SAMPLE INVALIDITY SEARCH REPORT

“A process for industrial preparation of [(s)-n-tert butoxycarbonyl-3-hydroxy] adamantylglycine”

Indian Patent Application no: 4256/CHE/2012

PCT Publication no: WO2014057495

1. Search Objective

Objective of this assignment is to determine validity of afore-mentioned Indian patent application titled “A process for industrial preparation of [(s)-n-tert butoxycarbonyl-3- hydroxy] adamantylglycine” vide Indian Patent Application No. 4256/CHE/2012 (herein afterIN ’256).

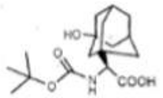
2. Understanding of the subject matter

The Invalidation search has been conducted with respect to the following:

Indian Patent Application Number	4256/CHE/2012
Title	A process for industrial preparation of [(s)-n-tert butoxycarbonyl-3-hydroxy]adamantylglycine
Inventors	Venkat Reddy Alla, Raghu Mitra ALLA, etal.
Original Assignee/Applicant	Lee Pharma Limited
Earliest Priority Date	11 Oct 2012
PCT Application Number	PCT/IN2012/000865
PCT Publication Number	WO/2014/057495
PCT Filing Date	31st December 2012

The independent Claim 1 of IN ’256 reads as follows:

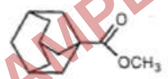
A process for industrial preparation of [(s)-n-tert butoxycarbonyl-3-hydroxy] adamantylglycine (compound-VI) with more than 99.5% HPLC purity



(VI)

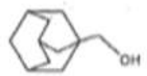
Comprising the steps of:

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



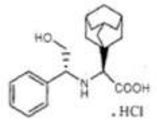
(I)

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



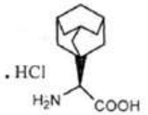
(II)

c) conversion of adamantane-1-methanol to 2-adamantane-2(R)-2-hydroxy-2-phenylethyl amino acetic acid (compound-Ill) of HP C purity above 98%;



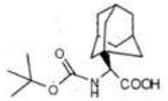
(III)

d) deprotection of compound-Ill by catalytic reduction to obtain an amino compound-IV



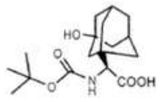
(IV)

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



(V)

f) oxidation of compound-V to obtain (α-S)- α-[[1,1-dimethylethoxy carbonyl]amino]-3- hydroxytricyclo [3.3.1.13,7]decane-1-acetic acid or commonly known as [(s)-n-tert butoxycarbonyl-3-hydroxy] adamantylglycine (compound-VI) having more than 99.5% of HPLC purity.



(VI)

3. Research Methodology

The following search methodology was adopted for finding relevant prior art documents

- Determining scope of claims of the subject patent
- Identifying keywords pertaining to the subject matter (Refer section 4)
- Identifying the right patent/non-patent databases to carry out the search (Refer section 6)
- Framing indicative search strategies for searching in the databases
- Analysis of retrieved patent/non-patent documents with a view to determine Validity of the claimed subject matter
- Report Preparation

4. Keywords

One or more of the key words listed below have been used in different combinations while conducting the prior art search.

Saxagliptin / (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl)acetyl]-2- azabicyclo[3.1.0]hexane-3-carbonitrile
Adamantine-1-carboxylic acid/ 1-carboxyladamantane/ 1-adamantylcarboxylic acid/ 1-Adamantanecarboxylic acid/ adamantane carboxylic acid/ 1-carboxyadamantane
Thionyl chloride/ SOCl2/ Sulfurous dichloride, Sulfinyl dichloride/ Dichloro sulfoxide
Adamantane-1-carboxylic methyl ester/ Methyl 1-Adamantanecarboxylate/ 1- Carbomethoxyadamantane/ 1-Adamantoic acid methyl/ 1- (Methoxycarbonyl)adamantane/ methyl adamantane-1-carboxylate/ 1- Methoxycarbonyladamantane/
1-Adamantanemethanol/ 1-Adamantylmethanol/ Adamantanemethanol/ Adamantane-1-methanol/ 1-adamantanemethol/ tricyclo(3.3.1.13,7)dec-1-ylmethanol/ 1-(Hydroxymethyl)Adamantane/ 1-tricyclo[3.3.1.1(3,7)]decanemethanol/ 1- adamantanol
LiAlH4/ Lithium aluminohydride/ Lithium aluminum tetrahydride/ Lithium Tetrahydridoaluminate/ Lithium Alminium Hydride
(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl/ Tempo/ (2,2,6,6-Tetramethylpiperidin-1- yl)oxyl

5. Exemplary International Patent Classifications (IPC)

One or more of the international classifications listed below have been used while conducting the search.

