A Highly Convergent Total Synthesis of Leustroducsin B

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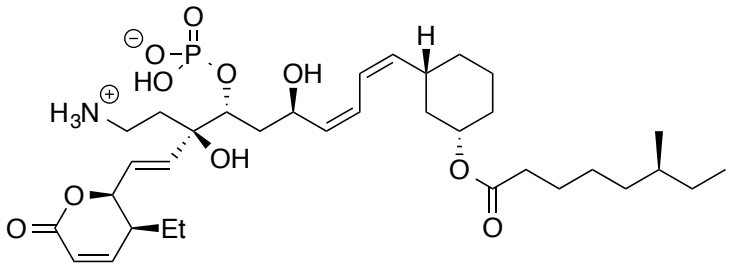
I. Introduction



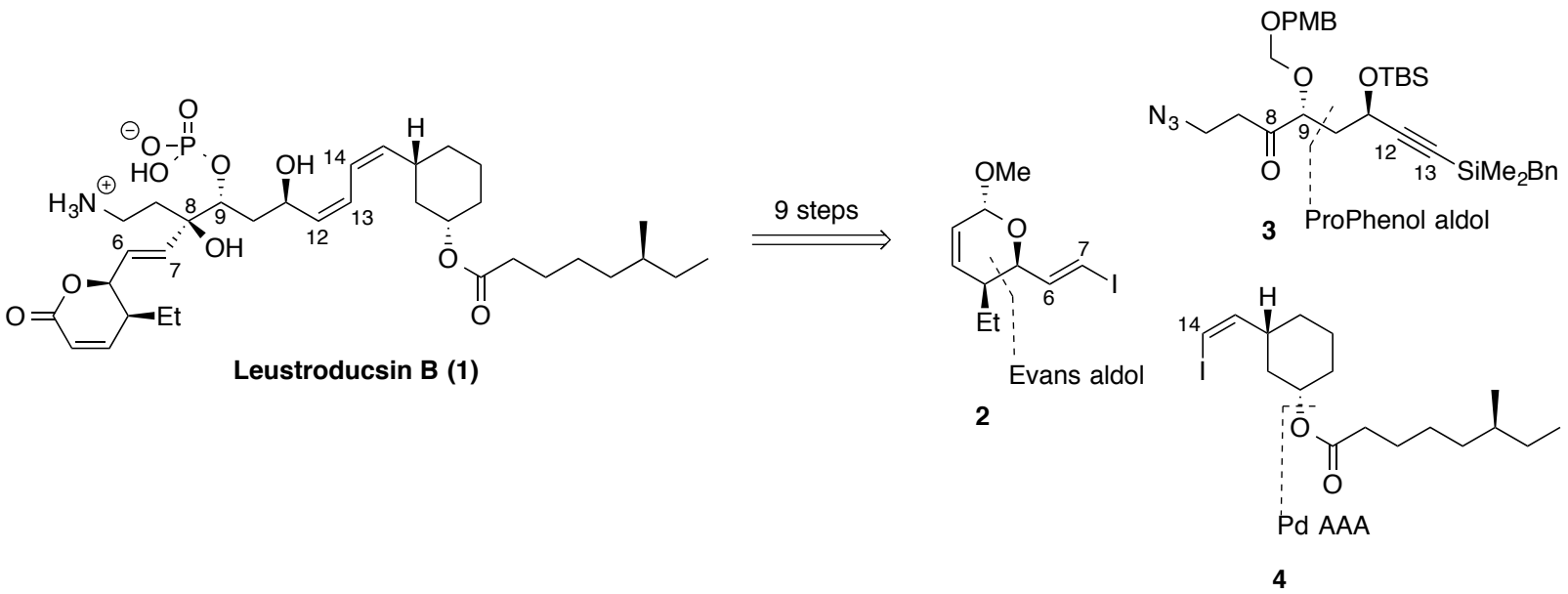
Leustroducsin B (1)

- Leustroducsins A-C isolated from soil bacterium *Streptomyces platensis* SANK 60191 in 1993 by Kohama et al.[2]
- Phoslactomycin family
- Leustroducsin B has shown:
  - *in vitro* induction of cytokine production by KM-102 cells
  - Increase of host *In vivo* resistance to *E. coli* infection
  - Thrombocytosis induction in mice
- 5 previous syntheses of Leustroducsin B, shortest one being 37 linear and 64 total steps[3]

1. Trost, B. M. et al. *J. Am. Chem. Soc.* **2015**, *137*, 11594–11597.
2. a. Kohama, T. et al. *J. Antibiot.* **1993**, *46*, 1503−1511. b. Kohama, T. et al. *J. Antibiot.* **1993**, *46*, 1512−1519.
3. a. Shimada, K. et al. *J. Am. Chem. Soc*. **2003**, *125*, 4048−4049. b. Miyashita, K. et al. *Tetrahedron Lett*. **2007**, *48,* 3829−3833. c. Miyashita, K. et al. *J. Org. Chem*. **2008**, *73*, 5360−5370. d. Mise, J. et al. *Synlett* **2008**, *2008*, 2617−2620. e. Druais, V. et al. *Tetrahedron* **2010**, *66*, 6358−6375. f. Grezler, S. N. et al. *Org. Lett*. **2011**, *13,* 3206−3209. g. Matsuhashi, H. et al. *Tetrahedron* **2002**, *58*, 5619−5626.

Retrosynthetic Analysis of Leustroducsin B

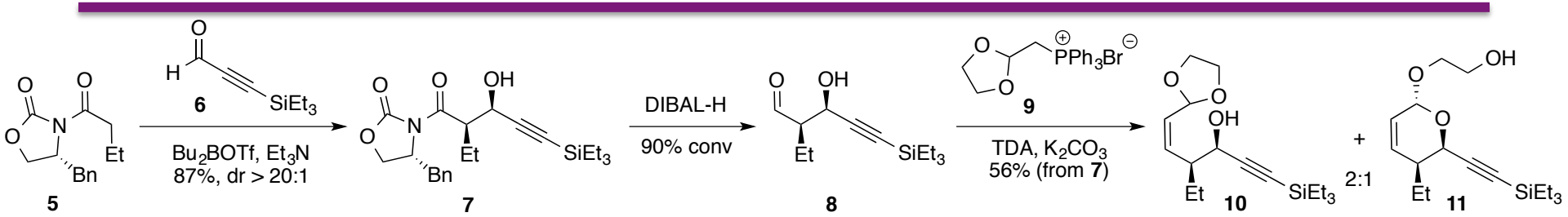
II. Retrosynthetic Analysis



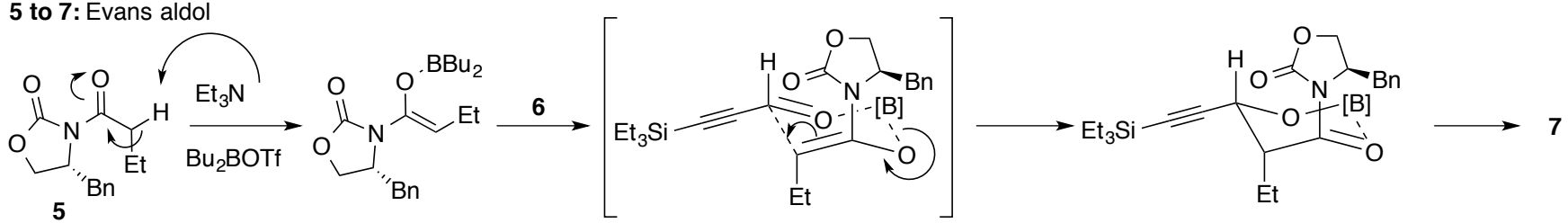
- C_7–C_8: α-alkoxy-directed diastereoselective vinyl zinc addition between **2** and **3**
- C_{13}–C_{14}: modified Hiyama cross-coupling to introduce **4**
- Eastern fragment **2**: Evans aldol
- Central fragment **3**: zinc-ProPhenol-catalyzed aldol reaction
- Western fragment **4**: Pd-catalyzed asymmetric allylic alkylation

