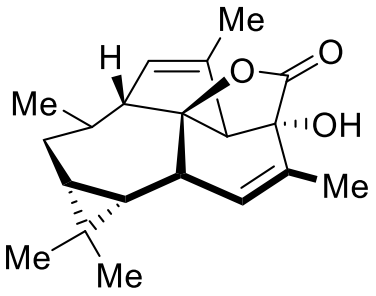
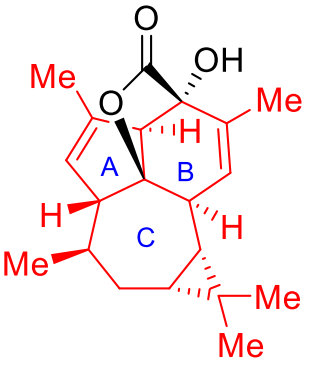
Enantioselective Total Synthesis of (+)-Euphorikanin A

Moritz J. Classen, Markus N. A. Böcker, Remo Roth, Willi M. Amberg,
and Erick M. Carreira* *J. Am. Chem. Soc.* **2021**, 143, 8261-8265.

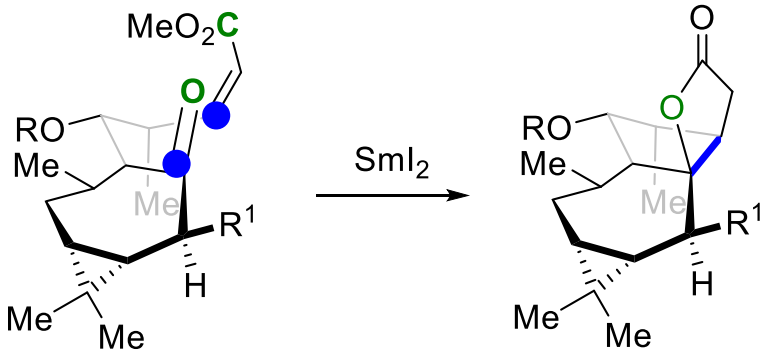
- First total synthesis of (+)-euphorikanin A, an ingenane-derived natural product
- Isolated in 2016 and identified as a novel diterpenoid from the roots of *Euphorbia kansui*, commonly known as kansui
- Extracts of the root have been widely used in traditional Chinese medicine. (+)-euphorikanin A has been shown to exhibit cytotoxicity against two human tumor cell lines (NCI-446 and HeLa)
- Features an unprecedented 5/6/7/3-fused tetracyclic skeleton
- Prepared in 19 steps from (+)-3-carene
- Key step is an SmI2-mediated ketyl-enoate cyclization cascade



(+)-Euphorikanin A (**1**)



