



(51) International Patent Classification:  
C07C 209/52 (2006.01)

(21) International Application Number:  
PCT/IN2009/000170

(22) International Filing Date:  
12 March 2009 (12.03.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
518/MUM/2008 13 March 2008 (13.03.2008) IN

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

**Published:**

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: A PROCESS FOR PREPARATION OF RAMIPRIL

(57) Abstract: Disclosed herein is a process for preparation of Ramipril; which comprises; reacting salts of (S,S,S)-azabicyclo[3.3.0]octane-3-carboxylate with N-[1-(S)-ethoxy carbonyl]-3- phenyl propyl]-L-alanine in presence of dicyclohexylcarbodiimide (DCC) and 1- hydroxybenzotriazole (HOBT) in a suitable solvent medium.

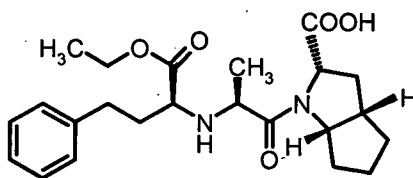


WO 2009/122433 A2

## “A PROCESS FOR PREPARATION OF RAMIPRIL”

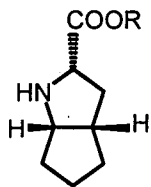
### Technical field:

The present invention relates to a process for preparation of Ramipril of formula (XII), or its pharmaceutical salts.



Formula (XII)

The invention also relates to optically pure intermediate (S,S,S)-2-azabicyclo [3.3.0]-octane-3-carboxylate of formula (VIII), its salts and its use in the synthesis of optically pure ramipril.



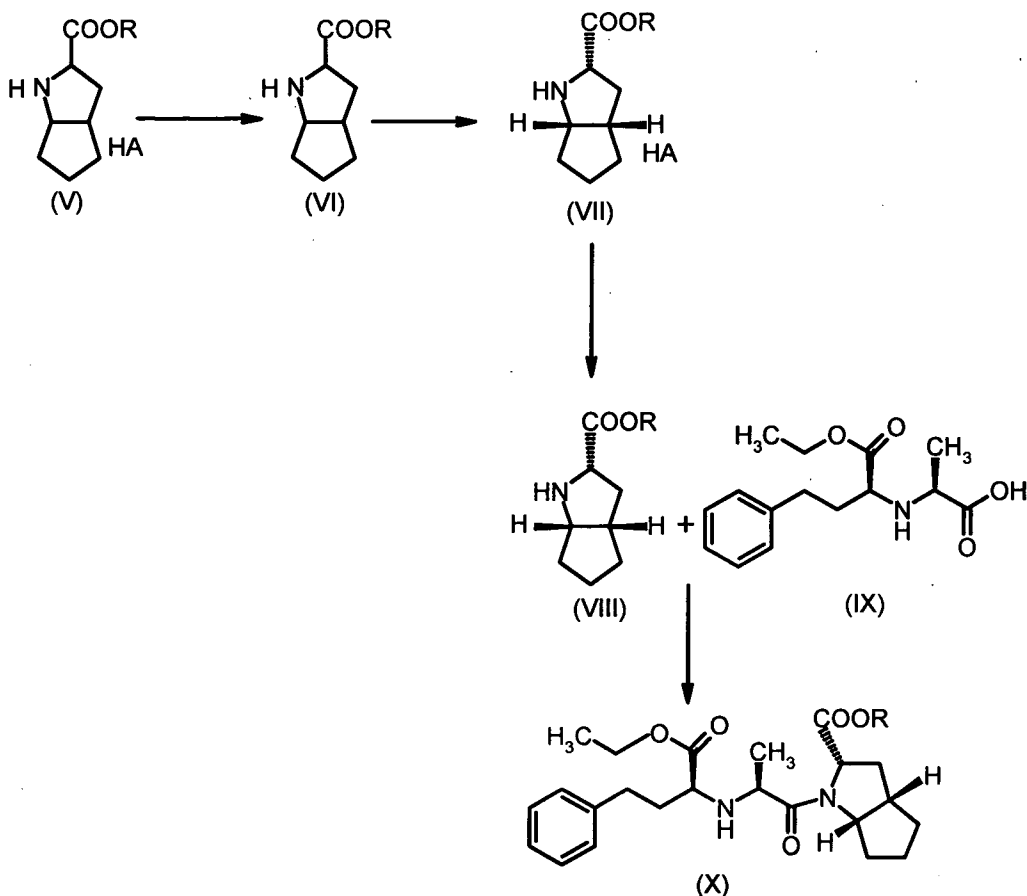
R=H, alkyl, benzyl, or any protecting group

