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(54) Title: PROCESS FOR THE PREPARATION OF CHIRAL AMINES

(57) Abstract: The invention relates to a process for the preparation of a chiral amine, whereby a ketone or aldehyde is contacted with an enantiomerically enriched phenylglycine amide to give an imine, whereby the imine is subsequently contacted with a Reformatsky reagent and the formed compound is subsequently converted into a chiral amine by means of hydrogenolysis, oxidation or a retro Strecker method.

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# PROCESS FOR THE PREPARATION OF CHIRAL AMINES

The present invention relates to a process for the preparation of chiral amines, which amines are defined in this application as chiral beta-amino acid esters or amides, or derivatives hereof e.g. acids, or chiral beta amino ketones or chiral beta amino nitriles. These compounds are used e.g. in the manufacture of pharmaceutical or agrochemically active compounds.

A process for the preparation of chiral amines is known from EP-A-0355819 which publication relates specifically to the preparation of chiral beta-amino acid esters. In this disclosure a process is given comprising the steps of 1) reacting an aldehyde with an amine to produce a Schiff base, 2) reacting said Schiff base with a methyl haloacetate and a metal such as Zn to produce a diastereomeric mixture of a beta-lactam, 3) hydrolysing said beta-lactam to produce a diastereomeric mixture of a first beta-amino acid, 4) esterifying said first beta-amino acid, 5) isolating one isomer of the ester of said diastereomeric mixture of said first beta-amino acid, 6) hydrogenolysing said ester to produce one stereoisomer of a second beta amino acid. This process however is known to give very low diastereoselectivities.

A process for the preparation of chiral amines is furthermore known from US 5,840,961. In this disclosure, a 4-step process is described in which process in a first step an aldehyde is reacted with (*R*)- or (*S*)-phenylglycinol as a chiral auxiliary to form an imino-alcohol; in a second step this imino-alcohol is reacted with $BrZnCH_2CO_2$-*t*Bu to form an amino-alcohol; in a third step the chiral auxiliary is removed from the amino alcohol by reaction with sodium periodate or lead tetraacetate to form an imine and finally in a fourth step, the imine is hydrolyzed in the presence of para toluene sulphonic acid to obtain an ester of an (*R*)-or (*S*)-beta amino acid.

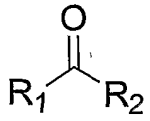
The $BrZnCH_2CO_2$-*t*Bu reagent, in US 5,840,961 referred to as a Reformatsky agent, is prepared separately by activation of zinc with dibromoethane in tetrahydrofuran, followed by reaction with tert-butyl bromoacetate and isolation by filtration. Given this Reformatsky agent's low stability it has to be stored at low temperature (i.e. -10 °C, as mentioned in Example 2 of US 5,840,961).

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Disadvantage of the process as disclosed in US 5,840,961 is that said process comprises many reaction steps resulting in a laborious process for the preparation of chiral beta-amino acids.

Object of the present invention is to provide a process for the preparation of chiral amines, which process has less process steps than the process as disclosed in US 5,840,961.

This object is achieved with a process according to the invention in which process a compound according to formula (I)

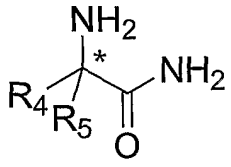


(I)

in which formula

$R_1$, $R_2$ = H, a substituted or unsubstituted: (cyclo)alkyl group, (cyclo)alkenyl group, aryl group, cyclic of acyclic heteroalkyl group or heteroaryl group with one or more N, O, S atoms whereby $R_1 \neq R_2$

is contacted with an enantiomerically enriched phenylglycine amide according to formula (II)



(II)

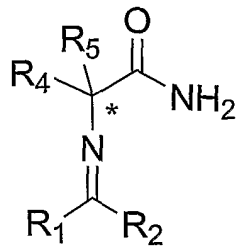
in which formula

$R_4$ = a substituted or unsubstituted phenyl or naphtyl group

$R_5$ = H or alkyl with 1-6 carbon atoms

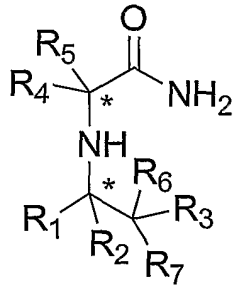
* = a chiral center, which may have the (*R*) or (*S*) configuration

to give an imine according to formula (III), in this application also referred to as a 'Schiff base',



(III)

The Schiff base of formula (III) is converted into a compound according to formula (IV)