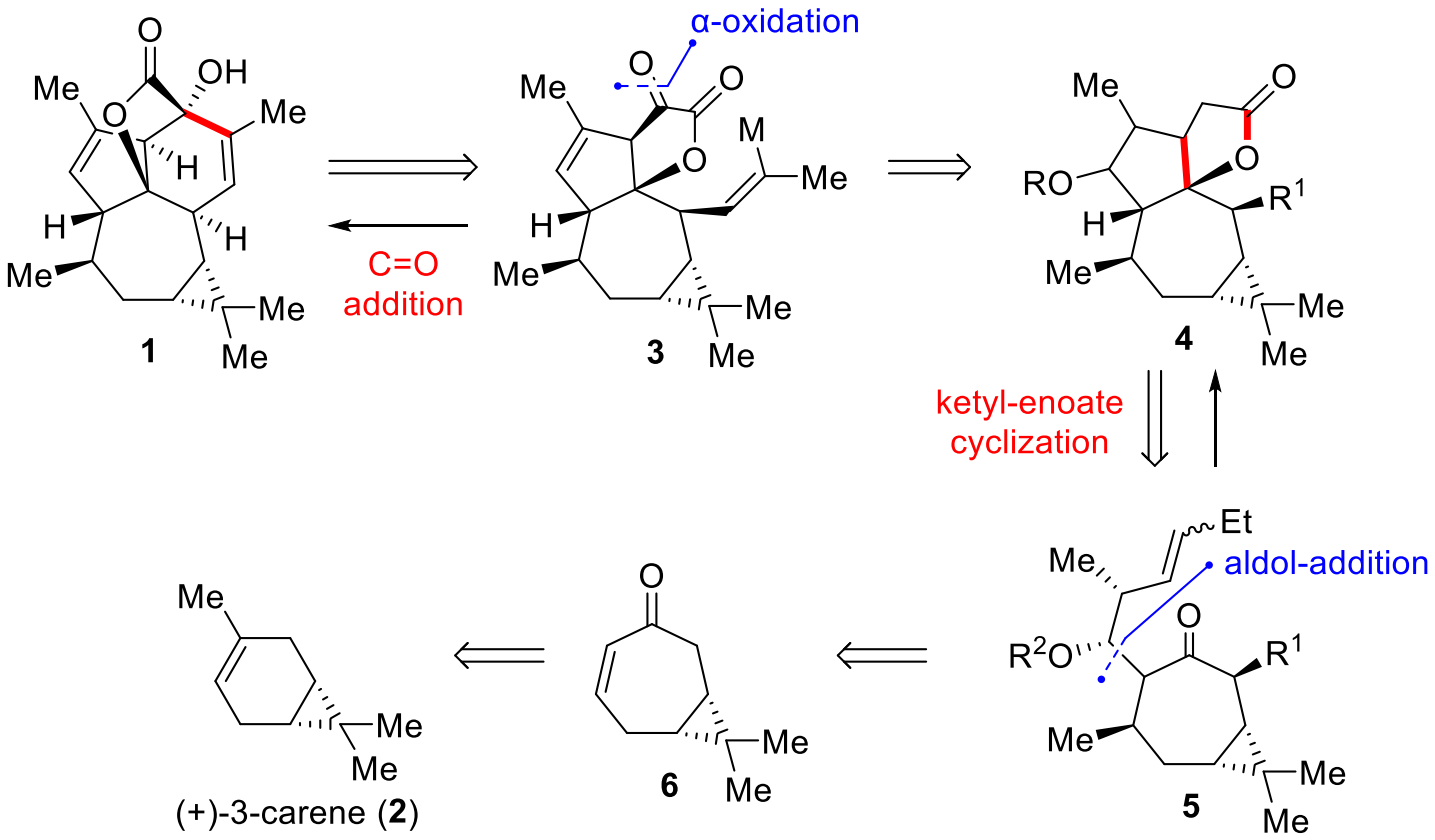
5/6/7/3-fused skeleton

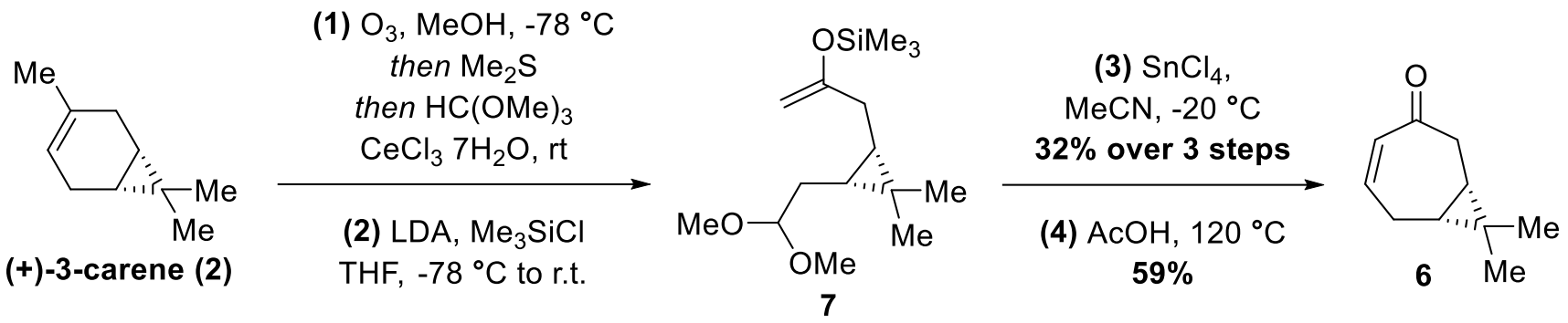


1-step Formation of A Ring & Lactone

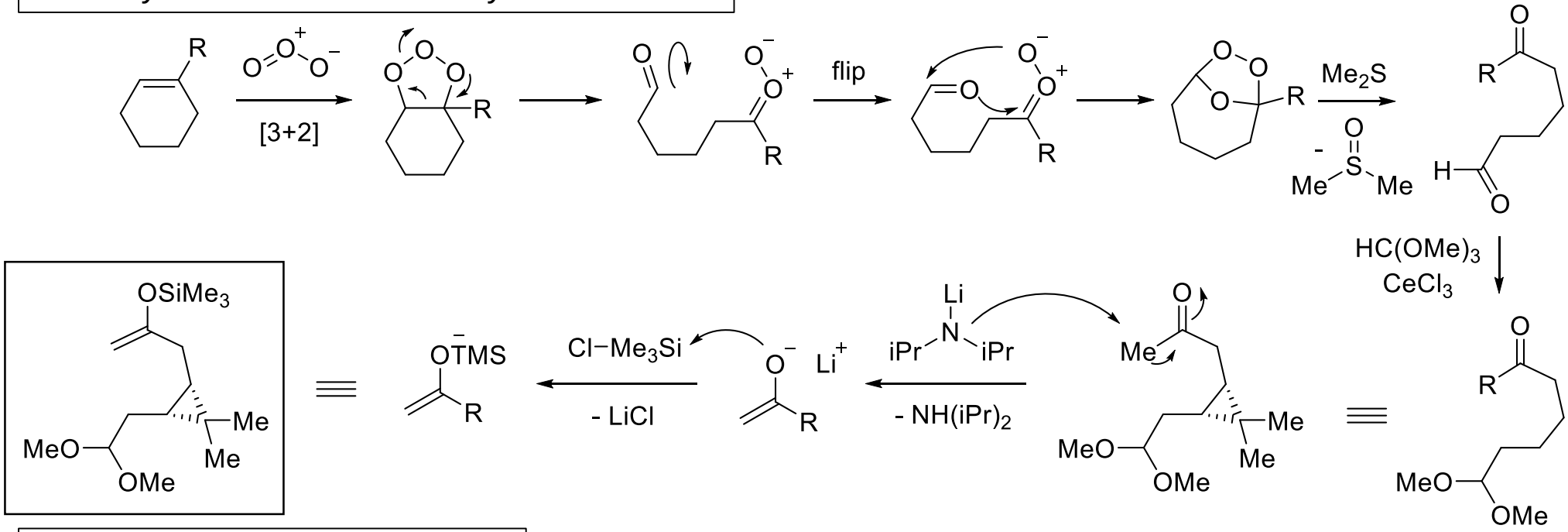
Ricky Alvarado
November 16th, 2021
Shih-Yuan Liu Group

