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# BIOCATALYTIC APPROACH TO CHEMOSELECTIVE ACYLATION OF SESQUITERPENE LACTONES FROM CHICORY: TOWARDS NEW ESTERS

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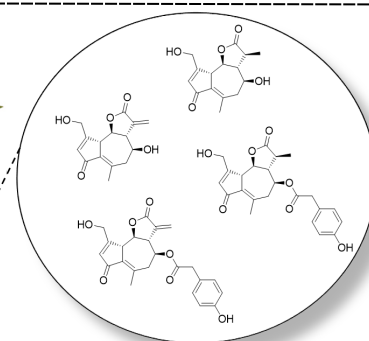
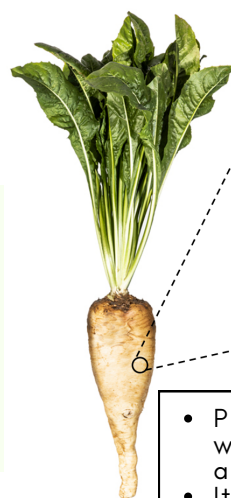
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## INTRODUCTION

- Terpenes are the largest family of natural compounds, with over 64,000 structures known.
- Sesquiterpene lactones (STL) are a very diverse group of terpenoids with 15-carbon skeletons commonly found in plants of the *Asteraceae* family. They serve as defence tools to help them cope with environmental stresses.
- STLs have shown a wide range of biological activities:



Anti-Inflammatory



*Cichorium intybus*

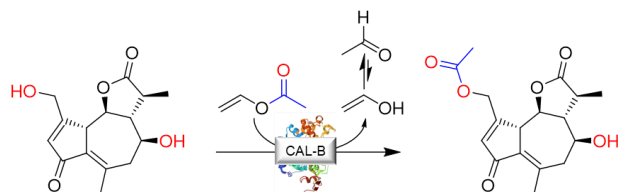
- Plant of the *Asteraceae* family widely cultivated in Belgium and in the north of France.
- Its root is rich in STLs such as lactucin (Lc), lactucopicrin (Lp) and their dihydro derivatives (DHLc, DHLp).

## Chemoselective acylation of DHLc catalyzed by lipase B from *Candida antarctica* (Novozym 435)

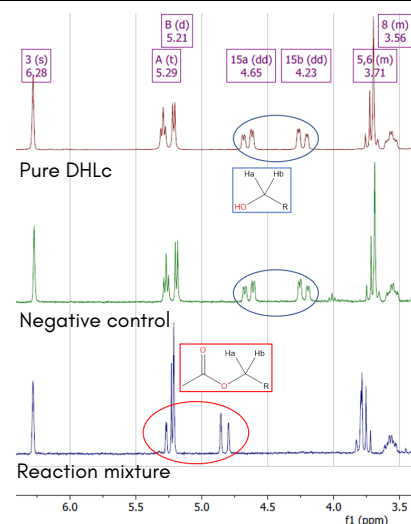
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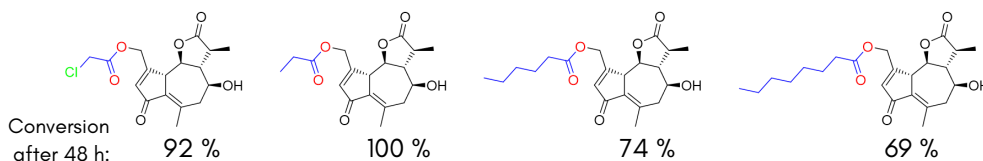
- 10 mM DHLc, 100 mM acyl donor, 2 mg N435, MS 5 Å, 37 °C, 35 RPM, 1 mL MTBE:ACN (3:1)
- **100 % conversion** in 24 h
- Pure product after filtration and concentration under vacuum (8 mbar)
- Complete chemoselectivity was observed for the primary allyl alcohol
- No hydrolysis of the lactone was observed at any time, neither spontaneous nor biocatalytical
- Acetic acid was also compatible as an acyl donor, giving 76 % conversion after 48 h



## Ester derivatives of DHLc synthesized from their corresponding vinyl esters via the same protocol

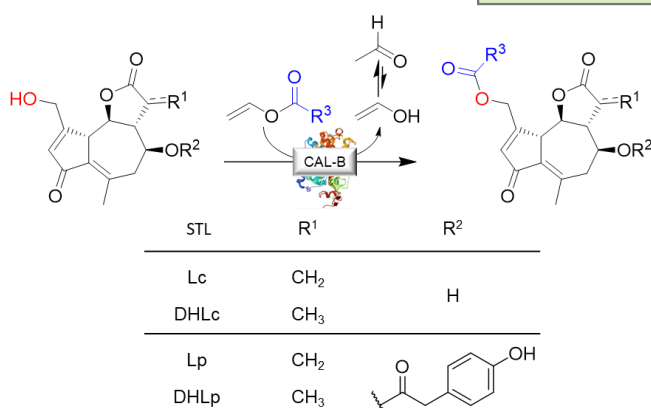
With short acyl chains (until propionate), the selectivity was due to the intrinsic reactivity of both hydroxy groups.

With longer chains such as those from vinyl hexanoate and octanoate, steric hindrance became significant and only the primary hydroxy group could reach the acyl enzyme carbonyl function. The reaction rate was also slower.



## Applicable to other STLs from chicory

- 100 % conversion
- Complete selectivity



## Binding modes & interactions between DHLc and N435

- The main enzyme-substrate interactions involving STLs and the different acyl donors are hydrophobic. Important residues at the cavity entrance (Ile189-285 and Val154) interact with the cycloheptene ring and the methyl group.
- Nevertheless, H-bonds were observed between the lactone and residues in the oxyanion hole
- Aliphatic acyl chains with a degree of flexibility tend to be preferred due to their better positioning over the hydrophobic wall of the cavity

