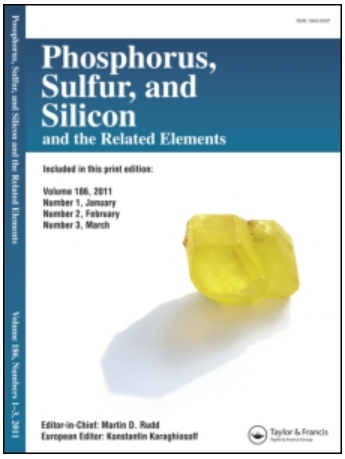

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Biocatalyzed Reactions in Optically Active Phosphonate Synthesis

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Biocatalyzed Reactions in Optically Active Phosphonate Synthesis

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With the dramatic growth in importance of asymmetric synthesis and application of optically pure organophosphorus compounds of defined absolute configuration, new approaches of gaining them become essential. This review is focused on representative and selected examples of recent achievements in enantioselective biotransformations of phosphoroorganic compounds.

Keywords Biotransformations; organophosphonates; chirality

INTRODUCTION

Organophosphonates are group of chemical compounds with a direct bond between phosphorus and carbon atoms. They effectively, structurally mimic carboxylic acids. The replacement of carboxylic group by phosphonic acid moiety has a number of important consequences deriving from their differences in shape (tetrahedral phosphonic versus flat carboxylic one); acidity (phosphonic being significantly more acidic) and steric bulk (phosphorus atom has bigger radius than carbon one). Phosphonates exert biological effect as antibacterials, antivirals, herbicides, neuromodulators or chelating agents. It is well known that enantiomers usually represent different biological activity. Biocatalysis is an effective, and in many cases preferable, alternative to the standard synthesis of optically active forms of fine chemicals, including phosphonates of defined structure and absolute configuration.

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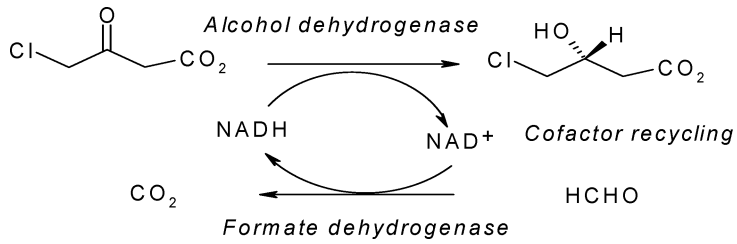
BIOCATALYSIS – SCOPE AND LIMITATIONS

Biotransformations—biocatalyzed conversion of non-physiological substrates into defined products of industrial meaning may be performed using whole cells of desired activity or isolated enzymes. Both methods have their advantages and disadvantages, but when compared to chemical catalysis they are exquisitely selective and highly precise due to their substrate selectivity. The use of bicatalysts allows distinguishing and acting on the subset of compounds within a larger group of chemically related compounds; their stereoselectivity—the ability to act on a single enantiomer or diastereoisomer selectively; their regioselectivity—ability to recognize one location in a molecule and finally their selectivity towards defined functional group in a presence of other equally reactive or more reactive one. Each type of selectivity shows advantages that can accrue to chemical processes because of the special properties of the enzymes. Furthermore, biocatalysts are able to carry out bioconversion under mild conditions—another benefit of using them as industrial catalysts.[1–3] Typically, they function at ambient temperatures, atmospheric pressure, and neutral pH. Additionally it is important to note the generation of side products a minimized, raising yield and facilitating the product recovery. Moreover, biocatalysis is environmentally friendly, obviously because of the nature of the catalyst and because of the reaction medium—usually water solutions. On the other hand, it has to be stressed that employing biocatalyst has restrictions, which is implied from their biological structure. The limitations are as follows: too low productivity, in many cases connected with the required low concentration of the substrates in the reaction medium; a narrow range of water-soluble substrates; and some special enzymes requirements such as cofactor regeneration systems, in the case of the oxidation or reduction reactions.[4–6] However, dynamic development of biological sciences including enzymes and microbes engineering allows implementing biocatalysis into many chemical syntheses. It also allows generating a new approach to scientifically based environment protection.[3,7] Employing whole-cell biocatalysts is a strategy that allowed overcoming many limitation of the biotransformation and, what is important, is usually cheaper than using purified enzymes. Additionally, microbial cells used as a catalysts, have their own cofactor regeneration systems, offer wide range of enzymatic activities towards a number of non-physiological substrates and moreover, usually there are no side reactions except the expected ones.[7,8] There are many ways of whole cell adaptation to catalyze desired chemical processes. One of the strategies includes the change of the reaction medium, that is water solutions into biphasic (water and organic solvent) or anhydrous systems.

