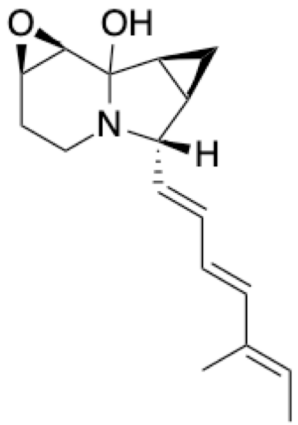
Total Synthesis of (±)-Indolizomycin (Chapter 27)



Keshav Prahalad

1/31/22

CEM 852

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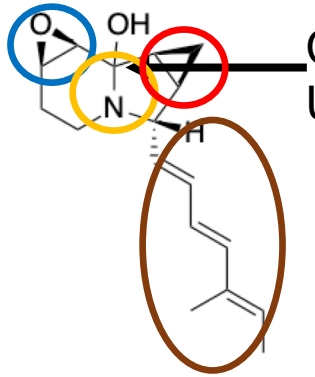
K. C. Nicolaou & E. J. Sorensen, VCH, 1996

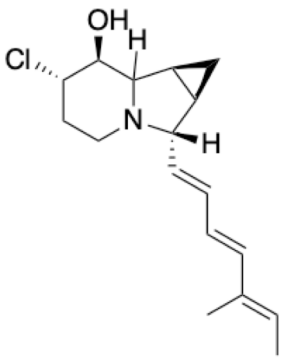
Background of (±)-Indolizomycin



Configuration Unconfirmed

(±)-Indolizomycin

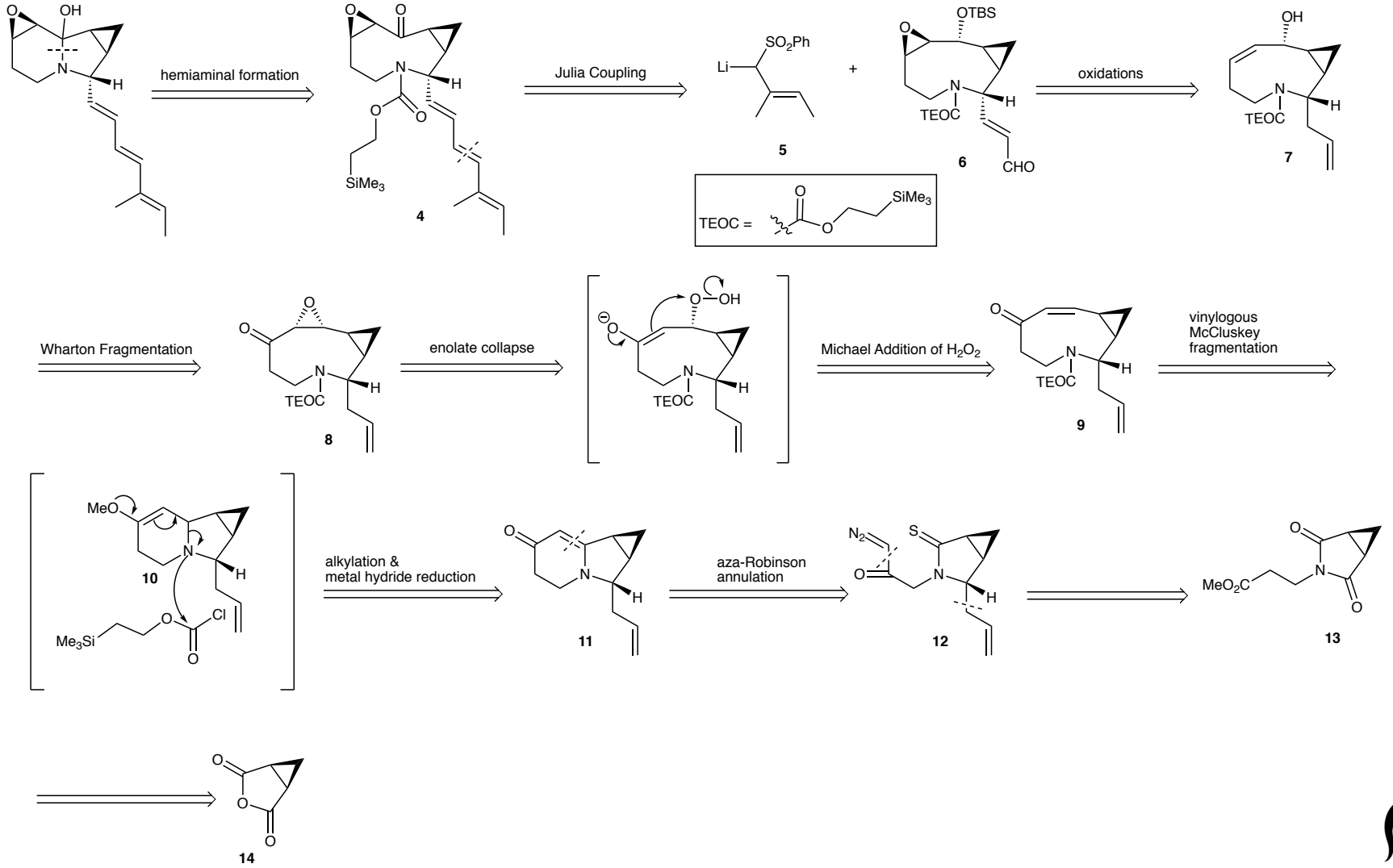
- Potent antibiotic produced by an active clone (SK2-52) in a fusion event between two *Streptomyces strains*
  - ➢ *Streptomyces tenjimariensis* (NM16) & *Streptomyces grisline* (NP1-1)
- Discovered in Japan, but the first total synthesis of the racemic compound was reported by the Danishefsky group in 1990
- Key structural features include an oxiranyl ring, cyclopropyl ring, hemiaminal linkage, and conjugated triene
- Compound is incredibly labile, decomposing at 25 °C under neutral conditions
- The structure was elucidated through a stable derivative of indolizomycin



