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(54) **Title:** PROCESS FOR PREPARING TRANDOLAPRIL AND INTERMEDIATES THEREOF

(57) **Abstract:** The present invention relates to an improved process for the preparation of Trandolapril and intermediate compounds useful in the preparation of Trandolapril.

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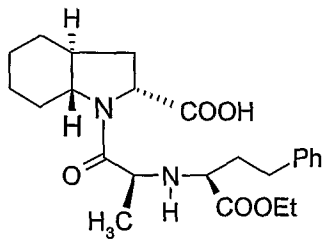
Process for preparing Trandolapril and intermediates thereof

Field of the invention

The present invention relates to an improved process for the preparation of Trandolapril and intermediate compounds useful in the preparation of Trandolapril

Background of the invention

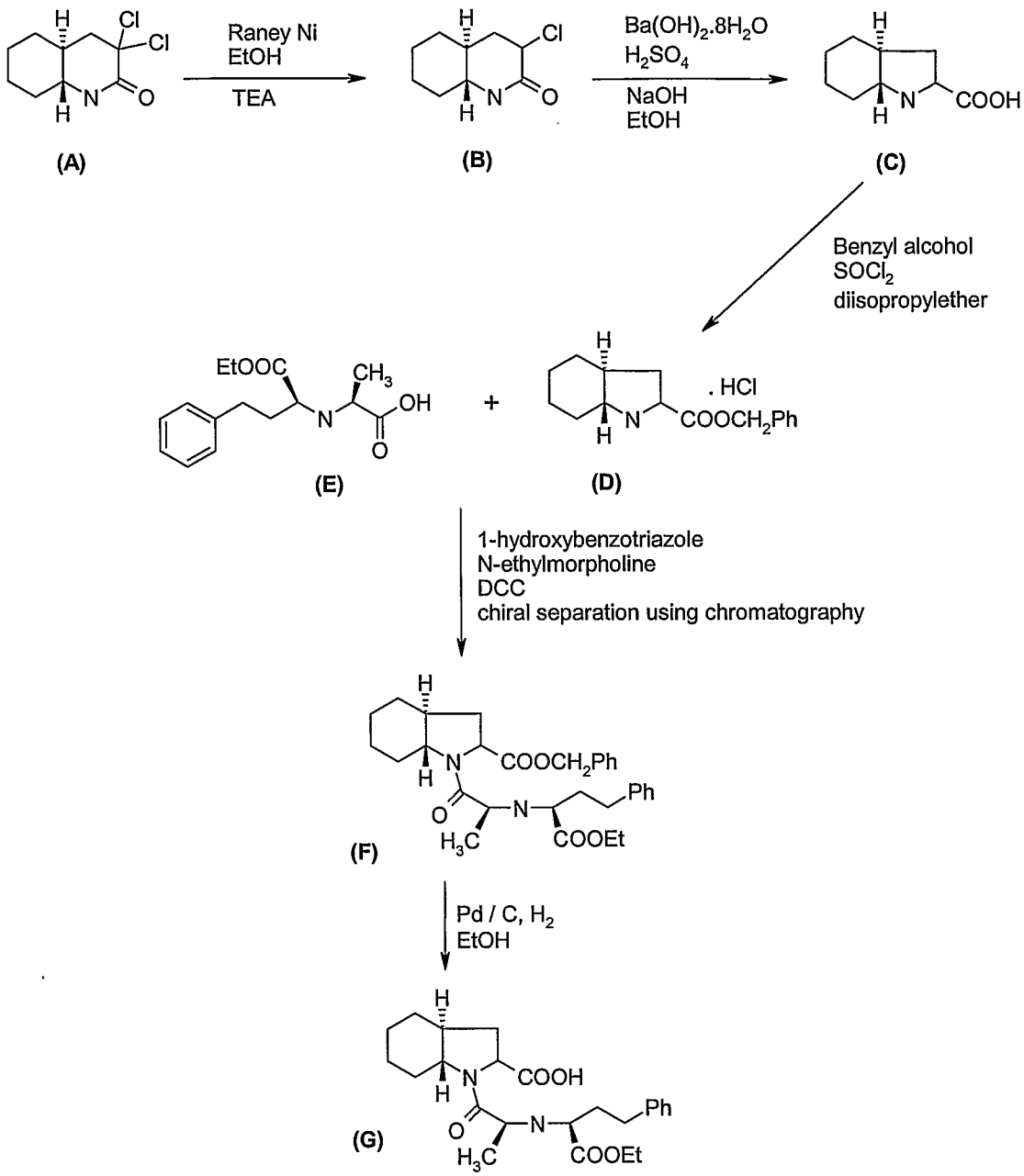
Trandolapril is an angiotensin converting enzyme inhibitor and was first disclosed in the US Patent No. 4,933,361, which is herein incorporated by reference. Chemically, Trandolapril is (2*S*, 3a*R*, 7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydro-1*H*-indole-2-carboxylic acid (Formula I)



Formula I

US Patent No. 4,933,361 also discloses a method of preparation of Trandolapril as summarized in the reaction **Scheme 1**. 3,3-dichloro-*trans*-octahydro-1*H*-quinoline-2-one (**A**) is selectively monodehalogenated to 3-chloro-*trans*-octahydro-1*H*-quinoline-2-one (**B**) in presence of a Raney nickel catalyst. The intermediate compound (**B**) on reaction with barium hydroxide at reflux temperature gives intermediate *dl*-octahydroindole-2-carboxylic acid (**C**), which is separated from the reaction mixture using hot ethanol. The intermediate acid (**C**) is further converted to *dl*-benzyloctahydroindole-2-carboxylic acid hydrochloride (**D**) in presence of thionyl chloride and benzyl alcohol and the intermediate hydrochloride (**D**) obtained is condensed with 1-(1*S*-carboethoxy-3-phenylpropyl)-*S*-alanine (**E**) in presence of 1-hydroxybenzotriazole, *N*-methylmorpholine and DCC to give diastereomeric mixture of benzyl protected Trandolapril. The diastereomeric mixture is separated into individual isomers using silica chromatography and the appropriate isomer (**F**) is debenzylated in presence of H_2-Pd/C to afford stereochemically pure Trandolapril (**G**).

Scheme 1



The process summarized in **Scheme 1** has several limitations when operated on an industrial scale. Firstly, the reaction using barium hydroxide produces a large amount undesired inorganic solids that need to be removed completely by repeated extractions in order to ensure the success of further reaction steps. Another industrial limitation is in the chiral separation using silica chromatography, which is time consuming and cost/energy intensive.

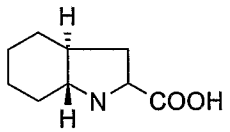
There have been a few efforts to improve the said conventional manufacturing process of Trandolapril and its intermediate compounds. For example, US Patent No. 6,559,318 also incorporated herein by reference, provides a process for chiral octahydro-1*H*-indole-2-carboxylic acids using enzymatic resolution approach. US Patent No. 5,011,940 also incorporated herein by reference provides a process for the preparation of bicyclic amino acids using radical cyclization.

A quick review of the available literature on this subject reveals that the synthetic processes currently available for the preparation of Trandolapril and its intermediates are tedious and cost/energy intensive. In view of this, there exists an urgent need to develop a simpler and efficient process for preparing Trandolapril and its intermediate. The applicants of the present invention have successfully investigated the possibility of designing such a novel process, which is described herein.

Summary of the invention

Accordingly the present invention provides an improved process for the preparation of Trandolapril and intermediate compounds useful in the preparation of Trandolapril.

