Review

Stereoselective Synthesis of Terpenoids through Lipase-Mediated Resolution Approaches

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Abstract: This review article focuses on the scientific developments concerning the lipase-mediated synthesis of terpenoids that have been reported in the literature during the last twenty years. More specifically, this review describes in depth the resolution approaches that allow the preparation of the chiral building blocks used for the stereoselective synthesis of bioactive terpenoids. The synthetic methods that have given new and innovative perspectives from a scientific standpoint, and the preparative approaches that possess industrial importance, are described thoroughly.

Keywords: biocatalysts; lipases; enzyme-mediated resolution; terpenoids; stereoselective synthesis; natural products

1. Introduction

Lipases (EC 3.1.1.3), also named triacylglycerol hydrolases, are the enzymes belonging to the esterase family that catalyze the hydrolysis of triglycerides [1]. They have been found in almost all organisms, from bacteria and fungi to animals and plants. These enzymes are very versatile since they accept a wide range of substrates, other than triglycerides, are quite stable at a high temperature, can be used both in water and in nonaqueous organic solvents [2], and do not require cofactors. In addition, different lipases are currently produced in large scale by overexpression in an appropriate microorganism and are commercially available [3]. Therefore, lipases have found many applications in biotechnology for use in applications such as foods, laundry detergents, to convert vegetable oil into fuel, and as catalysts in synthetic organic chemistry. It is worth noting that these enzymes catalyze the reaction of racemic esters or substrates with several hydroxyl groups in high enantio- and regioselectivity and are able to discriminate between enantiotropic groups and between the enantiomers of a racemate.

To this end, lipases have been successfully employed to catalyze the stereoselective hydrolysis or acylation of racemic starting materials, in order to accomplish the asymmetric synthesis of chiral building blocks. Since the stereoisomeric forms of a given compound usually show different biological activities, the industrial production of a number of active pharmaceutical ingredients (APIs), flavors, fragrances, natural products, and other bioactive chemicals [4–12] looks toward their stereoselective synthesis. In this context, the ‘green’ biocatalytic processes, and especially the approaches involving lipase-mediated resolution steps, have gained increasing relevance in the last forty years [13].

This review deals with the synthetic approaches for terpenoids synthesis based on the lipase-mediated resolution. Terpenoids are natural products that are widespread in nature, isolated from plants, animals, fungi, and bacteria. They display an astonishing diversity concerning both chemical structure and biological activity. Their properties as flavor and fragrance ingredients, synthetic building blocks, and pharmaceutical compounds are strictly related to their stereochemistry. Consequently, the development of synthetic methods for their stereoselective preparation is of pivotal relevance. Although the majority of these products were prepared by either chemical synthesis or by extraction from plants, the employment of biocatalyzed
processes for their synthesis or for their transformation has increased considerably. The most widely used enzymatic process is the lipase-mediated kinetic resolution of racemates [11,14]. Enzymatic kinetic resolution (EKR) is a process based on unequal reaction rates of enantiomers by means of an enzyme catalyst. EKR has high relevance in the preparation of terpenoids because it allows access to both enantiomers of the given synthetic building block and thus of the desired natural product.

In principle, the lipase-mediated resolution step is made up of three main approaches. The first consists of the esterification/hydrolysis of a racemic alcohol or its esters, which contains a stereogenic center in its molecular scaffold.

The second is based on the hydrolysis/esterification of a racemic esters/carboxylic acid, which contains a stereogenic center in its molecular scaffold.

The third consists of the lipase-mediated desymmetrization of meso compounds [15], which could be diols, diesters, or diacids. Formally, this approach is not properly based on a resolution reaction, as the starting meso compounds are not made up by two enantiomeric forms.

2. Lipase-Mediated Resolution of Racemic Alcohols or Their Esters

As mentioned above, the lipase-catalyzed esterification/hydrolysis of racemic alcohols or their esters can allow their resolution. This is the most-used method because both esterification and hydrolysis reactions are scalable and well suited to the industrial process requirements. In particular, when alcohols esterification is performed in organic solvents, the work-up procedure is very simple, and the lipase is usually recovered by filtration from the reaction mixtures. In addition, it is possible to accomplish the resolution by means of the kinetic irreversible acylation reaction, using vinyl-esters derivatives as acyl donors.

Lipases catalyze preferentially the transformation of one of two enantiomers of a racemic mixture, leaving the other unaffected. The stereoselectivity of this reaction depends on a number of factors, such as the enzyme specific activity/selectivity toward the substrate, the temperature, the concentration of the reagents, the solvent, and the nature of the acyl moiety.

The most relevant aspect concerns the chemical structure of the alcohol moiety. The steric crowding around the hydroxyl functional group and its distance from the stereogenic center affect the kinetic and the enantioselectivity of the reaction, respectively. Therefore, we can observe great differences among these resolution processes depending on whether the racemic moiety consists of a primary, secondary, or tertiary alcohol.

