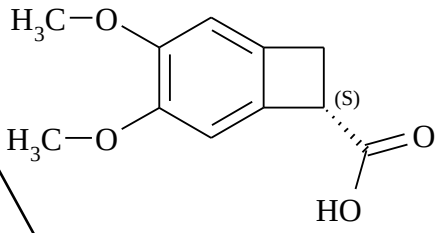
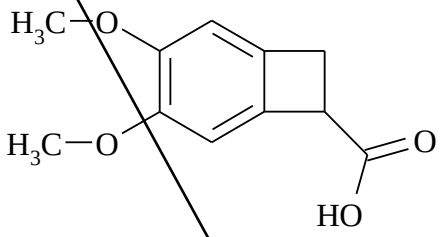
CLAIMS

1. Process for the synthesis of the optically pure compound of formula (Ia):



(Ia)

by enantioselective enzymatic esterification of the racemic, or other not optically pure, acid of formula (X):



(X)

using a lipase or esterase,

in a mixture of alcohol ROH wherein R represents a linear or branched C_1-C_6alkyl group, and an organic co-solvent,

at a concentration from 5 to 500 g/L of compound of formula (X) per litre of solvent mixture,

at an E/S ratio of from 10/1 to 1/100,

at a temperature from 25°C to 40°C.

2. Synthesis process according to claim 1, wherein the lipase or esterase is selected from lipases of *Candida antarctica*, of *Pseudomonas fluorescens*, of *Pseudomonas cepacia*, of *Rhizopus oryzae*, of *Aspergillus niger*, of *Mucor javanicus*, of *Aspergillus oryzae* and of *Penicillium camemberti*, and esterases of *Rhizopus oryzae*, of *Mucor miehei* and of *Rhizopus niveus.*

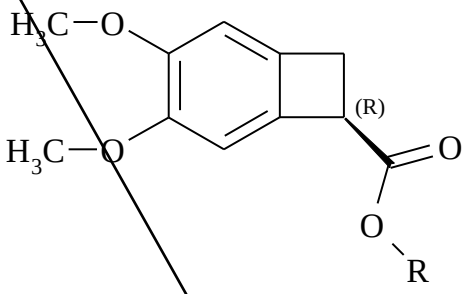
3. Synthesis process according to claim 2, wherein the lipase or esterase is a lipase of *Candida antarctica* or of *Pseudomonas fluorescens.*

4. Synthesis process according to any one of claims 1 to 3, wherein the E/S ratio is from 1/5 to 1/10.

5. Synthesis process according to any one of claims 1 to 4, wherein the alcohol ROH is methanol and the co-solvent is acetonitrile.

6. Synthesis process according to claim 5, wherein the acetonitrile/methanol ratio is from 8/2 to 9/1.

7. Synthesis process according to any one of claims 1 to 6, wherein the ester of configuration (R), the secondary product of the reaction:



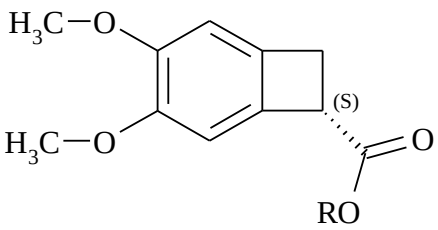
is hydrolysed by the action of a base to form the racemic acid of formula (X) in order to be recycled into the enzymatic esterification process.

8. Synthesis process according to claim 7, wherein the base is KOH.

9. Synthesis process according to either claim 7 or claim 8, wherein the hydrolysis/racemisation step is carried out *in situ*.

10. Synthesis process according to any one of claims 1 to 9, wherein the acid of formula (Ia) is isolated after one or more cycles of enzymatic esterification.

