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Biocatalysis Applied to the Preparation of Pharmaceuticals

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Abstract:

Biotransformations are now accepted as a methodology for the preparation of fine chemicals. The majority of enzyme-catalysed reactions involve the use of hydrolases, especially lipases, in hydrolysis, esterification or aminolysis reactions. Lyases, enzymes much less exploited in organic synthesis, are proving increasingly interesting, especially the use of (*R*)-oxynitrilases for the synthesis of optically active cyanohydrins which are intermediates of many compounds of pharmacological importance. In this account, we report the utility of four kinds of processes which we have carried out recently in our laboratory in the field of pharmaceutical chemistry. Enzymatic resolution of alcohols, enzymatic acylation of amines, regioselective acylation, and alkoxycarbonylation of natural products, and chemoenzymatic synthesis of products of high added value using (*R*)-oxynitrilase as biocatalyst are described.

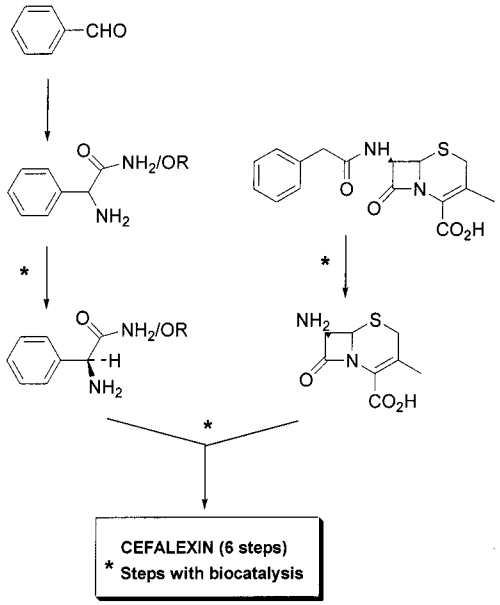
Introduction

In the past few years, there has been an ever-increasing trend for chiral drugs substances to focus on single stereosisomers, that is, enantiomers instead of racemic mixtures. The single most important reason for developing stereochemically pure and defined compounds is the difference of biological activity, displayed in many cases by each enantiomer of a chiral compound.[1] For this reason, worldwide sales of chiral drugs in single-enantiomer dosage forms continued growing at an annual rate of more than 13% to $133 billion in 2000.[2]

In this context, biocatalysis has been well recognized as an excellent strategy for the preparation of pharmaceuticals. Biocatalytic processes are environmentally friendly in contrast to conventional chemical catalytic processes, especially when these make use of heavy-metal catalysis. However, in many cases, the combination of chemical procedures with biocatalytic methods can be an excellent strategy for the production of fine chemicals. For instance, biocatalysis plays an important role in the production of antibiotics, an illustrative example being the preparation of cefalexin which has been shortened from 10 to 6 steps using a chemoenzymatic procedure (Scheme 1).[3]

Both isolated enzymes and whole cells, either in soluble form or immobilized, have been used successfully in the synthesis of pharmacologically valuable materials.[4] However,

Scheme 1



hydrolytic enzymes are widely used in organic synthesis as environmentally friendly catalysts that possess broad substrate specificities, display high stereoselectivity, are commercially available, and do not require the use of cofactors.[5]

These biocatalysts have been exploited for asymmetric synthesis transformations, fueled by the growing demand for enantiopure pharmaceuticals. Furthermore, lipase-catalyzed reactions are normally carried out under mild conditions and can be used in organic solvents. In addition, biocatalysis in nonaqueous media has been widely used for the resolution of alcohols, acids, or lactones through enzymatic transesterificacion reactions using hydrolytic enzymes, especially lipases.[6] Moreover, other processes such as the enzymatic acylation of amines or alkoxycarbonylation of alcohols and amines have shown themselves to be of great utility for the resolution of amines and the preparation of chiral amides, carbonates, or carbamates.[7] The mechanism of these processes is shown in Scheme 2.

The main difference between enzymatic aminolysis and transesterification reactions is the use of the corresponding acyl donor because activated esters which are of utility in acylation of alcohols react with amines in the absence of biocatalysts, and nonactivated esters must be used to carry out an enzymatic aminolysis or ammonolysis reaction. For

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(1) Ariens, E. J. *J. Med. Res. Rev.* **1986**, *6*, 451.
(2) Stinson, S. C. *Chem. Eng. News* **2001**, October 1, 79.
(3) Bruggink, A. Biocatalysis in the Synthesis of Semi-synthetic Antibiotics. In *Enzymes in Action: Green Solutions for Chemical Problems*; Zwanemburg, B., Mikolajcyky, M., Kielbasinski, P., Eds.; Nato Science Series; Kluwer Academic Publishers: Dordrecht, 2000; pg 449−458.
(4) Federsel, H.-J. *CHEMTECH* **1993**, 24.
(5) Faber, K. *Biotransformations in Organic Chemistry*, 4th. ed.; Springer-Verlag: Berlin, 2000.
(6) Carrea, G.; Riva., S. *Angew. Chem., Int. Ed.* **2000**, *39*, 226.
(7) Gotor, V. *Bioorg. Med. Chem.* **1999**, *7*, 2189.

