BIOTRANS
LA ROCHELLE 2023

N°1444 / PC
TOPIC(s) : Enzyme discovery and engineering / Industrial biocatalysis

Enchanted enzyme environments: The biocatalytic stereoconvergent cation-olefin cyclization

AUTHORS

Andreas SCHNEIDER / UNIVERSITY OF STUTTGART, ALLMMANDRING 31, STUTTGART
Christian CURADO / UNIVERSITAT DE GIRONA, INSTITUT DE QUÍMICA COMPUTACIONAL I CATÀLISI AND DEPARTAMENT DE QUÍMICA, GIRONA
Sergi RUIZ-BARRANGAN / UNIVERSITAT DE GIRONA, INSTITUT DE QUÍMICA COMPUTACIONAL I CATÀLISI AND DEPARTAMENT DE QUÍMICA, GIRONA
Thomas LYSTBAEK / UNIVERSITY OF STUTTGART, ALLMANDRING 31, STUTTGART
Silvia OSUNA / UNIVERSITAT DE GIRONA & ICREA, INSTITUT DE QUÍMICA COMPUTACIONAL I CATÀLISI AND DEPARTAMENT DE QUÍMICA, GIRONA
Corresponding author : Bernhard HAUER / bernhard.hauer@itb.uni-stuttgart.de

PURPOSE OF THE ABSTRACT

The stereocontrolled cationic cyclization cascade is one of nature's most elegant tools for generating molecular complexity in terpene metabolism and is unmatched by man-made catalysts. Moreover, it remains a major challenge for chemistry to harness the unique catalytic power of the enzymes that control such reactions for synthesis. Here we report the tailoring of the squalene-hopene cyclase (SHC) for cationic cyclization catalysis beyond the current state-of-the-art. Based on the promiscuous cyclization of homofarnesol to (–)-ambroxide as a model reaction, we demonstrated a rational enzyme engineering and application strategy that allowed us to exceed 105 catalytic turnovers. Moreover, we created a locally electron-enriched, active site that enables an unprecedented stereoconvergent cationic cyclization of a 50:50, 3E:3Z-homofarnesol mixture to sole (–)-ambroxide. Our results demonstrate how enzyme engineering can unlock and even extend the chemical wizardry of terpene cyclases.

FIGURES

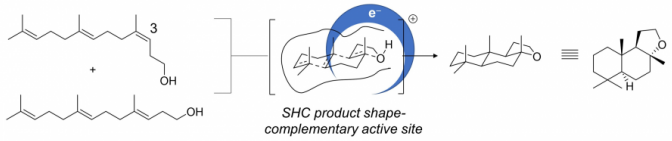

FIGURE 1

Scheme 1

The stereoconvergent head-to-tail cyclization of 3E/3Z-homofarnesol in an electronically enriched confined active site of the SHC results in the formation of sole (-)-ambroxide.

FIGURE 2

KEYWORDS

biocatalysis | cation-olefin cyclization | stereoconvergence | squalene-hopene cyclase

BIBLIOGRAPHY

[1] A. Schneider, C. Curado, T. B. Lystbaek, S. Osuna, B. Hauer, ChemRxiv 2022, DOI 10.26434/CHEMRXIV-2022-XWCQJ.

[2] A. Schneider, C. Curado, T. B. Lystbaek, S. Osuna, B. Hauer, Angew. Chem. Int. Ed. 2023, e202301607.