Formula (VIII)

### Background and Prior art:

Ramipril named chemically (2S,3aS,6aS)-1-[(S)-2-[[[(S)-1-(ethoxycarbonyl)-3-phenylpropyl]-aminopropyl] octahydrocyclopenta[b]pyrrole-2-carboxylic acid is an ACE inhibitor, and is used to treat hypertension and congestive heart failure.

Ramipril and its process for preparation is disclosed in US5061722. Synthesis of Ramipril is also disclosed in several other prior arts such as CA1338162, EP79022, US4668796, US5977380, US6541635, US5175306, WO2005121084, WO2005/049568, WO2005/108366, WO2005068422, US2007/0232680. A thorough study of the prior art for the synthesis of Ramipril indicates that the following route of synthesis (Scheme-I, wherein R means H, Alkyl, benzyl group; and HA means an inorganic or sulphonic acid) is widely used.

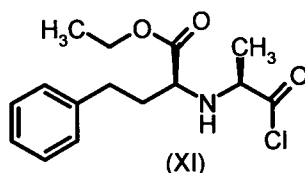


Scheme-I

According to our search, in all the preparative methods disclosed for Ramipril involving the usual DCC-HOBT mediated coupling of intermediate of formula VIII and compound of formula IX, obtainment of intermediate of formula (VIII) as free base from its salt (Formula VII) is common. Such processes comprise reaction of said salt (Formula VII) with an alkali followed by an extractive work-up prior to its use in the process of coupling with intermediate IX. It is seen that intermediate (VIII) being an oily substance, it is advantageous to convert into an acid addition salt for better handling, isolation/purification and storage and therefore, its conversion to a salt form is almost unavoidable for stable storage/handling. But, carrying out the conversion of salt into free base of Formula VIII before peptide coupling reaction makes the process lengthy and cumbersome due to the increased number of unit operations and therefore such process is not suitable from an industrial standpoint.

Yet another publication, US5055591 discloses use of alkane phosphonic acid anhydrides as coupling reagent in place of conventional dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) for preparation of ramipril using intermediate VII and IX, and stated that DCC and HOBT catalyzed reaction under similar condition results in poor yields of ramipril. However, the use of alkane phosphonic acid anhydride does not appear to be practical as it is expensive and not readily available in commercial quantities compared to DCC.

Although US2007/0232680 describes direct use of azabicycloester salt formula VII in the process for ramipril, but employ acid chloride of formula (XI) as reaction partner in place of intermediate (IX) which involves an additional step of preparing the compound of formula (XI)



Needless to say it is advantageous to develop a process which eliminates the necessity of converting the salt into a free ester in an additional step in the DCC mediated coupling of azabicycloester salt formula VII with IX, yet providing Ramipril in high yields and thereby making the overall process simpler and shorter.

Another major insufficiency in the literature process appeared to be related to the optical purity of Ramipril as the product obtained is contaminated with its optical antipodes, which is in contrast to the required pharmacopoeial purity criteria. The crystallization methods so far reported do not effectively remove the undesired optical isomers, unless a thorough repeated crystallization from organic solvents is done, which is not only unacceptable from stability point of the compound but also for economy of the process. Purification of ramipril to increase optical purity is troublesome mainly because of its susceptibility to degradation and forms the hydrolyzed diacid and/or intermolecular cyclised diketopiperazine impurities. These impurities may form during isolation, purification, formulation or storage as has been seen and documented in US2007/0232680, WO2005/121084, US20060159742, and WO2006052968. Most of the purification processes involves either solvent purification from an organic solvent, and

aqueous solvents, for example in US20070232680, WO2005/068422 or an acid/base treatment. This accelerates the possibility of hydrolysis or diketopiperazine formation and hence isolation and purification of ramipril appears to be a very delicate process and it is advantageous to avoid too many processing steps in final purification or finding a process that result in optically pure ramipril.

