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(54) Title: NOVEL PROCESS FOR PREPARATION OF OPTICALLY PURE NOREPHEDRINE AND ITS DERIVATIVES

(57) Abstract: The present invention relates to a novel process for preparation of norephedrine and its derivatives. The present invention also relates to a process for separation of individual isomers of norephedrine and its derivatives using suitable chiral resolving agents.

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"NOVEL PROCESS FOR PREPARATION OF OPTICALLY PURE NOREPHEDRINE AND ITS DERIVATIVES"

PRIORITY

This application claims the benefit under Indian Provisional Application No. 4906/CHE/2013 filed on 31 October 2013 and entitled "Novel process for preparation of optically pure Norephedrine and its derivatives", the content of which is incorporated by reference herein.

FIELD OF THE INVENTION

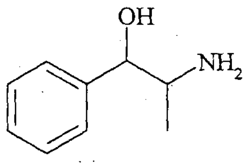
The present invention relates to a novel process for preparation of norephedrine and its derivatives, particularly norephedrine, pyrrolidinyl norephedrine and the like with high chiral purity; a chiral auxillary useful in the preparations of anti retroviral drugs like efavirenz.

The present invention also relates to a process for separation of individual isomers of norephedrine and its derivatives using suitable chiral resoluting agents.

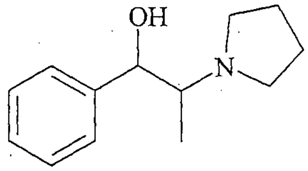
BACKGROUND OF THE INVENTION

Chiral amine derivatives like pyrrolidinyl norephedrine play an important role in the pharmaceutical and chemical industry. Chiral amine derivatives in general are frequently used as a resolving agents or intermediates or synthons for the preparation of various physiologically, for instance pharmaceutically active substances. In a great number of the various applications of chiral amine derivatives, only one particular optically active form has the desired physiological activity. Thus, there is a clear need to provide processes for the preparation of chiral amine derivatives in an optically active form.

Pyrrolidinyl norephedrine is a pyrrolidine derivative of Norephedrine, chemically known as 1-phenyl-2-(pyrrolidin-1-yl) propan-1-ol, represented by the following structural Formula:



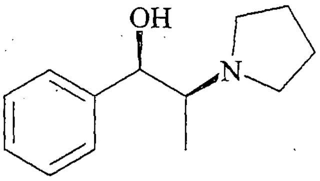
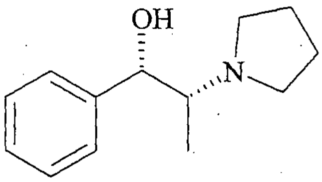
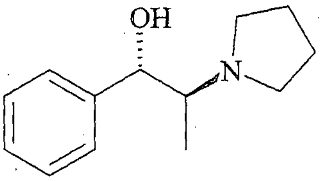
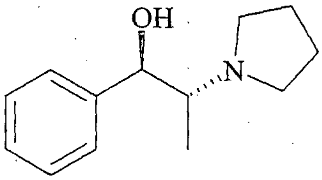
Norephedrine



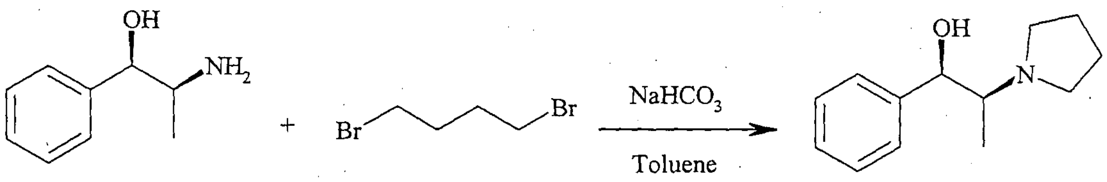
Pyrrolidinyl norephedrine

Norephedrine and its derivatives exhibits optical isomerism and have chiral centers, giving rise to four stereoisomers. By convention the pair of enantiomers with the stereochemistry (1R, 2S and 1S, 2R) is designated norephedrine derivatives, while the pair of enantiomers with the stereochemistry (1R, 2R and 1S, 2S) is called norpseudoephedrine derivatives.

The optical isomers of Pyrrolidinyl norephedrine, particularly the (1R, 2S) – enantiomer, is use as a resolving agents. The four enantiomers are represented by the following structural formula:

 (1R, 2S)	 (1S, 2R)
 (1S, 2S)	 (1R, 2R)

U.S. Patent No. 5,856,492 discloses a process for the preparation of pyrrolidinyl norephedrine by reacting (1R, 2S) - norephedrine with 1,4-dibromobutane as mentioned in the below scheme:



PCT Publication No. 2013/0244543 discloses a method of production of active chiral amines from alpha hydroxyl ketone using enzyme transaminase as the biocatalyst.

The reported literature disclose the use of norephedrine as intermediate or starting material, which is a controlled substance and thus having certain limitations when using in commercial scale operations and further the reported literature involves enzymatic reactions, which are not viable in commercial scale operations.

It would be desirable to provide a process for preparation of norephedrine and its derivatives with high chiral purity, which is simple and cost effective that would avoid the aforementioned difficulties.

The present invention provides a process for the preparation of norephedrine and its derivatives, particularly norephedrine, pyrrolidinyl norephedrine and the like with simple and commercially available starting materials that avoids controlled substances and enzymatic reactions.

SUMMARY OF THE INVENTION

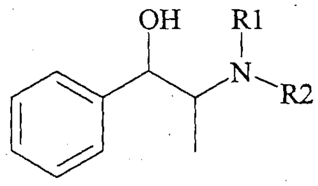
The present invention encompasses to a novel process for preparation of norephedrine and its derivatives with high chiral purity.

The present invention relates to a novel process for preparation of norephedrine with high chiral purity.

The present invention also relates to a novel process for preparation of pyrrolidinyl norephedrine with high chiral purity.

The present invention also relates to a process for separation of individual isomers of norephedrine and its derivatives using suitable chiral resoluting agents.

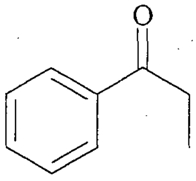
In accordance with one embodiment, the present invention provides a process for the preparation of norephedrine and its derivatives of Formula I,



Formula I

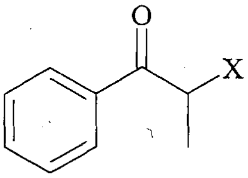
wherein R1 and R2 independently represent hydrogen or R1 and R2 combine to form a cyclic ring; comprising:

a) reacting propiophenone of Formula IV



Formula IV

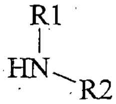
with a suitable halogenating agent to obtain halopropiophenone of Formula III,



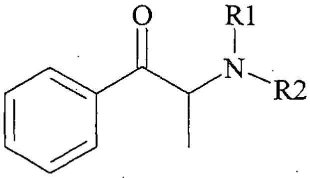
Formula III

wherein 'X' is a halogen selected from Cl, Br or I;

b) reacting the resulting halopropiophenone with a suitable amine source of Formula



wherein R1 and R2 independently represents hydrogen or a formyl group; or R1 and R2 combine to form a cyclic ring; to obtain a keto compound Formula II; and

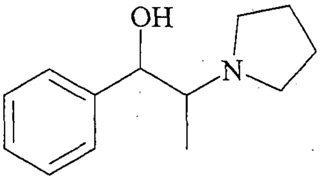


Formula II

wherein R1 and R2 independently represent hydrogen or R1 and R2 combine to form a cyclic ring;

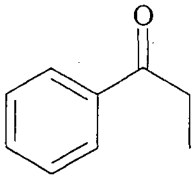
c) reducing the keto compound of Formula II with a suitable reducing agent to obtain norephedrine derivative of Formula I.

In accordance with a second embodiment, the present invention provides a process for the preparation of pyrrolidinyl norephedrine of Formula IA, comprising:



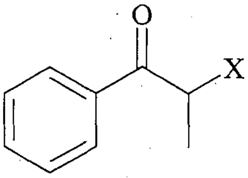
Formula IA

a) reacting propiophenone of Formula IV



Formula IV

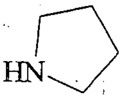
with a suitable halogenating agent to obtain halopropiophenone of Formula III,



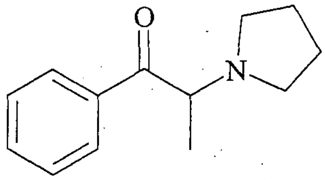
Formula III

wherein 'X' is a halogen selected from Cl, Br or I;

b) reacting the resulting halopropiophenone with pyrrolidine of Formula



to obtain a keto compound Formula IIA; and



Formula IIA

c) reducing the keto compound of Formula IIA with a suitable reducing agent to obtain pyrrolidinyl norephedrine.

In accordance with a third embodiment, the present invention provides a process for the preparation of optically pure pyrrolidinyl norephedrine of Formula IA, comprising:

a) reacting propiophenone of Formula IV with a suitable halogenating agent to obtain halopropiophenone of Formula III, wherein 'X' is a halogen selected from Cl, Br or I;
b) reacting the resulting halopropiophenone with pyrrolidine to obtain a keto compound Formula IIA;
c) reducing the keto compound of Formula IIA with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine; and
d) separating the optical isomers of pyrrolidinyl norephedrine.

In accordance with a fourth embodiment, the present invention provides a process for the preparation optically pure pyrrolidinyl norephedrine, comprising:

a) reacting propiophenone of Formula IV with a suitable halogenating agent to obtain halopropiophenone of Formula III, wherein 'X' is a halogen selected from Cl, Br or I;
b) reacting the resulting halopropiophenone with pyrrolidine to obtain a keto compound of Formula IIA;
c) reducing the keto compound of Formula IIA with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine; and
d) treating the resultant mixture with a suitable chiral acid to obtain pyrrolidinyl norephedrine.

In accordance with a fifth embodiment, the present invention provides a process for the preparation of optically pure pyrrolidinyl norephedrine, comprising:

a) reacting propiophenone of Formula IV with a suitable halogenating agent to obtain halopropiophenone of Formula III, wherein 'X' is a halogen selected from Cl, Br or I;
b) reacting the resulting halopropiophenone with pyrrolidine to obtain a keto compound of Formula IIA;
c) reducing the keto compound of Formula IIA with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine; and
d) treating the resultant mixture with a suitable chiral acid to obtain optically pure pyrrolidinyl norephedrine;

wherein the halogen is Chloro or Bromo;

wherein the suitable reducing agent is selected from the group comprising sodium borohydride, lithium aluminum hydride, vitride (Sodium bis(2-methoxyethoxy)aluminum hydride), DIBAL-H and the like;

wherein the metal salt is represented by the formula MX_2, wherein the 'M' represents a metal cation selected from zinc, beryllium, magnesium, calcium, cerium, strontium, manganese, copper and barium; 'X' represents halide, acetate or trifluoromethane sulfonate;

wherein the suitable chiral acid is selected from the group comprising D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, L(+)-tartaric acid, L(+)-malic acid, L(+)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

In accordance with a sixth embodiment, the present invention provides a process for the preparation of optically pure (1R, 2S) - pyrrolidinyl norephedrine, comprising: treating either any ratio of optical isomers of pyrrolidinyl norephedrine or its mixture with optical isomers of pyrrolidinyl norpseudoephedrine with a suitable chiral acid in an appropriate solvent to obtain (1R, 2S) - pyrrolidinyl norephedrine.

In accordance with a seventh embodiment, the present invention provides a process for the preparation of optically pure (1R, 2S) - pyrrolidinyl norephedrine, comprising: treating either any ratio of optical isomers of pyrrolidinyl norephedrine or its mixture with optical isomers of pyrrolidinyl norpseudoephedrine with a suitable chiral acid in an appropriate solvent to obtain (1R, 2S) - pyrrolidinyl norephedrine; wherein the suitable chiral acid is selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

In accordance with an eighth embodiment, the present invention provides a process for the preparation of (1R, 2S) - pyrrolidinyl norephedrine, comprising:

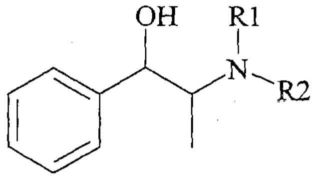
a) reacting propiophenone of Formula IV with a suitable halogenating agent to obtain halopropiophenone of Formula III, wherein 'X' is a halogen selected from Cl, Br or I;
b) reacting the resulting halopropiophenone with pyrrolidine to obtain a keto compound of Formula IIA;
c) reducing the keto compound of Formula IIA with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine;
d) treating the resultant mixture with a suitable chiral acid to obtain (1S, 2R) - pyrrolidinyl norephedrine; and
e) treating the mother liquors containing (1R, 2S) - pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine with a suitable chiral acid to obtain (1R, 2S) - pyrrolidinyl norephedrine.

In accordance with a ninth embodiment, the present invention provides a process for the isomer separation of (1R, 2S) - pyrrolidinyl norephedrine, comprising:

a) providing a solution of racemic mixture comprising optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine;
b) treating the resultant mixture with a suitable chiral acid to obtain salt of (1S, 2R) - pyrrolidinyl norephedrine,
c) neutralizing the mother liquors containing a salt of (1R,2S)-pyrrolidinyl norephedrine and salt of optical isomers of pyrrolidinyl norpseudoephedrine with a base to obtain (1R, 2S) - pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine;
d) treating the resultant mixture with a suitable chiral acid to obtain a salt of (1R, 2S) - pyrrolidinyl norephedrine, and
e) neutralizing the salt of (1R, 2S) - pyrrolidinyl norephedrine with a base to obtain optically pure (1R, 2S) - pyrrolidinyl norephedrine;

wherein the suitable chiral acid of step b) is selected from the group comprising L(+)-tartaric acid, L(+)-malic acid, L(+)-lactic acid and the like and suitable chiral acid of step d) is selected from the group comprising D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

In another embodiment, the present invention provides a chiral acid salt compound of Formula I,



Formula I

wherein R1 and R2 independently represent hydrogen or R1 and R2 combine to form a cyclic ring;

wherein the chiral acid is selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, L(+)-tartaric acid, L(+)-malic acid, L(+)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

In accordance with an eleventh embodiment, the present invention provides a chiral acid salt of pyrrolidinyl norephedrine; wherein the chiral acid is selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, L(+)-tartaric acid, L(+)-malic acid, L(+)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

In accordance with a twelfth embodiment, the present invention provides a process for the preparation of (1R, 2S) - pyrrolidinyl norephedrine, comprising:

a) providing mother liquors containing either any ratio of optical isomers of pyrrolidinyl norephedrine or its mixture with pyrrolidinyl norpseudoephedrine,
b) evaporating the solvent from the mother liquors to obtain a residue,
c) treating the residue with an oxidizing agent in an appropriate solvent to obtain keto compound of Formula IIA,
d) reducing the keto compound of Formula IIA with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and pyrrolidinyl norpseudoephedrine; and
e) treating the resulting mixture with a suitable chiral acid to obtain (1R, 2S) - pyrrolidinyl norephedrine.

In accordance with a thirteenth embodiment, the present invention provides a process for isomer enrichment of optical purity of (1R, 2S) - pyrrolidinyl norephedrine or a salt thereof, comprising:

a) combining (1R, 2S) - pyrrolidinyl norephedrine or a salt thereof with a suitable solvent;
a) heating to obtain clear solution,
b) optionally seeding the chiral acid salt of (1R, 2S) - pyrrolidinyl norephedrine,
c) cooling the solution to precipitation, and
d) isolating the pure (1R, 2S) - pyrrolidinyl norephedrine or salt thereof.

