Title: A PROCESS FOR INDUSTRIAL PREPARATION OF [(S)-N-TERT BUTOXYCARBONYL-3-HYDROXY]ADAMANTYLGLYCINE

(VI)

Abstract: A commercially viable process for industrial preparation of [(S)-n-tert butoxycarbonyl-3-hydroxy]adamantylglycine which is a key intermediate for saxagliptin synthesis and is represented by compound of Formula-VI. The compound-VI obtained by the process of present invention has more than 99.5% HPLC purity, not more than 0.15 % of dihydroxy impurity, not more than 0.05% of isomer impurity and not more than 0.1% of any unknown impurity. Formula (VI).
A PROCESS FOR INDUSTRIAL PREPARATION OF [(S)-N-TERT BUTOXycARBONYL-3-HYDROxy]ADAMANTyLGLYCINE.

FIELD OF INVENTION

The invention relates to a process for industrial preparation of [(S)-n-tert butoxy carbonyl-3-hydroxy]adamantylglycine. More particularly, the invention relates to a commercially viable process for industrial preparation of [(S)-n-tert butoxycarbonyl-3-hydroxy]adamantylglycine which is a key intermediate for saxagliptin synthesis and is represented by compound of Formula-VI. The compound-VI obtained by the process of present invention has more than 99.5% HPLC purity.

![Formula-VI](image)

BACKGROUND OF THE INVENTION

Saxagliptin is dipeptidyl peptidase-4 (DPP-4) chemically known as (1S, 3S, 5S)-2-((2S)-2-Am o-2-(3-hydroxyadamantan-1-yl)-acetyl)-2-azabicyclo[3.1.0]hexane-3-carbonitrile and represented by the compound of Formula-A.

![Formula-A](image)

Saxagliptin is an oral hypoglycemic drug used for the treatment of Type-2 diabetes and is disclosed in US 6,395,767 along with its hydrochloride and trifluoroacetic acid salts. Additionally,
US 7,420,079 discloses saxagliptin and its hydrochloride, trifluoroacetic acid and benzoate salts, as well as saxagliptin monohydrate.

The compound (α-S)-α-[[1,1-dimethylethoxy carbonyl]amino]-3-hydroxytricyclo[3.3.1.1³⁷] decane-1-acetic acid, commonly known as [(S)-n-tert butoxy carbonyl-3-hydroxy] adamantyl glycine, represented by the Compound-VI, is a key intermediate in synthesis of saxagliptin.

(VI)

Among the prior arts, WO 2005/012249 discloses a process for preparation of the [(S)-n-tert. butoxy carbonyl-3-hydroxy]adamantylglycine represented by a process of Scheme-I comprising an eight step process starting with adamantine-1-carboxylic acid.

Scheme-I
The process disclosed in this prior art comprises esterification of adamantine 1-carboxylic acid by an asymmetric Strecker reaction using either methanol with hydrochloric acid at reflux temperature or using trimethylsilyldiazomethane in solvent ether/methanol to give the corresponding methyl ester. The ester is reduced with LAH to alcohol and subsequently oxidized to aldehyde. The aldehyde is transformed into corresponding nitrile compound under asymmetric Strecker conditions with KCN, NaHSO₃ and R-(-)-2-phenylglycinol. The nitrile group of the obtained compound is hydrolyzed under strong acidic conditions, using, for example, 12M HCl in AcOH to give the corresponding carboxylic acids. The chiral auxiliary is removed by catalytic reduction using Pearlman's catalyst to give, after protection of the resulting amino group, protected adamantyl glycine amino acids.

It is observed that process disclosed in this prior art may be useful for lab scale synthesis but it is not commercially viable for industrial scale preparation of the intermediate Compound-VI.

The process disclosed in this prior art primarily comprises an eight step process wherein the intermediates obtained in each step are purified by column/flash chromatography which due to its high cost and complexities is not commercially viable for industrial scale preparation of this compound. If used in anyways, the cost of the end product would be very high.

Further, various steps in the prior art discloses use of either as solvent which due to its highly volatile and hazardous nature is found to be highly difficult and complicated in an industrial scale preparations.

Further, this prior art only discloses the weight % of various intermediates obtained in various steps but this prior art fails to provide HPLC purity/impurity details of those intermediates.

