Abstract:
The present invention relates to a process for producing an optically active (2S,3S)-3-(4-methoxyphenyl)glycidic acid methyl ester and (Cis-lactam) and uses thereof. More particularly, this invention relates to a process for making (2R,3S)-3-(4-methoxyphenyl)glycidic acid methyl ester employing enzymes, which is simple, industrially applicable and economically viable.
PROCESS FOR PREPARATION OF OPTICALLY ACTIVE (2R, 3S)-3-(4-METHOXYPHENYL)GLYCIC ACID METHYL ESTER AND CIS LACTAM AND USES THEREOF

Field of the Invention

The present invention is in the field of chemistry and more particularly the invention deals with an improved process for the preparation of an optically active (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (Cis-lactam).

Background of the Invention

Diftiazem, the chemical structure of which is shown in FIG. 1, is an optically active pharmaceutical compound. More specifically, diitiazem, the chemical name of which is (+)-5-[2-(dimethylamino)ethyl]-cis-2,3-dihydro-3-hydroxy-2-(p-methoxyphenyl)-1,5-benzothiazapin-4(5)-one acetate (ester), consists of a substituted benzothiazapene wherein both chiral carbon atoms have the S absolute stereo-configuration (H. Inoue et al, US Patent-No. 3,562,257). Diftiazem has proven useful for the treatment of angina due to coronary artery spasm, and for exertional angina. The beneficial therapeutic effects achieved with diitiazem are believed to be derived from the inhibition of calcium ion influx during depolarization of the ceil membrane in both cardiac and smooth muscle. Diftiazem is known to prevent coronary artery spasm, both spontaneous and ergonovine provoked, and to decrease peripheral vascular resistance. Diftiazem is marketed by Tanabe and by Marion Laboratories in the United States, where it is sold under the tradename Cardizem.RTM.

Analogues to diitiazem are also known to exist, e.g., wherein the benzothiazapene moiety has a single chlorine substituent on the aromatic ring.

![FIG. 1](image)

Diftiazem is currently being manufactured via a process similar to that shown in FIG. 2. The first step in the synthetic sequence involves the Lewis acid-catalyzed nucleophilic attack of o-
nitrothiophenol on methyl trans-3-(4-methoxyphenyl)glycidate, as a mixture of enantiomers, to give the threo compound shown (H. Inoue et al., J. Chem. Soc. Perkin Trans. I, 1984, 1725; H. Inoue et al., J. Chem. Soc. Perkin Trans. L 1985, 421; H. Inoue et al., US Patent No. 4,420,628). This threo compound then needs to be resolved at a subsequent step in the synthetic pathway in order to arrive at the optically active final product (diltiazem).

The 3-(4-methoxyphenyl)glycidic acid ester, shown in FIG. 3, contains two chiral centers at carbon atoms 2 and 3, both of which may assume either the R or S absolute configurations. Generally speaking, molecules containing n chiral centers and having no elements of reflective symmetry, will have $2^n$ stereoisomers, in a molecule with 2 chiral centers, there will thus be $2^2$ or 4 stereoisomers. Furthermore, in the case of a molecule having only two chiral centers, these four stereoisomers will be related as a diastereomeric pair of enantiomers, that is two diastereomers each existing as a mixture of its two enantiomers. In the specific case of 3-(4-methoxyphenyl)glycidic acid esters, the two diastereomeric forms are described as cis and trans isomers. The cis isomer is defined as the diastereomer in which the two hydrogen atoms bonded to the carbon atoms of the oxirane ring, that is carbon atoms 2 and 3, eclipse each other, that is, are on the same side of the plane defined by the oxirane ring substructure of the molecule. The trans isomer is defined as the diastereomer in which the hydrogen atoms bonded to carbon atoms 2 and 3 lie on opposite sides of the plane of the oxirane ring. Thus the relative configurations of carbon atoms 2 and 3 are fixed in each diastereomer, although each diastereomer will still exist as a pair of enantiomers. Because...
diastereomeric compounds are physically distinct entities, not related by symmetry operations performed on the entire molecule, they are physically distinguishable and may be produced separately by the appropriate conventional chemical methods.

