(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 January 2011 (06.01.2011)

PCT

(10) International Publication Number
WO 2011/001373 A1

(51) International Patent Classification:
C07D 217/18 (2006.01)

(21) International Application Number:
PCT/IB2010/052962

(22) International Filing Date:
29 June 2010 (29.06.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/IB2009/052835 30 June 2009 (30.06.2009) IB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

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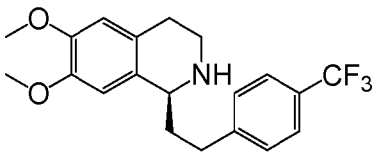
(54) Title: PROCESS FOR THE PREPARATION OF AN ENANTIOMERICALLY PURE TRISUBSTITUTED 1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVE



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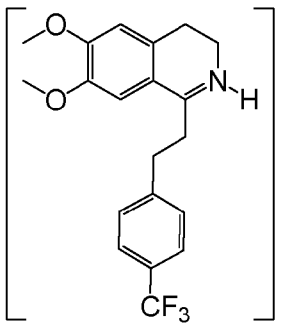

4 * HX

(57) Abstract: The present invention relates to a process for the preparation of the compound of formula 7, which process comprises: the asymmetric transfer hydrogenation of the compound of formula 4 * HX: wherein HX is as decribed in the description; in the presence of an optically active Noyori- type transfer hydrogenation catalyst, at a substrate to catalyst ratio of more than 100:1 mol equivalent; a reducing agent; and a solvent; to obtain the compound of formula 7.

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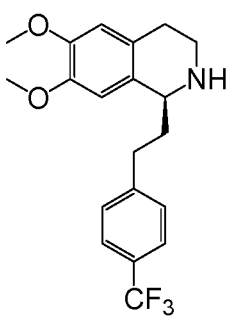
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

Process for the preparation of an enantiomerically pure trisubstituted 1,2,3,4-tetrahydroisoquinoline derivative

The present invention relates to a process for the preparation of the compound of formula 7 below starting from an iminium salt of formula 4 * HX below



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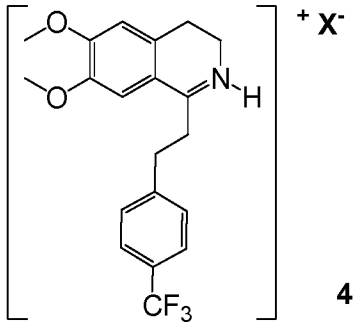
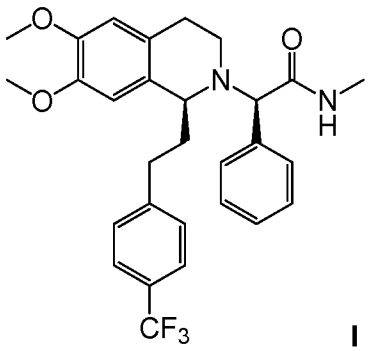


4 * HX .

The compound of formula 7 is useful in the preparation of (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide (almorexant), i.e. the compound of formula I drawn below, especially in form of the hydrochloride salt I * HCl,



I ,

which is known from WO2005/118548 and Nat. Med. (2007), **13**, 150-155 and which is especially useful as orexin receptor antagonist. It can be obtained through a multiple-step synthesis. The key intermediate in the synthesis of almorexant is the 1-substituted 1,2,3,4-tetrahydroisoquinoline derivative of formula 7. Accordingly, almorexant can be prepared by cyclisation of the respective N-phenethyl-propionamide derivative with $POCl_3$ leading to the imine of formula 4, followed by asymmetric transfer hydrogenation in the presence of a chiral Ru(II)-complex (Noyori catalyst, Uematsu et al. J. Am. Chem. Soc. 1996, **118**, 4916-4917) (see for example WO2005/118548, WO2004/085403) leading to the compound of formula 7, and coupling of the latter with the appropriate tosylate derivative. In WO2005/118548, the free imine was used as substrate to prepare the optically active

amines of formula 7. A further process which is a hydrogenation process using a different catalyst system and molecular hydrogen is disclosed in WO2009/083903 and WO2009/083899.

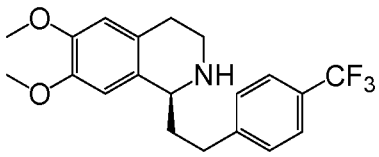
A drawback of the preparation process using the Noyori transfer hydrogenation process as described in the references cited above is that, especially when the process is performed using an appropriate substrate to catalyst ratio for industrial scale synthesis, relatively high amounts of side-product, such as the N-formylated optically active amine, may be formed. Thus, the above process may lead to unsatisfactory overall yields of the compound of formula 7, and in consequence, to unsatisfactory overall yields of the compound of formula I * HCl. In addition, the formation of side products may require more laborious purification steps.

It has now surprisingly been found that the compound of formula 7, and thus almorexant and its hydrochloride salt ("the compound of formula I*HCl"), can be manufactured in an improved way using the process of the present invention, wherein the substrate 4 in the asymmetric transfer hydrogenation reaction is a protonated imine, i.e. compound 4*HX.

Surprisingly, with the process of the invention the formation of side-product (the N-formylated optically active amine) is reduced significantly. For example the asymmetric transfer hydrogenation of the free imine 4 leading to full conversion may, depending on the reaction time, result in formation of > 10% N-formylated side-product (i.e. 6,7-Dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinoline-2-carbaldehyde), whereas the asymmetric transfer hydrogenation of the protonated imine according to the invention leading to full conversion may result in formation of less than 3% of the N-formylated side-product. In addition, it is an advantage of the process of the invention that when the substrate imine 4 is produced as a salt to ease purification, no separate process step is needed to remove the acid.

Various embodiments of the invention are presented hereafter:

i) In a first embodiment, the invention relates to a process for the preparation of the compound of formula 7



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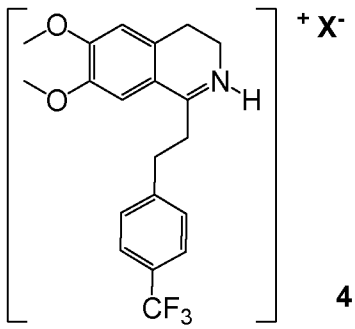
which process comprises:

the asymmetric transfer hydrogenation of the compound of formula 4 * HX:



4 * HX ,

wherein X^- represents the conjugate base of the acid HX; wherein the acid HX is selected from the group consisting of sulfuric acid, trifluoro acetic acid, methanesulfonic acid, benzene sulfonic acid, tetrafluoroboric acid and hydrochloric acid (in particular methanesulfonic acid);

in the presence of

- an optically active Noyori-type transfer hydrogenation catalyst (notably (R,R)-[*p*-($(CH_3)_2CH$)-C_6H_4-CH_3]RuH(NH_2-CHPh-CHPh-N-SO_2-C_6H_4-*p*-CH_3), or a precursor thereof,
- at a substrate to catalyst ratio of more than 100:1 mol equivalent;
- a reducing agent selected from the group consisting of formic acid, a mixture of formic acid and triethylamine, and sodium formate; and
- a solvent;

to obtain the compound of formula 7.

The acids HX that may be used in the process of the invention to form the protonated imine 4*HX have the common characteristic that they have a pK_a <3. It is well understood that equivalent acids having a pK_a < 3, said acids being well known to the skilled person, may also be used.

