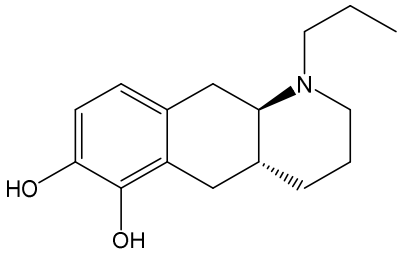
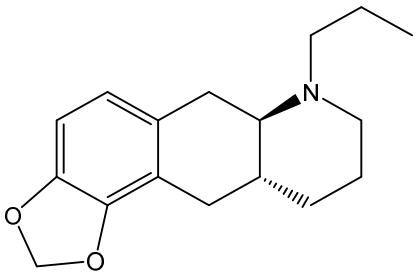
CLAIMS

1. A process for the manufacture of compound (I) with the formula below



(I)

from the compound (Ib) with the formula below



(Ib).

wherein compound (Ib) is prepared by a process comprising the steps of:

Step 0)

Substep (i) reacting compound (A1) with 3-chloropropan-1-amine to obtain compound (a2i); or

Substep (S1)

reacting compound (a6i) with tert-butyl 2-bromoacetate and zinc to form a mixture, followed by

treating the mixture from substep (S1) with acetic acid, followed by

reacting said mixture with 3-chloropropan-1-amine hydrochloride to afford compound (a2i);

followed by

Step 1)

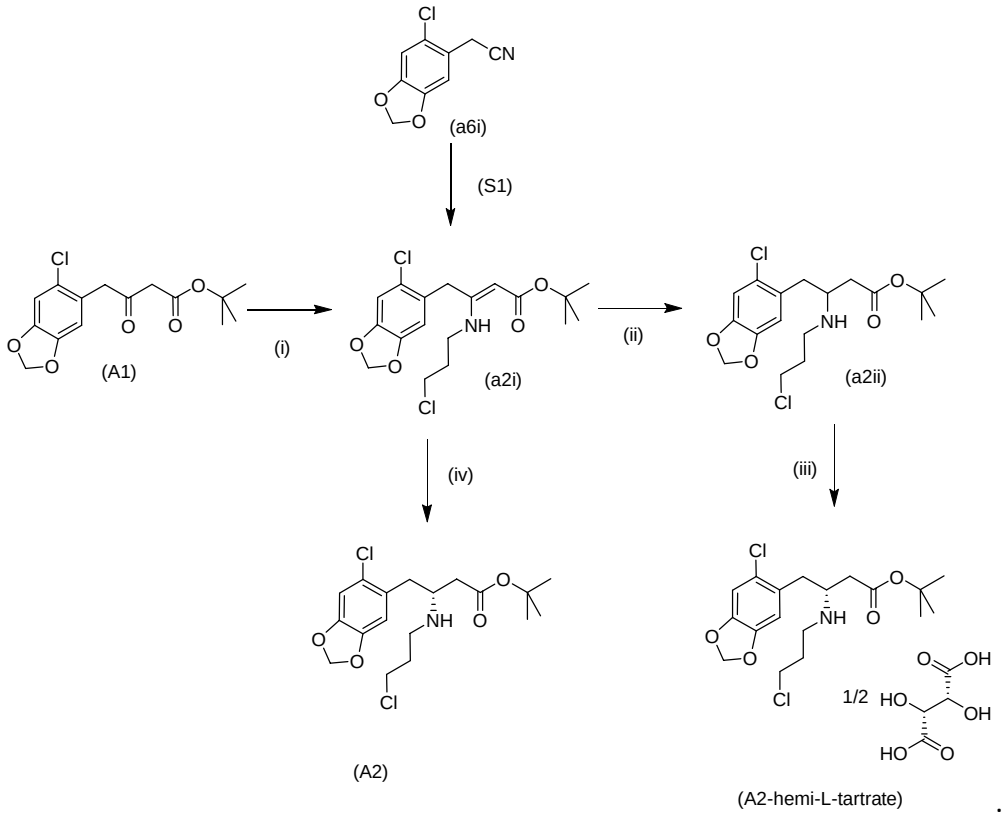
Substep (ii) reducing the compound (a2i) obtained in substep (i) or substep (S1) to obtain compound (a2ii), followed by

Substep (iii) resolving compound (a2ii) using L-tartaric acid to afford compound (A2-hemi-L-tartrate);

or

Substep (i) or substep (S1) is followed by substep (iv) comprising the step of subjecting compound (a2i) to a hydrogenation performed with a chiral catalyst in the presence of hydrogen and a solvent to afford compound (A2);

according to the reaction scheme below:



.

