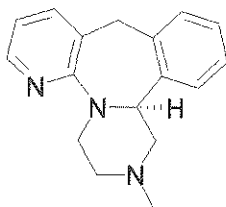


A method for the preparation of an enantiomerically pure benzazepine

The invention relates to a method for the preparation of an enantiomerically pure benzazepine, in particular of mirtazapine, in substantial enantiomeric excess of the R or S form. The invention further relates to novel intermediates and their use for the preparation of mirtazapine having a substantial enantiomeric excess of the R or S form.

Mirtazapine (1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3c][2]benzazepine) is a tetracyclic compound having the formula A:

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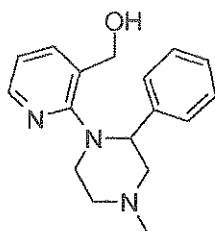
Formula A

The compound is chiral and the racemic mixture finds widespread use as a medicine for the treatment of depression. Other medical uses for mirtazapine have also been reported e.g., WO 99/25356 and WO 01/58453 disclose its use in the treatment of sleep disorders and apnea. Investigations into the biological effects of the enantiomers of mirtazapine (e. g. O'Connor and Leonard, Neuro-pharmacology, 1986, vol. 25, pp.267-270 ; Kooyman et al., 1994, vol. 33, pp. 501-507 ; De Boer et.al., Neuro-pharmacology, 1988, vol. 27, pp. 399-408 ; Gower et al., 1988, vol. 291, pp 185-201) mention properties of the compound in its pure enantiomeric forms. The present invention provides for an efficient production of large quantities of enantiomerically pure mirtazapine and related benzazepines.

The term "enantiomerically pure", "optically pure" and "having a substantial enantiomeric excess" are used interchangeably and all imply a mixture of R and S enantiomers comprising a substantial enantiomeric excess of the R or S enantiomer. In the context of the present invention a substantial enantiomeric excess preferably is an enantiomeric excess of at least 80%.

A variety of methods are known in the art for the preparation of mirtazapine in racemic or enantiopure form. According to the method described in US4062848 mirtazapine

can be obtained as a result of ring closure of a compound of Formula B using a variety of dehydrohalogenating agents.



5

Formula B

- Examples of such agents include acids such as sulphuric acid, concentrated hydrochloric acid, picric acid, trifluoroacetic acid, phosphoric acid, polyphosphoric acid (PPA), phosphorus oxychloride, phosphorus trioxide, phosphorus pentoxide and Lewis Acids such as aluminium chloride, ferric chloride, zinc chloride, tin chloride, titanium chloride, boron trifluoride, antimony pentachloride and zirconium tetrachloride. In US4062848 preparation of mirtazapine is exemplified by ring closure using concentrated sulphuric acid. In WO00/62782 it is indicated that concentrated sulphuric acid is most preferred. The optical resolution of racemic mirtazapine has also been addressed in US4062848. By the method disclosed in US4062848, enantiomerically pure mirtazapine is obtained by forming diastereomeric salts by reaction of racemic mirtazapine with enantiomerically pure dibenzoyltartaric acid in ethanol, filtering off the thus formed diastereomeric salt, followed by regeneration of the free base by treatment with aqueous ammonia.
- In document WO 2005/005410 is described that for the synthesis of enantiomerically pure mirtazapine by ring closure of an enantiomerically pure compound of above formula (A), stereochemical integrity in the starting material can be preserved by making a specific selection out of the above mentioned ring closing reagents. The method comprises a step of ring closure of a compound according to formula (A), said step comprising treatment, wherein mirtazapine with enantiomeric excess is formed by the ring closure of the compound of formula (A) with enantiomeric excess by treatment with a suitable acid in the absence of a solvent or a suitable combination of an acid and an organic solvent. The inventors have found that the reaction described in WO 2005/005410 can proceed without substantial racemisation by selection of the appropriate conditions, but that under such conditions a significant amount of side products is formed that complicates purification of the enantiopure mirtazapine and consequently diminishes the overall yield of the process. Reversely, preparation

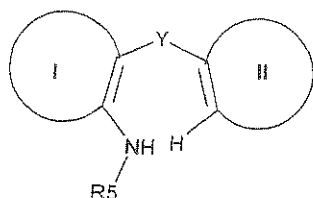
conditions that aim to reduce the amount of side products again proceed with substantial racemisation.

In the described prior art methods resolution occurs at the end of the synthetic pathway leading to the generation of a racemic mixture of mirtazapine. It follows therefore that the overall yield of each enantiomerically pure compound obtained is relatively low and can never be more than 50%. It would be beneficial to have a more economic method in which mirtazapine with substantial enantiomeric excess could be prepared with an overall improved yield. In US4062848 a general remark is made that pure enantiomers of mirtazapine may also be prepared directly by starting from optically active precursors. However, it is not described how to obtain such precursors in enantiomeric excess or how to retain the enantiomeric excess throughout the subsequent reaction steps for the manufacture of mirtazapine. The methods described in US4062848 and WO00/62782 with concentrated sulphuric acid do not sufficiently retain the enantiomeric excess. The skilled man still has the problem of choosing between a low yield or, when using optically pure precursors, a low enantiomeric excess.

It is a general object of the invention to provide an alternative method for the preparation of mirtazapine having substantial enantiomeric excess and which has a higher overall yield and can therefore be less expensive. It is a further object of the invention to provide intermediates for the preparation of mirtazapine that can be used in a process for the preparation of mirtazapine without substantial racemisation or side products formation and preferably can also easily be obtained in enantiomerically pure form.

Summary

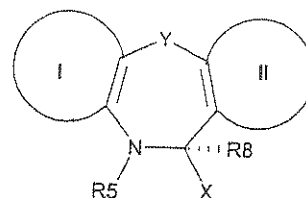
According to a first aspect, there is provided a method for the preparation of a cyclic compound according to Formula IIIa comprising reacting a compound according to Formula Ia and a compound according to Formula II,



Formula Ia



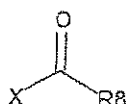
Formula II



Formula IIIa

wherein

- ring structure I represents a pyridine;
 - ring structure II represents a phenyl ring;
 - Y is O, N-R₉ or CR₉R₁₀ wherein R₉ and R₁₀ are hydrogen or substituents comprising saturated or unsaturated hydrocarbons optionally comprising hetero atoms;
 - R₅ is hydrogen or a hydrocarbon substituent group comprising one or more carbon atoms and optionally one or more hetero atoms;
- and wherein in Formula II,
- Z₁ and Z₂ are leaving groups, or together form oxygen creating the corresponding aldehyde or ketone as indicated in Formula IIb

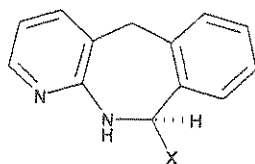


Formula IIb.

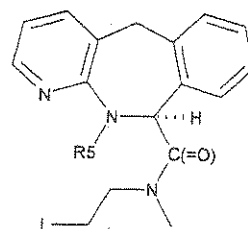
- X is a hydrocarbon group for subsequent ring closure, comprising one or more carbon atoms and optional hetero-atoms and a group Q and having a chain of between 1 to 6 atoms between the carbon atom attached to the central carbon atom of formula II and the group Q, or X is -C(=O)-Q, wherein Q is a hydrogen, halogen, a hydrocarbon substituent optionally comprising hetero atoms, or Q is -NHR or -OR, wherein R is hydrogen or a hydrocarbon substituent, or Q is L(CHR)_m-(NR)_p-(CRH)_n- wherein each R is independently hydrogen or a hydrocarbon substituent comprising one or more carbon atoms and/or hetero atoms, p is 0 or 1, n is 0 – 2, m is 1 - 3 and m + n is 1 – 3 and L is a leaving group.
- R₈ is hydrogen or a hydrocarbon substituent different from X making the central carbon atom of Formula II a chiral centre in Formula IIIa.

3b

According to a second aspect, there is provided a compound according to Formula IIIb or IVb in racemic, enantiomeric excess or enantiomeric pure R or S form,



Formula IIIb



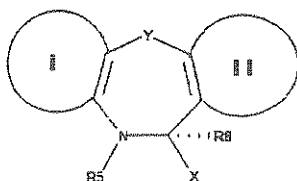
Formula IVb

(C(=O) here implies both CH₂ and C=O)

wherein X in Formula IIIb is a hydrocarbon group for subsequent ring closure, comprising one or more carbon atoms and optional hetero-atoms and a group Q and having a chain of between 1 to 6 atoms between the carbon atom attached to the central carbon atom of formula II and the group Q, or X is -C(=O)-Q, wherein Q is a hydrogen, halogen, a hydrocarbon substituent optionally comprising hetero atoms, or Q is -NHR or -OR, wherein R is hydrogen or a hydrocarbon substituent, or Q is L(CHR)_m-(NR)_p-(CRH)_n wherein each R is independently hydrogen or a hydrocarbon substituent comprising one or more carbon atoms and/or hetero atoms, p is 0 or 1, n is 0 - 2, m is 1 - 3 and m + n is 1 - 3 and L is a leaving group;

and whereby in Formula IVb, L is a leaving group and R₅ is hydrogen or a hydrocarbon substituent group comprising one or more carbon atoms and optionally one or more hetero atoms.

