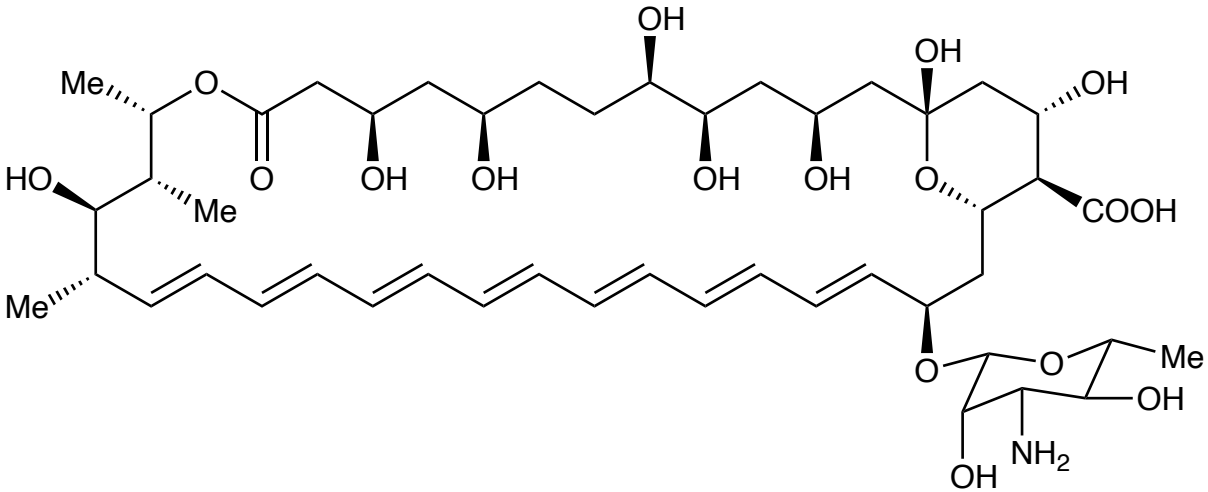
Total Synthesis of Amphotericin B

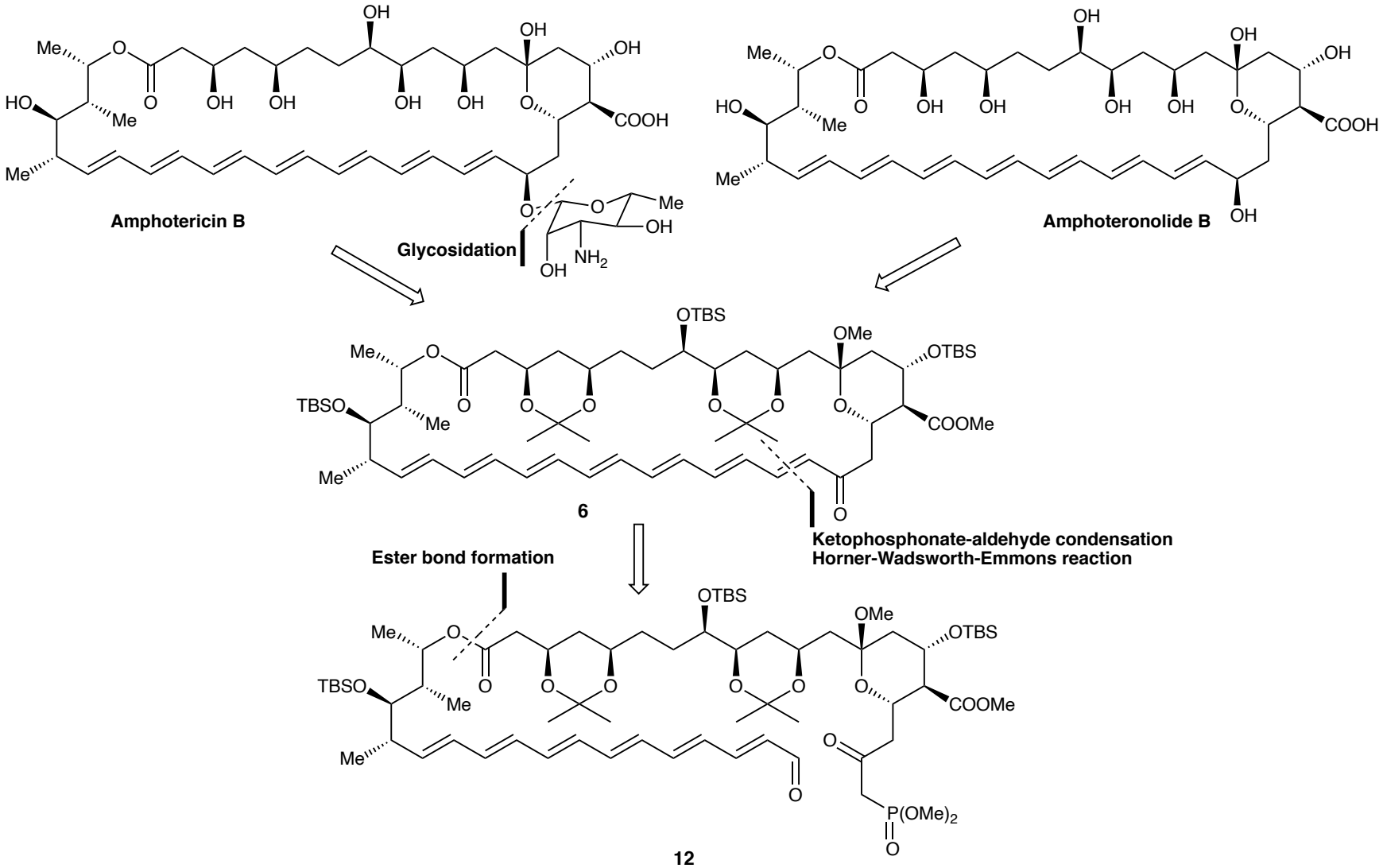
- Amphotericin B is one of the most prominent members of the clinically important polyene macrolide family of natural products.
- large macrolactone ring and conjugated all-trans polyolefinic region.
- A widely used antifungal agent.
- It is produced by *Streptomyces nodosus*.



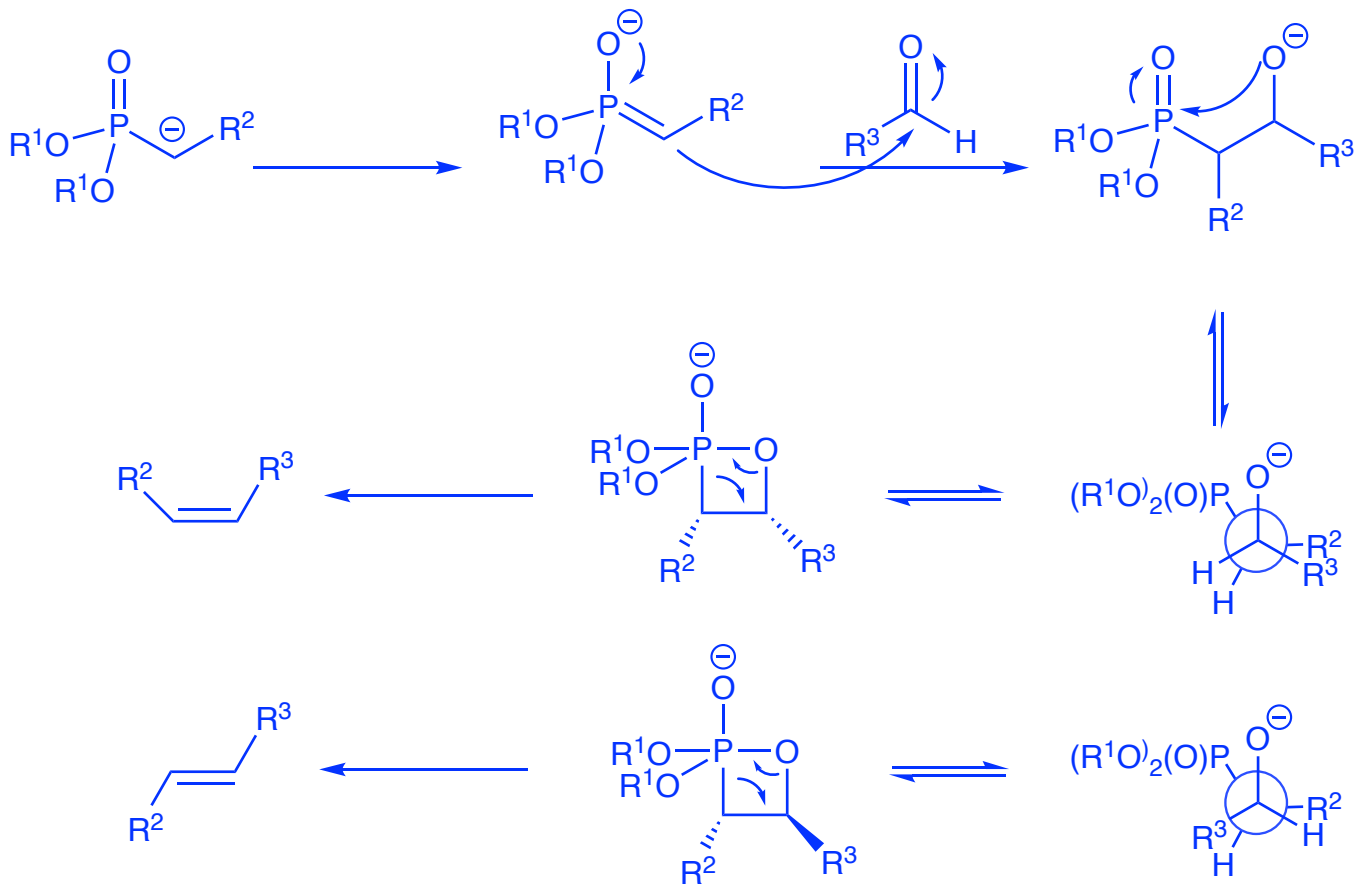
Isolation: Vandeputte, J.; Watchtel, J. L.; Stiller, E. T. *Antibiotic Annu.* **1956**, 587-591.
X-ray structure: a) Mechinski, W.; Shaffner, C. P.; Ganis, P.; Avitabile, G. *Tetrahedron Lett.* **1970**, 3873-3876. b) Ganis, P.; Avitabile, G.; Mechinski, W.; Shaffner, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 4560-4564.
Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2821-2822.