It allowed increasing the substrates spectrum with the water insoluble compounds, however requires special biocatalyst preparation such as lyophilization and/or immobilization—to stabilize the biocatalysts in such a reaction medium and protect the cells against toxic impact of organic solvent.[8,9] There is no doubt that the advantage of microbial biotransformations is the possibility to induce enzymes of defined, desired activity (which are not constitutively presented inside the microbe cells), simply by the suitable preincubation methods. This strategy includes temperature pretreatment, cultivation under anaerobic or starvation conditions, and the use of different sort of cultivation media with different source of supporting elements. Microbiological media in particular experiments, contain special chemical additives, which influence the particular enzymes activities or are an exogenous source of hydrogen for dehydrogenases cofactors regeneration systems[10–13] (Scheme 1).



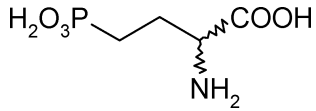
SCHEME 1

With the multiplicity of constitutive and inducible enzymes, microorganisms are capable of performing a vast number of chemical reactions, which are essential for maintaining the life functions of the cell. In fact, there exists an enzyme—catalyzed equivalent for almost every type of chemical reaction. As a consequence of increasing knowledge about the nature of biotransformations, many traditional chemical synthesis are replaced by bioprocesses or hybrid chemical/biocatalytic reactions.[14–16]

PHOSPHONATES OF BIOLOGICAL IMPORTANCE

Synthesis of chiral phosphonates has gathered considerable attention due to their usefulness for the synthesis of other phosphorus compounds of variable use[17–19] and because of their possible biological activity.[20] Phosphonates, as structural analogues of carboxylic acids, are known as an enzymes inhibitors and thus offer the possibility to control some metabolic pathways in living cells. Aminophosphonates affect enzymes involved in amino acids metabolism whereas hydroxyphosphonates display an inhibiting effect on fermentation pathways biocatalysts, which

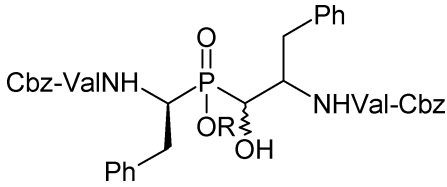
usually interact with natural hydroxycarboxylic acids.[19,20] This research field is still not fully explored, although it began more than 40 years ago with the first report on the inhibition of avian glutamine synthetase by phosphonic and phosphinic analogues of glutamic acid (Scheme 2).



SCHEME 2

Currently, there are many reported effective phosphonates derivatives acting as inhibitors of different enzymes, such as: urokinase plasminogen activator,[21] arabinosylotransferase,[22] human gastric lipase,[23] glutamate carboxypeptydase,[24] farnesyl diphosphate synthase,[25] and gamma-glutamyl transpeptidase.[26]

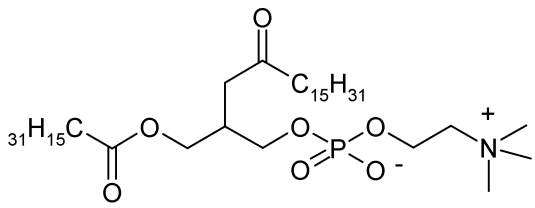
Among phosphonates there is a group of compounds of proven antiviral activity—this scientific field develops dynamically, offering rationally designed structures—mostly nucleoside analogues—phosphonated nucleosides[27–29] or hydroxyphosphonates acting as an antiviral factors against human immunodeficiency virus[30] (Scheme 3).



