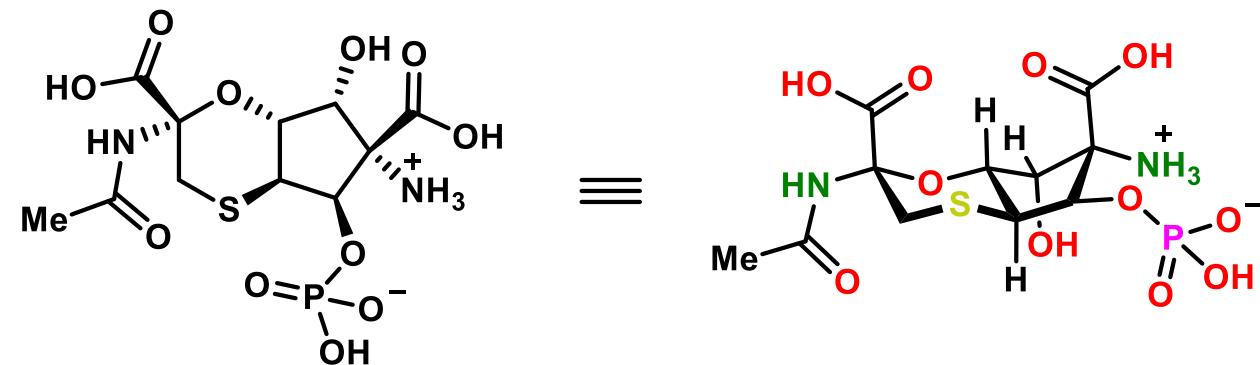


The Baran Total Synthesis of Tagetitoxin



J. Am. Chem. Soc. 2020, 142, 13683-13688

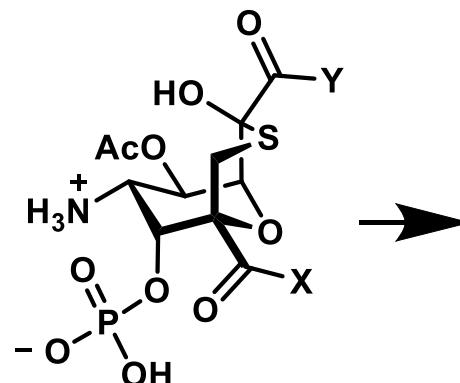
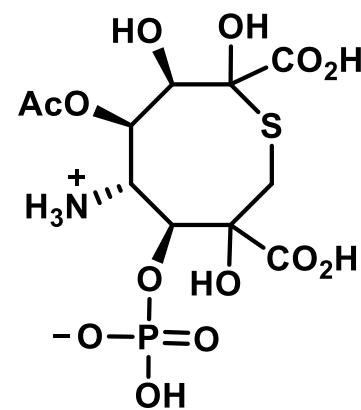
John Hoskin
2/05/2021

Tagetitoxin: a Structural Quagmire



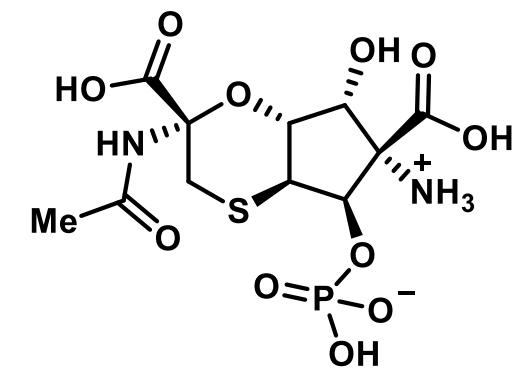
- causes apical chlorosis and leaf spot
- inhibits chloroplast RNA polymerase III and also bacterial RNA polymerase
- at least 7 attempted syntheses of the 1989 structure, none successful