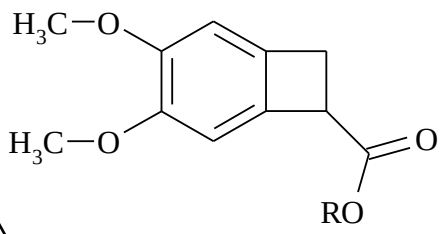
11. Process for the synthesis of the optically pure compound of formula (Ib):



(Ib),

wherein R represents a linear or branched C_1-C_6alkyl group,

by enantioselective enzymatic hydrolysis of the racemic, or other not optically pure, ester of formula (XI):



(XI),

wherein R represents a linear or branched C_1-C_6alkyl group,

using a lipase or esterase, in water, in a buffer solution of pH=5 to 8 or in a mixture of organic solvent and water or buffer of pH=5 to 8, at a concentration of from 1 to 200 g/L of compound of formula (XI) per litre of solvent or solvent mixture,

at an E/S ratio of from 10/1 to 1/100,

at a temperature from 25°C to 40°C,

followed by isolation of the ester of formula (Ib).

12. Synthesis process according to claim 11, wherein the lipase or esterase is selected from lipases of *Candida antarctica*, of *Pseudomonas fluorescens*, of *Pseudomonas cepacia*, of *Rhizopus oryzae*, of *Aspergillus niger*, of *Mucor javanicus*, of *Aspergillus oryzae* and of *Penicillium camemberti*, and esterases of *Rhizopus oryzae*, of *Mucor miehei* and of *Rhizopus niveus*.

13. Synthesis process according to claim 12, wherein the lipase or esterase is a lipase of *Candida antarctica* or of *Pseudomonas fluorescens*.

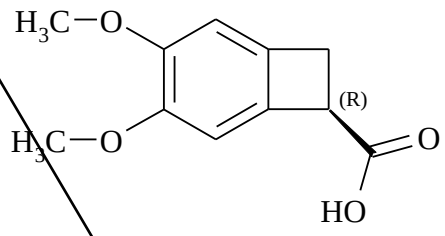
14. Synthesis process according to any one of claims 11 to 13, wherein the E/S ratio is from 1/5 to 1/10.

15. Synthesis process according to any one of claims 11 to 14, wherein R is a methyl group.

16. Synthesis process according to any one of claims 11 to 15, wherein the reaction is carried out in a mixture of acetonitrile and buffer of pH=7.

17. Synthesis process according to claim 16, wherein the acetonitrile/buffer pH=7 ratio is from 8/2 to 9/1.

18. Synthesis process according to any one of claims 11 to 17, wherein the acid of configuration (R):



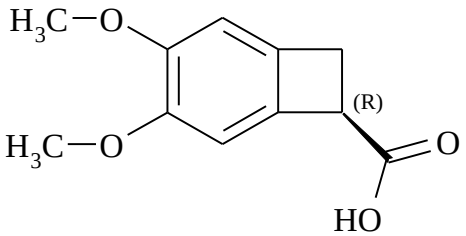
,

the secondary product of the reaction,

is racemised by the action of a base, and then the racemic acid thereby obtained is alkylated to form the racemic ester of formula (XI) in order to be recycled into the enzymatic hydrolysis process.

19. Synthesis process according to claim 18, wherein the acid of configuration (R) is racemised by the action of KOH in the hot state.

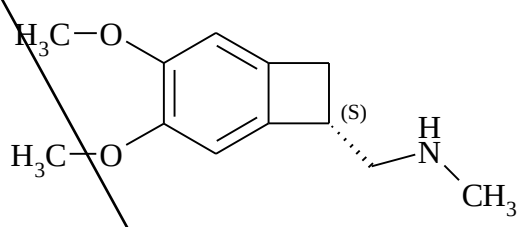
20. Synthesis process according to any one of claims 11 to 17, wherein the acid of configuration (R), the secondary product of the reaction:



is first alkylated and then the ester of configuration (R) thereby obtained is racemised by the action of a base in order to be recycled into the enzymatic hydrolysis process.

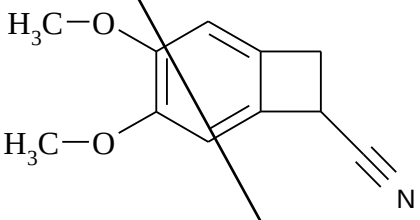
21. Synthesis process according to claim 20, wherein the ester of configuration (R) is racemised by the action of DBU in the hot state or of KOH at ambient temperature.

