Repurposing Enzymes from Nature as Catalysts in Chemoenzymatic Natural Product Synthesis

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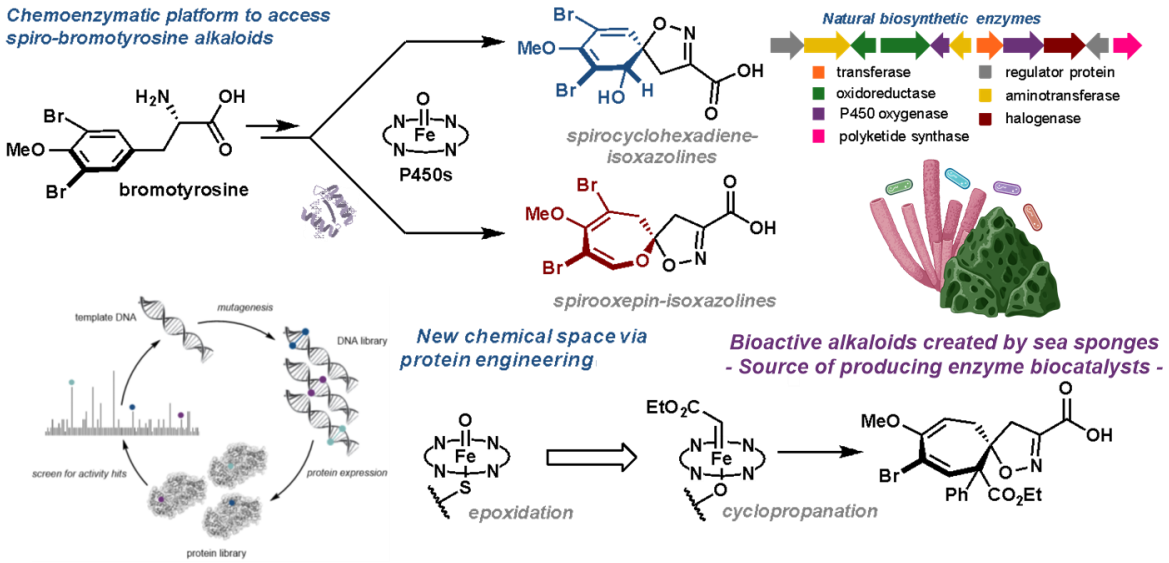
Nature uses enzymes, proteins that carry out chemical reactions, to construct structurally complex natural products with exceptional selectivity. Recently, there is a drive to use enzymes as "biocatalysts" for synthesis, in contrast to conventional chemocatalysts. Enzyme biocatalysts are powerful synthetic tools given both their ability to achieve highly chemo- and stereoselective reactions, and their use in simple reaction set-ups using environmentally benign reagents.

One project in the Smith group focuses on the synthesis of a class of marine, bromotyrosine-derived alkaloids produced by sea sponges. Bromotyrosine-derived spirocyclic alkaloids from marine sponge holobionts are promising targets for the development of new antiviral and anticancer therapeutics. Notably, members of this alkaloid family have exhibited inhibitory properties toward Haitian RF HIV-1 strains, and cytotoxity toward colorectal LOVO cells. Despite their promise as potential therapeutics, the isolation of these compounds from producing organisms is arduous, yielding insufficient quantities for further investigation. An alternative approach is to use the alkaloid-producing enzymes as biocatalysts in preparative scale reactions. In this case, the enzyme biocatalysts can be produced on-scale, allowing for both highly scalable and stereoselective syntheses of these natural products. Additionally, these enzyme biocatalysts can be further enhanced through protein engineering to access new molecular motifs. This project will use heterologous expression to produce enzymes from the biosynthesis of spirocyclic bromotyrosine alkaloids. These enzyme formulations will be optimized to maximize the production of a diverse class of these bioactive natural products.



REU students working in the Smith group are mentored in the techniques of modern organic synthesis. These include the use of Schlenk lines and anaerobic chambers for the use of air- and moisture-sensitive chemicals. Students also gain experience with microbiological and biochemical techniques, such as bacterial cell culturing, cloning, protein expression and purification. To analyze reactions, students receive hands-on training with LC-MS, NMR, and UV-VIS instrumentation.

Relevant and Related References:

1. Smith, K. L.; Arbuckle, M. A.; Kim, A. T.; Tsai, C.-Y.; McIntosh, J. A.; Verma, D.; Shim, E.; Narayan, A. R. H. *J. Am. Chem. Soc.* **2025,** *147,* 25191.
2. Romero, E. O.; Saucedo, A. T.; Hernández-Meléndez, J. R.; Yang, D.; Chakrabarty, S.; Narayan, A. R. H. *JACS Au* **2023,** *3,* 2073.