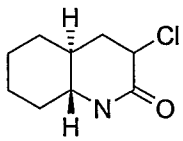
In one embodiment of the invention, there is provided an improved process for the preparation of *dl*-octahydroindole-2-carboxylic acid of formula II



Formula II

comprising

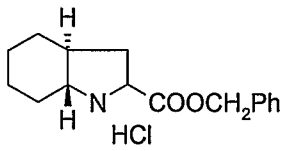
(a) contacting 3-chloro-*trans*-1*H*-quinoline-2-one of formula III with a basic compound, and



Formula III

(b) recovering the said *dl*-octahydroindole-2-carboxylic acid from the reaction mass using an ion exchange resin.

In another embodiment of the invention, there is provided a process for the preparation of *dl*-benzyloctahydroindole-2-carboxylate hydrochloride of formula (IV)



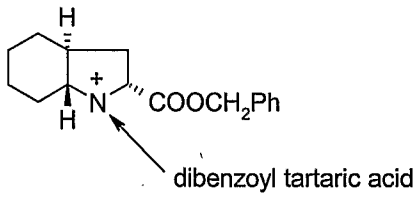
Formula IV

comprising

(a) contacting *dl*-octahydroindole-2-carboxylic acid of formula (II) with benzyl alcohol in presence of thionyl chloride, and

(b) isolating the said *dl*-benzyloctahydroindole-2-carboxylate hydrochloride.

In another embodiment of the invention, there is disclosed a compound L-(-)-benzyloctahydroindole -2-carboxylate-dibenzoyl-*L*-tartaric acid salt (V) which is an important intermediate in the preparation of Trandolapril.



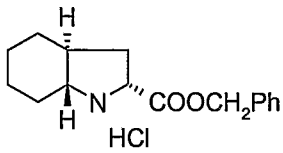
Formula V

In yet another embodiment of the invention, there is provided a process for the preparation of *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl- *L*-tartaric acid salt (V) comprising:

(a) contacting *dl*-benzyloctahydroindole-2-carboxylate or its hydrochloride salt with *L*(-)-dibenzoyl tartaric acid in presence of solvent, and

(b) isolating the *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl- *L*-tartaric acid salt (V).

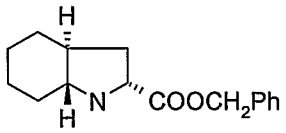
In a further embodiment of the invention, there is provided a process for the preparation of *L*-(-)- benzyloctahydroindole-2-carboxylate hydrochloride (VI)



Formula VI

comprising:

(a) contacting *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl- *L*-tartaric acid salt of formula V with a base in presence of a solvent to give *L*-(-)benzyloctahydroindole-2-carboxylate of formula VII,

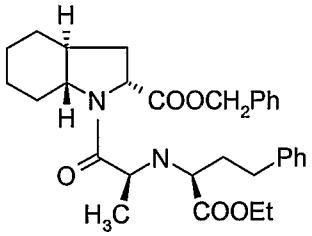


Formula VII

(b) converting the said *L*-(-)benzyloctahydroindole-2-carboxylate into its hydrochloride, and

(c) optionally purifying the said *L*-(-)benzyloctahydroindole-2-carboxylate hydrochloride

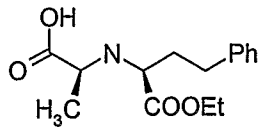
In a still further embodiment of the invention, there is provided a process for the preparation of benzyl protected Trandolapril of formula VIII



Formula VIII

comprising

(a) contacting *L*-(-)benzyloctahydroindole-2-carboxylate or its hydrochloride salt with *N*-(1-(*S*)-ethoxycarbonyl-3-phenylpropyl)- *L*-alanine of formula IX

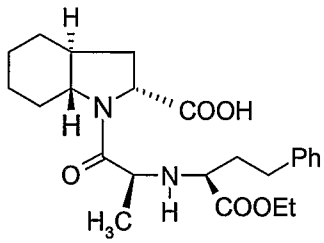


Formula IX

or it's reactive derivative in presence of a base and a solvent, and

(b) isolating, and optionally purifying, the said benzyl protected Trandolapril of formula VIII

In a still further embodiment of the invention, there is provided a process for the preparation of Trandolapril of formula I



Formula I

comprising

(a) debenylating the benzyl protected Trandolapril of formula VIII, and

(b) isolating, and optionally purifying, the obtained Trandolapril.

Further aspects and embodiment of the invention may become apparent to those skilled in the art from a review of the following detailed description, taken in conjugation with the examples and the claims. It must be understood that the present disclosure is intended as illustrative only and is not intended to limit the scope of the invention to the specific embodiments described herein

Brief description of the figures

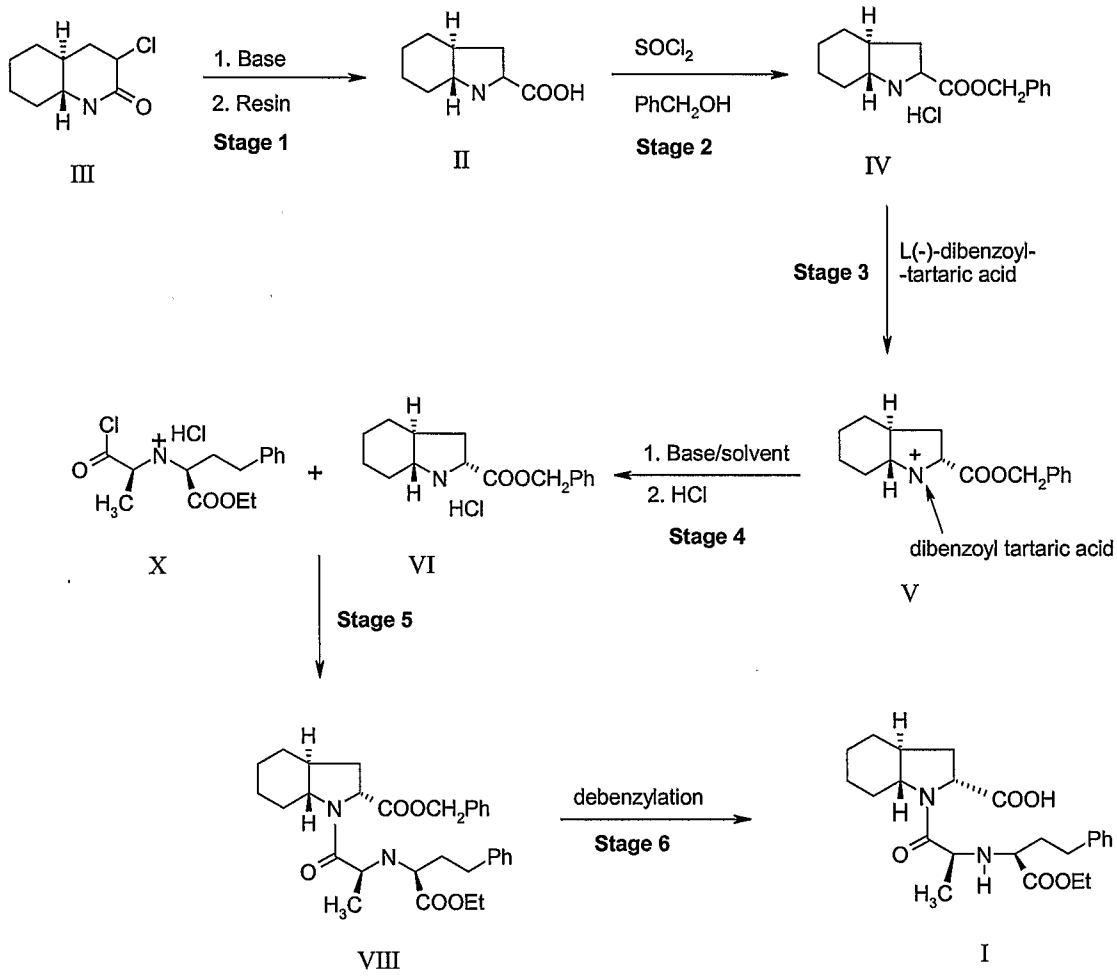
FIG 1 is DSC thermogram of *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl- *L*-tartaric acid salt (V)

