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(54) Title: PROCESS OF PREPARATION OF OPTICALLY ACTIVE ALPHA AMINOACETALS

(57) Abstract: The invention relates to a process for preparing optically active α-aminoacetals by resolution of a racemic mixture or of a mixture of enantiomers via the formation of diastereoisomeric salts, and also novel intermediates in the form of diastereoisomeric salts.

PROCESS OF PREPARATION OF OPTICALLY ACTIVE ALPHA AMINOACETALS

The invention relates to a process for preparing optically active α-aminoacetals, and also novel intermediates in the form of diastereoisomeric salts useful for this purpose.

More particularly, the invention relates to a process for resolving a racemic mixture or a mixture of enantiomers by the formation of diastereoisomeric salts, which makes it possible to access the two enantiomers with high optical purities.

Optically active α-aminoacetals are compounds that are particularly advantageous as direct precursors of optically active α-aminoaldehydes.

N-protected α-aminoaldehydes are commonly used as chiral reactants in the total synthesis of biologically active products, as described, for example, in J. Jurczak et al., Chem. Rev., (1989), 89 (1), 149-164 or M.T. Reetz, Angew Chem., Int. Ed. Engl., (1991), 30 (12), 1531-1546, but are not readily commercially available.

The synthetic pathways most commonly described for the preparation of α-aminoacetals use N-protected α-amino acids as reactants, in order to access N-protected α-aminoaldehydes and then α-aminoacetals, either by intermediate formation of a Weinreb amide, or by partial reduction to aldehyde, or by total reduction to α-aminoalcohols and partial reoxidation to N-protected α-aminoaldehydes. These methods for preparing optically active α-aminoacetals have various drawbacks, among which mention may be made of reaction conditions which are restricting for industrial exploitation, or the use of expensive reactants. The main restriction of these syntheses is the limited availability of the starting reactants, namely the natural α-amino acids.

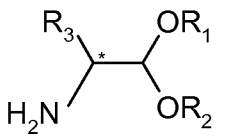
Other methods have been used, such as the asymmetric reduction of optically active imines, derived from α-keto acetals, as described, for example, in application EP 374647, which are difficult to access, with the exception of pyruvaldehyde dimethylacetal.

Finally, methods using a chiral inductor have been developed in order to access these optically active α-aminoacetals from dialkoxyethanals, such as the methodology using

the chiral auxiliaries SAMP, (S)-1-amino-2-(methoxymethyl)pyrrolidine, and RAMP, (R)-1-amino-2-(methoxymethyl)pyrrolidine, as described, for example, in D. Enders et al., Angew. Chem., Int. Ed. Engl., (1993), 32 (3), 418-21, or aminotriazoles, (S,S)-4-amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole, as described, for example, in application EP1527041. Nevertheless, these various syntheses use either reactants that are expensive or difficult to prepare, or synthesis, purification or optical enrichment steps which are restricting from the industrial point of view.

The technical problem to be solved therefore consists in providing a process for preparing optically active α-aminoacetals which makes it possible to solve the abovementioned problems while starting from commercially available and inexpensive materials.

The invention therefore relates to a process for preparing optically active α-aminoacetals of formula (R)-(I) or (S)-(I)



(R)-(I) or (S)-(I)

in which:

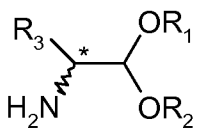
- R_1 and R_2, which may be identical or different, represent a linear or branched C_1-C_{12} alkyl group, or else R_1 and R_2 are joined so as to form a 1,3-dioxolan-2-yl group which is unsubstituted or substituted on positions 4 and/or 5 with one or more linear or branched C_1-C_6 alkyl substituents, or a 1,3-dioxan-2-yl group which is unsubstituted or substituted on positions 4 and/or 5 and/or 6 with one or more linear or branched C_1-C_6 alkyl substituents;

- R_3 represents a linear or branched C_1-C_{12} alkyl group; a C_2-C_{12} alkenyl group; a C_2-C_{12} alkynyl group; a C_3-C_{10} cycloalkyl group; a C_3-C_{10} cycloalkenyl group; a cycloalkylalkyl group in which the cycloalkyl and alkyl groups are as defined above; a heterocycloalkyl group containing 3 to 10 atoms; a heterocycloalkylalkyl group in which the heterocycloalkyl and alkyl groups are as defined above; a monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group; a heteroaryl group

containing 5 to 14 atoms; an arylalkyl group or a heteroarylalkyl group, in which the aryl, heteroaryl and alkyl groups are as defined above; a $C(=O)R_4$ group in which R_4 represents a linear or branched C_1-C_{12} alkyl group, a cycloalkyl group, a cycloalkenyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, as defined above, or an OR_5 group in which R_5 represents an H, a linear or branched C_1-C_{12} alkyl group, a C_3-C_{10} cycloalkyl group, a C_3-C_{10} cycloalkenyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, as defined above, or R_4 represents an NHR_6 group in which R_6 represents an H, a linear or branched C_1-C_{12} alkyl group, a C_3-C_{10} cycloalkyl group, a C_3-C_{10} cycloalkenyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, as defined above; all the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl radicals above being unsubstituted or substituted;

- the asterisk * signifies that the C atom is an asymmetrical carbon,

which process comprises the resolution of a compound of formula (I) in racemic form or in the form of mixtures of enantiomers

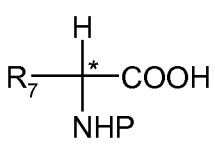


(I)

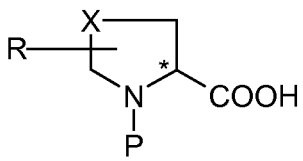
in which R_1, R_2, R_3 and the asterisk * are as defined above, with a resolving agent,

characterized in that said process comprises the steps consisting in:

a) reacting a compound of formula (I) with an optically active α-amino acid represented by general formulae (II) to (VI)



(II)



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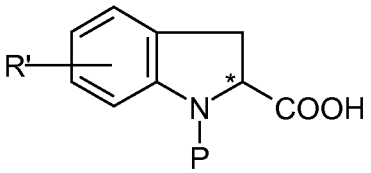

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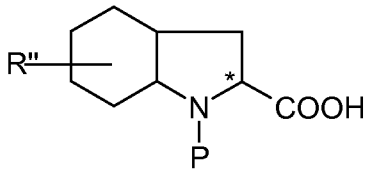

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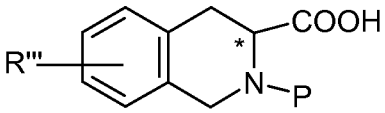


(VI)

in which:

- R_7 represents a linear or branched C_1-C_{12} alkyl group; a C_3-C_{10} cycloalkyl group; a cycloalkylalkyl group in which the cycloalkyl and alkyl groups are as defined above; a monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group; an arylalkyl group in which the alkyl and aryl groups are as defined above; a heteroaryl group containing 5 to 14 atoms; or a heteroarylalkyl group in which the alkyl and heteroaryl groups are as defined above; all the alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl radicals being unsubstituted or substituted;

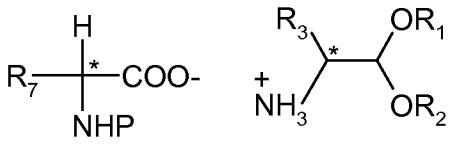
- P represents a 9-fluorenylmethoxycarbonyl protective group; a $-COR_8$ group in which R_8 represents hydrogen, a linear or branched C_1-C_6 alkyl group, a monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group or an OR_9 group in which R_9 represents a linear or branched C_1-C_6 alkyl group or an arylalkyl group in which the aryl and alkyl groups are as defined above; or an $-S(O_2)R_{10}$ group in which R_{10} represents a linear or branched C_1-C_6 alkyl group, a monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group or an arylalkyl group in which the aryl and alkyl groups are as defined above; all the 9-fluorenylmethoxycarbonyl, alkyl, aryl and arylalkyl groups being unsubstituted or substituted;

- X represents a carbon or sulphur atom;

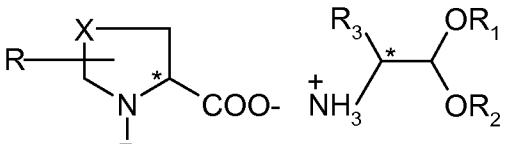
- R, R', R'' and R''', independently of one another, represent one or more hydrogen atom(s), halogen atom(s) or hydroxyl group(s) or an oxo (=O) group;

- the asterisk * signifies that the C atom is an asymmetrical carbon,

in a solvent, so as to form diastereoisomeric salts represented by formulae (VII) to (XI):