IPC	DESCRIPTION
C	Section C - Chemistry; Metallurgy
C07	Organic Chemistry
C07C	Acyclic or Carbocyclic Compounds
A	Section A- Human Necessities
A61	Medical or Veterinary Science; Hygiene
A61K	Preparation for Medical, Dental, or Toilet purpose

6. Databases Used

Patent Databases

- Questal Orbit
- Thomson Innovation
- USPTO
- Espacenet
- WIPO
- JPO
- Google Patents
- Patent Lens
- Sumobrain
- Free Patent Online
- Depatisnet
- KPO

Non Patent Databases

- Science Direct
- Google Scholar
- PubMed
- Freefull PDF

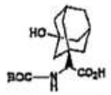
7. Search Results

Result 1

Patent No	EP2272825
Title	N-Protected amino hydroxy adamantane carboxylic acid and process for its preparation
Publication Date	26 Nov 2004
Priority Date	10 Mar 2000
Applicant	Bristol-Myers Squibb Company
Family members	CA2402894A1, CN1213028C, CN1427826A, CN1698601A, DE60134122D1, DE12201000000 8I1, DE1220120000 23I1, EP1261586A2, EP1559710A2, EP2272825A2, US6395767, US20020019411, USRE44186, WO2001068603A2

Abstract

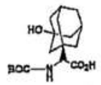
A compound having the structure



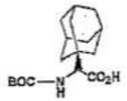
and a method for its preparation, which comprises:
providing a protected amino adamantane carboxylic acid of the structure treating the protected amino adamantane carboxylic acid with potassium permanagate and potassium hydroxide to form the protected amino hydroxy adamantane carboxylic acid.

Cited Portions

Claim 1: A compound having the structure

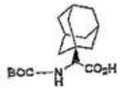


Claim 2: A method for preparing a protected amino hydroxy admantane carboxylic acid as defined in claim 1, which comprises: providing a protected amino adamantane carboxylic acid of the structure



treating the protected amino adamantane carboxylic acid with potassium permanagateand potassium hydroxide to form the protected amino hydroxy adamantane carboxylic acid.

Claim 3: A method for preparing the protected amino adamantane carboxylic acid of the structure

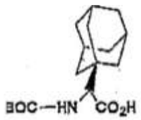


as defined in claim 2, which comprises treating adamantane-1-carboxylic acid with trimethylsilyl diazomethane to form adamantane-1-carboxylic acid methyl ester having the structure as defined in claim 2, which comprises treating adamantane-1-carboxylic acid with trimethylsilyl diazomethane to form adamantane-1-carboxylic acid methyl ester having the structure

treating adamantane-1-carboxylic acid methyl ester with lithium aluminum hydride to form 1-hydroxymethyl adamantane having the structure

treating the 1-hydroxymethyl adamantane with an activated DMSO adduct formed by treating DMSO with oxalyl chloride, to form the adamantane aldehyde of the structure

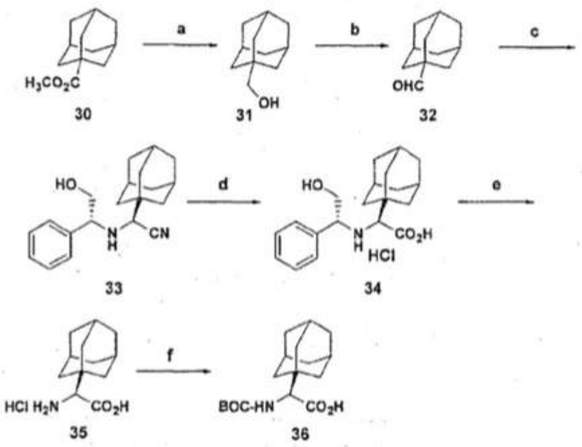
treating the adamantane aldehyde with potassium cyanide and (R)-(-)-phenylglycinol to form an adamantane nitrile compound of the structure