Bahareh Ghaffari
1/28/2022

Retrosynthesis

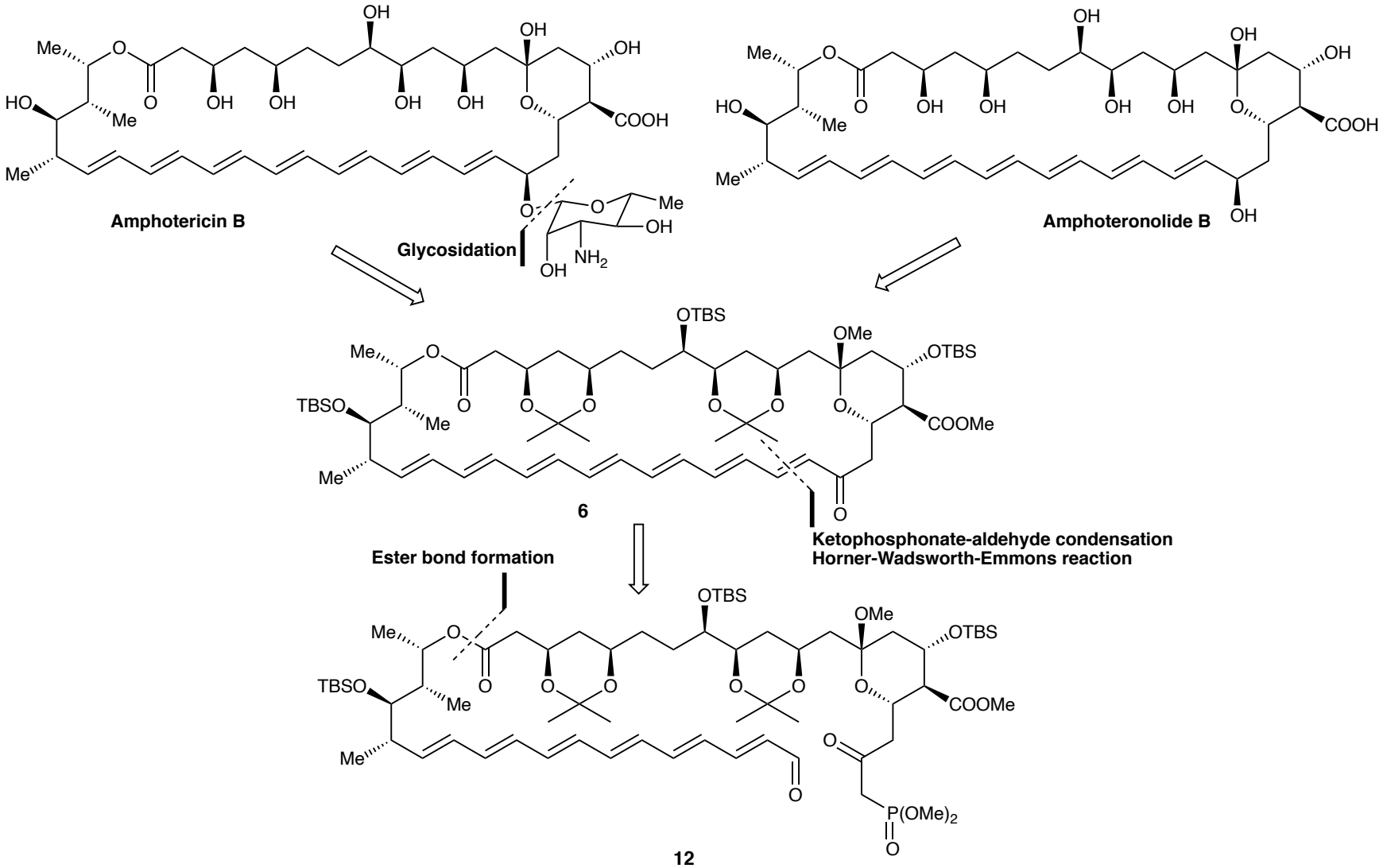


Horner-Wadsworth-Emmons Reaction

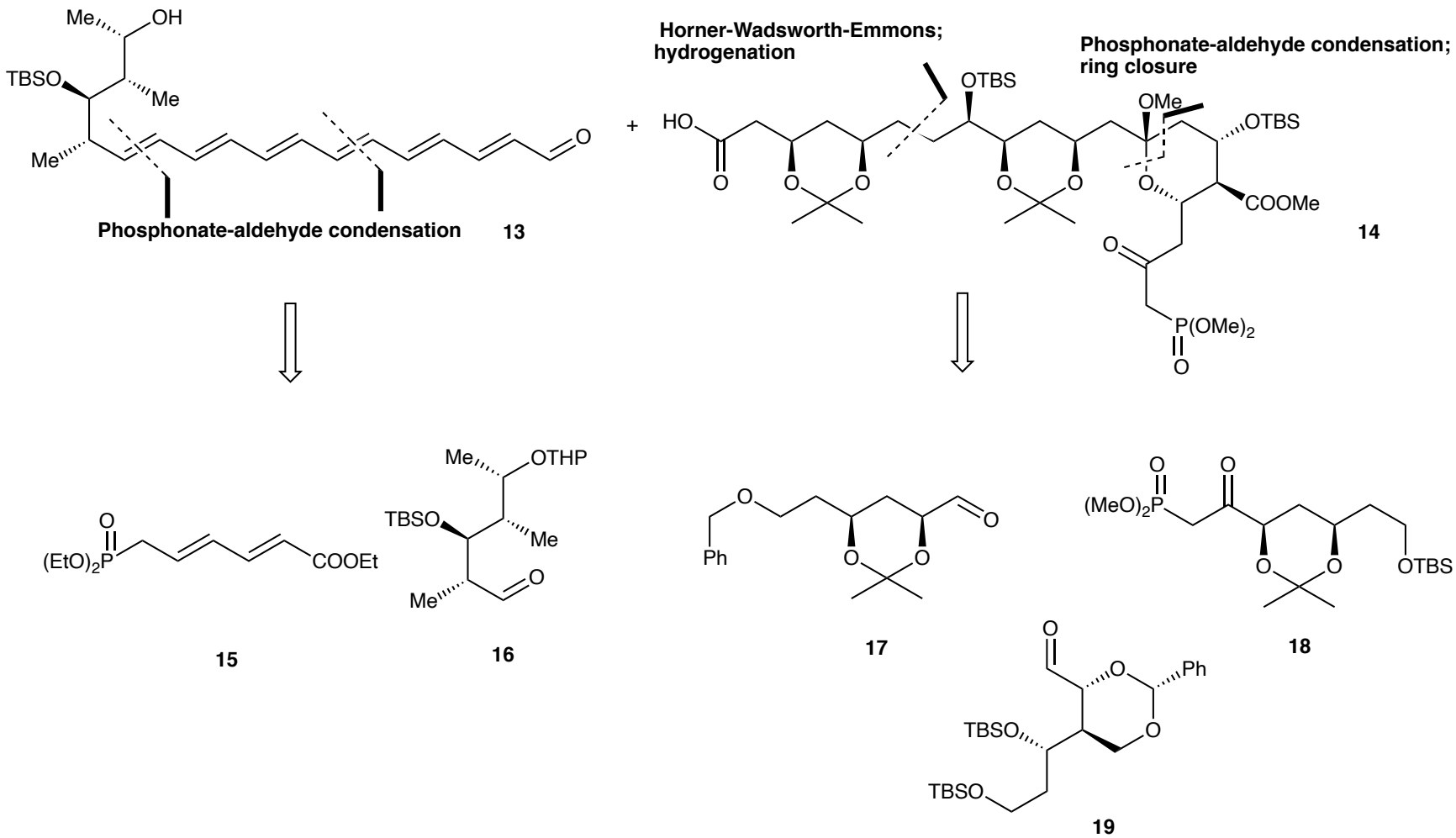


Wadsworth, W. S., *Jr. Org. React (N. Y.)* **1977**, *25*, 73.