Tagetes erecta : the African Marigold



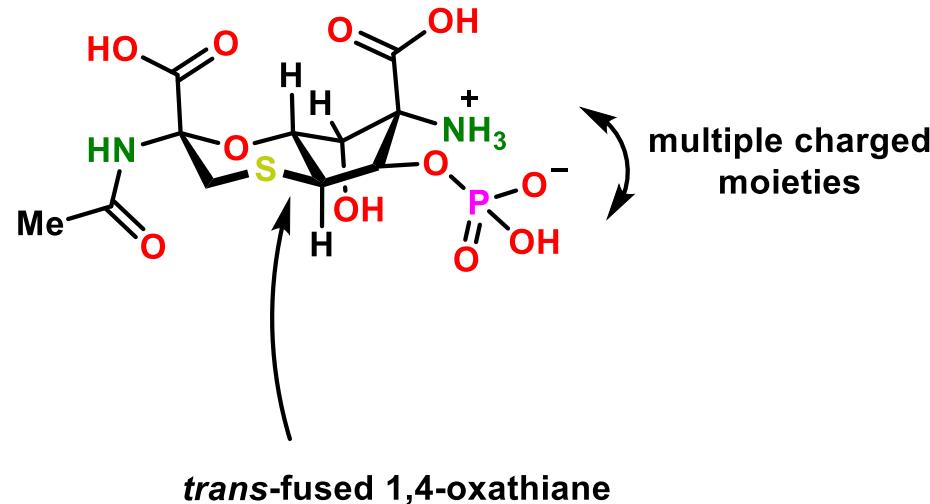
MW = 678
(no structure proposed)

Gronwald, 2005

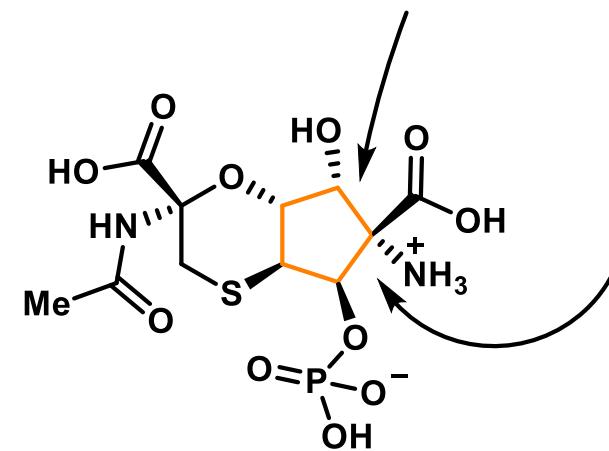


A True Synthetic Challenge

11 carbons, 15 heteroatoms !