Derivatized Indolizomycin

Gomi, S.; Ikeda, D.; Nakamura, H.; Naganawa, H.; Yamashita, F.; Hotta, K.; Kondo, S.; Okami, Y.; Umezawa, H.; Iitaka, Y. *J. Antibiot (Tokyo)* **1984**, *37*, 1491-1494.
Yamashita, F.; Hotta, K.; Kurasawa, S.; Okami, Y.; Umezawa, H. *J. Antibiot (Tokyo)* **1985**, *38*, 58-63.
Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30–39.
Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J. *J. Am. Chem. Soc.***1990**, *112*, 2003–2005.

Retrosynthesis of (±)-Indolizomycin



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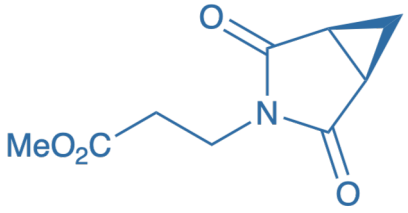
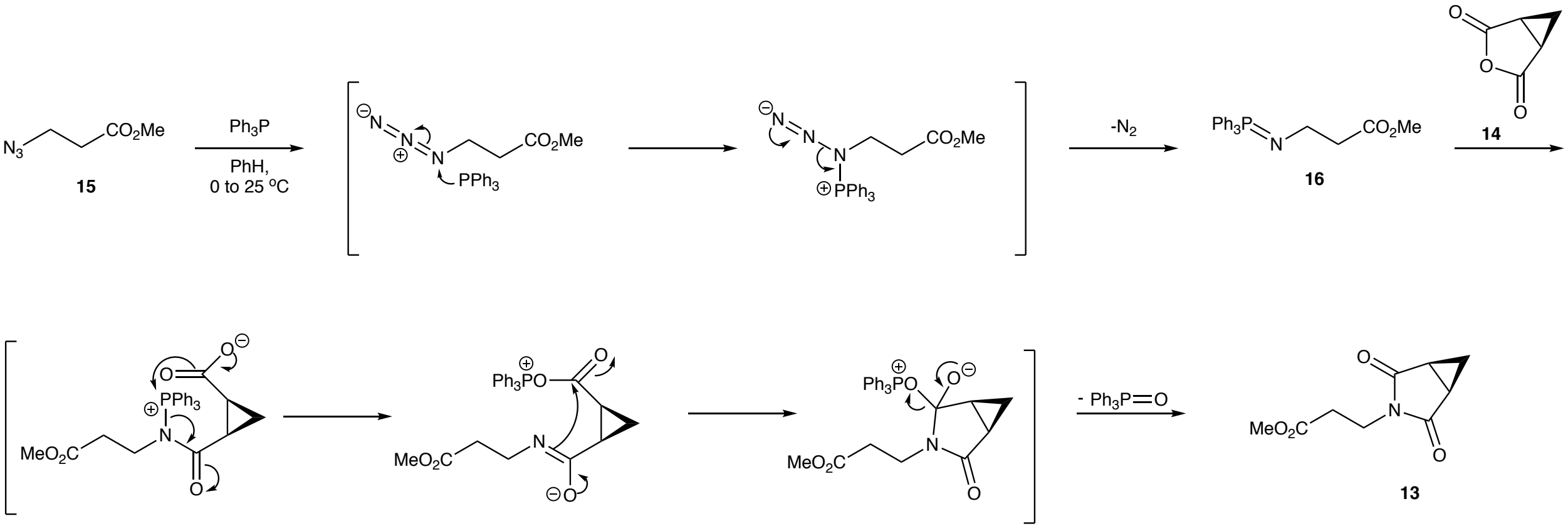
Formation of Substituted Imide **13**