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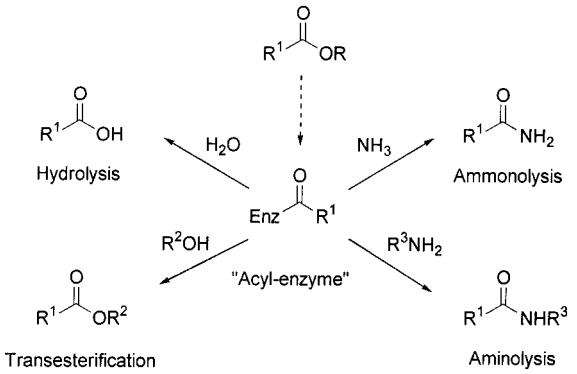
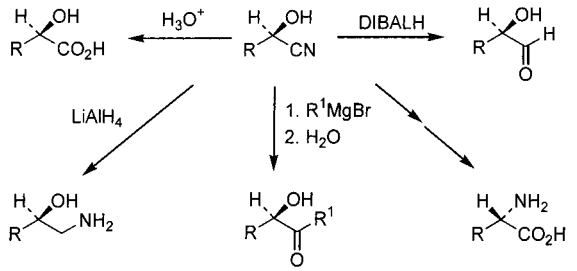
Scheme 2



Scheme 3



this reason, lipases are the most efficient hydrolases to catalyse the acylation of amines and ammonia because these hydrolytic enzymes have very low amidase activity.[8]

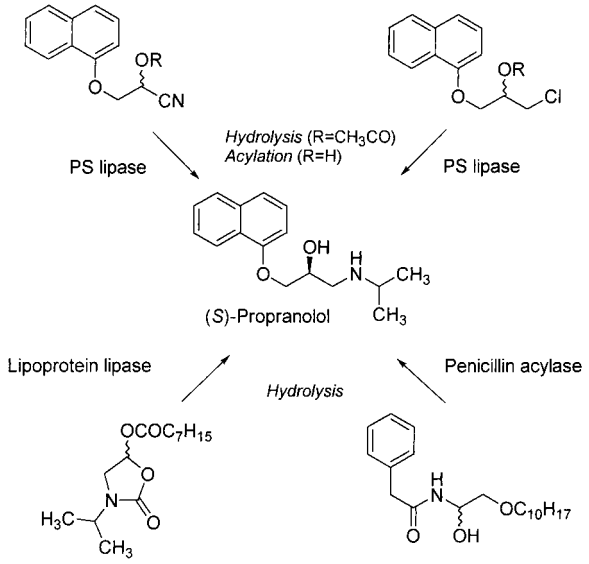
On the other hand, the addition of HCN to carbonyl compounds catalyzed by oxynitrilases (a type of lyase) to yield optically pure cyanohydrins[9] is a process of pharmacological interest, because cyanohydrins are precursosrs of amino acids, amino alcohols, and other compounds of high added value in pharmaceutical chemistry (Scheme 3).[10]

This review covers some reactions that we have carried out in our group, using lipases for the preparation of compounds with pharmacological activity through enantioselective and regioselective processes. Additionally, several examples of in-house-*R*-oxynitrilase-catalyzed reactions for the synthesis of nitrogen-containing heterocycles of biological interest are described.

Resolution of Alcohols. Enzymatic hydrolysis of acetylated alcohols or enzymatic transesterification reactions of many secondary alcohols have been exhaustively investigated for the preparation of a great number of synthons for the synthesis of chiral drugs.[11] For instance, β-adrenergic blocking agents, such as propanolol, have been synthesized by different chemoenzymatic methods (Scheme 4). The main reason to prepare these amino alcohols in an optically pure form is because the activity of these pharmaceuticals resides in the (*S*)-enantiomer.[12]

Another family of chiral drugs where biocatalysis has acquired a relevant role has been in the preparation of single enantiomers of arylpropionic acids (nonsteroidal antiinflamatory agents)[13] because the (*S*)-enantiomer is also more active than its (*R*)-counterpart. Optically pure 1,4-dihydropyridine derivatives are compounds of great interest as calcium antagonists and their preparation or resolution is one of the most important focal points in the pharmaceutical industry. The two enantiomers of the majority of dihydropyridines, including mimodipine or amlodipine, differ in their pharmacological effects. The enzymatic resolution of racemic 1,4-dihydropyridines has been accomplished through enzymatic hydrolysis and transesterification.[14]

Scheme 4

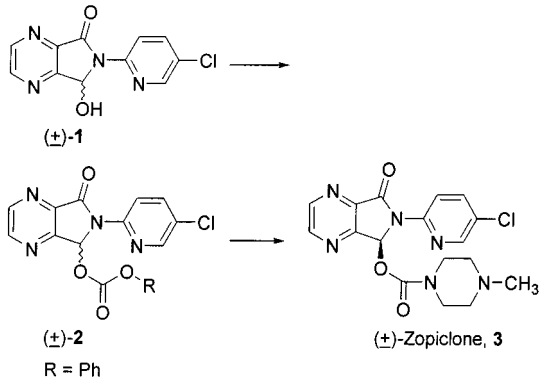


(±)-Zoplicone **3** is a chiral cyclopyrrolone with hypnotic properties, possessing a pharmaceutical profile of high efficacy and low toxicity, similar to that of benzodiazepines. Zoplicone has been commercialized as a racemic mixture. However the (*S*)-enantiomer is more active and less toxic than the (*R*)-enantiomer.[15] On the other hand, phase III clinical studies on the single enantiomer by Sepracor are being completed; the next step will be the filing of an NAD with the Food and Drug Administration.[2] Racemic zoplicone is currently produced by Astur Pharma[16] as outlined in Scheme 5, where the final step is the reaction of *N*-methylpiperazine with the carbonate **2**.

