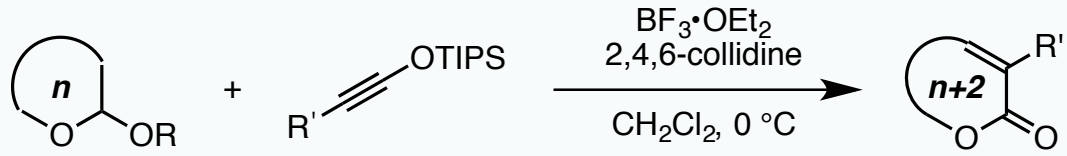
A New Strategy for Efficient Synthesis of Medium and Large Ring Lactones without High Dilution or Slow Addition

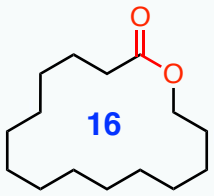


Zhao, W.; Li, Z; Sun, J. *J. Am. Chem. Soc.* **2013** ASAP

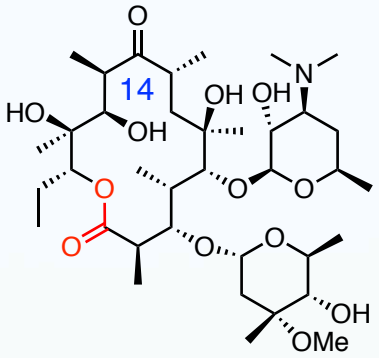
Joshua Sacher

23 March 2013

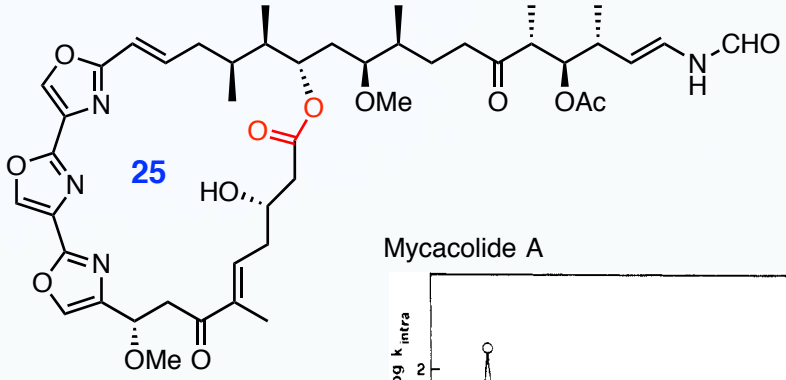
Macrolactonization



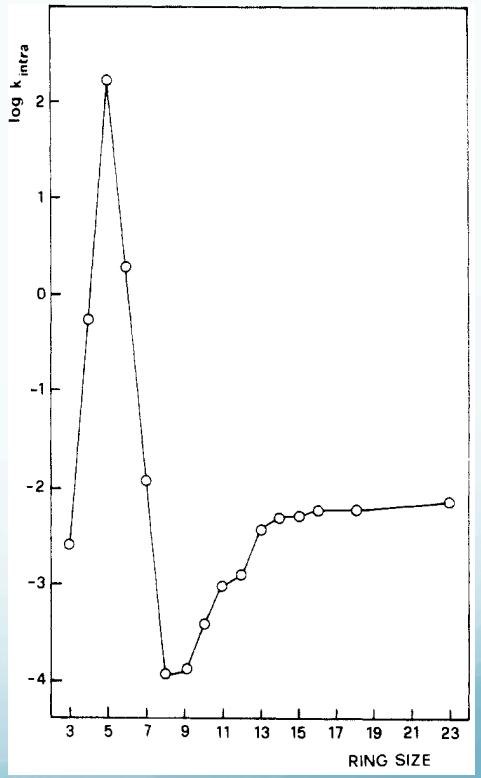
Exaltolide
(perfume–musk)



Erythromycin A
(antibiotic)



Mycacolide A



Direct lactonization:

