lacks the epivancosamine moiety on residue 6, the dimer consists of four hydrogen bonds at the interface. The antibiotic teicoplanin possesses a lipophilic moiety that imparts membrane-anchoring properties to it. The second-generation glycopeptide antibiotics (telavancin, dalbavancin, and oritavancin) exhibit enhanced antibacterial activity by virtue of the presence of lipophilic groups that facilitate localization of antibiotic on the membrane surfaces and also perturb the integrity of the bacterial membrane (Zhanel et al. 2010).

4.4 Resistance to Glycopeptides

It was found early on that bacteria found it difficult to develop resistance to vancomycin. The minimum inhibitory concentration (MIC) of vancomycin was found to show a meager eight-fold increase after 25 serial passages against *S. aureus* (McGuire et al. 1955). Resistance development to vancomycin by alteration of the target of glycopeptides (the D-Ala-D-Ala terminus of lipid II and/or the immature peptidoglycan) is difficult as the process involves simultaneous modifications of multiple enzymes in the pathway to peptidoglycan synthesis. Resistance to vancomycin was observed in enterococci 30 years after its approval (Murray 2000). The incidence of vancomycin-resistant enterococci (VRE) in hospitalized patients with enterococcal infections in the United States had increased to 30%. In 2001, hetero-resistant vancomycin-intermediate *S. aureus* (VISA) and the first vancomycin-resistant *S. aureus* (VRSA) were reported (Hiramatsu 2001; Hiramatsu et al. 1997). Resistance to vancomycin in enterococci (VRE) resulted from the transfer of resistance genes from other glycopeptide-resistant bacteria such as those resulting from the overuse of avoparcin as animal growth promoter (Bager et al. 1997). Courvalin and Walsh groups elucidated the mechanism of vancomycin resistance in enterococci in the 1990s (Arthur and Courvalin 1993; Bugg et al. 1991; Evers et al. 1996). Subsequent work on glycopeptide resistance in producer organisms has revealed that they consist of the same resistance genes as the resistant enterococcal strains. Nine gene clusters – *vanA*, *vanB*, *vanC*, *vanD*, *vanE*, *vanG*, *vanL*, *vanM*, and *vanN* – that confer resistance to vancomycin in enterococci in various ways have been identified (Binda et al. 2014; Boyd et al. 2008; Lebreton et al. 2011; McKessar et al. 2000; Xu et al. 2010). Resistance could result from the modification of D-Ala-D-Ala terminal to D-Ala-D-Ser as in the case of the *vanC*, *vanE*, *vanG*, *vanL*, and *vanN* or replacement of D-Ala-D-Ala with D-Ala-D-Lac in the case of *vanA*, *vanB*, *vanD*, and *vanM* genes. The replacement of the D-Ala-D-Ala terminal of the cell wall precursor pentapeptide with D-Ala-D-Lac (Figure 4.2b) leads to a 1000-fold loss of binding affinity and therefore resistance in these phenotypes (McComas et al. 2003). Resistance by mutation to D-Ala-D-Ser results in a sevenfold decrease in binding affinity (McKessar et al. 2000). The VanA and VanB resistance phenotypes are the