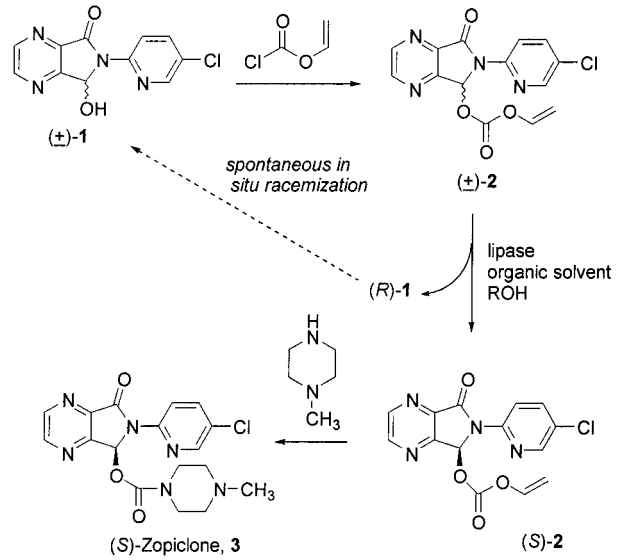
Enzymatic alkoxycarbonylation has been much less investigated than the corresponding transesterification reaction. We have developped a methodology for the preparation of carbonates and carbamates through the enzymatic alkoxycarbonylation of alcohols[17] and amines.[18] We found that direct enzymatic carbonation of the alcohol **1** was unsuccessful and therefore studied the enzymatic hydrolysis of carbonates **2** with the aim of preparing optically active zoplicone. The best results were obtained using *Candida*

(8) Castro, M. S.; Sinisterra Gago, J. V. *Tetrahedron* **1998**, *54*, 2877.
(9) Effenberger, F. *Stereoselective Biocatalysis*; Patel, R. N., Ed; Marcel Dekker: New York, 2000; Chapter 12, pp 321−342.
(10) Gregory, R. J. M. *Chem. Rev.* **1999**, *99*, 3649.
(11) Margolin, A. L. *Enzyme Microb. Technol.* **1993**, *15*, 266.
(12) Bevinakatti, H. S.; Banerji, A. A. *J. Org. Chem.* **1991**, *56*, 5372.
(13) Morrone, R.; Nicolasi, G.; Patti, A.; Piatelli, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1773.
(14) Soboled, A.; Franssen, M. C. R.; Makarova, N.; Duburs, G.; de Groot A. *Tetahedron: Asymmetry* **2000**, *11*, 4559.
(15) Blaschke, G.; Hempel, G.; Muller, W. *Chirality* **1993**, *5*, 419.
(16) Astur Pharma S.A. is a Spanish chemical company devoted since 1985 to the synthesis of raw materials and intermediates for the pharmaceuticals dosage and injectable forms.
(17) Pozo, M.; Pulido, R.; Gotor, V. *Tetrahedron* **1992**, *48*, 6477.
(18) Pozo, M.; Gotor, V. *Tetrahedron* **1993**, *49*, 4321.

Scheme 5



Scheme 6

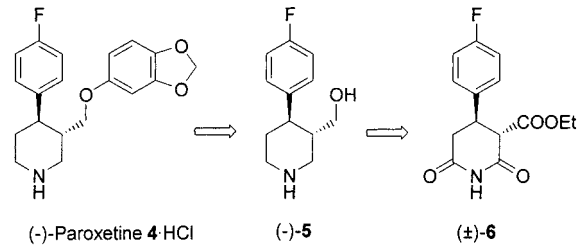


antarctica lipase B (CAL-B) and vinyl carbonate **2** (Scheme 6).[19] The reaction is very enantioselective in 1,4-dioxane, as indicated by the high enantiomeric purity of (*S*)-**2** (ee > 98%) at 50% conversion, which corresponds to $E > 100$. It should be noted that the substrate **1** is always recovered racemic, indicating that (*R*)-**1** spontaneously racemizes in the reaction mixture. Presently, we continue our research on the synthesis of new active carbonates which allows the preparation of (*S*)-zoplicone at multikilogram scale in collaboration with Astur Pharma.

