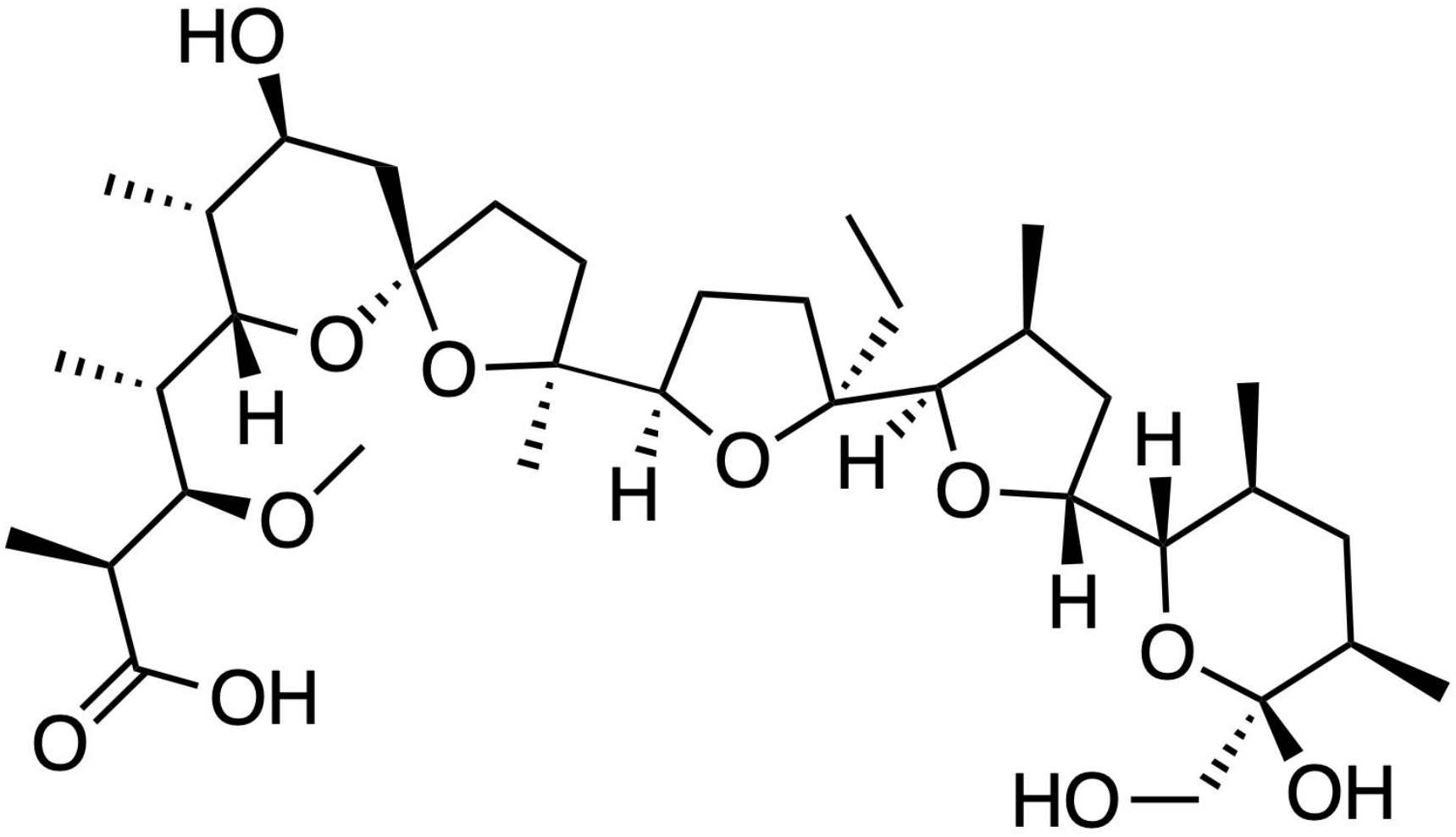
Discussion of the total synthesis of Monensin



Why Monensin?

A polyether antibiotic, Monensin was the first member of this class of molecules to be structurally characterized.[1]

The structural features of these polyethers comprise of a terminal carboxylic acid, multiple cyclic ether rings (ex. Tetrahydrofuran and tetrahydropyran), a large amount of stereocenters and (for many of these molecules) one or more spiroketal moieties.[2]

Monensin was introduced into the market in 1971 and is used to fight coccidial infections in poultry and as an additive in cattle feed.[3]

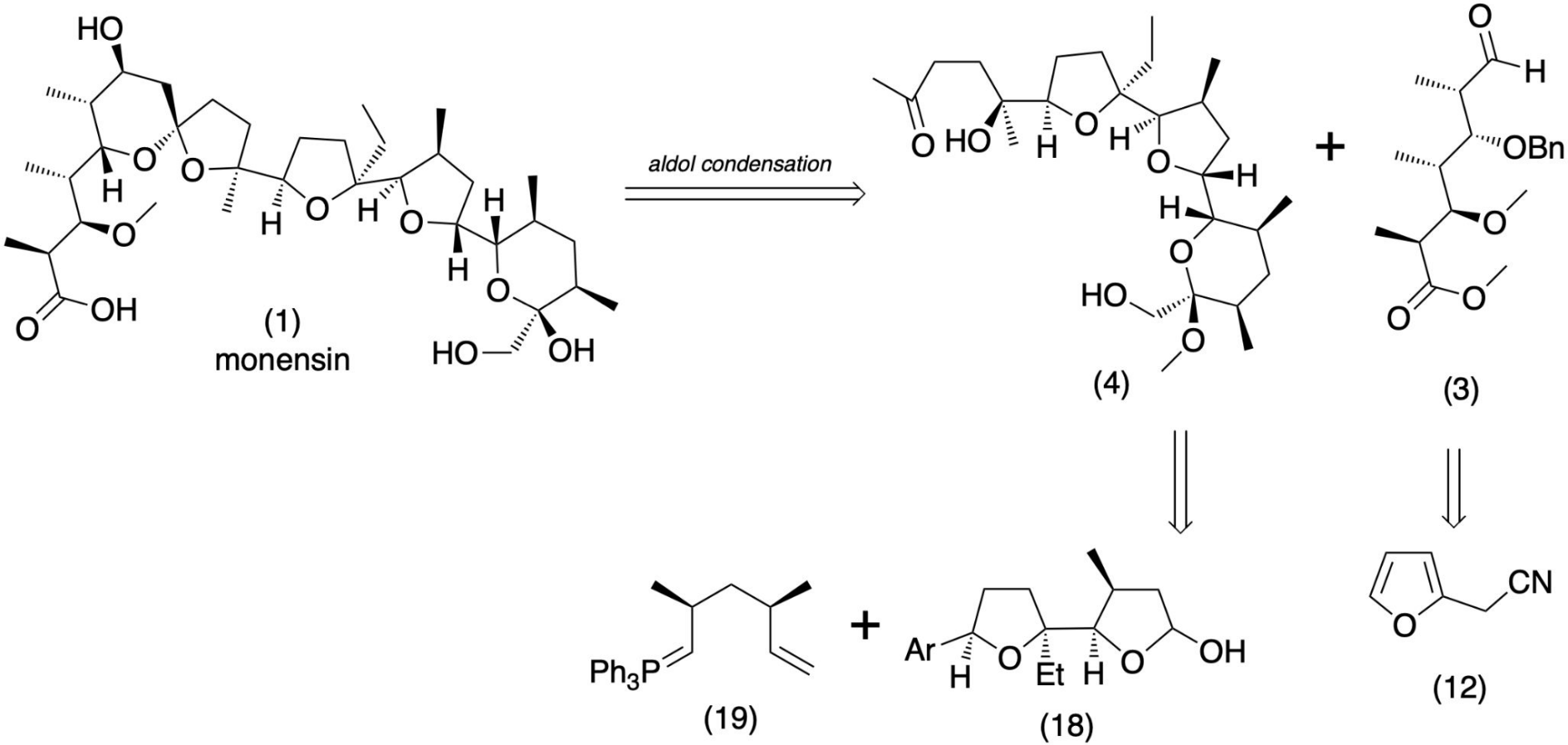
Of the 26 carbon atom's in Monensin's backbone, 17 are stereogenic and six of those are contiguous. Coupled with a spiroketal moiety, three hydrofuran rings and two hydropyran rings, the molecule was an attractive synthetic target.