FIG 2 is infrared spectrum of *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-L-tartaric acid salt (V)

Detailed description of the invention

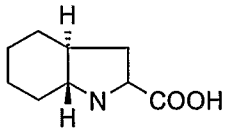
Accordingly, the present invention provides an improved process for the preparation of Trandolapril and several intermediate compounds useful in the preparation of Trandolapril as summarized in reaction **Scheme 2.**

Scheme 2



Stage 1: *dl*-octahydroindole-2-carboxylic acid

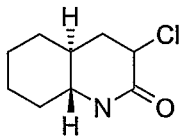
In one aspect of the invention there is provided an improved process for the preparation of *dl*-octahydroindole-2-carboxylic acid of formula II



Formula II

comprising:

(a) contacting 3-chloro-*trans*-1*H*-quinoline-2-one of formula III with a basic compound, and



Formula III

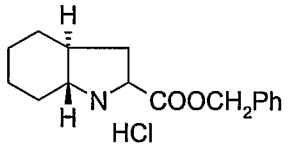
(b) recovering the said *dl*-octahydroindole-2-carboxylic acid from the reaction mass using an ion exchange resin.

The conversion of 3-chloro-*trans*-1*H*-quinoline-2-one into *dl*-octahydroindole-2-carboxylic acid may be achieved in presence of a basic compound, through a reaction commonly known as Favorski rearrangement. A basic compound is a compound, which can act as a base under the reactions conditions. Other compounds capable of effecting the said Favorski rearrangement reaction may also be advantageously used as basic compounds. Typical examples of such basic compounds without any limitation include barium hydroxide, sodium hydroxide, potassium hydroxide and alike. The rearrangement reaction may be conducted in the presence or absence a solvent. Preferred examples of solvents if used include, without any limitation, water, organic solvents or mixture thereof. The inorganic salts obtained during the rearrangement reaction may be removed by known techniques like acidifying the reaction mixture and isolating the inorganic solids. Especially, when barium hydroxide is used as a basic compounds for the rearrangement reaction, the reaction mass may be treated with an acid to form barium salts which may be filtered off before subjecting the reaction mass to the

resin treatment. It is an advantageous feature of the present invention that the reaction mass obtained in the rearrangement step (a) may as such be subjected to step (b) for resin treatment without isolating any solids. It is desirable that the *p*H of the reaction mass obtained in the step (a) is adjusted to about 6.5 before the contents are passed through an ion-exchange resin, which retains the desired product *dl*-octahydroindole-2-carboxylic acid. A wide variety of resins may be employed in the separation process. Preferably the resin employed is a cationic resin. Typical examples of such resins without any limitation include is Indion-170, Indion-130, Indion –190 and alike. After passing the reaction mass, the resin is eluted with an eluent capable of selectively eluting the said *dl*-octahydroindole-2-carboxylic acid. A variety of eluents may be used for the elution purpose depending on the requirement. It is preferred that the eluent used is ammonium hydroxide. The eluted solvent is collected and optionally distilled to afford a residue. The residue thus obtained is optionally treated with an organic solvent, preferably alcohol and the solids thus obtained are isolated. It is interesting to note that the filtrate obtained after the resin treatment is substantially free of any inorganic solvents (residue after ignition < 0.20%) as compared to that obtained without resin treatment (residue after ignition >20%). This exemplifies the exceptional performance of the resin treatment. It is noteworthy, that the removal of solids from the product *dl*-octahydroindole-2-carboxylic acid is very crucial. It has been observed that the presence of any solids in quantities more than 1% may lead to decomposition the said *dl*-octahydroindole-2-carboxylic acid in the subsequent process step.

Stage 2: *dl*-benzyloctahydroindole-2-carboxylate hydrochloride

In another aspect of the invention, there is provided a process for the preparation *dl*-benzyloctahydoindole-2-carboxylate hydrochloride of formula (IV)



Formula IV

comprising:

(a) contacting *dl*-octahydroindole-2-carboxylic acid of formula (II) with benzyl alcohol in presence of thionyl chloride, and

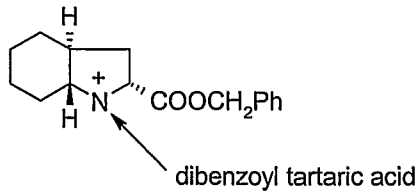
(b) isolating the said *dl*-benzyloctahydroindole-2-carboxylate hydrochloride.

The *dl*-octahydroindole-2-carboxylic acid used in step (a) above is preferably prepared according a process described in Stage 1. In a typical procedure, *dl*-octahydroindole-2-carboxylic acid is contacted with benzyl alcohol in presence of thionyl chloride optionally in the presence of an inert solvent at a temperature between about -20°C to about 25°C. More preferably, the temperature is between about -10°C to about 20°C. Temperatures beyond these may also be employed if desired. Other chlorinating agents such as $POCl_3$, PCl_5 and alike may also be employed in place of thionyl chloride in the above reaction if desired. The reaction mass thus obtained is stirred preferably at a temperature below about 20°C until the reaction is complete to a satisfactory extent. After the reaction is complete, the reactions mass is optionally brought to room temperature and the residual gases are degassed by applying a vacuum or purging an inert gas. Excess benzyl alcohol may be removed by a simple or vacuum distillation. It is preferred that the benzyl alcohol is removed at a temperature below 80°C because of the possibility of the product degradation. The residue thus obtained containing desired product may optionally be treated with an organic solvent, preferably an alcohol, ether or acetone, and the product obtained is filtered off. *dl*-Benzyloctahydroindole-2-carboxylate hydrochloride thus obtained may further be purified by treating with an organic solvent at an elevated temperature.

The inventors note that the amount of benzyl alcohol employed for benzylation reaction has a significant effect on the product yield. The product assay increases with increase in benzyl alcohol amount, but at higher amounts of benzyl alcohol than stoichiometry, the product assay drops down. This could be because benzyl alcohol is a high boiler and if present in large excess would require higher temperatures and longer time to remove. The product *dl*-benzyloctahydroindole-2-carboxylate or its hydrochloride salt may not be stable at high temperatures for longer times.

Stage 3: *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt

In another aspect of the invention, there is disclosed a compound *L*-(-)-benzyloctahydroindole-2-carboxylate-dibenzoyl- *L*-tartaric acid salt (V) which is an important intermediate in the preparation of Trandolapril.



Formula V

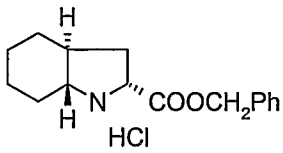
In a further aspect of the present invention, there is also provided a process for the preparation of *L*-(-)-benzyloctahydroindole-2-carboxylate-dibenzoyl- *L*-tartaric acid salt (V) comprising:

(a) contacting *dl*-benzyloctahydroindole-2-carboxylic acid or its hydrochloride salt with *L*-(-)-dibenzoyl tartaric acid in presence of solvent, and
(b) isolating the *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl- *L*-tartaric acid salt (V).

