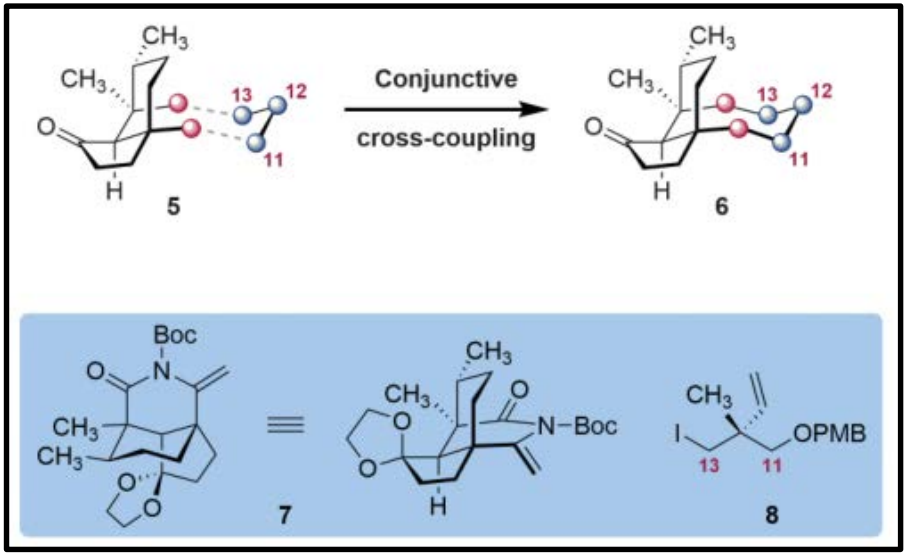


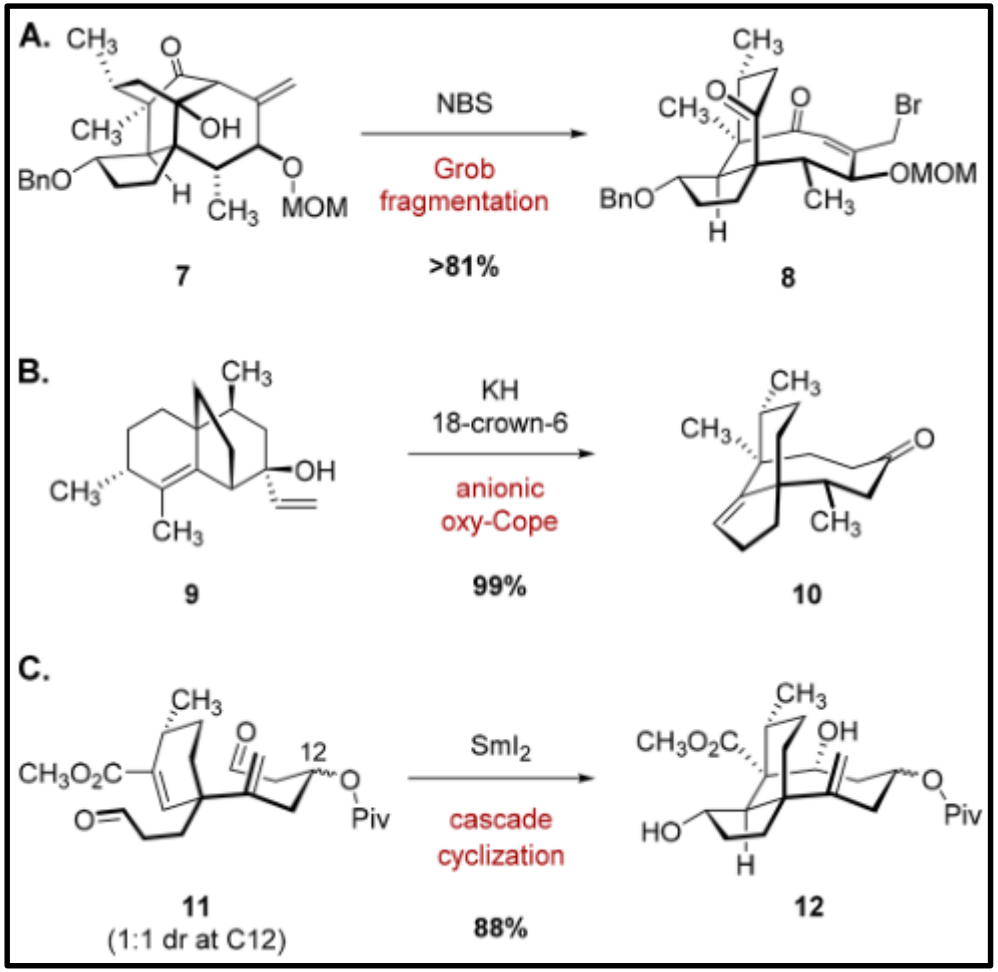
Figure 1. Structures of natural (+)-pleuromutilin (**1**) and the deacylated derivative (+)-mutilin (**2**), structures of the semisynthetic C14 derivatives tiamulin (**3**), retapamulin (**4**), and lefamulin (**5**), and the structure of a representative 12-*epi*-mutilin derivative **6**. Natural (+)-pleuromutilin (**1**) and the semisynthetic C14 derivatives **3**–**5** are active primarily against Gram-positive pathogens. 12-*epi*-Mutilin derivatives such as **6** possess extended spectrum activity against Gram-negative and drug-resistant pathogens.

Pleuromutilin



18 steps

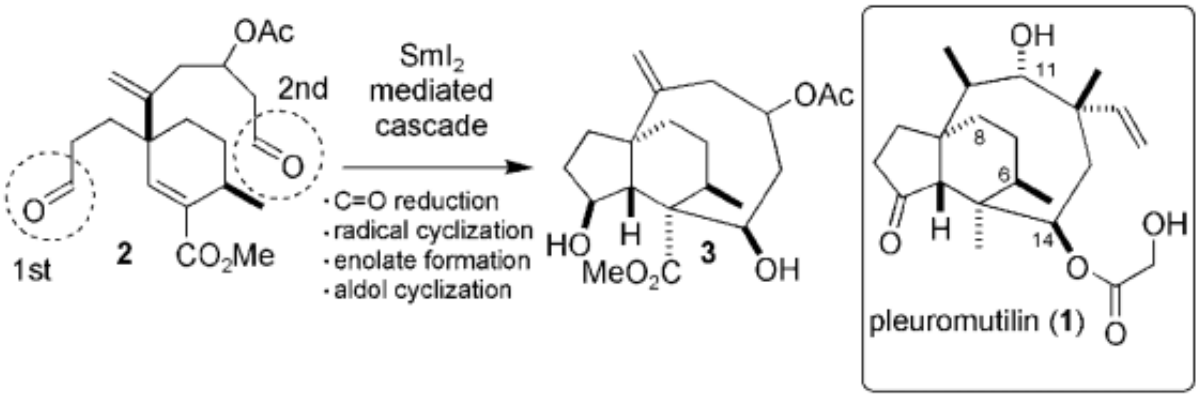
J. Am. Chem. Soc. 2017, 139, 16377−16388
Murphy et al., Science 356, 956–959 (2017)