2.1. Primary Alcohols

A large number of lipases catalyze the esterification/hydrolysis of the primary alcohol derivatives. The reduced steric crowding around the hydroxyl group usually facilitates the reaction, lowering the activation energy gap in the transition state and thus increasing the rate of the transformation. It is worth noting that the stereoselectivity of the lipase-mediated resolution of the primary alcohols is usually inferior if compared with that characterizing the same process, using secondary alcohol derivatives as substrates. This is due to the presence of at least one methylene unit that increases the distance between the hydroxyl group and the stereogenic center. In spite of this fact, other factors, such as the specific chemical structure of the substrate, can affect the stereoselectivity of the reaction. Overall, we can observe that, in the processes successfully used for the resolution of primary alcohol, the chemical framework of the substrate has shown an astonishing influence on the stereoselectivity of the resolution step.

In the field of terpenoids synthesis, a number of relevant studies have been reported to date [16–43], especially concerning the preparation of monoterpenes and sesquiterpenes. Substrates containing a cyclic or polycyclic framework in their chemical structure turned out to be the most suitable ones. An interesting exception was observed regarding the resolution of the acyclic terpene lavandulol (1) (Figure 1).
This fragrance occurs as (R)-enantiomer in lavender oil. The racemic alcohol is a cheap commodity, as it is produced by industrial chemical synthesis. In spite of this fact, the natural enantiomer proved to possess better odor quality [16], if compared with the racemic material or with the (S)-enantiomer. A first resolution method was developed, using immobilized Candida antarctica lipase (Novozym 435) as the catalyst and acetic acid as the acyl donor [17]. Even if the formed (R)-acetyl lavandulol was obtained in modest enantiomeric purity, the process holds industrial relevance, as it makes use of immobilized lipase and can be performed in supercritical carbon dioxide [18]. Interestingly, opposite stereoselectivity was observed while using porcine pancreas lipase (PPL) and vinyl acetate [19,20]. Using the latter enzyme, the acetate (S)-2 was formed in good enantiomeric purity. In addition, the reaction proceeded with high enantioselectivity, as confirmed by the assessment of an enantiomer ratio ($E$) value of about 42.

Concerning substrates that contain cyclic frameworks in their chemical structure, we report below a large number of noteworthy processes. A first, relevant approach takes advantage of the chemical transformation of an easily available industrial intermediate into a diastereoisomerically pure racemic alcohol derivative. The following lipase-mediated resolution step affords the enantioenriched forms of the same diastereoisomer. Accordingly, racemic diol 3 and 6, both possessing four stereocenters, were prepared from isopulegol and 4-methyl-tropolone, respectively (Figure 2).

The lipase-PS-mediated acetylation reactions were performed by using vinyl acetate and gave enantioenriched monoacetates (+)-4 [21] and (+)-7 [22], respectively, with complete regioselectivity toward the primary hydroxyl group and good enantioselectivity. The unreacted diol (−)-3 was oxidized to lactone (+)-5, which is a relevant flavor component of Italo-Mitcham black peppermint oil, whereas acetate (+)-7 is a chiral building block for the synthesis of the guaiane sesquiterpenes.
A second approach is based on the use of a substrate prepared through the chemical transformation of an easily available enantiopure terpene derivative. The latter compound is functionalized with a primary alcohol group, with concurrent introduction of a new stereocenter. The resulting mixture of enantiopure diastereoisomeric alcohols is submitted to the lipase-mediated resolution step. The overall process allows the separation of the two enantiopure diastereoisomers, with an efficiency that depends on the enantioselectivity of the enzymatic transformation.

Below are reported two examples of this approach (Figure 3). (+)-Limonene and (−)-carvone were chemically manipulated in order to obtain the two diastereoisomeric mixtures of the primary alcohol 8 [23] and 10 [24], both possessing 4R absolute configuration. A preliminary screening indicated that PPL catalyzes the acetylation of these alcohols with higher stereoselectivity and without noticeable diastereoselectivity. Therefore, this lipase was selected as the enzyme of choice to perform the separation of the diastereoisomers. Accordingly, the mixtures of alcohols 8a/8b and 10a/10b were acetylated, using vinyl acetate as acetyl donor and PPL as the catalyst, to afford acetates 9a and 11a and unreacted alcohols 8b and 10b. The diastereoisomeric purity of the four obtained compounds was increased by their transformation into the corresponding 3,5-dinitrobenzoyl esters, followed by crystallization from hexane. After chemical hydrolysis, the p-menth-1-en-9-ol isomers 8a and 8b and the p-menth-1,5-dien-9-ol isomers 10a and 10b were produced in very high diastereoisomeric purity. As (−)-limonene and (+)-carvone are easily available from the chiral pool, the described procedure gives access also to the enantiomeric form of the above-described terpenols, possessing 4S absolute configuration. Overall, all of these compounds can be regarded as chiral building blocks for the synthesis of p-menthane terpene and bisabolane sesquiterpene.

Figure 3. The PPL-mediated resolution of a mixture of two enantiopure diastereoisomeric alcohols. An application to the preparation of the chiral building blocks p-menth-1-en-9-ol (8) and p-menth-1,5-dien-9-ol (10). Reagents and conditions: (a) NaOH/MeOH; (b) 3,5-dinitrobenzoyl chloride/Py; (c) crystallization from hexane; and (d) BF3·Et2O.

A pertinent example is illustrated with the acid-catalyzed cyclization of alcohol 10a, to give the monoterpenes (−)-dill ether 12, which is the character-impact flavor of dill oil.

