ENGINEERING AN ARTIFICIAL PATHWAY FOR CIS-A-IRONE BIOSYNTHESIS

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Metabolic engineering has become an attractive method for the efficient production of natural products. However, one important pre-requisite is to establish the biosynthetic pathways. Many commercially interesting molecules cannot be biosynthesized as their native biochemical pathways are not fully elucidated. Cis-α-irone, a top-end perfumery molecule, is an example. To address this challenge, retrobiosynthetic pathway design by employing promiscuous enzymes provides an alternative solution. In this work, we have designed an artifical pathway to produce cis-α-irone with a promiscuous methyltransferase (pMT).Using structure-guided enzyme engineering strategies, we have improved pMT activity and specificity towards cis-α-irone by >10,000-fold and >1000-fold, respectively. About 120 mg l^{-1} cis- α-irone is produced by one-step biotransformation of synthetic psi-ionone. By incorporating one of the optimized methyltransferases into our engineered microbial cells, ~86 mg l^{-1} cis-α-irone is produced from glucose in a 5 l bioreactor. Our work illustrates that integrated artifical pathway design and enzyme engineering can offer opportunities to expand the scope of natural molecules that can be biosynthesized.

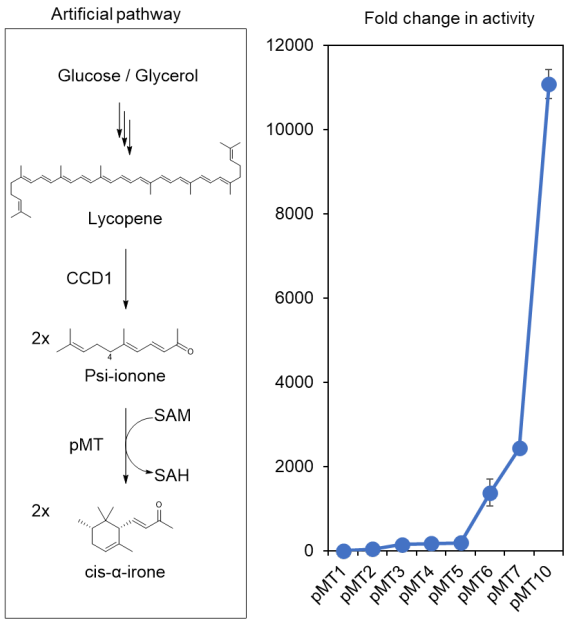

Figure 1: schematic representation of the artificial pathway to produce cis-α-irone from simple carbon source. It leverages on a promiscuous methyltransferase (pMT). Rational enzyme engineering has been applied to increase the pMT activity by > 10,000 fold.

Reference

Chen, X.; T, R.; Esque, J.; Zhang, C.; Shukal, S.; Lim, C. C.; Ong, L.; Smith, D.; André, I. Total Enzymatic Synthesis of Cis-α-Irone from a Simple Carbon Source. *Nat. Commun.* **2022**, *13* (1), 7421. https://doi.org/10.1038/s41467-022-35232-2