According to a third aspect, there is provided a compound according to Formula IIIa,



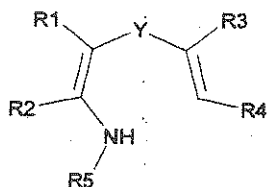
Formula IIIa

wherein

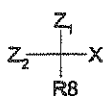
- ring structure I represents a pyridine;
- ring structure II represents a phenyl ring;
- Y is O, N-R₉ or CR₉R₁₀ wherein R₉ and R₁₀ are hydrogen or substituents comprising saturated or unsaturated hydrocarbons optionally comprising hetero atoms
- R₅ is hydrogen or a hydrocarbon substituent group comprising one or more carbon atoms and optionally one or more hetero atoms,
- X is -CO-Q wherein Q is a hydrogen, halogen, a hydrocarbon substituent optionally comprising hetero atoms, or Q is -NHR or -OR, wherein R is hydrogen or a hydrocarbon substituent, or Q is L(CHR)_m-(NR)_p-(CRH)_n- wherein each R is independently hydrogen or a hydrocarbon substituent comprising one or more carbon atoms and/or hetero atoms, p is 0 or 1, n is 0 – 2, m is 1 – 3 and m + n is 1 – 3 and L is a leaving group.
- R₈ is hydrogen or a hydrocarbon substituent different from X making the central carbon atom of Formula II a chiral centre in Formula IIIa.

Detailed Description of Embodiments

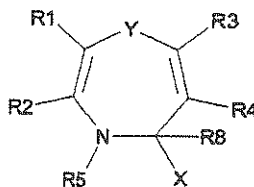
According to the invention there is provided a method for the preparation of a cyclic compound according to formula III comprising reacting a compound according to Formula I and a compound according to formula II,



Formula I



Formula II



Formula III

wherein in Formula I,

- R₁, R₂, R₃ and R₄ may be hydrogen or substituent groups comprising one or more carbon atoms and/or hetero-atoms, wherein R₁, R₂, R₃ and R₄ can be combined in aromatic or aliphatic ring structures,
 - Y is a ring element comprising 1 - 3 substituted or unsubstituted carbon atoms and/or heteroatoms in the ring and
 - R₅ is hydrogen or a hydrocarbon substituent group comprising one or more carbon atoms and optionally one or more hetero atoms,
- and wherein in Formula II,
- Z₁ and Z₂ are, leaving groups,
 - X is a reactive functional hydrocarbon group for subsequent ring closure, comprising one or more carbon atoms and a reactive functional group and having a chain of between 1 to 6 atoms between the carbon atom attached to the central carbon atom of formula II and the reactive functional group and
 - R₆ is hydrogen or a hydrocarbon substituent different from X making the central carbon atom of formula II a chiral centre in Formula III.

The compound according to formula I comprises a primary or secondary amine connected via 2 carbon atoms having an unsaturated bond, ring element Y and again to carbon atoms having an unsaturated bond to a reactive hydrogen atom. Said hydrogen atom is reactive because it is connected to an unsaturated bond. It is believed that the unsaturated bond adjacent to the amine group stereochemically facilitates the reaction between the amine and said reactive hydrogen atom. The ring element Y can optionally be combined with other substituent groups R₁, R₂, R₃ and R₄ to form a cyclic structure.

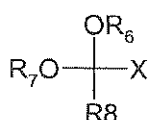
In a preferred embodiment R₃ and R₄ are combined forming a substituted or unsubstituted aromatic ring, preferably a phenyl or pyridine ring. It is considered that an aromatic ring promotes the reaction. The ring element Y may comprise 1, 2 or 3 ring atoms thus making the compound of formula III a seven, eight or nine membered ring. Preferably, Y is -O-, -NR₉- or -CR₉R₁₀- wherein R₉ and R₁₀ are hydrogen or hydrocarbon substituents that may be saturated or unsaturated and may optionally comprise hetero atoms.

The reaction between compound I and II is preferably carried out in the presence of a strong acid such as trifluoroacetic acid, methanesulfonic acid, toluenesulfonic acid, but most preferably sulphuric acid. The reaction between the compound of formula I and

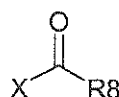
formula II proceeds by elimination of leaving groups Z_1 and Z_2 on compound II with the hydrogen on the amine and the reactive hydrogen. Although the substituents R_1 , R_2 , R_3 and R_4 are broadly defined, it is considered that preferably these substituents do not comprise primary or secondary amines or hydrogen atoms that are reactive with compound II. Suitable leaving groups Z_1 and Z_2 in formula II are each independently hydroxy, alkoxy, chloride, bromide, iodide, triflate, mesylate, tosylate or besylate.

Good results were obtained in a method wherein the compound II represents

- a (hemi-)acetal (for $R_8 = H$) or (hemi-)ketal (for $R_8 = \text{hydrocarbon}$) according to formula IIa wherein Z_1 and Z_2 are OR_6 and OR_7 respectively wherein R_6 and R_7 are hydrocarbon or hydrogen, or
- the corresponding aldehyde (for $R_8 = H$) or ketone (for $R_8 = \text{hydrocarbon}$) according to formula IIb:



Formula IIa



Formula IIb

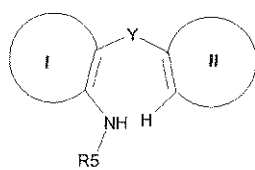
Suitable example of compounds according to formula IIa or IIb are alkylaminoacetaldehyde dialkylacetals, halogen acetaldehyde dialkylacetal, alkyl-2,2-dialkoxyacetate, 2,2- dialkoxyacetal alkylamide, 2,2- dialkoxyacetal (2-hydroxy ethyl) alkyl amide.

The method according to the invention is very suitable for preparing compounds having multi-cyclic structures. Such compounds often have biologic activity and can be used for the preparation of pharmaceutical formulations. The group X in the context of the present invention is chosen in view of further cyclization reaction, in one or more reaction steps, between reactive functional group X and the nitrogen in the ring in formula III. However, it is noted that compound of formula III wherein Y = oxygen or sulphur are novel irrespective of the choice of group X, so in this compounds X may also be hydrogen or hydrocarbon that is not substituted with a reactive functional group.

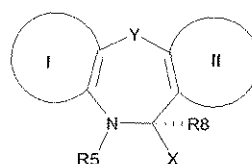
Bioorg. & Med. Chem. Lett., 2002, 12, 3573-3577 describes a method for the preparation of benzazepine antagonist for the neurotransmitters serotonin (5-HT) involving a reaction between paraformaldehyde and a compound according to formula
 5 Ia. Similarly, Journal of Combinatorial Chemistry, 8(3), 381-387; 2006 describes a method to prepare a polycyclic structure by ring closure between an amine and an aromatic hydrogen atom using an ethylaldehyde. However, these methods do not disclose or teach to prepare an intermediate according to formula IIIa comprising a group X that can be extended to achieve a further ring closure, in particular it does not
 10 disclose or teach the preparation of mirtazapine or any of its precursors, more particular having a substantial enantiomeric excess.

In view of preparing polycyclic compounds, the compound of Formula I is preferably a bicyclic compound according to general Formula Ia for forming, according to the
 15 method of the invention, a tricyclic compound according to Formula IIIa, wherein I and II represent ring structures, preferably comprising between five and eight ring atoms optionally comprising a hetero atoms N, S or O. The ring structures I and/or II may comprise one or more substitute groups preferably selected from alkyl, aryl, alkyl-aryl or alkoxy optionally comprising one or more ethylenically unsaturated bonds and/or
 20 optionally comprising one or more hetero atoms, halogen, hydroxy or sulphur containing groups.

25



Formula Ia

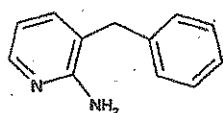


Formula IIIa

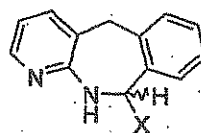
Most preferably, at least ring structure II, preferably both ring structure I and II represent a substituted or unsubstituted aromatic ring structure optionally comprising
 30 heteroatoms, preferably pyridine or phenyl, and wherein $Y = O, N-R_9$ or CR_9R_{10} (R_9 and R_{10} are hydrogen or substituents comprising saturated or unsaturated hydrocarbons optionally comprising hetero atoms). Most preferably ring II is a phenyl ring to form a benzazepine. Preferably, ring I is a phenyl or pyridine ring.

It is noted that all comments herein relating to generically described compounds similarly apply to the corresponding more specifically described compounds, for example comments to compounds of formulae I, II, III, IV and V similarly apply to compounds of formulae Ia, IIa, IIIa, IVa and comments to compounds IIIb apply to compounds IIIb1 and IIIb2 etc.

In a method for the preparation of mirtazapine, the compound according to Formula I is 2-amino-3-benzylpyridine of Formula Ib forming a novel mirtazapine precursor of formula IIIb. For the preparation of mirtazapine the group X is a reactive group comprising one or more carbon atoms and optional hetero-atoms chosen in view of one or more subsequent reaction steps to a following ring closure to form mirtazapine of Formula A.



Formula Ib

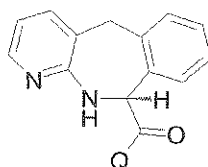


Formula IIIb

US 4062848 describes a method for the preparation of tetracyclic compounds according to formula IIIa starting from tricyclic compounds according to formula Ia wherein Y is CH_2 , R5 is H and ring II is a benzene ring. This method uses acid dihalogenide $\text{HalC(=O)(CH}_2)_n\text{Hal}$ to get ring closure forming an imine ring which is subsequently reduced to a benzazepine according to Formula IIIa. This preparation route has several disadvantages compared to the method according to the invention. First of all, this preparation route cannot be used to prepare mirtazapine starting from the compound of Formula Ib because the acid di-halogenide will also react with the nitrogen of the pyridine. This document does indeed not describe the preparation of mirtazapine following this method. Further, this preparation route has the general disadvantage that the preparation of the benzazepine with formula III, IIIa, or IIIb involves 2 reaction steps whereas the method according to the invention only comprises one reaction step.