Retrosynthesis

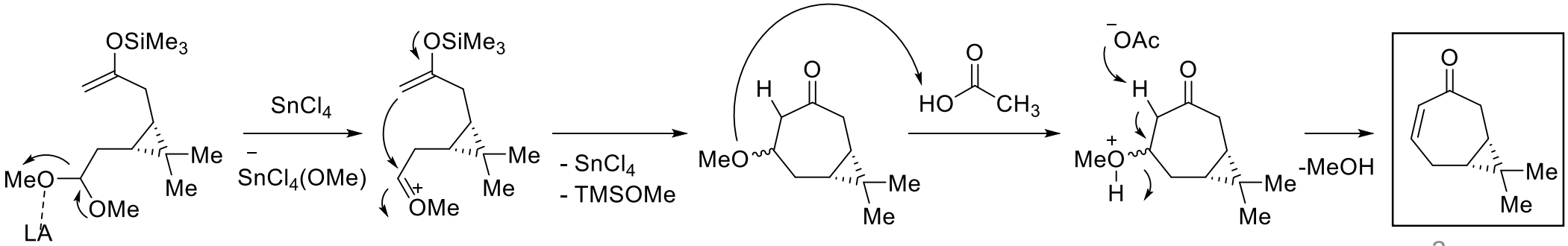


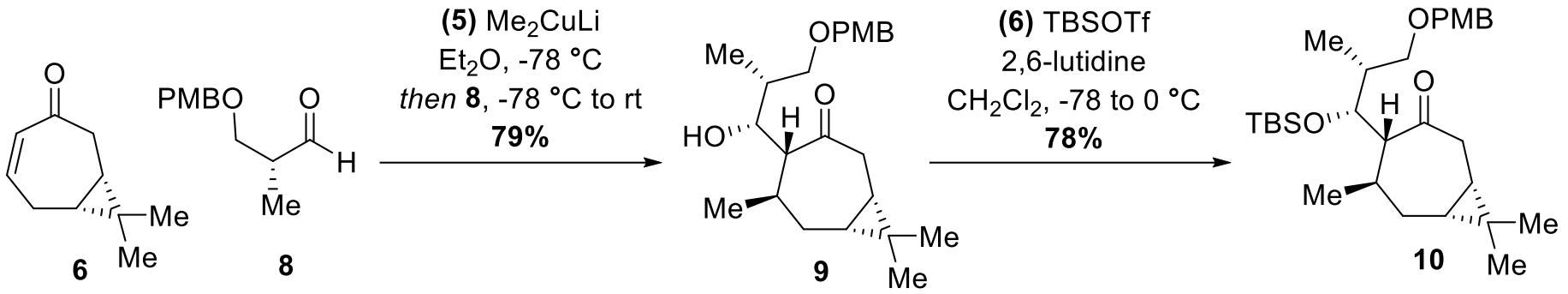


Ozonolysis and formation of silyl ketene acetal

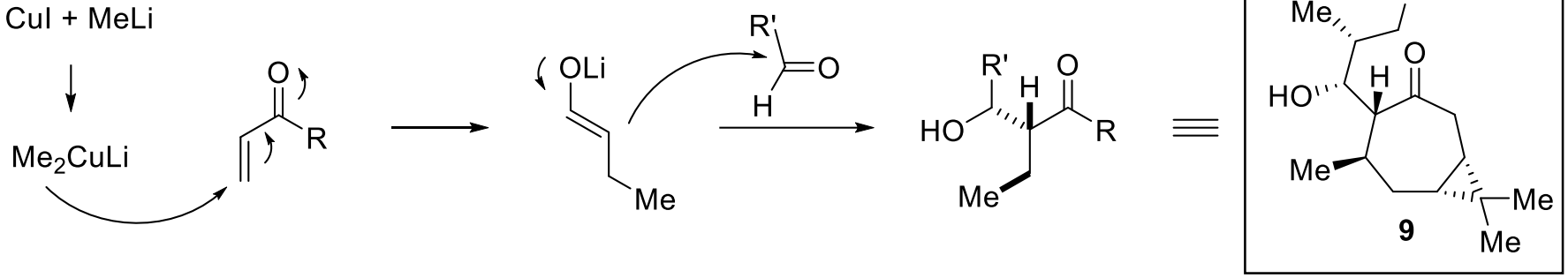


Acid-cyclization and dehydration

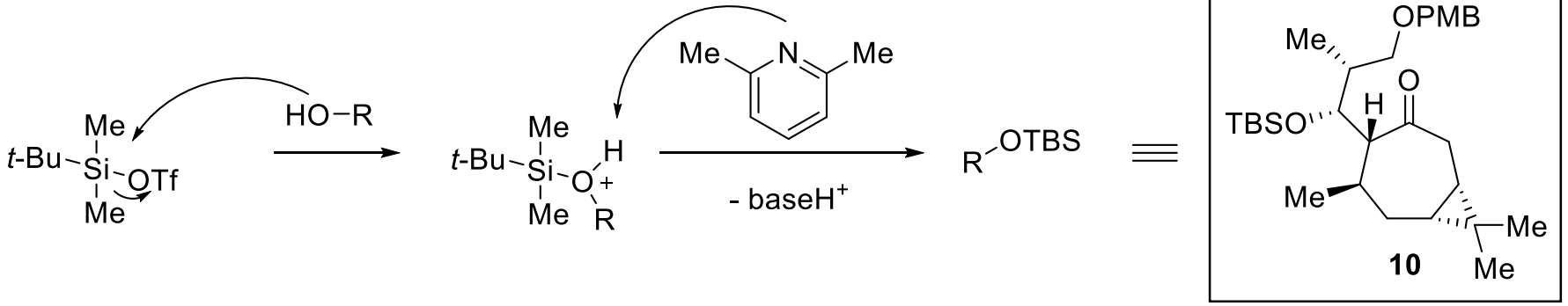