![Diagram of diastereomer](image)

Fig. 3

The thermodynamically favorable trans diastereomer of a given 3-(4-methoxyphenyl)glycidic acid ester can be synthesized via the Darzen's glycidic ester condensation, and rendered free of any cis diastereomer by conventional purification methods. The trans diastereomer exists in two enantiomeric forms, one having absolute configuration R at carbon atom 2, and absolute configuration S at carbon atom 3. This enantiomer is described as the (2R,3S) isomer. The other enantiomer of the trans diastereomer will have absolute configuration (2S,3R). The enantiomers of the cis diastereomer exhibit absolute configurations (2S,3S) and (2R,3R). The particular glycidic ester enantiomer having absolute configuration (2R,3S) is the compound desired as an optically purified synthetic precursor to diltiazem.

The production of (2R,3S)-3-(4-methoxyphenyl)glycidic acid methyl ester has previously been achieved through two fundamentally different procedures. The first procedure involves the synthesis of the chiral glycidic acid methyl ester from achiral precursors, with the creation of chirality during a specific reaction which utilizes a chiral oxidation reagent. Thus, trans-cinnamyl alcohol is asymmetrically epoxidized to give the desired oxirane ring structure, with the correct stereochemistry being created at carbon atoms 2 and 3 simultaneously (K. Igarashi et al., US Patent No. 4,552,695).

The second procedure, which is generally considered more classical, involves the use of an optically pure reagent used in stoichiometric quantities, to form diastereomeric adducts with the enantiomers of racemic esters or salts of trans-3-(4-methoxyphenyl)glycidic acid (M. Hayashi et al., Japan 5 Kokai Tokkyo Koho J P 61/145160 A2 [86/145160] (1986); \1 Hayashi et al, Japan Kokai Tokkyo Koho J P 61/145160 A2 [86/145160] (1986)). These adducts are physically distinguishable, and may be separated by conventional procedures.
such as fractional crystallization. The thus separated adducts are then decomposed under
controlled conditions to leave the separated enantiomers, and the recovered resolving reagent.

Both of these procedures suffer drawbacks, however. In particular, the first procedure
involves the use of an unusual catalyst, namely, diafkyf trtarate titanium(TV) isopropoxide,
which requires anhydrous conditions and concomitant handling procedures (K. B. Sharpless
589). More importantly, the reaction which creates the desired stereochemistry does not
produce the methyl ester directly. Two further reactions are required beyond the point at
which chirality is introduced, involving the production (by oxidation of the alcohol) and
esterification of the glycidic acid itself, which is an unstable compound requiring special
handling. The second procedure suffers from the need for stoichiometric quantities of
previously resolved chiral materials or resolving agents such as alpha-methylbenzylamine (S.
Nagao et al., US Patent No. 4,416,819). Because of the expense of such resolving agents,
there also exists a need to recover these materials in a quantitative manner after the resolution
step. Additionally, the energy and solvent requirements of large-scale crystallization
processes make them unattractive.

Another approach to the resolution of racemic mixtures of chiral compounds involves
subjecting racemic compounds to the enantioselective action of various enzymes. Enzymatic
resolution has been widely employed for the lab-scale, preparative-scale, and industrial-scale
production of many optically pure compounds including esters but not heretofore the
glycidate esters.

Many different classes of enzymes have been used for the resolution of stereoisomers on a
preparative scale, including hydrolases (especially the lipases, proteases and esterases such as
chymotrypsin), lyases and oxidoreductases (e.g., amino acid oxidases and alcohol
reductases). Generally speaking, enzymes for use in resolutions should ideally exhibit broad
substrate specificity, so that they will be capable of catalyzing reactions of a wide range of
"unnatural" substrates, and they should exhibit a high degree of stereoselectivity for
catalyzing the reaction of one isomer to the exclusion of others.

