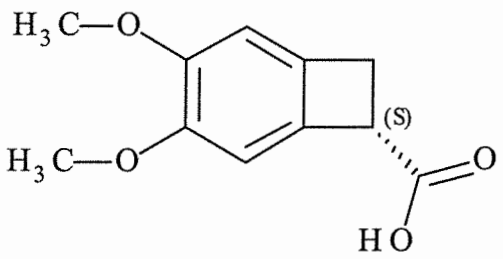
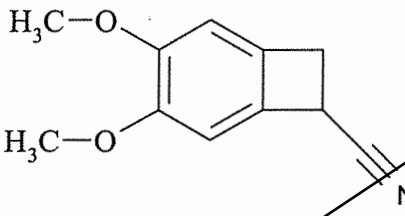
CLAIMS

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



(I)

by enantioselective enzymatic hydrolysis of the racemic, or not optically pure, nitrile of formula (IV):



(IV)

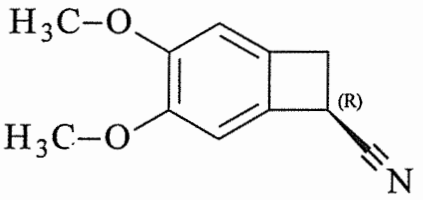
using the nitrilase of *Rhodococcus rhodochrous* NCIMB 11216 over-expressed in another organism having a competent biological system,
in a mixture of an organic solvent and an aqueous solution having a pH from 5 to 10,
at a concentration from 1 to 500 g of nitrile of formula (IV) per litre of solvent mixture,
at an E/S ratio of from 1/1 to 1/100,
at a temperature from 25°C to 40°C.

2. Process according to claim 1, wherein the organism having a competent biological system is a bacteria comprising a rearranged plasmid.

3. Process according to claim 2, wherein the bacteria over-expressing the nitrilase are used directly, in the form of a bacterial slurry or lyophilisate.

4. Process according to any one of claims 1 to 3, wherein the organic solvent is selected from dimethyl sulphoxide, DMF, acetone, acetonitrile, ethanol, isopropanol, THF and MTBE.

5. Synthesis process according to any one of claims 1 to 4, wherein the nitrile of configuration (R), the secondary product of the reaction:



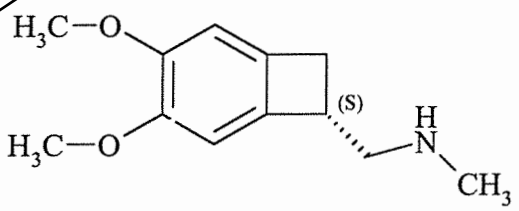
is racemised by the action of a base to form the racemic nitrile of formula (IV) in order to be recycled into the enzymatic hydrolysis process.

6. Synthesis process according to claim 5, wherein the base is DBU.

7. Synthesis process according to either claim 5 or claim 6, wherein the racemisation step is carried out *in situ*.

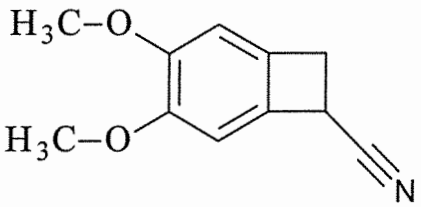
8. Synthesis process according to any one of claims 5 to 7, wherein the acid of formula (I) is isolated after one or more enzymatic hydrolysis cycles.