Therefore, there is a need for a commercially viable process which is simplified, cost effective and could be used for industrial scale preparation of Compound-VI.
OBJECTS OF THE INVENTION

Primary object of the invention is to provide a process for industrial preparation of [(S)-n-tert butoxy carbonyl-3-hydroxy] adamantylglycine, a key intermediate for saxagliptin synthesis.

Another object of the invention is to provide a simplified, cost effective and commercially viable process for industrial scale preparation of [(S)-n-tert butoxy carbonyl-3-hydroxy] adamantylglycine with more than 99.5% HPLC purity.

SUMMARY OF THE INVENTION

Accordingly, there is provided a simplified process for preparation of (α-S)-α-[1,1-dimethylethoxy carbonyl]amino]-3-hydroxytricyclo[3.3.1.13,7]decane-1-acetic acid, commonly known as [(S)-n-tert butoxy carbonyl-3-hydroxy] adamantyl glycine, represented by Compound-VI.

\[
\text{(VI)}
\]

The process uses adamantine-1-carboxylic acid as starting material and comprises following steps:

a). treating adamantine-1-carboxylic acid with thionyl chloride to obtain adamantane-1-carboxylic methyl ester (compound-I);

\[
\text{(I)}
\]

b). reducing adamantane-1-carboxylic methyl ester to obtain adamantane-1-methanol (compound-II);

\[
\text{(II)}
\]
c). conversion of adamantane-1-methanol to 2-adamantane-2(R)-2-hydroxy-2-phenylethyl amino acetic acid (compound-III);

\[
\text{(III)}
\]

5
d). catalytic reduction of compound-III to obtain an amino compound-IV;

\[
\text{(IV)}
\]

10
e). protecting amino moiety of compound-IV with di-tert butyl dicarbonate to obtain compound-V;

\[
\text{(V)}
\]

15
f). oxidation of compound-V to obtain [(S)-n-tert butoxy carbonyl-3-hydroxy] adamantylglycine (compound-VI) with more than 99% HPLC purity.

\[
\text{(VI)}
\]

5
The process of the invention is represented in Scheme-II below.

Scheme-II-

[Chemical reaction scheme showing the conversion of Adamantane-1-carboxylic acid and Thionyl chloride to (I), which is then reacted with LiAlH4 to form (II), followed by treatment with KBr/NaOCl/TEMPO/MDC to produce Adamantane-1-aldehyde (Step-I compound).]

[Further reactions showing the conversion of (I) to (II), (II) to (III), and (III) to (IV), followed by the formation of (V) through a series of reactions involving NaOH/THF, di-tert-butyl dicarbonate, and ethyl acetate.]

Stage VI

(alpha S)-alpha-[[1,1-dimethylethoxycarbonyl]amino]tricyclo[3.3.1.137]decane-1-acetic acid (V)

[Finally, the reaction with KMnO4 TRAB 2%aq KOH NaBH4 MDC results in (VI).]

DETAILED DESCRIPTION OF THE INVENTION

Detailed embodiments of the present invention are disclosed herein below. However, it is to be understood that the disclosed embodiments are merely exemplary of the invention, which can be embodied in various forms. The scope of the invention is not limited to the disclosed embodiments and terms and phrases used herein are not intended to be limiting but rather to provide an understandable description of the invention. The invention is defined by claims appended hereto.
The invention relates to a process for preparation of \((\alpha\text{-S})\alpha\)-[[1,1-dimethylethoxy carbonyl]amino]-3-hydroxytricyclo [3.3.1.1^{3,7}]decane-1-acetic acid, commonly known as \([(S)-n\text{-tert butoxy carbonyl-3-hydroxy}] adamantylglycine, represented by Compound-VI.

![Formula VI](image)

The process broadly comprises six stages which are summarized below. Each stage is described in details hereinafter in later paragraphs.

**Stage-I-**

**Esterification of adamantine-1-carboxylic acid to the corresponding ester.**

This comprises treating adamantine-1-carboxylic acid with thionyl chloride to obtain adamantine-1-carboxylic methyl ester (compound-I);

![Formula I](image)

**Stage-II-**

**Conversion of the ester to the corresponding alcohol.**

This comprises reducing adamantine-1-carboxylic methyl ester to obtain adamantine-1-methanol (compound-II);

![Formula II](image)
Stage-III-
Oxidation of alcohol to corresponding aldehyde, its coupling in-situ with R(-)-phenylglycinol followed by hydrolysis of the corresponding nitrile to corresponding acid.

