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(54) **PREPARATION METHOD OF RIVASTIGMINE, ITS INTERMEDIATES AND PREPARATION METHOD OF THE INTERMEDIATES**

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(58) **Field of Classification Search** 564/384, 564/389; 560/133, 136
See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides N-methylethylcarbamino-3-[(S)-1-(methyl-[(S)-1-phenylethyl]amino)ethyl]phenyl ester represented by formula (II) and its preparation method. The present invention also provides (S)-1-(3-methoxyphenyl)-N-methyl-N—[(S)-1-phenylethyl]ethylamine and 3-[(S)-1-(methyl-[(S)-1-phenylethyl]amino)ethyl]phenol as intermediates of the compound represented by formula (II), and the use of the compound represented by formula (II) for preparing rivastigmine used for treating Alzheimer disease.

6 Claims, No Drawings

PREPARATION METHOD OF RIVASTIGMINE, ITS INTERMEDIATES AND PREPARATION METHOD OF THE INTERMEDIATES

CROSS REFERENCE TO RELATED APPLICATION

This application is a 35 U.S.C. §371 national phase application of PCT Application No. PCT/CN2008/000072, filed on Jan. 10, 2008, the disclosures and contents of which are hereby incorporated by reference as if recited in full herein. The above-referenced PCT International Application was published in Chinese as International Publication No. WO 2009/086705 A1.

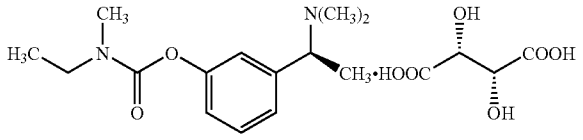
FIELD OF THE INVENTION

The present invention is related to N-methylethylcarbamino-3-[(S)-1-(methyl-[(S)-1-phenylethyl]amino) ethyl] phenyl ester (the compound represented by formula (II)) and its process of preparation. The present invention further describes (S)-1-(3-methoxyphenyl)-N-methyl-N—[(S)-1-phenylethyl]ethylamine and 3-[(S)-1-(methyl-[(S)-1-phenylethyl]amino) ethyl]phenol as intermediates for preparing the compound represented by formula (II), and the use of the compound represented by formula (II) for preparing rivastigmine which is used for treating Alzheimer disease.

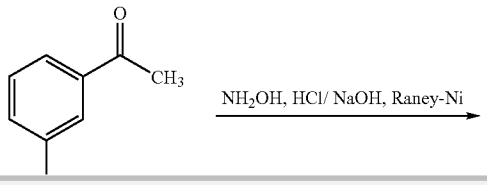
BACKGROUND OF THE INVENTION

It has been proved that rivastigmine has the activity of selective inhibitive central cholinesterase so that it is used for treating presenile dementia. The structure of rivastigmine is shown as formula (VIII):

(VIII)



The synthesis of rivastigmine was reported in U.S. Pat. No. 5,602,176, GB2409453, and Yonwen, Jiang et. al. [Journal of East China Normal University (Natural Science), 2001, 1, 61-65], in which the method is disclosed as: preparing racemic rivastigmine by a series of reactions, then salifying the result with D-(+)-O, o'-bis-p-tolyl formacyl tartaric acid monohydrate (D-DTTA) to separate the racemic mixture, and recrystallizing at least three time to obtain (S)-rivastigmine with an optical purity of above 99%. The final yield is only 5.14%.



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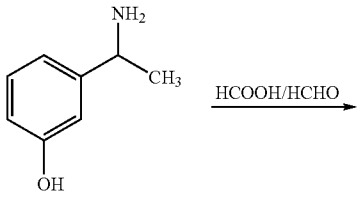
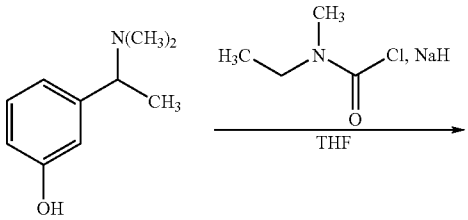
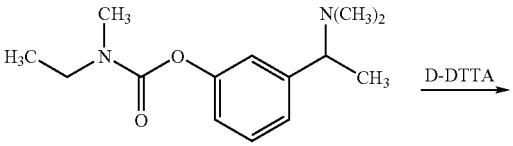
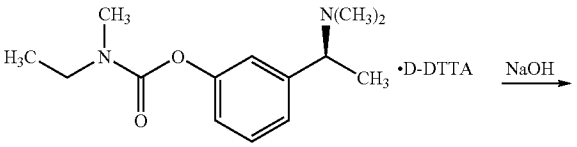
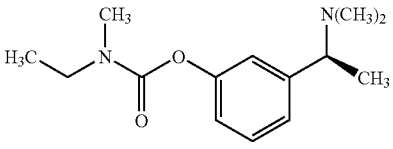


