Abstract: The present invention relates to a process for the preparation of 1-[2-amino-1-(4-substituted phenyl)ethyl]cyclohexanol (3) (where R is OMe, OH), said process comprising the steps of: subjecting a reaction mixture of substituted phenylethylcyanonitrile (2) in alcohol, an organic acid, and a hydrogenating catalyst in the presence of hydrogen gas pressure in the range of 0.5 kg/cm² to 30 kg/cm² and temperature in the range of 0-100°C; filtering and concentrating the cooled reaction mixture to obtain an acid addition salt of 1-[2-amino-1-(4-substituted phenyl)ethyl]cyclohexanol (4); and treating the acid addition salt of 1-[2-amino-1-(4-substituted phenyl)ethyl]cyclohexanol (4) with an ester in presence of a base to obtain 1-[2-amino-1-(4-substituted phenyl)ethyl]cyclohexanol (3).
A PROCESS FOR PREPARATION OF PHENETHYLAMINE DERIVATIVE

Field of Invention

The present invention relates to an improved process for preparation of phenethylamine derivatives of formula 3, particularly for the preparation of 1-[(2-amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol (3a), an important intermediate for the synthesis of the well-known antidepressant, Venlafaxine.

Background of the Invention

Tricyclic antidepressants that show potential, as cardiovascular and anticholinergic agents have been developed recently. Most of these compounds have shown promise in the treatment of cerebral function disorders such as Parkinson’s disease and senile dementia. Appropriate references are cited in patents viz. WO 94/00047 and WO 94/00014. Venlafaxine referred to in this invention is a non-tricyclic compound, chemically named as (+)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, an antidepressant studied extensively and described in U.S. Pat. No. 4,761,501 and by Pento, J.T. in Drugs of Future, 13(9): 839-840 (1988). Its hydrochloride salt is commercially available in the United States under the name Effexor® which is a racemate of (+) and (-) enantiomers of venlafaxine and is indicated for the treatment of depression.

The synthesis of venlafaxine and its derivatives has been described in J. Med.Chem. 33, 2899-2905 (1990) and U.S. patent No.5043466 by Yardley, J. P., et al., the disclosure of which is incorporated by reference. The referred method, which was adopted, for the synthesis of the compounds of invention, is shown in Scheme-1.

Scheme-1
wherein R is methoxy or hydroxy, R₁ is methyl and the reaction conditions are:

a. LDA in cyclohexanone at -78°C  
b. Rh/Al₂O₃ and hydrogen  
c. HCHO/HCOOH, H₂O and reflux.

The final product by step 'c' is isolated by methods known to those skilled in the art, including preparative high performance liquid chromatography (HPLC). The term "isolate" used herein encompasses the isolation of a compound from the reaction mixture and purification. This method suffers from the following drawbacks, which are not economical. The reaction requires very low temperature, -78°C, which is practically unattainable in tropical conditions or attained with great difficulty and excess of cyclohexanone is used as a solvent. The use of highly toxic and pyrophoric reagents like LDA (Lithiumdiisopropylamide) and highly expensive reduction catalyst Rhodium/Alumina makes the process economically unviable.

Hubbards et al. in U.S. Patent No. 4535186 (1985) and EP 0112669B describe a method for the synthesis of venlafaxine. Venlafaxine is prepared by the reaction of 4-methoxyphenyl acetonitrile (1) (where R is OMe), herein referred to as PMPA with cyclohexanone at -78°C under the influence of n-butyl lithium following the methods known in the literature (Sauvette et al., Tetrahedron, 34, 2135, 1978) to form 1-[cyano-(4-methoxyphenyl)methyl]cyclohexanol (2) (where R is OMe), as represented in Scheme-1, followed by reduction under high pressure to an amine (3) (where R is OMe), using Rhodium catalyst. Symmetrical N,N-dimethylation following the modified Eschweiler-Clarke procedure, employing formic acid, formaldehyde and large excess of water as illustrated by Tillord et al., and Jerussy Thomas in J. Am. Chem. Soc, 76, 2431, 1954 and WO 00159851 respectively, affords venlafaxine (4) (where R is OMe, R₁ is Me). The process suffers from the following major drawbacks; use of very low temperatures, pyrophoric lithium components and large volumes of water for isolating free amine. Moreover, the amine (3) (where R is OMe) viz., 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol, obtained from the above procedure, has been found to be highly unstable and needs to be processed immediately to venlafaxine. All these factors make this process unattractive for industry.