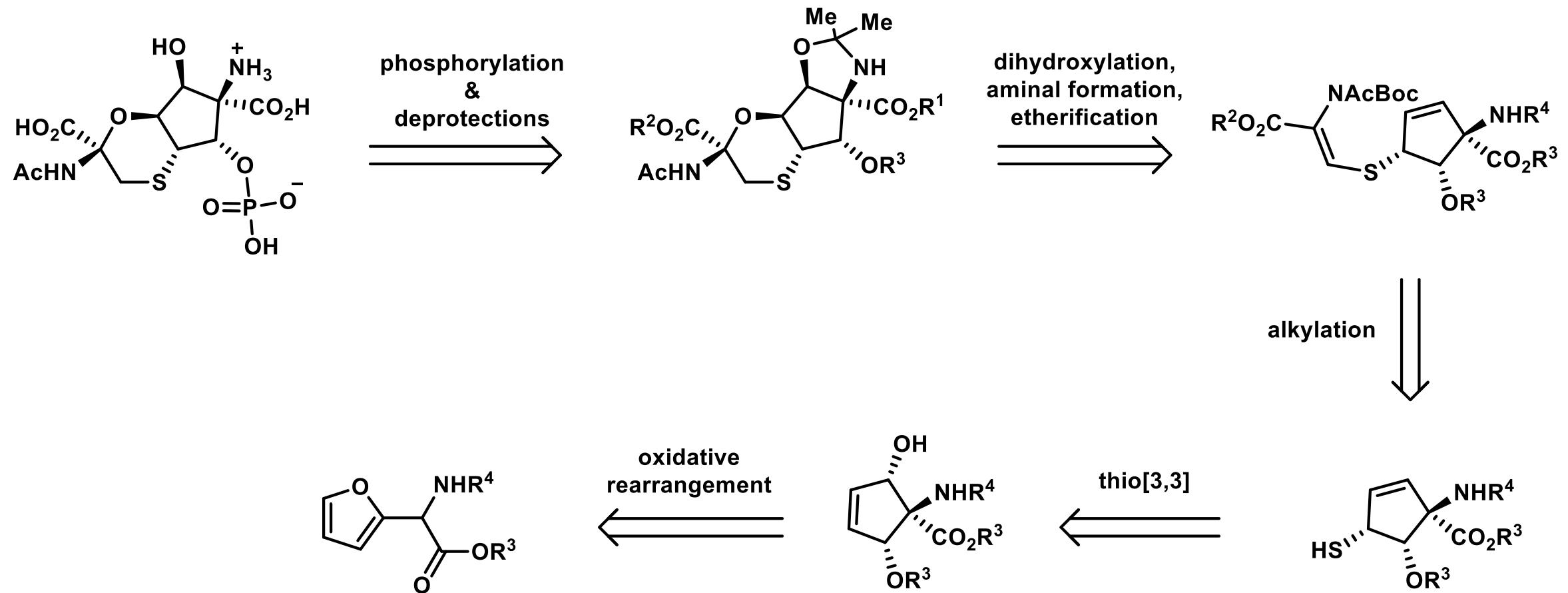


potential retro-aldol concerns

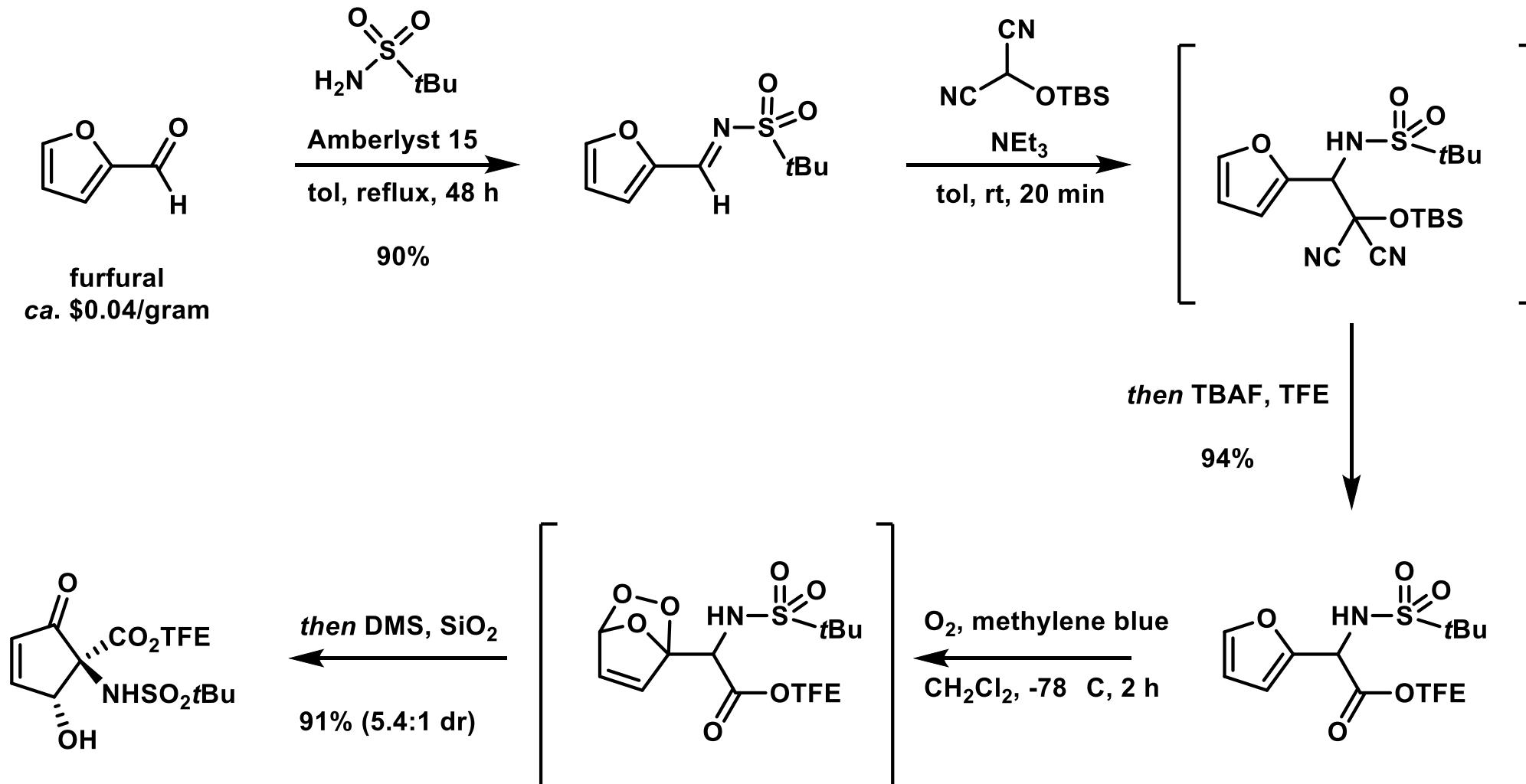


