In addition, other new antibacterial compounds based on vancomycin modification were also exhibited prominent biological activity against resistant pathogens. In 2000, Daniel Kahne and co-workers investigated the role of hydrophobic substituents in sugar moiety of vancomycin for overcoming drug resistance (Kerns et al. 2000). The MIC assays demonstrated that all the resultant products 14 have better bactericidal activity toward both sensitive and resistant strains. Comparing with the original vancomycin, the biological activity of these derivatives with hydrophobic groups increased by 50–100 times against sensitive *Enterococcus faecium* and by 15–200 times against resistant *E. faecium*. It is proved that the hydrophobic modification strategy is one of the rational approaches for improving vancomycin activity. From the above point of primary synthetic chemistry, modifying of clinical antibiotics is a classical and appropriate method for obtaining counterpart derivatives. By screening active ones from them, this strategy has applied many highly effective new antibiotics. These listed proper examples demonstrated that the semisynthetic modification strategy is advantageous in treating drug-resistant pathogens. But we should also clearly understand that not all the modified antibiotic derivatives could obtain a better biological function, so the semisynthetic method is a difficult and unpredicted way (Scheme 16.4).

With the specific study on the sterilization mechanism, more directional modification strategies have been introduced for promoting vancomycin activity. For example, in order to prevent the bacterial cell wall maturation, it has been demonstrated that vancomycin must form specific vancomycin homodimers driven by hydrogen bonding and hydrophobic interaction (Mackay et al. 1994a, b) firstly and then selectively contact with the terminal of *N*-acyl-D-Ala-D-Ala (Sheldrick et al. 1978; Perkins 1982). It also has been proved that one of the resistance mechanisms of vancomycin is that the terminal D-Ala-D-Ala is replaced by D-Ala-D-Lac. This little mutation resulted in the decrement of the binding ability between the original vancomycin and peptidoglycan. Fortunately, the constructed vancomycin dimers could bind with the mutated D-Ala-D-Lac (Bugg et al. 1991). Thus, it was a predictable approach that constructing vancomycin dimers to improve the affinity between vancomycin and original/mutated peptidoglycan sit, regaining the bactericidal activity of vancomycin. In 2003, Mu's group synthesized a kind of vancomycin dimer (**18**) bearing disulfide bonds (Mu et al. 2004). They also verified that the vancomycin dimer had great antibacterial activity against some selected pathogens. In 2015, Haldar's group prepared the vancomycin aglycon dimers (**19**), bis(vancomycin aglycon)carboxamides (Yarlagadda et al. 2015). The polyamine linker has a variable hydrophobicity, positive charge, and primary amine group, which could couple to the carboxyl group of vancomycin aglycon. The final product also recovered the vancomycin activity against MRSA and VRE.