

## Enzymatic amide tailoring expedites unusual retro-aldol-type amino acid conversion to form antifungal cyclopeptide.

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### Abstract

Aspirochlorine is an unusual antifungal cyclopeptide produced by *Aspergillus oryzae*, an important mold used for food fermentation. Whereas its structure suggested that a non-ribosomal peptide synthetase assembles the cyclopeptide from phenylalanine and glycine building blocks, labeling studies indicated that one Phe moiety is transformed into Gly after peptide formation. By means of genetic engineering, heterologous expression, biotransformations, and in vitro assays we dissected and reconstituted four crucial steps in aspirochlorine biosynthesis that involve two cytochrome P450 monooxygenases, (AclL and AclO), a methyltransferase (AclU), and a halogenase (AclH). We found that the installation of the N-methoxylation of the peptide bond sets the stage for a retro-aldol reaction that leads to the Phe-to-Gly conversion. The substrate scopes of the dedicated enzymes as well as bioassays revealed that the peptide editing has evolved to optimize the antifungal action of the natural product.

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