M. J. MOORE, S. QU, C. TAN, Y. CAI, Y. MOGI, D. J. KEITH, D. L. BOGER* (THE SCRIPPS RESEARCH INSTITUTE, LA JOLLA, USA)

Next-Generation Total Synthesis of Vancomycin
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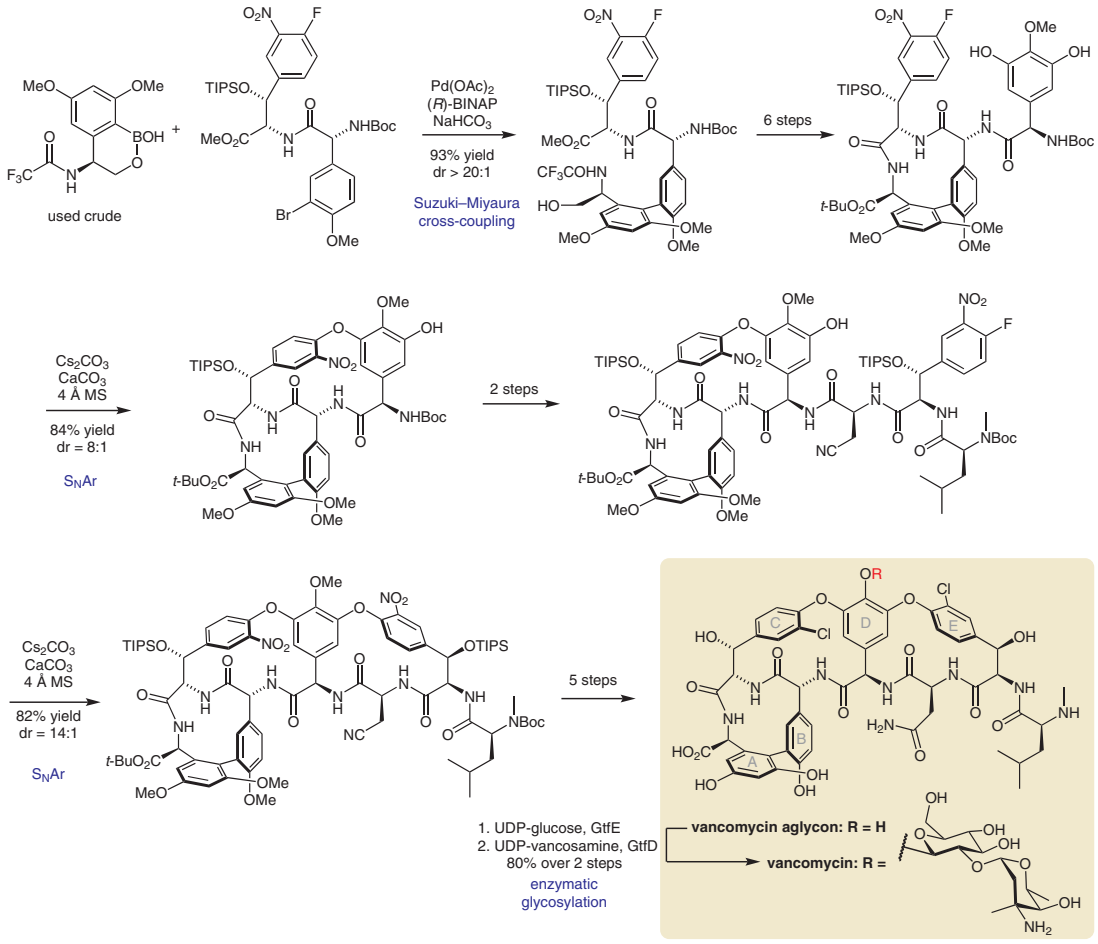
Next Generation Vancomycin Total Synthesis



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 S_NAr afforded the ABCD-ring system with excellent diastereoselectivity. Amide coupling with the next building block was followed by yet another highly atroposelective S_NAr. 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).

SYNFACTS Contributors: Dirk Trauner, Klaus-Peter Ruehmann
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glycopeptide
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atropisomerism

Synfact of the Month