Another important topic concerns the difference of the lipase enantioselectivity among regioisomers with very similar chemical frameworks. As a first instance, we reported the case of the cyclogeraniol isomers (Figure 4). α-Cyclogeraniol 13 was resolved, using vinyl acetate as acetyl donor and lipase PS...
as catalyst [25]. Using γ-cyclogeraniol 14 as the substrate, the same acetylation conditions and the same enzyme gave the corresponding acetate in very low enantioselectivity (E = 2.3). Other enzymes were screened [26], and only the combined use of lipase from Candida antartica and vinyl propionate allowed the resolution of this isomer, although with modest enantioselectivity (E = 6.7). Similarly, the resolution of the sesquiterpenes drimenol (15) and albicanol (16), by means of this enzymatic approach, was extensively studied [27–30]. Moreover, in these cases, to achieve suitable enantioselectivity, specific acylation conditions were identified. Accordingly, lipase PL 266/isopropenyl acetate [28] and lipase QL/vinyl myristate [29,30] allowed the resolution of alcohols 15 and 16. Overall, the obtained enantioenriched derivatives have been used for the synthesis of a number of bioactive terpenoids. As representative examples, the compounds (−)-13, (+)-14, (+)-17, and (8aS)-18 were used as chiral building blocks for the preparation of the fragrance (S)-α-ionone (19) [31], of the sesterpene (+)-luffarin P (20) [26], of the naturally occurring enantiomeric form of drimenol (15) [28], and of the sesquiterpene quinone (−)-tauranin (21) [30], respectively.

![Diagram](image_url)

**Figure 4.** The lipase-mediated resolution of the two couples of substituted cyclohexenylmethanol regioisomers 13, 14 and 15, 16. Compounds 19, 20, (−)-15, and 21 are the natural products synthesized by using the chiral building blocks 13, 14, 17, and 18, respectively.

The four substrates described above are two couples of regioisomers that differ from each other only for the position of the double bond. In these cases, the bonding patterns of the chiral centers are the same for all isomers. When the structural difference between regioisomers also involves the stereogenic center, the enzymatic transformation of two regioisomers could proceed with much more different enantioselectivity. As a representative example, we report the resolution of the two epoxy-cyclohexenylmethanols, 22 and 23 (Figure 5). Novozym 435 was identified as the most suitable lipase to perform the resolution of α-epoxyalcohol 22 [32], as it catalyzes the acetylation step with the higher enantiomer ratio (E = 10), if compared with other commercial lipases.
The application of this protocol leads to an overall increasing of the resolution process’s efficiency. Some relevant examples are described in Figure 6.

The chiral center of β-epoxyalcohol acetate 23 is part of the oxirane ring, and this structural difference leads to a huge modification of the reactivity. Actually, lipase P catalyzes the hydrolysis of this ester [33] with very high enantioselectivity ($E = 1600$), which is about 160 times higher than that measured for the acetylation of alcohol 22.

The obtained enantioenriched derivatives (+)-24 and (+)-25 were used as starting materials for the stereoselective synthesis of the two natural terpenoids, (+)-tetrahydroactinidiolide 26 and (+)-abscisic acid 27, which are a relevant vegetal flavor component and a plant hormone, respectively.

The problem of the low enantioselectivity of the lipase-mediated resolution of some primary alcohol derivatives can be overcome by employing a couple of lipases that catalyze the same chemical transformation of the same substrate with opposite stereoselectivity. In these cases, it is possible to sequentially run two opposite enzymatic reactions (e.g., acylation/hydrolysis). The lipase used as the catalyst in the first step must possess opposite selectivity of the lipase employed in the second one. The application of this protocol leads to an overall increasing of the resolution process’s efficiency. Some relevant examples are described in Figure 6.

![Figure 5](image-url)

**Figure 5.** The lipase-mediated resolution of the two substituted epoxy-cyclohexylmethanol regioisomers, 22 and 23. Chiral building blocks 24 and 25 was used for the synthesis of the flavor tetrahydroactinidiolide 26 and the vegetal hormone 27, respectively.

![Figure 6](image-url)

**Figure 6.** Example of resolution procedures that exploit the opposite selectivity of two different enzymes. Preparation of the two synthetic building blocks, 29 and 31, that were used for the synthesis of the terpenoids (−)-thallusin 30 and the enantiomers of the monoterpene linaloyl oxide 33, respectively.
A recent research study established [34] that the enantiomeric forms of the diol derivative 28 are useful chiral building blocks for the stereoselective synthesis of the algal growth factor thallusin 30. Unfortunately, the commercially available lipases transform substrate 28 with modest enantioselectivity. Therefore, the observation that lipase PS-30 and lipase M catalyze the hydrolysis of the acetate 28 with opposite enantioselectivity was exploited for its resolution. Accordingly, the hydrolysis of racemic 28 using lipase PS-30 gave (−)-diol 29 and the unreacted acetate (−)-28. The latter compound was then separated and submitted to lipase M-catalyzed hydrolysis, to afford diol (+)-29, whose absolute configuration is suitable for (−)-thallusin synthesis. Diol (+)-29 was obtained in good enantiomeric purity (92%) and was employed to accomplish the first stereoselective synthesis of natural thallusin.