As a modification to the prior art described in J. Med. Chem. 33, 2899-2905 (1990), Robin Gerald Shepherd et al. [U.K. Patent No.GB 2 227 743A (1990)] have condensed the PMPA with cyclohexanone in presence of LDA in hydrocarbon solvents such as hexane,
toluene, cyclohexane and like at ambient temperature thereby improving the yield of α-4-anisyl-α-(l-hydroxycyclohexyl)acetonitrile (2) (where R is OMe) to 71%. Further processing involved the reduction of the above nitrile to the amine, followed by dimethylation to produce venlafaxine. The disadvantages associated with this process are use of highly dangerous LDA, use of expensive reduction catalysts for reducing cyano compound, isolation of unstable 1-[2-amino-1-(4-methoxyphenyl) ethyl] cyclohexanol (3) (where R is OMe) and tedious work up procedures in the isolation and purification of venlafaxine.

Chinese researchers Zhou Jimpei et al. [J. China Pharm. Univ., 30(4), 249-50, 1999] have acylated anisole to the chloroacetyl derivative, which was then aminated using N,N-dimethylamine to obtain α-dimethylamino-4-methoxyacetophenone. The carbonyl group was reduced to alcohol and converted to the bromo compound using methods known to those skilled in the art. The bromo compound was converted to the Grignard reagent and reacted with cyclohexanone to obtain venlafaxine. This method is unattractive because it involves the use of obnoxious reagents and furthermore the product yields are poor.

Spanish workers, Nalot, I. A. et al., describe a process to obtain venlafaxine from 4-methoxyphenyl acetic acid in their patent (WO 01/07397). The method which can be adopted for the synthesis of venlafaxine is shown in Scheme-2.
This process involves Grignard reaction, which is cumbersome and hazardous and moreover yields are unattractive.

The use of reagents like Grignard reagent, LDA, n-butyl lithium, anhydrous AlCb, PBr₃, etc. pose several problems in the preparation of venlafaxine.

Indian chemists Chavan et al. (U.S. Patent No. 6,504,044 B2) came up with yet another modification for the synthesis of said compound under invention. The authors reacted PMPA (1) (where R is OMe), with cyclohexanone to generate compound of formula (2) (where R is OMe), Scheme-1, using a base selected from NaOH, KOH or 10% aqueous NaOH or 50% NaOH. The process uses a phase transfer catalyst and gives a solid, which needs to be crushed and purified further. On a large scale this type of operation leads to difficulties.

Furthermore, in the subsequent step, the nitrile (2) (where R is OMe) is reduced to the amino compound l-[2-amino-l-(4-methoxyphenyl)ethyl]cyclohexanol (3) (where R is OMe) using Raney Ni in yields as low as 15% and the maximum yield achieved was 30%.

The process further involves the separation of the amine (3) (where R is OMe), an air and light sensitive amine, and recycling the unreacted nitrile to optimize the yield. This type of operation is not only expensive but also cumbersome on an industrial scale and highly unattractive for large-scale preparation of compounds like Venlafaxine.

A similar process for the manufacture of Venlafaxine hydrochloride has been described in the U.S. Patent No. 6,620,960 B2. Reddy et al. in their patent application US 2005/0033088A1 describe a process by which the nitrile (2) (where R is OMe) is reduced in acetic acid medium with palladium catalyst. In this process, acetic acid is evaporated and the resulting compound is neutralized and extracted with an organic solvent to obtain the free base. The free base is then converted to the acetate salt by the addition of acetic acid. When this process was repeated at our end to obtain the acetate salt, it resulted in an impure product in poor yield. As the amine acetate is heated to higher temperature to remove traces of acetic acid, the salt tends to decompose rapidly forming impurities, which affect the final conversion to Venlafaxine hydrochloride. Removal of traces of acetic acid is very difficult and requires high vacuum and the conversion of acetate salt to pure amine by neutralization and isolation of the amine in the pure form is cumbersome and time consuming.