13



Garcia, J.; Vilarrasa, J.; Bordas, X.; Banaszek, A. *Tetrahedron Lett.* **1986**, *27*, 639-640.

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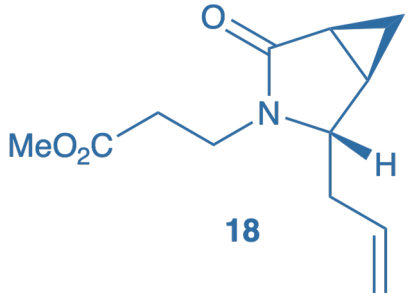
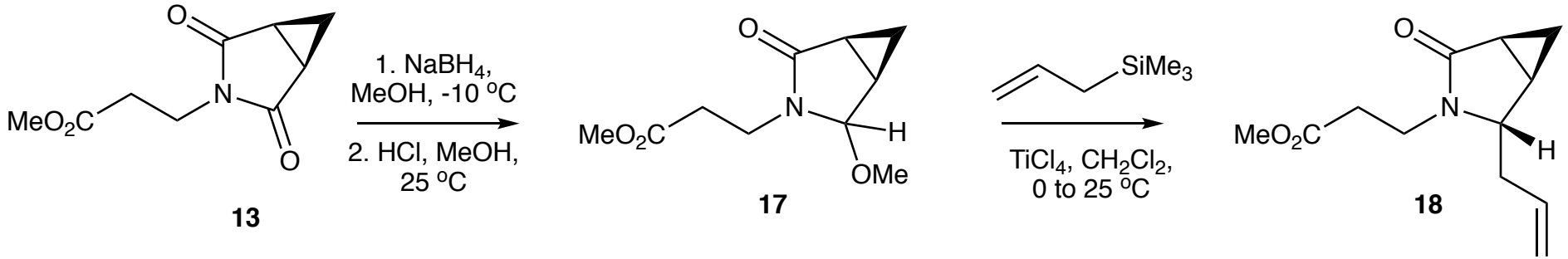
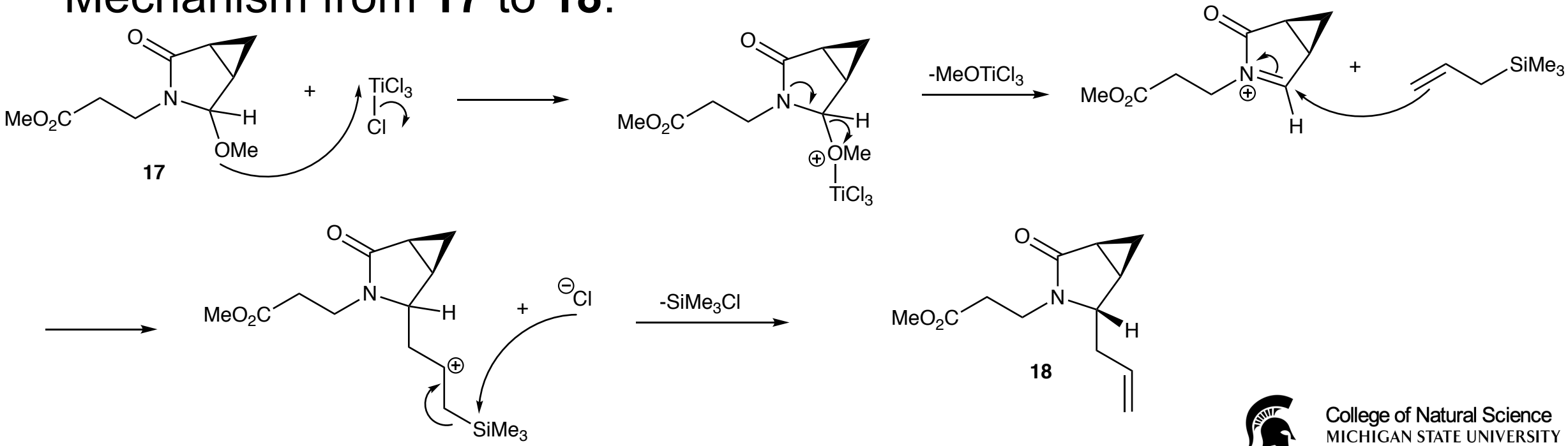
Formation of Intermediate **18**





