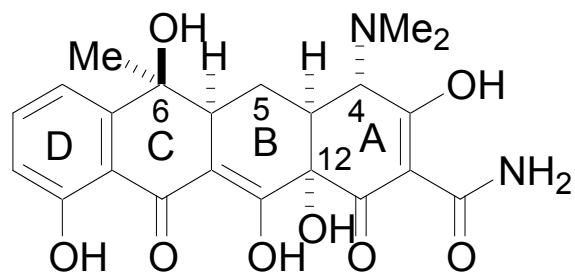


The Tetracyclines

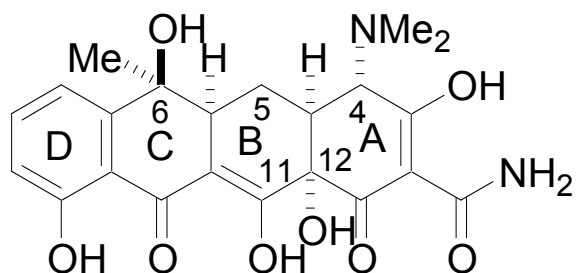


(-)-tetracycline

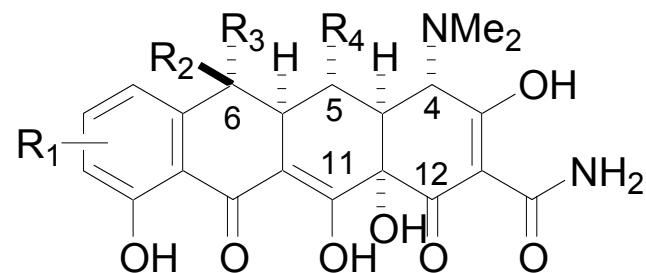
- Prepared from the cultures of several species of *Streptomyces*
- Once an enormously effective treatment for a wide range of bacterial infections
- Mode of action is binding to the 30S ribosome of the bacteria, preventing attachment of the aminoacyl tRNA to the RNA-ribosome complex
- Decades of clinical use have led to the emergence of widespread bacterial resistance
- Analogues generally prepared via semisynthesis
- First total synthesis of a tetracycline-like molecule reported by Woodward and a group from Pfizer
- Synthetic approaches by Woodward, Shemyakin, Muxfeldt, Stork, and Myers

Michael Ellis
November 30, 2005

Structure-Activity Relationships



(-)-tetracycline

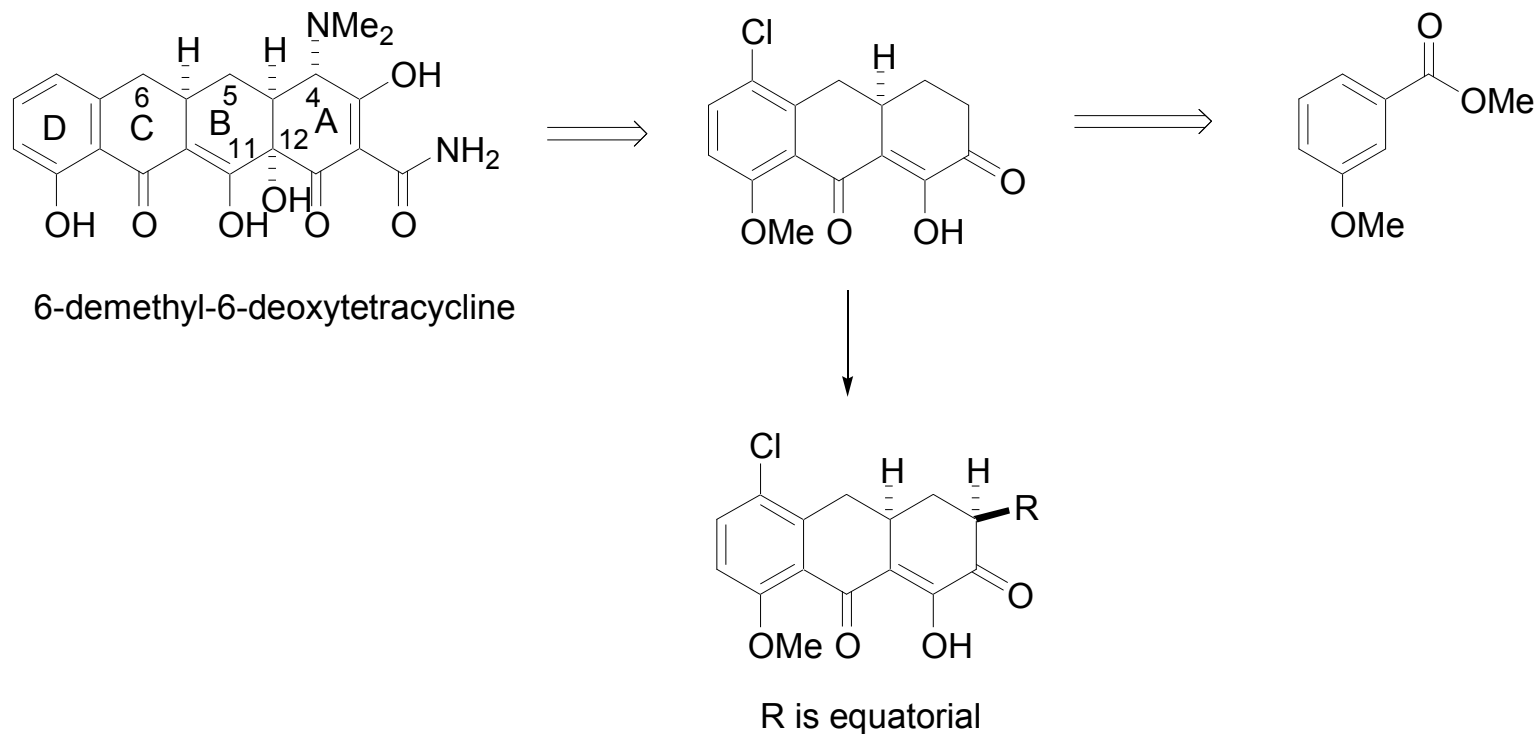


-R1-R4 can be substituted or removed without effecting a substantial decrease in antimicrobial activity