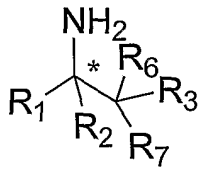
(IV)

by reaction with a Reformatsky reagent $XZnCR_6R_7R_3$

in which formula

| | | |
|---|---|---|
| X = | | Cl, Br or I |
| $R_3$ = | | $COOR_8$, $CONR_8R_9$, $COSR_8$, $COR_8$ or CN |
| $R_6$, $R_7$ | | independent of each other, H, halogen (for example Cl, Br, I or F), a substituted or unsubstituted: (cyclo)alkyl group, (cyclo)alkenyl group, aryl group, cyclic or acyclic heteroalkyl group or a heteroaryl group with one or more N, O, S atoms. |
| $R_8$, $R_9$ = | | independent of each other, a substituted or unsubstituted: (cyclo)alkyl group, (cyclo)alkenyl group, aryl group, cyclic or acyclic heteroalkyl group or a heteroaryl group with one or more N, O, S atoms. |

Finally the compound according to formula (IV) is then converted into the chiral amine according to formula (V) or an amine salt thereof by hydrogenolysis, oxidation or a retro Strecker method.



(V)

The process according to the invention has less process steps than the process as disclosed in US 5,840,961.

An additional advantage is that the process according to the invention uses less costly chiral auxiliaries than those disclosed in US 5,840,961.

Moreover the process according to the invention refrains from using environmentally undesirable compounds such as e.g. lead tetra acetate as used in US 5,840,961. Furthermore the process according to the invention is not restricted to the use of t-butylesters, as in US 5,840,961.

Suitable compounds according to formula (I) are aldehydes or ketones for example, benzaldehyde, 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, 4-fluorobenzaldehyde, 4-trifluoromethylbenzaldehyde, piperonal, acetaldehyde, cyclopropylaldehyde or isopropylaldehyde. Optionally the $R_1$, $R_2$ group may be substituted with for example alkoxy, halo, trifluoromethyl, alkyl or alkylamino groups or aryl or arylamino groups

Furthermore $R_1$ should not equal $R_2$ in order to obtain chiral amines with the process according to the invention.

Preferably $R_1$ is a (cyclo)alkyl or (hetero)aryl group with 3-10 carbon atoms. In the process according to the invention this gives a high yield of the compound according to formula (V).

Preferably $R_2$ comprises H or from 3 to 6 carbon atoms. In the process according to the invention this gives a high yield of the compound according to formula (V).

Compounds according to formula (II) are chiral compounds wherein $R_4$ is a substituted or unsubstituted phenyl- or naphthyl-group, and $R_5$ is H or an alkyl group

If so desired, the phenyl- or naphthyl-group of $R_4$ may be monosubstituted or polysubstituted with for example halogen, in particular chlorine or bromine, a hydroxy group, an alkyl or (hetero)aryl group with for example 1-10 carbon atoms and/or an alkoxy group or acyloxy group with for example 1-10 carbon atoms.

Preferably $R_5$ is H or an alkyl group with 1 to 6 carbon atoms, more preferably $R_5$ is H. In the process according to the invention this gives a high enantiomeric excess, as defined below, of a compound according to formula (V).

A particular preferred compound according to formula (II) is a compound where $R_4$ is a phenyl-group and $R_5$ is a H, hereinafter referred to as phenyl glycine amide (PGA). An advantage of PGA is that it gives compounds according to formula (V) that are generally solids. This means that compounds of formula (IV), which are not completely diastereomerically pure, can be purified to diastereomerically pure compounds in one crystallization step.

Examples of possible substituents on $R_6$, $R_7$, $R_8$ or $R_9$ are: alkoxy, halo, trifluoromethyl, alkyl, aryl, alkylamino and arylamino.

The enantiomeric excess (ee) is defined as the difference between the amounts of enantiomers divided by the sum of the amounts of the enantiomers, which quotient can be expressed as a percentage after multiplication by 100.

Depending on the desired chirality of the compound according to formula (V), either an (*R*)- or (*S*)-configuration of the compound according to formula (II) may be chosen.

In the present invention the compound according to formula (II) is an enantiomerically enriched compound, which means that the compound according to formula (II) has an enantiomeric excess of at least 80%, more preferably of at least 90%, most preferably of at least 98%.

In the process according to the invention the compounds according to formula (I) and (II) are contacted, preferably in a solvent. Preferably water, alcohols, esters, aliphatic or aromatic hydrocarbons or haloalkanes are used as solvents. More preferred solvents include methanol, ethanol, toluene, dichloromethane, ethylacetate or isopropylacetate. In these solvents the compounds according to formula (I) and (II) can be dissolved easily. Optionally a catalyst may be used upon contacting the compounds according to formula (I) and (II). Preferred catalysts include acids, such as for example p-toluenesulphonic acid, pyridinium-p-toluenesulphonate or Lewis acids such as for example titaniumtetrachloride, titaniumtetra-isopropoxide, $BF_3.O(CH_2CH_3)_2$ or $Si(OCH_2CH_3)_4$..

The temperature at which the compounds according to formula (I) and (II) are contacted preferably is between 0-140°C, more preferably between 20-120°C.