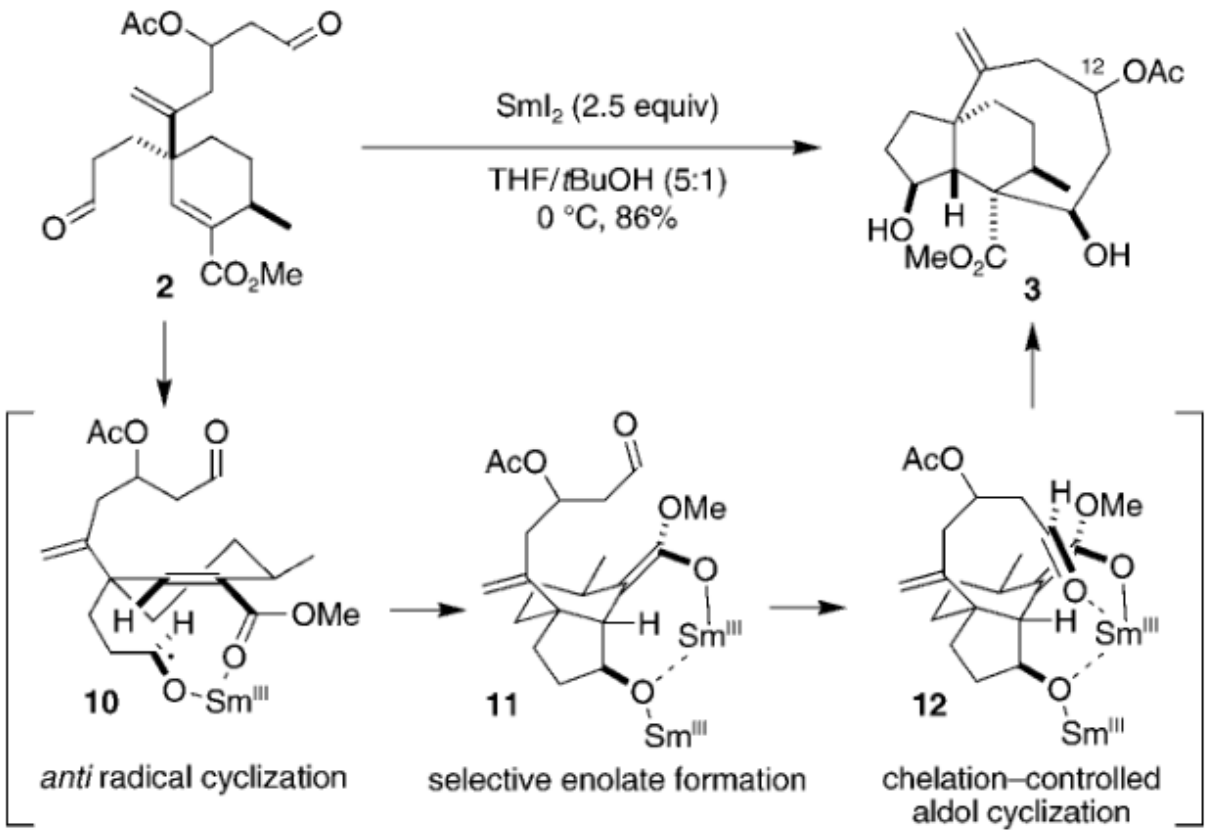


27 to 34 steps

E. G. Gibbons, J. Am. Chem. Soc. 104, 1767–1769 (1982).
R. K. Boeckman, D. M. Springer, T. R. Alessi, J. Am. Chem. Soc.111, 8284–8286 (1989).
N. J. Fazakerley, M. D. Helm, D. J. Procter, Chemistry 19, 6718–6723 (2013).

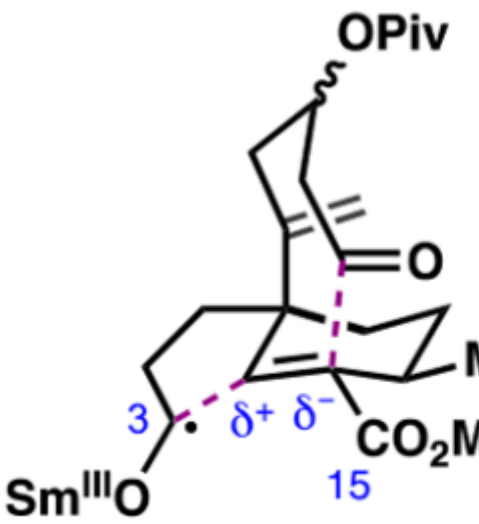
Total Synthesis of Pleuromutilin by David J. Procter





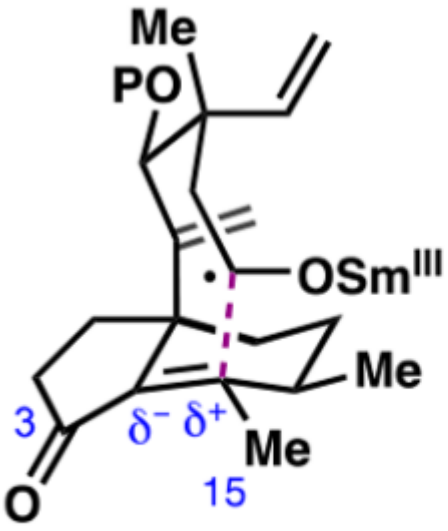
Angew. Chem. Int. Ed. **2009**, *48*, 9315 –9317

Comparison of SmI_2 Approaches to Pleuromutilin Framework



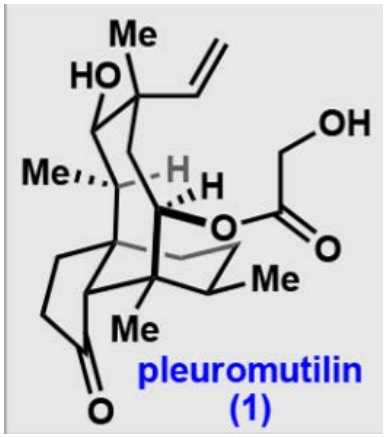
Procter et al.:

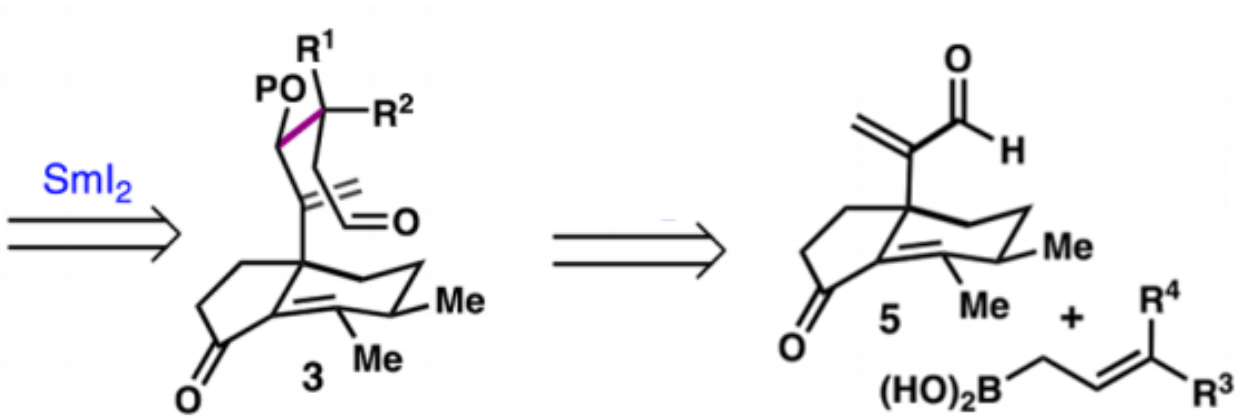
- 8-membered ring formed by **aldol**
- Cyclization product has C3 and C15 at **incorrect** oxidation states



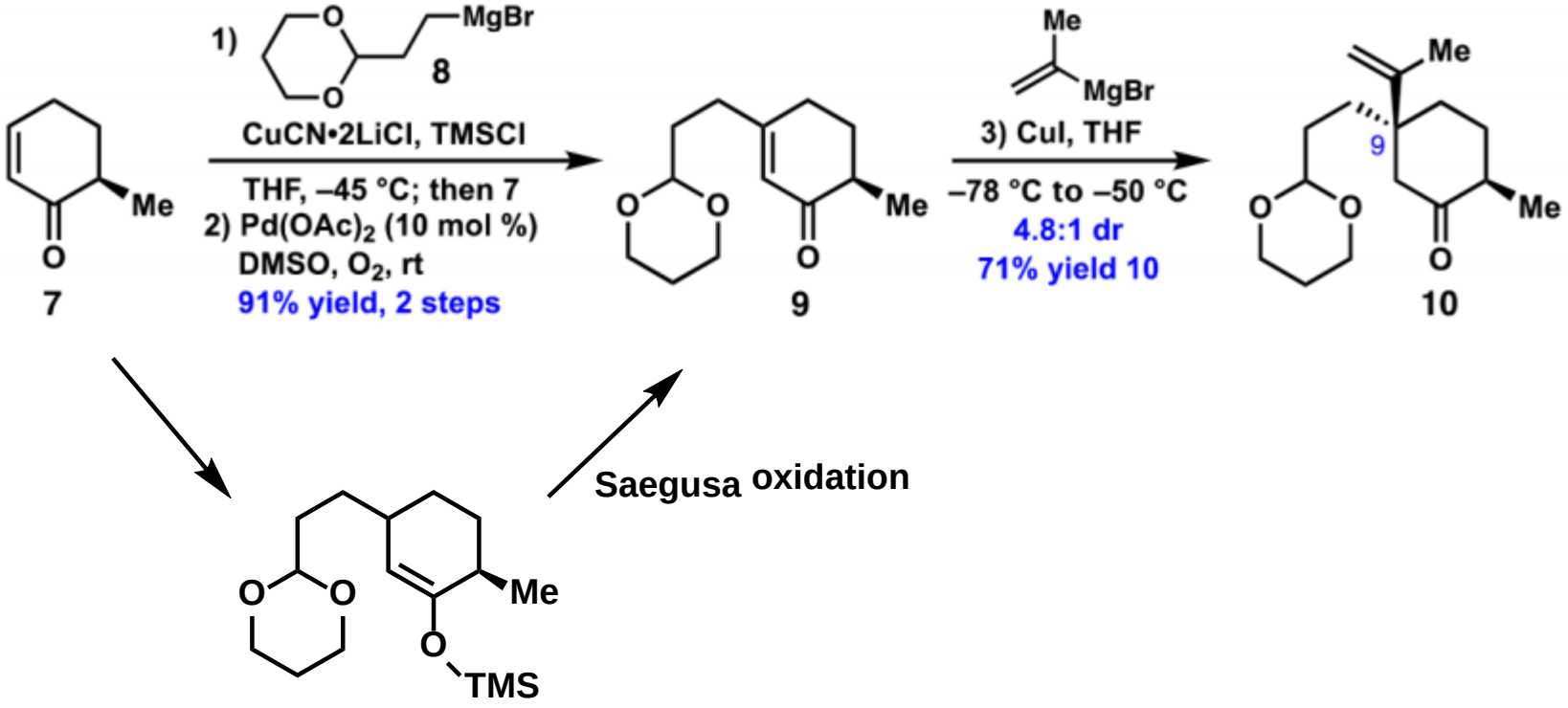
This Work:

