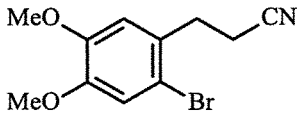
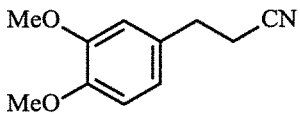
CLAIMS

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



(I),

characterised in that the compound of formula (VIII):



(VIII)

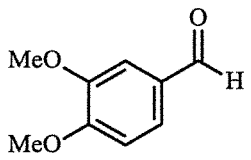
is subjected to the action of *N*-bromosuccinimide in the presence of an organic solvent to yield the compound of formula (I).

2. Process according to claim 1, characterised in that the organic solvent used to carry out the conversion of the compound of formula (VIII) into the compound of formula (I) is selected from *N*,*N*-dimethylformamide, tetrahydrofuran, acetonitrile, acetic acid, methanol, dichloromethane and toluene.

3. Process according to claim 2, characterised in that the organic solvent used to carry out the conversion of the compound of formula (VIII) into the compound of formula (I) is *N*,*N*-dimethylformamide.

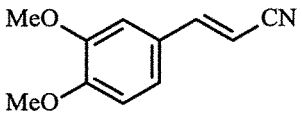
4. Process according to any one of claims 1 to 3, characterised in that the conversion of the compound of formula (VIII) into the compound of formula (I) is carried out at a temperature between -10°C and 30°C, inclusive.

5. Process according to claim 1, characterised in that the compound of formula (VIII) is prepared starting from the compound of formula (IX):



(IX),

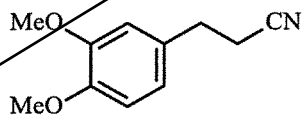
which is converted into the compound of formula (X):



(X)

in the presence of a phosphorus ylide and a base in an organic solvent,

which is converted into the compound of formula (VIII):



(VIII)

by a reduction reaction in the presence of a hydride donor agent in an organic solvent or mixture of organic solvents.

6. Process according to claim 5, characterised in that the phosphorus ylide used to carry out the conversion of the compound of formula (IX) into the compound of formula (X) is diethyl cyanomethyl phosphonate or (triphenylphosphoranylidene)acetonitrile.

7. Process according to claim 6, characterised in that the phosphorus ylide used to carry out the conversion of the compound of formula (IX) into the compound of formula (X) is diethyl cyanomethyl phosphonate.

8. Process according to any one of claims 5 to 7, characterised in that the base used to carry out the conversion of the compound of formula (IX) into the compound of

formula (X) is selected from potassium *tert*-butoxide, sodium hydride, triethylamine and potassium hydrogen carbonate.

9. Process according to claim 8, characterised in that the base used to carry out the conversion of the compound of formula (IX) into the compound of formula (X) is potassium *tert*-butoxide.

10. Process according to any one of claims 5 to 9, characterised in that the organic solvent used to carry out the conversion of the compound of formula (IX) into the compound of formula (X) is selected from tetrahydrofuran, acetonitrile and toluene.

11. Process according to claim 10, characterised in that the organic solvent used to carry out the conversion of the compound of formula (IX) into the compound of formula (X) is tetrahydrofuran.

12. Process according to any one of claims 5 to 11, characterised in that the conversion of the compound of formula (IX) into the compound of formula (X) is carried out at a temperature between -5°C and 120°C, inclusive.

13. Process according to any one of claims 5 to 12, characterised in that the hydride donor agent used to carry out the conversion of the compound of formula (X) into the compound of formula (VIII) is selected from sodium borohydride, ammonium formate in the presence of Pd/C, and formic acid in the presence of $Pd(OAc)_2$.

14. Synthesis process according to claim 13, characterised in that the hydride donor agent used to carry out the conversion of the compound of formula (X) into the compound of formula (VIII) is sodium borohydride.