Suitable optically active Noyori-type transfer hydrogenation catalysts, or transfer hydrogenation catalysts that may alternatively be used in the above process, are known from A.J. Blacker, Chapter 35, in "The Handbook of Homogeneous Hydrogenation" (Ed. J.G. de Vries, C. J. Elsevier, Wiley, 2007), T. Ikariya and A.J. Blacker (Accounts Chem. Res. 2007, 40, 1300) and references therein, W. Baratta et al. (Chem. Eur. J. 2009, 15, 726) and references therein, or Wang et al. (Chemistry: an Asian Journal, 2008, 3, 1750). These transition-metal based catalysts are commercially available, prepared beforehand, or can be prepared in situ from any commercially available transition-metal complex (also known as precursors) and an optically active ligand as known for example from S. Gladiali and E. Alberico (Chem. Soc. Rev. 2006, 35, 226) and references therein.

Particularly suitable for the process of embodiment i) are optically active Noyori-type transfer hydrogenation catalysts comprising

- a transition metal selected from iridium, rhodium and notably ruthenium (introduced via suitable precursors such as dichloro (pentamethylcyclopentadienyl) iridium(III) dimer, or especially dichloro (pentamethylcyclopentadienyl) rhodium(III) dimer, or (notably) $[RuCl_2(p\text{-cymene})]_2$);
- an optically active mono-*N*-sulfonated ethan-1,2-diamine derived ligand [which may be cyclic (such as 1-sulfonamido-(2-amino)-cyclohexane derivatives, such as especially (R,R)-N-(2-amino-cyclohexyl)-4-methyl-benzene-sulfonamide); or which may notably be acyclic (such as 1-sulfonamido-(2-amino-1,2-diphenyl)-ethane derivatives; such as especially (R,R)-N-(2-amino-1,2-diphenyl-ethyl)-2,4,6-trimethyl-benzenesulfonamide, (R,R)-N-(2-amino-1,2-diphenyl-ethyl)-methanesulfonamide, (R,R)-N-(2-amino-1,2-diphenyl-ethyl)-camphorsulfonamide and notably (R,R)-TsDPEN ((R,R)-N-(2-amino-1,2-diphenyl-ethyl)-4-methyl-benzenesulfonamide: (R,R)-NH_2-CHPh-CHPh-NH-SO_2-C_6H_4-*p*-CH_3]; and
- an η^5-cyclopentadienyl-, or notably an η^6-arene coordinating ligand (such as pentamethylcyclopentadiene, benzene, trimethylbenzene, toluene, or notably p-cymene (*p*-((CH_3)$_2$CH)-C_6H_4-CH_3)).

Preferred is the Noyori catalyst (R,R)-[*p*-((CH_3)$_2$CH)-C_6H_4-CH_3]RuH(NH_2-CHPh-CHPh-N-SO_2-C_6H_4-*p*-CH_3), or precursors thereof (such as for example (R,R)-[*p*-((CH_3)$_2$CH)-C_6H_4-CH_3]RuCl(NH_2-CHPh-CHPh-N-SO_2-C_6H_4-*p*-CH_3), which is commercial or obtained e.g. from the reaction of $[RuCl_2(p\text{-cymene})]_2$ with the appropriate ligand (R,R)-NH_2-CHPh-CHPh-NH-SO_2-C_6H_4-*p*-CH_3).

Suitable reducing agents are well known in the field of transfer hydrogenation of imines. Frequently, such reducing agents are based on formic acid, such as especially formic acid; mixtures of formic acid and triethylamine; or formic acid salts, such as ammonium formate or alkali metal formates (in particular sodium or potassium formate); or mixtures thereof. Well known equivalents to such reducing agents based on formic acid are for example isopropanol or Hantzsch ester, which reducing agents, when used for the reduction of iminium substrates, may require particular reaction conditions and the use of an appropriate catalyst such as for example a Noyori-type transfer hydrogenation catalyst comprising iridium or rhodium and a η^5-cyclopentadienyl ligand (see), or an equivalent catalyst comprising for example an aminoethanol derived ligand. Such particular reaction conditions and alternative combinations of reducing agent and catalyst are well known to the skilled person (see A.J. Blacker, Chapter 35, in the Handbook of Homogeneous Hydrogenation (Ed. J.G. de Vries, C. J. Elsevier, Wiley, 2007) and references cited above).

Preferably, the reducing agent is a mixture of formic acid and triethylamine; or sodium formate. In case the reducing agent is a mixture of formic acid and triethylamine, it is notably triethylamine/formic acid (i.e. the ratio of formic acid and triethylamine is 1:1 eq.) or a mixture of formic acid and triethylamine/formic acid; such mixture is optionally formed *in situ* from formic acid and triethylamine. In a sub-embodiment, the ratio of formic acid and triethylamine is less than 5:2 mol eq., preferably less than 2:1 mol eq., more preferably less than 1.5:1 mol eq.. In one variant, the reducing agent is triethylamine/formic acid (i.e. the ratio of formic acid and triethylamine is 1:1 eq.). In another variant, in case the reducing agent is a mixture of formic acid and triethylamine, the ratio of formic acid and triethylamine is less than 1:1 mol eq., notably about 4:5 mol eq.. In another embodiment of the invention sodium formate is applied as reducing agent. Preferably, the amount of reducing agent (as counted from the hydrogen donor) is less than 5.8 mol eq. compared to mol eq. of substrate, more preferably less than 4 mol eq., even more preferably less than 3 mol eq.. In one embodiment of the invention a mixture of formic acid and triethylamine is applied as reducing agent, at a concentration of about 3 mol eq. or less (such as e.g. 2 mol eq.). Sodium formate is preferably applied at a concentration of about 3 mol eq. or less.

In the process of the invention, the substrate to catalyst ratio is more than 100:1 mol eq.. More preferably, the ratio of substrate to catalyst is more than 500:1. Even more preferably, this ratio is more than 1000:1, notably more than 2000:1. In particular, the ratio

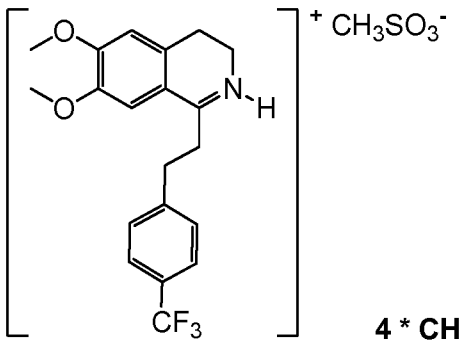
is between about 1000 and 3000, notably between about 1500 and 2500, especially about 2000.

Suitable solvents are for instance water, methanol, dichloromethane, isopropanol, methanol, ethylacetate, methylisobutylketone, toluene, 1,4-dioxane, acetonitrile, dimethylformamide, N-methylpyrrolidinone, 1,3-dimethyl-2-imidazolidinone, N,N-dimethylacetamide, 2,3,4,5-tetrahydrothiophene-1,1-dioxide, tetrahydrofuran, dimethylsulfoxide, sulfolane or mixtures thereof. Preferably, the solvent is water, methanol, dichloromethane, or any mixture thereof. In a sub-embodiment, the solvent is dichloromethane. In another sub-embodiment, the solvent is a mixture of water and methanol. In another aspect of the invention the reducing agent may also be the solvent, and has as such a double role.

In yet another embodiment of the invention, refluxing conditions are applied prior to the transfer hydrogenation reaction, or during the asymmetric transfer hydrogenation reaction, to remove undesired gases, such as oxygen, CO_2 and/or CO. Preferably, refluxing conditions are obtained by applying a small under-pressure (e.g. 200 to 800 mbar and preferably 400 to 500 mbar). Alternatively, the undesired gases can be removed by bubbling through any inert gas, e.g. nitrogen gas, or by applying an inert gas flow.