This comprises conversion of adamantane-1-methanol to 2-adamantane-2(R)-2-hydroxy-2-phenylethyl amino acetic acid (compound-III);

![III](image)

Stage-IV-
Deprotection of compound-III by catalytic reduction resulting the corresponding amine derivative.

This comprises catalytic reduction of compound-III to obtain an amino compound-IV;

![IV](image)

Stage-V-
Protection of the amino moiety of Compound-IV with t-butyl carbamate.

This comprises protecting amino moiety of compound-IV with di-tert-butyl di-carbamate to obtain compound-V;

![V](image)
Stage VI:
Oxidation to give corresponding hydroxyl derivative in presence of phase transfer catalyst.

This comprises of oxidation of compound-V to obtain [(S)-n-tert butoxy carbonyl-3-hydroxy] adamantylglycine (compound-VI) with more than 99% HPLC purity.

\[
\text{(VI)}
\]

The process of the invention is represented in Scheme II.

Scheme – II:
Detailed embodiments of various stages of the process are described below-

**Stage-I-**

**Esterification of adamantane-1-carboxylic acid to the corresponding ester.**

This stage comprises treating adamantane-1-carboxylic acid with thionyl chloride in methanol with stirring at room temperature for 2-6 hours. Removing excess of solvent and thionyl chloride under reduced pressure at temperature between 10-40°C to obtain adamantane-1-carboxylic methyl ester (compound-I) having more than 95% of GC purity.

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O
OCH₃
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(I)

**Stage-II-**

**Conversion of the ester to the corresponding alcohol.**

This comprises reducing adamantane-1-carboxylic methyl ester in presence of anhydrous THF and LiAlH₄ under inert and moisture free atmosphere at temperature between 0-5°C and obtaining adamantane-1-methanol (compound-II) with more than 99% of GC purity.

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O
OH
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(II)

**Stage-III-**

**Oxidation of alcohol to corresponding aldehyde, its coupling in-situ with R(-)phenylglycinol followed by hydrolysis of the corresponding nitrile to corresponding acid.**

This comprises conversion of adamantane-1-methanol to 2-adamantane-2(R)-2-hydroxy-2-phenylethyl amino acetic acid (compound-III);
The process of this stage comprises dissolving compound-II in MDC and adding sodium bi carbonate and KBr at room temperature and cooling the solution to 0 – 5°C and stirring for 15 min; adding TEMPO solution and sodium hypo chloride (11% chlorine content) at 0 – 5°C and stirring; adding 10% sodium thio sulphate solution at 0-5°C; slowly raising the temperature to room temperature; separating the organic layer and washing with saturated sodium chloride solution and drying over sodium sulphate; distilling the organic layer under vacuum at below 35°C to get a semi-solid Step-A product with more than 99 % of GC purity; suspending the step-A product in water and cooling the mixture to 0-5°C; treating the mixture with NaHSO₃and NaCN and a solution of (R)(-)-phenyl glycinol in methanol; stirring the resulting mixture at 0-5°C for 10-15min and then heating to 25-30°C and maintaining at this temperature for 1-2 hrs. raising the reaction temperature to 50-55°C and maintaining at this temperature for 4-5hrs; cooling the reaction temperature to 40-45°C and extracting the aqueous fraction with ethyl acetate; washing with saturated sodium chloride solution and drying over anhydrous Na₂SO₄ and concentrating the combined organic layer under vacuum at below 50°C to obtain Step-B nitrile compound having more than 95% HPLC purity; adding the Step-B nitrile compound in conc. HCl and acetic acid at room temperature and stirring for 10 minutes; slowly raising the temperature to 90-95°C and stirring for 8-10hrs; cooling the reaction mass to room temperature and stirring for 5-6 hrs; cooling the temperature of reaction mass to 0-5°C and maintaining at this temperature for 8 - 10 hrs; vacuum filtration and washing with chilled water and obtaining compound 2-adamantane-2(R)-2-hydroxy-2-phenylethyl amino acetic acid (compound-III) with more than 95% of HPLC purity.
Stage-IV
Deprotection of compound-III by catalytic reduction resulting the corresponding amine derivative.