(VII)



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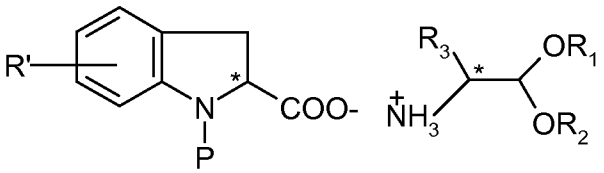

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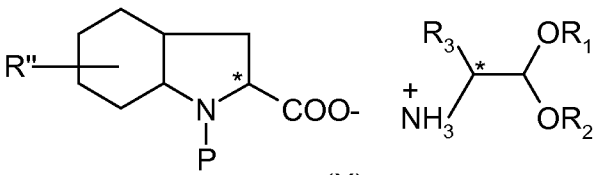
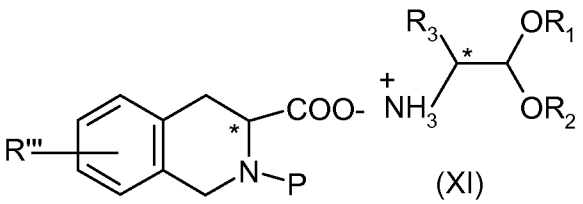


(X)



(XI)

in which R_1, R_2, R_3, R_7, P, X, R, R', R'', R''' and the asterisk * are as defined above,

b) separating the diastereoisomeric salts of formulae (VII) to (XI) formed in the medium, and

c) releasing the optically active α-aminoacetal of formula (R)-(I) or (S)-(I).

The expression “optically active” is intended to mean that the compound of formula (R)-(I) or (S)-(I) possesses an enantiomeric excess, relative to the other enantiomer, within the range of from 1% to 100%, preferably within the range of from 50% to 100%, and more preferably within the range of from 70% to 100%.

The term “enantiomeric excess” is intended to mean the ratio of the excess of the desired enantiomer relative to the undesired enantiomer.

This ratio is calculated according to one of the following equations:

% ee.(R) = ([R] - [S] / [R] + [S]) x 100
% ee.(S) = ([S] - [R] / [R] + [S]) x 100

in which:

- % ee.(R) represents the enantiomeric excess of R isomer
- % ee.(S) represents the enantiomeric excess of S isomer
- [R] represents the concentration of R isomer, and
- [S] represents the concentration of S isomer.

The term “releasing” is intended to mean that the optically active α-aminoacetal is no longer in the form of diastereoisomeric salts of formulae (VII) to (XI).

According to one preferred aspect of the invention, use will be made of a compound of formula (I) in racemic form or in the form of mixtures of enantiomers, in which

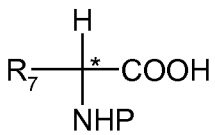
- R_1 and R_2, which may be identical or different, represent a linear or branched C_1-C_6 alkyl group, in particular methyl or ethyl;

- R_3 represents a group chosen from a substituted or unsubstituted, linear or branched C_1-C_6 alkyl group; a substituted or unsubstituted monocyclic, bicyclic

or tricyclic C_6-C_{14} aryl group, preferably phenyl; a substituted or unsubstituted arylalkyl group in which the aryl and alkyl groups are as defined above, preferably benzyl, or phenylethyl; a substituted or unsubstituted C_3-C_{10} cycloalkyl group, preferably cyclohexyl; and a substituted or unsubstituted cycloalkylalkyl group in which the cycloalkyl and alkyl groups are as defined above.

Optional substituents of the R_3, R_4, R_5 and R_6 groups may be independently chosen from the following groups: halogen, OH (optionally protected, for example in the form of an ether with tetrahydropyran or in the form of an ester with the acetyl group), NH_2, CO_2H, SO_3H, CF_3, alkoxycarbonyl (or alkyl-O-CO-), amide, alkyl-N-CO-, alkylenedioxy (or -O-alkylene-O-), alkylsulphonyl (or alkyl-SO_2-), alkylsulphonylcarbamoyl (or alkyl-SO_2-NH-C(=O)-), -O-cycloalkyl, acyloxy, acylamino, alkylamino, dialkylamino, aryl-amino, diarylamino, arylalkylamino, oxo protected in the form of a cyclic or noncyclic ketal, formyl protected in the form of a cyclic or noncyclic acetal, aryloxy, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl and alkoxy.

According to another preferred aspect of the process according to the invention, a compound of formula (I) in racemic form or in the form of mixtures of enantiomers is reacted with an optically active α-amino acid represented by general formula (II) or (III)



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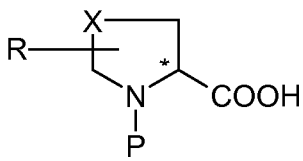


(III)

in which:

- R_7 represents a linear or branched C_1-C_6 alkyl group which is unsubstituted or substituted with one or more hydroxyl, -NHP', -C(O)NH_2, -NH-C(=NH)-NHP', -SH, -S-CH_3, -CO_2H or phenyl groups, in which P' represents hydrogen or an acetyl, propionyl, formyl, tosyl, benzoyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or 9-fluorenylmethoxycarbonyl group; a cyclohexyl group; a phenyl group; a benzyl or naphthyl group which is unsubstituted or substituted one or more times with a halogen atom, a hydroxyl group, an NO_2 group, a

phenyl group or a C_1-C_3 alkoxy group; a pyridyl group; an imidazolylmethyl group; a pyridylmethyl group; or a thiazolylmethyl or indolylmethyl group;

- P represents an acetyl, propionyl, formyl, tosyl, benzoyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or 9-fluorenylmethoxycarbonyl group;

- X represents a carbon atom;
- R represents a hydrogen atom.

In the products of formulae (I), (S)-(I), (R)-(I) and (II) to (XI), and also for the substituents, the groups indicated have the meanings which follow:

- the halogen group denotes fluorine, chlorine, bromine or iodine atoms;

- the linear or branched C_1-C_{12} alkyl group denotes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, sec-pentyl, tert-pentyl, neopentyl, hexyl, isohexyl, sec-hexyl, tert-hexyl, heptyl, octyl, nonyl, decyl, undecyl or dodecyl groups, linear or branched C_1-C_6 alkyl groups being preferred;

- the linear or branched C_2-C_{12} alkenyl group denotes, for example, ethenyl or vinyl, propenyl or allyl, 1-propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl, hexenyl, heptenyl, octenyl or decenyl groups, linear or branched C_2-C_4 alkenyl groups being preferred;

- the linear or branched C_2-C_{12} alkynyl group denotes, for example, ethynyl, propynyl or propargyl, butynyl, n-butynyl, i-butynyl, 3-methylbut-2-ynyl, pentynyl or hexynyl groups, linear or branched C_2-C_4 alkynyl groups being preferred;

- the linear or branched C_1-C_{12} alkoxy group denotes, for example, methoxy, ethoxy, propoxy, isopropoxy, linear, secondary or tertiary butoxy, pentoxy, hexoxy or heptoxy groups, linear or branched C_1-C_6 alkoxy groups being preferred;

- the cycloalkyl group denotes a monocyclic or bicyclic C_3-C_{10} carbocyclic group, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl groups;

- the cycloalkenyl group denotes a monocyclic or bicyclic C_3-C_{10} carbocyclic group containing at least one double bond, such as cyclobutenyl, cyclopentenyl or cyclohexenyl groups;

- the cycloalkylalkyl group denotes a group in which the cycloalkyl and alkyl residues have the meanings mentioned above, such as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclopropylethyl or cyclohexylethyl groups;

- the aryl group denotes a monocyclic, bicyclic or tricyclic C_6-C_{14} carbocyclic aromatic group, such as phenyl, naphthyl, indenyl or anthracenyl groups, and more particularly the phenyl group;

- the arylalkyl group denotes a group in which the aryl and alkyl residues have the meanings mentioned above, such as benzyl, phenylethyl, 2-phenylethyl or naphthylmethyl groups;

- the heterocycloalkyl group denotes a monocyclic or bicyclic carbocyclic group containing 3 to 10 atoms, interrupted with one or more heteroatoms, which may be identical or different, chosen from oxygen, nitrogen or sulphur atoms, such as the dioxolanyl, dioxanyl, dithiolanyl, thioxolanyl, oxiranyl, piperazinyl, piperidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, tetrahydrofuryl, tetrahydrothienyl or thiazolidinyl group;

- the heterocycloalkylalkyl group denotes a group in which the heterocycloalkyl and alkyl residues have the meanings mentioned above;

