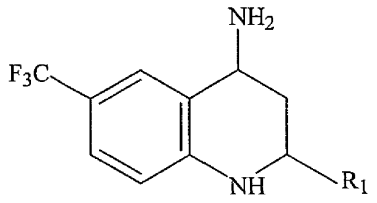
dosages than had to be used for other CETP-inhibitors. Moreover, clinical studies have also shown that Compound A is well tolerated and that it does not lead to serious side effects.

For the preparation of tetrahydroquinoline derivatives, such as Compound A, use has been made of the intermediates according to formula I



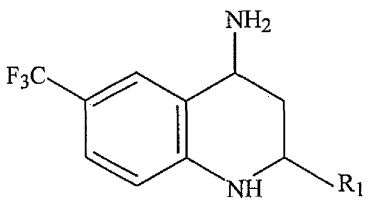
formula I

Although these kinds of intermediates are very useful in the preparation of tetrahydroquinoline derivatives, such as Compound A, with the current methods for preparing these kinds intermediates, such as described in WO2007/116922, the overall yield is relatively low. Moreover relatively expensive starting materials and catalysts have to be used, such as (*R*)-3-aminovaleric acid and palladium, respectively. Furthermore, in the current methods of manufacturing problems arise with residual fluorine corroding manufacturing equipment.

Hence, a need exists for an efficient and cost effective process for preparing intermediates according to formula I, which may be used in the further preparation of tetrahydroquinoline derivatives having CETP inhibiting properties, such as Compound A.

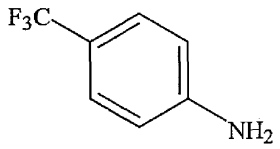
SUMMARY

A first aspect of the present invention relates to a process for preparing the racemic compound of formula I or a salt thereof:



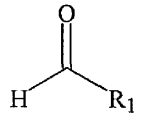
formula I

comprising the steps of: (a) simultaneously reacting 4-aminobenzotrifluoride according to formula II



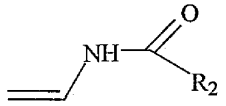
formula II

with an aldehyde according to formula III



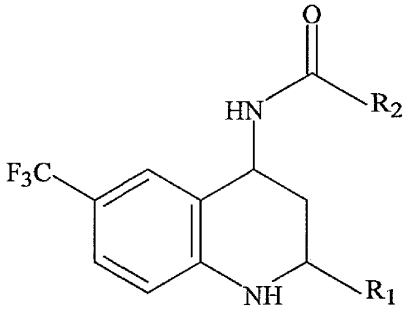
formula III

and with a compound according to formula IV



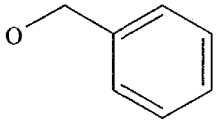
formula IV

in the presence of a solvent and optionally one or more catalysts to form the racemic compound of formula V

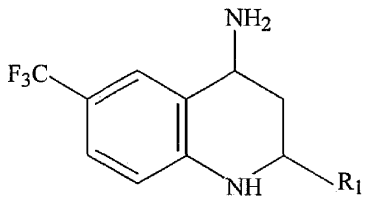


formula V

wherein
R_1 is H or C_1-C_3 alkyl, preferably CH_2CH_3;
R_2 is H, C_1-C_3 alkyl or



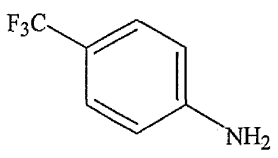
(b) hydrolyzing the racemic compound of formula V to form the racemic compound of formula (I); wherein prior to step (b) the racemic compound of formula V is separated from the reaction mixture of step (a). Also described herein is a process for preparing the compound of formula I or a salt thereof:



formula I

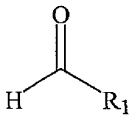
comprising the steps of:

(a) reacting 4-aminobenzotrifluoride according to formula II



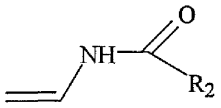
formula II

with an aldehyde according to formula III



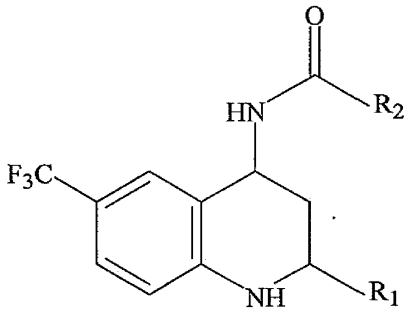
formula III

and with a compound according to formula IV



formula IV

in the presence of a solvent and optionally one or more catalysts to form the compound of formula V