IV. Forward Synthesis

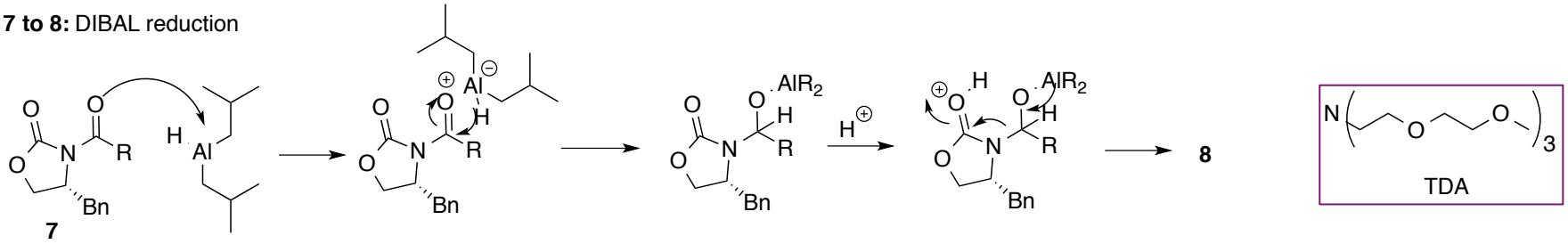
Synthesis of Eastern Fragment 2



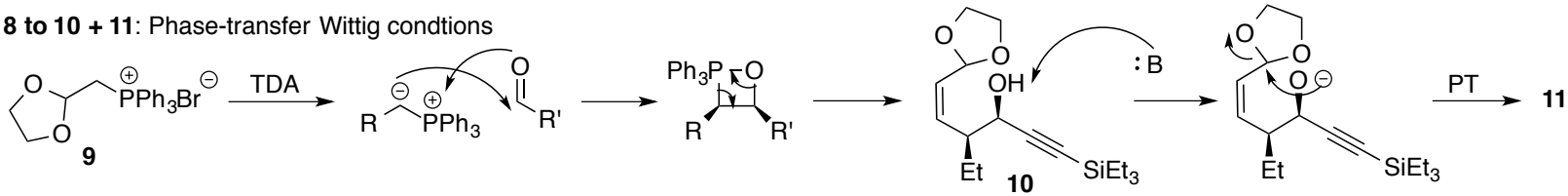
5 to 7: Evans aldol



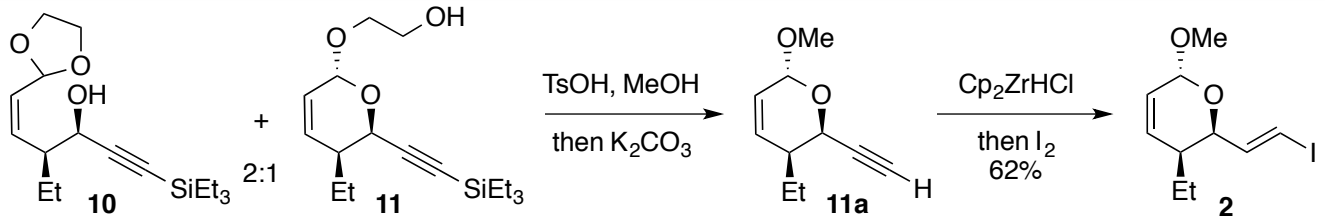
7 to 8: DIBAL reduction



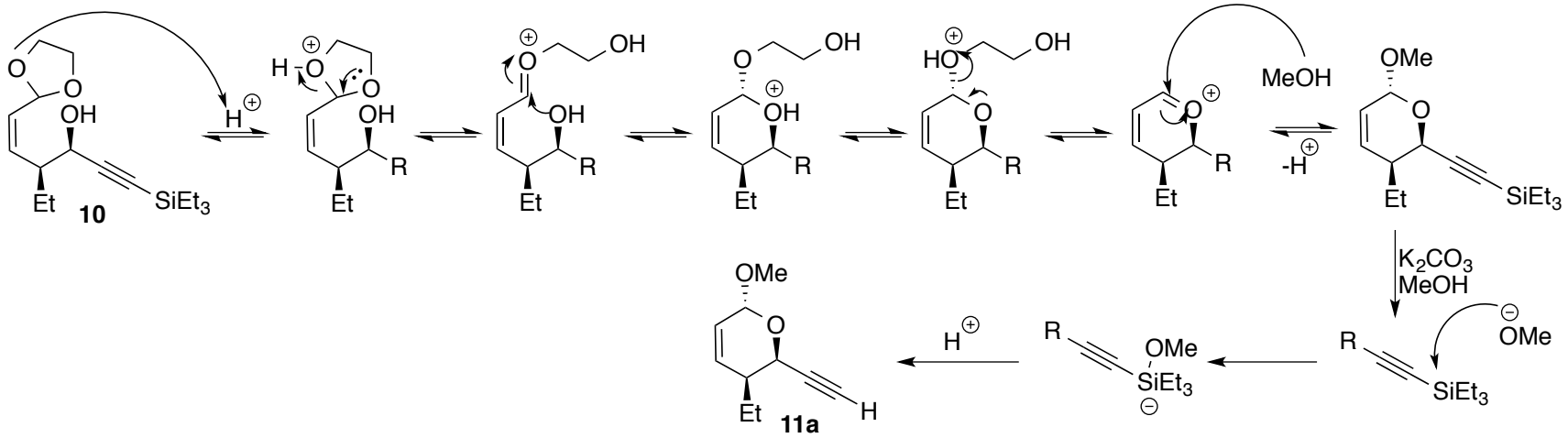
8 to 10 + 11: Phase-transfer Wittig condtions