-Configuration at C-5a and C-4 are crucial for activity

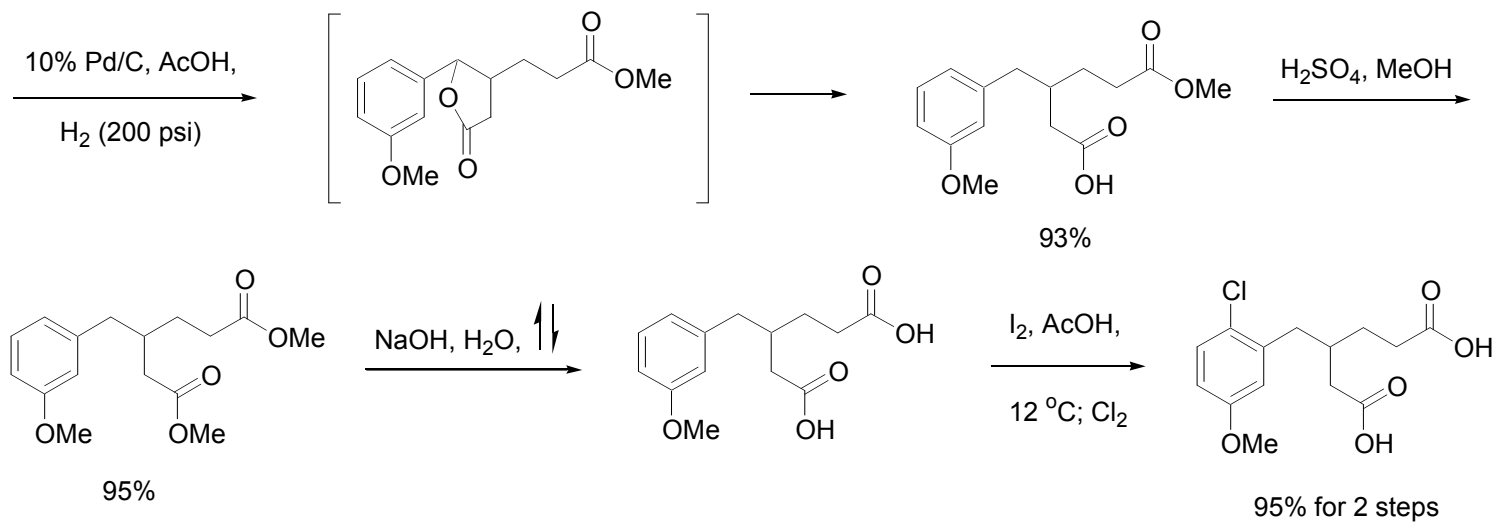
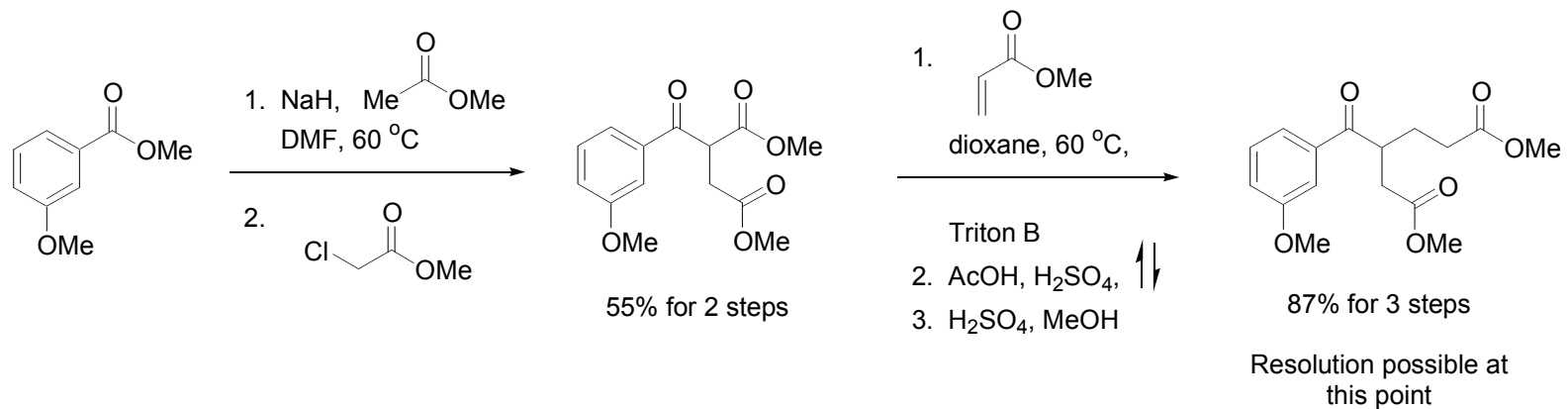
-Hypothesized that the principal active center is the C-11, C-12 diketone system of rings B and C

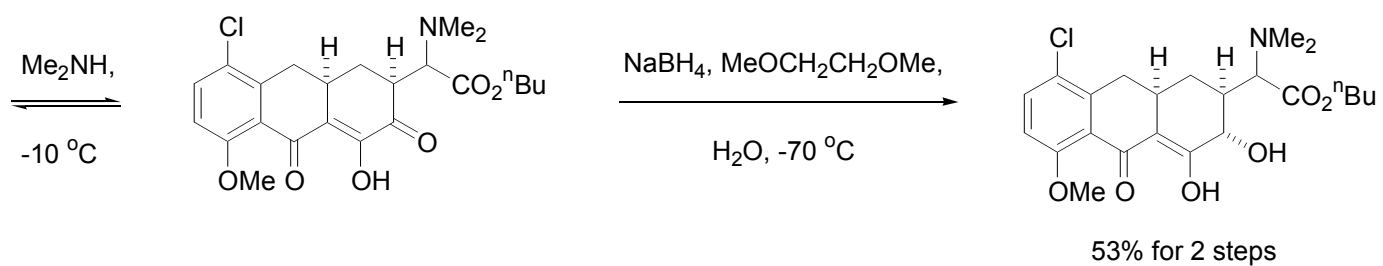
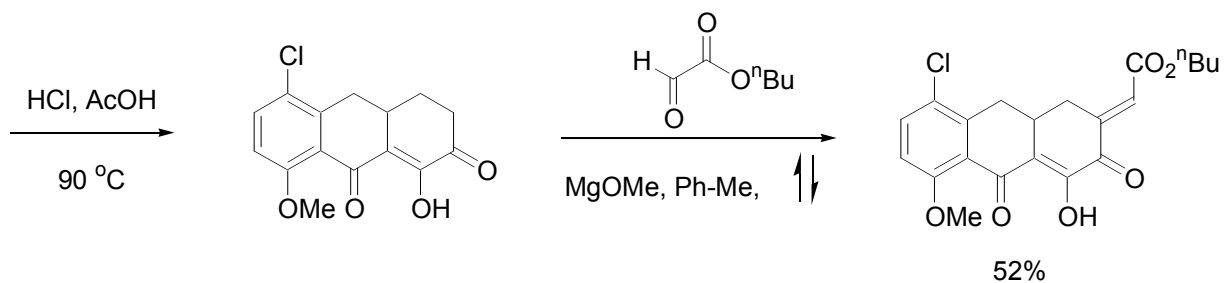
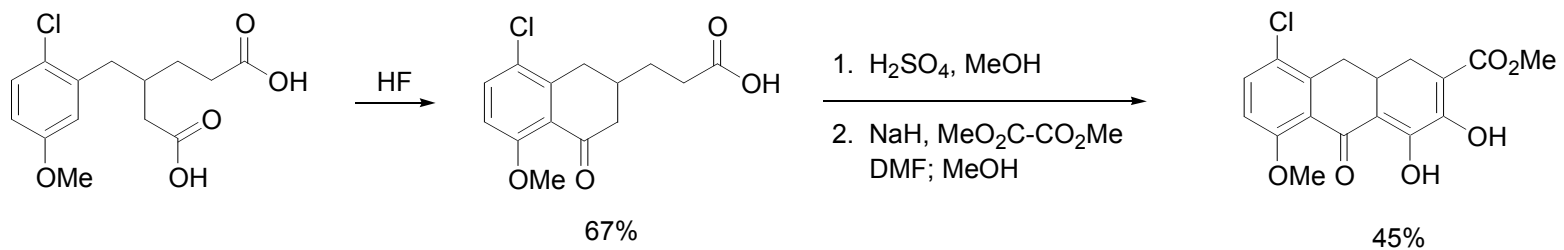
Woodward's Approach