Upon contacting the compounds according to formula (I) and formula (II) in the process according to the invention a reaction mixture comprising compound (III) is formed. Compound (III) is an imine, and in this application also referred to as a 'Schiff base'. The reaction mixture comprising compound (III) may be purified before the subsequent contacting with the Reformatsky reagent $XZnCR_6R_7R_3$.

In the next step, the Reformatsky reagent $XZnCR_6R_7R_3$, is contacted with the compound according to formula (III).

In the event that $R_3$ is $-COOR_8$, a beta amino acid ester is produced with the process according to the invention. If required the beta amino acid ester may be hydrolyzed to the beta amino acid with techniques well known to the skilled man.

In the event that $R_3$ is $CONR_8R_9$, or $COSR_8$, a beta amino acid amide respectively a beta amino acid thio ester is produced with the process according to the invention.

In the event that $R_3$ is $COR_8$, or CN a beta amino ketone respectively a beta amino nitril is produced with the process according to the invention.

*Preferably $R_3$ is $-COOR_8$, because the chiral beta amino acid esters* produced thereof can be incorporated directly into pharmaceutical or agrochemically active compounds.

The Reformatsky reagent $XZnCR_6R_7R_3$, may be prepared separately or may be prepared in situ in the process according to the invention. In the Reformatsky reagent $XZnCR_6R_7R_3$, preferably X = Br. The advantage hereof is that this gives the fastest reaction with the compound according to formula (III). Moreover these Reformatsky reagents $BrZnCR_6R_7R_3$ give the highest yield upon reacting with the compound according to formula (III).

In the case that the Reformatsky reagent $XZnCR_6R_7R_3$ is prepared separately this can suitably done with methods as disclosed in "Organozinc reagents in Organic Synthesis", Erdik, E, Ed., CRC Press, 1996, p 55-61.

The Reformatsky reagent $XZnCR_6R_7R_3$,is preferably prepared in situ in the process according to the invention by heating Zn and $XCR_6R_7R_3$ preferably at a temperature between 40 and 120 °C, which in situ formed Reformatsky reagent then subsequently reacts with the compound according to formula (III). Zinc may be used in any form, for example as dust, granules, foil or wire. The zinc may be used without prior activation, however if the reactivity of the zinc would not be sufficient and consequently

resulting in a low yield, the zinc may be activated in situ by methods known to the skilled man, for example by treatment of the zinc with dibromoethane, iodine, trimethylsilylchloride, HCl or by application of ultrasound. Zinc preferably is used in 0.8-10 equivalents related to compound (III), more preferably in 1.0-6 equivalents and most preferred in 1.2-4 equivalents. This results in a good balance between high speed of reaction and limited amounts of zinc to be removed.

A second method of in situ preparation of the Reformatsky reagent $XZnCR_6R_7R_3$, is by contacting $XCR_6R_7R_3$ with $(R_{10})_2Zn$, wherein $R_{10}$ is alkyl, alkenyl or aryl, in the presence of an additive comprising an element from group 4-12 of the periodic table with the compound according to formula III. Most preferred compounds of $(R_{10})_2Zn$ are $(C_2H_5)_2Zn$ and $(CH_3)_2Zn$ because these reagents give fast formation of the Reformatsky reagent $XZnCR_6R_7R_3$. Preferred additives are Cr(III)(acetylacetonatate)$_3$, Fe(III)(acetylacetonate)$_3$, Ni(II)(acetylacetonate)$_2$, $PdCl_2$, $RhCl(PPh_3)$, $IrCl_2$ and $CeCl_3$. More preferably, Fe(III)(acetylacetonate)$_3$ or Ni(II)(acetylacetonate)$_2$ are used, because a higher yield is obtained when these additives are present during contacting the Reformatsky reagent with the compound according to formula (III). The additive is preferably added in an amount of less than 20 mol% based on the total amount of compound according to formula (III), more preferably in an amount of less than 10 mol% and most preferred in an amount of less than 5 mol%.

An additional advantage of in situ preparation of the Reformatsky reagent $XZnCR_6R_7R_3$ is that the process according to the invention comprises even less process steps than the process as disclosed in US 5,840,961.

An additional advantage of the second method of in situ preparation is that a high yield in the compound according to formula (V) is obtained.

The reaction mixture comprising compound (III) is subsequently contacted with the Reformatsky reagent $XZnCR_6R_7R_3$ in the event that this reagent is produced separately. The temperature at which the compound according to formula (III) and the Reformatsky reagent are contacted preferably is between 0 and 140 °C, more preferably between 20-120°C.

Upon contacting the compound according to formula (III) and the Reformatsky reagent $XZnCR_6R_7R_3$ in the process according to the invention a reaction mixture comprising compound (IV) is formed.

In order to increase the diastereoselectivity or purity of the compound according to formula (IV), this compound may be recrystallized, with known techniques, as such or as a salt from a suitable solvent. Suitable salts include those formed with HCl, HBr, acetic acid, p-toluenesulphonic acid, benzenesulphonic acid, tartaric acid. Suitable solvents include heptane, methylisobutylketone, acetone, methyltertbutylether, isopropylacetate, ethylacetate, isopropanol, ethanol or methanol.