Plus, final structure is highly acid-sensitive

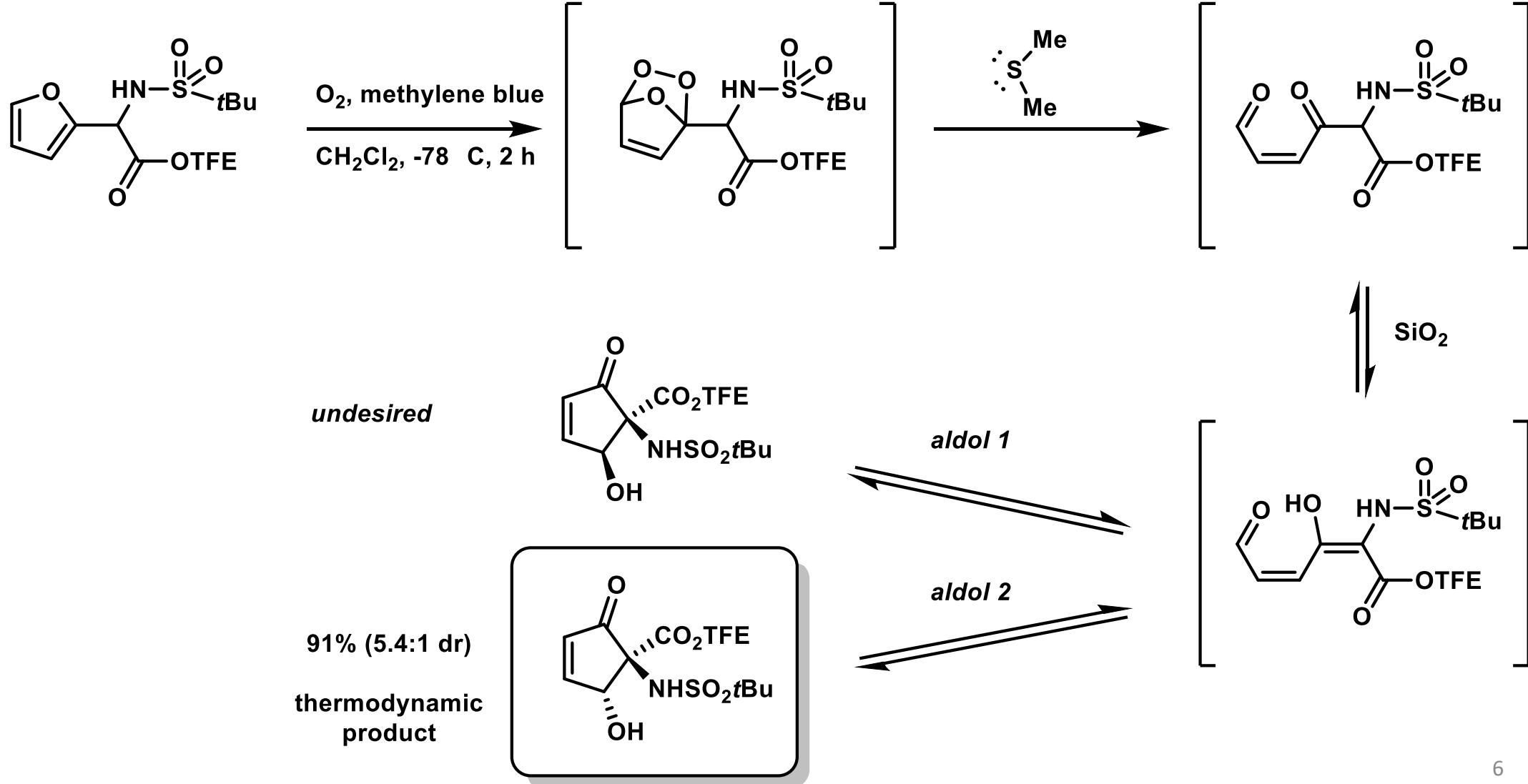