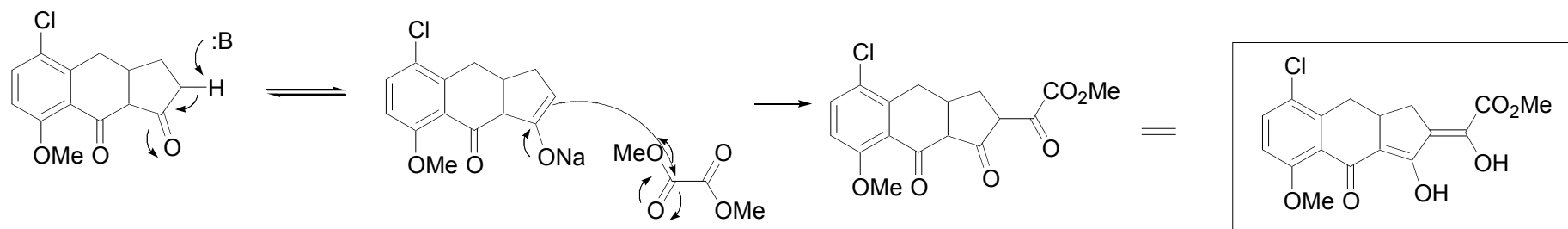
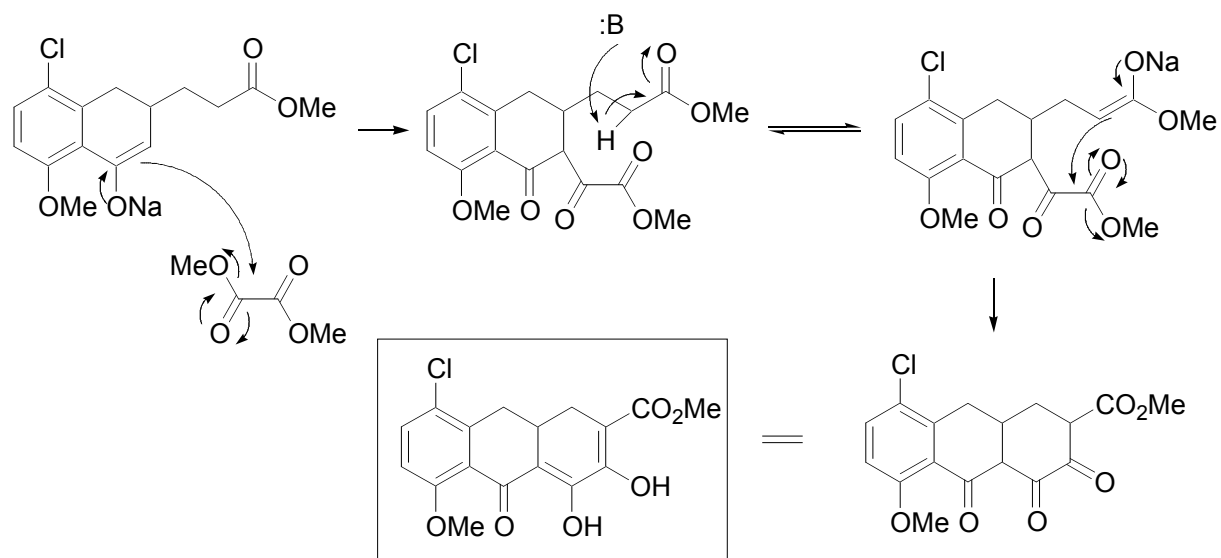
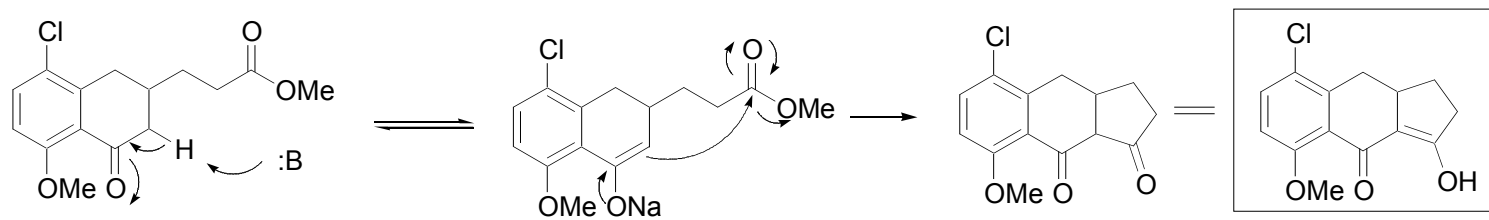


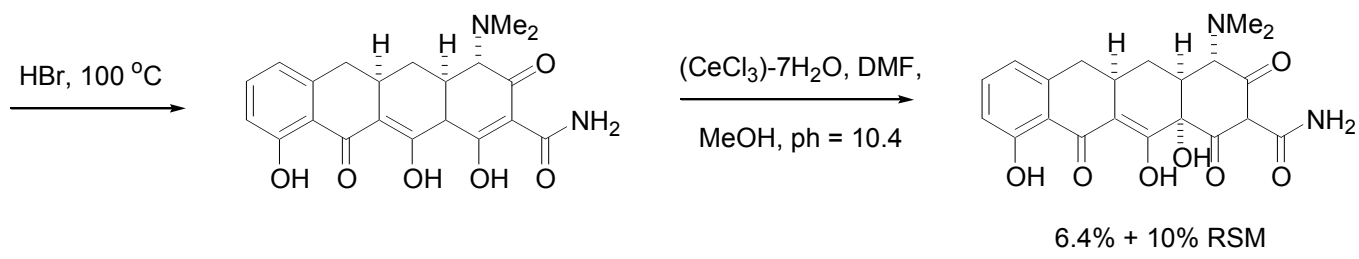
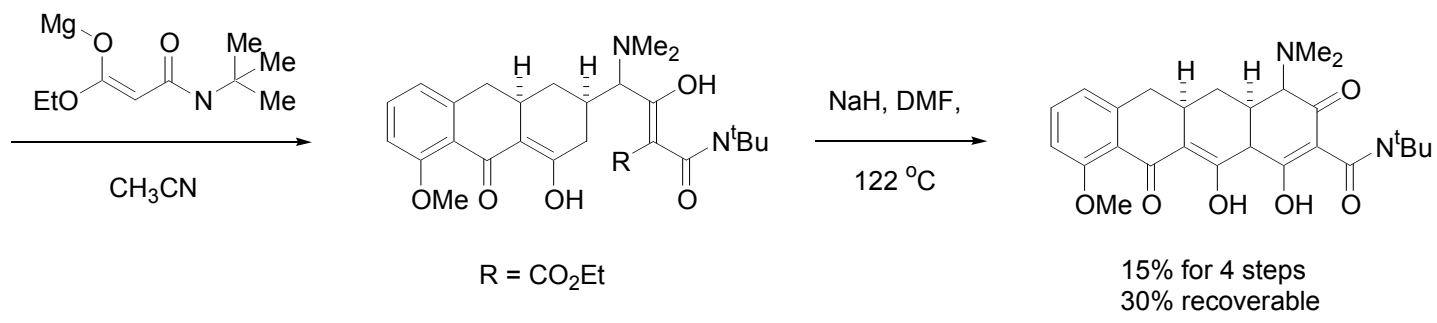
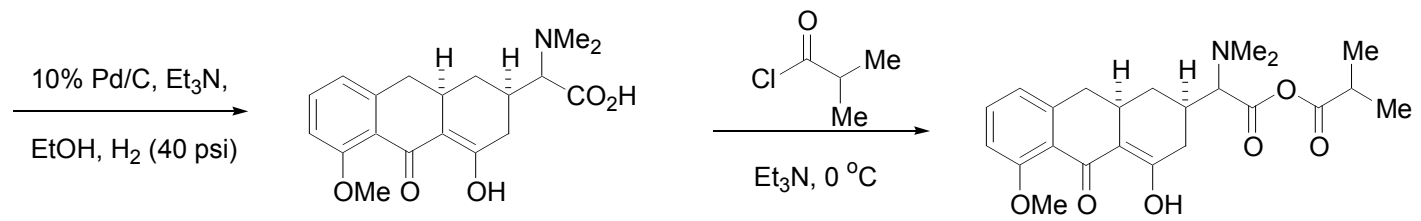
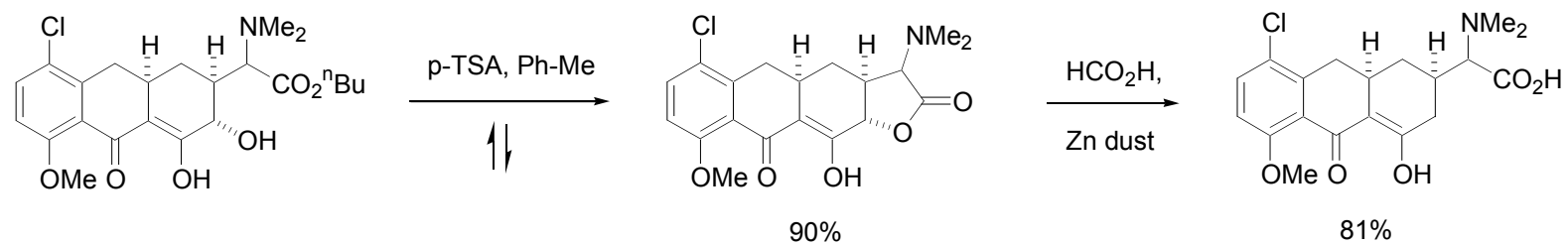
“The most formidable synthetic problems posed by the structure are concentrated in ring A: every carbon of the atom skeleton of that ring bears at least one substituent, and three of the four asymmetric centers of the molecule fall in the consecutive chain C4, C4a, C12a.” - Woodward

Korst, J. J.; Johnston, J. D.; Butler, K.; Bianco, E. J.; Conever, L. H.; Woodward, R. B.
J. Am. Chem. Soc. **1968**, *90*, 439.

