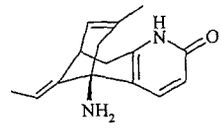
ABSTRACT:

The present invention relates to an improved and cost effective process for the preparation of (-)-Huperzine A. The present invention also relates to a process for separation of enantiomers using preparative HPLC.

WE CLAIM:

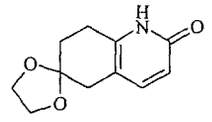
Claim 1: An improved process for the preparation of (-)-huperzine A of Formula I,



Formula I

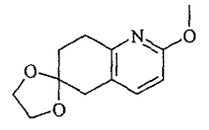
comprising;

a) reacting 1,4-cyclohexanedione monoethylene acetal with methyl propiolate in presence of ammonium source to provide a compound of Formula II,



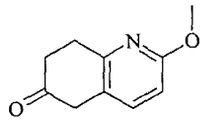
Formula II

b) reacting the compound of Formula II with silver carbonate and methyl iodide or dimethylsulfate in presence of a catalyst to provide a compound of Formula III;



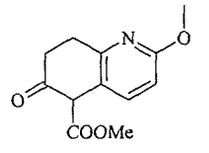
Formula III

c) hydrolyzing the compound of Formula III with phosphoric acid to provide a compound of Formula IV;



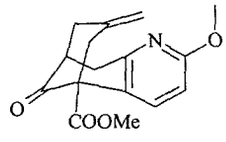
Formula IV

d) carboxymethylation of compound of Formula IV with dimethylcarbonate and a base to provide a compound of Formula V;



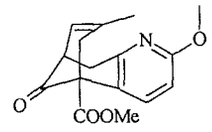
Formula V

e) annulating the compound of Formula V with 2-methylenepropane-1,3-diol diacetate to provide the compound of Formula VI,



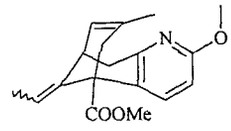
Formula VI

f) isomerizing the compound of Formula VI to provide a compound of Formula VII,



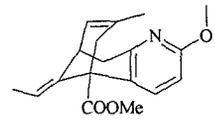
Formula VII

g) reacting the compound of Formula VII with ethyltriphenylphosphonium bromide and n-butyllithium to provide a compound of Formula VIII;



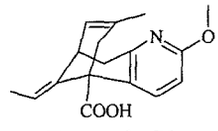
Formula VIII

h) isomerizing the compound of Formula VIII with 1-octanethiol and azobisisobutyronitrile (AIBN) to provide a compound of Formula IX;



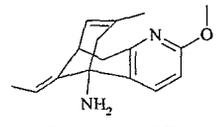
Formula IX

i) hydrolyzing the compound of Formula IX with a suitable base to provide a compound of Formula X;



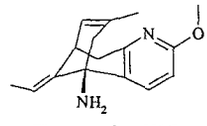
Formula X

j) converting the compound of Formula X into a compound of Formula XI;



Formula XI

k) resolving the compound of Formula XI to provide a compound of Formula XII; and



Formula XII

l) converting the compound of Formula XII to (-)-huperzine A of Formula I;
wherein the silver carbonate and the catalyst are used is less than about 0.8 and less than about 0.3 equivalents respectively to the compound of Formula II; wherein the phosphoric acid used is less than about 3 vol/wt to the compound of Formula III; wherein the dimethylcarbonate used is less than about 20 vol/wt to the compound of Formula IV; and wherein the ethyltriphenylphosphonium bromide and n-butyllithium are used are less than about 3.0 equivalents and less than about 2.0 equivalents respectively to the compound of Formula VII.

Claim 2: The process of claim 1, wherein the ammonium source is selected from either ammonia or methanolic ammonia.

Claim 3: The process of claim 1, wherein in the catalyst of step b) is a phase transfer catalyst and is selected from the group comprising tetrabutylammonium bromide, tetrabutylammonium iodide, tetrabutylammonium chloride, tetrabutylammonium tribromide, benzyltrimethylammonium bromide, benzyltriethylammonium bromide, benzyltrimethyl ammonium chloride, benzyltriethylammonium chloride and the like and mixtures thereof.

Claim 4: The process of claim 1, wherein the base used in step d) is selected from sodium hydride, potassium hydride, sodiumhexamethyldisilazane, lithiumhexamethyldisilazene or potassium hexamethyldisilazane.

Claim 5: The process of claim 1, wherein in the suitable base of step i) is alkali metal hydroxides selected from sodium hydroxide, potassium hydroxide or mixtures thereof.

Claim 6: The process of claim 1, wherein the silver carbonate and the catalyst are used in less than about 0.6 and less than about 0.1 equivalents respectively to the compound of Formula II; wherein the phosphoric acid used is less than 1 vol/wt to the compound of Formula III; wherein the dimethylcarbonate used is less than 10 vol/wt to the compound of Formula IV and wherein the ethyltriphenylphosphonium bromide and n-butyllithium are used each less than 2.0 equivalents to the compound of Formula VII.

Claim 7: An improved process for the preparation of (-)-huperzine A of Formula I, comprising

a) isomerizing the compound of Formula VIII with 1-octane thiol and azobisisobutyronitrile (AIBN) to provide a compound of Formula IX; and

Formula VIII

Formula IX

b) converting the compound of Formula IX into (-)-huperzine A.

Claim 8: An improved process for the preparation of (-)-huperzine A of Formula I, comprising

i) subjecting the racemic compound of Formula VI to preparative HPLC,
ii) separating the required (-)-enantiomer of Formula VI; and
iii) converting the (-)enantiomer of Formula VI into (-)-huperzine A.

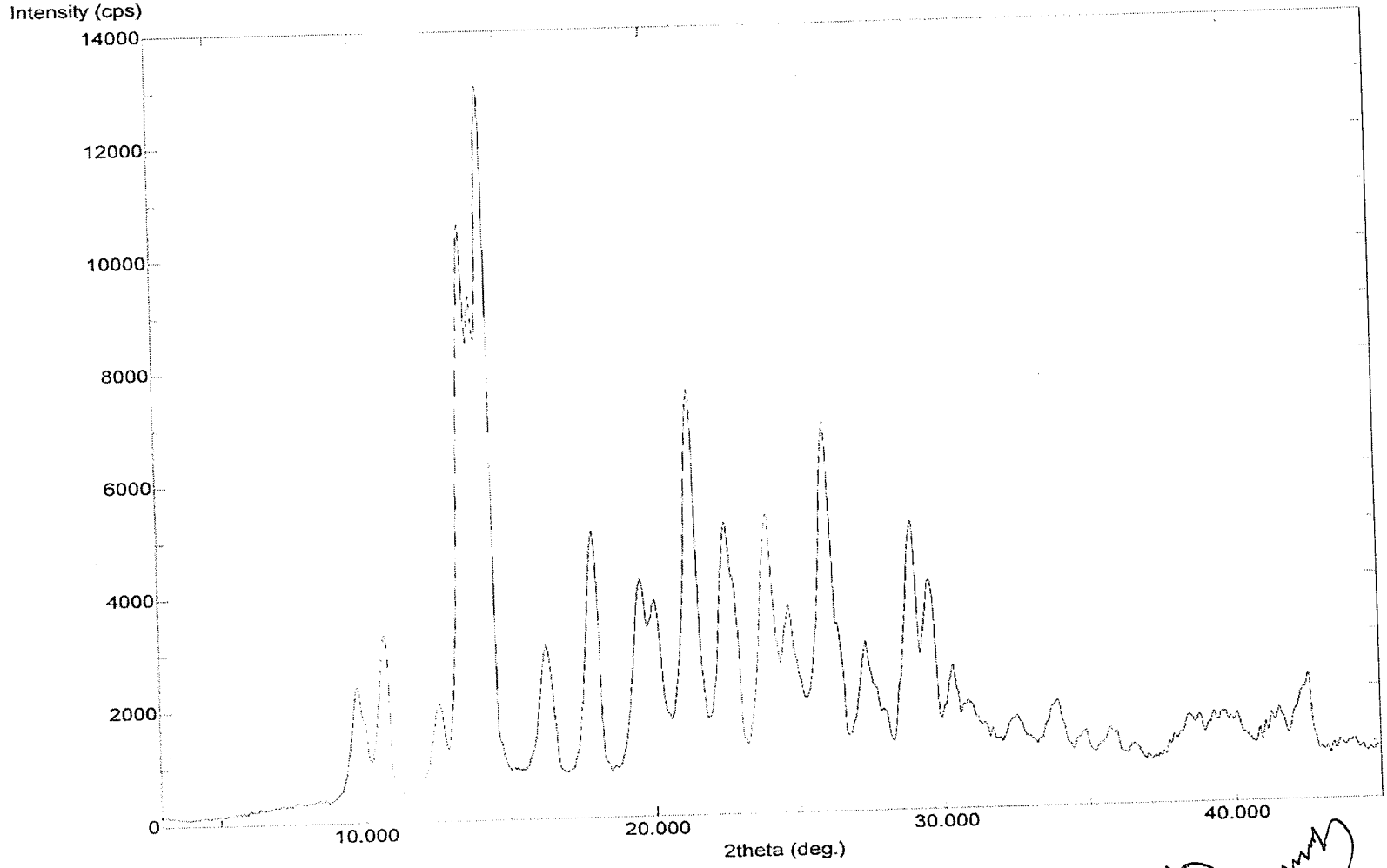
Claim 9: The process of claim 8, wherein the preparative HPLC is performed using a suitable eluent and is selected from the group comprising an alcohol, hydrocarbon solvent and mixtures thereof.

Claim 10: The process of claim 8, wherein the step of converting the (-)enantiomer of Formula VI into (-)-huperzine A is carried out through formation of corresponding isomer of Formula VII, Formula VIII, Formula IX, Formula X and Formula XI according to process of claim 1-7 except resolution process using a suitable resolving agent.