Generally speaking, the optical purity of ramipril can be controlled by the purity of intermediate (VII) and intermediate IX. Although intermediate IX can be obtained in reasonable optical purity, but obtaining the intermediate (VII) of high optical purity is difficult, because the diastereomeric resolution of the compound of formula (V) with optical acids and subsequent purification of the resulting diastereomeric salt known so far, for example from US4668796, WO2005/049568, IN191949, US2007/0232680, US4659838, WO2005/049568 invariably result into compound of formula (VIII) contaminated with 2-4% of the undesired (R,R,R)-stereoisomer. Another alternative, for example the enantioselective synthesis of compound (VII) or derivative reported in Tetrahedron Lett, 1993, 34 (41), 6603-6603 or Heterocyclic 1989 28(2),957-965, however, result in very low yield and is not economically feasible for large scale production, which is substantiated by the disclosure of US6407262 (column 3, line 45-65).

US2007/0232680 discloses preparation of (S,S,S)-azabicyclo [3.3.0]-octane-3-carboxylic acid benzyl ester hydrochloride having 100% HPLC purity, on the other hand, it is noticed by the present inventors as well as evident from several prior art processes that it is difficult to achieve high optical purity of azabicycloester either by resolution or subsequent purification of diastereomeric salt, meaning the mentioned purity might be related to chemical purity and not optical purity.

Thus it is evident from the above study that exclusive obtainment of (S,S,S)- isomer of 2-azabicyclo [3.3.0]-octane-3-carboxylic acid benzyl ester is not enabled by the prior art processes and using the same for obtaining optically pure Ramipril without the need for exhaustive purification measures. Thus there is still a need in the art for an improved process to prepare optically pure ramipril which reduces the processing steps involved in preparation and purification while using the inexpensive and readily available reagents

like DCC and HOBt for peptide condensation. The present invention ameliorates above problems in the prior art and also reduces a number of unit operations.

**Summary of the invention:**

The present invention thus provides a process for Ramipril by direct condensation of a salt of intermediate VII. According to one aspect, the present invention provides a process for preparation of ramipril comprising reacting an acid addition salt of bicyclic amino ester of formula (VII) with N-[1-(S)-(ethoxy carbonyl)-3-phenylpropyl]-L-alanine (IX) in presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) in a suitable solvent medium.

In one embodiment, the process comprises of reacting an optically pure acid addition salt of benzyl (S, S, S)-2-azabicyclo [3.3.0] octane-3-carboxylate of formula (VII) with N-[1-(S)-(ethoxy carbonyl)-3-phenylpropyl]-L-alanine (IX) in presence of a base and DCC and HOBt in a suitable solvent, followed by removal of benzyl ester to obtain optically pure ramipril. The optically pure acid addition salt of benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate of formula (VII) preferably contain no detectable amount of its (R,R,R)- optical isomer.

In a second aspect, the invention provides optically pure (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate of formula (VIII) or its salts preferably with no detectable amount of (R,R,R)- isomer and a process for preparing the same. The process according to the present invention, for optically pure benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate of formula (VIII) and its salts substantially free from other stereoisomers, especially R,R,R-isomer comprises isolating the compound of formula (VII) as an inorganic/sulfonic acid salt from solvents selected from C<sub>1</sub>-C<sub>4</sub> linear or branched chain alcohol.

**Detailed Description:**

Unless specified otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art, to which this invention belongs. To describe the invention, certain terms are defined herein specifically as follows:

The term "optically pure" in the context of the present invention means the chiral isomeric purity exceeding 99.5%.

The term "substantially free" in the context of the present invention means the stated product is free from contamination of stated thing or impurities at least less than 0.5%, preferably less than 0.1% and most preferably less than 0.05%.

The details of one or more embodiments in the practice of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the appended examples and claims.