2. The process according to claim 1, wherein compound (Ib) is prepared by a process comprising the steps of:

Step 0)

Substep (S1)

reacting compound (a6i) with tert-butyl 2-bromoacetate and zinc to form a mixture, followed by

treating the mixture from substep (S1) with acetic acid, followed by

reacting said mixture with 3-chloropropan-1-amine hydrochloride to afford compound (a2i);

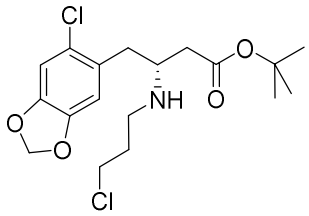
followed by

Step 1)

Substep (ii) reducing the compound (a2i) obtained in substep (S1) to obtain compound (a2ii), followed by

Substep (iii) resolving compound (a2ii) using L-tartaric acid to afford compound (A2-hemi-L-tartrate).

3. The compound of formula (A2) below



(A2)

or a salt thereof.

4. The process according to claim 1, wherein the chiral catalyst in Step 1 substep (iv) is selected from (2S)-1-[(1S)-1-[bis(1,1-dimethylethyl)phosphino]ethyl]-2-(diphenylphosphino)ferrocene and bis(2,5-norbornadiene)rhodium(I) tetrafluoroborate.

5. The process according to claims 1 and 4, wherein the solvent in Step 1 substep (iv) is 2,2,2-trifluoroethanol.

6. The process according to any one of claims 1-2, wherein the reduction in Step 1 substep (ii) takes place in the presence of a reducing agent selected from the group consisting of $NaBH_3CN$, sodium triacetoxyborohydride (STAB), a borane, 5-ethyl-2-methylpyridine borane (PEMB) and $NaBH_4$.

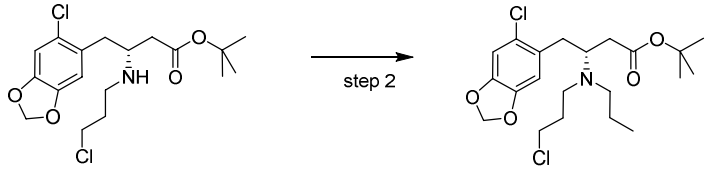
7. The process according to any one of claims 1-2, wherein the reduction in Step 1 substep (ii) takes place by use of a platinum catalyst, preferably platinum on carbon.

8. The process according to claims 1-2, and 4-7, wherein compound (Ib) is prepared by a process comprising the following step

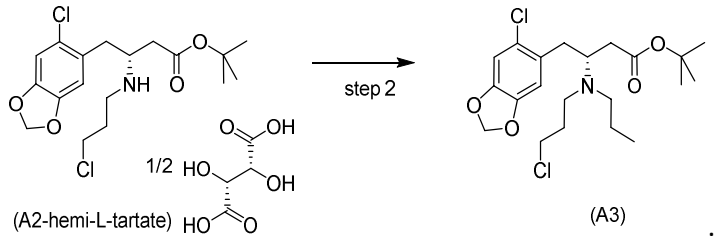
2) reacting compound (A2) or compound (A2-hemi-L-tartrate) with propanal in the presence of a reducing agent,

to afford compound (A3) according to reaction scheme a) or b) below

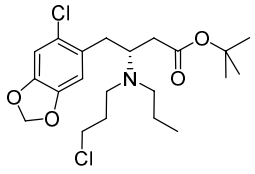
scheme a)



scheme b)



9. The compound of formula (A3) below

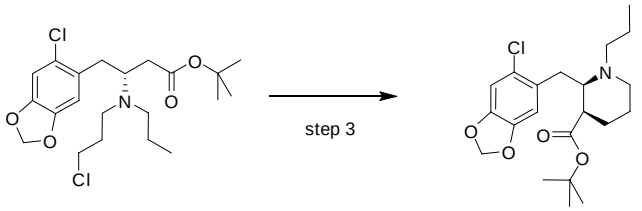


(A3)

or a salt thereof.

10. The process according to any one of claims 1-2, 4-8, wherein compound (Ib) is prepared by a process comprising the following step

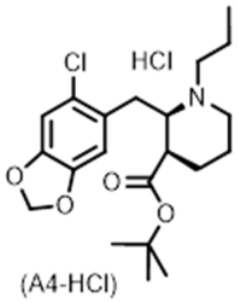
3) reacting compound (A3) with a strong base, to afford compound A4 according to the reaction scheme below



(A3) (A4)

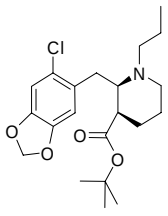
optionally followed by isolating compound (A4), or a salt thereof.

