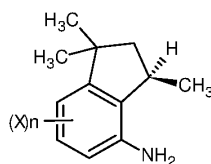


CLAIMS

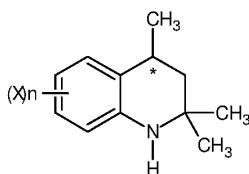
1. A process for preparing the compound 1,1,3-trimethylindan-4-amine of formula (I), or a salt thereof, enriched in the enantiomer (R)



(I)

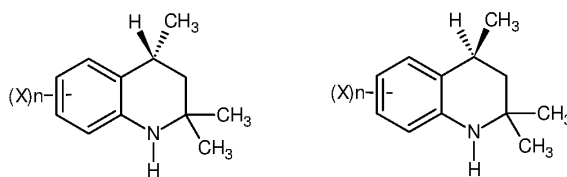
10 which comprises the following steps:

a) providing a racemic mixture of the optionally substituted 2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline compound of formula (IIIa)



(IIIa)

comprising the enantiomer (R) of formula (IVa) and the enantiomer (S) of formula
20 (Va)



(IVa)

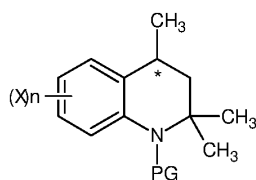
(Va),

b) treating said racemic mixture of the compound of formula (IIIa) according to an operating sequence A or an operating sequence B, wherein:

- the operating sequence A comprises:

b1) converting by means of a protection reaction the racemic mixture of the compound of formula (IIIa) into a racemic mixture of the compound of formula (IIIb) having a protective PG group to protect the nitrogen atom

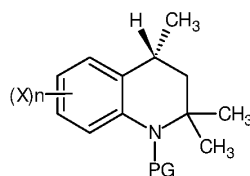
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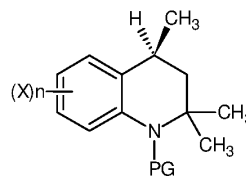
(IIIb),

said racemic mixture of the compound of formula (IIIb) comprising the
10 enantiomer (R) of formula (IVb) and the enantiomer (S) of formula (Vb)

15



(IVb)



(Vb),

b2) separating said enantiomer (R) of formula (IVb) from said enantiomer (S) of formula (Vb);

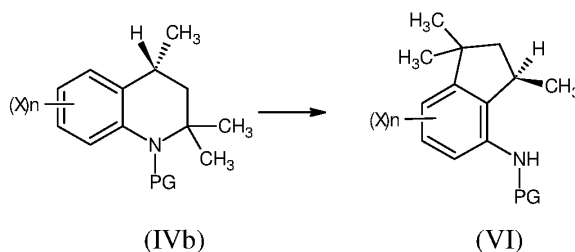
- the operating sequence B comprises:

20 b3) separating said enantiomer (R) of formula (IVa) from said enantiomer (S) of formula (Va);

b4) converting by means of a protection reaction said enantiomer (R) of formula (IVa) into an enantiomer (R) of formula (IVb);

25 c) subjecting said enantiomer (R) of formula (IVb) obtained in step b2 or in step b4 to an acid rearrangement reaction to form the compound of formula (VI)

30



(IVb)

(VI)

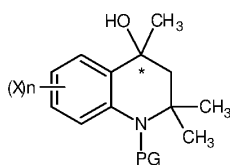
d) substituting the PG group of said compound of formula (VI) with a hydrogen atom to obtain the enantiomer (R) of the compound of formula (I);

where in the aforesaid formulas:

- * indicates an asymmetric carbon atom;
- X is a halogen atom;
- n is an integer selected from: 0, 1, 2 and 3;
- PG is a $-\text{COR}^1$ group or a $-\text{COOR}^2$ group,
- R^1 represents a linear or branched $\text{C}_1\text{-C}_6$ alkyl group;
- R^2 represents a linear or branched $\text{C}_1\text{-C}_6$ alkyl group or a benzyl group.