Similarly, the enantiomeric forms of the tetrahydropyranyl alcohol 31 have been used for the synthesis of both terpenes [35] and sesquiterpenes [36]. A practical large-scale resolution procedure [35] exploits the opposite enantioselectivity of Novozym 435 lipase and lipase AK in the acetylation of racemic 31. Hence, racemic 31 was treated with vinyl acetate in t-BuOMe, using Novozym 435 as the catalyst. The acetylation reaction was prolonged until about 65% conversion was reached. In accord with the specific lipase enantioselectivity (E = 16.3), the unreacted alcohol (−)-31 was isolated in about 34% yield and in very high enantiopurity (98% ee). On the contrary, the acetate (+)-32 possessed low optical purity and was hydrolyzed by using NaOH in methanol. The resulting alcohol was submitted to a second acetylation step, using lipase AK as the catalyst. Indeed, the latter enzyme catalyzed the esterification of (−)-31, which was transformed in the corresponding acetate. As (−)-31 is the minor component of the enantiomers’ mixture, the enzymatic reaction increased the enantiomeric purity of the unreacted alcohol.

After the acetylation reaction reached a conversion of about 60%, the alcohol (+)-31 was isolated in about 35% overall yield and with 98% ee. Nearly racemic acetate 32 was also obtained, and it could be hydrolyzed to recover further alcohol, to be used in a new resolution procedure. The two enantiomeric forms of the alcohol 31 were employed for the first stereoselective synthesis of both enantiomers of the flavor linaloyl oxide (33).

The enantioselectivity of the lipase-mediated resolution of primary alcohols can be affected by the presence of specific functional groups in the substrate framework, even if in a position very far from the stereogenic center.

A very singular case concerns the lipase-catalyzed acetylation of substituted 2-aryl-propanols. The enantioselectivity of these transformations was dependent on the type of lipase used, and a recent study [37] proves that PPL is the more versatile lipase, catalyzing the acetylation with an enantiomeric ratio value that ranges from 1 up to 144, depending on the substrate used (Figure 7).

The type of substituents, and particularly their position on the aromatic ring, strongly affected the selectivity of the reaction. Substituents situated at the para-position to the aliphatic chain greatly increased the enantioselectivity, whereas those placed at either the meta- or ortho-position displayed the opposite effect. Amongst the type of the substituents investigated, the methoxy group mostly increased the enantioselectivity. These results were exploited by the large-scale resolution of substituted 2-aryl-propanols 34c, 34d, 34e, 34f, and 34g, whose enantiomeric forms are relevant building blocks in the enantioselective synthesis of different phenolic sesquiterpenes and norsesquiterpene [37–40].

The combination of the aforementioned resolution processes with a few straightforward chemical transformations allowed the synthesis of the bisabolane sesquiterpenes turmeronol B (36) [37], curcuphenol, xanthorrhizol (37), glandulone A (38), curculiol, turmerone, curculiol-10-one (38), (−)-1,2,11-trihydroxy-1,3,5,9-bisabolatetraene (39) [39], and of the trinorsesquiterpene tetratones aristalegone and schiffnerone-B [40].
with good enantioselectivity. This resolution approach was applied in the stereoselective synthesis of the norsesquiterpene. The same enzyme catalyzes the reaction of vinyl 3-(4-trifluoromethylphenyl)propanoate with racemic 

Catalysts

bioactive sesquiterpene phenols were used for the asymmetric synthesis of the norsesquiterpene (+)-turmeronol B (36), (+)-xanthorrhizol (37), (+)-glandulone A (38), and (+)-1,2,11-trihydroxy-1,3,5,9-bisabolatetraene (39), respectively.

For some substrates, the enantioselectivity of the lipase-mediated resolution process can be increased through the selection of a suitable acylating reagent. The resolution of 2-aryl-heptanol 40 is a representative example (Figure 8) [41]. The acetylation of the latter alcohol with vinyl acetate and using lipase PS as catalyst affords preferentially the (S) enantiomer of the acetate 41 with an enantiomer ratio of 26. The same enzyme catalyzes the reaction of vinyl 3-(4-trifluoromethylphenyl)propanoate with racemic 40, to give the (S) enantiomer of the ester 42. The enantioselectivity of the latter reaction was about twelve times as high as that measured for the preparation of acetate 41. Enantiomerically pure derivative (S)-42 was used for the asymmetric synthesis of the norsesquiterpene (+)-5,6-dehydrosenedigal tale 43.

Lipases can catalyze chemical transformations in both a stereoselective and regioselective fashion. Both kinds of selectivity were exploited for the resolution of 5-acetoxy-4-aryl-(2E)-pentenoate derivatives [42]. These substrates contain a primary alcohol acetate and a α,β-unsaturated acid methyl ester. Some selected lipases are able to exclusively hydrolyze the acetate functional group with good enantioselectivity. This resolution approach was applied in the stereoselective synthesis of some bisabolane sesquiterpenes (Figure 9) [43]. Accordingly, racemic compound 44 was hydrolyzed, using diisopropyl ether/water and lipase OF 360 as the catalyst. Primary alcohol (−)-45 was obtained in good enantiomeric purity and was employed as a chiral building block for the synthesis of the bioactive sesquiterpene phenols (+)-curcuphenol (46) and (+)-curcudiol (47).
2.2. Secondary Alcohols

As mentioned in the previous paragraph, due to the reduced distance between the hydroxyl group and the stereogenic center, the stereoselectivity of the lipase-mediated resolution of the secondary alcohols is usually greater than those characterizing primary alcohol derivatives.