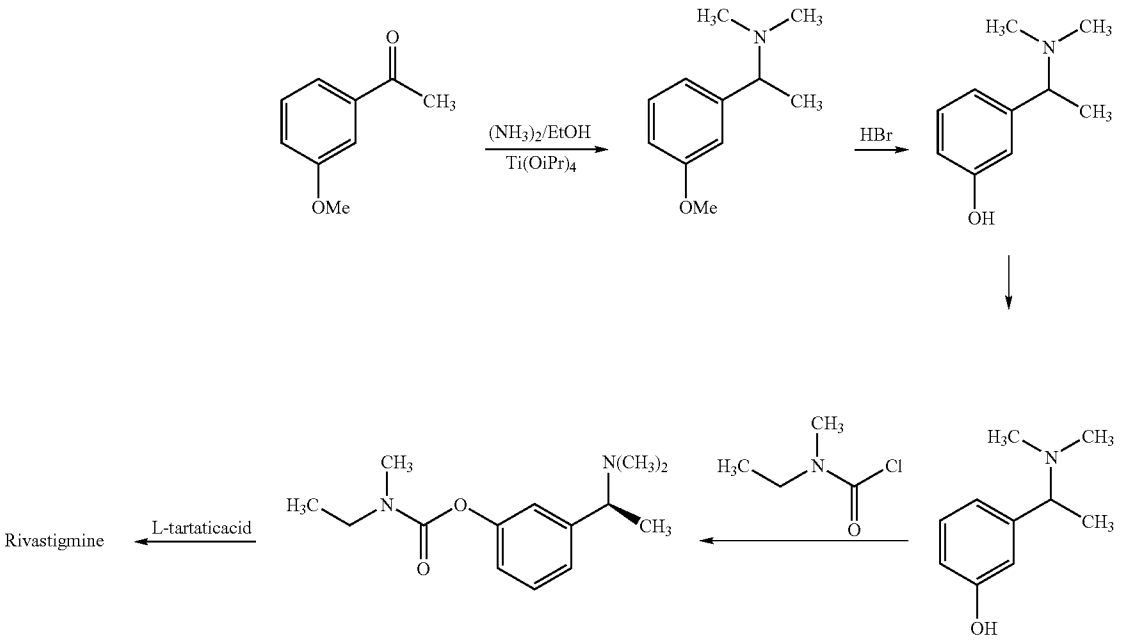








A method for resolution of a intermediate of rivastigmine is disclosed in WO200403771, in which S-(+)-camphor sulfonic acid is used to separate racemic intermediates of 3-(1-(S)—(N,N-dimethylamino) ethyl)phenol, and optically pure 3-(1-(S)—(N,N-dimethylamino) ethyl)phenol is obtained after three times recrystallization and then condensates with