- 8-membered ring formed by **ketyl addition**
- Cyclization product has C3 and C15 at **correct** oxidation states

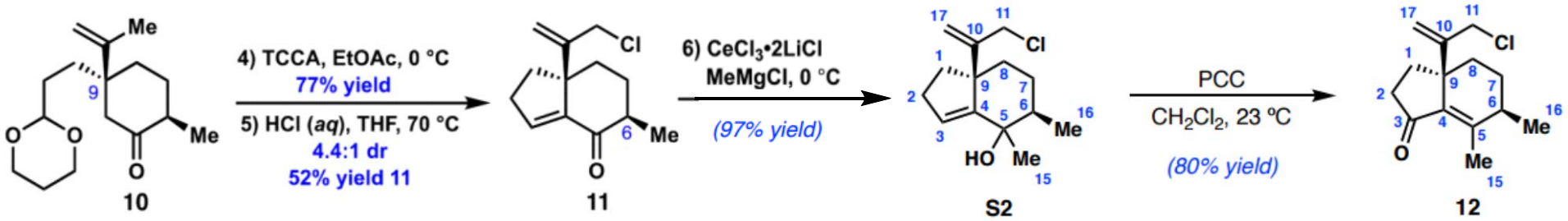


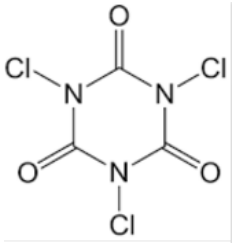


Total Synthesis of (+)-Pleuromutilin

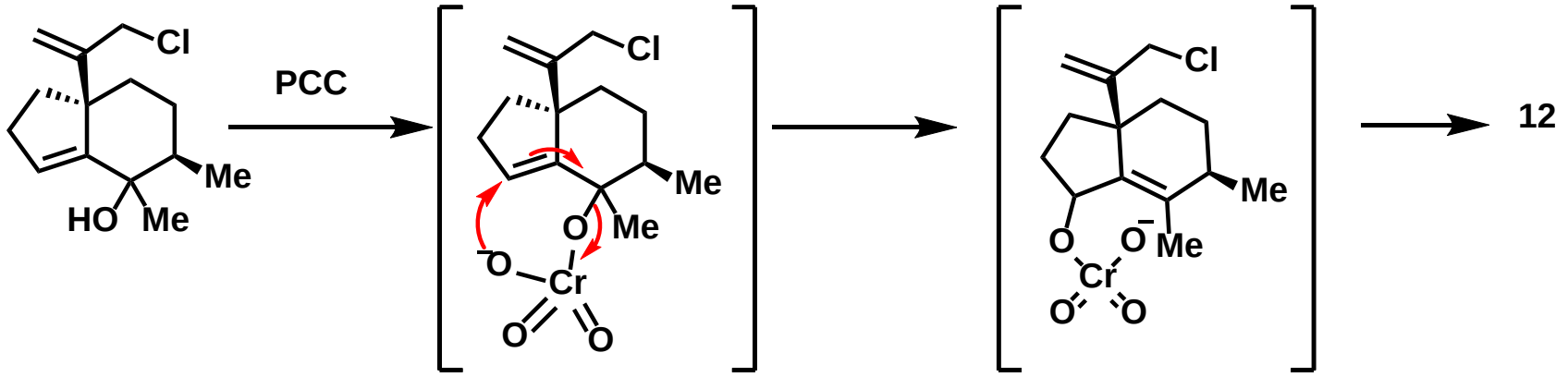


Total Synthesis of (+)-Pleuromutilin

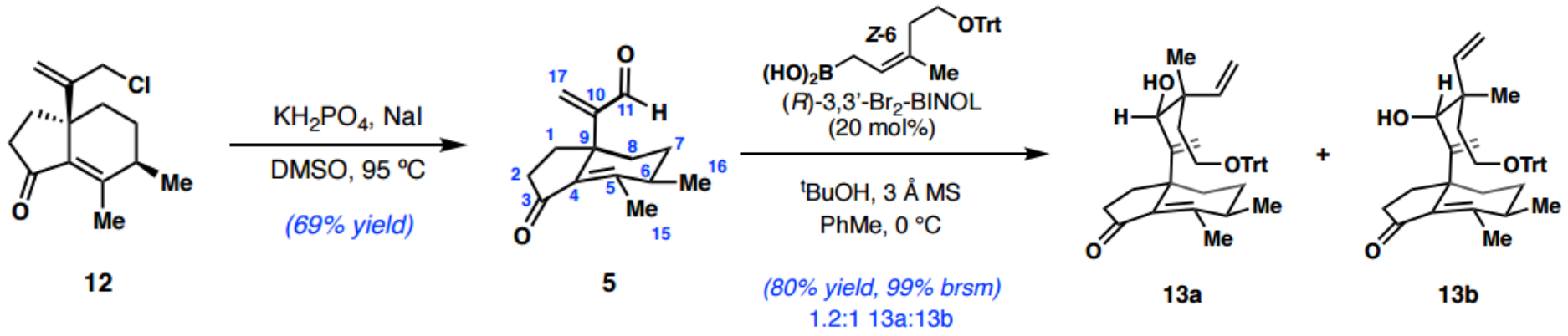




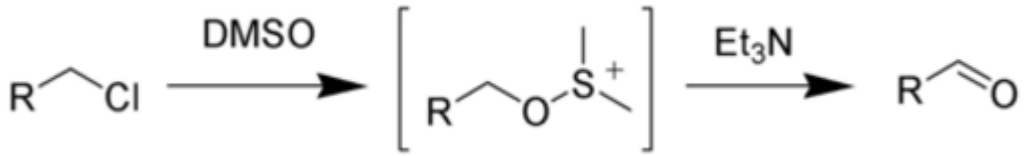
Trichloroisocyanuric acid (TCCA)