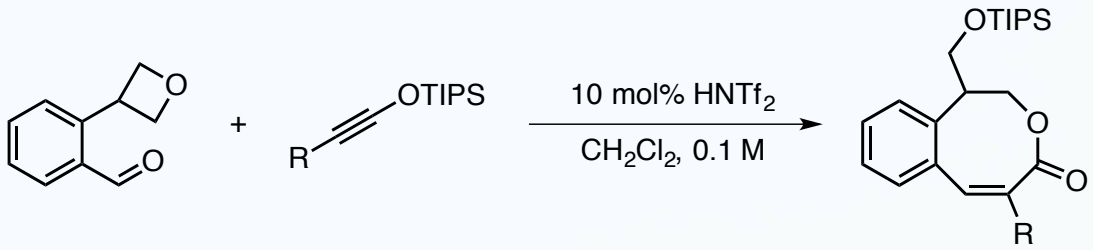
- Activated acids (Carbodiimides, P-based, Yamaguchi, etc.)
- Carboxylate attack (Mitsunobu, Iodolactonization, etc.)

Indirect formation:

- RCM
- Olefination (Wittig, HWE, Julia)
- Others (ex: heterocycles, couplings)

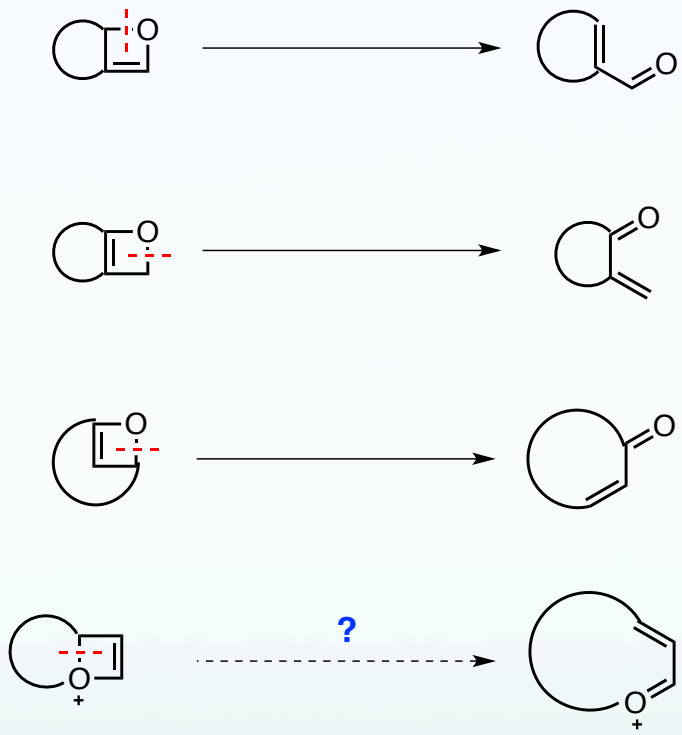
Parenty, A.; Moreau, X.; Niel, G.; Campagne, J.-M. *Chem. Rev.* **2013**, *113*, PR1
Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95