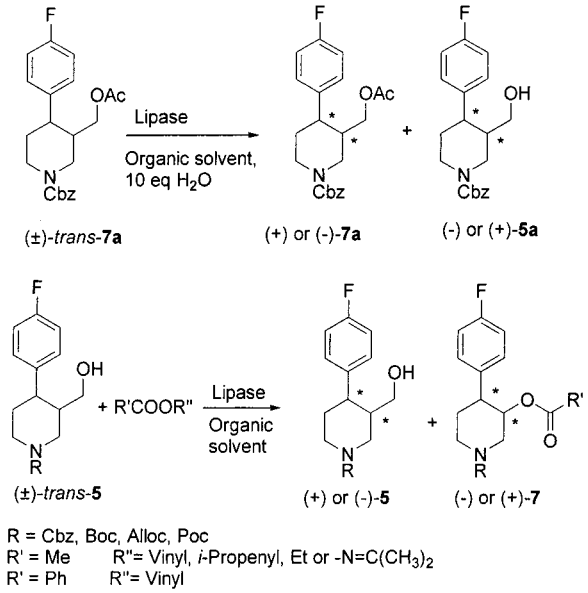
(−)-Paroxetine hydrochloride **4** is a selective serotonin (5-HT) reuptake inhibitor that is used as an antidepresant.[20] An inspection of a possible retrosynthetic pathway of (−)-paroxetine (Scheme 7) reveals that there are two intermediates that can be resolved by an enzymatic process. The enantioselective hydrolysis of *N*-methyl derivative imidoester (±)-*trans*-**6** catalyzed by biocatalytic methods[21] has been described. However, we envisaged a more convenient way to carry out the resolution of the compound **5**.

We have studied the enzymatic hydrolysis of acylated compound **7** with several hydrolases and different reaction

Scheme 7



Scheme 8

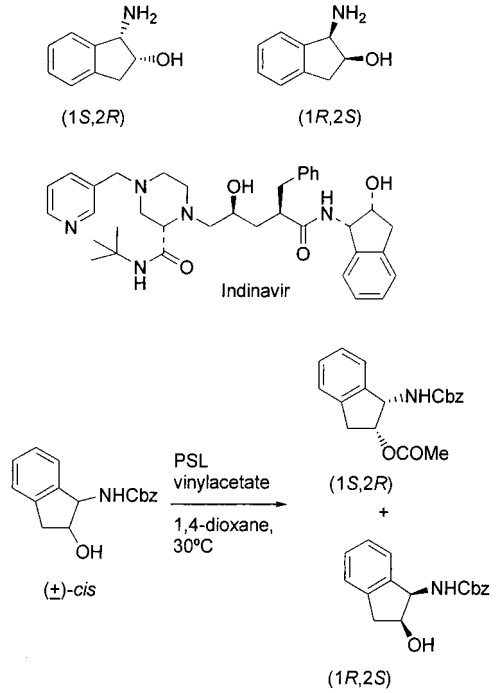


conditions. In most cases low enantioselectivities were observed except with *Candida antarctica* lipase A (CAL-A) where reaction conditions were carried out in hexane ($E = 68$)[22] giving rise to (3*S*,4*R*)-**7**. We also found that better enantioselectivities were obtained when CAL-B-catalyzed acylations of **5** were carried out in organic solvent rather than in water. Furthermore, the remaining alcohol (3*S*,4*R*)-**5** was the correct absolute configuration for the synthesis of (−)-paroxetine. On the other hand, CAL-A catalyzes the enantiomer with the correct configuration, giving (3*S*,4*R*)-**7**. Both enantiomers can be obtained with very high enantiomeric excesses, and both lipases show an opposite selectivity (Scheme 8).[22]

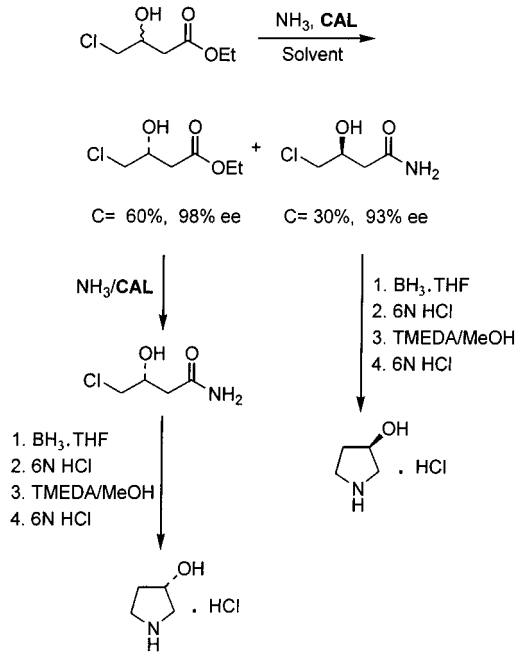
Chiral 1,2-amino alcohols have proved to be a functionally active class of compounds with a wide applicability in medicinal chemistry. For example, (*S*)-2-amino-1-butanol is the chiral precursor of the antitubercular drug ethambutol, and *cis*-(1*S*,2*R*)-1-aminoindan-2-ol is a key component of indinavir, which is a potent protease inhibitor of human inmunodeficency virus (HIV). Recently, we have developed a general strategy for the resolution of (±)-*trans*-[23] and (±)-*cis*-[24] 1,2-aminocyclopentanol and 1,2-aminocyclohexanol. In these studies, the best results were achieved through a lipase-catalysed *O*-acylation of the *N*-Cbz-protected amino

(19) Gotor, V.; Limeres, F.; Garcia, R.; Bayod, M.; Brieva, R. *Tetrahedron: Asymmetry* **1997**, *8*, 995.
(20) Dechant, K. L.; Clissold, S. P. *Drugs* **1991**, *41*, 225.
(21) Gledhill, L.; Kell, C. M. WO Patent 98/02556, 1998; *Chem. Abstr*. **1998**, *128*, 151093v.
(22) de Gonzalo, G.; Brieva, R.; Sánchez, V. M.; Bayod, M.; Gotor, V. *J. Org. Chem*. **2001**, *66*, 8947.
(23) Maestro, A.; Astorga, C.; Gotor, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3153.
(24) Luna, A.; Astorga, C.; Fülop, F.; Gotor, V. *Tetrahedron: Asymmetry* **1998**, *9*, 4483.