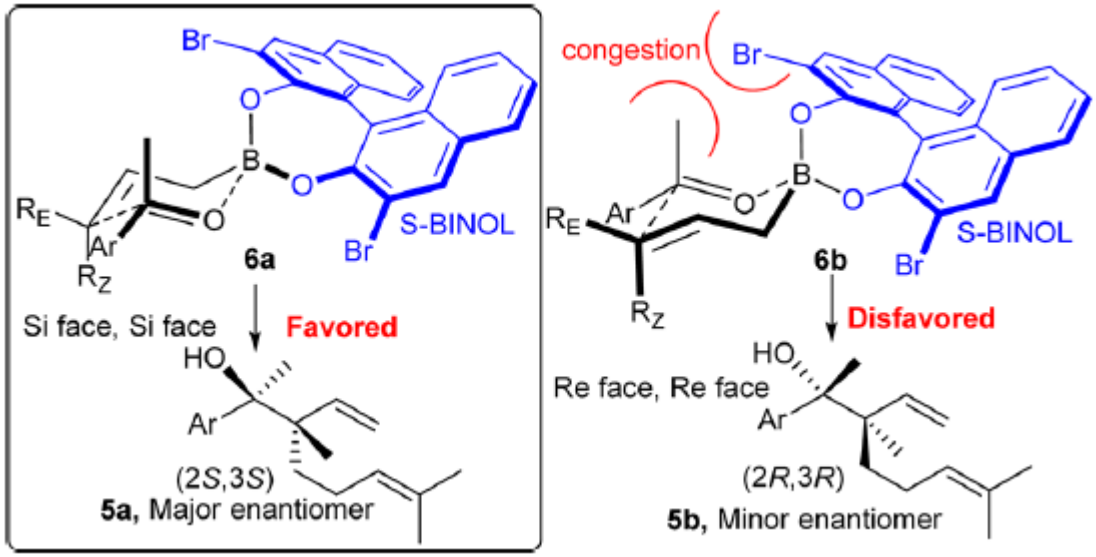
Total Synthesis of (+)-Pleuromutilin



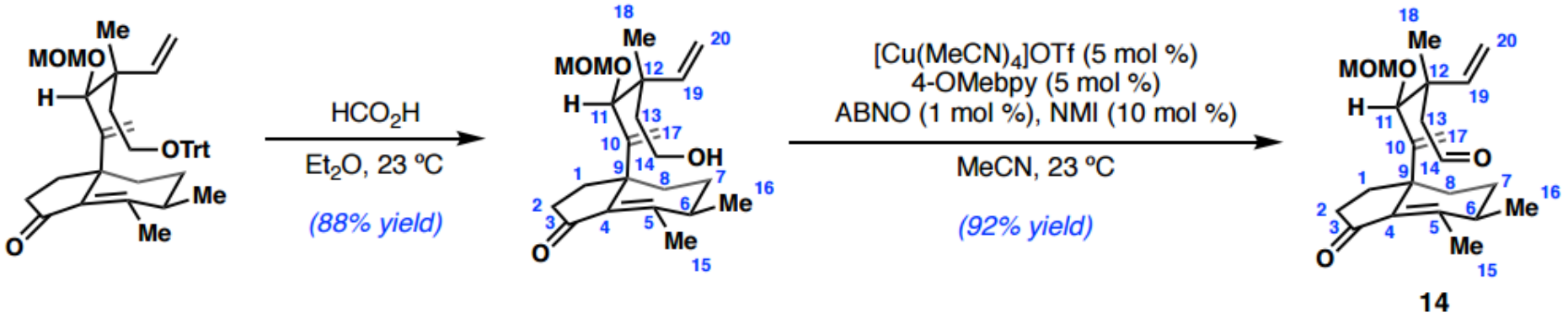
Kornblum oxidation

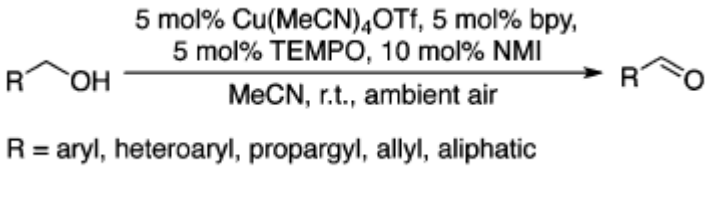


Asymmetric Allylation

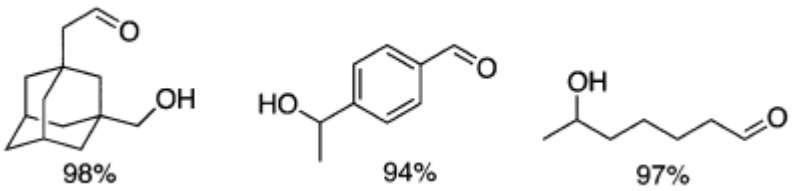


Total Synthesis of (+)-Pleuromutilin

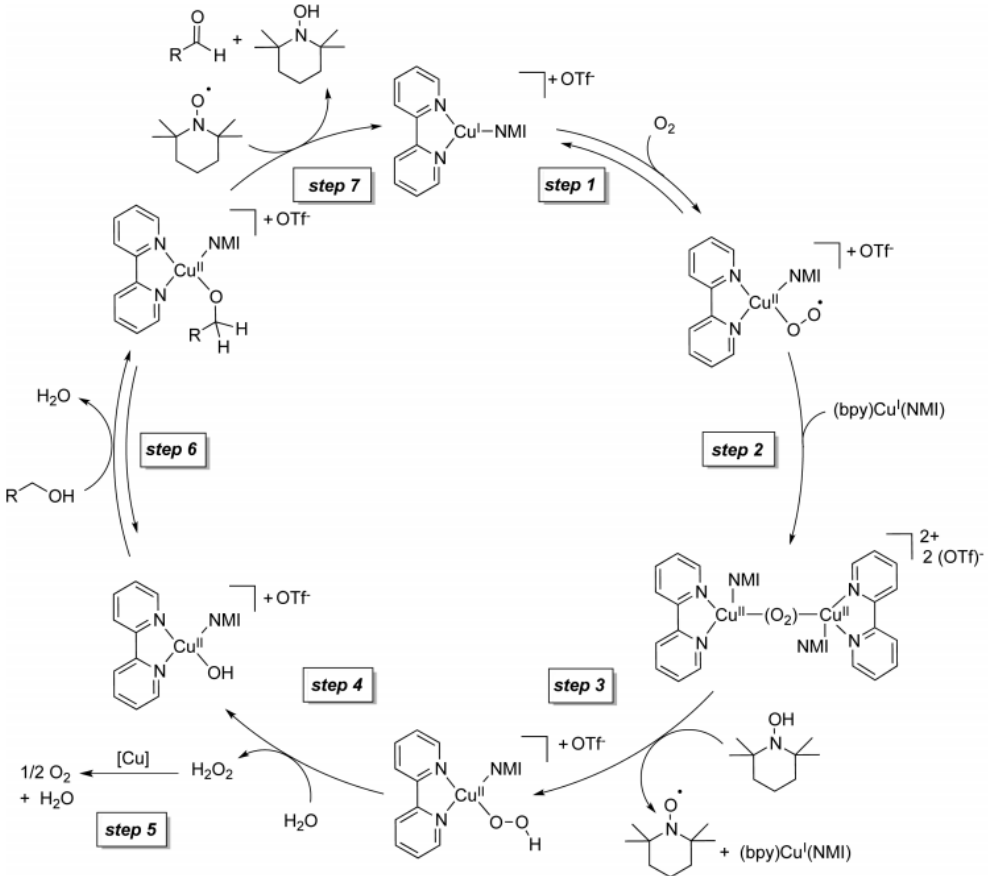




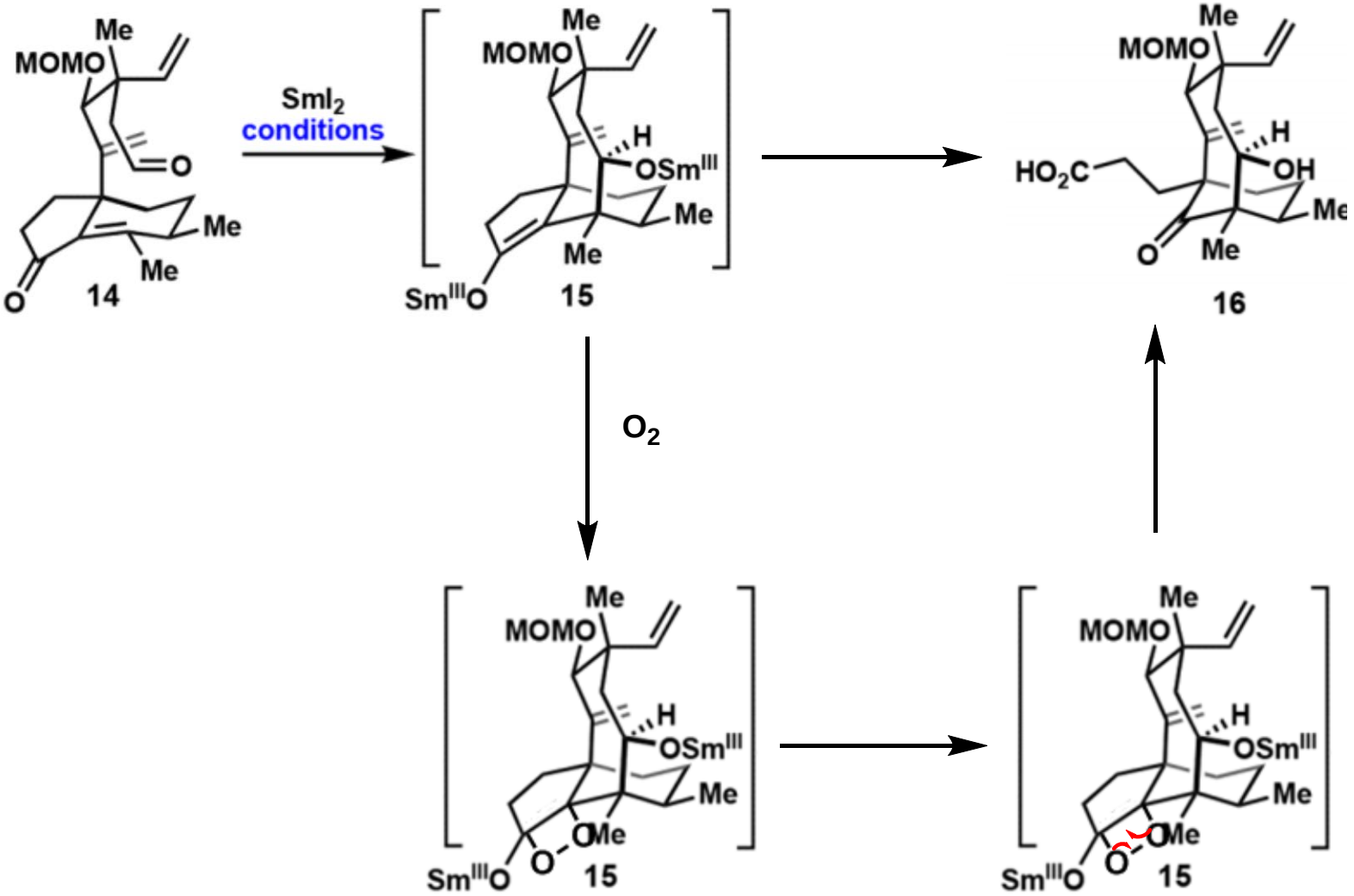
sterically selective alcohol oxidation



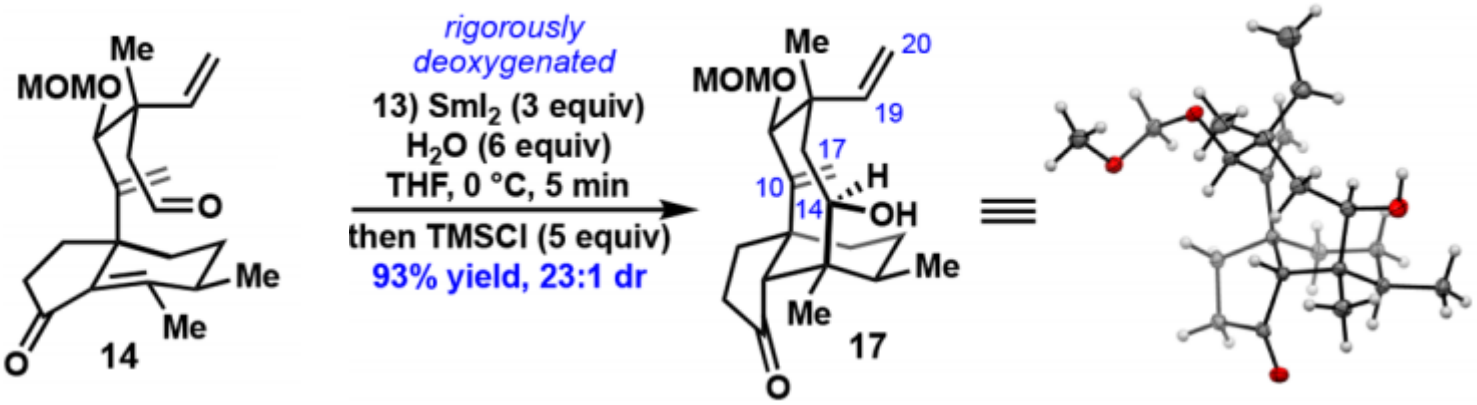