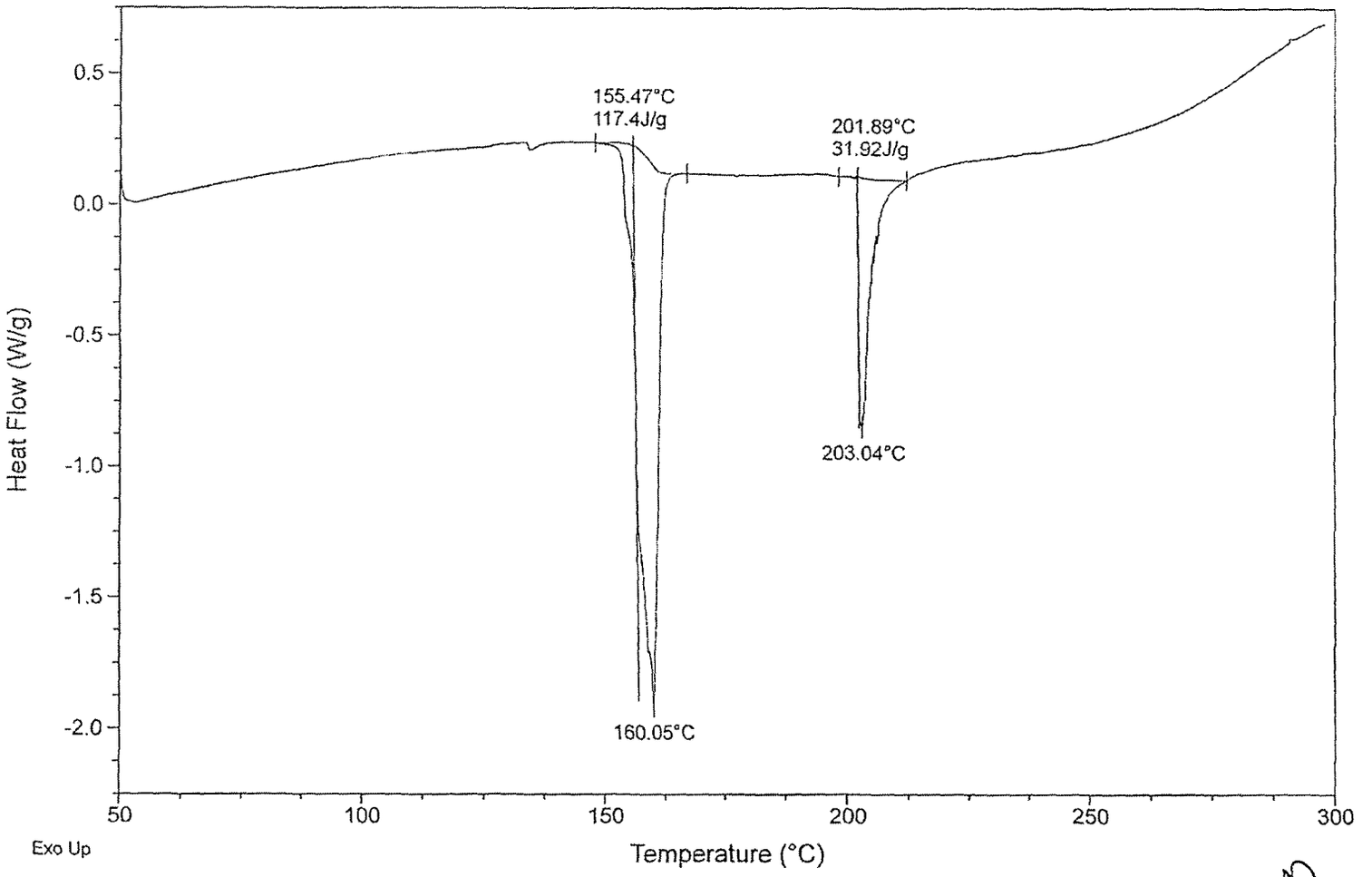
Dated this 20th day of March, 2015

Sign----------
(CH.V. Ramana Rao)
Asst.Vice President
Laurus Labs Pvt. Ltd

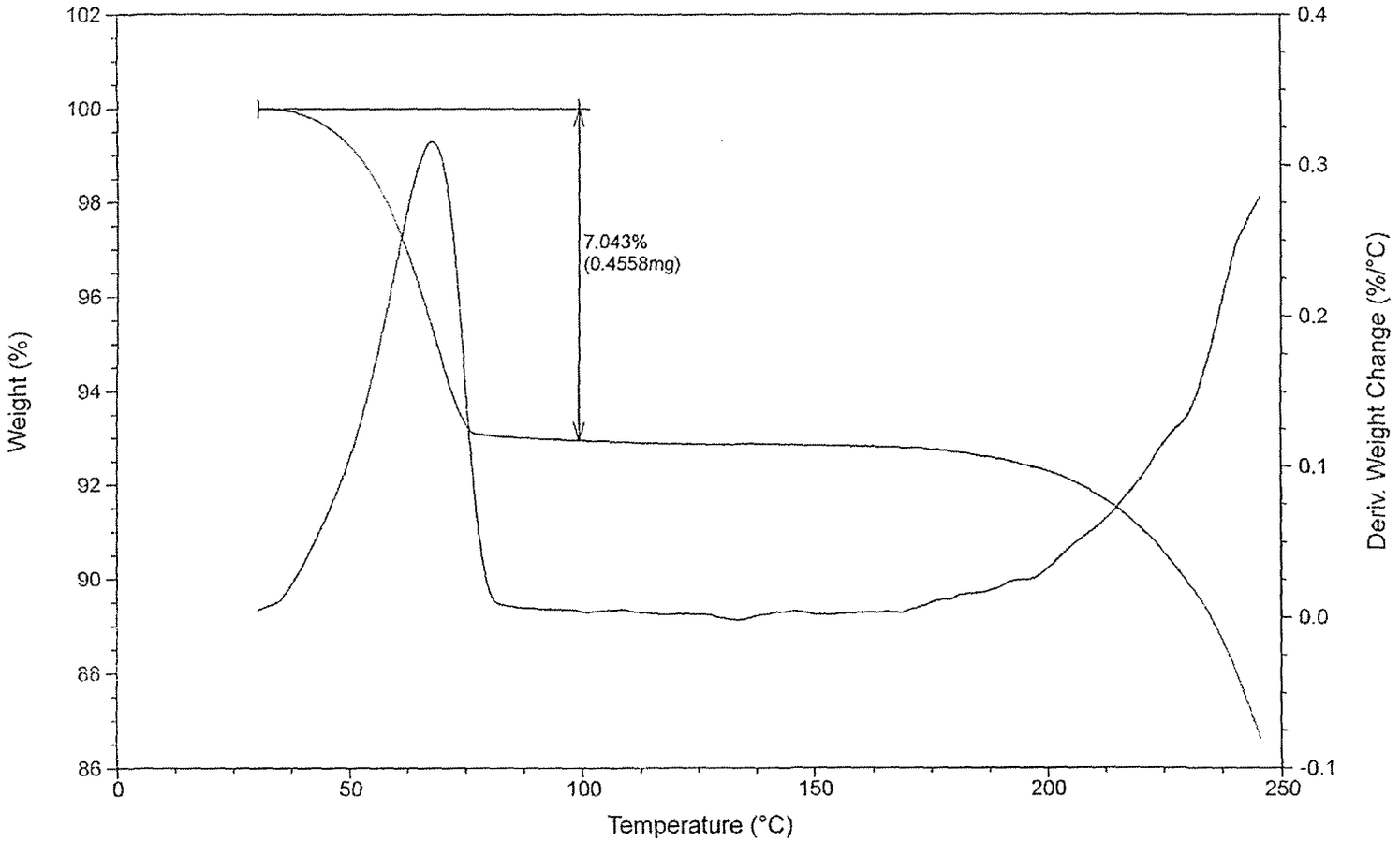
LAURUS LABS PVT LTD



(CH. V. Ramana Rao)
Laurus Labs Pvt Ltd



(CH. V. Ramana Rao)
Laurus Labs Pvt Ltd



(CH. V. Ramana Rao)
Laurus Labs Pvt Ltd

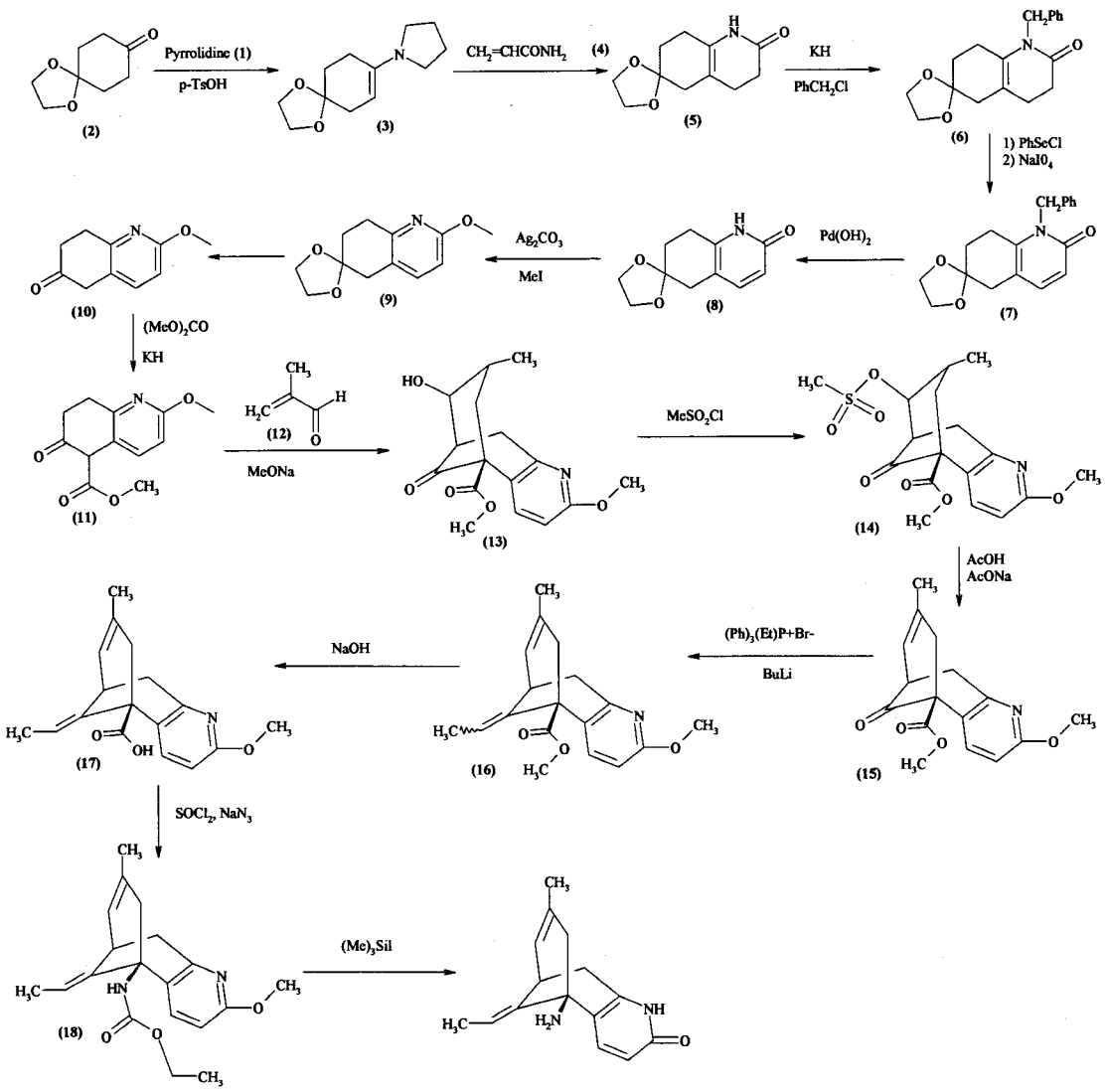
FIELD OF THE INVENTION:

The present invention relates to an improved and cost effective process for the preparation of (-)-Huperzine A.

BACKGROUND OF THE INVENTION:

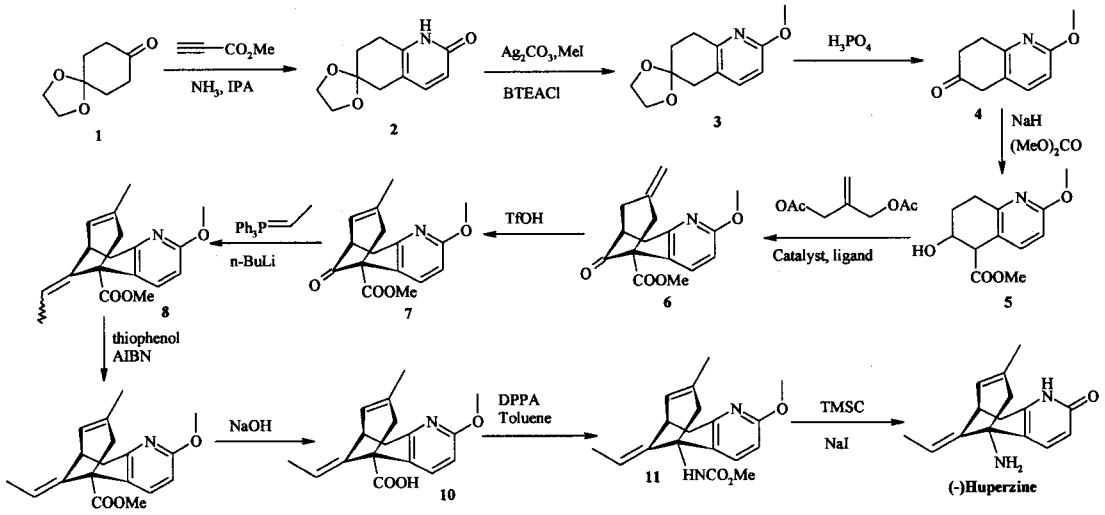
(-)-Huperzine A is a naturally occurring sesquiterpene alkaloid compound found in the plant firmoss Huperzia serrata. (-)-Huperzine A is also an acetyl cholinesterase inhibitor, which has a mechanism of action similar to donepezil, rivastigmine and galantamine. A pro-drug form of huperzine A (ZT-1) is under development as a treatment for Alzheimer's disease. In the US, (-)-huperzine A is sold as a dietary supplement for memory support. The botanical has been used in China for centuries for the treatment of swelling, fever and blood disorders. Clinical trials in China have shown it to be effective in improving cognitive performance in patients with Alzheimer's disease and enhancing memory in students. (-)-Huperzine A is naturally occurring one and is more potent than (+)-Huperzine A.

US4929731 disclosed a process for the preparation of racemic huperzine A. The disclosed process include: reaction of pyrrolidine (1) with cyclohexane-1,4-dione monoethyleneketal (2) in presence of p-toluenesulfonic acid in benzene at reflux to provide enamine (3), which is cyclized with acrylamide (4) in refluxing in dioxane to provide bicyclic pyridone (5). Benzylation of (5) with benzyl chloride in presence of KH in THF followed by dehydrogenation of the n-benzyl derivative (6) with phenyl selenium chloride in THF and then with $NaIO_4$ to provide protected pyridone (7). Removing the benzyl group with Pd(OH)2 in acetic acid to provide the free pyridone (7), which is aromatized with methyl iodide and silver carbonate to provide 2-methoxypyridine (9). Elimination of the ketal group of (9) with HCl in refluxing acetone and then carboxylating the tetrahydroquinolone (10) with dimethyl carbonate and KH to provide 2-methoxy-6-oxo-5,6,7,8-tetrahydroquinoline-5-carboxylic acid methyl ester (11). The compound (11) is cyclized with 2-methylacrolein (12) in presence of sodium methoxide in methanol or tetramethylguanidine in dichloromethane