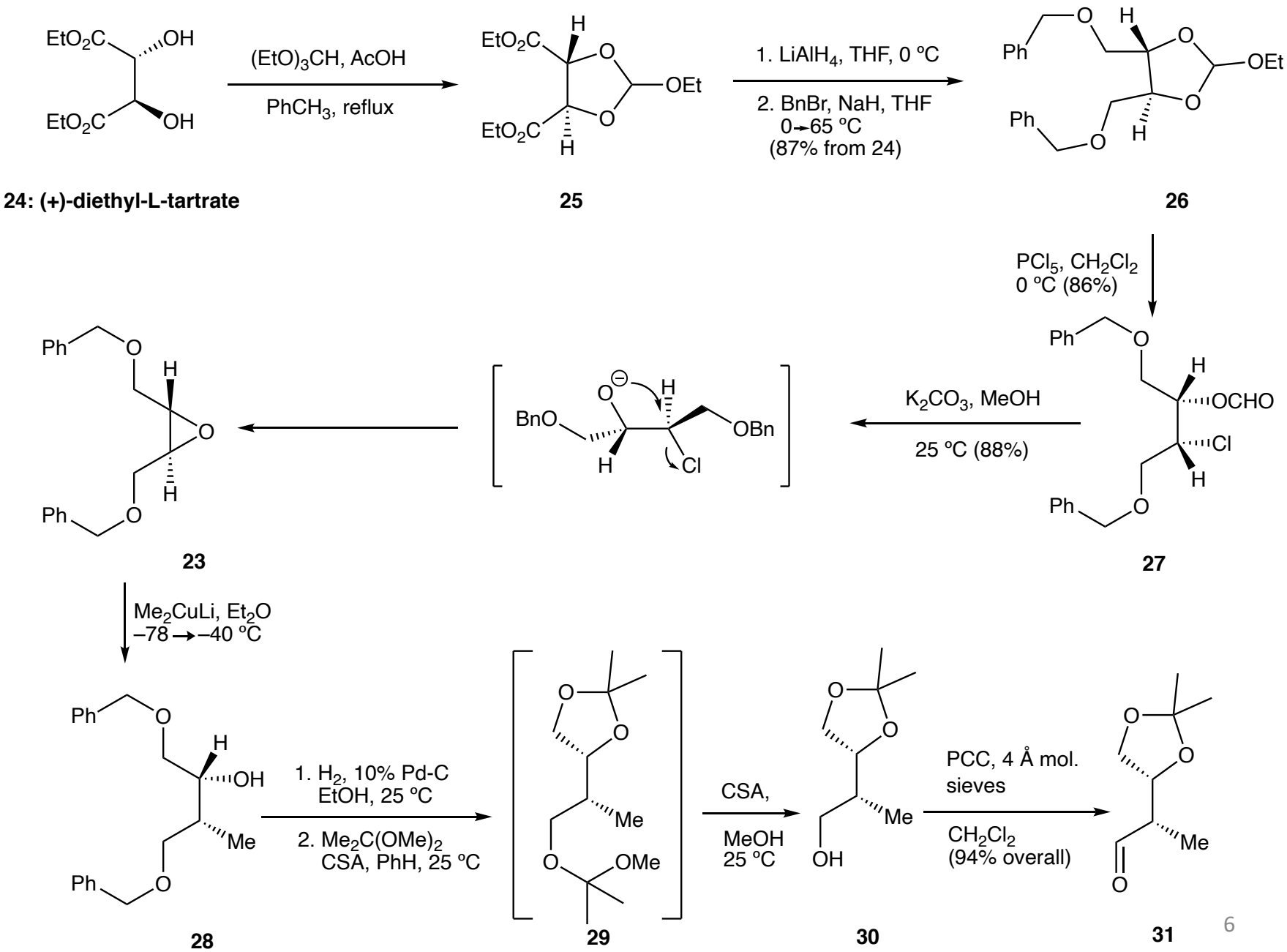
Retrosynthesis



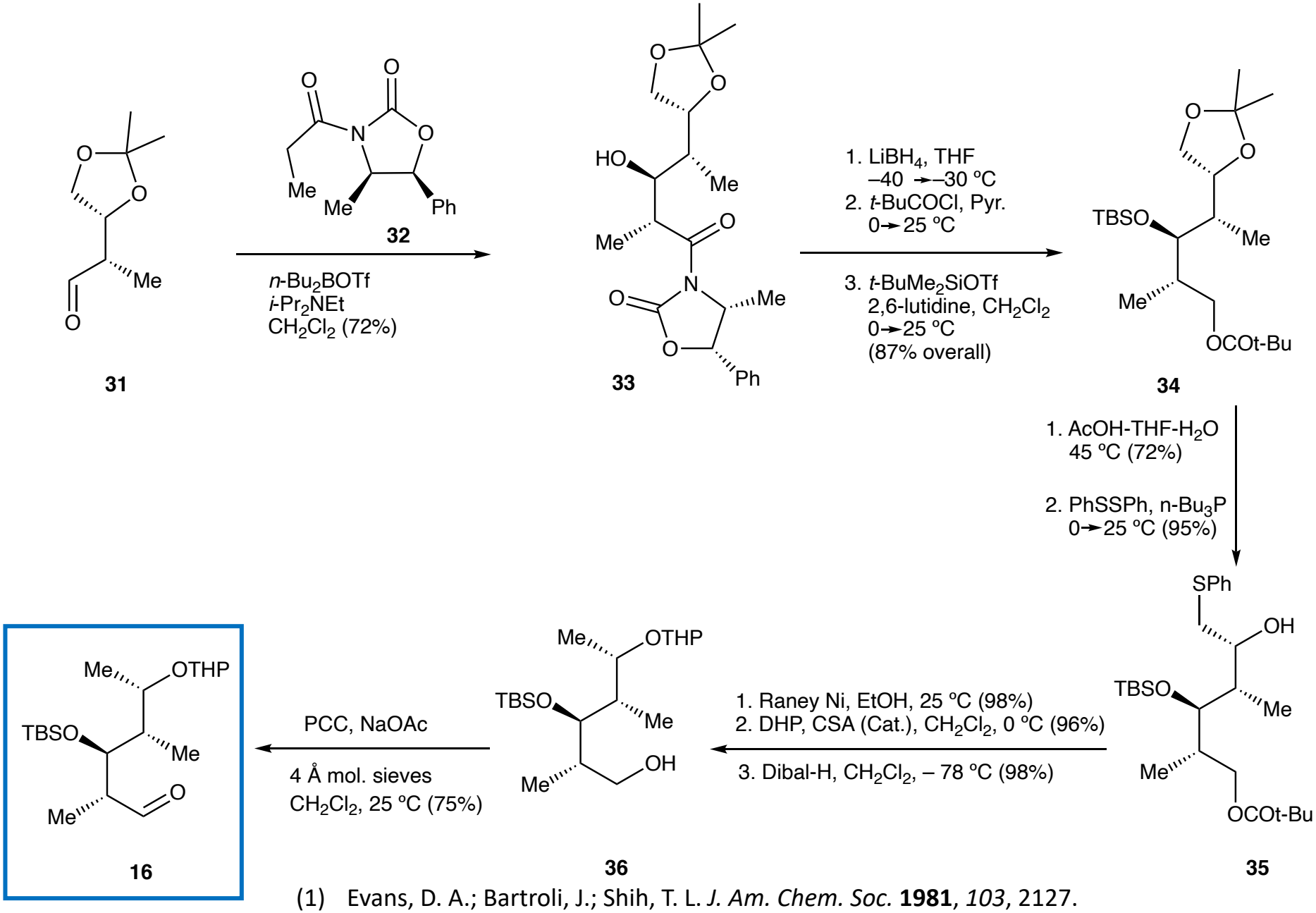
Retrosynthesis



Synthesis of substrate 16



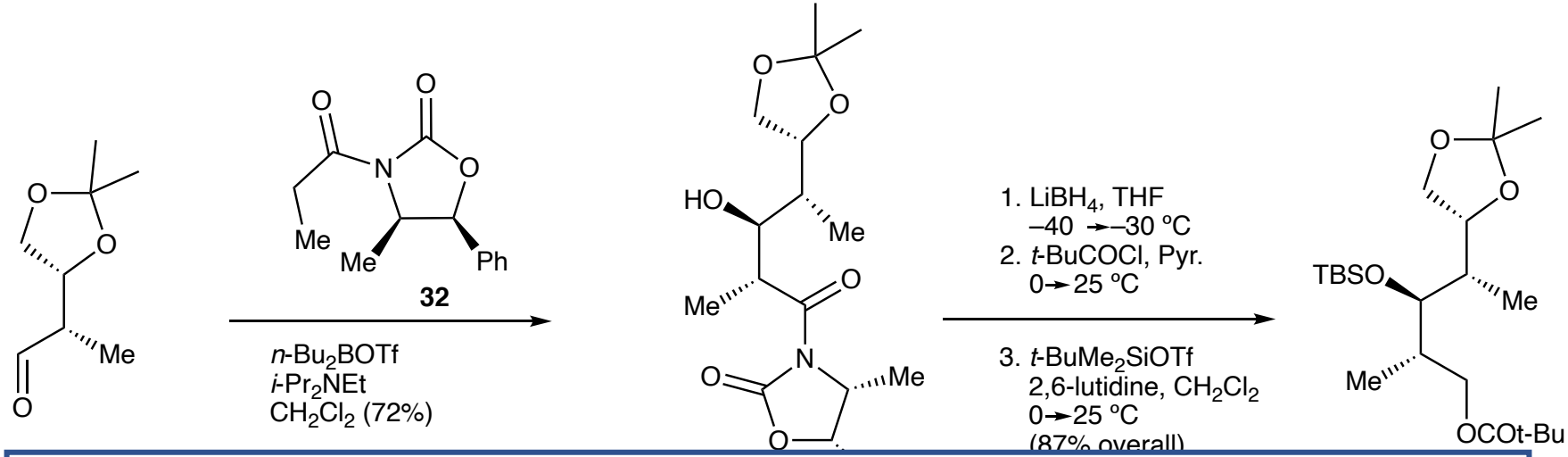
Synthesis of substrate 16

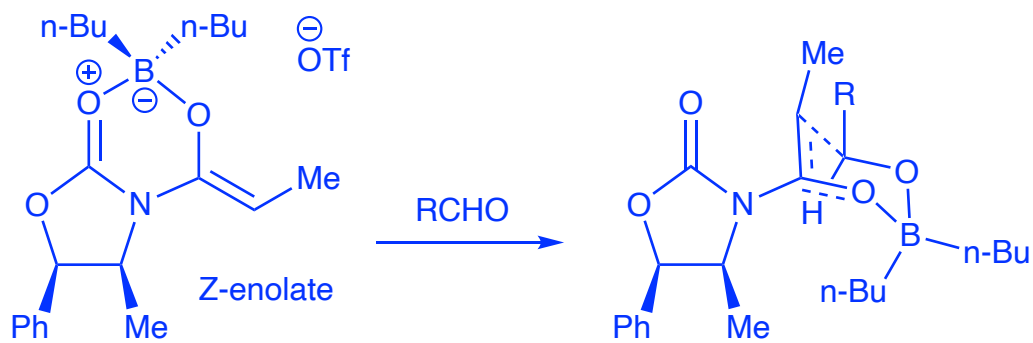


(1) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(2) Zhang. Z.; Collum, D. B. *J. Org. Chem.* **2017**, *82*, 7595.

Synthesis of substrate 16



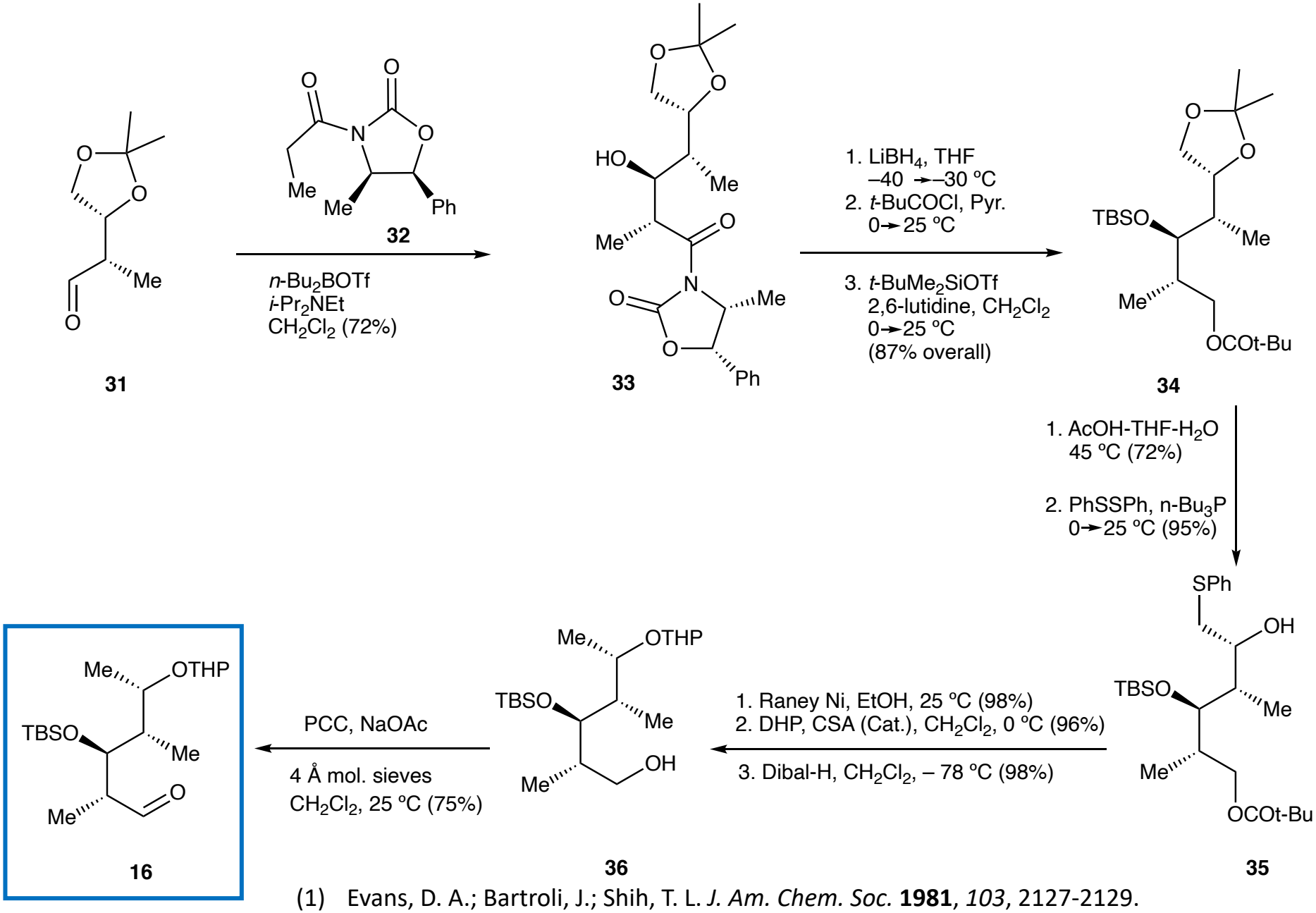


Evans asymmetric aldol reaction

The Z-enolate determines the relative stereochemistry of the product.
4-methyl, 5-phenyl groups determine the absolute stereochemistry of the product.

(1) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(2) Zhang. Z.; Collum, D. B. *J. Org. Chem.* **2017**, *82*, 7595.

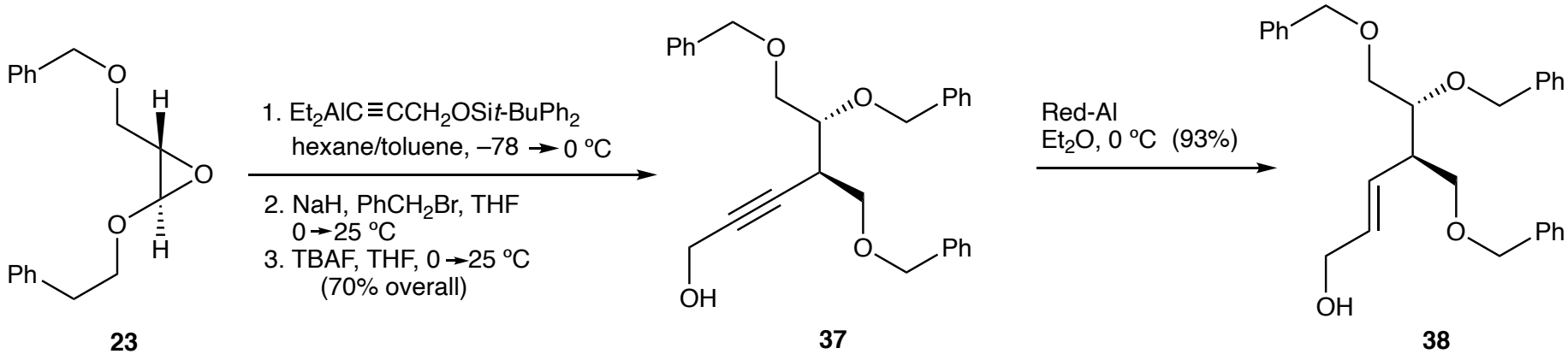
Synthesis of substrate 16



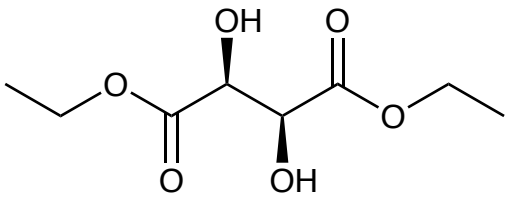
(1) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

(2) Zhang. Z.; Collum, D. B. *J. Org. Chem.* **2017**, *82*, 7595-7601.