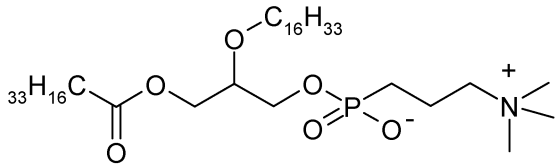
SCHEME 3

Aminophosphonates with the fluorine moiety are antifungal factors.[31] Other groups of phosphonates derivatives are used to construct haptens for the preparation of catalytic antybodies of desired acitivity.[32] Furthermore, during the last few years, another biological meaning of phosphonates was discovered and is intensively explored—he influence on the adsorption surfaces in lungs. Phosphonolipid **3** is promising for the future application in treating surfactant dysfunction in inflammatory lung injury.[33]

Finally, organophosphorus compounds with two phosphonates groups – bisphosphonates, are also known from their interesting biological properties such as: osteoporosis treatment drugs (Scheme 4);[34–36] inhibition of the protozoan parasite, *Toxoplasma gondii* growth (in vitro) .[37] Moreover, bisphosphonates are successfully used as a support



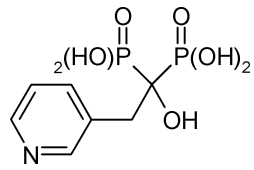
Dipalmitoyl phosphatidylcholine – native lung surfactant



Phosphonate analogue

SCHEME 4

material for the biomolecules immobilization.[38,39] These compounds are also capable to binding and masking metal ions that is why they can act as synthetic chelating agents in the aquatic environment (Scheme 5).[40]

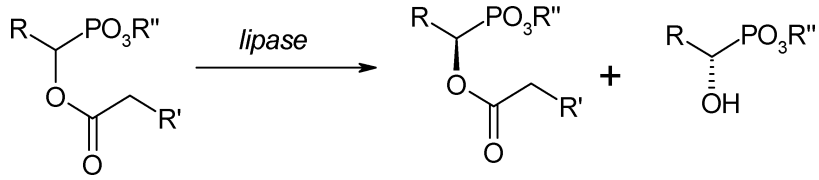


SCHEME 5

PHOSPHONATE BIOTRATNSFORMATIONS—KINETICALLY CONTROLLED BIOCATALYSIS

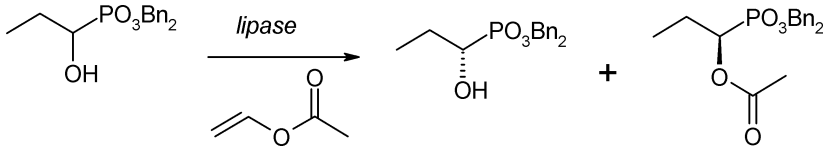
Whole-cell, as well as enzyme biocatalysis, is successfully applied in chemoenzymatic synthesis of phosphonates (phosphinates) of defined structures and absolute configurations. However, these biotransformations required carefully selected biocatalysts, concerning the wide spectrum of possible biological activities of organophosphorous compounds, especially enzymes inhibition. Bioconversion of these substrates base upon following enzymatic activities: esterification and hydrolysis of the racemic mixtures of starting materials—kinetically controlled resolution—and upon the reduction and oxidation of prochiral

substrates—dynamically controlled processes. Phosphonates (phosphinates) substrates are chemical moieties with one—on the carbon or phosphorus atom or two—on the phosphorus and carbon atoms—stereogenic centers. Biotransformations were introduced into phosphonic acids chemistry more than ten years ago and consist of the use of lipases for the esterification of hydroxyphosphonates or hydrolysis of acyloxyphosphonates.[41–44] Lipases from different sources natively require biphasic media for their activity. In some cases, it is an advantage because it allows using water insoluble substrates and often facilitates the products separation. Enantioselective hydrolysis of number of 1-acyloxyphosphonates resulted in effective kinetic resolution of racemic starting materials (Scheme 6).



