M. J. MOORE, P. QIN, N. YAMASAKI, X. ZENG, D. J. KEITH, S. JUNG, T. FUKAZAWA, K. GRAHAM-O'REGAN, Z.-C. WU, S. CHATTERJEE, D. L. BOGER* (THE SCRIPPS RESEARCH INSTITUTE, LA JOLLA, USA)

Tetrachlorovancomycin: Total Synthesis of a Designed Glycopeptide Antibiotic of Reduced Synthetic Complexity
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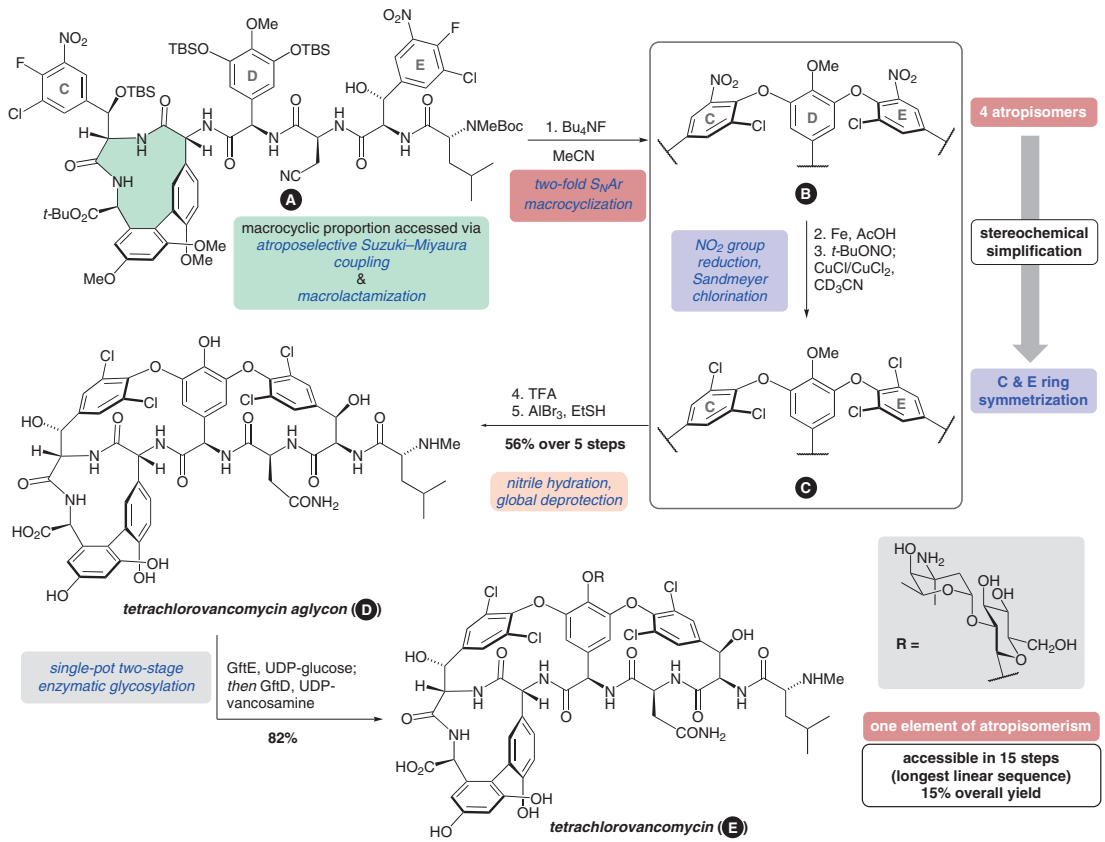
Total Synthesis of Tetrachlorovancomycin



Significance: Vancomycin has been the subject of significant synthetic efforts for decades, due to its potent antimicrobial properties. Its structure, harboring three elements of atropisomerism, poses a tremendous synthetic challenge. Removal of two elements of atropisomerism by addition of two aryl chlorides at rings C and E significantly reduced synthetic complexity and yielded the stereochemically simplified tetrachlorovancomycin (**E**), which retains significant antimicrobial activity. Peripherally modified derivatives further showed high potencies against vancomycin-resistant bacterial strains. This work is an important contribution to the development of new synthetic glycopeptide antibiotics to tackle the challenge of rising antibiotic resistances.

Comment: Building on their 2020 vancomycin synthesis, the Boger group prepared intermediate **A**, carrying additional chloro substituents at rings C and E. The macrocyclic proportion of **A** was constructed via atroposelective Suzuki–Miyaura coupling and macrolactamization. The vancomycin core structure **B** was generated by two-fold S_NAr macrocyclization after desilylation, yielding a mixture of four atropisomers. The mixture was converted into symmetrical tetrachloro intermediate **C** via nitro group reduction and Sandmeyer chlorination. TFA-mediated nitrile hydration and global deprotection afforded aglycon **D** in over 50% yield over five steps starting from **A**. Enzymatic glycosylation concluded the total synthesis of **E** with an exceptional yield of 15% over 15 steps.

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Category

Innovative Drug Discovery and Development

Key words

vancomycin
antibiotics
total synthesis
atropisomerism
S_NAr reaction
Sandmeyer chlorination
symmetrization

Synfact of the Month