*1. A*gtarap, A.; Chamberlain, J.W.; Pinkerton, M.; Stein-rauf, L. *J. Am. Chem. Soc.* **1967**, 89, 5737

2. Polyether Antibiotics : Naturally Occurring Acid Ionophores. Westley J.W.; Marcel Dekker: New York (**1982)** *Vol. 1-2.*

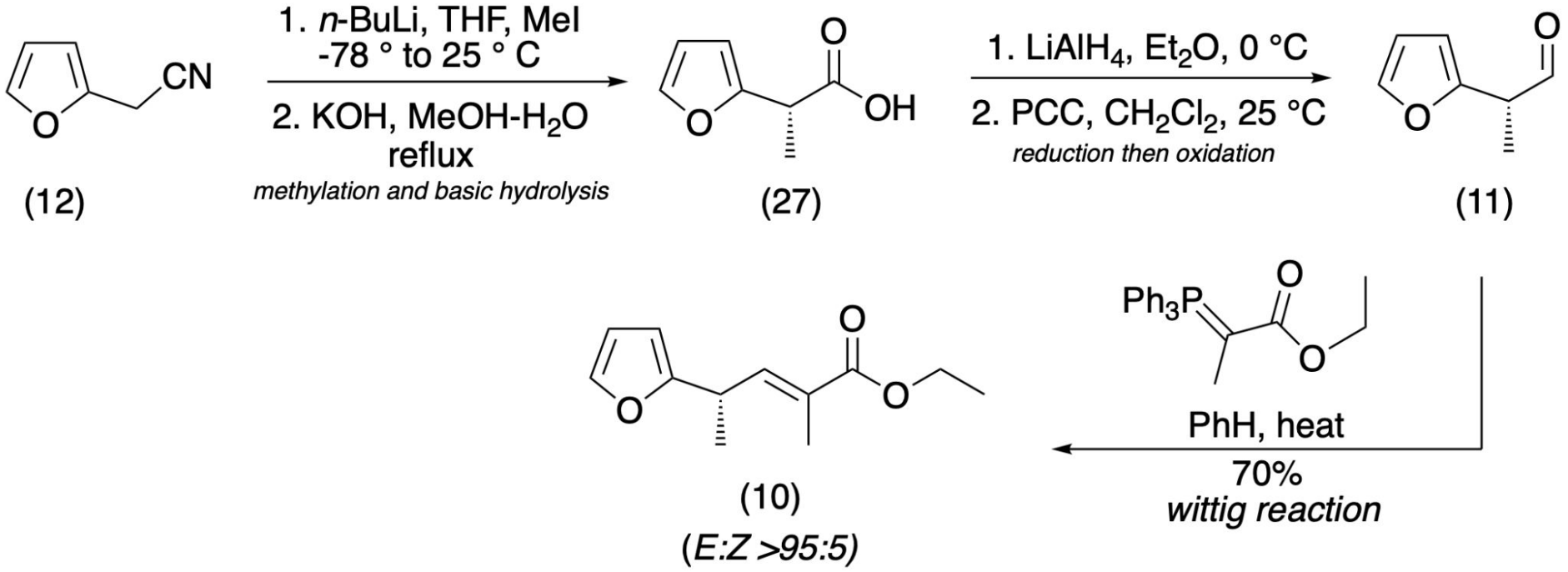
3. Stark, W.M. In *Fermentation Advances,* Perlman, D., Ed., Academic Press: New York, **1969**, 517

Retrosynthetic Analysis of Monensin



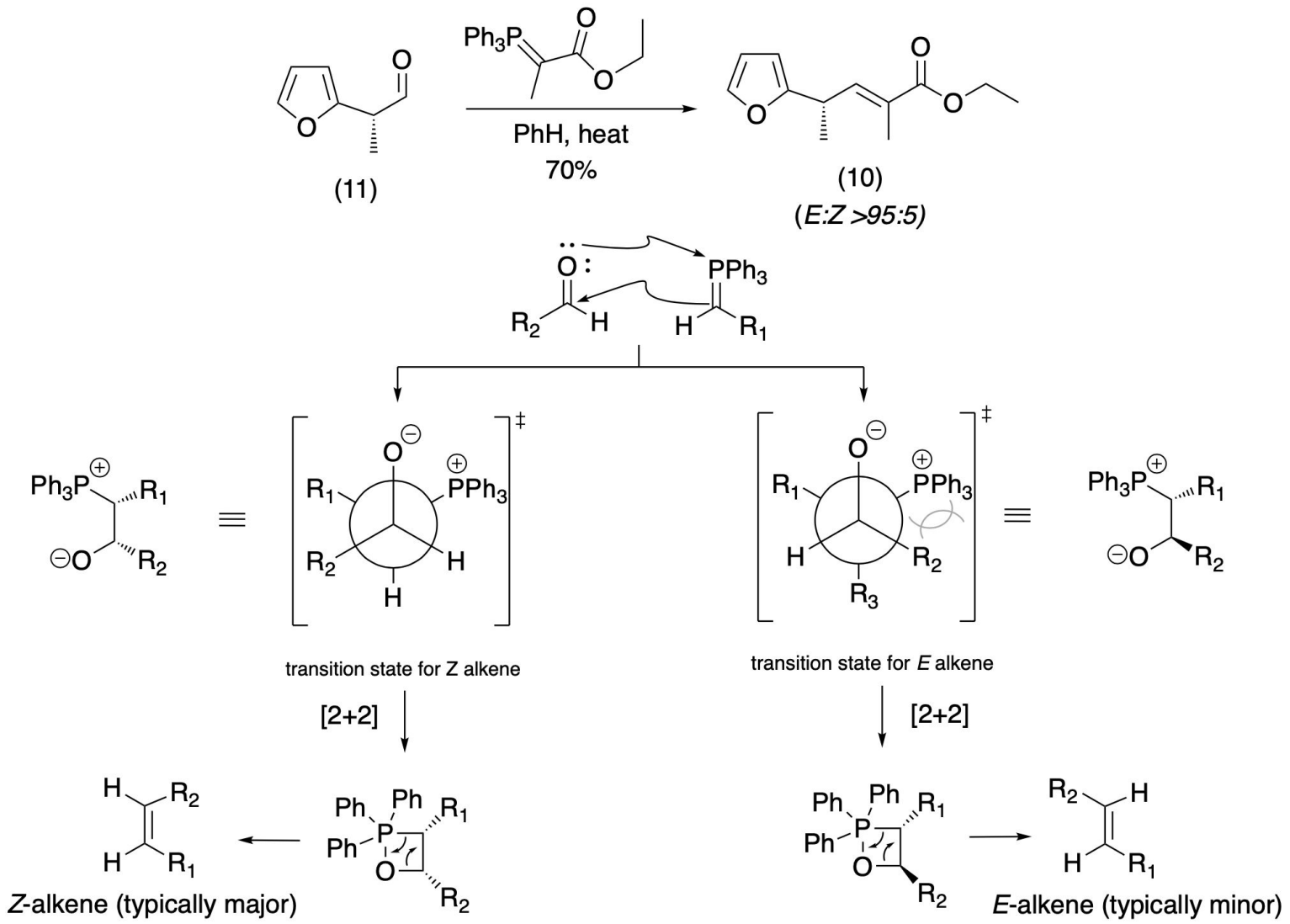
Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

Efforts Towards the Synthesis of Intermediate 3 (1)



Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

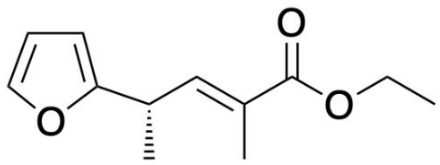
The Wittig Reaction



Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

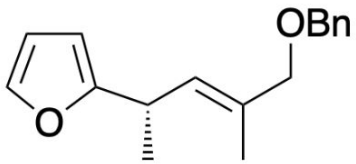
Valiulin, R. A. *Organic Chemistry: 100 must-know mechanisms*; De Gruyter: Berlin, 2020.