In a known hydrogenation process the formation of two major impurities viz. p-methoxy phenyl ethylamine and dehydro was observed during the preparation of l-[2-amino-1-(4-methoxy phenyl)ethyl]cyclohexanol.
In our previous patent application we have disclosed a novel process for the preparation of 1-[2-amino-1-(4-methoxy phenyl)ethyl]cyclohexanol said process comprising the steps of: dissolving 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol in an alcohol and ammonium salt to obtain a reaction mixture, and treating the reaction mixture with hydrazine hydrate in the presence of a noble metal catalyst to obtain 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol, an important intermediate for the synthesis Venlafaxine and its acid addition salts.

Summary of the Invention

Accordingly, the present invention provides an improved process for the preparation of 1-[2-amino-1-(4-substituted phenyl)ethyl]cyclohexanol (3),

wherein R is selected from a group consisting of C1-C4 alkoxy, C1-C4 alkyl, hydroxyl and H, said process comprising

i. subjecting a reaction mixture of substituted phenylacetonitrile (2) in alcohol, an organic acid, and a hydrogenating catalyst in the presence of hydrogen gas pressure in the range of 0.5 kg/cm² to 30 kg/cm² and temperature in the range 0°-100°C;

ii. filtering and concentrating the cooled reaction mixture to obtain an acid addition salt of 1-[2-amino-1-(4-substituted phenyl)ethyl]cyclohexanol (4'); and
iii. treating the acid addition salt of l-[2-amino-l-(4-substituted phenyl)ethyl]cyclohexanol (4') with an ester in presence of a base to obtain l-[2-amino-l-(4-substituted phenyl)ethyl] cyclohexanol (3).

These and other features, aspects, and advantages of the present subject matter will become better understood with reference to the following description and appended claims.

This Summary is provided to introduce a selection of concepts in a simplified form. This Summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter.

Detailed Description of the Invention

The present invention relates to an improved process for the preparation of phenethylamine derivative of compound of Formula-3,

![Chemical Structure](image)

wherein R is selected from a group consisting of C1-C4 alkoxy, C1-C4 alkyl, hydroxy and H, said process comprising

i. subjecting a reaction mixture of substituted phenylacetonitrile (2) in alcohol, an organic acid, and a hydrogenating catalyst in the presence of hydrogen gas pressure in the range of 0.5 kg/cm² to 30 kg/cm² and temperature in the range of 0-100°C;

![Chemical Structure](image)

ii. filtering and concentrating the cooled reaction mixture to obtain an acid addition salt of l-[2-amino-l-(4-substituted phenyl)ethyl]cyclohexanol (4'); and
Uf. treating the acid addition salt of 1-[2-amino-1-(4-substituted phenyl)ethyl]cyclohexanol (4') with an ester in presence of a base to obtain 1-[2-amino-1-(4-substituted phenyl)ethyl] cyclohexanol (3).

In an exemplary embodiment the Schematic representation for the preparation of phenethylamine derivatives of formula 3, by the process of the present invention is as shown in Scheme 3.

Scheme-3-

\[ \begin{align*}
\text{CN} & \quad \text{(a)} \quad \text{CN} \\
R & \quad 1 \quad R \\
\text{CN} & \quad (d) \quad \text{CN} \\
R & \quad 2 \quad R \\
\text{H}_2\text{N} & \quad \text{(e)} \quad \text{H}_2\text{N} \\
\text{OH} & \quad 3 \quad \text{OH} \\
R & \quad 4' \quad R
\end{align*} \]

wherein R is (Ci-C₄) alkoxy or hydroxyl, hydrogen, (Ci-C₄)alkyl. Step (a) is carried out using the reagents sodium methoxide, cyclohexanone in methanol; step (d) is the treatment of cyano alcohol as obtained from step (a) with noble metal catalyst or Cobalt or Raney nickel in alcohol, water, organic acid and inorganic salt; and step (e) is the treatment of the acid addition salt of formula (4') in an ester and addition of a base to obtain the phenethylamine derivatives of formula 3.