Previous Work

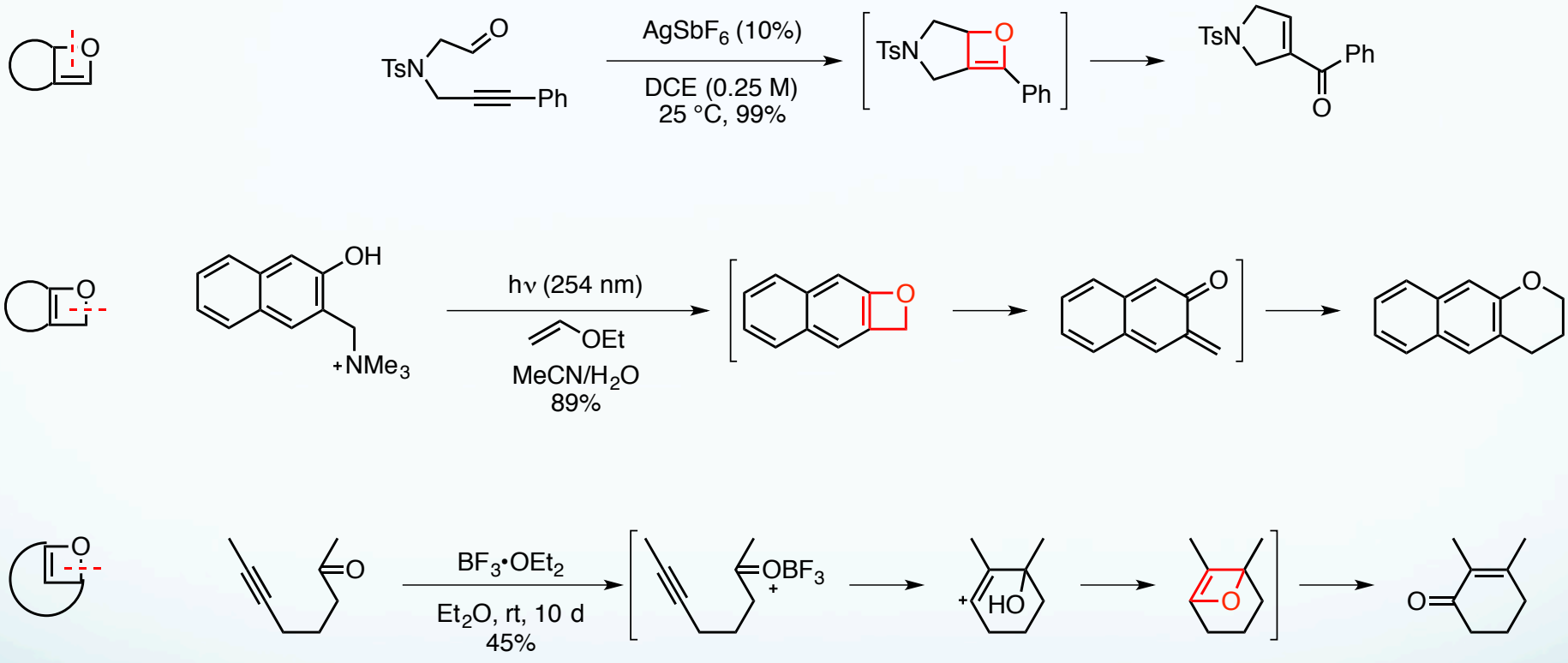


Zhao, W.; Wang, Z.; Sun, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 6209