In a particularly preferred embodiment of the invention X is $-\text{C(=O)}-\text{Q}$, wherein Q is a substituent, preferably nitrogen, oxygen, or hydrogen or a substituent group comprising one or more carbon or hetero-atoms. The invention relates in particular to the

mirtazapine precursor compound according to formula IIIb1 wherein X is $-C(=O)-Q$ in racemic form, but more preferably in enantiomeric excess or enantiomeric pure R or S form.



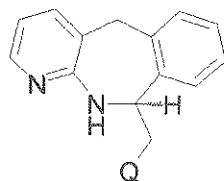
Formula IIIb1

The particular preference for this compound wherein X is $-C(=O)-Q$ follows from its property that the chiral center adjacent to the ketone/carbonyl ($>C=O$) group can easily be racemised at elevated temperatures and/or mildly basic or acidic conditions and therefore can be used in a dynamic enantiomer resolution to obtain either of the enantiomers in theoretically hundred percent yield. Accordingly, a preferred method for the preparation of the compound of formula III wherein X is $-C(=O)-Q$ in enantiomeric excess or enantiomeric pure form, comprises

- 1: subjecting a racemic mixture of said compound to an optical resolution step,
- 2: separating the desired enantiomer,
- 3: racemising the undesired enantiomer and
- 4: preferably recycling the racemised undesired enantiomer preferably to optical resolution step 1.

By racemising and recycling, the yield, defined as the amount in moles of the desired enantiomer divided by the amount in moles of the starting compounds of formula I or II is at least 70 %, preferably at least 80%, more preferably at least 85 %, more preferably at least 90 % and most preferably at least 95 %. The racemisation can be done preferably at slightly elevated temperatures under mildly basic or acidic conditions.

For the preparation of mirtazapine or other compounds of formula III having a methyl group adjacent to the chiral carbon, the method comprises a further step wherein the $C=O$ group is reduced to a methylene group, in particular wherein X is $-CH_2-Q$ is obtained by reduction of the compound wherein X is $-C(=O)-Q$ (formula IX).



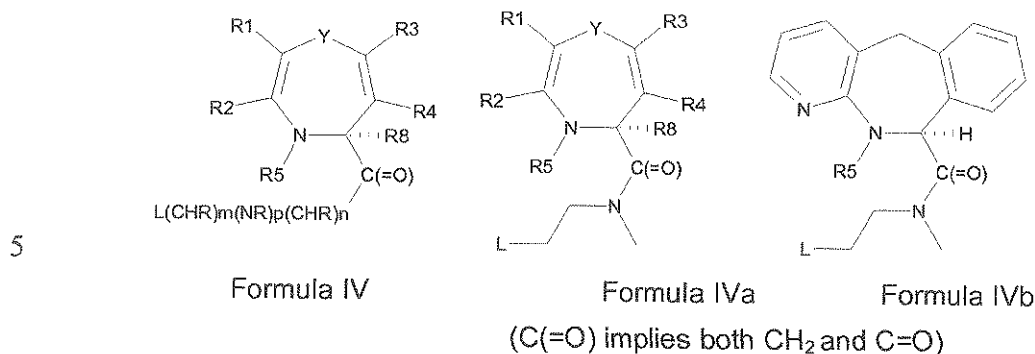
Formula IIIb2

It was found this can be done in an early stage or in any later stage during the
 5 preparation, preferably after ring closure where risk of racemization is less. In the
 method of the invention X can also be chosen to be $-\text{CH}_2\text{-Q}$, wherein Q is a substituent
 as defined above. In this method racemisation is not possible and optical resolution
 must be done using known methods, like diastereomer selective crystallisation.
 Although this inadvertently leads to a lower yield than the preparation route described
 10 above using the carbonyl precursor, it is still possible to obtain a good yield while
 producing considerably lower amounts of waste compared to prior art methods where
 the optical resolution step is done at a later stage in the preparation process.

The intermediate III is very useful for the preparation of optically pure mirtazapine and
 15 can be used for the preparation of S-mirtazapine, R-mirtazapine or for racemic
 mirtazapine. In principle all options presented can be applied for both enantiomerically
 pure or racemic mirtazapine. Esters ($\text{Q} = \text{OR}$ in formula IIIb1) can be resolved by using
 a chiral acid such as (-)-dibenzoyl-L-tartaric acid yielding the (S)-enantiomer. The
 amide enantiomers ($\text{Q} = \text{NRH}$) can be resolved by using a chiral acid, for example
 20 enantiopure mandelic acid. A bromide precursor can be resolved via diastereoselective
 crystallization, for one sample with R(+)-mandelic acid giving the S-enantiomer.
 Similarly the opposite R-enantiomer can be obtained by resolution with S(-)-mandelic
 acid.

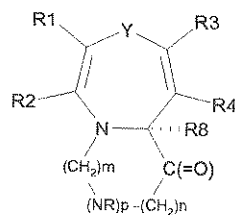
25 The group X in formula II is chosen in view of the subsequent reaction steps towards
 desired end products. In view of the general object to produce polycyclic structures, the
 intermediate compound according to formula IV can be prepared. Accordingly, in the
 preparation method a compound II is chosen wherein X is $-\text{C}(=\text{O})\text{Q}$ or $-\text{CH}_2\text{Q}$ and
 wherein Q is chosen to be $\text{L}(\text{CHR})_m(\text{NR})_p-(\text{CRH})_n-$ wherein each R may be the same
 30 or different substituent hydrogen or a hydrocarbon substituent comprising one or more
 carbon atoms and/or hetero atoms, p is 0 or 1, n is 0 – 2, m is 1 – 3 and $m + n$ is 1 – 3
 and L is a leaving group. For the formation of a six membered ring it is preferred that Q
 is $-\text{LC}_2\text{H}_4\text{NMe}-$, in order to obtain a precursor of formula IVa. In the preparation

process for mirtazapine, said intermediate compound is the compound according to formula IVb.



Alternatively, instead of choosing a compound II that directly produces a compound of
 10 Formulae IV, IVa or IVb, a method can be followed wherein Q comprises a reactive
 group which is reacted with an extender according to the formula $L(CHR)_m-(NR)_p-(CRH)_nA$, wherein A is a group reactive with Q. For the preparation of compound of
 formula IVa or IVb (from compounds III, IIIa, IIIb, IIIb1, or IIIb2), the group Q can be
 reacted with extension group $-AC_2H_4L$ to form a group $-NMeC_2H_4L$. Good results were
 15 obtained in preparations wherein Q is a halogen, $-NHR$ or $-OR$ wherein R is a
 hydrogen or hydrocarbon substituent, preferably a C1 – C4 alkyl. In case Q is a good
 leaving group, preferably halogen or $-OR$, A is $RHN-$ or, reversely, in case Q is a $RHN-$
 group, A is a good leaving group, preferably halogenide or OR wherein R comprises a
 tolylate or mesylate. It was found for mirtazapine preparation that this extension
 20 reaction proceeds with a very high retention of optical purity. If the synthesis is started
 from an enantiopure form of compound III, the compound of formula IV can be obtained
 in enantiopure form.

A compound of formula IV wherein L is a weak leaving group can be converted into a
 25 compound according to formula V by modification of said weak leaving group L into a
 strong leaving group and subsequent ring closure in the presence of a base through
 nucleophilic displacement of the leaving group by the amidine in the ring. The strong
 leaving group L is preferably chosen from the group of chloride, bromide, iodide,
 methanesulfonate, toluenesulfonate, triflate, etc.



formula V

Leaving group L can be chosen to be a weak leaving group, preferably hydroxyl, to
 5 prevent interference with the reaction between Q and A. However, it is also possible in
 the extension reaction to directly proceed to ring closure forming the compound
 according to formula V in one step. In this case L in the compound of formula IV is
 chosen to be a stronger leaving group that can react directly with the amine in the
 presence of a base. In the method for the preparation of mirtazapine via compounds of
 10 Formula Ib, IIIb or IVb this results in mirtazapine according to formula A.

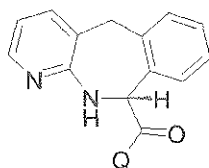
As described above, in case the compound is derived from an intermediate compound
 comprising a carbonyl group adjacent to the chiral center, a further reduction step can
 follow to reduce the carbonyl group $>C=O$ to an ethylene group $>CH_2$.

15

The invention also relates to the intermediate compounds for the preparation of
 mirtazapine according to formulae IIIb, IVb or Vb in racemic, enantiomeric excess or
 enantiomeric pure R or S form and to any method for the preparation of mirtazapine in
 racemic, enantiomeric excess or enantiomeric pure R or S form using any of these
 20 compounds. US 4, 062, 848 describes similar precursors only in generic terms, but not
 a preparation route specifically for the preparation of mirtazapine from such precursors.
 Mirtazapine precursor Ib indeed cannot be used because the acid di-halogenide will
 also react with the nitrogen of the pyridine ring resulting in an entirely different
 unwanted product.

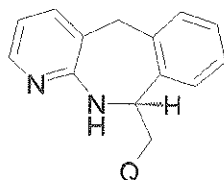
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Particularly preferred are intermediate compounds for the preparation of mirtazapine
 according to Formula IIIb1 in racemic form, in enantiomeric excess or enantiomeric
 pure R or S form, wherein Q is a reactive group for ring formation, preferably –
 NMeC₂H₄L, halogen, –NHMe or –OR wherein R is hydrogen or a hydrocarbon
 30 substituent, preferably a C1 – C4 alkyl. These components are preferred because they
 can easily be converted to a racemic state and recycled to the optical resolution step
 resulting in a very high yield.



