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Bioreduction of Phenyl Ketones for the Obtention of Enantiopure Alcohols

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Abstract: The demand for chiral intermediate compounds with high enantiomeric purity has increased markedly in industries. Chiral secondary alcohols are frequently required as important intermediates for the introduction of chiral center into the pharmaceuticals, flavor, aroma and agricultural chemicals, and specialty materials. Biocatalytic asymmetric reductions can offer highly selective reactions, environmentally benign processes, and energy-effective operations and thus of great interest. Alcohol dehydrogenases (ADH), are a class of nicotinamide dependent oxidoreductases, which can catalyze the reduction of carbonyl compounds to produce alcohols. Three different sources of oxidoreductase were tested (alberjon, alubia and ayocote) for the biotransformation of acetophenone (**1a**) and propiophenone (**1b**) to their respective alcohols (**2a,2b**), with alberjon as enzyme source, the reduction of both ketones was similar. With alubia and ayocote bean the enzyme was sensitive to the chain size of the ketone, the reduction of **1a** was almost the double than that of **1b** this could be because a steric effect. With regard to the ee, there was not a correlation between the chain size and the ee, it was more dependent on the enzyme source. Alberjon, **2a** 71%, **2b** (10%); alubia, **2b** had a 58% ee, 28% for **2a**; ayocote beans, **2a** 38% ee and 29% ee for **2b**.

Key words: Ketones, enantiopure alcohols, bioreduction, alcoholdeshidrogenase.

INTRODUCTION

The demand for chiral intermediate compounds with high enantiomeric purity has increased markedly in industries such as foods, chemicals, pharmaceuticals, and agrochemicals, because the chiral compounds

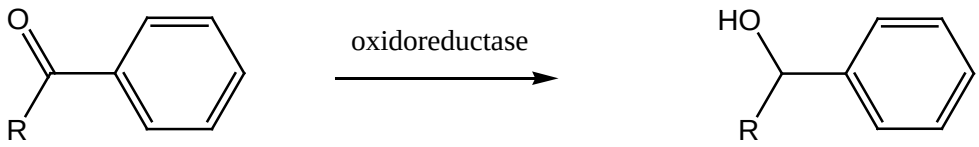
exhibit their biological activity often in only one enantiomeric form. Then the chemical industry has been enforced to face the challenge of efficiently producing enantiopure molecules.

Nowadays, most of the chiral molecules are being developed as single stereoisomers, and different forms of resolution techniques are still used for the separation of enantiomers. Enzymes have been accepted for the production in organic chemistry, not only for their chemo- and regioselectivity but most of all for their often incomparable stereoselectivity allowing the direct production of enantiomerically pure products[1-3]. Chiral secondary alcohols are frequently required as important intermediates for the introduction of chiral center into the pharmaceuticals, flavor, aroma and agricultural chemicals, and specialty materials[3]. Enantioselective ketone reduction is a reliable, scalable and straightforward route for the production of optically active alcohols. Biocatalytic asymmetric reductions can offer highly selective reactions, environmentally benign processes, and energy-effective operations and thus of great interest[4].

Alcohol dehydrogenases (ADH), also referred to as carbonyl reductases (CR), are a class of nicotinamide dependent oxidoreductases, which can catalyze the reduction of carbonyl compounds to produce alcohols. Due to their strict recognition of substrate and hence high enantiomeric excess products, ADH/CR are especially suitable for asymmetric synthesis of optically pure alcohols[5]. Most of the enzymes are of microbial origin, but plant sources are becoming more attractive lately because they are easily accessible and of low cost, oxidoreductases from plants have been used to reduce aldehydes and ketones[1, 5-7].

The purpose of the present work was to carry out the enantioselective reduction of acetophenone and propiophenone with the seeds of alberjon, alubia and ayocote bean, to the best of our knowledge the mentioned seeds have not been used as reductase sources.

Methods. The seeds of alberjon, alubia and ayocote were ground and stirred with phosphate buffer (0.1M pH 7.6), after one hour the mixture was centrifuged, the supernatant was used as enzyme source; the acetophenone or propiophenone dissolved in isopropyl alcohol was mixed with the supernatant, incubated at 35°C, stirred at 1300rpm; after 24h the mixture was extracted with ethyl acetate and analyzed by GC and HPLC, to determine the conversion and enantiomeric excess (ee) respectively.