Accordingly, the present invention provides a process to prepare ramipril. The process involves condensation of an acid addition salt of formula (VII) with an intermediate of formula (IX) in presence of DCC and HOBT in a suitable solvent. The process of the present invention is advantageously carried out in presence of a base substance.

The acid addition salt of formula (VII), which may be used in the present invention, is selected from an inorganic acid salt or sulfonic acid salts, such as hydrochloric acid, *p*-toluene sulphonic acid, benzene sulphonic acid, methane sulphonic acid. The preferred inorganic salt is hydrochloric acid salt and sulfonic acid salt is *p*-toluene sulfonic acid salt.

The base used in the present invention may be selected appropriately from an organic class of compounds. The most preferred bases are alkyl amines for example triethyl amine, diisopropyl ethylamine. The base is conveniently used in an amount, although not limited to, equal or greater than molar equivalents relative to the starting intermediate of Formula VII, preferably in a range between 1.5 to 3 moles, more preferably between 2.0 to 2.8 moles.

Dicyclohexylcarbodiimide (DCC) in the application of the present invention may be used in an amount ranges between 1.0 mole to 2.0 moles, preferably between about 1.1 to 1.5 moles with respect to intermediate (VII). The HOBT may be used in catalytic amounts or

in molar amounts in the range between 1.0 to 2.0 with respect to the starting intermediate (VII) salt.

The reaction is advantageously carried out in a solvent. The solvent may be selected from any inert organic solvent. Examples of solvents include, esters such as ethyl acetate; hydrocarbons such as toluene; chlorinated hydrocarbon such as dichloromethane, dichloroethane etc; polar aprotic solvent such as dimethylformamide. The especially preferred solvent is dichloromethane or ethyl acetate.

The reaction may be carried out at suitable temperature, either under cooling or at ambient temperature. Although the reaction can be carried out under heating, but to minimize the possible decomposition of product and impurity formation the reaction is carried out at room temperature. The especially preferred reaction temperature is between 25-30 °C.

On completion of the reaction, the intermediate benzyl ramipril can be recovered from the reaction in a conventional manner. The isolated benzyl ramipril may be purified from the by-products such as dicyclohexyl urea by treating in a suitable organic solvent. Purification may also be carried out by forming suitable acid addition salts. In the process, the benzyl ramipril is subjected to catalytic debenzylation to obtain Ramipril either by methods known in the art or the process as disclosed herein. In a typical procedure the benzyl ramipril is treated with a hydrogenation catalyst, for example Palladium charcoal, in a suitable organic solvent, and the reaction is carried under hydrogen pressure at a temperature in the range of 20-40°C. The solvents used herein can be selected from C<sub>1</sub>-C<sub>3</sub> linear or branched chain alcohol. Preferably ethanol is used in present process. On completion of debenzylation reaction, Ramipril can be isolated by removing catalyst followed by optional elimination of the solvent or precipitating and/or crystallizing from a suitable purification solvent to remove chemical impurities.

The suitable purification solvent is an organic solvent, especially selected from a group consisting of aliphatic ethers, aliphatic ketones, aliphatic or aromatic hydrocarbons, alkyl esters, aliphatic nitrile or aliphatic alcohols. A single solvent or mixture of suitable solvents can be used for purification/ recovery of ramipril.

The optical purity of Ramipril obtained by the present invention depends on the optical purity of intermediate VII. Thus by employing an intermediate salt obtained by any one of the process according to the US4668796, WO2005/049568, IN191949, US2007/0232680, US4659838, WO2005/049568, yielded Ramipril of about 96-98% optically pure. The inventors had recognized that purification of Ramipril to increase the optical purity from 96-98% by the known methods is not a reliable methodology to improve optical purity because changes in manufacturing parameters or presence of acid/alkali might lead to formation of impurities in the known methods. Although these methods may improve the optical purity but finally contaminate the product with those chemical impurities generated during purification.

Thus in a preferred embodiment of the present invention, an optically pure benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate of formula (VIII) and its salts formula (VII), substantially free from its other stereoisomers, especially with no detectable amount of (R,R,R)-isomer is provided in the present invention to use in the process for Ramipril.

