Next-Generation Macrolide Antibiotics

Significance: Since the discovery of erythromycin A in 1949 as a potent antibacterial natural product, many synthetic and semisynthetic approaches have been investigated to improve its activity or to reduce side effects. While some semisynthetic strategies were successful (e.g., azithromycin), total synthetic approaches mostly failed to efficiently generate larger quantities of analogues. 35 years after the celebrated synthesis of Woodward and co-workers, Seiple, Zhang et al. reported a highly diverse total synthetic approach towards new macrolide antibiotics that established more than 300 new variants of ketolides and azaketolides.

Comment: Macrolide antibiotics disrupt bacterial growth by inhibiting protein synthesis. The highly diverse synthetic approach of Myers and co-workers includes a vinylogous Mukaiyama aldol reaction, a glycosylation according to Woodward's protocol, and a Boeckman cyclization to elaborate the key macrolactone motif. All reactions have proven to be robust towards many functional groups, enabling this approach to establish new analogues that are no longer restricted by the functional groups required for semisynthetic derivatizations. Many of the synthesized macrolides showed high potencies.

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