22. Process for the synthesis of the compound of formula (III):



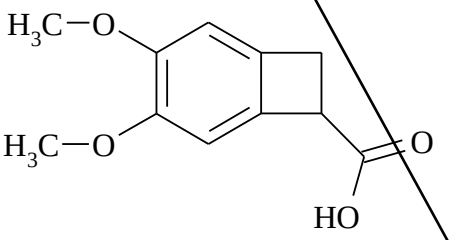
(III)

starting from the nitrile of formula (IV):



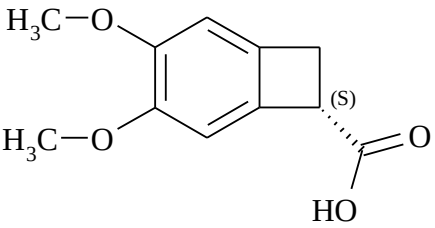
(IV),

which is hydrolysed to form the racemic acid of formula (X):



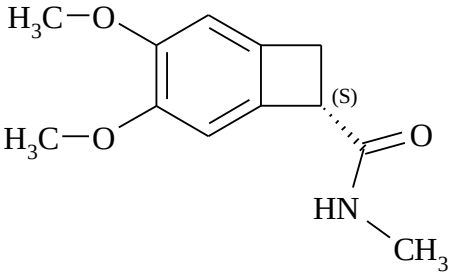
(X),

the enzymatic esterification of which in accordance with any one of claims 1 to 10 yields the optically pure acid of formula (Ia):



(Ia),

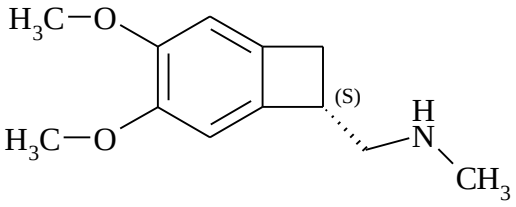
which is then converted into the optically pure amide of formula (XII):



(XII),

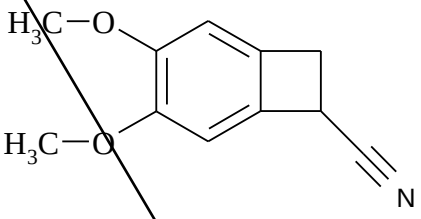
the reduction of which yields the compound of formula (III).

23. Process for the synthesis of the compound of formula (III):



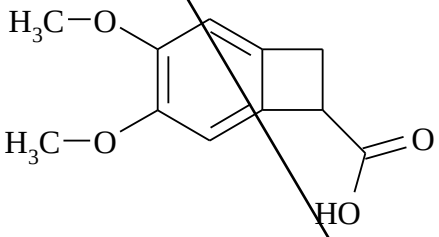
(III)

starting from the nitrile of formula (IV):



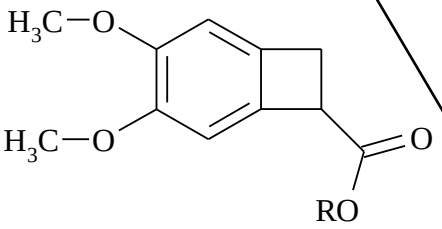
(IV),

which is hydrolysed to form the racemic acid of formula (X):



(X)

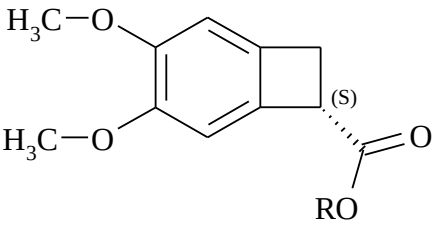
and then alkylated to form the racemic ester of formula (XI):