Synthesis of substrate 19

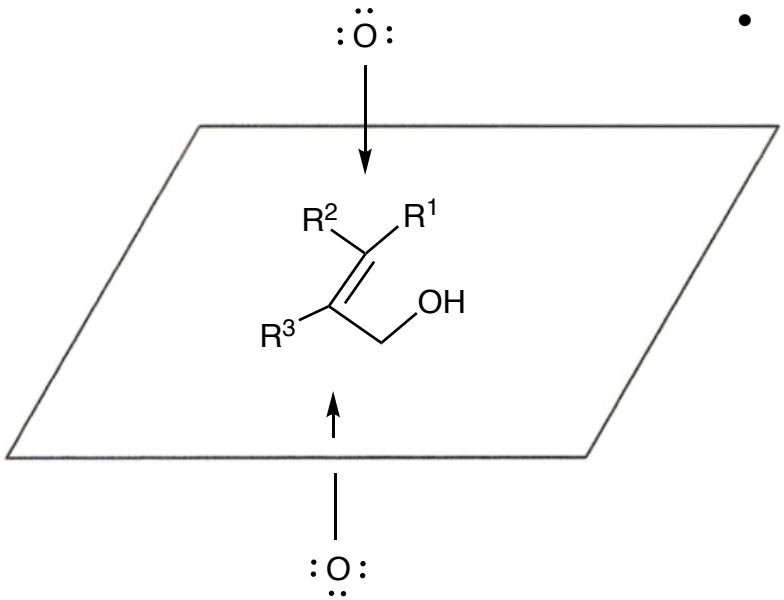


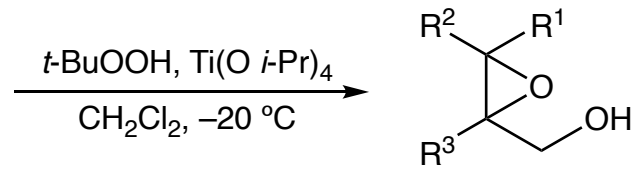
Sharpless Asymmetric Epoxidation



D-(-)-diethyl tartrate (unnatural)

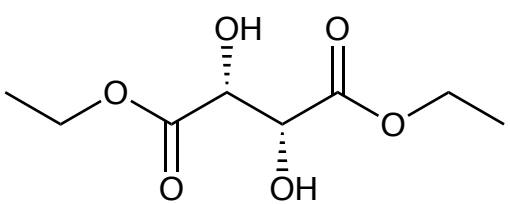
- Enantioselective
- Enantiomer formed depends on stereochemistry of catalyst
- Tolerates a wide variety of functional groups





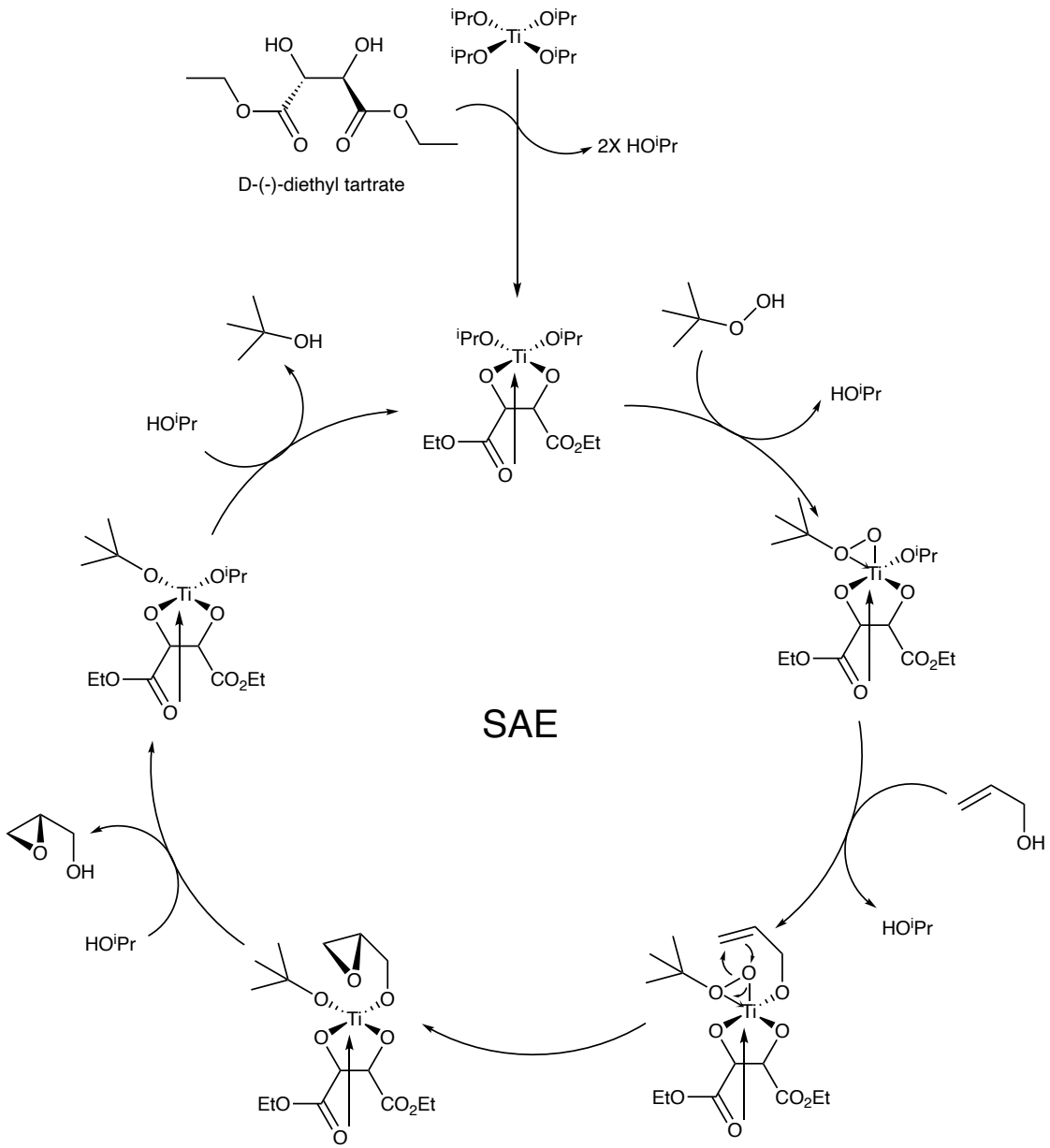
70-90% yield
≥ 90% ee

L-(+)-diethyl tartrate (natural)



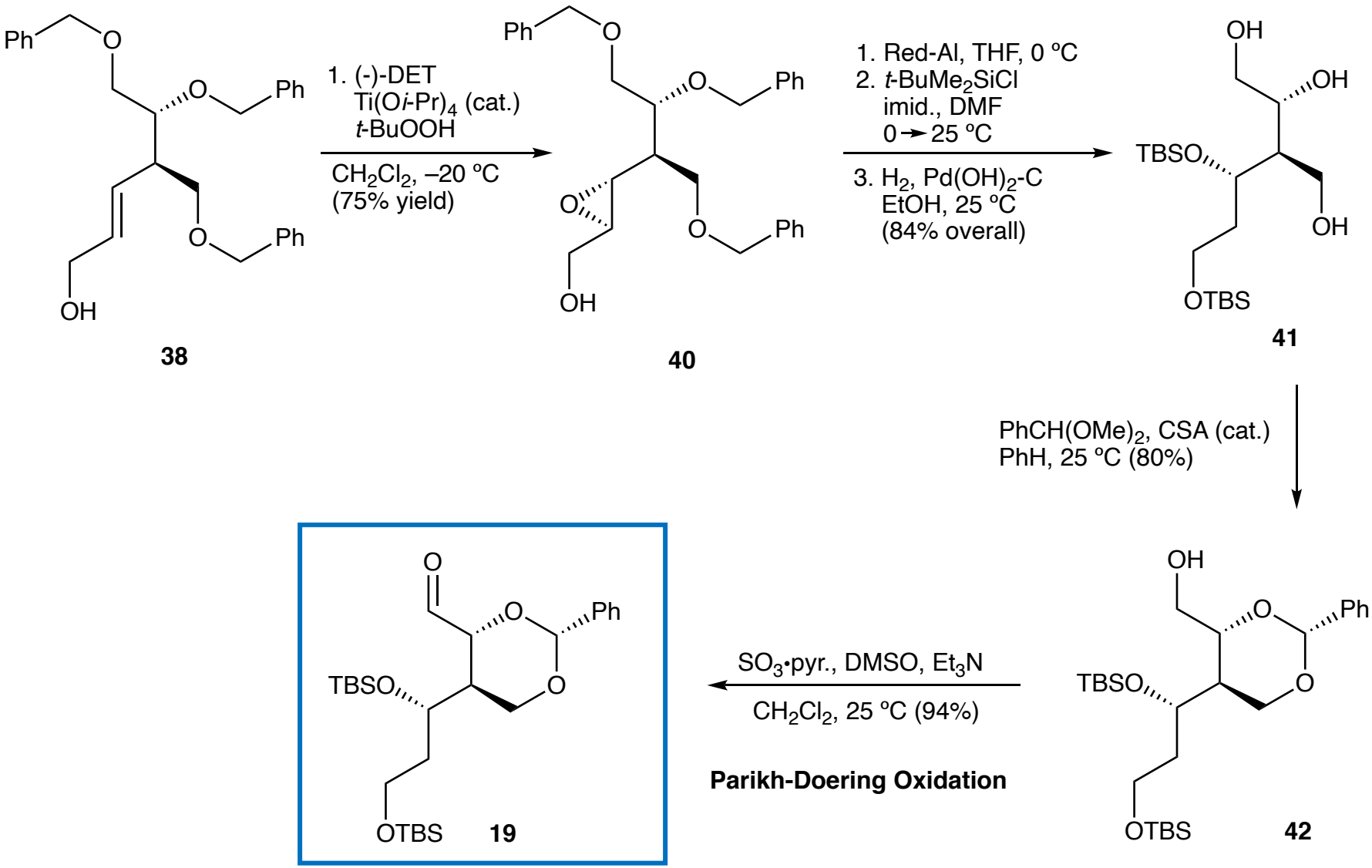
Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.
Katsuki, T.; Martin, V. *Org. React*, **2004**, *48*, 1-299.