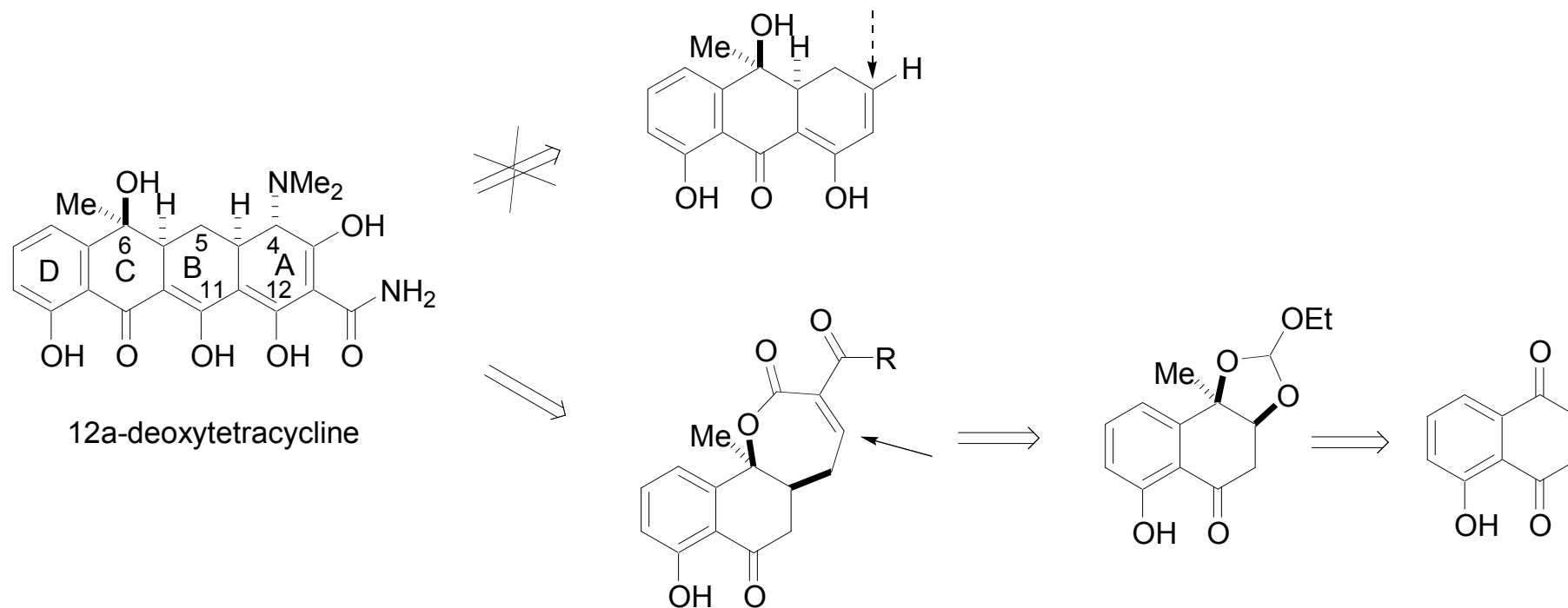




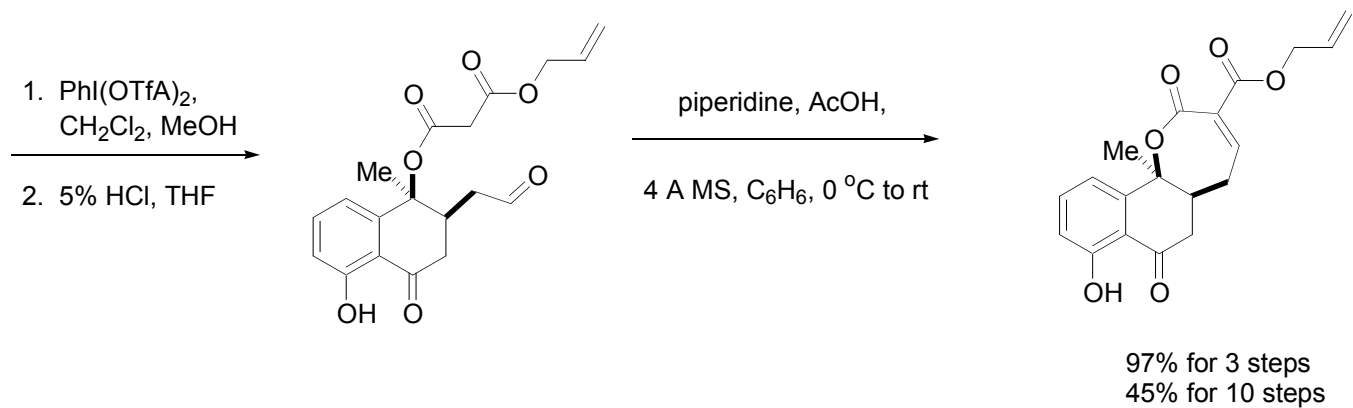
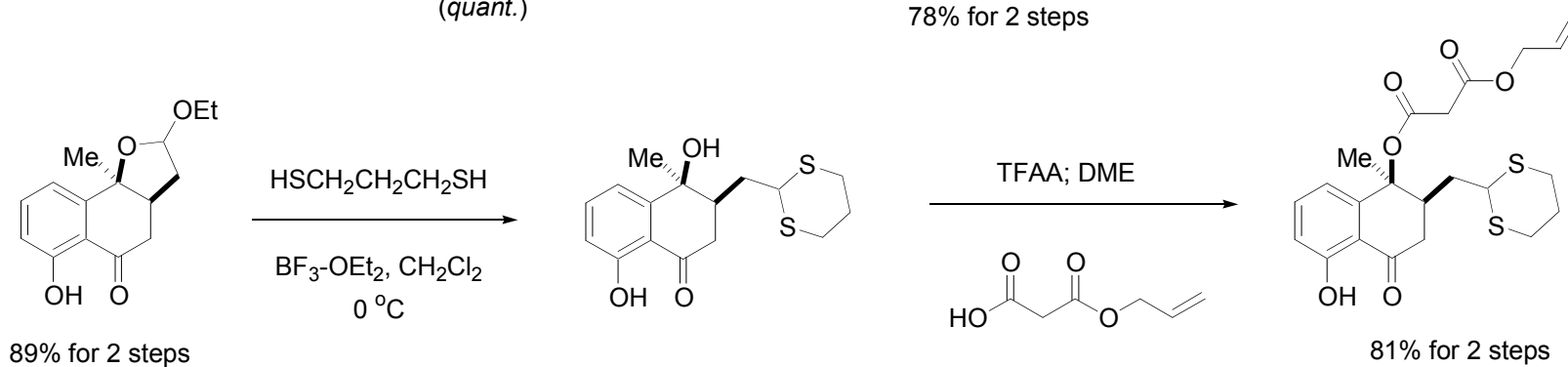
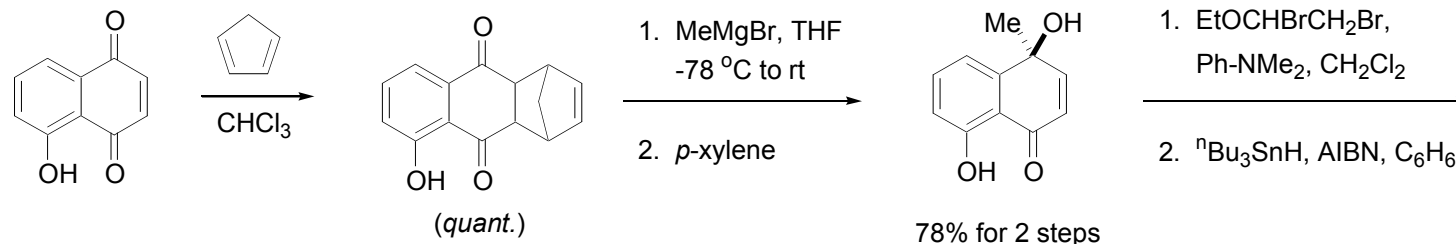