A wide variety of solvents may be employed in the above step (a) such as alkyl, aryl, heteroalkyl solvents which may optionally be substituted. Typical classes of such solvents include without any limitation alcohols, ketones, esters, ethers, chlorinated solvents and alike. Illustrative examples of such solvents without any limitation include toluene, xylene, dichloromethane, chloroform, ethanol, ether, ethyl acetate, hexane and alike. The choice of a suitable is very crucial for the satisfactory success of the reaction. Preferably such solvent should have significant difference in the solubility of *d* and *l* isomers of the said benzyloctahydroindole-2-carboxylate-dibenzoyl- *L*-tartaric acid salt. Preferably the solvent used is ethyl acetate. It should be noted that a skilled artisan might appreciate existence of another such preferable solvent or a mixture of solvents. The said *L*-(-)benzyloctahydroindole -2- carboxylate-dibenzoyl-L-tartaric acid salt thus obtained may be further purified by treating with an organic solvent or a mixture of solvents. Preferably the said *L*-(-)-benzyloctahydroindole-2-carboxylate-dibenzoyl-L-tartaric acid salt is purified by heating in alcohol-water mixture, cooling to the room temperature and filtering the pure compound.

Stage 4: *L*(-)benzyloctahydroindole-2-carboxylate hydrochloride

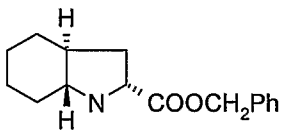
In a further aspect of the invention there is provided a process for the preparation of *L*-(-)-benzyloctahydroindole-2-carboxylate hydrochloride (VI)



Formula VI

comprising:

(a) contacting *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl- *L*-tartaric acid salt of formula V with a base in presence of a solvent to give *L*-(-)benzyloctahydroindole-2-carboxylate of formula VII,



Formula VII

(b) converting the said *L*-(-)benzyloctahydroindole-2-carboxylate into its hydrochloride salt, and

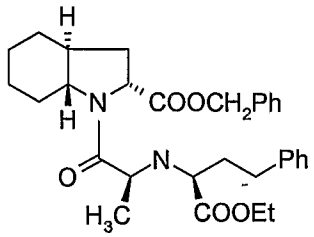
(c) optionally purifying the said *L*-(-)benzyloctahydroindole-2-carboxylate hydrochloride

A wide variety of bases can be used in step (a) above. The typical examples of such bases without any limitation include organic bases (such as triethylamine, pyridine, DBN, DABCO, DBU and alike), inorganic bases (such as potassium carbonate, sodium hydroxide, potassium hydroxide and alike). It is a further advantageous feature of the present invention that a wide variety of solvents may be employed in the above step (a) such as alkyl, aryl, heteroalkyl solvents which may optionally be substituted. Typical classes of such solvents include without any limitation alcohols, ketones, esters, ethers, chlorinated solvents and alike. Illustrative examples of such solvents with any limitation include toluene, xylene, dichloromethane, chloroform, ethanol, ether, ethyl acetate, hexane and alike. Preferably, the solvent used is isopropyl ether because it extracts only the product *L*-(-)benzyloctahydro-indole-2-carboxylate and not the liberated resolving agent. The *L*-(-)benzyloctahydroindole-2-carboxylate obtained may be isolated and purified or as such contacted with alcoholic hydrochloride solution to get the desire *L*-(-)benzyloctahydroindole-2-carboxylate hydrochloride. The alcoholic hydrochloride is preferably an isopropyl alcohol hydrochloride. The hydrochloride salt formation reaction is preferably carried out at a temperature between

about 10°C to about 40°C. The product *L*-(-)benzyloctahydroindole-2-carboxylate hydrochloride may be further purified if desired.

Stage 5: benzyl protected Trandolapril

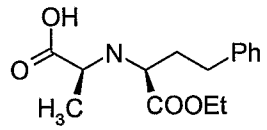
In a further aspect of the invention, there is provided a process for the preparation of benzyl protected Trandolapril of formula VIII



Formula VIII

comprising

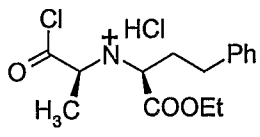
(a) contacting *L*-(-)benzyloctahydroindole-2-carboxylate or its hydrochloride salt with *N*-(1-(*S*)-ethoxycarbonyl-3-phenylpropyl)- *L*-alanine of formula IX or it's reactive derivative in presence of a base and a solvent, and



Formula IX

(b) isolating, and optionally purifying, the said benzyl protected Trandolapril of formula VIII

The *L*-(-)benzyloctahydroindole-2-carboxylate or its hydrochloride salt used herein is preferably prepared by a procedure given in Stage 4, although a different source may also be advantageously used. The *L*-(-)benzyloctahydroindole-2-carboxylate or its hydrochloride salt is contacted with *N*-(1-(*S*)-ethoxycarbonyl-3-phenylpropyl)- *L*-alanine of formula IX or it's reactive derivative in presence of a base and a solvent. Typical examples of reactive derivatives of *N*-(1-(*S*)-ethoxycarbonyl-3-phenylpropyl)- *L*-alanine include, without any limitation, *N*-(1-(*S*)-ethoxycarbonyl-3-phenylpropyl)- *L*-alanine hydrochloride, *N*-(1-(*S*)-ethoxycarbonyl-3-phenylpropyl)- *L*-alanine chloride hydrochloride (formula X) and a like.

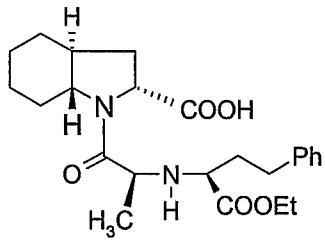


Formula X

The condensation reaction is conducted in presence of a base. A wide variety of bases can be used in step (a) above. Typical examples of such bases without any limitation include organic bases (such as triethylamine, pyridine, DBN, DABCO, DBU and alike), inorganic bases (such as potassium carbonate, sodium hydroxide, potassium hydroxide and alike). It is a further advantageous feature of the present invention that a wide variety of solvents may be employed in the above step (a) such as alkyl, aryl, heteroalkyl solvents which may optionally be substituted. Typical classes of such solvents include without any limitation alcohols, ketones, esters, ethers, chlorinated solvents and alike. Illustrative examples of such solvents with any limitation include toluene, xylene, dichloromethane, chloroform, ethanol, ether, ethyl acetate, hexane and alike. Preferably, the solvent used is dichloromethane. A skilled artisan would appreciate that variety of other solvents or their mixtures may be employed depending upon the requirement.

Stage 6: Trandolapril

In a still further aspect of the invention there is provided a process for the preparation of Trandolapril of formula I



Formula I

comprising

(a) debenylating the benzyl protected Trandolapril of formula VIII, and

(b) isolating, and optionally purifying, the obtained Trandolapril.