SCHEME 6

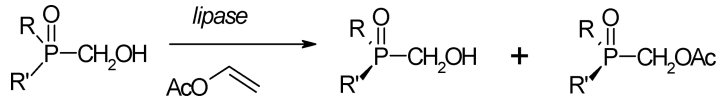
The best results (18–50% of yield and up to 98% of e.e.) were obtained using lipases of microbial origin (*Aspergillus niger*—AP 6 or *Rhisopus oryzae* – FAP 15) and for the substrates where R″ were as follows: substituted phenyl, 1-naphtyl, 2- and 3-thienyl, 3-furyl, 2- and 3- piridyl. The second strategy—lipolytic acylation—resulted in optically pure products (yields 44% and up to 99% of e.e.) (also with stereogenic centre on the carbon atom), employs lipase from *Pseudomonas fluorescens* for the transesterification carried out in anhydrous organic solvent[45,46] (Scheme 7).



SCHEME 7

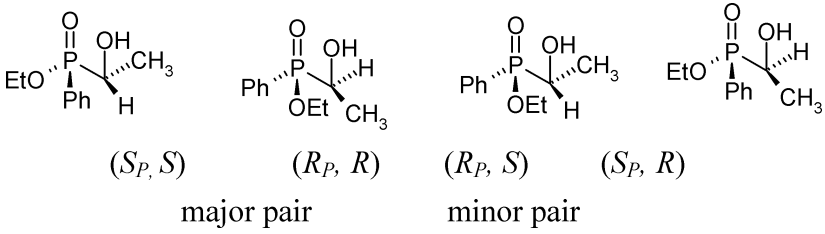
As it is clearly seen, in the case of asymmetric centre located on α-carbon, enzymes of various origins have different specificity. Fungal lipases prefer enantioselective hydrolysis whereas bacterial—enantioselective acylation. Lipases-catalyzed acylation was successfully used for the substrates with the chiral phosphorus atom in 1998. Kinetic resolution of the racemic mixture of hydroxyphosphinates was

performed by the enzyme from *Pseudomonas cepacia* (Scheme 8).[47] Final products—acetyl phosphinates were obtained with satisfactory yield (up to 42%) and of excellent optical purity—92%.



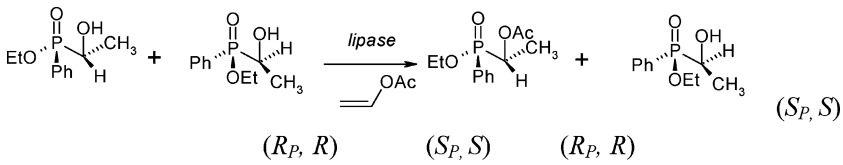
SCHEME 8

The best results were obtained for the following substituents: R - phenyl and R′- methoxy group and for the biotransformations carried out in organic medium. Also this time for enantioselective transesterification, lipases were purified from a bacterial strain. Enzyme -catalyzed acylation of *P*-chiral hydroxymethanephosphinates and hydroxymethylphosphine oxides was also performed in unusual reaction medium—in ionic liquids.[48] The modification of biotransformation conditions for the enzyme—promoted syntheses of chiral heteroatom compounds allowed improving the values of enantiomeric excess (three to six times, comparing to the biocatalysis carried out in common organic systems). This attempt was effective for substrates having larger organic substituents. The next challenge was to develop the methods for the enzymatic resolution of the substrates with two stereogenic center. This approach was introduced in 2003. 1-Hydroxy-P-phenylphosphinates were applied as starting compounds.[49] Such reactions are much more sophisticated than previously described because of the four possible diasteromeric forms of the phosphinates moiety (Scheme 9).