Sharpless Asymmetric Epoxidation

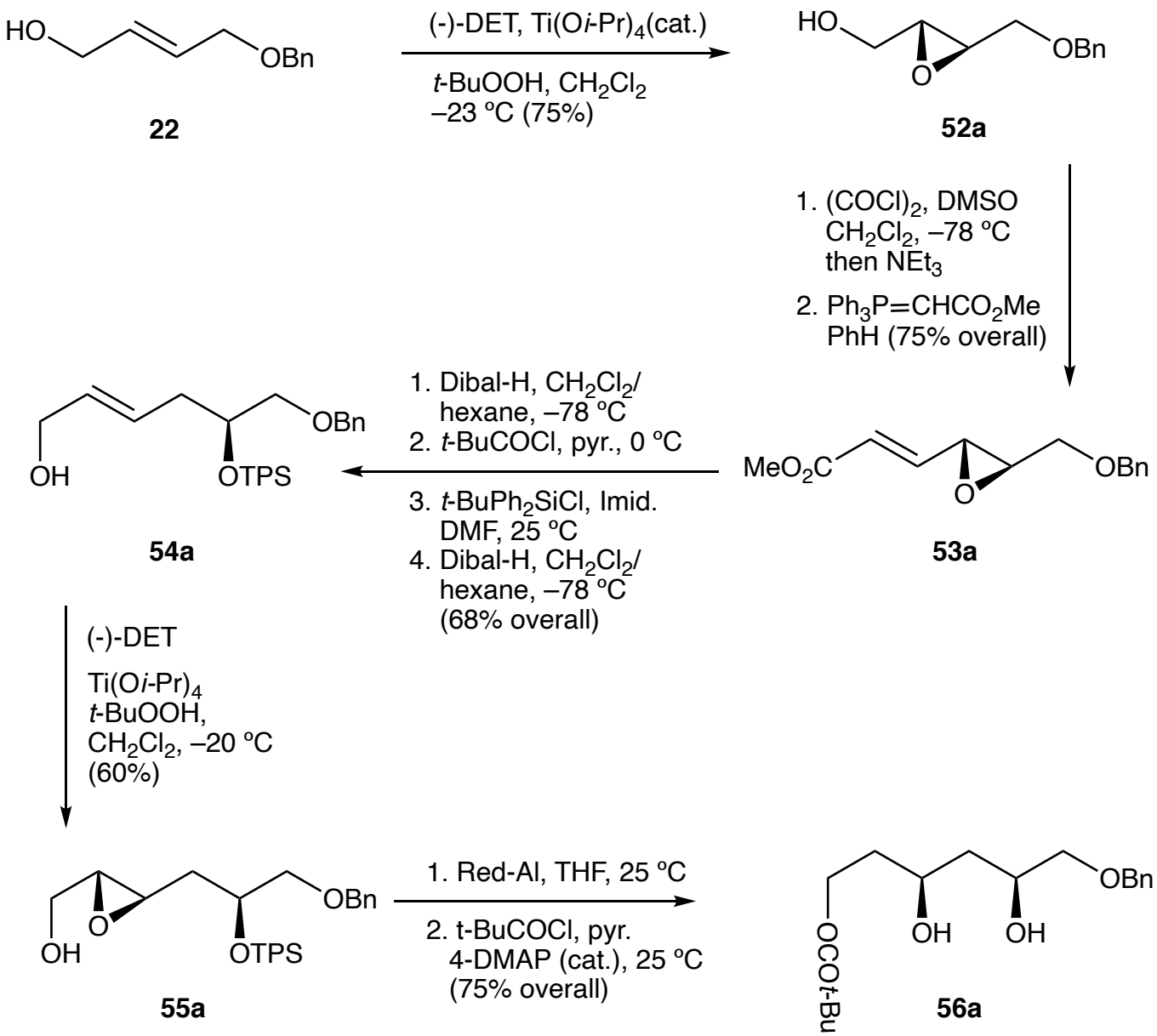


Finn, M.G.; Sharpless, K.B.; *J. Am. Chem. Soc.* **1991**, *113*, 113-126.