Formula IIIb1

- 5 The invention also specifically relates to intermediate compounds for the preparation of mirtazapine according to Formula IIIb2 in enantiomeric excess or enantiomeric pure R or S form, wherein Q is a reactive group for ring formation, preferably $-\text{NMeC}_2\text{H}_4\text{L}$, halogen, $-\text{NHMe}$ or $-\text{OR}$ wherein R is hydrogen or a hydrocarbon substituent, preferably a C1 – C4 alkyl.



Formula IIIb2

10 The invention also relates to precursor compounds in enantiomeric excess or enantiomeric pure R or S form according to general formula III, IV, and V. Although in the forementioned prior art document a broad statement is made that optically active compounds can be made from optically active precursors, it is considered that this broad statement does not provide a specific enabling pointer to enantiopure intermediate compounds. There is no disclosure of a specific optically active intermediate compound, no disclosure of a process to prepare such optically active compounds and no disclosure of a process using such optically active precursors. In fact all examples of enantiopure compounds were prepared only using an entirely different preparation route using entirely different precursors followed by optical resolution only of the end products. Further, inventors have found that a preparation method described in this prior art document results in considerable racemisation, so the broad statement is merely an unsubstantiated desideratum.

The invention further relates to compounds according to formula III or IIIa, wherein X is $-\text{C}(=\text{O})-\text{Q}$ or compounds according to formula IV, IVa, or V, comprising a $\text{C}=\text{O}$ group adjacent to the chiral carbon atom and their use for the manufacture of the

corresponding compounds having a substantial enantiomeric excess of the R or S enantiomer, optionally followed by reduction of the $-C(=O)-$ group to a $-CH_2-$ group. As described above these compounds having a $C=O$ group adjacent to the chiral carbon can relatively easily be racemised allowing recycling of the racemised
5 undesired enantiomer and a preparation process with a very high yield.

The invention will be illustrated by the following examples.

Example 1

- 10 A methylamine compound according to formula IIIb2 wherein Q = NHMe (10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepin-10-ylmethyl)-methyl-amine) was prepared as described below using two different methods A and B.

Method A.

- 15 A mixture of 2-amino-3-benzylpyridine (2.1 g, 11.4 mmol) and N-methylaminoacetaldehyde dimethyl acetal (3.7 g, 31.1 mmol, 2.7 eq.) in a 250 ml round-bottomed flask was treated at room temperature with concentrated sulphuric acid (30 ml) by quick addition while stirring. A vigorous exothermic reaction took place. After stirring for 45 minutes the dark mixture was poured on ice water (250 ml).
20 Concentrated ammonia (25% aq.; 150 ml) was added to basify the mixture. Extraction was done with ethyl acetate (3 x 150 ml). The combined organic layers were dried with Na_2SO_4 . Evaporation under vacuum gave the crude 10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepin-10-ylmethyl)-methyl-amine as a yellow oil (2.5 g, 10.5 mmol) in 92% yield.
25 Mass analysis: $M^{+1} = 240$ major peak.

- 1H -NMR ($CDCl_3$) δ (ppm) 2.16 1H, br s, NH; 2.54 3H, s, N-CH₃; 3.14-3.18 2H, m; 3.68 1H, d, J = 15.2 Hz, CHH; 4.45 1H, d, J = 15.2 Hz; 5.05 1H, dd, J = 2.4 and 6.0 Hz; 5.55 1H, br s, NH; 6.49 1H, dd, J = 5.1 and 7.5 Hz, ArH; 7.15 1H, m, ArH; 7.19-7.27 4H, m,
30 ArH; 7.86 1H, dd, J = 1.8 and 5.1 Hz, ArH.

Chiral HPLC analysis: column Chiralcel OJ (250 x 4.6 mm; 5 μ m), mobile phase: n-heptane/EtOH/Et₂NH (90:10:0.2), flow: 1.0 ml/min, UV: 248 and 308 nm, sample: ~ 1 mg/ml in 2-propanol, injection: 10 μ l, temp: 22 °C. Enantiomers at 13.8 and 18.0 min. The product was used in subsequent steps without further purification.

35

Method B. Via reduction of N-methylamide

N-methylamide (700 mg, 2.77 mmol) was dissolved in THF (20 ml). The solution was cooled to 0 °C while stirring $\text{BF}_3 \cdot \text{OEt}_2$ (1.0 ml, 7.89 mmol, 2.8 eq.) was added and the mixture was stirred for 30 minutes at 0 °C. Then $\text{BH}_3 \cdot \text{SMe}_2$ (3.0 ml, 2.0 M in THF; 6.0 mmol) was added. After stirring for 3 hours at room temperature the mixture was
5 heated to reflux for 3 hours to give almost complete conversion. The mixture was then cooled to room temperature and 2N HCl was added to quench the excess borane, followed by the addition of water (20 ml) and ethyl acetate (100 ml). The organic layer was separated. The aqueous layer was extracted with dichloromethane (2 x 25 ml). The combined organic layers were dried with Na_2SO_4 and concentrated under vacuum
10 to give an oil. Purification by chromatography on silica gel gave the pure product (298 mg, 1.25 mmol) in 45% yield.

Mass analysis: $M^{+1} = 240$ major peak.

Example 2

15 A bromine compound according to formula IIIb2 wherein Q = Br (10-bromomethyl-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine) was prepared as described below using two different methods A and B.

Method A. Neat

20 A mixture of 2-amino-3-benzylpyridine (12.0 g, 65.2 mmol) and bromoacetaldehyde dimethyl acetal (19 g, 112.4 mmol, 1.7 eq.) in a 250 ml round-bottomed flask was treated at room temperature with concentrated sulphuric acid (50 ml) by quick addition. A vigorous exothermic reaction took place. After stirring for one hour the dark mixture was poured on ice (ca. 500 ml). Concentrated ammonia was added to basify the
25 mixture. Extraction was done with ethyl acetate (100 ml) and dichloromethane (2 x 150 ml). The combined organic layers were dried with Na_2SO_4 . Evaporation under vacuum gave 10-bromomethyl-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine as a brown powder (14 g, 48.6 mmol) in 75% yield. Mass analysis: M^{+1} 289,291 (Br-isotope) major peak.
30 $^1\text{H-NMR}$ (CDCl_3) δ (ppm) 3.88 2H, d, $J = 6.9$ Hz, CH_2Br ; 3.95 1H, d, $J = 15.3$ Hz, CHH ; 4.05 1H, d, $J = 15.3$ Hz, CHH ; 5.01 1H, dd, $J = 6.9$ and 12.3 Hz, CH; 5.35 1H, br s, NH; 6.58 1H, dd, $J = 4.8$ and 6.9 Hz, ArH; 7.17-7.29 5H, m, ArH; 7.93 1H, dd, $J = 2.1$ and 4.8 Hz, ArH.

The product was used without further purification.

35

Method B. Dichloromethane solution

A mixture of 2-amino-3-benzylpyridine (11.6 g, 63.0 mmol) and bromoacetaldehyde dimethyl acetal (10.65 g, 63.0 mmol, 1.0 eq.) was dissolved in dichloromethane (100 ml). The stirred solution was cooled to 0°C with an ice bath. Concentrated sulphuric acid (50 ml) was added in portions over ca. one minute to the cooled solution while stirring. A vigorous exothermic reaction took place. Stirring was continued for 3 hours while warming to room temperature. The mixture was poured on ice (ca. 500 ml). The resulting mixture was basified with concentrated ammonia (250 ml). Extraction was done with dichloromethane (3 x 200 ml). The combined organic layers were dried with Na₂SO₄. Evaporation under vacuum gave 10-bromomethyl-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine as a brown powder (15.3 g, 53.1 mmol) in 84% yield and 98% purity (LC-MS). The product was used without further purification.

Example 3

The compounds obtained in example 2 (IIIb2, Q = Bromide) were optically resolved by diastereomeric salt resolution of the enantiomer mixture (10-bromomethyl-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine).

A solution of *S*(+)-mandelic acid (7.0 g, 46.2 mmol) in EtOH (100 ml) was added to a warm solution of bromide (13.3 g, 46.2 mmol) in EtOH (400 ml). The mixture was heated to reflux and then slowly cooled to room temperature while stirring in the heating mantle. After 4 hours the suspension was filtered over a P2-glass filter to give a pale brown solid. The solid was washed with 2-propanol (10 ml) and isopropyl ether (25 ml) and then dried under vacuum to give 7.7 g salt (17.5 mmol; $M_{\text{salt}} = 440$) in 38% yield with 59% d.e. (chiral HPLC). Recrystallization in EtOH (200 ml) gave 5.2 g salt with 74% d.e. Again recrystallization from EtOH (70 ml) gave 83% d.e. After two more recrystallizations the free base was liberated with aq. Na₂CO₃/dichloromethane to give bromide *R*(-)-10-bromomethyl-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine with 92% e.e.

The first filtrate from above was concentrated under vacuum to give 6.3 g salt (21.8 mmol). The free base was liberated and dissolved in EtOH (250 ml). *R*(-)-mandelic acid (0.8 eq., 2.66 g, 17.5 mmol) was added. The mixture was heated to reflux and then cooled to room temperature overnight. The suspension was filtered over a glass filter. The salts were washed with EtOH (10 ml) and isopropyl ether (25 ml). Drying under vacuum gave 3.9 g salt (8.9 mmol) in 19% yield with 86% d.e. Recrystallization from EtOH (40 ml) gave after hot filtration 3.2 g salt with 92% d.e.. After two more recrystallizations the salt was obtained with 97% d.e. Liberation of the free base gave

bromide S(+)-10-bromomethyl-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine with 97% e.e.