The hydrolases (e.g., lipases, proteases and esterases) are among the more attractive enzymes
for use in resolutions, because they are commercially available at reasonable cost, they do not
require expensive cefaclors, and some of them exhibit reasonable tolerance to organic
solvents. Additionally, chiral chemistry often involves alcohols, carboxylic acids, esters,
amides and amines with cbiral carbons, and carboxyl hydrolases are preferred choices as stereoselective catalysis for reactions of such species (Cambou, B. and A. M. Klibanov, *Biotechnol. Bioeng.*, 1984, 26, 1449). Many pharmaceuticals and their intermediates exhibit very low solubilities in water, and accordingly a number of enzyme-mediated optical resolutions have been conducted under multiphasic reaction conditions.

Enzymatic treatment has been applied to the resolution of racemic mixtures of amino acid esters. For example, Stauffer (US Patent No. 3,963,573) produced optically pure N-acyl-L-methionine by treating N-aeryl-D,L-methionine ester with microbial proteases and separating the product acid from the reaction mixture. Similarly, Bauer (US Patent No. 4,262,092) prepared optically pure D-phenylalanine ester by subjecting a racemic mixture of an N-acyl-D,L-phenylalanine ester to the action of a serine protease, separating the unaffected N-acyl-D-phenylalanine ester, and removing the N-acyl and ester groups. Malta et al. (*J. Org. Chem.*, 1974, 39, 2291) used chymotrypsin in the resolution of precursors of the drug 3-(3,4-dihydroxyphenyl)alanine or dopa.

Enzymes have also been explored for the resolution of other compounds such as agricultural chemicals, sometimes in biphasic reactions systems. In particular, Cambou and Klibanov (*Biotech. Bioeng.*, 1984, 26, 1449) examined the use of lipase immobilized in porous beads for the enzymatic resolution of mixtures of (R,S)-2-(p-chloro-phenoxy)propanoic acid (whose R isomer is a herbicide) and various esters thereof. The differing solubility properties of the acids and esters used in their studies required the dispersion and agitation of mixtures containing the immobilized solid-phase enzyme, an aqueous buffer, and the water-immiscible organic phase containing solvent and reactant—a relatively inefficient process.

In summary, there exists a need in the art for more efficient methods for production of optically purified diltiazem and its analogues, and in particular for improved processes for the optical resolution of racemic diltiazem precursors including the esters of trans-3-(4-methoxyphenyl) glycidic acid. Furthermore, while enzymatic resolution techniques have been employed for the production of many optically pure pharmaceuticals and their precursors, this technique has not yet been disclosed and successfully applied to the resolution of the glycidate esters that are chiral intermediates in the production of diltiazem. The present invention provides such an enzymatic resolution method.
Objective of the Invention

The main objective of the present invention is to provide a simple and cost effective process for the preparation of (2R,3S)-3-(4-methoxyphenyl)glycidic acid methyl ester with high purity and good yield on commercial scale.

A yet another objective of the present invention is to provide a process for the preparation of (2R,3S)-3-(4-methoxyphenyl)glycidic acid methyl ester by using enzyme and then conversion to Cis-lactam, which is simple, industrially applicable and economically viable.

A yet another objective of the present invention is to provide an improved process for the preparation of 4-methoxy phenylacetic acid with high yield and high purity.

Another objective of the present invention is to provide a process for the preparation of 4-methoxy phenylacetic acid, which is simple, industrially applicable and economically viable.

Summary of the Invention

The present inventors have proceeded with extensive research. As a result, it is to provide an improved process for the preparation of an optically active (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (Cis-lactam).

The present invention provides novel method for the resolution of racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate (racemic trans-MMPG) by using enzyme is selected from lipases and then conversion to Cis-lactam. This Cis-lactam can also be further used for the preparation of optically active Diltiazem.

Furthermore, the present invention provides that the unwanted isomer obtained from the resolution of racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate (racemic trans-MMPG) is inter-converted into /?-methoxyphenyl acetaldehyde which can be isolated and further chemically oxidized into its corresponding acid of /?-methoxy phenylacetic acid. This /?-methoxy phenylacetic acid can also be further used for the preparation of Dextromethorphan.
This compound of formula (I) can also be further used for the preparation of optically active Diltiazem.

**Scheme-1**

**Description of the Invention**

The present invention provides novel method for the resolution of racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate \((\text{racemic trans-MMPG})\) by using enzyme is selected from lipases and then converted to Cis-lactam. The compound of cis-lactam can also be further used for the preparation of optically active Diltiazem.