Compound (IV) is finally converted through hydrogenolysis, a retro Strecker method or oxidation into the chiral amine according to formula (V).

Hydrogenolysis may suitably be done with $H_2$ using for example Pd as a catalyst. Through hydrogenolysis the chiral centre comprising $R_4$ and $R_5$ is split off from the compound according to formula (IV), resulting in the corresponding chiral amine according to formula (V). Temperature during hydrogenolysis is chosen preferably between 0 and 40 °C, more preferably between 20 and 30 °C. This results in a high yield of the chiral amine according to formula (V)

Another method of converting the compound according to formula (IV) into the corresponding chiral amine is by means of a so-called retro Strecker reaction. This retro Strecker reaction is a one step reaction, in which the amide group of the compound according to formula (IV) is first converted to a nitril, by a dehydrating agent, for example by thionylchloride, phosphoroxy trichloride, phosphorpentachloride, p-toluenesulphonic acid/pyridine, Vilsmeyer reagent/$Et_3N$ or pyridine, cyanuric chloride, acetic acid anhydride, trifluoroacetic acid anhydride and other dehydrating agents, for example as described in March, Advanced Organic Chemistry, 5$^{th}$ Edition, Wiley Interscience, Eds,M.B. Smith and J. March, 2001, p1350 followed by a retro Strecker reaction, i.e. elimination of HCN, for example by addition of a base or by heating. Examples of suitable bases are (earth) alkali metal hydroxides, (earth) alkalimetal carbonates, (earth) alkalimetal phospates and organic bases. Suitable bases are for instance KOH, $Na_2CO_3$ or $K_2CO_3$,followed by hydrolysis with methods known to the skilled man of the obtained imine to the chiral amine. Hydrolysis may suitable be done by e.g. heating the imine to temperatures up to 120°C, addition of acids, or transimination by for example $NH_2OH.HCl$ or $NaHSO_3$. This retro Strecker reaction is carried out in one vessel without isolation of intermediates thereby making it a one step reaction.

A further method of converting the compound according to formula (IV) into the corresponding chiral amine is by means of oxidation followed by hydrolysis of the

imine to the chiral amine according to formula (V). With oxidation in this application is understood treatment with peracids, $O_3$, metal-based oxidative agents such as e.g. $KMnO_4$ and hypochlorites such as e.g. NaOCl. These oxidation methods as such are known and are described e.g. in March, Advanced Organic Chemistry, 5th Edition, Wiley Interscience Eds,M.B. Smith and J. March, 2001, Chapter19..

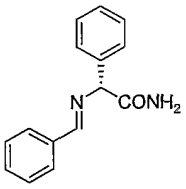
Preferably compound (IV) converted through hydrogenolysis into the chiral amine according to formula (V). The advantage hereof is that this method is less prone to side reactions.

The invention will now be further elucidated with the following examples, without being limited hereto.

Examples

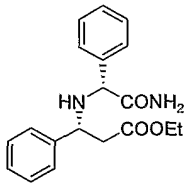
Example I: Synthesis of (*R*)-3-amino-3-phenyl-propionic acid ethyl ester

Ia. First step: Synthesis of (*R*)-2-[(phenylmethylene)-amino]-2-phenylacetamide according to formula:




Phenylglycine amide (50 g, 0.31 mol, assay 94%) and benzaldehyde (34.8 g, 0.33 mol were added to 250 mL of $CH_3OH$. The mixture was stirred at room temperature. After 15 min crystallization was observed. The mixture was stirred for 18 h. After filtration, washing with 2 x 25 mL of $CH_3OH$, a white solid was obtained (63.6 g, 81%). $^1H$ NMR ($CDCl_3$): δ 4.99 (s, 1H), 5.8 (bs, 1H), 7.0 (bs, 1H), 7.4 (m, 8H), 7.8 (m, 2H), 8.31 (s, 1H),

Ib-1. Second step: Synthesis of (*R*)-3-([(*R*)-2-amino-2-oxo-1-phenylethyl]amino)-3-phenyl-propionic acid ethyl ester: Reformatsky reaction of compound from Example Ia with Zn, $BrCH_2COOEt$ to form:



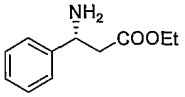

The Schiff base of Example Ia (4.8 g, 20 mmol) was dissolved in $CH_2Cl_2$ (50 mL) and Zn dust was added (5.2, 80 mmol). The reaction mixture was heated until reflux and $BrCH_2COOEt$ (10.4 g, 62 mmol) was dosed in ca 200 min. The mixture was then stirred under reflux (ca 42°C) for 2 h. After cooling the reaction mixture was filtered and added to a solution of 4N aqueous HCl (75 mL). After stirring for approximately 15 h, the precipitated solid was isolated by filtration to give the product as HCl salt (5.2 g, 72%, *de* 96%).$^1$H NMR ($CDCl_3$): δ 1.3 (m), 2.1 (s), 2.8 (m), 4.0 (s), 4.3 (m), 6.1 (br s), 7.2-7.5 (m), 7.9 (s).