The product of the process of the invention (i.e. the compound of formula 7) can be isolated in a number of ways. In general once the reaction is complete, the reaction mixture is worked up by aqueous extraction(s) and the product can be either used as is (in solution) for further reactions, or crystallized as amine or crystallized as a suitable salt. Preferably, the secondary amine product is crystallized as amine or as suitable salt. More preferably, the secondary amine product of the asymmetric transfer hydrogenation of the invention is treated with acetic acid, as such precipitating the product as the amine acetic acid salt.

ii) Another embodiment relates to the process according to embodiment i), characterized in that the compound of formula 4 * HX is the compound of formula 4 * methanesulfonic acid (4 * CH_3SO_3H):



4 * CH_3SO_3H

In a sub-embodiment, the compound 4*CH_3SO_3H as used according to embodiment ii) in the process according to embodiment i) is isolated from toluene or a mixture of toluene and acetone.

iii) Another embodiment relates to the process according to embodiments i) or ii), characterized in that the optically active Noyori-type transfer hydrogenation catalyst comprises a transition metal selected from iridium, rhodium and notably ruthenium; an optically active mono-*N*-sulfonated ethan-1,2-diamine derived ligand; and an η^5-cyclopentadienyl-, or notably an η^6-arene coordinating ligand.

iv) Another embodiment relates to the process according to any one of embodiments i) to iii), characterized in that the η^5-cyclopentadienyl- or η^6-arene coordinating ligand is selected from the group consisting of pentamethylcyclopentadiene, benzene, trimethylbenzene, toluene, and notably p-cymene (*p*-$((CH_3)_2CH)$-C_6H_4-CH_3).

v) Another embodiment relates to the process according to any one of embodiments i) to iv), characterized in that the transition metal and the η^5-cyclopentadienyl- or η^6-arene coordinating ligand of the optically active Noyori-type transfer hydrogenation catalyst are introduced via dichloro (pentamethylcyclopentadienyl) iridium(III) dimer, or especially dichloro (pentamethylcyclopentadienyl) rhodium(III) dimer, or (notably) $[RuCl_2(p\text{-cymene})]_2$.

vi) Another embodiment relates to the process according to any one of embodiments i) to v), characterized in that the optically active mono-*N*-sulfonated ethan-1,2-diamine derived ligand is (R,R)-N-(2-amino-cyclohexyl)-4-methyl-benzene-sulfonamide, (R,R)-N-(2-Amino-1,2-diphenyl-ethyl)-2,4,6-trimethyl-benzenesulfonamide, (R,R)-N-(2-Amino-1,2-diphenyl-ethyl)-methanesulfonamide, (R,R)-N-(2-Amino-1,2-diphenyl-ethyl)-camphorsulfonamide,

or notably (R,R)-TsDPEN ((R,R)-N-(2-Amino-1,2-diphenyl-ethyl)-4-methyl-benzenesulfonamide: (R,R)-NH_2-CHPh-CHPh-NH-SO_2-C_6H_4-*p*-CH_3) [In particular, the ligand is (R,R)-N-(2-Amino-1,2-diphenyl-ethyl)-2,4,6-trimethyl-benzenesulfonamide, (R,R)-N-(2-Amino-1,2-diphenyl-ethyl)-methanesulfonamide, (R,R)-N-(2-Amino-1,2-diphenyl-ethyl)-camphorsulfonamide, or notably (R,R)-TsDPEN ((R,R)-N-(2-Amino-1,2-diphenyl-ethyl)-4-methyl-benzenesulfonamide: (R,R)-NH_2-CHPh-CHPh-NH-SO_2-C_6H_4-*p*-CH_3)].

vii) Another embodiment relates to the process according to any one of embodiments i) to vi), characterized in that the optically active Noyori-type transfer hydrogenation catalyst is (R,R)-[*p*-((CH_3)$_2$CH)-C_6H_4-CH_3]RuH(NH_2-CHPh-CHPh-N-SO_2-C_6H_4-*p*-CH_3), or a precursor thereof.

viii) Another embodiment relates to the process according to any one of embodiments i) to vii), characterized in that the solvent is dichloromethane.

ix) Another embodiment relates to the process according to any one of embodiments i) to vii), characterized in that the solvent is a mixture of water and methanol.

x) Another embodiment relates to the process according to any one of embodiments i) to viii), characterized in that the reducing agent is triethylamine/formic acid, or a mixture of formic acid and triethylamine/formic acid.

xi) Another embodiment relates to the process according to any one of embodiments i) to viii), characterized in that the reducing agent is a mixture of formic acid and triethylamine wherein the ratio of formic acid and triethylamine is less than 5:2 mol eq..

xii) Another embodiment relates to the process according to any one of embodiments i) to viii), characterized in that the reducing agent is a mixture of formic acid and triethylamine, wherein the ratio of formic acid and triethylamine is less than 2:1 mol equivalent (notably less than 1.5:1 mol equivalent). In a sub-embodiment, the ratio is less than 1:1 mol eq., notably about 4:5 mol eq..

xiii) Another embodiment relates to the process according to any one of embodiments i) to viii), characterized in that the reducing agent is triethylamine/formic acid (i.e. the ratio of formic acid and triethylamine is 1:1 mol equivalent).

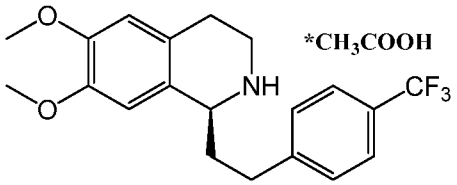
xiv) Another embodiment relates to the process according to any one of embodiments i) to vii) or ix), characterized in that the reducing agent is sodium formate.

xv) A process according to any one of embodiments i) to xiv), characterized in that the amount of reducing agent is less than 4 mol equivalents compared to mol equivalent of

substrate (in one sub-embodiment less than 3 mol equivalents, in another sub-embodiment about 3 mol equivalents).

xvi) Another embodiment relates to the process according to any one of embodiments i) to xv), characterized in that the ratio of substrate to catalyst is more than 500:1 (notably more than 1000:1; especially between about 1000 and 3000, and notably between about 1500 and 2500).

xvii) Another embodiment relates to the process according to any one of embodiments i) to xvi), characterized in that the compound of formula 7 is isolated as compound of formula 7*CH_3COOH:



7*CH_3COOH .

xviii) Another embodiment relates to the process according to any one of embodiments i) to xvii), wherein the compound of formula 7 is further transformed to (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide, or a salt thereof (especially the hydrochloride salt thereof).

The following paragraphs provide definitions of the various chemical moieties for the compounds according to the invention or of other terms used herein and are intended to apply uniformly throughout the specification and claims, unless an otherwise expressly set out definition provides a different definition:

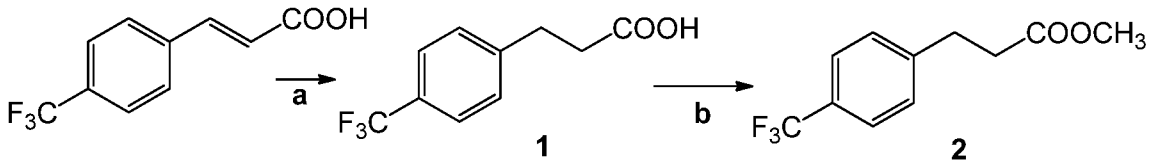
Whenever the symbol "*" is followed by the expression "acetate", "mesylate", "HCl", "CH_3SO_3H" or "CH_3COOH", it denotes the corresponding salt of the compound after which this combination is placed. For example, the expression "the compound of formula 4*mesylate" is the same as 4*CH_3SO_3H and denotes the methanesulfonic acid salt of the compound of formula 4.