Scheme 9



Scheme 10



alcohols. When the reaction was carried out without the protection of the amino group, the enantioselectivity was very low. In Scheme 9 is shown the resolution of *cis*-1-amino-2-indanol. The best reaction conditions for the resolution of all four stereosisomers of 1,2- and 2,1-aminoindanols[25] were using *Pseudomonas cepacia* lipase (PSL) in dioxane and vinyl acetate as the acyl donor ($E > 200$); however, in the case of the *trans*-2-aminoindan-1-ol the enantioselectivity was lower than 100.

Enzymatic Aminolysis and Ammonolysis Reactions. Over the past few years, we have shown[7] the value of the enzymatic aminolysis and ammonolysis reactions for the preparation of chiral amides and resolution of esters or amines. We describe here two procedures of pharmaceutical interest that we have studied in our laboratory: the preparation of both enantiomers of pyrrolidinol-3-ol[26] and the desymmetrization of prochiral diesters.[27] Until now, among tested enzymes, CAL-B is the most efficient biocatalyst for the enzymatic aminolysis and ammonolysis processes.

We have explored the potential of CAL-B for catalysing the resolution by ammonolysis of ethyl (±)-4-chloro-3-hydroxybutanoate. This is done with the aim of using the optically pure amides obtained as starting material for the preparation of both isomers of pyrrolidin-3-ol, since this compound has been employed as a precursor of different compounds of medicinal interest (Scheme 10). Although, the enantioselectivity is not very high, substrate and product can be obtained in enantiopure form to different conversions. The enantiomerically enriched ester (98% ee at 60% conversion) was better converted in the corresponding (*R*)-amide by biocatalytic reaction than by chemical reaction, because in this case the chemical ammonolysis reaction is very slow and other non-identified side products were formed. The cyclization to pirrolidinols takes place by reduction with BH_3 and subsequent heterocyclization.[26]

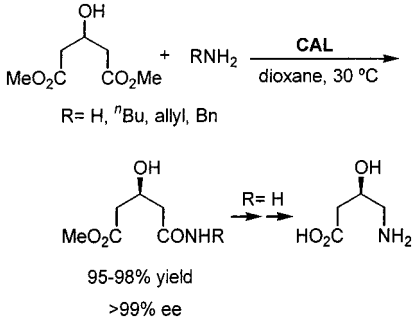
The desymmetrization of prochiral compounds is a process of special relevance in asymmetric synthesis because of the enantiopure compounds which can be obtained. Asymmetrization of diesters and diols has been carried out by enzymatic hydrolysis or transesterification reactions.[28] Reports on the corresponding aminolysis reactions are rather rare, however. Until now, only one example has been published by our group in this context (when we reported the utility of this process for the preparation of optically active amidoesters), and using this strategy we have carried out the synthesis of the biologically active (*R*)-4-amino-3-hidroxybutanoic acid precursor of L-carnitine.

The reaction of dimethyl 3-hydroxyglutarate with ammonia or amines yields the corresponding enantiomerically pure amido esters. The best biocatalyst to perform this reaction is CAL-B. In all solvents tested, the nucleophile reacts with the pro-(*R*) ester group, and the (*S*)-amidoester is always obtained.[27] The compound prepared by the corresponding enzymatic ammonolysis reaction is acetylated and subjected to Hoffmann rearrangement followed by other conventional chemical reactions, giving the corresponding amino acid. We have extended this reaction to different 3-substituted glutarates, and again CAL-B is the best biocatalyst (Scheme 11).

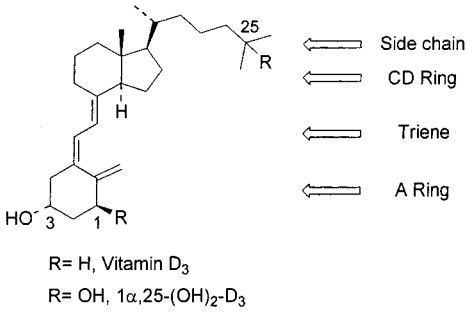
Enzymatic Regioselective Reactions of Natural Products. Selective modifications of natural products, which contain several functional groups with similar chemical reactivities, represent an interesting challenge for organic chemists. Normally, to modify one of these groups, several

(25) Luna A.; Maestro, A.; Astorga, C.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 1969.
(26) García-Urdiales, E.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 721.
(27) Puertas, S.; Rebolledo, F.; Gotor, V. *J. Org. Chem*. **1996**, *61*, 6024.
(28) Chênevenet, R.; Ziarani, G. M.; Morin, M. P.; Dasser, M. *Tetrahedron: Asymmetry* **1999**, *10*, 3117.