The method employs an enzyme is selected from lipase that catalyzes the **enantioselective** hydrolysis of racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate \((\text{racemic trans-MMPG})\). \((2R,3S)-3-(4\text{-methoxyphenyl})\text{glycic acid methyl ester having enantiomeric excess (e.e) of 90-99% in 45 to 47.5 yield has been produced by enantio-selective hydrolysis of the racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate \((\text{racemic trans-MMPG})\) with lipases as shown in scheme 1.**
The enzyme used according to the subject invention is a lipase originating from *Serratia marcescens, Candida cylindrecea*. These lipases can, for instance, also be produced via recombinant DNA technology. The gene coding for the lipase in question is heterologously expressed in a host microorganism, for instance *Serratia marcescens* and *Candida cylindrecea*. These enzymes (obtained from *Serratia marcescens* and *Candida cylindrecea*) are commercially available under the tradename of "Lipase A" and "Lipase OF" respectively.

The enzyme according to the invention is preferably applied in its immobilized form, i.e. on a solid phase, gel-type particles, ion exchange resins and crossed linked aggregate. This facilitates recovery of the enzyme, while enabling reuse of the enzyme. It has been found that a high activity and selectivity are also reached when the enzyme is used in immobilized form, said activity and selectivity being retained after the enzyme had been recycled several times.

The enantioselctive hydrolysis is preferably effected in a two-phase system comprising an aqueous phase and an organic phase. The aqueous phase contains buffers. The buffer is selected from the group consisting of potassium phosphate, sodium phosphates and TrisHCl or mixtures thereof. The organic phase contains an organic solvent. The organic solvent is selected from benzene, toluene, xylene, methyl t-butyl ether, methyl isobutyl ketone, cyclohexanone or mixtures thereof.

The hydrolysis according to the invention can be carried out at room temperature or at elevated temperature. The upper limit is determined by the stability of the substrate. In practice, the upper temperature limit is about 70°C. Preferably, the hydrolysis is carried out at a temperature of about 20-50°C. More preferably, the hydrolysis is carried out at a temperature of about 30-40°C.

During the hydrolysis, the pH is kept at a value of 5 to 10. Preferably the pH is maintained at 7-9. In particular, the pH is maintained at about 8. The pH is maintained by addition of a base. The base can be selected from inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, and sodium bicarbonate.

Furthermore the present invention provides the commercial/industrial use of the unwanted isomer for the preparation of Dextromethorphan or its starting material as shown in Scheme 1. The unwanted isomer obtained from the resolution of racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate (*racemic trans-MMPG*), is inter-converted (interconversion is a process in which two things are each converted into the other, often as the result of chemical or
physical activity) into /?-methoxyphenyl acetaldehyde which can be isolated and further chemically oxidized into its corresponding acid of /?-methoxy phenylacetic acid. This p-methoxy phenylacetic acid can also be further used for the preparation of Dextromethorphan.

In an embodiment, for chemically oxidizing /?-methoxyphenyl acetaldehyde, an oxidizing agent is used. The oxidizing agent is selected from the group consisting of hydrogen peroxide, sodium chlorite, periodate, chromic acid, permanganate, nitrogen dioxide, with air, alkali metal hypochlorites, \([\text{Fe(CN)}_5\text{H}_2\text{O}]^3\), \(\text{Ru-Co(OH)}_2\text{-CeO}_2\)-air, \(\text{Pd(II)-Bathophenanthroline, Ag}_2\text{O-CuO, NaClO-NiCl}_2\) or \(\text{Ni(OAc)}_2, \text{NaClO-TEMPO(cat.), NaIO}_4, \text{Na}_2\text{Cr}_2\text{O}_7\cdot\text{H}_2\text{O}_4, \text{hydrogen sulphuric acid, or mixtures thereof. More preferably, the oxidizing agent used is a mixture of hydrogen peroxide and sodium chlorite.}

The term "ee" refers to "optical purity" or "enantiomeric excess".