It is an embodiment of the present invention wherein the reaction mixture of step (i) comprises of an inorganic salt of the corresponding organic acid.
In an embodiment of the present invention, inorganic salt of organic acid is employed in a molar equivalent in the range from 1 to 1.5.

In an embodiment of the present invention, the alcohol is selected from a group consisting of methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol and ter-butanol or mixtures thereof, preferably methanol.

In an embodiment of the present invention, the volume of alcohol employed is 6 to 16 times as that of the compound of Formula 2. More preferably the volume of alcohol employed is 12 times as that of the compound of formula 2.

In another embodiment of the present invention, the organic acid is selected from a group consisting of each substituted or unsubstituted aliphatic, aryl, arylalkyl, heteroaryl carboxylic acids, unsaturated carboxylic acid and sulphonic acid, or a mixture thereof, preferably an aliphatic dicarboxylic acid.

In an embodiment of the present invention, the organic acid is employed in a molar equivalent in the range from 1 to 1.5 as that of the compound of formula 2.

In yet another embodiment, the organic acid is either oxalic acid or methanesulphonic acid.

In yet another embodiment, the inorganic salt is selected from a group consisting of salt of organic acid, salt of aliphatic dicarboxylic acid, salt of alkali metal and salt of alkaline earth metal or mixtures thereof, preferably salt of corresponding aliphatic dicarboxylic acid.

In another embodiment, the inorganic salt is ammonium oxalate when the organic acid is oxalic acid.

In yet another embodiment, wherein the hydrogenating catalyst is selected from a group consisting of noble metal catalyst, a cobalt catalyst, palladium on charcoal and Raney nickel catalyst. More preferably the catalyst Palladium on charcoal can be used as 5% or 10%.

In an embodiment of the present invention, Palladium on charcoal is employed in the range from 0.05 to 0.1 w/w as that of the compound of formula 2.

It is still another embodiment of the present invention, a process for the preparation of l-[2-amino-l-(4-methoxyphenyl)ethyl]cyclohexanol of Formula-3(a),

![Chemical Structure](image)
said process comprising

i. subjecting a reaction mixture of α-4-anisyl-α-(1-hydroxycyclohexyl)acetonitrile of Formula 2(a) in methanol, methanesulfonic acid and palladium on charcoal in the presence of hydrogen gas pressure 5kg/cm² and at temperature 20° to 25°C;

\[
\text{2a}
\]

ii. filtering and concentrating the cooled reaction mixture to obtain 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol methanesulfonate of formula (4'a)

\[
4\text{a}
\]

; and

iii. treating 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol methanesulfonate with ethyl acetate in presence of an ammonia to obtain 1-[2-amino-1-(4-methoxy phenyl) ethyl] cyclohexanol (3a).

It is an embodiment of the present invention wherein the acid addition salt of 1-[2-amino-1-(4-substituted phenyl) ethyl] cyclohexanol is suspended in solvent is ester or chlorinated solvent such as ethyl acetate, methylenechloride, dichloroethylene. Most preferably ethyl acetate.

In an embodiment of the present invention, the volume of an ester employed is 5 to 12 times as that of compound of formula (4'a). More preferably the volume of an ester employed is 10 times as that of compound of formula (4'a).

It is an embodiment of the present invention wherein the substituted phenylacetonitrile (2) is 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol or 1-[cyano(4-hydroxyphenyl)methyl]cyclohexanol.
Another embodiment of the present invention is using hydrogen gas in the pressure range of 0.5 \( \text{kg/cm}^2 \) to 30 \( \text{kg/cm}^2 \), preferably 2 \( \text{kg/cm}^2 \) to 10 \( \text{kg/cm}^2 \).