Instead of second step Ib-1, second step Ib-2 as given above may be employed:

Ib-2. Second step: Synthesis of (*R*)-3-([(*R*)-2-amino-2-oxo-1-phenylethyl]amino)-3-phenyl-propionic acid ethyl ester: Reformatsky reaction of compound from Example Ia with $Et_2Zn$, $BrCH_2COOEt$ in $CH_2Cl_2$ as solvent.

The Schiff base of Example Ia (8.6 g, 36 mmol) was dissolved in $CH_2Cl_2$ (100 mL) and cooled to *ca.* -30 °C. The following reagents were added in succession: $ZnEt_2$, 1 M in hexane (91 mL, 2.5 eq), $BrCH_2COOEt$ (4.9 mL, 1.2 eq) and Ni(acetylacetonatate)$_2$ (0.5 g, 5 mol%), either drop wise or in portions. The reaction mixture was allowed to warm to room temperature in a controlled fashion and stirred for 3 h, then poured onto about 150 g of crushed ice. The mixture was filtered over Celite, the layers were separated, the organic layer was dried on $Na_2SO_4$ and the volatiles were removed *in vacuo*, yielding a yellow oil. This oil was dissolved in methyl-*t*-butylether (250 mL) and $CH_3OH$ (25 mL), to which about 4.6 mL of 30% aqueous HCl (1.5 eq) was added then. $CH_3OH$ (50 mL) was added and the mixture was stirred for 16 h, after which a white suspension had formed. The solid was filtered off, washed with methyl-*t*-butylether (100 mL) and dried *in vacuo*, affording the product as HCl salt as white solid (8.10 g, 62%). HPLC-MS (Discovery C18): 97 assay % at 216 nm, 97 assay % at 286 nm, 98% *de*.

Ic-1: Third step: Synthesis of (*R*)-3-amino-3-phenyl-propionic acid ethyl ester via retro-Strecker method to form:



The compound of Example Ib (1.54 g, 4.7 mmol) was dissolved in THF (40 mL). $Et_3N$ (7.2 mL, 12 eq) was added and the mixture was cooled on ice. $POCl_3$ (0.9 mL, 2.2 eq) was added dropwise, then the mixture was allowed to warm to room temperature, stirred for 1 h and subsequently refluxed for 5 h. At room temperature, a solution of $NH_2OH \cdot HCl$ (0.91 g, 3 eq) in $H_2O$ (50 mL) was added and the resulting mixture was stirred for 16 h. The pH was adjusted to 1 with 30% HCl and THF was removed *in vacuo*. The aqueous layer was washed with methyl-*t*-butylether (40 mL), then $CH_2Cl_2$ was added (50 mL) and the pH was adjusted to 10 with 10% aqueous NaOH. The layers were separated, the organic layer was dried on $Na_2SO_4$ and the volatiles were removed *in vacuo*, affording a brown oil (0.51 g, 54%). $^1H$ NMR ($CDCl_3$): δ 1.5 (q, 3H), 2.6 (d, 2H), 3.9 (q, 2H), 4.4 (t, 1H), 7.4 (m, 5H). HPLC (Chiralcel OD): >99% *ee*.

Instead of third step Ic-1, third step Ic-2 as given above may be employed:

Ic-2: Third step: Synthesis of (*R*)-3-amino-3-phenyl-propionic acid ethyl ester via oxidation

The product of Example Ib (0.84 g, 2.37 mmol) was dissolved in acetone (40 mL). $KMnO_4$ (0.94 g, 2.5 eq) was added and the mixture was stirred for 16 h, then 6 mL of 1 M aqueous NaOH (2.5 eq) was added and the mixture was filtered over Celite. Acetone was removed *in vacuo* and the residue was partitioned between $CH_2Cl_2$ (40 mL) and $H_2O$ (40 mL). The layers were separated, the organic layer was dried on $Na_2SO_4$ and volatiles were removed *in vacuo*, yielding a yellow oil (1.03 g). This was dissolved in tetrahydrofuran (20 mL) and $H_2O$ (20 mL) and $NH_2OH \cdot HCl$ (0.50 g, 3 eq) was added. The mixture was stirred for 16 h, then THF was removed *in vacuo*. The pH was adjusted to 1 with 1 M HCl and the aqueous layer was washed with EtOAc (30 mL). The pH was adjusted to 10 with 10% aqueous NaOH and the aqueous layer was extracted with $CH_2Cl_2$ (50 mL). The organic layer was dried on $Na_2SO_4$ and the volatiles were removed *in vacuo*,

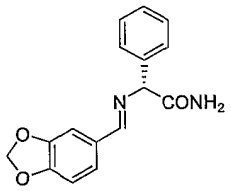
affording a yellow oil (0.23 g, 44%). $^1$H NMR ($CDCl_3$): *vide supra*. HPLC (Chiralcel OD): 99% *ee*.

