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(54) **Title:** PROCESS FOR THE SYNTHESIS OF PYRROLIDINES AND PYRROLES

(57) **Abstract:** The invention relates to pyrrolidines, pyrroles and processes for the preparation of pyrrolidines and pyrroles.



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Process for the synthesis of pyrrolidines and pyrroles

The invention relates to pyrrolidines, pyrroles and processes for the preparation of pyrrolidines and pyrroles, wherein the processes require less process steps, allow a more rapid access towards the pyrrolidines and pyrroles and/or do not require the use of advanced starting materials compared to several of the known processes. Some of the pyrrolidines and the pyrroles might be suitable as intermediates for the preparation of ethyl (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylate and/or the preparation of telaprevir or a pharmaceutically acceptable salt or solvate thereof.

Background prior art

2,3,4-Trisubstituted pyrrolidines and pyrroles are interesting and suitable building blocks for a wide range of active agents.

One of these agents is telaprevir. Telaprevir (CAS Number 402957-28-2; IUPAC Name: (1S,3aR,6aS)-2-[(2S)-2-[[[(2S)-2-Cyclohexyl-2-(pyrazine-2-carbonylamino)acetyl]amino]-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c] pyrrol-1-carboxamid) is a protease inhibitor that can be used as antiviral drug. By way of example, telaprevir inhibits the hepatitis C virus NS3-4A serine protease. Ethyl (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylate (CAS Number: 402958-25-2) is one of the building blocks of telaprevir.

WO 0218369 A2, WO 2007022459 A2, WO 2008090819 A1 and WO 2010008828 A2 disclose the preparation of 2,3,4-trisubstituted pyrrolidines such as ethyl (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylate. However, the preparation of them is often associated with complex syntheses that either start with already advanced starting materials (WO 2007022459 A2, WO 2008090819 A1) or require multistep syntheses (WO 0218369 A2, WO 2008090819 A1). In particular, advanced starting materials (such as octahydrocyclopenta[c]pyrrole) are often not commercially available, expensive, or require elaborate syntheses themselves. Multistep syntheses might be of academic interest but are often not suitable for technical scale up and industrial processes.

Therefore, it was an object of the present invention to provide processes for the preparation of 2,3,4-trisubstituted pyrrolidines, such as ethyl (1S,3aR,6aS)-

octahydrocyclopenta[c]pyrrole-1-carboxylate, and pyrroles, in particular enhanced processes that overcome at least one of the problems of the prior art processes.

It was a further object of the present invention to provide processes for the preparation of 2,3,4-trisubstituted pyrrolidines and pyrroles, in particular of 2,3,4-trisubstituted pyrrolidines and pyrroles suitable for the production of ethyl (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylate and/or telaprevir or a pharmaceutically acceptable salt or solvate thereof, in particular enhanced processes that overcome at least one of the problems of the prior art processes.

It was a further object of the present invention to provide processes for the preparation of 2,3,4-trisubstituted pyrrolidines and pyrroles, which might be suitable for the production of other buildings blocks than ethyl (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylate and/or other active agents than telaprevir or a pharmaceutically acceptable salt or solvate thereof.

It was another object of the present invention to provide new 2,3,4-trisubstituted pyrrolidines or pyrroles, in particular 2,3,4-trisubstituted pyrrolidines and pyrroles suitable for the production of ethyl (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylate and/or telaprevir or a pharmaceutically acceptable salt or solvate thereof.

It was yet another object of the present invention to provide new 2,3,4-trisubstituted pyrrolidines or pyrroles, which might be suitable for the production of other buildings blocks than ethyl (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylate and/or other active agents than telaprevir or a pharmaceutically acceptable salt or solvate thereof.

Summary of the invention

It was surprisingly found that processes can be provided, which allow a very general access towards 2,3,4-trisubstituted pyrrolidines and pyrroles. Therefore, the present invention relates to the overall processes, the single process steps and the compounds as defined below.

List of figures

Figure 1: shows a scheme of some of the processes as disclosed herein.

Figure 2: shows a further scheme of some of the processes as disclosed herein.

Figure 3: shows a chiral HPLC analysis.

Definitions

The term "electron withdrawing group" as used herein shall be understood as known in the art. In particular, it shall be understood as a group that draws electrons away from a reaction center. When this center is an electron rich position, the presence of the electron-
5 withdrawing substituent has a stabilizing effect. Examples of electron withdrawing groups are sulfones, nitriles (CN), carbonyls (CO), phosphonates (PO(OR)₂) and nitro groups (NO₂). Suitable electron withdrawing group are listed for example in standard text books such as *J. A. Joule and K. Mills, Heterocyclic Chemistry*, 4th edition, 2000, published by Blackwell Science Ltd., ISBN: 978-0-632-05453-4, pp. 259 – 260.

10 The term "protective group" as used herein shall be understood as known in the art. In particular, it shall be understood as a group which has been introduced into a molecule by chemical modification of a functional group of the molecule to avoid a reaction of said functional group in a subsequent reaction. The "protective group" is introduced in to the
15 molecule by a reaction of a functional group of the molecule and an "agent suitable for introducing a protective group". Particularly, the "protective group" may be selected from *t*-butyloxycarbonyl, carboxybenzyl, fluorenylmethyloxycarbonyl.

An "agent suitable for removing the protective group or the PG residue" as used herein shall
20 be understood as known in the art. In particular, it shall be understood as an agent, which cleaves the "protective group" from the said functional group and allows the functional group to react in a subsequent reaction. For example, it may be an acid, particularly a concentrated, strong acid. (such as HCl or CF₃COOH) when the "PG residue" or the "protective group" is a BOC-group.

25 A "protective group" that is "capable of protecting an amine group" as used herein shall be understood as a protective group which avoids a reaction of said amine group under the conditions of a step b²), a step e²) and/or a step c) as defined herein, especially as exemplified in the examples. In particular, a "protective group" that is "capable of protecting
30 an amine group" avoids between 95 to 100 %, particularly between 98 to 100 %, more particularly 100 %, of a reaction of said amine group in the presence of lithium diisopropylamide at 0 °C in THF for at least 1 hour, particularly between 1 and 2 hours, in the absence of an "agent suitable for removing the protective group or the PG residue".

The term "halide" or "halogenide" as used herein shall be understood as including at least
35 chlorine, iodine, and bromine.

The term "leaving group" as used herein shall be understood as known in the art. Suitable leaving groups are listed for example in standard text books such as March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 6th Edition; Wiley & Sons. Preferred leaving groups are *t*-butoxycarbonyl, halogenides, particularly chloride and bromide, alkyl sulfonates and aryl sulfonates.

The terms "ambient temperature" and "room temperature" used herein will be understood by the person skilled in the art as referring to a temperature between about 20 °C and about 25 °C, particularly between 20 °C and 25 °C.

All compounds as disclosed herein may, if possible, be present in form of a salt. In particular, all amines as disclosed herein may be present in form of a salt. Suitable salts may include, but are not limited to the group consisting of hydrochloride, hydrobromide, sulphates or phosphates as well as organic salts such as acetate, citrate, maleate, succinate, lactate, tartrate, *o*-substituted tartrate, mesylate, tosylate, trifluoroacetate, benzoate and salts of mandelic acid.

The term "comprising" as used herein shall in every embodiment, aspect, example, item or claim be interpreted as encompassing all the specifically mentioned features, components or steps as well as optional, additional, unspecified ones. In addition, the term "comprising" as used herein shall also be interpreted to mean "consisting of", therewith defining for every embodiment, aspect, example, item or claim that no further features, components or steps are present.

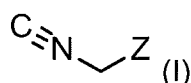
A "dry" solvent as used herein typically contains 0.005 % (50 ppm) or less water.

Detailed description

Processes for the preparation of pyrrolidines and pyrroles

According to one aspect the present invention relates to a process comprising the following steps:

a) reacting a compound of formula (I)



wherein Z is selected from carbonyl groups,

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

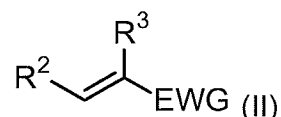
(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

- 5 -

or particularly from $-\text{CON-XY}$ groups, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

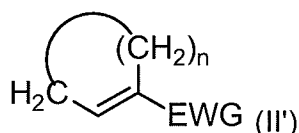
or particularly from $-\text{CON-QW}$ groups, wherein N-QW constitutes a fragment of any natural or non-natural amino acid;

with a compound of formula (II)



wherein R^2 and R^3

-form a ring and the compound of formula (II) is the compound of formula (II')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

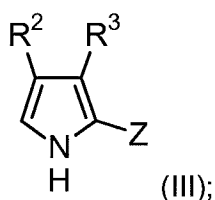
- are identical or different, and are independently selected from
(i) hydrogen,

(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

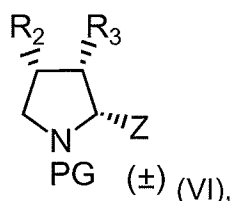
and wherein the EWG residue is an electron withdrawing group;

to obtain a compound of formula (III)



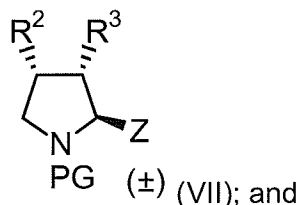
b) converting the compound of formula (III) to a compound of formula (VI)

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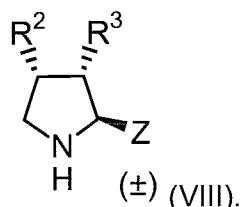


wherein the PG residue is a protective group, which is capable of protecting an amine group;

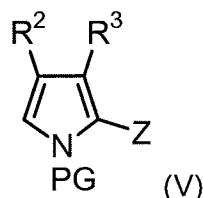
c) converting the compound of (VI) to a compound of formula (VII)



d) converting the compound of (VII) to a compound of formula (VIII)

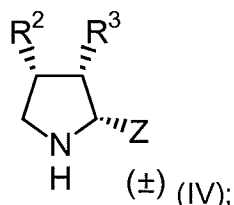


Specifically, step b) may comprise a step b¹) of converting the compound of formula (III) to a compound of formula (V)



wherein the PG residue is as defined herein; and a step b²) of converting the compound of (V) to the compound of formula (VI).

Step b) may, however, also comprise a step b³) of converting the compound of formula (III) to a compound of formula (IV)



and a step b⁴) of converting the compound of (IV) to the compound of formula (VI).

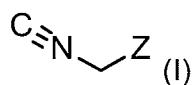
The process may start with commercially available starting material, e.g. a sulfone and an isocyanide. More specifically, isocyanides such as compound (I), particularly the compound of formula (Ia) defined below, and compounds such as compounds (II), particularly the

compound of formula (IIa) defined below, may be condensed in the presence of a suitable base to form pyrroles such as compound (III), particularly the compound of formula (IIIa) defined below. The pyrrole can be converted to pyrrolidines such as compounds (VI), particularly to the compound of formula (VIa) defined below, e.g. by the steps explained above. Upon treatment with a base, preferably a strong base such as lithium diisopropylamide (LDA), it is possible to convert the *cis*-compounds, particularly the compound of formula (VIa) defined below, to the corresponding *trans*-compound of formula (VII), particularly the compound of formula (VIIa) defined below ("exo-product"). Deprotection may give pyrrolidines of formula (VIII), particularly the compound of formula (VIIIa) defined below, which is ethyl (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylate. Therefore, the process allows the rapid preparation of a variety of 2,3,4-substituted pyrrolidines, e.g. compounds of formulae (VI), (VII) and (VIII), by a simple pyrrole-cyclization/hydrogenation strategy. The relative stereochemistry is *cis* after the hydrogenation but can be equilibrated to *trans* after treatment with a suitable base. Moreover, the process allows the rapid preparation of a variety of pyrroles, e.g. compounds of formulae (III) and (V).

The reaction sequence gives high yields: the substituted pyrroles of formula (III) may be formed in ~ 90% yield and the hydrogenation of pyrroles of formula (III) may give yields in a range of 50-90% (depending on the reaction conditions). For example, the hydrogenation of BOC-pyrroles of formula (V) proceeds almost quantitatively. Some of the reactions (pyrrole synthesis, hydrogenation) may give clean conversions (low amounts or even no side products). The route avoids critical solvents and reagents with respect to safety and should be well suited for large scale reactions. Additionally, some of the materials may be crystalline compounds (e.g. the compounds of formulae (IIa) and (IIIa) below).

According to a further aspect the present invention relates to a process comprising the following steps:

a) reacting a compound of formula (I)



wherein Z is selected from carbonyl groups,

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

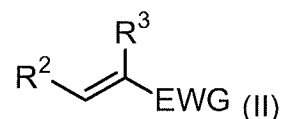
(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

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or particularly from $-\text{CON-XY}$ groups, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

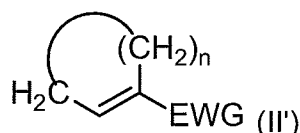
or particularly from $-\text{CON-QW}$ groups, wherein N-QW constitutes a fragment of any natural or non-natural amino acid;

with a compound of formula (II)



wherein R^2 and R^3

-form a ring and the compound of formula (II) is the compound of formula (II')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

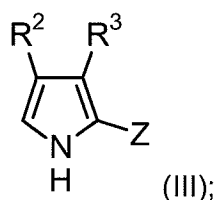
- are identical or different, and are independently selected from

(i) hydrogen,

(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

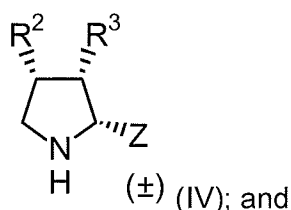
(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

and wherein the EWG residue is an electron withdrawing group; to obtain a compound of formula (III)



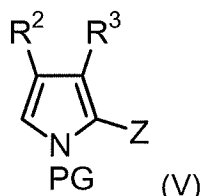
e) converting the compound of formula (III) to a compound of formula (IV)

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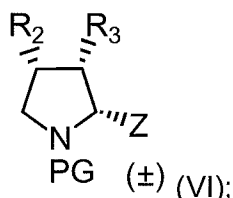


optionally f) performing chiral resolution.

Specifically, step e) may comprise a step e¹) of converting the compound of formula (III) to a compound of formula (V)



wherein the PG residue is as defined herein; a step e²) of converting the compound of formula (V) to a compound of formula (VI)



and a step e³) of converting the compound of (VI) to a compound of formula (IV). However, step e) may also comprise a step e⁴) of converting the compound of formula (III) to the compound of formula (IV).

The process may start with commercially available starting material, e.g. a sulfone and an isocyanide. More specifically, isocyanides such as compound (I), particularly the compound of formula (Ia) defined below, and compounds such as compounds (II), particularly the compound of formula (IIa) defined below, may be condensed in the presence of a suitable base to form pyrroles such as compound (III), particularly the compound of formula (IIIa) defined below. The pyrroles can e.g. be directly hydrogenated under pressure and temperature to give pyrrolidines of compounds (IV), particularly the compound of formula (IVa) defined below. Alternatively, the pyrroles can be protected to give PG-pyrroles such as compounds (V), particularly the compound of formula (Va) defined below, which can be hydrogenated under very mild conditions to yield PG-pyrrolidine such as compounds (VI), particularly the compound of formula (VIa) defined below. These can be easily converted into pyrrolidine such as compounds (IV), particularly the compound of formula (IVa) defined below under acidic conditions. In some cases, the racemic *cis*-products of compounds of formula (IV), particularly when the compound of formula (IVa) is obtained, may be obtained almost exclusively ("*endo*-products"). The reaction sequence gives high yields: the

substituted pyrroles of formula (III) may be formed in ~ 90% yield and the hydrogenation of pyrroles of formula (III) may give yields in a range of 50-90% (depending on the reaction conditions). For example, the hydrogenation of BOC-pyrroles of formula (V) proceeds almost quantitatively. Both reactions (pyrrole synthesis, hydrogenation) may give clean conversions (low amounts or even no side products). The route avoids critical solvents and reagents with respect to safety and should be well suited for large scale reactions. Additionally, some of the materials may be crystalline compounds (e.g. the compounds of formulae (IIa) and (IIIa) below).