- the heteroaryl group denotes a monocyclic, bicyclic or tricyclic, aromatic or partially unsaturated carbocyclic group interrupted with one or more heteroatoms, which may be identical or different, chosen from oxygen, nitrogen or sulphur atoms, containing 5 to 14 atoms, such as furyl (2-furyl, for example), thienyl (2-thienyl, 3-thienyl, for example), pyrrolyl, diazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, 3- or 4-isoxazolyl, imidazolyl, pyrazolyl, isoxazolyl, pyridyl (2- or 3- or 4-pyridyl, for example), pyrimidinyl, pyridizinyl, pyrazinyl, tetrazolyl, benzothienyl (3-benzothienyl, for example), benzofuranyl, indolyl, purinyl,

quinolyl, isoquinolyl, chromanyl or naphthyridinyl groups;

- the heteroarylalkyl group denotes a group in which the heteroaryl and alkyl residues have the meanings mentioned above;

- the alkyl-O-CO- group denotes a linear or branched C_2-C_{12} group in which the alkyl group has the meaning indicated above;

- the alkylene group denotes a divalent, linear or branched C_1-C_6 hydrocarbon-based group, such as methylene, ethylene, propylene or isopropylene;

- the -O-alkylene-O- group denotes a linear or branched C_1-C_6 group in which the alkylene group has the meaning indicated above;

- the alkyl-SO_2- group denotes a linear or branched C_1-C_{12} group in which the alkyl group has the meaning indicated above;

- the alkylsulphonylcarbamoyl group denotes a linear or branched C_2-C_{12} group in which the alkyl group has the meaning indicated above;

- the -O-cycloalkyl group denotes a group in which the cycloalkyl group has the meaning indicated above;

- the acyloxy group denotes an r-CO-O- group in which r represents an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, these groups having the values indicated above, such as acetoxy or propionyloxy;

- the acylamino group denotes an r-CO-N- group in which r has the meaning indicated above, such as acetamido;

- the alkyl-N-CO- group denotes a group in which the alkyl group has the meaning indicated above;

- the alkylamino, dialkylamino, arylamino, diarylamino, and arylalkylamino groups denote groups in which the alkyl and aryl groups have the meanings indicated above;

- the aryloxy group denotes an aryl-O- group in which the aryl group has the meaning indicated above, such as phenoxy or naphthyloxy.

As optically active α-amino acid, use will, for example, be made of an α-amino acid chosen from N-acetyl-(L)-phenylalanine, N-acetyl-(D)-phenylalanine, N-acetyl-(L)-leucine, N-acetyl-(D)-leucine, N-acetyl-(L)-valine, N-acetyl-(D)-valine, N-acetyl-(L)-tyrosine, N-acetyl-(D)-tyrosine, N-acetyl-(L)-methionine, N-acetyl-(D)-methionine, N-acetyl-(L)-asparagine, N-acetyl-(D)-asparagine, N-tosyl-(L)-phenylalanine, N-tosyl-(D)-phenylalanine, N-ethoxycarbonyl-(L)-phenylglycine and N-ethoxycarbonyl-(D)-phenylglycine.

N-Acetyl-(L)-phenylalanine or N-acetyl-(D)-phenylalanine are optically active α-amino acids which are preferred for the purposes of the invention.

The racemic α-aminoacetals used for the resolution in the process of the invention can be prepared by adaptation of methods described in the literature, for example starting from α-halogenated acetals followed by amination, as described, by way of indication, in Heterocyclic Compounds, (1962), 3425, J. Chem. Soc., 1957, 2146-2158, J. Med. Chem., 1987, 30(1), 150-156 and J. Org. Chem., 1981, 46(8), 1575-1585. They can also be obtained starting from α-amino acids and then by formation of a Weinreb amide, reduction and acetalization as described in Bioorg. & Med. Chem. Lett., 2002, 12(4), 701-704 and WO 9822496.

FR 2843112 describes the addition of organometallic compounds to aminotriazole derivatives for obtaining racemic α-aminoacetals or mixtures of enantiomers.

The reduction of oxime derivatives of α-keto acetals described in J. Heterocycl. Chem., 1978, 15(4), 665-670 and EP 367242 also makes it possible to obtain racemic α-aminoacetals.

In step a) of the process according to the invention, preferred implementation conditions are the following:

- the optically active α-amino acid is present in a molar ratio of between 0.1 and 1 molar equivalent, relative to the compound of formula (I), preferably 0.5 molar equivalent;

- the solvent is chosen from the group comprising isopropanol, ethanol, water, acetone, methyl isobutyl ketone, tetrahydrofuran, acetonitrile, ethyl acetate, toluene and methyl tert-butyl ether, and mixtures thereof;

- the concentration of the compound of formula (I) is between 1% and 40% by weight, preferably between 3% and 9% by weight;

- the reaction temperature is between 0°C and 120°C, preferably between 5°C and the boiling point of the reaction medium, in particular with temperature holds or gradients being performed during heating and cooling;

- the duration of the reaction is between 30 min and 48 h.

At the end of step a), the resolution is carried out by selective crystallization of the diastereoisomeric salts of formulae (VII) to (XI).

This is because, advantageously, during the reaction of step a), one of the two diastereoisomeric salts preferentially precipitates. The separation of the least soluble diastereoisomeric salt from the reaction medium is preferably performed by filtration during step b).

During step c), the optically active α-aminoacetal is obtained by treatment of the separated diastereoisomeric salt with an alkaline aqueous solution such as sodium hydroxide or potassium hydroxide, or an acidic aqueous solution such as hydrochloric acid. Preferably, treatment with a dilute aqueous solution of sodium hydroxide is used, optionally followed by extraction with an appropriate organic solvent for releasing the desired optically active α-aminoacetal. Neutralization of the alkaline solution makes it possible to recycle the optically active α-amino acid.

In preferred conditions for implementing the process according to the invention, it is possible, before releasing the optically active α-aminoacetal of formula (R)-(I) or (S)-(I) as defined above, to subject the diastereoisomeric salts of formulae (VII) to (XI)

obtained after step b) to at least one recrystallization or reslurrying step, in particular for improving the optical purity (ee≥95%).

According to one of its subsequent aspects, the invention therefore relates to a process for preparing optically active α-aminoacetals of formula (R)-(I) or (S)-(I) as defined above, in which the diastereoisomeric salts of formulae (VII) to (XI) obtained after step b) are subjected to at least one recrystallization or reslurrying step.

The recrystallization or the reslurrying may, for example, be carried out in an inert solvent or in a mixture of inert solvents, for instance isopropanol, ethanol, acetone, water, tetrahydrofuran, acetonitrile, ethyl acetate, methyl tert-butyl ether (MTBE), methyl isobutyl ketone (MIBK) or toluene, at a temperature of between 0°C and 120°C, preferably between ambient temperature and the boiling point of the reaction medium, in particular by optionally performing temperature holds or gradients during heating and cooling, for a period of between 30 min and 48 h. The dilution of the medium is generally between 1% and 20% by mass relative to the unit of mass of the salt to be recrystallized or reslurried, preferably between 3% and 9% by mass.

The reaction medium solution recovered after separation of the least soluble diastereoisomeric salt can be treated so as to obtain a mixture enriched in the enantiomer having the configuration opposite to that of the enantiomer obtained from the least soluble diastereoisomeric salt.

According to one of its subsequent aspects, the invention therefore relates to a process for preparing optically active α-aminoacetals of formula (R)-(I) or (S)-(I) as defined above, comprising the steps consisting in:

- recovering, from the reaction medium, a diastereoisomeric salt represented by general formulae (VI) to (XI), as defined above, which was not separated during step b), and

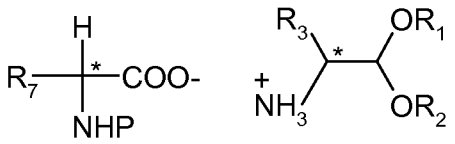
- releasing the optically active α-aminoacetal of formula (R)-(I) or (S)-(I).

Said diastereoisomeric salt may, for example, be recovered by concentration to dryness, and the release of the optically active α-aminoacetal may be carried out, for example, by treatment with an alkaline aqueous solution, optionally followed by

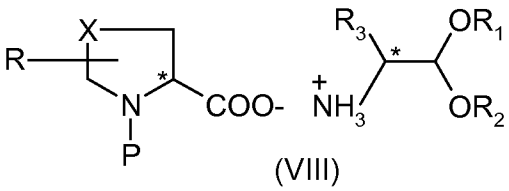
extraction with a suitable organic solvent, as described above for step c) of the process according to the invention.