The Retrosynthetic Plan



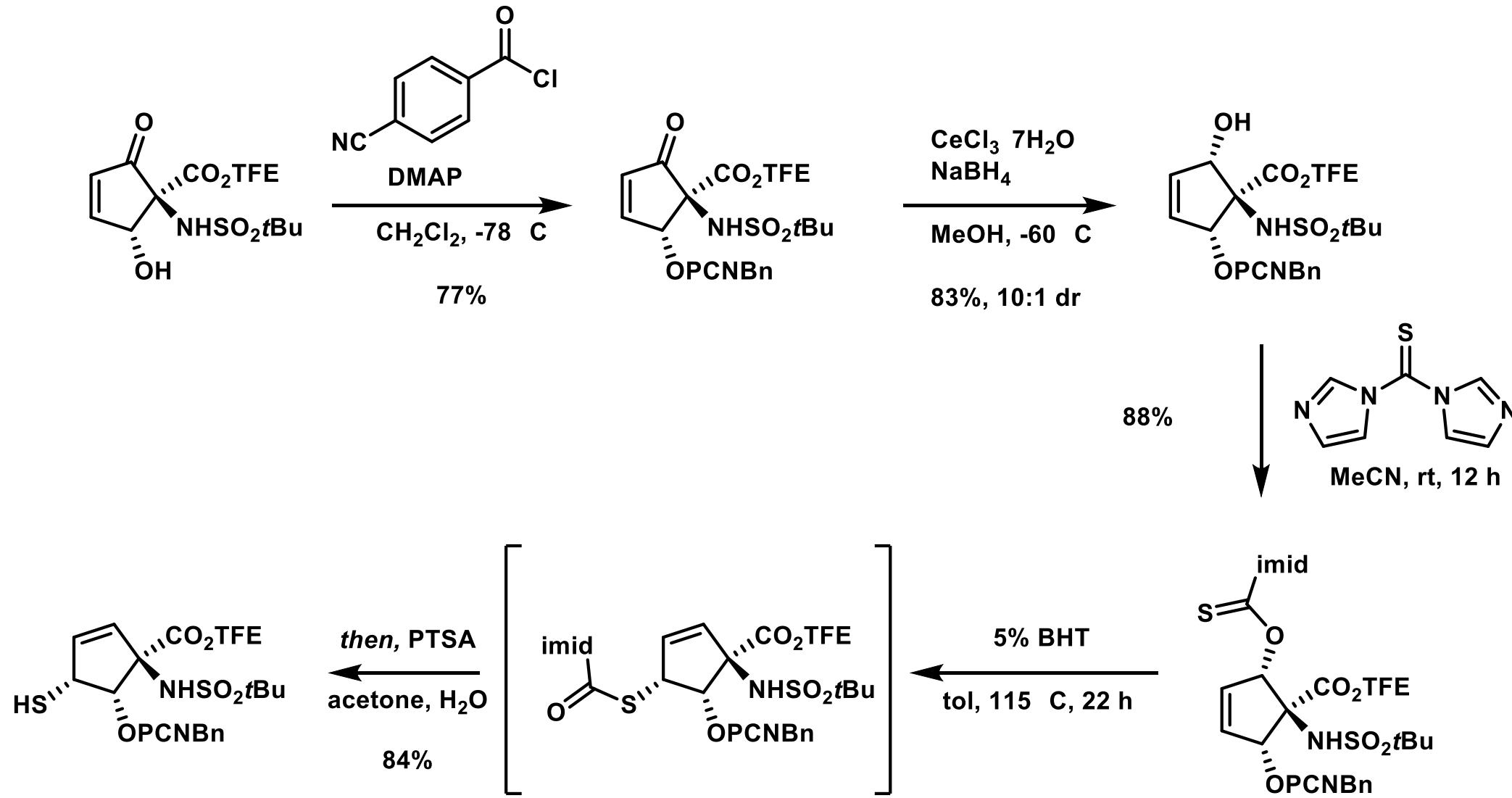
A 3-Step Synthesis of the Cyclopentene Core