Shannon S. Stahl. *J. Am. Chem. Soc.* **2013**, *135*, 15742−15745



Total Synthesis of (+)-Pleuromutilin

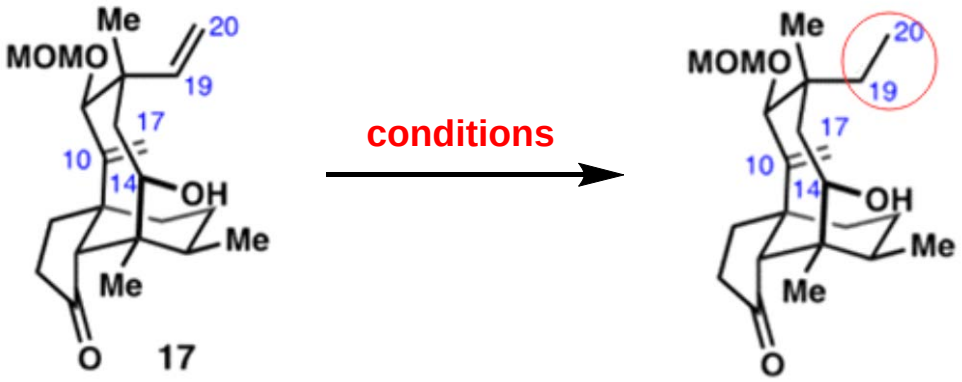


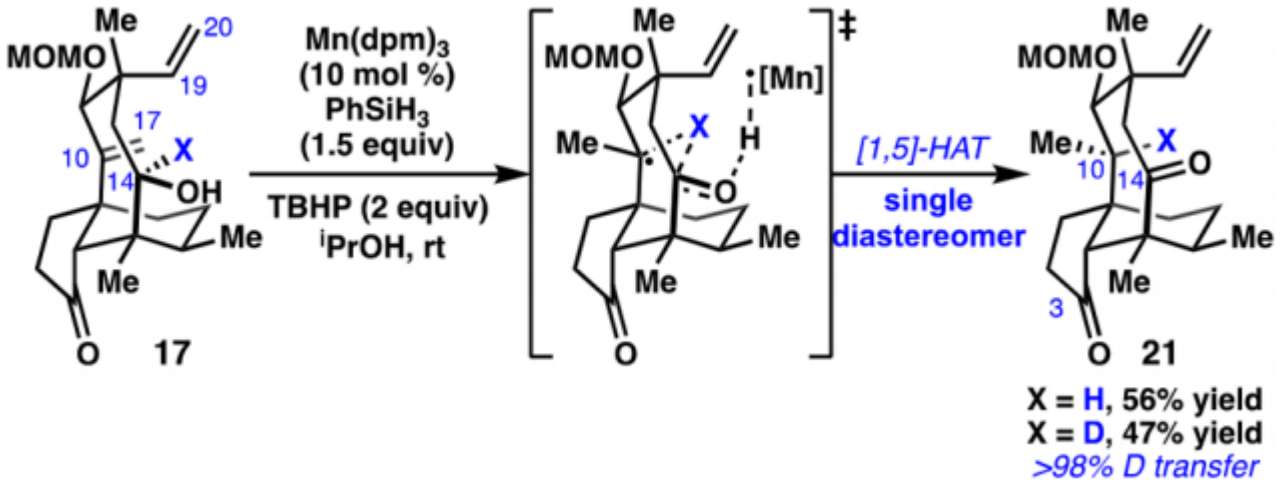
Total Synthesis of (+)-Pleuromutilin

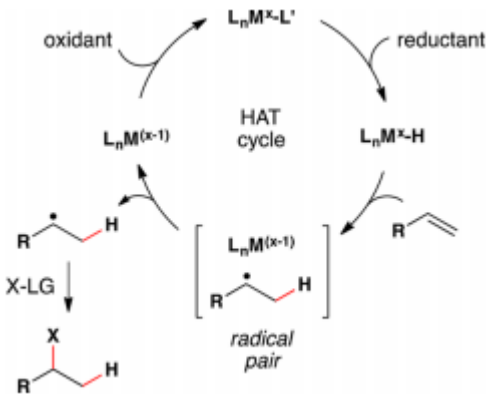


Under rigorously anaerobic conditions followed by quenching first with trimethylsilyl chloride (TMSCl) and then aqueous workup delivered tricycle 17 in 93% yield as a separable 23:1 mixture of diastereomers