to provide the tricyclic compound (13), which is then, mesylated with mesyl chloride to provide the mesylate (14). Elimination of the mesyl group of (14) with sodium acetate in refluxing acetic acid to provide the olefinic compound (15), which is then witttig condensation with ethylidenetriphenylphosphorane in ether to provide diolefinic compound (16) as a mixture of the E- and Z-isomers. Selective hydrolysis of (16) with sodium hydroxide in THF - methanol yields acid (17) as the E-isomer, which is treated with thionyl chloride and sodium azide in a modified Curtius reaction to provide urethane (18) followed by deprotection with trimethylsilyl iodide to provide huperzine A.



The above disclosed process involves large number of steps and huge quantities of costly reagents such as silver carbonate and dimethyl carbonate. Usage of huge quantities of such reagents necessitates huge quantity of solvents and reagents for further workup, thereby produces more effluent and difficult to handle, which results to an increase in the production cost. Further the said process involves the use of foul smelling liquid such as thiophenol, which is difficult to handle and not recommended in view of personal and environment safety. Hence this process is commercially not suitable.

US2009247754 disclosed an improved process for the preparation of (-)-huperzine A, which is schematically represented by the following scheme:

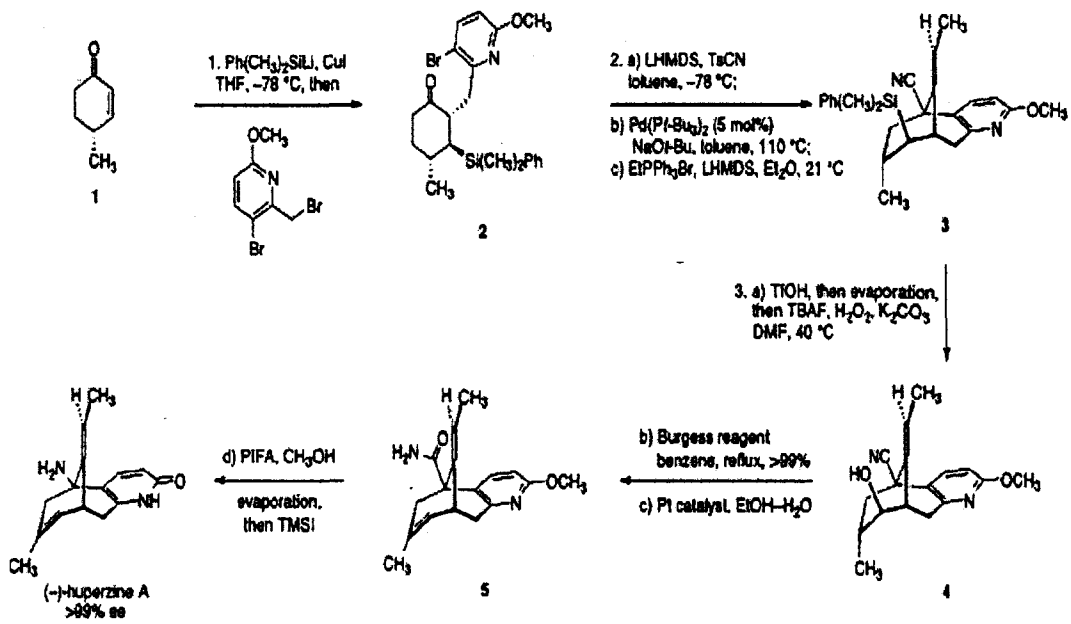


The process disclosed in US2009247754 has the following drawbacks:

a) involves usage of costly reagents such as silver carbonate and benzyl triethyl ammonium chloride in excess quantity for the conversion of compound 2 to compound 3. The usage of such costly reagents not only increases the cost of product and further leads to the formation of N-methyl compounds as an impurity.
b) involves usage of thiophenol for the conversion of compound 8 to compound 9. Thiophenol is an irritant and foul smelling liquid which is difficult to handle at commercial scale.
c) involves usage of huge volumes of dimethyl carbonate for the carboxymethylation of compound 4, which requires excess amount of solvent for workup process, which makes the process difficult to carry on large scale operations. Further it generates large quantity of effluent thereby increases the overall cost of the production;
d) it requires double the amount of trimethyl silyl chloride and sodium iodide i.e., almost 6 equivalents of each to carry out the final N- and O-deprotection of compound 11.