A subject of the present invention is also novel intermediates for preparing an optically active α-aminoacetal of formula (R)-(I) or (S)-(I), i.e. the diastereoisomeric salts of formulae (VII) to (XI) as defined above.

Among these, the diastereoisomeric salts of formula (VII) or (VIII) below



(VII)



(VIII)

in which:

- R_7 represents a linear or branched C_1-C_6 alkyl group which is unsubstituted or substituted with one or more hydroxyl, -NHP', $-C(O)NH_2$, -NH-C(=NH)-NHP', -SH, $-S-CH_3$, $-CO_2H$ or phenyl groups, in which P' represents hydrogen or an acetyl, propionyl, formyl, tosyl, benzoyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or 9-fluorenylmethoxycarbonyl group; a cyclohexyl group; a phenyl group; a benzyl or naphthyl group which is unsubstituted or substituted one or more times with a halogen atom, a hydroxyl group, an NO_2 group, a phenyl group or a C_1-C_3 alkoxy group; a pyridyl group; an imidazolylmethyl group; a pyridylmethyl group; or a thiazolylmethyl or indolylmethyl group;

- P represents an acetyl, propionyl, formyl, tosyl, benzoyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or 9-fluorenylmethoxycarbonyl group;

- X represents a carbon atom;
- R represents a hydrogen atom,

are preferred compounds.

Particularly preferred diastereoisomeric salts may be chosen from the following compounds:

- (R)-1-benzyl-2,2-dimethoxyethylammonium N-acetyl-(L)-phenylalaninate,
- (S)-1-benzyl-2,2-dimethoxyethylammonium N-acetyl-(D)-phenylalaninate,
- (R)-1-isobutyl-2,2-dimethoxyethylammonium N-acetyl-(L)-phenylalaninate,
- (S)-1-isobutyl-2,2-dimethoxyethylammonium N-acetyl-(D)-phenylalaninate,
- (S)-1-phenyl-2,2-dimethoxyethylammonium N-acetyl-(L)-phenylalaninate,
- (R)-1-phenyl-2,2-dimethoxyethylammonium N-acetyl-(D)-phenylalaninate,
- (R)-1-(4-methylbenzyl)-2,2-dimethoxyethylammonium N-acetyl-(L)-phenylalaninate,
- (S)-1-(4-methylbenzyl)-2,2-dimethoxyethylammonium N-acetyl-(D)-phenylalaninate, and
- (S)-1-(2-phenylethyl)-2,2-dimethoxyethylammonium N-acetyl-(L)-phenylalaninate.

The following examples illustrate the invention in a nonlimiting manner.

In the examples, the optical purity of the (R)- or (S)-α-aminoacetals is determined by chiral HPLC, either directly on the compounds of formula (I), or on derivatives, preferably on the carbamate derivatives in which the amine function is protected with a benzyloxycarbonyl (C(O)–O-Bz) group.

The optical purity is measured by the enantiomeric exess, ee, the value of which is given by the equation mentioned above.

EXAMPLE 1

resolution of racemic 1-benzyl-2,2-dimethoxyethylamine with N-acetyl-(L)-phenyl-alanine

1) Preparation of (R)-1-benzyl-2,2-dimethoxyethylammonium N-acetyl-(L)-phenyl-alaninate

(compound of formula (VII) – $R_1 = R_2$ = methyl, $R_3 = R_7$ = benzyl, P = acetyl)

In a 250 ml three-necked flask equipped with a mechanical stirrer, a condenser and a thermometer, 6 g (30.8 mmol, 1 mol. eq.) of racemic 1-benzyl-2,2-dimethoxyethylamine and 3.18 g (15.4 mmol, 0.5 mol. eq.) of N-acetyl-(L)-phenylalanine (Sigma Aldrich) are introduced into 94 g of isopropanol (solution at 6%). The medium is stirred and heated at 50°C for 3 h, and then a temperature hold is performed at 40°C for 2 h. At the end of this hold, the temperature is returned slowly to ambient temperature and stirring is continued overnight at this temperature.

The precipitate is filtered off under vacuum and the solid is washed with cyclohexane (approximately 100 ml) (filtrate 1), and then oven-dried at 40°C under vacuum. A mass of 3 g of (R)-1-benzyl-2,2-dimethoxyethylammonium N-acetyl-(L)-phenylalaninate is obtained in the form of a white solid, i.e. a yield of 50% relative to the N-acetyl-(L)-phenylalanine.

- Molecular formula: $C_{22}H_{30}N_2O_5$
- Molar mass: 402.49 $g.mol^{-1}$

- NMR (200MHz/DMSO-d^6):

  ^1H NMR: δ 1.78 (s, 3H, CH_3); 2.63-2.74 and 3.05-3.14 (syst. AB, 2H, CH_2); 2.79-2.92 (m, 2H, CH_2); 3.2-3.4 (m, 1H, CH); 3.33 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 4.2 (d, J=4.8Hz, 1H, CH), 4.32 (m, 1H, CH); 5.11 (broad s, NH_3^+); 7.1-7.4 (m, 10H, $H_{aromatic}$) and 7.86 (d, 1H, NH) ppm.

^{13}C NMR: δ 22.56 (CH_3); 36.06 (CH_2); 37.31 (CH_2); 53.36 (CH); 54.51 (CH); 54.85 (CH_3); 55.12 (CH_3); 105.25 (CH), 125.95-126.23-127.88-128.27-129.16-129.29 ($CH_{aromatic}$); 137.96-138.59 ($C_{aromatic}$), 168.66 (C=O) and 173.71 (C=O) ppm.

- Melting point: Mp=159°C
- Optical rotation: α^{25}_D= +42.2° (MeOH, c=1)

2) Preparation of the (R) and (S) enantiomers of 1-benzyl-2,2-dimethoxyethylamine

(compound of formula (R)-(I) or (S)-(I) – R_1 = R_2 = methyl, R_3 = benzyl)

The salt is taken up in 53 g of isopropanol (solution at 5.5%) and the medium is heated at 50°C for approximately 1 h 30. The temperature is allowed to return to ambient temperature slowly, and the medium is kept at this temperature overnight with stirring. After filtration, the solid is washed with 50 ml of cyclohexane and oven-dried at 40°C.

The salt is treated with an aqueous solution of sodium hydroxide and the aqueous phase is extracted with CH_2Cl_2. After concentration of the solvent, a mass of 1.23 g of (R)-1-benzyl-2,2-dimethoxyethylamine is obtained, i.e. a yield of 41% relative to the N-acetyl-(L)-phenylalanine, with an optical purity equal to: $ee_{(R)}$=97% (determined by chiral HPLC).

Filtrate 1 is concentrated and the solid residue is taken up, with stirring, in approximately 100 ml of cyclohexane, filtered under vacuum and washed with 60 ml of cyclohexane. After drying and treatment with an aqueous solution of sodium hydroxide, 1.29 g of optically active (S)-1-benzyl-2,2-dimethoxyethylamine are obtained with an optical purity $ee_{(S)}$ = 74% (determined by chiral HPLC), i.e. a yield of 43% relative to the N-acetyl-(L)-phenylalanine.

1-benzyl-2,2-dimethoxyethylamine (colourless oil)

- Molecular formula: $C_{11}H_{17}NO_2$
- Molar mass: 195.26g.mol^{-1}
- Boiling point: Bp =115-120°C under 5mmHg

- EI MS m/z (% relative intensity): 164 (M-31, 11); 120 (M-75, 96); 104 (M-91, 39); 91 (62); 75 (100).

- NMR (200MHz/$CDCl_3$):

  ^1H NMR: δ1.3 (s, 2H, NH_2); 2.5 (dd, 1H, syst AB CH_2); 3 (dd, 1H, syst AB CH_2); 3.15 (m, 1H, CH); 3.49 (s, 6H, CH_3); 4.14 (d, J=5.6Hz, 1H, CH) and 7.19-7.4 (m, 6H, $CH_{aromatic}$) ppm.

  ^{13}C NMR: δ 38.7 (CH_2); 54.2 (CH); 55.05 and 55.19 (CH_3); 107.9 (CH); 126.3-128.3-128.56-129.1-129.4 ($CH_{aromatic}$) and 139.1 ($C_{aromatic}$) ppm.