In accordance with a fourteenth embodiment, the present invention provides a process for the preparation of optically pure (1S, 2R) - pyrrolidinyl norephedrine, comprising: treating a mixture of (1S, 2R) and (1R, 2S) optical isomers of pyrrolidinyl norephedrine, with a suitable chiral acid in an appropriate solvent to obtain (1S, 2R) - pyrrolidinyl norephedrine;
wherein the suitable resoluting agent is selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl

phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

In accordance with a fifteenth embodiment, the present invention provides a process for the preparation of (1S, 2S) - pyrrolidinyl norpseudoephedrine, comprising:

a) reducing a keto compound of Formula IIA with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and pyrrolidinyl norpseudoephedrine;
b) separating the optical isomers of pyrrolidinyl norpseudoephedrine from the resulting mixture of step a) using a column chromatography with a suitable eluent,
c) treating the resultant optical isomers of pyrrolidinyl norpseudoephedrine with a suitable chiral acid to obtain (1S, 2S) - pyrrolidinyl norpseudoephedrine.

In accordance with a sixteenth embodiment, the present invention provides a process for the preparation of (1S, 2S) - pyrrolidinyl norpseudoephedrine, comprising:

a) reducing a keto compound of Formula IIA with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and pyrrolidinyl norpseudoephedrine;
b) separating the optical isomers of pyrrolidinyl norpseudoephedrine from the resulting mixture of step a) using a column chromatography with a suitable eluent,
c) treating the resultant optical isomers of pyrrolidinyl norpseudoephedrine with a suitable chiral acid to obtain (1S, 2S) - pyrrolidinyl norpseudoephedrine;

wherein the suitable chiral acid is selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

In accordance with a seventeenth embodiment, the present invention provides a process for enrichment of optical purity of (1S, 2S) - pyrrolidinyl norpseudoephedrine, comprising:

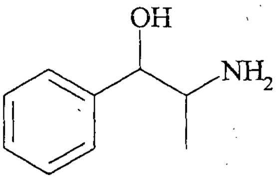
a) combining a chiral acid salt of (1S, 2S) - pyrrolidinyl norpseudoephedrine with a suitable solvent;
b) heating to obtain clear solution,
c) cooling the solution to precipitation,
d) isolating the pure chiral acid salt of (1S, 2S) - pyrrolidinyl norpseudoephedrine, and
e) neutralizing the salt of (1S, 2S) - pyrrolidinyl norephedrine.

In accordance with an eighteenth embodiment, the present invention provides a process for the preparation of (1R, 2R) - pyrrolidinyl norpseudoephedrine, comprising:

a) providing mother liquors containing any ratio of optical isomers of pyrrolidinyl norpseudoephedrine,
b) evaporating the solvent from the mother liquors to obtain a residue,
c) dissolving the residue in water and a water immiscible organic solvent,
d) adjusting the pH to basic with a suitable base,
e) separating the water immiscible organic solvent and evaporating the solvent to obtain a residue, and
f) treating the residue with a suitable chiral acid to obtain (1R, 2R) - pyrrolidinyl norpseudoephedrine.

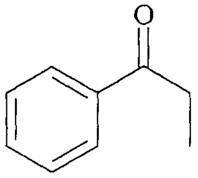
In accordance with a nineteenth embodiment, the present invention provides a process for the preparation of optically pure (1R, 2R) - pyrrolidinyl norpseudoephedrine, comprising: treating a mixture of (1S, 2S) and (1R, 2R) optical isomers of pyrrolidinyl norpseudoephedrine, with a suitable chiral acid in an appropriate solvent to obtain (1R, 2R) - pyrrolidinyl norpseudoephedrine;
wherein the suitable chiral acid is selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

In accordance with a twentieth embodiment, the present invention provides a process for the preparation of norephedrine of Formula IB, comprising:



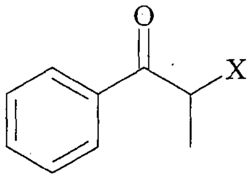
Formula IB

a) reacting propiophenone of Formula IV



Formula IV

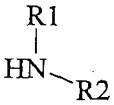
with a suitable halogenating agent to obtain halopropiophenone of Formula III,



Formula III

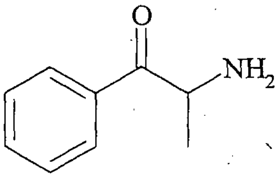
wherein 'X' is a halogen selected from Cl, Br or I;

b) reacting the resulting halopropiophenone with a suitable amine source of Formula



$\mathrm{HN(R1)(R2)}$

wherein R1 and R2 independently represent hydrogen or a formyl group; to obtain a keto compound Formula IIB; and



Formula IIB

c) reducing the keto compound of Formula IIB with a suitable reducing agent to obtain norephedrine of Formula IB.

In accordance with a twenty first embodiment, the present invention provides a process for the preparation of (1R, 2S) - norephedrine, comprising:

a) reacting propiophenone of Formula IV with a suitable halogenating agent to obtain halopropiophenone of Formula III, wherein 'X' is a halogen selected from Cl, Br or I;
b) reacting the resulting halopropiophenone with pyrrolidine to obtain a keto compound of Formula IIB;
c) reducing the keto compound of Formula IIB with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of norephedrine and norpseudoephedrine; and
d) treating the resultant mixture with a suitable chiral acid to obtain (1R, 2S) - norephedrine;

wherein the halogen is chloro or Bromo;

wherein the suitable reducing agent is selected from the group comprising sodium borohydride, lithium aluminum hydride, vitride (Sodium bis(2-methoxyethoxy)aluminum hydride), DIBAL-H and the like;

wherein the metal salt is represented by the formula MX_2, wherein the 'M' represents a metal cation selected from zinc, beryllium, magnesium, calcium, cerium, strontium,

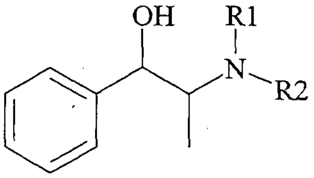
manganese, copper and barium; 'X' represents halide, acetate or trifluoromethane sulfonate;
wherein the suitable chiral acid is selected from the group comprising D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses to a novel process for preparation of norephedrine and its derivatives such as norephedrine, pyrrolidinyl norephedrine and the like with high chiral purity.

The present invention also relates to a process for separation of individual isomers of norephedrine and its derivatives using suitable chiral acids.

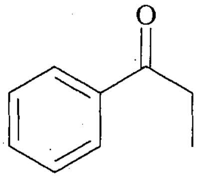
In one embodiment, the present invention provides a process for the preparation of norephedrine and its derivatives of Formula I,



Formula I

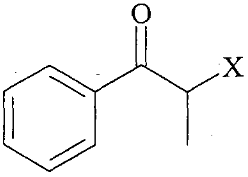
wherein R1 and R2 independently represent hydrogen or R1 and R2 combine to form a cyclic ring; comprising:

a) reacting propiophenone of Formula IV



Formula IV

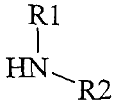
with a suitable halogenating agent to obtain halopropiophenone of Formula III,



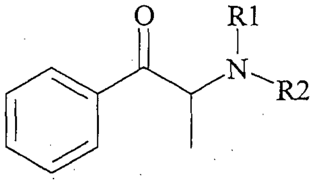
Formula III

wherein 'X' is a halogen selected from Cl, Br or I;

b) reacting the resulting halopropiophenone with a suitable amine source of Formula



wherein R1 and R2 independently represents hydrogen or a formyl group; or R1 and R2 combine to form a cyclic ring; to obtain a keto compound Formula II; and



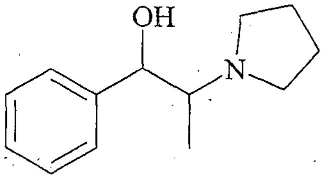
Formula II

wherein R1 and R2 independently represents hydrogen or R1 and R2 combine to form a cyclic ring;

c) reducing the keto compound of Formula II with a suitable reducing agent to obtain norephedrine and its derivative thereof.

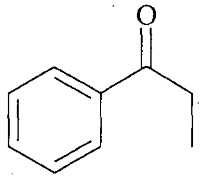
In a preferred embodiment, the present invention provides a process for the preparation of norephedrine and its derivatives of Formula I, wherein R1 and R2 independently represents hydrogen or R1 and R2 combine to form a cyclic ring such as pyrrolidine and the like.

In another preferred embodiment, the present invention provides a process for the preparation of pyrrolidinyl norephedrine of Formula IA, comprising:



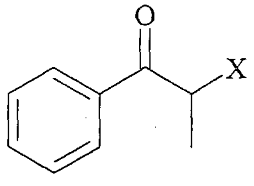
Formula IA

a) reacting propiophenone of Formula IV



Formula IV

with a suitable halogenating agent to obtain halopropiophenone of Formula III,

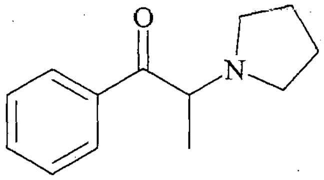


Formula III

wherein 'X' is a halogen selected from Cl, Br or I; preferably Cl, or Br;

b) reacting the resulting halopropiophenone with pyrrolidine of Formula

to obtain a keto compound Formula IIA; and



Formula IIA

c) reducing the keto compound of Formula IIA with a suitable reducing agent to obtain pyrrolidinyl norephedrine.

Step a) of foregoing process may be carried out by reacting propiophenone of Formula IV with a suitable halogenating agent in a suitable solvent to obtain halopropiophenone of Formula III. The suitable halogenating agent includes, but are not limited to bromine, N-halo succinimide such as N-bromo succinimide, N-chloro succinimide and the like; sulfuryl chloride, thionyl chloride, thionyl bromide, phosphorous trichloride, phosphorous tribromide and the like and mixtures thereof; preferably bromine or sulfuryl chloride.

The suitable solvent includes, but are not limited to halogenated hydrocarbons such as methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, chlorobenzene and the like; ethers such as diethyl ether, methyl tert-butyl ether, diisopropyl ether, tetrahydrofuran (THF), 1,4-Dixoane and the like and mixtures thereof; preferably methylene chloride, chloroform, toluene and mixtures thereof.

The reaction temperature should be sufficient to effect halogenation. Typically the reaction temperature may be from about ambient temperature to about reflux temperature. Preferably the reaction temperature is about 25°C to about 80°C; more preferably about 30°C to about 45°C.

Step b) of the foregoing process involves reaction of halopropiophenone of step a) with pyrrolidine in a suitable solvent in presence of a base to obtain a keto compound of Formula IIA.

The suitable solvent used herein for step b) is selected form the group consisting of halogenated hydrocarbons such as methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, chlorobenzene and the like; ethers such as diethyl ether, methyl tert-butyl ether, diisopropyl ether, THF, 1,4-Dixoane and the like; ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone; esters such as ethyl acetate, isopropyl acetate and the like; Nitriles such as acetonitrile, propionitrile, benzonitrile and the like; aromatic hydrocarbons such as toluene, xylene and the like and mixtures thereof; preferably methylene chloride, chloroform, toluene and the like and mixtures thereof.

The suitable base used herein for step b) is selected form the group consisting of alkali or alkaline metal hydroxides, carbonates, bicarbonates and the like; preferably sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and the like and mixtures thereof; more preferably potassium carbonate.

The reaction temperature should be sufficient to effect step b) reaction. Typically the reaction temperature may be from about ambient temperature to about reflux temperature. Preferably the reaction temperature is about 25°C to about 90°C; more preferably about 55° to about 85°C.

Step c) of the foregoing process is carried out by treating sufficient amount of a suitable reducing agent to the resultant product in order to carrying keto reduction in a solvent.

The suitable reducing agent in the foregoing process may be selected from the group comprising of sodium borohydride, lithium aluminum hydride, vitride (Sodium bis(2-methoxyethoxy)aluminum hydride), DIBAL-H and the like; preferably sodium borohydride.

The solvent for keto reduction includes, but is not limited to alcohols, ethers, halogenated hydrocarbons, nitriles, aromatic hydrocarbons and the like and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, n-propanol, t-butanol and the like and mixtures thereof; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, chlorobenzene and the like and mixtures thereof; ethers include, but are not limited to dimethyl ether, diethyl ether, methyl ethyl ether, diisopropyl ether, methyl tertiary butyl ether, THF, 1,4-dioxane and the like and mixtures thereof; nitriles include, but are not limited to acetonitrile, propionitrile and the like and mixtures thereof. Preferably the organic solvent is selected from the group consisting of methanol, ethanol, methylene chloride, chloroform, tetrahydrofuran, diisopropyl ether, methyl ethyl ether, methyl tertiary butyl ether, toluene and mixtures thereof; more preferably methanol, methylene chloride, chloroform, toluene and mixtures thereof.

The reaction temperature should be sufficient to effect reduction of keto to alcohol. Typically the reaction temperature may be from about ambient temperature to about reflux temperature. Preferably the reaction temperature is about -10°C to about 60°C; preferably about -5°C to about 10°C. The reaction may take from about 15 minutes to about 20 hours depending upon the reducing agent, solvent and temperature chosen, preferably about 30 minutes to about 6 hours.

The pyrrolidinyl norephedrine recovered using the process of the present invention having a chiral purity of about 10-35% each of four optical isomers i.e. pyrrolidinyl norephedrine isomers [(1R, 2S) and (1S, 2R)] and pyrrolidinyl norpseudoephedrine isomers [(1S, 2S) and (1R, 2R)].

The inventors of the present invention have found that norephedrine and its derivatives such as norephedrine, pyrrolidinyl norephedrine and the like with high chiral selectivity may be obtained by incorporating the process modifications such as use of a metal salt along with a suitable reducing agent in the keto reduction, yielding a product containing substantially higher selectivity of the optical isomers of norephedrines.

In a preferred embodiment, the keto reduction of step c) may be advantageously carried out with a suitable reducing agent and a metal salt.

The metal salt in the foregoing process may be represented by the following formula MX_2, wherein the 'M' represents a metal cation selected from the group comprising zinc, beryllium, magnesium, calcium, cerium, strontium, manganese, copper and barium; 'X' represents halide, acetate, sulfate, bisulfate, carbonate, bicarbonate or trifluoromethane sulfonate. The halide includes, but is not limited to fluoro, bromo, chloro, iodo and the like. Preferably, the metal salt is selected from the group consisting of zinc chloride, zinc bromide, zinc sulfate, zinc acetate, zinc trifluoromethane sulfonate, magnesium chloride, magnesium acetate, manganese chloride, calcium chloride, cerium chloride and the like.

The suitable reducing agent, organic solvent and the reaction temperature used for the keto reduction with a suitable reducing agent as described above can also be same as for the process of keto reduction with a suitable reducing agent along with a metal salt.

The norephedrines such as pyrrolidinyl norephedrine recovered using the process of the present invention having a chiral purity of about 20-45% of each of (1R, 2S) and (1S, 2R) isomers. The high selectivity of optical isomers of (1R, 2S) and (1S, 2R) enantiomers in the reduction stage may be obtained due to the presence of metal salt in the reduction stage.

The enantioselectivity of pyrrolidinyl norephedrine can be further improved by resolving pyrrolidinyl norephedrine obtained by the above procedure using a suitable resoluting agent such as suitable chiral acid.

In another embodiment, the present invention provides a process for the preparation of optically pure pyrrolidinyl norephedrine, comprising:

a) reacting propiophenone of Formula IV with a suitable halogenating agent to obtain halopropiophenone of Formula III, wherein 'X' is a halogen selected from Cl, Br or I;
b) reacting the resulting halopropiophenone with pyrrolidine to obtain a keto compound of Formula IIA;
c) reducing the keto compound of Formula IIA with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine; and
d) treating the resultant mixture with a suitable chiral acid to obtain optically pure pyrrolidinyl norephedrine.