Mechanism from **17** to **18**:



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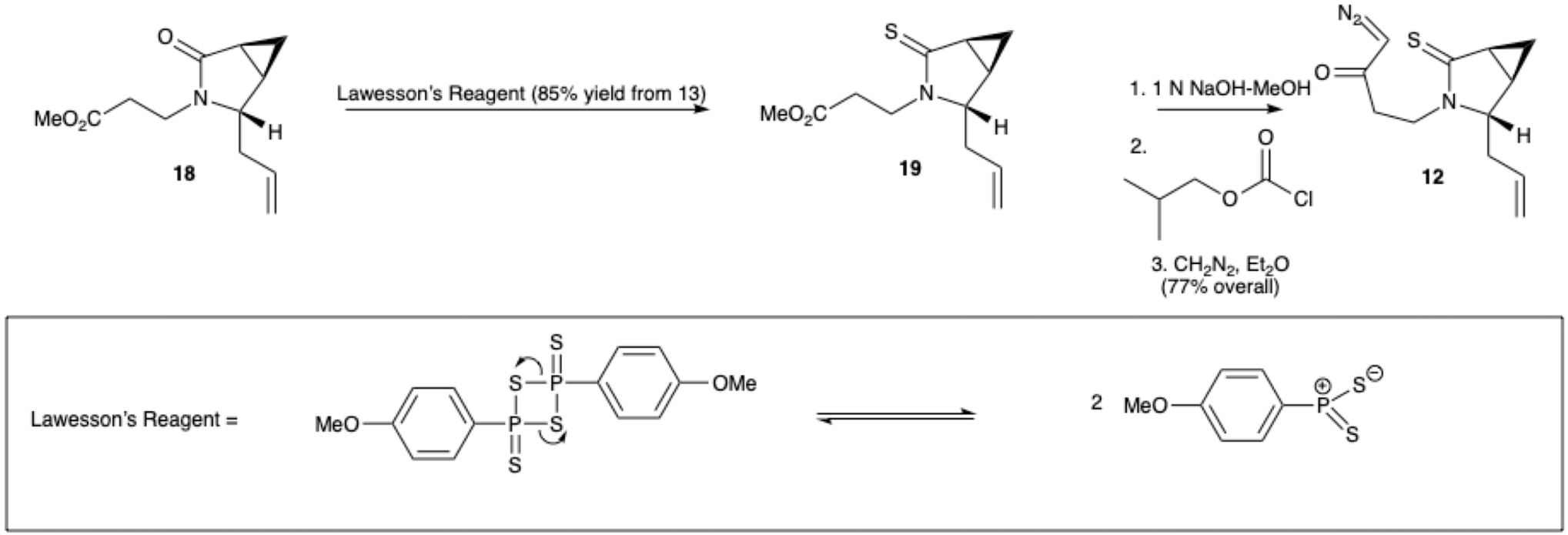
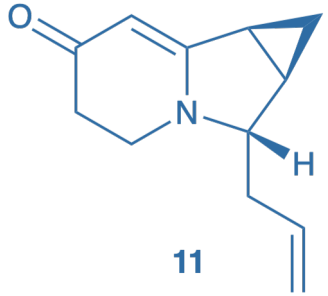
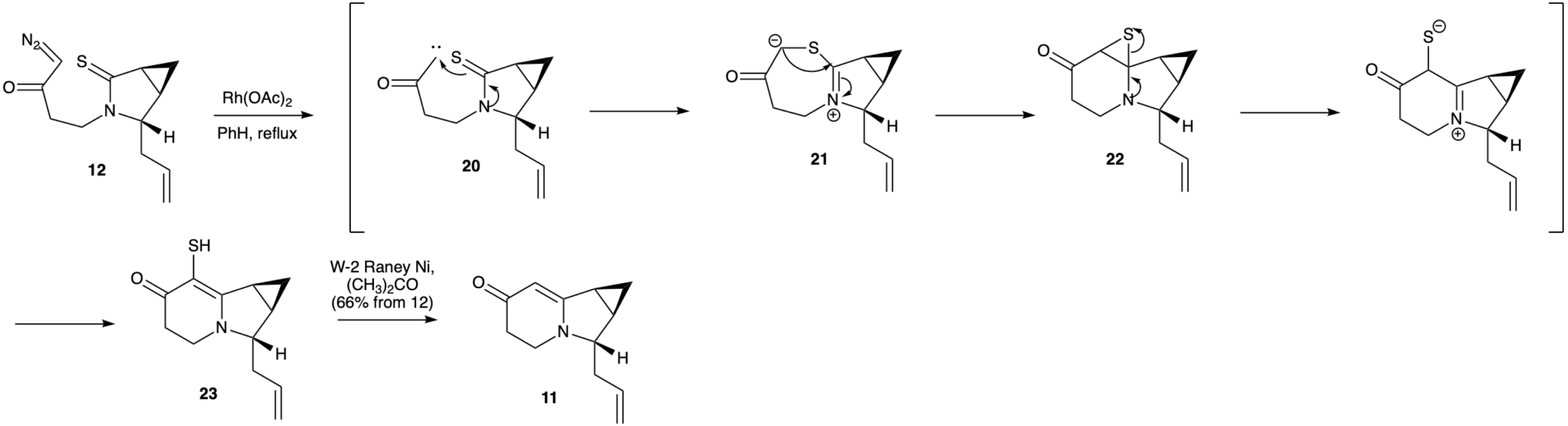
Formation of Diazo Ketone **12**