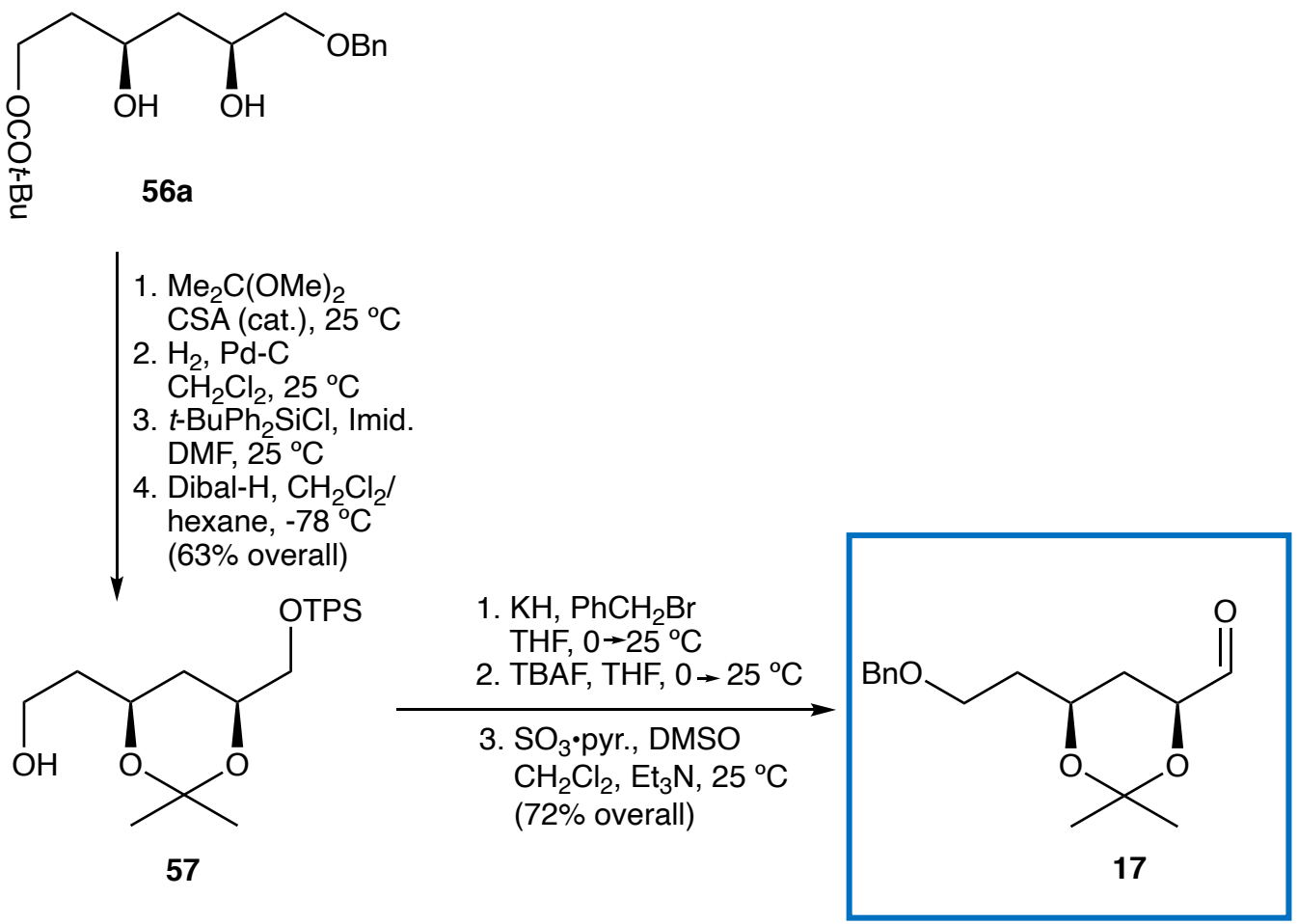
Synthesis of substrate 19



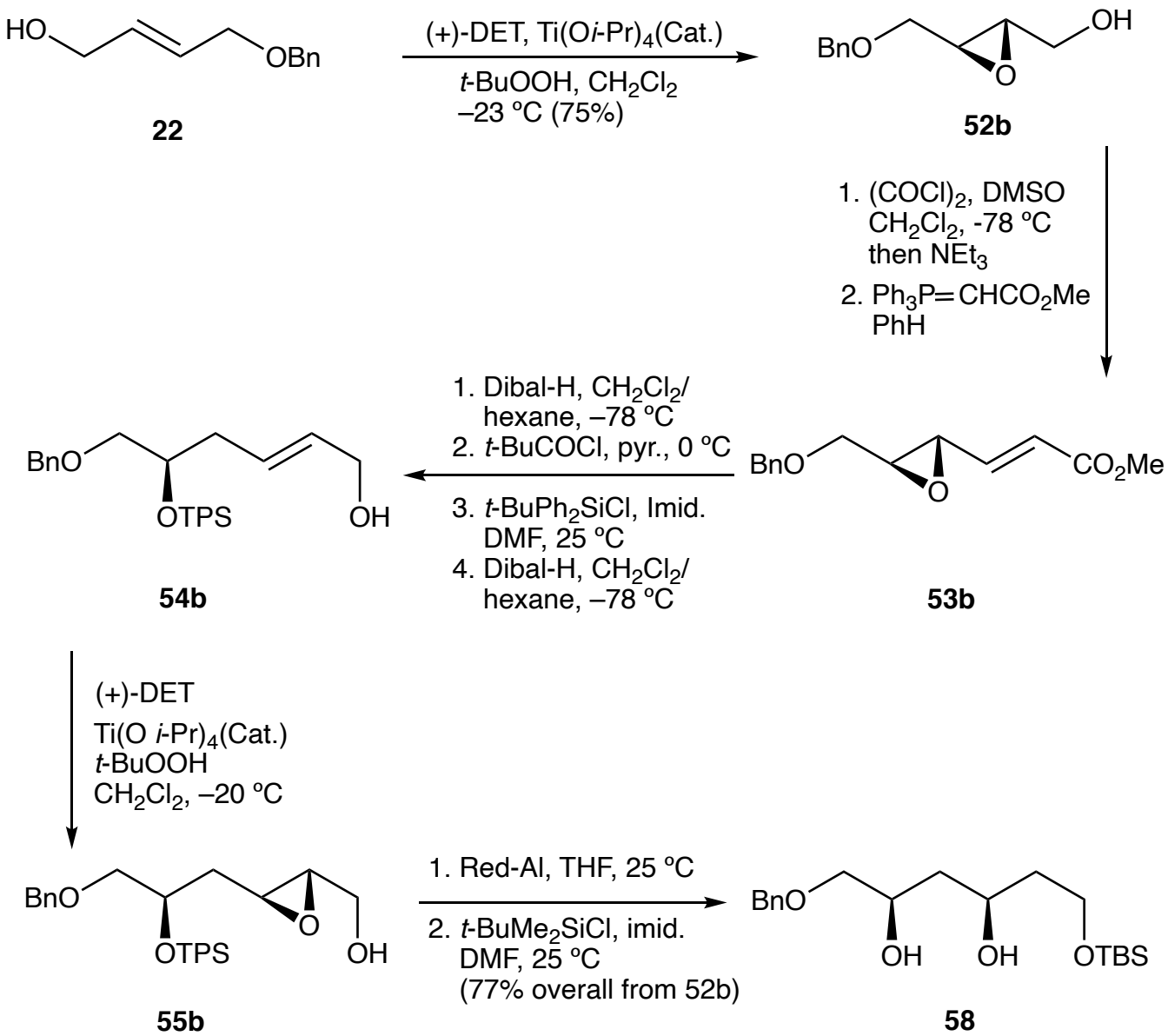
Synthesis of substrate 17



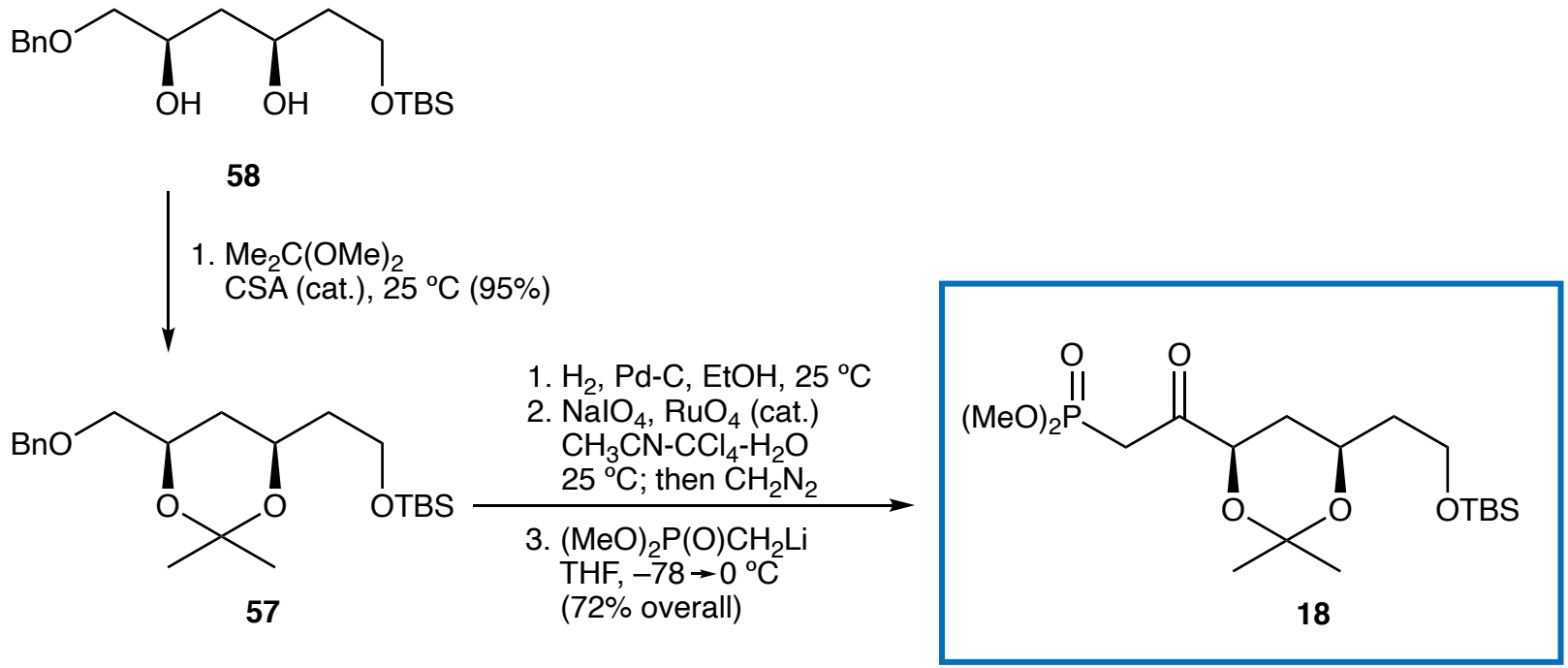
Synthesis of substrate 17



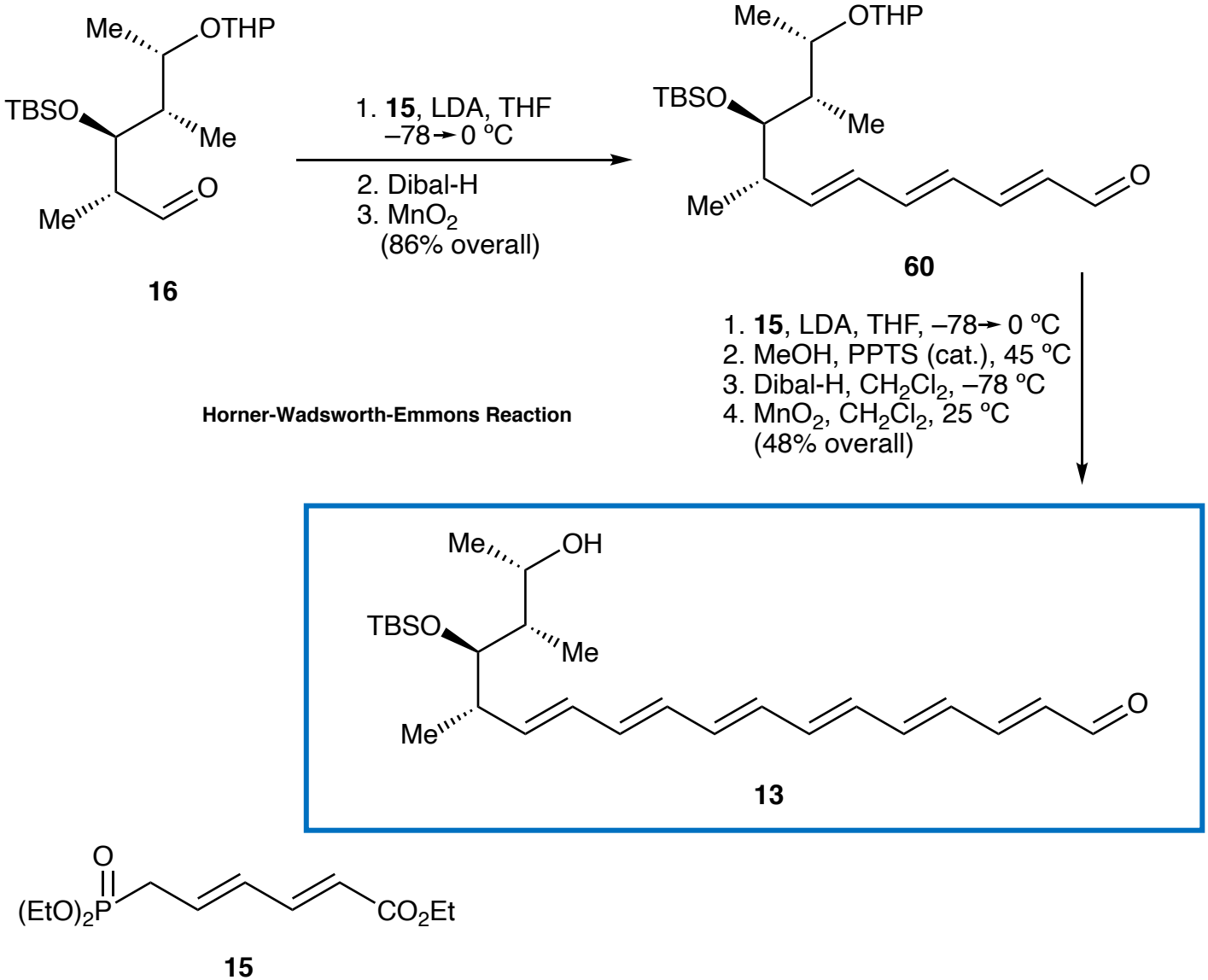
Synthesis of substrate 18



Synthesis of substrate 18

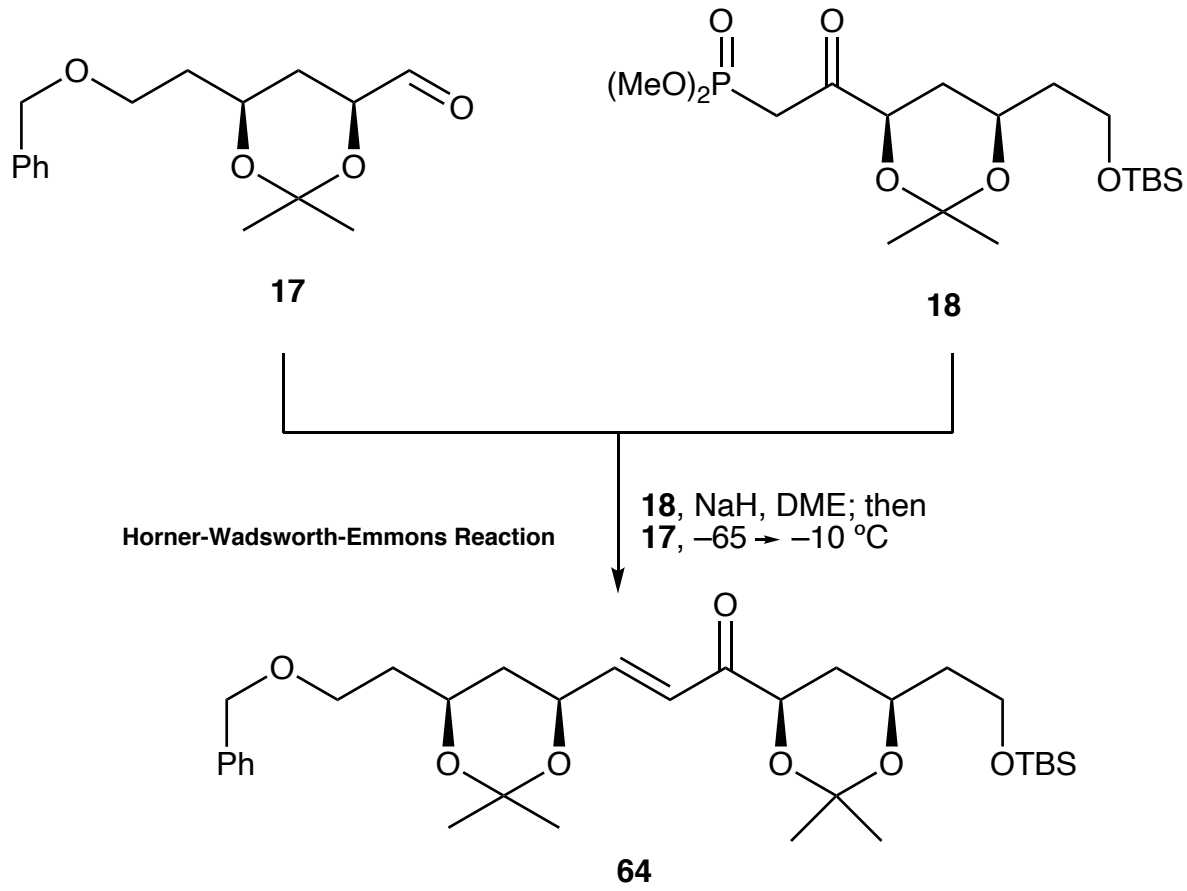


Synthesis of substrate 13 from building blocks 15 and 16

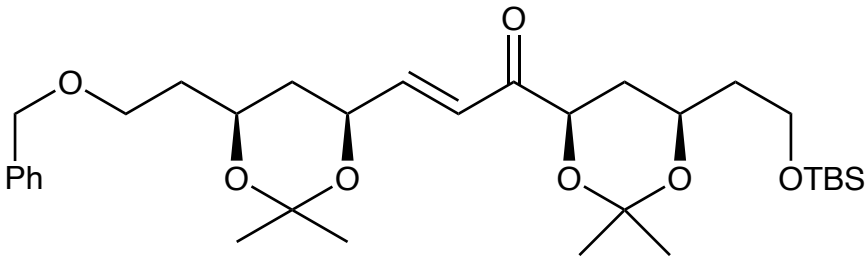


Wadsworth, W. S., *Jr. Org. React (N. Y.)* **1977**, *25*, 73.