In a preferred embodiment, the keto reduction of step c) may be advantageously carried out with a suitable reducing agent and a metal salt.

Starting mixture of optical isomers of pyrrolidinyl norephedrine and optical isomers pyrrolidinyl norpseudoephedrine of step d) is obtained by process of steps a) to c) as process described as above and then treating with a suitable chiral acid.

Alternatively any ratio of optical isomers of pyrrolidinyl norephedrine and pyrrolidinyl norpseudoephedrine as defined above or the same may be obtained by any known process can be used as starting material for the resolution.

In a preferred embodiment, the present invention provides a process for the preparation of optically pure (1R, 2S) - pyrrolidinyl norephedrine, comprising: treating either any ratio of optical isomers of pyrrolidinyl norephedrine or its mixture with optical isomers pyrrolidinyl norpseudoephedrine with a suitable chiral acid in an appropriate solvent to obtain (1R, 2S) - pyrrolidinyl norephedrine.

The resolution step of the present invention involves conversion of mixture of optical isomers of pyrrolidinyl norephedrine and pyrrolidinyl norpseudoephedrine to its corresponding pyrrolidinyl norephedrine chiral acid salt and then neutralizing the chiral acid salt.

The suitable chiral acid may be selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, L(+)-tartaric acid, L(+)-malic acid, L(+)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

Other suitable chiral acid resolving agents may be determined by testing and the use thereof in a process as described above falls within the scope of the present invention.

The appropriate solvent may be selected from the group consisting of alcohols such as methanol, ethanol, isopropanol, n-propanol and the like; nitriles such as acetonitrile, propionitrile and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; halogenated solvents such as methylene chloride, ethylene chloride, chloroform and the like; esters such as ethyl acetate, n-propyl acetate, isobutyl acetate and the like; ethers such as diethyl ether, dimethyl ether, tetrahydrofuran, methyl tertiary butyl ether and the like; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; amides such as dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide and the like; water and mixtures thereof; preferably methanol, ethanol, acetone, methylene chloride, chloroform, ethyl acetate and the like; more preferably methanol, ethanol, chloroform and mixtures thereof.

The resolution may be carried out at a temperature ranging from about 0°C to reflux temperature of the solvent used. The reaction time may range from about 30 minutes to about 30 hours, or longer, depending on the conditions chosen.

The obtained chiral salt of compound of pyrrolidinyl norephedrine (which is generally optically enriched as a single enantiomer) may be isolated by techniques, such as centrifugation, gravity filtration, or vacuum filtration or other techniques known in the art for the separation of solids; for example gravity filtration. Optionally, the solvent from the reaction mass may be removed completely or partially by distillation techniques such as atmospheric distillation, distillation under vacuum or evaporation before isolation. The chiral acid salt of pyrrolidinyl norephedrine thus obtained may be further purified to remove impurities, reaction byproducts, and the like by slurrying or crystallizing from a suitable solvent.

The chiral salt of pyrrolidinyl norephedrine recovered using the process of the present invention having a chiral purity of greater than about 95%, about 4% of (1R, 2S), (1S, 2R) respectively and about 0.5% each of (1S, 2S) and (1R, 2R) isomers.

The enantioselectivity of (1R, 2S) enantiomer can be further improved by purifying the pyrrolidinyl norephedrine chiral acid salt obtained by the above procedure using a suitable solvent.

The suitable solvent includes, but is not limited to alcohols, esters, ethers, halogenated solvents, hydrocarbon solvents, water and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, n-propanol and the like; esters include, but are not limited to ethyl acetate, isopropyl acetate and the like; ethers include, but are not limited to tetrahydrofuran, diisopropyl ether, diethyl ether and the like; halogenated solvents include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; hydrocarbon solvents include, but are not limited to toluene, xylene, hexane, heptane, cyclohexane and the like; preferably methanol, ethanol, ethyl acetate, toluene and the like and mixtures thereof.

The solvent may be heated to obtain a solution at a temperature of from about ambient temperature to about reflux temperature. The reaction solution may be cooled at a temperature from about 20°C or less such that chiral acid salt of (1R, 2S) - pyrrolidinyl norephedrine can be isolated by conventional techniques. This may allow for a high chiral purity level of the resulting chiral acid salt of (1R, 2S) - pyrrolidinyl norephedrine from the crude chiral acid salt of (1R, 2S) - pyrrolidinyl norephedrine, e.g., content of (1R, 2S) enantiomer of at least about 99% and other (1S, 2R) enantiomer is of less than about 0.5%.

Then, the obtained optically pure chiral acid salt of (1R, 2S) - pyrrolidinyl norephedrine may be neutralized to obtain free base of optically pure (1R, 2S) - pyrrolidinyl norephedrine.

The neutralization step may be carried out by any known procedure; for example optically pure chiral acid salt of (1R, 2S) - pyrrolidinyl norephedrine may be combined with water and a water immiscible organic solvent such as toluene, methylene chloride, ethyl acetate, chloroform, ethyl acetate and the like. Then the solution pH may be adjusted to basic with a suitable base such as sodium hydroxide and the like. The product containing organic layer may be separated and isolating the (1R, 2S)-pyrrolidinyl norephedrine free base by conventional methods such as evaporation, solvent crystallization or both.

In another embodiment, the present invention provides a process for the preparation of (1R, 2S) - pyrrolidinyl norephedrine, comprising:

a) reacting propiophenone of Formula IV with a suitable halogenating agent to obtain halopropiophenone of Formula III, wherein 'X' is a halogen selected from Cl, Br or I;

b) reacting the resulting halopropiophenone with pyrrolidine to obtain a keto compound of Formula IIA;
c) reducing the keto compound of Formula IIA with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine;
d) treating the resultant mixture with a suitable chiral acid to obtain (1S, 2R) - pyrrolidinyl norephedrine; and
e) treating the mother liquors containing (1R, 2S) - pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine with a suitable chiral acid to obtain (1R, 2S) - pyrrolidinyl norephedrine.

In a further embodiment, the present invention provides a process for the isomer separation of (1R, 2S) - pyrrolidinyl norephedrine, comprising:

a) providing a solution of racemic mixture comprising optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine;
b) treating the resultant mixture with a suitable chiral acid to obtain salt of (1S, 2R) - pyrrolidinyl norephedrine,
c) neutralizing the mother liquors containing a salt of (1R,2S)-pyrrolidinyl norephedrine and salt of optical isomers of pyrrolidinyl norpseudoephedrine with a base to obtain (1R, 2S) - pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine,
d) treating the resultant mixture with a suitable chiral acid to obtain a salt of (1R, 2S) - pyrrolidinyl norephedrine, and
e) neutralizing the salt of (1R, 2S) - pyrrolidinyl norephedrine with a base to obtain optically pure (1R, 2S) - pyrrolidinyl norephedrine.

Starting compound of racemic mixture comprising optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine is obtained by process of steps a) to c) as process described as above and then treating with a suitable chiral acid.

Alternatively any ratio of optical isomers of pyrrolidinyl norephedrine and optical isomers pyrrolidinyl norpseudoephedrine as defined above or the same may be obtained by any known process can be used as starting material for the resolution.

In another embodiment, the present invention provides a process for the preparation of optically pure (1R, 2S) - pyrrolidinyl norephedrine, comprising: treating either any ratio of optical isomers of pyrrolidinyl norephedrine or its mixture with pyrrolidinyl norpseudoephedrine with a suitable chiral acid in an appropriate solvent to obtain (1S, 2R) - pyrrolidinyl norephedrine and converting the mother liquors containing mixture of

(1R, 2S)-pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine in to pure (1R, 2S) - pyrrolidinyl norephedrine by treating it with another suitable chiral acid.

The resolution step of the present invention involves conversion of mixture of optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine to its corresponding pyrrolidinyl norephedrine chiral acid salt and then neutralizing the chiral acid salt.

The suitable chiral acid for step b) is selected from the group comprising L(+)-tartaric acid, L(+)-malic acid, L(+)-lactic acid and the like; preferably L(+)-tartaric acid. Other suitable chiral acid resolving agents may be determined by testing and the use thereof in a process as described above falls within the scope of the present invention.

The appropriate solvent for resolution of racemic mixtures of pyrrolidinyl norephedrine may be selected from the group consisting of alcohols such as methanol, ethanol, isopropanol, n-propanol and the like; nitriles such as acetonitrile, propionitrile and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; halogenated solvents such as methylene chloride, ethylene chloride, chloroform and the like; esters such as ethyl acetate, n-propyl acetate, isobutyl acetate and the like; ethers such as diethyl ether, dimethyl ether, tetrahydrofuran, methyl tertiary butyl ether and the like; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; amides such as dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide and the like; water and mixtures thereof; preferably methanol, ethanol, acetone, methylene chloride, chloroform, ethyl acetate and the like; more preferably methanol, ethanol, chloroform and mixtures thereof.

The resolution may be carried out at a temperature ranging from about 0°C to reflux temperature of the solvent used. The reaction time may range from about 30 minutes to about 30 hours, or longer, depending on the conditions chosen.

The obtained (1S, 2R) - pyrrolidinyl norephedrine chiral salt of compound of pyrrolidinyl norephedrine may be isolated by techniques, such as centrifugation, gravity filtration, or vacuum filtration or other techniques known in the art for the separation of solids; for example gravity filtration.

Step c) of the foregoing process involves neutralizing the mother liquors obtained from step b) containing a salt of (1R,2S)-pyrrolidinyl norephedrine and salt of optical isomers of pyrrolidinyl norpseudoephedrine to obtain (1R, 2S) - pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine.

The neutralization step c) may be carried out by removing the solvent form the mother liquors obtained from step b) under vacuum at ambient temperature to about 80°C obtain a residue, then adding water and water immiscible organic solvent to the residue and adjusting the pH to basic of about 10 with a suitable base such as sodium hydroxide, potassium hydroxide and the like. The organic layer may be separated and removing the water immiscible organic solvent completely under vacuum to obtain a residue containing free base of mixture of (1R, 2S) - pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine. The water immiscible organic solvent used herein for step c) is selected from the group consisting of toluene, ethyl acetate, methylene chloride, chloroform and the like, preferably toluene.

Alternatively, the neutralization step c) can be carried out by adding water to the mother liquors obtained from step b), if the solvent used in the step b) is water immiscible organic solvent, and adjusting the pH to basic of about 10 with a suitable base such as sodium hydroxide, potassium hydroxide and the like. The organic layer may be separated and proceed for next step.

Step d) of the foregoing process involves treating the resultant mixture of step c) with a suitable chiral acid in a suitable solvent to obtain a salt of (1R, 2S) - pyrrolidinyl norephedrine.

The suitable chiral acid used herein for step f) is selected from the group comprising D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like; preferably D(-)-tartaric acid.

The suitable solvent used herein for step d) is selected from the group comprising alcohols such as methanol, ethanol, isopropanol, n-propanol and the like; nitriles such as acetonitrile, propionitrile and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; halogenated solvents such as methylene chloride, ethylene chloride, chloroform and the like; esters such as ethyl acetate, n-propyl acetate, isobutyl acetate and the like; ethers such as diethyl ether, dimethyl ether, tetrahydrofuran, methyl tertiary butyl ether and the like; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; amides such as dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide and the like; water and mixtures thereof; preferably methanol, ethanol, acetone, methylene chloride, chloroform, ethyl acetate and the like; more preferably methanol, ethanol, chloroform and mixtures thereof.

The resolution may be carried out at a temperature ranging from about 0°C to reflux temperature of the solvent used. The reaction time may range from about 30 minutes to about 30 hours, or longer, depending on the conditions chosen.

The obtained chiral acid salt of (1R,2S)-pyrrolidinyl norephedrine can be isolated by techniques known in the art, such as centrifugation, gravity filtration, or vacuum filtration or other techniques known in the art for the separation of solids; for example gravity filtration. Optionally, the solvent from the reaction mass may be removed completely or partially by distillation techniques such as atmospheric distillation, distillation under vacuum or evaporation before isolation.

Optionally, the chiral acid salt of (1R,2S)-pyrrolidinyl norephedrine thus obtained may be further purified to remove impurities, reaction byproducts, and the like by slurrying or crystallizing from a suitable solvent.

In another embodiment, the present invention provides a process for isomer enrichment of (1R,2S)-pyrrolidinyl norephedrine or a salt thereof, comprising:

a) combining (1R, 2S) - pyrrolidinyl norephedrine or a salt thereof, obtained by the process described just as above in a suitable solvent;
b) heating to obtain clear solution,
c) optionally seeding the chiral acid salt of (1R, 2S) - pyrrolidinyl norephedrine,
d) cooling the solution to precipitation, and
e) isolating the pure (1R, 2S) - pyrrolidinyl norephedrine or a salt thereof.

The suitable solvent includes, but is not limited to alcohols, esters, ethers, halogenated solvents, hydrocarbon solvents, water and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, n-propanol and the like; esters include, but are not limited to ethyl acetate, isopropyl acetate and the like; ethers include, but are not limited to tetrahydrofuran, diisopropyl ether, diethyl ether and the like; halogenated solvents include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; hydrocarbon solvents include, but are not limited to toluene, xylene, hexane, heptane, cyclohexane and the like; preferably methanol, ethanol, ethyl acetate, toluene and the like and mixtures thereof; more preferably methanol, ethanol, toluene and mixtures thereof.

The solvent may be heated to obtain a solution at a temperature of from about ambient temperature to about reflux temperature, preferably about 35°C to 85°C. The reaction solution may be cooled at a temperature from about 20°C or less such that chiral acid salt of (1R, 2S) - pyrrolidinyl norephedrine can be isolated by conventional techniques, for example filtration. This may allow for a high chiral purity level of the resulting chiral acid salt of (1R, 2S) - pyrrolidinyl norephedrine from the crude chiral acid salt of

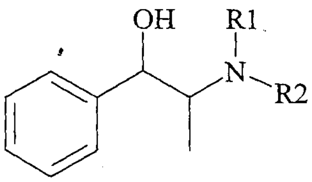
(1R, 2S) - pyrrolidinyl norephedrine, e.g., content of (1R, 2S) enantiomer of at least about 99% and other (1S, 2R) enantiomer is of less than about 0.5%.

Then, the obtained optically pure chiral acid salt of (1R, 2S) - pyrrolidinyl norephedrine may be neutralized to obtain free base of optically pure (1R, 2S) - pyrrolidinyl norephedrine.

The neutralization step may be carried out by any known procedure; for example optically pure chiral acid salt of (1R, 2S) - pyrrolidinyl norephedrine may be combined with water and a water immiscible organic solvent such as toluene, methylene chloride, ethyl acetate, chloroform, ethyl acetate and the like. Then the solution pH may be adjusted to basic with a suitable base such as sodium hydroxide and the like. The product containing organic layer may be separated and isolating the (1R, 2S)-pyrrolidinyl norephedrine free base by conventional methods such as evaporation, solvent crystallization or both.

The present invention provides a (1R, 2S)-pyrrolidinyl norephedrine, obtained by the process described herein, having a chiral purity of at least about 98%, as measured by HPLC, preferably at least about 99% as measured by HPLC, and more preferably at least about 99.5%, as measured by HPLC; contains less than about 1% of (1S, 2R)-enantiomer, as measured by HPLC, preferably less than about 0.5%, as measured by HPLC, more preferably less than about 0.2%, as measured by HPLC; and substantially free of enantiomers of norpseudoephedrine such as (1S, 2S) and (1R, 2R), wherein the word "substantially free" refers to (1R, 2S)-pyrrolidinyl norephedrine having less than about 0.1% of (1S, 2S) and (1R, 2R)-enantiomers, as measured by HPLC; more preferably less than about 0.05% of (1S, 2S) and (1R, 2R)-enantiomers, as measured by HPLC.