11. The process according to claim 10, wherein A4 is isolated as a HCl salt as depicted below



(A4-HCl) .

12. The compound of formula (A4) below

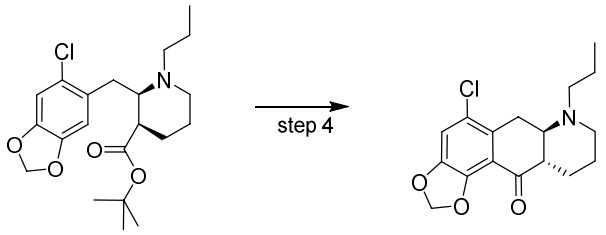


(A4)

or a salt thereof.

13. The process according to any one of claims 1-2, 4-8, and 10-11, wherein compound (Ib) is prepared by a process comprising the following step

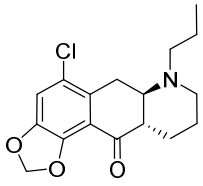
4) performing an intramolecular Friedel-Craft acylation of compound (A4) to afford compound (A5) according to the reaction scheme below:



(A4) (A5)

optionally followed by isolating compound (A5), or a salt thereof.

14. The compound of formula (A5) below

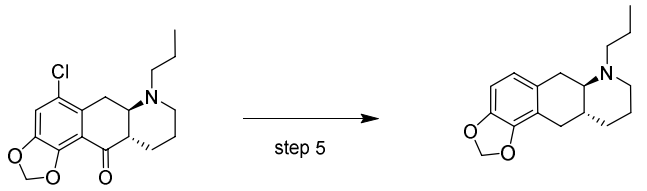


(A5)

or a salt thereof.

15. The process according to any one of claims 1-2, 4-8, 10-11, and 13, wherein compound (Ib) is prepared by a process comprising the following step

5) reducing compound (A5), or a salt thereof, to obtain compound (Ib), or a salt thereof according to the reaction scheme below

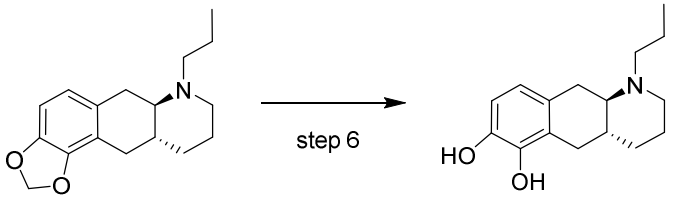


(A5) compound (Ib) .

16. The process according to any of claims 1-2, 4-8, 10-11, 13, and 15, wherein compound (I) is prepared from compound (Ib) by the following step

6) reacting compound (Ib) with a Lewis acid or Brønsted acid selected from the group consisting of BCl_3, BBr_3 and HBr,

to obtain compound (I) according to the reaction scheme below



compound (Ib) compound (I) .

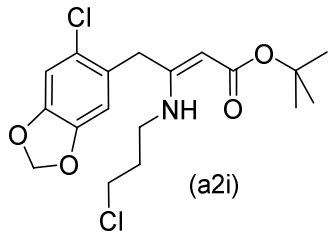
17. The process according to claim 16, wherein step 6 comprises reacting compound (Ib) with BCl_3 to obtain compound (I) or a salt thereof.

18. The process according to claim 16, wherein step 6 comprises reacting a salt of compound (Ib) with a base to obtain compound (Ib) as free base, followed by reacting compound (Ib) with BCl_3 to obtain compound (I) or a salt thereof.

19. The process according to claim 16, wherein step 6 comprises reacting a salt of compound (Ib) with an aqueous solution of Na_2CO_3, K_2CO_3 or ammonia to obtain compound (Ib) as free base followed by reacting compound (Ib) with BCl_3 to obtain compound (I) or a salt thereof.

20. The process according to claim 16, wherein step 6 comprises reacting the (-)-*O*,*O*'-di-p-toluoyl-L-tartaric acid salt (L-DTTA) salt of compound (Ib), with a base to obtain the free base of compound (Ib) followed by reacting compound (Ib) with BCl_3 to obtain compound (I) or a salt thereof, such as a HCl salt of compound (I).

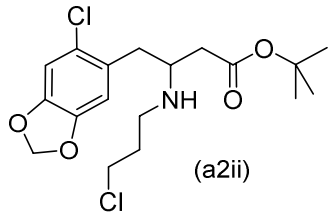
21. A compound of formula (a2i) below



(a2i)

or a salt thereof.

22. A compound of formula (a2ii) below



(a2ii)

or a salt thereof.