The benzyl protected Trandolapril is preferably prepared according to a procedure given in Stage 4. The debenzylation may be achieved using several methods including those reported in the prior art. In one of the preferred methods according to the present invention, the

debenzylation is achieved by contacting the benzyl protected Trandolapril with hydrogen in presence of a catalyst and a solvent. The catalyst used in this reaction is preferably a transition metal catalyst. Most preferably, the catalyst used is a palladium catalyst. As far as a solvent is concerned, again a wide variety of solvents can be used in this reaction including substituted or unsubstituted alkyl, aryl, heteroaryl solvents. It is preferred that the solvent used is a C_1-C_8 alcohol. Most preferably the solvent is selected from a group comprising methanol, ethanol or isopropyl alcohol. After the debenzylation reaction is complete, the crude Trandolapril is isolated from the reaction mass and optionally, further purified using single or a mixture of organic solvent. Preferably the crude Trandolapril is purified by crystallizing from a solvent mixture wherein at least one solvent is an alcohol. Typical examples of such solvent mixtures include methanol: ethyl acetate; ethanol: ethyl acetate; isopropyl alcohol: ethyl acetate and a like. More preferably, the crude Trandolapril is purified by crystallizing from a mixture of isopropyl alcohol: ethyl acetate

The present invention is described in more details with reference to the following examples that are only illustrative and should not be construed as a limitation on the scope of the invention.

Examples

Example-1: *dl*-octahydroinode-2-carboxylic acid.

A mixture of barium hydroxide (5.10 kg) and water (90.0 ltr) were heated to 75-80°C in SSR reactor and to it 3-chloro-*trans*-octahydro-1*H*-quinoline-2-one (5.17 Kg) was added and refluxed (95-98°C) for 4 hours. After cooling to 60°C, the reaction mixture was transferred to the GLR reactor and then added sulfuric acid (1.55 lit). The contents were further refluxed to reaction mixture for 1 hour and cooled to room temperature and filtered. Filtrate was adjusted to *p*H = 6.5 with 1N sodium hydroxide solution and the material passed through cationic resin (Indion-170). The resin column was eluted 2N ammonium hydroxide and the ammoniacal filtrate obtained was distilled under vacuum to get a solid residue. The residue was triturated with isopropyl alcohol (40 ltr) and filtered. A white solid thus obtained was dried (60-65°C) in vacuum oven to get *dl*-octahydroindole-2-carboxylic acid (3.74 kg). Assay determined by HPLC was more than 99.00 %.

Residue on ignition = 0.16 %.,

Melting point = 275-280°C

Example-2: *dl*-benzyloctahydroindole-2-carboxylate hydrochloride.

To a cooled solution of benzyl alcohol (6.75 ltr, -5°C) was drop wise added thionyl chloride (1.5 ltr) and the temperature was maintained at 0 to –5°C. After addition of thionyl chloride was completed, the reaction temperature brought to -8°C and the solid *dl*-octahydroindole-2-carboxylic acid (1.50 kg) was added below –5 °C in lot wise. The reaction mixture was stirred 0 to -5°C for 6 hours and brought to room temperature. The residual gases were degassed using industrial vacuum. Benzyl alcohol was distilled under high vacuum below 80°C. Residue thus obtained was triturated with isopropyl ether (15 ltr) and the reaction mixture was cooled and filtered. The wet material obtained was refluxed with acetone (10.0 ltr) for 1 hour and then cooled to room temperature, further cooled to 0 to 5°C and filtered to get (after drying) *dl*-benzyloctahydroindole-2-carboxylate hydrochloride as a white crystalline solid (2.05 kg). Assay determined by HPLC was 95.00%

Example-3: *L*(-) benzyloctahydroindole-2-carboxylate-dibenzoyl- *L*-tartaric acid salt.

To a solution of *dl*-benzyloctahydroindole-2-carboxylate (free base, 175.0 gm) in ethyl acetate (1.80 ltr) was drop wise added a solution of *L*-(-)dibenzoyltartaric acid (276.44 gm) in ethyl acetate (600 ml) between 25 to 40°C. A massive precipitation was obtained. The resultant suspension is then heated at 50 to 55°C for 8 to 10 hours and the mixture is then cooled to a temperature below 30°C and then maintained at this temperature for another 2 hours with stirring. The mixture is then filtered and residue is washed with fresh ethyl acetate (100 ml) and suck dried. The wet weight of tartarate salt was 400 to 450 gm, which was taken in isopropyl alcohol (3.0 ltr) and heated to 60-65 ^{0}C for 2.0 hours. Deionized water (600 ml) was added to the heterogeneous mixture and further maintained for 2 hours. The mixture was then cooled to a room temperature over a period of 30 minutes and then stirred at this temperature for an additional 60 minutes. The crystalline white solid material was filtered and dried under vacuum at 50°C to obtain the desired *L*-(-) benzyloctahydroindole-2-carboxylate-dibenzoyl- *L*-tartaric acid salt (160gm).

Melting point = 164 to 166°C.

Specific optical rotation = -99.81°(C = 0.2 % Methanol).

Assay by HPLC,

a) *L*-(-)benzyloctahydroindole-2-carboxylate base = 40.52 % (on anhydrous basis)
b) *L*-(-)dibenzoyl-L-tartaric acid = 59.80 % (on anhydrous basis)

Example-4: *L*-(-)-benzyloctahydroindole-2-carboxylate free base

L-(-)-Benzyloctahydroindole-2-carboxylate-dibenzoyl-(*L*)-tartaric acid (217 gm) is taken in isopropyl ether (2 ltr) and suspension is stirred at 20 to 30°C under nitrogen. To the mixture was added a pre-cooled solution of sodium hydroxide in (40 gm in 685 ml of water) over a period of 15 minutes while maintaining the temperature below 30°C. The resultant suspension was then stirred until all solids were dissolved (about 15 to 30 minutes) and the layers were separated. The aqueous layer was then extracted with isopropyl ether (500 ml). The combined organic layers were washed with water (750 ml) and dried over anhydrous sodium sulfate to afford *L*-(-) benzyloctahydroindole-2-carboxylate (free base) in a diisopropyl ether (2.55 ltr) and used as such in the next stage.

Example-5: *L*-(-)benzyloctahydroindole-2-carboxylate hydrochloride.

L-(-) benzyloctahydroindole-2-carboxylate (free base) in a diisopropyl ether (2.55 ltr) obtained in example 4 was cooled to a temperature below 20°C and was added over a period of 30 minutes, isopropyl alcoholic hydrochloride (30%, 40gm) to obtain a white hydrochloride salt. The resultant suspension was stirred furthermore for 2 hours, filtered and wet hydrochloride salt was washed with isopropyl ether (2 × 100 ml) to obtain the desired *L*-(-) benzyloctahydroindole-2-carboxilate hydrochloride (90 gm) as a white solid.

Specific optical rotation= - 49 to 51 (C = 1.0, methanol).

Melting point = 142 to 146°C.

Assay was determined by HPLC = 99.00 %.

Example-6: ECPP-Alanine chloride hydrochloride. (ECPP= *N*-(1-(*S*)-ethoxycarbonyl-3-phenylpropyl))

ECPP-alanine (600 gm) was taken in dichloromethane (2.40 ltr) and cooled to –5°C and HCl gas was bubbled into the reaction mixture below 0°C followed by addition of phosphorous pentachloride (581.50 gm) and the contents were maintained for 5 hrs. ECPP-alanine chloride hydrochloride (compound X) was precipitated by adding isopropyl ether (3.60ltr) and filtered. Wet weight of the material (1069gm) was taken in dichloromethane (4.80ltr) and used for coupling reaction in next stage.

Example-7: Benzyl protected Trandolapril

L(-)-benzyloctahydroindole-2-carboxylate hydrochloride (600 gm) was taken in dichloromethane (3 ltr) and cooled to –10°C . Triethylamine (768gm) was added dropwise below –5°C followed by addition of ECPP-alanine chloride hydrochloride (suspended in dichloromethane). Progress of reaction was monitored by HPLC. After completion of reaction, reaction mixture was diluted with water and the organic layer was separated. Dichloromethane was distilled off to afford benzyl protected Trandolapril as an oil (1088gm).