Efforts Towards the Synthesis of Intermediate 3 (2)



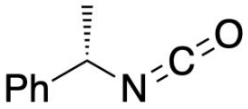
(±)-(10)
(*E:Z* >95:5)

1. $LiAlH_4$, Et_2O, 25 °C
2. BnBr, KH, DMF-THF, 0 °C
(95% overall)
oxidation and protection



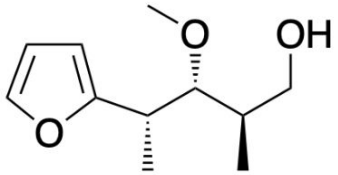
(±)-(9)

B_2H_6, THF, 0 °C; then KOH, H_2O_2
(85%)
hydroboration



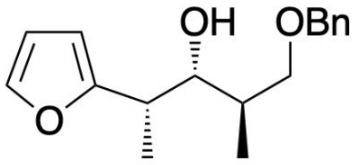
(*S*)-(-)-α-methyl-benzyiisocyanate

Et_2N, 50 °C
2. resolution
3. $LiAlH_4$

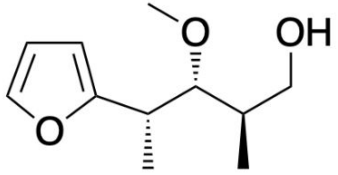


(±)-(29)

1. KH, MeI, DMF-THF
0 °C
2. H_2, 10% Pd/C
MeOH, 25 °C
(88% overall)
alkylation and deprotection

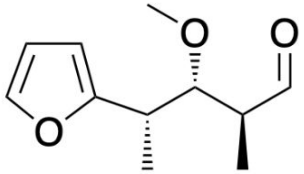


(±)-(28)
(8:1 mixture of diastereoisomers in favor of 28)



(-)-(29)

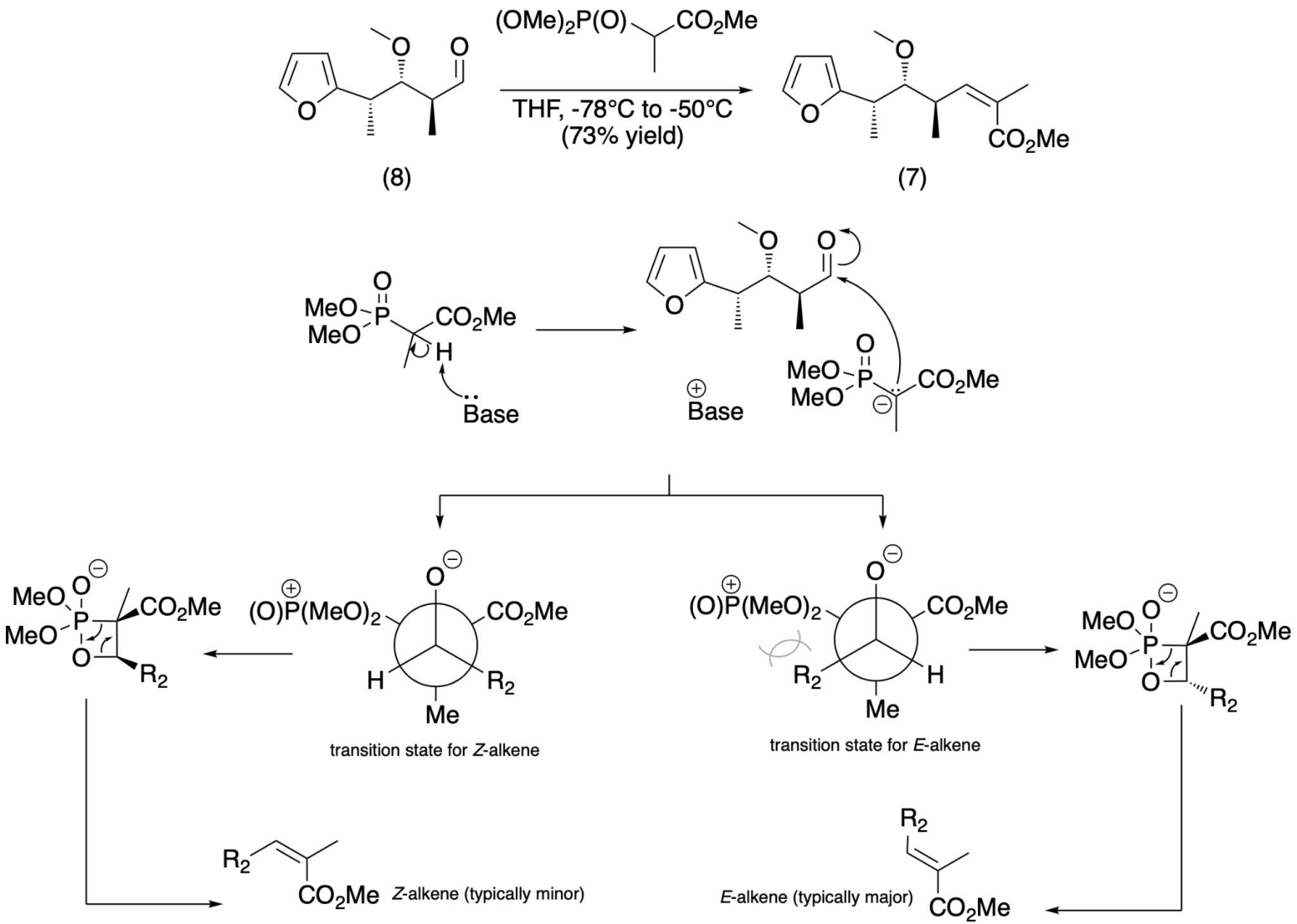
PCC, CH_2Cl_2, 25 °C
(88% yield)
oxidation



(8)

Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

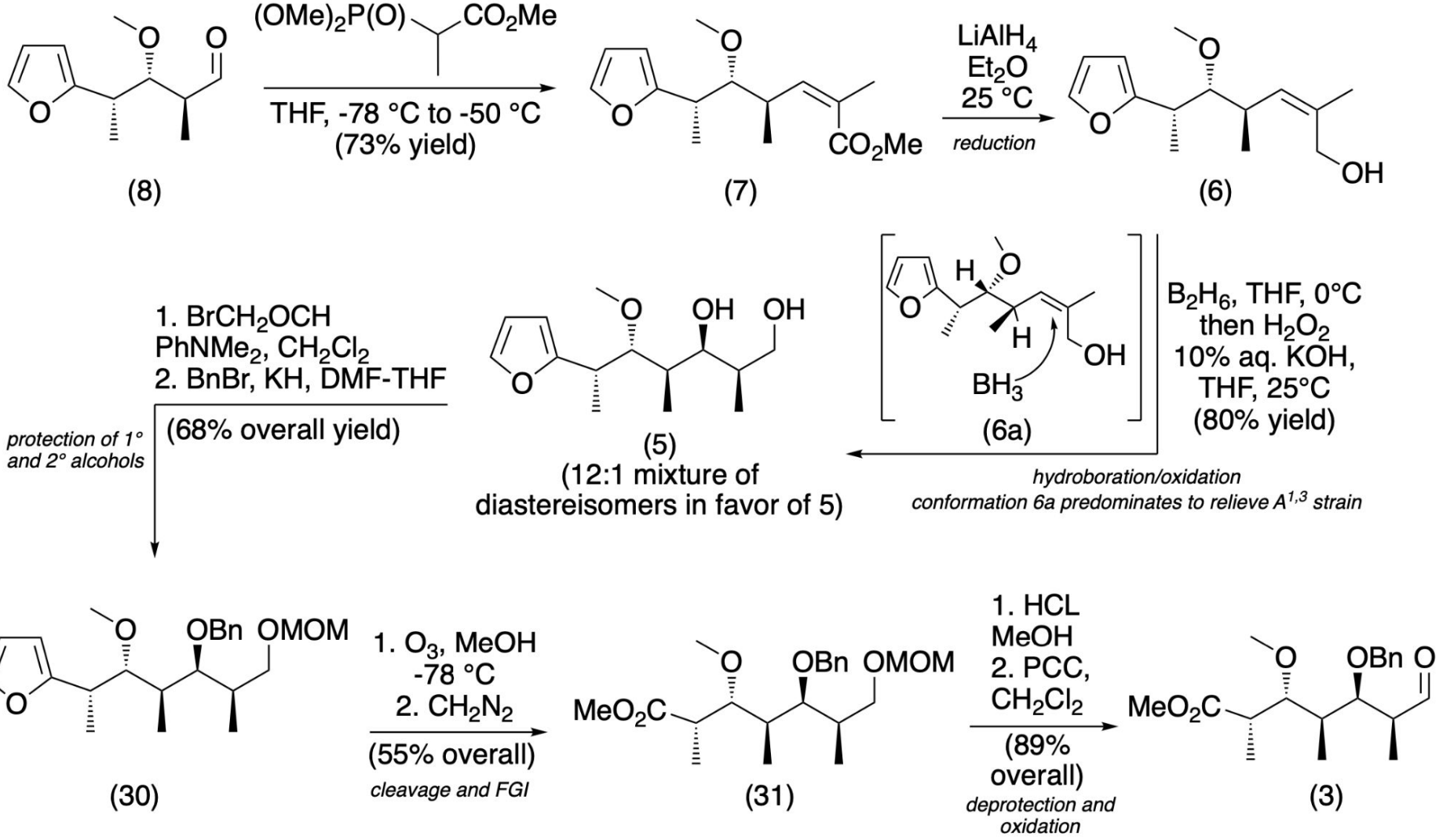
Horner-Wadsworth-Emmons Olefination



Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

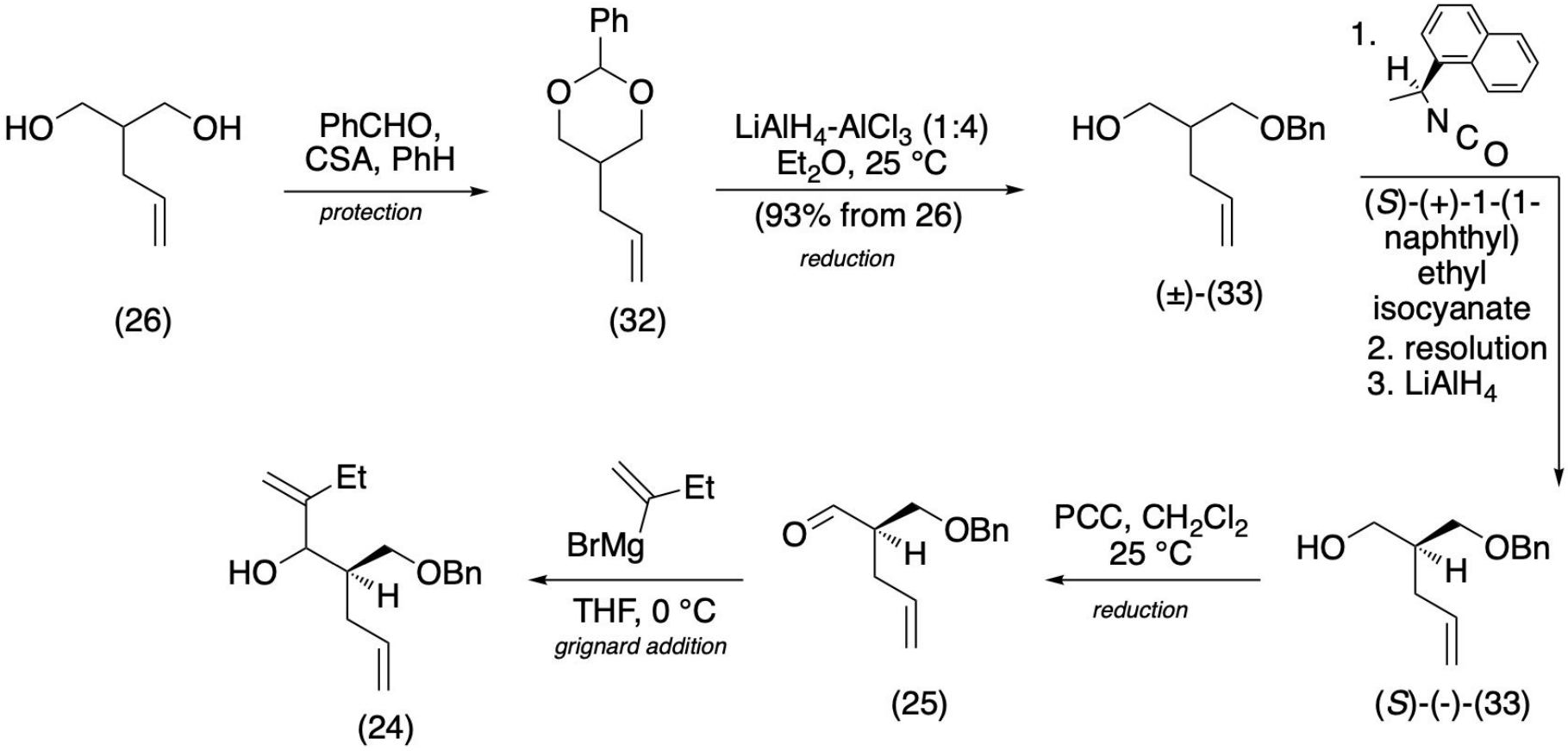
Valiulin, R. A. *Organic Chemistry: 100 must-know mechanisms*; De Gruyter: Berlin, 2020.

