BIOTRANS
LA ROCHELLE 2023

N°245 / OC
TOPIC(s) : (Chemo)enzymatic strategies

Lipase-catalyzed chemoselective acylation of sesquiterpene lactones: towards new ester derivatives

AUTHORS

Juan RODRIGUEZ MOSHEIM / UMR TRANSFRONTALIÈRE BIOECOAGRO N1158, UNIV. LILLE, INRAE, UNIV. LIÈGE, UPJV, JUNIA, UNIV. ARTOIS, UNIV. LITTORAL CÔTE D'OPALE, INSTITUT CHARLES VIOLLETTE, LILLE 1 UNIVERSITY OF SCIENCE AND TECHNOLOGY (CITÉ SCIENTIFIQUE), VILLENEUVE D'ASCQ
Francesca RUGGIERI / UNIVERSITY OF LILLE, INSERM, INSTITUT PASTEUR DE LILLE, LILLE 1 UNIVERSITY OF SCIENCE AND TECHNOLOGY (CITÉ SCIENTIFIQUE), LILLE
Egon HEUSON / UNIV. LILLE, CNRS, CENTRALE LILLE, UNIV. ARTOIS, UMR 8181—UCCS—UNITÉ DE CATALYSE ET CHIMIE DU SOLIDE, LILLE 1 UNIVERSITY OF SCIENCE AND TECHNOLOGY (CITÉ SCIENTIFIQUE), LILLE
Renato FROIDEVAUX / UMR TRANSFRONTALIÈRE BIOECOAGRO N1158, UNIV. LILLE, INRAE, UNIV. LIÈGE, UPJV, JUNIA, UNIV. ARTOIS, UNIV. LITTORAL CÔTE D'OPALE, INSTITUT CHARLES VIOLLETTE, LILLE 1 UNIVERSITY OF SCIENCE AND TECHNOLOGY (CITÉ SCIENTIFIQUE), VILLENEUVE D'ASCQ
Jean-Louis HILBERT / UMR TRANSFRONTALIÈRE BIOECOAGRO N1158, UNIV. LILLE, INRAE, UNIV. LIÈGE, UPJV, JUNIA, UNIV. ARTOIS, UNIV. LITTORAL CÔTE D'OPALE, INSTITUT CHARLES VIOLLETTE, LILLE 1 UNIVERSITY OF SCIENCE AND TECHNOLOGY (CITÉ SCIENTIFIQUE), VILLENEUVE D'ASCQ
Philippe HANCE / UMR TRANSFRONTALIÈRE BIOECOAGRO N1158, UNIV. LILLE, INRAE, UNIV. LIÈGE, UPJV, JUNIA, UNIV. ARTOIS, UNIV. LITTORAL CÔTE D'OPALE, INSTITUT CHARLES VIOLLETTE, LILLE 1 UNIVERSITY OF SCIENCE AND TECHNOLOGY (CITÉ SCIENTIFIQUE), VILLENEUVE D'ASCQ

PURPOSE OF THE ABSTRACT

Terpenes are the most abundant and diverse family of natural compounds with over 64000 structures identified to date. Plants rich in terpenes have been used for medicinal purposes by various human cultures around the world, and many terpenes and terpenoids are now recognized for their biological activities, such as antimicrobial, anti-inflammatory, and antitumor properties.

The chicory plant has a long medicinal history, as it was used as a herbal remedy by ancient civilizations for the treatment of various pathologies. Its root is rich in secondary metabolites with biological activities, mainly polyphenolic compounds and sesquiterpene lactones (STL). The functionalization of these compounds is a promising approach for pharmaceutical applications, as well as in the agri-food sector.

Out of the thousands of terpenoids compounds that have been characterized, it is notable that a primary allyl alcohol moiety is highly frequent among the terpene family, serving as a promising starting point for the addition of side chains or various linkers. Our global strategy was then to use the anchor points to substitute them with various chains and chemical functions, converting the STL into versatile building blocks bearing different physicochemical properties. Our approach is based on the use of enzymes to maximize the selectivity of the reactions, as terpenes often exhibit more than one accessible hydroxyl group on their structure. As an example, we present here one of our most promising achievements, based on the use of an immobilized lipase to introduce aliphatic esters onto STL, with the primary goal of modulating their lipophilicity. This precise reaction was selected in the perspective to later evaluate their antibiotic activity, as some terpenes already shown to exhibit interesting actions onto bacterial membranes.