The factors that affected the selectivity of the enzymatic transformations of the secondary alcohols are related to the specific chemical structure of the substrate, with special relevance of the symmetry degree of the molecule and of whether the stereogenic center is part of a ring.

The latter structural feature is seldom very important. We report, below, the description of the lipase-mediated resolution processes of two structurally related compounds (Figure 10).

(R)-6,7-Dihydroxylinalool 48, a naturally occurring triol, was treated with vinyl acetate in presence of lipase catalyst. Out of eleven commercial lipases tested, only Novozym 435 afforded the acetate 49 in good enantiomer excess (E = 38.5) [44]. Overall, all the acetylation experiments indicate a low reactivity of the substrate, which needs a very long time to reach a suitable conversion. On the contrary, different lipases catalyze the acetylation of racemic linalool oxide diastereoisomers with high efficiency and selectivity [45]. The latter compounds are important natural flavors, and their resolution was studied in depth. The reaction of trans-linalool oxide 50 with vinyl acetate and catalytic lipase PS afforded acetate (+)-52 in good enantioselectivity (E = 39), whereas cis-linalool oxide 51, in the same experimental conditions and using CRL as catalyst, was transformed into acetate (−)-53, with very high enantioselectivity (E = 261).

Figure 9. Lipase-mediated resolution of 5-acetoxy-4-aryl-(2E)-pentenoate derivatives. Regio- and stereoselective hydrolysis of the primary alcohol esters. Chiral building blocks (−)-45, prepared by resolution of racemic acetate 44, was used for the synthesis of the bisabolane sesquiterpene (+)-curcuphenol (46) and (+)-curcudiol (47).

Figure 10. Lipase-mediated resolution of (6R)-6,7-dihydroxylinalool (48) and of trans- and cis-linalool oxide 50 and 51, respectively.

We can observe that the secondary alcohol group of compound 48 (drawn in folder configuration) possesses a steric hindrance similar to those of linalool oxide diastereoisomers. Therefore, when the substrate conformation is blocked in the tetrahydropyranyl ring, both reactivity and selectivity of the acetylation increase considerably.

Less sterically crowded open-chain secondary alcohol derivatives were successfully resolved through lipase catalysis and then employed in terpenoids synthesis. In particular, compounds...
possessing the generic \((E)\)-4-aryl/cyclohexenyl-but-3-en-2-ol framework proved to be suitable substrates for lipase-mediated resolution.

As a first example, we report the resolution procedure of allyl alcohol \(54\), which was acetylated with very high enantioselectivity, using vinyl acetate in presence of lipase PS (Figure 11) \([46]\). The obtained enantiopure ester \((+)-55\) was transformed into acid \(56\) through a well-established procedure \([47]\) based on Claisen rearrangement. The latter compound, which possess a defined stereocenter in benzylic position, was used as a starting material for the stereoselective synthesis of the natural sesquiterpene \(cis\)-methoxy-calamene \((57)\).

The resolution of compounds possessing the \((E)\)-4-cyclohexenyl-but-3-en-2-ol framework was largely employed for the preparation of enantioenriched apocarotenoid and norterpenoid natural products, such as ionone \([31]\) and irone \([48]\) isomers, respectively. In addition, other enantiopure 4-substituted-butan-2-ol derivatives were obtained through the same resolution approach and were used as starting materials for the enantioselective synthesis of different apocarotenoid derivatives \([31]\). Selected representative example are illustrated in Figure 12. Accordingly, synthetic \(\alpha\)-ionone \((19)\) and \(\gamma\)-ionone \((58)\) isomers were transformed into the diastereoisomerically pure racemic alcohols \(59-66\). The following lipase-PSmediate acetylation afforded enantioenriched derivatives \(63-66\), respectively. The latter compounds were chemically manipulated, in order to obtain the single isomeric forms of the natural fragrances \(\alpha\)-ionone \((19)\) \([49]\), \(\alpha\)-damascone \((67)\) \([50]\), \(\gamma\)-dihydroionone \((68)\) \([51]\), and 7,11-epoxymegastigma-5(6)-en-9-one \((69)\) \([52]\), which are the olfactory active component of the violet, rose, ambergris, and passiflora scent, respectively.

A larger number of terpenes and terpenoids have been prepared by using enantioenriched building blocks obtained by lipase-mediated resolution of cyclic secondary alcohols. This approach has been exploited for the synthesis of the \(p\)-menthane terpenes. In particular, \(p\)-menthan-3-ol monoterpens are suitable substrates for the enzymatic resolution process (Figure 13).