Yet another embodiment of the present invention is to perform the reaction at a temperature in the range of 0-100°C, preferably 60°C.

The invention is further defined by reference to the following examples describing in detail the preparation and composition of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practised without departing from the purpose and interest of the invention.

The process of the present invention is described by the following examples, which are illustrative only and should not be construed as limit to the scope of the reaction in manner.

**EXAMPLES**

**Example 1:**

**Preparation of \( \alpha \)-4-anisyl- \( \alpha \)-(1-hydroxycyclohexyl)acetonitrile**

4-Methoxyphenylacetonitrile (100kg, 679.44 mol) is mixed with cyclohexanone (153.2Kg, 1561 mol) in a clean stainless steel reactor. The mixture is stirred at room temperature for 15-20 min and then cooled to 0°C by applying brine in the reactor.

In another stainless steel reactor sodium methoxide solution (25%, commercial, 400 L) is charged and cooled to 20°C. To this solution is added methanol (400 L) whose moisture content has been determined previously. The mixture is stirred and mixed thoroughly and cooled to -5°C. To the chilled sodium methoxide solution is added the mixture of PMPA and cyclohexanone at such a rate that the temperature of the reaction mixture does not go above -2°C. Once the addition is complete the reaction mixture is stirred for 4-5hr or until there is no more of starting material as indicated by TLC. Once the reaction is complete, the reaction mass is centrifuged at -5 to 0°C and the wet product is slurried in 600L of water containing 15L of acetic acid at 25-30°C and centrifuged, and washed with 200L of water. The material is unloaded and dried at room temperature to obtain a free flowing white crystalline solid (145Kg, 589.4 mol, 86.75%).

**Example-2:** **Preparation of 1-[(2-amino)-l-(4-methoxyphenyl)ethyl]cyclohexanol oxalate salt.**

The \( \alpha \)-4-anisyl- \( \alpha \)-(1-hydroxycyclohexyl)acetonitrile (25g, 0.102 mole), methanol (300ml), oxalic acid (12.86g, 0.102 mole) and 10% Palladium on charcoal (2.5g, 50% wet)
are charged into autoclave. Nitrogen gas is purged in and vented out to replace air. The operation is repeated twice and then with nitrogen gas thrice. The autoclave is pressurized with hydrogen gas to 1 kg/sq. cm and vented out to replace nitrogen, and then autoclave is pressurized with hydrogen gas to 5 kg/sq. cm and maintained with stirring at this pressure and about 60°C for 16h.

After completion of reaction is ascertained by TLC, the contents are cooled to 25-28°C and filtered. The bed is washed with methanol (30 ml). The combined filtrate are concentrated to give 1-[(2-amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol oxalate salt as a white solid, which is slurried in ethyl acetate. Yield - 29g (84%).

Example-3:

Preparation of 1-[(2-amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol oxalate salt.

The α-4-anisyl-α-(l-hydroxycyclohexyl)acetonitrile (25g, 0.102 mole), 300ml of methanol (12V), oxalic acid (12.86g, 0.102 mole), ammonium oxalate (28.99 g, 0.204 moles) and 10% Palladium on charcoal (2.5g, 50% wet) are charged into autoclave. Nitrogen gas is purged in and vented out to replace air. The operation is repeated twice and then with nitrogen gas thrice. The autoclave is pressurized with hydrogen gas to 1 kg/sq. cm and vented out to replace nitrogen, and then autoclave is pressurized with hydrogen gas to 5 kg/sq. cm and maintained with stirring at this pressure and about 60°C for 16hr.

After completion of reaction is ascertained by TLC, the contents are cooled to 25-28°C and filtered. The bed is washed with methanol (30 ml). The combined filtrate are concentrated to give 1-[(2-amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol oxalate salt as a white solid, which is slurried in ethyl acetate. Yield - 31.0 g (89.8%).

Example-4:

Preparation of 1-[(2-amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol methane sulfonate salt.

