A Streamlined Chemoenzymatic One-Pot Process for the Enantioselective Total Synthesis of Tenuipesone A/B

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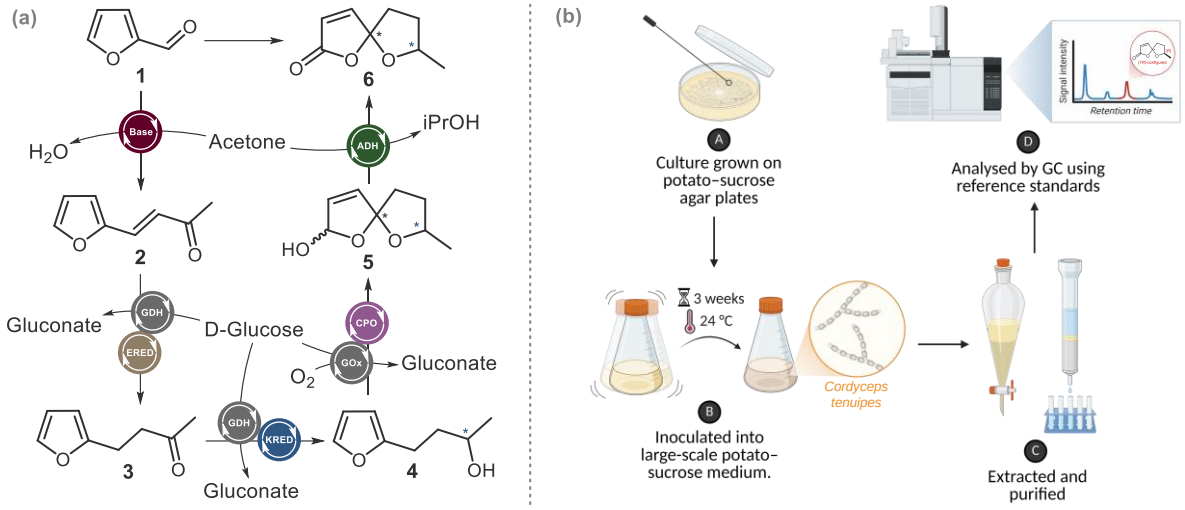
Biocatalysis is now a well-established branch of catalysis and has become a versatile tool in the synthetic chemist's toolbox. The growing demand for more sustainable synthetic methodologies has driven the discovery and development of enzymes for application in organic synthesis.[1] An underutilised property of enzymes in synthesis is their broad cross-compatibility, which lends itself well to one-pot artificial metabolisms for complex natural product synthesis. This type of approach can eliminate the need for intermediate purification, significantly enhancing the efficiency of multi-step syntheses.[2] The power of this strategy was demonstrated through a single-pot operation for the total synthesis of the fungal spirolactone metabolites, tenuipesone A/B (**6**), directly from the biorefinery side stream furfural (**1**). This multi-enzyme system integrates six biocatalysts over five linear steps to produce the tenuipesones in overall yields of up to 72% (i.e. 94% per individual step), and careful selection of specific enzyme combinations allows for the synthesis of each enantiomeric pair in excellent optical purities, enabling the reassignment of the natural products' absolute configurations.[3]



Scheme 1. (a) One-pot chemoenzymatic cascade for the synthesis of tenuipesone A/B, depicting each intermediate. (b) Cultivation and isolation of natural tenuipesones from *Cordyceps tenuipes* for stereochemical assignment.

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2. K. Faber, *Biotransformations in Organic Chemistry: A Textbook*, 6th ed., Springer, **2004**.
3. M. Hallamaa, A. O'Connell, J. Björklund, Y.C. Liu, J. Deska, *ChemRxiv*, **2025**, 10.26434/chemrxiv-2025-rbj31.