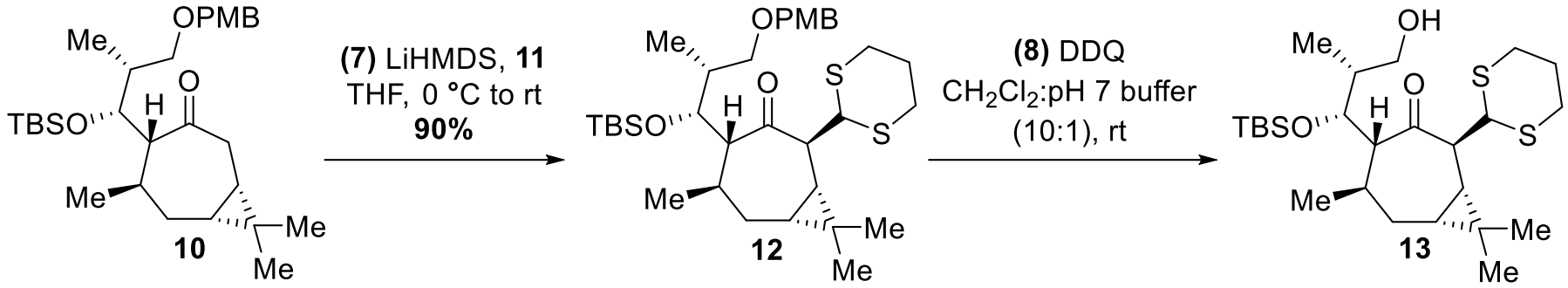


Conjugate addition – Aldol addition

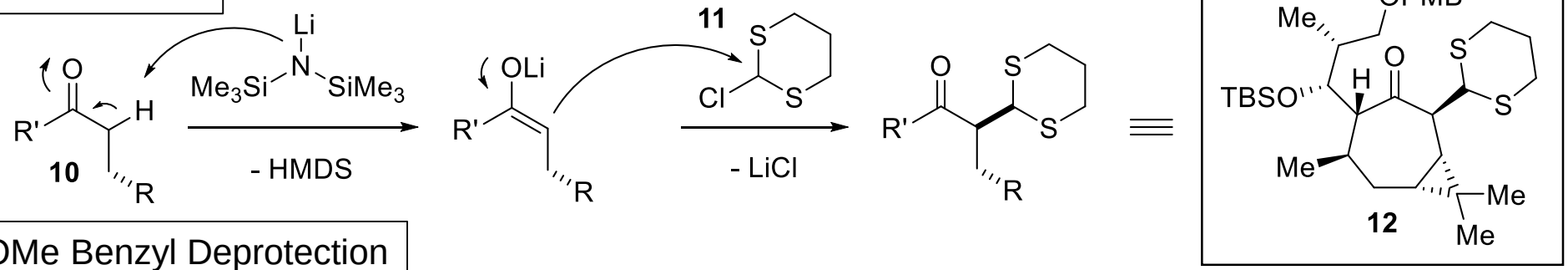


Alcohol protection with TBSOTf

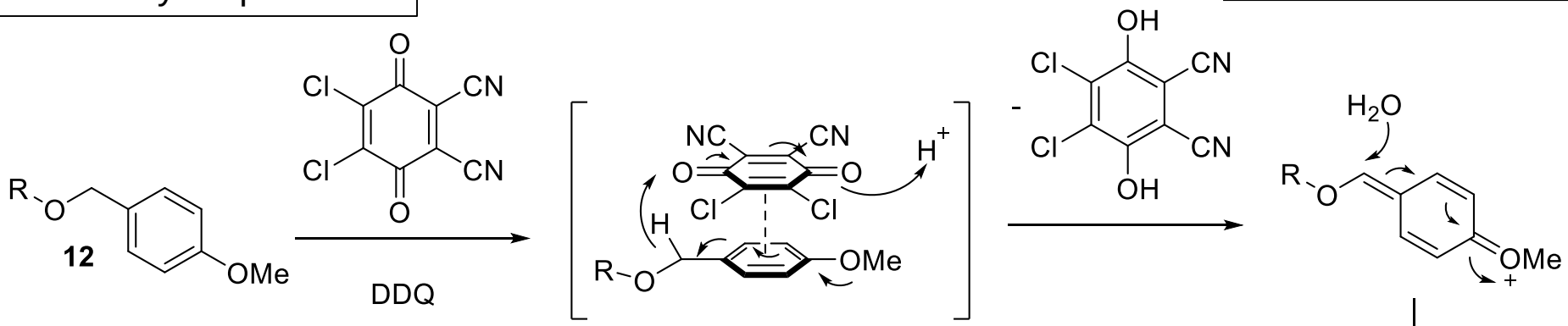


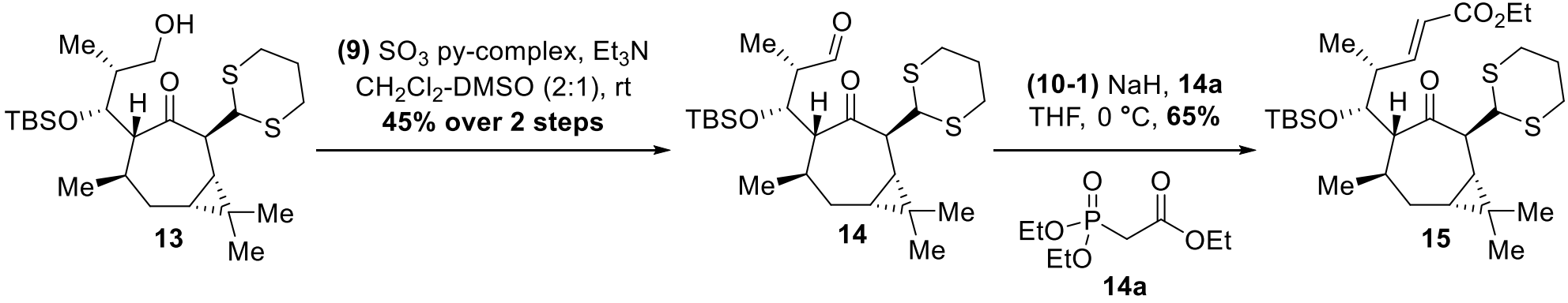


Enolate addition

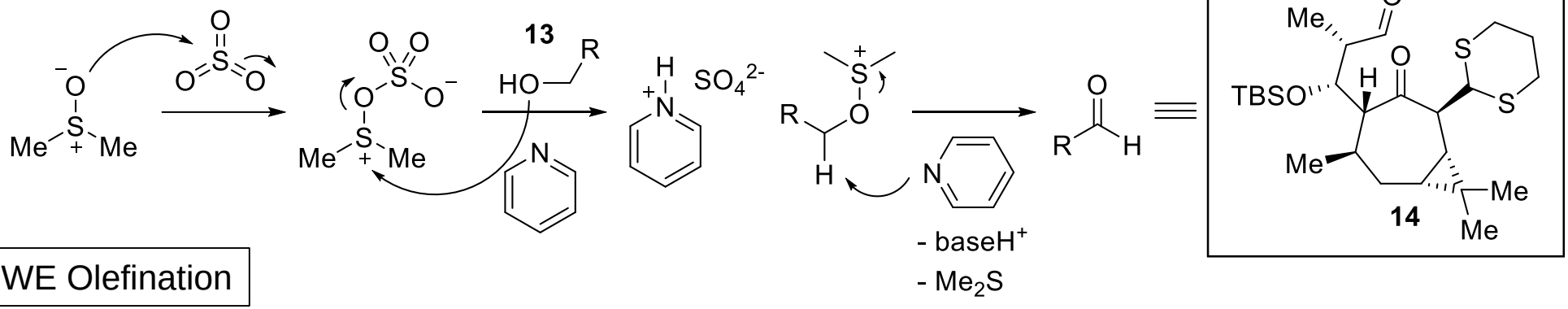