Synthesis of Diazo Indolizidine **11**





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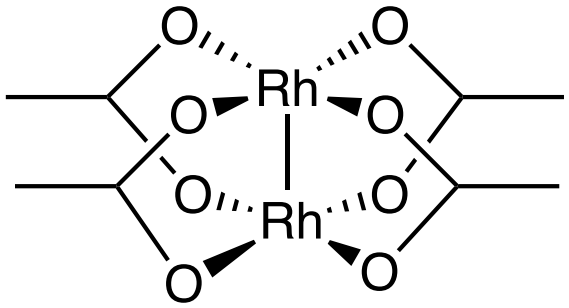
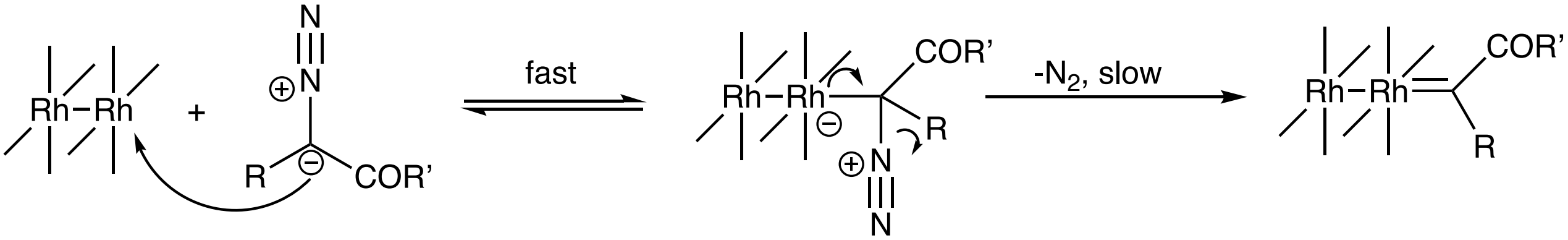
Mechanism of Carbene Insertion with $Rh(OAc)_2$