- Chiral HPLC analyses (Chiralcel OD-H, hexane/isopropanol 90/10, 1 ml/min, detection UV 254 nm and polarimeter):

  (S)-(-) enantiomer t_R= 5.6 min

  (R)-(+) enantiomer t_R= 6.5 min

- Optical rotation:

  (S)-(-) enantiomer: α^{25}_D= -27.7° (MeOH, c=1)

  (R)-(+) enantiomer: α^{25}_D= +27.6° (MeOH, c=1)

EXAMPLE 2

resolution of racemic 1-benzyl-2,2-dimethoxyethylamine with N-acetyl-(D)-phenylalanine

In a 250 ml three-necked flask equipped with a mechanical stirrer, a condenser and a thermometer, 6 g (30.8 mmol, 1 mol. eq.) of racemic 1-benzyl-2,2-dimethoxyethylamine and 3.18 g (15.4 mmol, 0.5 mol. eq.) of N-acetyl-(D)-phenylalanine (Sigma Aldrich) are introduced into 94 g of isopropanol (solution at 6%). The medium is stirred and heated at 50°C for 3 h, and then a temperature hold is performed at 40°C for 2 h. At the end of this hold, the temperature is allowed to return to ambient temperature slowly and stirring is continued overnight at this temperature.

The precipitate is filtered off under vacuum and the solid is washed with 100 ml of cyclohexane (filtrate 1), and then oven-dried at 40°C under vacuum. A mass of 3.85 g of (S)-1-benzyl-2,2-dimethoxyethylammonium N-acetyl-(D)-phenylalaninate is obtained,

i.e. a yield of 62% relative to the N-acetyl-(D)-phenylalanine.

The solid is taken up in 66 g of isoopropanol (solution at 5.5%) and the medium is heated at 50°C for approximately 1 h 30. The temperature is allowed to return to ambient temperature slowly and the medium is maintained at this temperature overnight with stirring. After filtration, the solid is washed with 50 ml of cyclohexane and oven-dried at 40°C.

The solid is treated with an aqueous solution of sodium hydroxide and the aqueous phase is extracted with CH_2Cl_2. After concentration of the solvent, 1.32 g of (S)-1-benzyl-2,2-dimethoxyethylamine are obtained, i.e. a yield of 44% relative to the N-acetyl-(D)-phenylalanine, with an optical purity equal to: $ee_{(S)}$ ≥99% (determined by chiral HPLC).

The filtrate 1 is concentrated and the solid residue is stirred in approximately 100 ml of cyclohexane, filtered under vacuum and washed with 60 ml of cyclohexane. After drying, the precipitate (1 g, i.e. a yield of 35% relative to the N-acetyl-(D)-phenylalanine) is taken up in 37 g of isoPrOH (5.5% dilution) and the medium is kept stirring for 1 h 30. After filtration, drying of the solid and basic treatment, 0.66 g of optically active (R)-1-benzyl-2,2-dimethoxyethylamine is obtained with an optical purity equal to: $ee_{(R)}$=91% (determined by chiral HPLC), i.e. a yield of 22% relative to the N-acetyl-(D)-phenylalanine.

<u>(S)-1-benzyl-2,2-dimethoxyethylammonium N-acetyl-(D)-phenylalaninate</u> (white solid)

(compound of formula (VII) – R_1 = R_2= methyl, R_3 = R_7 = benzyl, P = acetyl)

- Molecular formula: $C_{22}H_{30}N_2O_5$
- Molar mass: 402.49 $g.mol^{-1}$

- NMR (200MHz/DMSO-d^6):

  ^{1}H NMR: δ 1.78 (s, 3H, CH_3); 2.63-2.74 and 3.05-3.14 (syst. AB, 2H, CH_2); 2.79-2.92 (m, 2H, CH_2); 3.2-3.4 (m, 1H, CH); 3.33 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 4.2 (d, J=4.8Hz, 1H, CH), 4.32 (m, 1H, CH); 5.11 (broad s, NH_3^+); 7.1-7.4 (m, 10H, $H_{aromatic}$) and 7.86 (d, 1H, NH) ppm.

^{13}C NMR: δ 22.56 (CH_3); 36.06 (CH_2); 37.31 (CH_2); 53.36 (CH); 54.51 (CH); 54.85 (CH_3); 55.12 (CH_3); 105.25 (CH), 125.95-126.23-127.88-128.27-129.16-129.29 ($CH_{aromatic}$); 137.96-138.59 ($C_{aromatic}$), 168.66 (C=O) and 173.71 (C=O) ppm.

- Melting point: Mp=159°C
- Optical rotation: α^{25}_D= -39.6° (MeOH, c=1)

EXAMPLE 3

Preparation of compounds of formula (R)-(I) or (S)-(I) in which:

$R_1 = R_2$ = methyl

R_3 = isobutyl, phenyl, 4-methylbenzyl or Ph-CH_2-CH_2-

The operating conditions of example 1 or 2 are repeated, using N-acetyl-(L)- or -(D)-phenylalanine as resolving agent, various solvents or solvent mixtures, various concentrations by mass of product of formula (I), various temperature conditions and various reaction durations, and performing one or more recrystallizations of the precipitated salts formed, from isopropanol, with various concentrations by mass.

The results obtained are reported in table 1 below.

Table 1

R_3	resolving agent	solvent (concentration by mass)	conditions	Number of recrystallizations (concentration by mass)	ee (%) [a]	yield/resolving agent (%)
isoBu	(L) 0.5 mol. eq.	acetone / isoPrOH 87/13 (6%)	(I) 50°C 3h (II) Ta[c]	2 (7%)	96 (R)[b]	50-55
isoBu	(D) 0.5 mol. eq.	acetone / isoPrOH 87/13 (9%)	(I) 50°C 3h (II) Ta	2 (7%)	96 (S)[b]	50
Ph	(L) 0.5 mol. eq.	isoPrOH (6%)	(I) 50°C 3h (II) Ta	2 (3%)	98 (S)	56
Ph	(D) 0.5 mol. eq.	isoPrOH (6%)	(I) 50°C 3h (II) Ta	2 (5.5%)	97 (R)	70-75
4-MeBn	(L) 0.5 mol. eq.	isoPrOH (9%)	(I) 50°C 3h (II) Ta	2 (5.5%)	99 (R)	65
4-MeBn	(D) 0.5 mol. eq.	isoPrOH (9%)	(I) 50°C 3h (II) Ta	1 (5.5%)	98 (S)	68
$PhCH_2CH_2$	(L) 0.5 mol. eq.	isoPrOH (6%)	(I) 28°C 2h (II) 50°C (III) 30°C	2 (3%)	96 (S)	19
$PhCH_2CH_2$	(D) 0.5 mol. eq.	isoPrOH (6%)	(I) 19°C 2h (II) 50°C (III) 30°C	2 (3%)	96 (R)	23

(a) determined by chiral HPLC

(b) determined by chiral HPLC on the carbamate derivatives of N-Cbz type

(c) Ta = ambient temperature

The results show that, under all the operating conditions used, an optical purity of greater than or equal to 96% is obtained.

EXAMPLE 4

Resolution of racemic 1-benzyl-2,2-dimethoxyethylamine with N-acetyl-(L)-leucine

In a 100 ml two-necked flask equipped with a magnetic stirrer, a condenser and a thermometer, 1 g (5.1 mmol, 1 eq.mol.) of racemic 1-benzyl-2,2-dimethoxyethylamine is introduced into a 6% solution of N-acetyl-(L)-leucine (Sigma Aldrich) in iso-PrOH (2.5 mmol, 0.5 eq.mol.). The medium is stirred at ambient temperature overnight.

The precipitate obtained is filtered off under vacuum and the solid is washed with 10 ml of cyclohexane, and then oven-dried at 40°C under vacuum.

The solid is treated with an aqueous solution of sodium hydroxide and the aqueous phase is extracted with dichloromethane. After concentration of the organic phase, 0.14 g of (R)-1-benzyl-2,2-dimethoxyethylamine is obtained, i.e. a yield of 28% relative to the N-acetyl-(L)-leucine, with an optical purity equal to: $ee_{(R)}$ = 83% (determined by chiral HPLC).

EXAMPLE 5

Resolution of racemic 1-benzyl-2,2-dimethoxyethylamine with N-acetyl-(L)-methionine

In a small flask, 0.13 g (0.6 mmol, 1 eq.mol.) of racemic 1-benzyl-2,2-dimethoxyethylamine and 0.06 g (0.3 mmol, 0.5 eq.mol.) of N-acetyl-(L)-methionine are introduced into 1 g of iso-PrOH (11% solution). The flask is subjected to orbital shaking at ambient temperature overnight.

The medium is filtered and the solid is washed with cyclohexane, and then oven-dried at 40°C under vacuum.