Example-8: Trandolapril

Benzyl protected Trandolapril (1085 gm) obtained above was debenzylated in presence of Pd/C catalyst (120 gm) and hydrogen (50 psi) in isopropyl alcohol (6 ltr) at 20 to 25°C for 8 to 10 hours. After hydrogenation, catalyst was filtered and isopropyl alcohol was distilled out under vacuum to get and oily mass which is diluted with isopropylether and stirred for 3 hours at room temperature and filtered the white solid crude Trandolapril. Crude Trandolapril was purified in a mixture of isopropyl alcohol: isopropyl ether to give a white crystalline pure Trandolapril.

Assay and purity are determined by HPLC was above 99.80 %

SOR = - 16.50 to 18.50 (C= 2, ethanol)

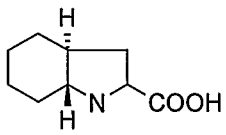
Advantageous features of the present invention

1. The present provides an improved process for isolation of *dl*-octahydroindole-2-carboxylic acid by using an ion exchange resin, which limits the inorganic solid content in the product to less than 0.2%. The resin can be reused again after a simple regeneration step.
2. The invention provides an improved process for the Trandolapril using a novel intermediate *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt, which affords high stereoselective yields
3. The present invention also for the first time discloses synthesis of Trandolapril using *N*-(1-(*S*)-ethoxycarbonyl-3-phenylpropyl)-*L*-alanine chloride hydrochloride (formula X).

Claims

We claim

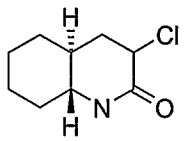
1. A process for the preparation of *dl*-octahydroindole-2-carboxylic acid of formula II



Formula II

comprising:

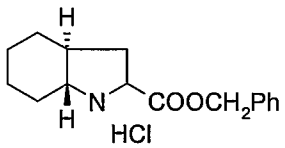
(a) contacting 3-chloro-*trans*-1*H*-quinoline-2-one of formula III with a basic compound, and



Formula III

(b) recovering the said *dl*-octahydroindole-2-carboxylic acid from the reaction mass using an ion exchange resin.

2. A process according to claim 1 wherein the basic compound is selected from a group comprising of sodium hydroxide, potassium hydroxide and barium hydroxide.
3. A process according to claim 1 or 2 wherein the resin used is a cationic resin
4. A process according to claim 3 wherein the cationic resin is selected from a group comprising of Indion-130, Indion-170 and Indion-190.
5. A process for the preparation *dl*-benzyloctahydoindole-2-carboxylate hydrochloride of formula (IV)



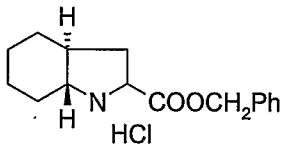
Formula IV

comprising:

(a) contacting *dl*-octahydroindole-2-carboxylic acid of formula (II) with benzyl alcohol in presence of thionyl chloride, and

(b) isolating the said *dl*-benzyloctahydroindole-2-carboxylate hydrochloride.

6. A process for the preparation *dl*-benzyloctahydoindole-2-carboxylate hydrochloride of formula (IV)



Formula IV

comprising:

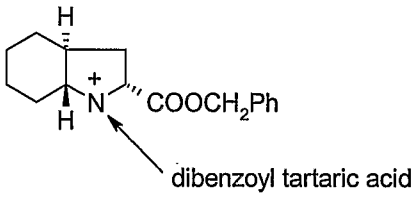
(a) preparing *dl*-octahydroindole-2-carboxylic acid of formula (II) according to any of the claims 1 to 4

(b) contacting the said *dl*-octahydroindole-2-carboxylic acid obtained in step (a) above with benzyl alcohol in presence of thionyl chloride, and

(c) isolating the said *dl*-benzyloctahydroindole-2-carboxylate hydrochloride.

7. A process for the preparation *dl*-benzyloctahydoindole-2-carboxylate hydrochloride of formula (IV) according to claim 5 or 6 further comprising purifying the said *dl*-benzyloctahydoindole-2-carboxylate hydrochloride by refluxing in an organic solvent

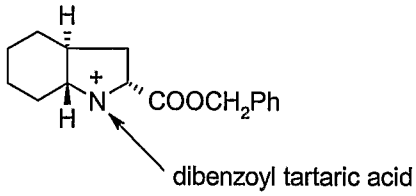
8. A compound which is *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt of formula (V).



Formula V

9. A process for the preparation of Trandolapril using *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt of formula (V) claimed in claim 8, as an intermediate

10. A process for the preparation of *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt of formula V



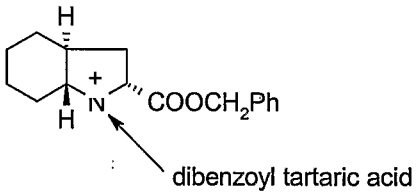
Formula V

comprising

(b) contacting *dl*-benzyloctahydroindole-2-carboxylic acid or its hydrochloride salt with *L*(-)-dibenzoyl tartaric acid in presence of solvent, and

(c) isolating the *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt (V).

11. A process for the preparation of *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt of formula V



Formula V

comprising

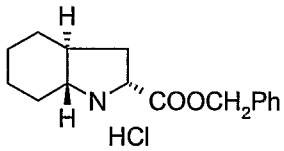
(a) preparing *dl*-benzyloctahydroindole-2-carboxylic acid or its hydrochloride salt according any of the claims 5, 6 or 7

(b) contacting the said *dl*-benzyloctahydroindole-2-carboxylic acid or its hydrochloride salt obtained in step (a) above with L(-)-dibenzoyl tartaric acid in presence of solvent, and

(c) isolating the *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt (V).

12. A process according to claim 10 or 11 wherein the solvent used in step (b) is ethyl acetate
13. A process according to claim 10, 11 or 12 wherein the step (b) further comprises heating the reaction contents at about 20°C to 60°C for about 5 to about 30 minutes
14. A process according to claim 13 wherein step (b) further comprises cooling the reaction contents to room temperature and stirring at room temperature for about 1 to about 5 hours.
15. A process according to any of the claims 10 to 14 further comprising a purification step wherein the crude *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt of formula V is heated in presence of isopropyl alcohol and water for about 2 hours, cooling to room temperature and isolating the said pure *L*-(-)- benzyl - octahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt.

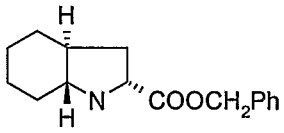
16. A process for the preparation of *L*-(-)- benzyloctahydroindole-2-carboxylate hydrochloride (VI)



Formula VI

comprising:

(a) contacting *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt of formula V with a base in presence of a solvent to give *L*-(-) benzylocta – hydroindole-2-carboxylate of formula VII,

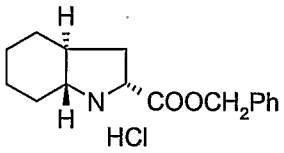


Formula VII

(b) converting the said *L*-(-)benzyloctahydroindole-2-carboxylate into its hydrochloride salt, and

(c) optionally purifying the said *L*-(-)benzyloctahydroindole-2-carboxylate hydrochloride

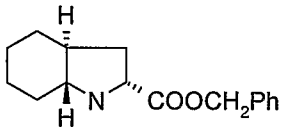
17. A process for the preparation of *L*-(-)- benzyloctahydroindole-2-carboxylate hydrochloride (VI)



Formula VI

comprising:

(a) preparing *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt of formula V according to any of the claims 10 to 15 and contacting the said *L*-(-)- benzyloctahydroindole-2-carboxylate-dibenzoyl-*L*-tartaric acid salt with a base in presence of a solvent to give *L*-(-) benzyloctahydroindole-2-carboxylate of formula VII,



Formula VII

(b) converting the said *L*-(-)benzyloctahydroindole-2-carboxylate into its hydrochloride salt, and

(c) optionally purifying the said *L*-(-)benzyloctahydroindole-2-carboxylate hydrochloride

18. A process according to claim 16 or 17 wherein the base used is selected from a group comprising of sodium hydroxide, potassium hydroxide, potassium carbonate, triethylamine and pyridine.