According to further aspects, the present invention relates to the following processes:

-a process of reacting a compound of formula (I) with a compound of formula (II) to obtain a compound of formula (III) in a step a) as defined herein, converting the compound of formula (III) to a compound of formula (VI) in a step b) as defined herein and converting the compound of (VI) to a compound of formula (VII) in a step c) as defined herein;

-a process of reacting a compound of formula (I) with a compound of formula (II) to obtain a compound of formula (III) in a step a) as defined herein and converting the compound of formula (III) to a compound of formula (VI) in a step b) as defined herein;

-a process of reacting a compound of formula (I) with a compound of formula (II) to obtain a compound of formula (III) in a step a) as defined herein and converting the compound of formula (III) to a compound of formula (V) in a step b¹) or a step e¹) as defined herein;

-a process of converting the compound of formula (III) to a compound of formula (VI) in a step b) as defined herein, converting the compound of (VI) to a compound of formula (VII) in a step c) as defined herein and converting the compound of (VII) to a compound of formula (VIII) in a step d) as defined herein;

-a process of converting the compound of formula (III) to a compound of formula (VI) in a step b) as defined herein and converting the compound of (VI) to a compound of formula (VII) in a step c) as defined herein;

-a process of converting the compound of formula (III) to a compound of formula (VI) in a step b) as defined herein and converting the compound of (VI) to a compound of formula (VII) in a step c) as defined herein;

-a process of converting the compound of formula (III) to a compound of formula (V) in a step b¹) or a step e¹) as defined herein and converting the compound of formula (V) to a compound of formula (VI) in a step b²) or a step e²) as defined herein;

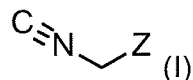
-a process of converting the compound of formula (III) to a compound of formula (IV) in a step b³) or a step e⁴) as defined herein and converting the compound of formula (IV) to a compound of formula (VI) in a step b⁴) as defined herein;

-a process of converting the compound of formula (III) to a compound of formula (V) in a step b¹) or a step e¹) as defined herein, converting the compound of formula (V) to a compound of formula (VI) in a step b²) or a step e²) as defined herein and converting the of formula (VI) to a compound of formula (IV) in a step e³) as defined herein.

5

Step a

According to all aspects, step a) comprises reacting a compound of formula (I)



wherein Z is selected from carbonyl groups,

10

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

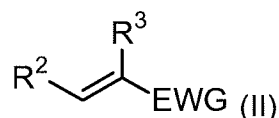
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or particularly from $-\text{CON}-\text{XY}$ groups, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

or particularly from $-\text{CON}-\text{QW}$ groups, wherein N-QW constitutes a fragment of any natural or non-natural amino acid;

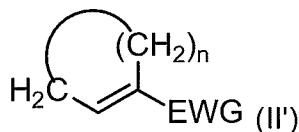
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with a compound of formula (II)



wherein R^2 and R^3

-form a ring and the compound of formula (II) is the compound of formula (II')



25

with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

- are identical or different, and are independently selected from

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(i) hydrogen,

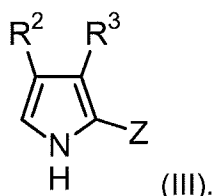
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(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

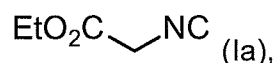
and wherein the EWG residue is an electron withdrawing group;

to obtain a compound of formula (III)

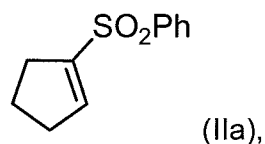


Step a) may be carried out at a temperature of -10 °C to 30 °C, particularly 0 °C to room temperature, more particularly first at 0 °C and then at room temperature. Furthermore, step a) may be carried out in a solvent, particularly an aprotic solvent, more particularly a dry aprotic solvent. The solvent may be selected from tetrahydrofuran (THF), acetonitrile, dimethylacetamide (DMAc), dimethylformamide (DMF), methyl tert-butyl ether, 2-methyltetrahydrofuran, *N*-methyl-2-pyrrolidone (NMP), and any combination thereof, and is particularly THF, and more particularly dry THF. Step a) may be carried out under an inert gas atmosphere, particularly under a nitrogen or argon gas atmosphere. Moreover, step a) may be carried out in the presence of a base. The base may be selected from KOBut, NaOEt, diazabicycloundecene (DBU), lithium diisopropylamide, potassium hexamethyldisilazide, sodium hexamethyldisilazide, lithium hexamethyldisilazide, NaOBut, K₂CO₃, Na₂CO₃, KOAc, NaOAc, tetramethylguanidine, diazabicyclononene, and any combination thereof, and is particularly KOBut.

According to a preferred embodiment, step a) comprises reacting a compound of formula (Ia)

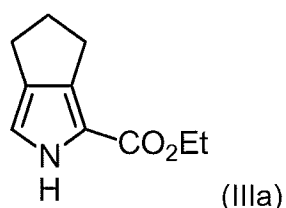


with a compound of formula (IIa)



to obtain a compound of formula (IIIa)

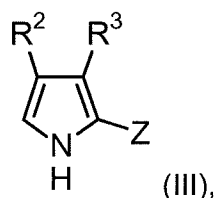
- 13 -



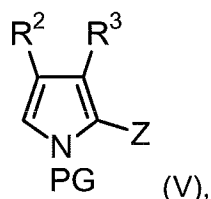
wherein step a) is carried out in the presence of KOBut first at 0 °C and then at room temperature in dry THF.

5 Step b¹ or step e¹

According to all aspects, step b¹) or step e¹) as defined herein comprise converting a compound of formula (III)

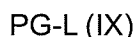


to a compound of formula (V)



wherein the PG residue is a protective group, which is capable of protecting an amine group. Said steps may be carried out at a temperature of 15 °C to 40 °C, particularly from 20 °C to 30 °C, and more particularly at room temperature. The converting is typically carried out by adding an agent suitable for introducing a protective group, particularly by adding a

15 compound of formula (IX)



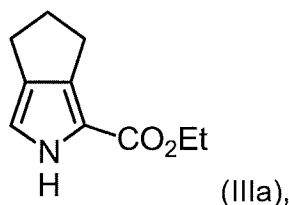
wherein the PG residue is as defined herein and wherein L is a leaving group. L may be selected from *t*-butoxycarbonyl, halogenides, particularly chloride and bromide, and is particularly *t*-butoxycarbonyl. Particularly, the PG residue may be selected from *t*-

20 butyloxycarbonyl, carboxybenzyl, fluorenylmethyloxycarbonyl, and is particularly *t*-butyloxycarbonyl. The compound of formula (IX) may be selected from di-*t*-butyl dicarbonate, carboxybenzylchlorid, fluorenylmethyloxycarbonyl chloride, and is particularly di-*t*-butyl dicarbonate. Said steps may be carried out in a solvent, particularly an aprotic solvent. The solvent may be selected from tetrahydrofuran (THF), dimethylformamide (DMF),

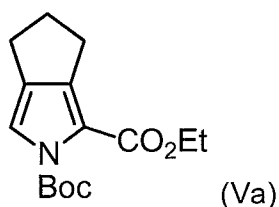
25 dimethylacetamide (DMAc), dichloromethane, ethyl acetate, 2-methyltetrahydrofuran, *N*-methyl-2-pyrrolidone (NMP), and any combination thereof, and is particularly THF. Said step b¹) or e¹) may be carried out in the presence of a base. The base may be selected from

tertiary and secondary amines, particularly dimethylaminopyridine, diisopropylethylamine, isopropylmethylamine, butylmethylamine, and triethylamine; cyclic tertiary amines, particularly *cis*-2,6-dimethylpiperidine, 1,4-diazabicyclo[2.2.2]octane, N-methylpiperidine and N-methylmorpholine; and any combination thereof, and is particularly dimethylaminopyridine.

According to a preferred embodiment, said step b¹) or e¹) comprises converting a compound of formula (IIIa)



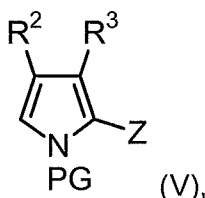
to a compound of formula (Va)



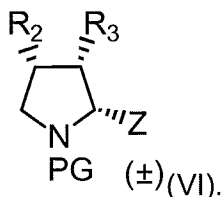
with di-*t*-butyl dicarbonate in the presence of dimethylaminopyridine at room temperature in THF.

Step b² and step e²

A process comprising a step b²) or a step e²) as defined herein comprises converting a compound of (V)

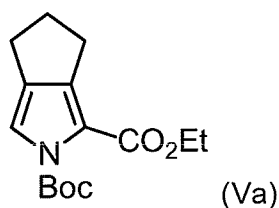


wherein the PG residue is a protective group, which is capable of protecting an amine group; to a compound of formula (VI)

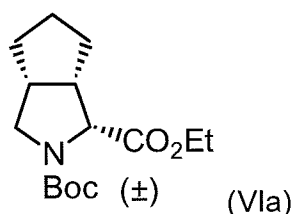


Said step b²) or e²) may be carried out at a temperature of 20 °C to 100 °C, particularly from 50 °C to 70 °C, and more particularly 60 °C. Said step b²) or e²) may be carried out with hydrogen at a pressure of 1 to 100 bar, particularly between 2 bar and 10 bar, more particularly at 2 bar or at 10 bar. Moreover, said step b²) or e²) may be carried out in the

presence of a catalyst. Particularly, the catalyst is a solid-supported catalyst. The catalyst may be selected from rhodium, palladium, platinum, platinum oxide, or nickel, and is particularly rhodium and the solid support may be selected from activated charcoal, carbon, alox, and is particularly activated charcoal. Particularly, the solid-supported catalyst is selected from rhodium-on-activated charcoal, palladium-on-activated charcoal, raney nickel, and is particularly rhodium-on-activated charcoal. Then, step b²) or e²) is typically carried out in the presence of a base and the base may be selected tertiary and secondary amines, particularly triethylamine, dimethylaminopyridine, diisopropylethylamine, isopropylmethylamine, and butylmethylamine; cyclic tertiary amines, particularly *cis*-2,6-dimethylpiperidine, 1,4-diazabicyclo[2.2.2]octane, N-methylpiperidine and N-methylmorpholine; and any combination thereof, and is particularly triethylamine. Typically, said step b²) or e²) is carried out in a solvent, particularly selected from ethanol, methanol, propanol, isopropanol, butanol, and any combination thereof, and is particularly ethanol. According to a preferred embodiment, said step b²) or e²) comprises converting a compound of (Va)



to a compound of formula (VIa)

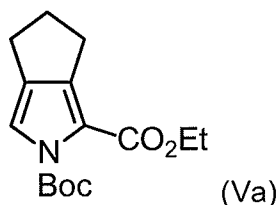


with hydrogen at a pressure of 2 bar or 10 bar in the presence of rhodium-on-activated charcoal and triethylamine at 60 °C in ethanol.

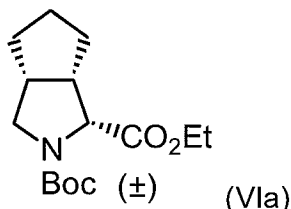
However, said step b²) or e²) may also be carried out with hydrogen at a pressure of 20 to 100 bar, particularly of 40 to 60 bar, and more particularly 50 bar. Said step b²) or e²) is then typically carried out in the presence of a catalyst. The catalyst is then a homogenous catalyst comprising a transition metal compound and at least one ligand. The transition metal compound may be selected from Rhodium complexes, particularly Rh(III)-chloronorbornadiene-dimer, and Ruthenium complexes, particularly [(Ru(η^3 -methylallyl)(cod))], and any combination thereof, and is particularly [(Ru(η^3 -methylallyl)(cod))]. The at least one ligand may selected from phosphine ligands, particularly diphosphine and

monophosphine ligands, and any combination thereof. The at least one ligand may also be selected from Josiphos ligands, Walphos-type ligands, Taniaphos-type ligands, Mandyphos-type ligands and Du-Phos-type ligands. Particularly, the at least one ligand is selected from diphosphine ligands, particularly from 2,2-bis(diphenylphosphino)-1,1-binaphthale, 1,2-bis(diphenylphosphino)benzene, (Oxydi-2,1-phenylene)bis-(diphenylphosphine), (*R*)-2,2-bis(diphenylphosphino)-1,1-binaphthalene, (*S*)-2,2-bis(diphenylphosphino)-1,1-binaphthale, and any combination thereof. The homogenous catalyst may also comprise [(Ru(η^3 -methylallyl)(cod))] and a Josiphos ligand or [(Ru(η^3 -methylallyl)(cod))] and 2,2-bis(diphenylphosphino)-1,1-binaphthale. Said step b²) or e²) may be carried out in the presence of a base and the base may selected tertiary and secondary amines, particularly triethylamine, dimethylaminopyridine, diisopropylethylamine, isopropylmethylamine, and butylmethylamine; cyclic tertiary amines, particularly *cis*-2,6-dimethylpiperidine, 1,4-diazabicyclo[2.2.2]octane, N-methylpiperidine and N-methylmorpholine; and any combination thereof, and is particularly triethylamine. Further, said step b²) or e²) may be carried out in a solvent, particularly selected from methanol, ethanol, propanol, isopropanol, butanol, and any combination thereof.

According to a further embodiment, said step b²) or e²) may then comprise converting a compound of (Va)



to a compound of formula (VIa)

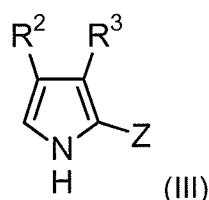


with hydrogen at a pressure of 50 bar in the presence of [(Ru(η^3 -methylallyl)(cod))] and a Josiphos ligand, and triethylamine at 60 °C.

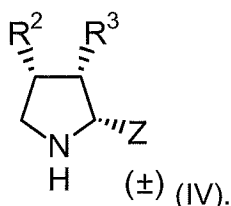
Step b³ und e⁴

According to all aspects, a process comprising a step b³) or a step e⁴) as defined herein comprises converting a compound of formula (III)

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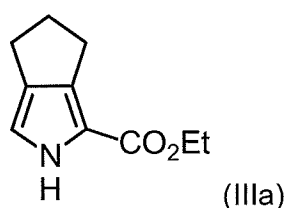


to a compound of formula (IV)

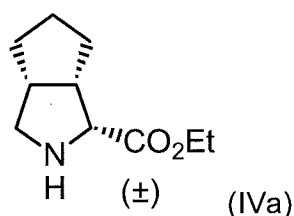


Said step b³) or e⁴) may be carried out at a temperature of 40 °C to 80 °C, particularly from 50 °C to 70 °C, and more particularly 60 °C. Said step b³) or e⁴) may be carried out with hydrogen at a pressure of 30 to 70 bar, particularly of 40 to 60 bar, more particularly 50 bar. Said step b³) or e⁴) may be carried out in the presence of a catalyst. Particularly, the catalyst is a solid-supported catalyst, typically selected from rhodium, palladium, platinum, platinum oxide, and nickel, and is particularly rhodium. The solid support may be selected from activated charcoal, carbon, and alox, and is particularly activated charcoal. Particularly, the solid-supported catalyst is selected from rhodium-on-activated charcoal, palladium-on-activated charcoal, raney nickel, and is more particularly rhodium-on-activated charcoal. Said step b³) or e⁴) may be carried out in the presence of an acid, wherein the acid may be selected from sulfuric acid, HCl and acetic acid and any combination thereof, and is particularly sulfuric acid. Said step b³) or e⁴) may be carried out in a solvent, particularly selected from ethanol, methanol, ethanol, propanol, isopropanol, butanol, and any combination thereof, and is particularly ethanol.

According to a preferred embodiment, said step b³) or e⁴) comprises converting a compound of formula (IIIa)



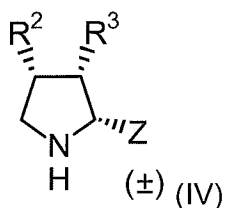
to a compound of formula (IVa)



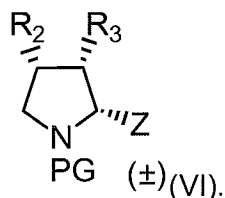
with hydrogen at a pressure of 50 bar in the presence of rhodium-on-activated charcoal and sulfuric acid at 60 °C in ethanol.

Step b⁴

- 5 A process comprising a step b⁴) as defined herein comprises converting a compound of formula

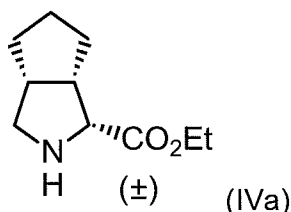


to a compound of formula (VI)

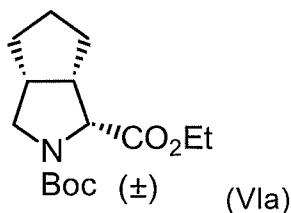


Step b⁴) may be carried out as step b¹) or e¹) as defined herein.