In this embodiment, the process for Ramipril comprises purifying an optically impure inorganic/sulfonic acid salt of benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate of formula (VII) from selected solvents to provide corresponding optically pure benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate salt; treating said optically pure benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate salt and intermediate of Formula IX in presence of a base and a peptide coupling catalyst in a suitable solvent; and hydrogenation of the resulting benzyl Ramipril to obtain optically pure Ramipril. The reagents and conditions may be used as illustrated before and further exemplified in the accompanying examples.

Thus in the second aspect, the invention provides optically pure benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate or its salt, especially an inorganic/sulfonic salt substantially free from other stereoisomers, especially with no detectable amount of (R,R,R)-isomer for the first time. Said optically pure intermediate finds use in the synthesis of optically pure ramipril.

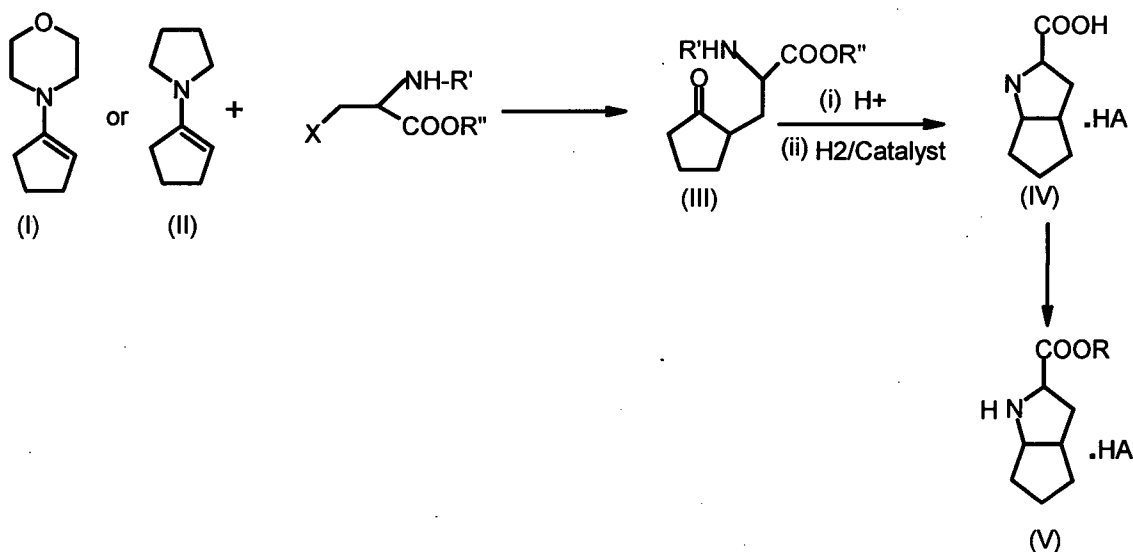
In this aspect of the invention, the present invention provides an efficient purification process for preparing the optically pure intermediate of formula (VII) which comprises isolating an inorganic/sulfonic acid salt of benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate from solvents selected from the group of C<sub>1</sub>-C<sub>4</sub> linear or branched chain alcohol. Especially preferred solvent is isopropyl alcohol or ethanol or methanol or their mixture. The salts thus obtained can be converted to their free form by methods known conventionally; the ester other than benzyl can be used as well for the present process.

The process, according to the present invention comprises mixing benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate or its inorganic/sulfonic acid salt contaminated of (R,R,R)-isomer; optionally adding an inorganic acid or sulfonic acid; and recovering an optically pure benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate as inorganic/sulfonic acid salt from solvents selected from the group of C<sub>1</sub>-C<sub>4</sub> linear or branched chain alcohol, especially ethanol or isopropyl alcohol; and if desired converting to benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate. In a preferred embodiment, the process comprises treating benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate or its inorganic/sulfonic acid salt contaminated of corresponding (R,R,R)-isomer in a solvent selected from the group of C<sub>1</sub>-C<sub>4</sub> linear or branched chain alcohol, especially ethanol or isopropyl alcohol, and recovering the optically pure benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate or its inorganic/sulfonic acid salt.