In another embodiment, the present invention provides a chiral acid salt compound of Formula I,



Formula I

wherein R1 and R2 independently represent hydrogen or R1 and R2 combine to form a cyclic ring;

wherein the chiral acid is selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, L(+)-tartaric acid, L(+)-malic acid, L(+)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

In a preferred embodiment, the present invention provides a chiral acid salt of pyrrolidinyl norephedrine; wherein the chiral acid is selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, L(+)-tartaric acid, L(+)-malic acid, L(+)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

In a preferred embodiment, the present invention provides a chiral acid salt of pyrrolidinyl norephedrine, which include:

i) pyrrolidinyl norephedrine L(+)-tartaric acid salt
ii) pyrrolidinyl norephedrine D(-)-tartaric acid salt,
iii) pyrrolidinyl norephedrine S(+)-mandelic acid salt, and
iv) pyrrolidinyl norephedrine dibenzoyl-d-tartaric acid salt.

In a preferred embodiment, the present invention provides (1S, 2R)-pyrrolidinyl norephedrine L(+)-tartaric acid salt.

In a preferred embodiment, the present invention provides (1R, 2S)-pyrrolidinyl norephedrine D(-)-tartaric acid salt.

In a preferred embodiment, the present invention provides (1S, 2S)-pyrrolidinyl norpseudoephedrine S(+)-mandelic acid salt.

In a preferred embodiment, the present invention provides (1S, 2S)-pyrrolidinyl norpseudoephedrine dibenzoyl-d-tartaric acid salt.

In another embodiment, the present invention provides a process for the preparation of (1R, 2S) - pyrrolidinyl norephedrine, comprising recycling the mother liquors containing unwanted optical isomers of pyrrolidinyl norephedrine as obtained by the process described above or may be obtained by any known process, as a starting material by means of oxidation to obtain keto compound of Formula IIA and converting the compound of Formula IIA into optically pure (1R, 2S)- pyrrolidinyl norephedrine.

In another embodiment, the present invention provides a process for the preparation of (1R, 2S) - pyrrolidinyl norephedrine, comprising:

a) providing mother liquors containing either any ratio of optical isomers of pyrrolidinyl norephedrine or its mixture with pyrrolidinyl norpseudoephedrine,
b) evaporating the solvent from the mother liquors to obtain a residue,
c) treating the residue with an oxidizing agent in an appropriate solvent to obtain keto compound of Formula IIA,
d) reducing the keto compound of Formula IIA with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and pyrrolidinyl norpseudoephedrine; and
e) treating the resulting mixture with a suitable resoluting agent to obtain (1R, 2S) - pyrrolidinyl norephedrine.

The starting mother liquors containing mixed enantiomers of pyrrolidinyl norephedrine and pyrrolidinyl norpseudoephedrine such as (1R, 2S), (1S, 2R), (1S, 2S) and (1R, 2R) obtained by the process described above or may be obtained by any known process may be evaporated to remove solvent completely under reduced pressure to obtain a residue. The residue may be taken into an appropriate solvent such as water and treating with an oxidizing agent to obtain a ketopyrrolidine compound of Formula IIA, which is further converted into optically pure (1R, 2S) - pyrrolidinyl norephedrine by the process of keto reduction and then chiral resolution process as described herein as above.

The suitable oxidizing agent in the foregoing process may be selected from the group consisting of chromium trioxide, sodium dichromate, potassium dichromate, potassium permanganate, pyridinium chlorochromate, dess-martin periodinane, pyridinium dichromate, magnesium dioxide, manganese (IV) oxide, dichromate (VI), chromium (VI) oxide and the like; preferably sodium dichromate.

In another embodiment, the present invention provides a process for the preparation of optically pure (1S, 2R) - pyrrolidinyl norephedrine, comprising: treating a mixture of (1S, 2R) and (1R, 2S) optical isomers of pyrrolidinyl norephedrine, with a suitable resoluting agent in an appropriate solvent to obtain (1S, 2R) - pyrrolidinyl norephedrine; wherein the suitable resoluting agent is selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

In a preferred embodiment, wherein the starting mixture of (1S, 2R) and (1R, 2S) optical isomers of pyrrolidinyl norephedrine contains excess of (1S, 2R) isomer.

The starting mixture of (1S, 2R) and (1R, 2S) optical isomers of pyrrolidinyl norephedrine, may be obtained by the process described as above or may be obtained by any known process. Preferably mother liquors containing mixture of (1S, 2R) and (1R, 2S) optical isomers of pyrrolidinyl norephedrine, wherein the content of (1S, 2R) isomer is greater than the other isomer, may be evaporated to remove solvent completely under reduced pressure to obtain a residue. Then, the residue may be taken into an appropriate solvent and treating with a suitable resoluting agent to obtain optically pure (1S, 2R) - pyrrolidinyl norephedrine.

The appropriate solvent may be selected from the group consisting of alcohols such as methanol, ethanol, isopropanol, n-propanol and the like; nitriles such as acetonitrile, propionitrile and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; halogenated solvents such as methylene chloride, ethylene chloride and the like; esters such as ethyl acetate, n-propyl acetate, isobutyl acetate and the like; ethers such as diethyl ether, dimethyl ether, tetrahydrofuran, methyl tertiary butyl ether and the like; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; amides such as dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide and the like; water and mixtures thereof; preferably ethanol, chloroform and mixtures thereof.

The enantioselectivity of the obtained (1S, 2R) enantiomer can be further improved by purifying the pyrrolidinyl norephedrine chiral acid salt obtained by the above procedure using a suitable solvent for example, a purification process as described for (1R, 2S) enantiomer.

The obtained optically pure chiral acid salt of (1S, 2R) - pyrrolidinyl norephedrine may be neutralized to obtain free base of optically pure (1S, 2R) - pyrrolidinyl norephedrine. The neutralization step may be carried out any known procedure; for example neutralization process as described above for the process of (1R, 2S) - pyrrolidinyl norephedrine.

The (1S, 2R)- pyrrolidinyl norephedrine recovered using the process of the present invention having a chiral purity of at least about 98%, as measured by HPLC, preferably at least about 99% as measured by HPLC, and more preferably at least about 99.5%, as measured by HPLC; contains less than about 1% of (1R, 2S)-enantiomer, as measured by HPLC, preferably less than about 0.5%, as measured by HPLC, more preferably less than about 0.2%, as measured by HPLC.

In another embodiment, the present invention provides a process for the preparation of (1S, 2S) - pyrrolidinyl norpseudoephedrine, comprising:

a) reducing a keto compound of Formula IIA with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and pyrrolidinyl norpseudoephedrine;
b) separating the optical isomers of pyrrolidinyl norpseudoephedrine from the resulting mixture of step a) using a column chromatography with a suitable eluent,
c) treating the resultant optical isomers of pyrrolidinyl norpseudoephedrine with a suitable resoluting agent to obtain (1S, 2S) - pyrrolidinyl norephedrine.

The step of reduction of keto compound of Formula IIA may be carried out by adding sufficient amount of a suitable reducing agent to the keto compound of Formula IIA in order to carrying keto reduction in an organic solvent.

The use of suitable reducing agent, organic solvent and the reaction temperature for the keto reduction with a suitable reducing agent optionally in presence of a metal salt can also be the same as the process of keto reduction described as above.

The pyrrolidinyl norephedrine recovered using the process of the present invention having a chiral purity of about 10-35% each of four optical isomers i.e. pyrrolidinyl norephedrine isomers [(1R, 2S) and (1S, 2R)] and pyrrolidinyl norpseudoephedrine isomers [(1S, 2S) and (1R, 2R)].

The step b) of foregoing process involves separating the optical isomers of pyrrolidinyl norpseudoephedrine from the resulting mixture of step a) using a column chromatography with a suitable eluent. The suitable eluent is selected from the group consisting of halogenated solvents such as methylene chloride, chloroform and the like; alcohols such as methanol, ethanol and the like and mixtures thereof. The fractions containing mixture of pyrrolidinyl norpseudoephedrine isomers [(1S, 2S) and (1R, 2R)] are separated first and then other isomers pyrrolidinyl norephedrines [(1R, 2S) and (1S, 2R)]. Then the solvent fractions containing mixture of (1S, 2S) and (1R, 2R) isomers are evaporated under reduced pressure to obtain a residue.

The step c) of foregoing process involves resolution of pyrrolidinyl norpseudoephedrine isomers obtained from step b) using a suitable resoluting agent in a suitable solvent to obtain pure (1S, 2S) - pyrrolidinyl norpseudoephedrine.

The suitable resoluting agent may be selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like; preferably S(+)-mandelic acid or dibenzoyl-D-tartaric acid.

The suitable solvent may be selected from the group consisting of alcohols such as methanol, ethanol, isopropanol, n-propanol and the like; nitriles such as acetonitrile, propionitrile and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; halogenated solvents such as methylene chloride, ethylene chloride and the like; esters such as ethyl acetate, n-propyl acetate, isobutyl acetate and the like; ethers such as diethyl ether, dimethyl ether, tetrahydrofuran, methyl tertiary butyl ether and the like; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; amides such as dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide and the like; water and mixtures thereof; preferably ethanol, chloroform, ethyl acetate and mixtures thereof; more preferably ethanol.

The resolution may be carried out at a temperature ranging from about 0°C to reflux temperature of the solvent used. The reaction time may range from about 30 minutes to about 30 hours, or longer, depending on the conditions chosen.

The obtained (1S, 2S) - pyrrolidinyl norpseudoephedrine chiral salt may be isolated by techniques known in the art, such as centrifugation, filtration, or vacuum filtration or other techniques known in the art for the separation of solids; for example filtration.

The (1S, 2S) - pyrrolidinyl norpseudoephedrine chiral salt recovered using the process of the present invention having a chiral purity of about 97% and 3% of (1S, 2S) and (1R, 2R) respectively.

The enantioselectivity of (1S, 2S) enantiomer can be further improved by purifying the (1S, 2S)-pyrrolidinyl norpseudoephedrine chiral acid salt obtained by the above procedure using a suitable solvent.

In another embodiment, the present invention provides a process for isomer enrichment of optical purity of (1S, 2S) - pyrrolidinyl norpseudoephedrine, comprising:

a) combining a chiral acid salt of (1S, 2S) - pyrrolidinyl norpseudoephedrine with a suitable solvent;
b) heating to obtain clear solution,
c) cooling the solution to precipitation, and
d) isolating the pure chiral acid salt of (1S, 2S) - pyrrolidinyl norpseudoephedrine.

The suitable solvent includes, but is not limited to alcohols, esters, ethers, halogenated solvents, hydrocarbon solvents, water and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, n-propanol and the like; esters include, but are not limited to ethyl acetate, isopropyl acetate and the like; ethers include, but are not limited to tetrahydrofuran, diisopropyl ether, diethyl ether and the like; halogenated solvents include, but are not limited to methylene chloride, ethylene chloride and the like; hydrocarbon solvents include, but are not limited to toluene, xylene, hexane, heptane, cyclohexane and the like; preferably ethanol, isopropanol, ethyl acetate and mixtures thereof; more preferably ethanol.

The solvent may be heated to obtain a solution at a temperature of from about ambient temperature to about reflux temperature. The reaction solution may be cooled at a temperature from about 20°C or less such that chiral acid salt of (1S, 2S) - pyrrolidinyl norpseudoephedrine can be isolated by conventional techniques. This may allow for a high chiral purity level of the resulting chiral acid salt of (1S, 2S) - pyrrolidinyl norpseudoephedrine from the corresponding crude chiral acid salt, e.g., content of (1S, 2S) enantiomer of at least about 99% and other (1R, 2R) enantiomer is of less than about 1%.

Then, the obtained optically pure chiral acid salt of (1S, 2S) - pyrrolidinyl norpseudoephedrine may be neutralized as per the procedure known in the art to obtain free base of optically pure (1S, 2S) - pyrrolidinyl norpseudoephedrine.

The (1S, 2S)- pyrrolidinyl norpseudoephedrine recovered using the process of the present invention having a chiral purity of at least about 98%, as measured by HPLC, preferably at least about 99% as measured by HPLC, and more preferably at least about 99.5%, as measured by HPLC; contains less than about 1% of (1R, 2R)-enantiomer, as measured by HPLC, preferably less than about 0.5%, as measured by HPLC, more preferably less than about 0.2%, as measured by HPLC.

In another embodiment, the present invention provides a process for the preparation of (1R, 2R) - pyrrolidinyl norpseudoephedrine, comprising:

a) providing mother liquors containing any ratio of optical isomers of pyrrolidinyl norpseudoephedrine,
b) evaporating the solvent from the mother liquors to obtain a residue,
c) dissolving the residue in water and a water immiscible organic solvent,
d) adjusting the pH to basic with a suitable base,
e) separating the water immiscible organic solvent and evaporating the solvent to obtain a residue, and
f) treating the residue with a suitable resoluting agent to obtain (1R, 2R) - pyrrolidinyl norpseudoephedrine.

The step a) of starting mother liquors containing mixed enantiomers of pyrrolidinyl norpseudoephedrine such as (1S, 2S) and (1R, 2R) obtained by the process described above or may be obtained by any known process may be evaporated to remove solvent completely under reduced pressure to obtain a residue. The residue may be taken into water and a water immiscible organic solvent such as toluene and then adjusting the pH to basic with a suitable base such as sodium hydroxide and the like. The water immiscible organic solvent layer may be separated and evaporating under reduced pressure to obtain a mixture of (1S, 2S) and (1R, 2R) isomers as residue, which is further treating with a suitable resoluting agent in a suitable solvent to obtain (1R, 2R) - pyrrolidinyl norpseudoephedrine.

The resolution of step f) involves conversion of mixture of optical isomers of (1S, 2S) and (1R, 2R) - pyrrolidinyl norpseudoephedrine to its corresponding chiral acid salt and then neutralizing the chiral acid salt.

In a preferred embodiment, wherein the mixture of (1S, 2S) and (1R, 2R) optical isomers of pyrrolidinyl norpseudoephedrine contains excess of (1R, 2R) isomer.

The suitable resoluting agent may be selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like; preferably S(+)-mandelic acid.

The suitable solvent may be selected from the group consisting of alcohols such as methanol, ethanol, isopropanol, n-propanol and the like; nitriles such as acetonitrile, propionitrile and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; halogenated solvents such as methylene chloride, ethylene chloride and the like; esters such as ethyl acetate, n-propyl acetate, isobutyl acetate and the like; ethers such as diethyl ether, dimethyl ether, tetrahydrofuran, methyl tertiary butyl ether and the like; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; amides such as dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide and the like; water and mixtures thereof; preferably ethanol, chloroform, ethyl acetate and mixtures thereof; more preferably ethanol.

The resolution may be carried out at a temperature ranging from about 0°C to reflux temperature of the solvent used. The reaction time may range from about 30 minutes to about 30 hours, or longer, depending on the conditions chosen.

The obtained chiral acid salt of compound of (1R, 2R)-pyrrolidinyl norpseudoephedrine may be isolated by techniques known in the art, such as centrifugation, filtration, or vacuum filtration or other techniques known in the art for the separation of solids; for example filtration.

The chiral acid salt of (1R, 2R)-pyrrolidinyl norpseudoephedrine recovered using the process of the present invention having a chiral purity of about 97% and 3% of (1R, 2R) and (1S, 2S) respectively.

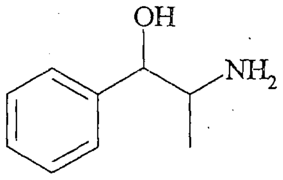
The enantioselectivity of (1R, 2R) enantiomer can be further improved by purifying the pyrrolidinyl norpseudoephedrine chiral acid salt obtained by the above procedure using a suitable solvent system as per the procedure described for (1S, 2S) enantiomer.