The α-4-anisyl-α-(l-hydroxycyclohexyl)acetonitrile (500g), 6 liter of methanol (12V), methane sulphonic acid (159ml) and 5% Palladium on charcoal (50g, 50% wet) are charged into autoclave. Nitrogen gas is purged in and vented out to replace air. The operation is repeated twice and then with nitrogen gas thrice. The autoclave is pressurized with hydrogen gas to 1 kg/sq. cm and vented out to replace nitrogen, and then autoclave is pressurized with hydrogen gas to 5 kg/sq. cm and maintained with stirring at this pressure and about 25°C. After completion of reaction is ascertained by TLC, the reaction mass is
filtered, recover the catalyst and distill the methanol under vacuum at 45 to 50°C. The resulting reaction mass is cooled to 0 to -5°C and filtered. The filtrate is washed with isopropyl alcohol (500ml) and dried at 50-55°C to obtain 557g of 1-[(2-amino)-1-(4-methoxyphenyl) ethyl] cyclohexanol methanesulfonate salt. (Yield- 79%, Purity 98.6%)

**Example 5:**

**Preparation of 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol of formula (3a)**

Ethyl acetate (690ml) and 1-[2-amino-1-(4-methoxyphenyl) ethyl] cyclohexanol methanesulfonate salt (69.3g) are charged into R.B. flask and stirred for 15 minutes at room temperature. The reaction mixture is basified with aqueous ammonia till pH 9 is achieved and stirred for 10 minutes at room temperature. The aqueous and organic layers are separated and the aqueous layer is extracted twice with ethyl acetate (60ml). The combined organic layer is washed twice with water and concentrated under vacuum at 50°C to obtain 50g of crude 1-[2-amino-1-(4-methoxyphenyl) ethyl] cyclohexanol.(Yield 100%, purity greater than 98%)

Although the subject matter has been described in considerable detail with reference to certain preferred embodiments thereof, other embodiments are possible. As such, the spirit and scope of the appended claims should not be limited to the description of the preferred embodiment contained therein.

**Advantages**

The previously described versions of the subject matter and its equivalent thereof have many advantages, including those which are described below:

1) The process of the present invention is a convenient and commercially viable process for the preparation of 1-[2-amino-1-(4-substitutedphenyl)ethyl]cyclohexanol (3) (where R is OMe).

2) The present invention provides a process for the preparation of 1-[2-amino-1-(4-substitutedphenyl) ethyl]cyclohexanol (3) (where R is OMe, OH) in high yield with enhanced purity.

3) The present invention provides a process for the preparation of 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol which reduces the formation of p-methoxy phenyl ethylamine and dehydro impurities.
I/We claim:

1. A process for the preparation of phenethylamine derivative of compound of Formula-3,

   \[
   \begin{array}{c}
   \text{H}_2\text{N} \\
   \text{OH} \\
   \text{R} \\
   \end{array}
   \]

   wherein R is selected from a group consisting of C1-C4 alkoxy, C1-C4 alkyl, hydroxyl and H, said process comprising

   i. subjecting a reaction mixture of substituted phenylacetonitrile (2) in alcohol, an organic acid, and a hydrogenating catalyst in the presence of hydrogen gas pressure in the range of 0.5 kg/cm² to 30 kg/cm² and temperature in the range of 0-100°C;

   \[
   \begin{array}{c}
   \text{CN} \\
   \text{OH} \\
   \text{R} \\
   \end{array}
   \]

   ii. filtering and concentrating the cooled reaction mixture to obtain an acid addition salt of 1-[2-amino-1-(4-substituted phenyl)ethyl]cyclohexanol (4');

   \[
   \begin{array}{c}
   \text{H}_2\text{N} \\
   \text{OH} \\
   \text{R} \\
   \end{array}
   \]

   iii. treating the acid addition salt of 1-[2-amino-1-(4-substituted phenyl)ethyl]cyclohexanol (4') with an ester in presence of a base to obtain 1-[2-amino-1-(4-substituted phenyl)ethyl] cyclohexanol (3).