Chiral HPLC analysis: column Chiralcel OJ (250 x 4.6 mm; 5 μ m), mobile phase: 5 *n*-heptane/2-PrOH/Et₂NH (60:40:0.2), flow: 1.0 ml/min, UV: 248 and 308 nm, sample: ~ 1 mg/ml in 2-propanol, injection: 10 μ l, temp: 22 °C. Enantiomers at 10.3 min (minor) and 24.9 min. (major *R*-isomer).

Example 4

10 A methyl ester compound according to formula IIIb1 wherein Q = OMe (10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-carboxylic acid methyl ester) was prepared as described below.

A mixture of 2-amino-3-benzylpyridine (18.3 g, 99.4 mmol; crude) and methyl 2,2-dimethoxyacetate (22 g, 21.6 mmol, 1.9 eq.) in a 250 ml round-bottomed flask was 15 treated at room temperature with concentrated sulphuric acid (50 ml) by quick addition while stirring. A vigorous exothermic reaction took place. After stirring for 30 minutes the dark mixture was poured on ice water (1000 ml). Concentrated ammonia (25% aq.; 250 ml) was added to basify the mixture. Extraction with dichloromethane (2 x 150 ml). 20 The combined organic layers were dried with Na₂SO₄. Evaporation under vacuum gave 10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-carboxylic acid methyl ester as a yellow foam (18.5 g, 72.8 mmol) in 73% yield. An analytically pure sample can be obtained by chromatography on silica gel. *R*_f = 0.3 (EtOAc/*n*-heptane = 1:1).

25 Mass analysis: *M*⁺ = 255 major peak.

¹H-NMR (CDCl₃) δ (ppm) 3.84 3H, s, OCH₃; 3.86 1H, d, *J* = 15.5 Hz, CHH; 4.11 1H, d, *J* = 15.5 Hz, CHH; 5.51 1H, d, *J* = 5.7 Hz; 5.87 1H, br s, NH; 6.52 1H, dd, *J* = 5.1 and 7.2 Hz, ArH; 7.08 1H, m, ArH; 7.20-7.31 4H, m, ArH; 7.88 1H, dd, *J* = 1.5 Hz and 4.8 Hz, ArH.

30 M.p. 130.6 °C

Chiral HPLC analysis: column Chiralpak AD-H (250 x 4.6 mm; 5 μ m), mobile phase: *n*-heptane/EtOH/Et₂NH (50:50:0.2), flow: 0.5 ml/min, UV: 248 and 308 nm, sample: ~ 1 mg/ml in 2-propanol, injection: 10 μ l, temp: 22 °C. Enantiomers at 44.8 35 ((+)-isomer) and 68.5 min. ((-)-isomer).

The product was used without further purification.

Example 5

The methyl ester compound obtained in example 4 (IIIb1, Q = OMe) was optically resolved by diastereomeric salt resolution.

5

A mixture of methyl ester (10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-carboxylic acid methyl ester) (2.14 g, 8.41 mmol) in EtOH (35 ml) and (-)-dibenzoyl-L-tartaric acid (3.01 g, 8.41 mmol) was stirred at 70 °C until a clear solution was obtained. While cooling to room temperature salts precipitated. After 18 hours the precipitated
10 salts were filtered over a glass filter. The solids were washed with EtOH (10 ml), isopropanol (10 ml) and isopropyl ether (25 ml). Drying under vacuum gave the diastereomeric salt (1.54 g, 2.52 mmol) in 30% yield with 80% d.e. The ee was determined as follows. Treatment of a sample of the salt with aq. Na₂CO₃ and extraction with CH₂Cl₂ gave after evaporation an oil. Chiral HPLC analysis showed that
15 the sample had 80% ee of the (-)- isomer. Repeated recrystallization of the salt from EtOH gave (-)- with >99% ee.

Example 6

An ethyl ester compound according to formula IIIb1 wherein Q = OEt (10,11-dihydro-
20 5H-benzo[e]pyrido[2,3-b]azepine-10-carboxylic acid ethyl ester) was prepared as described below.

A mixture of 2-amino-3-benzylpyridine (2.1 g, 11.4 mmol) and ethyl 2,2-diethoxyacetate (3.8 g, 21.6 mmol, 1.9 eq.) in a 250 ml round-bottomed flask was treated at room
25 temperature with concentrated sulphuric acid (10 ml) by quick addition while stirring. A vigorous exothermic reaction took place. After stirring for 30 minutes the dark mixture was poured on ice water (100 ml). Concentrated ammonia (25% aq.; 25 ml) was added to basify the mixture. Extraction with ethyl acetate (2 x 50 ml). The combined organic layers were dried with Na₂SO₄. Evaporation under vacuum gave 10,11-dihydro-5H-
30 benzo[e]pyrido[2,3-b]azepine-10-carboxylic acid ethyl ester as a dark yellow oil (2.4 g, 8.9 mmol) in 79% c.y. An analytically pure sample can be obtained by chromatography on silica gel. R_f = 0.3 (EtOAc/n-heptane = 1:1).

Mass analysis: M⁺ = 269 major peak.

¹H-NMR (CDCl₃) δ (ppm) 1.28 3H, d, J = 7.2 Hz, CH₃; 3.80 1H, d, J = 15.5 Hz, CHH;
35 4.18 1H, d, J = 15.5 Hz, CHH; 4.32 2H, q, J = 7.2 Hz, OCH₂; 5.54 1H, d, J = 5.1 Hz;

5.86 1H, br d, J = 5.1 Hz, NH; 6.50 1H, dd, J = 4.8 and 7.2 Hz, ArH; 7.08 1H, m, ArH; 7.20-7.30 4H, m, ArH; 7.88 1H, dd, J = 1.5 Hz and 4.8 Hz, ArH.

Chiral HPLC analysis: column Chiralcel OF (250 x 4.6 mm; 5 μ m), mobile phase: *n*-heptane/2-PrOH/Et₂NH (95:5:0.2), flow: 1.0 ml/min, UV: 248 and 310 nm, sample: ~

- 5 1 mg/ml in 2-propanol, injection: 10 μ l, temp: 22 °C. Enantiomers at 75.3 ((+)-isomer and 83.6 min. ((-)-isomer).

The product was used without further purification.

Example 7

- 10 The ethyl ester compound obtained in example 6 (IIIb1, Q = OEt) was optically resolved by diastereomeric salt resolution.

A warm solution of the ethyl ester (3.2 g, 11.94 mmol) in EtOH (50 ml) at 70 °C was treated with (-)-dibenzoyl-L-tartaric acid (4.27 g, 11.94 mmol). The mixture was stirred

- 15 at 70 °C for 30 minutes. The resulting clear solution was stirred while cooling to room temperature. The precipitated salts were filtered over a glass filter. The solids were washed with EtOH (10 ml), isopropanol (10 ml) and isopropyl ether (25 ml). Drying under vacuum gave the diastereomeric salt (2.2 g, 3.51 mmol) in 29% c.y. with 88% d.e. The ee was determined as follows. Treatment of a sample of the salt with aq.
- 20 Na₂CO₃ and extraction with CH₂Cl₂ gave after evaporation an oil. Chiral HPLC analysis showed that the sample had 88% ee of the (-)-enantiomer. Repeated recrystallization of the salt from EtOH gave (-)- with >99% ee. The absolute configuration of the (-)- isomer is not known.

- Evaporation of the combined filtrates, basifying with aq. Na₂CO₃ and extraction with
- 25 CH₂Cl₂ gave 2.2 g (8.2 mmol) of the opposite enantiomer (+)- (39% e.e.) with 69% recovery.

Example 8

- 30 A carboxamide compound according to formula IIIb1 wherein Q = NHMe (10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-N-methylcarboxamide) was prepared as described below using 2 different methods A and B

Method A. From methyl ester compound obtained in example 4:

- 35 Methylamine (250 ml 40% in water) was added to the crude methyl ester compound (22.5 g, 88.6 mmol) at room temperature. The mixture was heated to 65 °C on a water

bath for 5 minutes. The obtained solution was stirred overnight while cooling to room temperature. The reaction mixture was heated to reflux for one hour and then evaporated under vacuum to dryness. Toluene (50 ml) was added and the mixture was evaporated to dryness. Acetone (50 ml) was added and the mixture was again
5 evaporated to dryness to give the crude racemic carboxamide nearly quantitatively.

Mass analysis: $M^{+1} = 254$ major peak

$^1\text{H-NMR}$ (CDCl_3) δ (ppm) 2.88 3H, quasi d, N-CH₃; 3.49 1H, d, $J = 15.0$ Hz, CHH; 4.15 1H, d, $J = 15$ Hz, CHH; 4.92 1H, br s, CH; 5.95 1H, br s, NH; 6.58 1H, dd, $J = 5.1$ and 7.5 Hz, ArH; 6.96 1H, br s, NH; 7.16-7.32 5H, m, ArH; 7.90 1H, dd, $J = 1.2$ and 5.1 Hz,
10 ArH.

The crude product was used without further purification.

Method B. From ethyl ester compound obtained in example 6

A mixture of ethyl ester (500 mg, 1.87 mmol) and 40% aqueous methylamine (50 ml)
15 was stirred at room temperature overnight to give complete conversion to the N-methylamide. Extraction was done with toluene (2 x 50 ml) and dichloromethane (2 x 50 ml). The combined organic extracts were dried with Na_2SO_4 . Evaporation under vacuum gave pure amide in nearly quantitative yield according to $^1\text{H-NMR}$ and mass analysis: $M^{+1} = 254$ found

20

Example 9

The carboxamide compound obtained in example 8 (IIIb1, Q = NHMe) was optically resolved by diastereomeric salt resolution.