Example II: Synthesis of (*R*)-3-amino-3-benzo[1,3]dioxol-5-yl-propionic acid ethyl ester

IIa. First step: Synthesis of (*R*)-2-[(benzo[1,3]dioxol-5-ylmethylene)-amino]-2-phenylacetamide

Phenylglycine amide (50 g, 0.31 mol, assay 94%) and piperonal (50 g, 0.30 mol) were added to 400 mL of $CH_3OH$. After heating to 30°C a clear solution was obtained. The mixture was stirred at room temperature for 18 h and a precipitate was observed. After filtration, washing with 2 x 25 mL of $CH_3OH$, a white solid was obtained (73 g, 86 %). $^1$H NMR ($CDCl_3$): δ 4.9 (s, 1H), 6.0, (m, 3H), 6.8 (m, 1H), 7.01 (br s, 1H), 7.3 (m, 7H), 8.2 (s, 1H)

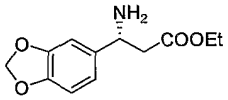
IIb. Second step: Synthesis of (*R*)-3-([(*R*)-2-amino-2-oxo-1-phenylethyl]amino)-3-[(benzo[1,3]dioxol-5-yl)-3-propionic acid ethyl ester: Reformatsky reaction of compound from Example IIa with $Et_2Zn$, $BrCH_2COOEt$ to form:




The Schiff base of example IIa (10.3 g, 36 mmol) was dissolved in $CH_2Cl_2$ (100 mL) and cooled to about -30 °C. The following reagents were added in succession: $Et_2Zn$ (1 M in hexane. 91 mL, 2.5 eq), $BrCH_2COOEt$ (4.9 mL, 1.2 eq) and Ni(acetylacetonatate)$_2$ (0.5 g, 5 mol%), either dropwise or in portions. The reaction mixture was allowed to warm to room temperature in ca 30 min and stirred for 3 h, then poured onto *ca*. 150 g of crushed ice. The mixture was filtered over Celite, the layers were separated, the organic layer was dried on $Na_2SO_4$ and the volatiles were removed *in vacuo*, yielding yellow oil. This was dissolved in methyl-*t*-butylether (250 mL) and $CH_3OH$ (25 mL), to which *ca*. 4.6 mL of 30% aqueous HCl (1.5 eq) was added. A precipitate formed initially, but rapidly oiled out. $CH_3OH$ (25 mL) was added and the mixture was

stirred for 16 h, after which a white suspension had formed. The solid was filtered off, washed with methyl-*t*-butylether (100 mL) and dried *in vacuo*, affording a white solid (7.89 g, 59%). HPLC-MS (Discovery C18): 97 assay % at 216 nm, 97 assay % at 286 nm, 98% *de*.

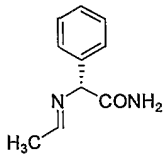
IIc: Third step: Synthesis of (*R*)-3-amino-3-benzo[1,3]dioxol-5-yl-propionic acid ethyl ester via hydrogenolysis to form:




The compound of example IIb (6 g, 0.13 mol) was dissolved in dry EtOH (100 mL) and 5% Pd/C (1.9 g, 50 % $H_2O$) was added. The mixture was shaken at 9 bar $H_2$ for 16h. The Pd/C was removed by filtration over Celite and after addition of 5 mL of concentrated aqueous HCl the solvent was removed by evaporation. To the residu EtOAc (150 mL) was added and the solvent removed by evaporation. Then again EtOAc was added, stirred for 15 h to give the product as HCl salt (3.1 g, 87%, *ee* 96% containing a small amount (8%) of phenylacetamide. $^1$H NMR ($CDCl_3$): δ 1.3 (t, 3H), 1.8 (br s, 2H), 2.6 (d, 2H), 4.2 (q, 2H), 4.4 (t, 1H), 6.0 (s, 2H), 6.8-7.0 (m, 3H).

Example III: Synthesis of (*S*)-3-amino-butyric acid ethyl ester.

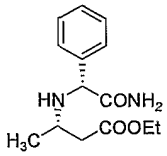
IIIa. First step: Synthesis of (*R*)-2-[(ethylidene)-amino]-2-phenylacetamide:




Phenylglycine amide (30 g, 0.19 mol, assay 94%) and 5 g $Na_2SO_4$ were added to 250 mL of $CH_2Cl_2$. To the stirred mixture was added acetaldehyde (8.8 g, 0.20 mol). The mixture was stirred at room temperature for 1 h and the solids were removed by filtration. The $CH_2Cl_2$ was removed by evaporation and the residu stirred in 150 mL EtOAc.