This comprises dissolving compound-III in methanol and acetic acid and hydrogenating with H₂ and Pearlman’s catalyst (10% palladium hydroxide) or Palladium carbon and maintaining the reaction mass for 10-12hrs at room temperature; filtering and washing the filter with methanol; completely distilling the methanol and acetic acid under reduced pressure at below 50° C and co-distilling with n-hexane and stirring at this temperature for 15 minutes and cooling to room temperature and obtaining the amino compound-IV with more than 90% of HPLC purity.

\[
\begin{align*}
\text{HCl} \\
\text{H₂N} \\
\text{COOH}
\end{align*}
\]

(IV)

Stage-V-
Protection of the amino moiety of Compound-IV with t-butyl carbamate.

This comprises dissolving compound-IV in sodium hydroxide at room temperature and cooling the temperature to 0-5°C and stirring for 15 minutes; adding THF at 0-5°C and maintaining the reaction mass at this temperature for 4-5 hrs.; raising the temperature to room temperature; separating the aqueous layer and washing with n-hexane; cooling the aqueous layer to 0-5°C and adding ethyl acetate; adjusting the pH of reaction mass to 2-4 with HCl and extracting the aqueous layer with ethyl acetate and washing with saturated sodium chloride solution and drying over sodium sulphate and obtaining compound-V with more than 99% HPLC purity and less than 0.1% impurity.

\[
\begin{align*}
\text{O} \\
\text{H} \\
\text{COOH}
\end{align*}
\]

(V)
Stage-VI -

Oxidation to give corresponding hydroxyl derivative in presence of phase transfer catalyst.

This comprises treating compound-V with potassium permanganate, KOH and TBAB at 20-25°C and stirring at this temperature for 1 hour at 40-45 RPM; maintain the reaction mass at this temperature for 20-25 hrs with intermittent stirring for 15 to 20 seconds after every one hour; adding sodium bi sulphate solution to reduce the oxidizing agent and adjusting the pH to 2-3 with HCl and extracting the reaction mass with MDC; distilling the MDC layer and dissolving the residue in ethyl acetate and isolating the [(S)-n-tert butoxy carbonyl-3-hydroxy] adamantylglycine (compound-VI) with more than 99% HPLC purity and less than 0.1% impurity.

![Chemical Structure](VI)

15 Examples

Various embodiments of the invention are further exemplified with the help of given examples. However, these examples are only for the purpose of explanation of the process to a person of ordinary skill and various parameters of the examples are illustrative only and should not be taken as limitation to the claims.

Example-1-Esterification of adamantane-1-carboxylic acid to obtain adamantane-1-carboxylic methyl ester (compound-I)

![Chemical Structure](I)
0.55 Moles (100g) of adamantane-1-carboxylic acid in 500mL of methanol was treated with 1.42 moles of thionyl chloride and stirred at room temperature for 3hr till compliance of TLC and later the excess of solvent and thionyl chloride was removed up to traces under reduced pressure below 40°C to yield the product (100g) having the purity above 95% by GC.

Example-2- Conversion of adamantane-1-carboxylic methyl ester to adamantane-1-methanol (compound-II)

\[ \text{II} \]

In an oven dried 3 neck flask, 70mL of anhydrous THF was charged under inert and moisture free atmosphere and 335 mL of LiAlH4 (1M solution in THF) was added. After stirring at room temperature for 1hr the reaction mass was cooled to 0-5°C and slowly 50 g of compound-I solution in THF was added at 0-5°C The reaction temperature was slowly raised to room temperature. After stirring for 2hrs, TLC was checked. If TLC complied, temperature of the reaction mass was cooled to 0-5°C. Slowly DM water and 15% sodium hydroxide solution was added at 0-5°C. After stirring for 15minutes at 0-5°C, the slurry was vacuum filtered and the solids were washed with ethyl acetate and the filtrate was concentrated by evaporation and 20mL of pet ether was charged and stirred for 30-45 minutes at 40-45°C and 35-40gms of the product was isolated (70% yield w/w) having purity above 99% by GC analysis.