25 A mixture of the racemic carboxamide compound (19.2 g, 75.9 mmol) and S(+)-mandelic acid (11.54 g, 1.0 eq.) was mixed with ethanol (100 ml). The suspension was shortly heated to 65 °C to give a clear solution. The warm solution was stirred while cooling to room temperature. After 24 hours the salts were filtered over a glass filter under suction. The finely divided powder was washed with ethanol (10 ml) and then
30 washed with isopropyl ether (2 x 40 ml). The residual solid was dried under vacuum to give the S(+)-mandelic acid salt (9.4 g, 23.2 mmol) as an off-white solid in 31% yield with 74% d.e., according to chiral HPLC of the liberated S(+)-carboxamide. The salt was recrystallized from ethanol to give 6.8 g salt with 86% d.e.

The combined filtrates were basified with aqueous Na_2CO_3 and the corresponding R(-)-
35 isomer was extracted with dichloromethane. The organic layer was dried with Na_2SO_4 . Evaporation under vacuum gave R(-)-enantiomer (6.4 g, 25.3 mmol) with 44% e.e.

Then, *R*(-)-mandelic acid (2.88 g, 18.95 mmol, 0.72 eq.) and ethanol (25 ml) were added. The mixture was warmed to give a clear solution. Upon stirring while cooling to room temperature precipitation of the *R*(-)-mandelic acid salt of *R*(-)-enantiomer took place. The salt was filtered over a glass filter and washed with ethanol (5 ml) and isopropyl ether (2 x 25 ml). After drying under vacuum 4.0 g (9.88 mmol) of the *R*(-)-mandelic acid salt of *R*(-)-enantiomer was obtained in 39% yield, with 98% d.e. Treatment of the salt with aqueous Na₂CO₃ and extraction with CH₂Cl₂ gave pure *R*(-)-amide.

10 **Example 10**

An extended compound hydroxyethyl-carboxamide compound (according to formula IIIb1 with Q = HOC₂H₄NMe-) (10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-N-(2-hydroxyethyl)-carboxamide) was prepared as described below using 2 different methods A and B.

15

Method A. From methyl ester compound obtained in Example 4:

2-(N-methyl)-aminoethanol (25 g, 330 mmol) was added to a preheated solution of 10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-carboxylic acid methyl ester (27.5 g, 108.3 mmol) in THF (100 ml) at 75 °C while stirring. After 30 minutes ca. 15% conversion was observed by LC-MS. The reaction mixture was stirred for 3 days at room temperature. Concentration under vacuum (at 95 °C) gave a brown solid. Dichloromethane (200 ml) was added and after stirring for 5 minutes the mixture was filtered over a glass filter. The solid residue was washed with ethyl acetate (300 ml) and acetone (50 ml). Drying under vacuum gave the amide as an off-white solid (18.4 g, 61.95 mmol) in 57% yield. From the combined filtrates a second crop of amide was isolated by filtration and drying.

Mass analysis: M⁺ = 298 major peak.

¹H-NMR (dmso-d₆) δ (ppm) (appears as a mixture of amide rotamers) 2.80 1.8H, s, N-CH₃; 3.05 1.2H, s, N-CH₃; 3.16-3.70 6H, m; 4.71 1H, d, J = 15 Hz, CHH; ; 4.83 1H, d, J = 15 Hz, CHH; 5.96, 1H, dd, J = 5.1 and 9.9 Hz; 6.23 1H, dd, J = 5.1 and 10.2 Hz; 6.46 1H, dd, J = 4.8 and 6.9 Hz, ArH; 6.88 0.34H, m, NH; 7.00 0.66H, m, NH; 7.21-7.31 5H, m, ArH; 7.75 1H, d, J = 5.1 Hz, ArH.

Method B. From ethyl ester compound obtained in Example 6:

35 A mixture of 2-(N-methyl)-aminoethanol (10 g, 133.2 mmol) and 10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-carboxylic acid ethyl ester (2.0 g, 7.46 mmol) was

heated for 15 minutes at 70 °C while stirring. The resulting mixture was stirred for 5 days at room temperature. The mixture was concentrated under vacuum (at 90 °C) to give the amide as a brown solid in nearly quantitative yield.

Mass analysis: $M^{+1} = 298$ major peak. The product was used without further purification.

Example 11

A hydroxyethylmethylamide compound (according to formula IIIb2 with Q = $\text{HOC}_2\text{H}_4\text{NMe-}$) according to formula IIIb2 (10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-yl-(2-hydroxyethyl)-methylamine), was prepared as described below using 2 different methods A and B

Method A. From the bromide compound obtained in Example 2 and N-methylaminoethanol

A solution of 10-bromomethyl-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine (13.4 g, 46.5 mmol), 2-(methylamino)ethanol (31 g, 413.3 mmol; 8.9 eq.) and K_2CO_3 (26 g, 188.4 mmol; 4 eq.) was heated to reflux in acetonitrile (50 ml) for 15 minutes and then stirred over the weekend (3 days) while cooling to room temperature in the shut-off heating mantle. The reaction mixture was concentration under vacuum. Water was added and the crude product was extracted with dichloromethane (2 x 25 ml). The dichloromethane solution was dried with Na_2SO_4 , filtered and concentrated to give the crude hydroxyethylamine, which could be used directly in the following step. A sample of 4 g crude material was purified by automated ISCO chromatography and afforded 510 mg (1.77 mmol) analytically pure product.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm) 2.39 3H, s, CH_3 ; 2.58-2.86 3H, m; 3.12 1H, t, $J = 11.7$ Hz; 3.52 1H, d, $J = 15.0$ Hz, CHH ; 3.61-3.75 3H, m; 4.64 1H, d, $J = 15.0$ Hz, CHH ; 5.17 1H, dd, $J = 3.9$ and 10.8 Hz; 6.01 1H, br s, NH; 6.45 1H, m, ArH; 7.12-7.30 5H, m, ArH; 7.77 1H, d, $J = 4.8$ Hz.

Method B. From the methyl amine compound obtained in Example 2 and bromoethanol

Potassium carbonate (14.6 g, 105.8 mmol, 2 eq.) was added to a mixture of amine 10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepin-10-ylmethyl)-methyl-amine (13.7 g, 57.3 mmol) and bromoethanol (1.0 eq., 7.16 g) in DMF (50 ml). The mixture was heated to reflux for 5 hours. Evaporation of the solvent under vacuum, addition of

dichloromethane and washing with water gave after drying of the organic layer with Na₂SO₄ and concentration under vacuum the product in nearly quantitative yield.

Example 12

- 5 Mirtazapine was prepared from 10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-yl-(2-hydroxyethyl)-methylamine obtained in Example 11

10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-yl-(2-chloroethyl)-methylamine

- Thionyl chloride (2 ml) was added to a solution of 10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-yl-(2-hydroxyethyl)-methylamine in dichloromethane (15 ml) at room temperature to replace the hydroxy group with a stronger leaving group. After stirring for one hour the reaction mixture was concentrated under vacuum to give the crude chloride compound as a brown oil. Mass analysis: M⁺¹ = 302,304 (Cl-isotope).

15 ***Mirtazapine***

- The crude 10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-yl-(2-chloroethyl)-methylamine obtained (some starting material present) was dissolved in DMF (10 ml). K₂CO₃ (800 mg) and KI (500 mg) were added. The mixture was refluxed for 4 hours. Dilution with water (100 ml) and extraction with dichloromethane (2 x 100 ml) gave after drying with Na₂SO₄ and evaporation crude racemic mirtazapine as an oil.

- ¹H-NMR (CDCl₃) δ (ppm) 2.32 1H, dd, J = 3.3 and 10.8 Hz, H-3; 2.37 3H, s, N-CH₃; 2.51 1H, t, J = 10.2 Hz, H-1; 2.86 1H, m, H-1; 2.96 1H, m, H-3; 3.42 1H, d, J = 13.2 Hz, H-10; 3.50 1H, m, H-4; 3.69 1H, m, H-4; 4.35 1H, dd, J = 2.4 and 9.9 Hz, H-14b; 4.52 1H, d, J = 13.5 Hz, H-10; 6.72 1H, dd, J = 4.8 and 7.2 Hz, H-8; 7.14 4H, m, ArH; 7.30 1H, m, H-9; 8.15 1H, dd, J = 1.8 and 5.1 Hz, H-7.

Example 13

Mirtazapine was prepared from 10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-N-(2-hydroxyethyl)-carboxamide obtained in example 10.

30

10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-N-(2-chloroethyl)-carboxamide

- Thionyl chloride (13.5 ml) was added to a suspension of 10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-N-(2-hydroxyethyl)-carboxamide (18.6 g, 61.95 mmol) in chloroform (100 ml) at room temperature. The mixture was stirred overnight at room temperature. Evaporation under vacuum gave an oily product. The residue was

35

coevaporated with toluene (50 ml) under vacuum to give the crude chloride as a beige solid in quantitative yield. Mass analysis: $M^{+1} = 316,318$ (Cl-isotope).

The chloride was used without further purification.