[1] [2]

R= (a)CH_3 (b) CH_3CH_2

Figure 1: Reduction of acetophenone (**1a**) and 1-phenyethanol (**1b**) to their corresponding alcohols using alberjon, alubia and ayocote beans as oxidoreductase sources.

RESULTS

Three different sources of oxidoreductase were tested for the biotransformation of acetophenone (**1a**) and propiophenone (**1b**) to their respective alcohols (**2a**, **2b**), these seeds were chosen because in a previous work they showed good conversion of benzaldehyde to benzyl alcohol. In figure 2, can be observed that with

alberjon as enzyme source, the reduction of both ketones was similar. But with alubia and ayocote bean the enzyme was sensitive to the chain size of the ketone, the reduction of **1a** was almost the double than that of **1b**, in both cases, the largest the chain the lowest the reduction this could be because a steric effect.

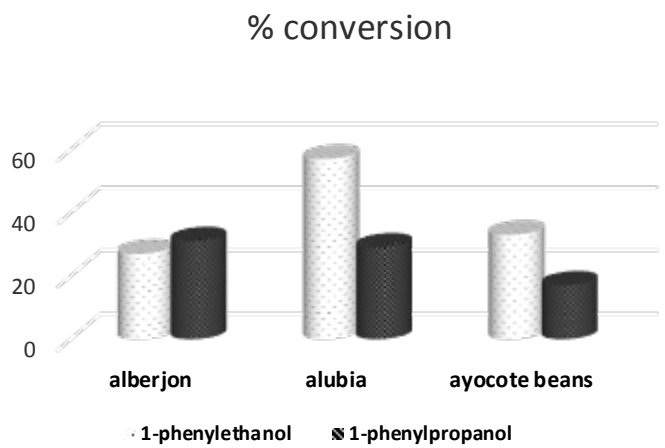


Figure 2: % conversion of 1-phenylethanol and 1-phenylpropanol with three different sources of oxidoreductases.

With regard to the ee, the situation was completely different, there was not a correlation between the chain size and the ee, and it was more dependent on the enzyme source. In figure 3, can be observed that with alberjon as oxidoreductase source, **2a** had the highest ee (71%) but the lowest for **2b** (10%). In the case of alubia, **2b** had a 58% ee and only 28% for **2a**. Ayocote beans did not the enantioselectivity of the reduction was los the %ee of **2a** was 38% and 29% for **2b**.

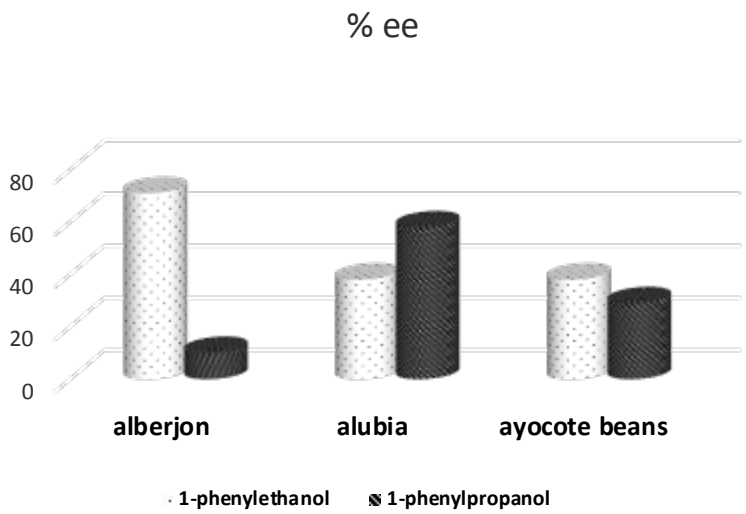


Figure 3: % ee for 1-phenyl ethanol and 1-phenylpropanol with alberjon, alubias and ayocote beans.

CONCLUSIONS

The seeds of alberjon, alubia and ayocote bean are accessible and readily accessible reductase sources. Although the enantiomeric excess was not very high, the results can be improved with modifications on the reaction conditions.

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