Efforts Towards the Synthesis of Intermediate 3 (3)



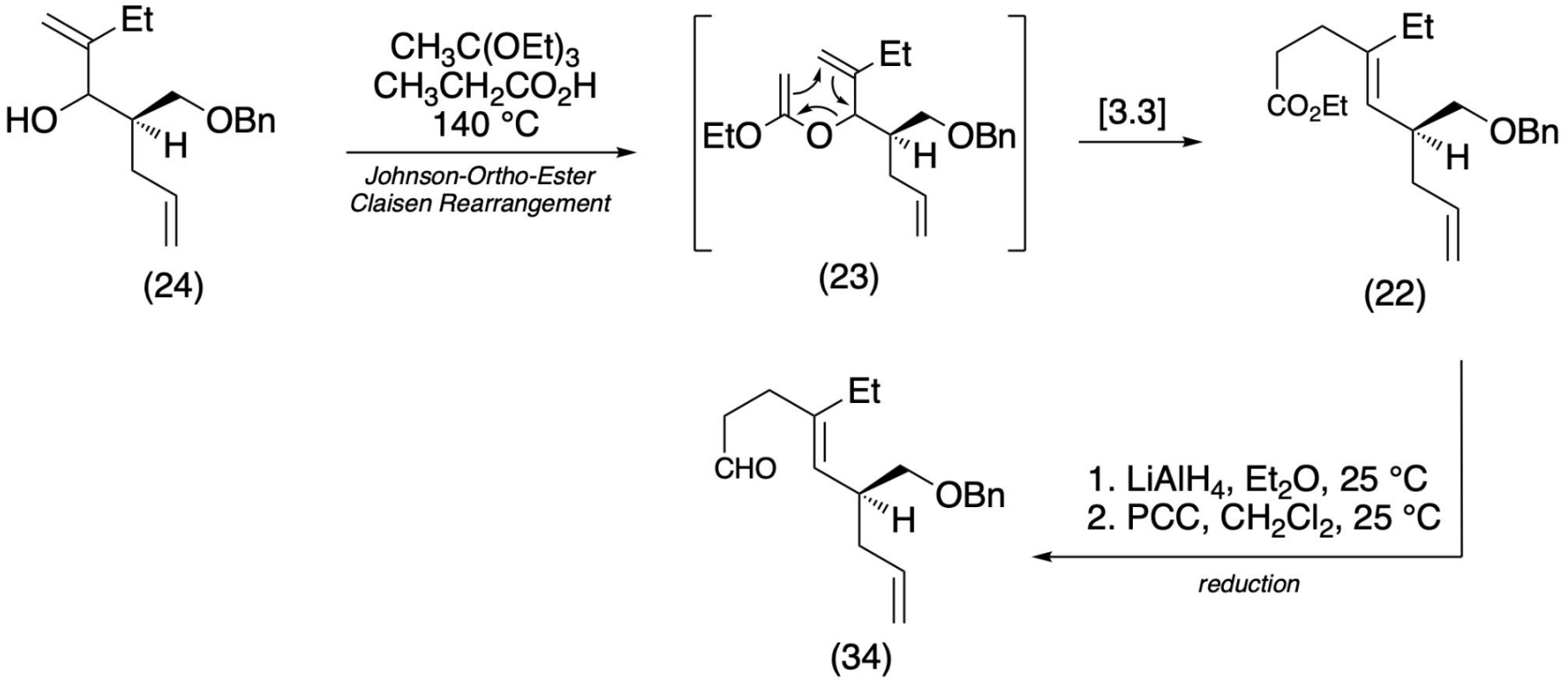
Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

Efforts Towards the Synthesis of Intermediate 4 (1)



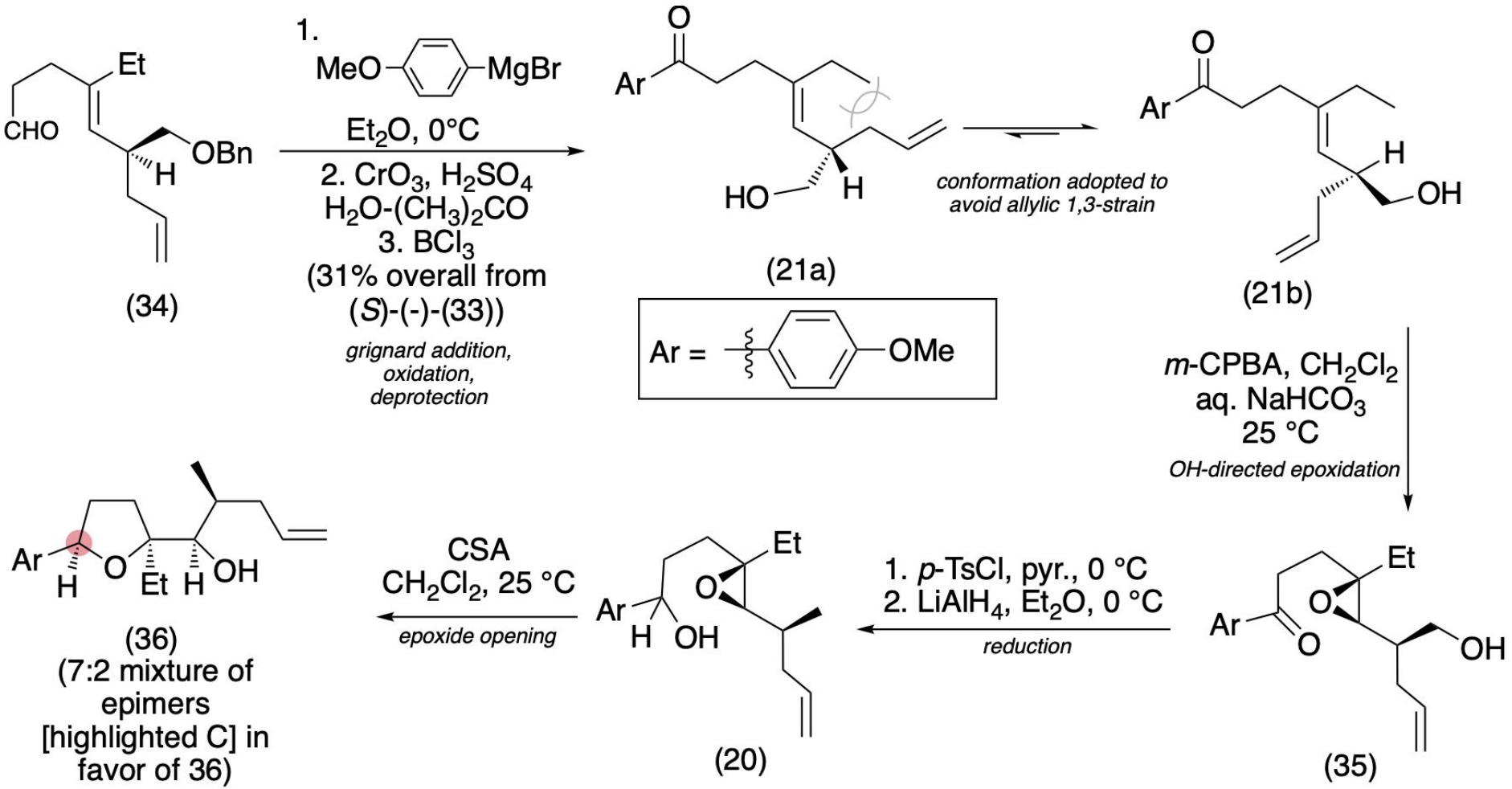
Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

Efforts Towards the Synthesis of Intermediate 4 (2)



