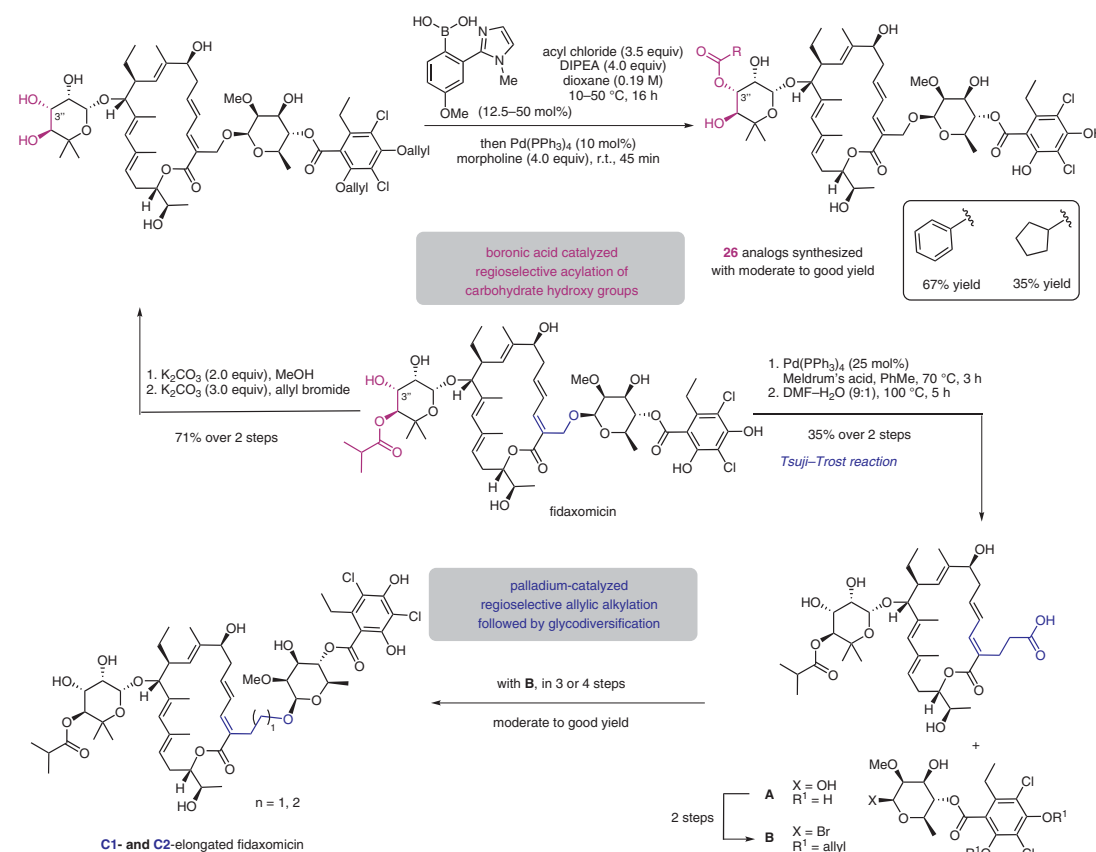


Novel Antibiotics by Late-Stage Derivatization of Marketed Fidaxomicin



Significance: Fidaxomicin shows antibacterial activity against Gram-positive bacteria. In 2011, fidaxomicin was approved by the FDA for the treatment of *C. difficile* infection, the main cause of hospital-acquired diarrhea. The development of second-generation fidaxomicin derivatives cannot only expand its therapeutic applications, such as the treatment of *Mycobacterium tuberculosis*, but can be a potential candidate against multidrug-resistant bacteria. The authors developed two strategies for the synthesis of novel analogues with promising antibacterial activities directly from fidaxomicin.

Comment: Two strategic, site-selective reactions were used for late-stage functionalization of fidaxomicin. A boronic acid catalyzed regioselective acylation can acylate the C3''-OH in the presence of six other hydroxy groups, based on previous work (*Org. Lett.* 2019, 21, 3789). A palladium-catalyzed regioselective allylic alkylation can replace the right part glucose with Meldrum's acid, and further manipulations allow for glycodiversifications at the right side. Considering the complexity of fidaxomicin, the achieved selectivity is quite impressive.