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 SNAr macrocyclization after desilylation, yielding a mixture of four atropisomers. The mixture was converted into symmetrical tetrachloro intermediate C via nitro group reduction, 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.