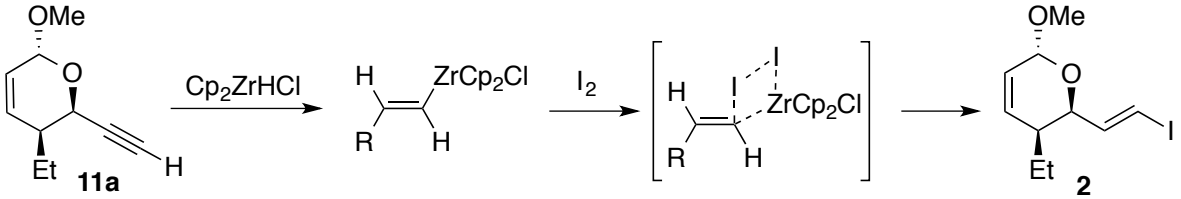
Synthesis of Eastern Fragment 2



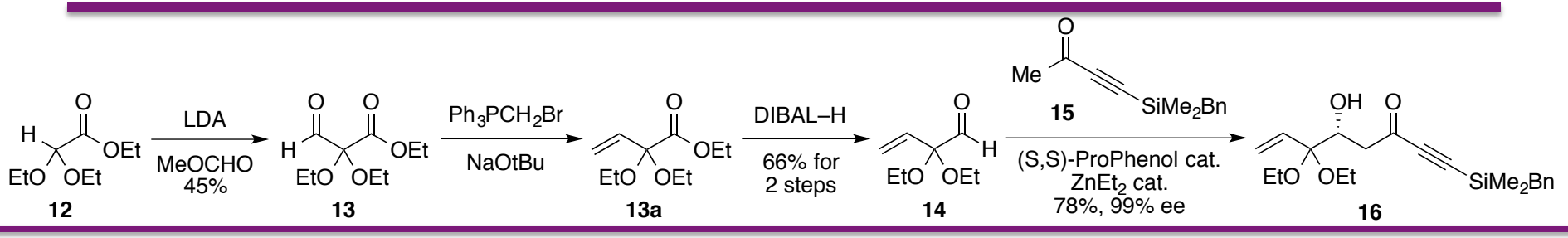
10+11 to 11a: Ketalization



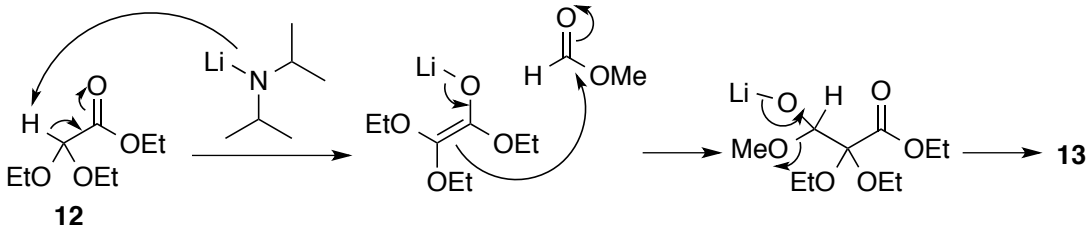
11a to 2: Hydrozirconation/iodination



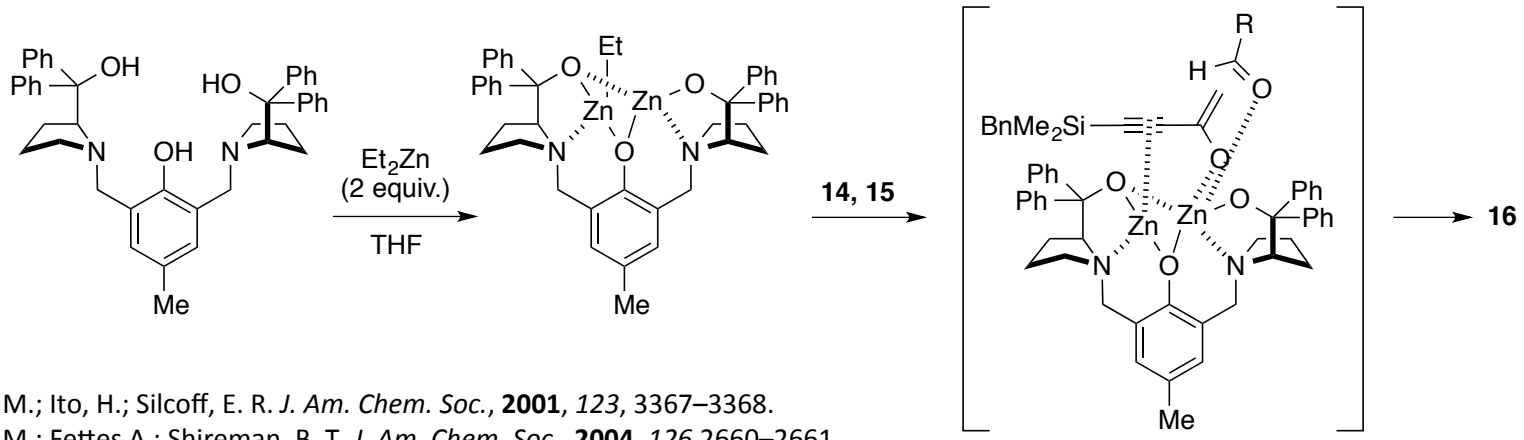
Synthesis of Central Fragment 3



12 to 13: Aldol addition

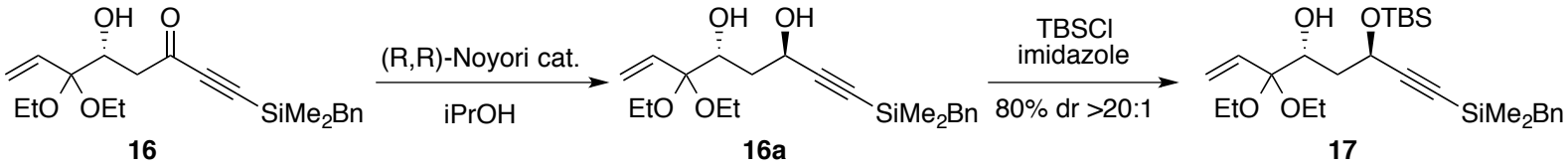


14 to 16: Zinc--ProPhenol-catalyzed aldol reaction

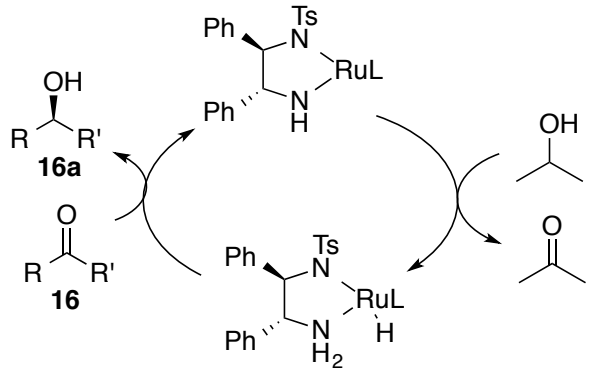


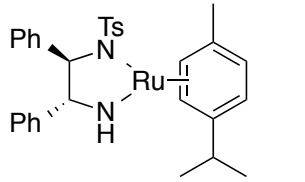
Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.*, **2001**, *123*, 3367–3368.
Trost, B. M.; Fettes A.; Shireman, B. T. *J. Am. Chem. Soc.*, **2004**, *126*,2660–2661.