The abbreviations "aq.", "ee", "eq.", "mol%", "wt%", and RT refer respectively to the aqueous, enantiomeric excess of an enantiomeric mixture, equivalent(s), to the molar percentage of a component in a mixture, to the weight percentage of a component in a mixture, and to room temperature. The abbreviation "MIBK" refers to methylisobutylketone. "DCM" refers to dichloromethane.

Unless used regarding temperatures, the term “about” placed before a numerical value “X” refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term “about” placed before a temperature “Y” refers in the current application to an interval extending from the temperature Y minus 10°C to Y plus 10°C, and preferably to an interval extending from Y minus 5°C to Y plus 5°C. For example room temperature (RT) refers to about 25°C.

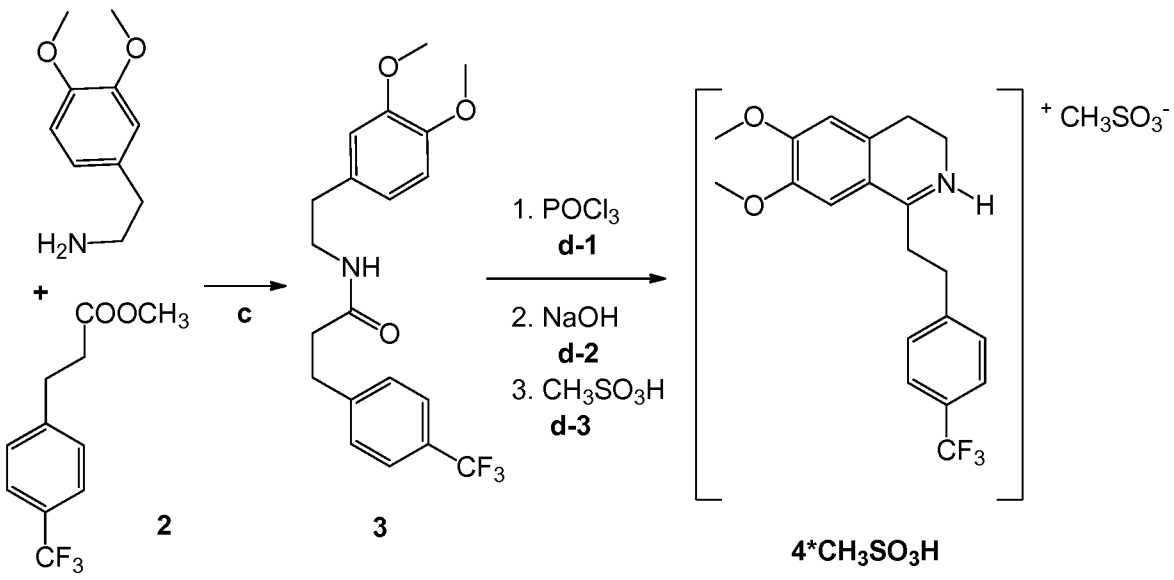
The present invention is further described by reaction schemes 1-5.

Reaction scheme 1:



In step a of the reaction, commercially available 4-trifluoromethylcinnamic acid is hydrogenated (e.g. in methanol at 2 bar hydrogen pressure, in the presence of 2 wt% Pd/C, having 5% Pd on charcoal at 15 to 25°C), to obtain compound of formula 1. In step b of the reaction, the compound of formula 1 is reacted with methanol (e.g. in the presence of 5 mol% H_2SO_4, at the boiling point of the mixture) to obtain the corresponding ester of formula 2. In a preferred embodiment of the reaction, the compound of formula 1 is not isolated after step a (only the catalyst is removed by filtration), and the reaction is continued with step b.

Reaction scheme 2:



In step c of the reaction, compound of formula 2 is reacted with commercially available 2-(3,4-dimethoxy-phenyl)-ethylamine (e.g. 30% sodium methoxide in methanol, toluene, 100°C) to obtain the compound of formula 3.

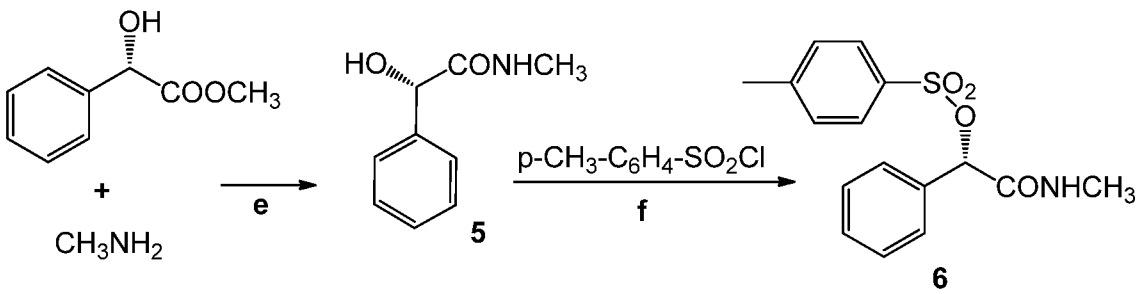
In step d-1 of the reaction, the compound of formula 3 is reacted e.g. in the presence of phosphorus oxychloride in an amount of 0.5 to 1.5 eq. (notably 0.7 to 1.0 eq.) per eq. of compound of formula 3 to obtain the compound of formula 4*HCl (said compound is a mixture of phosphorus imine salts and/or chlorophosphorous imine salts). Suitable solvents are aromatic solvents such as benzene, xylene, mesitylene, or toluene (preferably toluene), and a suitable reaction temperature is between 60 to 120°C (notably 80 - 110°C). In subsequent step d-2 of the reaction, the reaction mixture of step d-1 is reacted with a solution of an alkaline hydroxide (preferably a sodium hydroxide solution), to obtain the compound of formula 4.

In step d-3 of the reaction, the reaction mixture of step d-2 is reacted with methanesulfonic acid (preferably 0.9 – 1.5 eq.; particularly 1.0 – 1.2 eq.) to obtain the compound of formula 4*mesylate. The reaction is carried out at a reaction temperature from -5 to 60°C, preferably between 0 to 40 °C, in another embodiment preferably 0 to 10°C. Suitable solvent systems for the crystallization of compound 4*mesylate are aromatic solvents (notably toluene) and ketones (notably acetone) as well as mixtures thereof.

The technical advantages of step d-3, compared to the prior art, are the following:

- The surprising advantage of the 4*mesylate compound (as compared to the HCl analogue) is that it precipitates in high yield and sufficient purity for the subsequent enantioselective transfer hydrogenation; notably from solvents like toluene, acetone or mixtures thereof. As a consequence, the 4*mesylate can be used directly in the subsequent step.
- There is only one precipitation and isolation necessary yielding to good product quality, and improvement of the process and reduction of unit steps is achieved.