Scheme 11



Scheme 12



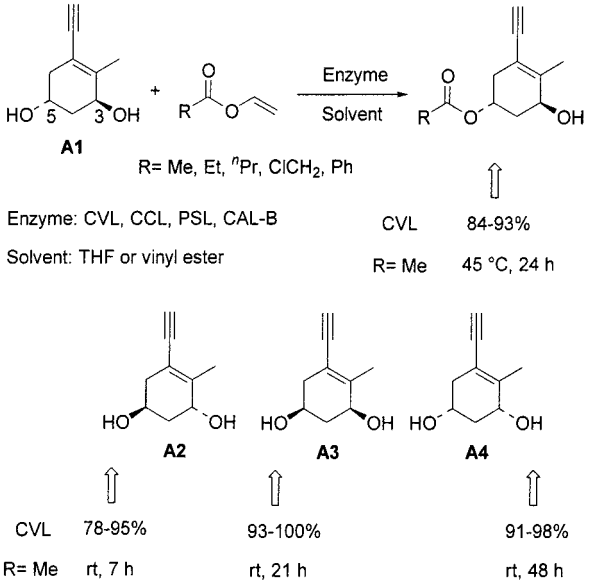
steps of protection and deprotection are necessary. For this reason, it is always of interest to find new regioselective processes, and in this case, biocatalysis offers opportunities that are not possible by chemical catalysis.

Recently, we have reviewed the utility of biocatalysis in two important families of natural products, stereoids[29] and nucleosides.[30] Vitamin D_3 through its hormonally active form 1α,25-dihydrovitamin D_3 (Scheme 12) plays an important role in the endocrine system, and this metabolite exhibits a much broader spectrum of biological activity than the expected. We have worked in chemoenzymatic transformations on the A-ring synthon of 1α,25-dihydrovitamin D_3, with the aim of preparing different kinds of derivatives in a regioselective manner, for the synthesis of new analogues of vitamin D, and of carrying out a biological evaluation of the new compounds obtained.

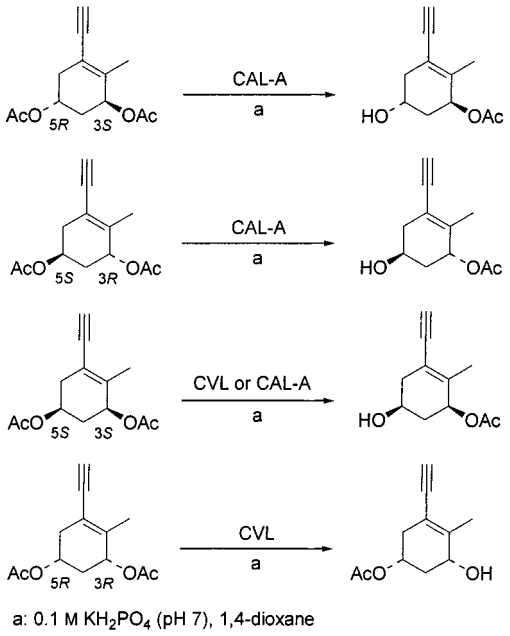
We have studied the enzymatic regioselective acylation[31] and alkoxycarbonylation[32] of the A-ring synthon of the natural isomer (**A1**) and the other three diasteroisomers[33] using different enzymes with several vinyl esters. In Scheme 13 is showed the enzymatic acylation of the four isomers. The best biocatalyst was *Chromobacterium viscosum* lipase (CVL), and this lipase showed a great selectivity towards the hydroxyl group at the five position. However, in the case of the *cis*-isomer (**A4)** an opposite regioselectivity was discovered.[31]

Normally, enzymatic hydrolysis is a complementary reaction of the acylation reaction; for this reason, we have

Scheme 13



Scheme 14

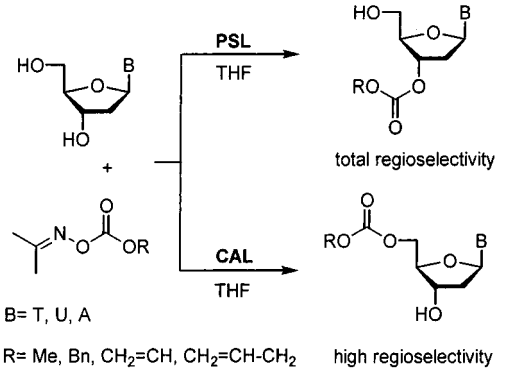


considered it interesting to study the enzymatic hydrolysis of the corresponding diacylated sterosisomers with the aim of obtaining the acylated compound with a regioselectivity the opposite of that achieved in the enzymatic acylation. In fact, this reaction allows the preparation of the other four monoacylated stereoisomers in the opposite position from those obtained in the enzymatic acylation of the diols.[34] The best results were achieved with CAL-A and CVL (Scheme 14). These biotransformations can achieve new derivatives of vitamin D with possible new applications in medicinal chemistry.

