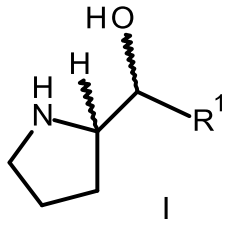
Process for the preparation of chiral pyrollidine-2-yl- methanol derivatives

The invention relates to a novel process for the preparation of a chiral pyrollidine-2-yl-methanol derivative or a salt thereof of the formula I



I

wherein R^1 is aryl or heteroaryl and both aryl or heteroaryl are optionally substituted by C_{1-4}-alkyl, halo-C_{1-4}-alkyl, C_{1-4}-alkoxy or halogen.

Chiral pyrollidine-2-yl- methanol derivatives of the formula I are versatile building blocks in the synthesis of pharmacologically active compounds, such as for the stereospecific synthesis of oligonucleotides carrying chiral phosphonate moieties (see e.g. Int. PCT Publication WO 2010/064146).

A process for the preparation of chiral pyrollidine-2-yl- methanol derivatives of the formula I has been described in Soai et al.; J.Chem.Soc., Chem.Commun. 1986, 412-413. The three step process starts from S-proline and is characterized by the reduction of a chiral benzoyl pyrrolidine with various reducing agents which affords, depending on the reducing agent, erythro/threo mixtures of the chiral pyrollidine-2-yl-methanol.

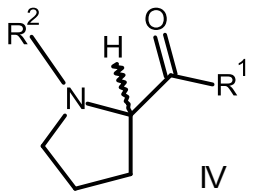
There is a need for a scalable process which affords the desired chiral building block in good yields and high enantiomeric purity. Object of the embodiments disclosed herein accordingly was to overcome the flaws of the state of the art processes.

The object could be achieved with the new process as described below.

There is provided a process for the preparation of a chiral pyrollidine-2-yl- methanol derivative or a salt thereof of the formula I

R^1MgHal

wherein R^1 is as above and Hal stands for a halogen atom to form the aroyl pyrrolidine derivative of formula IV

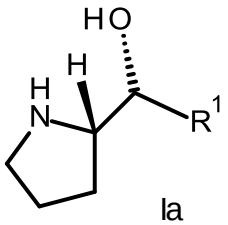


IV

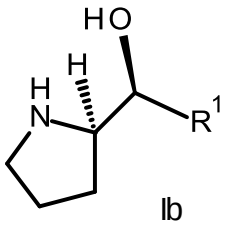
wherein R^1 and R^2 are as above and;

c) the aroyl pyrrolidine derivative of formula IV is first freed from the amino protecting group R^2 and subsequently hydrogenated in the presence of a hydrogenation catalyst to form the chiral pyrollidine-2-yl- methanol derivative of the formula I.

In one aspect, there is provided a process for the preparation of a chiral pyrollidine-2-yl-methanol derivative or a salt thereof of the formula Ia or Ib



Ia

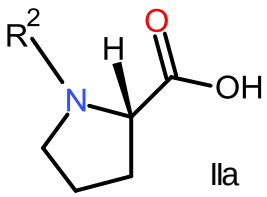


Ib

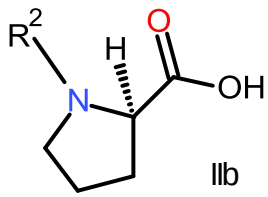
wherein R^1 is aryl or heteroaryl and both aryl or heteroaryl are optionally substituted by C_{1-4}-alkyl, halo-C_{1-4}-alkyl, C_{1-4}-alkoxy or halogen;

comprising the steps

a) a pyrrolidine carboxylic acid derivative of formula IIa or IIb



IIa

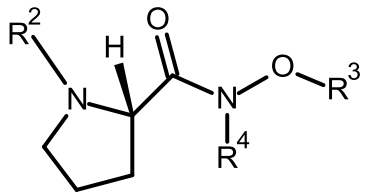


IIb

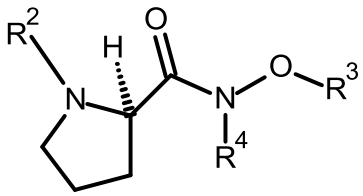
wherein R^2 is an amino protecting group is transformed with an N,O-dialkylhydroxylamine of the formula IV

$$R^4ONHR^3 \qquad IV$$

wherein R^3 and R^4 independently of each other are C_{1-4}-alkyl into the carbamoyl pyrrolidine derivative of formula IIIa or IIIb



IIIa



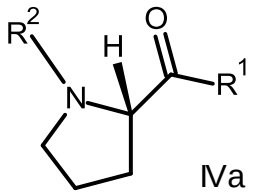
IIIb

wherein R^2 is as above and R^3 and R^4 independently of each other are C_{1-4}-alkyl ;

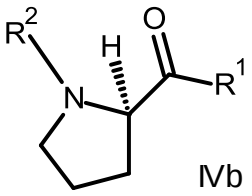
b) the carbamoyl pyrrolidine derivative of formula IIIa or IIIb is reacted with a Grignard reagent of the formula

R^1MgHal

wherein R^1 is as above and Hal stands for a halogen atom to form the aroyl pyrrolidine derivative of formula IVa or IVb



IVa



IVb

wherein R^1 and R^2 are as above and:

c) the aroyl pyrrolidine derivative of formula IVa or IVb is first freed from the amino protecting group R^2 and subsequently hydrogenated in the presence of a hydrogenation catalyst to form the chiral pyrollidine-2-yl- methanol derivative of the formula Ia or Ib.

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term “chiral” signifies that the molecule can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

In a preferred embodiment of the invention the term “chiral” denotes optically pure enantiomers.