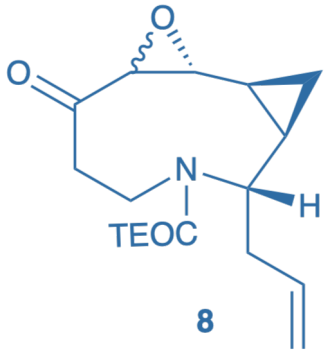


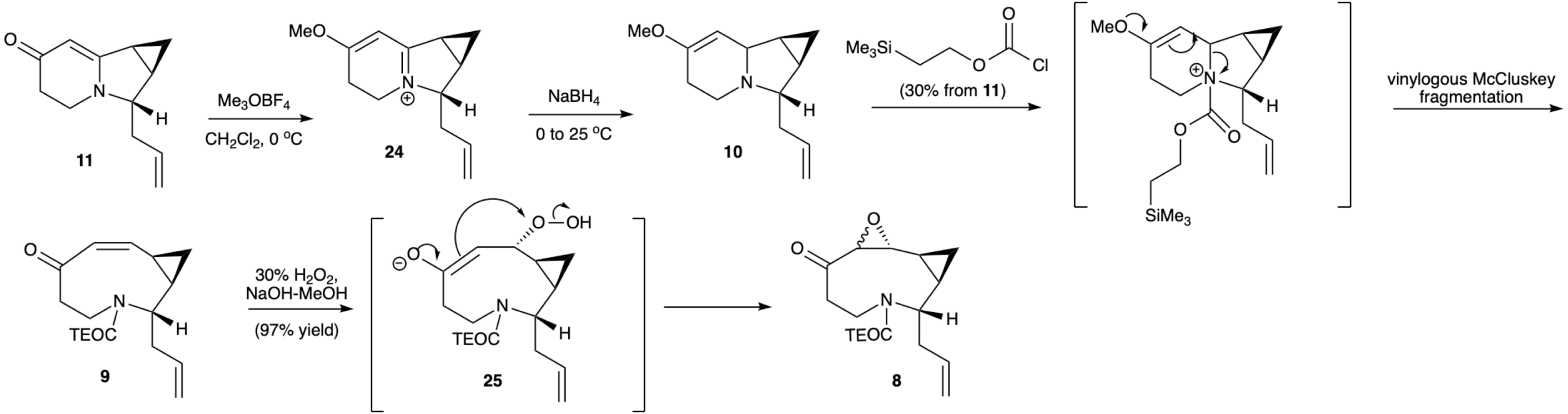
Rhodium (II) acetate dimer



Wong, F. M.; Wang, J.; Hengge, A. C.; Wu, W. *Org Lett* **2007**, *9*, 1663-1665.

Synthesis of Epoxy Ketone **8**





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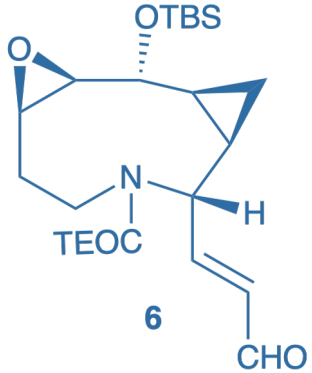
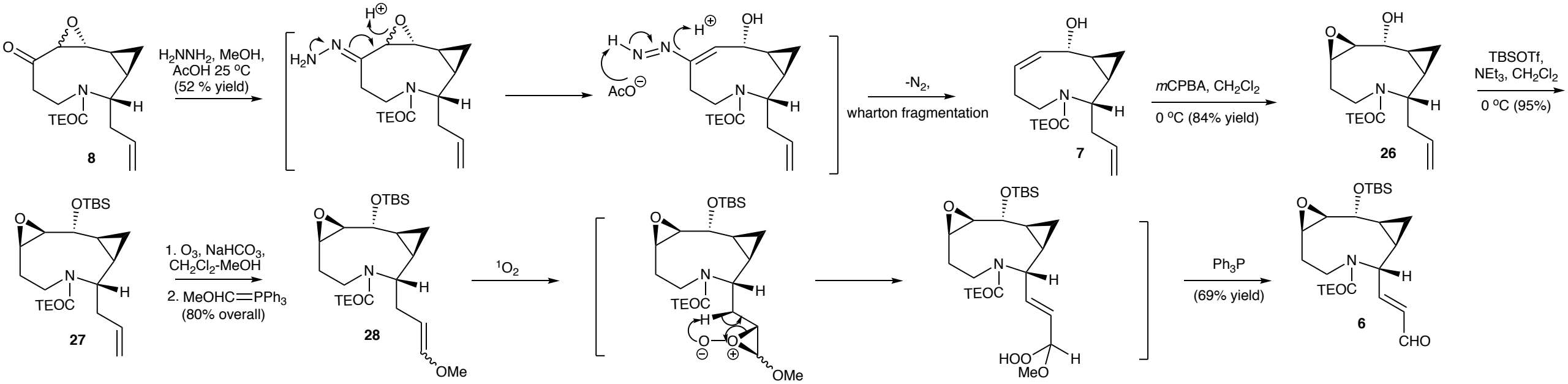
Synthesis of Enal **6**