(XI),

wherein R represents a linear or branched C_1-C_6alkyl group,

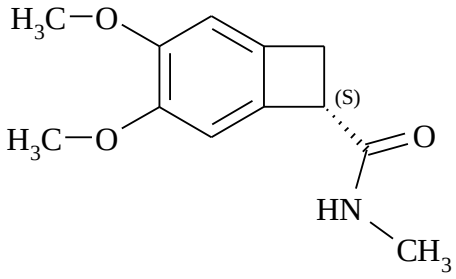
the enzymatic hydrolysis of which in accordance with any one of claims 11 to 21 yields the optically pure ester of formula (Ib):



(Ib),

wherein R represents a linear or branched C_1-C_6alkyl group,

which is converted into the optically pure amide of formula (XII):

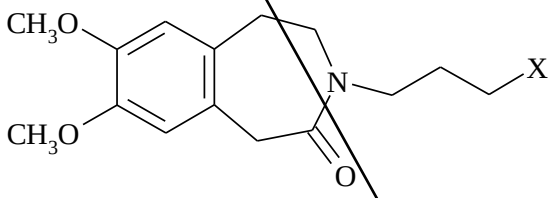


(XII),

the reduction of which yields the compound of formula (III).

24. Synthesis process according to either claim 22 or claim 23, wherein the reduction of the compound of formula (XII) to form the compound of formula (III) is carried out by BH_3, $NaBH_4$ or $LiAlH_4$.

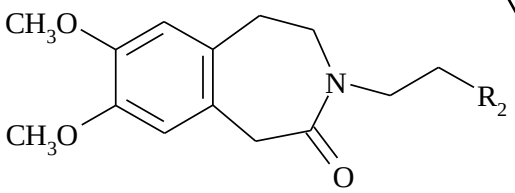
25. Synthesis process according to any one of claims 22 to 24, wherein the compound of formula (III) is subsequently either coupled with a compound of formula (XIII) :



(XIII),

wherein X represents a halogen atom,

or subjected to a reductive amination reaction with a compound of formula (XIV) in the presence of a reducing agent:



(XIV),

wherein R_2 represents a group selected from CHO and CHR_3R_4,

wherein R_3 and R_4 each represent a linear or branched (C_1-C_6)alkoxy group or form, together with the carbon atom carrying them, a 1,3-dioxane, 1,3-dioxolane or 1,3-dioxepane ring,

to yield ivabradine, which is then converted into an addition salt with a pharmaceutically acceptable acid, said salt being in anhydrous or hydrate form.

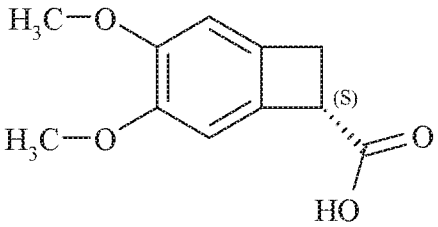
26. Synthesis process according to claim 25, wherein X is an iodine atom.

27. Synthesis process according to claim 25, wherein the compound of formula (III) is used in the reductive amination reaction in the form of its hydrochloride to yield ivabradine in the form of the hydrochloride.

28. Synthesis process according to either claim 25 or claim 27, wherein the reductive amination reaction with a compound of formula (XIV) is carried out in the presence of dihydrogen catalysed by palladium-on-carbon.

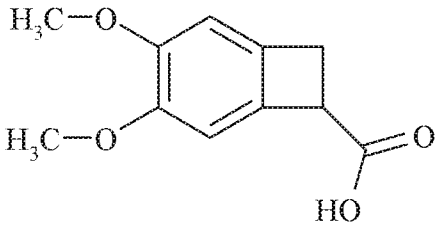
The claims defining the invention are as follows:

1. A process for the synthesis of the optically pure compound of formula (Ia):



(Ia)

by enantioselective enzymatic esterification of the racemic, or other not optically pure, acid of formula (X):



(X)

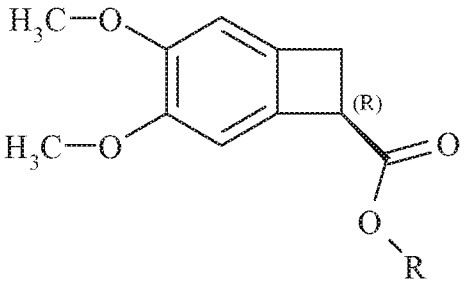
using a lipase of *Candida antarctica* or of *Pseudomonas fluorescens*,
in a mixture of alcohol ROH wherein R represents a linear or branched C_1-C_6alkyl group, and an organic co-solvent,
at a concentration from 5 to 500 g/L of compound of formula (X) per litre of solvent mixture,
at an E/S ratio of from 10/1 to 1/100,
at a temperature from 25°C to 40°C.