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



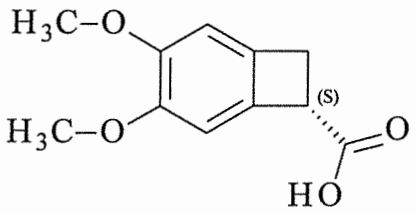
(III)

starting from the nitrile of formula (IV):



(IV),

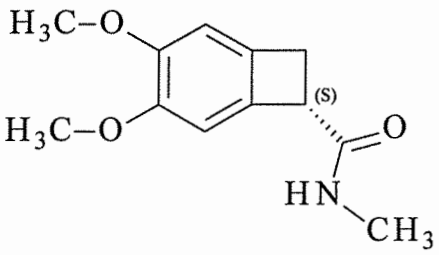
which is hydrolysed to form the optically pure acid of formula (I):



(I)

in accordance with any one of claims 1 to 8,

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

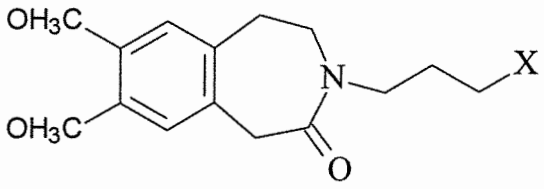


(XI),

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

10. Synthesis process according to claim 9, wherein the reduction of the compound of formula (XI) to form the compound of formula (III) is carried out by BH_3, $NaBH_4$ or $LiAlH_4$.

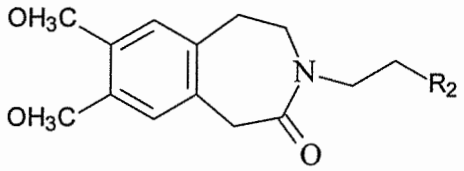
11. Synthesis process according to either claim 9 or claim 10, wherein the compound of formula (III) is subsequently either coupled with a compound of formula (XII):



(XII),

wherein X represents a halogen atom,

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



(XIII),

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 $(C_1\text{-}C_6)$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 in anhydrous or hydrate form.

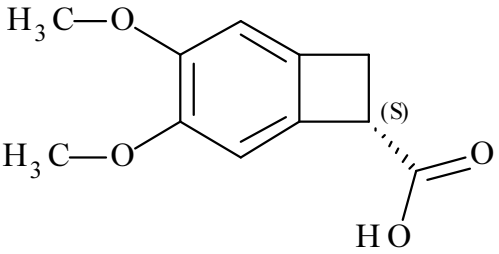
12. Synthesis process according to claim 11, wherein X is an iodine atom.

13. Synthesis process according to claim 11, 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.

14. Synthesis process according to either claim 10 or claim 13, wherein the reductive amination reaction with the compound of formula (XIII) is carried out in the presence of dihydrogen catalysed by palladium-on-carbon.

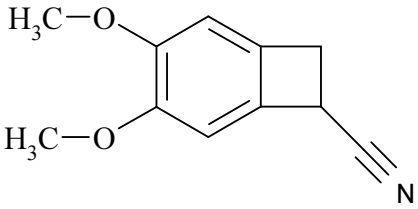
WHAT WE CLAIM IS:

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



(I)

by enantioselective enzymatic hydrolysis of the racemic, or not optically pure, nitrile of formula (IV):



(IV)

using the nitrilase of *Rhodococcus rhodochrous* NCIMB 11216 over-expressed in a bacteria, a yeast or a fungus,

in a mixture of an organic solvent and an aqueous solution having a pH from 5 to 10,

at a concentration from 1 to 500 g of nitrile of formula (IV) per litre of solvent mixture,

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

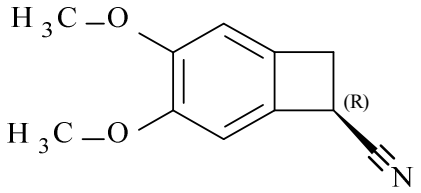
at a temperature from 25°C to 40°C.

2. Process according to claim 1, wherein the bacteria, yeast or fungus is a bacteria comprising a rearranged plasmid.

3. Process according to claim 2, wherein the bacteria over-expressing the nitrilase are used directly, in the form of a bacterial slurry or lyophilisate.

4. Process according to any one of claims 1 to 3, wherein the organic solvent is selected from dimethyl sulphoxide, DMF, acetone, acetonitrile, ethanol, isopropanol, THF and MTBE.