p-OMe Benzyl Deprotection

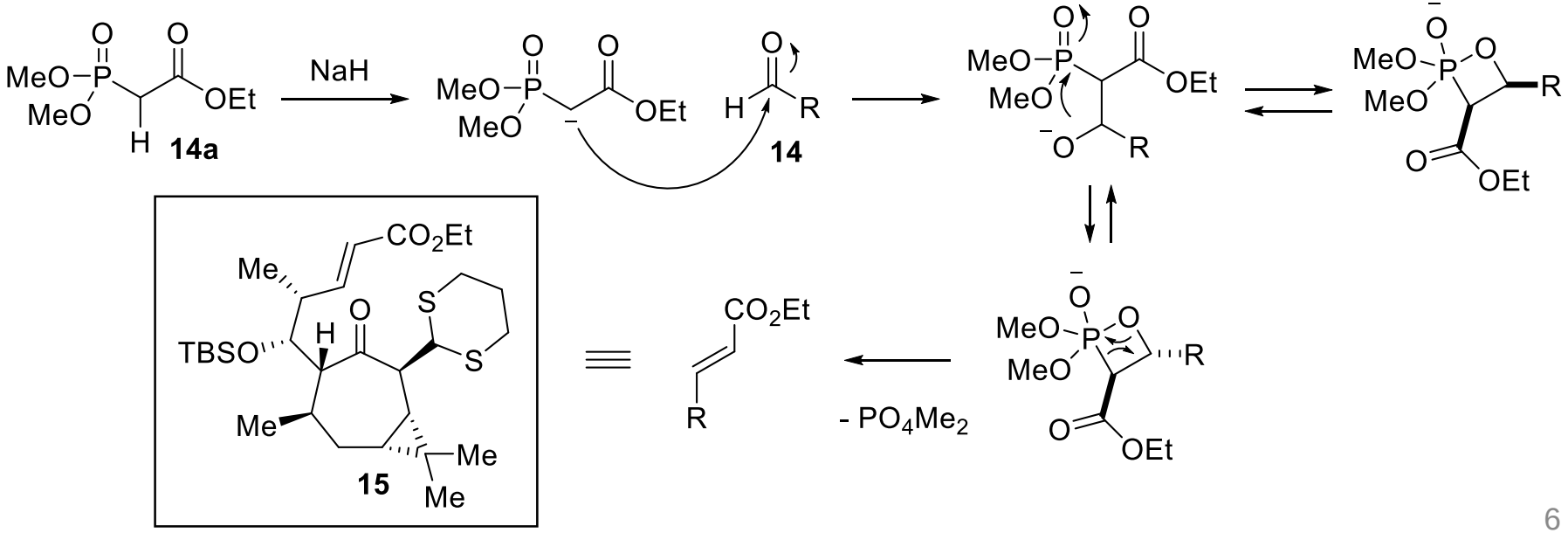


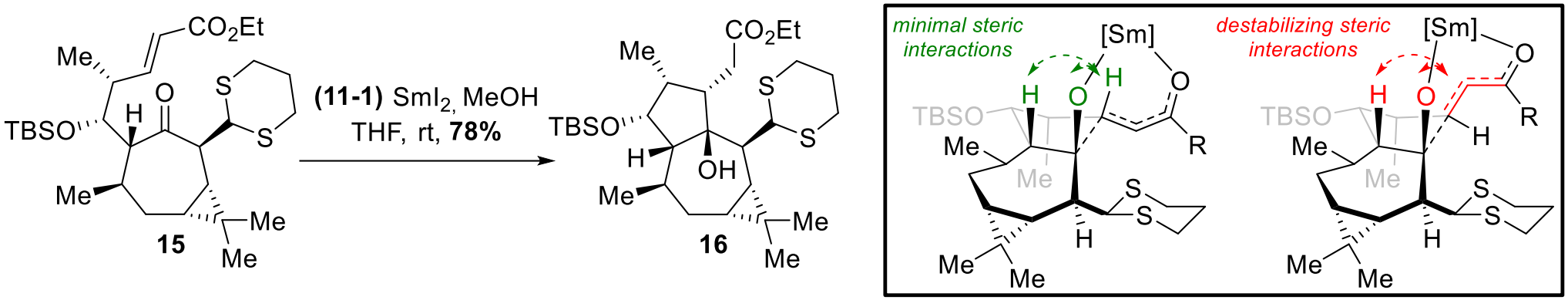


Parikh-Doering Oxidation

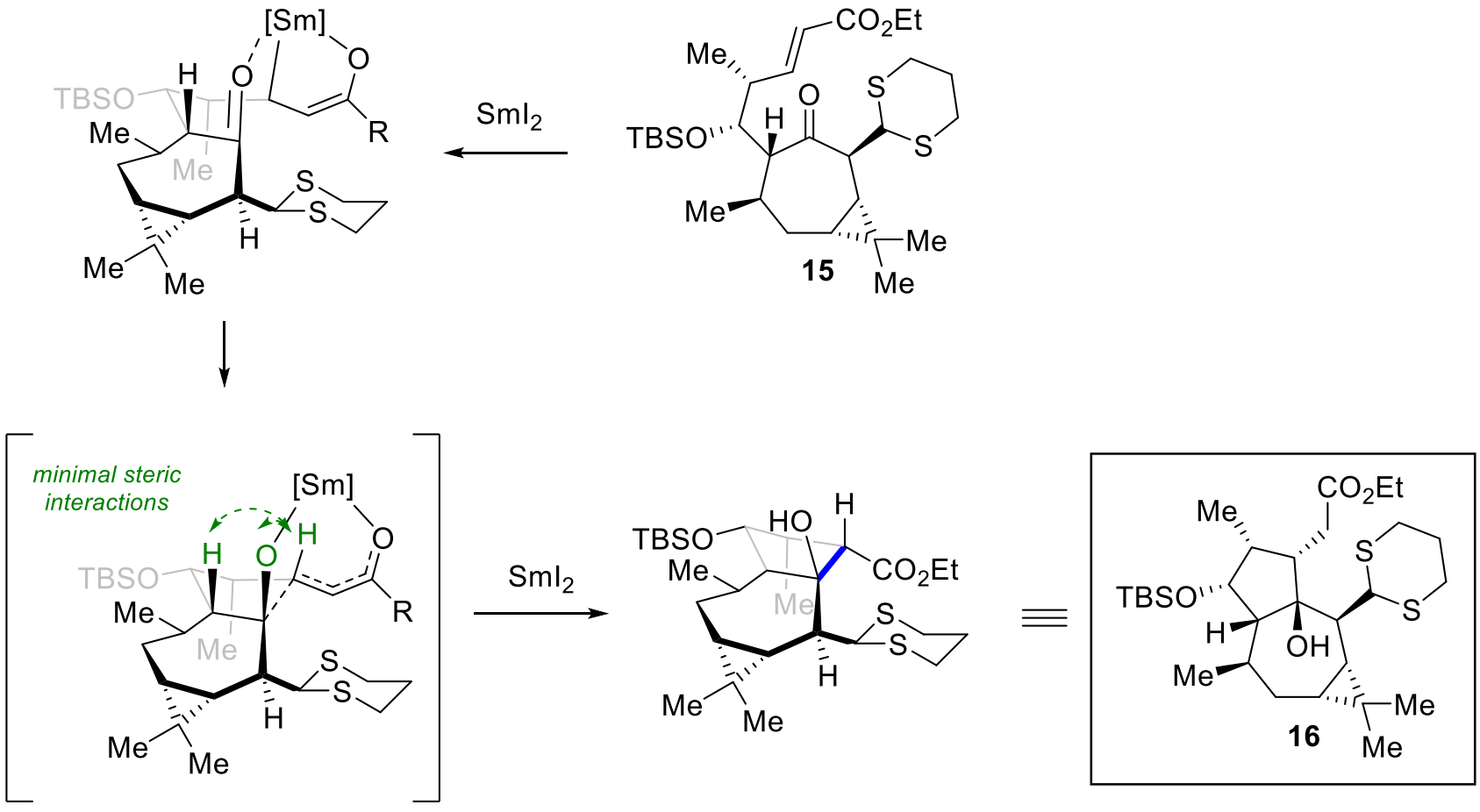


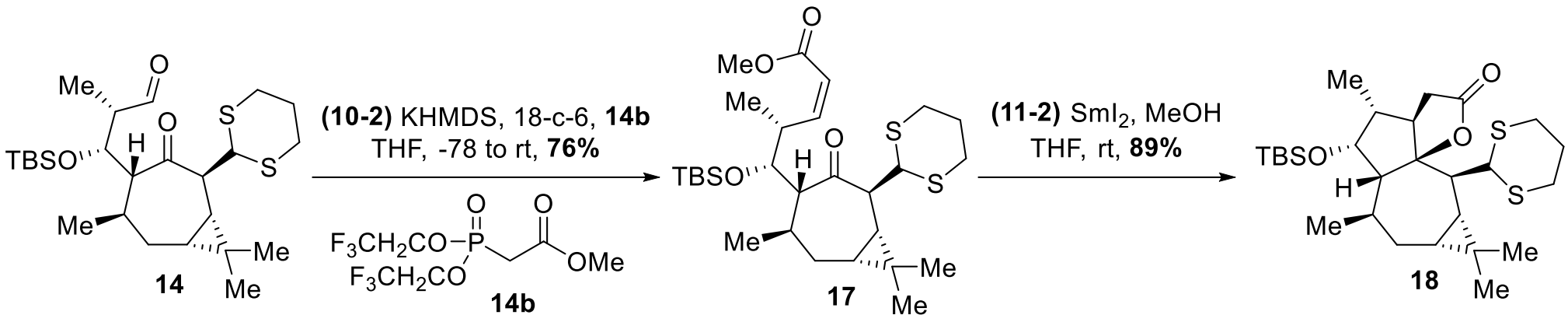
HWE Olefination



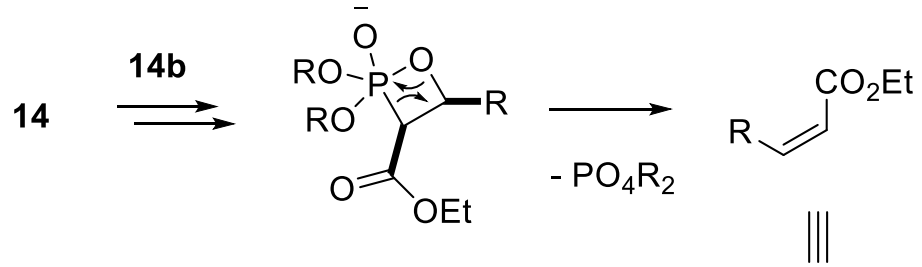