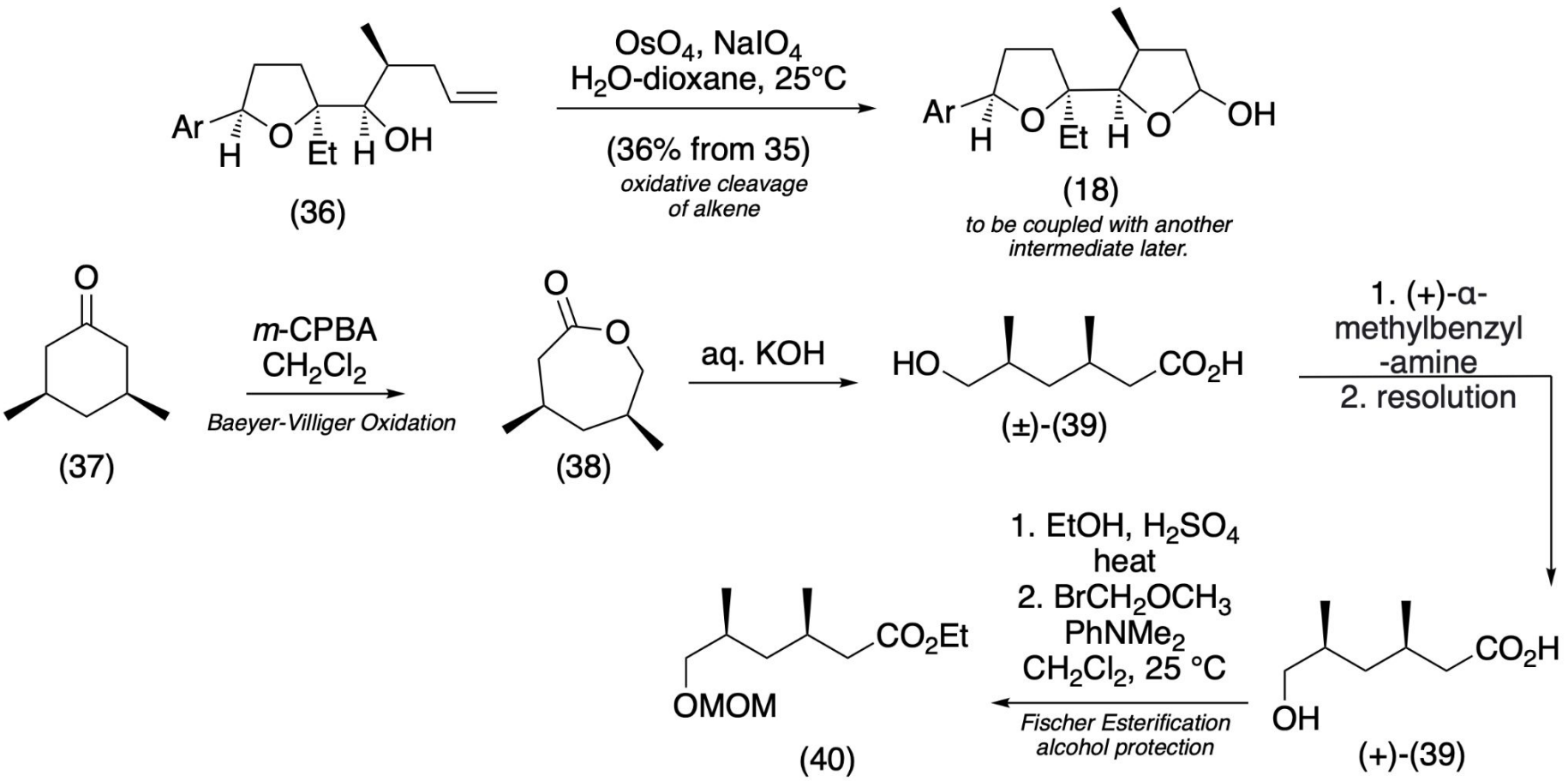
Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

Efforts Towards the Synthesis of Intermediate 4 (3)



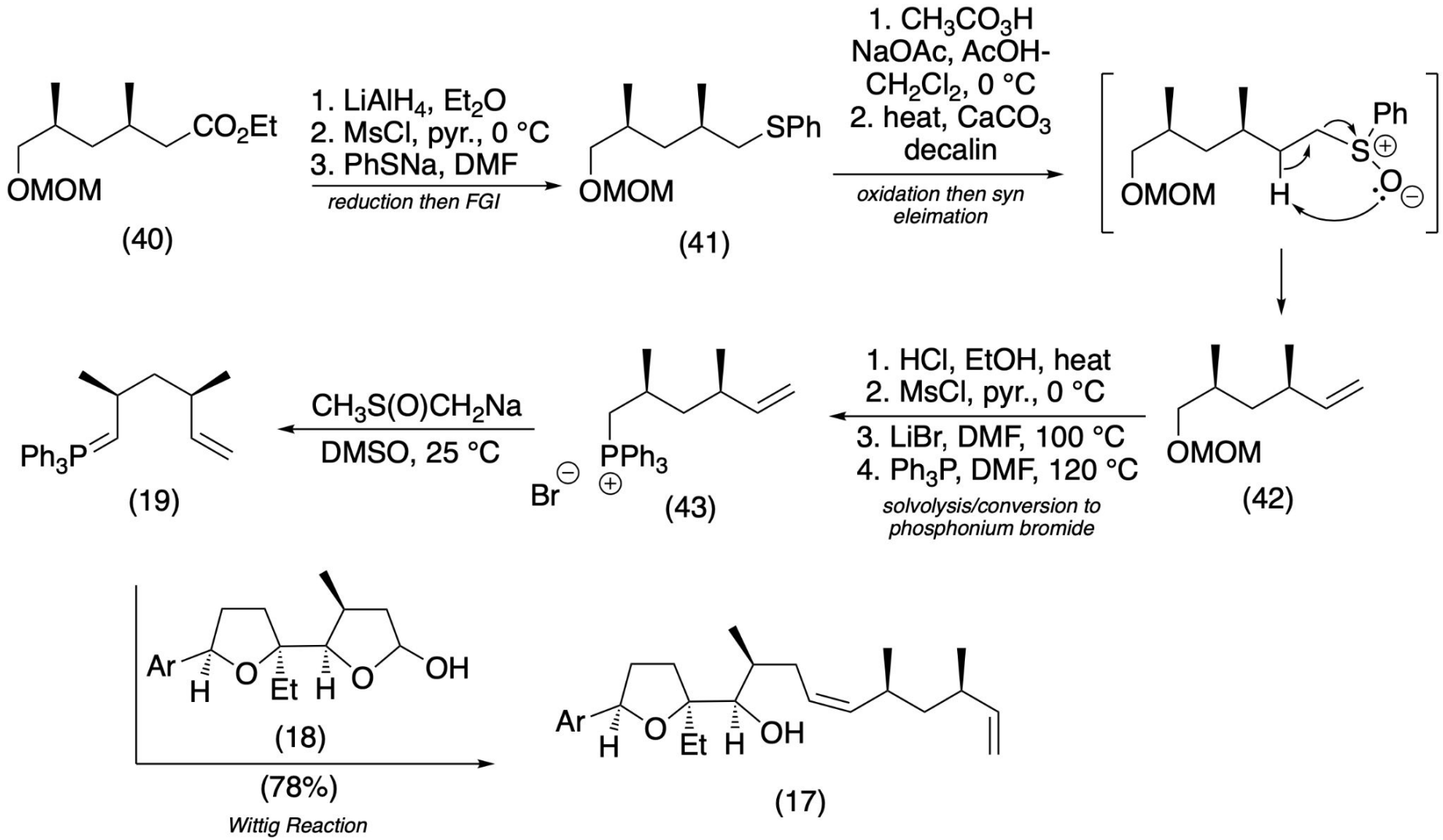
Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

Efforts Towards the Synthesis of Intermediate 4 (4)