5 **3,4,10,14b-tetrahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2]benzazepin-1(2H)-one**

A mixture of crude 10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-N-(2-chloroethyl)-carboxamide (2.4 g, 7.46 mmol), K_2CO_3 (3.5 g, 25.4 mmol) and KI (2.7 g, 16.3 mmol) in DMF (100 ml) was heated to reflux while stirring. After 3 hours the
10 heating was stopped and the mixture was stirred overnight while cooling to room temperature. The mixture was evaporated under vacuum at 85 °C. Water (50 ml) was added and the mixture was extracted with a mixture of dichloromethane/methanol (95:5, 100 ml). The organic extract was concentrated under vacuum. The obtained brown oil was dissolved in acetone (10 ml). Upon addition of t-butyl methyl ether (50
15 ml) a beige precipitate was formed which was filtered over a glass filter under suction. Drying under vacuum gave 0.28 g of the title compound (13% yield) as a white solid. The remaining filtrate was evaporated under vacuum and the residue was purified by chromatography on silica gel, eluting with dichloromethane/methanol = 9:1 ($R_f = 0.1$) to give another crop of the title compound as a white solid.

20 Mass analysis: $M^{+1} = 280$.

1H -NMR ($CDCl_3$) δ (ppm) 3.19 3H, s, N-CH₃; 3.30-3.44 2H, m; 3.49 1H, d, J = 16.2 Hz, CHH; 3.71 1H, m; 4.42 1H, m; 4.83 1H, d, J = 16.2 Hz, CHH; 5.90 1H, s; 6.63 1H, dd, J = 5.1 and 7.5 Hz, ArH; 7.09 1H, m, ArH; 7.23 3H, m, ArH; 7.33 1H, d, J = 6.9 Hz, ArH; 8.01 1H, dd, J = 0.9 and 5.1 Hz, ArH.

25

Mirtazapine

3,4,10,14b-tetrahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2]benzazepin-1(2H)-one (200 mg, 0.72 mmol) was dissolved in dichloromethane (40 ml). $BF_3 \cdot OEt_2$ (0.5 ml) was added while cooling to 0 °C with an ice-water bath under stirring. A yellow precipitate
30 was formed. After 15 minutes $BH_3 \cdot SMe_2$ (10 ml 2.0 M in THF) was added in one portion. The mixture was stirred overnight while warming to room temperature. Water was added, followed by addition of an aqueous Na_2CO_3 solution. The water phase was extracted with dichloromethane (3 x 25 ml) and the organic extract was dried with Na_2SO_4 . Evaporation under vacuum gave crude mirtazapine as a yellow solid (246
35 mg). Purification by chromatography gave pure mirtazapine (105 mg, 0.4 mmol) in 55% yield.

Mass analysis: $M^{+1} = 266$

Example 14

(R)-mirtazapine is prepared from R(-)-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-N-methylcarboxamide obtained in example 9

R-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepin-10-ylmethyl)-methyl-amine

Method A. LiAlH_4 reduction of amide

The R(-)-mandelic acid salt of R(-)-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-N-methylcarboxamide (2.75 g, 6.79 mmol; 98% d.e.) was mixed with saturated aqueous Na_2CO_3 (25 ml) and dichloromethane (50 ml). After vigorous mixing the dichloromethane layer was separated, dried with Na_2SO_4 and concentrated under vacuum to give the free base of R(-)-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-N-methylcarboxamide as a foam. THF (25 ml) was added and a clear solution was obtained. This THF solution was added dropwise to a stirred suspension of LiAlH_4 (516 mg, 13.58 mmol; 2 eq.) in dry THF (25 ml) under inert nitrogen atmosphere. After 90 minutes stirring at room temperature no reaction had taken place and the mixture was heated to reflux for 2 hours while stirring. The reaction mixture was quenched by careful addition of water (10 ml) and a concentrated aqueous potassium sodium tartrate solution (50 ml). The mixture was extracted with dichloromethane. The organic layer was dried with Na_2SO_4 and concentrated under vacuum to give an oil (1.3 g), containing of 30% starting material and 70% ***R-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepin-10-ylmethyl)-methyl-amine***, according to LC-MS. Chiral HPLC analysis on ***R-4b*** 87% ee. Enantiomers at 13.8 (major) and 18.0 min. (minor).

Method B. $\text{BH}_3\cdot\text{SMe}_2$ reduction of amide

The R(-)-mandelic acid salt of amide R(-)-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-N-methylcarboxamide (1.0 g, 2.47 mmol; 98% d.e.) was mixed with saturated aqueous Na_2CO_3 (20 ml) and dichloromethane (50 ml). After vigorous mixing the dichloromethane layer was separated. The aqueous layer was extracted with dichloromethane (25 ml). The combined organic fractions were dried with Na_2SO_4 and concentrated under vacuum to give the free amide R(-)-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-N-methylcarboxamide as a foam. The amide was mixed with dichloromethane (25 ml) and $\text{BF}_3\cdot\text{OEt}_2$ (0.5 ml, 2.35 mmol) was added while stirring at 0 °C. After 5 minutes $\text{BH}_3\cdot\text{SMe}_2$ (6.0 ml, 2.0 M in THF; 12.0 mmol) was added. After 18 hours at room temperature very low conversion was observed and

again $\text{BF}_3 \cdot \text{OEt}_2$ (3 ml, 14.1 mmol) was added under vigorous gas evolution. After 20 hours the mixture was poured in ice water (100 ml). Sat. aq. Na_2CO_3 (100 ml) was added and the mixture was extracted with dichloromethane (2 x 100 ml). The organic extracts were dried with Na_2SO_4 and concentrated under vacuum to give the crude product (443 mg, 1.85 mmol) in 75% yield as a yellow oil. Purification by chromatography on silica gel gave the pure product **4b** (266 mg, 1.11 mmol) in 45% c.y.

Chiral HPLC analysis on **R-4b**: 98% e.e.

10 ***R-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-yl-(2-hydroxyethyl)-methylamine***

Crude **R-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepin-10-ylmethyl**-methyl-amine was dissolved in DMF (25 ml) and 2-bromoethanol (0.85 g, 6.8 mmol), K_2CO_3 (3.9 g, 28.3 mmol) and KI (2.0 g, 12.0 mmol) were added. The mixture was heated overnight while stirring. The mixture was filtered over a glass filter and the filtrate was concentrated under vacuum to give the crude alcohol. Purification by chromatography on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ mixtures (100:0-90:10), gave **R-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-yl-(2-hydroxyethyl)-methylamine** (1.4 g, 4.95 mmol) in 73% yield.

20

R-mirtazapine

R-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-yl-(2-hydroxyethyl)-methylamine was dissolved in dichloromethane (50 ml). Thionyl chloride (3 ml) was added at room temperature. After stirring for 15 minutes the mixture was evaporated under vacuum. Toluene (50 ml) was added and the mixture was again concentrated under vacuum. The resulting clear brown oil (the intermediate chloride) was dissolved in DMF (50 ml). K_2CO_3 (6.0 g, 43.5 mmol) and KI (3.0 g, 18.1 mmol) were added and the resulting mixture was heated to reflux for 90 minutes, stirred overnight at room temperature and heated to reflux for one hour. The mixture was evaporated under vacuum at 85 °C with a rotary evaporator. CH_2Cl_2 (50 ml) was added to the residue and the resulting slurry was filtered over a glass filter. Evaporation under vacuum gave crude **R(-)-mirtazapine** as an oil. Purification by chromatography on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ = 9:1 (TLC: R_f = 0.45; staining with I_2 vapor), gave **R(-)-mirtazapine** (1.0 g, 3.7 mmol) in 78% yield. Chiral HPLC analysis: 98% e.e. **R(-)-mirtazapine**.

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Example 15

S(+)-mirtazapine is prepared from S(+)-10-bromomethyl-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine as obtained in example 3

5 **S-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-yl-(2-hydroxyethyl)-methylamine**

S(+)-10-bromomethyl-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine (1 g, 3.53 mmol; 97% e.e.), 2-(methylamino)ethanol (1 g, 13.3 mmol; 3.8 eq.) and K₂CO₃ (1 g, 7.3 mmol; 2 eq.) was heated to reflux in acetonitrile (50 ml) overnight. After one hour MS-analysis
10 showed the formation of S-7 (M⁺ = 284 found). The reaction mixture was concentrated under vacuum. Water was added and the crude product S-7 was extracted with dichloromethane (2 x 25 ml). The dichloromethane solution was dried with Na₂SO₄ and filtered. Purification by chromatography gave S-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-yl-(2-hydroxyethyl)-methylamine 599 mg, 2.21 mmol) in 60% yield.

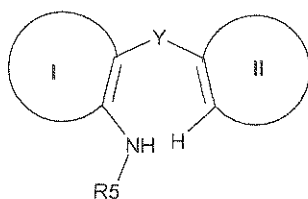
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S-mirtazapine

Thionyl chloride (2 ml) was added to a dichloromethane solution (20 ml) of S-10,11-dihydro-5H-benzo[e]pyrido[2,3-b]azepine-10-yl-(2-hydroxyethyl)-methylamine at room temperature. After stirring for one hour, the reaction mixture was concentrated under
20 vacuum to give the crude intermediate chloride. The crude chloride was dissolved in acetonitrile (100 ml). K₂CO₃ (1.5 g, 10.9 mmol) and KI (1 g, 6.0 mmol) were added. The mixture was refluxed overnight while stirring. Evaporation under vacuum. Water (50 ml) was added. Extraction with dichloromethane (3 x 50 ml), drying with Na₂SO₄ and concentration under vacuum gave an oil. Mass analysis: M⁺ = 266 (mirtazapine) found.
25 An analytically pure sample of S(+)-mirtazapine (439 mg, 1.65 mmol; 75% yield) was obtained by chromatography on silica gel. Chiral HPLC analysis (Chiralcel OF column): 97% e.e. S(+)-mirtazapine.