According to another embodiment, step b⁴) comprises converting a compound of formula (IVa)



to a compound of formula (VIa)

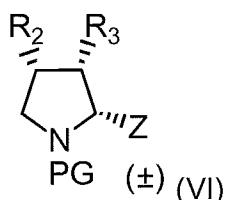


with di-*t*-butyl dicarbonate in the presence of dimethylaminopyridine at room temperature in THF.

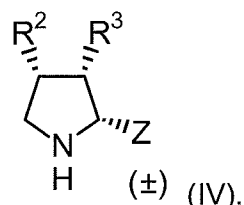
Step e³

- 20 According to all aspects, a process comprising a step e³) as defined herein comprises converting a compound of (VI)

- 19 -

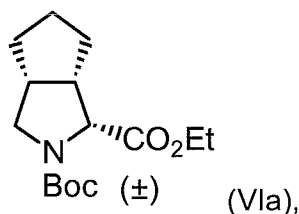


to a compound of formula (IV)

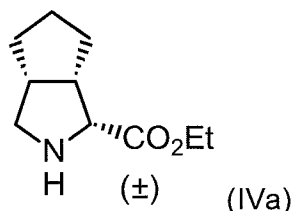


Step e³) may be carried out at a temperature of between room temperature and 100 °C, particularly 20 °C to 30 °C, more particularly at room temperature. Step e³) may be carried out in a solvent, particularly selected from water, dichloromethane, ethanol, methanol, dioxane, THF, ethyl acetate, and any combination thereof. Step e³) is typically carried out in the presence of an agent suitable for removing the PG residue, particularly an acid, a base or hydrogen, depending on the PG residue.

According to a preferred embodiment, step e³) comprises converting a compound of formula (VIa)



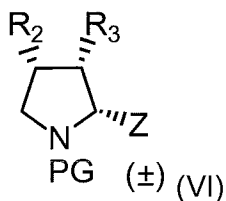
to a compound of formula (IVa)



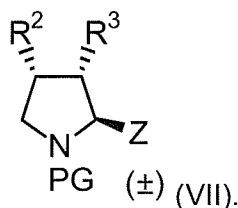
in the presence of HCl at room temperature in dioxane.

Step c

A process comprising a step c) as defined herein comprises converting a compound of formula (VI)

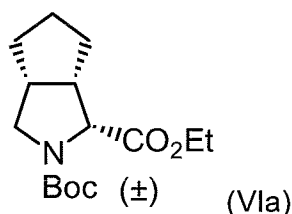


to a compound of formula (VII)

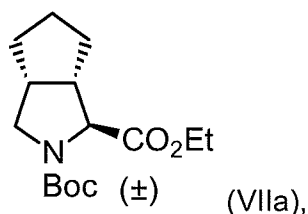


Step c) may be carried out at a temperature of -10 °C to 10 °C, particularly -5 °C to +5 °C, more particularly at 0 °C. Step c) may be carried out in a solvent, particularly an aprotic solvent. Typically, the solvent is selected from tetrahydrofuran (THF), dimethylacetamide (DMAc), dimethylformamide (DMF), 2-methyltetrahydrofuran, *N*-methyl-2-pyrrolidone (NMP), and any combination thereof, and is particularly THF. Moreover, step c) may be carried out in the presence of a base, wherein the base may be selected from lithium diisopropylamide, lithium hexamethyldisilazide, potassium hexamethyldisilazide, sodium hexamethyldisilazide, and any combination thereof, and is particularly lithium diisopropylamide.

According to a preferred embodiment, step c) comprises converting the compound of (VIa)



to a compound of formula (VIIa)



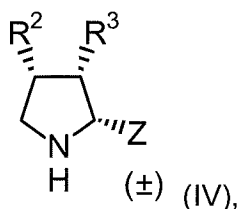
in the presence of lithiumdiisopropylamide at 0 °C in THF.

Step d

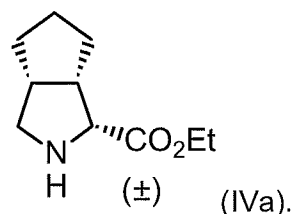
Step d) as defined herein may be carried out as a step e³) as defined herein.

Step f

A process comprising a step f) as defined herein comprises performing chiral resolution with a mixture of compounds of formula (IV)



preferably compounds of formula (IVa)



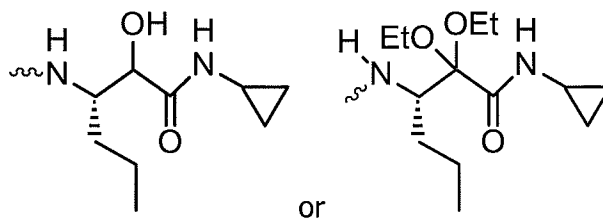
Step f) is typically carried out by performing a crystallizing step in the presence of dibenzoyl tartaric acid and acetonitrile. Particularly, a dibenzoyl tartrate salt of the compound of formula (IV), particularly the compound of formula (Iva) is obtained. Step f) may be carried out at a temperature of -25 to + 25 °C, particularly 0 to +8 °C, more particularly at 4 °.

According to all aspects, the Z group as defined herein is selected from carbonyl groups, particularly from $-\text{CO}_2\text{R}^1$ groups or $-\text{CON-QW}$ groups as defined herein. In particular, Z may be $-\text{CO}_2\text{R}^1$ and R^1 may be selected from ethyl, methyl, i-propyl, n-propyl, n- t-butyl, i- t-butyl, s- t-butyl, t-butyl, pentyl, hexyl benzyl, cyclohexyl, and is particularly ethyl. Furthermore, R^1 may be a phenyl group substituted with: NO_2 , F, Cl, OPh, SPh, SO_2 -alkyl, SO_2 -aryl, alkyloxy, aryloxy, alkyl, aryl, $\text{CH}(\text{Oalkyl})_2$, or tertiary amines.

Z may also be a $-\text{CON-XY}$ group, wherein X and Y may be independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly ethyl, ethyloxy, hydrogen, methyl, methyloxy, i-propyl, i-propyloxy, n-propyl, n-propyloxy, n- t-butyl, n- t-butyloxy, i- t-butyl, i- t-butyloxy, s- t-butyl, s- t-butyloxy, t-butyl, t-butyloxy, phenyloxy, and benzolxy. Particularly, X is methoxy and Y is methyl.

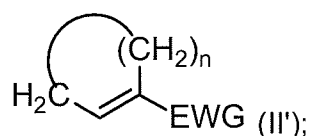
Z may also be a $-\text{CON-QW}$ group, wherein Q and W constitute a fragment of any natural or non-natural amino acid. This includes, but is not limited to, $-\text{CON-QW}$ groups wherein one of Q and W is hydrogen and the other one constitutes the remaining fragment of glycine, alanine, valine, leucine, isoleucine, serine, cysteine, threonine, methionine, phenylalanine, tyrosine, tryptophan, histidine, lysine, arginine, aspartate, glutamate, asparagine, glutamine, either in their L or their D form. Q and W may also constitute the remaining proline fragment.

Furthermore, in $-\text{CON-QW}$, $\sim\text{N-QW}$ may be



According to all aspects, R^2 and R^3 may form a ring analogous to the compound of formula (II')

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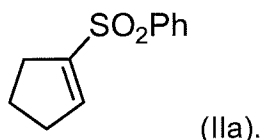
with $n = 1, 2, 3, 4$ or 5 ; particularly with $n = 2$. Alternatively, R^2 and R^3 are identical or different, and are independently selected from hydrogen, alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted; cycloalkyl residues having from 3 to 12 carbon atoms, wherein the cycloalkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted, aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted; aryl residues constituting a heterocycle, or a phenyl group substituted with: NO_2 , F, Cl, OPh, SPh, SO_2 -alkyl, SO_2 -aryl, alkyloxy, aryloxy, alkyl, aryl, $\text{CH}(\text{Oalkyl})_2$, or tertiary amines.

According to all aspects, the EWG residue may be selected from SO_2R^4 groups, wherein R^4 is selected from

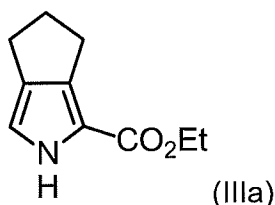
- (i) aryl residues having from 6 to 24 carbon atoms, particularly phenyl, chlorophenyl, particularly p-chlorophenyl, bromophenyl, particularly p-bromophenyl, fluorophenyl, particularly p-fluorophenyl, nitrophenyl, particularly p-nitrophenyl, and toluenyl, particularly p-toluenyl, wherein the aryl residues are optionally alkyl substituted;
- (ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

and NO_2 .

The compound of formula (II) as disclosed herein may in all aspects be the compound of formula (IIa)

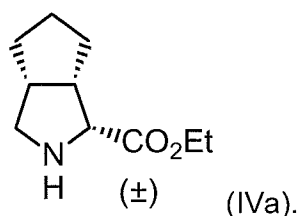


The compound of formula (III) as disclosed herein may in all aspects be the compound of formula (IIIa)

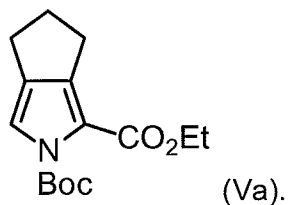


The compound of formula (IV) as disclosed herein may in all aspects be the compound of formula (IVa)

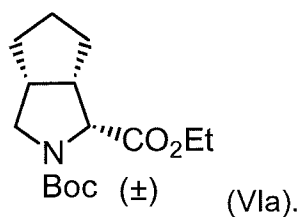
- 23 -



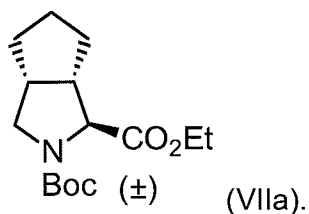
The compound of formula (V) as disclosed herein may in all aspects be the compound of formula (Va)



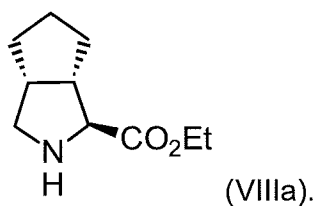
- 5 The compound of formula (VI) as disclosed herein may in all aspects be the compound of formula (VIa)



The compound of formula (VII) as disclosed herein may in all aspects be the compound of formula (VIIa)



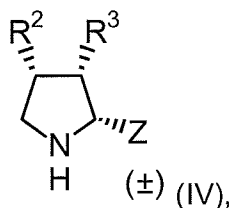
10 The compound of formula (VIII) as disclosed herein may in all aspects be the compound of formula (VIIIa)



15 **Pyrrolidines and pyrroles of the invention**

All definitions, e.g. the definitions of the Z, R¹, R², R³, R⁴, PG and the EWG groups, provided above may apply likewise for the pyrrolidines and pyrroles of the invention.

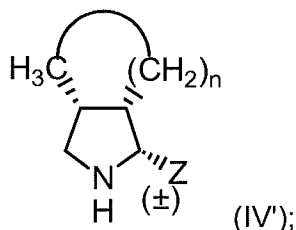
A further aspect of the present invention relates to a compound of formula (IV)



wherein Z is as defined herein and

wherein R^2 and R^3

- 5 -form a ring and the compound of formula (IV) is the compound of formula (IV')



10 with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

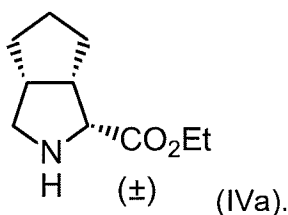
- are identical or different, and are independently selected from

(i) hydrogen,

15 (ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted.

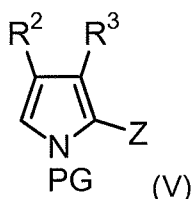
Particularly, the compound is the compound of formula (IVa)



20 The compound of formula (IV') with $n = 2$ may be used in a process for the preparation of compounds suitable as building blocks for (1S,3aR,6aS)-2-[(2S)-2-[(2S)-2-Cyclohexyl-2-(pyrazine-2-carbonylamino)acetyl]amino]-3,3-dimethylbutanoyl]-N-[(3S)-1-

(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c] pyrrol-1-carboxamid.

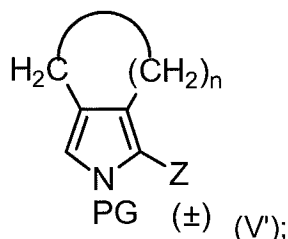
A further aspect of the present invention relates to a compound of formula (V)



wherein Z is as defined herein an

wherein R² and R³

-form a ring and the compound of formula (V) is the compound of formula (V')



with n = 1, 2, 3, 4 or 5, wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

- are identical or different, and are independently selected from

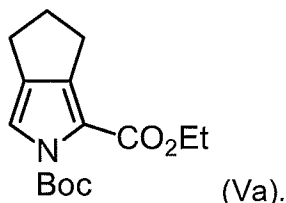
(i) hydrogen,

(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

wherein the PG residue is as defined herein.

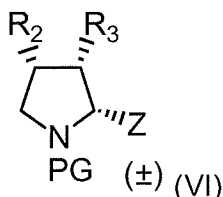
Particularly, the compound of formula (V) is the compound of formula (Va)



The compound of formula (V') with n= 2 may be used in process for the preparation of compounds suitable as buildings blocks for (1S,3aR,6aS)-2-[(2Sv)-2-[(2S)-2-Cyclohexyl-2-

(pyrazine-2-carbonylamino)acetyl]amino]-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c] pyrrol-1-carboxamid.

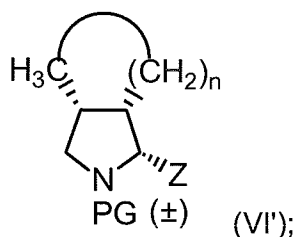
- 5 Another aspect of the present invention relates to a compound of formula (VI)



wherein Z is as defined herein and

wherein R² and R³

-form a ring and the compound of formula (VI) is the compound of formula (VI')



with n = 1, 2, 3, 4 or 5, wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

- are identical or different, and are independently selected from

(i) hydrogen,

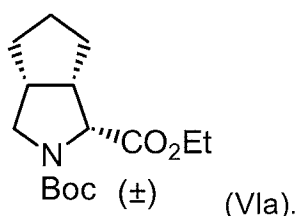
(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

wherein the PG residue is as defined herein.

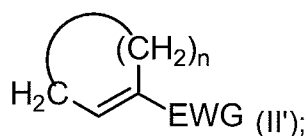
The PG residue is particularly selected from *t*-butyloxycarbonyl, carboxybenzyl, fluorenylmethyloxycarbonyl, and is particularly *t*-butyloxycarbonyl. Particularly, the compound of formula (VI) is the compound of formula (VIa)

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The compound of formula (VI') with $n = 2$ may be used in a process for the preparation of compounds suitable as building blocks for (1S,3aR,6aS)-2-[(2S)-2-[(2S)-2-Cyclohexyl-2-(pyrazine-2-carbonylamino)acetyl]amino]-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c] pyrrol-1-carboxamid.

Another aspect of the present invention relates to a compound of formula (II')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; wherein the EWG residue is an electron withdrawing group and is selected from SO_2R^4 groups, wherein R^4 is selected from aryl groups selected from phenyl, chlorophenyl, particularly p -chlorophenyl, bromophenyl, particularly p -bromophenyl, fluorophenyl, particularly p -fluorophenyl, nitrophenyl, particularly p -nitrophenyl, and toluenyl, particularly p -toluenyl, wherein the aryl residues are optionally alkyl substituted, under the proviso that when $n = 1$ R^4 is not phenyl, when $n = 2$ R^4 is not phenyl or p -toluenyl, when $n = 3$ R^4 is not phenyl or p -toluenyl and when $n = 4$ R^4 is not phenyl. R^4 may also be selected from alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

This compound with $n=2$ may be used in a process for the preparation of compounds suitable as building blocks for (1S,3aR,6aS)-2-[(2S)-2-[(2S)-2-Cyclohexyl-2-(pyrazine-2-carbonylamino)acetyl]amino]-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c] pyrrol-1-carboxamid.