Example-3- Oxidation of the adamantane-1-methanol (compound-II) to corresponding aldehyde and hydrolysis of the nitrile to corresponding 2-adamantane-2(R)-2-hydroxy-2-phenylethyl amino acetic acid (compound-III);

\[ \text{III} \]
The 50g, (0.3 moles) of compound-II was dissolved in 500mL of MDC and 76g (0.9M) of sodium bi carbonate and 7.2g (0.06M) of KBr were added at room temperature and reaction mass was cooled to 0-5°C and stirred for 15 minutes. 0.1g of TEMPO solution was added at 0-5°C and then 225mL of sodium hypo chloride (11% chlorine content) solution was slowly added for 60-90 minutes at 0-5°C. Reaction mass was stirred for 2-3 hours at 0-5°C till reaction was completed. After completion of the reaction, 10% (500 ml) sodium bi sulphate solution was added at 0-5°C. Temperature was slowly raised to room temperature and 350mL of DM water was added and reaction mass was stirred for 30 minutes and both the layers were separated. The aqueous layer was extracted with 300mL of MDC and total organic layer was combined and organic layer was washed with 25mL saturated sodium chloride solution. The organic layer was dried over sodium sulphate and the organic layer was distilled under vacuum at below 35°C to obtain 41gm of semi-solid Step-A aldehyde compound having 99 % of purity by GC analysis.

200 g, (1.217M) of the semi solid Step-A aldehyde compound obtained from the above step was suspended in 2.5L of water and mixture was cooled to 0-5°C. The mixture was treated with 140.0g (1.66M) of NaHSO₃ and 110.0 g (1.692M) of NaCN and a solution of (R)-phenyl glycinol in methanol (200 g,1.457M dissolved in 1600mL of methanol). The resulting mixture was stirred at 0-5°C for 10-15min, then heated to 25-30°C and maintained for 1–2 hrs. Again the temperature was raised to 50-55°C and maintained for 4-5 hours at 50 – 55°C. When reaction was completed, reaction mass was cooled to 40-45°C, and 1000 mL of ethyl acetate was charged and mixed. After mixing for 15minutes, the layers were separated. The aqueous fraction was extracted with 500mL of ethyl acetate. The combined ethyl acetate layer was washed with 1000mL saturated sodium chloride solution and dried over anhydrous Na₂SO₄. Combined organic layer was concentrated under vacuum at below 50°C and 287 g of the desired Step-B nitrile compound having HPLC purity above 95 % was obtained.

The 285 g (0.918M) Step-B nitrile compound obtained from the above step was added in 3.42 L of Conc. HCl and 855 mL of acetic acid at room temperature and stirred for 10 minutes at room temperature. Temperature was slowly raised raise to 90-95°C and stirred for 8–10 hours up to completion of the reaction, after completion of the reaction, the reaction mass was cooled to room
temperature and stirred for 5 – 6 hrs. The reaction mass was cooled to 0-5°C and maintained at this temperature for 8 - 10 hrs. Reaction mass was vacuum filtered and washed with 300mL of chilled DM water and the desired product was obtained from resulting precipitate as 195 g white solid having HPLC purity of above 98%.

Example-4- Catalytic reduction of compound-III resulting the corresponding amine derivative (Compound - IV).

![IV](image)

The 100 g of compound-III was dissolved in 1000 mL of methanol and 200 mL of acetic acid and was hydrogenated with H₂ and Pearlman’s catalyst (10% palladium hydroxide 10 g,0.07M) or Palladium carbon and the reaction mass was maintained for 10 -12 hrs at room temperature. Upon completion of the reaction, the mass was filtered and the carbon cake was washed with 100mL of methanol. Methanol and acetic acid combined filtrate was completely distilled under reduced pressure at below 50°C and 100 mL of n-hexane was added to the crude and distilled again. Again to the crude residue 300 ml of n-hexane was added and the reaction mass was maintained for 4-5 hrs at room temperature for the formation of material and was filtered later. The resulting solid was washed with 50mL of n - hexane. The 42 g of while solid compound-IV having HPLC purity above 98% was obtained.

Example-5- Protection of the amino moiety of Compound-IV with t-butyl carbamate to obtain compound-V.