Claims

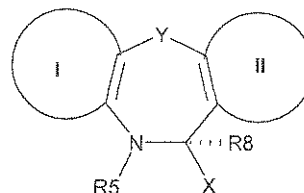
1. A method for the preparation of a cyclic compound according to Formula IIIa comprising reacting a compound according to Formula Ia and a compound according to Formula II,



Formula Ia



Formula II



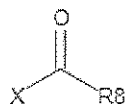
Formula IIIa

wherein

- ring structure I represents a pyridine;
- ring structure II represents a phenyl ring;
- Y is O, N-R₉ or CR₉R₁₀ wherein R₉ and R₁₀ are hydrogen or substituents comprising saturated or unsaturated hydrocarbons optionally comprising hetero atoms;
- R₅ is hydrogen or a hydrocarbon substituent group comprising one or more carbon atoms and optionally one or more hetero atoms;

and wherein in Formula II,

- Z₁ and Z₂ are leaving groups, or together form oxygen creating the corresponding aldehyde or ketone as indicated in Formula IIb

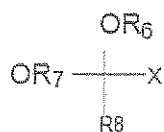


Formula IIb.

- X is a hydrocarbon group for subsequent ring closure, comprising one or more carbon atoms and optional hetero-atoms and a group Q and having a chain of between 1 to 6 atoms between the carbon atom attached to the central carbon atom of formula II and the group Q, or X is -C(=O)-Q, wherein Q is a hydrogen, halogen, a hydrocarbon substituent optionally comprising hetero atoms, or Q is -NHR or -OR, wherein R is hydrogen or a hydrocarbon substituent, or Q is L(CHR)_m-(NR)_p-(CRH)_n- wherein each R is independently hydrogen or a hydrocarbon substituent comprising one or more carbon atoms and/or hetero atoms, p is 0 or 1, n is 0 – 2, m is 1 - 3 and m + n is 1 – 3 and L is a leaving group.
- R₈ is hydrogen or a hydrocarbon substituent different from X making the central carbon atom of Formula II a chiral centre in Formula IIIa.

2. The method according to claim 1 wherein the leaving groups Z₁ and Z₂ in Formula II each independently are hydroxide, alkoxide, chloride, bromide, iodide, triflate, mesylate, tosylate or besylate.

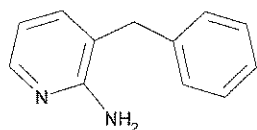
3. The method according to claim 2 wherein formula II represents a (hemi-)acetal (for $R_8 = H$) or (hemi-)ketal (for $R_8 = \text{hydrocarbon}$) according to formula IIa



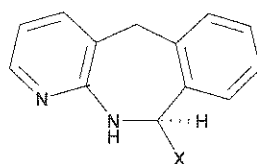
Formula IIa

wherein R_6 and R_7 are hydrocarbon or hydrogen.

4. The method according to claim 1 for the preparation of mirtazapine precursor of Formula IIIb, wherein the compound of Formula Ia is 2-amino-3-benzylpyridine according to Formula Ib

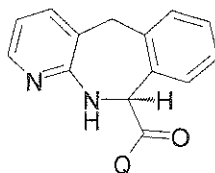


Formula Ib



Formula IIIb.

5. The method according to claim 4, wherein X is $-\text{CO}-Q$ and R_5 and R_8 are H, according to Formula IIIb1,



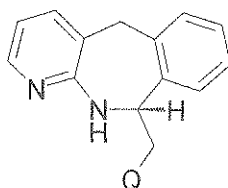
Formula IIIb1

wherein Q is a hydrogen, halogen, a hydrocarbon substituent optionally comprising hetero atoms, or $-\text{NHR}$ or $-\text{OR}$ wherein R is hydrogen or a hydrocarbon substituent.

6. The method according to claim 5 for the preparation of the compound of Formula IIIb1 in enantiomeric excess comprising the steps:

- 1: subjecting a racemic mixture of said compound to an optical resolution step,
- 2: separating the desired enantiomer,
- 3: racemising the undesired enantiomer and
- 4: recycling the racemised undesired enantiomer to the optical resolution step 1.

7. The method according to claim 6, wherein the compound of Formula IIIb1 is further reduced to a compound of Formula IIIb2



Formula IIIb2.

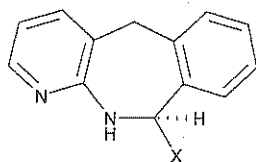
8. The method according to anyone of claims 1 to 6, wherein X is $-\text{CO}-\text{Q}$ wherein Q is $\text{L}(\text{CHR})_m-(\text{NR})_p-(\text{CRH})_n-$ wherein each R independently is hydrogen or a substituent group comprising one or more carbon atoms and/or hetero-atoms, p is 0 or 1, n is 0 – 2, m is 1 – 3 and m + n is 1 – 3 and L is a leaving group.

9. The method according to claim 8, wherein Q is $-\text{NMeC}_2\text{H}_4\text{L}$ and R₈ is hydrogen.

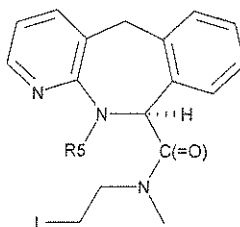
10. The method according to anyone of claim 5 to 7, wherein Q is reacted with an extender compound according to the Formula $\text{L}(\text{CHR})_m-(\text{NR})_p-(\text{CRH})_n\text{A}$, wherein each R independently is hydrogen or hydrocarbon optionally comprising hetero atoms, p is 0 or 1, n is 0 – 2, m is 1 – 3 and m + n is 1 – 3, L is a leaving group, and
 - A is $\text{RHN}-$, wherein R is hydrogen or a hydrocarbon substituent, if Q is a leaving group, or
 - A is a leaving group, if Q is an $\text{RHN}-$ group, wherein R is hydrogen or a hydrocarbon substituent.

11. The method according to claim 10, wherein Q is a halogen, $-\text{NHR}$ or $-\text{OR}$ wherein R is hydrogen or a hydrocarbon substituent.

12. A compound according to Formula IIIb or IVb in racemic, enantiomeric excess or enantiomeric pure R or S form,



Formula IIIb



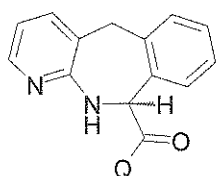
Formula IVb

(C(=O) here implies both CH_2 and $\text{C}=\text{O}$)

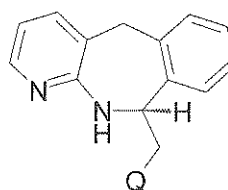
wherein X in Formula IIIb is a hydrocarbon group for subsequent ring closure, comprising one or more carbon atoms and optional hetero-atoms and a group Q and having a chain of between 1 to 6 atoms between the carbon atom attached to the central carbon atom of formula II and the group Q, or X is $-C(=O)-Q$, wherein Q is a hydrogen, halogen, a hydrocarbon substituent optionally comprising hetero atoms, or Q is $-NHR$ or $-OR$, wherein R is hydrogen or a hydrocarbon substituent, or Q is $L(CHR)_m-(NR)_p-(CRH)_n-$ wherein each R is independently hydrogen or a hydrocarbon substituent comprising one or more carbon atoms and/or hetero atoms, p is 0 or 1, n is 0 – 2, m is 1 – 3 and $m + n$ is 1 – 3 and L is a leaving group;

and whereby in Formula IVb, L is a leaving group and R_5 is hydrogen or a hydrocarbon substituent group comprising one or more carbon atoms and optionally one or more hetero atoms.

13. The compound according to claim 12 in racemic form, in enantiomeric excess or enantiomeric pure R or S form having Formula IIIb1 or Formula IIIb2



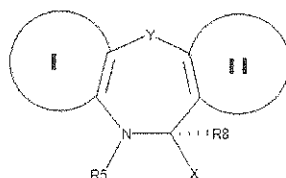
Formula IIIb1



Formula IIIb2,

wherein Q is a hydrogen, halogen, a hydrocarbon substituent optionally comprising hetero atoms, or Q is $-NHR$ or $-OR$, wherein R is hydrogen or a hydrocarbon substituent, or Q is $L(CHR)_m-(NR)_p-(CRH)_n-$ wherein each R is independently hydrogen or a hydrocarbon substituent comprising one or more carbon atoms and/or hetero atoms, p is 0 or 1, n is 0 – 2, m is 1 – 3 and $m + n$ is 1 – 3 and L is a leaving group.

14. A compound according to Formula IIIa,



Formula IIIa

wherein

- ring structure I represents a pyridine;
 - ring structure II represents a phenyl ring;
- Y is O, N-R₉ or CR₉R₁₀ wherein R₉ and R₁₀ are hydrogen or substituents comprising saturated or unsaturated hydrocarbons optionally comprising hetero atoms
- R₅ is hydrogen or a hydrocarbon substituent group comprising one or more carbon atoms and optionally one or more hetero atoms,
 - X is -CO-Q wherein Q is a hydrogen, halogen, a hydrocarbon substituent optionally comprising hetero atoms, or Q is -NHR or -OR, wherein R is hydrogen or a hydrocarbon substituent, or Q is L(CHR)_m-(NR)_p-(CRH)_n- wherein each R is independently hydrogen or a hydrocarbon substituent comprising one or more carbon atoms and/or hetero atoms, p is 0 or 1, n is 0 – 2, m is 1 - 3 and m + n is 1 – 3 and L is a leaving group.
 - R₈ is hydrogen or a hydrocarbon substituent different from X making the central carbon atom of Formula II a chiral centre in Formula IIIa.