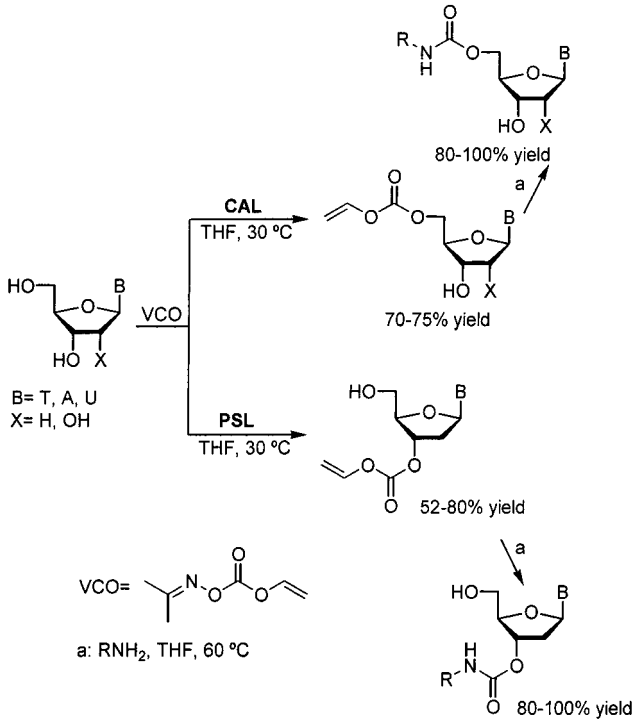
Nucleosides and deoxynucleosides are an important class of compounds because they have important applications in pharmaceutical chemistry, especially because of their anti-

(29) Ferrero, M.; Gotor, V. *Stereoselective Biocatalysis*; Patel, R. N., Ed.; Marcel Dekker: New York, 2000; Chapter 11, p 289.
(30) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319.
(31) Fernández, S.; Ferrero, M.; Gotor, V.; Okamura, W. *J. Org. Chem.* **1995** , *60*, 6057.
(32) Ferrero, M.; Fernández, M.; Gotor, V. *J. Org. Chem.* **1997**, *62*, 4358.
(33) Gotor-Fernández, V.; Ferrero, M.; Fernández, S.; Gotor, V. *J. Org. Chem.* **1999**, *64*, 7504.
(34) Gotor-Fernández, V.; Ferrero, M.; Fernández, S.; Gotor, V. *J. Org. Chem.* **2002**, *67*, 1266.

Scheme 15



Scheme 16



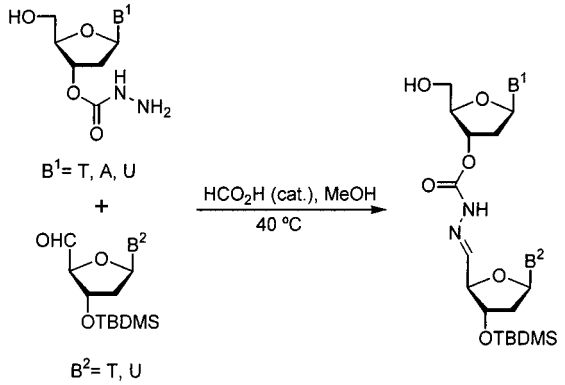
viral and antitumoral properties. Several years ago, we began to apply biotransformations to these compounds; some of these processes are now described.

We reported the utility of the enzymatic alkoxycarbonylation in 2′-deoxynucleosides. Using oximecarbonates as alkoxycarbonylation agents, it was possible to protect the 5′-OH group when CAL catalysed this reaction.[35] However PSL showed the opposite regioselectivity, and the 3′-carbonates were obtained.[36] This reaction allows the alkoxycarbonylation of both hydroxyl groups without needing the previous protection steps (Scheme 15).

Using this strategy we have carried out the introduction of an vinylalkoxycarbonyl group. These compounds allow the preparation of other deoxynucleoside derivatives, and different kinds of nucleoside carbamates can be obtained[37] (Scheme 16). The value of both the nucleoside and carbamate groups in some areas of medicinal chemistry is of note.

(35) Morís, F.; Gotor, V. *Tetrahedron* **1992**, *48*, 9869.
(36) Morís, F.; Gotor, V. *J. Org. Chem.* **1992**, *57*, 2490.
(37) García-Allés, L.; Gotor, V. *Tetrahedron* **1995**, *51*, 307.

Scheme 17



Modulation of gene expression by antisense technologies requires the design of modified oligonucleotides showing enhanced cellular uptake, resistance toward degradation nucleases, and appropriate hybridization to target natural oligonucleotides. It is of interest to consider backbone linkages that contain carbazate groups, because this type of linkage may serve as an attractive surrogate to the phosphodiester linkage, being nonionic, hydrolytically stable, and nonchiral.

The synthesis of backbone-modified dinucleotide analogues is shown in Scheme 17, where the natural phosphodiester linkage is replaced by a 3′-5′-carbazoyl linkage.[38] The bridge is formed via a coupling reaction between an appropriate 3'carbazoyl nucleoside analogue and an aldehyde nucleoside derivative. At the moment, we are using these new dinocleotides as starting material for the synthesis of *antisense* oligonucleotides.

