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A Short Review on Chiral Alcohols Verses Bio-Catalysis

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Abstract

Catalyst is a chemical molecule or metal substance which enhances the rate of reaction is called catalyst, the catalyst present in the living organisms to carryout biochemical reactions or metabolic pathways. Exames oxidoreductases, lyases, ligages, proteases, hydrolases, esterases, pectinases etc. are Different methodologies available in synthesis of chiral molecules chemical/biocatalysis. The enormous potential of biocatalysts (microorganisms and enzymes) in synthesis of chiral molecules in mild conditions (pH and temperate) with high chemo-, regio-, enantio and functional selectivity with decrease formation of by-products, with short reaction steps (reactions which are not easily conducted classical organic reactions) (Long chemical processes with tedious blocking and de-blocking steps). Thus the use of biocatalyst has attracted a great attention from the green chemistry perspective (expensive chiral reagents/ environmentally hazardous heavy metals).

Biocatalysts are well known for their enzymatic activity towards numerous reactions ranging from in-vivo living cells (biochemical pathways) to in-vitro chemical reactions (reduction and transesterification) with enantiomeric purity and specificity. In this review the discussion is about synthesis of chiral using different kinds of biocatalysts. *Daucus Carota*, *Pisum Sativa*, *Novazyme P-435*, as biocatalysts for chiral alcohols.

Keywords: Biocatalysis; Biocatalysts; Sterio selectivity; Chiral alcohols; Anti-fungal; Antimicrobial; Active pharma ingredients; Pharma intermediates; Agrochemicals; Flavours; Lactonization; Bioreduction; Trans-esterification; Lipase; *Novazyme P-435*

Overview of the Chiral Alcohols Verses Bio-catalysis

Life and chirality are strictly connected in carrying out different metabolic functions of the living organism, thus chirality plays an important role in the life of plants and animals. Louis Pasteur (1853) coined the name dissymmetric. Later the term was changed to asymmetry and later it was replaced by the term chirality, a familiar analogy of the mirror image relationship like left and right [1-14]. The chemical complexity is the fundamental from of life and thus the chirality occupies the main features of the living world. Chirality is a phenomenon of geometrical or spatial arrangement of an object which is a non-super imposable mirror image. Chiral molecules that consist of a tetrahedral carbon atom attached to four different groups are called stereo-isomers, and possess identical chemical properties [12-25].

Chiral molecules are widely distributed in nature, and these enantioselective compounds are known to have selective/specific potent biological activities with reduced side effects compared to their racemates [26-29]. Hence, the synthesis of chiral molecules has drawn immense attention in the pharmaceutical industry as well as by drug regulatory authorities (FDA). A majority of naturally obtained compounds are chiral molecules that are active single isomers. For e.g., between the two enantiomers of Ketamine, S(+) Ketamine is the active anesthetic whereas the other isomer, R(-)Ketamine show undesirable side effects [30-38].

Reduction of different classes of prochiral ketones ranging from aromatic, heterocyclic and aliphatic ketones to their corresponding chiral alcohols. These chiral secondary alcohols are being used as drug intermediates in pharmaceuticals and also as toxophores in agrochemicals. These chiral synthons can be synthesized by economically viable and eco-friendly methods by using biocatalysts [39-48]. The use of biocatalyts from plant sources as enzymes have been well recognized for the synthesis of chiral products. Among the plant enzymes, sprouted seeds (e.g., *Pisum sativum*) have been considered as suitable biocatalytic systems for the reduction of aliphatic and aromatic prochiral ketones. an enzymatic approach for synthesis of (S)-1-phenethyl alcohol in 72% yield with 98% ee, by selective reduction of acetophenones, using sprouted *Pisum sativum* in an aqueous medium. Similarly substituted acetophenone derivatives, aliphatic and hetero cyclic ketones, tetrahydro pyran-4-ones and β-keto esters were taken up for selective bio reduction by sprouted *Pisum sativum* to obtain chiral secondary alcohols with a high degree purity with 91-98% enantioselectivity (ee) showing (S) configuration, following Prelog's rule. Enzymatic approach for the synthesis of chiral tetrahydropyranols by enantioselective reduction of 2-substituted tetrahydropyran-4-ones using *Daucus carota*. Reduction of (±)-2-phenyl-tetrahydro-2H-pyran-4-ones with *Daucus carota* afforded (2S, 4S)-2-phenyl-tetrahydropyranol and (2R,4S)-2-phenyl-tetrahydropyranol in a 1:1 ratio. The enantiomeric excesses 92% was observed in both the cis- & trans-tetrahydropyranols as determined by HPLC using chiral columns. The absolute stereochemistry of (2R, 4S)- & (2S, 4S)-2-aryl- or 2-alkyl-tetrahydropyranols was established by comparison with authentic samples. This methodology has wide substrate selectivity like alkyl and aryl pro chiral ketones to give corresponding chiral alcohols with optical purity and enantio & stereo selectivity. Acetyl-pyridines which are known as aromatic components