The inorganic acid/sulfonic acid may be selected from any known ones, especially preferred acid are hydrochloric acid, methane sulphonic acid, benzene sulfonic acid and *p*-toluene sulphonic acid. The process is carried out at a temperature in the range of 20°C to reflux temperature, preferably under heating to reflux temperature of solvent; and the purified salt is obtained by cooling the reaction mixture to a convenient temperature, for example room temperature or below. The cooled reaction mixture is then filtered to give salt of formula (VII) free of undesired isomers. The benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate or its inorganic/sulfonic acid salt may be prepared separately in a suitable solvent or in situ in the purification solvents disclosed before.

In the process of purification, the starting benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate or its salt may contain a significant amount of corresponding (R,R,R)-isomer, especially in the range of above 1-5% , more preferably it may contain 2-3%.

The starting benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate or its salt may contain a significant amount of corresponding (R,R,R)-isomer can be prepared by any one of the process known in literature, for example according to the following scheme. The racemic benzyl-2-azabicyclo [3.3.0] octane-3-carboxylate or its salt may be obtained according to any one of the process in the following scheme.



Scheme II

X=any leaving group; R'=any protecting group; R''=alkyl or benzyl; R=any protecting group

HA=represents an acid capable of forming salts

The racemic benzyl-2-azabicyclo [3.3.0] octane-3-carboxylate or its salt is further resolved to obtain the benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate or its salt of about 96-98% optical purity by treating the racemic mixture with an optically active acid, followed by diastereomeric crystallization.

Suitable optically active acids for resolution are selected from mandelic acid, N-benzyloxycarbonyl-L-phenyl alanine, wherein mandelic acid is especially preferred. The solvent for resolution is selected from alkyl acetate, cyclohexane, alcohols like isopropyl

alcohol, ethanol, aromatic hydrocarbon like toluene or their mixtures thereof. The preferred solvent is ethyl acetate, or a mixture of ethyl acetate and cyclohexane. The optically enriched diastereomeric salt is crystallized by cooling the reaction mixture. This is then isolated, and optionally recrystallized from said solvents to increase optical purity followed by treatment with an alkali to liberate the free (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate with an optical purity of 96-98%. The alkali is selected from sodium hydroxide or sodium bicarbonate.

The optically pure intermediate of formula (IX) can be obtained from any commercial source or prepared by any conventional known method, for example US4925969.

The pure ramipril or its salt obtained by the process of the present invention may be formulated into a dosage form, e.g., tablet, capsule, etc., by combining with one or more pharmaceutically acceptable excipients using known techniques. Further, the dosage form may be immediate release or extended release.

The following experimental examples are illustrative of the invention but not limitative of the scope thereof.

**Example 1. Preparation of cis, endo,-2-azabicyclo-[3.3.0]-octane-3-carboxylic acid hydrochloride (R=H)**

40 gm of methyl-3-chloro-2-acetyl amino propionate, 45.8gm of cyclopentenopyrrolidine, 27 gm of triethyl amine and 120 ml of toluene were charged in a reaction flask at 0° C. The temperature of reaction mixture was increased to 25° C and it was stirred at the same till the completion of reaction. After completion the reaction mixture was concentrated under vacuum. The residue thus obtained was acidified with concentrated hydrochloric acid and the resultant mixture was extracted with ethyl acetate, after separation of layers the organic layer was concentrated under vacuum, 5N HCl (135ml) was added to the residue and the mixture was stirred for 5 hr, distillation of water gave the residue which was taken into 400ml glacial acetic acid followed by addition of 4gm Pd/C. The reaction mixture was hydrogenated under pressure of 5kg/cm<sup>2</sup> and at a temperature of 60°C± 2 °C, after completion of reaction the catalyst was filtered and the filtrate was distilled to obtain a residue which was slurried with acetone to get the title product.

