

Stereochemical aspects of polyketide antibiotic biosynthesis

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One of the central goals of research on modular polyketide synthases (PKSs) is to understand the way in which the structure of the multienzyme dictates the precise chemical and stereochemical outcome of polyketide chain synthesis. In particular, much remains to be learned about the mechanisms of stereocontrol mediated by ketosynthase (KS), acyltransferase (AT), ketoreductase (KR), dehydratase (DH) and enoylreductase (ER) domains. We have approached this question by studying the reactivity of individual recombinant domains in vitro against surrogate substrates, as well as the effects of selective active-site mutations of intact model PKS systems in vivo. It appears that the observed differences arise from different modes of presentation of the substrate to a highly conserved catalytic apparatus. We have, for example, now identified residues important in determining the stereochemical course of ER-catalysed reduction, which allows straightforward prediction of (and potentially engineered changes in) the configuration of a methyl branch in a fully reduced extension unit. Additional stereochemical complexity arises in the biosynthesis of polyethers, where the initially-formed polyketide chain undergoes an origami-like process of oxidative cyclization to form multiple rings. We have attempted to probe the stereochemical aspects of this process by comparing the biosynthesis of the polyether tetronate ionophores tetronasin and tetronomycin, which chemically are “near-identical twins” but which have opposite configurations at every comparable stereocentre.

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