Synthesis of Central Fragment 3

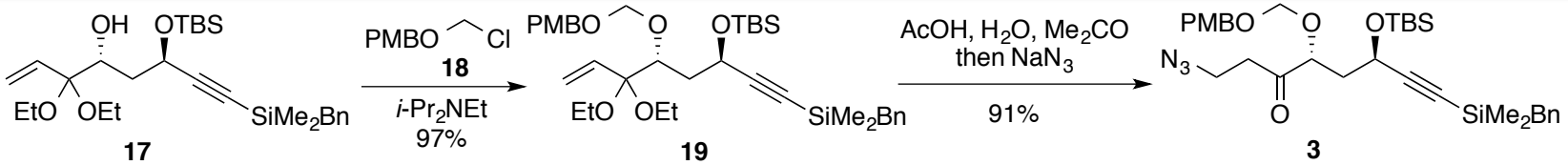


16 to 16a: Noyori asymmetric transfer hydrogenation

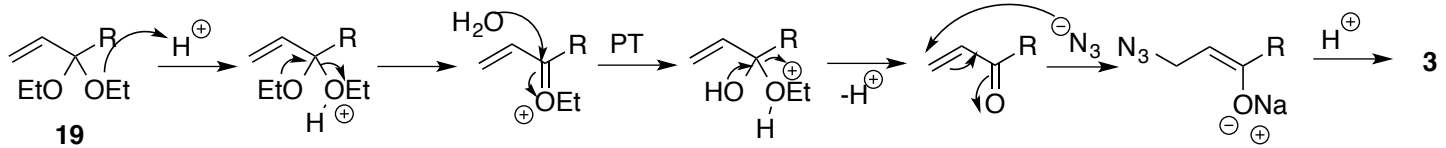




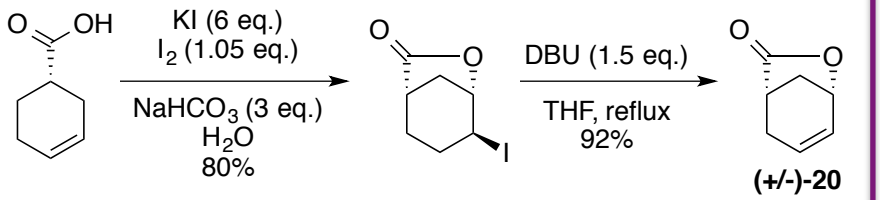
(*R,R*)-TsDPEN-Ru(*p*-cymene)

