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Stereoselective Directed Cationic Cascades Enabled by Molecular Anchoring in Terpene Cyclases

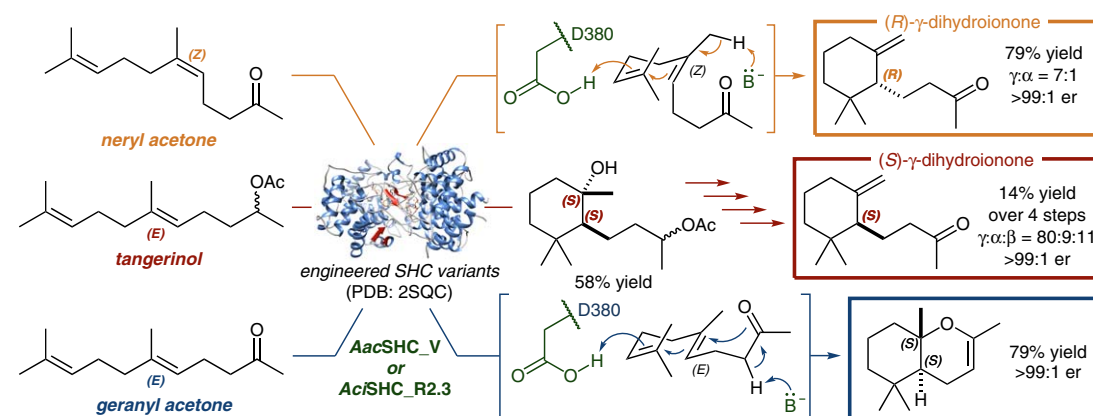
Angew. Chem. Int. Ed. **2021**, *60*, 13251–13256, DOI: 10.1002/anie.202101228.

M. EICHENBERGER, S. HÜPPI, D. PATSCH, N. AEBERLI, R. BERWEGE, S. DOSSENBACH, E. EICHORN, F. FLACHSMANN, L. HORTENCIO, F. VOIROL, S. VOLLENWEIDER, U. T. BORNSCHEUER, R. BULLER* (ZURICH UNIVERSITY OF APPLIED SCIENCES, WÄDENSWIL, SWITZERLAND)

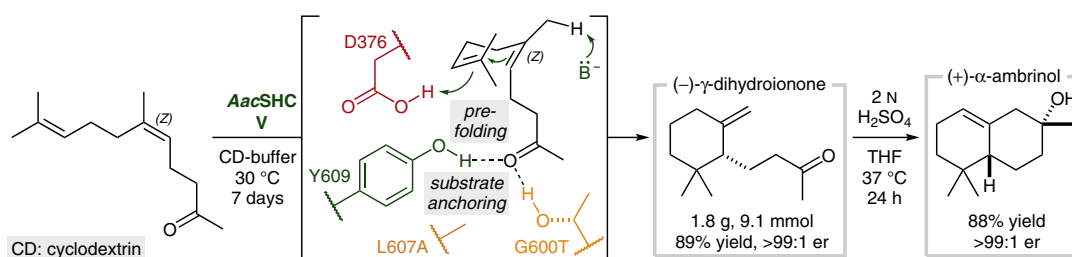
Asymmetric Cation-Olefin Monocyclization by Engineered Squalene-Hopene Cyclases

Angew. Chem. Int. Ed. **2021**, DOI: 10.1002/anie.202108037.

Biocatalytic Directed Cationic Cyclization Cascades toward Fragrance Ingredients



— Directed cascade approach | proposed mechanism for the stereoselective monocyclization



Significance: The Hauer group and a collaborative effort between the groups of Buller and Bornscheuer and Givaudan independently report the development of engineered squalene-hopene cyclases (SHCs) for stereoselective, cationic cyclization cascades toward natural products and, in particular, fragrance ingredients. The Hauer group describes a biocatalytic monocyclization of neryl acetone by using an engineered SHC from *Alicyclobacillus acidocaldarius* (AacSHC) to give (R)-γ-dihydroionone in excellent yield and enantioselectivity. Buller and collaborators report a complimentary stereodivergent approach from either neryl or geranyl acetone by using variants based on a previously unidentified SHC from *Acidothermus cellulolyticus* (AcSHC).

Comment: Cationic cyclization cascades serve as powerful tools for the rapid assembly of complex carbon skeletons in a highly efficient manner. However, stereoselective methods to interrupt the cascade at a desired intermediate to preferentially access monocyclic products are challenging and underdeveloped. The Hauer group devised a strategy to overcome this limitation by engineering the active site of an SHC. Specific addition of stabilizing hydrogen-bonding interactions for substrate anchoring favors deprotonation over the usual bicycle formation. Buller and collaborators demonstrated that the stereoselectivity of the cyclization is governed by the double-bond geometry of the starting material, due to identical pre-folding of the chair.

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Synfacts 2021, 17(10), 1137 Published online: 17.09.2021
DOI: 10.1055/s-0040-1719990; Reg-No.: B07921SF

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Category

Organo- and Biocatalysis

Key words

squalene-hopene cyclase

directed cyclization

cascade reaction

molecular anchoring

monocyclization

fragrances

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