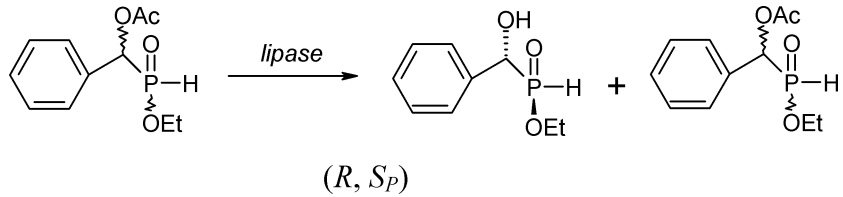
SCHEME 9

The kinetic resolution of the major phosphinates (see **Scheme 9**) was catalyzed by *Candida antarctica* lipase, using vinyl acetate as an acyl donor. Acylation of the mixture of (S_P,S) and (R_P, R) isomers afforded the corresponding, enantiomerically pure esters (conversion 50%, e.e. -98%) (Scheme 10).



SCHEME 10

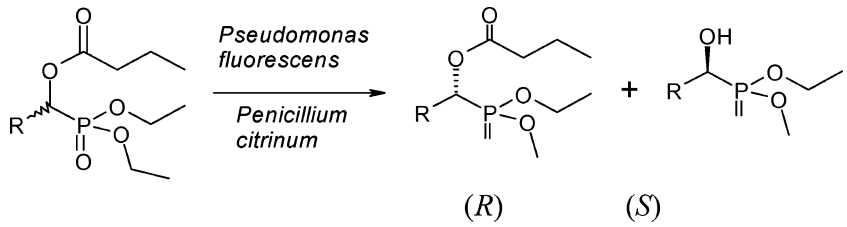
It has to be noted that in this case, fungi constitute the appropriate source of enzymes for the lipase-performed acylation. As a consequence of reported bioconversions, lipases were successfully applied for the preparation of other, optically pure 1-heteroatom phosphinates, as well as 1-hydroxy-P-phenylphosphinates[50] and 1-hydroxy-H-phosphinates.[51] In this case, chemically acylated substrates were enzymatically hydrolyzed. From the mixture of four stereo isomers of 1-hydroxy-H-phosphinates, one was obtained selectively with the yield of 9–14% and of high optical purity (Scheme 11).[51] *Pseudomonas cepacia* served as a source of enzyme of hydrolytic activity.



SCHEME 11

Unfortunately, application of the lipases has limitations such as too low enantioselectivity or unsatisfactory yield or finally lack of the activity towards particular substrates. These restrictions redirect the attention to whole-cell biocatalysts, however, since lipase rank among the least expensive enzymes the use of microbial cultures is less competitive than in other cases. Application of microorganisms of induced or constitutive lipolytic activity allowed carrying particular biotransformations, as well as in biphasic, anhydrous and in buffer media without any organic solvent addition, what was indispensable in the case of pure lipases. This approach was introduced in 1996[52] and since than, have resulted in many successful, steroselective bioconversions of phosphonates (phosphinates). The cells of bacteria—*Pseudomonas fluorescens* and fungi—*Penicillium citrinum* were applied as biocatalysts for the kinetic resolution of 1-butyryloxyphosphonates (Scheme 12).[52,53]

The certain selectivity was observed among microorganisms used—fungal strain efficiently hydrolyzed substrates containing aliphatic