CN101130520 disclosed a process for resolution of (13E)-13-ethylidene-5-methoxy-11-methyl-6-azatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6,10-tetraene-1-amine using (-)-2,3-dibenzoyl tartaric acid followed by demethylation of resolved intermediate to provide natural (-)-huperzine A.

WO2012121863 disclosed a process for preparation of (-)-huperzine A through novel intermediate compounds, which is schematically represented as follows:



WO2013139195 disclosed crystalline forms of (-)-huperzine A designated as crystalline Form I, Form II, Form III, Form IV and Form V. This publication also disclosed process for preparation of novel crystalline forms and their characteristic details.

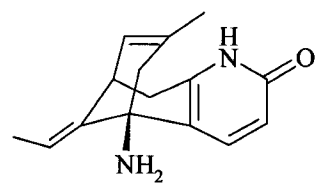
In general, the reported process involves the usage of excess amount of costly reagents such as silver carbonate and dimethyl carbonate and preventable reagents such as thiophenol; hence the reported process is not viable in view of cost and safety at industrial level.

There is a need in the art for an improved process for the preparation of (-)-huperzine A, which is cost effective, eco-friendly and easy to scale up in commercial level and avoids the aforesaid problems associated with the prior art.

SUMMARY OF THE INVENTION:

Accordingly the present invention provides an improved process for the preparation of (-)-huperzine A which is cost effective, eco-friendly and easy to scale up.

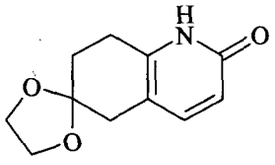
In a first aspect, the present invention provides an improved process for the preparation of (-)-huperzine A of Formula I,



Formula I

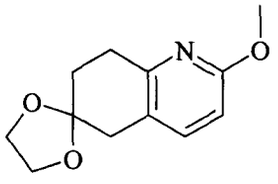
comprising;

a) reacting 1,4-cyclohexanedione monoethylene acetal with methyl propiolate in presence of ammonium source to provide a compound of Formula II,



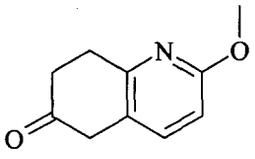
Formula II

b) reacting the compound of Formula II with silver carbonate and methyl iodide or dimethylsulfate in presence of a catalyst to provide a compound of Formula III, wherein the silver carbonate and the catalyst are used in less than about 0.8 and less than about 0.3 equivalents respectively to the compound of Formula II;



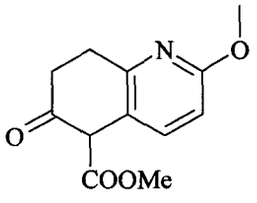
Formula III

c) hydrolyzing the compound of Formula III with phosphoric acid to provide a compound of Formula IV, wherein the phosphoric acid is used in less than about 3 vol/wt to the compound of Formula III;



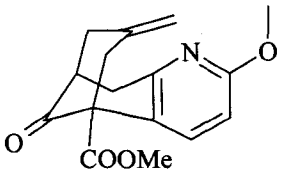
Formula IV

d) carboxymethylation of compound of Formula IV with dimethylcarbonate and a base to provide a compound of Formula V, wherein the dimethylcarbonate is used in less than about 20 vol/wt to the compound of Formula IV;



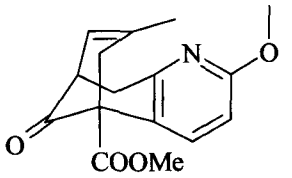
Formula V

e) annulating the compound of Formula V with 2-methylenepropane-1,3-diol diacetate to provide the compound of Formula VI,



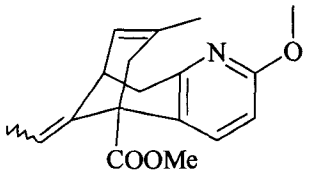
Formula VI

f) isomerizing the compound of Formula VI to provide a compound of Formula VII,



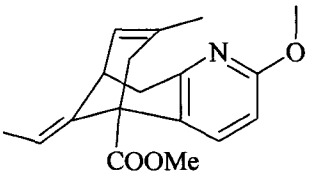
Formula VII

g) reacting the compound of Formula VII with ethyltriphenylphosphonium bromide and n-butyllithium to provide a compound of Formula VIII, wherein the ethyltriphenylphosphonium bromide and n-butyllithium are used in less than about 3.0 equivalents and less than about 2.0 equivalents respectively to the compound of Formula VII;



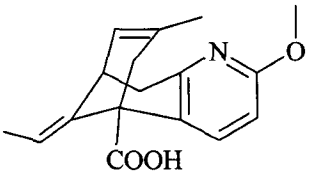
Formula VIII

h) isomerizing the compound of Formula VIII with 1-octane thiol and azobisisobutyronitrile (AIBN) to provide a compound of Formula IX;



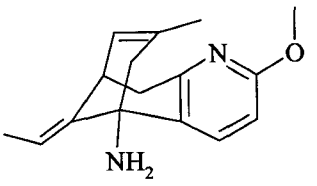
Formula IX

i) hydrolyzing the compound of Formula IX with a suitable base to provide a compound of Formula X;



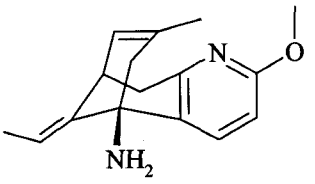
Formula X

j) converting the compound of Formula X into a compound of Formula XI;



Formula XI

k) resolving the compound of Formula XI to provide a compound of Formula XII; and



Formula XII

l) converting the compound of Formula XII to (-)-huperzine A of Formula I.

In a second aspect, the present invention provides an improved process for the preparation of (-)-huperzine A of Formula I, comprising

a) reacting the compound of Formula II with silver carbonate and methyl iodide or dimethylsulfate in presence of a catalyst to provide a compound of Formula III, wherein the silver carbonate and the catalyst are used in less than about 0.8 and less than about 0.3 equivalents respectively to the compound of Formula II; and
b) converting the compound of Formula III into (-)-huperzine A.

In a third aspect, the present invention provides an improved process for the preparation of (-)-huperzine A of Formula I, comprising

a) carboxymethylation of compound of Formula IV with dimethylcarbonate and a base to provide a compound of Formula V, wherein the dimethylcarbonate is used in less than about 20 vol/wt to the compound of Formula IV; and
b) converting the compound of Formula V into (-)-huperzine A.

In a fourth aspect, the present invention provides an improved process for the preparation of (-)-huperzine A of Formula I, comprising

a) reacting the compound of Formula VII with ethyltriphenylphosphonium bromide and n-butyllithium to provide a compound of Formula VIII, wherein the ethyltriphenylphosphonium bromide and n-butyllithium are used in less than about 3.0 equivalents and less than about 2.0 equivalents respectively to the compound of Formula VII; and
b) converting the compound of Formula VIII into (-)-huperzine A.

In a fifth aspect, the present invention provides an improved process for the preparation of (-)-huperzine A of Formula I, comprising

a) isomerizing the compound of Formula VIII with 1-octane thiol and azobisisobutyronitrile (AIBN) to provide a compound of Formula IX; and
b) converting the compound of Formula IX into (-)-huperzine A.

In a sixth aspect, the present invention provides an improved process for the preparation of (-)-huperzine A of Formula I, comprising

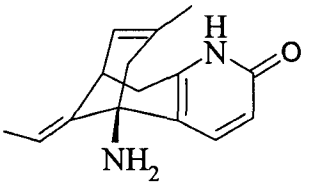
i) subjecting the racemic compound of Formula VI to preparative HPLC,
ii) separating the required (-)-enantiomer of Formula VI; and
iii) converting the (-)enantiomer of Formula VI into (-)-huperzine A.

BRIED DESCRIPTION OF THE DRAWINGS:

Figure 1: shows the powder X-ray diffraction (PXRD) pattern of (-)-huperzine A obtained by the present invention.
Figure 2: shows the Differential Scanning Calorimetry (DSC) thermogram of (-)-huperzine A obtained by the present invention.
Figure 3: shows the Theromo gravimetric Analysis (TGA) thermogram of (-)-huperzine A obtained by the present invention.