15. Process according to any one of claims 5 to 14, characterised in that the organic solvent used to carry out the conversion of the compound of formula (X) into the compound of formula (VIII) is selected from methanol, ethanol, tetrahydrofuran and the mixture pyridine/methanol.

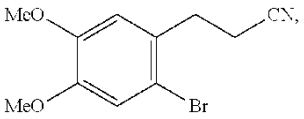
16. Process according to claim 15, characterised in that the organic solvent used to carry out the conversion of the compound of formula (X) into the compound of formula (VIII) is the mixture pyridine/methanol.

17. Process according to any one of claims 5 to 16, characterised in that the conversion of the compound of formula (X) into the compound of formula (VIII) is carried out at a temperature between 25°C and 110°C, inclusive.

18. Process for the synthesis of ivabradine, pharmaceutically acceptable salts thereof and hydrates thereof, characterised in that the compound of formula (VIII) is converted into the intermediate of formula (I) according to the process of claim 1, and then the intermediate of formula (I) is converted into ivabradine, which may be converted into addition salts thereof with a pharmaceutically acceptable acid selected from hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, benzenesulphonic acid and camphoric acid, and into hydrates thereof.

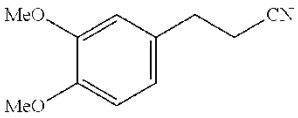
The invention claimed is:

1. A process for the synthesis of a compound of formula (I):



wherein a compound of formula (VIII):

(VIII)



is subjected to the action of N-bromosuccinimide in the presence of an organic solvent to yield the compound of formula (I).

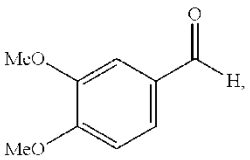
2. The process according to claim 1, wherein the organic solvent used to carry out the conversion of the compound of formula (VIII) into the compound of formula (I) is selected from N,N-dimethylformamide, tetrahydrofuran, acetonitrile, acetic acid, methanol, dichloromethane and toluene.

3. The process according to claim 2, wherein the organic solvent used to carry out the conversion of the compound of formula (VIII) into the compound of formula (I) is N,N-dimethylformamide.

4. The process according to claim 1, wherein the conversion of the compound of formula (VIII) into the compound of formula (I) is carried out at a temperature between −10°C. and 30°C., inclusive.

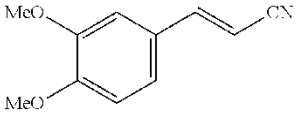
5. The process according to claim 1, wherein the compound of formula (VIII) is prepared starting from the compound of formula (IX):

(IX)



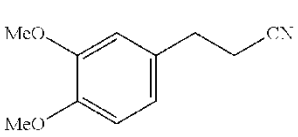
which is converted into a compound of formula (X):

(X)



in the presence of a phosphorus ylide and a base in an organic solvent,

which compound of formula (X) is converted into the compound of formula (VIII)



(VIII)

by a reduction reaction in the presence of a hydride donor agent in an organic solvent or mixture of organic solvents.

6. The process according to claim 5, wherein the phosphorus ylide used to carry out the conversion of the compound of formula (IX) into the compound of formula (X) is diethyl cyanomethyl phosphonate or (triphenylphosphoranylidene)acetonitrile.

7. The process according to claim 6, wherein the phosphorus ylide used to carry out the conversion of the compound of formula (IX) into the compound of formula (X) is diethyl cyanomethyl phosphonate.

8. The process according to claim 5, wherein the base used to carry out the conversion of the compound of formula (IX) into the compound of formula (X) is selected from potassium tert-butoxide, sodium hydride, triethylamine and potassium hydrogen carbonate.

9. The process according to claim 8, wherein the base used to carry out the conversion of the compound of formula (IX) into the compound of formula (X) is potassium tert-butoxide.

10. The process according to claim 5, wherein the organic solvent used to carry out the conversion of the compound of formula (IX) into the compound of formula (X) is selected from tetrahydrofuran, acetonitrile and toluene.