Yield= 14gm; 33% yield

**Example 2.** Preparation of benzyl cis-endo-2-azabicyclo-[3.3.0]-octane-3-carboxylate hydrochloride

37.3 gm of thionyl chloride and 76.3 gm of benzyl alcohol were mixed in a reaction flask at 0° C, to this mixture 15 gm of carboxylic acid obtained as per example (1) was added. The temperature of reaction mixture was raised to 25° C and it was further stirred till the completion of reaction. The solvent was distilled off followed by addition of diisopropyl ether to precipitate the product. The precipitated product was filtered and dried.

Yield=18.4gm; 83%

**Example 3.** Preparation of benzyl cis-endo-2-azabicyclo-[3.3.0]-octane-3-carboxylate *p*-toluene sulphonic acid salt

15 gm of carboxylic acid obtained as per example (1) and 150 ml of toluene were mixed in a reaction flask followed by addition of 16.6 gm of *p*-toluenesulphonic acid and 29.6 gm of benzyl alcohol. The reaction mixture was heated to reflux and water was removed by dean stark. Once the theoretical amount of water was collected, solvent was distilled off from reaction mixture under vacuum, diisopropylether (45 ml) was added to the residue and the precipitated product was collected by filtration.

Yield 23gm; 70%

**Example 4.** Preparation of mandelic acid salt of 2-azabicyclo [3.3.0] octane-3-carboxylic acid benzyl ester

Sodium hydroxide (25.5 gm) was dissolved in 150ml water and to the resultant solution 100 gms of racemic -2-azabicyclo [3.3.0] octane-3-carboxylic acid benzyl ester hydrochloride in 400 ml of ethyl acetate were added. The reaction mixture was stirred and layers were separated. To the ethyl acetate layer 29.7 gm of S-(+) -mandelic acid in 400ml of ethyl acetate was added. The reaction mixture was cooled to 0°C, the precipitated mandelic acid salt was filtered and dried.

Yield 57.0gm (81% of required isomer)

**Examples 5.** Preparation of (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylic acid benzyl ester hydrochloride

50.0 gms of mandelic acid salt of 2-azabicyclo [3.3.0] octane-3-carboxylic acid benzyl ester and 137.5 ml water were mixed, to this mixture a solution of sodium hydroxide (5.53 gm sodium hydroxide+50ml water) and 250 ml of dichloromethane were added. The reaction mixture was stirred at 25-30° C, layers separated and organic layer was concentrated to obtain a residue, to this 250 ml isopropyl alcohol and 50 ml of isopropanolic solution of hydrochloric acid was added. The reaction mixture was cooled to about 0° C the product thus crystallized was filtered and dried.

Yield 32.5gm (91%)

Purity SSS isomer 98%, RRR isomer 2% (HPLC area %)

30 gm of salt obtained as above mentioned process step was dissolved in 1200ml of isopropyl alcohol the reaction mixture was heated to reflux followed by cooling to about 30° C, the reaction mixture was filtered and the product thus obtained was dried under vacuum

Yield 27.5 gm; 91%

Purity SSS isomer 100%. RRR isomer nil (HPLC area %)

#### **Example 6. Preparation of benzyl ramipril**

40 gms of (S,S,S)-2-azabicyclo[3.3.0]-octane-3-carboxylic acid benzyl ester hydrochloride was charged in a round bottom flask to this 40 gms of triethylamine, 26gms of 1-hydroxybenzotriazole, 46 gms of N-[1-(S)-(ethoxy carbonyl)-3-phenylpropyl]-L-alanine, 33 gms of N,N dicyclohexyl carbodimide and 700ml of dichloromethane were added. The reaction mixture was stirred at 25-30° C for 16 hrs. Dicyclohexyl urea precipitated out and was removed by filtration. The filtrate was washed with 1200ml of water followed by distillation of solvent to obtain benzyl ramipril as oil.

Yield=71.9gm

#### **Example 7. Preparation of ramipril**

15 gms of benzyl ramipril, 100ml of ethanol, and 1.5 gm of Pd/C were taken in an autoclave. The hydrogenation was carried out at 30° C and a pressure of 5.0 kg/Cm<sup>2</sup> till completion of reaction, after completion of reaction the catalyst was filtered out, the filtrate was distilled off to obtain residue. To the residue 75ml of acetonitrile was added, the product was crystallized, reaction mixture was filtered and the crystalline product thus obtained was dried. It was further purified using acetonitrile.