According to the present invention, which relates to pure solid compounds of an optically active \((2R, 3S)-3-(4\text{-methoxyphenyl})\text{glycidic acid methyl ester} ((2R,3S)-\text{MMPG})\), wherein \((2R, 3S)-3-(4\text{-methoxyphenyl})\text{glycidic acid methyl ester} has a purity of more than 98%. Preferably, the purity is more than 99%. More preferably, the purity is more than 99.9%.

The present invention also provides an optically active \((2S, 3S)-3\text{-hydroxy-2-(4-methoxyphenyl)-}2,3\text{-dihydro-1,5-benzothiazepin-4(5H)-one} \) (Cis-Lactam), wherein an optically active \((2S, 3S)-3\text{-hydroxy-2-(4-methoxyphenyl)-}2,3\text{-dihydro-1,5-benzothiazepin-4(5H)-one} has a purity of more than 98%. Preferably, the purity is more than 99%. More preferably, the purity is more than 99.9%.

The following examples illustrate the nature of the invention and are provided for illustrative purposes only and should not be construed to limit the scope of the invention.

**Example 1: Synthesis of racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate (racemic trans-MMPG)**

A mixture of /?-anisaldehyde (100 g) and methyl chloroacetate (108 g) solution was added slowly to a cold solution (26%) of sodium methoxide (250 mL) at 0-5 °C. The reaction mass was stirred and maintained for 4 hrs at 0-5 °C. After completion of the reaction, the mass was transferred to another flask containing cold water and maintained the temperature at below 12
with agitation for 30 minutes. Further the reaction mass was centrifuged and washed with water and dried to yield the title compound as a solid. Yield: 136.0 g.

Example 2: Synthesis of (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (Cis lactam 1)

The racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate (racemic trans-MMPG) (100 g) was dissolved in toluene (350 mL) and mixed with phosphate buffer (150 mL) (pH-7.5, 100 mmol). To the mixture 20 g of *Serratia marcescens* lipase (Lipase A) was added and the pH was adjusted to 7.2-7.5 with 5% sodium hydroxide solution with stirring at 30 °C and maintained for 6-7 hrs. The reaction was stopped after 50 to 52% conversion of racemic trans MMPG. The enzyme was filtered and washed with toluene (50 mL). Layers were separated and the organic layer was washed twice with 8% solution of NaHSO₃ (420 mL) (pH 6.3-6.4), organic and aqueous layers were separated (the aqueous layer was used for the recovery of 4-methoxy phenyl acetaldehyde which was further converted into 4-methoxy phenyl acetic acid). The organic layer containing (2R,3S)-3-(4-methoxyphenyl)glycidic acid methyl ester ((2R,3S)-MMPG) was washed with water (2x100 mL). The organic layer was refluxed at 110-115 °C for 1 hr, 2-amino thio-phenol (25.2 g) was added with agitation and maintained at 110 °C for 3-4 hrs. Further methanesulfonic acid (3.69 g) was added into the reaction mixture and maintained for 15-18 hrs. The reaction mixture was cooled to 0-5 °C and stirred for 30 mins, the solid was filtered and washed with toluene. The wet cake was dissolved in methanol (120 mL) and stirred for 30 min at 40-45 °C. The reaction mixture was cooled to 0-5 °C, filtered, washed with methanol and dried to obtain (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (Cis lactam 1).

Yield: 67 g; Chiral Purity: ee >99.9 %. ¹H NMR (300 MHz, DMSO-d₆, solvent): δ 9.24 (s, 1H, NH), 7.69 (d, J=6.0 Hz, 1H), 7.49 (d, J=9.0 Hz, 2H), 7.41-7.36 (m, 1H), 7.27-7.20 (m,1H), 7.13 (d, J=9.0 Hz, 1H), 6.77 (d, J=9.0 Hz, 2H), 5.11-5.09 (d, J=6.0, Hz, 1H), 4.48 (d, J=6.0 Hz, 1H), 3.75 (s, 3H, OMe), 2.90 (br. 1H, OH); ¹³C NMR (75 MHz, CDCl₃, solvent): δ 174.015, 160.10, 140.54, 134.39, 131.36, 130.28, 127.51, 127.14, 126.43, 123.30, 113.84, 69.42, 57.75 and 55.42.