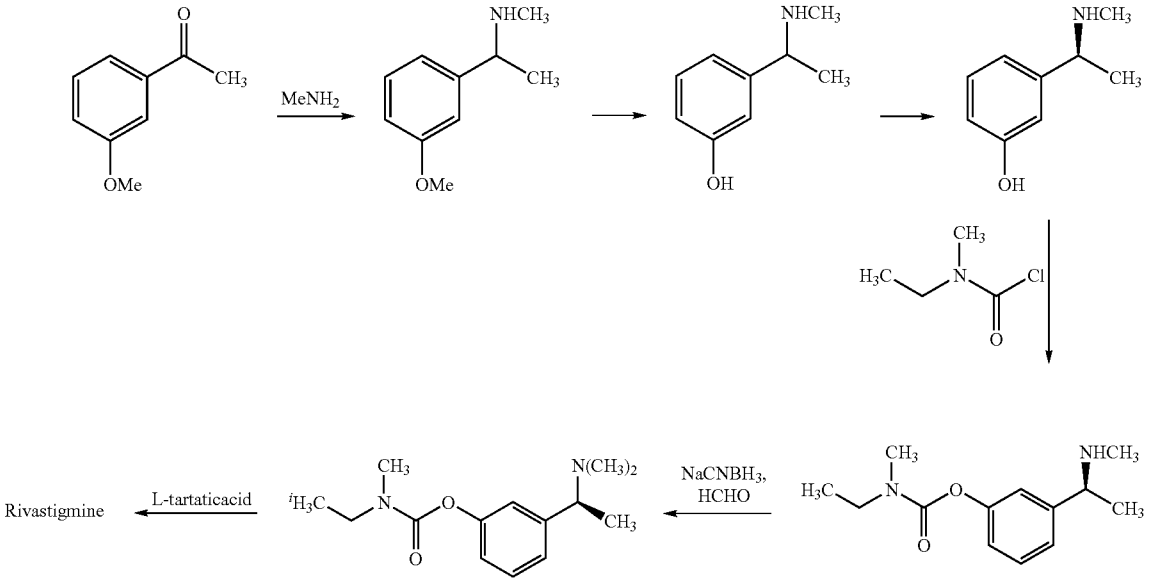


A method for resolution of a intermediate of rivastigmine is also disclosed in WO2007014973, in which S-(+)-camphor sulfonic acid is used to separate racemic intermediates of 3-(1-(methylamino) ethyl)phenol, and the result condensates with N-methyl-N-ethyl-amino formacyl chloride to obtain N-methylethylcarbamino-3-[(S)-1-(methylamino)-ethyl] phenyl ester, and a methylation is then performed on the nitrogen atom followed by salifying with L-(+)-tartaric acid so that rivastigmine is obtained. The methylation needs a reduction system of sodium cyanoborohydride/formaldehyde, in which sodium cyanoborohydride is highly toxic, so that the method is not suitable for industrial production. The specific synthesis route is shown below:

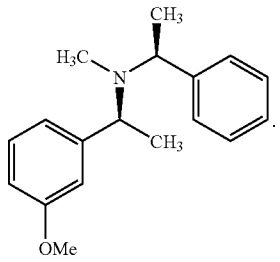
The resolution methods mentioned above are time consuming with low yields, so that final yields are reduced and costs are increased, which are not beneficial for industrial production and the optical purity of rivastigmine cannot be guaranteed.

SUMMARY OF THE INVENTION

The present invention provides a compound having a structure represented by formula (IV) below, i.e. [(S)-1-(3-methoxyphenyl)-N-methyl-N—[(S)-1-phenylethyl]ethylamine]:

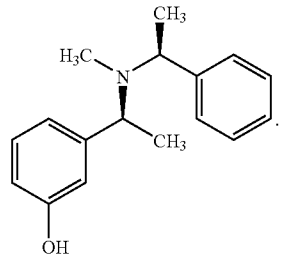


(IV)



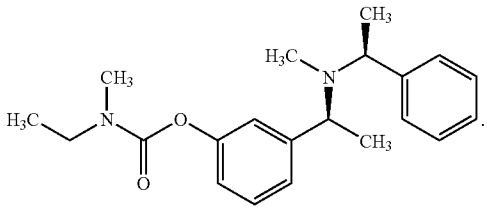
The present invention also provides a compound having a structure represented by formula (V) below, i.e. [3-[(S)-1-(methyl-[(S)-1-phenylethyl]amino) ethyl]phenol]:

(V)



The present invention also provides a compound having a structure represented by formula (II) below, i.e. [N-methyl-ethylcarbamino-3-[(S)-1-(methyl-[(S)-1-phenylethyl] amino) ethyl]phenyl ester]:

(II)

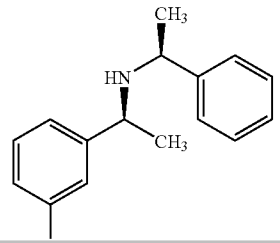


The compound represented by formula (IV) and the compound represented by formula (V) above are key intermediates for the preparation of the compound represented by formula (II).

The present invention further provides a preparation method of the compound represented by formula (II) comprising the steps of:

a) methylating a compound having a structure represented by formula (III) below, i.e. [(S)-1-(3-methoxyphenyl)-N—((S)-1-phenylethyl)ethylamine], to obtain a compound represented by formula (IV);

(III)



b) demethylating the compound represented by formula (IV) to obtain the compound represented by formula (V); and

c) carrying out a condensation reaction of the compound represented by formula (V) and N-methyl-N-ethyl-amino formacyl chloride to provide the compound represented by formula (II).