Out of the eight menthol stereoisomers, \((-)\)-menthol \((70)\) is the only enantiomer that can be used as flavor/fragrance. Since the racemic mixture of this alcohol is an affordable commodity secured by the chemical industry, a number of studies on its resolution have been reported, both in the academic and patent literature \([53-64]\). To this end, lipase from \(Candida\) \(rugosa\) (CRL LIP1), lipase PS, lipase from \(Candida\) \(cilindracea\) (CCL), lipase from \(Pseudomonas\) \(alcaligenes\), lipase AK, and lipase from \(Thermomyces\) \(lanuginosus\) were successfully employed. In addition, some of the latter processes take advantage of the use of reverse micelle system \([56]\), specific immobilization procedures \([57,58]\), ionic liquids \([59]\), green organic solvents \([62]\), and deep eutectic solvents \([64]\).
The resolution of other $p$-menthan-3-ol monoterpenes, although less investigated, has given very good results [55]. The lipase-PS-mediated acetylation of the eight stereoisomers of isopulegol afforded regio- and stereoselectively only the acetate of ($-$)-isopulegol (71) in high enantipurity. The same enzyme was successfully used for the resolution of the allyl alcohols trans-piperitol (72), cis-piperitol (73), and cis-isopiperitenol (74), whose acetylation reactions are characterized by a very high enantioslectivity ($E > 500$). Similarly, the enantiomeric forms of the trans-$p$-menthan-1,8-dien-5-ol (75) [65] were obtained by the same resolution procedure and were used in the synthesis of paeonilactone B [66].

Another relevant resolution procedure concerns $p$-menthan-3,9-diol isomers (Figure 14) [21]. In this case, the enzymatic acetylation affords both monoacetate and diacetate derivatives. The reaction proceeds stepwise, with two different kinetics. The primary alcohol is esterified rapidly, without stereoselectivity, whereas the secondary alcohol is acetylated slower, with a very high enantioslectivity ($E > 650$). Overall, starting from a diastereoisomerically pure $p$-menthan-3,9-diol, the acetylation process

Figure 12. Lipase-mediated resolution of the racemic ionol derivatives 59–62, applied to the enantioselective synthesis of the apocarotenoids $\alpha$-ionone (19), $\alpha$-damascone (67), $\gamma$-dihydroionone (68), and 7,11-epoxymegastigma-5(6)-en-9-one (69).

Figure 13. Compounds 70–75 are $p$-menthan-3-ol monoterpenes obtained by lipase-mediated resolution. The lipase used and its stereoselectivity are indicated next to the alcohol.
allows for the separation of the two enantiomeric forms as monoacetate and diacetate derivatives. Accordingly, racemic diols 76 and 80, easily available by chemical synthesis, were submitted to the lipase-PS-mediated resolution process, to afford monoacetate 77 and 81 and diacetate 78 and 82, respectively. Enantiopure compounds (−)-78 and (+)-81 have been used as chiral building blocks for the stereoselective synthesis of the natural monoterpenes (−)-mintlactone (79) and (−)-wine lactone (83) [67], respectively, which are relevant flavor components of the peppermint oil and white wines.

![Figure 14](image)

Figure 14. Lipase-mediated resolution of the racemic p-menthan-3,9-diol derivatives 76 and 80 and use of the chiral building blocks 78 and 81 for the enantioselective synthesis of the natural flavors mintlactone (79) and wine lactone (83), respectively.

The lipase-mediated resolution was applied to different ionone or damascone derivatives possessing a secondary alcohols functional group belonging to the cyclohexene ring. The developed processes provided a number of valuable chiral building blocks that are suitable for the synthesis of apocarotenoids and terpenoids (Figure 15). The enantiomers of 4-hydroxy-β-ionone and 4-hydroxy-β-damascone were separated by means of PPL-catalyzed acetylation reaction, which affords derivatives 84 and 85 [68]. Similarly, compound 86 was obtained by acetylation of the corresponding racemic diol, using lipase PS as catalyst [69]. The fractional crystallization of the enantioenriched acetate that followed afforded enantiopure 86, which was transformed into (−)-8,9-dehydrotheaspirone (87), a component of nectarine flavor.

Ultimately, 4-hydroxy-γ-ionone turned out to be a very useful synthetic precursor of different terpenoids. The racemic cis diastereoisomeric form of the latter compound is available by chemical synthesis [70]. The resolution of this alcohol was successfully performed by using lipase-PS-mediated acetylation reaction. The obtained enantiopure acetate (+)-88 is a versatile chiral building block that has been employed for the synthesis of a number of natural compounds that possess different chemical frameworks. Some representative examples include the ambergis components (+)-γ-dihydroionone (68) and (−)-α-ambrinol (89) [71], the sesquiterpene (+)-trans-monocyclofarnesol (90) [72], the meroterpene hydroquinone (+)-metachromin V (91) [73], and different diterpene derivatives, [74] such as (+)-ambliol A (92) [75].

Further terpenes and terpenoids have been prepared by using enantioenriched building blocks obtained by lipase-mediated resolution of cyclic secondary alcohols. This large group of natural compounds possesses chemical frameworks very different from each other, and the features of the developed enzymatic processes are strictly dependent on the structures of the substrates involved in the resolution step. The most representative secondary alcohols are cyclohexane or cyclopentane derivatives [76–89], even if cycloheptane [90] and cycloundecane [91] derivatives have been resolved by using lipases (Figure 16).
Concerning cyclohexane secondary alcohols, the chiral building blocks 93–97 were obtained by acetylation or hydrolysis of the corresponding alcohols (93, 95, and 96), diol (94), and butyrate (97) derivatives. More in detail, enantioenriched acetates 93 [76] and 94 [77] were transformed in different γ-cyclogeraniol derivatives, which are synthetic precursors of a number of natural products, such as the marine terpenenes luffarin P (20) [26] and pallescensin-2 (98) [78]. Optically active alcohol 95 [79] was employed in the synthesis of many terpenes [10], of which the sesquiterpene (+)-dehydro-β-monocyclonerolidol (99) is reported as a representative example. Bicyclic esters 96 [80] and 97 [81] were used as starting compounds, to accomplish the first synthesis of the cytotoxic sesquiterpene (+)-glaucescenolide (100) and of the formal synthesis of the antitumor sesquiterpene (+)-confertin (101), respectively.