5. Synthesis process according to any one of claims 1 to 4, wherein the nitrile of configuration (R), the secondary product of the reaction:



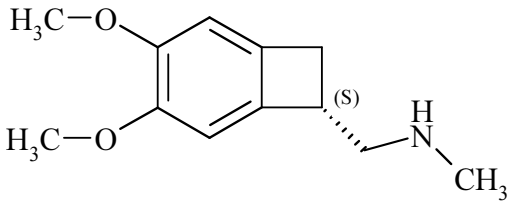
is racemised by the action of a base to form the racemic nitrile of formula (IV) in order to be recycled into the enzymatic hydrolysis process.

6. Synthesis process according to claim 5, wherein the base is DBU.

7. Synthesis process according to either claim 5 or claim 6, wherein the racemisation step is carried out *in situ*.

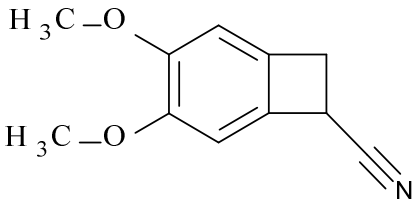
8. Synthesis process according to any one of claims 5 to 7, wherein the acid of formula (I) is isolated after one or more enzymatic hydrolysis cycles.

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



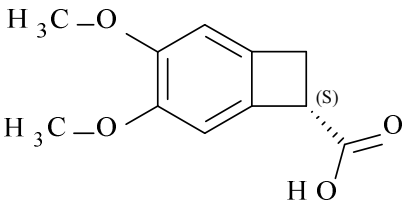
(III)

starting from the nitrile of formula (IV):



(IV),

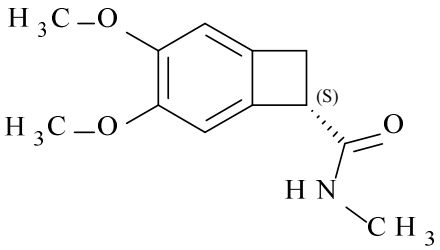
which is hydrolysed to form the optically pure acid of formula (I):



(I)

in accordance with any one of claims 1 to 8,

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

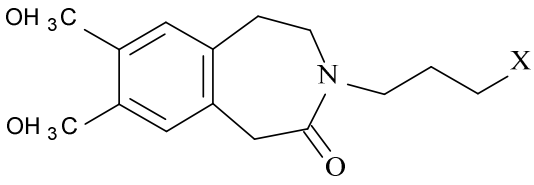


(XI),

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

10. Synthesis process according to claim 9, wherein the reduction of the compound of formula (XI) to form the compound of formula (III) is carried out by BH_3, $NaBH_4$ or $LiAlH_4$.

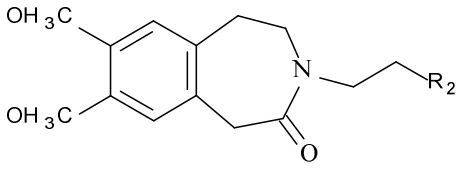
11. Synthesis process according to either claim 9 or claim 10, wherein the compound of formula (III) is subsequently either coupled with a compound of formula (XII):



(XII),

wherein X represents a halogen atom,

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



(XIII),

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 in anhydrous or hydrate form.

12. Synthesis process according to claim 11, wherein X is an iodine atom.

13. Synthesis process according to claim 11, 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.

14. Synthesis process according to either claim 10 or claim 13, wherein the reductive amination reaction with the compound of formula (XIII) is carried out in the presence of dihydrogen catalysed by palladium-on-carbon.

15. An optically pure compound of formula (I) as defined in claim 1, when prepared by the process of claim 1.

16. A compound of formula (III) as defined in claim 9, when prepared by the process of claim 9.

17. A process according to claim 1 or claim 9, substantially as herein described with reference to any example thereof.

18. A compound according to claim 15 or claim 16, substantially as herein described with reference to any example thereof.