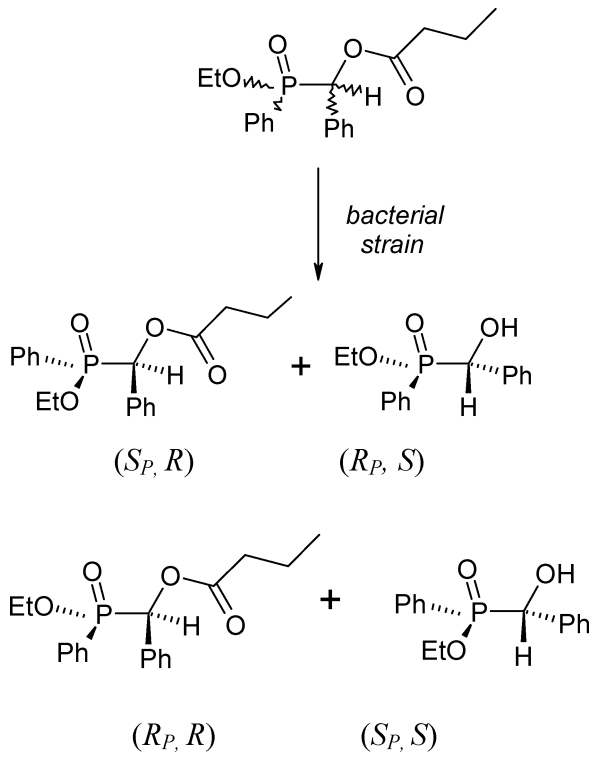
SCHEME 12

substituents at the 1-position, whereas bacterial cells were effective towards substrates substituted with an aromatic moiety at this position. On the other hand, both biocatalysts performed the same enantioselectivity. Despite that, described strategy allowed obtaining optically pure products via quite cheap and simple methods. Examples mentioned, represent microbial biotransformations of phosphonates derivatives with one asymmetric center—on carbon atom. It was obvious that whole-cell biocatalysis of the compounds with two stereogenic centers was the matter of time. The first application of microbial cultures for the biocatalysis of ethyl hydroxy(phenyl)methane(P-phenyl)phosphinate was reported last year, in 2006.[54] Substrate-chemically acylated with butyryl chloride—was hydrolyzed using whole cells of following bacterial strains: *Bacillus subtilis, Acinetobacter baumanni, Serratia liquefaciens* and *Pseudomonas aeruginosa* (Scheme 13).

Microorganisms preferentially hydrolyzed compound with the *S* configuration of α-carbon whereas the lack of stereoselectivity was observed toward phosphorous atom. The best results (yield 50% and e.e. – 90%) were obtained with the cells of *Bacillus subtilis.* It is necessary to stress that the final results of the biocatalyzed, asymmetric synthesis of phosphonic or phosphinic acids derivatives are tightly connected with the kind of microorganism, which is the source of the enzyme of particular activity or which serves as a whole-cell catalyst.

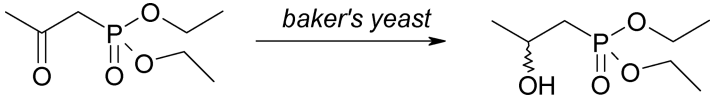
PHOSPHONATE BIOTRANSFORMATIONS—THERMODYNAMICALLY CONTROLLED BIOCATALYSIS

The most important advantage of thermodynamically controlled biotransformations is the possibility to convert whole amount of prochiral substrate into desired product of excellent yield, enantiomeric excess and defined absolute configuration. This strategy was reported for the first time in 1995.[55] Application of the commercially available baker's yeast cells as a biocatalyst and using 2-ketophosphonates as substrates afforded in obtaining corresponding hydroxyphosphonates with



SCHEME 13

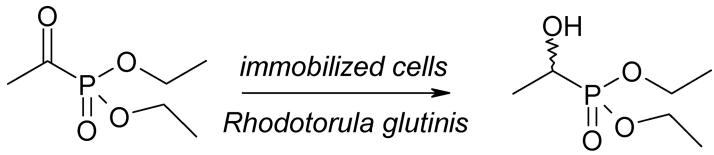
satisfactory yield of 80% and in optically pure form of *S* configuration. Biotransformation effectiveness was strongly correlated with the structure and steric hindrance of phosphonate moiety. The best results were obtained for the enantioselective reduction of 2-ketopropylphosphonate diethyl ester (Scheme 14).