Concerning cyclopentane secondary alcohols, the enantioenriched compounds 102–106 were obtained by acetylation or hydrolysis of the corresponding racemic alcohols. Acetate 102 [82] was specially prepared and used in the multistep synthesis affording the optically active azulene derivative 109, useful for terpenoid synthesis. The ester 103 [83] has been employed for the preparation of the herbetane sesquiterpenes (−)-α-herbetenol (110), (−)-herbetenediol, and (+)-1,14-herbetenediol. A very similar chiral building block [84] was used for the synthesis of the cuparene sesquiterpene β-cuparenone [85], whereas the alcohol 104 [86] was employed in the synthesis of the monoterpene (−)-β-necrodol (111). Diol 105 [87] was transformed into tricyclic sesquiterpene kelsoene (112), while lactone 106 [88] was converted into bicyclic lactone 113, which is a useful key intermediate in the synthesis of isoprostane-like cyclopentanoids and of natural iridoids.

A singular resolution process regards the preparation of hemiacetal 107 [89]. The lipase-mediated hydrolysis of the corresponding racemic acetate afforded enantiopure 107, which was transformed into natural iridoid lactone (−)-nepetalactone (114).

Lastly, other cyclohexane secondary alcohols have been resolved by means of lipase. As relevant examples, we report only the studies on the preparation of the cycloheptenol karahanaenol [90] and of the cycloundecatrienol acetate 108. The latter compound is a precursor of (+)-zerumbol (115) [91], a sesquiterpene that is present in ginger and is a potential starting material for conversion to the anticancer-agent paclitaxel.
2.3. Tertiary Alcohols

The esterification/hydrolysis of the tertiary alcohol derivatives is very difficult. The high steric crowding around the hydroxyl group hampers this reaction. Both chemical and enzymatic catalysts allow the transformation ratio to be increased. Despite this fact, the natural substrates of the lipases are glycerides, which do not contain tertiary alcohols in their chemical frameworks. Consequently, only few tertiary alcohols are lipase substrates.

Due to the high synthetic relevance of the resolution processes involving tertiary alcohol derivatives, the catalytic activity of a huge number of lipases have been investigated. Concerning terpene derivatives, the most studied substrate is the monoterpene linalool. This compound possesses a simple chemical structure, is easily available in racemic form, and is a natural product of large industrial use. Therefore, linalool has been used as a substrate model, to check the lipase selectivity and activity [92–94]. Even with these premises, only a limited number of lipases allow linalool resolution, and no resolution
processes of further terpenes are worth mentioning. To date, the resolution of the above-mentioned terpene has been successfully accomplished by using esterases [95,96], instead of lipases.

3. Lipase-Mediated Resolution of Racemic Acid Derivatives

As mentioned in the introduction, lipases can preferentially catalyze the transformation of one of the two enantiomers of a racemic esters/carboxylic acid, which contains a stereogenic center in its molecular scaffold. In principle, this approach can be used to perform resolution processes, as described for primary alcohol derivatives. Despite this fact, racemic acids are usually resolved by using other techniques, such as the preparation of diastereoisomeric mixtures of poorly soluble derivatives. The salts obtained by reaction of the racemic acids with a suitable enantiopure amine are submitted to fractional crystallization, in order to collect the less soluble diastereoisomer.

Therefore, a limited number of lipase-mediated resolution processes of carboxylic acid derivatives have been employed for terpenoids synthesis. The most interesting applications concern the resolution of 3-aryl-butanoic acid derivatives (Figure 17). Accordingly, ethyl ester 116 [97] was hydrolyzed by using lipase PS-C as the catalyst. The resulting acid (117) was obtained in very high enantiomeric purity, and the carboxylic acid functional group was manipulated in order to allow the transformation of 117 into bisacumol acetate, as a mixture of the two diastereoisomers 118 and 119. The target sesquiterpene bisacumol (120) possesses a defined S configuration at the secondary alcohol stereocenter. Therefore, the mixture of the acetates 118 and 119 was hydrolyzed, using lipase-PS-C as the catalyst, again. The unreacted ester 119 was then hydrolyzed to afford natural (S,S)-bisacumol (120). Similarly, enantiopure acid 122 was obtained by lipase-PS-IM-mediated hydrolysis of the methyl ester 121 [98]. The obtained chiral building block was then used for the stereoselective synthesis of the naturally occurring enantiomer of trans-trikentrin A (123), an indole terpenoid possessing potent antitumor activity.