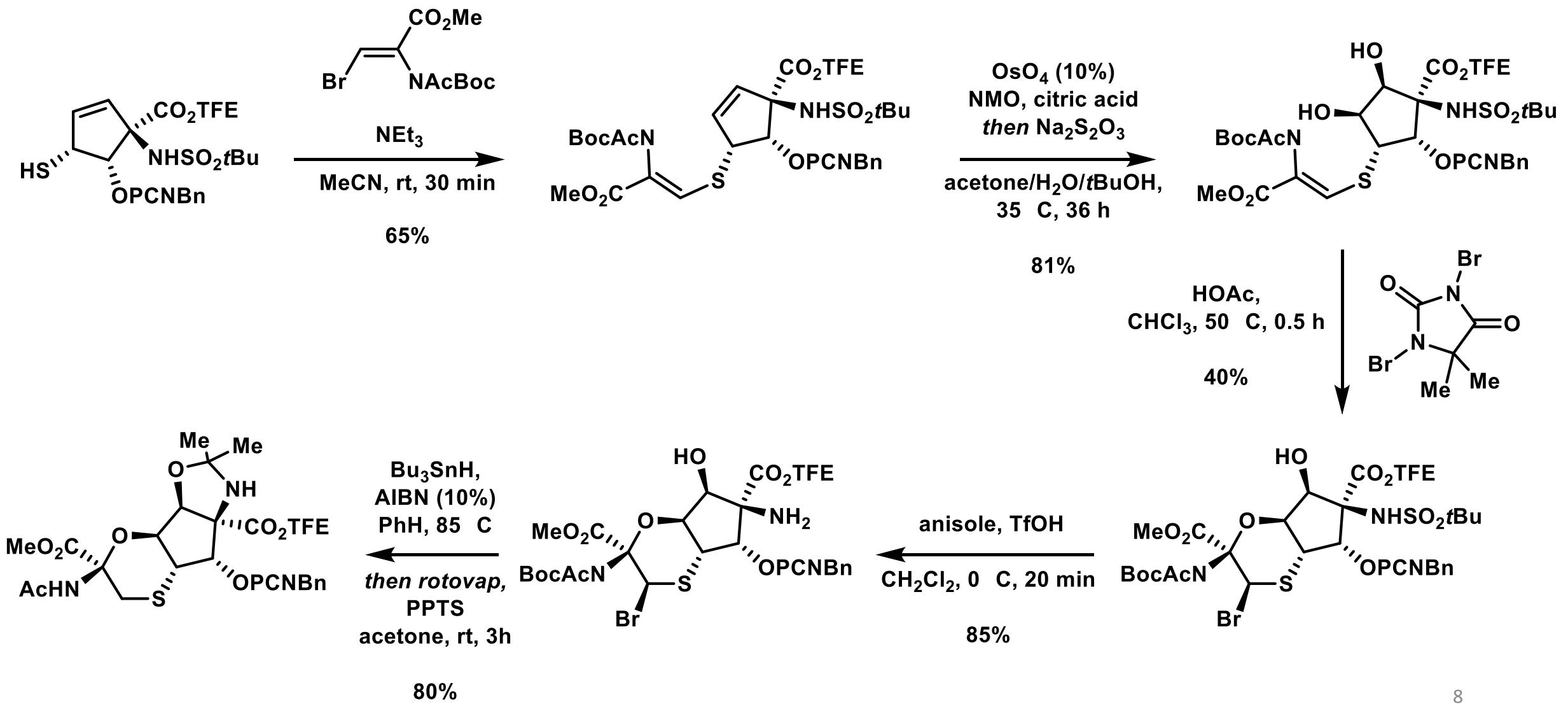
A Fortuitous Stereochemical Outcome



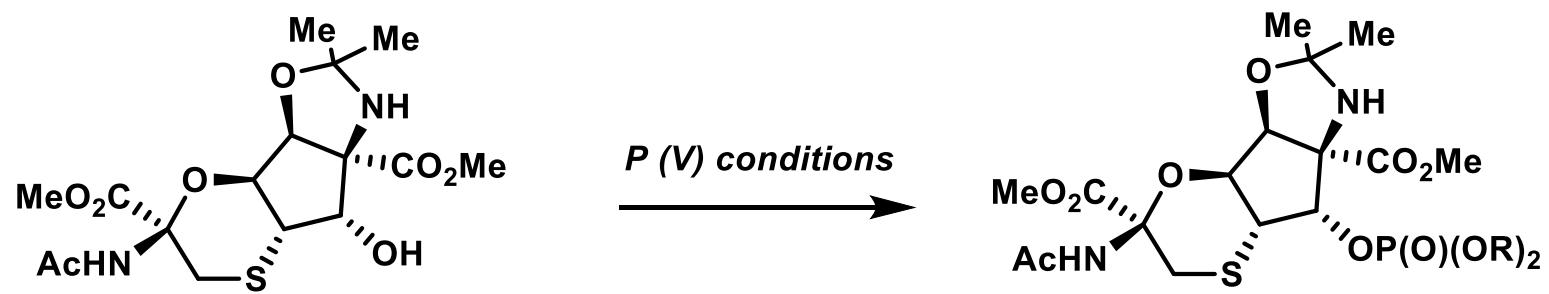
A Net Reductive Transposition to Install the Sulfer



