



Fig. 14 Structures of antibacterial natural products actinorhodin (**27**) and granaticin (**28**), and recombinant antibiotic dihydrogranaticin (**29**)

products easier, this also means that the different types of natural products is probably limited, assuming no fundamentally new, unique biosynthetic pathways will be discovered.

For the biosynthesis of entirely new natural products, a common method used is to introduce mutations into the producing enzymes in order to either modify the produced natural product or to diversify the precursors that the enzymes will accept to incorporate into the natural product structure. The first example of this method was published in 1985, where the combination of PKS gene clusters for producing enzymes of the antibiotics actinorhodin (**27**) and granaticin (**28**) led to the production of dihydrogranaticin (**29**), which includes structural features from both antibiotics (Fig. 14) (Hopwood et al. 1985).

Another well-known example is the biosynthesis of analogues of the antibiotic erythromycin. Through mutation of the PKS, it became possible to introduce various functional groups which resembled the original precursors through feeding experiments, giving rise to a number of deglyco-erythromycin analogues (McDaniel et al. 1999, Fig. 15). In a similar way, metabolic engineering of PKS and feeding experiments has resulted in the successful production of various enniatin analogues (Feifel et al. 2007).

Metabolic engineering of NRPS has also been investigated, where it was found that rearrangement of the modules within the gene clusters could be employed to create a large diversity of peptide natural products (Mootz et al. 2002). Not long after this discovery, extensive manipulation studies of various modules from the NRPS responsible for the biosynthesis of daptomycin resulted in a range of new daptomycin analogues (Nguyen et al. 2006). Further recent examples include the