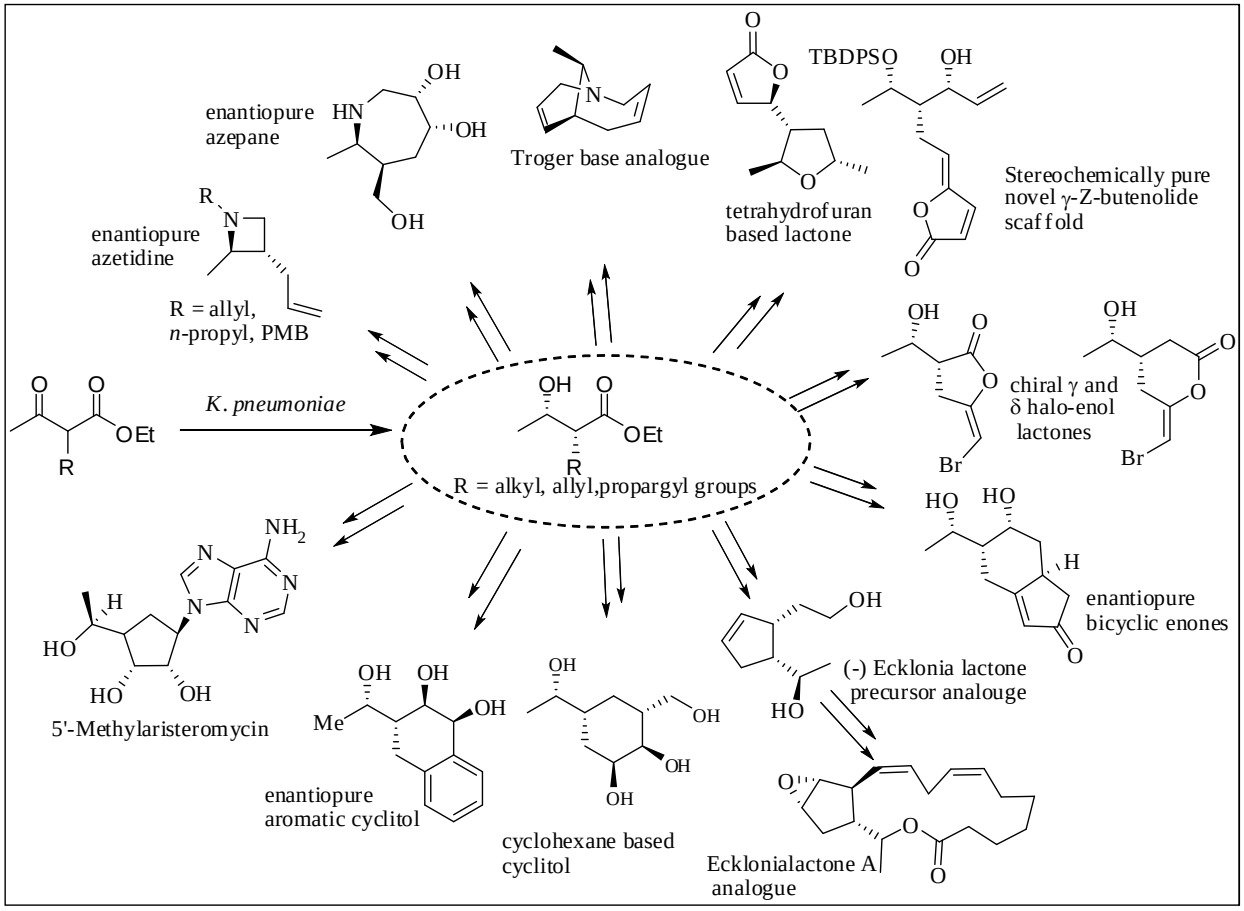
Abstract:

"Synthetic exploration of ketoreductase from *Klebsiella pneumoniae*: Asymmetric synthesis of small ring carbocyclic, heterocyclic scaffolds and an indirect desymmetrization reaction"

The secondary alcohols act as a potential building block in organic synthesis, and they can be synthesized in various processes such as chemical process and enzymatic process. In the chemical process, it can be synthesized from various routes like reduction of carbonyl groups, oxidation of hydrocarbons hydrolysis of alkyl halides, epoxides ring opening, etc. In the enzymatic process, the secondary alcohols can be synthesized from ketones by reductase enzymes, from esters by esterase enzymes, from phosphate by phosphatase enzymes, from sulfate by sulfatase enzymes, etc. Optically pure secondary alcohol functionality is present in many biologically active natural products and active pharmaceutical ingredients (APIs). Asymmetric bioreduction processes for the synthesis of enantiopure secondary alcohols by ketoreductases enzymes have explored extensively in the last two decades. We have demonstrated that Ketoreductases from *Klebsiella pneumoniae* (NBRC 3319) selectively reduce several 2-substituted ethyl 3-oxobutyrates to yield the corresponding *syn*-β-hydroxy esters with remarkable stereocontrol (de >99%, ee > 99%). At a later stage, the enzymatically synthesized enantiopure β-hydroxy esters can be used for the effective construction of many useful small molecular scaffolds. Such important and useful scaffolds are enantiopure azetidine, enantiopure azepane, Troger base analogue, tetrahydrofuran based lactones, chiral γ and δ lactones with exocyclic bromethylene group, (-) Ecklonia lactone precursor, enantiopure aromatic cyclitol, enantiopure bicyclic enones, small ring carbocycles, 5'-methylaristeromycin functionalized carbocyclic and heterocyclic scaffolds as shown in the following scheme (**Scheme 1**).

Ethyl 2, 2-disubstituted-3-oxobutanoates were biocatalytically reduced to the corresponding (*S*)-ethyl 3-hydroxy-2, 2-disubstituted butanoate with the growing cells of *Klebsiella pneumoniae* (NBRC 3319) with excellent enantioselection. The biocatalytically derived enantiopure hydroxyl esters are then synthetically manipulated to (*S*)-4-hydroxy -3, 3-disubstituted pentane- 2-ones. The whole process can be regarded as an indirect enantioselective enzymatic desymmetrization (EED) and diastereoselective enzymatic desymmetrization (DED) method for the synthesis of (*S*)-4-hydroxy -3, 3-disubstituted pentane- 2-ones.



Scheme 1: *Klebsiella pneumonia* (NBRC 3319) mediated synthesis of various 2-substituted-β-hydroxy esters and further synthetic manipulation.

Key Words: Asymmetric bioreduction, Enantiopure cyclitols, Enantiopure bicyclic enones, Enantiopure azetidine and azepane, γ-Z butenolides, Ring closing metathesis, Johnson orthoester rearrangement, enantiopure small ring carbocycles, Indirect desymmetrization, Enantioselective enzymatic desymmetrization.