Umpolung Cyclization via Reduction with SmI2 – Undesired Stereoisomer

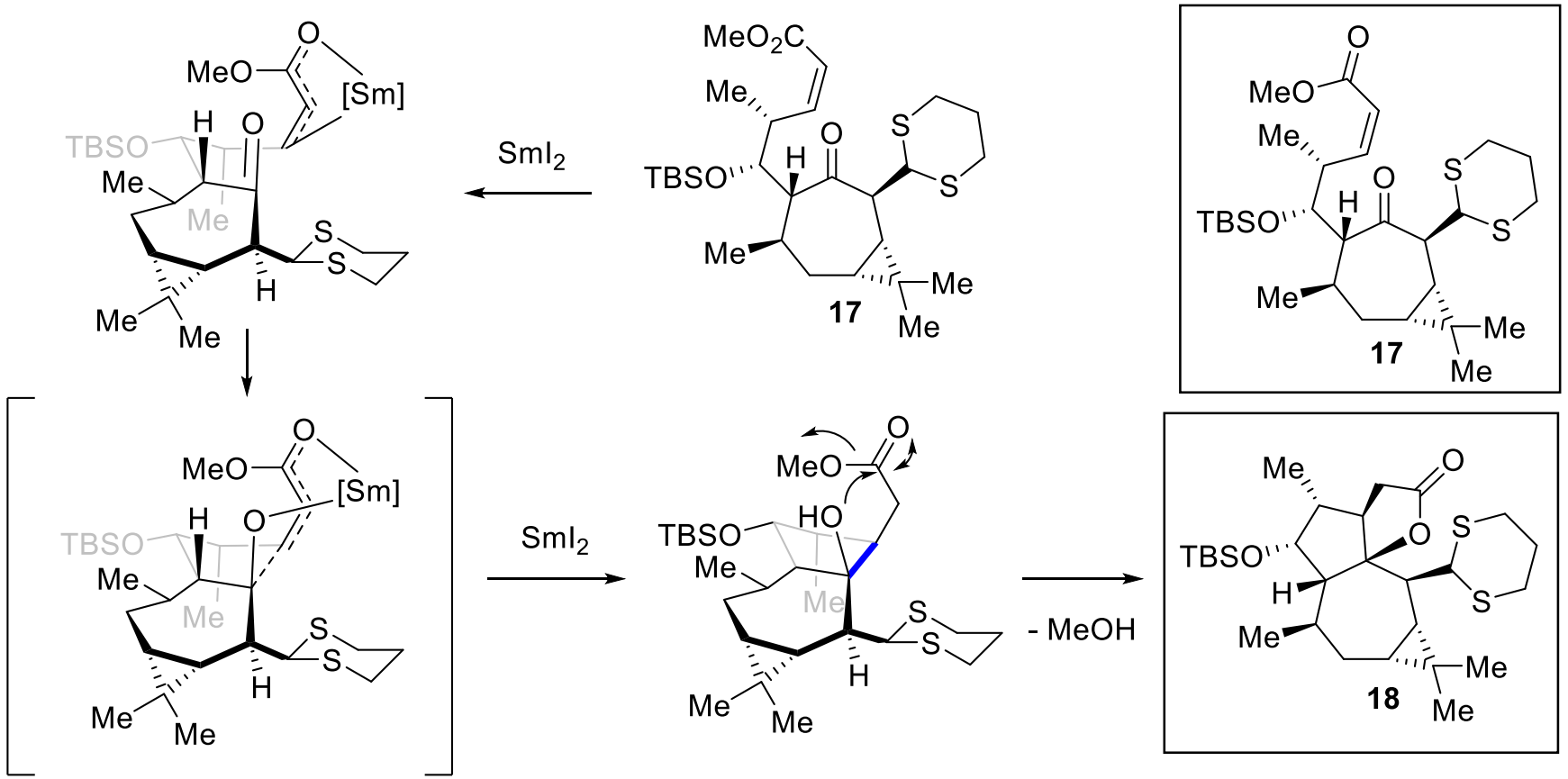


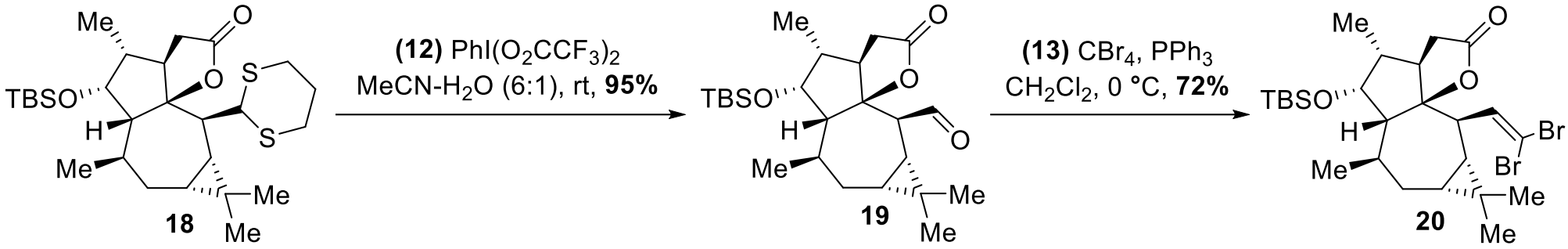


Olefination – Still-Gennari Modification

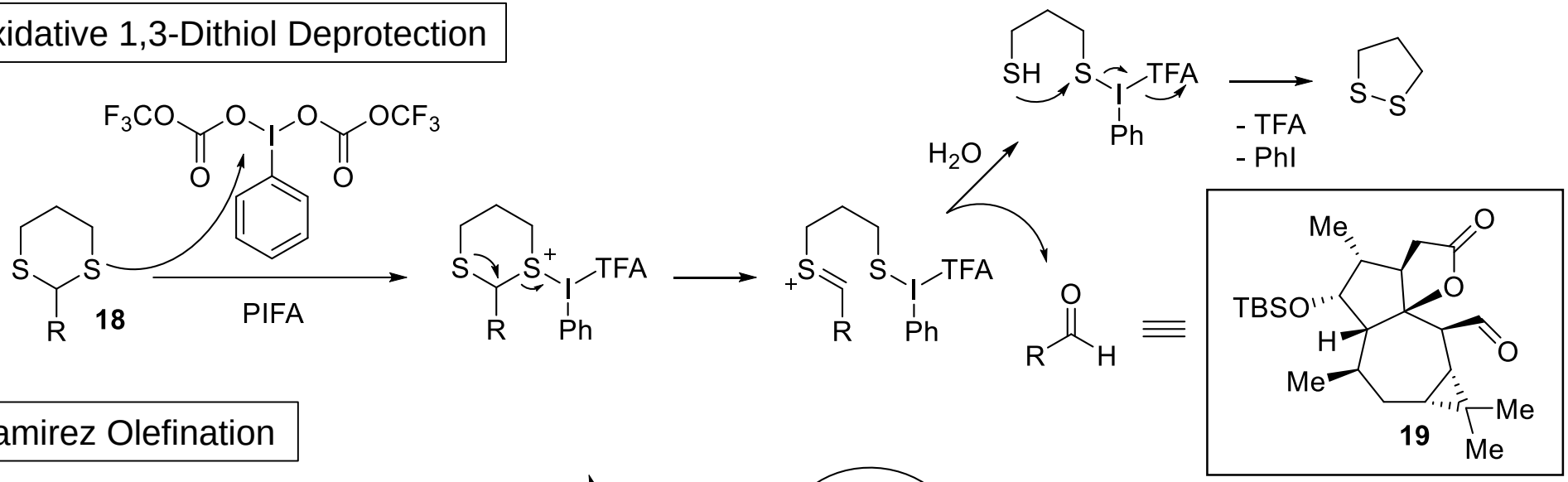


SmI2 Reduction – Desired Stereoisomer