Synthesis of Pharmaceuticals with (*R*)-Oxynitrilases. Oxynitrilases are lyases which catalyse the formation and cleavage of cyanohydrins. The cyanohydrin formation reaction proceeds by stereoselective addition of hydrogen cyanide to aldehydes or methyl ketones to give enantipure α-hydroxynitriles. The use of (*R*)-oxynitrilase for the preparation of chiral cyanohydrins which are used as precursors for the synthesis of many compounds with physiological properties has been growing in the past decade.[9]

Some years ago, we reported a double process of cyanation−transcyanation of *ω*-bromoaldehydes and racemic cyanohydrins[39] as a source of HCN (Scheme 18). This reaction was the first example where it was possible to obtain, in *one pot*, optically active (*S*)-ketone- and (*R*)-aldehyde-cyanohydrins. The reaction was carried out in diisopropyl ether using a crude extract of almond containing (*R*)-oxynitrilase as the biocatalyst. The optically active *ω*-bromocyanohydrins prepared by this method were used as starting materials for the synthesis of (*R*)-2-cyanotetrahydrofuran and (*R*)-2-cyanotetrahydropyran. These functionalized heterocycles are important since they are common structural components of interesting biologically active compounds.

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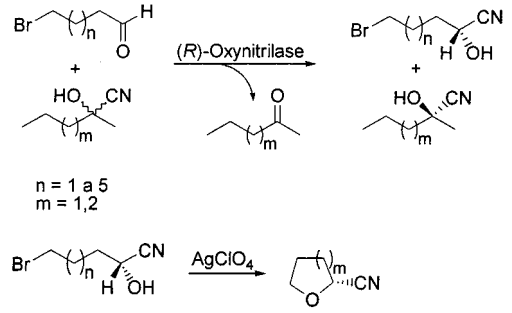
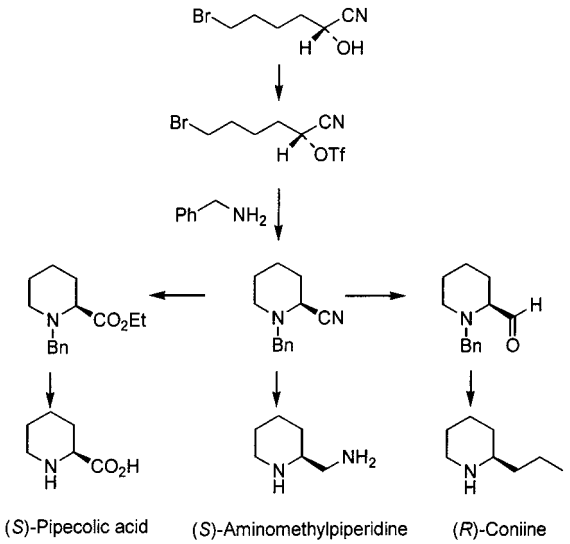
Scheme 18



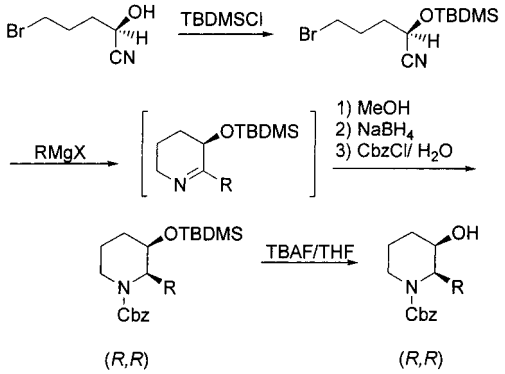
Scheme 19



The use of this kind of lyase has been exploited in organic synthesis by several groups using (*R*)- and (S)-oxynitrilases widely for the synthesis of a great variety of organic compounds. A representative example of the utility of this reaction in the synthesis of pharmaceuticals is the preparation of adrenergic bronchodilators.[40] Recently, we demonstrated the utility of (*R*)-optically active *ω*-bromocyanohydrins for the synthesis of piperidine ring forms, an integral feature of many compounds and synthetic derivatives that exhibit interesting biological activities (Scheme 19). For example, we carried out the preparation of optically active coniine and (*S*)-pipecolic acid.[41]

We extended our methodology to the preparation of 2,3-disubstituted piperidines using (*R*)-(+)-5-bromo-2-hydroxypentanitrile. An enantioselective (*R*)-oxynitrilase-catalyzed

Scheme 20



transcyanation was used to prepare the starting cyanohydrin. The 2,3-substituted piperidine structure constitutes the basic skeleton of many physiologically interesting compounds and occurs, for example, in special nonpeptidic tachykinin receptor antagonists[42] and cardiovascular agents.[43] The chemoenzymatic preparation of these piperidines is depicted in Scheme 20.[44] In these chemical transformations of cyanohydrins to achieve the corresponding heterocycles racemization was not observed.

The enzyme-catalysed cyanohydrin reaction offers new and interesting perspectives for the synthesis of different kinds of chiral cyanohydrins because over the next few years the continued development of new modified oxynitrilases will be, without doubt, of a great utility for the preparation of pharmaceuticals.

Conclusions

At present, many research groups employ biotransformations for the preparation of different kind of organic compounds, and it is well recognized that biocatalysis is of special relevance in pharmaceutical industry for the manufacture of enantiopure compounds. Among the enzymes tested, lipases have demonstrated a great versatility in organic synthesis, and over the past few years, oxynitrilases have emerged as a versatile tool for the synthesis of chiral cyanohydrins, which are important intermediates for the synthesis of products with physiological activity.

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