Next Generation Vancomycin Total Synthesis

**Significance:** The glycopeptide vancomycin has been used successfully to treat various infections of Gram-positive bacteria for more than 60 years. Vancomycin resistant bacteria have developed a clever alternative peptidoglycan assembly strategy that resulted in significant reduction in binding affinity of the antibiotic. Successful SAR-studies established analogues with high potencies against these resistant strains (J. Am. Chem. Soc. 2015, 137, 3693). However, a lengthy and low yielding synthesis hampered further clinical investigations of these promising candidates. The authors now describe a scalable, practical, and modular synthetic approach, containing 19 linear steps with high yields and atroposelectivities.

**Comment:** The first key step of their synthetic approach is a one-pot, atroposelective Miyaura borylation/Suzuki cross-coupling sequence. After macrolactamization and coupling with the central D-ring fragment, an SNAr afforded the ABCD-ring system with excellent diastereoselectivity. Amide coupling with the next building block was followed by yet another highly atroposelective SNAr. Further functional group manipulations afforded the aglycon of vancomycin. Its conversion into the natural product via enzymatic glycosylation has been previously reported (Org. Lett. 2014, 16, 3572).