The solid is treated with an aqueous solution of sodium hydroxide and the aqueous phase is extracted with dichloromethane. After concentration of the organic phase, the (S)-1-benzyl-2,2-dimethoxyethylamine is obtained with an optical purity equal to: $ee_{(S)}$ = 70% (determined by chiral HPLC).

EXAMPLE 6

Resolution of racemic 1-benzyl-2,2-dimethoxyethylamine with N-tosyl-(L)-phenylalanine

In a small flask, 0.1 g (0.5 mmol, 1 eq.mol.) of racemic 1-benzyl-2,2-dimethoxyethylamine and 0.08 g (0.25 mmol, 0.5 eq.mol.) of N-tosyl-(L)-phenylalanine are introduced into 0.15 g of MTBE (approximately 30% solution). The flask is subjected to orbital shaking overnight at ambient temperature.

The medium is filtered and the solid is washed with cyclohexane, and then oven-dried at 40°C under vacuum.

The solid is treated with an aqueous solution of sodium hydroxide and the aqueous phase is extracted with dichloromethane. After concentration of the organic phase, the (R)-1-benzyl-2,2-dimethoxyethylamine is obtained with an optical purity equal to: $ee_{(R)}$ = 50% (determined by chiral HPLC).

EXAMPLE 7

Resolution of racemic 1-isobutyl-2,2-dimethoxyethylamine with N-ethoxycarbonyl-(D)-phenylglycine

In a 50 ml round-bottomed flask equipped with a magnetic stirrer, a condenser and a thermometer, 0.26 g (1.6 mmol, 1 eq.mol.) of racemic 1-isobutyl-2,2-dimethoxyethylamine is introduced into a solution of 0.18 g (0.8 mmol, 0.5 eq.mol.) of N-ethoxycarbonyl-(D)-phenylglycine in 0.6 g of a mixture of MTBE/EtOH solvents (76/24, approximately 25% solution). The medium is kept stirring at ambient temperature

overnight.

The medium is filtered and the solid is washed with cyclohexane, and then oven-dried at 40°C under vacuum.

The solid is treated with an aqueous solution of sodium hydroxide and the aqueous phase is extracted with dichloromethane. After concentration of the organic phase, the (R)-1-isobutyl-2,2-dimethoxyethylamine is obtained with an optical purity equal to: $ee_{(R)}$ = 39% (determined by chiral HPLC after formation of the N-Cbz-type carbamate derivative).

EXAMPLE 8

Resolution of racemic 1-(2-phenylethyl)-2,2-diethoxyethylamine with N-acetyl-(L)-phenylalanine

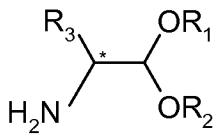
In a 50 ml three-necked flask equipped with a mechanical stirrer, a condenser and a thermometer, 0.22 g (0.93 mmol, 1 eq.mol.) of 1-(2-phenylethyl)-2,2-diethoxyethyl-amine and 0.1 g (0.46 mol, 0.5 eq.mol.) of N-acetyl-(L)-phenylalanine are introduced into 3.45 g of iso-PrOH (6% solution). The medium is stirred for 2 h at ambient temperature and then brought to 50°C, and the return to ambient temperature is carried out slowly. The stirring is maintained overnight.

The medium is filtered and the solid is washed with cyclohexane, and then oven-dried at 40°C under vacuum.

The solid is treated with an aqueous solution of sodium hydroxide and the aqueous phase is extracted with dichloromethane. After concentration of the organic phase, 0.19 g of 1-(2-phenylethyl)-2,2-diethoxyethylamine (colourless oil) is obtained with an enantiomeric excess of 28% (determined by chiral HPLC).

CLAIMS

1. Process for preparing optically active α-aminoacetals of formula (R)-(I) or (S)-(I)



(R)-(I) or (S)-(I)

in which:

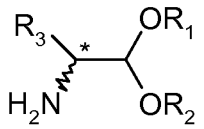
- R_1 and R_2, which may be identical or different, represent a linear or branched C_1-C_{12} alkyl group, or else R_1 and R_2 are joined so as to form a 1,3-dioxolan-2-yl group which is unsubstituted or substituted on positions 4 and/or 5 with one or more linear or branched C_1-C_6 alkyl substituents, or a 1,3-dioxan-2-yl group which is unsubstituted or substituted on positions 4 and/or 5 and/or 6 with one or more linear or branched C_1-C_6 alkyl substituents;

- R_3 represents a linear or branched C_1-C_{12} alkyl group; a C_2-C_{12} alkenyl group; a C_2-C_{12} alkynyl group; a C_3-C_{10} cycloalkyl group; a C_3-C_{10} cycloalkenyl group; a cycloalkylalkyl group in which the cycloalkyl and alkyl groups are as defined above; a heterocycloalkyl group containing 3 to 10 atoms; a heterocycloalkylalkyl group in which the heterocycloalkyl and alkyl groups are as defined above; a monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group; a heteroaryl group containing 5 to 14 atoms; an arylalkyl group or a heteroarylalkyl group, in which the aryl, heteroaryl and alkyl groups are as defined above; a C(=O)R_4 group in which R_4 represents a linear or branched C_1-C_{12} alkyl group, a cycloalkyl group, a cycloalkenyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, as defined above, or an OR_5 group in which R_5 represents an H, a linear or branched C_1-C_{12} alkyl group, a C_3-C_{10} cycloalkyl group, a C_3-C_{10} cycloalkenyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, as defined above, or R_4 represents an NHR_6 group in which R_6 represents an H, a linear or branched C_1-C_{12} alkyl group, a C_3-C_{10} cycloalkyl group, a C_3-C_{10} cycloalkenyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, as defined above; all the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, heterocycloalkyl, heterocyclo-

alkylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl radicals above being unsubstituted or substituted;

- the asterisk * signifies that the C atom is an asymmetrical carbon,

which process comprises the resolution of a compound of formula (I) in racemic form or in the form of mixtures of enantiomers

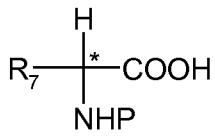


(I)

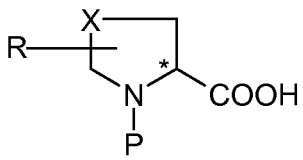
in which R_1, R_2, R_3 and the asterisk * are as defined above, with a resolving agent,

characterized in that said process comprises the steps consisting in:

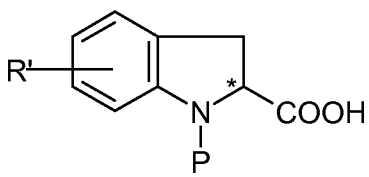
a) reacting a compound of formula (I) with an optically active α-amino acid represented by general formulae (II) to (VI)



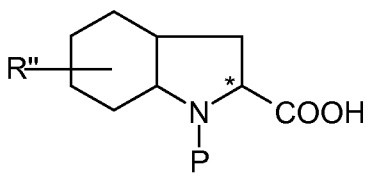
(II)



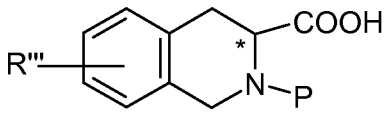
(III)



(IV)



(V)



(VI)

in which:

- R_7 represents a linear or branched C_1-C_{12} alkyl group; a C_3-C_{10} cycloalkyl group; a cycloalkylalkyl group in which the cycloalkyl and alkyl groups are as defined above; a monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group; an arylalkyl group in which the alkyl and aryl groups are as defined above; a heteroaryl group containing 5 to 14 atoms; or a heteroarylalkyl group in which the alkyl and heteroaryl groups are as defined above; all the alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl radicals being unsubstituted or substituted;

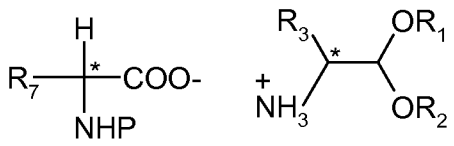
- P represents a 9-fluorenylmethoxycarbonyl protective group; a $-COR_8$ group in which R_8 represents hydrogen, a linear or branched C_1-C_6 alkyl group, a monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group or an OR_9 group in which R_9 represents a linear or branched C_1-C_6 alkyl group or an arylalkyl group in which the aryl and alkyl groups are as defined above; or an $-S(O_2)R_{10}$ group in which R_{10} represents a linear or branched C_1-C_6 alkyl group, a monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group or an arylalkyl group in which the aryl and alkyl groups are as defined above; all the 9-fluorenylmethoxycarbonyl, alkyl, aryl and arylalkyl groups being unsubstituted or substituted;

- X represents a carbon or sulphur atom;