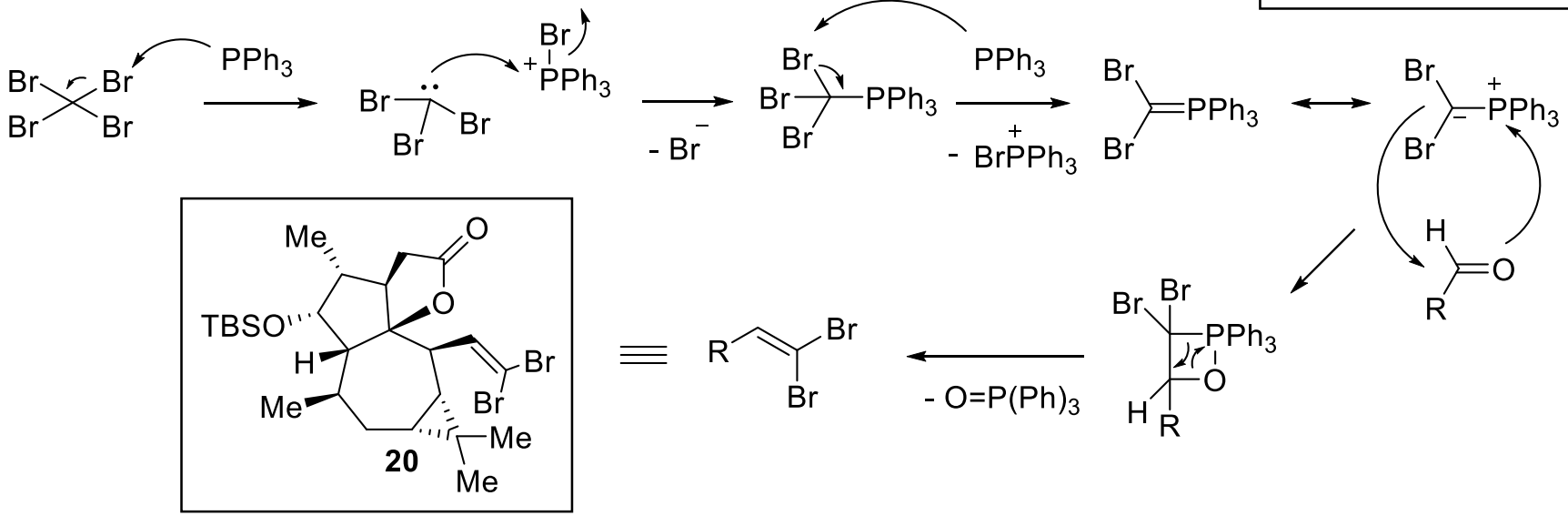


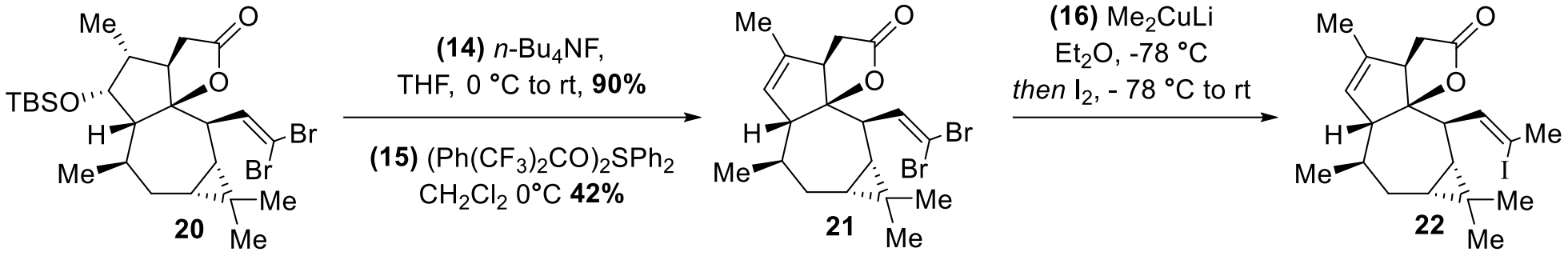


Oxidative 1,3-Dithiol Deprotection

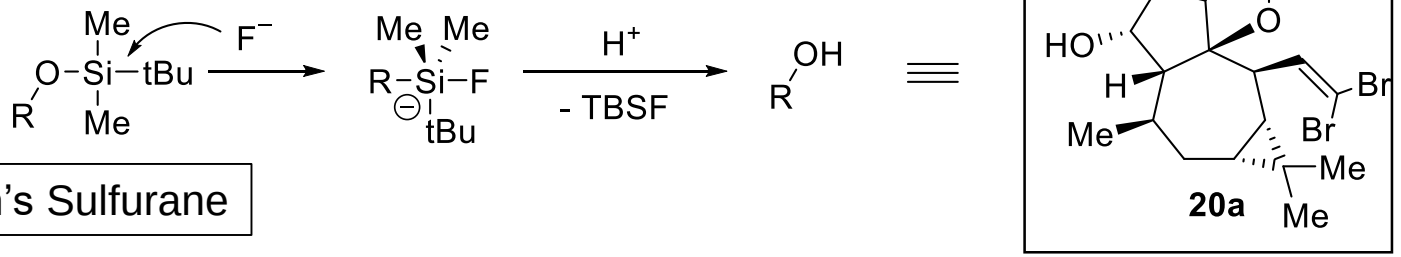


Ramirez Olefination

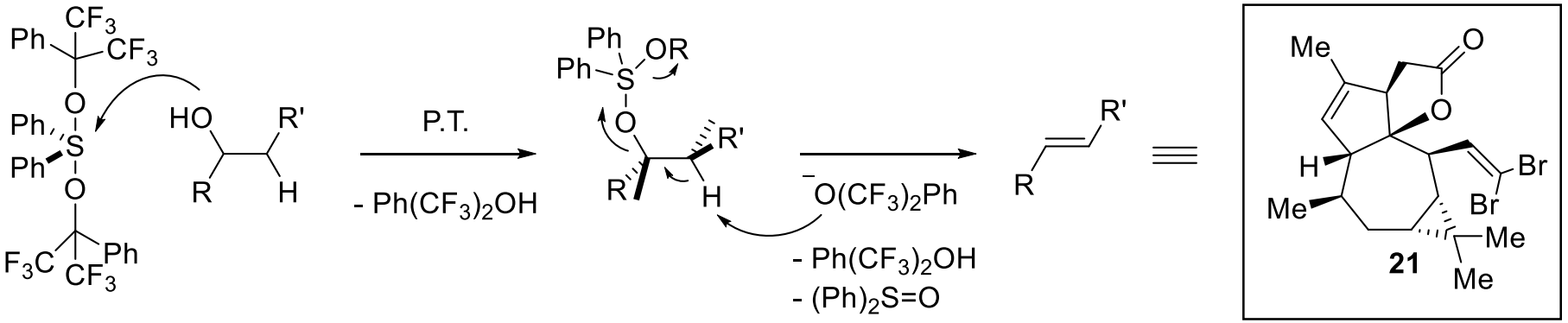




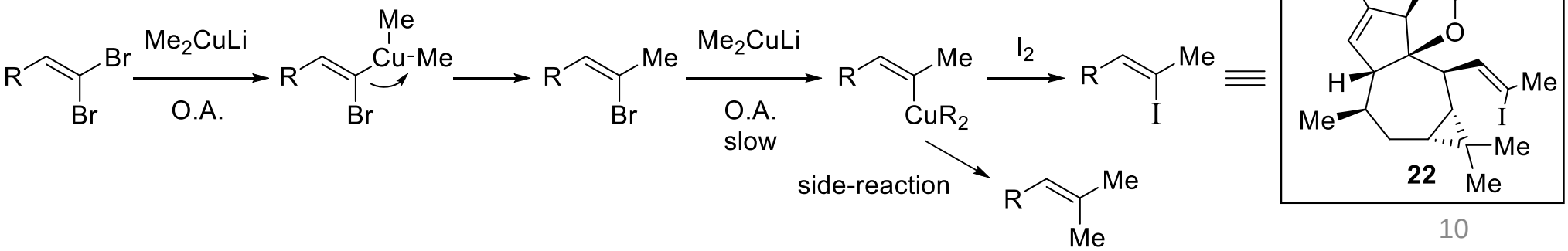
TBS Deprotection

