Total Chemical Synthesis of Lantibiotics

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The emergence of drug-resistant microbial pathogens has driven the search for new antibiotics. One such family is the lantibiotics: ribosomally-produced peptide natural products with promising antimicrobial activity against many clinically-relevant pathogens. The activity and stability of these compounds arise from multiple thioether-containing rings, termed lanthionine and methyllanthionine, installed posttranslationally throughout each peptide sequence. Chemical synthesis provides a means to access these compounds and a wide variety of analogues for structure-activity relationship, mode-of-action and engineering studies, but to date only a small handful of lantibiotic total syntheses have been reported. Here, a general approach to lantibiotic structures was enabled by solid-phase synthesis incorporating orthogonally-protected (methyl)lanthionine amino acids. These building blocks were synthesized in high yield from simple amino acid starting materials and successfully address the problems of stereo- and site-selectivity in the construction of multiple (methyl)lanthionine rings. To highlight this approach, a panel of analogues of epilancin 15X was synthesized in order to probe the currently unknown mode-of-action of this potent lantibiotic.