![V](image)
26.2 g, (0.655M) of sodium hydroxide and 665 mL of DM water were charged at room temperature in an oven dried 3 neck flask. The solution was cooled to 0-5°C and 80g (0.325M) of compound-IV was added into it at 0-5°C and stirred for 15 minutes. 400mL of THF was charged at 0-5°C and then slowly 86.8 g of di-tert butyl di-carbonate was added at 0-5°C for 30-45 minutes and maintained for 4-5 hours at 0-5°C up to completion of the reaction. After completion of the reaction, temperature of the reaction mass was raised to room temperature. Aqueous and organic layers were separated and aqueous layer was washed with 150mL of n-hexane. Separated aqueous layer was cooled to 0-5°C and 413mL of ethyl acetate was added. The pH was adjusted to 3.0 with 700mL of 1N HCl at 0-5°C. The reaction mixture was stirred for 10-15 minutes and both layers were separated. Aqueous layer was extracted with 600mL of ethyl acetate and total organic layer was combined and washed with saturated sodium chloride solution and dried over sodium sulphate. Organic layer was concentrated under vacuum at 35-40°C and co-distilled with 68.9 mL of ethyl acetate and 82.7mL of n-hexane was added at room temperature. Stirred for 1-2 hrs at room temperature, filtered and washed with 80 mL of n-hexane. The 80g of compound-V was obtained as white solid as resulting precipitate having HPLC purity above 99%.

Example-6- Oxidation of compound-V to give corresponding hydroxyl derivative[(S)-n-tert butoxy carbonyl-3-hydroxy] adamantyl glycine (compound-VI) in presence of phase transfer catalyst.

![VI]

In an oven dried 3 neck flask, 46.4 g (0.293M) of potassium permanganate was dissolved at room temperature in 500 mL of DM water. And 9.9 g (0.176M) of KOH was added at room temperature and under stirring 0.5g (0.003M) of TBAB was added at room temperature. The reaction mass was cooled to 20-25°C. Slowly 50g (0.162M) of compound-V was added lot wise at 20 - 25°C for 1 hour by maintaining the temperature at 20 – 25°C and RPM of 40 – 45. The reaction mixture was
maintained at 20-25°C for 20-25 hours with intermittent stirring for about 30 seconds after every one hour and maintaining for 20-25 hours in these conditions for completion of reaction. Upon completion of the reaction, mass was filtered, the filtrate ML’s was cooled to 10-15°C and sodium bi sulphate solution was added to reduce the oxidizing agent followed by pH adjustment to 2.5 with 1N HCl. The reaction mass was extracted with 300mL of MDC. The MDC layer was then distilled out and the residue was dissolved in ethyl acetate and material was isolated from ethyl acetate layer on cooling. The compound thus obtained was purified with ethyl acetate. The 18.6 g of desired compound-VI was obtained as white solid having HPLC purity more than 99.5%, any known dihydroxy impurity not more than 0.15%, any unknown impurity not more than 0.1% and isomer impurity not more than 0.05%

Definitions: wherever used in the above description, the expression-

“DM water” refers to demineralized water.

“MDC” refers to methylene dichloride.

“TBAB” refers to Tetra Butyl Ammonium Bromide

“KOH” refers to potassium hydroxide

“THF” refers to Tetra hydro furan.

“TLC” refers to Thin Layer chromatography

“Di hydroxy impurity” refers to (alphaS)-alpha-[[([1,1-Dimethylethoxy)carbonyl]amino]-3,5-

Dihydroxytricyclo[3.3.1.13,7] decane-1-acetic acid

“R – Isomer” refers to (R)-N-boc-3-hydroxyadaman-1-yl glycine
We claim:

1. A process for industrial preparation of \((s)-n\text{-tert butoxycarbonyl-3-hydroxy}\) adamantylglycine (compound-VI) with more than 99.5% HPLC purity

\[
\text{(VI)}
\]

Comprising the steps of:

a). treating adamantane-1-carboxylic acid with thionyl chloride to obtain adamantane-1-carboxylic methyl ester (compound-I);

\[
\text{(I)}
\]

b). reducing adamantane-1-carboxylic methyl ester to obtain adamantane-1-methanol (compound-II);

\[
\text{(II)}
\]

c). conversion of adamantane-1-methanol to 2-adamantane-2(R)-2-hydroxy-2-phenylethyl amino acetic acid (compound-III) of HPLC purity above 98%;

\[
\text{(III)}
\]
d). deprotection of compound-III by catalytic reduction to obtain an amino compound-IV of HPLC purity above 98%;

![](image)

(IV)

e). protecting amino moiety of compound-IV with di-tert-butyl dicarbonate to obtain compound-V of HPLC purity above 99%;

![](image)

(V)

f). oxidation of compound-V to obtain \((\alpha\text{-S})\text{-}[1,1\text{-dimethylethoxy carbonyl]amino}\text{-}3\text{-hydroxytricyclo}\ [3.3.1.1^{3,7}]\text{decane-1-acetic acid or commonly known as (s)-n-tert}}\text{butoxycarbonyl-3-hydroxy] adamantylglycine (compound-VI) having more than 99.5\% of HPLC purity.}