2. The process as claimed in claim 1, wherein the reaction mixture of step (i) comprises

   of an inorganic salt of the corresponding organic acid.
3. The process as claimed in claim 1, wherein the alcohol is selected from a group consisting of methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol and ter-butanol or mixtures thereof.
4. The process as claimed in either claim 1 or 3, wherein the alcohol is methanol.
5. The process as claimed in claim 1, wherein the organic acid is selected from a group consisting of each substituted or unsubstituted aliphatic, aryl, arylalkyl, heteroaryl carboxylic acids, unsaturated carboxylic acid and sulphonic acid, or a mixture thereof.
6. The process as claimed in either claim 1 or 5, wherein the organic acid is either oxalic acid or methanesulphonic acid.
7. The process as claimed in claim 2, wherein the inorganic salt is selected from a group consisting of salt of organic acid, salt of aliphatic dicarboxylic acid, salt of alkali metal and salt of alkaline earth metal or mixtures thereof, preferably salt of corresponding aliphatic dicarboxylic acid.
8. The process as claimed in claim 2, wherein the inorganic salt is ammonium oxalate when the organic acid is oxalic acid.
9. The process as claimed in claim 1, wherein the hydrogenating catalyst is selected from a group consisting of noble metal catalyst, a cobalt catalyst, palladium on charcoal and Raney nickel catalyst.
10. The process as claimed in claim 9, wherein the catalyst is either 5% or 10% palladium on charcoal, more preferably 5% palladium on charcoal.
11. The process as claimed in claim 9 and 10, wherein said palladium on charcoal is used in an amount 0.05 to 0.1 w/w as that of the compound of formula 2.
12. The process as claimed in any of the preceding claims, wherein the volume of alcohol employed is 6 to 16 times that of the compound of formula 2.
13. The process as claimed in claim 12, wherein the volume of alcohol employed is 12 times that of the compound of formula 2.
14. The process as claimed in any of the preceding claims, wherein the organic acid is employed in a molar equivalent in the range from 1 to 1.5 as that of the compound of formula 2.
15. A process for the preparation of 1-[2-amino-1-(4-ethoxyphenyl)ethyl]cyclohexanol of Formula-(3a), as claimed in claim 1.
said process comprising
i) subjecting a reaction mixture of α-4-anisyl-α-(l-hydroxycyclohexyl)acetonitrile of Formula 2a in methanol, methanesulphonic acid, 5% palladium on charcoal in the presence of hydrogen gas pressure 5kg/cm² and at temperature 20°-25°C.

ii) filtering and concentrating the cooled reaction mixture to obtain 1-[2-amino-l-(4-methoxy phenyl)ethyl]cyclohexanol methanesulfonate of formula (4'a)

iii) treating 1-[2-amino-l-(4-methoxyphenyl)ethyl]cyclohexanol methanesulfonate with ethyl acetate in presence of an ammonia to obtain 1-[2-amino-l-(4-methoxy phenyl) ethyl] cyclohexanol (3a).
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C213/02 C07C217/74

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and where practical search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document with indication where appropriate of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
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<tr>
<td>Y</td>
<td>WO 2007/047972 A (TEVA PHARMA [US]; KANSAL VINOD KUMAR [IN]; CHAURASIA BRIJNATH P [IN]); 26 April 2007 (2007-04-26) examples and claims; page 5, line 1 - page 9, line 2</td>
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<td>Y</td>
<td>WO 2008/059525 A (CALYX CHEMICALS AND PHARMACEUT [IN]; LAL BANSI [IN]; GUND VITTHAL GEMB) 22 May 2008 (2008-05-22) examples and claims</td>
<td>1-15</td>
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<td>Y</td>
<td>EP 1 870 395 A (KRKA D D NOVO MESTO [SI]) 26 December 2007 (2007-12-26) examples and claims</td>
<td>1-15</td>
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X Further documents are listed in the continuation of Box C

X See patent family annex

* Special categories of cited documents
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  'S' document member of the same patent family

Date of the actual completion of the international search: 20 October 2009

Date of mailing of the international search report: 30/10/2009

Name and mailing address of the ISA/ European Patent Office P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040 Fax (+31-70) 340-3016

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