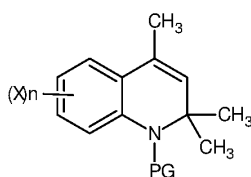
2. The process according to claim 1, which further comprises the following steps in sequence:

i) oxidizing, by means of an oxidizing agent, the enantiomer (S) of formula (Vb) obtained in step b2 to form the compound of formula (VII)



(VII);

ii) dehydrating said compound of formula (VII) in an acid environment to obtain a compound of formula (VIII)



(VIII);

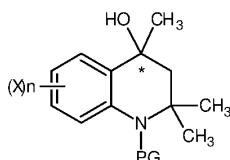
iii) hydrogenating said compound of formula (VIII) to obtain a racemic mixture of the compound of formula (IIIb) comprising the enantiomer (R) of formula (IVb) and the enantiomer (S) of formula (Vb).

3. The process according to claim 1, which comprises the following steps in sequence:

- converting by means of a protection reaction said enantiomer (S) of formula (Va) obtained in step b3 into an enantiomer (S) of formula (Vb);

i) oxidizing, by means of an oxidizing agent, said enantiomer (S) of formula (Vb) to form the compound of formula (VII)

5

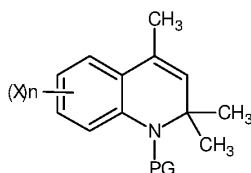


(VII);

10

ii) dehydrating said compound of formula (VII) in an acid environment to obtain a compound of formula (VIII)

15



(VIII);

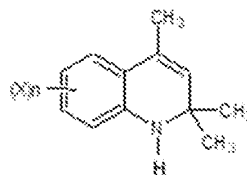
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iii) hydrogenating said compound of formula (VIII) to obtain a racemic mixture of the compound of formula (IIIb) containing the enantiomer (R) of formula (IVb) and the enantiomer (S) of formula (Vb).

4. The process according to claim 2, wherein said step iii is replaced by the following steps in sequence:

ii-bis) converting by means of a deprotection reaction said compound of formula (VIII) to obtain a compound of formula (IX)

25



(IX);

iii-bis) hydrogenating said compound of formula (IX) to obtain a racemic mixture of the compound of formula (IIIa) containing the enantiomer (R) of formula (IVa) and the enantiomer (S) of formula (Va).

5 5. The process according to any one of claims 2 or 3, wherein said racemic mixture of the compound of formula (IIIb) obtained in said step iii is fed to said step b2.

6. The process according to claim 4, wherein said racemic mixture of the compound of formula (IIIa) obtained in said step iii-bis is fed to said step a.

10 7. The process according to any one of the preceding claims, wherein said step d for substituting the PG group with a hydrogen atom is carried out by hydrolysis or catalytic hydrogenation.

8. The process according to any one of the preceding claims, wherein said step b2 or said separation step b3 is carried out by means of a chiral column chromatographic technique.

15 9. The process according to claim 1, wherein said separation step b3 of said racemic mixture of the compound of formula (IIIa) comprises the following steps:

- reacting said racemic mixture of formula (IIIa) with an optically active acid to obtain a mixture of a corresponding enantiomeric salt (R) and a corresponding enantiomeric salt (S);

20 - separating said enantiomeric salt (R) from said enantiomeric salt (S);

- subjecting said enantiomeric salt (R) to basic hydrolysis to obtain said enantiomer (R) of formula (IVa) to be fed to said step b4.

25 10. The process according to any one of the preceding claims, wherein said enantiomer (R) of formula (IVb) which is subjected to said acid rearrangement step c has an enantiomeric excess (ee%) with respect to said enantiomer (S) of general formula (Vb) greater than 90%, preferably greater than 98%, more preferably greater than 99.5%.

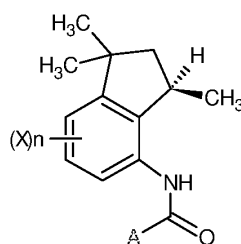
30 11. The process according to any one of the preceding claims, wherein said acid rearrangement reaction comprises reacting said enantiomer (R) of formula (IVb) in the presence of an inorganic acid, preferably selected from sulfuric acid and orthophosphoric acid.

12. The process according to any one of the preceding claims, wherein said compound of formula (I) obtained from said step d has an enantiomeric excess (ee%) of the enantiomer (R) with respect to the enantiomer (S) of formula greater than 97%, preferably greater than 99%, more preferably greater than 99.5%.