![](image)

(VI)

2. A process as claimed in claim 1, wherein said adamantine-1-carboxylic acid is treated with thionyl chloride in presence of methanol to obtain Compound-I with more than 95% of GC purity.
3. A process as claimed in claim 1, wherein said reduction of adamantane-1-carboxylic methyl ester is done in presence of anhydrous THF and LiAlH4 under inert and moisture free atmosphere at temperature between 0-5°C to obtain compound-II with more than 99% of GC purity.

4. A process as claimed in claim 1, wherein step (c) comprises:

A). dissolving compound-II in MDC, adding sodium bi carbonate and KBr at room temperature and cooling the solution to 0 – 5°C and stirring for 15 min; adding TEMPO solution and sodium hypo chloride at 0 – 5°C and stirring; adding 10% sodium bisulphate solution at 0-5°C; slowly raising the temperature to room temperature; separating the organic layer and washing with saturated sodium chloride solution and drying over sodium sulphate; distilling the organic layer under vacuum at below 35°C to get a semi-solid Step-A aldehyde compound with more than 99 % of GC purity;

B). suspending the step-A aldehyde compound in water and cooling the mixture to 0 - 5°C; treating the mixture with NaHSO3 and NaCN and a solution of (R)-phenyl glycinol in methanol; stirring the resulting mixture at 0 – 5°C for 10-15min and then heating to 25-30°C and maintaining at this temperature for 1–2 hours; raising the reaction temperature to 50–55°C and maintaining at this temperature for 4-5hrs; cooling the reaction temperature to 40 -45°C, and extracting the aqueous fraction with ethyl acetate; washing with saturated sodium chloride solution and drying over anhydrous Na2SO4 and concentrating the combined organic layer under vacuum at below 50°C to obtain Step-B nitrile compound having more than 95% HPLC purity;

C). adding the step-B nitrile compound in conc. HCl and acetic acid at room temperature and stirring for 10 minutes; slowly raising the temperature to 90 -95°C and stirring for 8 – 10hrs; cooling the reaction mass to room temperature and stirring for 5 – 6 hrs.; cooling the temperature of reaction mass to 0-5°C and maintaining at this temperature for 8 - 10 hours; vacuum filtration and washing with chilled water and obtaining compound 2-
adamantane-2(R)-2-hydroxy-2-phenylethyl amino acetic acid (compound-III) with more than 98% of HPLC purity.

5. A process as claimed in claim 1, wherein said deprotection of compound-III is done by catalytic reduction with Pearlman's catalyst.

6. A process as claimed in claim 1, wherein said deprotection of compound-III is done by catalytic reduction with Palladium carbon.

7. A process as claimed in claim 1, wherein said step (e) comprises BOC protection in sodium hydroxide and in presence of polar solvent like THF and removing the impurities by washing with n-hexane to obtain compound-V of HPLC purity above 99%.

8. A process as claimed in claim 1, wherein step (f) comprises treating compound-V with potassium permanganate, KOH and TBAB at 20-25°C, stirring the reaction mass and maintaining the reaction mass for 20-25 hours.

9. A process as claimed in claim 8, wherein said stirring is done for 1 hour at 40-45 RPM.

10. A process as claimed in claim 8, wherein said reaction mass is maintained for 20-25 hours at 20-25°C with intermittent stirring.

11. A process as claimed in claim 10, wherein said intermittent stirring is done is for 15 to 120 seconds after every one hour at temperature between 20-25°C.

12. (α-S)-α-[[1,1-dimethylethoxy carbonyl]amino]-3-hydroxytricyclo[3.3.1.13,7]decane-1-acetic acid (compound-VI) commonly known as [(s)-n-tert butoxycarbonyl-3-hydroxy] adamantylglycine obtained from the process as claimed in claim 1 wherein the compound
has more than 99.5% HPLC purity, not more than 0.15 % of dihydroxy impurity, not more than 0.05% of isomer impurity and not more than 0.1% of any unknown impurity.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C269/06  C07C271/22

ADD.

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 practicable, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>Y</td>
<td>the whole document</td>
<td>1-11</td>
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Date of the actual completion of the international search

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