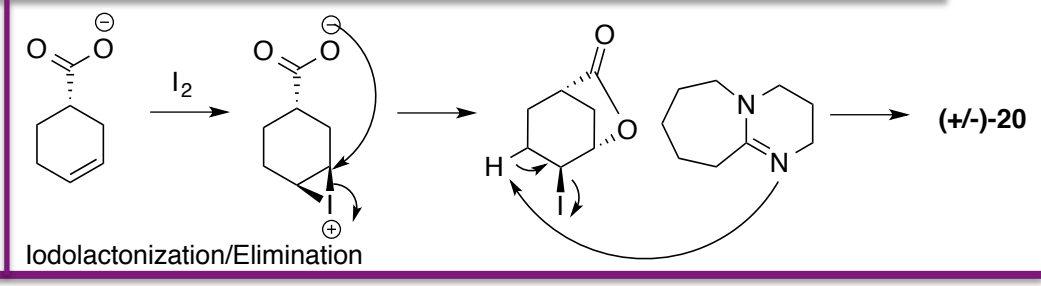


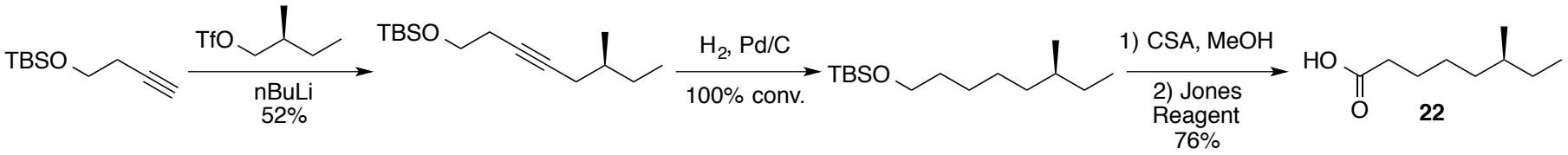
19 to 3

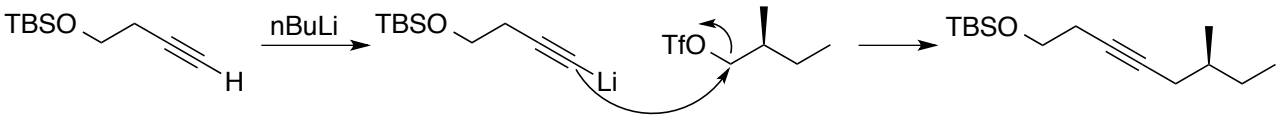


Synthesis of Western Fragment 4: Starting Materials

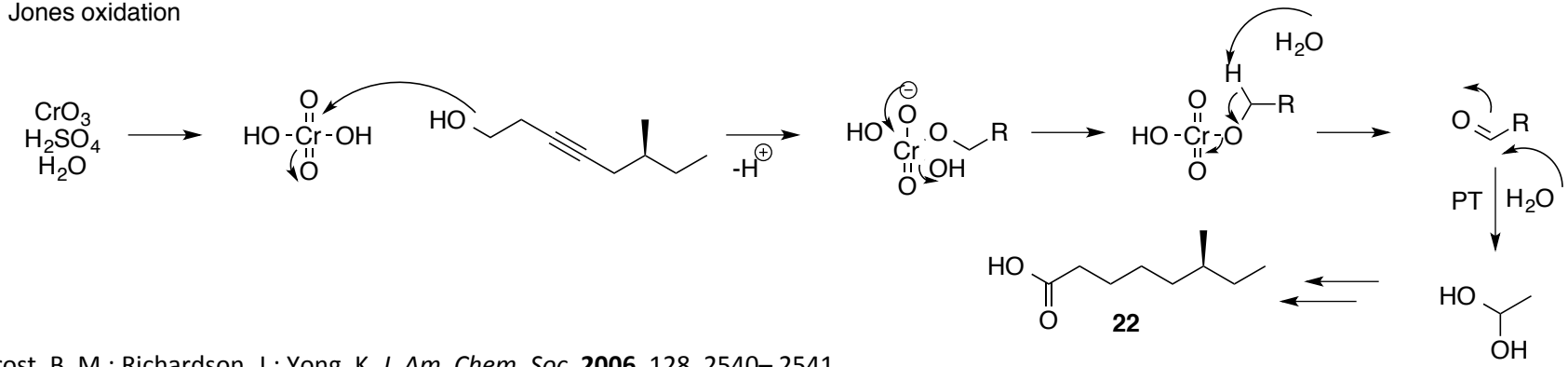






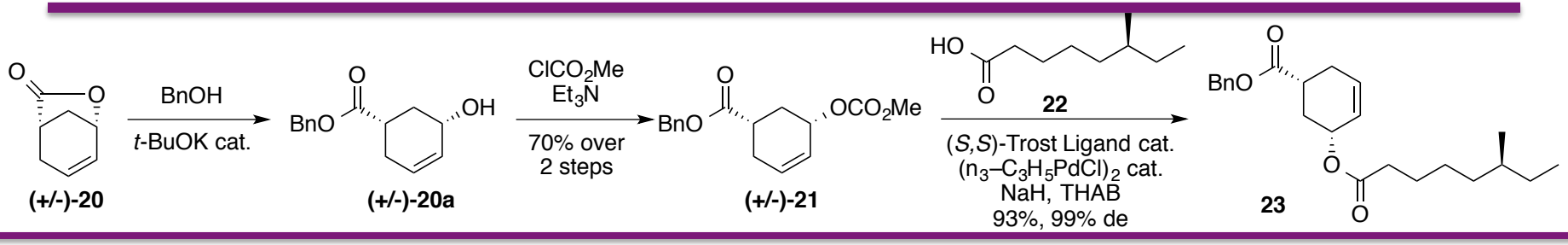


Jones oxidation

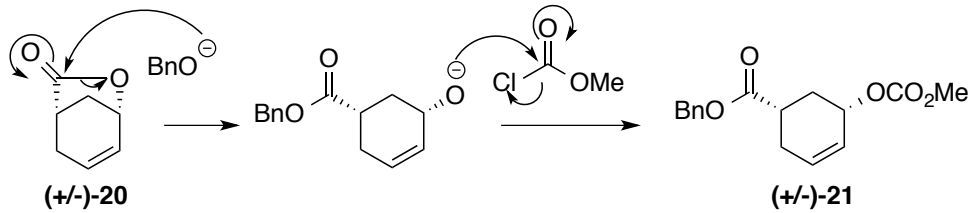


Trost, B. M.; Richardson, J.; Yong, K. *J. Am. Chem. Soc.* **2006**, 128, 2540– 2541.
Marshall, J. A.; Xie, S. *J. Org. Chem.* **1995**, *60*, 7230-7237.