DETAILED DESCRIPTION OF THE INVENTION:

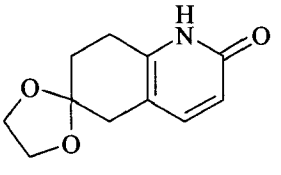
In one embodiment, the present invention provides an improved process for the preparation of (-)-huperzine A of Formula I,



Formula I

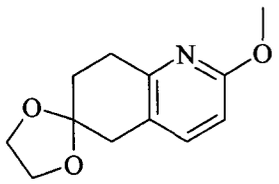
comprising;

a) reacting 1,4-cyclohexanedione monoethylene acetal with methyl propiolate in presence of ammonium source to provide a compound of Formula II,



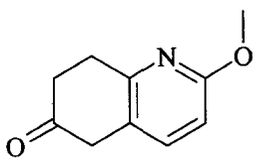
Formula II

b) reacting the compound of Formula II with silver carbonate and methyl iodide or dimethylsulfate in presence of a catalyst to provide a compound of Formula III, wherein the silver carbonate and the catalyst are used in less than about 0.8 and less than about 0.3 equivalents respectively to the compound of Formula II;



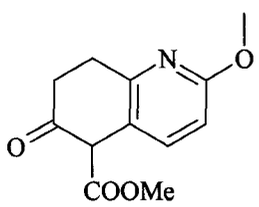
Formula III

c) hydrolyzing the compound of Formula III with phosphoric acid to provide a compound of Formula IV, wherein the phosphoric acid is used in less than about 3 vol/wt to the compound of Formula III;



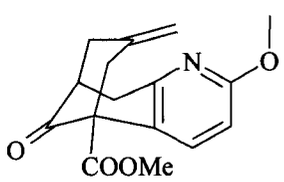
Formula IV

d) carboxymethylation of compound of Formula IV with dimethylcarbonate and a base to provide a compound of Formula V, wherein the dimethylcarbonate is used in less than about 20 vol/wt to the compound of Formula IV;



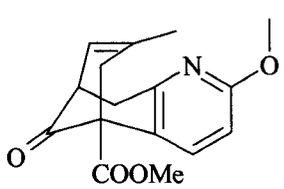
Formula V

e) annulating the compound of Formula V with 2-methylenepropane-1,3-diol diacetate to provide the compound of Formula VI,



Formula VI

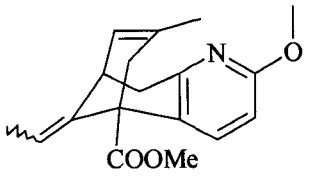
f) isomerizing the compound of Formula VI to provide a compound of Formula VII,



Formula VII

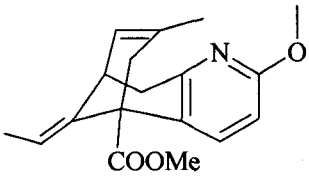
g) reacting the compound of Formula VII with ethyltriphenylphosphonium bromide and n-butyllithium to provide a compound of Formula VIII, wherein the

ethyltriphenylphosphonium bromide and n-butyllithium are used in less than about 3.0 equivalents and less than about 2.0 equivalents respectively, to the compound of Formula VII;



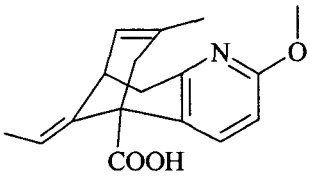
Formula VIII

h) isomerizing the compound of Formula VIII with 1-octane thiol and azobisisobutyronitrile (AIBN) to provide a compound of Formula IX;



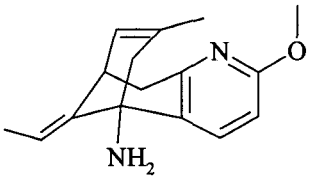
Formula IX

i) hydrolyzing the compound of Formula IX with a suitable base to provide a compound of Formula X;



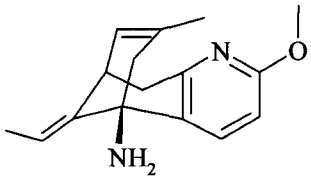
Formula X

j) converting the compound of Formula X into a compound of Formula XI;



Formula XI

k) resolving the compound of Formula XI to provide a compound of Formula XII; and



Formula XII

l) converting the compound of Formula XII to (-)-huperzine A of Formula I.

Step a) of the foregoing process involves the reaction of 1,4-cyclohexanedione monoethylene acetal with methyl propiolate in presence of ammonium source to provide the compound of Formula II.

Preferably the ammonium source used is ammonia or alcoholic ammonia and more preferably methanolic ammonia.

The step a) reaction is suitably carried out in presence of suitable solvent selected from alcohols such as methanol, ethanol, isopropanol and the like and mixtures thereof; preferably isopropanol.

The reaction of step a) is suitably carried out at a temperature of about 70-140°C, preferably at about 120-130°C for the period of about 10-12 hrs under 140-150 psi pressure.

Reported process involves the distillation of the reaction mass after reaction completion to isolate the compound of Formula II, which significantly affects the yield. The present invention avoids the distillation of the reaction mass and isolating the compound of Formula II by simply cooling the reaction mass after reaction completion.

Step b) of the forgoing process involves the reaction of compound of Formula II with silver carbonate and methyl iodide in presence of a catalyst in suitable solvent to provide the compound of formula III.

The catalyst used herein step b) is a phase transfer catalyst and is selected from tetra butyl ammonium bromide, tetra butyl ammonium iodide, tetra butyl ammonium chloride, tetrabutyl ammoniumtribromide, benzyltrimethylammonium bromide, benzyltriethylammonium bromide, benzyltrimethyl ammonium chloride, benzyltriethylammonium chloride and the like and mixtures thereof; preferably benzyl triethyl ammonium chloride.

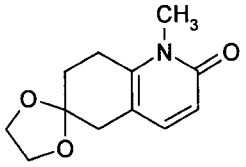
The solvent used herein step b) is selected from methylene chloride, ethylene chloride, chloroform and the like and mixtures thereof; preferably methylene chloride.

The step b) reaction may be carried out in presence of a base such as sodium hydroxide, potassium hydroxide and the like and mixtures thereof; preferably sodium hydroxide.

The step b) reaction may be carried out at a suitable temperature of about 10°C to about reflux temperature. Preferably, the reaction is carried out at 20-35°C. The reaction is allowed to stir for a period of time from about 30 mins to until completion of the reaction, preferably about 6 to 10 hrs.

It has been observed that the conventional methods involve the usage of higher amount of silver carbonate as well as phase transfer catalyst such as benzyl triethyl ammonium chloride. The usage of higher quantity of costly silver carbonate and benzyl triethyl ammonium

chloride (BTEACl) not only increases the cost of production but also leads to the formation of N-methyl impurity represented by the following structural formula



The inventors of the present invention have surprisingly found that usage of minimum amount of silver carbonate and phase transfer catalyst controlled the formation of N-methyl impurity to about less than 0.1% even after the prolonged maintenance and at the same time cost of production also minimized due to minimum quantities of reagents used when compared to the prior art process.

Preferably the silver carbonate used in the ratio of less than about 0.8 equivalents, more preferably about 0.6 equivalents to the compound of Formula II.

Preferably the phase transfer catalyst used in the ratio of less than about 0.3 equivalents, more preferably about 0.1 equivalents to the compound of Formula II.

Step c) of the forgoing process involves the hydrolysis of compound of Formula III with a suitable acid, preferably phosphoric acid to provide the compound of Formula IV. Further this step was carried out in presence of water. Phosphoric acid used herein is aqueous phosphoric acid and having the concentration of about 80-90%; preferably about 85%.

The process disclosed in the art involves the usage of about 4 vol/wt of phosphoric acid to the compound of Formula III for the hydrolysis reaction. Due to use of high volume of phosphoric acid in the reaction, it requires huge amount of base and solvent for workup. This makes the workup process not only tedious, but also results in large quantity of effluents, thereby increases the overall cost of production.

The inventors of the present invention have surprisingly found that usage of less volume of phosphoric acid such as 1 vol/wt to the compound of Formula III is sufficient to complete the hydrolysis and provide a compound of Formula IV with good yields and purity. Further usage of ammonia in place of sodium hydroxide as reported in the prior art for basification eases the workup process and provides the final compound with high purity and yield. Thereby present invention reduces the production cost and also reduces the generation of excess effluents which affects the environment.

The step c) reaction can be carried out at a suitable temperature such as 30°C to about reflux temperature. Preferably, the reaction is carried out at 70-85°C. The reaction is allowed to stir for a period of time from about 30 mins to until completion of the reaction, preferably 2-3 hrs.

Step d) of the forgoing process involves the carboxymethylation of compound of Formula IV with dimethyl carbonate and a suitable base such as sodium hydride, potassium hydride, sodiumhexamethyldisilazane, lithiumhexamethyldisilazene, potassium hexamethyldisilazane and the like; preferably sodium hydride to provide the compound of Formula V.

The process disclosed in the art involves the reaction of compound of Formula IV with 30-40 vol/wt of dimethyl carbonate in presence of sodium hydride at 85-90°C. After completion of the reaction, distillation of the dimethyl carbonate under vacuum followed by isolating the compound of Formula V.

The usage of excess volumes of dimethyl carbonate requires more amounts of solvents and reagents for workup, which not only increases the cost of production and also produces more effluent and is difficult to handle, particularly on commercial scale. Further, distillation of dimethylcarbonate in the presence of sodium hydride may lead to serious safety concerns and thus requires more labour and utmost care to use.

The inventors of the present invention have surprisingly found that reaction of compound of Formula IV with less than about 20 vol/wt of dimethyl carbonate to the compound of Formula IV, preferably less than about 15 vol/wt and more preferably 10 vol/wt, in presence of a base such as sodium hydride may completed the reaction within 2 hrs and resulting product having high purity and yield. The reduction in amount of dimethyl carbonate avoids the distillation of the reaction mass in presence of precarious sodium hydride. Further reduction of quantity of dimethyl carbonate avoids tedious workup difficulty and minimizing the effluent generation, thereby reduces the overall cost of production.

The step d) reaction may be carried out at a suitable temperature such as 30°C to about reflux temperature. Preferably, the reaction is carried out at 80-95°C. The reaction is allowed to stir for a period of time from about 30 mins to until completion of the reaction, preferably 2-3 hrs.

Step e) of the forgoing process involves annulation of the compound of Formula V with 2-methylenepropane-1,3-diol diacetate can be carried out in presence of 1,1,3,3-tetramethyl guanidine and palladium catalyst such as tetrakis triphenyl phosphine palladium in a suitable solvent to provide the compound of Formula VI.