Examples

The following examples describe the present invention in detail, but are not to be construed to be in any way limiting for the present invention. In the examples below, the following abbreviations have the following meanings. Any abbreviations not defined have their

generally accepted meaning. Unless otherwise stated, all temperatures are in degrees Celsius (°C).

1. Preparation of the compound of formula (IIIa)

5 The formation of the compound of formula (IIIa) was done as follows: a solution of the compound of formula (Ia) (36.0 g, 318 mmol) in tetrahydrofuran (THF) (635 mL) was added within 15 minutes to a stirred suspension of potassium *tert.*-butoxide (47.5 g, 423 mmol) in dry THF (1279 mL) at 0 °C under N₂-atmosphere and stirring was continued for 15 minutes. A solution of the compound of formula (IIa) (52.2 g, 251 mmol) in THF (1253 mL) was then
10 added within 20 minutes and the reaction mixture was stirred at 0 °C for 10 minutes and at room temperature for 180 minutes. The reaction progress was monitored by HPLC. The reaction was quenched by the addition of H₂O (1566 mL) and dichloromethane (1566 mL) was added. HCl (5.0 M, 153 g) were added in order to adjust the pH-value of the solution from pH = 13.0 to pH = 1.0. The two phases were separated and the organic layer was
15 washed with NaOH (0.5 M, 2.2 L). The solvent was removed under reduced pressure at 40 °C and the residue was dried in vacuum at room temperature. The crude product (46.6 g) was recrystallized: Heptane (373 mL) was added and the solution was warmed to 75 °C. The hot solution was filtered (K150) and then slowly cooled to 0 °C. The compound of formula (IIIa) was filtered (G3 filter) and dried under reduced pressure at room temperature. Yield:
20 38.7 g (86%).

The compound of formula (IIIa) has the following spectroscopic data: ¹H NMR (300 MHz, CDCl₃): δ = 9.06 (very br. s, 1H, NH), 6.59 (d, *J* = 2.4 Hz, 1H, NCH=C), 4.30 (q, *J* = 7.1 Hz, 2H, OCH₂), 2.83 (t, *J* = 7.2 Hz, 2H, CH₂), 2.64 (t, *J* = 7.2 Hz, 2H, CH₂), 2.34 (quint, *J* = 7.2 Hz, 2H, CH₂), 1.34 (t, *J* = 7.1 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 161.5, 138.4,
25 132.1, 114.8, 114.7, 59.8, 31.0, 26.2, 24.9, 14.5.

2. BOC-Protection of the compound of formula (IIIa)

Triethylamine (70.7 g, 699 mmol) and Boc₂O (30.75 g, 141 mmol) were added to a stirred solution (IIIa) (12.5 g, 70 mmol) and dimethylaminopyridine (0.85 g, 7 mmol) in
30 dichloromethane (700 mL) at room temperature. The reaction mixture was stirred for three hours and the reaction progress was monitored by HPLC. The reaction was quenched by the addition of H₂O (280 mL), the organic phase was separated and washed two more times with H₂O (280 mL each) and brine (280 mL). The combined aqueous layers were extracted with dichloromethane (280 mL) and the combined organic phases were dried over Na₂SO₄.
35 After filtration the solution was concentrated under reduced pressure at 30 °C and the residue was dried in vacuum overnight to give 20.1 g crude product which was purified by

flash column chromatography (300 g silica gel, heptane/ethyl acetate = 30/1) to give the compound of formula (Va). Yield: 19.1 g (98%).

The compound of formula (Va) has the following spectroscopic data: ^1H NMR of CCI01-96-C (300 MHz, CDCl_3): δ = 6.97 (s, 1H, NCH), 4.27 (q, J = 7.1 Hz, 2H, OCH_2), 2.75 (t, J = 7.3 Hz, 2H, CH_2), 2.58 (t, J = 7.2 Hz, 2H, CH_2), 2.29 (quint, J = 7.2 Hz, 2H, CH_2), 1.56 (s, 9H, *tert*-Bu), 1.33 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR of CCI01-096-C (75 MHz, CDCl_3): δ = 160.8, 148.9, 145.3, 132.0, 118.3, 117.2, 83.7, 60.2, 30.5, 27.7, 26.3, 24.5, 14.4.

3. Hydrogenation of the compound of formula (IIIa)

Neat sulfuric acid (1.1 g) and Rh/C (220 mg, 5w% Rh on activated charcoal) were added to a solution of the compound of formula (IIIa) in EtOH (20 mL). The reaction mixture was hydrogenated at a pressure of 50 bar and a temperature of 60 °C. In this case the conversion was approximately 50% after 24 hours as determined by GC. After basic work-up (NaHCO_3) spiking experiments and NMR experiments confirmed the formation of the compound of formula (IVa): The data of the compound of formula (IVa) are in complete agreement with the data obtained in experiment #6 (deprotection of the compound of formula (VIa)).

4. Hydrogenation of the compound of formula (Va)

The following reaction has been carried out twice in an autoclave at a hydrogen pressure of 10 bar and of 2 bar. To a solution of the compound of formula (Va) (1.0 g, 3.58 mmol) in EtOH (20 mL) in an autoclave was added triethylamine (125 μL , 0.9 mmol) and Rh/C (186 mg, 5% Rh on activated charcoal). The hydrogenation was performed with stirring at 10 bar pressure (or 2 bar, respectively) at 60 °C. The reaction was monitored by GC and the starting material was already consumed after one hour. The reaction mixture was filtered. Dichloromethane (50 mL) and aqueous NH_4Cl solution (10 %, 40 mL) were added to the solution and stirred. The organic layer was separated, washed with H_2O and dried over Na_2SO_4 . The solvent was then removed and the remaining slightly yellow and highly viscous oil compound of formula (VIa) was dried. Yield: 0.87 g, 86%.

The compound of formula (VIa) has the following spectroscopic data: ^1H NMR (300 MHz, CDCl_3): δ = 4.38 (m, 1H), 4.13 (m, 2H), 3.73 (m, 1H), 3.02 (t, J = 9.7 Hz, 1H), 2.88 (quint, J = 8.3 Hz, 1H), 2.66 (m, 1H), 1.70 (m, 2H), 1.35 – 1.59 (series of m, 4H), 1.35 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 171.8, 171.5, 154.1, 153.6, 79.6, 62.6, 60.4, 51.9, 46.9, 45.7, 43.3, 42.3, 29.6, 28.2, 27.8, 26.1, 14.2. Due to the formation of rotamers caused by the bulky BOC-group the signals in the ^1H NMR appear unusually broad (multiplett) and in the ^{13}C NMR spectra some signals appear as doublets.

5. Homogeneous hydrogenation of the compound of formula (Va) with Josiphos ligands and [(Ru(η^3 -methylallyl)(cod))]

In a round-bottom flask, a Josiphos-type ligand (45 mg, 49 μ mol), [(Ru(η^3 -methylallyl)(cod))]
(14.5 mg, 45 μ mol), triethylamine (TEA) (12.5 μ L, 89.5 mmol) and the compound of formula
(Va) (100 mg, 0.36 mmol) were placed and dissolved in isopropanol (2 mL, analytical grade).
This mixture was degassed three times by freezing under high vacuum, thawing and venting
with nitrogen. Then, it was transferred into a hydrogenation autoclave under nitrogen
atmosphere. The autoclave was evacuated, flushed twice with nitrogen and finally twice with
hydrogen. The hydrogen pressure was raised to 50 bar and the temperature was elevated to
approximately 60 °C. The reaction mixture was stirred for a period of 72h under these
conditions. Reaction control by HPLC indicated complete consumption of the starting
material. After releasing the overpressure, the mixture was concentrated under reduced
pressure and the crude product was dried overnight under vacuum at 40 °C and <50 mbar.
The structure of the pyrrolidine product was confirmed by ¹H-NMR spectroscopy (data see
above).

6. Deprotection of the compound of formula (VIa)

HCl (36%, 0.42 mL) was added to a stirred solution of the compound of formula (VIa) in
dichloromethane (5 mL) and H₂O (4 mL). The reaction mixture was stirred at 40 °C and the
progress was monitored by HPLC. In this case an additional aliquot HCl (36%, 0.2 mL) was
added and stirring at 40 °C was continued. The resulting homogeneous solution was cooled
to room temperature. Dichloromethane (5 mL) and H₂O (5 mL) were added. The organic
phase was separated and the aqueous phase was extracted with dichloromethane (5 mL).
Dichloromethane (10 mL) was then added to the aqueous phase and the pH-value was
adjusted from pH = 0.6 to pH = 10 with aqueous NaOH (2 M). The organic layer was
separated and washed with H₂O (5 mL). The combined organic phases were dried over
Na₂SO₄, filtered and the solvent was removed under reduced pressure to give crude
compound of formula (IVa) as an oil. Yield: 80 mg, 44%. The compound of formula (IVa) has
the following spectroscopic data: ¹H NMR (300 MHz, CDCl₃): δ = 4.13 (m, 2H, OCH₂), 3.63
(d, J = 7.4 Hz, 1H, NCH), 2.66 – 2.86 (overlapping signals, 3H, CH, NCH_A, NCH_B), 2.52 (m,
1H), 1.85 (m, 1H), 1.61 (m, 2H, CH), 1.02 – 1.40 (series of m, 3H), 1.21 (t, J = 7.2 Hz, 3H,
CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 172.6, 64.6, 60.4, 52.9, 46.9, 44.3, 33.7, 29.2, 27.7,
14.2.

7. Process for racemic resolution:

100 mg of compound IVa and 196 mg of dibenzoyltartaric acid are mixed in 1.0 mL of acetonitrile at room temperature. The clear solution is then stored for at least 16h in the fridge at 4 °C. During this time, a precipitate is formed which is isolated by filtration and washed with a little amount of ice-cold acetonitrile. The wet salt is dried overnight (~16h) under vacuum (<50 mbar) at RT. NMR spectroscopy of the DB-tartrate salt of compound IVa:

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 7.94 – 8.02 (m, 4H, Ar-H), 7.62 – 7.72 (m, 2H, Ar-H), 7.49 – 7.59 (m, 4H, Ar-H), 5.69 (m, 2H, CH), 4.28 – 4.41 (m, 1H, CH), 3.96 – 4.25 (m, 2H, OCH₂), 3.00 – 3.17 (m, 1H, CH), 2.77 – 2.92 (m, 2H, CH), 2.56 – 2.74 (m, 1H, CH), 1.85 (m, 1H), 1.51 – 1.84 (m, 3H, CH), 1.24 – 1.42 (m, 2H, CH), 1.16 (t, J = 7.2 Hz, 3H, CH₃) 1.01 – 1.11 (m, 1H, CH).

¹³C-NMR: (75 MHz, DMSO-d₆): δ (ppm) = 168.3, 168.0, 164.9, 133.4, 129.5, 129.2, 128.7, 72.7, 61.9, 61.4, 49.6, 44.3, 41.2, 31.9, 28.3, 26.4, 13.9.

Determination of the enantiomeric excess:

Enantiomeric excess: 77%, chiral HPLC analysis (see figure 3).

Chiral HPLC analysis of the salt: since a suitable chiral HPLC method was only available for compound VIa, a derivatization of compound IVa towards VIa was necessary. Therefore, the enantiomerically enriched dibenzoyl tartrate salt of compound IVa was dissolved in dichloromethane and washed once with 1N NaOH in order to remove the dibenzoyl tartrate. The thus obtained free base of compound IVa was then derivatized by conversion with BOC-anhydride, TEA and DMAP to give compound VIa. The procedure for this derivatization is the same as in steps b⁴ or e³.

Column: 5μ 4.6*250mm Lux Amylose-2 (Phenomenex), Part.No.: 00G-4472-E0. Flow rate: 0.5 mL/min. Mobile phase: 20mM 40:60:0.1 ammonium acetate:acetonitrile:trifluoroacetic acid. Wavelength: 230 nm. Temperature: 30 °C.

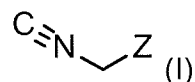
Cited literature

WO 0218369 A2
WO 2007022459 A2
WO 2008090819 A1
WO 201000882

The following pages of the description refer to the embodiments of the invention listed as separate items:

1. A process comprising the following steps:

a) reacting a compound of formula (I)



wherein Z is selected from carbonyl groups,

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

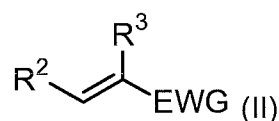
(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

or particularly from $-\text{CON}-\text{XY}$ groups, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

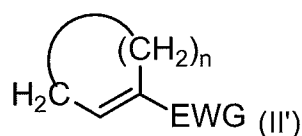
or particularly from $-\text{CON}-\text{QW}$ groups, wherein Q and W constitute a fragment of any natural or non-natural amino acid;

with a compound of formula (II)



wherein R^2 and R^3

-form a ring and the compound of formula (II) is the compound of formula (II')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

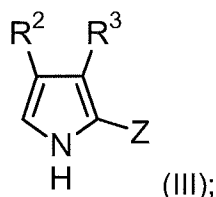
- are identical or different, and are independently selected from

(i) hydrogen,

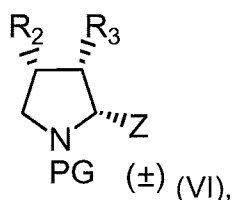
(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

- 33 -

(iii) aryl residues having from 6 to 24 carbon atoms,
wherein the aryl residues are optionally alkyl substituted;
and wherein the EWG residue is an electron withdrawing group;
to obtain a compound of formula (III)

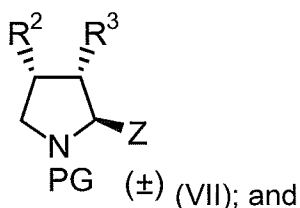


b) converting the compound of formula (III) to a compound of formula (VI)

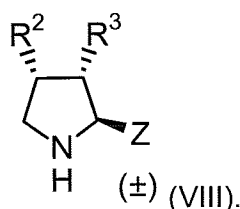


wherein the PG residue is a protective group, which is capable of protecting
an amine group;

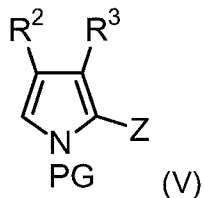
c) converting the compound of (VI) to a compound of formula (VII)



d) converting the compound of (VII) to a compound of formula (VIII)



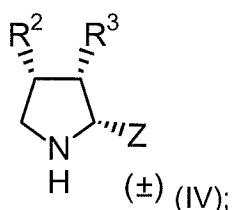
2. The process of item 1, wherein step b) comprises a step b¹) of converting the
compound of formula (III) to a compound of formula (V)



wherein the PG residue is as defined in item 1;
and a step b²) of converting the compound of (V) to the compound of formula (VI).

3. The process of item 1, wherein step b) comprises a step b³) of converting the
compound of formula (III) to a compound of formula (IV)

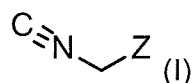
- 34 -



and a step b⁴) of converting the compound of (IV) to the compound of formula (VI).

4. A process comprising the following steps:

a) reacting a compound of formula (I)



wherein Z is selected from carbonyl groups,

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

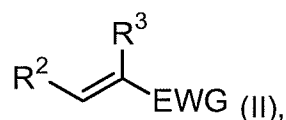
(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

or particularly from $-\text{CON}-\text{XY}$ groups, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

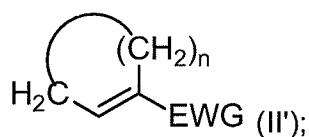
or particularly from $-\text{CON}-\text{QW}$ groups, wherein Q and W constitute a fragment of any natural or non-natural amino acid;

with a compound of formula (II)



wherein R^2 and R^3

-form a ring and the compound of formula (II) is the compound of formula (II')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

- 35 -

- are identical or different, and are independently selected from

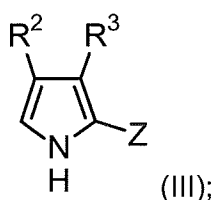
(i) hydrogen,

(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

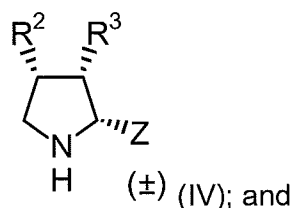
(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

and wherein the EWG residue is an electron withdrawing group;

to obtain a compound of formula (III)

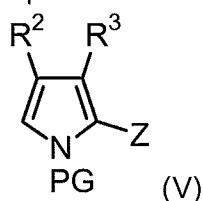


e) converting the compound of formula (III) to a compound of formula (IV)



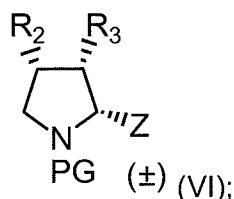
optionally f) performing chiral resolution.