11. The process according to claim 10, wherein the organic solvent used to carry out the conversion of the compound of formula (IX) into the compound of formula (X) is tetrahydrofuran.

12. The process according to claim 5, wherein the conversion of the compound of formula (IX) into the compound of formula (X) is carried out at a temperature between −0.5°C. and 120°C., inclusive.

13. The process according to claim 5, characterised in that the hydride donor agent used to carry out the conversion of the compound of formula (X) into the compound of formula (VIII) is selected from sodium borohydride, ammonium formate in the presence of Pd/C, and formic acid in the presence of $Pd(OAc)_2$.

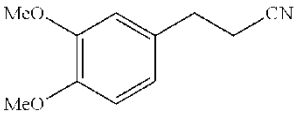
14. The process according to claim 13, wherein the hydride donor agent used to carry out the conversion of the compound of formula (X) into the compound of formula (VIII) is sodium borohydride.

15. The process according to claim 5, wherein the organic solvent used to carry out the conversion of the compound of formula (X) into the compound of formula (VIII) is selected from methanol, ethanol, tetrahydrofuran and a mixture pyridine/methanol.

16. The process according to claim 15, wherein the organic solvent used to carry out the conversion of the compound of formula (X) into the compound of formula (VIII) is the mixture pyridine/methanol.

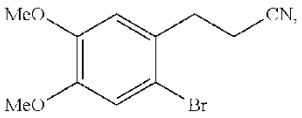
17. The process according to claim 5, wherein the conversion of the compound of formula (X) into the compound of formula (VIII) is carried out at a temperature between 25°C. and 110°C. inclusive.

18. A process for the synthesis of ivabradine, or a pharmaceutically acceptable salt thereof, wherein a compound of formula (VIII)



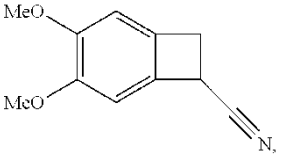
(VIII)

is subjected to the action of N-bromosuccinimide in the presence of an organic solvent to yield a compound of formula (I):



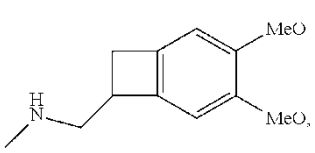
(I)

which compound of formula (I) is subjected to an intramolecular cyclization reaction in a basic medium to yield a compound of formula (III):



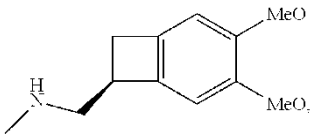
(III)

which compound of formula (III) is subjected to reduction conditions to yield a compound of formula (IV):



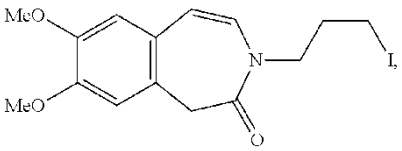
(IV)

which compound of formula (IV) is subjected to optical resolution conditions to yield a compound of formula (V):



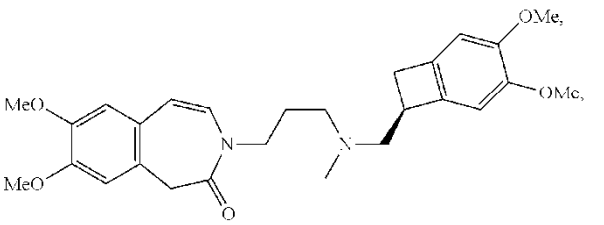
(V)

which compound of formula (V) is reacted with a compound of formula (VI):



(VI)

to yield a compound of formula (VII):



(VII)

which compound of formula (VII) is subjected to catalytic hydrogenation conditions to yield ivabradine, which may optionally be converted into an addition salt thereof via treatment with a pharmaceutically acceptable acid selected from hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, benzenesulphonic acid and camphoric acid.