[Para 271]

General Method G:L-Amino acids synthesized by Asymmetric Strecker Reaction. Commercially available adamantyl carboxylic acid was esterified either in MeOH with HCl at reflux or using trimethylsilyldiazomethane in Et2O/methanol to give 30. The ester was reduced to the alcohol 31 with LAH in THF and then subjected to a Swern oxidation to give aldehyde 32. Aldehyde 32 was transformed to 33 under asymmetric Strecker conditions with KCN, NaHSO3 and R-(-)-2-phenylglycinol. The nitrile of 33 was hydrolyzed under strongly acidic conditions using 12M HCl in HOAc to give 34. The chiral auxiliary was removed by catalytic reduction using Pearlman's catalyst in acidic methanol under 50 psi hydrogen to give 35 and the resulting amino group was protected as the t-butylcarbamate to give 36.

Scheme 9, General Method G, Examples 59-64



a. LAH, THF, 0 C to RT, 96% b. ClCOCOCl, DMSO, CH_2Cl_2, -78 C, 98% c. R-(-)-2-Phenylglycinol, $NaHSO_3$, KCN d.12M HCl, HOAc, 80 C, 16h, 78 % e. 20% $Pd(OH)_2$, 50 psi H_2, MeOH:HOAc, 5:1 f. $(Boc)_2O$, K_2CO_3, DMF, 92%, 2 steps

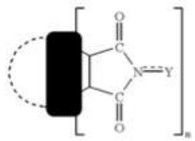
Result 2

Patent No	US6468487
Title	Nitration or carboxylation catalysts
Publication Date	22 Oct 2002
Priority Date	14 Jan 1997
Applicant	Daicel Chemical Industries, Ltd.
Family members	DE69834077D1, EP0897747B1, EP1574494A1, EP1574495A1, WO1998030329A1

Abstract

In the presence of an imide compound (e.g., N-hydroxyphthalimide) shown by the following formula (1):

(1)



wherein R1 and R2 represent a hydrogen atom, a halogen atom, an alkyl group, an aryl group and a cycloalkyl group, and R1 and R2 may bond together to form a double bond, or an aromatic or non-aromatic ring, and Y is an O or OH, and n denotes 1 to 3;

a substrate is allowed to contact with at least one reactant selected from (i) a nitrogen oxide and (ii) a mixture of carbon monoxide and oxygen to be introduced with at least one functional group selected from a nitro group and a carboxyl group. The nitrogen oxide includes, for example, a compound represented by the formula NxOy(e.g., N2O3, NO2).

The substrate includes, for example, a compound having a methine carbon atom (e.g., adamantane), a compound having a methyl group or a methylene group at an adjacent moiety of an aromatic ring. According to such reaction, the substrate can be efficiently nitrated or carboxylated even in a mild or moderate condition.

[Col. 25, Line 55-Col. 26, Line 6]

When a substituted hydroxyl group (e.g., an alkoxy group) protects a carboxyl group [(i.e., when a substituted hydroxycarbonyl group (an ester group)] is formed), the carboxyl group may be protected by reacting a carboxyl group-containing compound or derivative thereof (e.g., an acid halid such as an acid chloride) with an alcohol (e.g., methanol, ethanol) or reactive derivative thereof (e.g., lower alkyl ester), if necessary, in the presence of an acid (e.g., a mineral acid such as hydrochloric acid and sulfuric acid) or an base (e.g., the base exemplified above) to produce a compound having the corresponding ester group. The lower alkyl ester inclu des, for example, acetic acid-C1-4alkyl ester such as methyl acetate and ethyl acetate or the corresponding propionate (e.g., methyl propionate, ethyl propionate). For example, 1-methoxycarbonyl-3-nitroadamantane may be obtained by reacting 1-carboxy-3- nitroadamantane with methanol in the presence of an acid, or by acting thionyl chloride on 1- carboxy-3-nitroadamantane followed by reacting with methanol in the presence of a base.