19. A process according to any of the claims 16, 17 or 18 wherein the solvent used is selected from a group comprising diethyl ether, ethyl methyl ether and isopropyl ether.

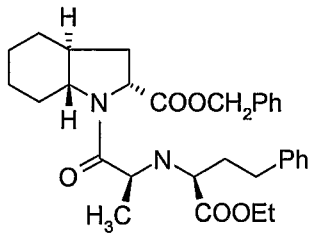
20. A process for the preparation of *L*-(-)- benzyloctahydroindole-2-carboxylate hydrochloride (VI) according to any of the claims 16 to 19 wherein the said *L*-(-)

benzyloctahydroindole-2-carboxylate is converted into its hydrochloride salt by contacting with alcoholic hydrochloride

21. A process for the preparation of *L*-(-)- benzyloctahydroindole-2-carboxylate hydrochloride (VI) according to claim 20 wherein alcoholic hydrochloride used is isopropyl alcohol hydrochloride

22. A process for the preparation of *L*-(-)- benzyloctahydroindole-2-carboxylate hydrochloride (VI) according to any of the claims 16 to 21 wherein the hydrochloride salt formation reaction is conducted at a temperature between about 10°C to about 40°C

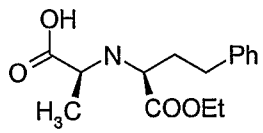
23. A process for the preparation of benzyl protected Trandolapril of formula VIII



Formula VIII

comprising:

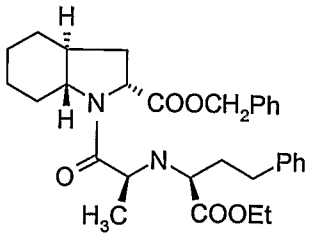
(a) contacting *L*-(-)benzyloctahydroindole-2-carboxylate or its hydrochloride salt with *N*-(1-(*S*)-ethoxycarbonyl-3-phenylpropyl)-*L*-alanine of formula IX or it's reactive derivative in presence of a base and a solvent, and



Formula IX

(b) isolating, and optionally purifying, the said benzyl protected Trandolapril of formula VIII

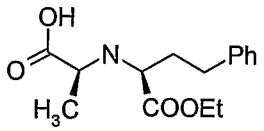
24. A process for the preparation of benzyl protected Trandolapril of formula VIII



Formula VIII

comprising

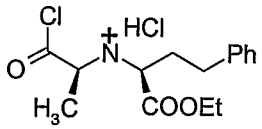
(a) preparing *L*-(-)benzyloctahydroindole-2-carboxylate or its hydrochloride salt according to any of the claims 16 to 22 and contacting with *N*-(1-(*S*)-ethoxycarbonyl-3-phenylpropyl)-*L*-alanine of formula IX or it's reactive derivative in presence of a base and a solvent, and



Formula IX

(b) isolating, and optionally purifying, the said benzyl protected Trandolapril of formula VIII

25. A process for according to claim 23 or 24 wherein the reactive derivative of *N*-(1-(*S*)-ethoxycarbonyl-3-phenylpropyl)-*L*-alanine is *N*-(1-(*S*)-ethoxycarbonyl-3-phenylpropyl)-*L*-alanine chloride hydrochloride (formula X).



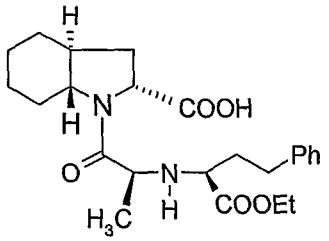
Formula X

26. A process according any of the claims 23 to 25 wherein the base used is an organic amine

27. A process according any of the claims 23 to 25 wherein the bases used is selected from a group comprising of triethylamine, pyridine, DBU, DABCO, DBN, sodium hydroxide, potassium hydroxide, potassium carbonate.

28. A process according to any of the claims 23 to 27 wherein the solvent used is selected from a group comprising of ethyl acetate, hexane, ethylene dichloride and dichloromethane.

29. A process for the preparation of Trandolapril of formula I



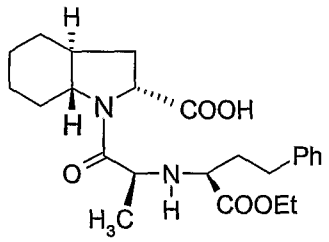
Formula I

comprising

(a) debenylating the benzyl protected Trandolapril of formula VIII, and

(b) isolating, and optionally purifying, the obtained Trandolapril.

30. A process the preparation of Trandolapril of formula I



Formula I

comprising

(a) preparing benzyl protected Trandolapril according to any of the claims 26 to 31 and debenylating the said benzyl protected Trandolapril, and

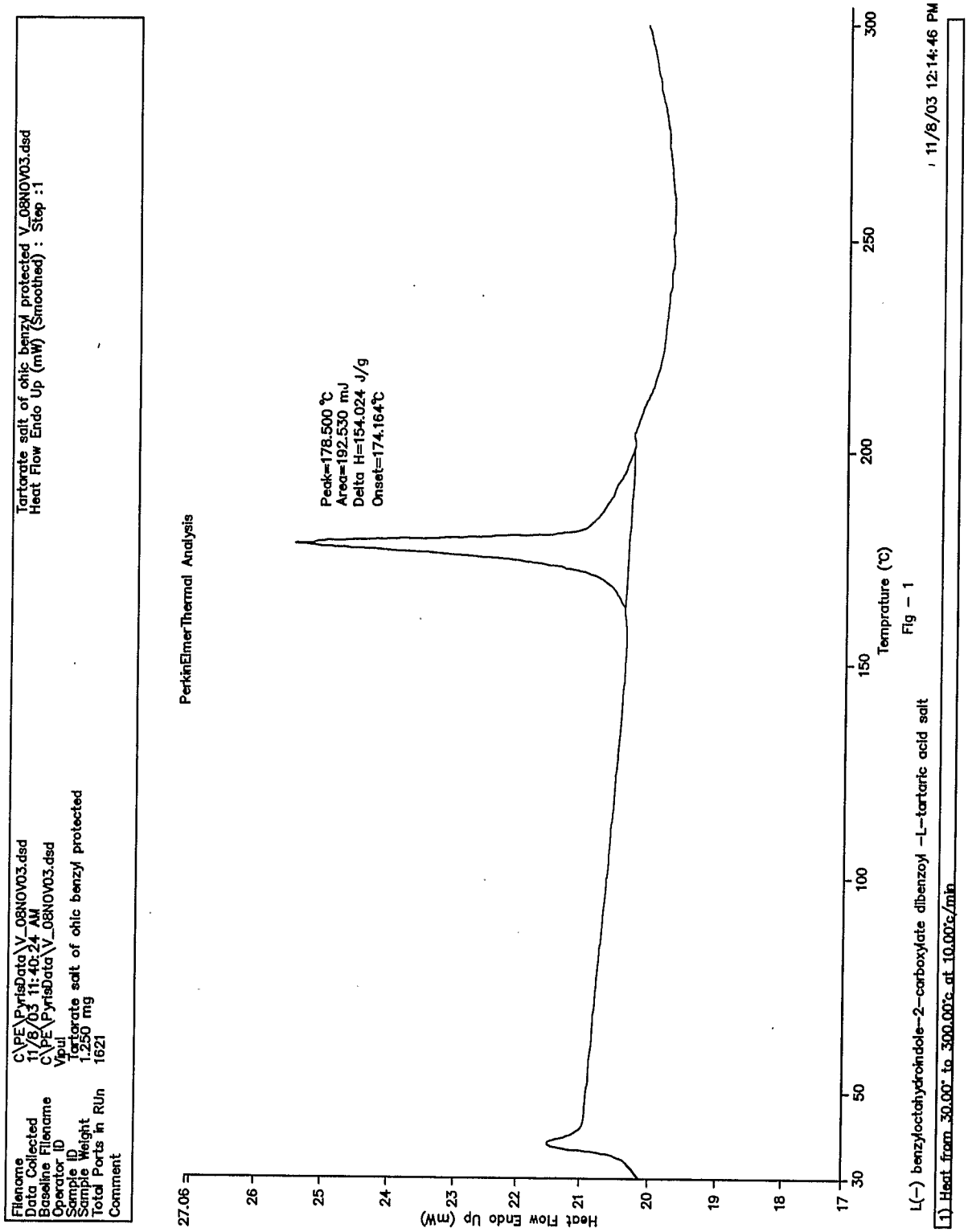
(b) isolating, and optionally purifying, the obtained Trandolapril.