The purification process may provide a high chiral purity level of the resulting chiral acid salt of (1R, 2R) - pyrrolidinyl norpseudoephedrine from the corresponding crude chiral acid salt, e.g., content of (1R, 2R) enantiomer of at least about 99% and other (1S, 2S) enantiomer is of less than about 1%.

Then, the obtained optically pure chiral acid salt of (1R, 2R) - pyrrolidinyl norpseudoephedrine may be neutralized as per the procedure known in the art to obtain free base of optically pure (1R, 2R) - pyrrolidinyl norpseudoephedrine.

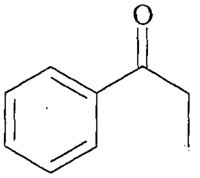
The (1R, 2R)- pyrrolidinyl norpseudoephedrine recovered using the process of the present invention having a chiral purity of at least about 98%, as measured by HPLC, preferably at least about 99% as measured by HPLC, and more preferably at least about 99.5%, as measured by HPLC; contains less than about 1% of (1S, 2S)-enantiomer, as measured by HPLC, preferably less than about 0.5%, as measured by HPLC, more preferably less than about 0.2%, as measured by HPLC.

In another embodiment, the present invention provides a process for the preparation of norephedrine of Formula IB, comprising:



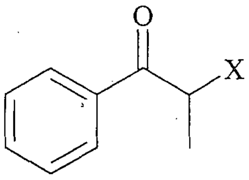
Formula IB

a) reacting propiophenone of Formula IV



Formula IV

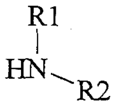
with a suitable halogenating agent to obtain halopropiophenone of Formula III,



Formula III

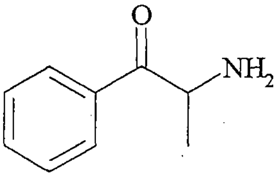
wherein 'X' is a halogen selected from Cl, Br or I;

b) reacting the resulting halopropiophenone with a suitable amine source of Formula



$\mathrm{HN(R1)R2}$

wherein R1 and R2 independently represents hydrogen or a formyl group; to obtain a keto compound Formula IIB; and

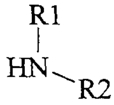


Formula IIB

c) reducing the keto compound of Formula IIB with a suitable reducing agent to obtain norephedrine of Formula IB.

The step a) of halogenation of propiophenone of Formula IV is carried out with a suitable halogenating agent as process described above for pyrrolidinyl norephedrine.

The step b) of the foregoing process may involve reaction of halopropiophenone of step a) with a suitable amine source of Formula:



$\mathrm{HN(R1)R2}$

wherein R1 and R2 independently represent hydrogen or a formyl group; preferably the suitable amine source can be selected from ammonia, diformylimide and the like; in a suitable solvent to obtain a keto compound of Formula IIB. The suitable solvent may be selected form the group consisting of halogenated hydrocarbons such as methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, chlorobenzene and the like; ethers such as ethers such as diethyl ether, methyl tert-butyl ether, diisopropyl ether, THF, 1,4-Dioxane and the like; ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone; esters such as ethyl acetate, isopropyl acetate and the like; Nitriles such as acetonitrile, propionitrile, benzonitrile and the like; aromatic hydrocarbons such as toluene, xylene and the like; and mixtures thereof.

The reaction temperature should be sufficient to effect step b) reaction. Typically the reaction temperature may be from about ambient temperature to about reflux temperature. Preferably the reaction temperature is about 25°C to about 90°C.

The step c) of foregoing process may be carried out by adding sufficient amount of a suitable reducing agent and optionally in presence of a metal salt to the resultant product in order to carrying keto reduction in an organic solvent.

The use of suitable reducing agent, organic solvent and the reaction temperature for the keto reduction with a suitable reducing agent optionally in presence of a metal salt can also be the same as the process of keto reduction described as above for pyrrolidinyl norephedrine.

The norephedrine of Formula 1B recovered using the process of the present invention having a chiral purity of about 10-35% of each four optical isomers i.e. norephedrine isomers [(1R, 2S) and (1S, 2R)] and norpseudoephedrine isomers [(1S, 2S) and (1R, 2R)].

The individual optical isomers of norephedrine [(1R, 2S) and (1S, 2R)] and norpseudoephedrine isomers [(1S, 2S) and (1R, 2R)] may be separated by resolution process using a suitable resoluting agents as per the process described above for separation of optical isomers of its corresponding pyrrolidine derivative.

The present invention provides norephedrine and its derivatives, obtained by the process described herein, as analyzed using the chiral high performance liquid chromatography ("chiral HPLC") with the conditions described below:

Column:	Chiralpak IA, 250 x 4.6 mm x 5μm
Flow rate:	0.8 mL / min
Detection wavelength:	220 nm
Injection volume:	20μL
Elution Mode:	Isocratic
Column temperature:	30°C
Mobile phase:	n-Hexane: Ethanol: diethylmaine (95: 5: 0.1), v/v/v
Sample concentration:	1 mg / mL
Run time:	15 min

In another embodiment, the enantiomerically pure norephedrine and its derivatives obtained by the process of the present invention can be used in the preparation of many pharmaceutically active medicaments, for example as chiral auxiliary in the preparation of anti retroviral drugs like efavirenz.

In another embodiment, the present invention provides a method for preparing pharmaceutically active medicaments, for example anti retroviral agent such as Efavirenz with high enantiomeric purity from (1R, 2S)-enantiomer of pyrrolidinyl norephedrine, obtained by the process of the present invention. The processes of the invention allow for economical synthesis, shorter reaction times, and yields of high purity.

EXAMPLES

The following non limiting examples illustrate specific embodiments of the present invention. They are not intended to be limiting the scope of the present invention in any way.

Seed Preparation:
Preparation of (1S, 2R)- pyrrolidinyl norephedrine L(+)-tartaric acid salt.

(1S, 2R)-pyrrolidinyl norephedrine (1 gm), obtained from Embio Ltd, was dissolved in isopropyl alcohol (6 ml) at 25°C to 35°C. L(+)-tartaric acid (0.73 gm) was added to the above solution at 25°C to 35°C and stirred for 30 mins. The solid obtained was filtered off, washed with isopropanol and dried the compound at 60-65°C for 4 hours (Yield: 0.95 gm); chiral purity: 100%.

Preparation of (1R, 2S)- pyrrolidinyl norephedrine D(-)-tartaric acid salt.

(1R, 2S)-pyrrolidinyl norephedrine (1 gm), obtained from Embio Ltd, was dissolved in ethanol (6 ml) at 25°C to 35°C. D(-)-tartaric acid (0.73 gm) was added to the above solution at 25°C to 35°C and stirred for 30 mins. The solid obtained was filtered off, washed with ethanol and dried the compound at 60-65°C for 4 hours (Yield: 0.90 gm); chiral purity: 100%.

Example 1: Preparation of 1-phenyl-2-(pyrrolidin-1-yl)propan-1-one.

A 1 L round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged methylene chloride (300 ml) and Propiophenone (100 gms; sourced from CAFFARO INDUSTRIE SPA) at a temperature of about 25°C to 35°C. The reaction mixture was allowed to cool to 15°C and Bromine (125 gms) was added to the reaction mass at same temperature over a period of about 2 hours. The reaction mass was heated to reflux temperature and stirred for 2 hours. After completion of the reaction, the reaction mass was allowed to cool to 30°C and washed with 10% aqueous sodium metabisulfite solution (100 ml) followed by with 10% aqueous sodium bicarbonate solution (100 ml). Organic and aqueous layers were separated and washed product containing organic layer with water (100 ml). The organic layer was taken into a 2 L round bottom flask and pyrrolidine solution (100 gms of pyrrolidine + 60 ml of water) was added at 25°C to 35°C. The reaction mixture was stirred for 4 hours at same temperature and reaction completion was monitored by TLC. To the reaction mass, water (390 ml) was charged and adjusted pH to about 2 with dilute HCl (125 ml) and then washed with methylene chloride (150 ml). The organic and aqueous layers were separated and aqueous layer pH was adjusted to about 9.0 to 9.5 with 10% sodium hydroxide solution (225 ml) and then extracted the product with methylene chloride (450 ml). The organic and aqueous layers were separated and the organic layer was washed with water and dried with sodium sulfate followed by concentrated completely under vacuum at below 40°C to obtain the title compound as residue (Yield: 140 gms).

Example 2: Preparation of 1-phenyl-2-(pyrrolidin-1-yl) propan-1-ol (pyrrolidinyl norephedrine) using sodium borohydride and zinc chloride.

A 1 L round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (350 ml) and zinc chloride (16.8 gms) at a temperature of about 25°C to 35°C. The reaction mixture was allowed to cool to about 0°C to 5°C and sodium borohydride (22.45 gms) was added at same temperature and stirred for 15 minutes. To the reaction mass, solution of 1-phenyl-2-(pyrrolidin-1-yl) propan-1-one (100 gms in 350 ml ethanol) was added at 0°C to 5°C and stirred for about 1 hour at same temperature. The reaction mass was heated to about 25°C to 30°C and stirred for about 12 hours at same temperature and reaction completion was monitored by TLC. The reaction mass pH was adjusted to about 4 with dilute HCl (210 ml) and the reaction mass was concentrated under vacuum at below 60°C to obtain residue. The residue was allowed to cool to 30°C to 35°C, water (900 ml) was charged and adjusted pH to about 2 with dilute HCl (10 ml) then heated to about 50°C. The reaction mass was washed with toluene (200 ml) and the aqueous layer pH was adjusted to about 10 with aqueous sodium hydroxide (290 ml) and then extracted the product with toluene (2×300 ml). The organic layer was washed with 10% sodium chloride solution and the organic layer was concentrated under vacuum at below 60°C to obtain the title compound as residue (Yield: 92 gms)

Chiral Purity: (1R, 2S):43.44%, (1S, 2R):46.42%, (1S, 2S):4.67%, (1R, 2R):5.46%

Example 3: Preparation of pyrrolidinyl norephedrine using sodium borohydride and zinc bromide.

A 1 L round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (350 ml) and Zinc bromide (27.6 gms) at a temperature of about 25°C to 35°C. The reaction mixture was allowed to cool to about 0°C to 5°C and sodium borohydride (22.45 gms) was added at same temperature and stirred for 15 minutes. To the reaction mass, solution of 1-phenyl-2-(pyrrolidin-1-yl) propan-1-one (100 gms in 350 ml ethanol) was added at 0°C to 5°C and stirred for about 5 hours at same temperature and reaction completion was monitored by TLC. The reaction mass pH was adjusted to about 4 with dilute HCl (210 ml) and the reaction mass was concentrated under vacuum at below 60°C to obtain residue. The residue was allowed to cool to 30°C to 35°C, water (900 ml) was charged and adjusted pH to about 2 with dilute HCl (10 ml) then heated to about 50°C. The reaction mass was washed with toluene (200 ml) and the aqueous layer pH was adjusted to about 10 with aqueous sodium hydroxide (290 ml) and then extracted the product with toluene (2×300 ml). The organic layer was washed with 10% sodium chloride solution and the organic layer was concentrated under vacuum at below 60°C to obtain the title compound as residue (Yield: 94 gms).

Chiral Purity: (1R, 2S):46.33%, (1S, 2R):47.48%, (1S, 2S):3.13%, (1R, 2R):3.06%

Example 4: Preparation of pyrrolidinyl norephedrine using sodium borohydride and zinc acetate.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (25 ml) and Zinc acetate (1.12 gms) at a temperature of about 25°C to 35°C. The reaction mixture was allowed to cool to about 0°C to 5°C and sodium borohydride (1.12 gms) was added at same temperature and stirred for 15 minutes. To the reaction mass, solution of 1-phenyl-2-(pyrrolidin-1-yl) propan-1-one (5gms in 17.5 ml ethanol) was added at 0°C to 5°C and stirred for about 2 hours at same temperature and reaction was not completed when monitored by TLC. Then raised the reaction mass to 25°C to 30°C and maintained for 18 hrs and the reaction completion was monitored by TLC. The reaction mass pH was adjusted to about 4 with dilute HCl (11 ml) and the reaction mass was concentrated under vacuum at below 60°C to obtain residue. The residue was allowed to cool to 30°C to 35°C, water (45 ml) was charged and adjusted pH to about 2 with dilute HCl (0.5 ml) then heated to about 50°C. The reaction mass was washed with toluene (10 ml) and the aqueous layer pH was adjusted to about 10 with aqueous sodium hydroxide (15 ml) and then extracted the product with toluene (2×25 ml). The organic layer was washed with 10% sodium chloride solution and the organic layer was concentrated under vacuum at below 60°C to obtain the title compound as residue (Yield: 3.7 gms).

Chiral Purity: (1R, 2S):41.71%, (1S, 2R):45.98%, (1S, 2S):6.12%, (1R, 2R):6.2%

Example 5: Preparation of pyrrolidinyl norephedrine using sodium borohydride and manganese chloride.

A 250 round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged methanol (100 ml) and 1-phenyl-2-(pyrrolidin-1-yl) propan-1-one (10 gms) at a temperature of about 25°C to 35°C. Anhydrous Manganese (II) chloride (1.23 gm) was charged to the reaction mass at about 25°C. The reaction mixture was allowed to cool to about 0°C to 5°C and sodium borohydride (1.86 gms) was added at same temperature. The reaction mass was stirred for 30 minutes at same temperature and reaction completion was monitored by TLC. The reaction mass pH was adjusted to about 4 with dilute HCl (20 ml) and the reaction mass was concentrated under vacuum at below 60°C to obtain residue. The residue was allowed to cool to 30°C to 35°C, water (90 ml) was charged and adjusted pH to about 2 with dilute HCl (1 ml). The reaction mass was washed with toluene (20 ml) and the aqueous layer pH was adjusted to about 10 with aqueous sodium hydroxide (26 ml) and then extracted the product with toluene (2×30 ml). The organic layer was washed with 10% sodium chloride solution and the organic layer was concentrated under vacuum at below 60°C to obtain the title compound as residue. Yield: 8.2 gms.

Chiral Purity: (1R, 2S):36.69%, (1S, 2R):42.55%, (1S, 2S):10.14%, (1R, 2R):10.62%

Example 6: preparation of pyrrolidinyl norephedrine D(-)-tartaric acid.

A 2 L round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (200 ml) and pyrrolidinyl norephedrine (100 gms) at a temperature of about 25°C to 35°C. The reaction mass was heated to about 40°C to get a clear solution. The resultant solution was allowed to cool to 25°C to 30°C and D(-)-tartaric acid solution (73 gms of D(-)-tartaric acid dissolved in 800 ml ethanol) was added at same temperature. The reaction mass was stirred for 60 minutes at same temperature and precipitated solids was filtered and washed with chilled ethanol (100 ml) to provide the title compound. Yield (wet): 59gm.

Chiral Purity: (1R, 2S):94.79%, (1S, 2R):4.74%, (1S, 2S):0.15%, (1R, 2R):0.32%

Example 7: purification of pyrrolidinyl norephedrine D(-)-tartaric acid.

A 1 L round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (550 ml) and wet material at a temperature of about 25°C to 35°C. The reaction mass was heated to reflux to get a clear solution and stirred for 30 minutes at same temperature. The resultant solution was allowed to cool to 0°C to 5°C and stirred for 30 minutes at same temperature. The precipitated solids was filtered and washed with chilled ethanol (50 ml). The wet product was dried at 50°C to 55°C under reduced pressure to provide the title compound. Yield: 43 gms.