In the structural formulae presented herein a broken bond (a) denotes that the substituent is below the plane of the paper and a wedged bond (b) denotes that the substituent is above the plane of the paper.

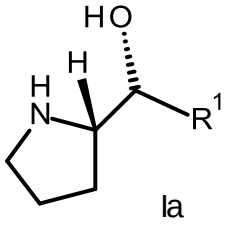
a) b) 

The spiral bond (c) denotes both options i.e. either a broken bond (a) or a wedged bond (b).

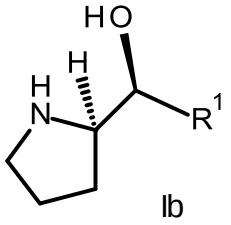
c)

Claims:

1. Process for the preparation of a chiral pyrollidine-2-yl- methanol derivative or a salt thereof of the formula Ia or Ib



Ia

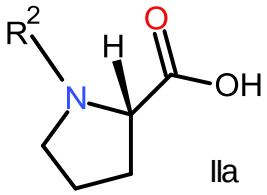


Ib

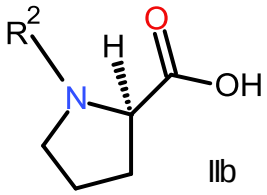
wherein R^1 is aryl or heteroaryl and both aryl or heteroaryl are optionally substituted by C_{1-4}-alkyl, halo-C_{1-4}-alkyl, C_{1-4}-alkoxy or halogen;

comprising the steps

a) a pyrrolidine carboxylic acid derivative of formula IIa or IIb



IIa

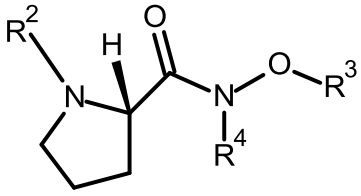


IIb

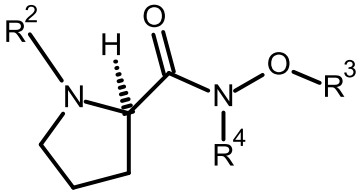
wherein R^2 is an amino protecting group is transformed with an N,O-dialkylhydroxylamine of the formula IV

$$R^4ONHR^3 \qquad IV$$

wherein R^3 and R^4 independently of each other are C_{1-4}-alkyl into the carbamoyl pyrrolidine derivative of formula IIIa or IIIb



IIIa



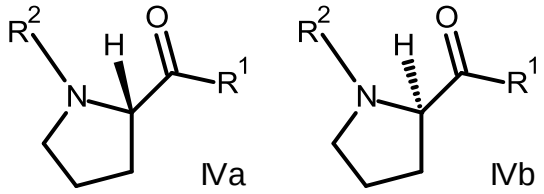
IIIb

wherein R^2 is as above and R^3 and R^4 independently of each other are C_{1-4}-alkyl ;

b) the carbamoyl pyrrolidine derivative of formula IIIa or IIIb is reacted with a Grignard reagent of the formula

$$R^1MgHal$$

wherein R^1 is as above and Hal stands for a halogen atom to form the aroyl pyrrolidine derivative of formula IVa or IVb



wherein R^1 and R^2 are as above and:

c) the aroyl pyrrolidine derivative of formula IVa or IVb is first freed from the amino protecting group R^2 and subsequently hydrogenated in the presence of a hydrogenation catalyst to form the chiral pyrollidine-2-yl- methanol derivative of the formula Ia or Ib.

2. Process of claim 1, wherein R^1 is aryl, optionally substituted by C_{1-4}-alkyl, halo-C_{1-4}-alkyl or C_{1-4}-alkoxy.

3. Process of claim 2, wherein R^1 is phenyl.

4. Process of any one of claims 1 to 3, wherein the transformation in step a) is performed in the presence of a coupling agent, an amine base and an organic solvent at a reaction temperature between 0°C and 60°C.

5. Process of claim 4, wherein the coupling agent is selected from DCC (N,N'-dicyclohexylcarbodiimide), EDC (N-(3-dimethylaminopropyl)-N`-ethylcarbodiimide-hydrochloride), TBTU (N,N,N′,N′-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate, HBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) together with an additive selected from HOBt (1-hydroxybenztriazole), HOSu (N-hydroxysuccinimide) or HOAt (1-hydroxy-7-azabenzotriazole) or is n-propylphosphonic acid anhydride (T3P®).

6. Process of claim 4, wherein the amine base is a tertiary amine and the organic solvent is a polar aprotic solvent.

7. Process of any one of claims 1 to 6, wherein the Grignard reaction in step b) is performed in an organic solvent, or mixtures thereof at a reaction temperature between -10°C and 50°C.

8. Process of any one of claims 1 to 7, wherein the amino protecting group R^2 is a group cleavable under acidic conditions.

9. Process of any one of claims 1 to 8, wherein R^2 is tert-butoxycarbonyl (BOC).

10. Process of any one of claims 1 to 9, wherein the freeing from the amino protecting R^2 group in step c) is performed with a strong acid.

11. Process of any one of claims 1 to 10, wherein the hydrogenation in step c) is performed in the presence of a hydrogenation catalyst consisting of a platin group metal selected from ruthenium, osmium, rhodium, iridium, palladium and platin.

12. Process of claim 11, wherein the hydrogenation takes place in a polar protic solvent at a reaction temperature between 0°C and 60°C and a hydrogen pressure between 1 and 10 bar.

13. Process of any one of claims 1 to 12, wherein the chiral pyrollidine-2-yl- methanol derivative or a salt thereof of the formula Ia or Ib is obtained in the form of its hydrochloride salt.