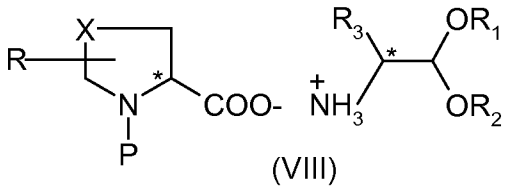
- R, R', R'' and R''', independently of one another, represent one or more hydrogen atom(s), halogen atom(s) or hydroxyl group(s) or an oxo (=O) group;

- the asterisk * signifies that the C atom is an asymmetrical carbon,

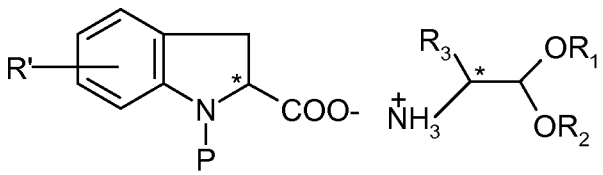
in a solvent, so as to form diastereoisomeric salts represented by formulae (VII) to (XI):



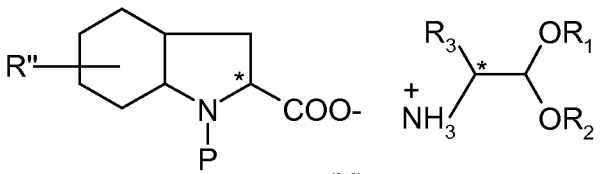
(VII)



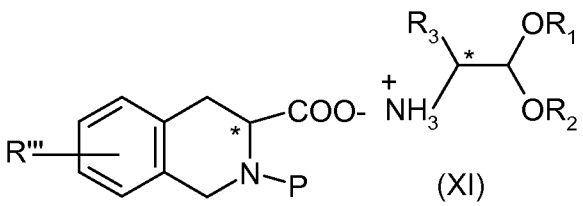
(VIII)



(IX)



(X)



(XI)

in which R_1, R_2, R_3, R_7, P, X, R, R', R'', R''' and the asterisk * are as defined above,

b) separating the diastereoisomeric salts of formulae (VII) to (XI) formed in the medium, and

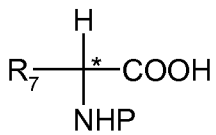
c) releasing the optically active α-aminoacetal of formula (R)-(I) or (S)-(I).

2. Process according to Claim 1, characterized in that use is made of a compound of formula (I) in racemic form or in the form of mixtures of enantiomers, in which

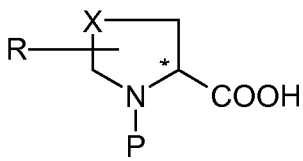
- R_1 and R_2, which may be identical or different, represent a linear or branched C_1-C_6 alkyl group;

- R_3 represents a group chosen from a substituted or unsubstituted, linear or branched C_1-C_6 alkyl group; a substituted or unsubstituted monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group; a substituted or unsubstituted arylalkyl group in which the aryl and alkyl groups are as defined above; a substituted or unsubstituted C_3-C_{10} cycloalkyl group; and a substituted or unsubstituted cycloalkylalkyl group in which the cycloalkyl and alkyl groups are as defined above.

3. Process according to either of Claims 1 and 2, characterized in that a compound of formula (I), in racemic form or in the form of mixtures of enantiomers, is reacted with an optically active α-amino acid represented by general formula (II) or (III)



(II)



(III)

in which:

- R_7 represents a linear or branched C_1-C_6 alkyl group which is unsubstituted or substituted with one or more hydroxyl, -NHP', -C(O)NH_2, -NH-C(=NH)-NHP', -SH, -S-CH_3, -CO_2H or phenyl groups, in which P' represents hydrogen or an acetyl, propionyl, formyl, tosyl, benzoyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or 9-fluorenylmethoxycarbonyl group; a cyclohexyl group; a phenyl group; a benzyl or naphthyl group which is unsubstituted or substituted one or more times with a halogen atom, a hydroxyl group, an NO_2 group, a

phenyl group or a C_1-C_3 alkoxy group; a pyridyl group; an imidazolylmethyl group; a pyridylmethyl group; or a thiazolylmethyl or indolylmethyl group;

- P represents an acetyl, propionyl, formyl, tosyl, benzoyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or 9-fluorenylmethoxycarbonyl group;

- X represents a carbon atom;
- R represents a hydrogen atom.

4. Process according to any one of Claims 1 to 3, characterized in that the optically active α-amino acid is chosen from N-acetyl-(L)-phenylalanine, N-acetyl-(D)-phenylalanine, N-acetyl-(L)-leucine, N-acetyl-(D)-leucine, N-acetyl-(L)-valine, N-acetyl-(D)-valine, N-acetyl-(L)-tyrosine, N-acetyl-(D)-tyrosine, N-acetyl-(L)-methionine, N-acetyl-(D)-methionine, N-acetyl-(L)-asparagine, N-acetyl-(D)-asparagine, N-tosyl-(L)-phenylalanine, N-tosyl-(D)-phenylalanine, N-ethoxyäcarbonyl-(L)-phenylglycine and N-ethoxycarbonyl-(D)-phenylglycine.

5. Process according to any one of Claims 1 to 4, characterized in that the optically active α-amino acid is chosen from N-acetyl-(L)-phenylalanine or N-acetyl-(D)-phenylalanine.

6. Process according to any one of Claims 1 to 5, characterized in that a molar ratio of optically active α-amino acid of between 0.1 and 1 molar equivalent, relative to the compound of formula (I), preferably 0.5 molar equivalent, is used.

7. Process according to any one of Claims 1 to 6, characterized in that the solvent is chosen from the group comprising isopropanol, ethanol, water, acetone, methyl isobutyl ketone, tetrahydrofuran, acetonitrile, ethyl acetate, toluene and methyl tert-butyl ether, and mixtures thereof.

8. Process according to any one of Claims 1 to 7, characterized in that the concentration of the compound of formula (I) in step a) is between 1% and 40% by weight, preferably between 3% and 9% by weight.

9. Process according to any one of Claims 1 to 8, characterized in that the reaction temperature in step a) is between 0°C and 120°C, preferably between 5°C and the boiling point of the reaction medium.

10. Process according to any one of Claims 1 to 9, characterized in that the separation in step b) is carried out by precipitation of the diastereoisomeric salt which is the least soluble of the diastereoisomeric salts formed in the reaction medium, and filtration of the precipitated diastereoisomeric salt from the reaction medium.

11. Process according to any one of Claims 1 to 10, characterized in that step c) is carried out by treatment of the separated diastereoisomeric salt with an alkaline or acidic aqueous solution.

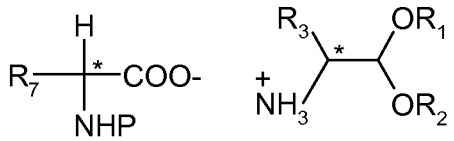
12. Process according to any one of Claims 1 to 11, characterized in that, before releasing the optically active α-aminoacetal of formula (R)-(I) or (S)-(I), as defined in Claim 1, the diastereoisomeric salts of formulae (VII) to (XI) obtained after step b) are subjected to at least one recrystallization or reslurrying step.

13. Process according to any one of Claims 1 to 12, characterized in that it comprises the steps consisting in:

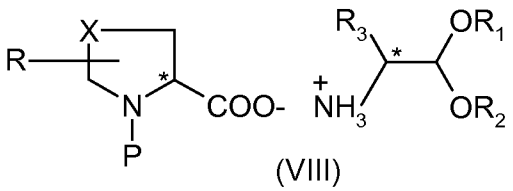
- recovering, from the reaction medium, a diastereoisomeric salt represented by general formulae (VI) to (XI) as defined in Claim 1, which was not separated during step b), and

- releasing the optically active α-aminoacetal of formula (R)-(I) or (S)-(I).