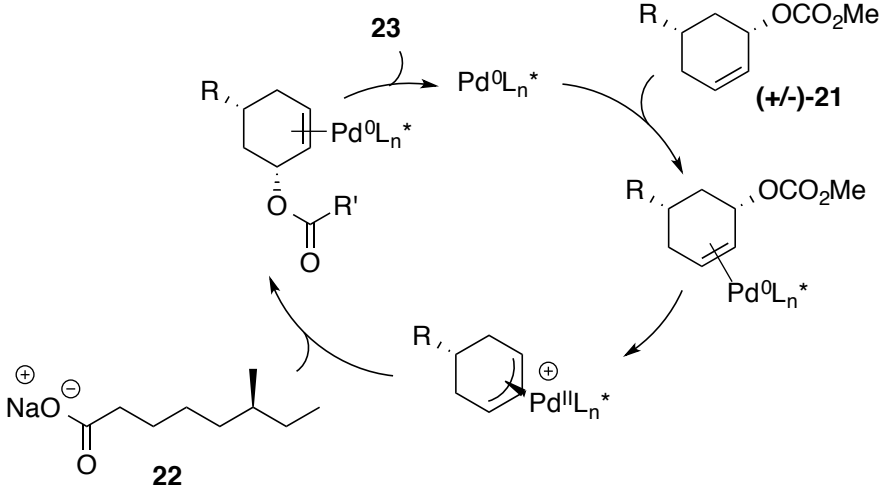
Synthesis of Western Fragment 4

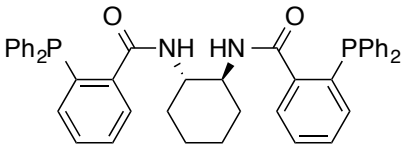


20 to 21

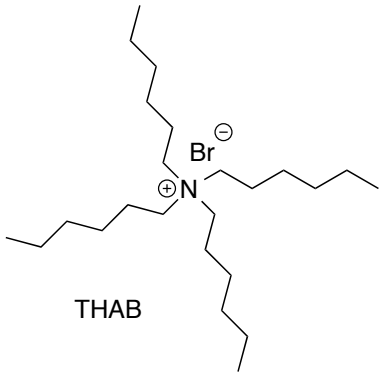


21 to 23: Allylic asymmetric alkylation

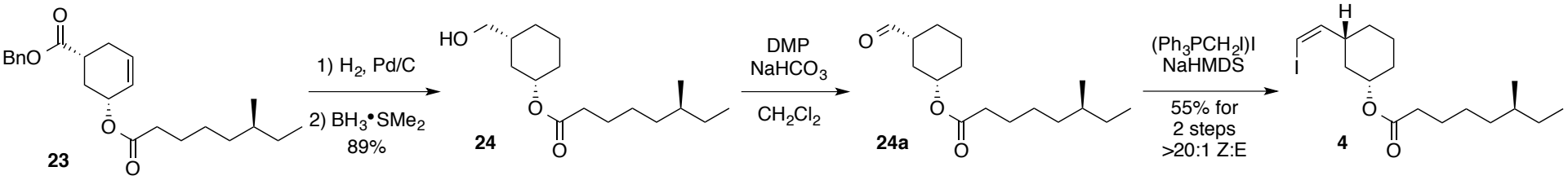




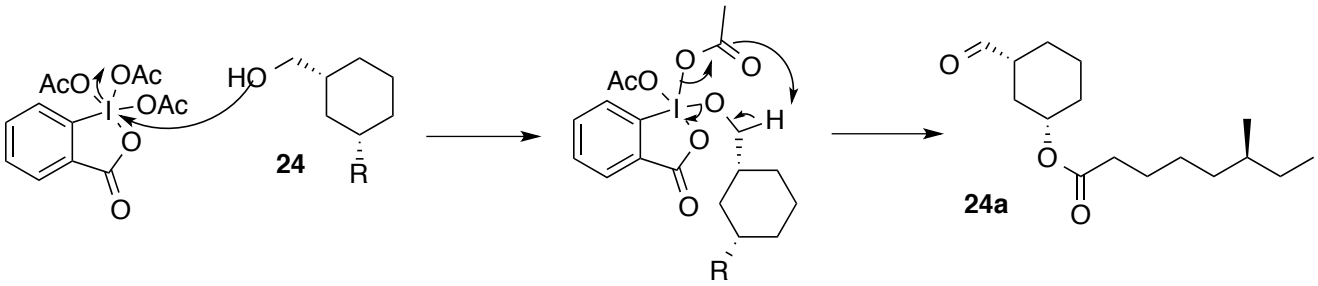
(*S,S*)-Trost ligand



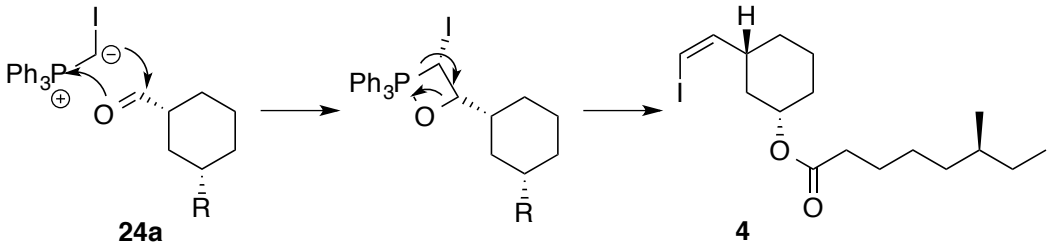
Synthesis of Western Fragment 4



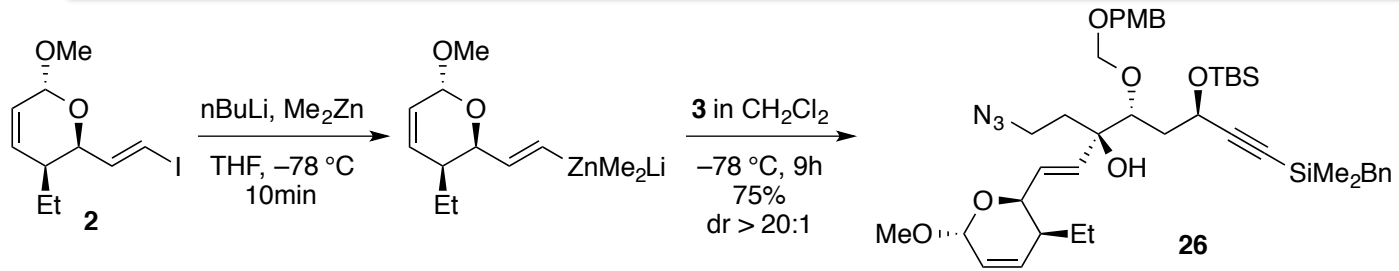
24 to 24a: Dess Martin oxidation

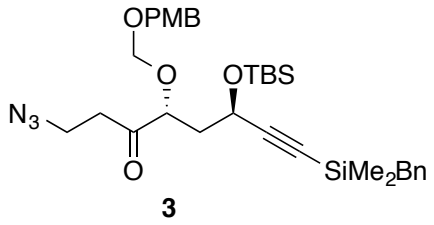


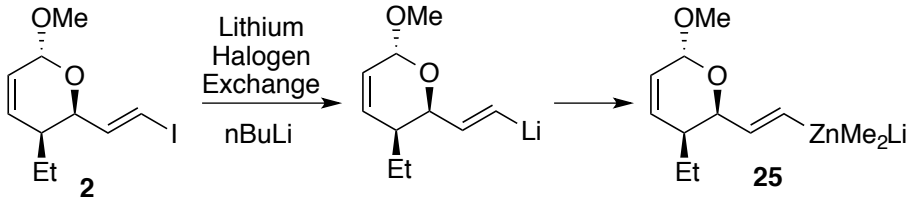
24a to 4: Stork-Zhao olefination