SCHEME 14

Since than, many other derivatives of 2-ketophosphonates were successfully reduced with the baker's yeast cells served as a source of reductive activity.[56,57] The approach mentioned above has many advantages such as, the simplicity of the procedure, which does not requires an expert in microbiology; the applied method is cheap because biotransformations are carried out in water or buffers; and finally,

column chromatography is the mean of the products recovery and purification. It is noteworthy, that this simple, baker's yeast—catalyzed bioreduction resulted in obtaining another valuable group of optically pure phosphonates—with the hydroxy group at γ – position.[58] This report also showed that the efficiency of the microbial enantioselective conversion under particular conditions strongly depends on the nature of the substrate. Steric hindrances introduced by substituents, which are in close proximity to the carbonyl moiety either totally abort or significantly decrease the reaction yield. The best results (85% of yield and 95% of e.e.) occurred for the biotransformation of γ-oxophenylpropylphosphonate diethyl ester, carried out under aerobic condition using fresh baker's yeast as a catalyst whereas the lack of the reaction was observed for the substrate with the aliphatic side chain. In this case, anaerobic biocatalyst preincubation allowed inducing dehydrogenases of different substrate specificity and bioconversion of 3-oxo-4-methylbutylphosphonate diethyl ester afforded in obtaining corresponding hydroxyphosphonate with enantiomerical excess of 85%. Succeeded application of the reductive potential of the yeast cells in phosphonates biocatalysis, stimulates the examination of a number of structurally diverse substrates and another fungal cells as potential biocatalysts.[59–62] The following fungal strains turned out to be effective: *Rhodotorula rubra, R. glutinis, Cladosporium sp., Verticillium sp.* and *Geotrichum candidum.* The most difficult biocatalytic challenge was the enantioselective reduction of 1-ketophosphonates—compounds extremely unstable in water and easily decomposed. Corresponding hydroxy acids are valuable not only due to their biological possible activity but also because they are chiral substrates for further chemical synthesis of optically active aminophosphonates. To perform the enantioselective reduction of 1-oxophosphonates, it was necessary to modify the biocatalyst cells in the way allowing carrying the bioconversion under completely anhydrous conditions. The best results were obtained for the biotransformation carried out in dried hexane with immobilized (via adsorption on the celite particles) cells of *Rhodotorula glutinis*. 1-Oxoethylphosphonate occurred with the yield of 81% and e.e of 99% (Scheme 15).



SCHEME 15

As it is clearly seen, the best sources of the reductases active towards oxophosphonates are different kinds of fungi imperfecti. The most important purpose in the chemistry of asymmetric compounds is the ability to synthesize desired optical isomer with good yield and of satisfactory optical purity. The next aim was to invent the method of control the stereochemistry of enantioselective bioreduction to obtain hydroxyphosphonates of defined absolute configuration in both enantiomeric forms. 2-Oxopropylphosphonate diethyl ester was used as a model substrate. There are at least two strategies that allow achieving mentioned purpose. The first one is based on the modification of the biotransformation conditions mostly by supplementation of the reaction medium by chemical additives, which affect the activity of dehydrogenases of particular enantioselectivity. The second attempt includes the screening of microorganisms of opposite enantioselectivity towards the same substrate.[62–63] In the case of the bioconversion of 2-oxophosphonate, both approaches were effective. The addition of ethyl chloroacetate or methylvinyl ketone to the reaction medium resulted in changing the stereochemistry of the baker's yeast—catalyzed bioreduction leading to the *R*-enantiomer of 2-hydroxyphosphonate whereas without any additives this bioprocess resulted only in the *S*-form of the product—the enantiomeric excess was excellent up to 99%.[62] It is noteworthy that also the second strategy was efficient - two kinds of microbial cells were found as an effective biocatalysts: *Saccharomyces cerevisiae*—allowed obtaining the *S*-isomer of 2-hydroxypropylphosphonate while *Rhodotorula rubra*—catalyzed enantioselective reduction resulted in the *R*-form; optical purity of the products was up to 99%. Described studies of many scientist proves, that there is a great potential in every single living cell, potential which is hidden and which is waiting to be discovered. Biocatalytic synthesis of asymmetric compounds, including phosphonates (phosphinates) will develop as a part of green chemistry, giving the solution of chemically unsolved problems.

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