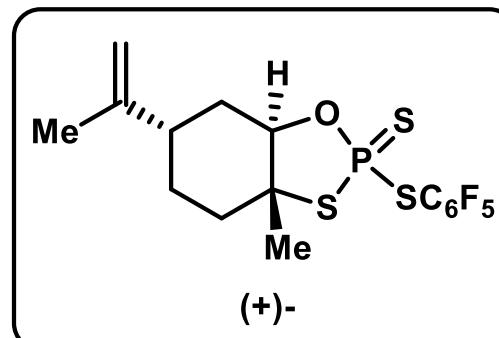
Obtaining the Correct Oxidation States



An Unexpectedly Challenging Phosphorylation



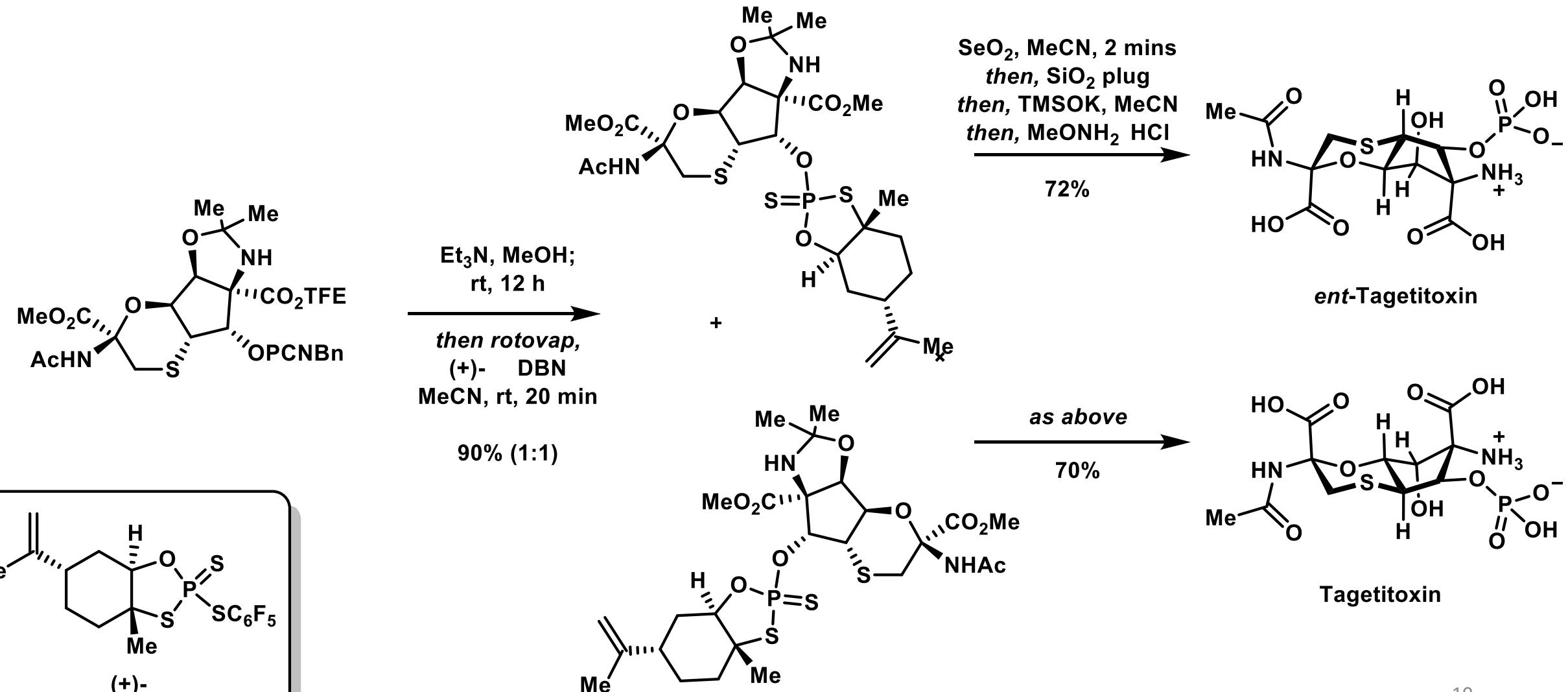
- | | |
|--|---|
| • POCl_3 , Et_3N , THF, 0°C ; H_2O | decomposition |
| • $\text{Bu}_4\text{N}^+\text{H}_2\text{PO}_4^-$, Cl_3CCN , CH_3CN , rt | decomposition |
| • $(\text{PhO})_2\text{POCl}$, Pyr., CH_2Cl_2 , rt | no reaction |
| • $(\text{PhO})_2\text{POCl}$, $t\text{BuOLi}$, THF, -78°C - rt | full conversion of SM, trace of product |
| • $(\text{PhO})_2\text{POCl}$, Et_3N , TiCl_4 (cat.), THF, rt | no reaction |