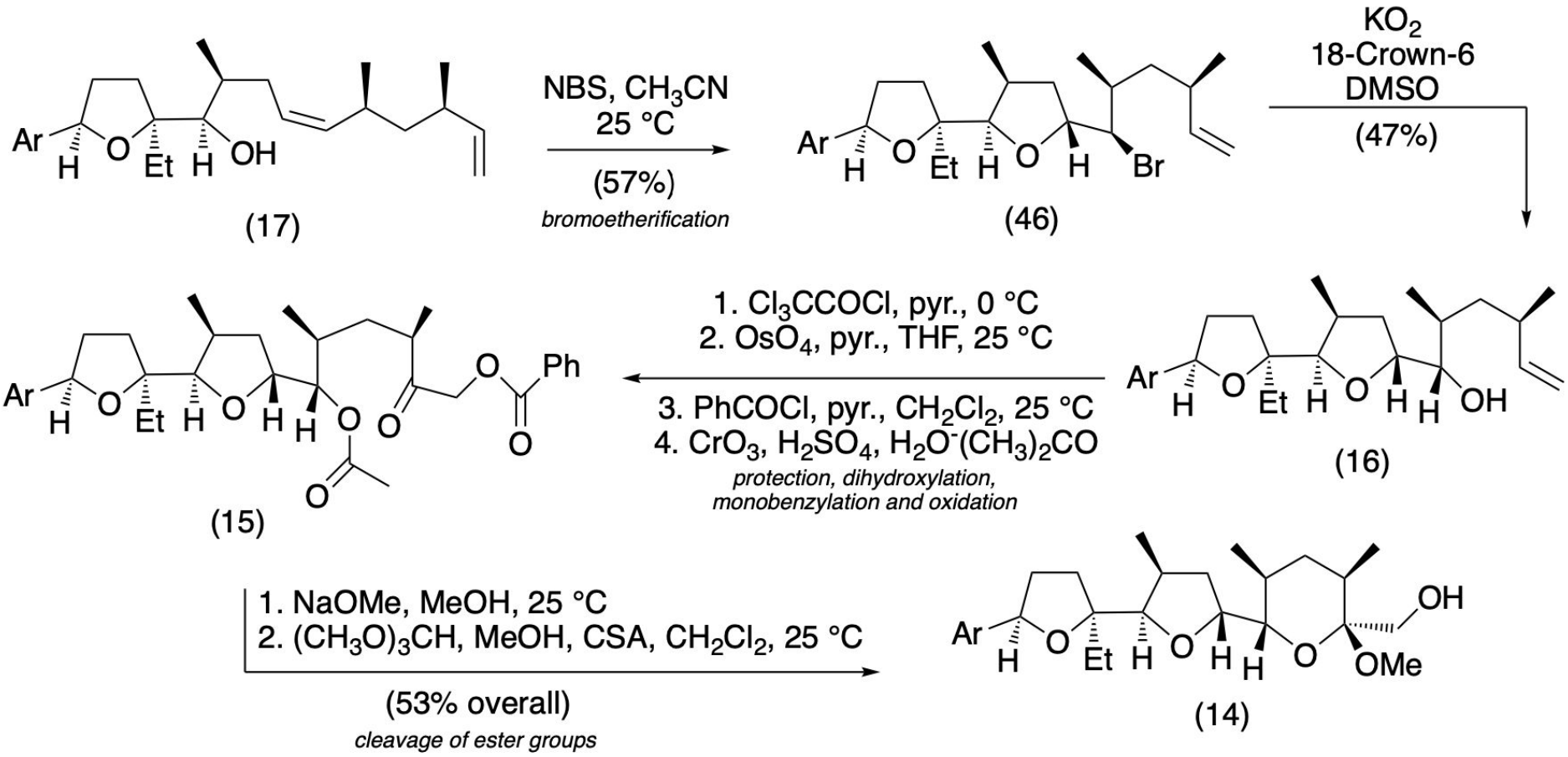
Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

Efforts Towards the Synthesis of Intermediate 4 (5)



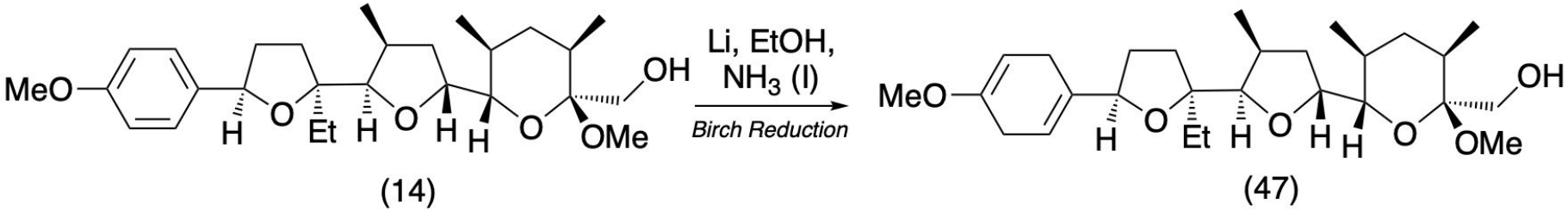
Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

Efforts Towards the Synthesis of Intermediate 4 (6)

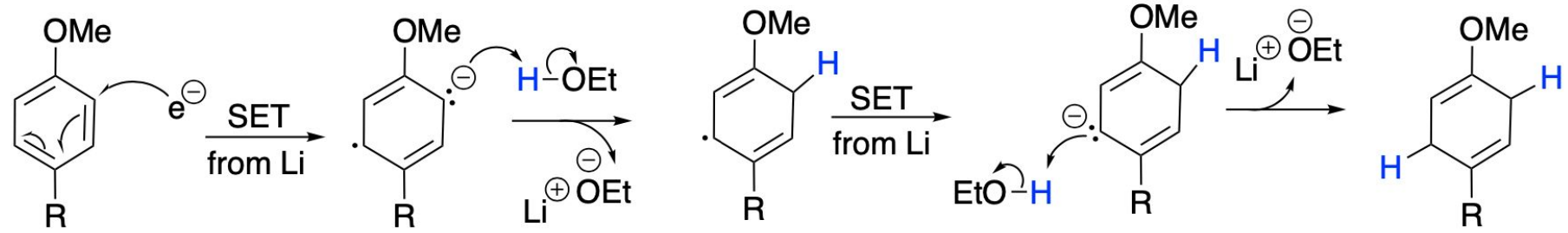


Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

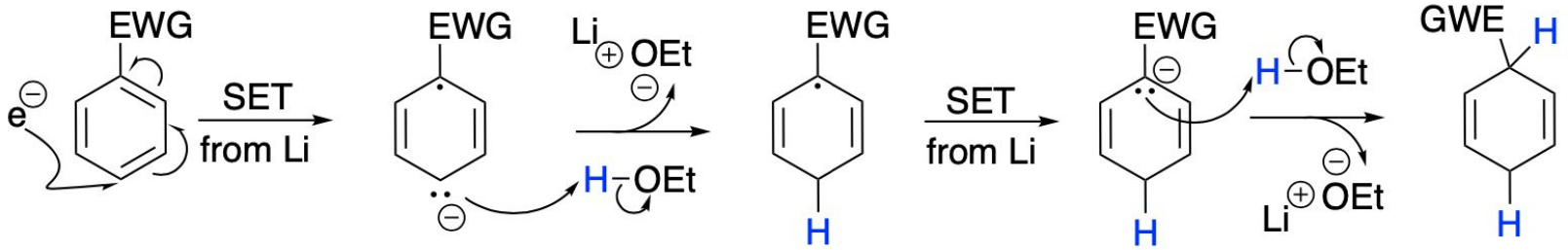
The Birch Reduction



General Mechanism (with EDG attached):



