(2018) reported that by using β,γ-diaminoacids as a β-turn mimic, they could synthesize analogues (**6** and **7**) that minimized the hemolytic activity effectively to less than 1% compared with 74–83% at comparable concentrations to GS, though the antibiotic activity was now between 2 and 8 times less effective against comparable microbes. However, the essential point is that these analogues are effectively non-hemolytic, thus expanding their potential for use other than as topical medications.

14.3.2 Streptogramins and Derivatives: Cyclic Peptides

Relatively recently, modifications of other peptide-based compounds from natural sources resulted in potential antibiotics, in particular the reassignment for human use of a class of agents (streptogramins) that were initially used solely for agricultural purposes. These compounds were divided into two distinct subgroups, group A (23-membered macrocyclic polyketide/non-ribosomal peptide hybrids) and group B (19-membered cyclic depsipeptides), which had a synergistic relationship. However, it was not until 1999 that the slightly modified compounds known as dalfopristin (**8**) (from virginiamycin M1; **9**), and quinupristin (**10**) (from virginiamycin S1; **11**) in a 70 : 30 mixture began clinical use as an IV formulation against multidrug resistance caused by vancomycin-resistant *Enterococcus faecium*. These compounds were produced via semisynthesis of the natural products, but in 2017, Li and Seiple (2017) published a modular and scalable synthesis of, in particular, virginiamycin M1 and maduramycin (structure not shown), as virginiamycin M1 has a dehydroproline moiety that may serve as a "handle" for the installation of side chains that could improve water solubility, as in the case of the semisynthesis of dalfopristin. The 2018 review by Luther et al. (2018) should also be consulted as it gives excellent coverage of the streptogramins and related compounds still under preclinical and early clinical studies.

14.3.3 Arylomycins (Lipopeptide and Modification, Preclinical)

Among the agents covered by Luther et al. are lipopeptides that target signal peptidase I, thus adding yet another bacterial target to the well-known earlier ones. None of these agents are yet in clinical trials, including the modified arylomycins, originally isolated from the soil bacterium *Streptomyces* Tü 6075 (Holtzel et al. 2002; Schimana et al. 2002) and shown to be active against the signal peptidase by workers at Lilly (Kulanthaivel et al. 2004). Genentech used the arylomycin structure (**12**) and modified it to produce G0775 (**13**) that covalently binds to a lysine in the *LepB* target as described in the recent *Nature* paper by Smith et al. (2018). Although these agents are still at the preclinical stage, their target is one that few agents have been tested against; therefore the possibilities are significant, and Genentech is the only major US-based company still "actively looking" for natural product-based antibiotics, with an active program with Lodo Therapeutics (see genetic methods below).