(3:2 mixture of olefin stereoisomers)

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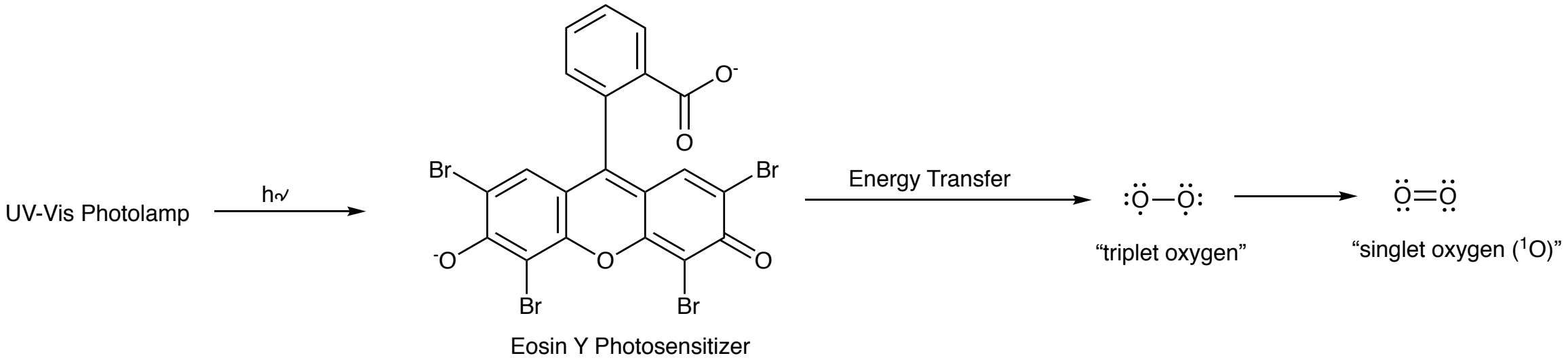
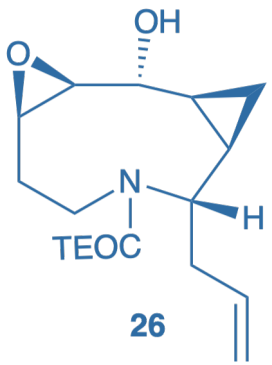
Generation of Singlet Oxygen ($^1O_2$)

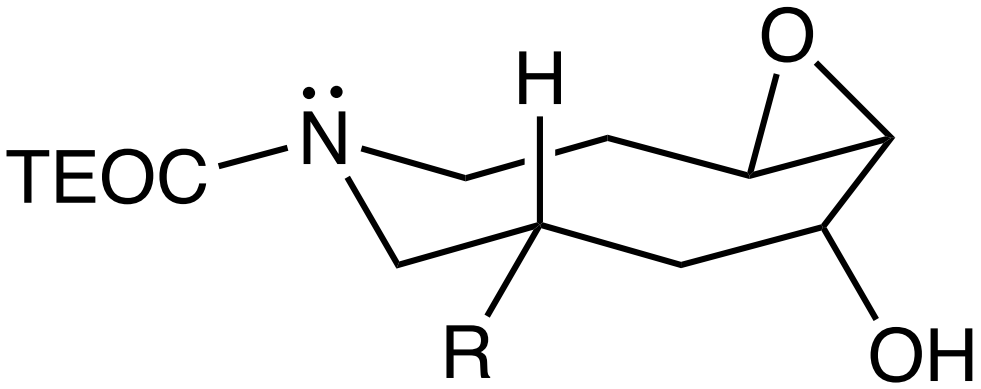


*Note that this specific photooxygenation takes place in acetone with the olefin according to Rousseau et al.

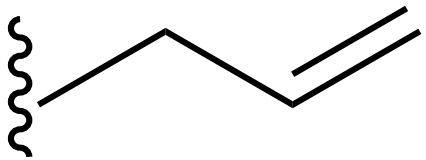
Rousseau, G.; Le Perchec, P.; Conia, J.M.; *Tetrahedron Lett.* **1977**, *18*, 45-48.