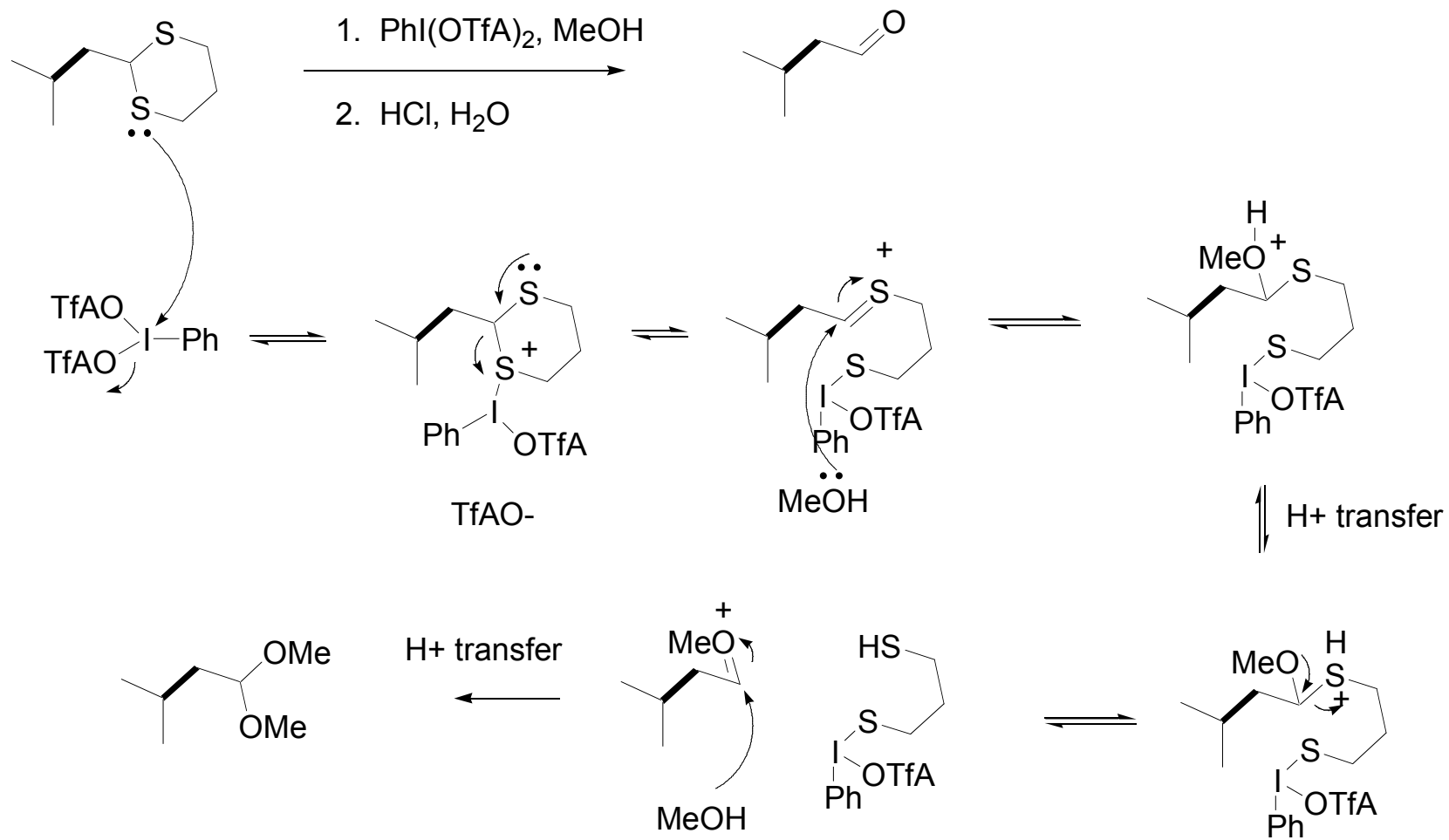


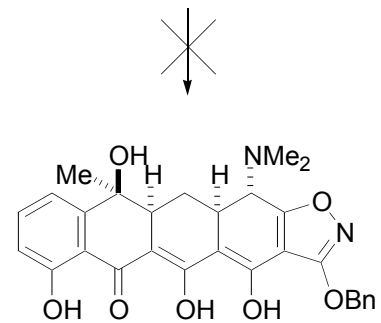
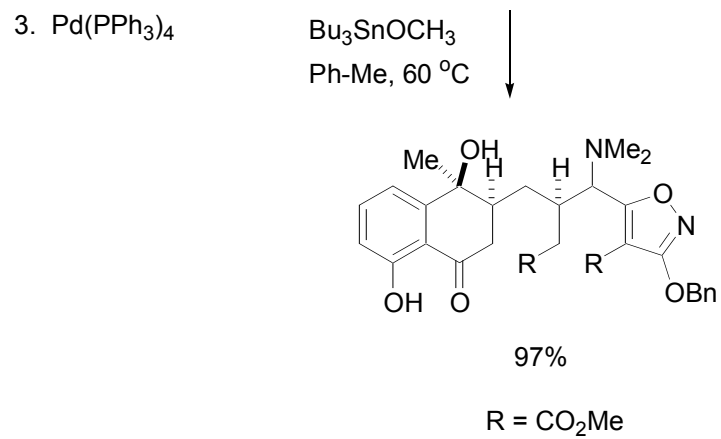
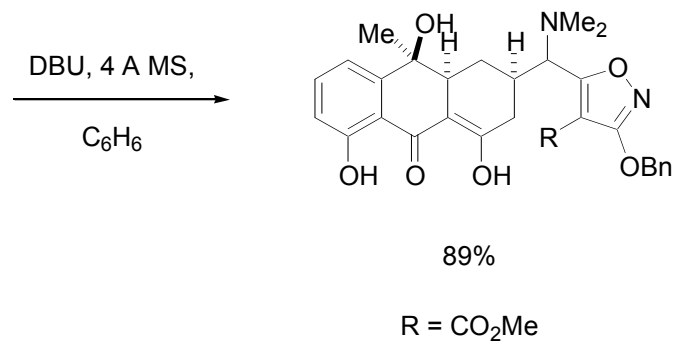
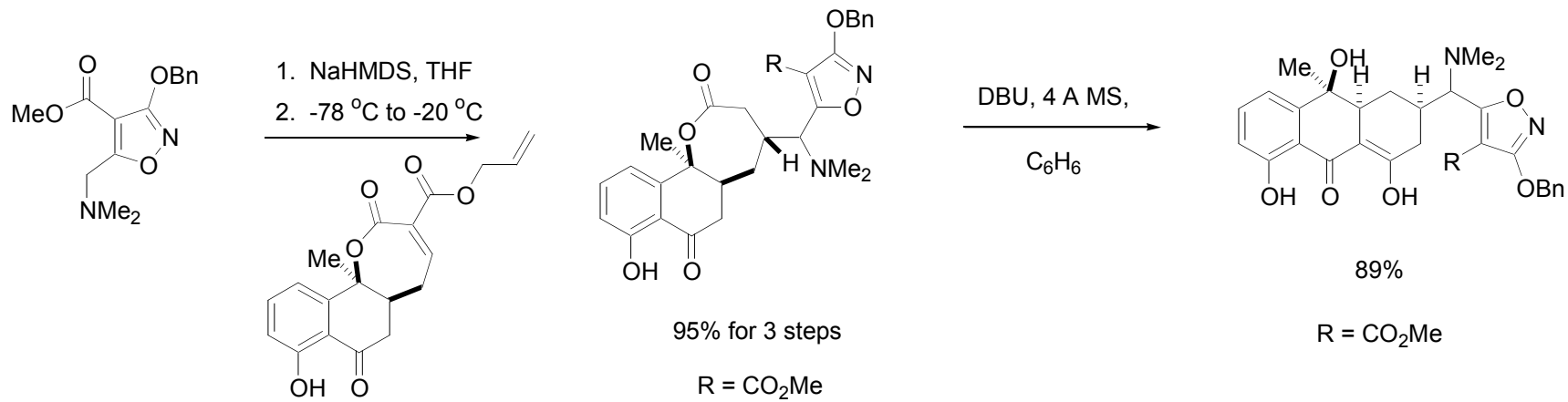
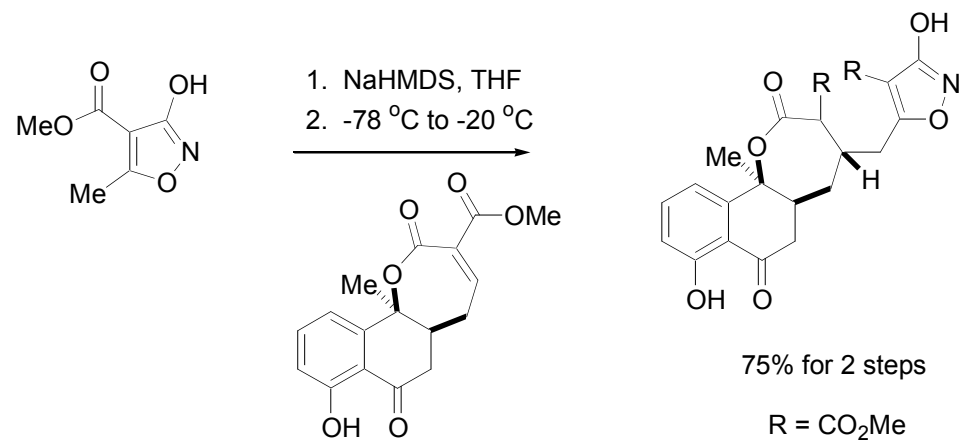
Stork's Approach