5. The process of item 4, wherein step e) comprises a step e¹) of converting the compound of formula (III) to a compound of formula (V)



wherein the PG residue is as defined in item 1;

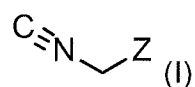
a step e²) of converting the compound of formula (V) to a compound of formula (VI)



and a step e³) of converting the compound of (VI) to a compound of formula (IV).

6. The process of item 4, wherein step e) comprises a step e⁴) of converting the compound of formula (III) to the compound of formula (IV).
7. A process comprising a step a) of reacting a compound of formula (I)

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wherein Z is selected from carbonyl groups,

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

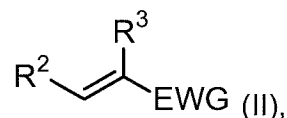
(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

or particularly from $-\text{CON-XY}$ groups, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

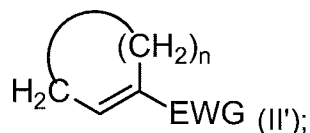
or particularly from $-\text{CON-QW}$ groups, wherein Q and W constitute a fragment of any natural or non-natural amino acid;

with a compound of formula (II)



wherein R^2 and R^3

-form a ring and the compound of formula (II) is the compound of formula (II')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

- are identical or different, and are independently selected from

(i) hydrogen,

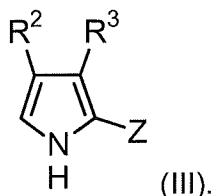
(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

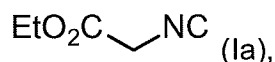
and wherein the EWG residue is an electron withdrawing group;

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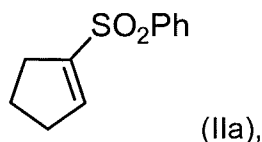
to obtain a compound of formula (III)



8. The process of items any of the preceding items, wherein step a) is carried out at a temperature of -10 °C to 30 °C, particularly 0 °C to room temperature, more particularly first at 0 °C and then at room temperature.
9. The process of any of the preceding items, wherein step a) is carried out in a solvent, particularly an aprotic solvent, more particularly a dry aprotic solvent
10. The process of any of the preceding items, wherein step a) is carried out in a solvent selected from tetrahydrofuran (THF), acetonitrile, dimethylacetamide (DMAc), dimethylformamide (DMF), methyl tert-butyl ether, 2-methyltetrahydrofuran, *N*-methyl-2-pyrrolidone (NMP), and any combination thereof, and is particularly THF, and more particularly dry THF.
11. The process of any of the preceding items, wherein step a) is carried out under an inert gas atmosphere, particularly under a nitrogen or argon gas atmosphere.
12. The process of any of the preceding items, wherein step a) is carried out in the presence of a base.
13. The process of item 12, wherein the base is selected from KOBut, NaOEt, diazabicycloundecene (DBU), lithium diisopropylamide, potassium hexamethyldisilazide, sodium hexamethyldisilazide, lithium hexamethyldisilazide, NaOBut, K₂CO₃, Na₂CO₃, KOAc, NaOAc, tetramethylguanidine, diazabicyclononene, and any combination thereof, and is particularly KOBut.
14. The process of any of items 1 to 6, wherein step a) comprises reacting a compound of formula (Ia)

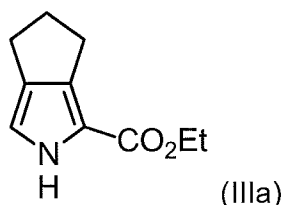


with a compound of formula (IIa)



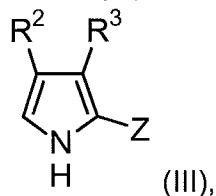
to obtain a compound of formula (IIIa)

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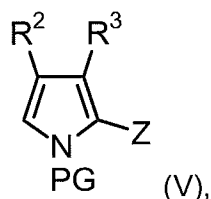


wherein step a) is carried out in the presence of KOBut first at 0 °C and then at room temperature in dry THF.

15. A process comprising a step b¹) as defined in item 2 or a step e¹) as defined in item 5 of converting a compound of formula (III)

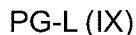


to a compound of formula (V)



wherein the PG residue is a protective group, which is capable of protecting an amine group.

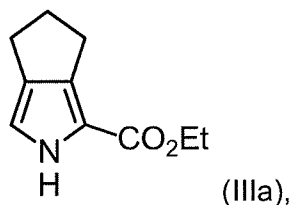
16. The process of any of items 2, 3, 5 or 15, wherein said step b¹) or e¹) is carried out at a temperature of 15 °C to 40 °C, particularly from 20 °C to 30 °C, and more particularly at room temperature.
17. The process of any of items 2, 3, 5, 15 or 16, wherein converting the compound of formula (III) to the compound of formula (V) is carried out by adding an agent suitable for introducing a protective group.
18. The process of any of items 2, 3, 5, or 15 to 17, wherein converting the compound of formula (III) to the compound of formula (V) is carried by adding a compound of formula (IX)



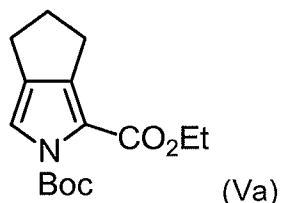
wherein the PG residue is as defined in item 1 and wherein L is a leaving group.

19. The process of item 18, wherein L is selected from *t*-butyloxycarbonyl, halogenides, particularly chloride and bromide, and is particularly *t*-butyloxycarbonyl.
20. The process of item 18 or 19, wherein the PG residue is selected from *t*-butyloxycarbonyl, carboxybenzyl, fluorenylmethyloxycarbonyl, and is particularly *t*-butyloxycarbonyl.

21. The process of any of items 18 to 20, wherein the compound of formula (IX) is selected from di-*t*-butyl dicarbonate, carboxybenzylchlorid, fluorenylmethyloxycarbonyl chloride, and is particularly di-*t*-butyl dicarbonate.
22. The process of any of items 12 to 15, 18 to 26, and 35 to 42, wherein said step b¹) or e¹) is carried out in a solvent, particularly an aprotic solvent.
23. The process of any of items 2, 3, 5, or 15 to 22, wherein step b¹) or e¹) is carried out in a solvent selected from tetrahydrofuran (THF), dimethylformamide (DMF), dimethylacetamide (DMAc), dichloromethane, ethyl acetate, 2-methyltetrahydrofuran, *N*-Methyl-2-pyrrolidone (NMP), and any combination thereof, and is particularly THF.
24. The process of any of items 2, 3, 5, or 15 to 23, wherein said step b¹) or e¹) is carried out in the presence of a base.
25. The process of item 24, wherein the base is selected tertiary and secondary amines, particularly dimethylaminopyridine, diisopropylethylamine, isopropylmethylamine, butylmethylamine, and triethylamine; cyclic tertiary amines, particularly *cis*-2,6-dimethylpiperidine, 1,4-diazabicyclo[2.2.2]octane, *N*-methylpiperidine and *N*-methylmorpholine; and any combination thereof, and is particularly dimethylaminopyridine.
26. The process of any of items 2, 3, 5, or 15, wherein said step b¹) or e¹) comprises converting a compound of formula (IIIa)



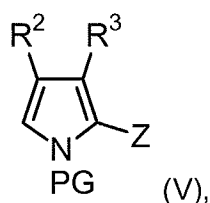
to a compound of formula (Va)



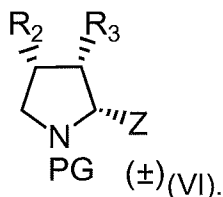
with di-*t*-butyl dicarbonate in the presence of dimethylaminopyridine at room temperature in THF.

27. A process comprising a step b²) as defined in item 2 or a step e²) as defined in item 5 of converting a compound of (V)

- 40 -

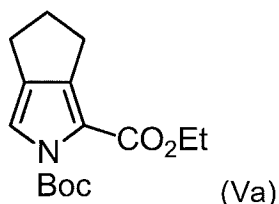


wherein the PG residue is a protective group, which is capable of protecting an amine group; to a compound of formula (VI)

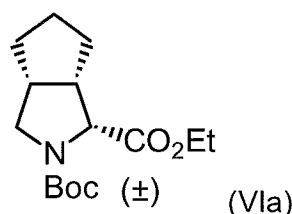


28. The process of any of items 2, 5 or 27, wherein said step b²) or e²) is carried out at a temperature of 20 °C to 100 °C, particularly from 50 °C to 70 °C, and more particularly 60 °C.
29. The process of any of items 2, 5, 27 or 28, wherein said step b²) or e²) is carried out with hydrogen at a pressure of 1 to 100 bar, particularly between 2 bar and 10 bar, more particularly at 2 bar or at 10 bar.
30. The process of any of items 2, 5 or 27 to 29, wherein said step b²) or e²) is carried out in the presence of a catalyst.
31. The process of any of items 2, 5 or 27 to 30, wherein the catalyst is a solid-supported catalyst.
32. The process of item 30 or 31, wherein the catalyst is selected from rhodium, palladium, platinum, platinum oxide, or nickel, and is particularly rhodium.
33. The process of item 31, wherein the solid support is selected from activated charcoal, carbon, alox, and is particularly activated charcoal.
34. The process of items 31 or 33, wherein the solid-supported catalyst is selected from rhodium-on-activated charcoal, palladium-on-activated charcoal, raney nickel, and is particularly rhodium-on-activated charcoal.
35. The process of any of items 2, 5, or 27 to 34, wherein said step b²) or e²) is carried out in the presence of a base.
36. The process of item 35, wherein the base is selected tertiary and secondary amines, particularly triethylamine, dimethylaminopyridine, diisopropylethylamine, propylmethylamine, and butylmethylamine; cyclic tertiary amines, particularly *cis*-2,6-dimethylpiperidine, 1,4-diazabicyclo[2.2.2]octane, N-methylpiperidine and N-methylmorpholine; and any combination thereof, and is particularly triethylamine.

37. The process of any of items 2, 5, or 27 to 36, wherein said step b²) or e²) is carried out in a solvent, particularly selected from ethanol, methanol, propanol, isopropanol, butanol, and any combination thereof, and is particularly ethanol.
38. The process of any of items 2, 5, or 27, wherein said step b²) or e²) comprises
- 5 converting a compound of (Va)



to a compound of formula (VIa)

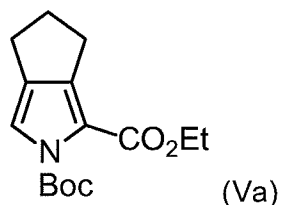


with hydrogen at a pressure of 2 bar or 10 bar in the presence of rhodium-on-activated charcoal and triethylamine at 60 °C in ethanol.

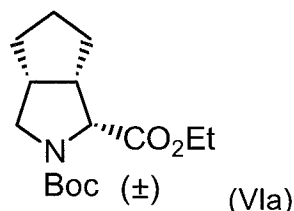
39. The process of item 2, 5, 27 or 28, wherein said step b²) or e²) is carried out with hydrogen at a pressure of 20 to 100 bar, particularly of 40 to 60 bar, and more particularly 50 bar.
40. The process of any of items 2, 5, 27, 28 or 39, wherein said step b²) or e²) is carried out in the presence of a catalyst.
41. The process of any of items 2, 5, 27, 28, 39 or 40, wherein the catalyst is a homogenous catalyst comprising a transition metal compound and at least one ligand.
42. The process of item 41, wherein the transition metal compound is selected from Rhodium complexes, particularly Rh(III)-chloronorbornadiene-dimer, and Ruthenium complexes, particularly [(Ru(η³-methylallyl)(cod))], and any combination thereof, and is particularly [(Ru(η³-methylallyl)(cod))].
43. The process of item 41 or 42, wherein the at least one ligand is selected from phosphine ligands, particularly diphosphine and monophosphine ligands, and any combination thereof.
44. The process of item 41 or 42, wherein the at least one ligand is selected from Josiphos ligands, Walphos-type ligands, Taniaphos-type ligands, Mandyphos-type ligands and Du-Phos-type ligands.
45. The process of item 41 or 42, wherein the at least one ligand is selected from diphosphine ligands, particularly from 2,2-bis(diphenylphosphino)-1,1-binaphthale, 1,2-

bis(diphenyl-phosphino)benzene, (Oxydi-2,1-phenylene)bis-(diphenylphosphine), (*R*)-2,2-bis(diphenylphosphino)-1,1-binaphthalene, (*S*)-2,2-bis(diphenylphosphino)-1,1-binaphthalene, and any combination thereof.

46. The process of item 41, wherein the homogenous catalyst comprises
 5 [(Ru(η^3 -methylallyl)(cod))] and a Josiphos ligand or [(Ru(η^3 -methylallyl)(cod))] and 2,2-bis(diphenylphosphino)-1,1-binaphthalene.
47. The process of any of items 2, 5, 27, 28 or 39 to 46, wherein said step b²) or e²) is carried out in the presence of a base.
48. The process of item 47, wherein the base is selected tertiary and secondary amines,
 10 particularly triethylamine, dimethylaminopyridine, diisopropylethylamine, isopropylmethanamine, and butylmethanamine; cyclic tertiary amines, particularly *cis*-2,6-dimethylpiperidine, 1,4-diazabicyclo[2.2.2]octane, N-methylpiperidine and N-methylmorpholine; and any combination thereof, and is particularly triethylamine.
49. The process of any of items 2, 5, 27, 28 or 39 to 48, wherein said step b²) or e²) is
 15 carried out in a solvent, particularly selected from methanol, ethanol, propanol, isopropanol, butanol, and any combination thereof.
50. The process of any of items 2, 5, or 27, wherein said step b²) or e²) comprises converting a compound of (Va)



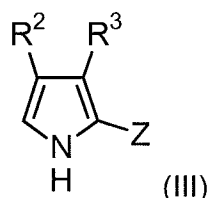
20 to a compound of formula (VIa)



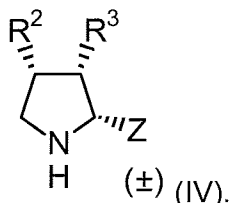
with hydrogen at a pressure of 50 bar in the presence of [(Ru(η^3 -methylallyl)(cod))] and a Josiphos ligand, and triethylamine at 60 °C.

51. A process comprising a step b³) as defined in item 3 or a step e⁴) as defined in item 6
 25 of converting a compound of formula (III)

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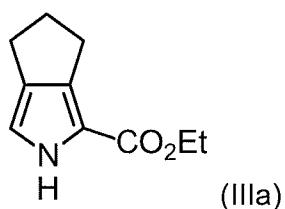


to a compound of formula (IV)

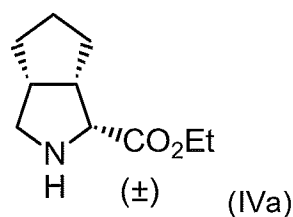


52. The process of any of items 3, 6 or 51, wherein said step b³) or e⁴) is carried out at a temperature of 40 °C to 80 °C, particularly from 50 °C to 70 °C, and more particularly 60 °C.
53. The process of any of items 3, 6, 51 or 52, wherein said step b³) or e⁴) is carried out with hydrogen at a pressure of 30 to 70 bar, particularly of 40 to 60 bar, more particularly 50 bar.
54. The process of any of items 3, 6, or 51 to 53, wherein said step b³) or e⁴) is carried out in the presence of a catalyst.
55. The process of item 54, wherein the catalyst is a solid-supported catalyst.
56. The process of item 54 or 55, wherein the catalyst is selected from rhodium, palladium, platinum, platinum oxide, and nickel, and is particularly rhodium.
57. The process of any of items 55 to 56, wherein the solid support is selected from activated charcoal, carbon, and alox, and is particularly activated charcoal.
58. The process of item 54, wherein the solid-supported catalyst is selected from rhodium-on-activated charcoal, palladium-on-activated charcoal, raney nickel, and is particularly rhodium-on-activated charcoal.
59. The process of any of items 3, 6, or 51 to 58, wherein said step b³) or e⁴) is carried out in the presence of an acid.
60. The process of item 59, wherein the acid is selected from sulfuric acid, HCl and acetic acid and any combination thereof, and is particularly sulfuric acid.
61. The process of any of items 3, 6, or 51 to 60, wherein said step b³) or e⁴) is carried out in a solvent, particularly selected from ethanol, methanol, ethanol, propanol, isopropanol, butanol, and any combination thereof, and is particularly ethanol.
62. The process of any of items 3, 6, or 51, wherein said step b³) or e⁴) comprises converting a compound of formula (IIIa)

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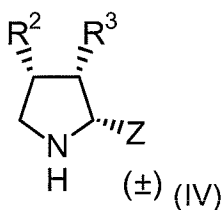


to a compound of formula (IVa)

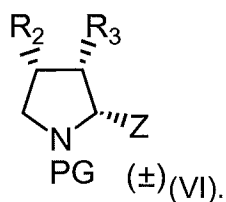


with hydrogen at a pressure of 50 bar in the presence of rhodium-on-activated charcoal and sulfuric acid at 60 °C in ethanol.