The suitable solvent used herein step e) is selected from ester solvent such as ethyl acetate, methyl acetate, propylacetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, isopropyl acetate and the like and mixtures thereof; preferably ethyl acetate.

The reaction of step e) is suitably carried out at a temperature of about 20-50°C, preferably about 20-30°C for the period of about 30 min to till completion of reaction, preferably about 2-3 hrs.

The usage of ester solvent such as ethyl acetate for this step e) makes the workup process simple compared to the acetone and dioxane mixture of the reported process.

The step f) of the forgoing process involves the isomerisation of compound of Formula VI to provide the compound of Formula VII, which can be carried out according to the methods known in the art.

For example, isomerisation reaction can be carried out by treating the compound of Formula VI with trifluoromethane sulfonic acid in a suitable solvent such as methylene chloride at a temperature of about 20-30°C for the period of about 2-3 hrs and the obtained compound of Formula VII can further purified using a suitable alcoholic solvent such as isopropanol.

Step g) of the forgoing process involves the reaction of compound of Formula VII with ethyltriphenylphosphonium bromide and n-butyllithium to provide a compound of Formula VIII, wherein the ethyltriphenylphosphonium bromide and n-butyllithium are used in less than about 3.0 equivalents and less than about 2.0 equivalents respectively to the compound of Formula VII.

The reported process for the conversion of Formula VII to Formula VIII involves the usage of 4 equivalents of ethyltriphenylphosphonium bromide and 3.5 equivalents of n-butyllithium to compound of Formula VII, whereas the present invention using only half of the reported equivalents and provides the final compound with required yield and purity.

The crude compound of Formula VIII obtained may be further purified by acid-base treatment. The suitable acid and base used is known in the art; for instance, treating the crude compound of Formula VIII with hydrochloric acid in a suitable solvent such as toluene followed by treating with sodium hydroxide to provide the pure compound of Formula VIII.

The reaction step g) is suitably carried out in presence of ether solvent such as tetrahydrofuran, diethylether and the like; preferably tetrahydrofuran, at a temperature of about 20-50°C, preferably at about 20-30°C for about 2-3 hrs.

Step h) of the forgoing process involves isomerization of compound of Formula VIII with 1-octane thiol and azobisisobutyronitrile (AIBN) to provide a compound of Formula IX.

The isomerisation reaction of step h) suitably carried out in presence of a suitable solvent such as toluene, hexane, heptane and the like and mixtures thereof; preferably toluene.

Reported process for the isomerisation of compound of Formula VIII or its isomers thereof involves the usage of thiophenol (about 1.5 equivalents to compound of Formula VIII). Thiophenol is an irritant and foul smelling liquid and usage of the same at commercial scale

may leads to problems associated with handling and further inhaling raises serious health concerns.

The inventors of the present invention have surprisingly found that usage of 1-octane thiol in place of thiophenol avoids the above said problems. Further, the present invention only involves substantially less amount of about 0.30 equivalent of 1-octane thiol to the compound of Formula VIII thereby avoiding the problems associated with the prior art.

The crude compound of Formula IX obtained may be further purified by acid-base treatment using suitable acids and bases known in the art; for instance, treating the compound of Formula IX with hydrochloric acid followed by treatment with sodium hydroxide to provide the pure compound of Formula IX.

The reaction of step h) is suitably carried out at a temperature of about 60-100°C, preferably at about 75-85°C for the period of about 30 mins to until completion of the reaction, preferably 2-4 hrs.

Step i) of the forgoing process involve hydrolysis of Formula IX using suitable base selected from sodium hydroxide, potassium hydroxide and the like and mixtures thereof; preferably sodium hydroxide, in presences of a suitable solvent to provide the compound of Formula X; wherein the base used in the ratio of about 15 equivalents to the compound of Formula IX.

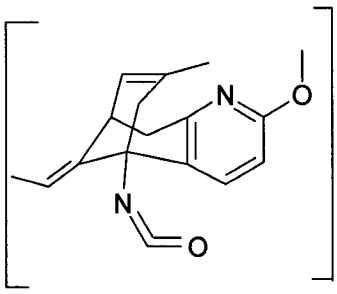
The suitable solvent used herein is selected from methanol, ethanol, isopropanol, water, tetrahydrofuran and mixtures thereof.

The reported process of hydrolysis of compound of Formula IX involves excess of sodium hydroxide such as about 30 equivalents with respect to the starting compound. This makes the workup tedious due to huge volumes and increases the cost of production and effluents.

The present inventors have surprisingly found that even half of the reported volume may sufficient to complete the hydrolysis of compound of Formula IX. The present invention thereby reduces cost of production and effluent and the same time reduces the burden of huge volume workups.

The hydrolysis reaction of step i) is suitably carried out at a temperature of about 30°C to reflux temperature, preferably about 60-65°C for the period of about 10 hrs to until the completion of reaction, preferably about 30-40 hrs.

Step j) of the forgoing process involves conversion of compound of Formula X into compound of Formula XI, which can be carried out by the methods known in the art. For example, reacting the compound of Formula X with diphenyl phosphorylazide in presence of a base such as triethyl amine in solvent such as toluene to provide the isocyanate intermediate having the following structure



Isocyanate Intermediate

which on in-situ treatment with suitable acid such as hydrochloric acid at reflux temperature to provide the compound of Formula XI.

Step k) of the forgoing process involves resolution of Formula XI to provide the compound of Formula XII can be carried out by the methods known in the art.

The resolution of Formula XI can be carried out with suitable resolving agents known in the art. For example, treating the compound of Formula XI with a suitable chiral acid such as (-)2,3-dibenzoyl tartaric acid in a suitable solvent to provide corresponding chiral acid salt of compound of Formula XI and then treating the obtained chiral acid salt compound with a suitable base in a suitable solvent to provide the compound of Formula XII.

Preferably the suitable solvent used for resolution herein selected from alcoholic solvent such as methanol, ethanol, n-propanol, isopropanol and n-butanol and the like; ketone solvents such as acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone, isobutylmethyl ketone and the like; chloro solvents such as methylene chloride, ethylene dichloride, carbon tetra chloride, chloroform and the like; and mixture thereof; and the base used herein is selected from sodium hydroxide, potassium hydroxide and the like, preferably sodium hydroxide.

Conversion of compound of Formula XII to (-)-huperzine of step l) of the forgoing process can be carried out by treating the compound of Formula XII with trimethyl silyl chloride, sodium iodide in a suitable solvent such as acetonitrile to provide the (-)-huperzine A of Formula I.

The reported process involves the deprotection of both N- and O- protecting groups at final stage to get the required huperzine A or its isomer and hence involves double the quantity of about 6.0 equivalents of trimethyl silyl chloride and sodium iodide. The present invention involves only single demethylation there by reducing the amount of reagents used to 3.0 equivalents each.

The reaction of step l) is suitably carried out at a temperature of about 30 to reflux temperature, preferably about 70-80°C for the period of about 2-3 hrs.

The (-)-huperzine A of Formula I was further purified using a suitable solvent such as methanol, ethanol, isopropanol, water and mixtures thereof to provide the pure (-)-huperzine A of Formula I.

Thus the present invention provides advantageous process for the preparation of (-)-huperzine A, which involves fewer amount of costly reagents, which not only reduces the cost of production also reduces the effluents which affects the environment and also avoids the usage of foul smelling and difficult to handle reagent such as thiophenol.

(-)-Huperzine A prepared by the present invention is characterized by the following; Powder X-ray diffraction (PXRD) pattern shown in figure-1; Differential Scanning Calorimetry (DSC) thermogram shown in figure-2; and Thermo gravimetric Analysis (TGA) thermogram shown in figure-3.

In another embodiment, the present invention provides an improved process for the preparation of (-)-huperzine A of Formula I, comprising

i) subjecting the racemic compound of Formula VI to preparative HPLC,
ii) separating the required (-)-enantiomer of Formula VI; and
iii) converting the (-)enantiomer of Formula VI into (-)-huperzine A.

The starting material of Formula VI is known in the art and can be prepared by any known methods, for example starting compound of Formula VI may be synthesized by a process as described just as above.

The preparative HPLC of step i) of the foregoing process can be performed using preparative chiral column and an eluent comprising an alcohol, hydrocarbon solvent and mixtures thereof; preferably the eluent is selected from the group consisting of ethanol, methanol, isopropanol, hexane, heptane and mixtures thereof. The preparative chromatography column may be selected from any column known in the art suitable for preparative chromatography, for example, CHIRALCEL OJ. Flow rate of the eluent may be selected from about 1 mL to 10 mL per minute. Conditions for the preparative HPLC are known to the person skilled in the art.

The separation of required (-) enatiomer of Formula VI and conversion of (-) enantiomer of compound of Formula VI to (-)-huperizine –A can be done by the methods known in the art.

The present invention provides compound of Formula VI, obtained by the preparative HPLC described herein, having enantiomeric purity of at least about 98% as measured by chiral HPLC, preferably at least about 99% as measured by chiral HPLC; more preferably at least about 99.5% as measured by chiral HPLC.

