BIOTRANS
LA ROCHELLE 2023

N°1709 / PC
TOPIC(s) : (Chemo)enzymatic strategies / Biocatalytic cascade reactions

Development of Convergent Biocatalytic Transformations for the Synthesis of Complex Alkaloids

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PURPOSE OF THE ABSTRACT
Biocatalysis involves the use of catalytic proteins (enzymes) to perform chemical transformations of simple, cheap, achiral materials into high value, chiral products. Nature uses enzymes, often in cascade approaches, to synthesise important building blocks and to assemble complex natural products. The selectivity of enzymes, their tuneability and compatibility with aqueous solvents, have led to their use in the pharmaceutical and fine chemical industry, offering a more attractive alternative to traditional catalysts and as an important synthetic tool in target retrosynthesis. [1] Biocatalysis has been suggested as a greener approach to synthesis, following some of the 12 Principles of Green Chemistry, including mild reaction conditions, production of less waste and the inherent biodegradability of enzymes. Biocatalysts enable more sustainable synthetic routes to access synthetically challenging compounds, offering high levels of chemo-, regio- and stereoselectivity. [2]

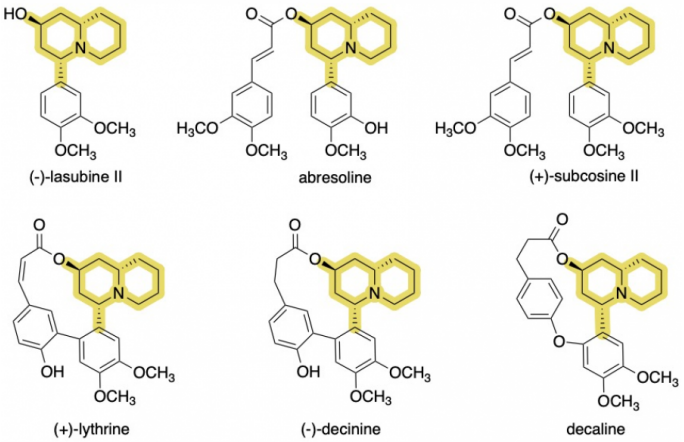
Alkaloids are a class of naturally occurring nitrogen-containing organic compounds that are known to exhibit many physiological effects, including anticancer and neuroprotective properties. [3,4] Synthetic methodologies accessing natural product N-heterocycles structural motifs and their derivatives is of interest to chemists due to the important therapeutic properties they possess and difficulties in extracting sufficient quantities from natural sources. Previous chemical synthetic routes developed to access such structures often require expensive precious metal catalysts and non-environmentally friendly reaction conditions.

The design of a hybrid bio-organocatalytic cascade was envisaged to enable assembly of complex quinolizidine alkaloid structural scaffolds (Figure). Lythraceae alkaloids are a plant derived class of quinolizidine-type alkaloids, [1] containing a 4-arylquinolizidine structural motif 1–6. Alkaloids from this class have shown biological activity, possessing anti-inflammatory, diuretic, sedative, antimalarial, antifungal and antithrombotic properties. The biomimetic cascade approach is initiated by a transaminase catalysed transformation of cadaverine 1 into the naturally occurring reactive cyclic imine, Δ1-piperideine 4, [5] which can subsequently undergo an L-proline 6 facilitated Mannich-aza-Mannich reaction, with an aryl enone 5, forming the 4-arylquinolizidine-2-one scaffold 7, [6] a key structural intermediate in the proposed cascade. The alkaloid 7 has the potential to be further derivatised using additional enzymes, such as a transaminase or alcohol dehydrogenase to generate the amine 8 or alcohol 9 products respectively, providing a chemical handle to further react.

The cascade has the potential to be significantly expanded by using alternative enones and incorporating additional enzymes to further functionalise the products, enabling access to a panel of natural products. The stereoselectivity and chemoselectivity of enzymes can enable a one-pot approach under mild conditions, forming complex alkaloid structures.

BiOrbic is funded under the Science Foundation Ireland Research Centres Programme and is co-funded under the European Regional Development Fund. The A2P CDT is supported by Science Foundation Ireland (SFI) and the Engineering and Physical Sciences Research Council (EPSRC) under the Grant No. 18/EPSRC-CDT/3582

FIGURES



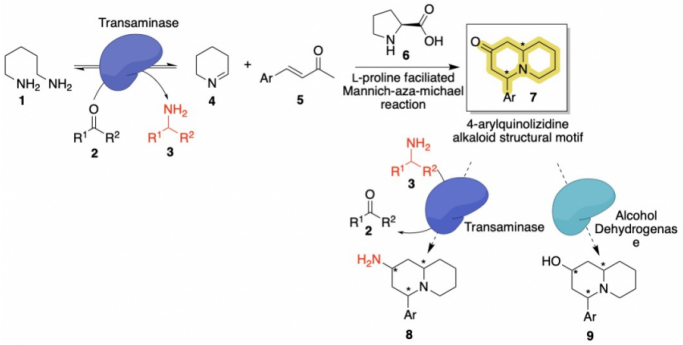


FIGURE 1

Plant derived Lythraceae alkaloids containing 4-arylquinolizidine ring structure motif.

Plant derived Lythraceae alkaloids containing 4-arylquinolizidine ring structure motif.

FIGURE 2

Proposed hybrid bio-organocatalytic route for the synthesis of quinolizidine alkaloids.

KEYWORDS

Bio-organocatalytic | Transaminase | Quinolizidine alkaloid | Cascade

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