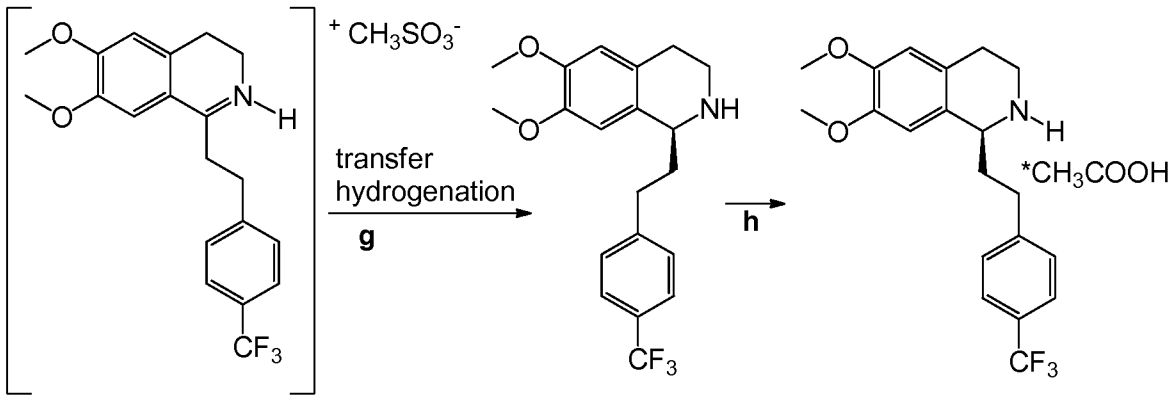
Reaction scheme 3:



In step e of the reaction, commercially available methylamine is reacted with commercially

available methyl (*S*)-mandelate to obtain the compound of formula 5 (e.g. 3.8 eq. methylamine, 30% in aqueous solution, at 0 to 10°C). After the reaction has been judged complete, excess methylamine may for example be distilled off at reduced pressure. In step f of the reaction, the compound of formula 5 is reacted with *p*-toluene sulfonic acid chloride in the presence of a base such as N-ethyldiisopropylamine (e.g. 1.0 eq. *p*-toluene sulfonic acid chloride and 1.1 eq. N-ethyldiisopropylamine in DCM at 5 to 30°C, preferably below 25°C), to obtain the compound of formula 6. Alternatively, a base like aqueous sodium hydroxide may be used. In a preferred embodiment of the invention, after a solvent switch to ethyl acetate the solution is concentrated, cooled to –2 °C and the precipitate is filtered. Alternatively, toluene may be used in the above procedure and the solution is cooled to 0 to 10°C.

Reaction scheme 4:



In step g of the reaction, the compound of formula 4 * HX, especially 4*mesylate is hydrogenated in the presence of a chiral transfer hydrogenation catalyst, especially an optically active Noyori-type transfer hydrogenation catalyst); a reducing agent, especially a formic acid based reducing agent; and a solvent, to yield the compound of formula 7.

Said catalysts or their precursors are commercially available, prepared beforehand, or prepared in situ, from a commercially available Ru, Ir and Rh complex (also known as precursor complex), and a commercially available chiral ligand, especially an optically active mono-*N*-sulfonated ethan-1,2-diamine derived ligand using methods well known in the art.

The preferred chiral transfer hydrogenation catalyst of the invention is the optically active Noyori catalyst (R,R)-[*p*-((CH$_3$)$_2$CH)-C$_6$H$_4$-CH$_3$]RuH(NH$_2$-CHPh-CHPh-N-SO$_2$-C$_6$H$_4$-*p*-CH$_3$), or a precursor thereof {such as (R,R)-[*p*-((CH$_3$)$_2$CH)-C$_6$H$_4$-CH$_3$]RuCl(NH$_2$-CHPh-CHPh-N-SO$_2$-C$_6$H$_4$-*p*-CH$_3$)}.

The amount of catalyst compared with the amount of substrate is preferably as low as possible. In practice for industrial production, molar substrate to catalyst ratio's are preferably at least 1000.

The transfer hydrogenation reaction is carried out at a temperature between -10°C and 100°C, preferably between 10°C and 75°C and more preferably between 15 and 35°C.

Particular solvents for the transfer hydrogenation reaction are water, methanol, DCM or any mixture thereof. In case a mixture of formic acid and triethylamine is applied as reducing agent, DCM is preferably used as solvent. However, such combination may lead to the formation of a potentially genotoxic side product: chloromethyl-triethylammonium chloride. In addition, the presence of said side product may require more laborious purification steps. DCM may also cause formation of side products derived from its reaction with the amine of formula 7. Formation of DCM related side products may be avoided by using a mixture of methanol and water as solvent, preferably using sodium formate as reducing agent.

The technical advantages of step g, compared to the prior art (e.g. Uematsu et al. J. Am. Chem. Soc. 1996, 118, 4916-4917 and WO2005/118548), are the following:

- The substrate 4 * HX, especially 4*mesylate is used directly in the transfer hydrogenation reaction without prior free-basing of the imine. Thus, reduction of unit steps (free-basing step) is achieved.
- The process of the prior art using the free imine substrate (compound of formula 4) leads, when done on industrially applicable scale (i.e. using a suitable substrate to catalyst ratio), to the formation of N-formyl side-products. Formation of such side products can be reduced when the compound of formula 4 * HX, especially 4*mesylate is used as substrate.
- Formation of side-products may necessitate an additional purification step. In such case, reduction of unit steps (isolation of the compound of formula 7) is achieved.
- The optical purity of the isolated compound of formula 7*acetate (steps g and h) is surprisingly high, ee of > 99%.
- Additionally, in large scale quantities, the process of the present invention gives reproducible ee.
- The process of the present invention is high yielding.

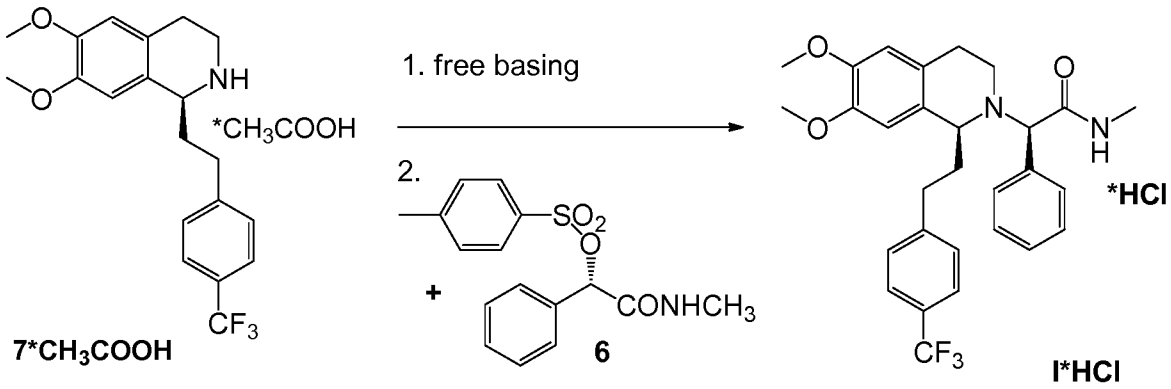
In step h of the reaction, the compound of formula 7 is reacted with acetic acid, to obtain the compound of formula 7*acetate. The reaction is carried out in a suitable solvent, such as any aromatic solvent (such as benzene, toluene and/or xylene) or mixture of aromatic

solvents and distillation fractions containing mainly heptane. Preferably toluene and pure heptane are used. More preferred is a 4 to 1 mixture of toluene and heptane. The reaction is carried out at a reaction temperature between -10 to 55°C preferably between 0 and 20 °C. The reaction is carried out with 0.9 to 1.3 eq. of acetic acid, more preferred with 1.0 eq. of acetic acid.