The present invention provides (-)-huperzine-A, 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
Mobile Phase	: n-Hexane: Ethanol: DEA (90:10:0.1)
Column Temperature	: 40 °C
Wave length	: 310 nm
Flow rate	: 1.0 mL/min
Injection Volume	: 10 µL
Diluent	: Mobile phase
Elution	: Isocratic

The present invention provides (-)-huperzine-A, obtained by the process described herein, as analyzed using the high performance liquid chromatography ("HPLC") with the conditions described below:

Column	: XTerra RP18
Buffer	: 0.01M K_2HPO_4
Mobile Phase	: A) Buffer: Acetonitrile (95:5, v/v) B) Methanol: Acetonitrile (80:20, v/v)
Column Temperature	: 30 °C
Wave length	: 280 nm
Flow rate	: 1.0 mL/min
Injection Volume	: 10 µL
Elution	: Gradient

Gradient Programme:

Time (min)	% A	% B
0	95	5
5	95	5
20	60	40
30	20	80
40	20	80
45	95	5
50	95	5

The following examples are provided by way of illustration only, and are not intended to be limiting of the present invention. Further, the present invention covers all the possible combinations of particular and preferred embodiments indicated herein.

EXAMPLES:

EXAMPLE-1: Preparation of 1',5',7',8'-tetrahydrospiro(1,3-dioxolane-2,6'(2'H)-quinolin)-2'-one.

Methyl propiolate (678.25 g) and methanolic ammonia (6.3 Lt) was added to a solution of 1,4-cyclohexanedione mononethylene acetal (600 g) in isopropanol (6 Lt) taken in a autoclave at 25-30°C and stirred for 30 min. The reaction mass was heated to 125-130°C and stirred for 12 hrs under 140-150psi pressure. After reaction completion, the reaction mass was cooled to 10-15°C and stirred for 4 hrs. The solid obtained was filtered, washed with isopropanol and dried at 50°C for 5 hrs to get the title compound;
Yield: 310 g; Purity by HPLC: 99.29%

EXAMPLE-2: Preparation of 7',8'-dihydro-2'-methoxyspiro(1,3-dioxolane-2,6'(5'H)-quinoline.

Aqueous sodium hydroxide solution (42.46 g in 1 Lt of water) was added to 1',5',7',8'-tetrahydrospiro(1,3-dioxolane-2,6'(2'H)-quinolin)-2'-one (200 g) in methylene chloride (2 Lt) at 20-25°C. Benzyl triethyl ammonium chloride (21.98 g, 0.1eq) followed by silver carbonate (159.6 g 0.6eq) was added to the reaction mass at 20-25°C and stirred for 30 min. Methyliodide (410.9 g) was slowly added to the reaction mass over the period of 30 min. at 20-25°C and stirred for 10 hrs. After reaction completion, the reaction mass was filtered and was washed with methylene chloride. The organic and aqueous layers were separated and the aqueous layer was extracted with methylene chloride. Organic layers were combined, washed with water and then distilled off the solvent completely under vacuum at 40°C. DM water (600 mL) was added to the obtained residue at 25-30°C and stirred for an hour. The solid obtained was filtered, washed with water and dried to get the title compound.
Yield: 190 g: Purity by HPLC: 99.87%; N-methyl impurity: Not detected

EXAMPLE-3: Preparation of 2-methoxy-7,8-dihydro-5H-quinolin-6-one.

Mixture of 7',8'-dihydro-2'-methoxyspiro(1,3-dioxolane-2,6'(5'H)-quinoline (175 g), DM water (1.75 Lt), phosphoric acid(175 mL (85%), 1V) was stirred for 30 min. at 25-30°C. The reaction mass was heated to 75-80°C and stirred for 3 hrs. After reaction completion, the reaction mass was cooled to 5-10°C and pH of the reaction mass was adjusted to 7-7.5 with aqueous ammonia. The reaction mass temperature was raised to 25-30°C and stirred for 15 min. Methylene chloride (875 mL), DM water (350 mL) was added to the reaction mass and stirred for 15 min. The organic and aqueous layers were separated and the aqueous layer was extracted with methylene chloride. Organic layers were combined, washed with brine solution and then distilled off the solvent up to 1.5 vol. under vacuum at 40°C. Hexane (525 mL) was added to the obtained crude and distilled off the hexane up to 1.5 vol. The reaction mass was stirred for 30 min. at 25-30°C then cooled to 0-5°C and stirred for an hour. The solid obtained was filtered, washed with chilled hexane and dried at 25-30°C for 3-4 hrs under vacuum to get the title compound.
Yield: 122.5 g; Purity by HPLC: 99.38%

EXAMPLE-4: Preparation of 2-methoxy-5-methoxycarbonyl-6-oxo-5,6,7,8-tetrahydroquinoline.

Mixture of dimethyl carbonate (850 mL, 5 V) and sodium hydride (28.77 g) was heated 85-90°C and stirred for 15 min. A solution of 2-methoxy-7,8-dihydro-5H-quinolin-6-one (170 g) in dimethyl carbonate (850 mL, 5 V) was slowly added to the reaction mass at 85-90°C over the period of 60-90 min. and stirred for 2 hrs at 85-90°C. After reaction completion, the reaction mass was cooled to 0-5°C and acetic acid (14.38 g) in dimethyl carbonate (170 mL) was added to it then stirred for 15 min. 10% ammonium chloride solution (1.7 Lt) was added to the reaction mass at 0-5°C. The reaction mass temperature was raised to 25-30°C and DM water (850 mL) was added to it then stirred for 15 min. The organic and aqueous layers were separated and the dimethyl carbonate layer was distilled up to 1 vol. under vacuum at 45-50°C. Isopropanol(850 mL) was added to the obtained residue and was distilled up to 1 vol. Isopropanol (850 mL) was again added to the obtained residue at 45-50°C and stirred for 10 min. The reaction mass was cooled to 25-30°C and stirred for 30 min. The reaction mass was further cooled to 0-5°C and stirred for an hour. The solid obtained was filtered, washed with isopropanol and dried at 50°C for 3-4 hrs under vacuum to get the title compound.
Yield: 183 g; Purity by HPLC: 99.84%

EXAMPLE-5: Preparation of (±)-7,8,9,10-tetrahydro-2-methoxy-7-methylene-11-oxo-5,9-methanocycloocta[b]pyridine-5(6H)-carboxylic acid methyl ester.

A solution of 2-methylene propane-1,3-diol acetate (100.6 g) and 2-methoxy-5-methoxycarbonyl-6-oxo-5,6,7,8-tetrahydroquinoline (125 g) was dissolved in ethyl acetate (625 mL) and was added to a solution of tetrakis triphenyl phosphine palladium(0) (36.84 g) in ethyl acetate (1.25 Lt) at 25-30°C then stirred for 20 min. A solution of 1,1,3,3-tetramethyl guanidine (159.16 g) in ethyl acetate (625 mL) was added to the reaction mass and stirred for 3 hrs at 25-30°c. After reaction completion, DM water (1.25 Lt) was added to the reaction mass and stirred for 15 min. at 25-30°C. The organic and aqueous layers were separated and the organic layer was washed with water followed by brine solution. The solvent from the organic layer was distilled off completely under vacuum to get the title compound as crude. The crude compound was further purified by silica gel column using hexane and ethyl acetate as eluent. The pure fractions was collected and distilled under vacuum at 40-45°C up to 1 vol and isopropanol (250 mL) was added and distilled off completely to remove ethyl acetate traces. Isopropanol (250 mL) was added at 40-45°C and stirred for 15 min. DM water (1.25 Lt) was added to the reaction mass and stirred for an hour at 25-30°C. The solid obtained was filtered and dried at 50°C for 7 hrs to get the pure title compound.
Yield: 118 g; Purity by HPLC: 99.23% (Keto + enol form)

EXAMPLE-6: Preparation of (±)-5-methoxy-11-methyl-13-oxo-6-aza-tricyclo [7.3.1.0] trideca-2(7),3,5,10-tetraene-1-carboxylic acid methyl ester.

Trifluoromethyene sulfonic acid (150 mL) was added to a solution of (±)7,8,9,10-tetrahydro-2-methoxy-7-methylene-11-oxo-5,9-methanocycloocta[b]pyridine-5(6H)-carboxylic acid methyl ester (150 g) in methylene chloride (1.05 Lt) at 20-25°C and stirred for 3 hrs. After reaction completion, the reaction mass was cooled to 0-5°C.Aqueous sodiumbicarbonate solution (8%, 2.25 Lt) was added to it over 30 min. and stirred for 15 min. The organic and aqueous layers were separated and the aqueous layer was extracted with methylene chloride. Organic layers were combined, washed with water and then distilled off under reduced pressure at 40-50°C up to 1 vol. Isopropanol (300 mL) was added to the reaction mass and was distilled up to1 vol. Isopropanol (225 mL) was again added to the obtained residue and stirred for 15 min at 45-50°C. The reaction mass was initially cooled to 25-30°C, stirred for 30 min then further cooled to 0-5°C and stirred for an hour. The solid obtained was filtered, washed with isopropanol and dried at 50°C for 3-4 hrs to get the title compound.
Yield: 124 g; Purity by HPLC: 96.92%

EXAMPLE-7: Preparation of (±)-11-ethylidene-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocyclo-octa[b]pyridine-5(6H)-carboxylic acid methyl ester.

Ethyltriphenylphosphonium bromide (43.92 g, 2 eq) followed by 15% n-butyl lithium in hexane (50.4 mL, 2 eq) was slowly added to tetrahydrofuran (340 mL) at 25-30°C over the period of 30 min. under nitrogen atmosphere and stirred for 30 min. The reaction mass was cooled to 0-5°C and (±)-5-methoxy-11-methyl-13-oxo-6-aza-tricyclo[7.3.1.0]trideca-2(7),3,5,10-tetraene-1-carboxylic acid methyl ester (17 g) was added it over 45 min. then stirred for 30 min. at 0-5°C. The reaction mass temperature was raised to 25-30°C and stirred for 3 hrs. After reaction completion, the reaction mass was cooled to 0-5°C and DM water (230 mL) was added to it. The reaction mass was stirred for 20 min. at 25-30°C and the layers were separated. Organic layer was distilled off under vacuum at 45-50°C and the obtained residue was co-distilled with toluene (85 mL). The obtained residue was dissolved in toluene (255 mL). 6N hydrochloric acid (170 mL) was added to the reaction mass and stirred for 30 min. at 25-30°C. Organic layer was separated and extracted with 6N hydrochloric acid. Both the acidic aqueous layers were combined and was washed with toluene. The aqueous layer was cooled to 0-5°C and the pH was adjusted 7-7.5 with 6N sodium hydroxide solution. The reaction mass was stirred for 30 min. at 25-30°C. The solid obtained was filtered, washed with water and dried at 50°C for 6-8 hrs to get the title compound.
Yield: 14.4 g; Purity by HPLC: 75.10% + 22.90% (Z:E-isomer)

EXAMPLE-8: Preparation of (E)-(±)-11-ethylidene-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocyclo-octa[b]pyridine-5(6H)-carboxylicacid methyl ester.

