CABBI
CENTER FOR ADVANCED BIOENERGY AND BIOPRODUCTS INNOVATION

Reshaping the 2-Pyrone Synthase Active Site for Chemoselective Biosynthesis of Polyketides

Background/Objective

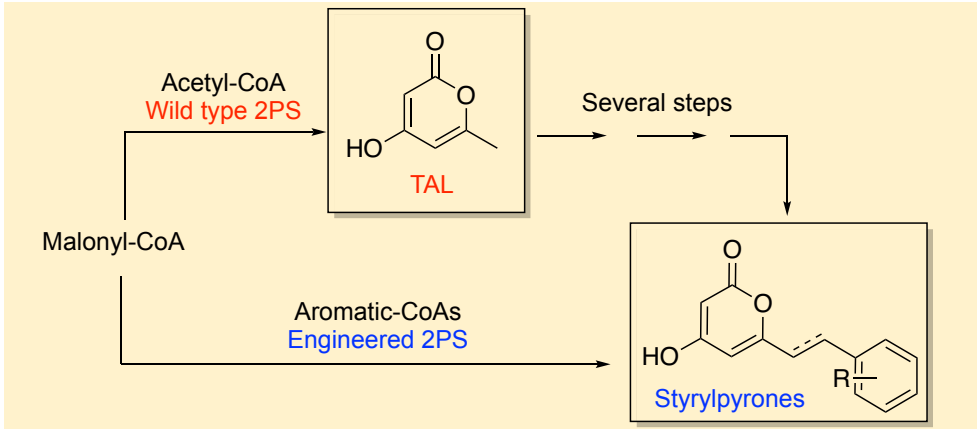
Triacetic acid lactone (TAL), naturally generated by 2-pyrone synthase (2PS), is a platform molecule that can be produced via microbial fermentation and further converted into value-added chemicals. However, these conversions require extra synthetic steps under harsh conditions. We herein report a biocatalytic system for direct generation of TAL derivatives under mild conditions with controlled chemoselectivity by rationally engineering the 2PS active site and then rewiring the biocatalytic pathway to produce high-value chemicals, such as kavalactone precursors.

Approach

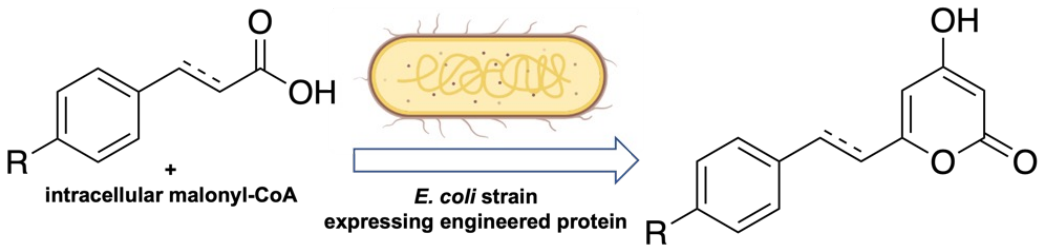
- Protein engineering of 2PS active site by computational homology modeling.
- Metabolic engineering utilizing intracellular malonyl-CoA.

Results

- Computer modeling indicated that sterics and hydrogen-bond interactions play key roles in tuning the selectivity, efficiency, and yield of pyrone generation.
- Yielded up to 17 mg/L TAL-derived pyrone biosynthesis by whole-cell transformation.



Engineered 2PS catalyzes TAL-derived polyketides generation.



Significance/Impacts

Rationally engineered 2-pyrone synthase with novel reactivity not only outperforms *in vitro* for TAL-derived value-added pyrone generation, but also can be implemented into complex metabolic networks to achieve one of the highest reported titers of the corresponding bioproducts.

Zhou, Y., Mirts, E.N., Yook, S., Waugh, M., Martini, R., Jin, Y.S., Lu, Y. Nov. 18, 2022. "Reshaping the 2-Pyrone Synthase Active Site for Chemoselective Biosynthesis of Polyketides." *Angewandte Chemie International Edition*. DOI: 10.1002/anie.202212440.