Synthesis and Mutasynthesis of Lanthionine-Containing Cyclic Peptides

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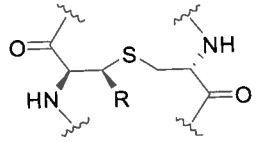
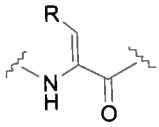
Lantibiotics are a diverse family of antibiotic cyclic peptides which contain post-translational modifications installed by lantibiotic synthetases. These modifications include thioether formations (lanthionine, methyllanthionine) and unsaturated amino acids (dehydroalanine, dehydrobutyrine). While this class of antibiotic peptides has shown promise for clinical use, their *in vitro* synthesis has proven difficult. We have approached this challenge using a combination of both chemical and enzymatic techniques in order to produce lantibiotics and sequence mutants. *In vitro* reconstitution of lantibiotic synthetase activity has been utilized to produce post-translational modifications on synthetic linear peptides. Alternatively, thioether-containing amino acids have been synthesized with proper orthogonal protection for solid-phase synthesis of such cyclic peptides. We have also expanded our methods to include synthesis of novel thioether-containing analogues of other biologically-active cyclic peptides.



R = H, lanthionine
R = Me, 3-methyllanthionine



R = H, dehydroalanine
R = Me, Z-dehydrobutyrine

Allylic C—H Amination for the Preparation of syn-1,3-Amino Alcohol Motifs

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We report a palladium/sulfoxide catalyzed allylic C—H amination to furnish *syn*-oxazinanone heterocycles *en route* to *syn*-1,3-amino alcohols. Key to the high reactivity observed under mild conditions (45 °C, 24h) is the use of an electron deficient *N*-nosyl carbamate nitrogen nucleophile that enables high concentrations of the active anionic species to be reached using endogenous catalytic acetate base. The scope for this C—H amination reaction is very broad and orthogonal to both classical C—C bond forming/reduction sequences and metal nitrene-based C—H amination methods for furnishing this motif. The reaction proceeds in stereochemically dense settings with predictable diastereomeric outcomes, making it well-suited for applications at late-stages of complex molecule synthesis. The streamlining potential of this method is highlighted in the concise and high yielding total synthesis of (+)-allosedridine.