Oxetene Fragmentation

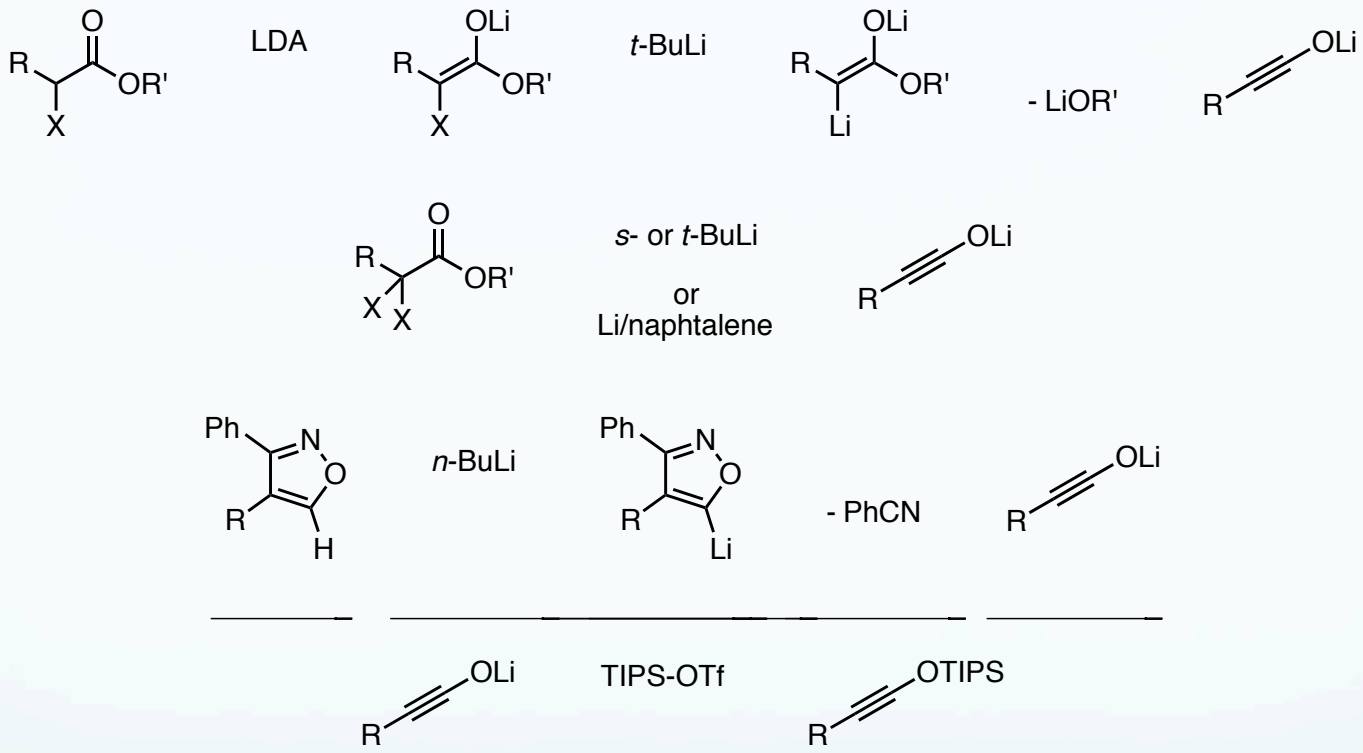


Real Examples



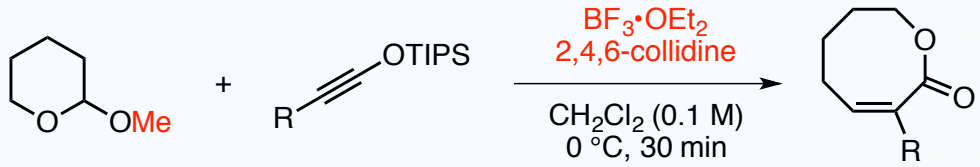
Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, *7*, 2493
Arumugam, S.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 11892
Harding, C. E.; King, S. L. *J. Org. Chem.* **1992**, *57*, 883

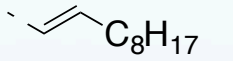
Ynolates



Shindo, M. *Tetrahedron*, **2007**, *63*, 10
Shindo, M.; Mori, S. *Synlett*, **2008**, 2231