Experiment 3: Synthesis of p-methoxy phenylacetic acid.

The aqueous layer separated as in Example 2 (recovery aqueous layer; 420 mL) was mixed with dichloromethane (250 mL) at 15-20 °C, to this 10% solution of NaOH (105 ml) was
added drop wise while stirring and maintained for 2 hrs. Layers were separated, the organic layer was mixed with sodium dihydrogen phosphate buffer (105 mL), 35 % hydrogen peroxide solution (24 mL) and thereafter 10% sodium chlorite solution (360 ml) was added slowly in to the above mixture at 5-10 °C. After completion of reaction basified with 20 % NaOH solution and layers were separated, the pH of aqueous layer was adjusted to 4 to 5 with HCl, cooled to 0-5 °C and stirred for 1 hr. The solid was filtered, washed with water and dried under vacuum at 45-50 °C to obtain 4-methoxy phenylacetic acid (36.0 g).

MP: 86-88.5° C. 1H NMR (300 MHz, CDCl₃): δ: 11.54 (s, 1H, COOH), 7.24 (d, J = 9.0 2H), 6.89 (d, J = 6.0, 2H), 3.79 (s, 3H), 3.59 (s, 2H); 13C NMR (75 MHz, CDCl₃) δ: 178.57, 159.03, 130.60, 125.54, 114.26, 55.44, and 40.3.

**Experiment 4: Enzymatic resolution of racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate (racemic trans-MMPG)**

The racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate (racemic trans-MMPG) (100 g) was dissolved in toluene (350 mL) and mixed with phosphate buffer (150 mL) (pH-7.5, 100 mmol), there after 20 g of *Serratia marcescens* lipase (Lipase A) was added. The pH was adjusted to 7.2-7.5 with 5 % sodium hydroxide solution with stirring at 30 °C and maintained for 6-7 hrs. The reaction was stopped after 50 to 52 % conversion of racemic trans MMPG. The enzyme was filtered and washed with toluene (50 mL). Layers were separated and the organic layer was washed twice with 8 % solution of NaHSO₃ (420 mL) (pH 6.3-6.4), organic and aqueous layers were separated (the aqueous layer was used for the recovery of 4-methoxy phenyl acetaldehyde which was further converted into of 4-methoxy phenyl acetic acid). The organic layer was washed with water (2x100 mL) and distilled the solvent to get the solid compound of (2R,3S)-3-(4-methoxyphenyl)glycidic acid methyl ester ((2Pv,3S)-MMPG) (48g).

Chiral Purity: ee>99.90 %; 1H-NMR (300 MHz, CDC13): δ 7.18-7.10 (m, 2 H), 6.83-6.78 (m, 2 H), 3.96 (d, J = 3.0 Hz, 1 H), 3.80& 3.72 (2s, 6 H, lxoMe and lxoCOOMe), 3.42 (d, J = 3.0 Hz, 1 H)

**Experiment 5: Synthesis of 4-methoxyphenylacetic acid**

4-Methoxy phenyl acetaldehyde (100.0 g) was dissolved in dichloromethane (500mL) and mixed with sodium dihydrogen phosphate buffer (350 mL), 35 % hydrogen peroxide solution (80 mL). Further 10% sodium chlorite solution (1200 mL) was added slowly in to the above
reaction mixture at 5-10 °C. After completion of reaction basified with 20 % NaOH sol and layers were separated, the pH of aqueous layer was adjusted to 4 to 5 with HCl further cooled to 0-5 °C and stirred for 1 hr. The solid was filtered, washed with water and dried under vacuum at 45-50 °C to obtain 4-methoxy phenylacetic acid (105 g).

MP: 86-88.5°C; 1H NMR (300 MHz, CDC13): δ: 11.54 (s, 1H, COOH), 7.24 (d, J = 9.0 2H), 6.89 (d, J = 6.0, 2H), 3.79 (s, 3H), 3.59 (s, 2H); 13C NMR (75 MHz, CDC13) δ: 178.57, 159.03, 130.60, 125.54, 114.26, 55.44, 40.3.

