Biosynthesis study of mycotoxin cyclochlorotine

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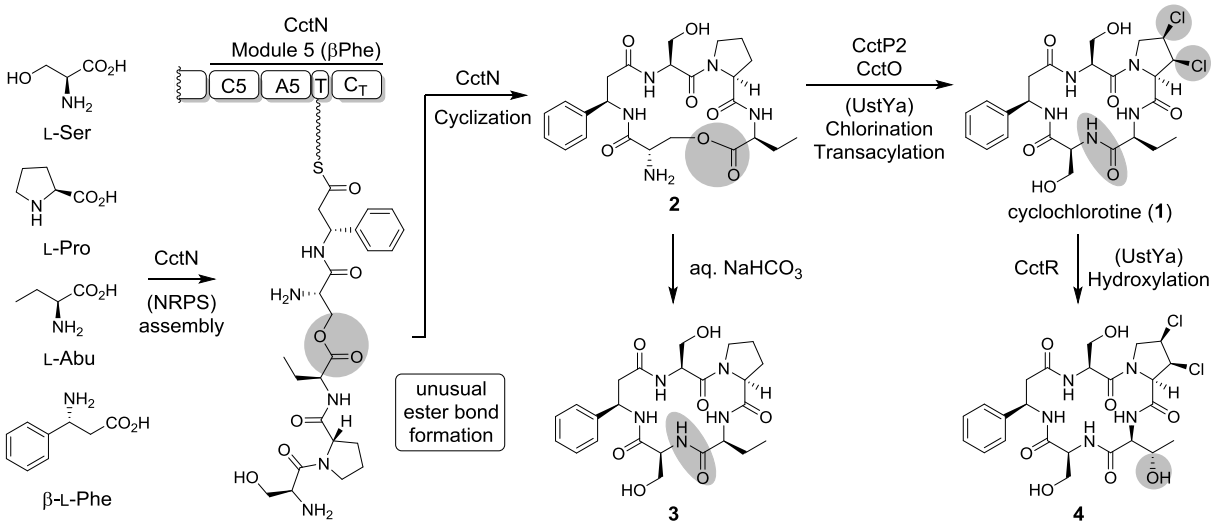
(Introduction) Cyclochlorotine (**1**) is a secondary metabolite of the fungal pathogen *Talaromyces islandicus* (*Penicillium islandicum*),[1] containing nonproteinogenic amino acids, 2-aminobutyric acid (Abu), β-phenylalanine (βPhe) and 3,4-dichloroproline. Although the nonribosomal peptide synthetase (NRPS) CctN responsible for amino acid assembly was identified in the previous study[2], the biosynthetic pathway for **1** and related metabolites remained elusive. In the present study, we identified the genes encoding tailoring enzymes involved in biosynthesis and elucidated their function.

(Results) We initially analyzed metabolites of producing strain and isolated **2**, which is a cyclic depsipeptide consisting of the same amino acids as those in **1**. Ester **2** readily underwent intramolecular *O*,*N*-transacylation to cyclotine (**3**) by treatment of $NaHCO_3$, suggesting that **2** is a biosynthetic precursor of **1** and **3**. Gene-knockout and heterologous expression experiments revealed that three UstYa family proteins, CctP2, CctO and CctR are responsible for chlorination, *O*,*N*-transacylation and hydroxylation. The detailed biosynthetic pathway leading to **1** and its hydroxylated product **4** will be presented.



References:
(1) Yoshioka, H. *et al.*, *Chem. Lett.* **1973**, 2, 1319–1322; (2) Schafhauser, T. *et al.*, *Environ. Microbiol.*, **2016**, 18, 3728-3741.