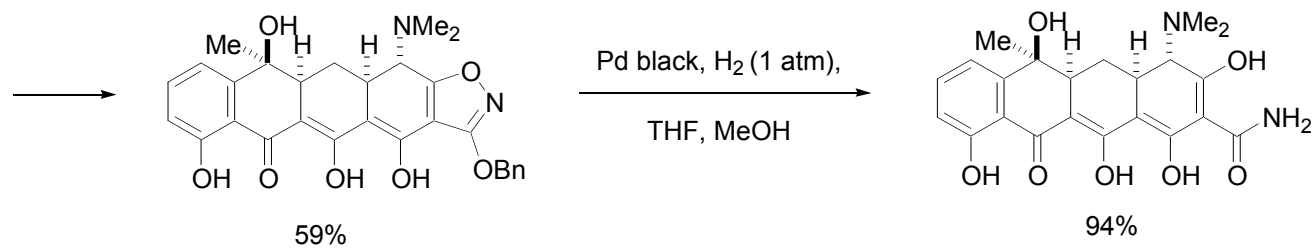
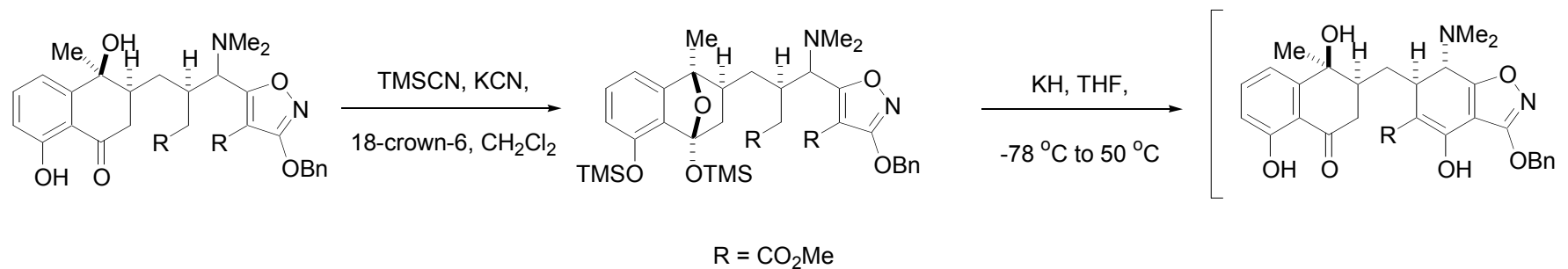


Stork, G.; La Clair, J. L.; Spargo, P.; Nargund, R. P. Total, N. *J. Am. Chem. Soc.* **1996**, *118*, 5304.

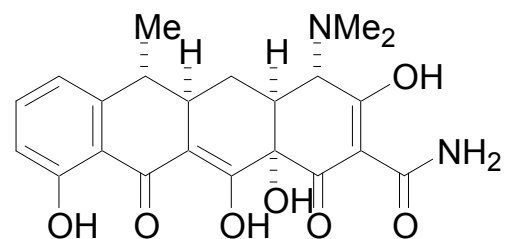






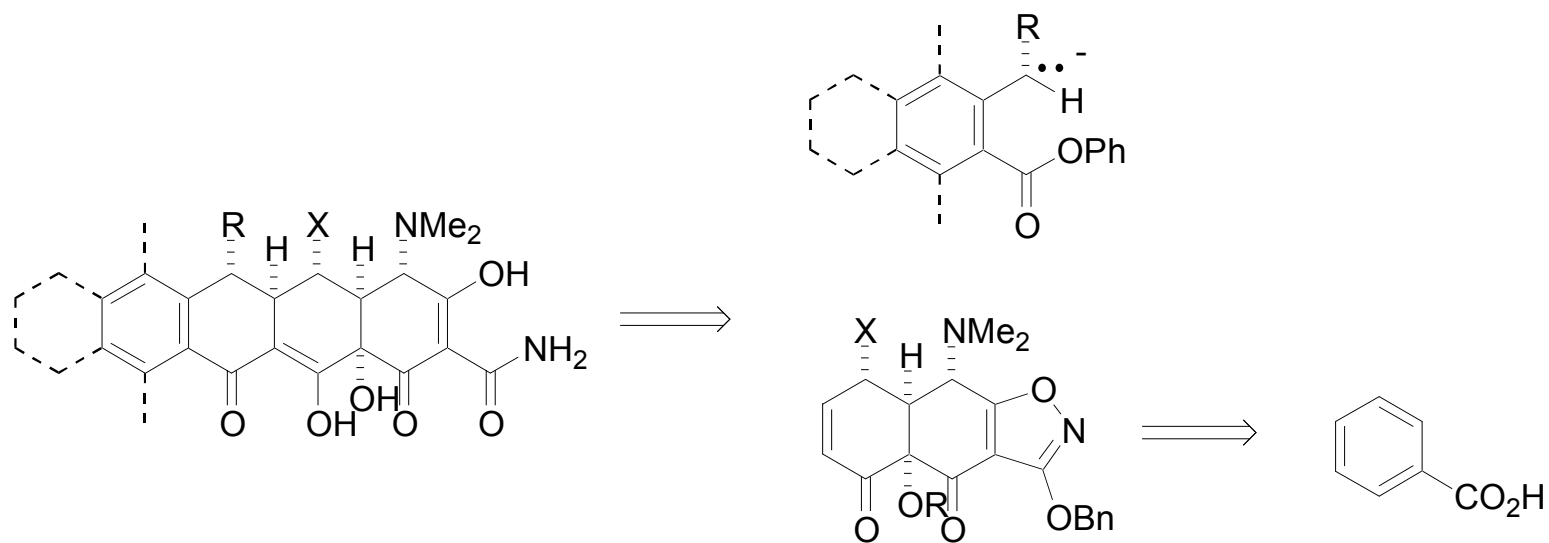


Myers' Approach

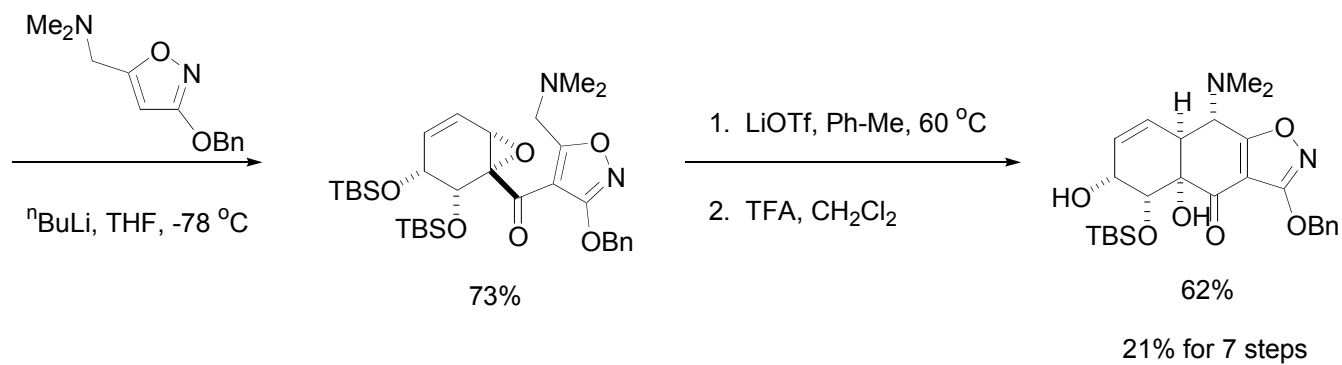
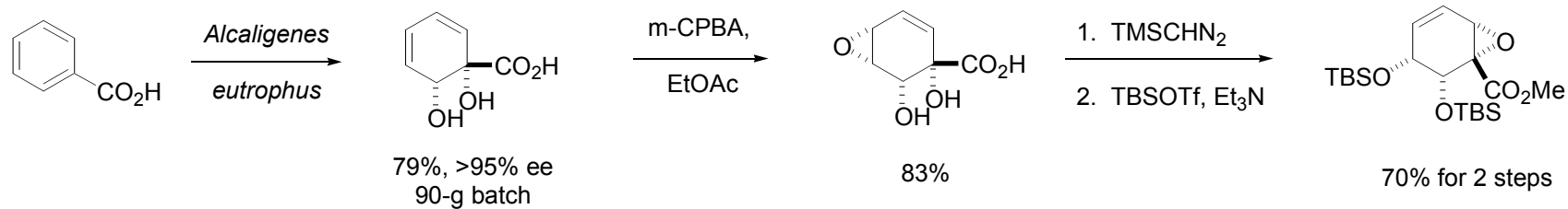