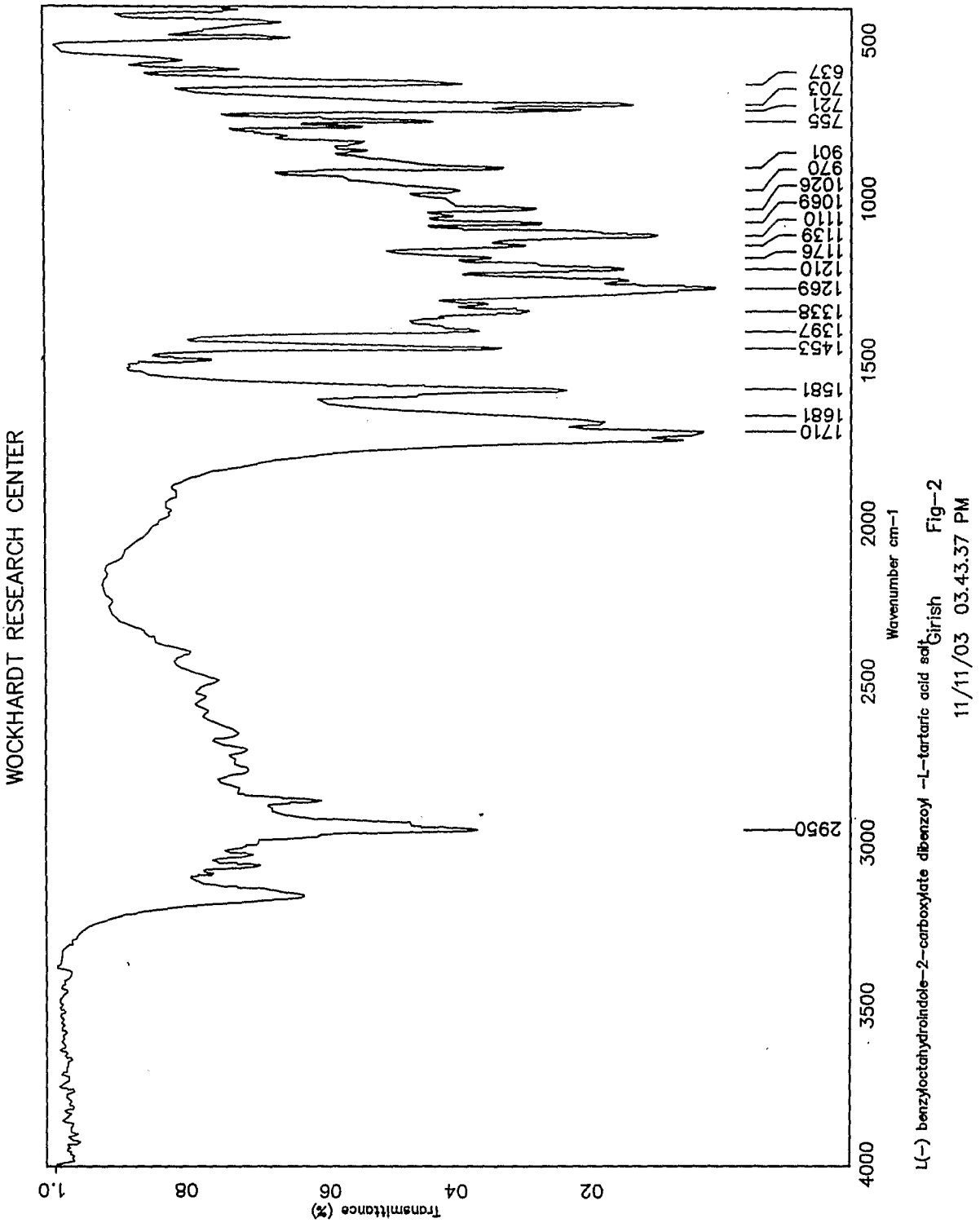
31. A process according to claim 29 or 30 wherein the debenzylation comprises of contacting the said benzyl protected Trandolapril with hydrogen in presence of a catalyst.

32. A process according to claim 31 wherein the transition metal catalyst is selected from a group comprising of palladium, platinum, rhodium and nickel catalyst.

33. A process according to claim 32 wherein the catalyst is Pd/C

34. A process according to claim any of the claims 31 to 33 wherein the solvent used is an alcohol.
35. A process according to claim 37 wherein the solvent is selected isopropyl alcohol.
36. A process according to any of the claims 31 to 35 wherein the reaction temperature is between about 10°C to about 80°C.


Filename C\PE\PyrisData\V_08NOV03.dsd
Data Collected 11/8/03 11:40:24 AM
Baseline Filename C\PE\PyrisData\V_08NOV03.dsd
Operator ID Vipul
Sample ID Tartarate salt of ohic benzyl protected
Sample Weight 1.250 mg
Total Ports in RUn 1621
Comment
Tartarate salt of ohic benzyl protected V_08NOV03.dsd
Heat Flow Endo Up (mW) (Smoothed) : Step :1
PerkinElmerThermal Analysis
Peak=178.500 °C
Area=192.530 mJ
Delta H=154.024 J/g
Onset=174.164°C
Heart Flow Endo Up (mW)
27.06
26
25
24
23
22
21
20
19
18
17
30
50
100
150
200
250
300
Temprature (°C)
Fig – 1
L(–) benzyloctahydroindole–2–carboxylate dibenzoyl –L–tartaric acid salt
1) Heat from 30.00° to 300.00°c at 10.00°c/min
11/8/03 12:14:46 PM


WOCKHARDT RESEARCH CENTER
Transmittance (%)
1.0
0.8
0.6
0.4
0.2
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
2950
1710
1681
1581
1453
1397
1338
1269
1210
1176
1139
1110
1069
1026
970
901
755
721
703
637
L(-) benzyloctahydroindole-2-carboxylate dibenzoyl -L-tartaric acid salt
Girish
Fig-2
11/11/03 03.43.37 PM