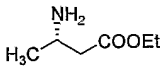
The solid was filtrated and washed with 2 x 25 mL of EtOAc. After drying the imine was obtained as a white solid (26.2 g, 78.4%). $^1$H NMR ($CDCl_3$): δ 2.1 (d, 3H), 4.7 (s, 1H), 5.9 (br s, 1H), 6.9 (br s, 1H), 7.4 (m, 5H), 7.8 (q, 1H).

IIIb; Second step: (*S*)-3-([(*R*)-2-amino-2-oxo-1-phenylethyl]amino)-butyric acid ethyl ester: Reformatsky reaction of compound from Example IIIa with $Et_2Zn$, $BrCH_2COOEt$ and $CH_2Cl_2$ to form:




The Schiff base of Example IIIa (67.3 g, 0.38 mol) was dissolved in $CH_2Cl_2$ (1500 mL) and cooled on ice-NaCl. The following reagents were added in succession: $Et_2Zn$ (1 M in hexane, 955 mL, 2.5 eq), $BrCH_2COOEt$ (63.5 mL, 1.2 eq) and Ni(acetylacetonatate)$_2$ (4.91 g, 5 mol%), either dropwise or in portions. The deep-orange solution was allowed to warm to room temperature and stirred for 2 h, then poured onto about 2000 g of crushed ice. The mixture was stirred to room temperature over 16 h and then filtered over Celite. The layers were separated, the organic layer was dried on $Na_2SO_4$ and the volatiles were removed *in vacuo*, yielding a brown oil (81.5 g, 81%). $^1$H NMR ($CDCl_3$): δ 1.2 (d, 3H), 1.3 (t, 3H), 1.7 (br, 1H), 2.3-2.6 (m, 2H), 3.2 (m, 1H), 4.2 (m, 3H), 4.4 (s, 1H), 6.1 (br s, 1H), 7.2-7.4 (m, 5H), 7.6 (br s, 1H). HPLC-MS (Discovery C18): 73 assay % at 218 nm, >99% *de*.

IIIc: Third step: Synthesis of (*S*)-3-amino-butyric acid ethyl ester via hydrogenolysis



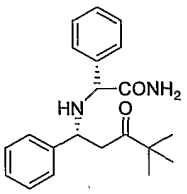

The compound of example IIIb (33.3 g, 0.13 mol) was dissolved in dry EtOH (160 mL). AcOH (36.5 mL, 5 eq) and dry reduced 10% Pd/C (3.33 g, 10% w/w) were added with care. The mixture was shaken at 5 bar $H_2$ for 24 h, then filtered over Celite. The residue was extracted with $H_2O$ (250 mL) and EtOH was removed *in vacuo* until a crystalline white precipitate formed ($PhCH_2CONH_2$). This was filtered off and washed with

$H_2O$ (50 mL). $CH_2Cl_2$ (400 mL) was added to the combined filtrates, then the pH was adjusted to 9 with 10% aqueous NaOH. The layers were separated, the organic layer was dried on $Na_2SO_4$ and the volatiles were removed *in vacuo* without external heating. The residue was extracted with pentane (2 x 125 mL) and the pentane removed *in vacuo* without heating. This afforded a yellow oil (8.81 g, 53%). $^1H$ NMR ($CDCl_3$): δ 1.1 (d, 3H), 1.2 (t, 3H), 1.6 (s, 2H), 2.2-2.4 (m, 2H), 3.4 (m, 1H), 4.1 (q, 2H). HPLC (Crownpak): 92% *ee*.

Example IV: Synthesis of (*R*)-1-Amino-4,4-dimethyl-1-phenyl-pentane-3-one

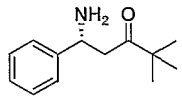
Step IVa: Synthesis of Schiff base: see example Ia

Step IVb: Synthesis of (*R*)-1-([(*R*)-2-amino-2-oxo-1-phenylethyl]amino)-4,4-dimethyl-1-phenyl-pentane-3-one: Reformatsky reaction of compound from Example IVa with $Et_2Zn$, $BrCH_2COOEt$ in $CH_2Cl_2$ as solvent to form:




The Schiff base of Example.IVa (0.87 g, 3.65 mmol) was dissolved in $CH_2Cl_2$ (40 mL). The following reagents were added in succession: $Et_2Zn$, (1 M in hexane, (9.1 mL, 2.5 eq), $BrCH_2CO$*t*-Bu (0.59 mL, 1.2 eq), Ni(acetylacetonatate)$_2$ (0.05 g, 5 mol%) and $PPh_3$ (0.10 g, 10 mol%). The resulting orange solution was stirred for 2 h, then saturated $NH_4Cl$ (50 mL) was added. The layers were separated, the organic layer was dried on $Na_2SO_4$ and the volatiles were removed *in vacuo*, affording a yellow oil (1.52 g), HPLC-MS (Discovery C18): 58 assay %, 99% *de*. $^1H$ NMR ($CDCl_3$): δ 1.3 (s, 9H), 2.2 (bm, 1H) 2.6-3.4 (m, 2H), 4.1 (s,1H), 4.3-4.4 (m, 1H), 6.2 (br s, 1H), 7.2-7.9 (m, 10H), 8.1 (bs, 1H).