Due to the unfavourable compound properties of enantiomeric 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline hydrochloride, the enantiomeric pure synthesis is limited. Surprisingly, the acetic acid salt of 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline (compound 7*CH_3COOH) has improved compound properties, that enables the enantiomeric pure synthesis. Additionally, based on the improved compound properties of the compound 7*CH_3COOH a more complete crystallisation of the acetate salt is achieved, and therefore a higher yield is obtained; compared to the hydrochloride salt the eutectics were surprisingly shifted by the choice of a suitable salt (like the acetic acid salt) and solvent (aromatic solvent, e.g. toluene) towards the desired direction.

The subsequent steps to produce almorexant, i.e. the compound of formula I*HCl are shown in Scheme 5 below.

Reaction scheme 5:



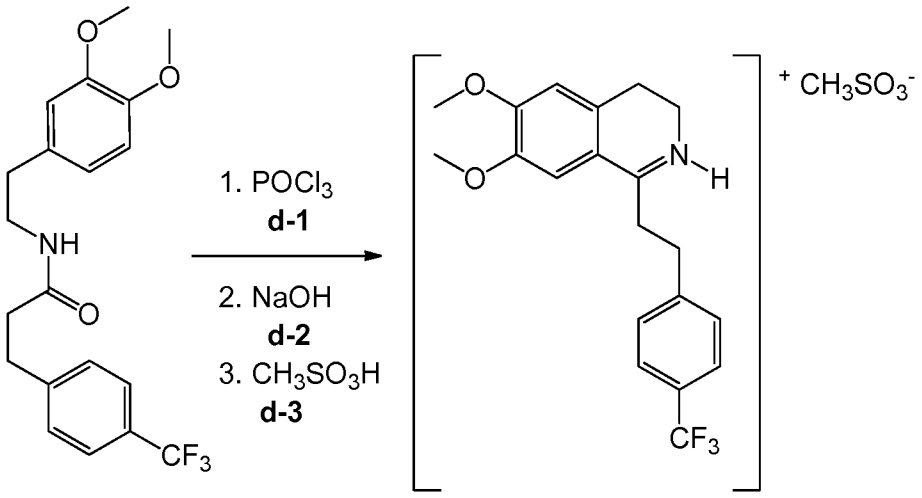
Free basing is preferably performed with an aqueous solution of sodium hydroxide. Suitable solvents are acetone, ethyl methyl ketone, tert.-butyl methyl ether, DCM, or MIBK, preferably MIBK. The reaction is carried out at a reaction temperature between 0-50°C, preferably between 15-25°C. The coupling with the compound of formula 6 is carried out with 1.1-2.0 eq. (preferably 1.2 eq.) of compound of formula 6. Appropriate bases are Li_2CO_3, Cs_2CO_3, the corresponding bicarbonates, caustic soda, potassium carbonate, and mixtures thereof. In a preferred embodiment, caustic soda is used in an

amount of 0-2.2 eq. (more preferred 1.2 eq. of caustic soda), and potassium carbonate is used in an amount of 0-2.2 eq. (more preferred 1.2 eq. of potassium carbonate). Suitable solvents are MIBK, tert.-butyl methyl ether or DCM (preferably MIBK). The reaction is carried out at a reaction temperature between 30-120°C, preferably between 70-90 °C. Preferably, the compound of formula I*HCl is formed by reaction with 0.95-1.1 eq. (preferably 1.0 eq.) of aqueous hydrochloric acid.

Experimental Part:

Particular embodiments of the invention are described in the following examples, which serve to illustrate the invention in more detail without limiting its scope in any way. The compounds 3 and 6 may be synthesized according to WO2005/118548 as outlined above.

Steps d-1 to d-3: Synthesis of 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-isoquinoline methanesulfonic acid (compound 4*mesylate)

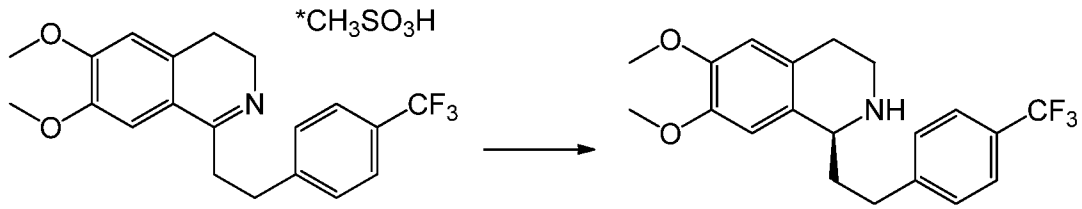


3 **4*CH_3SO_3H**

The compound 3 is suspended in toluene and heated to 80 - 100 °C. After addition of 1.5 eq. phosphorus oxychloride the mixture is heated for 6 hours to 80 - 100 °C and then cooled within 3 hours to 20 °C. The suspension is added to water while maintaining the pH of the aqueous layer during addition and subsequent stirring between 7-8 by addition of a sodium hydroxide solution. The mixture is stirred until all precipitate is dissolved. After phase separation the water is removed by azeotropic distillation. Then 1.0 eq. of methanesulfonic acid is added and the formed suspension stirred for some time. At this point parts of the solvent may be replaced by acetone, and the mixture is slowly cooled to

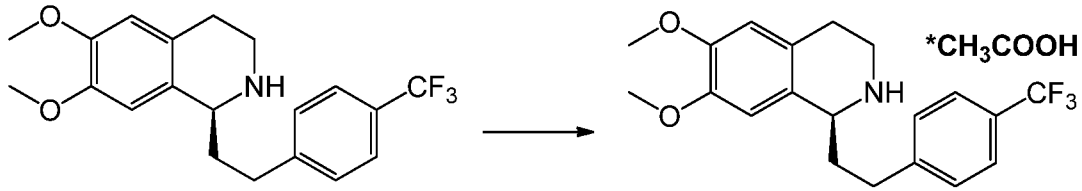
0 – 10 °C and stirred at this temperature for another couple of hours. After filtration the product is washed with toluene and dried in vacuo.

Step g: Synthesis of (*1S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline (compound 7)



4*CH_3SO_3H **7**

Step h: Synthesis of (*1S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline acetic acid salt (compound 7*CH_3COOH)



7 **7*CH_3COOH**

Reference Example:

6,7-Dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-isoquinoline (compound **4**, free base) (32 kg, 88 mol) is dissolved in DCM (497 L) and concentrated under vacuum to a volume of approximately 160 L. A solution of the Noyori catalyst {prepared from (R,R)-TsDPEN (64g), dichloro-bis-(p-cymene)ruthenium(III) (53.9 g) in acetonitrile (6 L), and addition of triethylamine (98 mL), followed by reflux (80°C) for 1 hour, then cooling to RT} is added, followed by a mixture of triethylamine and formic acid (45 L) {prepared from formic acid (5 eq., 28.2 L) and triethylamine (2 eq.) at a temperature below 15°C}, and the mixture is stirred at 20°C for ca. 60 hours. After dilution and aqueous work-up (aq. $NaHCO_3$ and stirring with water) (intermediate analysis indicates an enantiomeric ratio of 88:12 and an amount of 16-18% of N-formyl impurity, i.e. 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinoline-2-carbaldehyde) the solvent is switched to methanol (148 L) and HCl in isopropanol (5-6 N, 12 L) is added at a temperature of 40°C to yield after addition of isopropanol (85 L) and cooling to 0°C 31.8 kg of wet crude material with a chiral purity of 92:8 and a chemical purity of 92%.

Purification {slurry in methanol (140 L) at 45°C and cooling to 20°C, filtration} leads to 23.5 kg of wet product with chemical and optical purity >99%.