Chiral Purity: (1R, 2S):99.55%, (1S, 2R):0.45%, (1S, 2S): Not detected, (1R, 2R): Not detected

Example 8: preparation of pyrrolidinyl norephedrine free base.

A 1 L round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged toluene (100 ml), water (100 ml) and pyrrolidinyl norephedrine D(-)-tartaric acid (100 gms) at a temperature of about 25°C to 35°C. The reaction mass pH was adjusted to about 10 with 10% aqueous sodium hydroxide solution (250 ml) at 25°C to 35°C. The layers were separated and the aqueous layer was extracted with

toluene. The combined organic layer was concentrated under vacuum at below 60°C and degassed for 30 minutes to obtain the title compound (Yield: 57 gms).
Chiral Purity: (1R, 2S):99.55%, (1S, 2R):0.45%, (1S, 2S): Not detected, (1R, 2R): Not detected

Example 9: Preparation of 1-phenyl-2-(pyrrolidin-1-yl) propan-1-one from pyrrolidinyl norephedrine.

Step-1:

A 3 L round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged 1700 ml of ethanol mother liquors obtained from Example -6 & 7 were concentrated under reduced pressure to obtain a residue (120 gms). A 1 L round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged toluene (100 ml), water (100 ml) and the above residue (120 gms) at a temperature of about 25°C to 35°C. The reaction mass pH was adjusted to about 10 with 10% aqueous sodium hydroxide solution (250 ml) at 25°C to 35°C. The layers were separated and the aqueous layer was extracted with toluene. The combined organic layer was concentrated under vacuum at below 60°C and degassed for 30 minutes to obtain racemate of pyrrolidinyl norephedrine as residue. (Yield: 57 gms).
Chiral Purity: (1R, 2S):20.89%, (1S, 2R):57.09%, (1S, 2S):11.02%, (1R, 2R):11.01%

Step-2:

A 1L round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged DM Water (150 ml) and pyrrolidinyl norephedrine residue (57 gms) at a temperature of about 25°C to 35°C.The reaction mass was allowed to cool to 20°C to 25°C and sulphuric acid (63.9 gms) was added at 20°C to 25°C and stirred for 10 min. at same temperature. Sodium dichromate solution (72.6 gm of sodium dichromate was pre-dissolved in 73 ml of DM Water) was added to the reaction mass at 20°C to 25°C and the reaction mass was stirred for 6 hrs at same temperature. Reaction completion was monitored by TLC and after completion of reaction; DM water (50 ml) & Toluene (125 ml) were charged into the reaction mass and was cooled to 0°C to 5°C. The reaction mass pH was adjusted to about 10-11 with 50% sodium hydroxide solution (95 ml) at 0°C to 5°C. The reaction mass was stirred for 30 min. and undissolved dichromate salts were filtered and washed with Toluene (50ml). The layers were separated and the organic layer was washed with DM Water (100ml). The organic layer was concentrated under vacuum at below 60°C and degassed for 30 minutes to obtain the title compound. Yield: 50 gms.

Example 10: Preparation of pyrrolidinyl norephedrine.

A 0.5 L round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (175 ml) and Zinc bromide (13.8 gms) at a

temperature of about 25°C to 35°C. The reaction mixture was allowed to cool to about 0°C to 5°C and sodium borohydride (11.3 gms) was added at same temperature and stirred for 15 minutes. To the reaction mass, solution of 1-phenyl-2-(pyrrolidin-1-yl) propan-1-one (50 gms in 175 ml ethanol; obtained from Example-9) was added at 0°C to 5°C and stirred for about 5 hours at same temperature and reaction completion was monitored by TLC. The reaction mass pH was adjusted to about 4 with dilute HCl (105 ml) and the reaction mass was concentrated under vacuum at below 60°C to obtain residue. The residue was allowed to cool to 30°C to 35°C, water (450 ml) was charged and adjusted pH to about 2 with dilute HCl (5 ml). The reaction mass was washed with toluene (100 ml) and the aqueous layer pH was adjusted to about 10 with aqueous sodium hydroxide (145 ml) and then extracted the product with toluene (2×150 ml). The organic layer was washed with 10% sodium chloride solution and the organic layer was concentrated under vacuum at below 60°C to obtain the title compound as residue (Yield: 44 gms).
Chiral Purity: (1R, 2S): 59.12%, (1S, 2R): 29.8%, (1S, 2S):7.7%, (1R, 2R):3.31%

Example 11: Preparation of pyrrolidinyl norephedrine using sodium borohydride.

A 3.0L round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged methanol (600 ml) and 1-phenyl-2-(pyrrolidin-1-yl) propan-1-one (100 gms) at a temperature of about 25°C to 35°C. The reaction mixture was allowed to cool to about 0°C to 5°C and sodium borohydride (18.6 gms pre-dissolved in 56 ml of 0.2N sodium hydroxide solution) was added at same temperature and stirred for 15 minutes. The reaction mass was heated to 20-25°C and stirred for about 4 hours at same temperature and reaction completion was monitored by TLC. The reaction mass pH was adjusted to about 4 with dilute HCl (210 ml) and the reaction mass was concentrated under vacuum at below 60°C to obtain residue. The residue was allowed to cool to 30°C to 35°C, water (900 ml) was charged and adjusted pH to about 2 with dilute HCl (10 ml). The reaction mass was washed with toluene (200 ml) and the aqueous layer pH was adjusted to about 10 with aqueous sodium hydroxide (290 ml) and then extracted the product with toluene (2×300 ml). The organic layer was washed with 10% sodium chloride solution and the organic layer was concentrated under vacuum at below 60°C to obtain the title compound as residue (Yield: 96 gms).
Chiral Purity: (1R, 2S):13.32%, (1S, 2R):13.88%, (1S, 2S):35.94%, (1R, 2R):36.86%

Example 12: Separation of mixture of (1R,2S) & (1S,2R) isomers of pyrrolidinyl norephedrine & mixture of (1S,2S) & (1R,2R) isomers of pyrrolidinyl norpseudoephedrine.

A 2 Feet length and 3” diameter glass column was loaded with silica gel (500 gms) using methylene chloride. Pyrrolidinyl norephedrine (95 gms pre adsorbed on 47.5 gms of silica gel using methylene chloride) was loaded. The column was eluted with

methylene chloride using 0.5% methanol concentration. The fractions were combined and distilled out the solvent under vacuum to obtain mixture of (1S, 2S) & (1R, 2R) isomers as residue (35 gms).
Chiral Purity: (1R, 2R):47.27%, (1S, 2S):52.63%

Then again the column was eluted with methylene chloride using 0.5% - 1.0% methanol concentration. The fractions were combined and distilled out the solvent under vacuum to obtain mixture of all four isomers (1S, 2S), (1R, 2R), (1R, 2S) & (1S, 2R) as residue (20 gms).
Further the column was eluted with methylene chloride using 1.0-2.0% methanol concentration. The fractions were combined and distilled out the solvent under vacuum to obtain mixture of (1R, 2S) & (1S, 2R) isomers as residue (20 gms).
Chiral Purity: (1R, 2S):47.45%, (1S, 2R):52.55%

Example 13: preparation of (1S, 2S)-pyrrolidinyl norpseudoephedrine S(+)-mandelic acid.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (30 ml) and mixture of (1S, 2S) & (1R, 2R) isomers (10 gms) at a temperature of about 25°C to 35°C. S(+) Mandelic acid (7.4 gm dissolved in 30 ml of ethanol) was charged into the reaction mass at same temperature. The reaction mass was stirred for 30 min. at same temperature. The reaction mass was allowed to cool to 0°C to 5°C and stirred for 60 minutes at same temperature and precipitated solids was filtered and washed with chilled ethanol (5 ml) to provide the title compound. Yield (wet): 3.5 gms
Chiral Purity: (1S, 2S):97.86%, (1R, 2R):2.14%

Example 14: purification of (1S, 2S)-pyrrolidinyl norpseudoephedrine S(+)-mandelic acid.
A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (17.5 ml) and (1S, 2S)-pyrrolidinyl norpseudoephedrine S(+)-mandelic acid (3.5 gms wet) at a temperature of about 25°C to 35°C. The reaction mass was heated to reflux to get a clear solution and stirred for 30 minutes at same temperature. The resultant solution was allowed to cool to 0°C to 5°C and stirred for 30 minutes at same temperature. The precipitated solids was filtered and washed with chilled ethanol (2.5 ml). The wet product was dried at 50°C to 55°C under reduced pressure to provide the title compound. Yield: 3.0 gms.
Chiral Purity: (1S, 2S):99.60%, (1R, 2R):0.40%

Example 15: preparation of (1S, 2S)-pyrrolidinyl norpseudoephedrine free base.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged toluene (10 ml), water (10 ml) and (1S, 2S)-pyrrolidinyl norpseudoephedrine S(+)-mandelic acid (3.0 gms) at a temperature of about 25°C to 35°C. The reaction mass pH was adjusted to about 10 with 10% aqueous sodium hydroxide solution (7.5 ml) at 25°C to 35°C. The layers were separated and the aqueous layer was extracted with toluene (10 ml). The combined organic layer was concentrated under vacuum at below 60°C and degassed for 30 minutes to obtain the title compound. Yield: 1.73 gms.
Chiral Purity: (1S, 2S):99.63%, (1R, 2R):0.42%

Example 16: preparation of (1S, 2S)-pyrrolidinyl norpseudoephedrine dibenzoyl-d-tartaric acid.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (30 ml) and mixture of (1S, 2S) & (1R, 2R) isomers (10 gms) at a temperature of about 25°C to 35°C. Dibenzoyl-d-tartaric acid (17.4 gm dissolved in 30 ml of Ethanol) was charged into the reaction mass at same temperature. The reaction mass was stirred for 30 min. at 25°C to 35°C. The reaction mass was allowed to cool to 0°C to 5°C and stirred for 60 minutes at same temperature and precipitated solids was filtered and washed with chilled ethanol (5 ml) to provide the title compound. Yield (wet): 3.5 gms
Chiral Purity: (1S, 2S):96.37%, (1R, 2R):3.63%

Example 17: purification of (1S, 2S)-pyrrolidinyl norpseudoephedrine dibenzoyl-d-tartaric acid.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (17.5 ml) and (1S, 2S)-pyrrolidinyl norpseudoephedrine dibenzoyl-d-tartaric acid (3.5 gms wet) at a temperature of about 25°C to 35°C. The reaction mass was heated to reflux to get a clear solution and stirred for 30 minutes at same temperature. The resultant solution was allowed to cool to 0°C to 5°C and stirred for 30 minutes at same temperature. The precipitated solids was filtered and washed with chilled ethanol (2.5 ml). The wet product was dried at 50°C to 55°C under reduced pressure to provide the title compound. Yield: 3.0 gms.
Chiral Purity: (1S, 2S):99.70%, (1R, 2R):0.30%

Example 18: purification of (1S, 2S)-pyrrolidinyl norpseudoephedrine free base.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged toluene (10 ml), water (10 ml) and (1S, 2S)-pyrrolidinyl norpseudoephedrine dibenzoyl-d-tartaric acid (3.0 gms) at a temperature of about 25°C to 35°C. The reaction mass pH was adjusted to about 10 with 10% aqueous sodium

hydroxide solution (7.5 ml) at 25°C to 35°C. The layers were separated and the aqueous layer was extracted with toluene (10ml). The combined organic layer was concentrated under vacuum at below 60°C and degassed for 30 minutes to obtain the title compound.
Yield: 1.75 gms
Chiral Purity: (1S, 2S):99.68%, (1R, 2R):0.32%

Example 19: Preparation of mixture of (1S, 2S) & (1R, 2R) isomers of pyrrolidinyl norpseudoephedrine.

A 3 L round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol mother liquors obtained from Example -13 & 14 were concentrated under reduced pressure to obtain a residue (12 gms). In another 250 ml round bottom flask was charged toluene (60 ml), water (60 ml) and the residue (12 gms) at a temperature of about 25°C to 35°C. The reaction mass pH was adjusted to about 10 with 10% aqueous sodium hydroxide solution (15 ml) at 25°C to 35°C. The layers were separated and the aqueous layer was extracted with toluene (10ml). The combined organic layer was concentrated under vacuum at below 60°C and degassed for 30 minutes to obtain the title compound. Yield: 6.7 gms
Chiral Purity: (1S, 2S):31.5%, (1R, 2R):68.5%

Example 20: preparation of (1R, 2R)-pyrrolidinyl norpseudoephedrine S(+) Mandalic acid.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (15 ml) and mixture of (1S, 2S) & (1R, 2R) isomers of pyrrolidinyl norpseudoephedrine (5 gms) at a temperature of about 25°C to 35°C. S (+) Mandelic acid (3.7 gm) was charged into the reaction mass at same temperature. The reaction mass was stirred for 30 min. at 25°C to 35°C. The reaction mass was allowed to cool to 0°C to 5°C and stirred for 60 minutes at same temperature and precipitated solids was filtered and washed with chilled ethanol (2.5 ml) to provide the title compound. Yield (wet): 1.75 gms
Chiral Purity: (1S, 2S):2.85%, (1R, 2R):97.15%

Example 21: purification of (1R, 2R)-pyrrolidinyl norpseudoephedrine S(+) Mandalic acid.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (9 ml) and (1R, 2R)-pyrrolidinyl norpseudoephedrine S(+) Mandalic acid (1.75 gms wet) at a temperature of about 25°C to 35°C. The reaction mass was heated to reflux to get a clear solution and stirred for 30 minutes at same temperature. The resultant solution was allowed to cool to 0°C to 5°C and stirred for 30 minutes at same temperature. The precipitated solids was filtered and

washed with chilled ethanol (1.5 ml). The wet product was dried at 50°C to 55°C under reduced pressure to provide the title compound. Yield: 1.5 gms.
Chiral Purity: (1S, 2S):0.30%, (1R, 2R):99.7%

Example 22: preparation of (1R,2R) pyrrolidinyl norpseudoephedrine free base.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged toluene (5 ml), water (5 ml) and (1R,2R) pyrrolidinyl norpseudoephedrine S(+) Mandalic acid (1.5 gms) at a temperature of about 25°C to 35°C. The reaction mass pH was adjusted to about 10 with 10% aqueous sodium hydroxide solution (3.3 ml) at 25°C to 35°C. The layers were separated and the aqueous layer was extracted with toluene (5 ml). The combined organic layer was concentrated under vacuum at below 60°C and degassed for 30 minutes to obtain the title compound.
Yield: 0.85 gms.
Chiral Purity: (1S, 2S): 0.32%, (1R, 2R): 99.68%

Example 23: preparation of (1R,2S)-pyrrolidinyl norephedrine D(-)-tartaric acid.