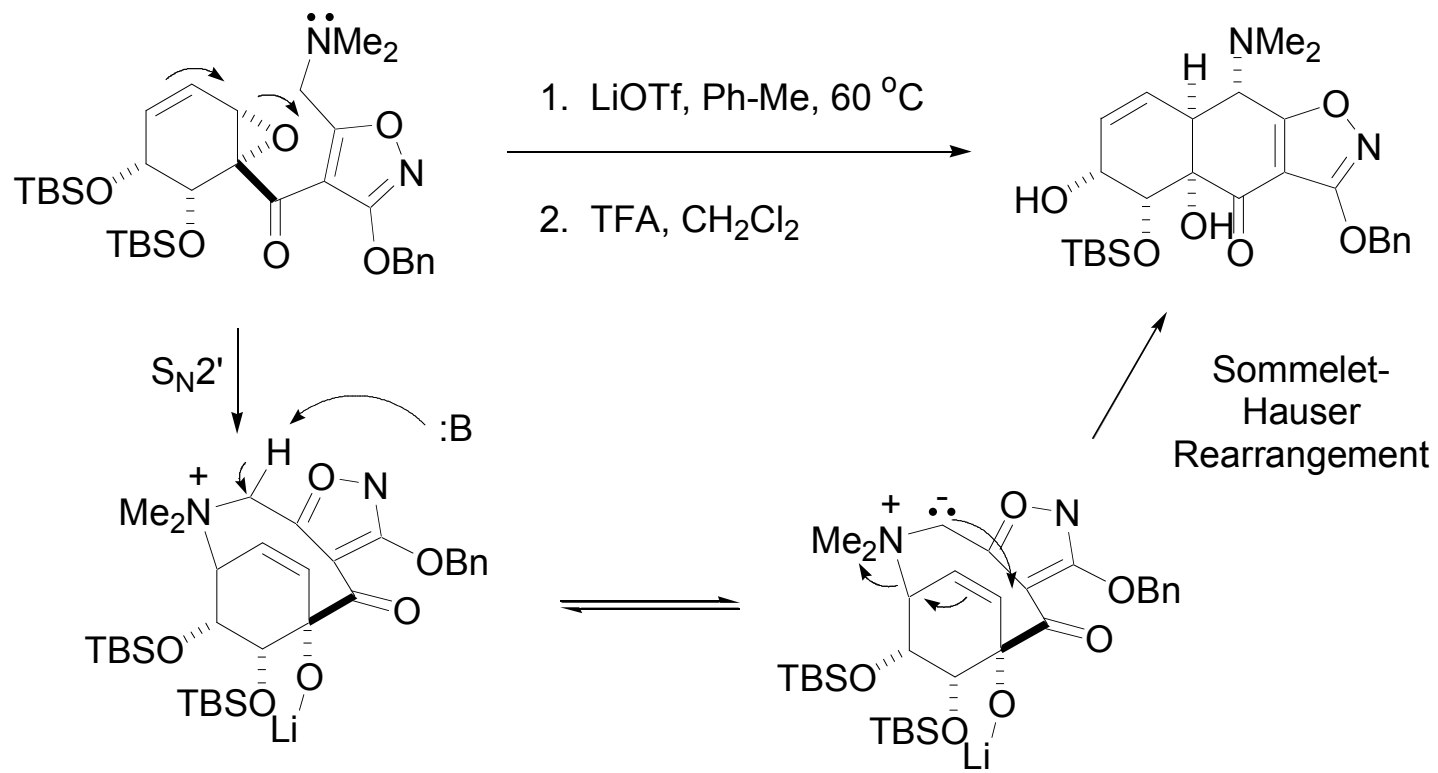
and analogs...

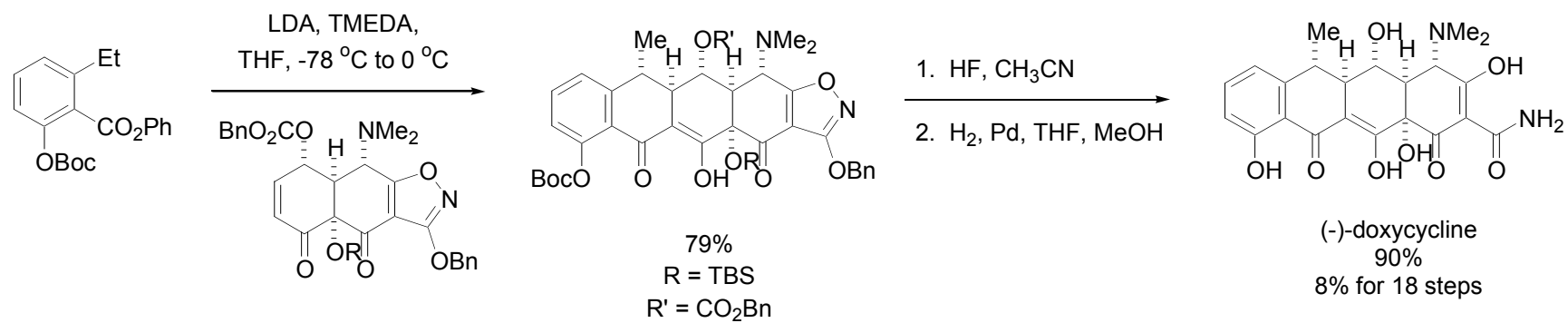
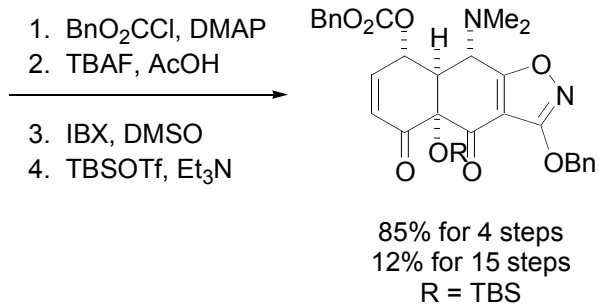
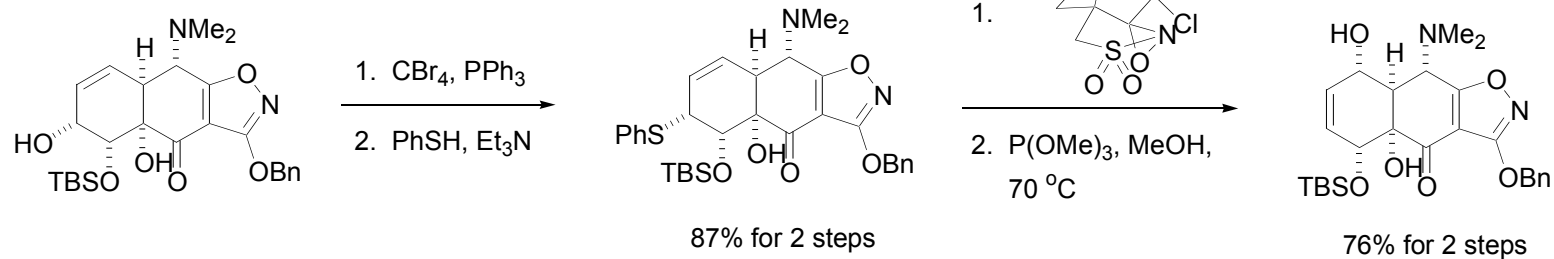
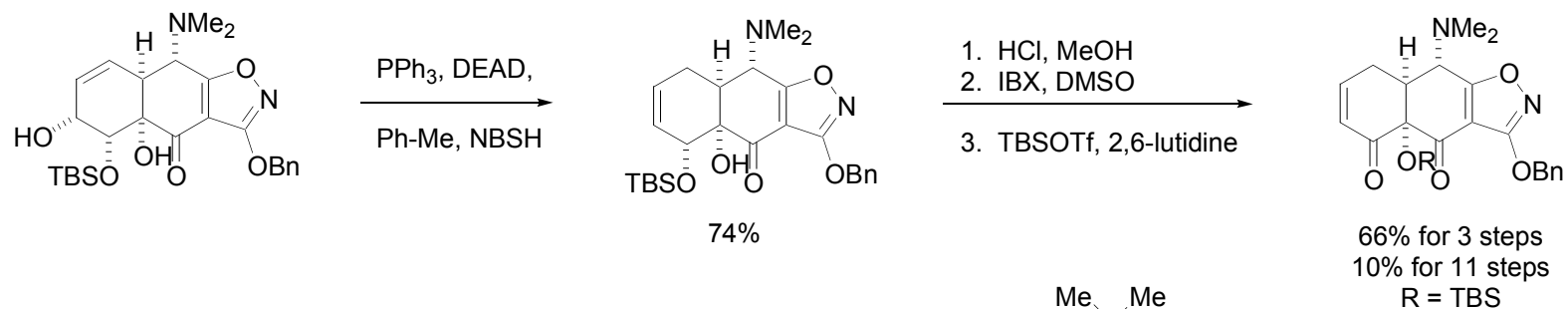
(-)-6-deoxytetracycline