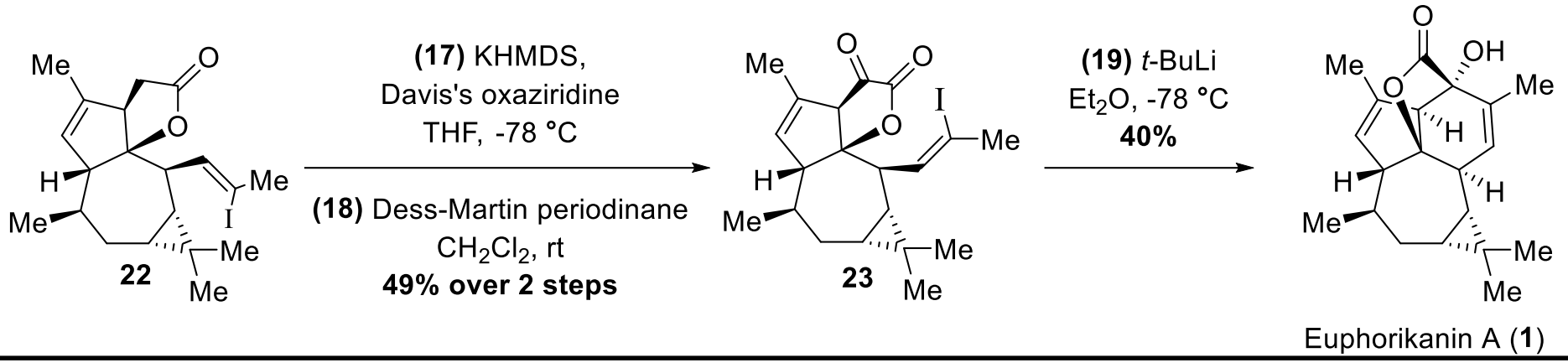


Dehydration with Martin's Sulfurane

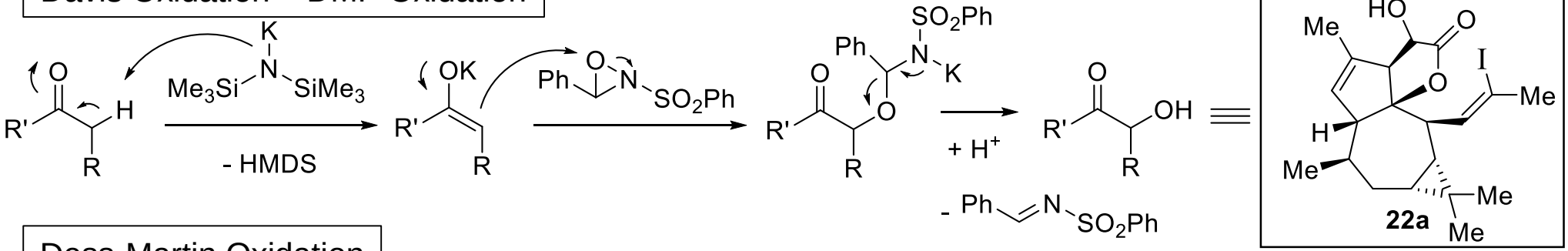


Methylation – Iodination

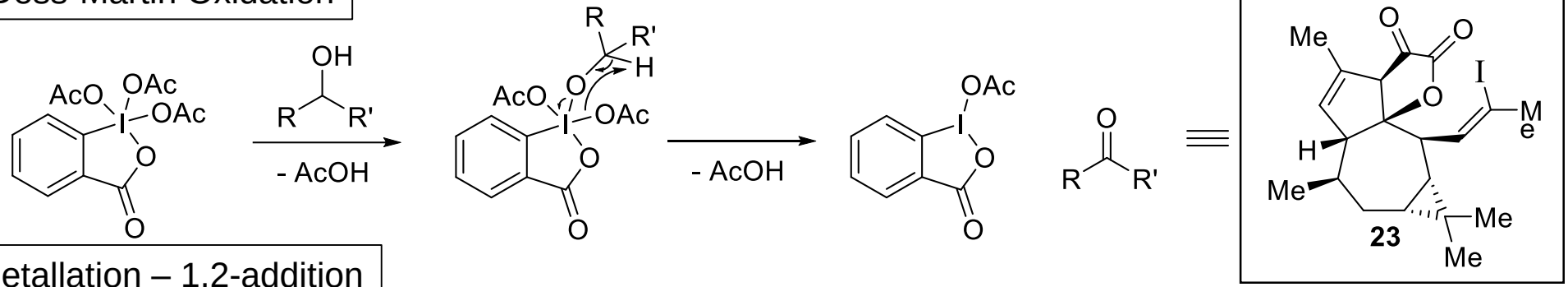




Davis Oxidation – DMP Oxidation



Dess-Martin Oxidation



Metallation – 1,2-addition