of perfumes, smoking suppressants and flavours used in foods [5,6,49-54]. Heterocyclic aromatic compounds contain nitrogen or oxygen or sulfur in the heterocyclic ring is important core groups found in natural and synthetic products of biological interest. Chiral hetero aryl alcohols have numerous applications as important intermediates in the synthesis of biologically active molecules and also act as chiral ligands/auxiliaries in a number of asymmetric addition reactions. This study highlights the selective asymmetric reduction of the heteroaryl prochiral ketones to the corresponding chiral alcohols using *Daucus carota*. The results confirms that the production of high yields of chiral alcohols (60% - 95%) with high enantioselectivity (76% - 99%) for (S)-configuration following the Prelog's rule. Only a single isomer was obtained, as confirmed through HPLC using a chiral column (no second isomer was present in the reaction medium.The un-reacted starting compound was recovered [7-13, 55-67].

Total Synthesis of Some Chiral γ-Lactones

Current discussion highlights the total synthesis of γ-Lactones like the fungicide Paecilocin A, (-)-3-butyl-7-hydroxyphthalide and the insect pheromones (4R)-Dodecanolide and (4R)-Octanolide molecules. Total synthesis of polyketide Paecilocin A which was isolated from the fungus Paecilomyces variotii. This molecule is known to exhibit inhibitory activity against pathogenic bacteria including methicillin-resistant bacteria. The molecule 3-butyl-7-hydroxyphthalide was isolated from a culture broth of Penicillium vulpinum. Furthermore, the lactones are known to function such as hormones, pheromones, and antibiotics [14,68-72]. Therefore the synthesis of these natural products taken up in an elegant way using lipase mediated kinetic resolution of propargyl alcohol (to create the stereo center of the target molecule) followed by Alder-Rickert reaction (to construct the functionalized aromatic precursor) as the key steps. The synthesis of target molecules, Paecilocin A and (-)-3-butyl-7-hydroxyphthalide were accomplished by the trans-esterification of racemic compounds respectively, which were easily synthesized by alkyne esters and anisole derivative of diene via Alder-Rickert reaction [73]. The optically pure esters were formed from secondary alcohols via the Enzymatic kinetic trans-esterification of racemic propargylic alcohols using Novozym-435 in the presence of vinyl acetate in tert-butyl methyl ether afforded enantioselective (S)-acetates. Propargylic alcohols were synthesized from the commercially available aldehydes respectively [74]. In summary, we have successfully demonstrated the enantioselective total synthesis of Paecilocin A & (-)-3-butyl-7-hydroxyphthalide using lipase mediated kinetic resolution of racemic propargyl alcohol and Alder-Rickert reaction. The synthesized chiral molecules possess a potent anti-fungal activity.

Synthesis of (R)-Dodecan-4-olide & (R)-Octan-4-olide Molecules

This Section describes the total synthesis of γ-lactones; optically active 5- and 6-alkyl-substituted (or) γ- and δ-lactones which are important scaffolds in medicinal chemistry and also attractive building blocks in the synthesis of natural products. Lactones contain structural moieties that are frequently present in insect pheromones, cardenolides, lignans and flavor components [16-18]. Among various γ-lactones, 4(R)-Dodecanolide is a unique and naturally occurring butanolide; it is isolated from fruits and butterfat. It is a defensive secretion of the pygidial glands of rove beetles, Bledius mandibularis and Bledius spectabilis and is also produced during the bioconversion of soya bean fatty acids by Pencillium roqueforti spores in the presence of an exogenous lipase. These lactones were used as a flavouring agent. The γ-lactones, (4R)-Octanolide is found in strawberry, peach and apricot, it exhibits significant physiological activities [19,75]. The synthesis of target molecules, γ-lactones were accomplished from alkyne esters respectively, which were easily prepared from secondary alcohols via the enzymatic kinetic resolution of racemic propargylic alcohols using Novozym-435 in the presence of vinyl acetate in tert-butyl methyl ether afforded (R)-alcohols. Propargylic alcohols were synthesized from the commercially available aldehydes respectively.

Summary

The current review successfully demonstrated chemo enzymatic total synthesis of wide variety of chiral alcohols such as aromatic and aliphatic chiral alcohols via bio-reduction and synthesis of γ-lactones such as (4R)-Dodecanolide and (4R)-Octanolide using lipase mediated kinetic resolution followed by lactonization as the key steps.

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