A 250 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (20 ml) and mixtures of (1R,2S) & (1S, 2R)-pyrrolidinyl norephedrine (10 gms) at a temperature of about 25°C to 35°C. The reaction mass was heated to about 40°C to get a clear solution. The resultant solution was allowed to cool to 25°C to 30°C and D(-)-tartaric acid solution (7.3 gms of D(-)-tartaric acid dissolved in 80 ml ethanol) was added at same temperature. The reaction mass was stirred for 60 minutes at same temperature and precipitated solids was filtered and washed with chilled ethanol (10 ml) to provide the title compound.
Yield (wet): 5.5gm
Chiral Purity: (1R, 2S):95.26%, (1S, 2R):4.74%

Example 24: purification of (1R,2S)-pyrrolidinyl norephedrine D(-)-tartaric acid.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, and addition funnel was charged ethanol (55 ml) and (1R,2S)-pyrrolidinyl norephedrine D(-)-tartaric acid (5.5 gms wet) at a temperature of about 25°C to 35°C. The reaction mass was heated to reflux to get a clear solution and stirred for 30 minutes at same temperature. The resultant solution was allowed to cool to 0°C to 5°C and stirred for 30 minutes at same temperature. The precipitated solids was filtered and washed with chilled ethanol (5 ml). The wet product was dried at 50°C to 55°C under reduced pressure to provide the title compound. Yield: 4.1 gms.
Chiral Purity: (1R, 2S):99.65%, (1S, 2R):0.35%

Example 25: preparation of (1R,2S)-pyrrolidinyl norephedrine free base.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged toluene (10 ml), water (10 ml) and (1R,2S)- pyrrolidinyl norephedrine D(-)-tartaric acid (4 gms) at a temperature of about 25°C to 35°C. The reaction mass pH was adjusted to about 10 with 10% aqueous sodium hydroxide solution (100 ml) at 25°C to 35°C. The layers were separated and the aqueous layer was extracted with toluene (5 ml). The combined organic layer was concentrated under vacuum at below 60°C and degassed for 30 minutes to obtain the title compound. Yield: 2.3 gms
Chiral Purity: (1R, 2S):99.63%, (1S, 2R):0.37%

Example 26: Preparation of mixture of (1R,2S) & (1S, 2R) isomers of pyrrolidinyl norephedrine.

170 ml of ethanol mother liquors obtained from Example 22 & 23 were concentrated under reduced pressure to obtain residue (12 gms). A 100 ml round bottom flask fitted with a mechanical stirrer was charged toluene (10 ml), water (10 ml) and the above residue (12 gms) at a temperature of about 25°C to 35°C. The reaction mass pH was adjusted to about 10 with 10% aqueous sodium hydroxide solution (20 ml) at 25°C to 35°C. The layers were separated and the aqueous layer was extracted with toluene (10ml). The combined organic layer was concentrated under vacuum at below 60°C and degassed for 30 minutes to obtain the title compound. Yield: 5.7 gms
Chiral Purity: (1R, 2S):29.63%, (1S, 2R):70.37%

Example 27: preparation of (1S,2R)- pyrrolidinyl norephedrine D(-) tartaric acid.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (10 ml) and mixture of (1R,2S) & (1S, 2R) isomers of pyrrolidinyl norephedrine (5 gms) at a temperature of about 25°C to 35°C. The reaction mass was heated to about 40°C to get a clear solution. The resultant solution was allowed to cool to 25°C to 30°C and D(-)-tartaric acid solution (3.65 gms of D(-)-tartaric acid dissolved in 40 ml ethanol) was added at same temperature. The reaction mass was stirred for 60 minutes at same temperature and precipitated solids was filtered and washed with chilled ethanol (10 ml) to provide the title compound. Yield (wet): 2.9gm
Chiral Purity: (1R, 2S):4.65%, (1S, 2R):95.35%

Example 28: purification of (1S,2R)-pyrrolidinyl norephedrine D(-)-tartaric acid.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged ethanol (50 ml) and (1S,2R)- pyrrolidinyl norephedrine D(-) tartaric acid (2.9 gms wet) at a temperature of about 25°C to 35°C. The reaction mass was heated to reflux to get a clear solution and stirred for 30 minutes at same

temperature. The resultant solution was allowed to cool to 0°C to 5°C and stirred for 30 minutes at same temperature. The precipitated solids was filtered and washed with chilled ethanol (5 ml). The wet product was dried at 50°C to 55°C under reduced pressure to provide the title compound. Yield: 2.1 gms.
Chiral Purity: (1R, 2S):0.55%, (1S, 2R):99.45%

Example 29: preparation of (1S,2R)-pyrrolidinyl norephedrine free base.

A 100 ml round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged toluene (5 ml), water (5 ml) and (1S,2R)-pyrrolidinyl norephedrine D(-) tartaric acid (2 gms) at a temperature of about 25°C to 35°C. The reaction mass pH was adjusted to about 10 with 10% aqueous sodium hydroxide solution (5 ml) at 25°C to 35°C. The layers were separated and the aqueous layer was extracted with toluene (5 ml). The combined organic layer was concentrated under vacuum at below 60°C and degassed for 30 minutes to obtain the title compound. Yield: 1.14 gms
Chiral Purity: (1R, 2S):0.57%, (1S, 2R):99.43%

Example 30: Preparation of pyrrolidinyl norephedrine using a procedure analogous to that employed in Example 2 with using sodium borohydride and different metal salts as described in the following table:

S. No	Reducing agent	Metal salt	Chiral Purity: (1R,2S), (1S,2R), (1S,2S), (1R,2R)
01	Sodium borohydride	Calcium chloride	16.28%, 20.03%, 31.18%, 32.51%
02	Sodium borohydride	Cerium chloride	23.46%, 23.88%, 24.65%, 28.01%
03	Sodium borohydride	Barium chloride	18.46%, 21.75%, 27.46%, 32.33%
04	Sodium borohydride	Magnesium sulfate	22.58%, 20.65%, 23.35%, 33.42%

Example 31: Preparation of (1R, 2S)- pyrrolidinyl norephedrine D(-)-tartaric acid.

A round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged Propiophenone (100 gms) and chloroform (300 ml) at 25°C to 35°C. Sulfuryl chloride (111 gms) was added to the reaction mass at 25°C to 35°C and stirred for 2 hours at same temperature. After completion of reaction, water (200 ml) was added to the reaction mass at 25°C to 35°C and stirred for 30 mins. The organic and aqueous layer was separated and Water (200 ml) and aqueous sodium hydroxide 50% solution (20 ml) was added to the organic layer at 25°C to 35°C, stirred for 30 mins then organic and aqueous layer was separated. To the organic layer, potassium carbonate (154.50 gms) and water (290 ml) was added at 25°C to 35°C followed by Pyrrolidine (60 gms) was added to the reaction mass and was heated to 60-65°C then stirred for 16 hours at same temperature. After completion of reaction, the reaction mass was allowed to cool to 25°C to 35°C and the organic layer was separated from the reaction mass. Methanol (280 ml) was added to the organic layer then the reaction mass was allowed to cool to -2°C to 2°C and Zinc chloride (40 gm) was added at -2°C to 2°C and stirred for 15 mins at same temperature. Sodium borohydride (30 gms) was added to the reaction mass at -2°C to 2°C and stirred for 2 hours at same temperature. After completion of reaction, the reaction mass pH was adjusted to 2-2.5 with concentrated hydrochloric acid at -2°C to 2°C and Water (1000 ml) was added to the reaction mass at -2°C to 2°C and heated to 25-35°C. The organic and aqueous layer was separated and then the aqueous layer pH was adjusted to 10-10.5 with aqueous sodium hydroxide solution at 25°C to 35°C. Chloroform ((300 ml) was added to the reaction mass and stirred for 15 mins at 25°C to 35°C and organic layer was separated. The organic layer was heated and water was removed by azeotrope distillation and the reaction mass was allowed to cool to 25°C to 35°C. Chloroform (260 ml) and methanol (44 ml) was added to the reaction mass and was heated to 40°C to 45°C. L(+)-tartaric acid (64 gms) was added to the reaction mass at 40°C and stirred for 30 mins at 40°C to 45°C. To the reaction mass, seed crystals of (1S, 2R)- pyrrolidinyl norephedrine L-(+)-tartaric acid salt (0.1 gm) was added and the reaction mass was allowed to cool to 25°C to 35°C and stirred for 2 hours at same temperature. The precipitated solid was filtered, washed with chloroform and suck dried for 30 mins. The filtrate was taken in to RBF and water was added to it at 25°C to 35°C then stirred for 15 mins. The reaction mass pH was adjusted to 9.5-10.5 with aqueous sodium hydroxide solution at 25°C to 30°C. The aqueous and organic layer was separated and the organic layer was allowed to cool to 40°C to 45°C. D(-)-tartaric acid (51 gms) was added to the reaction mass at 40°C to 45°C and stirred for 30 mins. The reaction mass was allowed to cool to 25°C to 35°C and stirred for 2 hours. The solid formed was filtered off, washed with chloroform and dried the compound at 50°C to 55°C for 4 hours to obtain the title compound.

Yield: 77.2 gms.
Chiral Purity: (1R, 2S): 96.05%, (1S, 2R): 2.03%, (1S, 2S):0.96% & (1R, 2R): 0.89%

Example 32: Purification of (1R, 2S)- pyrrolidinyl norephedrine D(-)-tartaric acid.

A round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged (1R, 2S)-pyrrolidinyl norephedrine D(-)-tartaric acid (100 gms) and methanol (200 ml) and was heated to reflux temperature. The reaction mass was stirred at reflux for 30 mins and toluene (500 ml) was added to it at 60-65°C. The reaction mass was cooled to 45°C to 50°C and seed crystals of (1R, 2S)-pyrrolidinyl norephedrine D-(-)-tartaric acid salt (0.1 gm) was added and stirred for 30 mins at 45°C to 50°C. The reaction mass was allowed to cool to 33-37°C and stirred for 60 mins. The reaction mass was further allowed to cool to 10°C to 15°C and stirred for 60 mins. The precipitated solid was filtered off, washed with a mixture of methanol and toluene and then dried at 50°C to 60°C to obtain the title compound.

Yield: 41.15 gms.

Chiral Purity: (1R, 2S): 99.7%, (1S, 2R): 0.3%.

Example 33: Preparation of (1R, 2S) pyrrolidinyl norephedrine.

A round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged (1R, 2S)-pyrrolidinyl norephedrine D(-)-tartaric acide (100 gms) obtained from example 32 and water (300 ml) and stirred for 10 mins at 25°C to 30°C. The reaction mass pH was adjusted to 9.5 to 10 with aqueous sodium hydroxide solution at 25°C to 30°C and was stirred for 30 mins. The reaction mass was allowed to cool to 20°C to 25°C and stirred for 60 mins. The solid obtained was filtered off, washed with water and dried at 40°C to obtain the title compound.

Yield: 28 gms.
Chiral Purity: (1R, 2S): 99.75%, (1S, 2R): 0.25%

Example-34: Preparation of (1R, 2S)- pyrrolidinyl norephedrine D(-)-tartaric acid.

A round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged with propiophenone (100 gms) and methylene chloride (300 ml) at 25°C to 35°C. The reaction mass was allowed to cool to 20°C to 25°C and sulfuryl chloride (110.65 gms) was added to the reaction mass. The reaction mass was heated to 30°C to 35°C and stirred for 2 hours. After completion of reaction, chilled water (200 ml) was added to the reaction mass and stirred for 15 mins at 25°C to 35°C. Organic and aqueous layer was separated and 10% Sodium bicarbonate (200 ml) solution was added to the organic layer at 25°C to 35°C and stirred for 15 mins. Organic and aqueous layer was separated and the organic layer was washed with water (200 ml). The Organic layer was concentrated under vacuum at below 40°C to obtain a residue. To the residue, Toluene (300 ml) and potassium carbonate solution (144.2 gms in 288 ml of water) was charged followed by pyrrolidine solution (74.19 gms in 38.2 ml water) was added at 25°C to 35°C. The reaction mass was heated to 80°C to 85°C and stirred for 12 hours. After completion of reaction, the reaction mass was allowed to cool to 25°C to 35°C and water (400 ml) was added to it. The reaction mass pH was adjusted to 2-2.5 with aqueous hydrochloric acid solution at 25°C to 35°C and stirred for 15 mins. The aqueous and organic layer was separated and the organic layer was extracted with water (100 ml). To the combined aqueous layer, sodium hydroxide solution was added to adjust the pH to 9-9.5 at 25°C to 35°C followed by Toluene (300 ml) was added to the reaction mass and stirred for 15 mins. The organic layer was separated and the aqueous layer was extracted with toluene (150 ml). The combined organic layer was washed with water and the organic layer was concentrated under vacuum till 5 vol remains in the flask. The reaction mass was allowed to cool to 0°C to 5°C and Zinc bromide (38.7 gms) was added at 0°C to 5°C and stirred for 15 mins. Sodium borohydride (33.8 gms) was added to the reaction mass at 0-5°C and stirred for 15 mins. Methanol (280 ml) was added to the reaction mass and stirred for 2 hours at 0-5°C. After completion of reaction, the reaction mass pH was adjusted to 2-2.5 with aqueous hydrochloric acid at 0-5°C and then Water (980 ml) was added to the reaction mass. The reaction mass was heated to 45°C to 50°C and stirred for 15 mins and organic and aqueous layer was separated. Water (140 ml) was added to the organic layer at 45°C to 50°C, stirred and the aqueous layer was separated. The aqueous layers were combined and pH was adjusted to 10-10.5 with sodium hydroxide solution at 45°C to 50°C and extracted the product with Toluene (2×420 ml) at 45°C to 50°C. The organic layer was washed with sodium chloride solution and the organic layer was concentrated under vacuum at below 60°C to obtain a residue. The residue was dissolved in ethanol and was further concentrated under vacuum at below 60°C to obtain a residue (130 gms).

To the residue (100 gms), ethanol (100 ml) was added at 25°C to 35°C and heated to 33°C to 37°C. L(+)-tartaric acid (51.2 gms) was added to the reaction mass at 33°C to 37°C and the reaction mass was seeded with (1S, 2R)- pyrrolidinyl norephedrine L-(+)-tartaric acid salt (0.1 gm) and stirred for 30 mins at 40°C to 45°C. The reaction mass was allowed to cool to 25°C to 35°C and further to 3°C to 7°C and stirred for 60 mins. The precipitated solid was filtered off, washed with chilled ethanol and suck dried. The filtrate was distilled off the solvent completely under vacuum at below 50°C and the obtained residue was allowed to cool to 40°C to 50°C. Water (100 ml) and toluene (300 ml) was added to the residue and stirred for 15 mins. The reaction mass pH was adjusted to 9.5-10 with aqueous sodium hydroxide solution and stirred for 15 mins at 25-30°C. The organic and aqueous layer was separated and aqueous layer was extracted with toluene (100 ml). Organic layer were combined and was washed with 5% sodium chloride solution at 25-30°C. The organic layer was concentrated under vacuum at below 60°C to obtain a residue. To the residue, ethanol (420 ml) was added and stirred for 10 mins at 35248C to 40°C. D(-)-tartaric acid (41 gms) was added to the reaction mass at 33°C to 37°C and the reaction mass was seed with (1R, 2S)- pyrrolidinyl norephedrine D-(-)-tartaric acid salt (0.1 gm) at 37°C to 43°C and stirred for 30 mins. The reaction mass was allowed to cool to 25°C to 35°C and further to 13°C to 17°C then stirred for 2 hours. The precipitate solid was filtered off, washed with chilled ethanol and suck dried. To the wet compound, ethanol (840 ml) was added and heated to 72°C to 82°C and stirred for 30 mins. The reaction mass was allowed to cool to 33°C to 37°C and further to 10°C to 15°C then stirred for 60 mins. The precipitated solid was filtered off, washed with chilled ethanol and dried at 50-55°C to obtain the title compound.

Yield: 60 gms
Chiral Purity: (1R, 2S): 99.89 %, (1S, 2R): 0.12%

Example 35: Preparation of (1R, 2S)-pyrrolidinyl norephedrine.

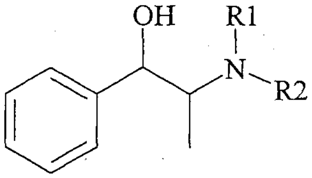
A round bottom flask fitted with a mechanical stirrer, thermometer socket, addition funnel was charged with (1R, 2S)-pyrrolidinyl norephedrine D(-)-tartaric acid (50 gms), obtained from example-34, toluene (150 ml) and water (50 ml) at 25°C to 30°C and stirred for 10 mins. Reaction mass pH was adjusted to 9.5-10 with aqueous sodium hydroxide solution and stirred for 30 mins. The organic and aqueous layers were separated and extracted the aqueous layer with toluene. The organic layer was combined and washed with 5% sodium chloride solution. The organic layer was concentrated under vacuum at below 60°C followed by degas for 30 mins. The obtained residue was allowed cool to 25°C to 35°C (Yield: 30 gms)..