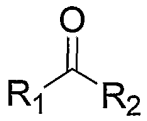
Step IVc: Synthesis of (*R*)-1-Amino-4,4-dimethyl-1-phenyl-pentane-3-one via retro Strecker method to form:



Procedure as described in Example Ic gives 0.34 g brown oil (54 %, assay 90%). $^1$H NMR ($CDCl_3$): δ 1.2 (s, 9H), 1.9 (bm, 2H) 2.8-3.2 (m, 2H), 4.5-4.6 (m,1H), 7.3-7.6 (m, 5H).

CLAIMS

1. Process for the preparation of a chiral amine whereby a compound according to formula (I)

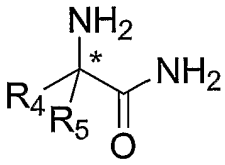


(I)

in which formula

$R_1$, $R_2$ = H, a substituted or unsubstituted: (cyclo)alkyl group, (cyclo)alkenyl group, aryl group, cyclic of acyclic heteroalkyl group or heteroaryl group with one or more N, O, S atoms, whereby $R_1 \neq R_2$

is contacted with an enantiomerically enriched phenylglycine amide according to formula (II)



(II)

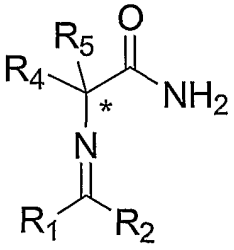
in which formula

$R_4$ = a substituted or unsubstituted phenyl or naphthyl group

$R_5$ = H or alkyl with 1-6 carbon atoms

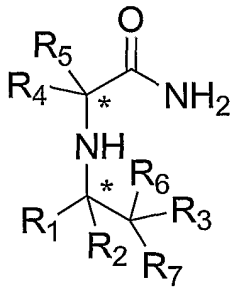
* = a chiral center, which may have the (*R*) or (*S*) configuration

to give an imine according to formula (III),



(III)

whereby the compound of formula (III) is subsequently converted into a compound according to formula (IV)
wherein

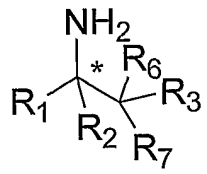


(IV)

by contacting with a Reformatsky reagent $BrZnCR_6R_7R_3$,
in which formulas

| | | |
|---|---|---|
| X = | | Cl, Br or I |
| $R_3$ = | | $COOR_8$, $CONR_8R_9$, $COSR_8$, $COR_8$ or CN |
| $R_6$, $R_7$ | | independent of each other, H, halogen, a substituted or unsubstituted: (cyclo)alkyl group, (cyclo)alkenyl group, aryl group, cyclic of acyclic heteroalkyl group or a heteroaryl group with one or more N, O, S atoms |
| $R_8$,$R_9$ = | | independent of each other, a substituted or unsubstituted: (cyclo)alkyl group, (cyclo)alkenyl group, aryl group, cyclic of acyclic heteroalkyl group or a heteroaryl group with one or more N, O, S atoms |

and finally the compound according to formula (IV) is converted into a chiral amine according to formula (V) by means of hydrogenolysis, oxidation or a retro Strecker method



(V)

2. Process according to claim 1, where, in the compound according to formula (II), $R_4$ is a phenyl-group and $R_5$ is a H.

3. Process according to claim 1 or 2, where the compound according to formula (II) has an enantiomeric excess of at least 80%.

4 Process according to any one of claims 1-3, whereby said Reformatsky reagent $XZnCR_6R_7R_3$ is prepared in situ by contacting $XCR_6R_7R_3$ with $(R_{10})_2Zn$, wherein $R_{10}$ is alkyl, alkenyl or aryl and additive comprising an element from group 4-12 of the periodic table is present

5. Process according to claim 4, wherein $(R_{10})_2Zn$ is $(C_2H_5)_2Zn$.

6. Process according to claim 4 or 5 wherein the additive is $Cr(III)(acetylacetonatate)_3$, $Fe(III)(acetylacetonate)_3$ or $Ni(II)(acetylacetonate)_2$.

7. Process according to any one of claims 1-6, where, in the Reformatsky reagent $XZnCR_6R_7R_3$, X is Br and $R_3$ is $COOR_8$.

8. Process according to claim 7 whereby the obtained compound according to formula (V) is subsequently hydrolysed.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/014170

A. CLASSIFICATION OF SUBJECT MATTER
C07C227/32 C07C231/18 C07C221/00 C07C253/30 C07B53/00
C07C229/34 C07C229/08 C07C225/16

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 C07B

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

[X] See patent family annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 3 March 2006 | 13/03/2006 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Rufet, J |

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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