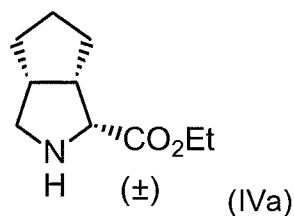
63. A process comprising a step b⁴) as defined in item 3 of converting a compound of formula



to a compound of formula (VI)

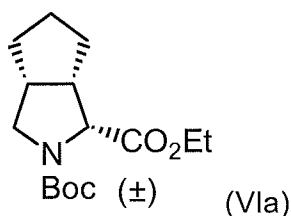


64. The process of item 3 or 63, wherein step b⁴ is carried out as defined in any of items 16 to 25.
65. The process of any of items 3 or 64, wherein step b⁴ comprises converting a compound of formula (IVa)



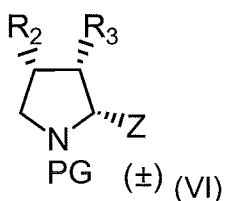
to a compound of formula (VIa)

- 45 -

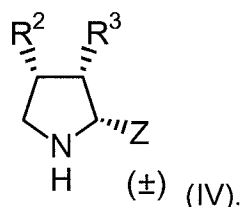


with di-*t*-butyl dicarbonate in the presence of dimethylaminopyridine at room temperature in THF.

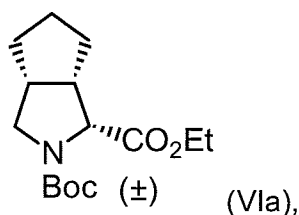
66. A process comprising a step e³) as defined in item 5 of converting a compound of (VI)



to a compound of formula (IV)

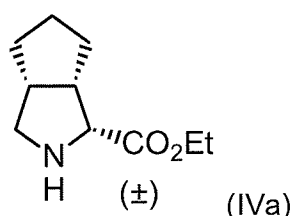


67. The process of item 3 or 66, wherein step e³) is carried out at a temperature of between room temperature and 100 °C, particularly 20 °C to 30 °C, more particularly at room temperature.
68. The process any of items 3, 66 or 67, wherein step e³) is carried out in a solvent, particularly selected from water, dichloromethane, ethanol, methanol, dioxane, THF, ethyl acetate, and any combination thereof.
69. The process of any of items 3, or 66 to 68, wherein step e³) is carried out in the presence of an agent suitable for removing the PG residue, particularly an acid, a base or hydrogen, depending on the PG residue.
70. The process of item 3 or 66, wherein step e³) comprises converting a compound of formula (VIa)



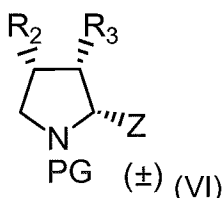
to a compound of formula (IVa)

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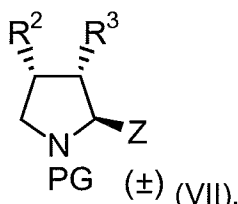


in the presence of HCl at room temperature in dioxane.

71. A process comprising a step c) as defined in item 1 of converting a compound of formula (VI)

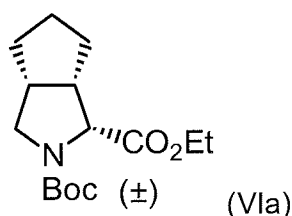


to a compound of formula (VII)

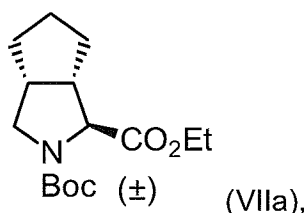


72. The process of item 1 or 71, wherein step c) is carried out at a temperature of -10 °C to 10 °C, particularly -5 °C to +5 °C, more particularly at 0 °C.
73. The process any of items 1, 71 or 72, wherein step c) is carried out in a solvent, particularly an aprotic solvent.
74. The process of any of items 1, or 71 to 73, wherein step c) is carried out in a solvent selected from tetrahydrofuran (THF), dimethylacetamide (DMAc), dimethylformamide (DMF), 2-methyltetrahydrofuran, *N*-methyl-2-pyrrolidone (NMP), and any combination thereof, and is particularly THF.
75. The process of any of items 1, or 71 to 74, wherein step c) is carried out in the presence of a base.
76. The process of item 75, wherein the base is selected from lithium diisopropylamide, lithium hexamethyldisilazide, potassium hexamethyldisilazide, and sodium hexamethyldisilazide, and any combination thereof, and is particularly lithium diisopropylamide.
77. The process of item 1 or 72, wherein step c) comprises converting the compound of (VIa)

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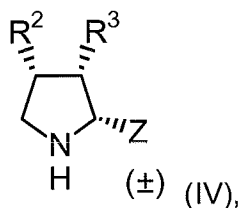


to a compound of formula (VIIa)

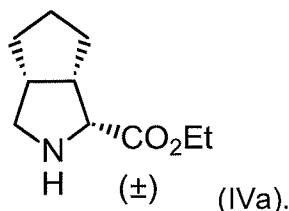


in the presence of lithiumdiisopropylamide at 0 °C in THF.

78. The process of item 1, wherein step d) is carried out as defined in any of items 67 to 69.
79. A process comprising a step f) as defined in item 4 of performing chiral resolution with a mixture of compounds of formula (IV)



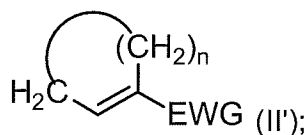
- preferably compounds of formula (IVa)



80. The process of item 79, wherein step f) is carried out by performing a crystallizing step in the presence of dibenzoyl tartaric acid and acetonitrile.
81. The process of any of the preceding items, wherein Z is $-\text{CO}_2\text{R}^1$ and R^1 selected from ethyl, methyl, i-propyl, n-propyl, n- t-butyl, i- t-butyl, s- t-butyl, t-butyl, pentyl, hexyl benzyl, cyclohexyl, and is particularly ethyl, or wherein Z is $-\text{CON-QW}$, wherein Q and W constitute a fragment of any natural or non-natural amino acid.
82. The process of any of items 1 to 80, wherein Z is $-\text{CON-XY}$, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly selected from ethyl, ethyloxy, hydrogen, methyl, methyloxy, i-propyl, i-propyloxy, n-propyl, n-propyloxy, n- t-butyl, n- t-butyloxy, i- t-butyl, i- t-butyloxy, s- t-butyl, s- t-

butyloxy, t-butyl, t-butyloxy, phenoxy, and benzoyloxy, more particularly wherein X is methoxy and Y is methyl.

83. The process of any of items 1 to 80, wherein R^2 and R^3 form a ring analogous to the compound of formula (II')



with $n = 1, 2, 3, 4$ or 5 ; particularly with $n = 2$.

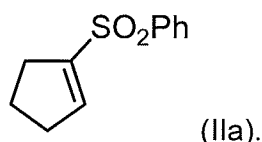
84. The process of any of items 1 to 13, wherein the EWG residue is selected from SO_2R^4 groups, wherein R^4 is selected from

(i) aryl residues having from 6 to 24 carbon atoms, particularly phenyl, chlorophenyl, particularly p-chlorophenyl, bromophenyl, particularly p-bromophenyl, fluorophenyl, particularly p-fluorophenyl, nitrophenyl, particularly p-nitrophenyl, and toluenyl, particularly p-toluenyl, wherein the aryl residues are optionally alkyl substituted;

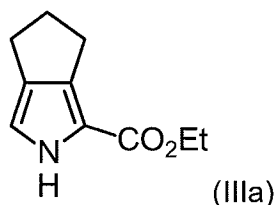
(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

and NO_2 .

85. The process of any of items 1 to 13, wherein the compound of formula (II) is the compound of formula (IIa)

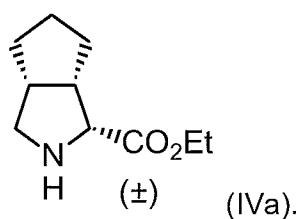


86. The process of any of items 1 to 28 or 51 to 62, wherein the compound of formula (III) is the compound of formula (IIIa)

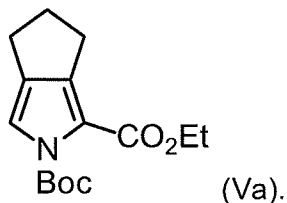


87. The process of any of items 4 to 6, 51 to 61, 63, 64, or 66 to 69, wherein the compound of formula (IV) is the compound of formula (IVa)

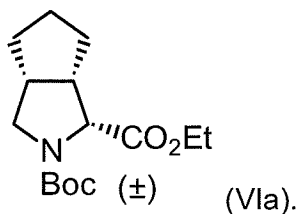
- 49 -



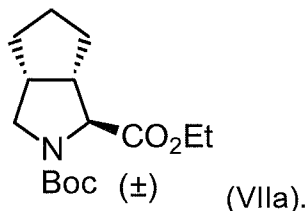
88. The process of any of items 2, 15 to 25, or 27 to 49, wherein the compound of formula (V) is the compound of formula (Va)



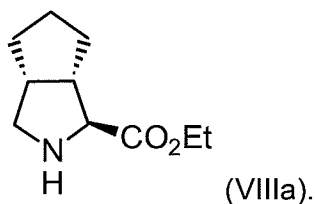
89. The process of any of items 1 to 3, 5, 27 to 39, 63, 64, 66 to 69, or 71 to 76, wherein the compound of formula (VI) is the compound of formula (VIa)



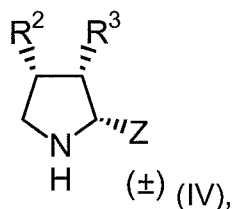
90. The process of any of items 1 to 3, 71 to 76, or 78, wherein the compound of formula (VII) is the compound of formula (VIIa)



91. The process of any of items 1 to 3, or 78, wherein the compound of formula (VIII) is the compound of formula (VIIIa)



92. A compound of formula (IV)



wherein Z is selected from carbonyl groups,

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

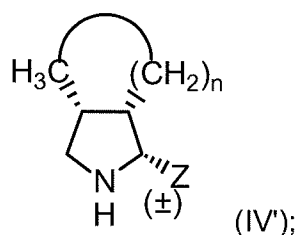
(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

or particularly from $-\text{CON-XY}$ groups, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

or particularly from $-\text{CON-QW}$ groups, wherein Q and W constitute a fragment of any natural or non-natural amino acid;

wherein R^2 and R^3

-form a ring and the compound of formula (IV) is the compound of formula (IV')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

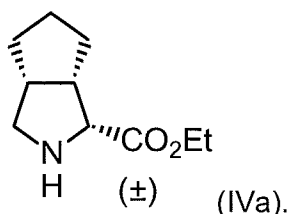
- are identical or different, and are independently selected from

(i) hydrogen,

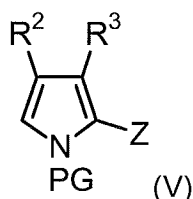
(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted.

93. A compound of formula (IV) wherein the compound is the compound of formula (IVa)



94. Use of a compound of item 93 or 92 when the compound is the compound of formula (IV') with $n=2$ in a process for the preparation of compounds suitable as building blocks for (1S,3aR,6aS)-2-[(2S)-2-[[[(2S)-2-Cyclohexyl-2-(pyrazine-2-carboxylamino)acetyl]amino]-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c] pyrrol-1-carboxamid.
95. A compound of formula (V)



wherein Z is selected from carbonyl groups,

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

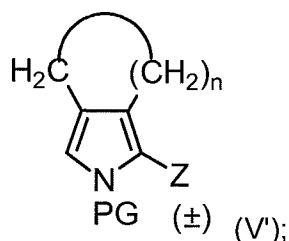
(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

or particularly from $-\text{CON-XY}$ groups, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

or particularly from $-\text{CON-QW}$ groups, wherein Q and W constitute a fragment of any natural or non-natural amino acid;

wherein R^2 and R^3

-form a ring and the compound of formula (V) is the compound of formula (V')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

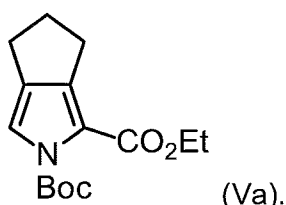
- are identical or different, and are independently selected from
(i) hydrogen,

(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

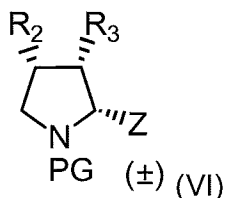
wherein the PG residue is a protective group, which is capable of protecting an amine group.

96. The compound of item 95, wherein the compound of formula (V) is the compound of formula (Va)



97. Use of a compound of item 96 or 95 when the compound is the compound of formula (V') with $n = 2$ in a process for the preparation of compounds suitable as building blocks for (1S,3aR,6aS)-2-[(2S)-2-[(2S)-2-Cyclohexyl-2-(pyrazine-2-carboxylamino)acetyl]amino]-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c] pyrrol-1-carboxamid.

98. A compound of formula (VI)



wherein Z is selected from carbonyl groups,

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

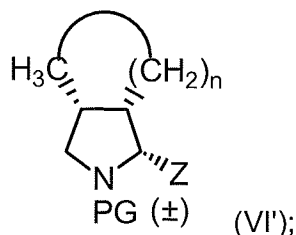
(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

or particularly from $-\text{CON-XY}$ groups, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

or particularly from $-\text{CON-QW}$ groups, wherein Q and W constitute a fragment of any natural or non-natural amino acid;

wherein R^2 and R^3

-form a ring and the compound of formula (VI) is the compound of formula (VI')



5 with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

- are identical or different, and are independently selected from

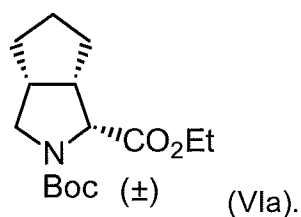
(i) hydrogen,

10 (ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

15 wherein the PG residue is a protective group, which is capable of protecting an amine group.

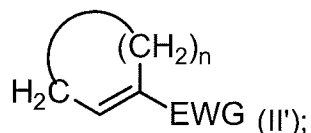
99. The compound of item 98, wherein the compound of formula (VI) is the compound of formula (VIa)



20 100. Use of a compound of item 98 or item 99 when the compound is the compound of formula (VI') with $n = 2$ in a process for the preparation of compounds suitable as buildings blocks for (1S,3aR,6aS)-2-[(2Sv)-2-[(2S)-2-Cyclohexyl-2-(pyrazine-2-carboxylamino)acetyl]amino]-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c] pyrrol-1-carboxamid.

25 101. The compound of item 95 or 98, wherein the PG residue is selected from *t*-butyloxycarbonyl, carboxybenzyl, fluorenylmethyloxycarbonyl, and is particularly *t*-butyloxycarbonyl.

102. A compound of formula (II')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms;

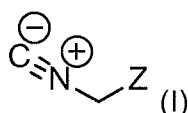
wherein the EWG residue is an electron withdrawing group and is selected from SO_2R^4 groups, wherein R^4 is selected from phenyl, chlorophenyl, particularly p-chlorophenyl, bromophenyl, particularly p-bromophenyl, fluorophenyl, particularly p-fluorophenyl, nitrophenyl, particularly p-nitrophenyl, and toluenyl, particularly p-toluenyl, under the proviso that when $n = 1$ R^4 is not phenyl, when $n = 2$ R^4 is not phenyl or p-toluenyl, when $n = 3$ R^4 is not phenyl or p-toluenyl and when $n = 4$ R^4 is not phenyl.