Chiral Purity: (1R, 2S): 99.96%, (1S, 2R): 0.04%

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of the specification appended hereto.

CLAIMS:

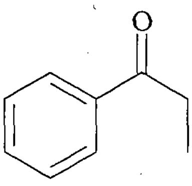
Claim 1: A process for the preparation of norephedrine and its derivatives of Formula I,



Formula I

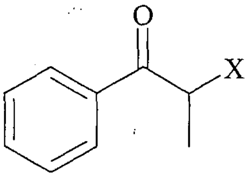
wherein R1 and R2 independently represent hydrogen or R1 and R2 combine to form a cyclic ring; comprising:

a) reacting propiophenone of Formula IV



Formula IV

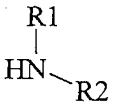
with a suitable halogenating agent to obtain halopropiophenone of Formula III,



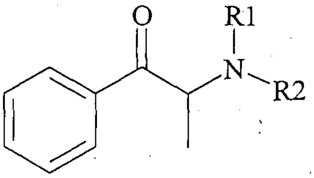
Formula III

wherein 'X' is a halogen selected from Cl, Br or I;

b) reacting the resulting halopropiophenone with a suitable amine source of Formula



wherein R1 and R2 independently represents hydrogen or a formyl group; or R1 and R2 combine to form a cyclic ring; to obtain a keto compound Formula II; and

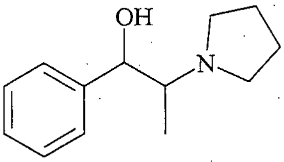


Formula II

wherein R1 and R2 independently represents hydrogen or R1 and R2 combine to form a cyclic ring;

c) reducing the keto compound of Formula II with a suitable reducing agent to obtain norephedrine and its derivative thereof.

Claim 2: The process according to claim 1, wherein the compound of Formula I is a compound of Formula IA:



Formula IA

Claim 3: The process according to claim 1, wherein the suitable halogenating agent is selected from the group comprising bromine, N-halo succinimide such as N-bromo succinimide, N-chloro succinimide; sulfuryl chloride, thionyl chloride, thionyl bromide, phosphorous trichloride, phosphorous tribromide and mixtures thereof.

Claim 4: The process according to claim 3, wherein the suitable halogenating agent is bromine or sulfuryl chloride.

Claim 5: The process according to claim 1, wherein the step a) is carried out in a suitable solvent selected from halogenated hydrocarbons such as methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, chlorobenzene; ethers such as diethyl ether, methyl tert-butyl ether, diisopropyl ether, tetrahydrofuran (THF), 1,4-Dixoane and mixtures thereof.

Claim 6: The process according to claim 5, wherein the solvent is selected from the group consisting of methylene chloride, chloroform, toluene and mixtures thereof.

Claim 7: The process according to claim 1, wherein the suitable amine source is pyrrolidine.

Claim 8: The process according to claim 1, wherein the step b) is carried out in presence of a base and a solvent.

Claim 9: The process according to claim 8, wherein the base is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and mixtures thereof.

Claim 10: The process according to claim 8, wherein the solvent is selected from the group comprising halogenated hydrocarbons such as methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, chlorobenzene; ethers such as diethyl ether, methyl tert-butyl ether, diisopropyl ether, THF, 1,4-Dixoane; ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone; esters such as ethyl acetate, isopropyl acetate; Nitriles such as acetonitrile, propionitrile, benzonitrile; aromatic hydrocarbons such as toluene, xylene; and mixtures thereof.

Claim 11: The process according to claim 10, wherein the solvent is selected from the group consisting of methylene chloride, chloroform, toluene and mixtures thereof.

Claim 12: The process according to claim 1, wherein the suitable reducing agent is selected from the group comprising sodium borohydride, lithium aluminum hydride, vitride, and DIBAL-H.

Claim 13: The process according to claim 12, wherein the suitable reducing agent is sodium borohydride.

Claim 14: The process according to claim 1, wherein the step c) is carried out in presence of a solvent selected from the group comprising alcohols, ethers, halogenated hydrocarbons, nitriles, aromatic hydrocarbons and mixtures thereof.

Claim 15: The process according to claim 14, wherein the solvent is selected from the group consisting of methanol, methylene chloride, chloroform, toluene and mixtures thereof.

Claim 16: A process for the preparation of optically pure pyrrolidinyl norephedrine, comprising:

a) reacting propiophenone of Formula IV with a suitable halogenating agent to obtain halopropiophenone of Formula III, wherein 'X' is a halogen selected from Cl, Br or I,

b) reacting the resulting halopropiophenone with pyrrolidine to obtain a keto compound of Formula IIA,

c) reducing the keto compound of Formula IIA with a suitable reducing agent optionally in presence of a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine, and

d) treating the resultant mixture with a suitable chiral acid to obtain optically pure pyrrolidinyl norephedrine.

Claim 17: The process according to claim 16, wherein the steps a) and b) are carried out according to process of claim 1.

Claim 18: The process according to claim 16, wherein the suitable reducing agent is selected from the group comprising sodium borohydride, lithium aluminum hydride, vitride, and DIBAL-H.

Claim 19: The process according to claim 16, wherein the step c) is carried out with a suitable reducing agent in presence of a metal salt.

Claim 20: The process according to claim 16, wherein the suitable reducing agent is selected from the group comprising sodium borohydride, lithium aluminum hydride, vitride, and DIBAL-H.

Claim 21: The process according to claim 19, wherein the metal salt is a compound of Formula MX_2, wherein the 'M' represents a metal cation selected from the group comprising zinc, beryllium, magnesium, calcium, cerium, strontium, manganese, copper and barium; 'X' represents halide, acetate, sulfate, bisulfate, carbonate, bicarbonate or trifluoromethane sulfonate.

Claim 22: The process according to claim 20, wherein the metal salt is selected from the group consisting of zinc chloride, zinc bromide, zinc sulfate, zinc acetate, zinc trifluoromethane sulfonate, magnesium chloride, magnesium acetate, manganese chloride, calcium chloride, cerium chloride and mixtures thereof.

Claim 23: The process according to claim 16, wherein the chiral acid is selected from the group comprising D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, L(+)-tartaric acid, L(+)-malic acid, L(+)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

Claim 24: The process according to claim 16, wherein the chiral acid is D(-)-Tartaric acid.

Claim 25: The process according to claim 16, wherein the step d) is carried out in a suitable solvent selected from the group comprising alcohols, nitriles, ketones, halogenated solvents, esters, ethers, hydrocarbon solvents, amides, water and mixtures thereof.

Claim 26: The process according to claim 25, wherein the solvent is selected from the group consisting of methanol, ethanol, acetone, methylene chloride, chloroform, ethyl acetate and mixtures thereof.

Claim 27: The process according to claim 16, wherein the optically pure pyrrolidinyl norephedrine is (1R, 2S) - pyrrolidinyl norephedrine.

Claim 28: The process according to claim 27, wherein the (1R, 2S) - pyrrolidinyl norephedrine containing less than 0.2% by HPLC of (1S, 2R)-enantiomer.

Claim 29: A process for the isomer separation of (1R, 2S) - pyrrolidinyl norephedrine, comprising:

a) providing a solution of racemic mixture comprising optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine;

b) treating the resultant mixture with a suitable chiral acid to obtain salt of (1S, 2R) - pyrrolidinyl norephedrine,

c) neutralizing the mother liquors containing a salt of (1R,2S)-pyrrolidinyl norephedrine and salt of optical isomers of pyrrolidinyl norpseudoephedrine with a base to obtain (1R, 2S) - pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine,

d) treating the resultant mixture with a suitable chiral acid to obtain a salt of (1R, 2S) - pyrrolidinyl norephedrine, and

e) neutralizing the salt of (1R, 2S) - pyrrolidinyl norephedrine with a base to obtain optically pure (1R, 2S) - pyrrolidinyl norephedrine.

Claim 30: The process according to claim 29, wherein the step a) is obtained according to process of claim 1 or claim 16.

Claim 31: The process according to claim 29, wherein the step a) is obtained by dissolving the racemic mixtures of optical isomers of pyrrolidinyl norephedrine and optical isomers of pyrrolidinyl norpseudoephedrine in a suitable solvent.

Claim 32: The process according to claim 31, wherein the solvent is selected from the group comprising alcohols, nitriles, ketones, halogenated solvents, esters, ethers, hydrocarbon solvents, amides, water and mixtures thereof.

Claim 33: The process according to claim 32, wherein the solvent is selected from the group consisting of methanol, ethanol, acetone, methylene chloride, chloroform, ethyl acetate and mixtures thereof.

Claim 34: The process according to claim 29, wherein the suitable chiral acid for step b) is selected from L(+)-tartaric acid, L(+)-malic acid or L(+)-lactic acid.

Claim 35: The process according to claim 34, wherein the suitable chiral acid is L(+)-tartaric acid.

Claim 36: The process according to claim 29, wherein the salt of (1S, 2R) - pyrrolidinyl norephedrine is separated by filtration.

Claim 37: The process according to claim 29, wherein the suitable chiral acid for step d) is selected from the group comprising D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like; preferably D(-)-tartaric acid.

Claim 38: The process according to claim 37, wherein the chiral acid is D(-)-tartaric acid.

Claim 39: The process according to claim 29, wherein the step d) is carried out in a suitable solvent selected from the group comprising alcohols, nitriles, ketones, halogenated solvents, esters, ethers, hydrocarbon solvents, amides, water and mixtures thereof.

Claim 40: The process according to claim 39, wherein the solvent is selected from the group consisting of methanol, ethanol, acetone, methylene chloride, chloroform, ethyl acetate and mixtures thereof.

Claim 41: The process according to claim 29, wherein the salt of (1R, 2S) - pyrrolidinyl norephedrine is separated by filtration.

Claim 42: The process according to claim 29, wherein the base used in step c) and e) is selected from sodium hydroxide, potassium hydroxide and mixtures thereof.

Claim 43: The process according to claim 29, further comprising purifying the salt of (1R, 2S) - pyrrolidinyl norephedrine using a suitable solvent.

Claim 44: The process according to claim 43, wherein the suitable solvent is selected from the group comprising methanol, ethanol, ethyl acetate, toluene and mixtures thereof.

Claim 45: A process for isomer enrichment of (1R,2S)-pyrrolidinyl norephedrine or a salt thereof, comprising:

a) combining (1R, 2S) - pyrrolidinyl norephedrine or a salt thereof in a suitable solvent,

b) heating to obtain clear solution,

c) optionally seeding the chiral acid salt of (1R, 2S) - pyrrolidinyl norephedrine,

d) cooling the solution to precipitation, and

e) isolating the pure (1R, 2S) - pyrrolidinyl norephedrine or a salt thereof.

Claim 46: The process according to claim 45, wherein the (1R, 2S) - pyrrolidinyl norephedrine salt is (1R, 2S) - pyrrolidinyl norephedrine D(-)-tartaric acid salt.

Claim 47: The process according to claim 45, wherein the suitable solvent is selected from the group comprising alcohols, esters, ethers, halogenated solvents, hydrocarbon solvents, water and mixtures thereof.

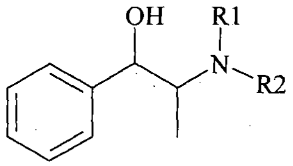
Claim 48: The process according to claim 47, wherein the solvent is selected from the group consisting of methanol, ethanol, ethyl acetate, toluene and mixtures thereof.

Claim 49: The process according to claim 45, wherein the heating is about ambient temperature to about reflux temperature.

Claim 50: The process according to claim 45, wherein the cooling the solution to less than 20°C.

Claim 51: The process according to claim 45, wherein the isolation is carried out by filtration.

Claim 52: A chiral acid salt compound of Formula I,



Formula I

wherein R1 and R2 independently represent hydrogen or R1 and R2 combine to form a cyclic ring; wherein the chiral acid is selected from the group comprising: D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, L(+)-tartaric acid, L(+)-malic acid, L(+)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like.

Claim 53: The chiral acid salt compound of Formula I is a chiral acid salt pyrrolidinyl norephedrine.

Claim 54: (1S, 2R)-pyrrolidinyl norephedrine L(+)-tartaric acid salt.

Claim 55: (1R, 2S)-pyrrolidinyl norephedrine D(-)-tartaric acid salt.

Claim 56: 1S, 2S)-pyrrolidinyl norpseudoephedrine S(+)-mandelic acid salt.

Claim 57: (1S, 2S)-pyrrolidinyl norpseudoephedrine dibenzoyl-d-tartaric acid salt.

Claim 58: A process for the preparation of (1R, 2S) - pyrrolidinyl norephedrine, comprising:

a) providing mother liquors containing either any ratio of optical isomers of pyrrolidinyl norephedrine or its mixture with pyrrolidinyl norpseudoephedrine,

b) evaporating the solvent from the mother liquors to obtain a residue,

c) treating the residue with an oxidizing agent in an appropriate solvent to obtain keto compound of Formula IIA,

d) reducing the keto compound of Formula IIA with a suitable reducing agent and a metal salt to obtain a mixture of optical isomers of pyrrolidinyl norephedrine and pyrrolidinyl norpseudoephedrine; and

e) treating the resulting mixture with a suitable resoluting agent to obtain (1R, 2S) - pyrrolidinyl norephedrine.

Claim 59: The process according to claim 58, wherein the oxidizing agent is selected from the group consisting of chromium trioxide, sodium dichromate, potassium dichromate, potassium permanganate, pyridinium chlorochromate, dess-martin periodinane, pyridinium dichromate, magnesium dioxide, manganese (IV) oxide, dichromate (VI) and chromium (VI) oxide.

Claim 60: The process according to claim 59, wherein the oxidizing agent is sodium dichromate.

Claim 61: The process according to claim 58, wherein the appropriate solvent is water.

Claim 62: The process according to claim 58, wherein the suitable reducing agent is selected from the group comprising sodium borohydride, lithium aluminum hydride, vitride, and DIBAL-H.

Claim 63: The process according to claim 58, wherein the metal salt is a compound of Formula MX_2, wherein the 'M' represents a metal cation selected from the group comprising zinc, beryllium, magnesium, calcium, cerium, strontium, manganese, copper and barium; 'X' represents halide, acetate, sulfate, bisulfate, carbonate, bicarbonate or trifluoromethane sulfonate.

Claim 64: The process according to claim 63, wherein the metal salt is selected from the group consisting of zinc chloride, zinc bromide, zinc sulfate, zinc acetate, zinc trifluoromethane sulfonate, magnesium chloride, magnesium acetate, manganese chloride, calcium chloride, cerium chloride and mixtures thereof.

Claim 65: The process according to claim 58, wherein the suitable chiral acid is selected from the group comprising D(-)-tartaric acid, D(-)-malic acid, D(-)-lactic acid, S(+)-mandelic acid, pyroglutamic acid, di-p-toluyl tartaric acid, dibenzoyl-D-tartaric acid, camphor sulfonic acid, naproxen, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, Di-p-anisoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid monodimethyl amide, S(+)-1,1'-binaphthalene-2,2'-dihydrogen phosphate and the like; preferably D(-)-tartaric acid.

Claim 66: The process according to claim 65, wherein the chiral acid is D(-)-tartaric acid.

Claim 67: A method for preparing pharmaceutically active medicaments with high enantiomeric purity using pyrrolidinyl norephedrine, obtained by the process of any of claims 1 – 66.