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Valuable chemicals by the enzymatic modification of molecules of natural origin: Terpenoids, steroids, phenolics and related compounds

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ABSTRACT

A renewed interest for using natural organic molecules for the production of valuable chemicals is observed in current organic processes. Natural compounds provide the access to natural grade chemicals when submitted to physical treatments or biotechnological processes. Dealing with structurally complex molecules, they can provide complex core structures for hemisynthesis purposes, and in many instances they offer the advantage of providing sustainable processes when using renewable resources. These assets could be synergistic with the assets of biocatalytic processes, to end-up with efficient and sustainable processes in the organic synthesis of valuable products.

In this review, we have gathered a selection of examples on the use of enzymes for the modification of molecules of natural origin being either purified compounds (terpenoids, steroids, phenolics) or mixtures (essential oils, natural extracts) to access fine chemicals or organic polymers.

1. Introduction

Natural products have probably been, and remain, the main source of investigations and discoveries for organic chemists to date. The discipline of organic chemistry is considered to be born in 1828 when Friedrich Wöhler serendipitously achieved the synthesis of urea from cyanic acid and ammonia in an attempt to prepare ammonium cyanate, thereby breaking the dogma of the vital force theory of the influential Swedish Professor Jons J. Berzelius. Following this discovery, natural organic molecules such as glucose, quinine, camphor, indigo, have attracted the interest of renowned chemists for the study of their structure, synthesis and properties. Organic chemistry was born, and the 20th century has witnessed an exponential increase of activity in the field, providing the scientific community with problems to solve and questions to address in the structural elucidation of complex molecules, the description and understanding of their stereochemistry and of the stereoselectivity of their biosynthesis, their mode of interaction with their environment including living organisms, and the total synthesis of these complex molecules. As a reward, many conceptual and practical progresses were made, including biosynthetic pathways elucidation, analytical chemistry at the molecular level, the development of a plethora of efficient synthetic methodologies, including enantioselective catalysis, transition metals-catalysed coupling reactions, in addition to the access to bioactive natural products and relatives. In one and a half century, the status of organic compounds thus shifted from Nature-made to Man-made, and with the ever growing ability of organic chemists to create new molecules, their interests also shifted towards synthetic and/or artificial molecules, in other words molecules with no natural equivalents. This attraction for artificial molecules culminated in the nineties in particular in medicinal chemistry with the development of combinatorial chemistry. For several scientific and cultural reasons, a renewed interest for natural molecules has been observed lately.

This trend has also been observed in applied biocatalysis. While in its infancy, the focus of biochemists and chemists interested in using enzymes in organic synthesis was put on the natural metabolic substrate, a trend largely supported by Emil Fisher's dogma 1 enzyme = 1 substrate = 1 reaction. Many studies of the substrate scopes of enzymes followed, and showed that some enzymes could accommodate various structurally related substrates. The idea of a larger substrate scope was significantly improved with the use of enzyme in organic solvents and the pioneering work of Klibanov (Zaks and Klibanov, 1985), in particular for lipases with the interfacial activation phenomenon (Schmid and Verger, 1998). Synthetic substrates of artificial origin could thus be used in enzymatic reactions performed in biomimetic media or in non-conventional media as well (organic solvents, gas phase, RTILs, supercritical fluids, fluorinated solvents). Today, the novel interest for using natural organic molecules for the production of natural

Abbreviations: API, active pharmaceutical ingredient; CaLB, *Candida antartica* lipase B; CPDMO, cyclopentadecanone monooxygenase; CPO, chloroperoxidase; CrL, *Candida rugosa* lipase; DMF, dimethylformamide; LOX, lipoxygenase; PLE, pig liver esterase; RTIL, room temperature ionic liquid; SEM, scanning electron microscopy; XO, xanthine oxidase.

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