103. Use of a compound of item 102 with $n=2$ in a process for the preparation of compounds suitable as building blocks for (1S,3aR,6aS)-2-[(2Sv)-2-[(2S)-2-Cyclohexyl-2-(pyrazine-2-carbonylamino)acetyl]amino]-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-1-carboxamidichloromethane.

Claims

1. A process comprising the following steps:

a) reacting a compound of formula (I)



wherein Z is selected from carbonyl groups,

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

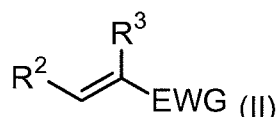
(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

or particularly from $-\text{CON-XY}$ groups, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

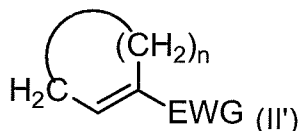
or particularly from $-\text{CON-QW}$ groups, wherein Q and W constitute a fragment of any natural or non-natural amino acid;

with a compound of formula (II)



wherein R^2 and R^3

-form a ring and the compound of formula (II) is the compound of formula (II')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

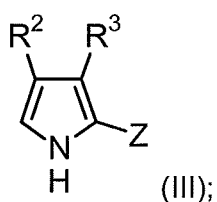
- are identical or different, and are independently selected from
(i) hydrogen,

(ii) alkyl residues having from 1 to 12 carbon atoms,
wherein the alkyl residues are optionally aryl, aryloxy,
alkoxy, and/or carbonyl substituted;

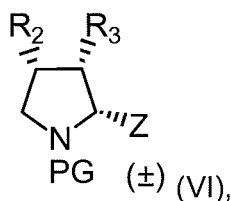
(iii) aryl residues having from 6 to 24 carbon atoms,
wherein the aryl residues are optionally alkyl substituted;

and wherein the EWG residue is an electron withdrawing group;

in the presence of a suitable base to obtain a compound of formula (III)

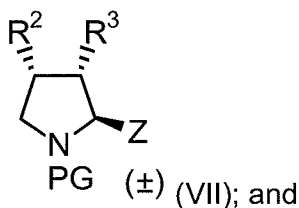


b) converting the compound of formula (III) to a compound of formula (VI)

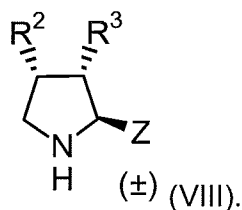


wherein the PG residue is a protective group, which is capable of protecting
an amine group;

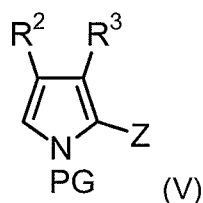
c) converting the compound of (VI) in the presence of a strong base to a compound of
formula (VII)



d) converting the compound of (VII) via deprotection to a compound of formula (VIII)



2. The process of claim 1, wherein step b) comprises a step b¹) of converting the
compound of formula (III) in the presence of a base to a compound of formula (V)

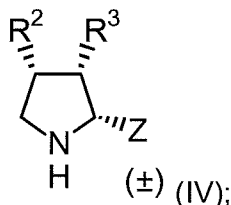


wherein the PG residue is as defined in claim 1;

and a step b²) of converting the compound of (V) via hydrogenation in the presence of a catalyst to the compound of formula (VI).

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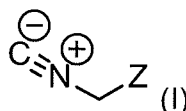
3. The process of claim 1, wherein step b) comprises a step b³) of converting the compound of formula (III) via hydrogenation in the presence of a catalyst to a compound of formula (IV)



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and a step b⁴) of converting the compound of (IV) in the presence of a base to the compound of formula (VI).

4. A process comprising the following steps:
a) reacting a compound of formula (I)



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wherein Z is selected from carbonyl groups,

particularly from -CO₂R¹ groups, wherein R¹ is selected from

(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

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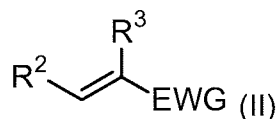
(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

or particularly from -CON-XY groups, wherein X and Y are independently selected from the R¹ groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

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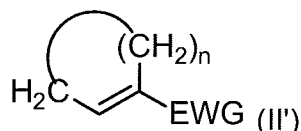
or particularly from -CON-QW groups, wherein Q and W constitute a fragment of any natural or non-natural amino acid;

with a compound of formula (II)



wherein R² and R³

-form a ring and the compound of formula (II) is the compound of formula (II')



with n = 1, 2, 3, 4 or 5, wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

- are identical or different, and are independently selected from

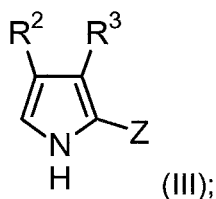
(i) hydrogen,

(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

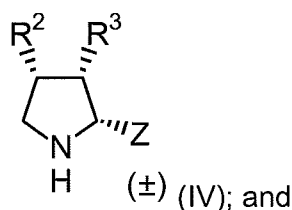
(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

and wherein the EWG residue is an electron withdrawing group;

in the presence of a suitable base to obtain a compound of formula (III)

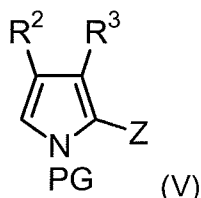


e) converting the compound of formula (III) via hydrogenation to a compound of formula (IV)



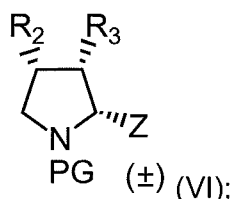
optionally f) performing chiral resolution.

5. The process of claim 4, wherein step e) comprises a step e¹) of converting the compound of formula (III) in the presence of a base to a compound of formula (V)



wherein the PG residue is as defined in claim 1;

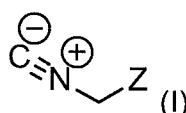
- a step e²) of converting the compound of formula (V) via hydrogenation in the presence of a catalyst to a compound of formula (VI)



and a step e³) of converting the compound of (VI) in the presence of an agent suitable for removing the PG residue to a compound of formula (IV).

6. The process of claim 4, wherein step e) comprises a step e⁴) of converting the compound of formula (III) via hydrogenation in the presence of a catalyst to the compound of formula (IV).

7. A process comprising a step a) of reacting a compound of formula (I)



wherein Z is selected from carbonyl groups,

particularly from -CO₂R¹ groups, wherein R¹ is selected from

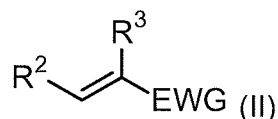
(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

or particularly from -CON-XY groups, wherein X and Y are independently selected from the R¹ groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

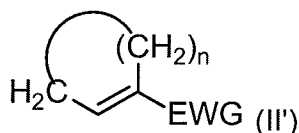
or particularly from -CON-QW groups, wherein Q and W constitute a fragment of any natural or non-natural amino acid;

with a compound of formula (II)



wherein R² and R³

-form a ring and the compound of formula (II) is the compound of formula (II')



with n = 1, 2, 3, 4 or 5, wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

- are identical or different, and are independently selected from

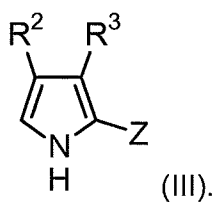
(i) hydrogen,

(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

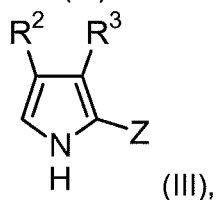
(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

and wherein the EWG residue is an electron withdrawing group;

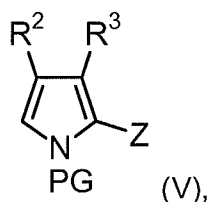
in the presence of a suitable base to obtain a compound of formula (III)



8. A process comprising a step b¹) as defined in claim 2 or a step e¹) as defined in claim 5 of converting a compound of formula (III)

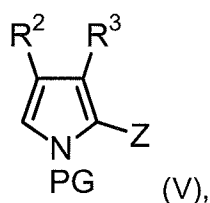


in the presence of a base to a compound of formula (V)

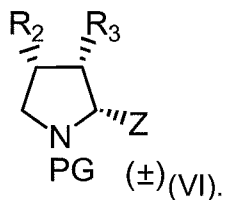


wherein the PG residue is a protective group, which is capable of protecting an amine group.

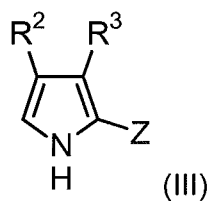
- 5 9. A process comprising a step b²) as defined in claim 2 or a step e²) as defined in claim 5 of converting a compound of (V)



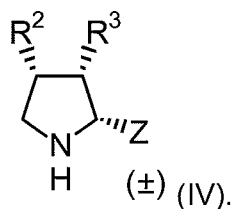
wherein the PG residue is a protective group, which is capable of protecting an amine group; via hydrogenation in the presence of a catalyst to a compound of formula (VI)



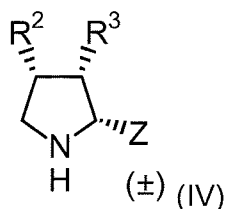
10. A process comprising a step b³) as defined in claim 3 or a step e⁴) as defined in claim 6 of converting a compound of formula (III)



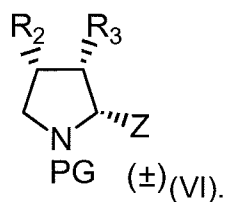
15 via hydrogenation in the presence of a catalyst to a compound of formula (IV)



11. A process comprising a step b⁴) as defined in claim 3 of converting a compound of formula

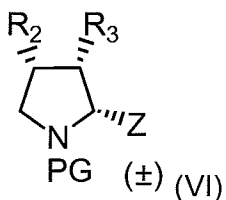


in the presence of a base to a compound of formula (VI)

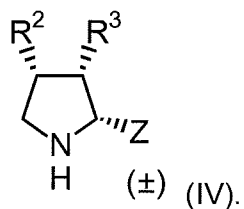


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12. A process comprising a step e³) as defined in claim 5 of converting a compound of (VI)

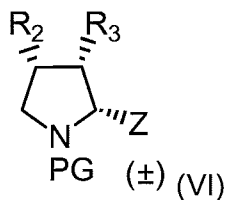


in the presence of an agent suitable for removing the PG residue to a compound of formula (IV)



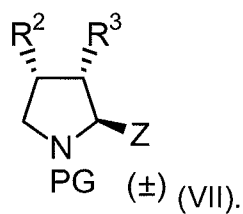
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13. A process comprising a step c) as defined in claim 1 of converting a compound of formula (VI)

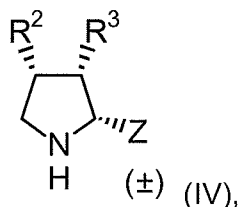


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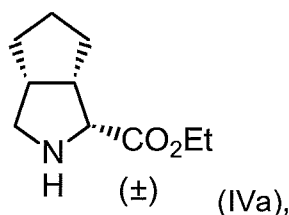
in the presence of a strong base to a compound of formula (VII)



14. A process comprising a step f) as defined in claim 4 of performing chiral resolution with a mixture of compounds of formula (IV)

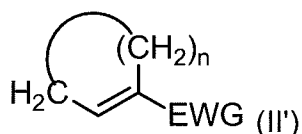


preferably compounds of formula (IVa)



preferably by performing a crystallizing step in the presence of dibenzoyl tartaric acid and acetonitrile.

15. The process of any of claims 1 to 14, wherein R^2 and R^3 form a ring analogous to the compound of formula (II')



with $n = 1, 2, 3, 4$ or 5 , particularly with $n = 2$.

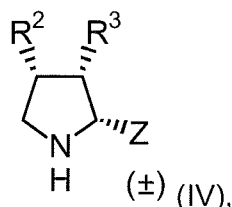
16. The process of any of claims 1 to 7 and 15, wherein the EWG residue is selected from SO_2R^4 groups, wherein R^4 is selected from

(i) aryl residues having from 6 to 24 carbon atoms, particularly phenyl, chlorophenyl, particularly p-chlorophenyl, bromophenyl, particularly p-bromophenyl, fluorophenyl, particularly p-fluorophenyl, nitrophenyl, particularly p-nitrophenyl, and toluenyl, particularly p-toluenyl, wherein the aryl residues are optionally alkyl substituted;

(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

and NO_2 .

17. A compound of formula (IV)



wherein Z is selected from carbonyl groups,

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

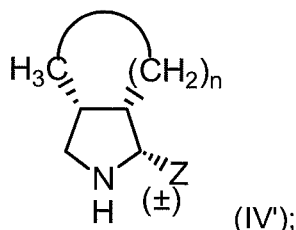
(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

or particularly from $-\text{CON-XY}$ groups, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

or particularly from $-\text{CON-QW}$ groups, wherein Q and W constitute a fragment of any natural or non-natural amino acid;

wherein R^2 and R^3

-form a ring and the compound of formula (IV) is the compound of formula (IV')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms; or

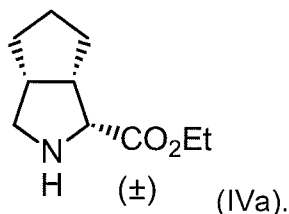
- are identical or different, and are independently selected from

(i) hydrogen,

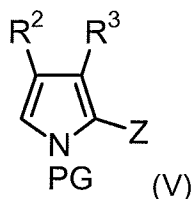
(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

wherein the compound is particularly the compound of formula (IVa)



18. A compound of formula (V)



wherein Z is selected from carbonyl groups,

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

(i) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl substituted;

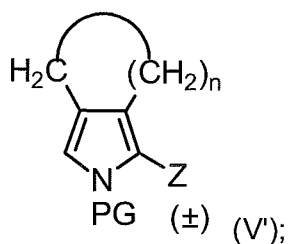
(ii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

or particularly from $-\text{CON-XY}$ groups, wherein X and Y are independently selected from the R^1 groups, alkyloxy or aryloxy groups, particularly wherein X is methoxy and Y is methyl;

or particularly from $-\text{CON-QW}$ groups, wherein Q and W constitute a fragment of any natural or non-natural amino acid;

wherein R^2 and R^3

-form a ring and the compound of formula (V) is the compound of formula (V')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms: or

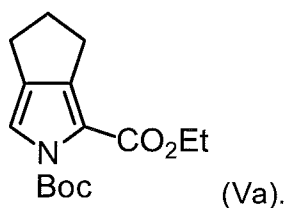
- are identical or different, and are independently selected from

(i) hydrogen,

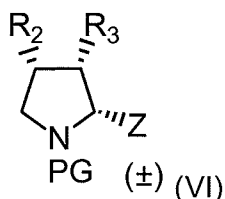
(ii) alkyl residues having from 1 to 12 carbon atoms,
wherein the alkyl residues are optionally aryl, aryloxy,
alkoxy, and/or carbonyl substituted;

(iii) aryl residues having from 6 to 24 carbon atoms,
wherein the aryl residues are optionally alkyl substituted;

wherein the PG residue is a protective group, which is capable of protecting an amine
group; wherein the compound is particularly the compound of formula (Va)



19. A compound of formula (VI)



wherein Z is selected from carbonyl groups,

particularly from $-\text{CO}_2\text{R}^1$ groups, wherein R^1 is selected from

(i) alkyl residues having from 1 to 12 carbon atoms, wherein the
alkyl residues are optionally aryl substituted;

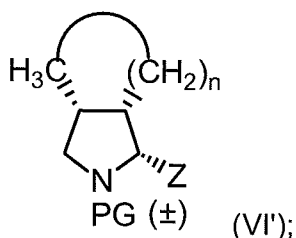
(ii) aryl residues having from 6 to 24 carbon atoms, wherein the
aryl residues are optionally alkyl substituted;

or particularly from $-\text{CON-XY}$ groups, wherein X and Y are
independently selected from the R^1 groups, alkyloxy or aryloxy groups,
particularly wherein X is methoxy and Y is methyl;

or particularly from $-\text{CON-QW}$ groups, wherein Q and W constitute a
fragment of any natural or non-natural amino acid;

wherein R^2 and R^3

-form a ring and the compound of formula (VI) is the compound of formula
(VI')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms: or

- are identical or different, and are independently selected from

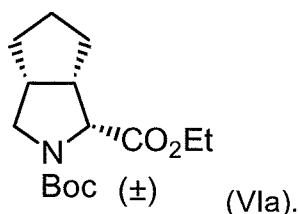
(i) hydrogen,

(ii) alkyl residues having from 1 to 12 carbon atoms, wherein the alkyl residues are optionally aryl, aryloxy, alkoxy, and/or carbonyl substituted;

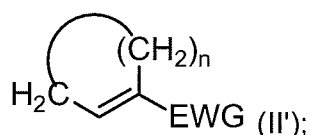
(iii) aryl residues having from 6 to 24 carbon atoms, wherein the aryl residues are optionally alkyl substituted;

wherein the PG residue is a protective group, which is capable of protecting an amine group;

wherein the compound is particularly the compound of formula (VIa)



20. A compound of formula (II')



with $n = 1, 2, 3, 4$ or 5 , wherein the ring is optionally substituted at at least one position with an alkyl residue having from 1 to 12 carbon atoms and/or an aryl residue having from 6 to 14 carbon atoms;

wherein the EWG residue is an electron withdrawing group and is selected from SO_2R^4 groups, wherein R^4 is selected from phenyl, chlorophenyl, particularly p-chlorophenyl, bromophenyl, particularly p-bromophenyl, fluorophenyl, particularly p-fluorophenyl, nitrophenyl, particularly p-nitrophenyl, and toluenyl, particularly p-toluenyl, under the proviso that when $n = 1$ R^4 is not phenyl, when $n = 2$ R^4 is not phenyl or p-toluenyl, when $n = 3$ R^4 is not phenyl or p-toluenyl and when $n = 4$ R^4 is not phenyl.