![Figure 17. Lipase-mediated resolution of the racemic esters 116 and 121. Transformation of the obtained chiral building blocks into sesquiterpenes (S,S)-bisacumol (120) and (+)-trans-trikentrin A (123).](image)

4. Lipase-Mediated Desymmetrization of Meso Compounds

The desymmetrization of meso compounds consists of chemical transformations that eliminates one or more elements of symmetry of the substrate. Enantioselective enzymatic desymmetrizations constitute a very interesting alternative to kinetic resolution. Actually, resolution processes allow enantiomers’ separation, with a maximum yield of 50%, whereas, in principle, desymmetrization reactions can give a maximum yield of 100%. For this reason, an increasing number of enzymatic desymmetrization studies applied to synthesis have been published in the literature [15] during the recent past years. The downside of these processes lies in the inherent symmetry of the substrates themselves that can be reflected into low enantioselectivity of the lipase-catalyzed transformations.
Despite this aspect, different lipase-mediated desymmetrization procedures have been successfully employed for terpenoids synthesis.

The lipase-mediated acetylation of substituted 2-aryl-propane-1,3-diols was exploited for the synthesis of a number of terpenes (Figure 18). These meso derivatives proved to be very versatile substrates for the desymmetrization procedure. For example, monoacetate 124 with R absolute configuration was obtained in 90% yield and 99% ee through acetylation of 2-(p-tolyl)propane-1,3-diol, using vinyl acetate and PPL as the catalyst [99]. Compound 124 was then used for the synthesis of the bisabolane sesquiterpene (R)-turmerone (127). Similarly, the same lipase allowed the preparation of the monoacetate (R)-125 [100], which has been employed as starting compound for the preparation of (−)-heliannuol A (128), a sesquiterpenoid exhibiting strong allelopathic activity. Remarkably, the meso diol precursor of (R)-125 was transformed into monoacetate (S)-125 [101], using CRL and vinyl acetate. Enantioenriched compound (S)-125 was then converted into the sesquiterpene quinone (S)-curcuquinone (129). These two studies demonstrate that it is possible to obtain both R and S enantiomers of the monoacetate 125 by using PPL or CRL, respectively. These two enantiomers were then employed in a number of studies aimed at stereoselective sesquiterpenes synthesis [102–106].

![Diagram of lipase-mediated desymmetrization of meso compounds](image)

Figure 18. Lipase-mediated desymmetrization of meso compounds. The figure describes the enantioenriched compounds obtained by desymmetrization (124, (R)-125, (S)-125, 131, and 132) and resolution (126), the lipase used (below chemical structure), and the terpene derivatives prepared by using the described chiral building blocks (127–130, 133, and 134).

The example of compound 126 [107] is completely different. The meso diol cis-cyclopent-4-ene-1,3 diol was derivatized in order to give cis-1,4-4-cumyloxy-2-cyclopenten-1-ol that was devoid of a symmetry plan. Therefore, the following lipase-PS-mediated acetylation proceeded with very high enantioselectivity (>99% ee), but the conversion cannot exceed 50% yield. The obtained acetate 126, which possesses a latent meso structure, was used as a chiral building block for the synthesis of the sesquiterpene (−)-α-cuparenone (130) and was claimed to be a potential precursor of other terpenoids.
Other 2-substituted-propane-1,3-diols are suitable substrates for desymmetrization processes. For instance, monoacetate (R)-131 [108] was obtained in high enantiomeric purity (98% ee), by reaction of the corresponding diol with vinyl acetate and CRL as catalyst. The primary alcohol functional group of the compound (R)-131 was transformed in a methyl group, and the following coupling with the farnesyl moiety afforded (S)-α-tocotrienol (133), a natural terpenoid that inhibits the cholesterol biosynthesis. Similarly, the compound (R)-132 [109] is a further example of a useful chiral building block.

5. Conclusions

The present review article is aimed to give a comprehensive overlook of the lipase-mediated resolution procedures in the field of terpenoids synthesis. The importance of the latter synthetic approach has been demonstrated by the many achievements accomplished during the last twenty years.

Overall, we can remark that the procedures based on the use of lipases are by now well established and have become customary in laboratory practice. In addition, lipases catalyze chemical transformation with high chemo- and stereoselectivity, and their use is well suited to the principles of green chemistry. Thus, the current state of art represents a solid basis for the development of a range of new industrial processes involving the preparation of terpenoids of commercial interest.

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Abbreviations

For enzymes abbreviations the reader is referred to the following list:

- PPL: porcine pancreas lipase;
- Novozyme 435: immobilized lipase B from Candida antarctica;
- lipase PS: lipase from Burkholderia cepacia;
- CAL-B: Candida antarctica lipase B;
- lipase PL-266: lipase from Alcaligenes sp.;
- lipase QL: lipase from Alcaligenes sp.;
- lipase P: lipase from Pseudomonas cepacia;
- lipase PS-30: lipase from Pseudomonas cepacia;
- lipase M: lipase from Mucor javanicus;
- lipase AK: lipase from Pseudomonas fluorescens;
- lipase OF-360: lipase from Candida cylindracea;
- CRL: Candida rugosa lipase;
- CCL: Candida cylindracea lipase;
- CRL LIP1: Candida rugosa lipase;
- Chirazyme L-2: immobilized lipase from Candida Antarctica;
- lipase PS-C: lipase from Burkholderia cepacia immobilized on ceramic;
- lipase PS-IM: lipase from Burkholderia cepacia immobilized on diatomaceous heart.

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