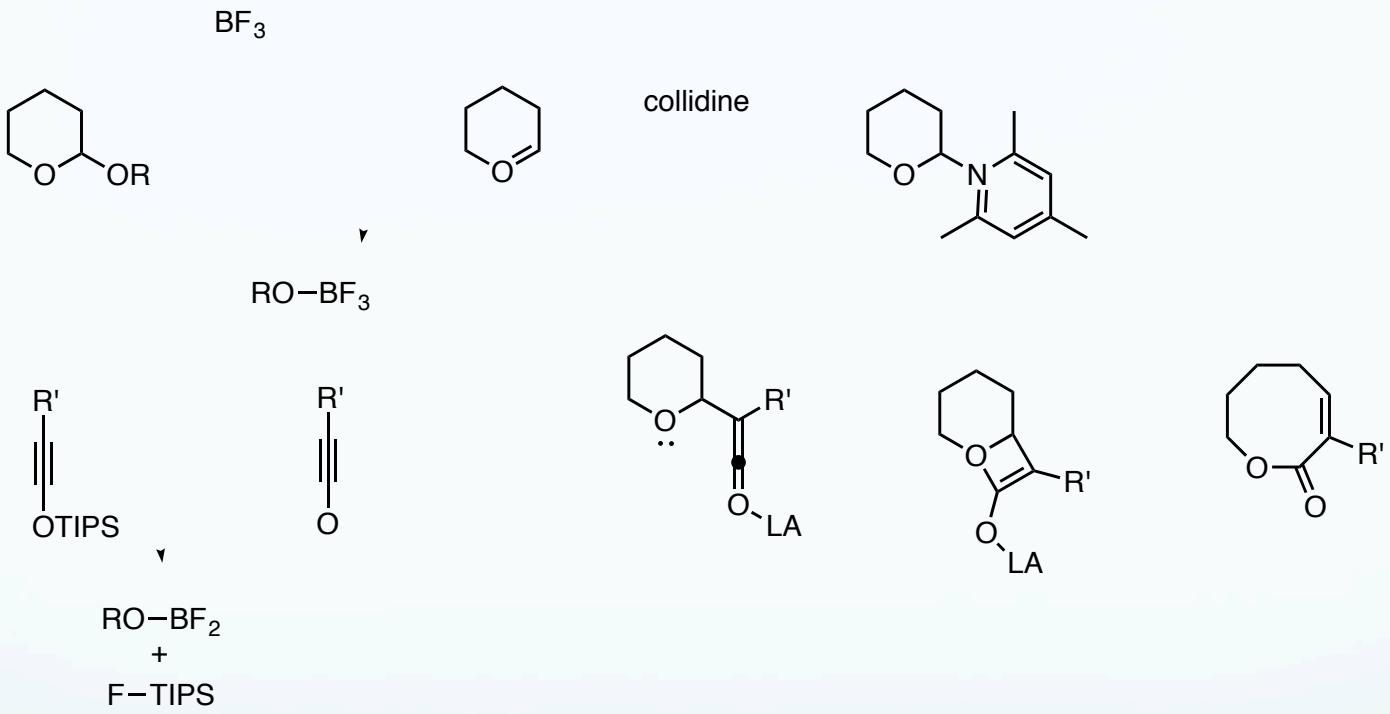
Ynol Ether Scope



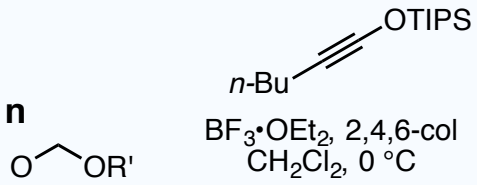
Entry	R	yield
1	*n*-Bu	91%
2	*n*-Oct	85%
3	$(CH_2)_3Ph$	77%
4	*c*-Pr	89%
5	*t*-Bu	84%
6	Ph	64%
7	$(CH_2)_3OTIPS$	62%
8		58%

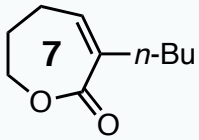
- Optimized acetal, Lewis acid, additive
- Sterics not an issue
- Conjugation problematic
- R ≠ H (unstable ynol ether)

Proposed Mechanism

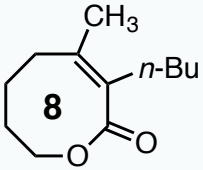


Ketals: Selected Examples

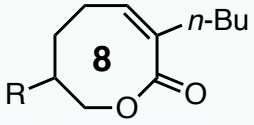




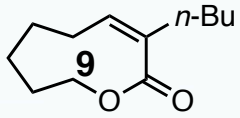
93%



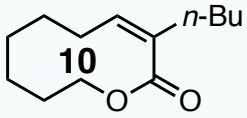
77%



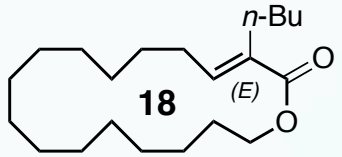
R	yield
OTBS	75%
OBz	56%
N_3	52%
O-allyl	65%
O-propargyl	63%