Total Synthesis of (+)-Pleuromutilin

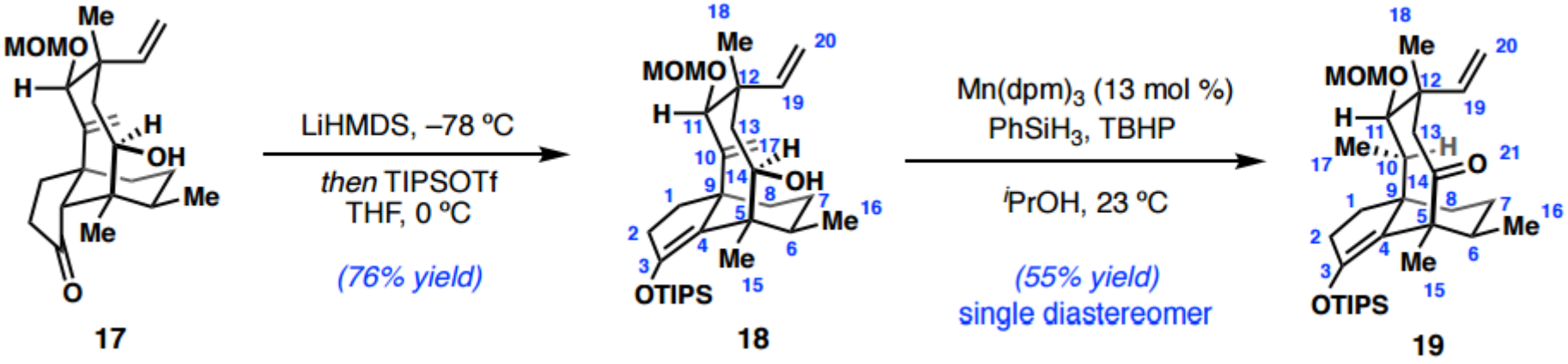


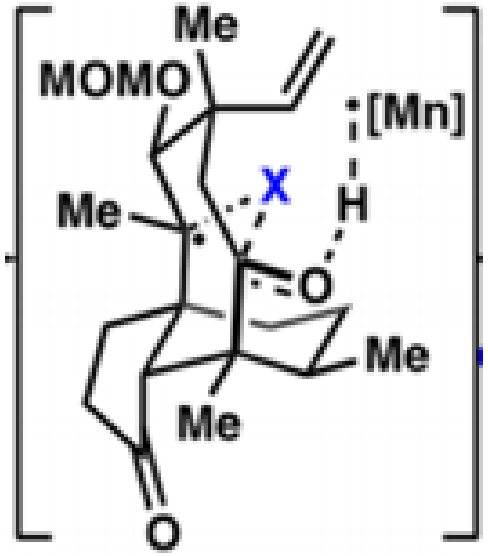


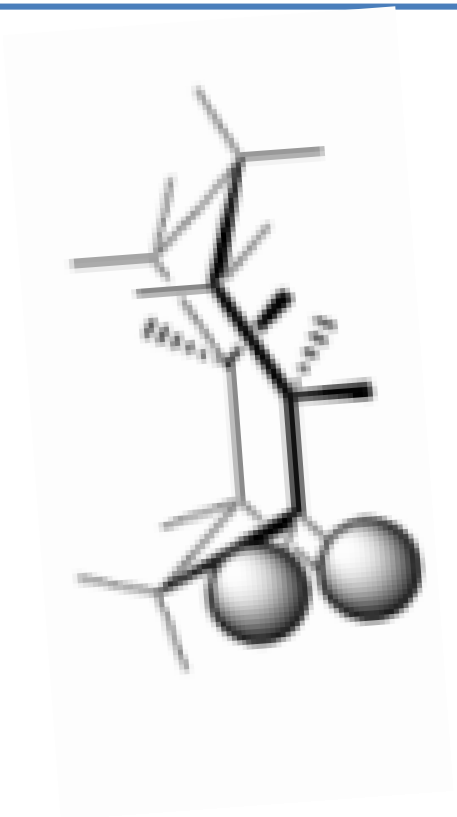


Shenvi, R. A. *Chem. Rev.* **2016**, *116*, 8912.