It may be noted that the embodiments illustrated and discussed in this specification are intended only to teach to those skilled in the art the best way known to the Inventors to make and use the invention. In describing embodiments of the Invention, specific terminology is employed merely for the sake of clarity. However, the invention is not intended to be restricted to specific terminology so-used. The above-described embodiments of the invention may be modified or varied, without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.
5 What Claimed is:

1. A process for the preparation of an optically active \((2R,3S)-3-(4\text{-methoxyphenyl})\)glycidic acid methyl ester, which comprises enantioselective hydrolysis of racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate with an enzyme, wherein the enzyme is obtained from *Serratia marcescens* and/or *Candida cylindracea*.

2. Process according to claim 1, wherein the hydrolysis is in a two-phase system comprising an aqueous phase and an organic phase.

3. Process according to claim 2, wherein the aqueous phase contains buffer solution, the buffer solution used in hydrolysis is selected from the group consisting of potassium phosphate, sodium phosphates and TrisHCl or mixtures thereof.

4. Process according to claim 2, wherein the organic phase contains an organic solvent, the organic solvent used in hydrolysis is selected from the group consisting of benzene, toluene, xylene, methyl t-butyl ether, methyl isobutyl ketone, and cyclohexanone or mixtures thereof.

5. Process according to claim 1, wherein the optically active \((2R,3S)-3-(4\text{-methoxyphenyl})\)glycidic acid methyl ester is being obtained with an ee. higher than 99%.

6. A process for the preparation of an optically active \((2S,3S)-3\text{-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one}\) of formula (I)

\[
\text{Formula (I)}
\]

which comprises

(a) enantioselective hydrolysis of racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate of formula racemic trans-MMPG

\[
\text{racemic trans-MMPG}
\]
with an enzyme, wherein the enzyme is obtained from *Serratia marcescens* and/or *Candida cylindracea*,

(b) optionally isolating non-hydrolyzed (2R,3S)-3-(4-methoxyphenyl)glycidic acid methyl ester of formula (2R,3S)-MMPG of step (a)

(c) treating said (2R,3S)-3-(4-methoxyphenyl)glycidic acid methyl ester with 2-aminothio-phenol to obtain an optically active (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one of formula (I).

7. Process according to claim 6, wherein the optically active (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one is being obtained with an ee. higher than 99%.

8. Process according to claim 6, wherein the optically active (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one so obtained is used for synthesis of diltiazem.

9. A process for the preparation of 4-methoxy phenylacetic acid, wherein the process comprises the steps of:
   (a) enantioselective hydrolysis of racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate with an enzyme, wherein the enzyme is obtained from *Serratia marcescens* and/or *Candida cylindracea*,
   (b) inter-converting the hydrolyzed (3R,2S)-3-(4-methoxyphenyl)glycidic acid of step (a) to 4-methoxy phenyl acetaldehyde,
   (c) optionally isolating 4-methoxy phenyl acetaldehyde of step (b), and
   (d) treating the 4-methoxy phenyl acetaldehyde with oxidizing reagent to obtain 4-methoxy phenylacetic acid.

10. Process according to claim 9, wherein the oxidizing agent is selected from the group consisting of hydrogen peroxide, sodium chlorite, periodate, chromic acid, permanganate, nitrogen dioxide, with air, alkali metal hypochlorites, [Fe(CN)5H2O]3-, Ru-Co(OH)3-CeO2-air, Pd(II)-Bathophenanthroline, Ag2O-CuO, NaClO-NiCl2 or
Ni(OAc)₂, NaCl0-TEMPO(cat.), NaI0₄, Na₂Cr₂O₇.7H₂O₄, hydrogen sulphuric acid,
or mixtures thereof.

11. Process according to claim 10, wherein the 4-methoxy phenylacetic acid so obtained
is used for synthesis of Dextromethorphan.

12. Process according to any of claims 1, 6, or 9, wherein the enzyme is used as whole

13. Process according to claim 12, wherein the enzyme is selected from Lipase A or

Lipase OF.