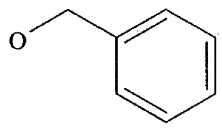


formula V

wherein

R_1 is H or C_1-C_3 alkyl, preferably CH_2CH_3;

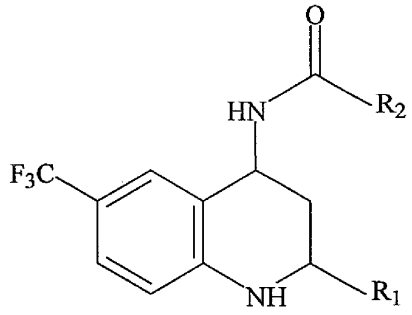
R_2 is H, C_1-C_3 alkyl or



(b) hydrolyzing the compound of formula V to form the compound of formula I.

With the process of the present invention it is now possible to prepare efficiently, with relatively cheap starting materials, with few byproducts and with a good yield the intermediate compounds according to formula I. As mentioned above, these compounds may be used in the further preparation of tetrahydroquinoline derivatives, such as Compound A.

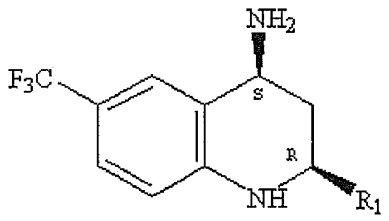
In the process described herein, use is made of a so-called three component Povarov reaction. A key step in this process is the formation of the so-called Povarov product according to formula V:



formula V

This intermediate may be prepared with relatively cheap starting materials and may efficiently be hydrolyzed to form the compound according to formula I. Hence, the disclosure also relates to the intermediate according to formula V as such as this intermediate has not been prepared before.

Also described herein is the use of the intermediate according to formula V in the preparation of a compound according to formula I, in particular in the preparation of the 2*R*,4*S* enantiomers thereof according to formula I-a, which enantiomers may be used in the preparation of Compound A.



formula I-a

Hence, the disclosure also relates to the use of the compound according to formula V in the preparation of Compound A.

DEFINITIONS

The term '*pharmaceutically acceptable*' as used herein has its conventional meaning and refers to compounds, material, compositions and/or dosage forms, which are, within the scope of sound medical judgment suitable for contact with the tissues of mammals, especially humans, without excessive toxicity, irritation, allergic response and other problem complications commensurate with a reasonable benefit/risk ratio.

The term '*salt*' as used herein has its conventional meaning and includes the acid addition and base salts.

The term '*treatment*' as used herein has its conventional meaning and refers to curative, palliative and prophylactic treatment.

The term '*cardiovascular disease*' has its conventional meaning and includes arteriosclerosis, peripheral vascular disease, hyperlipidemia, mixed dyslipidemia betalipoproteinemia, hypoalphalipoproteinemia, hypercholesteremia, hypertriglyceridemia, familial-hypercholesteremia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, restenosis after angioplasty, hypertension, cerebral infarction and cerebral stroke.

The term "*halo*", "*halogen atom*" or "*halogen*" refers to fluorine, chlorine, bromine or iodine.

The term "*alkyl*" or "*alkyl group*" as used herein has its conventional meaning and refers to a straight or branched saturated hydrocarbon chain having 1 to 10 carbon atoms and a cyclic saturated hydrocarbon chain having 3 to 10 carbon atoms.

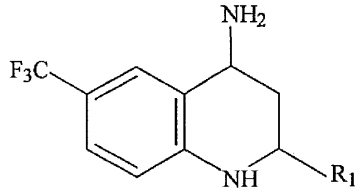
The term "C_1-C_3 *alkyl*" as used herein has its conventional meaning and refers to an alkyl group having 1 to 3 carbon atoms. Examples of such alkyl groups are methyl, ethyl, propyl and isopropyl.