Example 1:

Step g: DCM and formic acid are charged and cooled to 0-10°C. Triethylamine is dosed slowly to keep the temperature below 15°C. The resulting mixture is stirred for one hour at 20-25°C. 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-isoquinoline methanesulfonic acid salt (compound **4***CH_3SO_3H) is charged and the reaction mixture is degassed at reflux. The solution is cooled to RT and the Noyori catalyst precursor ((R,R)-[*p*-((CH_3)$_2$CH)-C_6H_4-CH_3]RuCl(NH_2-CHPh-CHPh-N-SO_2-C_6H_4-*p*-CH_3)) is charged (typical conditions are for example: 3 eq. triethylamine/formic acid (1:1); substrate to catalyst ratio: 1500:1 to 2000:1) under inert conditions. The mixture (8-9 wt% substrate) is stirred for 15-20h until full conversion is obtained (max. 2% remaining substrate, typically ~5% N-formyl impurity, i.e. 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinoline-2-carbaldehyde). Workup (7 wt %): Water is added and phases are separated, the aqueous layer is discarded. To the organic layer sodium bicarbonate solution is added, stirred and phases are separated again, the aqueous layer is discarded. The organic phase is extracted a third time with water.

Step h: Solvent is switched from DCM to toluene and the concentration is adjusted to 12 wt%. Afterwards, heptane is added to target at 4:1 mixture of toluene to heptane, 9-10 wt%. The product (*1S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline acetic acid salt (compound 7*CH_3COOH) is precipitated by addition of 1eq. of concentrated acetic acid at 20°C. The resulting product suspension is stirred for 2-3 hours at 20°C, filtered off and washed with heptane. The wet product is dried under reduced pressure at 40°C. Isolated Yield: about 80%.

Side reactions / by-products: (R)-Enantiomer, is depleted during crystallization step. N-Formyl impurity: typically ~5 area% of N-formyl impurity is formed. This impurity is well depleted during work up.

Example 2:

Step g: 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-isoquinoline methanesulfonic acid salt (compound **4***CH_3SO_3H) (40 g) is added at RT to DCM (120 g), followed by formic acid (8 g, 2 eq.). The solution is cooled to 0-10°C. Triethylamine (22 g, 2.5 eq.) is dosed slowly to keep the temperature below 15°C. The resulting mixture is warmed up to 25-30°C and stirred for 10 minutes under vacuum (500 mbar) at 25-30°C. The flask is charged with nitrogen and the Noyori catalyst precursor ((R,R)-[*p*-((CH_3)$_2$CH)-

C_6H_4-CH_3]RuCl(NH_2-CHPh-CHPh-N-SO_2-C_6H_4-*p*-CH_3)) is charged (27 mg, substrate to catalyst ratio: 2000:1) as a solution in degassed DCM (0.5 mL). The mixture is stirred at 25-30°C under reflux (450-550 mbar) until full conversion is obtained and then cooled to RT.

Intermediate process control shows 1-2% of N-formyl impurity.

Workup: Water is added and the mixture is stirred vigorously for 30 minutes at RT, phases are separated, the aqueous layer is discarded. To the organic layer sodium bicarbonate solution (35 g) is added, the mixture stirred and phases are separated again, the aqueous layer is discarded.

Step h: Solvent is switched from DCM to toluene and the concentration is adjusted. The product (*1S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline acetic acid salt (compound 7*CH_3COOH) is precipitated by addition of concentrated acetic acid (4.96 g, 0.95 eq.) at 20-30°C. The resulting mixture is stirred for 1 hour at RT, then cooled to 10-20°C and further stirred. The product is filtered off and washed with toluene. The wet product is dried under reduced pressure at 40°C.

Example 3:

Step g: 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-isoquinoline methanesulfonic acid salt (compound **4***CH_3SO_3H) (0.8 - 1.2 kg) is mixed at RT with methanol (1.0 - 2.1 kg), followed by water (0.85 - 2.0 kg) and formic acid sodium salt (0.18 - 0.75 kg). The solution is warmed to 25-45°C and the Noyori catalyst precursor ((R,R)-[*p*-((CH_3)$_2$CH)-C_6H_4-CH_3]RuCl(NH_2-CHPh-CHPh-N-SO_2-C_6H_4-*p*-CH_3)) (0.46 - 1.37 g, substrate to catalyst ratio of 1000-3000) is charged as a solution in methanol (0.5 - 3 w%). The mixture is stirred at 25-45°C, optionally under reflux, for up to 72 hours (leading to a loss of methanol/water of 0-30%).

Intermediate process control shows a maximum of 10area% of **4***CH_3SO_3H and N-formyl impurity at low level, in general <0.1%. No DCM related side products are formed as no DCM is present.

0-2.1 L of methanol/water per kg **4***CH_3SO_3H are distilled off. Then the mixture is cooled to 10-40°C. Workup: Toluene (2.5 - 4.5 kg per kg **4***CH_3SO_3H) and 50% aqueous NaOH (0.05 - 0.2 kg per kg **4***CH_3SO_3H) are added and the mixture stirred at RT, phases are separated, and the organic layer washed with water (1 - 5 times 0.5 - 2.0 kg water per kg **4***CH_3SO_3H). Water is removed by azeotropic distillation at 20-70°C and the concentration is adjusted to 8 - 18 wt% of compound **7**.

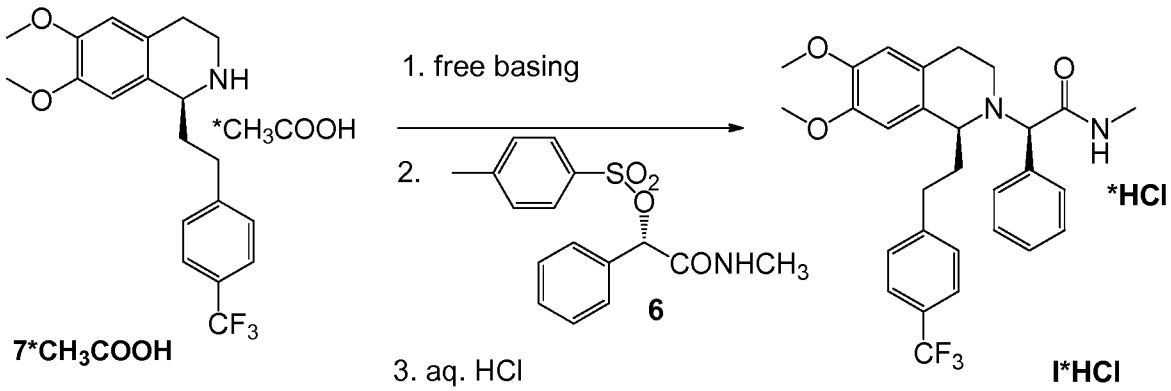
Step h: The product (*1S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline acetic acid salt (compound 7*CH_3COOH) is precipitated by addition of concentrated acetic acid (0.09 - 0.17 kg per kg **4***CH_3SO_3H) at 0-40°C. The resulting mixture is stirred for 0 - 48 hours at RT, then cooled to 10°C and further stirred for 0 to 48 hours. The product is filtered off and washed with toluene (0 - 3 kg per kg **4***CH_3SO_3H). The wet product is dried, optionally under reduced pressure, at 20-70°C.