In some embodiments, in step a), there may be two possible approaches for the methylation reaction:

In one embodiment, the first approach: Reductive N-methylation is performed using formaldehyde in the presence of a reducing agent. In one embodiment, (S)-1-(3-methoxyphenyl)-N—((S)-1-phenylethyl)ethylamine as a raw material, and formic acid or a borohydride of a metal of group I or group II as a reducing agent react with formaldehyde to perform the reductive N-methylation reaction, and (S)-1-(3-methoxyphenyl)-N-methyl-N—[(S)-1-phenylethyl]ethylamine is obtained. When formic acid is used as the reducing agent, the reaction is Eschweiler-Clarke reaction, the process of which is simple and common in the art. See J. Am. Chem. Soc., 1933, 55, 4571, which is incorporated herewith by reference. When the borohydride of a metal of group I or group II is used as the reducing agent, the reaction is usually performed in an aqueous solution, acetic acid and sodium acetate are used as a buffer, and a mixture of (S)-1-(3-methoxyphenyl)-N—((S)-1-phenylethyl)ethylamine and formaldehyde are added in batches into the borohydride under cooling. See J. Am. Chem. Soc., 1974, 96, 7812, which is incorporated herewith by reference in its entirety.

In another embodiment, the second approach: The methylation reaction is carried out using (S)-1-(3-methoxy phenyl)-N—((S)-1-phenylethyl)ethylamine as a raw material, and methyl iodide or dimethyl sulfate as a methylation agent, so as to obtain (S)-1-(3-methoxyphenyl)-N-methyl-N—[(S)-1-phenylethyl]ethylamine. Methyl iodide or dimethyl sulfate are conventional methylation agents, and the method is common in the art. See OS, CV4, 836 (1963); OS, CV3, 753 (1955), which are incorporated herewith by reference in their entireties.

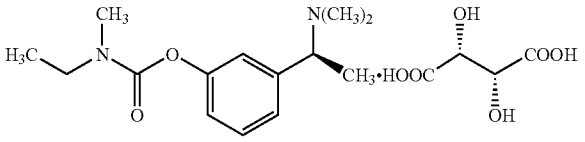
In step b), said demethylation reaction may be performed in hydrobromic acid. In some embodiments, a phase-transfer catalyst may be added during the demethylation reaction to accelerate the reaction. The phase-transfer catalyst may be any one selected from tetrabutyl ammonium bromide, tetraethyl ammonium bromide, tetrabutyl ammonium iodide or triethyl benzyl ammonium chloride. See J Labelled Compd. Radiophatin, 1997, 39(8): 651-668, which is incorporated herewith by reference in its entirety.

In step c), at least one basic reagent may be added during the condensation reaction. The basic reagent may be one or more of the following compounds: inorganic basic compounds selected from sodium carbonate, potassium carbonate, sodium amide, sodium hydride; alkali metal alcohol-based compounds selected from sodium methanol, sodium ethanol, potassium t-butanol; organic basic compounds selected from triethylamine, pyridine, quinoline, diisopropylethylamine. In some embodiments, at least one inert solvent is used as a solvent in the condensation reaction. The inert solvent may include, but is not limited to, any of ether-based solvents selected from tetrahydrofuran, ethyl ether, ethylene glycol dimethyl ether, dioxane, dimethyl tetrahydrofuran; aromatic hydrocarbon-based solvents selected from benzene, toluene, xylene; halogenated hydrocarbon-based solvents selected from dichloromethane, trichloromethane, dichloroethane; dimethylformamide, dimethyl acetamide and acetone. See WO2004/037771 and WO2006/068386, which are incorporated herewith by reference in their entireties. In some embodiments, a phase-transfer catalyst may be added

nium bromide, tetraethyl ammonium bromide, tetrabutyl ammonium iodide or triethyl benzyl ammonium chloride.

The present invention also provides a process of preparing a compound having the structure represented by formula (VIII) below, i.e. rivastigmine:

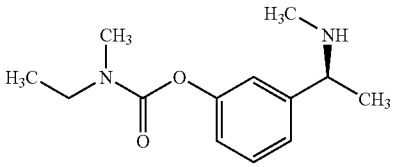
(VIII)



comprising the steps of:

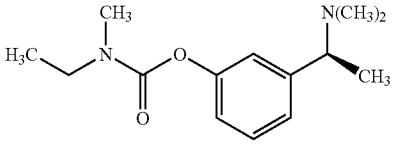
a) debenzylating the compound represented by formula (II) to obtain a compound having the structure represented by formula (VI) below, i.e. [N-methylethylcarbamino-3-[(S)-1-(methylamino) ethyl]phenyl ester];

(VI)



b) methylating the compound represented by formula (VI) to obtain a compound having the structure represented by formula (VII) below, i.e. [N-methylethylcarbamino-3-[(S)-1-(dimethylamino) ethyl]phenyl ester];

(VII)



c) reacting the compound represented by formula (VII) with L-(+)-tartaric acid to provide the compound represented by formula (VIII).