DETAILED DESCRIPTION OF THE INVENTION

A process for the preparation of tetrahydroquinoline derivatives has been described in WO 2007/116922. Although tetrahydroquinoline derivatives, such as

CLAIMS

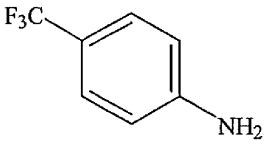
1. A process for preparing the racemic compound of formula I or a salt thereof:



formula I

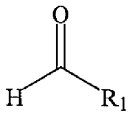
comprising the steps of:

(a) simultaneously reacting 4-aminobenzotrifluoride according to formula II



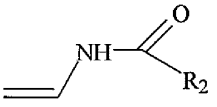
formula II

with an aldehyde according to formula III



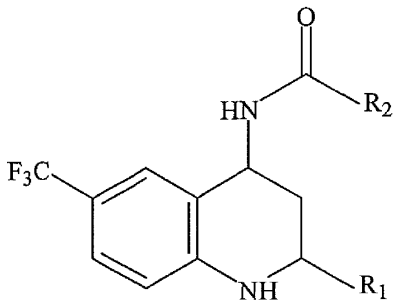
formula III

and with a compound according to formula IV



formula IV

in the presence of a solvent and optionally one or more catalysts to form the racemic compound of formula V

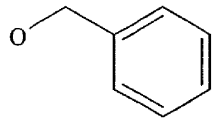


formula V

wherein

R_1 is H or C_1-C_3 alkyl, preferably CH_2CH_3;

R_2 is H, C_1-C_3 alkyl or



(b) hydrolyzing the racemic compound of formula V to form the racemic compound of formula (I); wherein prior to step (b) the racemic compound of formula V is separated from the reaction mixture of step (a).

2. Process according to claim 1, wherein R_1 is CH_2CH_3 and R_2 is H.

3. Process according to claim 1 or 2, wherein the solvent used is dichloromethane, acetonitrile, ethyl acetate, toluene or a mixture thereof.

4. Process according to any of the previous claims, wherein the catalyst used in step a) is an acid, preferably a Brønsted acid, or a Lewis acid.

5. Process according to claim 4, wherein the catalyst is 4-toluenesulfonic acid.

6. Process according to any of the previous claims, wherein prior to step (b) the racemic compound of formula V is separated from the reaction mixture of step (a) by means of

precipitation and/or filtration.

7. Process according to claim 6, wherein the racemic compound of formula V is precipitated from the reaction mixture by means of the addition of a non-polar solvent to said reaction mixture.

8. Process according to claim 7, wherein the non-polar solvent is a heptane, cyclohexane or a mixture thereof.

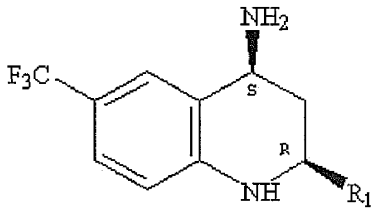
9. Process according to any of the previous claims, wherein in step (b) the racemic compound of formula V is hydrolyzed by warming a mixture comprising said compound for 1 to 3 hours at a temperature of 45°C to 80°C in the presence of an aqueous acid.

10. Process according to claim 9, wherein the racemic compound of formula V is hydrolyzed is in the presence of an aqueous acid and alcohol.

11. Process according to claim 9 or 10, wherein the acid is hydrochloric acid.

12. Process according to claim 10 or 11, wherein the alcohol is ethanol.

13. Process according to any of the previous claims, wherein in a further step c) the 2R,4S-enantiomer according to formula I-a is separated



formula I-a

wherein, R_1 is H or C_1-C_3 alkyl.

14. Process according to claim 13, wherein the separation of the enantiomer according to formula I-a is carried out by means of resolution with a chiral resolving agent, such as L-

tartaric acid or a derivative thereof, such as di-*p*-toluoyl-L-tartaric acid.

15. Process according to claim 13 or 14, wherein R_1 is CH_2CH_3.

16. The process according to claim 13, wherein the compound according to formula I-a is obtained with a purity of at least 99% enantiomeric excess (e.e).