Ortholactone Spiroketal Fragment Couplings: A Convergent Approach to Complex Natural Products.

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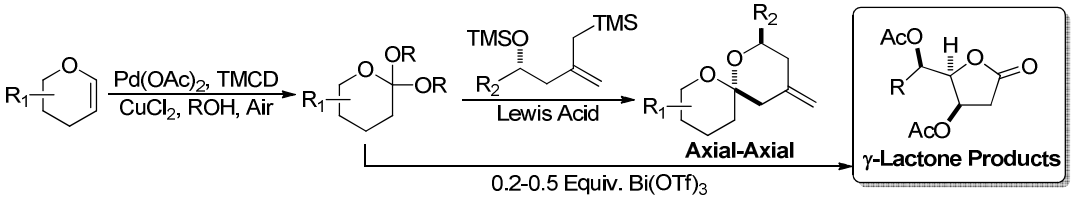
Spiroketals are ubiquitous in nature occurring in many complex macrolides which exhibit potent biological activity. Most methods for their construction are linear approaches requiring long synthetic sequences to install functional groups prior to a cyclization to form the spiroketal. Although effective, these methods are not convergent and lead to high linear step counts and issues with both material throughput and structure diversification.[1] Our approach was to develop a modular fragment-coupling based strategy whereby the sprioketalization is also the fragment coupling step. This convergent approach uses the coupling of an ortholactone and a δ-hyroxyallylsilane to form the sprioketal in a single step, a strategy reported by Markó on very simple substrates.[2]

The major synthetic challenges were to develop an efficient and functional group tolerant synthesis of ortholactones followed by optimization of the fragment coupling in complex systems. The ortholactone synthesis was achieved through a palladium catalyzed Wacker-type oxidation of dihydropyrans.[3] This method was particularly efficient for the construction of both methoxy and spirocyclic variants. These ortholactones could be coupled very efficiently with the allylsilanes to form the spiroketals in high yields as a single stereoisomer. When $Bi(OTf)_3$ was used as a Lewis acid, a fragmentation reaction occurred to form a rearranged γ-lactone product which occurs with a wide range of functionality.[4]



[1] Review: Yeung, K. –S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237.

[2] Markó: *Tetrahedron Lett.* **1991**, *32*, 4783; *J. Org. Chem.* **1992**, *57*, 2211;

[3] Baddeley, K. A.; Cao, Q.; Muldoon, M. J.; Cook, M. J. *Chem. Eur. J.* **2015**, *21*, 7726.

[4] Baddeley, K. A.; Cook, M. J. *Submitted for Publication.*