Example 4:

Step g: 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-isoquinoline methanesulfonic acid salt (compound **4***CH_3SO_3H) (210 g) is mixed at RT with methanol (367 g), followed by a solution of formic acid sodium salt (94 g, 3 eq.) in water (262 g). The solution is warmed to 35°C and the Noyori catalyst precursor ((R,R)-[*p*-((CH_3)$_2$CH)-C_6H_4-CH_3]RuCl(NH_2-CHPh-CHPh-N-SO_2-C_6H_4-*p*-CH_3)) is charged (144 mg, substrate to catalyst ratio: 2000:1) as a solution in methanol (10 mL). The mixture is stirred at 35°C under reflux (reduced pressure) until full conversion is obtained and a total of approximately 150 mL of solvent has been distilled off. Then the mixture is cooled to RT. Workup: Toluene (761 g) and 50% aqueous NaOH (21 g) are added and the mixture stirred for 30 minutes at RT, phases are separated, and the organic layer washed with water (2 x 210 g). Water is removed by azeotropic distillation and the concentration is adjusted.

Step h: The product (*1S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline acetic acid salt (compound 7*CH_3COOH) is precipitated by addition of concentrated acetic acid (27.3 g, 1 eq.) at 20-30°C. The resulting mixture is stirred for 2 hour at RT, then cooled to 10°C and further stirred. The product is filtered off and washed with toluene. The wet product is dried under reduced pressure at 40°C.

Synthesis of (*2R*)-2-{(*1S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide hydrochloride (compound I hydrochloride)



1. To a suspension of compound 7*CH_3COOH in MIBK is added sodium hydroxide solution (20%) and stirred at RT until the precipitate is dissolved. After phase separation, the organic layer is washed with water. After removal of the water from the organic phase by azeotropic distillation, the solution is diluted with MIBK to a concentration of 9 – 16%.

2. To the solution of the compound 7 in MIBK are added 1.2 eq. of the compound 6, 1.1 eq. caustic soda and 1.1 eq. potassium carbonate and heated to 70-90 °C. Water is added and the mixture is heated at the same temperature for 0.5 to 3 hours and then cooled to RT. Alternatively, after full conversion the solution is cooled to RT and water is added. Phase separation is followed by a second washing of the organic phase with water and again phase separation.

3. To the organic phase of step 2 is added 1 eq. aqueous hydrochloric acid and then the water removed by azeotropic distillation *in vacuo*.

Then, either:

- The precipitate is dissolved by addition of 2-propanol at 75 °C. Concentration of the solution leads to crystallisation and the suspension is then cooled to RT. To ensure complete crystallisation, the suspension is aged at RT, then filtered and washed with a MIBK - 2-propanol mixture.

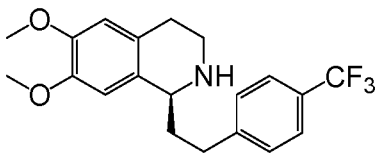
or:

- The compound I *HCl is obtained by crystallization from the organic phase of step 2 (MIBK) containing an adjusted amount of residual water (0.4 - 1.5%, e.g. 0.7%) without using 2-propanol at a temperature of above 40°C (e.g. about 65°C) using seeding crystals.

The product is isolated e.g. on an inverting bag centrifuge and dried *in vacuo* at 50°C.

Claims

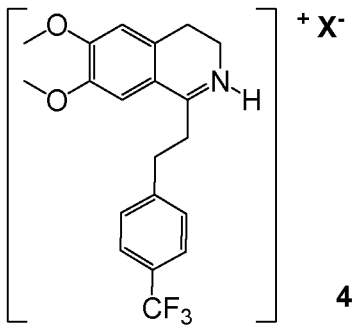
1. Process for the preparation of the compound of formula 7



7

which process comprises:

the asymmetric transfer hydrogenation of the compound of formula 4 * HX:



4 * HX ,

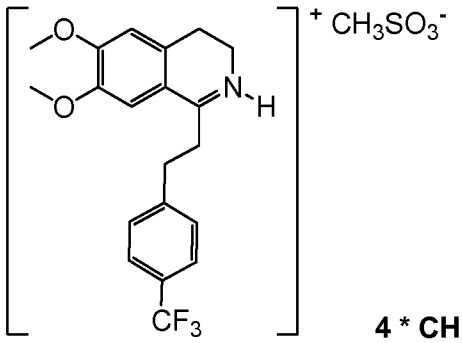
wherein X^- represents the conjugate base of the acid HX; wherein the acid HX is selected from the group consisting of sulfuric acid, trifluoro acetic acid, methanesulfonic acid, benzene sulfonic acid, tetrafluoroboric acid and hydrochloric acid;

in the presence of

- an optically active Noyori-type transfer hydrogenation catalyst, or a precursor thereof,
- at a substrate to catalyst ratio of more than 100:1 mol equivalent;
- a reducing agent selected from the group consisting of formic acid, a mixture of formic acid and triethylamine, and sodium formate; and
- a solvent;

to obtain the compound of formula 7.

2. The process according to claim 1, characterized in that the compound of formula 4 * HX is the compound of formula 4 * methanesulfonic acid (4 * CH_3SO_3H):



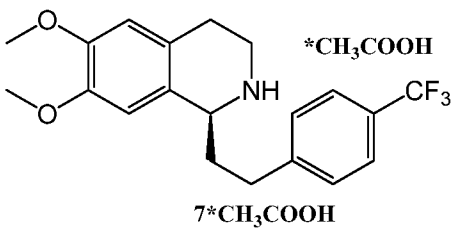
4 * CH_3SO_3H

3. The process according to claims 1 or 2, characterized in that the optically active Noyori-type transfer hydrogenation catalyst is (R,R)-[*p*-((CH_3)$_2$CH)-C_6H_4-CH_3]RuH(NH_2-CHPh-CHPh-N-SO_2-C_6H_4-*p*-CH_3), or a precursor thereof.

4. The process according to any one of claims 1 to 3, characterized in that the solvent is water, methanol, dichloromethane or any mixture thereof.

5. The process according to any one of claims 1 to 4, characterized in that the reducing agent is a mixture of formic acid and triethylamine; or sodium formate.

6. The process according to any one of claims 1 to 5, characterized in that the compound of formula 7 is isolated as compound of formula 7*CH_3COOH:



7*CH_3COOH

7. Process according to any one of claims 1 to 6, wherein the compound of formula 7 is further transformed to (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide, or a salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/052962

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D217/18
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/118548 A1 (ACTELION PHARMACEUTICALS LTD [CH]; WELLER THOMAS [CH]; KOBERSTEIN RALF) 15 December 2005 (2005-12-15) cited in the application Page 9, lines 20-22example G2.1	1-7
Y	WO 00/18708 A1 (AVECIA LTD [GB]; BLACKER ANDREW JOHN [GB]; CAMPBELL LYNNE [GB]) 6 April 2000 (2000-04-06) Page 2, lines 10-11. Page 4, lines 20-25. Page 6, lines 10-34. Page 10, lines 9-13.claims 1-14; examples 1-6	1-7
Y	WO 03/095426 A1 (YUN-CHOI HYE-SOOK [KR]; CHANG KI CHURL [KR]; LEE DUCK HYUNG [KR]) 20 November 2003 (2003-11-20) Step 3. Page 23, lines 21-23.claim 4	1-7

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 September 2010	09/09/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Von Daacke, Axel

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/052962

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2009/083899 A2 (ACTELION PHARMACEUTICALS LTD [CH]; BAPPERT ERHARD [CH]; DE VRIES ANDRE) 9 July 2009 (2009-07-09) cited in the application Page 2, line 20 - page 3, line 4. Page 8, lines 17-21.	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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