[Col. 41, Lines 33- 46]

Example 84

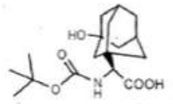
In an atmosphere of nitrogen, 10 mmole of 1,3-dicarboxyadamantane obtained by the method of Example 64 was dissolved in 10 ml of DMF. To the mixture, 30 mmole of thionyl chloride was added drop wise over 30 minutes and the mixture was heated to begin to reflux around the conclusion of addition. After refluxing for 2 hours, the mixture was cooled. To the mixture, 40 mmole of triethylamine was added followed by 22 mmole of methanol over 30 minutes while retaining the temperature of the mixture at 10° C. or less, and then stirred for more 2 hours. As a result, the conversion of 1, 3-dicarboxyadamantane was 99%, and 1,3-bis(methoxycarbonyl)adamantane (yield 95%) was formed.

8. Claim Mapping

Result 1: EP2272825

Subject Patent: 4256/CHE/2012(WO2014057495)	**Prior art: EP2272825**
Priority Date: 11th October 2012	**Publication Date:** 12 Jan 2011

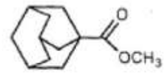
A process for industrial preparation of [(s)-n-tert butoxycarbonyl-3 - hydroxy] adamantyiglycine (compound-VI) with more than 99.5% HPLC purity



(VI)

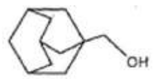
Comprising the steps of:

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



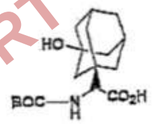
(I)

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



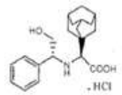
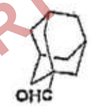
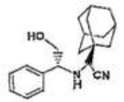
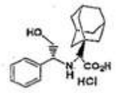
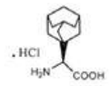
(II)

[Claim 1]
A compound having the structure

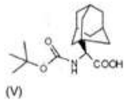
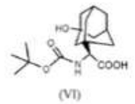
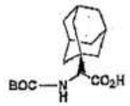


[Claim 3]
treating adamantane-1-carboxylic acid methyl esterwith lithium aluminum hydride to form 1-hydroxymethyl adamantane having the structure

Result 1: EP2272825

Subject Patent: 4256/CHE/2012(WO2014057495)	**Prior art: EP2272825**
Priority Date: 11th October 2012	**Publication Date:** 12 Jan 2011
c) conversion of adamantane- 1 - methanol to 2-adamantane-2(R)-2- hydroxy-2-phenylethyl amino acetic acid (compound-Ill) of HP C purity above 98%;  (III)	**[Claim 3]** treating the 1-hydroxymethyl adamantanewith an activated DMSO adduct formed by treating DMSO with oxalyl chloride, to form the adamantane aldehyde of the structure  treating the adamantane aldehyde with potassium cyanide and (R)-(-)-phenylglycinol to form an adamantane nitrile compound of the structure  treating the adamantane nitrile compound withhydrochloric acid and acetic acid to form the phenylglycine adamantane carboxylic acid salt of the structure 
d) deprotection of compound-Ill by catalytic reduction to obtain an amino compound-IV  (IV)	**[Claim 3]** treating the phenylglycine adamantane carboxylic acid salt with H2to form the corresponding amino adamantane carboxylic acid salt of the structure 

Result 1: EP2272825

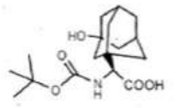
Subject Patent: 4256/CHE/2012(WO2014057495)	**Prior art: EP2272825**
Priority Date: 11th October 2012	**Publication Date:** 12th Jan 2011
e) protecting amino moiety of compound-IV with di-tert-butyl dicarbonate to obtain compound-V of HPLC purity above 99%;  (V) f) oxidation of compound-V to obtain (a-S)-a-[[l ,l -dimethylethoxy carbonyl]amino]-3- hydroxytricyclo [3.3.1.1 ']decane-l -acetic acid or commonly known as [(s)-n-tert butoxycarbonyl-3-hydroxy] adamantylglycine (compound-VI) having more than 99.5% of HPLC purity.  (VI)	**[Claim 3]** treating the amino adamantane carboxylic acid saltwith di-tert butyl dicarbonate under argon to form the protected amino adamantane carboxylic acid of the structure  **[Claim 2]** A method for preparing a protected amino hydroxy admantane carboxylic acid as defined in claim 1, which comprises: providing a protected amino adamantane carboxylic acid of the structure  treating the protected amino adamantane carboxylic acid with potassium permanagate and potassium hydroxide to form the protected amino hydroxy adamantane carboxylic acid.