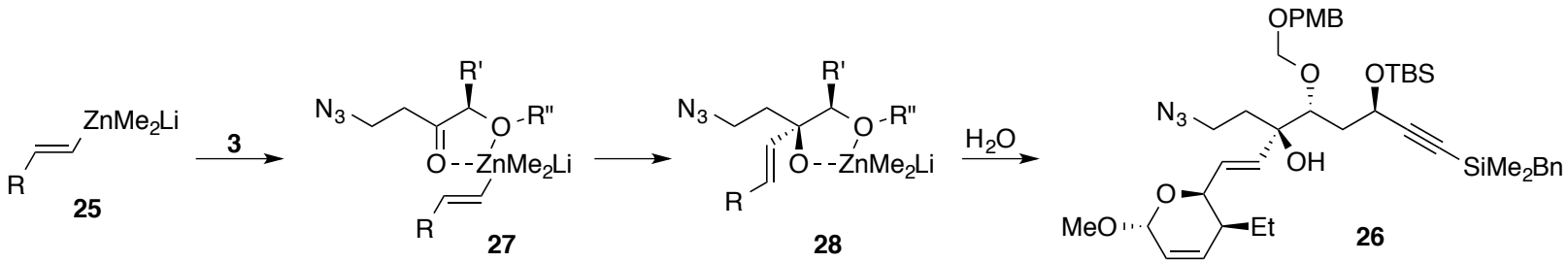


Chelation Controlled Addition of 2 to 3

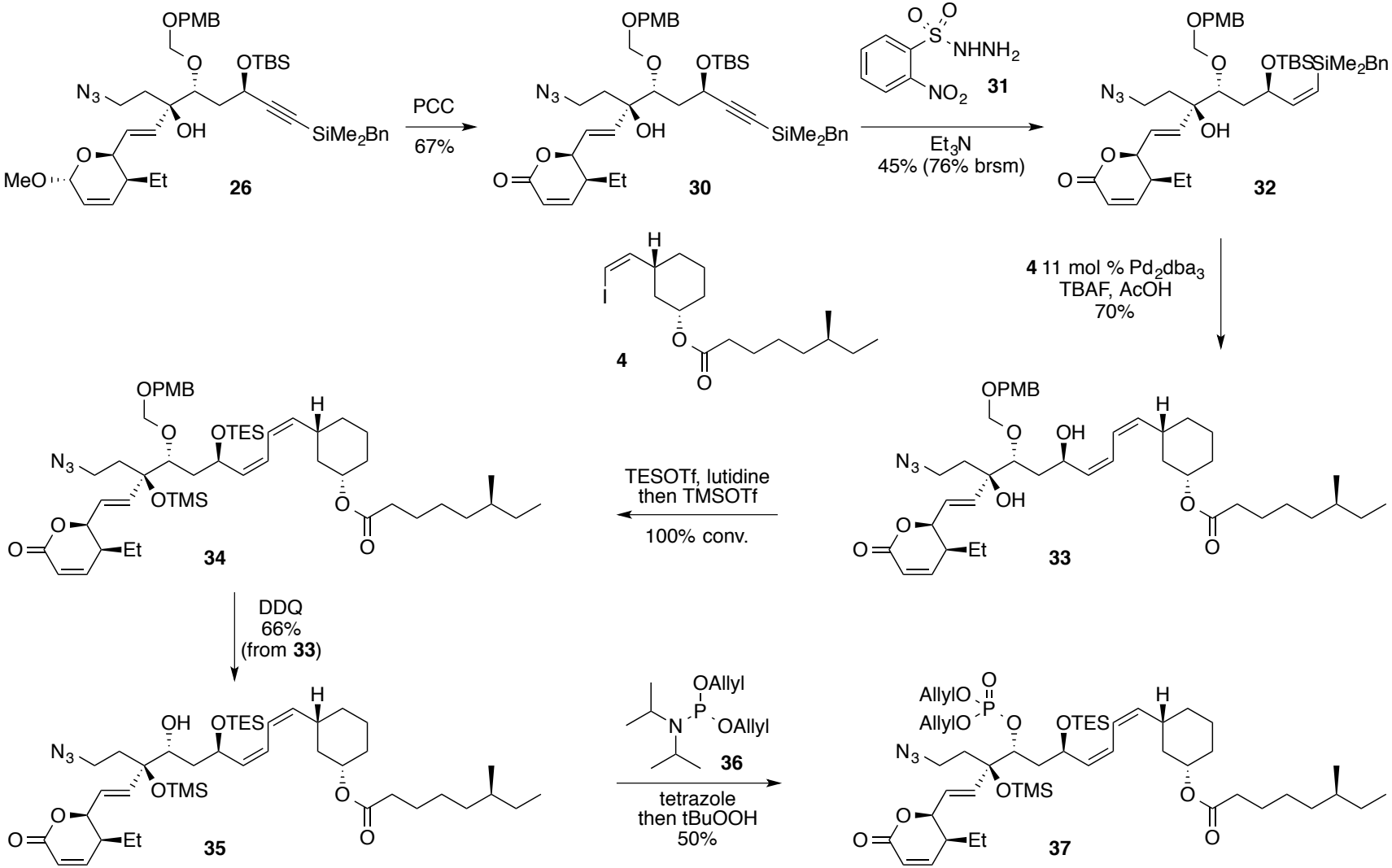






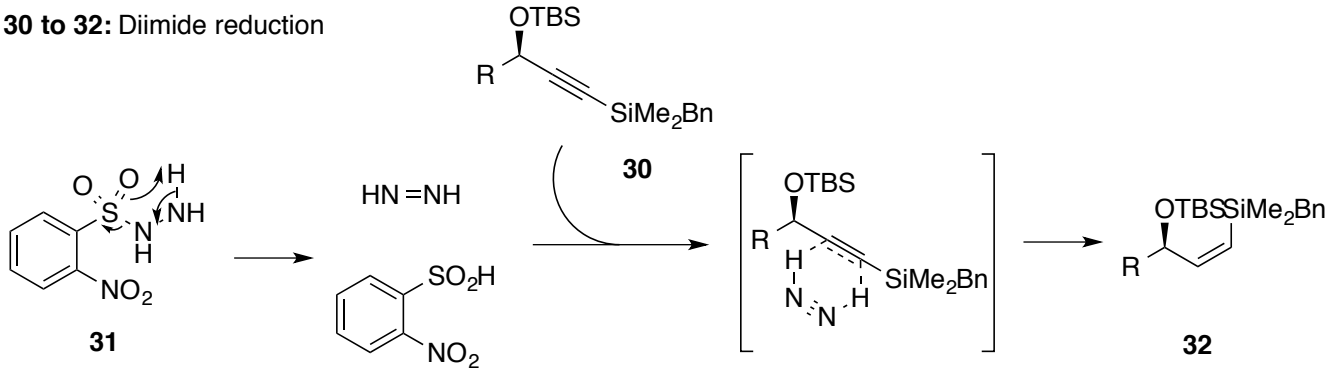


Completion of the Synthesis of Leustroducsin B

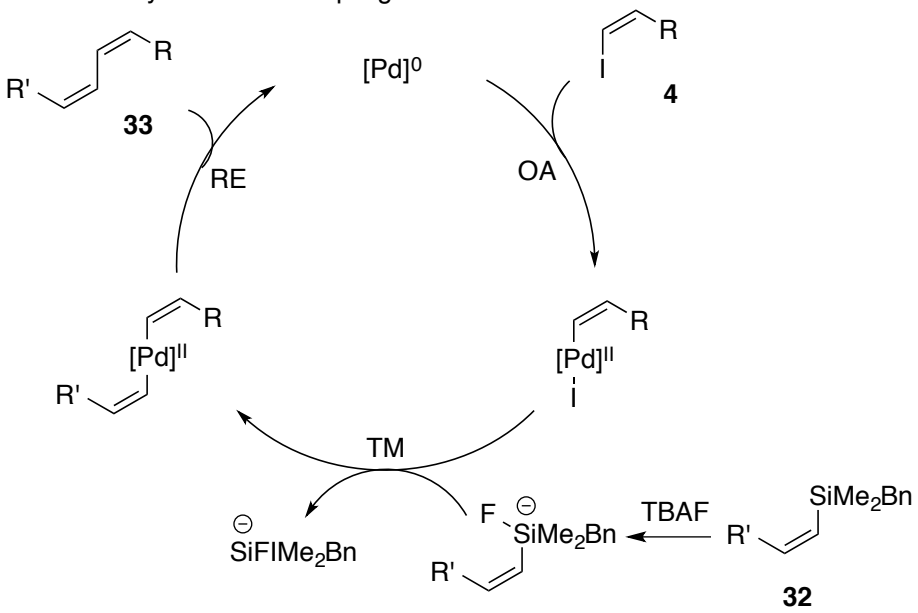


Completion of the Synthesis of Leustroducsin B

30 to 32: Diimide reduction

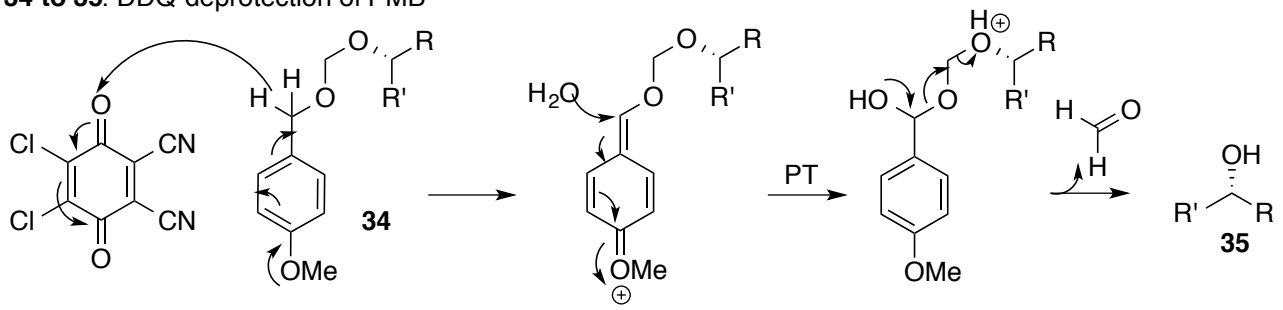


32 to 33: Hiyama cross-coupling

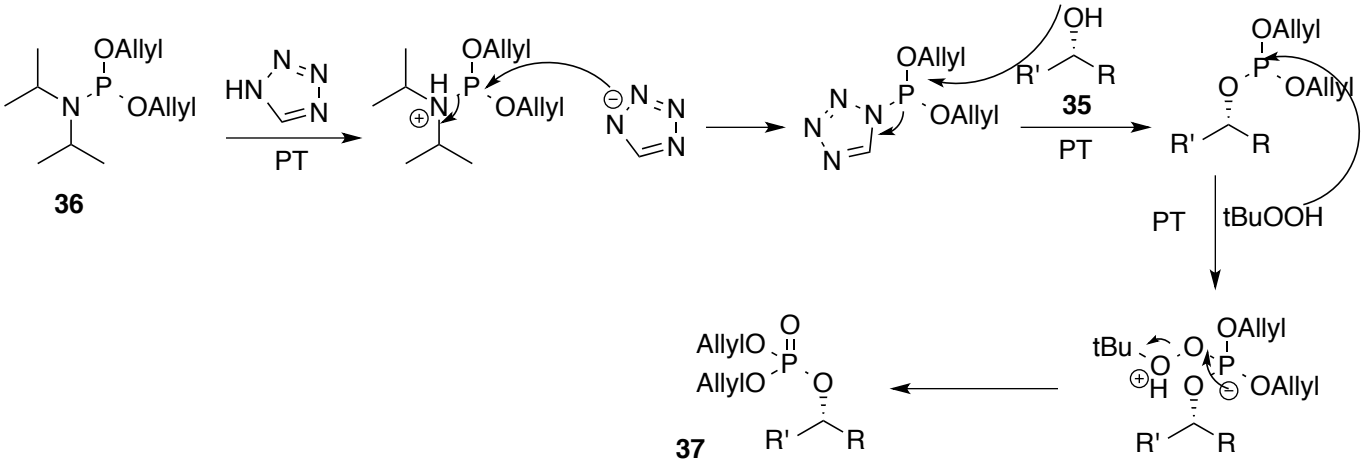


Completion of the Synthesis of Leustroducsin B

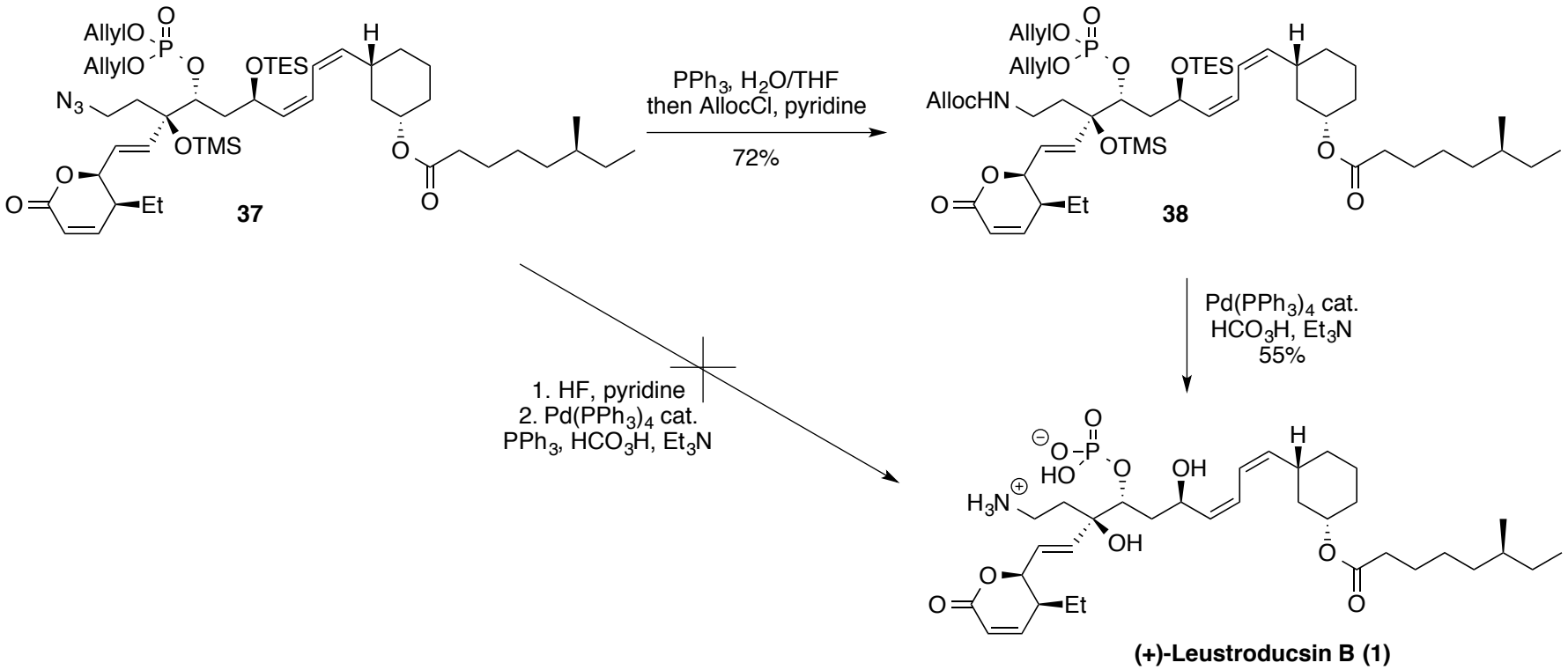
34 to 35: DDQ deprotection of PMB