2. The process according to claim 1, wherein the E/S ratio is from 1/5 to 1/10.

3. The process according to any one of claim 1 or 2, wherein the alcohol ROH is methanol and the co-solvent is acetonitrile.

4. The process according to claim 3, wherein the acetonitrile/methanol ratio is from 8/2 to 9/1.

5. The process according to any one of claims 1 to 3, wherein the ester of configuration (R), the secondary product of the reaction:



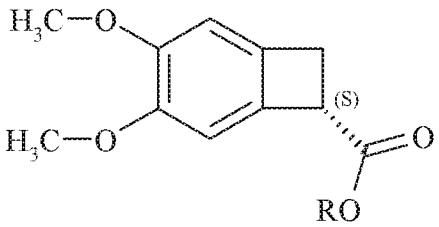
is hydrolysed by the action of a base to form the racemic acid of formula (X) in order to be recycled into the enzymatic esterification process.

6. The process according to claim 5, wherein the base is KOH.

7. The process according to claim 5, wherein the hydrolysis/racemisation step is carried out *in situ*.

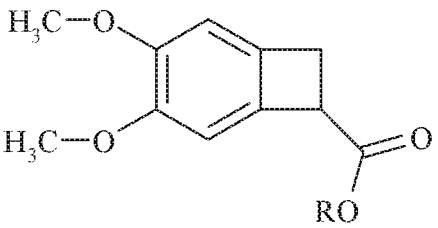
8. The process according to any one of claims 1 to 3, wherein the acid of formula (Ia) is isolated after one or more cycles of enzymatic esterification.

9. A process for the synthesis of the optically pure compound of formula (Ib):



(Ib),

wherein R represents a linear or branched C_1-C_6alkyl group,
by enantioselective enzymatic hydrolysis of the racemic, or other not optically pure, ester of formula (XI):



(XI),

wherein R represents a linear or branched C_1-C_6alkyl group,
using a lipase of *Candida antarctica* or of *Pseudomonas fluorescens*, in water, in a buffer solution of pH=5 to 8 or in a mixture of organic solvent and water or buffer of

pH=5 to 8, at a concentration of from 1 to 200 g/L of compound of formula (XI) per litre of solvent or solvent mixture,
at an E/S ratio of from 10/1 to 1/100,
at a temperature from 25°C to 40°C,
followed by isolation of the ester of formula (Ib).

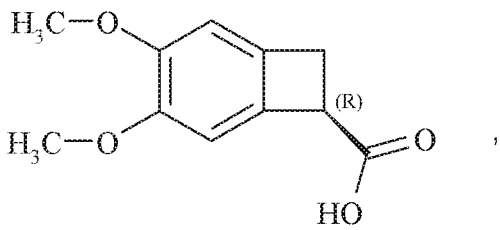
10. The process according to claim 9, wherein the E/S ratio is from 1/5 to 1/10.

11. The process according to any one of claim 9 or 10, wherein R is a methyl group.

12. The process according to claim 9 or 10, wherein the process is carried out in a mixture of acetonitrile and buffer of pH=7.

13. The process according to claim 12, wherein the acetonitrile/buffer pH=7 ratio is from 8/2 to 9/1.

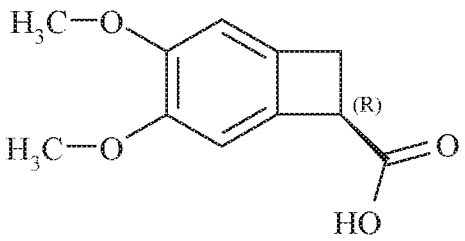
14. The process according to claim 9 or 10, wherein the acid of configuration (R):



the secondary product of the reaction,
is racemised by the action of a base, and then the racemic acid thereby obtained is alkylated to form the racemic ester of formula (XI) in order to be recycled into the enzymatic hydrolysis process.

