Actinomycetes are excellent sources for novel bioactive compounds, which serve as potential drug candidates for antibiotics development. While industrial efforts to find and develop novel antimicrobials have been severely reduced during the past two decades, the increasing threat of multidrug-resistant pathogens and the development of new technologies to find and produce such compounds have again attracted interest in this field. Based on improvements in whole-genome sequencing, novel methods have been developed to identify the secondary metabolite biosynthetic gene clusters by genome mining, to clone them, and to express them in heterologous hosts in much higher throughput than before. These technologies now enable metabolic engineering approaches to optimize production yields and to directly manipulate the pathways to generate modified products.