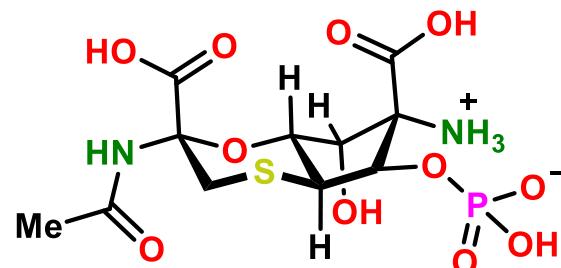
Phosphorous Sulfur Incorporation (PSI) Reagent

- designed for diastereoselective (at P) syntheses of phosphorothioate nucleotides
- in this case used for chiral separation

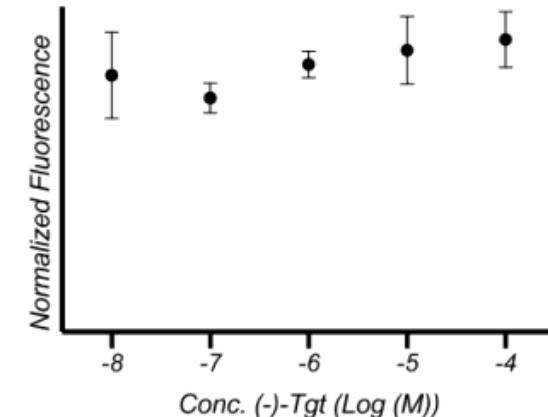
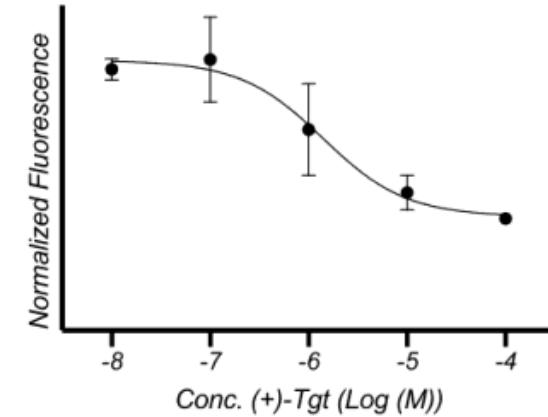
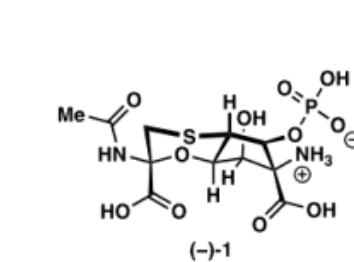
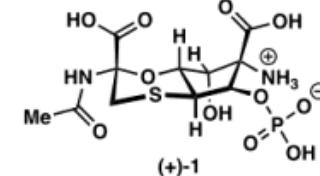
Completion and Determination of Absolute Stereochemistry



The Tagetitoxin Story can be Brought to a Close



- Structure solved nearly 80 years after initial disclosure
- 15 steps from furfural
- first use of the - reagent in total synthesis



Only natural Tagetitoxin inhibited e. coli RNA polymerase