Result 2: US6468487

Subject Patent: 4256/CHE/2012 (WO2014057495)	**Prior art: US6468487**
Priority Date: 11th October 2012	**Publication Date:** 22nd Oct 2002

[Claim 1]

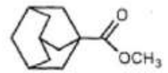
A process for industrial preparation of [(s)-n-tert butoxycarbonyl-3 - hydroxy] adamantyiglycine (compound-VI) with more than 99.5% HPLC purity



(VI)

Comprising the steps of:

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



(I)

[Col. 41, Lines 33- 46]

Example 84

In an atmosphere of nitrogen, 10 mmole of 1,3- dicarboxyadamantane obtained by the method of Example 64 was dissolved in 10 ml of DMF. To the mixture, 30 mmole of thionyl chloride was added dropwise over 30 minutes and the mixture was heated to begin to reflux around the conclusion of addition. After refluxing for 2 hours, the mixture was cooled. To the mixture, 40 mmole of triethylamine was added followed by 22 mmole of methanol over 30 minutes while retaining the temperature of the mixture at 10° C. or less, and then stirred for more 2 hours. As a result, the conversion of 1, 3-dicarboxyadamantane was 99%, and 1,3-bis(methoxycarbonyl)adamantane (yield 95%) was formed.

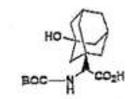
9. Conclusion

A comprehensive prior art search was executed for the subject matter disclosed and claimed in Indian Patent Application No. 4256/CHE/2012 (IN ’256). The International PCT application WO2014057495 was filed on 31st December 2012 taking priority from IN ’256. The prioritydate of IN ’256 patent application is 11th October 2012. The IN ’256 application contains a total of 12 claims including one independent claim i.e. claim 1.

Our search based on a set of identified keywords (Refer Section 4) has resulted in 2 prior art references which may be considered relevant and are listed below:

1. R1, EP2272825
2. R2, US6468487

R1 discloses a compound of formula 1 and its method of preparation starting from adamantane-1-carboxylic acid.



(Formula 1)

R2 discloses a method of preparing 1,3-bis(methoxycarbonyl)adamantane by treating 1,3-dicarboxyadamantane with thionyl chloride in presence of methanol.

Regarding Independent claim 1, R1 discloses a process for preparation of [(s)-n-tert butoxycarbonyl-3 -hydroxy] adamantyiglycine starting from adamantine-1-carboxylic acid (Compound I). All the process steps of IN ’256 are disclosed in R1 as clearly depicted in the claim mapping table above. The only difference in IN ’256 is the use of thionyl chloride in place of trimethylsilyl diazomethane as a reagent in step 1 of the process as shown in the claim mapping table above. However, R2 discloses a preparation of 3-bis(methoxycarbonyl)adamantane by treating 1,3-dicarboxyadamantane with thionyl chloride in presence of methanol. Thus the person skilled in the art would be motivated to combine the teachings of R1 and R2 to arrive at the claimed invention with reasonable expectation of success. Thus the process for industrial preparation of [(s)-n-tert butoxycarbonyl-3 -hydroxy] adamantylglycine as claimed in IN ’256 should be rendered obvious and not inventive.

Note: More relevant references could be identified and more grounds could be formulated in order to oppose the subject patent application at the Indian patent office under section 25 of the Indian Patent Act. You may contact iiprd@iiprd.com should you decide to oppose this or similar other patent application at the Indian patent office.

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Contact Us

Email: iiprd@iiprd.com
Tel : +91-(120) 4296878 , 4909201 , 4516201
Fax: +91-(120) 4516201