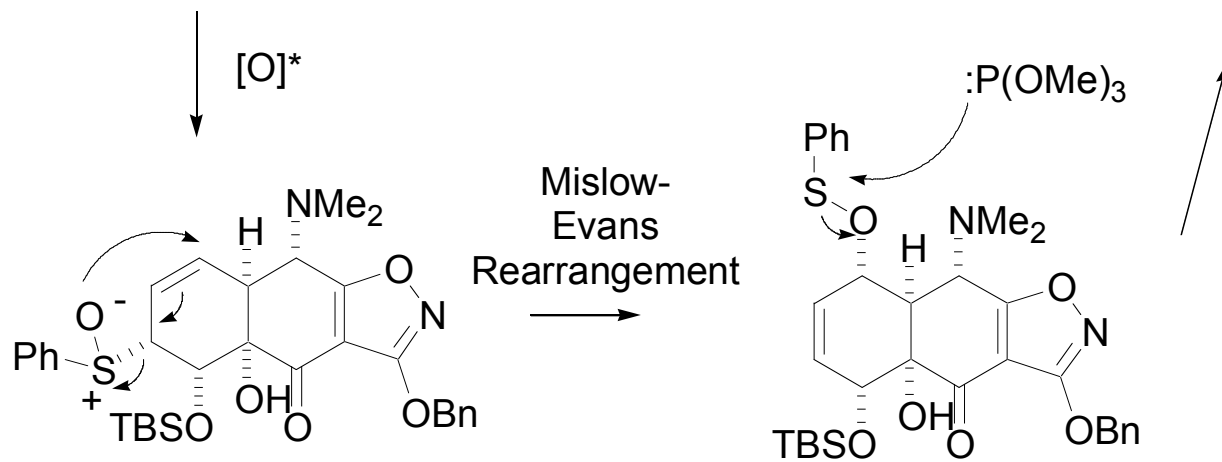
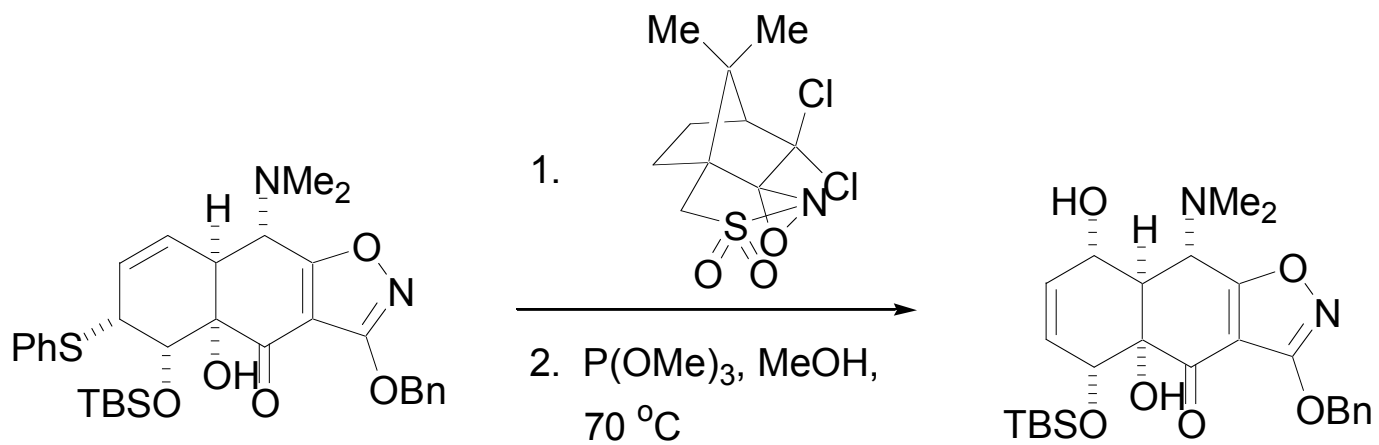


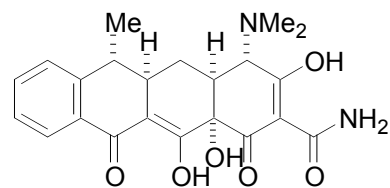
Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D. R. Myers, A. G. *Science* **2005**, 308, 395.



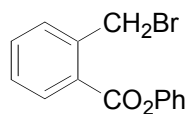




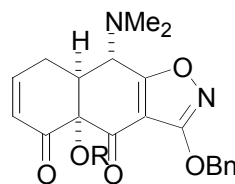




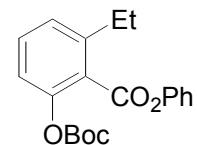
10-deoxysancycline
68% for 3 steps
7% for 14 steps



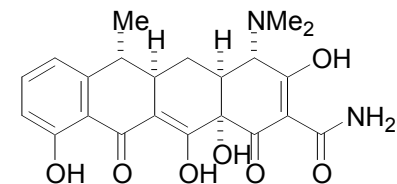
1. $n\text{BuLi}$, $-100\text{ }^\circ\text{C}$
to $-70\text{ }^\circ\text{C}$
2. HF , CH_3CN
3. H_2 , Pd



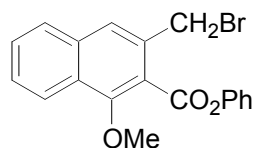
R = TBS



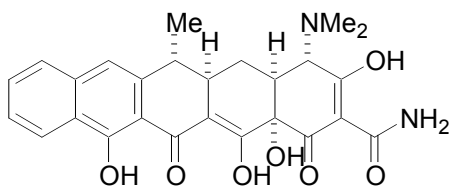
1. LDA , TMEDA ,
 $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$
2. HF , CH_3CN
3. H_2 , Pd



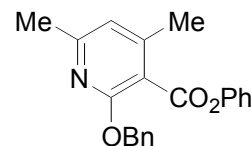
(-)-6-deoxytetracycline
69% for 3 steps
7% for 14 steps



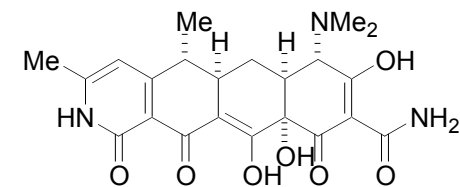
1. $n\text{BuLi}$, $-100\text{ }^\circ\text{C}$
to $0\text{ }^\circ\text{C}$
2. HF , CH_3CN
3. H_2 , Pd
4. BBr_3 , CH_2Cl_2
 $-78\text{ }^\circ\text{C}$ to rt



pentacycline derivative
56% for 4 steps
6% for 15 steps



1. LDA , TMEDA ,
 $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$
2. H_2 , $\text{Pd}(\text{OH})_2$
3. HCl , MeOH



pyridone derivative
50% for 3 steps
5% for 14 steps