Total Synthesis of (+)-Pleuromutilin

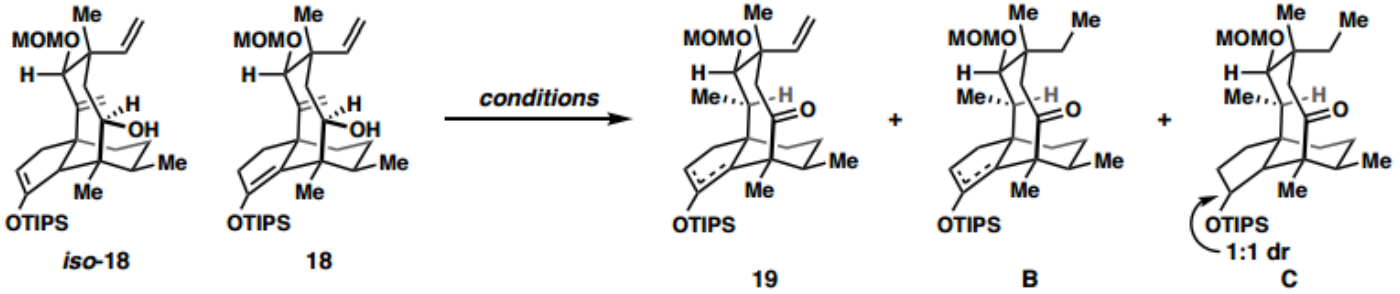






Total Synthesis of (+)-Pleuromutilin

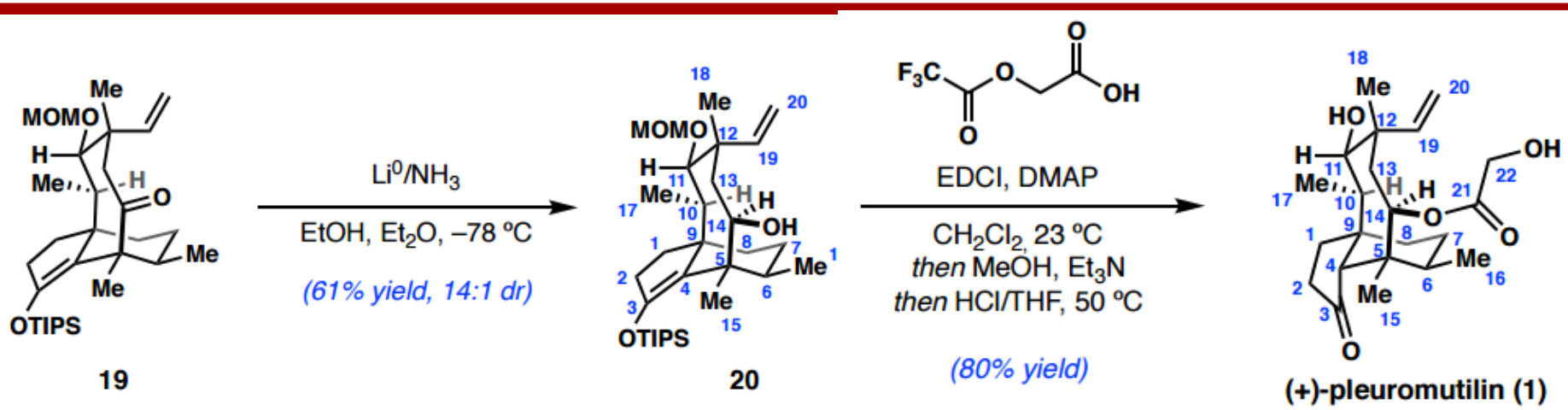
Table S2. Radical 1,5-HAT conditions



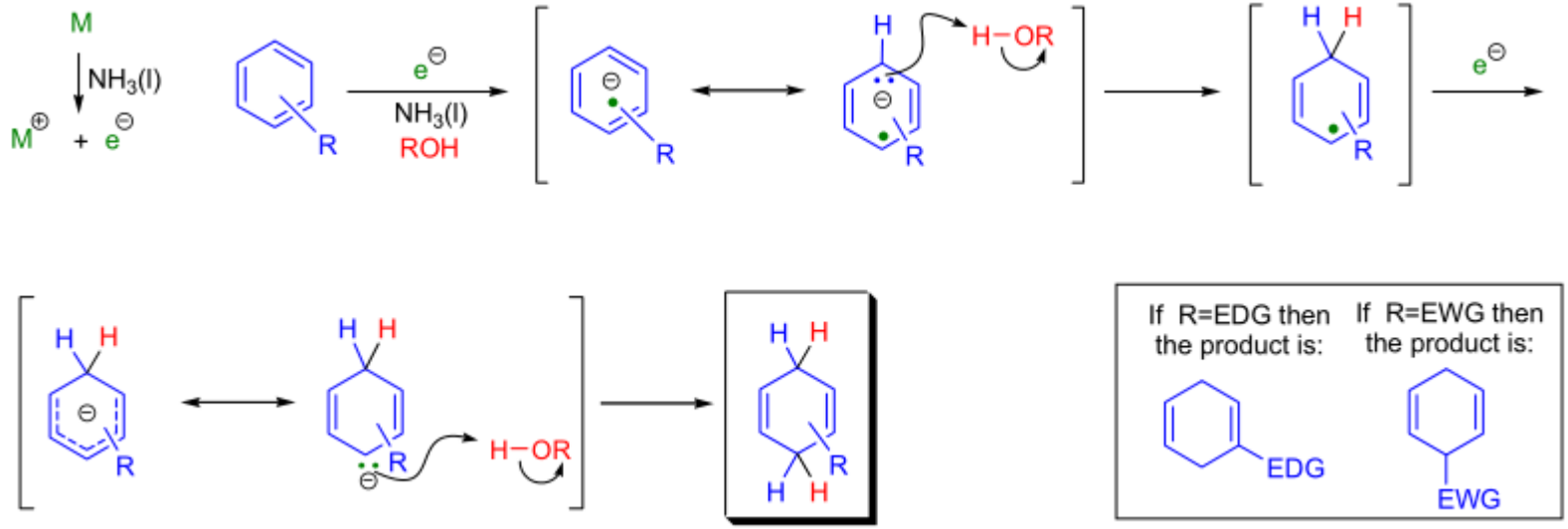
Entry	Substrate	[M]	[H·]	TBHP[a]	solvent	conc.	T	*t*	conv.	Yield (19)	Yield (B)	Yield (C)
1	*Iso*-18	$Mn(dpm)_3$ (10 mol % x 2)	$Ph(O^iPr)SiH_2$ (1 equiv)	Yes	hexanes	0.2 M	23 °C	5 min	80%	36%	22%	22%
2	*Iso*-18	$Mn(dpm)_3$ (10 mol % x 2)	$PhSiH_3$ (1.5 equiv)	Yes	^{i}PrOH	0.2 M	23 °C	1 h	69%	38%	5%	–
3	*Iso*-18	$Mn(dpm)_3$ (10 mol % x 2)	$PhSiH_3$ (1.5 equiv)	Yes	^{i}PrOH	0.04 M	23 °C	1 h	66%	50%	6%	–
4	*Iso*-18	$Mn(dpm)_3$ (10 mol %)	$PhSiH_3$ (1.5 equiv)	Yes	^{i}PrOH	0.04 M	23 °C	1 h	88%	66%	6%	–
5[b]	18	$Mn(dpm)_3$ (10 mol %)	$PhSiH_3$ (1.5 equiv)	Yes	^{i}PrOH	0.04 M	23 °C	1 h	82%	58%	8%	4%
6[b,c]	18	$Mn(dpm)_3$ (10 mol % + 3 mol %)	$PhSiH_3$ (1.5 equiv)	Yes	^{i}PrOH	0.04 M	23 °C	1 h	77%	55%	8%	4%
7	18	$Mn(dpm)_3$ (10 mol % x 2)	$Ph(O^iPr)SiH_2$ (1 equiv)	Yes	hexanes	0.2 M	23 °C	5 min	ND	30%	ND	ND
8	18	$Mn(dpm)_3$ (10 mol % x 2)	$Ph(O^iPr)_2SiH$ (1 equiv)	Yes	hexanes	0.2 M	23 °C	5 min	14%	14%	ND	ND
9	18	$Co(Salen^{tBu,\ tBu})Cl$ (3 mol % x 2)	$PhSiH_3$ (6 mol %)	No	PhH	0.05 M	23 °C	30 min	10%	<5%	–	–
10	18	$Co(Salen^{tBu,\ tBu})Cl$ (3 mol % x 2)	$PhSiH_3$ (6 mol %)	No	PhH	0.05 M	60 °C	30 min	10%	<5%	–	–
11	18	$Co(Salen^{tBu,\ tBu})Cl$ (10 mol %)	$PhSiH_3$ (6 mol %)	No	PhH	0.05 M	23 °C	30 min	ND	10%	–	7%

[a]1.5 equiv. [b]Under rigorously degassed conditions using freshly-distilled anhydrous ^{i}PrOH. [c]Reaction conducted on 0.224 mmol scale.

