Total Synthesis and Study of 6-deoxyerythronolide B by Late-Stage C—H Oxidation

Erik M. Stang and M. Christina White

The interconnected goals of increasing synthetic efficiency and diversity in the construction of complex molecules remain a frontier challenge in chemistry in the 21st century. C—H Oxidation reactions, particularly when applied at late-stages of complex molecule syntheses, hold special promise for achieving both these goals. A late-stage C—H oxidation strategy will be presented in the total synthesis of 6-deoxyerythronolide B (6-dEB), the aglycone precursor to the erythromycin antibiotics. An advanced linear alkenoic acid intermediate is cyclized to the 14-membered macrocyclic core of 6-dEB using a late-stage (step 19 of 22) C—H oxidative macrolactonization reaction that proceeds with high regio-, chemo-, and diastereoselectivity (>40:1). A chelate-controlled model for macrolactonization was used to predict the stereochemical outcome of C—O bond formation and led to the discovery of conditions for synthesizing the first diastereomeric 13-epi-6-dEB precursor. Overall, this C—H oxidation strategy affords a highly efficient and stereochemically versatile synthesis of the erythromycin core.