15. The process according to claim 14, wherein the acid of configuration (R) is racemised by the action of KOH in the hot state.

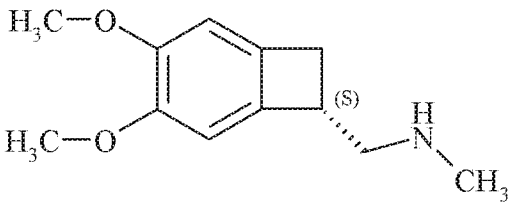
16. The process according to claim 9 or 10, wherein the acid of configuration (R), the secondary product of the reaction:



is first alkylated and then the ester of configuration (R) thereby obtained is racemised by the action of a base in order to be recycled into the enzymatic hydrolysis process.

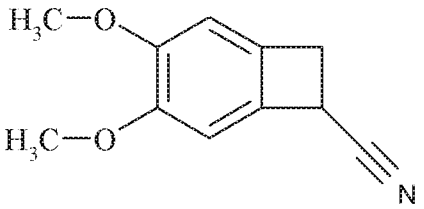
17. The process according to claim 16, wherein the ester of configuration (R) is racemised by the action of DBU in the hot state or of KOH at ambient temperature.

18. A process for the synthesis of the compound of formula (III):



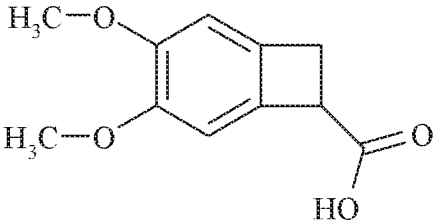
(III)

starting from the nitrile of formula (IV):



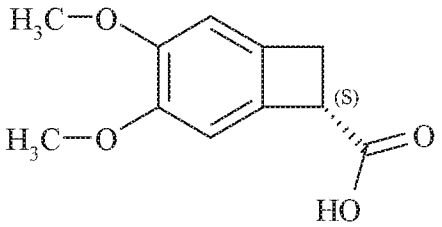
(IV),

which is hydrolysed to form the racemic acid of formula (X):



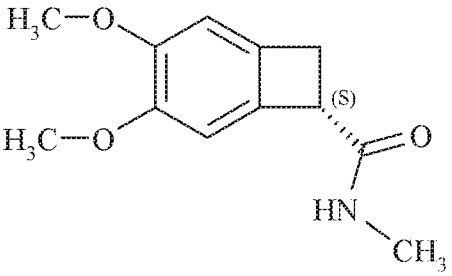
(X),

the enzymatic esterification of which in accordance with any one of claims 1 to 8 yields the optically pure acid of formula (Ia):



(Ia),

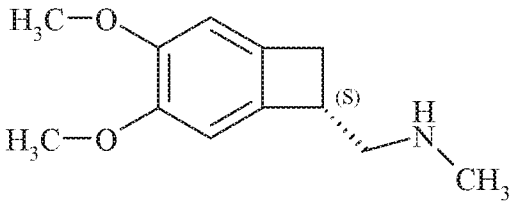
which is then converted into the optically pure amide of formula (XII):



(XII),

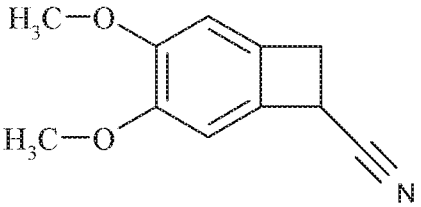
the reduction of which yields the compound of formula (III).

