Substrate-Guided Investigation of Lanthipeptide Synthetase ProcM

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In an era of widespread antimicrobial resistance in bacteria, there is a severe shortage of novel antibiotics in the drug development pipeline. A class of ribosomally synthesized and posttranslationally modified peptide natural products called the lanthipeptides have shown potential for treating infections caused by drug resistant pathogens. The lanthionine rings found in these natural products are formed by intramolecular Michael-type addition of cysteine thiols onto dehydrated serine/threonine residues. The thioether rings are important for the rigidity, stability and antimicrobial activity of lanthipeptides, it is important to further probe the molecular level details of the cyclization events that lead to the formation of these rings.

In *Prochlorococcus marinus* MIT9313, a single lanthipeptide synthetase (ProcM) catalyzes the posttranslational modification of twenty nine different prochlorosin peptides (ProcAs), thereby generating many distinct thioether ring topologies within these 29 native substrates. As such, the prochlorosin biosynthetic system is ideal for elucidating the details of thioether ring formation. To address how a single enzyme modifies several substrates with variable ring topologies, we probed the roles of both enzymatic and non-enzymatic cyclization in prochlorosin maturation using orthogonal protection of cysteine residues. We investigated the directionality of dehydration of substrates by ProcM. Insights gained within this study into the highly substrate-tolerant synthetase, ProcM, will aid in the design of lanthipeptides with improved properties.

Iron-Catalyzed Intramolecular Allylic C—H Amination

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We have developed the first general C—H amination reaction under iron catalysis, which employs an inexpensive, non-toxic [Fe^{III}Pc] catalyst. [Fe^{III}Pc] is highly chemo- and site-selective, displaying a strong preference for allylic C—H amination over aziridination and amination of all other C—H bond types (i.e. allylic > benzylic > ethereal > 3° > 2° >> 1°). Further, observed reactivity trends are orthogonal to those observed under rhodium catalysis. In polyolefinic substrates, site selectivities for [Fe^{III}Pc]–catalyzed C—H amination can be controlled by the electronic and steric character of the allylic C—H bond.