Fig. 1:

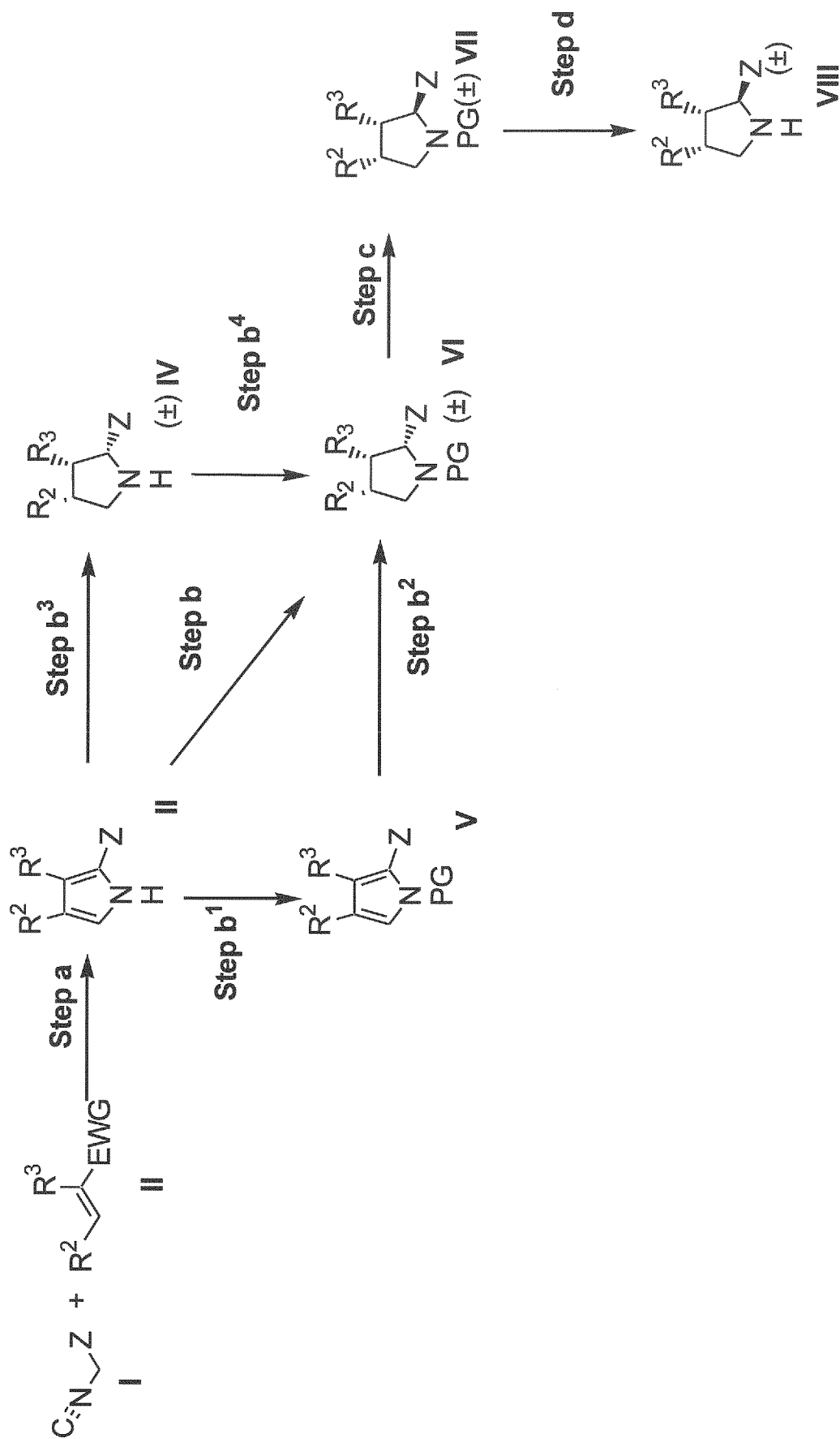


Fig. 2:

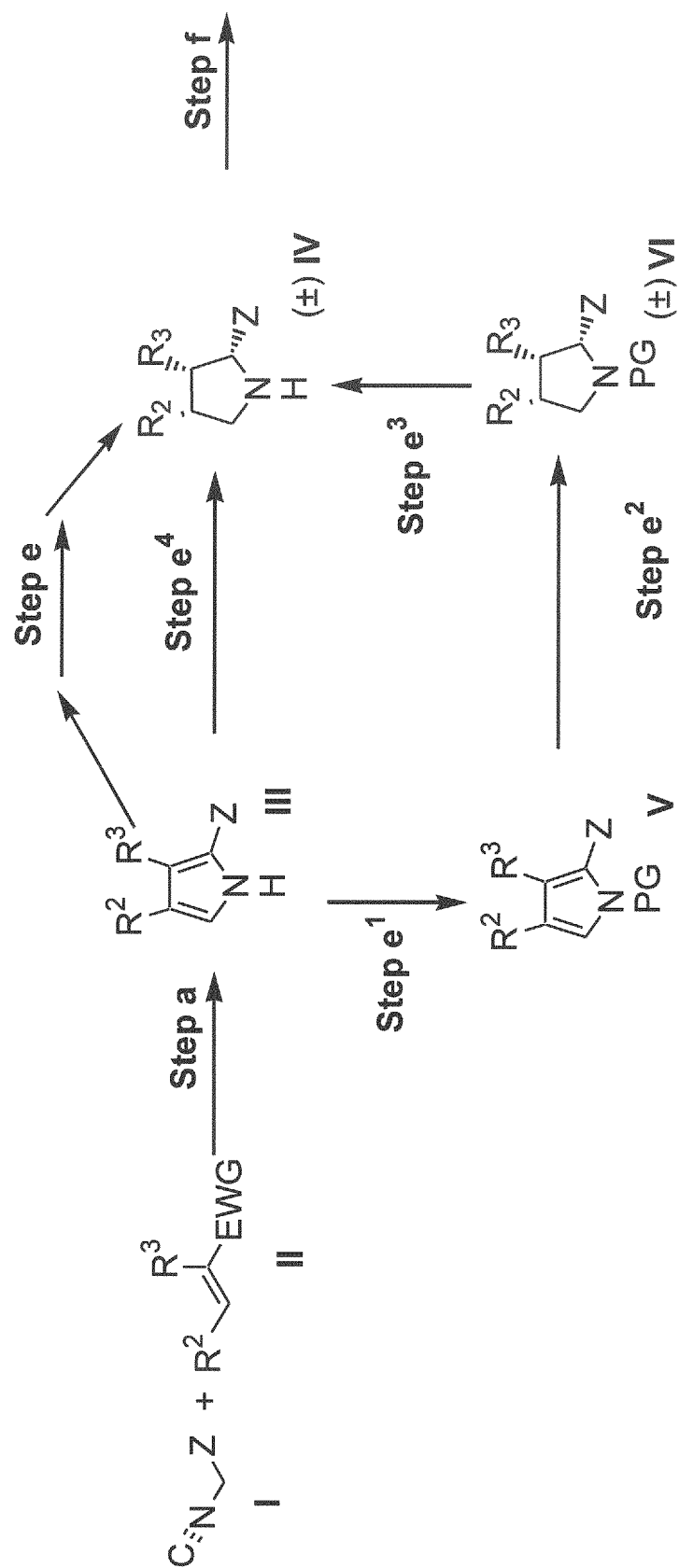
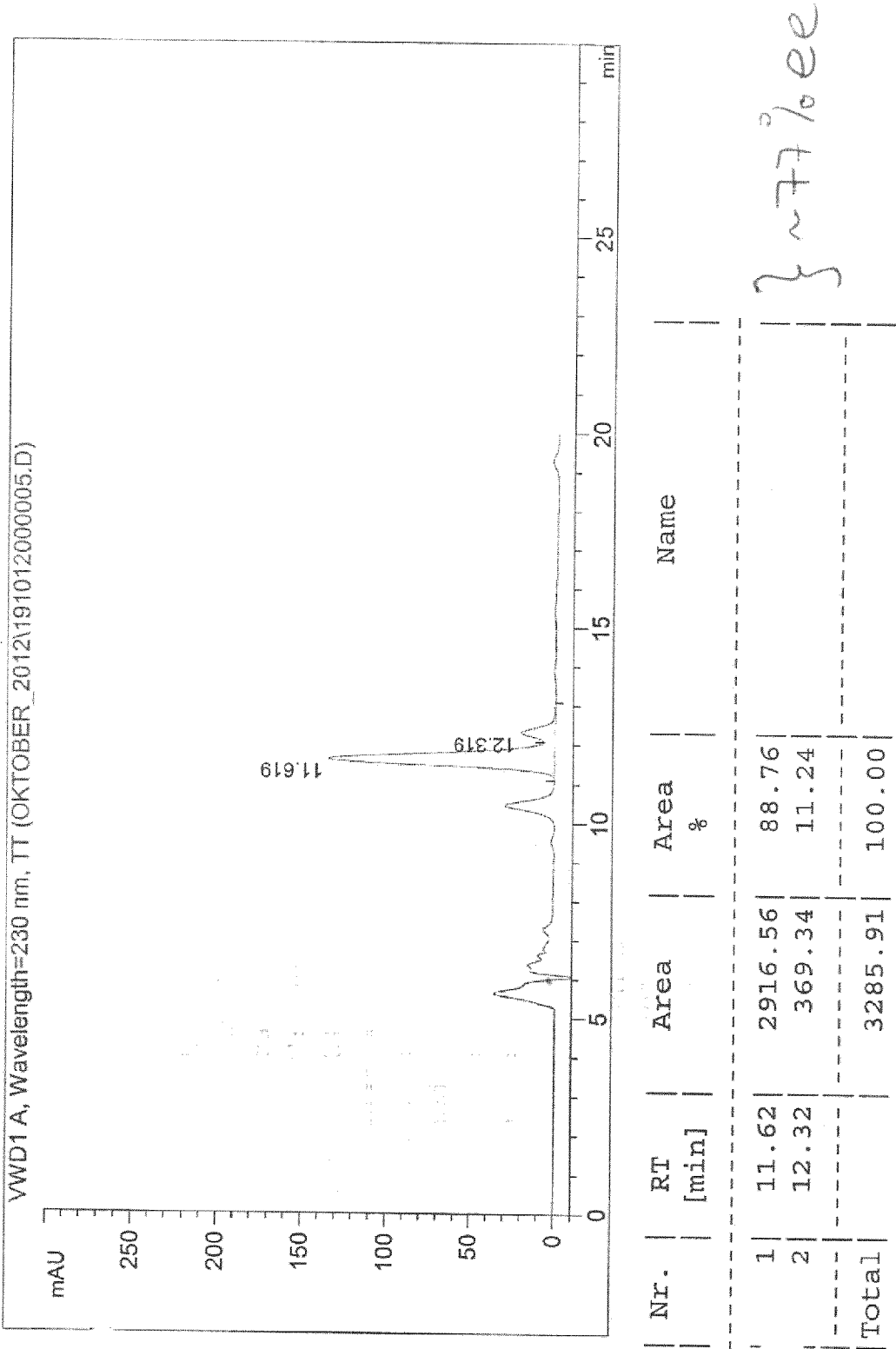


Fig.3



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/077726

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D207/04 C07D207/30
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IAIN COLDHAM ET AL: "Dynamic Thermodynamic and Dynamic Kinetic Resolution of 2-Lithiopyrrolidines", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 128, no. 33, 1 August 2006 (2006-08-01), pages 10943-10951, XP055053038, ISSN: 0002-7863, DOI: 10.1021/ja061963m page 10947; examples 33,34 ----- -/--	17,19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

6 February 2014

Date of mailing of the international search report

12/02/2014

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Gettins, Marc

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/077726

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FEI WANG ET AL: "Asymmetric Direct Aldol Reaction of [alpha]-Keto Esters and Acetone Catalyzed by Bifunctional Organocatalysts", ADVANCED SYNTHESIS & CATALYSIS, vol. 349, no. 17-18, 10 December 2007 (2007-12-10), pages 2665-2668, XP055053062, ISSN: 1615-4150, DOI: 10.1002/adsc.200700285 5 in Scheme 1 on page 2666 -----	17
X	KUDUK S D ET AL: "Synthesis of 2,3-diaminodihydropyrroles via thioimide cyclopropane rearrangement", TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 44, no. 7, 10 February 2003 (2003-02-10), pages 1437-1440, XP004405238, ISSN: 0040-4039, DOI: 10.1016/S0040-4039(02)02847-2 First reactant in scheme 2 on page 1439; examples 1-8 -----	17
X	SAGARA YUFU ET AL: "Identification of a novel 4-aminomethylpiperidine class of M3 muscarinic receptor antagonists and structural insight into their M3 selectivity", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 49, no. 19, 21 September 2006 (2006-09-21), pages 5653-5663, XP009100971, ISSN: 0022-2623, DOI: 10.1021/JM051205R 6 and 7 in Scheme 2 on page 5655 -----	17,19
X	DEATON D N ET AL: "Novel and potent cyclic cyanamide-based cathepsin K inhibitors", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 15, no. 7, 1 April 2005 (2005-04-01), pages 1815-1819, XP027800911, ISSN: 0960-894X [retrieved on 2005-04-01] 6g in scheme 1 on page 1816; examples 7a,7b,7f,7g; table 1 -----	17,19
A	WO 2011/103932 A1 (VERENIGING VOOR CHRISTELIJK HOGER ONDERWIJS WETENSCHAPPELIJK ONDERZOEK) 1 September 2011 (2011-09-01) examples 1-20 -----	18
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/077726

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/055467 A2 (VIROBAY INC [US]; HOLSINGER LESLIE JEAN [US]; ELROD KYLE [US]; LINK JO) 30 April 2009 (2009-04-30) (9) in reaction scheme II on page 15 -----	17
A	S.W. LEE: "Controlled endocyclic and exocyclic [gamma]-metalations of [beta]-substituted cyclohexenyl sulfones. Regiospecific syntheses of [gamma]-oxygenated cyclohexenyl sulfones", TETRAHEDRON LETTERS, vol. 32, no. 25, 1 January 1991 (1991-01-01), pages 2861-2864, XP055053177, DOI: 10.1016/0040-4039(91)80632-G page 2862; compound 2 -----	20
A	JOSEPH LAMBERT: "Phenylsulfonyl as a [beta] Participating Group", J. ORG. CHEM., vol. 64, 1 January 1999 (1999-01-01), pages 9241-9246, XP055053183, DOI: 10.1021/jo991536+ table 3; compound 4 -----	20
A	FUNK R L ET AL: "Stereoselective preparation of vinyl sulfones by protodesilylation of allyl silanes", TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 34, no. 18, 30 April 1993 (1993-04-30), pages 2867-2870, XP028087248, ISSN: 0040-4039, DOI: 10.1016/S0040-4039(00)60467-7 [retrieved on 1993-04-30] table 1; compound g -----	20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/077726

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WO 2011103932 A1	01-09-2011	CA 2790930 A1	01-09-2011
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		WO 2011103932 A1	01-09-2011
		WO 2011103933 A1	01-09-2011

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