most common and differ in their susceptibility to vancomycin and teicoplanin. Although the VanA phenotype shows reduced susceptibility to both teicoplanin and vancomycin, the VanB phenotype retains sensitivity to teicoplanin. The genes *vanRSHAX* encode for an alternate biosynthetic pathway that produces the mutated cell wall precursors (Walsh et al. 1996). In VISA the thickening of the bacterial cell wall leads to an increase in the number of binding sites for vancomycin binding and hence resistance (Hiramatsu 2001). Genotypic analysis of VRSA indicated that the resistance genes were acquired from VRE (Weigel et al. 2003). In some strains of VRSA, resistance was found to be due to both thickening of cell wall and mutation of the pentapeptide terminal (Hiramatsu 2001).

4.5 Second-Generation Glycopeptides

The second-generation glycopeptides are semisynthetic lipoglycopeptide antibiotics with enhanced antibacterial activity over vancomycin in both vancomycin-sensitive and vancomycin-resistant strains. There are three antibiotics that belong to this generation, namely, telavancin, dalbavancin, and oritavancin (Figure 4.1b). These glycopeptides possess a hydrophobic side chain that serves as a membrane anchor. The anchoring to the bacterial membrane increases localization in the membrane region and enhances the binding affinity to the membrane-associated lipid II. They strongly inhibit both transglycosylation and transpeptidation. This leads to enhanced antibacterial activity. All the three antibiotics have been briefly discussed below.

4.5.1 Telavancin

Telavancin (**3**) is a semisynthetic derivative of vancomycin consisting of a lipophilic decylaminoethyl moiety conjugated to the vancosamine sugar and a (phosphomethyl)aminomethyl moiety at the *para* position of the aromatic ring of the C-terminal dihydroxyphenylglycine residue (Charneski et al. 2009). The presence of the lipophilic moiety provides membrane interaction properties. This leads to permeabilization and depolarization of the bacterial cell membrane and a dual mechanism of action (Higgins et al. 2005). This membrane activity leads to improved bactericidal activity in comparison with the first-generation of glycopeptides against MRSA and methicillin-susceptible *S. aureus* (MSSA) as well as activity vancomycin-resistant strains such as VISA, VRSA, and VRE (Karlowsky et al. 2015). The hydrophilic (phosphomethyl)aminomethyl moiety enhances tissue distribution and clearance, hence reducing nephrotoxicity (Leadbetter et al. 2004). Telavancin has a half-life of approximately 8 hours in humans and is hence administered intravenously once daily for the required time duration of treatment. It was approved by the US FDA for the treatment