19. A process for the synthesis of the compound of formula (III):



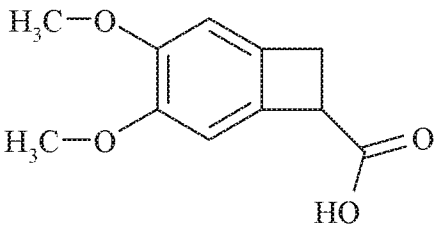
(III)

starting from the nitrile of formula (IV):



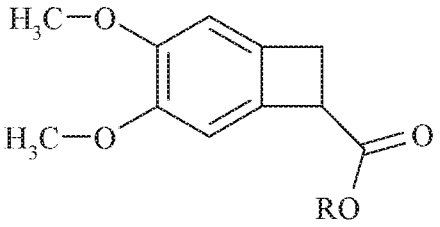
(IV),

which is hydrolysed to form the racemic acid of formula (X):



(X)

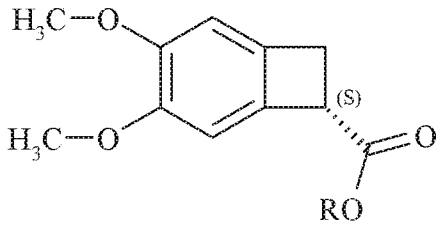
and then alkylated to form the racemic ester of formula (XI):



(XI),

wherein R represents a linear or branched C_1-C_6alkyl group,

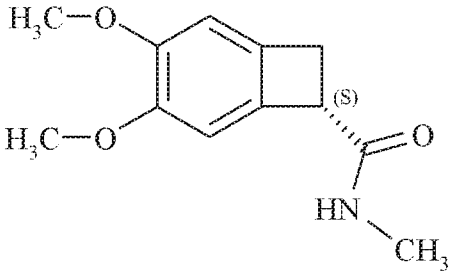
the enzymatic hydrolysis of which in accordance with any one of claims 9 to 17 yields the optically pure ester of formula (Ib):



(Ib),

wherein R represents a linear or branched C_1-C_6alkyl group,

which is converted into the optically pure amide of formula (XII):

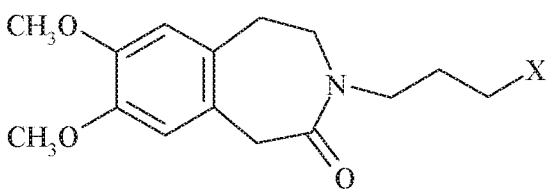


(XII),

the reduction of which yields the compound of formula (III).

20. The process according to claim 18 or 19, wherein the reduction of the compound of formula (XII) to form the compound of formula (III) is carried out by BH_3, $NaBH_4$ or $LiAlH_4$.

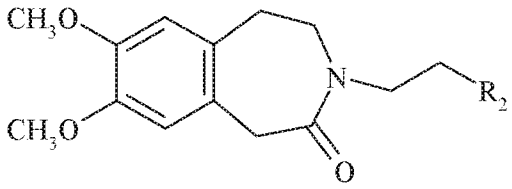
21. The process according to claim 18 or 19, wherein the compound of formula (III) is subsequently either coupled with a compound of formula (XIII) :



(XIII),

wherein X represents a halogen atom,

or subjected to a reductive amination reaction with a compound of formula (XIV) in the presence of a reducing agent:



(XIV),

wherein R_2 represents a group selected from CHO and CHR_3R_4,

wherein R_3 and R_4 each represent a linear or branched (C_1-C_6)alkoxy group or form, together with the carbon atom carrying them, a 1,3-dioxane, 1,3-dioxolane or 1,3-dioxepane ring,

to yield ivabradine, which is then converted into an addition salt with a pharmaceutically acceptable acid, said salt being in anhydrous or hydrate form.

22. The process according to claim 21, wherein X is an iodine atom.

23. The process according to claim 21, wherein the compound of formula (III) is used in the reductive amination reaction in the form of its hydrochloride to yield ivabradine in the form of the hydrochloride.

24. The process according to claim 21, wherein the reductive amination reaction with a compound of formula (XIV) is carried out in the presence of dihydrogen catalysed by palladium-on-carbon.