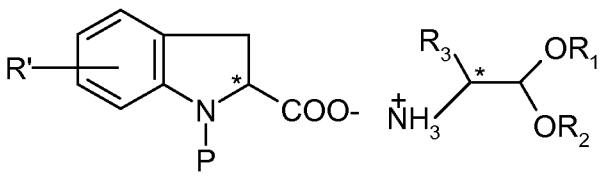
14. Diastereoisomeric salt represented by general formulae (VII) to (XI)



(VII)



(VIII)



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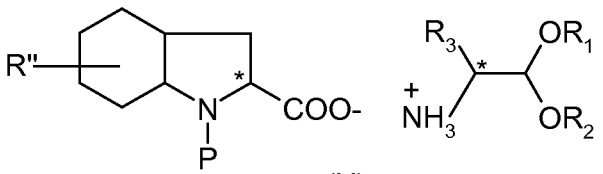
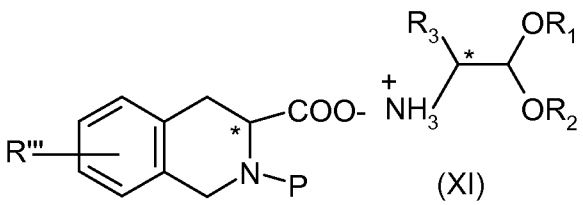


(X)



(XI)

in which:

- R_1 and R_2, which may be identical or different, represent a linear or branched C_1-C_{12} alkyl group, or else R_1 and R_2 are joined so as to form a 1,3-dioxolan-2-

yl group which is unsubstituted or substituted on positions 4 and/or 5 with one or more linear or branched C_1-C_6 alkyl substituents, or a 1,3-dioxan-2-yl group which is unsubstituted or substituted on positions 4 and/or 5 and/or 6 with one or more linear or branched C_1-C_6 alkyl substituents;

- R_3 represents a linear or branched C_1-C_{12} alkyl group; a C_2-C_{12} alkenyl group; a C_2-C_{12} alkynyl group; a C_3-C_{10} cycloalkyl group; a C_3-C_{10} cycloalkenyl group; a cycloalkylalkyl group in which the cycloalkyl and alkyl groups are as defined above; a heterocycloalkyl group containing 3 to 10 atoms; a heterocycloalkylalkyl group in which the heterocycloalkyl and alkyl groups are as defined above; a monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group; a heteroaryl group containing 5 to 14 atoms; an arylalkyl group or a heteroarylalkyl group, in which the aryl, heteroaryl and alkyl groups are as defined above; a $C(=O)R_4$ group in which R_4 represents a linear or branched C_1-C_{12} alkyl group, a cycloalkyl group, a cycloalkenyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, as defined above, or an OR_5 group in which R_5 represents an H, a linear or branched C_1-C_{12} alkyl group, a C_3-C_{10} cycloalkyl group, a C_3-C_{10} cycloalkenyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, as defined above, or R_4 represents an NHR_6 group in which R_6 represents an H, a linear or branched C_1-C_{12} alkyl group, a C_3-C_{10} cycloalkyl group, a C_3-C_{10} cycloalkenyl group, a heterocycloalkyl group, an aryl group or a heteroaryl group, as defined above; all the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl radicals above being unsubstituted or substituted;

- the asterisk * signifies that the C atom is an asymmetrical carbon,

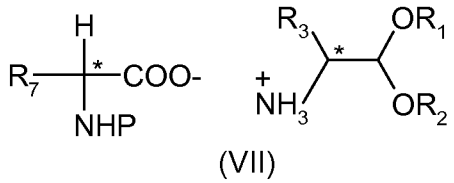
- R_7 represents a linear or branched C_1-C_{12} alkyl group; a C_3-C_{10} cycloalkyl group; a cycloalkylalkyl group in which the cycloalkyl and alkyl groups are as defined above; a monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group; an arylalkyl group in which the alkyl and aryl groups are as defined above; a heteroaryl group containing 5 to 14 atoms; or a heteroarylalkyl group in which the alkyl and heteroaryl groups are as defined above; all the alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl radicals being unsubstituted or substituted;

- P represents a 9-fluorenylmethoxycarbonyl protective group; a -COR_8 group in which R_8 represents hydrogen, a linear or branched C_1-C_6 alkyl group, a monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group or an OR_9 group in which R_9 represents a linear or branched C_1-C_6 alkyl group or an arylalkyl group in which the aryl and alkyl groups are as defined above; or an -$S(O_2)R_{10}$ group in which R_{10} represents a linear or branched C_1-C_6 alkyl group, a monocyclic, bicyclic or tricyclic C_6-C_{14} aryl group or an arylalkyl group in which the aryl and alkyl groups are as defined above; all the 9-fluorenylmethoxycarbonyl, alkyl, aryl and arylalkyl groups being unsubstituted or substituted;

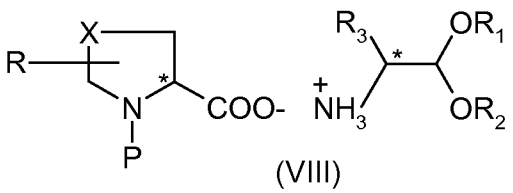
- X represents a carbon or sulphur atom;

- R, R', R" and R"', independently of one another, represent one or more hydrogen atom(s), halogen atom(s) or hydroxyl group(s) or an oxo (=O) group.

15. Diastereoisomeric salt according to Claim 14, represented by general formula (VII) or (VIII)



(VII)



(VIII)

in which:

- R_7 represents a linear or branched C_1-C_6 alkyl group which is unsubstituted or substituted with one or more hydroxyl, -NHP', -$C(O)NH_2$, -NH-C(=NH)-NHP', -SH, -S-CH_3, -CO_2H or phenyl groups, in which P' represents hydrogen or an acetyl, propionyl, formyl, tosyl, benzoyl, ethoxycarbonyl, tert-butoxycarbonyl,

benzyloxycarbonyl or 9-fluorenylmethoxycarbonyl group; a cyclohexyl group; a phenyl group; a benzyl or naphthyl group which is unsubstituted or substituted one or more times with a halogen atom, a hydroxyl group, an NO_2 group, a phenyl group or a C_1-C_3 alkoxy group; a pyridyl group; an imidazolylmethyl group; a pyridylmethyl group; or a thiazolylmethyl or indolylmethyl group;

- P represents an acetyl, propionyl, formyl, tosyl, benzoyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or 9-fluorenylmethoxycarbonyl group;

- X represents a carbon atom;
- R represents a hydrogen atom.

16. Salt according to either of Claims 14 and 15, characterized in that it is chosen from the following compounds:

- (R)-1-benzyl-2,2-dimethoxyethylammonium N-acetyl-(L)-phenylalaninate,
- (S)-1-benzyl-2,2-dimethoxyethylammonium N-acetyl-(D)-phenylalaninate,
- (R)-1-isobutyl-2,2-dimethoxyethylammonium N-acetyl-(L)-phenylalaninate,
- (S)-1-isobutyl-2,2-dimethoxyethylammonium N-acetyl-(D)-phenylalaninate,
- (S)-1-phenyl-2,2-dimethoxyethylammonium N-acetyl-(L)-phenylalaninate,
- (R)-1-phenyl-2,2-dimethoxyethylammonium N-acetyl-(D)-phenylalaninate,
- (R)-1-(4-methylbenzyl)-2,2-dimethoxyethylammonium N-acetyl-(L)-phenyl-alaninate,
- (S)-1-(4-methylbenzyl)-2,2-dimethoxyethylammonium N-acetyl-(D)-phenyl-alaninate, and
- (S)-1-(2-phenylethyl)-2,2-dimethoxyethylammonium N-acetyl-(L)-phenyl-alaninate.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/050665

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C213/10 C07C217/40 C07C229/36

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)
C07C

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 practical, search terms used)
EPO-Internal, WPI Data, PAJ, INSPEC, COMPENDEX, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 59 170058 A (TANABE SEIYAKU CO) 26 September 1984 (1984-09-26) abstract -----	1-16
Y	GUILLAUMIE F ET AL: "Solid-phase synthesis of C-terminal peptide aldehydes from amino acetals anchored to a backbone amide linker (BAL) handle" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, vol. 41, no. 32, 5 August 2000 (2000-08-05), pages 6131-6135, XP004243528 ISSN: 0040-4039 schémas 1 et 2 et parties du texte correspondantes ----- -/--	1-16

[X] Further documents are listed in the continuation of Box C.

[X] 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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 2009	10/03/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Seelmann, Marielle

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/050665

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 374 647 A (BASF AG [DE]) 27 June 1990 (1990-06-27) cited in the application the whole document -----	1-16
Y	D. ENDERS ET AL.: "Enantioselective synthesis of alpha-aminoacetals and alpha-aminoacids by nucleophilic substitution 1,2-addition to diethoxyacetaldehyde SAMP hydrazone." ANGEW. CHEM. INT. ED. ENGL., vol. 32, no. 3, 1993, pages 418-421, XP002500593 cited in the application schéma 1, page 419 et passages pertinents correspondants dans le texte -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/050665

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 59170058 A	26-09-1984	JP 1647716 C	13-03-1992
		JP 3012051 B	19-02-1991
EP 0374647 A	27-06-1990	DE 3843390 A1	05-07-1990