(±)-11-ethylidene-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocyclo-octa[b]-pyridine-5(6H)-carboxylic acid methyl ester (100 g), azobisisobutyronitrile(AIBN) (16.45 g), 1-octanethiol (14.72 g) was added to toluene (1.0 Lt) at 25-30°C under nitrogen atmosphere.

The reaction mass was heated to 75-80°C and stirred for 2-4 hrs. After reaction completion, the reaction mass was cooled to 25-30°C. 6N hydrochloric acid (1.0 Lt) was added to the reaction mass and stirred for 30 min. The organic and aqueous layers were separated; aqueous layer was again washed with 6N HCl (500 mL). Both the acidic aqueous layers were combined and washed with toluene to remove impurities. The aqueous layer was cooled to 0-5°C and pH was adjusted to 7.5-8 with aqueous sodium hydroxide solution at 0-5°C. The reaction mass stirred for 20 min at 25-30°C and extracted thrice with methylene chloride. The organic layers were combined and was washed with brine solution and then distilled off under vacuum at 45-50°C. Heptane (200 mL) was added to the residue and distilled off under vacuum. Heptane (200 mL) was again added to the obtained residue and stirred for 10 min at 40-45°C. The reaction mass was cooled to 0-5°C and stirred for an hour. The solid obtained was filtered, washed with water and dried at 40-45°C for 3 hrs to get the title compound.
Yield: 79.0 g; Purity by HPLC: 96.68% (E-isomer), 2.19% (Z-isomer).

EXAMPLE-9: Preparation of (13E)-13-ethylidene-5-methoxy-11-methyl-6-azatricyclo [7.3.1.$0^{2,7}$] trideca-2,4,6,10-tetraene-1-carboxylic acid.

(E)-(±)-11-ethylidene-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocyclo-octa[b]pyridine-5(6H)-carboxylicacid methyl ester (80 g), aqueous sodium hydroxide (160.3 g in 480 mL of DM water), methanol (720 mL) was added to tetrahydrofuran (480 mL) at 25-30°C. The reaction mass was heated to 60-65°C and stirred for 40 hrs at reflux. After reaction completion, the reaction mass was cooled to 45-50°C and the solvent was distilled off under vacuum. The obtained residue was dissolved in water (1.6 Lt) at 25-30°C. Aqueous layer was washed with methylene chloride and pH of the aqueous layer was adjusted to 3-4 with concentrated hydrochloric acid at 0-5°C. The reaction mass was stirred for 15 min at 25-30°C and extracted thrice with methylene chloride. Organic layers were combined, washed with DM water followed by brine solution. The organic layer was concentrated under vacuum at 40°C, striped off the crude with heptane. Heptane (800 mL) was added to the obtained residue and stirred for 15 min at 25-30°C. The reaction mass was further cooled to 0-5°C and stirred for 30 min. The solid obtained was filtered, washed with heptane and dried at 50°C for 3-4 hrs under vacuum to get the title compound.
Yield: 67 g; Purity by HPLC: 99.70%

EXAMPLE-10: Preparation of (13E)-13-ethylidene-5-methoxy-11-methyl-6-azatricyclo[7.3.1.$0^{2,7}$] trideca-2,4,6,10-tetraene-1-amine.

(13E)-13-ethylidene-5-methoxy-11-methyl-6-azatricyclo[7.3.1.$0^{2,7}$] trideca-2,4,6,10-tetraene-1-carboxylic acid (65 g), diphenyl phosphoryl azide (75.31 g), triethylamine (30.0 g) was added to toluene (1.30 Lt) at 25-30°C and stirred for 3 hrs. After reaction completion, 8N hydrochloric acid (260 mL) was added to the reaction mass at 25-30°C and stirred for 10 min. The reaction mass was heated to reflux temperature and stirred for 2 hrs. The reaction mass was cooled to 25-30°C and the organic layer was separated. Aqueous layer was washed with

toluene and pH of the aqueous layer adjusted to 10-11with sodium hydroxide solution. The reaction mass was then extracted with methylene chloride and the extracted layer was washed with water followed by brine solution. Organic layers were combined and concentrated under vacuum to get the crude compound. The crude compound was further purified by silica gel column (using 30% ethyl acetate in hexane as eluent) to get the title compound.
Yield: 34 g; Purity by HPLC: 95.7%

EXAMPLE-11: Preparation of (1R,13E)-13-ethylidene-5-methoxy-11-methyl-6-azatricyclo [7.3.1.$0^{2,7}$]trideca-2,4,6,10-tetraen-1-amine(2R,3R)-2,3-bis[(phenylcarbonyl)oxy]butanedioic acid.

(13E)-13-ethylidene-5-methoxy-11-methyl-6-azatricyclo[7.3.1.$0^{2,7}$] trideca-2,4,6,10-tetraene-1-amine (50 g) and (-)2,3-dibenzoyl tartaric acid anhydrous (76.9 g) was added to acetone (1 Lt) at 25-30°C. The reaction mass was heated to 50-55°C and stirred for 90 min. The reaction mass was cooled to 25-30°C and stirred for 30 min. The solid obtained was filtered and washed with acetone and suck dried. The obtained compound was recrystallised from acetone to get the pure title compound.
Yield: 45.0 g; chemical Purity: 99.76%; chiral purity: 99.98%

EXAMPLE-12: Preparation of (1R,13E)-13-ethylidene-5-methoxy-11-methyl-6-azatricyclo [7.3.1.$0^{2,7}$]trideca-2,4,6,10-tetraen-1-amine.

A mixture of (1R,13E)-13-ethylidene-5-methoxy-11-methyl-6-azatricyclo [7.3.1.$0^{2,7}$]trideca-2,4,6,10-tetraen-1-amine(2R,3R)-2,3-bis[(phenylcarbonyl)oxy]butanedioic acid (49 g) and methylene chloride (490 mL) was cooled to 5-10°C. The pH of the reaction mass was adjusted to 11-11.5 with aqueous sodium hydroxide solution at 5-10°C and stirred for 20 min. at 25-30°C. The aqueous and organic layers were separated and the aqueous layer was extracted with methylene chloride. Organic layers were combined and washed with water followed by brine solution. Organic layer was distilled off completely under vacuum to get the title compound.
Yield: 20 g; chiral purity: 99.93%; Chemical purity: 99.84%

EXAMPLE-13: Preparation of (-)-Huperzine A

(1R,13E)-13-ethylidene-5-methoxy-11-methyl-6-azatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6,10-tetraen-1-amine (10 g), sodium iodide (17.5 g) and trimethylsilyl chloride (12.6 g) was added to acetonitrile (110 mL) at 25-30°C. The reaction mass was heated to reflux temperature and stirred for 2.5 hrs at reflux. After reaction completion, the reaction mass was cooled to 25-30°C and diluted with methylene chloride (200 mL). The reaction mass was extracted twice with 1.5M hydrochloric acid. Acidic aqueous layers were combined and washed with methylene chloride. Acidic aqueous layer was cooled to 0-5°C and pH was adjusted to 12-13 with sodium hydroxide. Aqueous layer was extracted four times with methylene chloride. The organic layers were combined and washed with 5% dibasic sodium phosphate. The

organic layer was concentrated under vacuum to get the crude. The obtained crude was dissolved in methanol (100 mL) at 40-45°C and distilled off the solvent under vacuum up to 1 vol. Methanol (100 mL) was added to the residue and again distilled off methanol up to 1 vol. DM water (150 mL) was added to the residue and stirred for 30 min at 25-30°C.The solid obtained was filtered, washed with water and then dried under vacuum at 50-55°C for 3-4 hrs to get the title compound.
The PXRD of obtained (-)-huperzine-A having 2 theta peaks at about 9.78, 10.80, 12.62, 13.62, 13.94, 14.42, 16.32, 17.98, 19.58, 20.10, 21.38, 22.54, 23.98, 24.72, 26.02, 27.34, 28.00, 29.00, 29.60, 30.34, 32.48 and 33.94 ± 0.2 degree 2 theta.
Yield: 8.4 g; Chiral purity: 99.97%; Chemical purity: 99.80%.

Example 13: Chiral separation of (-) enantiomer from racemic compound of Formula VI:

Chiral separation of required (-) enatiomer of Formula VI from its racemic compound was carried out by preparative HPLC using CHIRALCEL OJ column under the following chromatography conditions:

Column	CHIRALCEL OJ
Mobile phase	Hexane: Ethanol (1:1, v/v)
Flow rate	1 mL/min
Detection	By UV at 300 nm
Sample concentration	~35 mg/mL

Chiral HPLC:
(-)-enantiomer: 99.8%
(+)-enantiomer: 0.2%

Dated this 21st day of March, 2014

Sign----------

(CH.V. Ramana Rao)
Asst.Vice President
Laurus Labs Pvt. Ltd

ABSTRACT:

The present invention relates to an improved and cost effective process for the preparation of (-)-Huperzine A. The present invention also relates to a process for separation of enantiomers using preparative HPLC.