Synthesis of substrate 14 from building blocks 17 and 18 and 19



Synthesis of substrate 14 from building blocks 17 and 18 and 19



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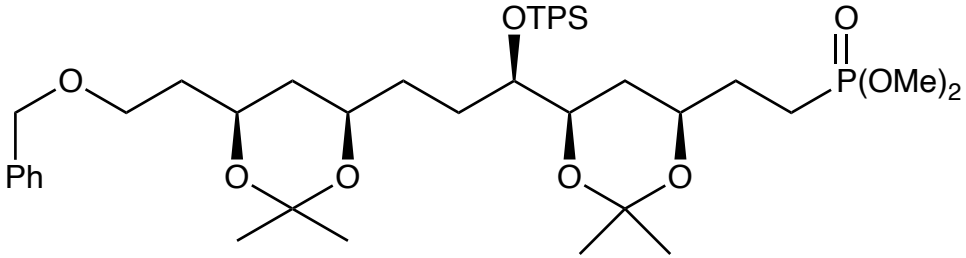
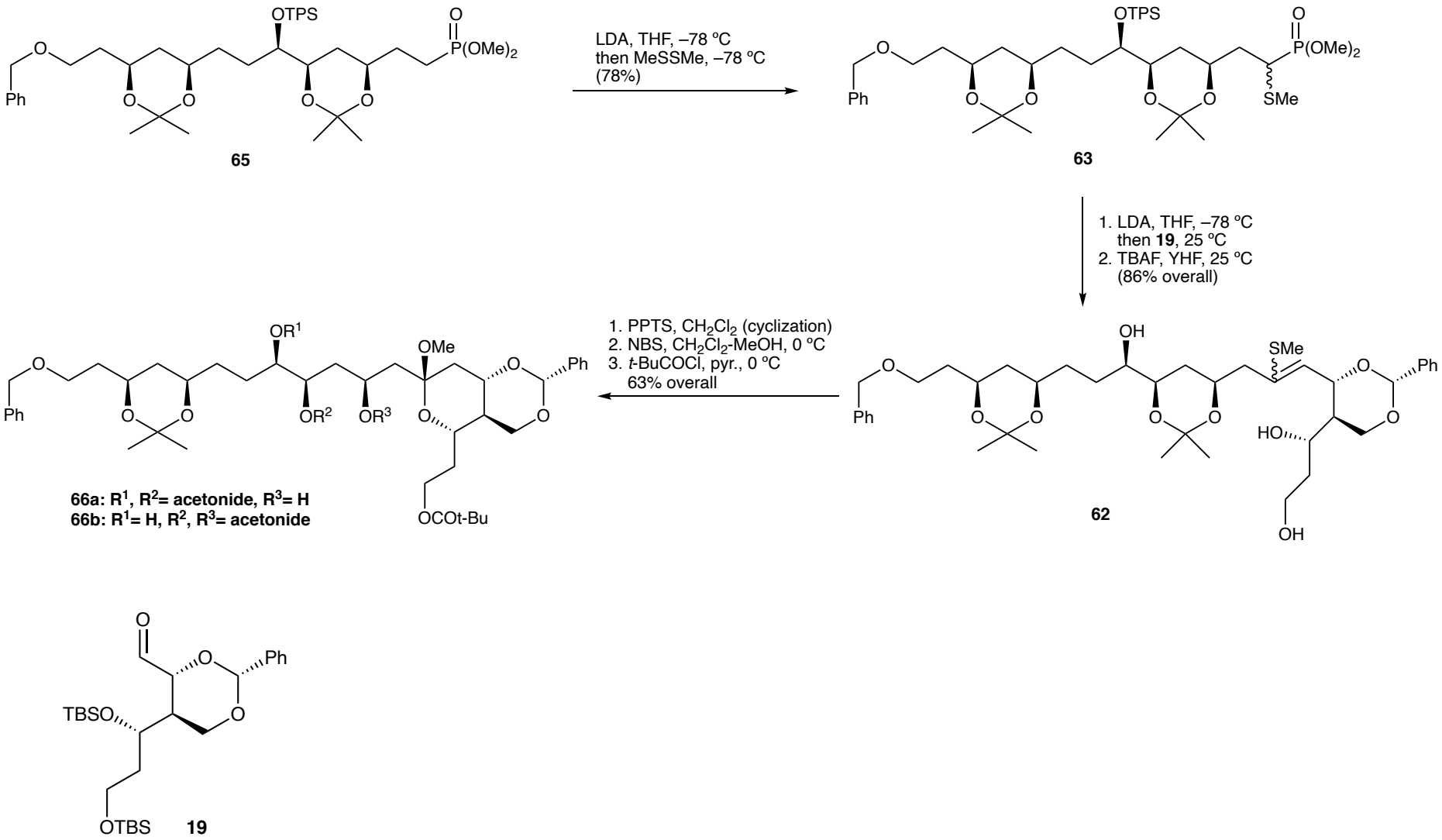
1. H_2, Pd-C, EtOAc, 25 ºC
2. L-Selectride, THF, –110 ºC
3. *t*-$BuPh_2SiCl$, imid., DMF, 50 ºC
4. TBAF, THF, 0 ºC (TBS cleavage)
5. MsCl, Et_3N, CH_2Cl_2, –15 ºC
6. NaI, acetone, 25 ºC
7. $(MeO)_2P(O)H$, NaH, DME/DMF (3:2), 45 ºC (75% overall)

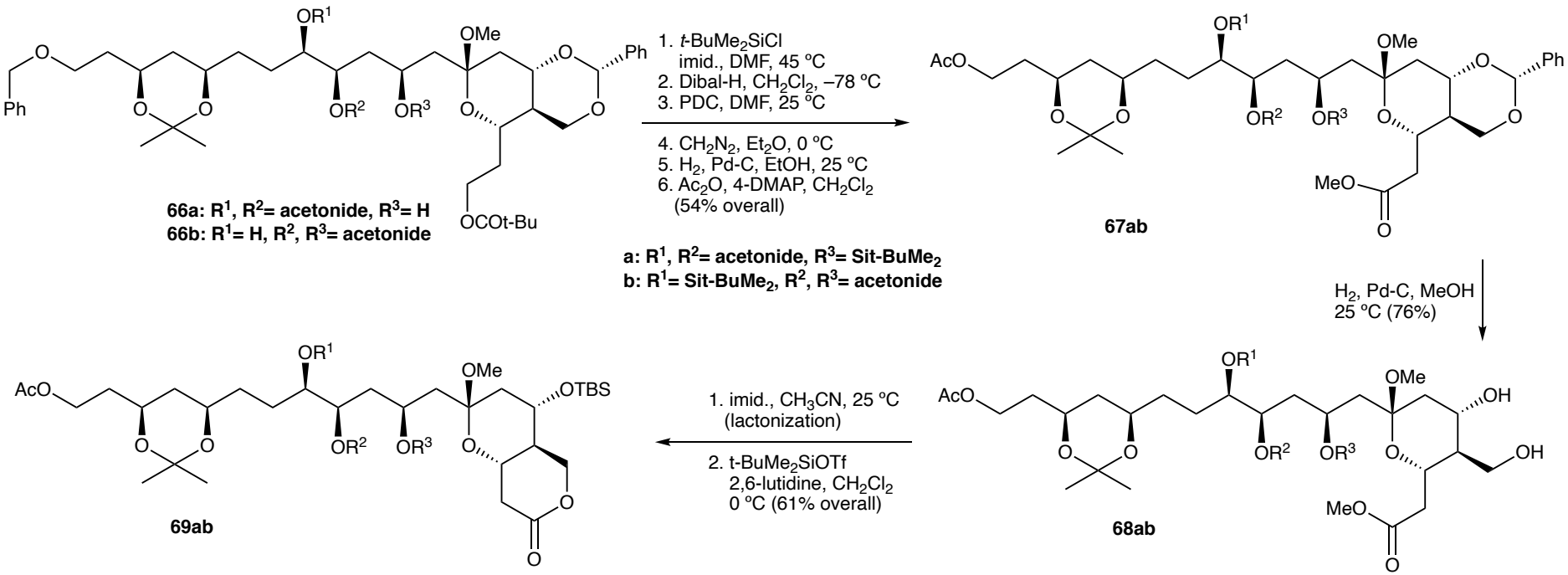


65

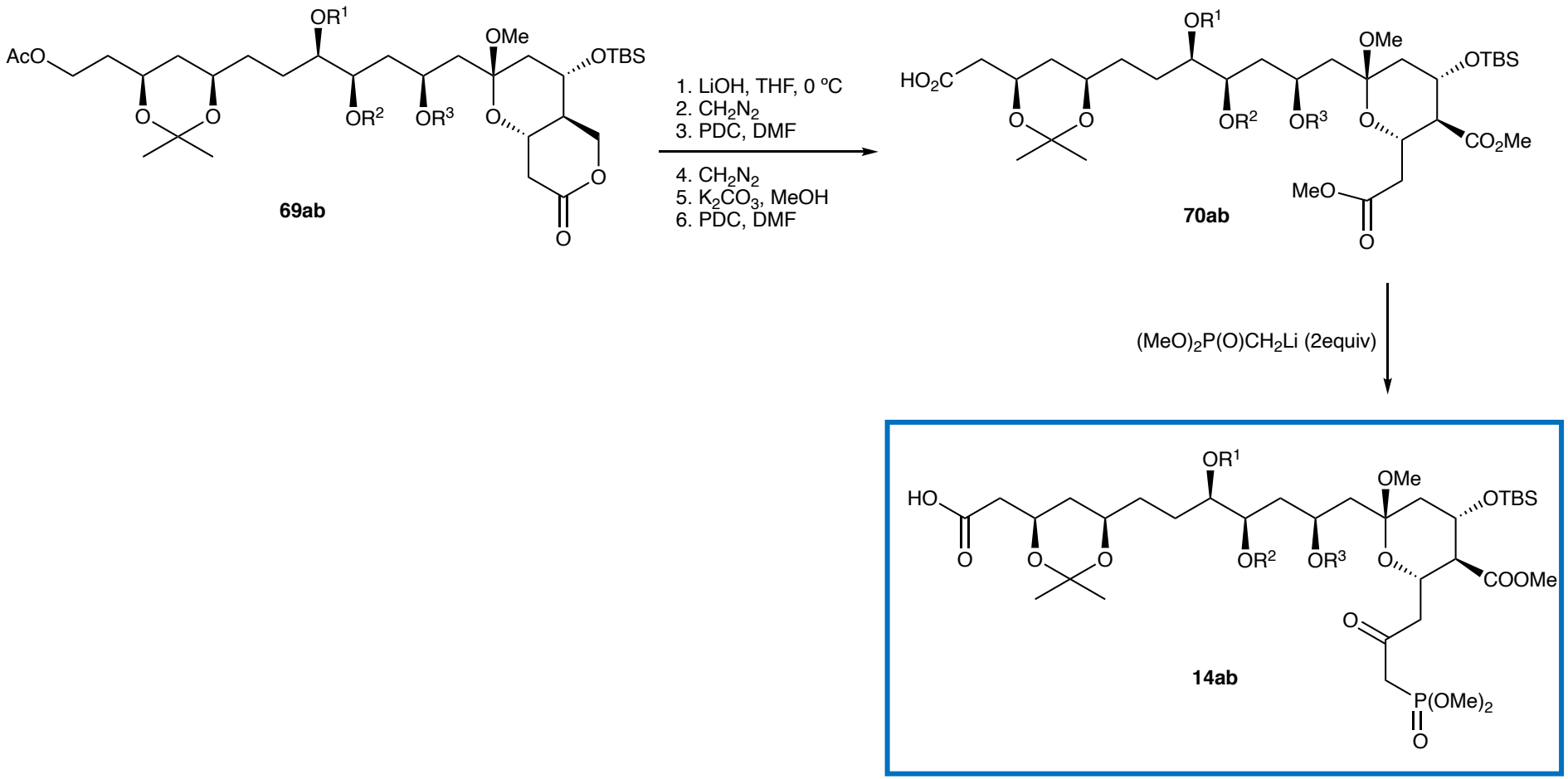
Synthesis of substrate 14 from building blocks 17 and 18 and 19