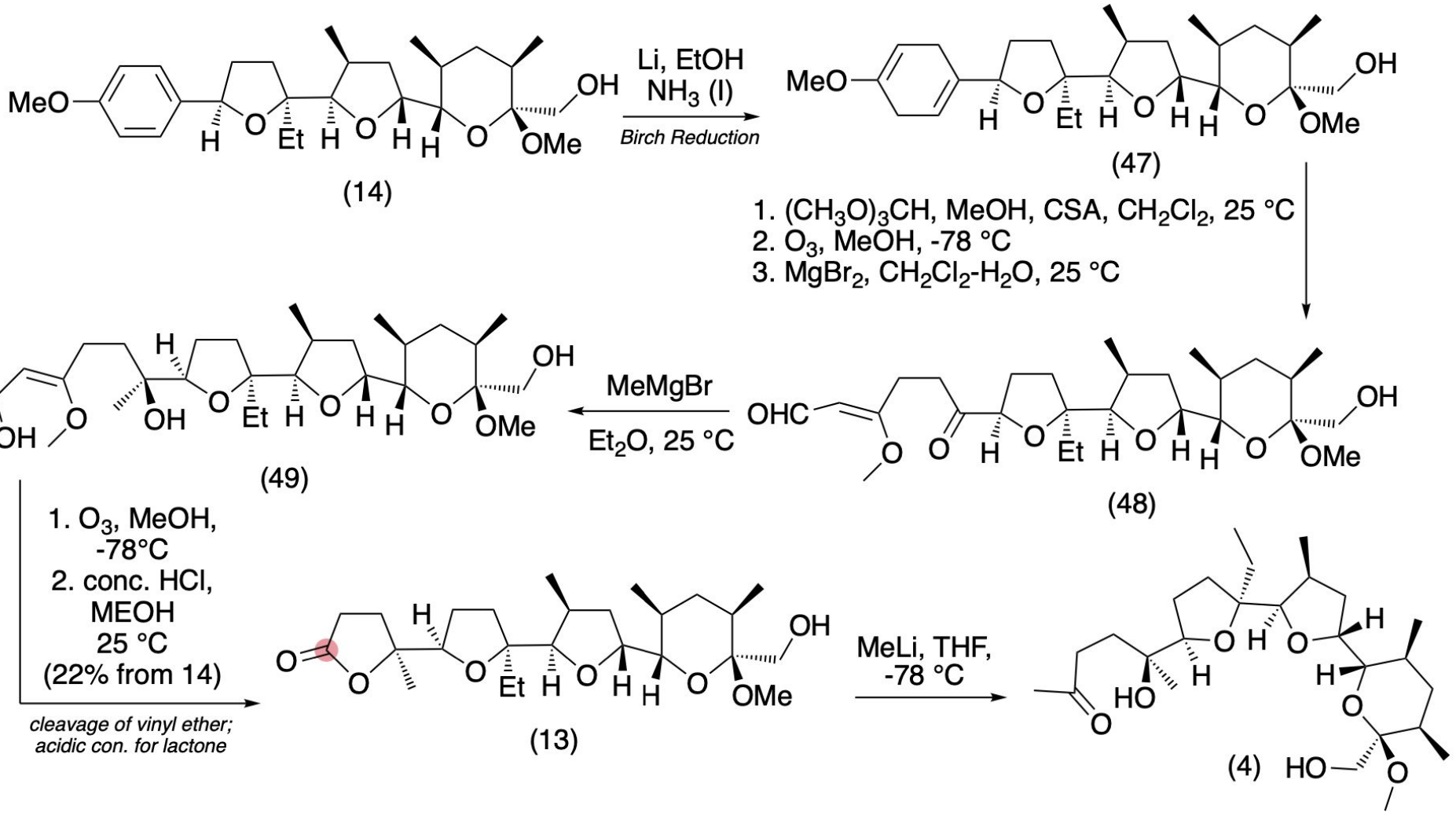
General Mechanism (with EWG attached):



Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

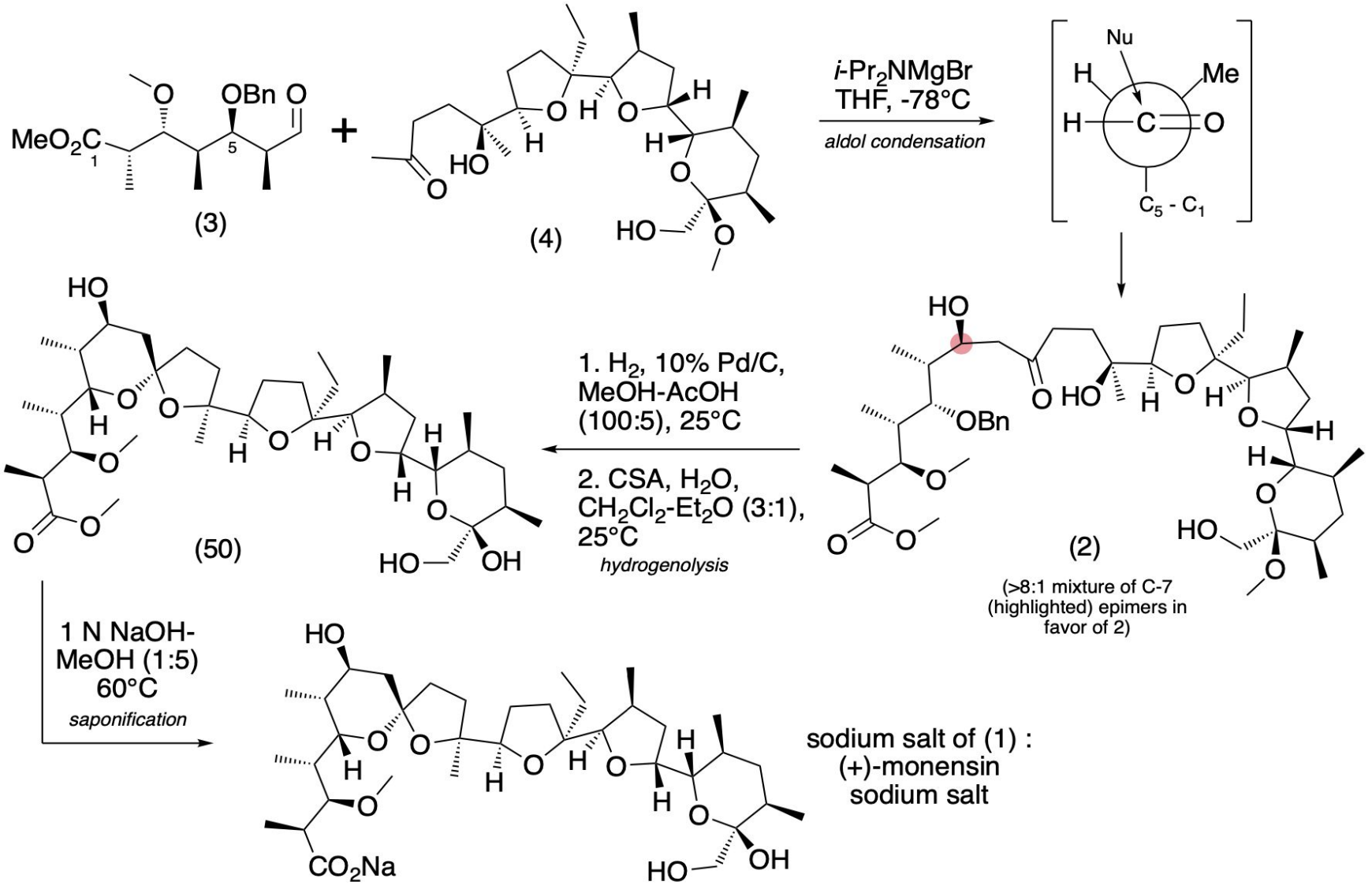
Valiulin, R. A. *Organic Chemistry: 100 must-know mechanisms*; De Gruyter: Berlin, 2020.

Efforts Towards the Synthesis of Intermediate 4 (7)



Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

The Final Steps to the Synthesis of Monensin



Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.

The Conclusion

- The Kishi group reported the first total synthesis of Monensin.
- The synthesis was especially noted for two things:
  - Its convergence and, more importantly,
  - Exploitation of acyclic stereocontrol (particularly allylic 1,3-strain) in order to create the desired stereogenic centers within the molecule.

Nicolaou, K. C.; Sorensen, E. J.; Chen, J. S.; Snyder, S. A. *Classics in total synthesis*; VCH: Weinheim Allemagne, 1996.