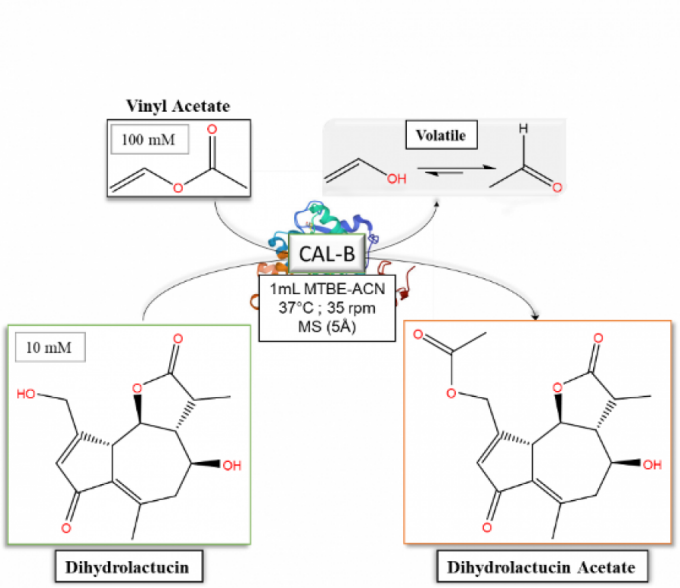
For this study, the rather classical Novozyme 435 (immobilized CAL-B), well known for its successful application in ester synthesis, was selected among a lipase panel based on preliminary tests on several monoterpenes, but also for its high availability, stability and ease of use, for further industrial development. Following our first screening, the enzymatic reaction conditions were first optimized (1mL of a mixture of MTBE and ACN (3:1) at 37 °C with 5 angstrom

molecular sieves) using (S)-perillyl alcohol, a cheap cyclic monoterpenoid carrying an allyl alcohol moiety. Afterward, we applied our synthesis to the transformation of the very expensive main four STL found in chicory root (lactucin, dihydrolactucin, lactucopicrin and dihydrolactucopicrin), which were never functionalized enzymatically by any means until then.

We started with the simplest ester derivative, a methyl ester, for which we compared the reactivity of two common types of acetyl donors, acetic acid and vinyl acetate. While 76 % yield could be achieved with the first in our conditions, a complete transformation could be observed with the latter, as we could expect from its higher reactivity. In both cases, acyl donors were introduced in 10:1 equivalent to maximize the consumption of the expensive STL. Then, we continued with dihydrolactucin, varying the length of the aliphatic chain in order to study both the selectivity of the lipase, but also to target a range of different properties for the synthesized products. Chloroacetate (92 % yield), propanoate (100 % yield), hexanoate (74 % yield) and octanoate (69 % yield) ester derivatives could be obtained after 48h hours of reaction. In addition to these high yields, very high selectivity was observed with no substitution on the secondary alcohol of our 4 STL, and the naturally present ester groups of lactucopicrin and dihydrolactucopicrin were not hydrolyzed during the reaction.

In conclusion, we report here the first example of enzymatic synthesis methodology to functionalize STLs from chicory with very high selectivity and a range of aliphatic esters.

FIGURES



	VINYL ACETATE	VINYL PROPIONATE	VINYL HEXANOATE	VINYL OCTANOATE	VINYL CHLOROACETATE	ACETIC ACID
DHLC	100%	100%	74%	69%	92%	76%

FIGURE 1

Representation of the selective transesterification of DHLc

Selective transesterification of DHLc, a sesquiterpene lactone from chicory, using Novozyme 435. 100% conversion was obtained within 24h

FIGURE 2

Yield of different alkyl esters of dihydrolactucin for each acyl donor

Conversion (%) after 48h at 37□C, 35rpm in 1mL MBTE-ACN (3:1) with 10mM of DHLc, 100mM of vinyl ester, 20mg of N435 and 2 molecular sieves 5 angstrom. Error margin = +/- 5%

KEYWORDS

lipase acylation | terpenoids | chicory | biocatalytic functionalization

BIBLIOGRAPHY

[1] Matsumi, R.; Atomi, H.; Driessen, A. J. M.; van der Oost, Research in Microbiology 2011, 162 (1), 39-52.

[2] Gershenzon, J.; Dudareva, N., Nat Chem Biol 2007, 3 (7), 408-414.

[3] Salakhutdinov, N. F.; Volcho, K. P.; Yarovaya, O. I., Pure and Applied Chemistry 2017, 89 (8), 1105-1117.

[4] Yang, W.; Chen, X.; Li, Y.; Guo, S.; Wang, Z.; Yu, X., Natural Product Communications 2020, 15 (3), 1934578X20903555.

[5] Zielinska-Blajet, M.; Feder-Kubis, J., IJMS 2020, 21 (19), 7078.

[6] Chaturvedi, D., In Discovery and Development of Therapeutics from Natural Products Against Neglected Tropical Diseases; Elsevier, 2019; pp 49-85.

[7] Al-Snafi, A., IOSR Journal of Pharmacy 2016, 6, 41-56.

[8] Wang, Q. P, African Journal of Biotechnology 2011, 10 (11), 1966-1977.

[9] Baert, J. R. A.; Van Bockstaele, E. J., Industrial Crops and Products 1992, 1 (2-4), 229-234.

[10] Gupta, A. K.; Mamta; Bhatia, I. S., Phytochemistry 1985.

[11] Ortiz, C.; Ferreira, M. L.; Barbosa, O.; dos Santos, J. C. S.; Rodrigues, R. C.; Berenguer-Murcia, □.; Briand, L. E.; Fernandez-Lafuente, R., Catal. Sci. Technol. 2019, 9 (10), 2380-2420.