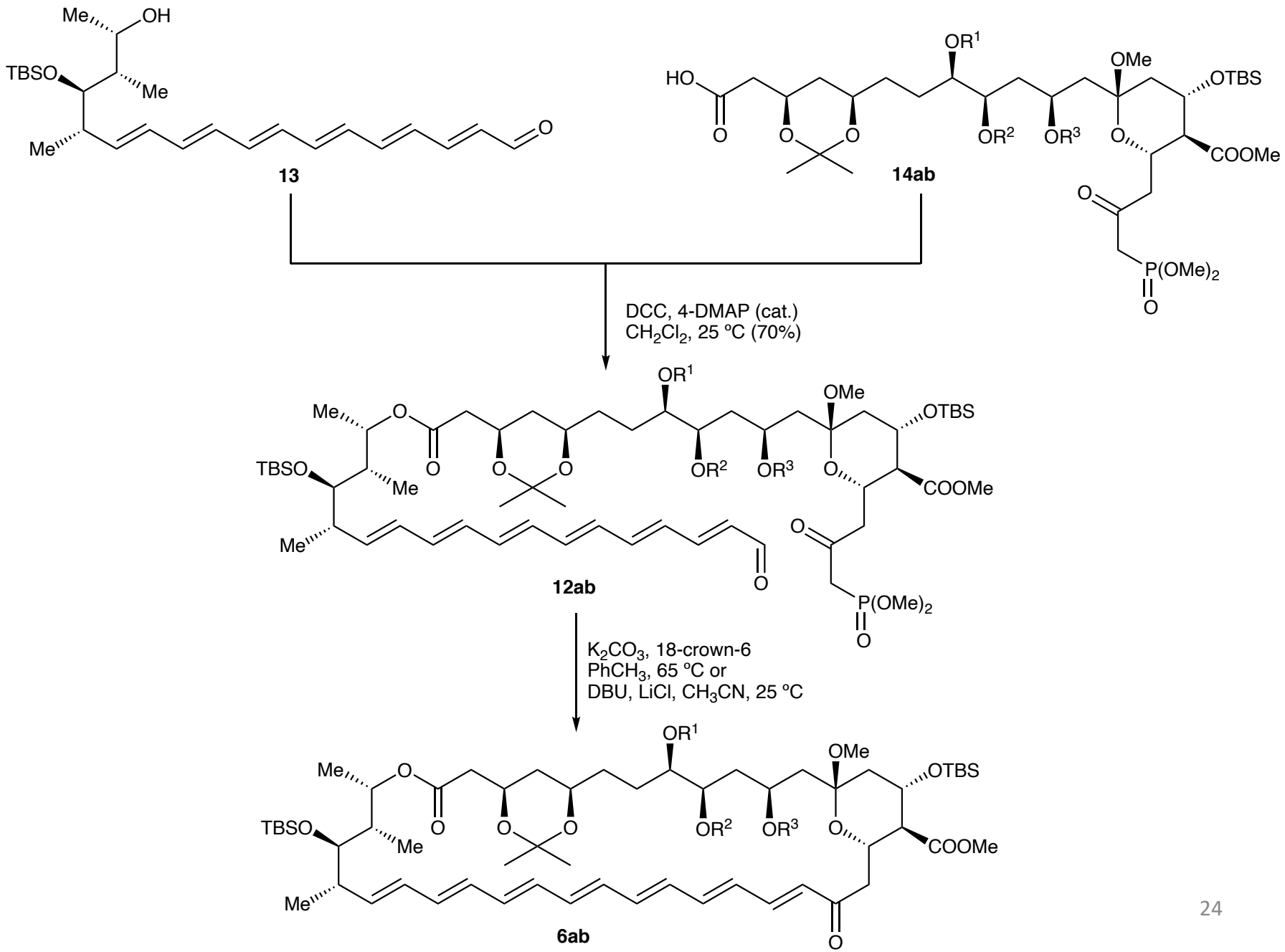
Synthesis of substrate 14 from building blocks 17 and 18 and 19



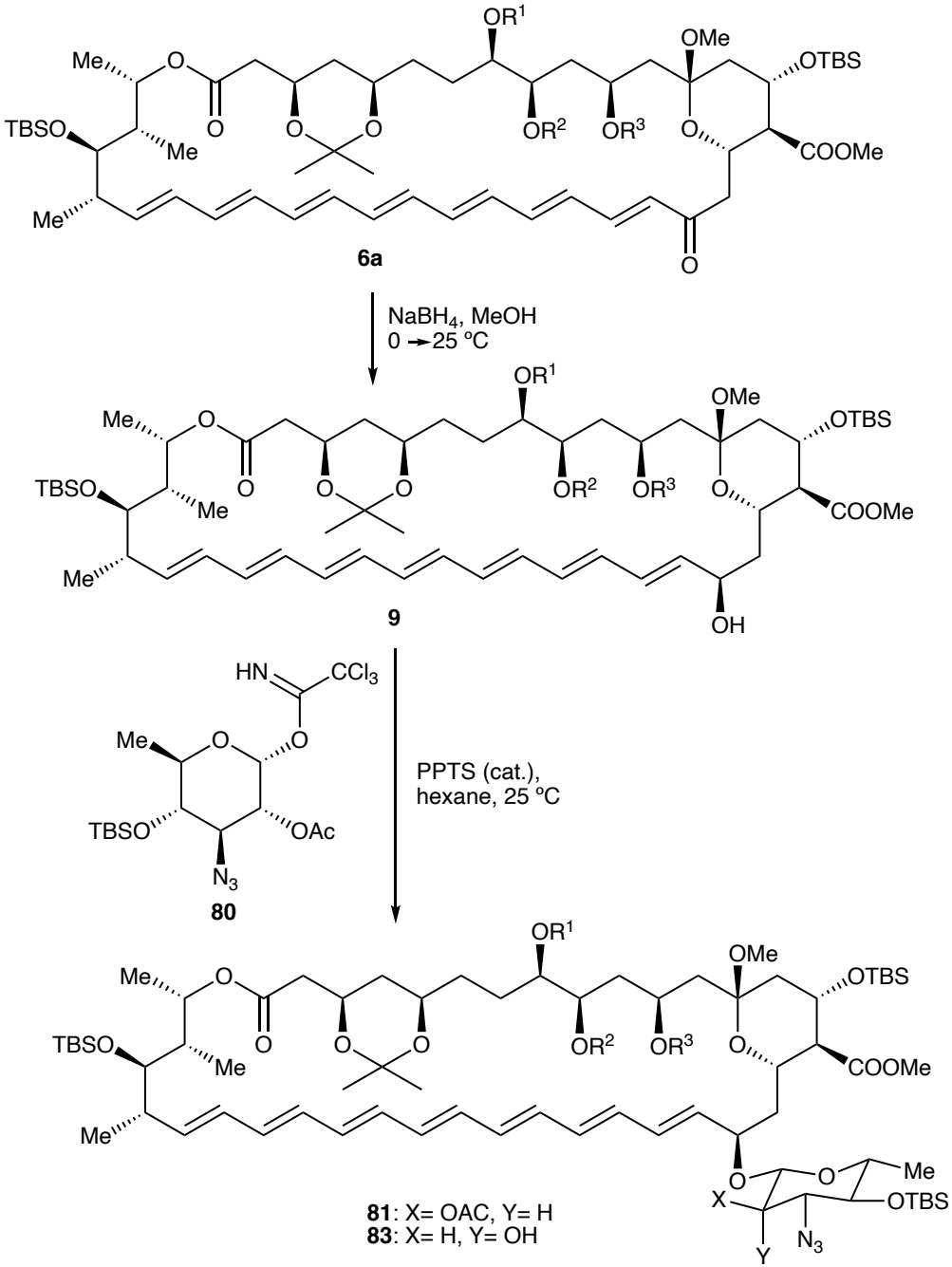
Synthesis of substrate 14 from building blocks 17 and 18 and 19



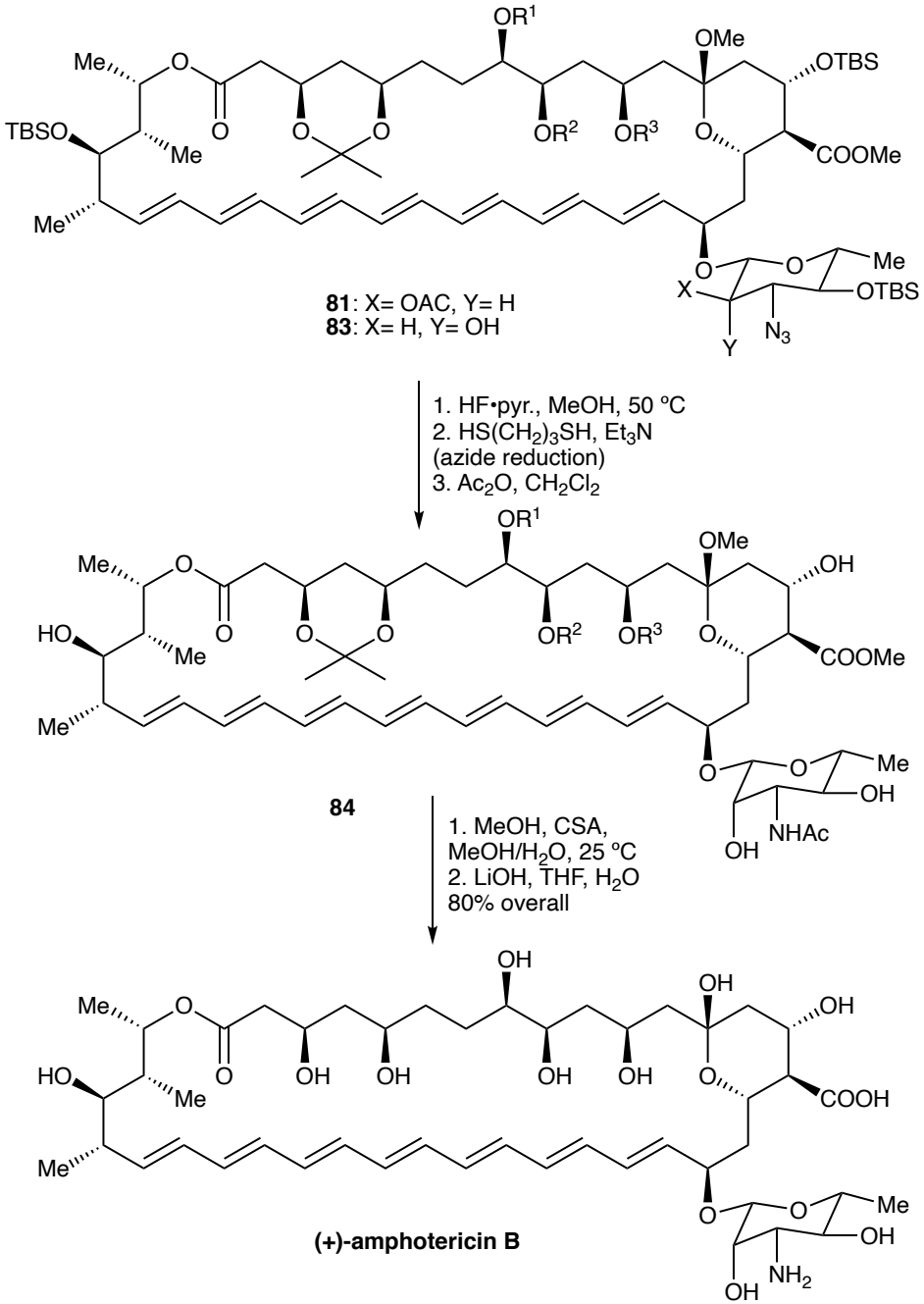
Synthesis of Amphotricin B from building blocks 13, 14, and 80



Synthesis of Amphotricin B from building blocks 13, 14, and 80



Synthesis of Amphotricin B from building blocks 13, 14, and 80



Amphotericin B, Conclusion

Noteworthy features of this strategy:

i. The recognition and utilization of subtle symmetry elements in the target molecule by careful retrosynthetic analysis.
ii. The employment of powerful Sharpless asymmetric epoxidation reaction.
iii. The Horner-Wadsworth-Emmons reaction emerged as the most useful carbon-carbon bond forming reaction.