Yield 8.4 gm, (68%)

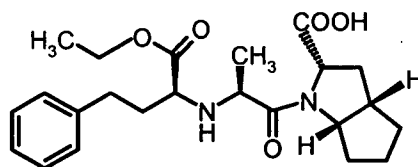
**Example 8. Preparation of ramipril**

25 gms of benzyl ramipril, 250 ml of ethanol and 2.5 gms of Pd/C were taken in an autoclave. The hydrogenation was carried out at 30°C and a pressure of 5.0 kg/cm<sup>2</sup> till completion of the reaction, after completion of reaction the catalyst was filtered out, the filtrate was distilled off to obtain the residue. To the residue 75 ml of ethyl acetate was added. The product was crystallized, the reaction mixture was filtered and the crystallized product thus obtained was dried. It was further purified using ethyl acetate.

Yield 13.9 gms; (68 %).

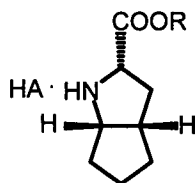
**We Claim,**

1. A process for preparing ramipril of formula (XII) comprising :

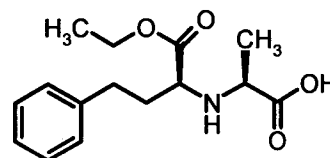


Formula (XII)

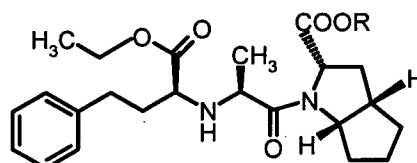
- a. reacting a compound of formula (VII) wherein R=H, alkyl, benzyl, or any protecting group, and HA represents an acid capable of forming salt, with N-[1-(S)-(ethoxy carbonyl)-3-phenylpropyl]-L-alanine of formula (IX) in presence of dicyclohexylcarbodiimide and 1-hydroxybenzotriazole to form a compound of formula (X) wherein R is as defined above and;



Formula(VII)



Formula (IX)



Formula (X)

- b. converting the compound of formula (X) obtained in step (a) to ramipril.
2. A process for preparation of ramipril as claimed in claim 1, wherein compound of formula (VII) is consisting essentially of (S,S,S)- isomer.
  3. A process as claimed in claim 1 or 2 wherein (S,S,S)- isomer of compound of formula (VII) contains no detectable amount of (R,R,R)- isomer.

4. A process as claimed in any of the preceding claim, wherein the compound of formula (VII) is benzyl (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylate or salt with no detectable amount of (R,R,R)- isomer.
5. A process as claimed in any of the preceding claim, wherein the reaction is in presence of a base.
6. A process as claimed in claim 4, wherein the base is selected from organic bases.
7. A process as claimed in any of the preceding claim, wherein the reaction is in presence of an inert organic solvent.
8. A process as claimed in claim 6, wherein the organic solvent is selected from a group comprising of esters, hydrocarbon, polar aprotic solvent or mixtures thereof.
9. A process as claimed in claim 1, wherein the step (b) is in presence of hydrogenation catalyst and a suitable solvent.
10. A process as claimed in claim 1, wherein the HA of formula VII is selected from hydrochloric acid, *p*-toluenesulfonic acid, benzenesulfonic acid, methane sulfonic acid.
11. A process as claimed in claim 1, wherein the compound of formula VII is purified from a solvent selected from linear or branched chain alcohol.
12. A process as claimed in claim 10, wherein solvent is methanol, ethanol or isopropyl alcohol.
13. A process as claimed in claim 1, further comprising isolating ramipril from a solvent selected from a group consisting of aliphatic ethers, aliphatic ketones,

aliphatic alcohols, aliphatic or aromatic hydrocarbons, alkyl esters or aliphatic nitrile or mixture thereof.

14. A process as claimed in claim 1, wherein recovered ramipril is free of (R,R,R,S,S)- isomer.
15. Use of (S,S,S)-2-azabicyclo [3.3.0] octane-3-carboxylic acid, esters or its salt with no detectable amount of (R,R,R) - isomer in the preparation of ramipril.