Relative Stereochemistry of **26**





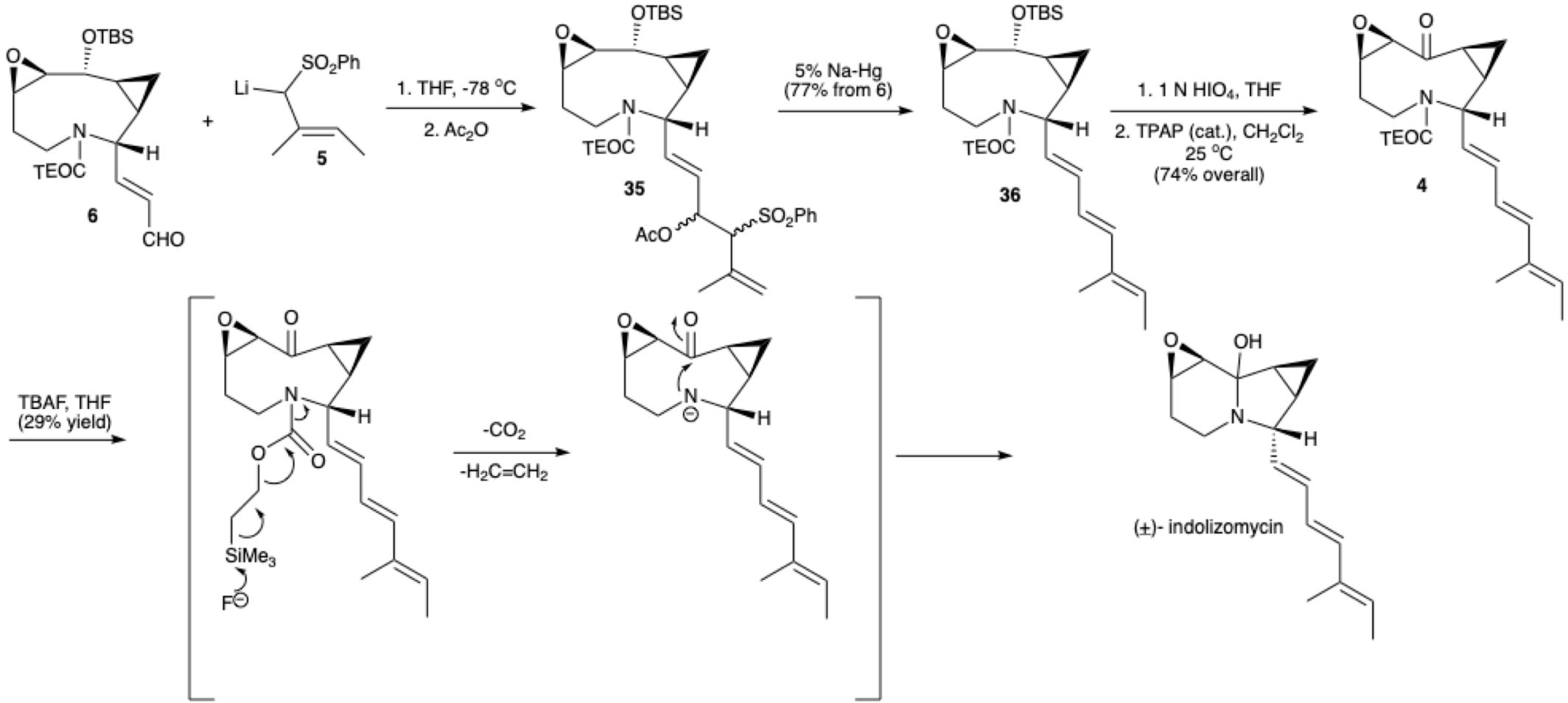
R =



*Note that the hydroxyl is *trans* to the epoxide, but 6 membered cyclic allylic alcohols will afford *cis* epoxide as intramolecular H-bonding between a pseudoequatorial OH stabilizes the peroxybenzoic acid.

Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S.; *J. Am. Chem. Soc.* **1979**, *101*, 159-169.

Synthesis of (±)-Indolizomycin



Ley, S. V.; Norman, J.; Griffith W. P.; Marsden S. P. *Synthesis* **1994**, 639

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Final Thoughts

- Danishefsky's synthesis of (±)-Indolizomycin featured many interesting transformations
- Intramolecular carbene insertion and sulfide contraction was used to generate intermediate **11** via an aza-Robinsion annulation
- Vinylogous McCluskey fragmentation was used to introduce azonine groups to indolizidine to form intermediate **9**
- Wharton fragmentations of the epoxy ketone afforded intermediate **7**