Macrolactonization via Hydrocarbon Oxidation

Kenneth J. Fraunhoffer and M. Christina White

Macrolides are important structural units due to their prevalence in numerous small molecules having significant and diverse biological and medicinal properties. While hydroxyacid lactonization reactions are powerful methods for the synthesis of complex macrolides, they often require the use of multiple biasing elements and high-dilution techniques to promote cyclization. In addition, the selective lactonization of polyhydroxylated compounds can require the heavy use of time-consuming functional group manipulations and oxidation state changes.

We report a novel Pd/sulfoxide-catalyzed macrolactonization method for the cyclization of linear ω-alkenoic acids that may streamline the overall synthesis of macrolides. The scope of this macrolactonization appears to be very broad. Aryl, alkyl, and (*Z*)-α,β-unsaturated acids are all competent nucleophiles for this reaction, with the latter undergoing macrolactonization with no olefin isomerization. High functional group compatibility is observed that includes biologically and medicinally relevant functionality such as ortho-substituted salicylate esters, bis(indolyl)maleimides, and peptides. Evidence is provided to support the hypothesis that macrolactonization proceeds through inner-sphere functionalization from a templated π-allylPd carboxylate intermediate. Notably, this Pd-templated macrolactonization method does not require the use of high-dilution techniques or biasing elements.