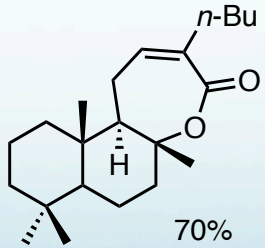
86%



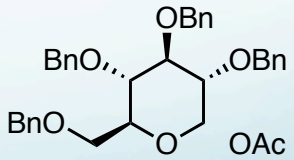
88%
(1:1 *E/Z*)



87%



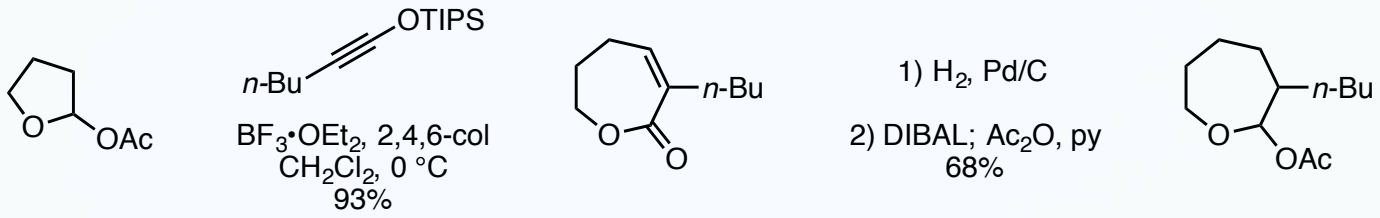
70%

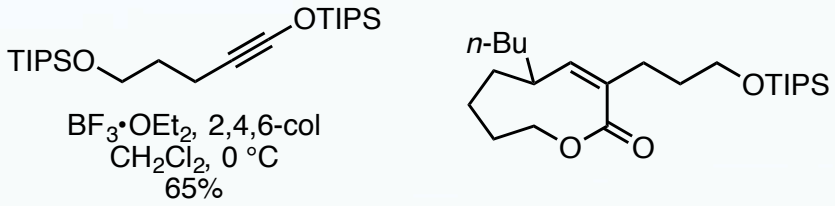


No Reaction

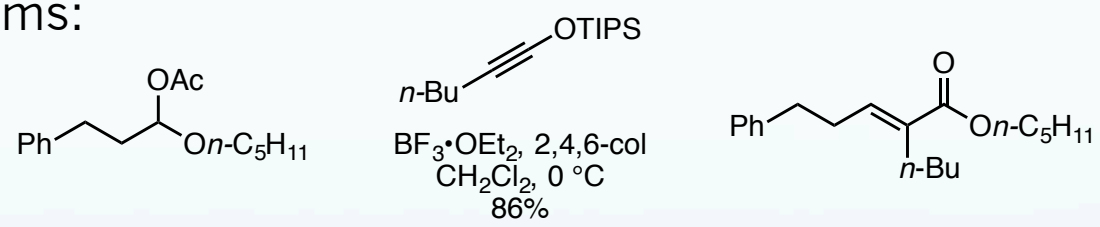
Extensions

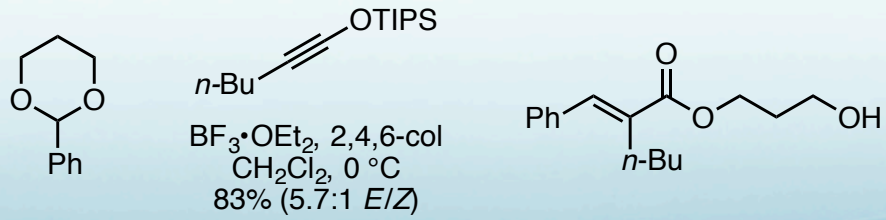
Iterative Ring Expansion:





Acyclic Systems:





Conclusion

- New methodology for forming medium- and large-ring lactones
- Unprecedented ring expansion reaction manifold for oxetenes
- Normal reaction concentrations, no slow addition
- Iterative process possible to generate large rings from inexpensive material

- Must use substituted alkynes due to instability
- Potential problems with electronics of alkyne
- Limited use in complex systems to date.