13. The process according to any one of the preceding claims, wherein in said compound of formula (IIIa) or (IIIb):

- X is a hydrogen or fluorine atom;
- n is equal to 1;
- PG is an acetyl group, a tert-butoxycarbonyl group or a carbobenzyloxy group.

14. The process for the preparation of an amide of formula (II), enriched in the enantiomer (R),



(II)

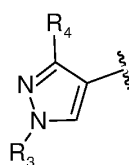
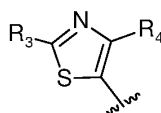
which comprises the following steps:

- preparing a compound 1,1,3-trimethylindan-4-amine of formula (I), or a salt thereof, enriched in the enantiomer (R) according to any one of the preceding claims;
- condensing said compound of formula (I) with at least one compound of formula $AC(O)Y$

wherein:

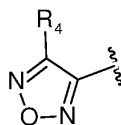
- A represents a C_6 - C_{10} aryl group or a heterocyclic group with 5 or 6 terms containing from 1 to 3 heteroatoms selected from N, O, S, said groups being optionally substituted with one or more R_3 and R_4 groups;
- R_3 represents a C_1 - C_6 alkyl group or a C_1 - C_6 , haloalkyl group, said groups being optionally substituted with one or more groups selected from R' , OR' ,

- S(O)_mR'; or R₃ represents a C₃-C₆ cycloalkyl group, a C₄-C₉ cycloalkylalkyl group, a C₂-C₆ alkenyl group, a C₂-C₆ alkynyl group, a C₆-C₁₀ aryl group, a C₇-C₁₂ arylalkyl group or a heterocyclic group with 5 or 6 terms containing from 1 to 3 heteroatoms selected from N, O, S, said groups being optionally substituted with one or more groups selected from a halogen atom, R', OR', NR'R'', S(O)_mR', CONR'R'', COR', CO₂R', CN, NO₂;
- R₄ represents a C₁-C₆ alkyl group or a C₁-C₆, haloalkyl group, said groups being optionally substituted with one or more groups selected from R', OR', S(O)_mR'; or R₄ represents a C₃-C₆ cycloalkyl group, C₄-C₉ cycloalkylalkyl group, C₆-C₁₀ aryl group or a C₇-C₁₂ arylalkyl group, said groups being optionally substituted with one or more groups selected from a halogen atom, R', OR', NR'R'', S(O)_mR', CONR'R'', COR', CO₂R', CN, NO₂;
- R' and R'', equal or different from each other, represent a hydrogen atom, a C₁-C₄ alkyl group or a C₁-C₄ haloalkyl group;
- Y represents a hydroxyl group, a halogen atom, a C₁-C₆, alkoxy group, a C₁-C₆ alkylsulfonyloxy group or a C₆-C₁₀, arylsulfonyloxy group, said C₁-C₆ alkoxy, C₁-C₆ alkylsulfonyloxy and C₆-C₁₀ arylsulfonyloxy groups being optionally substituted with one or more halogen atoms;
- m is an integer selected from: 0, 1, 2 and 3.
15. The process for the preparation of an amide of formula (II), according to claim 14, wherein A represents one of the following A₁-A₅ heterocycles:

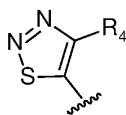
A₁

A₂

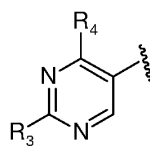
5

A₃

10

A₄

15

A₅

- 20 – R₃ and R₄, equal or different from each other, represent a C₁-C₆ alkyl group, a C₁-C₆ haloalkyl group or a phenyl optionally substituted with at least one from: halogen atom, C₁-C₄ alkyl group, C₁-C₄ haloalkyl group, C₁-C₄ alkoxyl group or a C₁-C₄ haloalkoxy group.

25 16. The process for the preparation of an amide of formula (II), according to claim 14 or 15, wherein in the A₁-A₅ heterocycles:

- R₃ represents a C₁-C₆ alkyl group or a phenyl optionally substituted with halogen atoms;
- R₄ represents a methyl, a difluoromethyl, a trifluoromethyl or a phenyl optionally substituted with halogen atoms.

30 17. The process for the preparation of an amide of formula (II) according to any of the claims from 14 to 16, wherein:

- A represents A_1 ;
- R_3 represents a methyl;
- R_4 represents a methyl, a difluoromethyl or a trifluoromethyl.