In step a), palladium-carbon hydrogenation catalyst in an amount ranging from 2% to 50% is used in the debenzylation reaction under a pressure ranging from 1 to 40 atm. In one embodiment, the pressure for the debenzylation reaction is ranging from 3 to 30 atm, and at a reaction temperature ranging from 20° C. to 100° C., or from 40° C. to 80° C. An organic solvent used in the reaction may be an alcohol selected from methanol, ethanol, propanol, isopropanol, butanol and t-butanol; or an ether selected from ethyl ether, isopropyl ether, tetrahydrofuran; or any mixtures of above said solvents. See EP257787, which is incorporated herewith by reference in its entirety.

In step b), the method for the methylation reaction is the same as that used for preparing the compound represented by formula (IV), In some embodiments, the methylation uses Eschweiler-Clarke reaction or methyl iodide or dimethyl sulphate is used as a methylating agent in the methylation reaction.

The compound represented by formula (VII) may react

The present application describes that the preparation of (S)-1-(3-methoxyphenyl)-N—((S)-1-phenylethyl)ethylamine (i.e, the compound represented by formula (III)) or the salt thereof. An asymmetric reductive amination reaction is performed using o-methoxyl acetophenone and S-α-phenylethylamine in ethyl acetate in the presence of the reduction system of tetraiospropyl titanate/Raney-Ni/H_2 to obtain the compound of formula (III). See J. Org. Chem., 1986, 51, 3635; Letters in Organic Chemistry, 2007, 4(2), 126-128; and Chinese patent application No. 200610116949.3, which are incorporated herewith by reference in their entireties. Based on the above, the benzyl of the compound represented by formula (III) or its salt is not removed, and methylation by multiple steps is used to prepare rivastigmine. The compounds represented by formulas (IV), (V) and (II) of the present invention are isomers with single configuration, which can be conveniently purified by utilizing the differences between the compounds and impurities which are not enantiomers thereof.

The synthesis process of the invention for preparing rivastigmine is reasonably designed and is very simple. In addition, raw materials can be easily obtained. The process avoids a waste caused by optical resolutions and has a high final yield (above 45% with respect to the compound represented by formula (III)). The product, rivastigmine, has a high chemical and optical purity (HPLC purity is above 99.7%, optical purity is above 99.8%). Therefore, the process can be easily industrialized for mass production.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will be further illustrated below in conjunction with examples, which do not form any limitation to the invention.

^{1}H-NMR is measured by AM 400 nuclear magnetic resonance analyzer, chemical shift is represented by δ (ppm). Mass spectrum is measured by Shimadzu LCMS-2010 mass spectrometer, Optical rotation is measured by Perkin-Elmer 341 polarimeter,

EXAMPLE 1

Preparation of (S)-1-(3-methoxyphenyl)-N-methyl-N—[(S)-1-phenylethyl]ethylamine (the compound represented by formula (IV))

38 g (0.149 mol) (S)-1-(3-methoxyphenyl)-N—((S)-1-phenylethyl)ethylamine (the compound represented by formula (III)) and 27.42 g (0.596 mol) formic acid were mixed at room temperature, and then 24.84 g (0.298 mol) formaldehyde aqueous (37 mass %) was added therein. The mixture was fluxed for 5 hours. After the mixture was cooled to room temperature, 265 ml water was added followed by adding sodium carbonate (20.33 g) in batches. Then the result was extracted with 250 ml ethyl acetate twice. The combined organic layers was washed with 50 ml water, and then dried with anhydrous magnesium sulfate. Colorless liquid (40.2 g) was obtained after filtering and recovering the solvent under a reduced pressure, which was used directly for the next reaction.

Optical rotation $[\alpha]^{20}_D$=−75.6°, C=2, ethanol.

^{1}H NMR ($CDCl_3$) δ ppm: 1.33 (q, 6H), 2.01 (s, 3H), 3.82

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