35 to 37

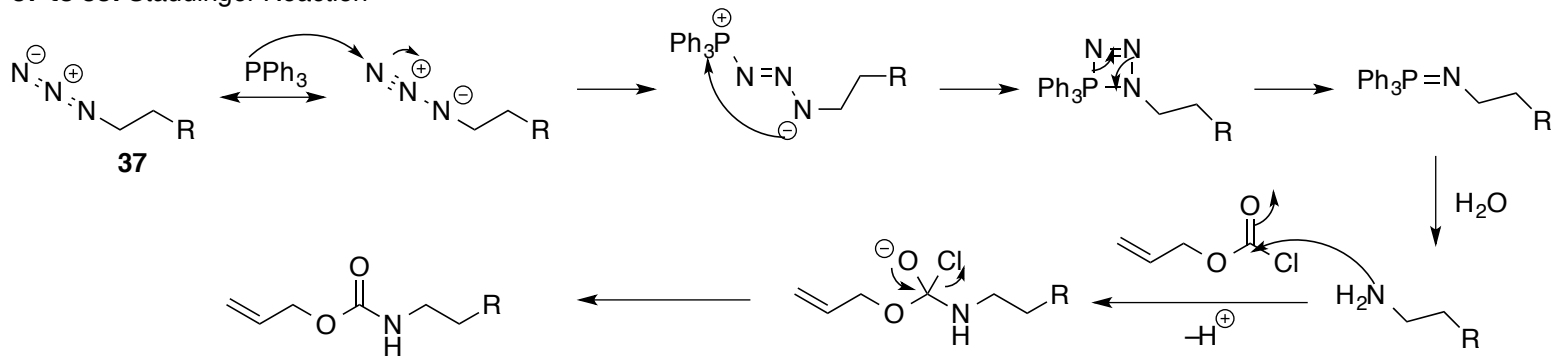


Completion of the Synthesis of Leustroducsin B

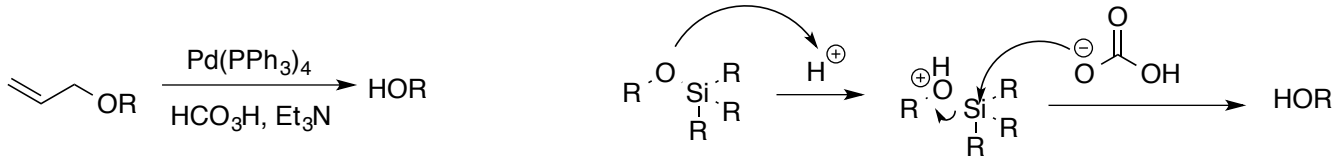


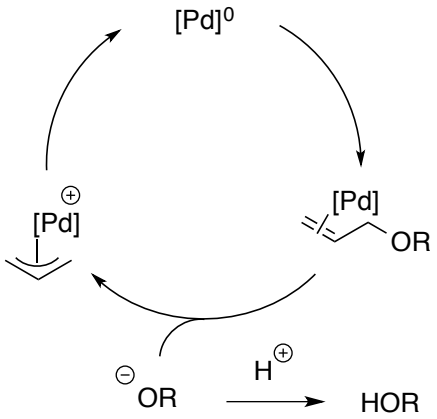
Completion of the Synthesis of Leustroducsin B

37 to 38: Staudinger Reaction



37 to 38: Allyl deprotection and acidic desilylation





Conclusion:

- Synthesis of Leustroducsin B achieved in 17 longest linear sequence and 39 total steps
- Highly efficient and convergent
  - United 3 fragments for convergent synthesis
  - Last step involved removal of 3 allyl and 2 silyl groups in one step