Polyketides constitute a large family of natural products that display various biological activities. Polyketides exhibit a high degree of structural diversity, although they are synthesized from simple acyl building blocks. Recent biochemical and structural studies provide a better understanding of the biosynthetic logic of polyketide diversity. This review highlights the biosynthetic mechanisms of structurally unique polyketides, β-amino acid-containing macrolactams, enterocin, and phenolic lipids. Functional and structural studies of macrolactam biosynthetic enzymes have revealed the unique biosynthetic machinery used for selective incorporation of a rare β-amino acid starter unit into the polyketide skeleton. Biochemical and structural studies of cyclization enzymes involved in the biosynthesis of enterocin and phenolic lipids provide mechanistic insights into how these enzymes diversify the carbon skeletons of their products.