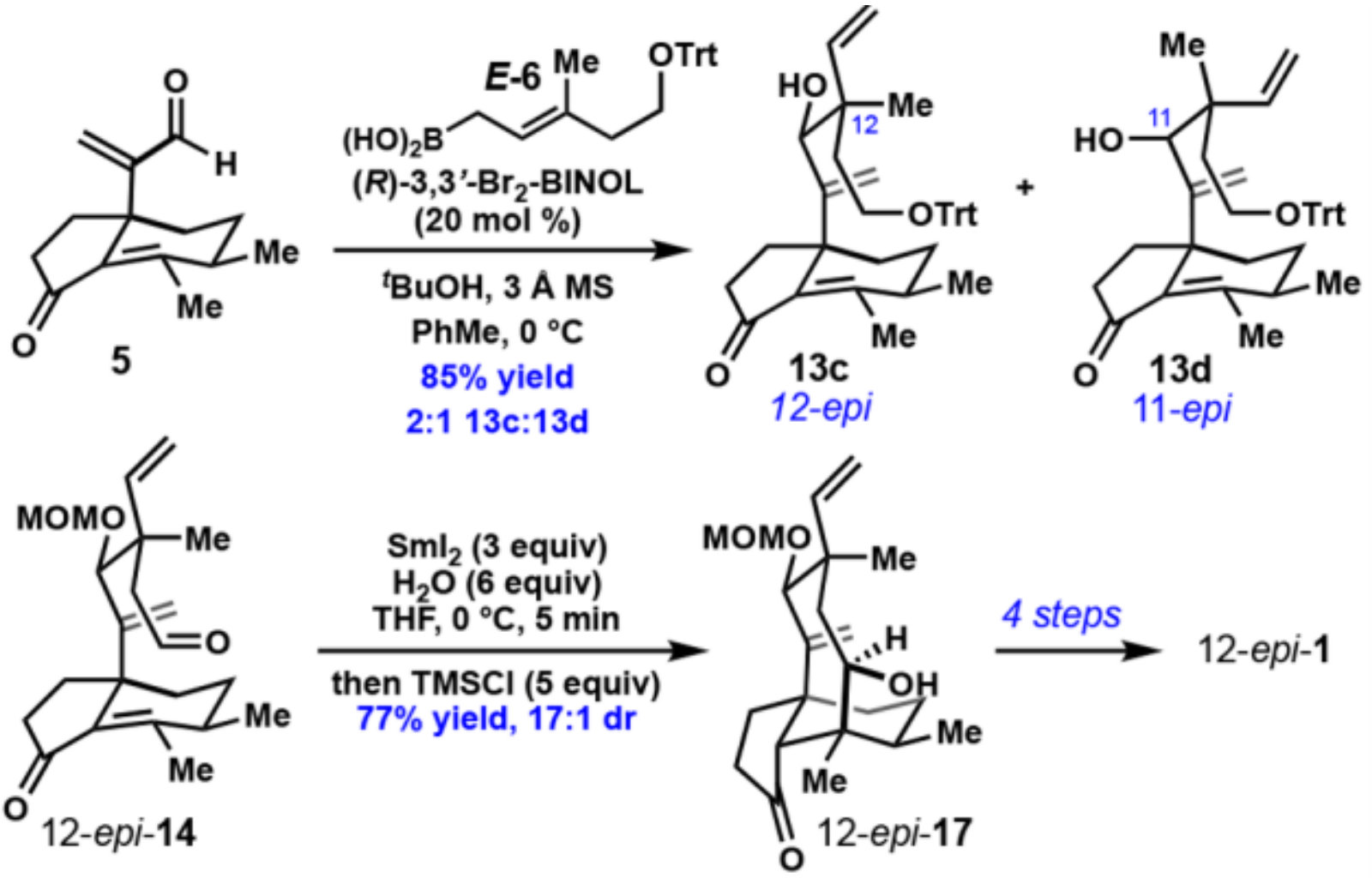
Total Synthesis of (+)-Pleuromutilin



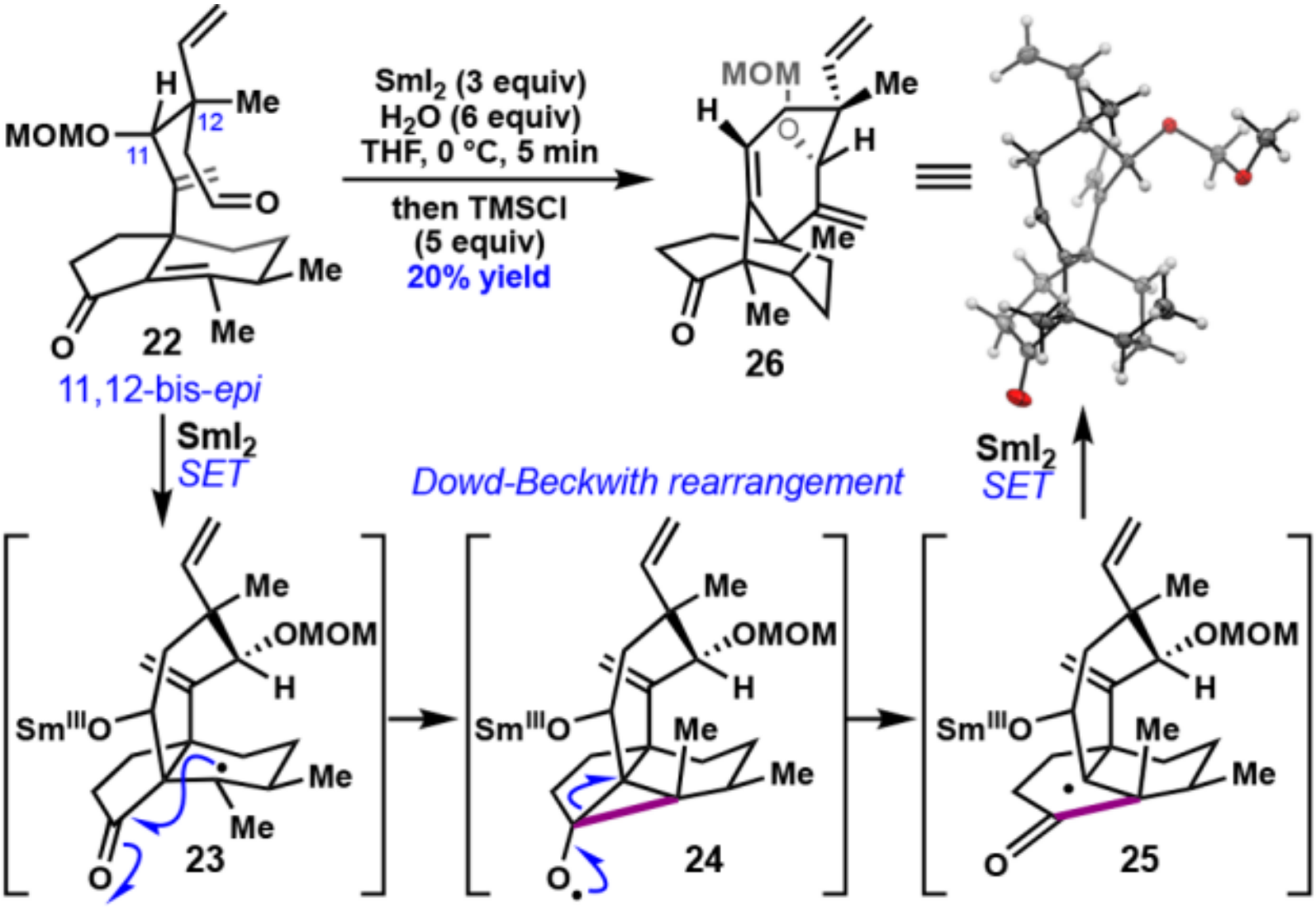
Birch reduction



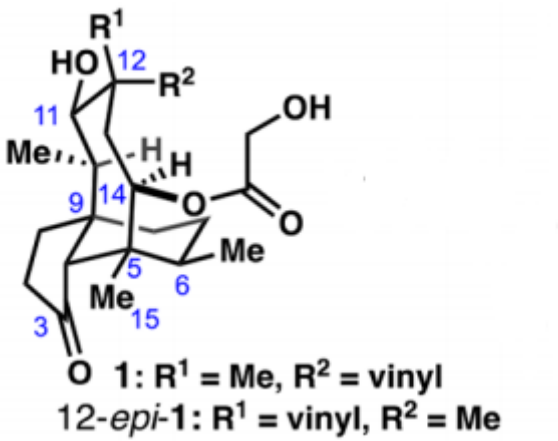
Total Synthesis of 12-*epi*-Pleuromutilin



Synthesis of 11,12-bis-*epi*-Pleuromutilin



Synthesis of 11,12-bis-*epi*-Pleuromutilin

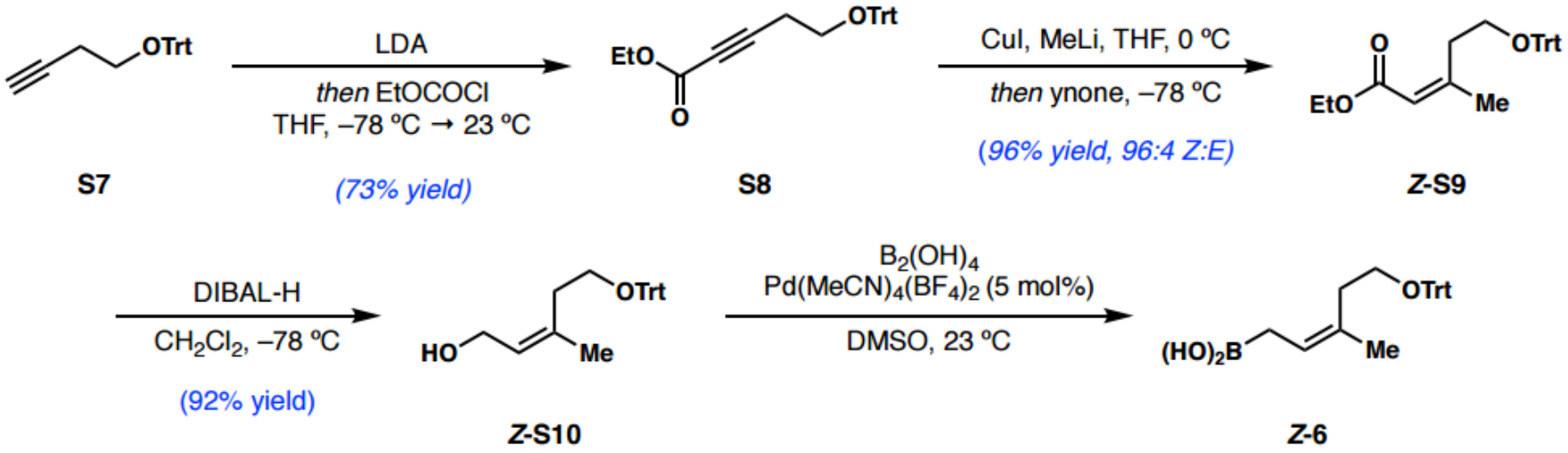


1: R^1 = Me, R^2 = vinyl

12-*epi*-**1**: R^1 = vinyl, R^2 = Me

- Total syntheses of (+)-pleuromutilin and (+)-12-epi-pleuromutilin were each completed in 18 steps (longest linear sequence) from (+)-trans-dihydrocarvone.
- Highly diastereoselective SmI_2-mediated radical cyclization
- Transannular [1,5]-HAT that effects a stereospecific redox relay to set the C10 stereocenter.

Synthesis of allylboronic acid



S7 **S8** ***Z*-S9** ***Z*-S10** ***Z*-6**